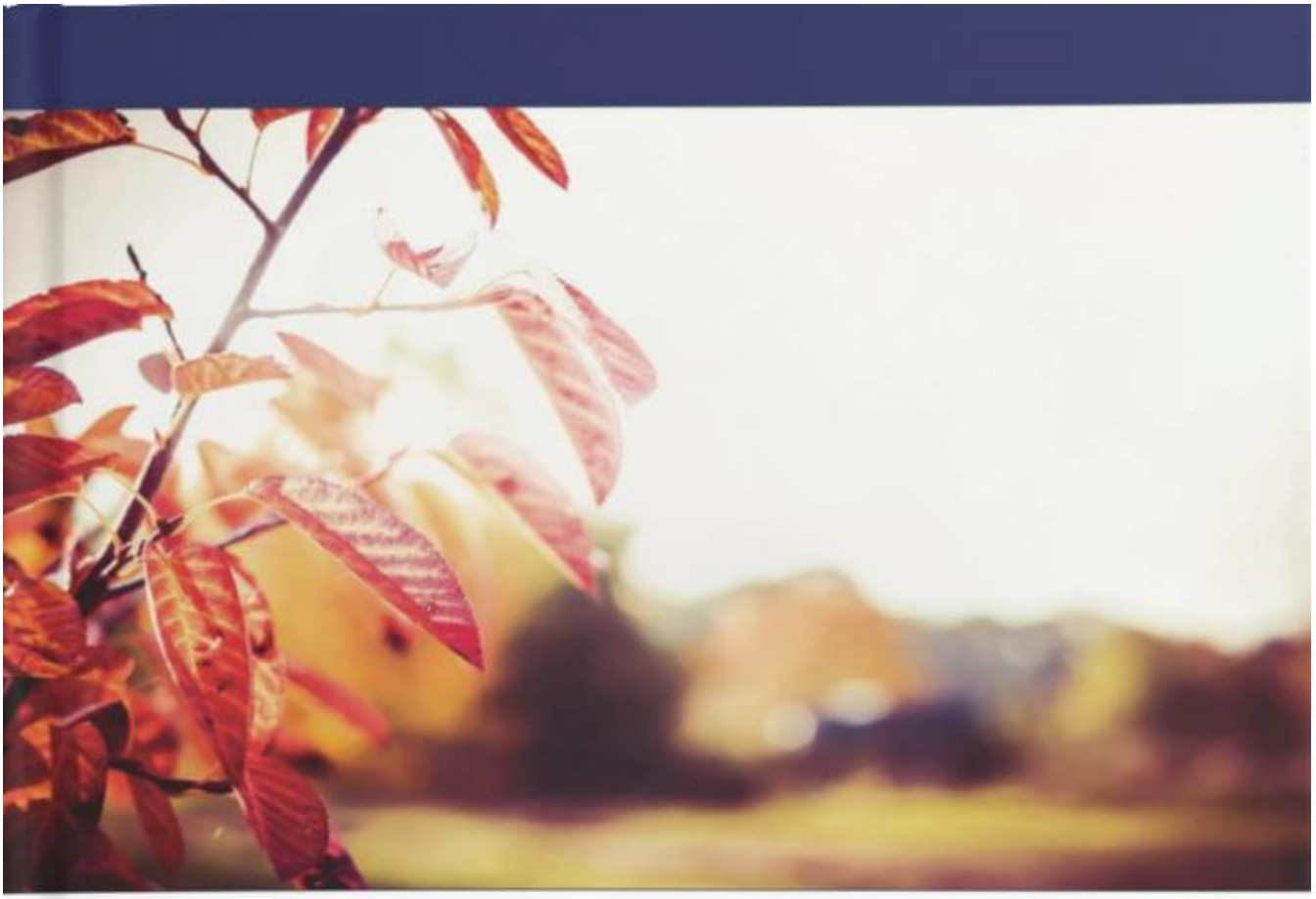

Costas Demetzos

The Voice of Science - The Silence of Nature

LAP LAMBERT Academic Publishing

Make a leap faster than decay[1]

Odysseas Elytis
Maria Nephele

[1] Elytis, O. (1981) *Maria Nephele*: *a Poem In Two Voices* / translated from the Greek by Athan. Anagnostopoulos. Houghton Mifflin.

Translated by: Eleni Vlachou

Edited by: Dr Vilelmini Sosoni and John O'Shea

FOREWORD

This wonderful book, "The Voice of Science, the Silence of Nature", written with loving care by Professor Costas Demetzos, is a journey through the Cosmos and its evolution over time. It deals with fundamental concepts of how it was born, of what the laws that dictate its function are, of what life is, and of how one could unify our current understanding of our position as human beings in this apparently infinite and eternal universe that appears to exist among other universes, participating in the so-called "multiverse".

He started by explaining the basic concepts of complex systems theory as a discussion with a wise old man, his "grandpa", an alter ego, explaining hard concepts in a simple, but not simplistic, actually quite accurate, didactic, grasping manner. These concepts historically were first intuitively examined and defined by Pythagoras of Samos and his student Alkmaeon of Croton, a Greek colony in Southern Italy. Pythagoras introduced the "harmony" of the Cosmos, the latter understood as a complex dynamic system in equilibrium or balance, between disturbing and re-establishing forces, an idea that was later extrapolated by Alkmaeon to human beings and called "isonomia". It is worth mentioning here the definition of a "complex system" as expressed by Alkmaeon: "Αρμονία δ'εστί πολυμιγέων ένωσις και δίχα φρονεόντων συμφρόνησις", Αλκμαίων Κροτωνιάτης (i.e., "Harmony is the union of multiple, mixed, components, and the agreement of the opposites", Alkmaeon of Croton). This concept was later presented by Epicurus as "eustatheia": "Ευστάθεια" το της "σαρκός και ψυχής ευσταθές κατάστημα", Επίκουρος Αθηναίος ("Eustatheia", the balanced state of the flesh and the soul", Epicurus of Athens). The concept was presumably lost during the so-called "dark ages" and reappeared as "homeostasis" in the 20th century, described by the legendary American physiologist Walter Cannon.

The author continued his discussion with grandpa with explaining the Cosmos as a complex system calling it "macrocosm", consisting of smaller ("microcosm", "nanocosm", etc.) and larger ("megacosm") complex systems, with novel properties emerging from the smaller to the larger physical dimensions of their constituents. He described the laws of thermodynamics, quantomechanics, etc., and proceeded to explain the creation of life via molecular self-assembly and cellular and multi-cellular organismal self-organization ("autopoiesis"), and then, by making unifying syntheses and using useful metaphors, he inter-connected the inanimate with the animate world, including the human individual and its societies. Here, he discussed and then used the biophysical concepts of "metastable phases" and "lyotropy" to explain changes in the macrocosm.

As our universe most likely started out as a singularity, -an infinitesimally small, ordered ball of energy, which has ballooned out and continued to expand as time progresses-, “entropy”, i.e., disorder, has been constantly growing with time, granted that there is more space and, therefore, a larger number of potential states of disorder. On the other hand, the total complexity (or information density) of our universe has been increasing with time, both because of the inevitable expansion of its parts, while, specifically, on our, at present, “unique” intelligent life-bearing planet, the “negative entropy” (order) that is life, adds another enormous amount of complexity to our Cosmos. In fact, if one plots complexity, expressed as “power density”, over the time of about 14.4 billion years that took our universe to reach its present state, there is an exponential curve, with life rapidly evolving on the time scale of the last 4.2 billion years, to ever more complex living organisms, with pinnacle the human beings and their immensely complex brains and civilization.

This beautifully written, erudite, and approachable book has a lot to teach and it does so with aplomb. It is a simplified, understandable tour-de-force, that will educate students and professionals alike. I enjoyed reading it and I recommend it with great enthusiasm.

George P. Chrousos, MD, MACP, MACE, FRCP,
Professor of Pediatrics and Endocrinology Emeritus,
Holder, UNESCO Chair on Adolescent Health Care,
Director, University Research Institute of Maternal and Child Health and Precision Medicine,
National and Kapodistrian University of Athens, Athens, Greece

PREFACE

There are many reasons to write a book. They may depend on the writer's intellectual and philosophical needs, on his experiences and world view, on the means chosen to express his feelings and, in the final analysis, on the means chosen to share those feelings with the world. The reason, though, is often silence, or an attempt to approach matters of concern through the medium of the written words. Another reason for capturing thoughts in digital format or on paper may be the need to ensure that the views continue to be heard over time, or simply to let go of them/get them out of your head, or to let them stand trial, open to whatever fair or unfair judgment may come their way.

I believe that publishing a book comes as the result of prolonged effort; an effort measured not only in scientific and writing "time", but also in terms of various parameters that cannot be quantitatively assessed. Maturity, self-consciousness, responsibility, education gained over the course of many years and experience come together to create a *starting point in time* from which one can begin to process the scientific data, philosophical questions and international bibliographical references one has amassed, which begin to "ferment" in some credible way.

This book is not a novel or a scientific missive, nor a dissertation or an account of events in narrative form.

It is a conversation with... Grandpa.

Grandpa, will sometimes appear as someone who takes us by surprise, and other times as the kind of elf you might meet in the sort of library where he roams. Grandpa is the sort of person we all avoid facing up to and listening to. He's the sort of person who is always there in our life. It's up to us whether or not we choose to talk to him.

Grandpa's knowledge is vast. He can guide us depending on our human needs and social expectations. We meet him the moment we are born. He follows us everywhere, waiting for us to cast a glance in his direction from time to time, seek out his advice, talk to him. And what might we talk about? Maybe about our sense of melancholy – not our familiar sense of how we behave, but rather the melancholy of our dialectic oppositions.

The conversation with Grandpa recounted in this book is a demanding one. It calls for perseverance as you come to understand the challenging concepts discussed. Science has been chosen as the channel for conveying these ideas and, in several places, I draw philosophical allusions. It has been proven through the ages that science and philosophy pave a safe way into and out of the study of inquiries and the pursuit of answers to difficult questions. This is a demanding

endeavor and the approach taken needs to be consistent with the process of data analysis and synthesis so as to properly organize and inform our inquiries. Years of devotion, perseverance and patience are required to identify those scientific tools which can be used to pursue knowledge; knowledge which we might never fully possess.

Moreover, this book presents a game with the Mirror of Time; the Mirror that everybody is called upon to face so they can learn who they truly are. Look into it and you will see either a monster or a saint. In this Mirror, you won't see yourself as some image you can boast about or whose shape you can modify to reflect some archetype –probably not of virtue but– of beauty. Rather, what you see is your trajectory over time and the experiences you carry with you as your consciousness, your past. You choose or change your destination and then mature based on the choices you make. The decision to face the Mirror of Time calls for maturity and decisiveness; factors which will most likely contribute to the end result in some positive way. It is often not right to look into the Mirror early on in one's life; that is to say before deciding that the time for this test has really come. Deciding on when to take the test can take many –too many– years, or it might not even ever happen. The Mirror can also be something to play around with. You can analyze the reflections you see and interpret them, or even change the lighting, see yourself in different colors and choose the reflections or the reality that suit you. The Mirror will show you your level of knowledge and awareness; it will reflect your present and project your future, not as some reflection of a blurry reality, but rather as a projection of truth.

But what else can you see in there apart from yourself? The experiences of other people who looked into the Mirror's depths lead us to Grandpa.

The Mirror and Grandpa will always be there, next to us. The Mirror will reflect the results of our own personal conflicts and changes to our own qualities. Grandpa will be there to encourage and guide us through our choices.

The Mirror and Grandpa will never lie to us and nor should we lie to them. Otherwise, a blurry image will be proof that we were mistaken, or that we are not following what Nature is whispering to us; what is echoed in Grandpa's words.

If you are lucky enough to meet him, remember that Grandpa is strict, yet also encouraging and fair – all at the same time. He will not ask you to interpret everything. Although you may ask yourself demanding questions and set yourself difficult problems, you won't necessarily find an answer to every single question. What Grandpa will ask for, though, is consistency and devotion to the conversation. You can't fool him because he's the one who has all the tools at his disposal. Even the technology we use can't fool him, for he has his own witches and fairies at his beck and call...

But you'll definitely learn a lot by talking to him.

I learnt a lot myself.

Every reader can meet Grandpa if they so wish, and every reader can talk openly with him. I am certain that they will find, if not all the answers they are looking for, then at least some knowledge. It is my wish that every reader sees themselves through Grandpa's eyes and that they become better persons by looking straight into the Mirror of their life.

Costas Demetzos

Athens 2022

Dedicated to my parents,
Nikos and Maria,
the primordial past of my own *creation*
and to
Voula, Katerina and Maria,
the living present of my own *evolution*.

Acknowledgments

I owe my gratitude to all those who taught me and continue to teach me, even without knowing it, either by offering me their knowledge, or through their actions. All of them were the driving force that activated my thinking and influenced my daily life and inspired me in my creative expressions.

I would like to thank my students and colleagues who, through their discussions and fruitful observations in the university auditoriums and research laboratories confirmed the anguish of my primordial questions and helped me make the decision to write this treatise. I owe them a lot.

I would like to warmly thank my mentor and companion during my spiritual wanderings, Professor Panagiotis Mitropetros, for his corrections and pertinent remarks in the first draft of this book which were key to its successful completion and presentation.

I would also like to extend my warm thanks to my dear colleague and Professor of Chemistry at the National and Kapodistrian University of Athens, Kyriakos Vyras, for his willingness to accept to read and correct this work mainly as regards the scientific parts.

My heartfelt gratitude goes out to Professor Costas Papailiou, who as a scientist and friend agreed to read the book and lend a listening ear to my scientific anxieties and social concerns. His remarks were the catalyst for its completion.

I also owe a warm thank you to the publisher Ms Margarita Parisianou from the PARISIANOU S.A. Publishing House in Greece for our constructive discussions and the continuous encouragement during the writing of the book.

I would also like to thank Ms Eleni Vlachou, who worked on the translation of the book.

I would also like to thank Dr. Vilelmini Sosoni and John O'Shea for their editing work on the English manuscript.

I would also like to thank Mr. Nikos Fikioris and In-Touch Health for their support.

Finally, I would like to thank everyone in my life who taught me to be sensitive and to hear and smell the beautiful world around me[2].

[2] **Conflicts of interest**: The author declares that there is no conflict of interest. The figures, schemes, pictures, and mathematical equations original or modified as well as the text as a whole or in parts, are adapted from the Greek original version with written permission from the Greek publisher PARISIANOU S.A

ABSTRACT

The book *The Voice of Science - The Silence of Nature* seeks to highlight the silent and soundless evolutionary processes and phenomena that dynamically unfold in nature without us being able to perceive them due to the scale on which they take place. Furthermore, it aims to showcase the scientific research and the timeless scientific tools and turning points in human thought, which are used in the macrocosm and constitute the voice of the scientific community in our effort to understand those silent natural processes and evolution.

This dialogue between macrocosm and microcosm as a means of understanding creation and the evolution of all species constitutes the underlying wisdom of the natural order, its determinism so to speak. The Silence of Nature 'carries' the creations that human beings attempt to examine through The Voice of Science. Philosophy constitutes the means that men and women use to build an understanding of the processes of creation and evolution, in order not to lose themselves in the endless process of 'the foundation of the cosmos' and creation, and in order to surpass their inherent imperfections and weaknesses.

THE ESSENCE OF THIS BOOK

This book is about a young scientist who tries to grasp the meaning of demanding scientific concepts, put them in order and connect them to everyday life. Our young scientist's natural habitat is the library, where Grandpa, appears either as a memory from the past or a vision from the future. From the challenges that the young scientist faces in his conversation with Grandpa and the demands of the scientific discourse he engages in, images emerge in an imaginary Mirror. This imaginary Mirror keeps on depicting blurry reflections. Thus, blurriness signifies the insufficiency of the images that appear with each new piece of knowledge acquired. While discussing demanding scientific, social and philosophical concepts with Grandpa, the young scientist comes to understand that each new image that emerges as a result of new knowledge acquired is always smaller and even more insignificant compared to the one which comes right after, that is the one that emerges and appears in the imaginary Mirror as a result of the conversation with Grandpa and the acquisition of new knowledge. The dead end –in reality, the evolution of the young scientist's knowledge– between Grandpa and the Mirror depicts man's endless conflict in the effort to grasp the 'truth' and his need for an endless journey, an Odyssey into the universal world surrounding us.

MY WISH TO YOU

It is my wish and hope that this book will inspire the young but also the more experienced to feel these quiet natural processes and to understand them as ‘projections’ of the microcosm into the macrocosm that surrounds us.

Reviews

The book by Professor Costas Demetzos is an original and deeply personal scientific quest for the origins of the creation of natural laws in the microcosm, but also for the visible results in the macrocosm. The book is a unique attempt to combine science with philosophical and social references and constitutes a highly original piece of writing.

Kyriakos Viras
Emeritus Professor of Chemistry
National & Kapodistrian University of Athens

This book is a true introspection, an internal monologue presented externally as a dialogue with ‘Grandpa’ in a library dominated by a peculiar Mirror, the Mirror of time and self-consciousness. It explores complex scientific issues in a literary way. The book constitutes a fascinating scientific discussion, which touches upon all aspects of scientific knowledge and human sensitivities.

Panagiotis Mitropetros
Professor of Ancient Greek, Headmaster of Lyceum

Fascinating stuff! And a very difficult exercise in the philosophy of science and intellectual thinking, generally speaking. A task in which I am confident you will succeed as I am aware of the power of your intellect and its versatility.

Gregory Gregoriadis
Professor, University of London - University College London

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PART I

THE BEGINNING

Night had just fallen when I opened the door of the room. Grandpa, as always, was sitting on the edge of the sofa eyes closed, probably asleep. At least he looked like he was asleep. I was used to seeing him like this and was no longer afraid... In the past, I used to think he had passed away, without even telling me!

Now, Grandpa, in his familiar pose, was probably trying to dream up answers to the questions that had nestled in his mind throughout the previous days or years; questions that tortured him incessantly.

"*Perhaps not all things need to have an answer*", he would say.

Over all the years I've known him –or, to put it better, the years that I have been aware of his existence and have been observing him– he even asked questions that appeared to have straightforward answers. Grandpa would not easily accept any 'answer', though. He would listen to it and then make clear that this was merely one approach to the inquiry at hand. He would refuse to answer, and would probably even mock not the answerer, but rather the answer itself. Especially when the answerer was young, he was highly appreciative of the answerer's endeavors to find an answer. He understood young people, perhaps because he saw himself as forever young, as if he was on some teenage trajectory into the field of inquiries; enjoying the unknown. He is engaged in a constant attempt to understand the natural environment, human beings, nature in general and to solve the primordial unanswered questions. Those questions are often so simplistic that they are the sort of things children ask.

Key Point

Yet as long as questions remained unanswered, they remain great.

Picture 1

"*Why is it that a centipede never stumbles*?", he would occasionally say to himself. He'd ask himself and other people similar questions out of his desire to poke fun at nature's quirks; quirks that most people think that have no answer, or not a serious one at least. But what serious answer could there be to a question like that? Is it the one concomitant with our level of knowledge? One that reflects our own experiences, our studies, our expectations for the future? Naturally, there are answers to everything. It's just that the answer you get might not be the ideal one. Yet the answer exists. If that were not so, we might become depressed by the sheer amount of questions and queries that arise in our day-to-day lives. Still, it's not easy to answer seemingly simple everyday questions.

Take for example the spontaneous questions children ask. Adults are often left dumbstruck with what they ask. Usually, too, they are unable to respond with the seriousness that is required. The questions little children ask are always so serious and so vital. Have you ever seen a child laugh when they ask something? Just look at them. They pull a very serious face and demand an answer. They insist. They just have to know so they can get on with their lives. Every answer to their everyday questions is a step forward for them. And we can see how seriously they take this. Respect and clear answers are required.

I was thinking about Grandpa, about how many questions he has answered, how many answers he must have been given in his life. An infinite number, I guess. But is the world we live in so utterly unknown to us? What memories do we have? What if there is no memory, we can associate with each and every single thing in our past? Everything is probably new and unknown when we are born, and our memories, our primordial memories... may be –or in fact definitely are–

embedded in our genes and express when the conditions and the environment allow it.

But I should check with Grandpa, just to see what he is doing now.

Ok, he's still sitting in the same position. I am trying to discern what features of his face and body shape time has preserved like imprints of a unique existence; imprints that have been transferred to me as well.

Yes, maybe to me as well. I would love that, so I know what I'm referring to when I reflect on my past and my origins. Often, I try to find the ways in which I resemble Grandpa, whether it's in my forehead, my gaze, my choices... It is very hard to identify behaviors, but not so hard to discover similarities when it comes to the face and body.

When people are young, and later too when they grow up to be middle-aged, they usually look into their deep past to see what 'paths' their family walked. They do so mainly by looking to their grandparents, and less so to their parents. This is perhaps because with the passing of time the prevalent features that serve as markers of a generation become firmly fixed. And it is those features that we try to find.

Why am I thinking about these things, anyway? Grandpa is still sitting on the couch, ignoring my presence, perhaps even unaware that I am here.

I will keep thinking about Grandpa. In doing so, I think that I am getting to know him better and that I have enough time to do so. It is still very early to start 'the' conversation with him. The conversation! I don't know if it is going to be a conversation, a lecture or a study on complex concepts and paths of the mind that will require great effort and personal labor to navigate.

Grandpa was a scientist. He still is. Even though he is of pensionable age he hasn't really retired in professional or scientific terms. It's common to refer to retired people as grandpas... Anyway... Being a scientist, Grandpa was –and still is– interested in simple things, not great things, as he is would like to say. I'm sure though that he has important things to say, important things to learn. I know that there are important books in his library, which he surely must have read.

He said that what is important or not is defined by the value the individual attaches to it. Small and 'humble' books can contain important concepts and thoughts in just a few pages. It is important to read these works yourself and to draw ideas and approaches from them that had previously never been thought about. That's helpful in forming your own opinion on different objective or subjective matters. It seems Grandpa couldn't grasp complex matters because according to him, his brain lacked the 'metastable phases' to allow something like that. In other words, "*there weren't enough mechanisms for accelerated and effective data processing, meaning inefficient statistical analysis, and a brain that*

didn't function as well as other people did", Grandpa used to say. He took the view that his own brain had limited computing power and was inherently incapable of understanding complex mathematical concepts. And he also said that he possessed more cerebral meta-functionality for data processing and synthesis, which created simple, understandable results. It was later on that I came to understand what these 'metastable phases' meant. They are 'rafts' or, to put it more simply, biophysical 'wrinkles', like the ones on our forehead, which are related to the morphology and behavior of cell membranes. Grandpa would say that his 'intelligence' was limited to mere 'phase transitions' of the brain cell membranes. A brain function of no limited value at all, I'd say. Everyone has their own set of skills; all you have to do is recognize what they are or seek help in discovering what they are. Once that's done, they are bound to be useful to society and science. I have often thought how useful a person who hated math might be, or someone who dislikes and avoids the theoretical subjects of philosophy, languages and history. Substantially useful I'd say, in my experience. Every single person is useful, provided those around them allow them to understand how important they are in a professional or social setting. Why was it then that when I was in school, student's skills and abilities were not discovered to help them grow? I do understand that the educational model includes general and necessary knowledge for integrating into society and into any profession, since knowledge is common and necessary. But, what about skills? Everyone needs guidance in developing their skills or a potential talent, even though that skill/talent may be of lesser importance to others. Perhaps it is the personal 'metastable phases' of cell membranes, as Grandpa would say, that are hard to recognize and precisely identified, or perhaps science does not yet possess the tools to acknowledge their importance and to handle them.

Why am I thinking about these things, anyway?

Grandpa said that society, educational systems and people advance and adjust themselves based on developments, on the evolution at every level of the complexity of life and of its functions, and on social phenomena.

The truth is I didn't really understand what Grandpa was saying, especially when he mentioned things like the 'metastable phases' of cell membranes. For what it's worth, he seemed to have studied the science of biophysics, judging by what he said, and his understanding of that science led him to new issues. I tried very patiently to understand what he was talking about and, above all to tie it back into the matters we had previously discussed. I always liked to create a web of well-developed thoughts and to situate it within a larger context; and then, within an even larger one, until the picture became blurred, and I returned to the previous one. I would remain staring at that picture for God knows how long, and then,

with the data I had acquired, the picture would shrink and form part of a larger one that now became visible. It meant playing around with knowledge and the results of years of studies. This only gave me temporary answers though. I generally liked combinatory thinking, blending together concepts of complementary hues.

Grandpa felt very happy every time he shared a new line of inquiry with me when he had discovered something. He said he didn't care about the answer, which could have many aspects to it; what interested him was to talk about the line of inquiry.

So, it is a strange thing that, while school and the educational process as a whole are based on ‘answering’ questions other people have had, i.e., school exams, questions to prove some kind of competence in a cognitive field and so on, what is of extreme importance in the end is the process of how to formulate questions, or as Grandpa prefers to put it, to talk about inquiries. It is also remarkable that discovering inquiries and not asking questions is the one thing that constitutes real research activity, since in research ‘inquiries’ are the quintessence of and the driving force in human evolution. On the contrary, everyday questions need to be answered quickly because they are simply part and parcel of our everyday life and we need to have correct, ‘approved’ answers. Let me think about this for a moment, just to get it clear in my mind. Asking somebody a question in order to get some objective information is a different thing from disclosing a line of inquiry of scientific or social importance. Before approaching Grandpa, I should also probably make it clear that inquiries with well-proven answers, such as natural laws, math, chemistry, social sciences, and the laws of society and many more, constitute answers to questions which had been posed at some unknown point in time and were later given an answer. Therefore, inquiries in their original expression, i.e., many years, perhaps even centuries or millions of years ago, today constitute questions in our everyday lives. Of course, it was these answers that created human civilization and led to all growth and human well-being on our planet. Therefore, questions and answers are of value at school, in education and in our everyday life; however, in mine and Grandpa's world, ‘identifying inquiries is a creative pastime and calls for a scientific approach’. No, it is not selfish. Thousands of human beings try to identify inquiries about our planet – and even non-human beings do so. Living organisms evolve within completely controlled mechanisms, posing their own inquiries while already having answers to everyday questions that their survival process poses.

I'd say I'm happy because I’ve managed to work out the key terms (at least how I understand them) and define them and put them in some sort of order. Now, when the conversation with Grandpa begins, I will have my own opinions and we

won’t waste time. But in any event, time is never wasted. It is only time not gained.

Key Point

Identifying inquiries rather than asking questions, is central to research activity. It is those ‘inquiries’ that are the quintessence of and the driving force pushing science forward.

PREPARING FOR THE CONVERSATION

I slowly approached Grandpa and sat next to him, trying not to disturb him. Perhaps I hoped that he might share with me some of the issues that he certainly thought or dreamed of. Grandpa doesn't waste time. Even in his sleep, he dreams about important matters, processing them, trying to find answers. I knew that because he had told me.

“*Time, as we have learned to experience it, must constitute for us the regulator of our everyday lives and we have to respect it. We need to know its limits, because it is there where human activity takes place; the activities which allow us to think, to wonder, to identify inquiries. It is important, then, to communicate with the rest of the world –humans, nature, events– based on time as we have defined it as a society. In this framework of time, we will be given the opportunity to understand the timeless essence of real events*.”

Grandpa talked to me about the concept of time in those words. I didn't get it. I was so young, and my knowledge was limited back then. But I believe that it is now time I talked to him again about the concept of time. Let's see what I can do while he is asleep.

Oh, I know! Let me enter his thoughts while he is asleep. I can use technology to help me. I will only have to embed his thoughts into my smartphone after downloading the right app. I will search for an *app* that allows you to download human thoughts. Oh, what superficial expectations I have... But let’s try. I immediately tried to download the *app* called Human Mind Hacker or HMH[3] and to create a hologram of his thoughts... It would be a complex process, I thought to myself, with millions of ‘wrinkles’ (i.e., ‘metastable phases’) depicted on my phone; but still I hoped that I could discern something. By searching the relevant databases, I hoped to retrieve the information I needed. Technology wouldn’t fail me, I thought to myself. This was my own technology, one that

[3] HMH: is not a real *app*

Grandpa could not experience, or could it be that he had experienced it before me? Grandpa was always so unpredictable!

I also thought that I could identify the inquiries Grandpa had identified, perhaps some of his answers to queries, to dream the future through the past and to learn about scientific data I didn't know about, that could help me understand what is real and objective and what is not. It was as simple as that: I learned from Grandpa that if I studied, as I did, I would have more chances of becoming less selfish and of understanding my own imperfections through my own knowledge. With this new *app* on my smartphone, I would have just such an ability. I would enter Grandpa's thoughts. Grandpa did not have to be awake, as long as I could detect the hologram of his thoughts and could read the inquiries, he had identified through that, and then... I'd have the answers, I assume. I'd then have to think what my next steps would be.

My thinking was probably way too simplistic, failing to take into account the complexity of the human brain, the complex networks of brain synapses and functions which are largely still unexplored by science. How could a smartphone *app* ever have this potential? Still, I hoped technology would have a solution.

"*Technological leaps impress us*", Grandpa had once told me, "*but the reality of human nature surpasses us.*"

He had also advised me not to count solely on technological advances, but more so on the abilities and skills that I discovered within myself every day. It is in them that all of nature's wisdom can be found. "*Technology will simply help you discover, organize and use them for yourself, as well as for society*" he said.

Key Point

Technological advances impress us, but the reality of human nature surpasses us.

I knew that one of Grandpa's foibles was his interest in the correlation between science and social phenomena and their interpretation through the scientific data of exact sciences and economics. He was also interested in culture and how it manifested through various forms of human behavior: art, theatre, poetry... and of course, exact sciences and economics. "*Science is mankind's great culture*," he said. "*Without science, we would not be able to explain natural phenomena, to know ourselves and our imperfections, to be more efficient.*"

I thought that a painting or a poem can depict not just the artist's need to express themselves, nature and its beauty. The so-called abstract art, and any form of art is nothing more than the depiction of reality by pushing beyond the limitations of our brain. It is the beauty of the real picture that we cannot perceive in the macrocosm we live in. So, why abstract? Perhaps because we live in our three-dimensional world and based on the 'approved' scientific and social order, we can 'see' the projections of another world or worlds as a fictional reality. Only an artist, or an artistically sensitive scientist can perceive or experience –even if only subconsciously– the real dimension and to a certain degree describe it. It is very hard for other people to understand or experience what an artist feels and describes. So, they dub it 'abstract art', 'surrealism' and so on, to capture the sense of what lies beyond.

I had once asked him, "Grandpa, are there other dimensions, unseen by us?" "*Of course*," he had replied, "*there are other dimensions where space and time unite, giving birth to a space-time continuum, a 'soup' of events which curve the space-time*; *we see the objects in the form we know, but in the three-dimensional space that was decided as the most prevalent for our planet, for the human species.*"

I had not understood any part of what Grandpa had said... 'A space-time continuum'? I took up studying and after a long time I began to understand what it was that Grandpa had meant. But there is a host of questions or even lesser inquiries that emerged through the course of those studies: Does inanimate nature (i.e., biomaterials) bear the imprint of time or, to put it better, of the space-time continuum? Do living creatures, animate beings, hide a 'silent' imprint of their space-time continuum in their genetic makeup which is 'transcribed' into the macrocosm like a projection of the being, and this being is perceived as a curvature in space-time continuum?

So, it seems that examining the terms 'creation' and 'evolution' will be important in the conversation with Grandpa, who has still not woken up. This is a hard approach to take. I don't know if we are going to be able –or if we will have time– to go through such things. As far as I know, the relevant literature touches on philosophy and theology as well as the classical principles of the sciences. I'd say that these approaches are important and I hope Grandpa will be happy with them when our conversation starts... just as soon as he wakes up.

Key Point

There are other dimensions where space and time unite, giving birth to a space-time continuum, a 'soup' of events which curve space-time.

" *The entropy of a system is deterministic evolution and leads to qualitatively higher levels of organization*'', Grandpa would often say to himself. He thought that the collision and struggle of the opposing sides and the laws of dialectics were directly linked to the laws of thermodynamics as well as to statistical physics and thermodynamics. "*Yes*", he would say, "*and here comes the great art of philosophy, which can lead you to paths of thought where the 'metastable phases*' –here they come again, the 'metastable phases' of the brain cell membranes, Grandpa's obsessive thoughts, I'd think to myself– "*present you with stimuli and images that nobody can imagine. It is in these 'metastable phases' of the brain that philosophical thinking, opinions, the depiction of art on canvas and poetry, are all based. These thoughts are not familiar to everyone, because the 'metastable phases' are a product of the primordial past and it is they who choose to whom they are going to show themselves... and certainly they do not reveal themselves to everybody*", as Grandpa says.

How does this selection take place? I' d wonder. How could somebody be a philosopher and convey great meaning, or look at the sea and its thousands of shades of blue and express them in a poem, while others cannot? Of course, personal endeavor and dedication to the goal you set, gives you the biophysical and thermodynamic 'advantage', according to Grandpa's views.

He often talked to himself and would break into a smile every time he identified similar correlations. It was as if he approached the social and natural phenomena in his own way; a way that people next to him could not imagine. This made him happy and posed new lines of inquiry and new ways of approaching them. He would share them with people next to him when the chance came and I had heard him do so many times, though I have to admit I did not pay much attention.

"*The evolution of society follows natural laws – which are transformed into social laws and rules to create any social organization. Social changes evolve macroscopically so very slowly and confirm the laws of thermodynamics and the battle against entropy, in an ever-changing, extremely complex system*", he said.

Strange words and phrases, I would think every time I thought of Grandpa.

What did he mean? I guess I should study a lot to understand him. I would often ask him when I found him sitting in his armchair, there in the library.

That library was not really the bookcases, as you might expect, or the books inside it. It was accumulated knowledge, some sense of a place of concentration, contemplation and creation. A place for personal quests and inquiries, a place where thousands of hours would pass in front of my eyes, yet I was unable to hold onto those hours... My whole lifetime inside Grandpa's books, inside a room where ignorance slowly and painstakingly, year by year, step by step gave its way to knowledge. Grandpa was always there, rallying me on in my efforts.

I often thought to myself how lucky I had been. I'd been given the chance to have a library and to have a Grandpa I inherited from the past, so full of memories, so willing to hold my hand. I constantly asked him questions, although he preferred to use the term 'inquiries'. Later on, he taught me that inquiries are more important and that it would be a great blessing and satisfaction if I could identify at least one major inquiry. It takes much work and study, it takes practice and devotion; there is much to overcome and many sacrifices to be made to acquire a more profound knowledge of nature and the data we have, and to fill in the large or small missing parts of the puzzle that help in solving the issue you've identified.

"What is a system, Grandpa?" I had once asked him.

"*Nothing more than mathematical variables which are self-assembled, based on exterior stimuli, into a piece of information is statistically perceptible to people as prevalent. In the background the chaotic process remains, but we can perceive only its deterministic outcome'*. In science, a system can be defined as the set of data in a network of integrated processes which is subject to laws and constraints. For example, living beings are organized in a system, and cells are the basic unit of life.

When I was still a newcomer to the library, I used to think to myself that Grandpa was so wise. There was no Internet back then, only a primitive little computer and even before that only a calculator. I used to count on my fingers. How old was I then?

Grandpa says things that other people do not understand. "But I have my smartphone application now and I'll be able to see everything through the hologram of his thoughts", I thought, and I kept on pressing buttons on my smartphone trying to complete the download of the application which would allow me to engage in this 'biological reading'.

Then I remembered what he had replied to me when I had asked him in the past:

"Are you wise, Grandpa?"

"Who is wise?" he had replied. "*Could it be the one who is aware of the things he does not know and of the imperfection of his objective, limited senses and of his mental capacity? 'I know that I know nothing', the philosopher Socrates had said in ancient times."*

"I am not wise", he had replied, *"because I talk about things without seeing them. I do not have the direct experience of the processes of life and my knowledge derives solely from the result that I can observe in the macrocosm where I live. I have an opinion, not knowledge."*

And he had added, *"Do you also see the variables I mentioned? Or do you see time or the space-time continuum?"*

"Hey, Grandpa", I had replied, "I'm not scared of the stuff you talk about."

In all my insolence I would think to myself some people have worked hard up to now so we can live and contemplate about centipedes and stuff.

"Imagine what happens 'deep down'", he had told me showing me a seed, *"and what happens 'up high'",* and he had pointed at the sky. *"Do you know, can you tell me?"*

He had replied to the question I was thinking about! Grandpa could read my thoughts! I was petrified, but I quickly came to.

But these also happened to be the same answers that he had given to me in the past. So, I was to assume everything was fine... Or was it not? Grandpa was asleep yet chatting to me at the very same time. Something wasn't quite right.

Grandpa kept on sleeping and I kept thinking about how I could interpret the hologram of his thoughts and dreams. I was mad at him and at my technology's failure to penetrate his innermost thoughts. Oh boy, how is it possible that the very same people who are trying to convince us about the smartness of their devices have failed to think of a single effective application for this common thing; reading somebody else's thoughts? Is it possible that what they lack is the ability to create an intelligent device, not just a smart one?

THE CONVERSATION WITH GRANDPA BEGINS

I was about to leave his side when he moved his hand and touched mine.

"*Wait,*" he said. "*Take a seat. I will tell you a story I have been thinking about for a long time now. I didn't have all the tools at my disposal to develop it into a system of thought and reflection. You know, there have been times when everything I wanted to tell you lay within me. Nobody knew about it, but we were developing it nonetheless, each one in his own way, even just by existing on Earth; with wars, with everyday battles and, of course, with human weaknesses... which*

have always been there. However, civilization advanced and, through conflict, new qualitative leaps led to new behaviors and to a new way of organizing everyday human life. There are places on this Earth that are called 'blessed', but to me it is the people who live in those places who are blessed, as long as they understand this and accept this blessing, study and transmit to future generations what was bestowed upon them, what they developed or are called to develop: knowledge and culture, science and philosophy, social progress and the improvement of people's lives. A long time ago – I can't say exactly how long or I would do a disservice to the clock of time– new ideas were burnt at the stake, people were forced to live in ignorance... a primitive form of 'civilization', that was bound to evolve. Yet would it develop for better or for worse? That, I don't know. There is no absolute truth. According to Protagoras' (490 BC – ca 420 BC), 'Man is the measure of all things'. That means that people are the measure of everything and are the ones to define the limits of each other's behavior."

Picture 2: Protagoras

Protagoras, from Abdera, Thrace, was an important classical philosopher. He was a contemporary of Democritus, who was also from Abdera, and was the greatest among all sophists and the founder of the sophist movement.

Protagoras introduced relativism and subjectivism into philosophy. Protagoras thought that knowledge is not defined objectively, but rather through the senses.

Protagoras introduced the concept of 'anthropocentrism', with his characteristic statement "Man is the measure of all things". This statement means that man is the measure of truth and knowledge, and for this reason every subjective view on a given subject is of value (https://en.wikipedia.org/wiki/Protagoras)**.**

"*However*", Grandpa went on, "*I think it seems that I had already 'known' everything I wanted to tell you, in the past, my very distant past, without knowing why. Maybe culture and science have been following me as a part of my primeval existence.*"

"Grandpa, do you now possess all the tools you lacked to transmit to me

what you hold inside, i.e., science and culture? Have you activated the 'metastable phases' in your brain, as you put it, to categorize and organize what you wish to tell me, so that I can carry them as tools, and both know and understand my primordial lines of inquiries?" I asked him.

"*Not exactly, but I know how to describe what I wish to tell you. I can better organize what I want to tell you. So, I propose that we walk around the magical realm of science, or rather a very small part of it, and have a conversation. What do you think? Perhaps we will need to borrow some useful, classical books from the library. What do you think? But you have to put your mind and your scientific skills to work. Only then will you be able to understand everything I wish to tell you. You will see that some demanding scientific concepts will be familiar to you too; you will feel like you already know them.*"

"That would be amazing, Grandpa! Will it be, I wonder?"

"*We will proceed with great concepts, which we need to think of as the building blocks of our conversation. Who knows? Various lines of inquiry might also arise. If we manage to do that and be able to conclude our conversation then, my dear boy, we will be successful. That remains to be seen, though.*

Furthermore, we should also take into consideration in our conversation – without entering too deep in this field, which is the field of theology– that, according to the narrative in Genesis, there are four important fields: nature, life, man and society. In these fields, important processes take place, resulting from differences and conflicts that occur there and constitute the evolutionary engine driving our world.[4] *It is in these fields that all the important, mystery-packed events in the microcosm and the macrocosm take place. And just like Einstein says in the book The Evolution of Physics, 'nature is a big book full of mysteries, and it has yet to reveal all of them'.*"

All that Grandpa suggests is important, but here come those lines of inquiry again! I thought to myself. Isn't he going to give me answers? Any answer whatsoever to the questions I will be asking him? Anyway, let' s move on. So be it. I will keep him company... His hand held mine as if he didn't want to let it go and I felt its warmth.

[4] N. Matsouka, "Επιστήμη, Φιλοσοφία και Θεολογία στην Εξαήμερο του Μ. Βασιλείου", [Epistími, Philosophía kai Theología stin Exaímero tou M. Vasilíou / Science, Philosophy and Theology in Saint Basil's Hexaemeron], p. 200, Kyriakidis publications, 2016, vol. 7, "Θεολογία και Οικουμένη" (Theología kai Ikouméni) series, 2016 (in Greek).

Picture 3

I made myself more comfortable and gazed over at him. Grandpa was staring at the opposite wall. He looked like he was trying to gather his thoughts.

"*What is the highest power we should always be seeking out; a power that holds all answers and truths*?", he asked me.

Oh dear, I thought. We're going to spend our nights and days having conversations that won't lead to any answers, talking about centipedes and things like that...

"*I see*", Grandpa said, "*that a question like that belongs at the end of our journey and that we'll have to do a lot of talking before we can get to that point. But what if this question of mine also happens to be a line of inquiry? I should tell you that if you ask me I'm not going to give you a single answer or even the multiple answers that may exist, because I simply don't have them.*"

Oh dear, I thought to myself again. We're at the very same point that I suspected we were at before he woke up. Grandpa has brought up a line of inquiry for exploration. Just brilliant! I can follow what he's saying. I understand him... If he has an answer, he formulates it as a question. If he doesn't have an answer, then he formulates it as line of inquiry. If that's the case, things will be hard, for there are no answers.

"*What is the highest power we should always be seeking for? A power that holds all answers and truths*?" That is not a line of inquiry! That's the quest for

some universal science and philosophy! You can spend an entire lifetime trying to get a grip on it and still fail to come up even with the simplest of answers! What is Grandpa trying to tell me? What is he trying to tell me by raising this line of inquiry?

He has posed a great line of inquiry indeed and I guess you could say we have a long way ahead of us. Yet, all I can see is a dead end in front of me. So, we're led to an important line of inquiry, not to a question, since there is no answer...

I kept those thoughts to myself. Let's just say they constitute my first success in my conversation with Grandpa, and I was feeling especially happy about that. He obviously wouldn't have a single answer or even multiple answers for this line inquiry, at least today. So, I thought it was best to move on.

Grandpa continued,

"*I have a road map, my boy, a scientific journey that I suggest that you take... In any case we have a lot of time ahead of us... Not the sort of time you can measure on a clock. The time it takes for a change to occur is slow. Yet it's also very quick when we observe it in our macrocosm, by which I mean in the world we see. So, we can measure it. Which type of clock do you prefer?*"

Once again, I didn't quite understand what Grandpa meant... I thought that if I picked up his clock, I might understand... I was curious to see where this would lead.

"*Look*", he said, "*I can assure you that the conversation that follows requires you to free your imagination and dream of what is happening 'deep down' within you. And when I tell you that you'll be creating the narrative, I mean it. I won't have to talk at all. At the very least I won't be talking so as not to confuse you. I'll only talk when it's necessary. You should know that a conversation doesn't always need two or more people speaking to each other; one can do most of the talking; that is more than enough. In the end, you'll see that I'll have said very little. That's the way it should be.*"

"Where can I find this 'deep down' place within myself, Grandpa?", I ask him to kick-start the conversation.

"*It is a place where the world is very small. We cannot see it. It's where all efforts are made for the survival of our species and for the creation of natural laws. The foundation of natural laws is an astonishingly harmonious process, which also includes the evolutionary process of creation. As a process, it is the 'uterus' containing the primordial and multifaceted genetic information of everything; as an evolutionary process, it includes the development of new features in biosystems and their adaptation to environmental conditions. New features emerge out of a need of this 'hidden' information to express itself;*

information that exists primordially and is expressed as the need for evolution and adaptation, creating new phenotypes which become visible in the macrocosm. As a building block for how we interpret genetic evolution, molecular biology provides us with an understanding of evolutionary processes as a result of genetic diversity and genetic polymorphism. This is achieved by creating new structures and organizing matter in new ways, but on an already existing genetic canvas. In this way, the 'statistically' prevalent genetic 'opinions' (i.e., genetic polymorphisms), that have been expressed due to environmental needs as the statistically prevalent polymorphic structures and as bionetworks, express the theory of evolution and of the heredity of acquired –yet predestined– genetic modifications. The initial 'birthing pains' of any new feature in a biosystem lead to the 'gestation' –or put differently creation– of new features, and to the adaptation and evolution of the bio-society'. According to the Greek philosopher Cornelius Castoriadis [5]*, the creation of a being is related to its morphology. According to Castoriadis, in essence this means that new forms emerge. In the context of everything we've already mentioned before about evolution and creation, given the genetic canvas of the structural polymorphism of genes and the evolution of information into new forms and features of biosystems and bionetworks, we can observe the following: the philosophical approach goes hand in hand with the scientific one. That's to say, hand in hand with the viewpoint of molecular biology and biophysics, but also thermodynamics, as we'll see later on. This creates a 'statistical advantage' in the way new features express themselves in organisms. Castoriadis also mentions the issue of scaling between physical and biological phenomena, but he moves even further, and refers to scaling between psychological and socio-historical phenomena. 'Statistical physics' leads to natural laws based on the dispersion of the variables around the mean value all of us perceive. Our brain perceives physical reality functioning in a locally Euclidean space ("as sufficient according to the need", to quote Aristotle) even if in reality it is not Euclidean at the microcosmic level. The forces through which two particles at a non-interacting distance actually interact, and which, despite that, act as if they are in constant interaction, signal the high –or even extreme– importance of the concept of locality* [6]*. Imagine, my boy that the interactions might occur between both biosystems and bionetworks with information about creation and evolution embedded in them.*

[5] Cornelius Castoriadis, "Φιλοσοφία και Επιστήμη. Ένας διάλογος με τον Γεώργιο Λ. Ευαγγελόπουλου" (Philosophía kai Epistími. Énas diálogos me ton Yeóryio L. Evangelópoulou / Philosophy and Science; A Conversation with Georgios L. Evangelopoulos), Eurasia publications, Athens 2010 (in Greek).

[6] Cornelius Castoriadis, "Φιλοσοφία και Επιστήμη. Ένας διάλογος με τον Γεώργιο Λ. Ευαγγελόπουλου" (Philosophía kai Epistími. Énas diálogos me ton Yeóryio L. Evangelópoulou / Philosophy and Science; A Conversation with Georgios L. Evangelopoulos), Eurasia publications, Athens 2010 (in Greek).

But let's get back to what we were talking about before and see, which one is more important, shall we? The mean value? Or the dispersion of values around the mean value? Which system is chosen by nature as the most stable, and therefore the most functional? Is it a system stable for nature, so it has the highest entropy thereby making it not especially functional on a macrocosmic level, i.e., in our own world? Or is it a system that is stable for us, with minimum entropy, which means we perceive minimum variability, contrary to the precepts of nature which constantly opts for complexity and system variability? If nature knows the truth about what will survive through complex and ever-changing systems, why don't we let it function? It is incontestable that entropy will be the prevalent 'opinion' in the end. It's just that we as a society –in fact ever since we emerged as human beings after billions of years of evolution and adaptation– have been noticing –yet finding it hard to grasp– events 'projected' into our reality, and not for the very same events, which are hard to perceive due to the limits our senses impose. In this way, in our effort to adapt, we manage to survive and communicate, to create networks and civilizations by means of 'agreed laws' and regulations which are temporarily 'tolerated' by nature –much as we believe that nature itself has created them for us– based on our human potential, or rather on our human weaknesses."

"Grandpa, that is tough going, and hard to grasp. But let's go on. I'll try to simplify things and keep track of what you're saying. I understand my own weaknesses and my limitations. I also get the Mirror that you've started to show to me so I can take a look at myself and my own weaknesses. You can be sure this isn't going to get me down. I'll try to get a handle on it. I'll try hard because even though it is something I don't exactly understand yet, I still feel that somehow it belongs to me. The effort to control how I think, to construct my own world of knowledge and emotions belongs to me. At present the image in the Mirror is blurred and I'll have to put effort to figure out what the first message written as an image on the Mirror is saying."

Grandpa acted as if he hadn't even heard what I'd said. It's true that I had been mumbling things to myself. He went on, ignoring my comments. Perhaps he already knew!

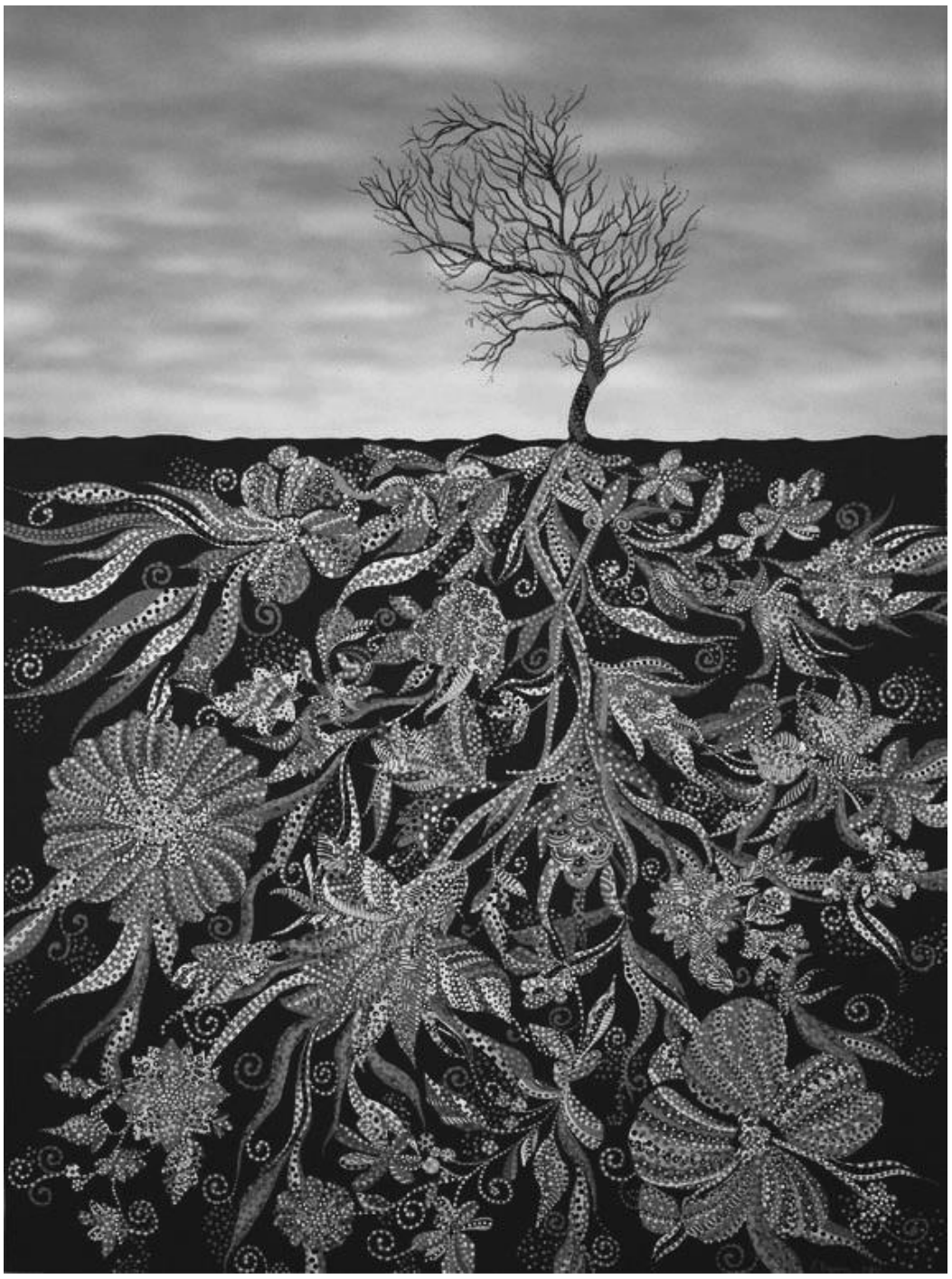
"*And then come the decisions 'up high' in our world, the macrocosm*," Grandpa went on. "*The decisions pertaining to nature, thermodynamics, statistical physics, statistical distributions and biology, and then maths, chemistry and bioreactions. We perceive all of the above as very slow changes over long periods of time through our limited senses. It takes years for a change to occur and centuries for an ecosystem to develop. And when it comes to society, changes are also very slow, excruciatingly slow. How will we ever manage to change the*

world? Will we live to see the changes? Those are the sorts of things we wondered about when we were young, when we couldn't wait to be not so young. So, what force is driving all these changes which leads to modifications in natural laws, to natural and social changes and revolutions. What force leads to changes in human behavior, and to the creation of laws and regulations so that we humans can go on with our journey through time; of course, time as we have defined it ourselves; this concept of time we have chosen and through which we perceive our own senses?"

"Grandpa, do you mean to say there are two worlds? One visible to our eyes and one invisible?"

"*Exactly, now we are starting to be on the same wavelength. The world we don't perceive is where natural laws are 'made'. 'Deep down' is where decisions are made –by whom, I don't know– about what will keep on existing, what are the prerequisites for its survival, and what is going to perish in the big world –the macrocosm– that we're able to perceive.*

"And if we don't like something, how can we intervene, Grandpa?"



Picture 4: Tree with branches and roots; the macrocosm and microcosm, respectively.

"*That's a good question. In the world we see, i.e., in the world we live in, the macrocosm, how can we adjust ourselves and evolve in order to survive based on microcosm's decisions? We neither control, nor are able to predict those decisions. All we can do is posit that they evolve and at a certain point they will manifest and we'll have to be ready to cope with them. It's is no easy task to cope with the microcosm's decisions, especially when they appear abruptly and suddenly. We don't possess any mechanism that allows us to adapt to abrupt,*

sudden and brutal changes. In the macrocosm we need adjustment time, and then, as scientists would say, relaxation time."

"But that's a question, not an answer. And you also add even more concepts into the mix! Like relaxation time... Luckily, I've already heard of it; it's the thermodynamic behavior of what we call 'soft matter'... and maybe in another context too. I can't recall."

"*I've already given you the answer, young boy. Stop muttering. Talking with me will not be easy. You see that I'm trying to say less, and you keep on talking to yourself. You're constantly talking. But I'll let it pass on this occasion. I've to admit I understand where you're coming from... My dear boy, look at the seed of a plant, look deep inside it. Life and its laws reside deep within this seed. This is what Aristotle dubbed 'entelechy' or 'εντελέχεια' in his own tongue. If you let this phenomenon, the evolution of life itself within a plant seed, slip by, you'll not be the lucky one studying transcription codes and the silence functionality of a biosystem, of an organism, if that is what you're looking for. You'll not give yourself a chance to see your own weaknesses and to make your own reflections in the Mirror clearer, even by just a little bit."*

Key Point

(...) Evolution is carried out through the transcription codes and the silence functionality of a biosystem or an organism (...)

"Is it possible that technology will help me study everything you're trying to tell me, Grandpa? Will it help me understand without struggling? You know, Grandpa, I've tried hard to become a scientist, get my degree and pursue postgraduate studies. Do you think that my efforts in that regard will help me understand our conversation better? I think this is going to be a tough conversation. Everybody is aware of the existence of technology, and that it evolves in order to make life easier, to solve our problems."

"*Of course, it will help you. But it is not the solution. Technology comes from and evolves through our constant, better understanding of the principles and laws of nature, through scientific methodology. What humans have been striving for centuries now is to be able to better study what natural laws dictate. Either way, it's when we, as human beings, read nature correctly that we have the biggest light bulb moments. We transmit our findings to society and make other people's lives better. But, if we're good scientists, we always understand that each new*

light bulb moment gives rise to new questions and yields few answers. Actually, it does not provide any answers at all. We come up with answers in order to satisfy our own human weaknesses and cope with the finite nature of human existence, and also in order to solve small, everyday problems. People's everyday life dictates how answers are used, in order for them to survive and be happy".

"That's how we mature, Grandpa. That's how we get better."

"*Yes, indeed. We become less self-centered against what is a natural process and against evolution faced with which we are powerless. Our interventions in the macrocosm seem to be small, yet they are long-lasting. They hardly ever impact on the entropic processes decided by nature, they just transpose it into the future. But things are not like that. If they were, we wouldn't have any reason to exist on this planet. And why did nature decide it? How? What hides behind decisions of this kind? Why were we not asked about it? Why? The questions are endless."*

"Grandpa, I'm starting to understand what you're trying to say. I simply lack the tools. Actually, I have to confess I'm afraid this is going to get me down, even though I promised myself I wouldn't let it."

"*No, it won't get you down. You'll only become wiser, because you'll start to understand how vulnerable and small everybody is. You need to learn everything that man has discovered thus far; human advances, not only scientific and technological ones, but also ones of intellect, thought and even culture. You need to keep on studying, keep on learning, and in that way you'll understand and be able to get a handle on what happens 'deep down' in the microcosm. You'll understand how subatomic particles 'live' and what kind of powers and interactions exist and influence the world, the universe... but which exactly is the universe? How big is it? I don't know, but we need to put it into words it in order to be able to talk about it*".

"You mean that anything happens 'deep down' in the microcosm and the nanocosm, also happens in the megacosm (i.e., the Universe)? Does it mean that it's the same powers and interactions that create evolution and adaptation, and the same natural laws? How are natural laws created? How do they evolve? What is the driving force behind this evolutionary process? Does entropy exist there too, in the megacosm?"

"*Just as we cannot see the changes that happen in the microcosm, in a similar way we cannot see them in the megacosm. But that doesn't mean that they don't exist. It's us who don't see those changes. We can only see some of the results from applying those "primordial decisions" of the micro- macro- and megacosms during our lifetime. Light takes time to reach us. It takes hundreds, maybe thousands of years –I don't even know how many year– to see an event that no*

longer exists, when we observe it in our visible world. It is in the past. This means that we are observing the past in our present. Do you think we can change things, given that when we see them they already old or gone? You can draw your own, personal conclusions. You'll see that you'll be very happy when you draw no conclusion at all, and instead only end up making certain findings. You'll be so happy about that."

"No conclusions? But why are you saying that, Grandpa?"

"*Alas! If we find the answers we've been waiting for, there will be no tomorrow, entropy will engulf us. We won't even try to provide an answer, so as to give ourselves one more enthalpic chance, 'warming' ourselves with new inquiries. They may be small ones. It doesn't matter how small, but we'll be constantly providing ourselves with 'negative entropy' and keeping ourselves in 'thermodynamic instability', which means alive, fighting against the second law of thermodynamics. But you'll be so happy and content because you were blessed with a journey towards knowledge, and that can be a never-ending journey.*

I believe you're familiar with the poem Ithaka written by Constantine Cavafy in 1894. Our poet from Alexandria writes 'As you set out for Ithaka/ hope that the voyage is a long one/ full of adventure, full of discovery. […] And if you find her poor, Ithaka won't have fooled you. / Wise as You'll have become, so full of experience, / You'll have understood by then what these Ithakas mean'" [7]**.**

Picture 5: Constantine Cavafy

Constantine Cavafy (Alexandria, April 29, 1863 – Alexandria, April 29, 1933) was one of the most eminent modern Greek poets. He was born in Alexandria, where he spent his life. Alexandria is often mentioned in his poems, and for this reason he is frequently referred to as the 'Alexandrian poet'.

He published poems, while there are also dozens of unpublished sketches. His most important works were created after the age of forty

(https://en.wikipedia.org/wiki/Constantine_P._Cavafy) .

[7] Translator's note: The quotation from the poem is taken from C.P. Cavafy, "Collected Poems", Translated by Edmund Keeley and Philip Sherrard. Edited by George Savidis. Revised Edition. Princeton University Press, 1992.

"Right, Grandpa, I understand. Luckily, I have a degree in the natural sciences, and I can at least understand the scientific terms you've mentioned: thermodynamics, instability, entropy, enthalpy... But now you've decided to throw some poetry into our conversation.

This conversation is turning into something quite interesting. It's my view that poetry that features challenging concepts, like Cavafy's, serves as compass that will help orientate us correctly. It will help us tell the difference between what's precious and useless and allow us to maintain the ability to think critically when coping with any challenges we might encounter in our lives. Even challenges will be welcome if they were decided 'deep down', as you say, as long as we possess weapons and tools - like knowledge and intellect- to understand what they mean.

Where do you want us to start, Grandpa?"

"*Let's go outside then. Out to where nature makes her choices without even asking us. Out where the microcosm's variability materializes as a visible fact in the macrocosm. What season is my boy? Is it still winter? Can you look out the window and tell me whether nature is frozen? Is it cold? Oh how the changes in nature, the change of the seasons, influence our mood! What's happening all around us is magical.*

Complexity in nature, the changes in the seasons, in temperature and even of our mood, and also the complex processes that take place, are linked to the non-linearity and to the stochasticity of the events that develop within a system. Non-linearity and in specific deterministic chaotic dynamics is the prevalent trend in natural events and processes; and it is the necessary condition for self-assembly[8] *process to take place. As we'll see below, in order to perceive the concept of complexity through our current objective capabilities – meaning our senses, cerebral function etc.– nature has to function at a complex systems level. To put it in a simple way, biological processes need to have a polyatomic character instead of a monatomic one, with numbers of atoms, i.e., of participants,*

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[8] Self-assembly identifies the high degree of organization of a structure, while self-organization identifies phase separation in a structure that has a lower degree of organization. The self-assembly of a system, e.g., a biosystem, is brought to a state of equilibrium through natural interactions, whereas self-organization is a steady state process, dynamic but of lower quality compared to the self-assembly process. The self-assembly process is driven by the entropy (Gibbs free energy change: $\Delta G = \Delta H - T\Delta S$ where ΔS is the change in entropy of the system and the index of the hierarchy of the structures created; ΔH is the enthalpy change and T is the temperature in Kelvin), because entropy serves as a guide to design self-assembled structures. Also, the kinetic energy of formation of the system (e.g., the biosystem) is decisive for the evolution of self-assembly. If it is slow, the formation of biosystems is practically very slow and probably not visible; if it is rapid, it will never take place. The understanding of these concepts requires deep scientific knowledge, but also philosophical thinking. Finally, it should be mentioned that the process of self-assembly is driven by entropy (entropy driven process). Chan C.C., Chan F.C., Tu D. *Energy and information correlation: towards sustainable energy*, Journal of International Council on Electrical Engineering, 5 (2015), pp. 29-33, https://doi.org/10.1080/22348972.2015.1050773.

sufficient to yield the statistical result that we'll see macroscopically, and which will constitute the driving force of any evolution whatsoever in the microcosm. This is a constant, dynamic process which never stops in a feedback sense and whose results are perceived by us as events in our limited lifetime. We consider these events to be invariable and unchanging within the constraints of our senses or rather we perceive them to be evolving at a very slow pace. We're so selfish that we think that nothing changes, and whatever we do on a macroscopic level will not impact on the process of evolution. And yet, the process of evolution and adaptation is an event and we can participate in it even if we won't live to see the result of our intervention, even if we consider it move extremely slowly in terms of time. Life and events move on and evolve without 'bothering' about our fleeting presence on planet Earth, except when each and every one of us works in order to create our own 'opinion' in the process of evolution, which will be taken into account in the final timeless statistical result 'deep down' in the microcosm."

Key Point

Non-linearity is the 'prevalent opinion' in nature and in the evolution of natural phenomena. The result of it is the self-assembly of biosystems.

"Grandpa, when you say, 'polyatomic character', do you mean that the number of the atoms which participate must be sufficient in order to yield the 'prevalent' statistical result in a way that will affect the expression of information?"

"*That's exactly right. Actually, if we accept that individual cells constitute a polyatomic unit –and it is just like that, if we take a look at the structure and the complex function and functionality of each cell– then the 'statistical decisions' concern them, too.* Furthermore, if we look at the sub-cellular organelles *like the mitochondria, from the same viewpoint, then they function on a 'statistical decisions' level too, contributing to the overall 'statistical natural decision' of a biological system that is construction or revision. This system is ordered – or, let's put that differently, it is required – to be self-assembled on a qualitatively higher level in order to be 'prevalent' in the midst of hundreds, millions or even uncountable other numerical quantities for a given stability period that the entropic process will allow for. I understand, it is fairly complex to perceive this from the world of our senses. But in the end, as you'll see, this cascade of monatomic systems (each one of which is in fact a polyatomic one in the final*

analysis), allows 'statistical physics' to yield results that can create a viable biological result with utmost precision, thanks to the immense number of participants. What do you have to say about that?"

"Alright, but don't we see any of those systems, don't we participate in any of them? Don't we have free will? Or is it the case that free will is the result of a certain ongoing statistical process? Perhaps this will never end. Why don't we see that? Why won't we see it in the brief span of our biological presence on earth?"

"*Oh, my dear boy, you're introducing an even higher level of complexity into our conversation. Free will is the subject of extremely tentative investigations into the realms of science and philosophy, and the careful expression of opinion with a sociological dimension. Let me quote what Dr. Stathis Gonos, Research Director at the National Hellenic Research Foundation (NHRF), writes in the book Philosophy and Natural Sciences in the 20th century* [9]*. He says: 'When it comes to free will, we wonder if it resides somewhere. And if so, then where'. He goes on to say: 'The following question persists, a question outdated to some. In the end, does the cell have a will? It is a hypothetical question, to which we don't have an answer'* [10]**.** *Then, he goes on to describe protein p53, which has been known to the scientific community for 25 years and has been shown to have an important role in cell survival. So, Dr. Gonos mentions that when the cell finds itself in a hostile environment, this protein has to decide what to do, and how to react. In fact, Dr. Gonos mentions that it will act according to the importance of the external enemy, which means that it understands the external stimuli and the significance of the decision it will make – it is related to the cell's survival and ability to function. Depending on the importance of the hostile external stimulus, this protein activates the relevant biochemical cascade which could in the end have an apoptotic effect. It may opt to do so in order not to transmit any mutations to descendant cells, for example. Dr. Gonos also says: 'So, we have a molecule [and he probably means a structurally self-organized system, and not a chemical molecule] which has a decision to make[...] We slowly begin to understand, on the basis of the logic of complex systems, that decisions differ depending on certain conditions, the given damage exposure, the given biological substrate', and he goes on to say that '[...] if we know in which system of reference we are working, the experiment gives us an answer which leaves hardly any room for doubt. At the same time, we need to challenge our own selves and stop believing that current knowledge is a panacea, because new lines of inquiries arise as soon as a given inquiry is answered. […]. Furthermore, we need to examine the degree*

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9 S. Gonos 'Philosophy and Natural Sciences in the 20th century', ed. H. Grammatikopoulou, p. 61. National Hellenic Research Foundation (NHRF), 2004 (in Greek).

10 Translator's note: our translation.

to which a living organism, when exposed to an environment, can adapt by producing the same molecules, but in a different structure'. In my opinion, in that short excerpt Dr. Gonos refers to a different type of polymorphism, better defined as the 'lyotropism of biosystems', which is related to the 'metastable phases' that have taken place on the cell membranes of the living cell. These 'metastable phases' are related to the biophysical and thermotropic behaviors of living cells and they act as promoters, modulators or retarders of biological phenomena that are observed macroscopically. It is important to understand that the 'metastable phases' could be defined as 'thermodynamic vehicles' able to deliver information to the target tissue [11]*. This is a unique approach. The combination of biophysics and thermodynamics as scientific elements could be considered as the building blocks that are able to transport information through bionetworks to living objects. However, the latter could also be capable of preserving their functionality and consequently their evolution process."*

Grandpa then adds:

"*Perhaps by learning all this stuff, and everything we'll talk about later, we'll have chance to talk about that point too, to talk about the existence of free will in human beings. Indeed, it is something challenging from a scientific point of view and it is related, to my mind, with how much the existing natural laws, which we have understood insofar as they allow us to understand them, are constantly creating or have created the prerequisites for individual decision-making in biosystems. We have inherited our past through nature's complexity, biodiversity and variability. However, our future is nothing but our descendants, to whom we bequeath greater complexity and more complex communication and decision-making networks. Free will at an atomic or subatomic level, at a level of 'small' biosystems (though we need to define what small means), is defined by the need for the survival and evolution of each bio-unit, individual, organism, biosystem, society and –ultimately– the survival and evolution of our planet."*

Key Point

(…) Our future is nothing but our descendants, to whom we bequeath greater complexity and diversity in the biosystems and the bionetworks of communication and bio-information transmission (…).

[11] C. Demetzos "Biophysics and Thermodynamics: The Scientific Building Blocks of Bio-inspired Drug Delivery Nanosystems", AAPS PharmSci Tech, 2015, 16(3):491-5

Grandpa stops for a while and ponders. Perhaps he too understands that this is an interesting, yet extremely complex subject for the current 'metastable phases' of the human brain which have not yet been incorporated into the neuro-network communication channels, so as to activate and transmit the feelings one needs to feel the satisfaction from understanding these complex –and yet fundamental– concepts. The factors that lead to knowledge include that sense of satisfaction, curiosity and the search for what comes next, which is how an event evolves. This is how science evolves and produces technology. But I see that Grandpa took the time he might have needed to relax and is now ready to resume our conversation. I also observe that he has moved to the library, perhaps in order to stretch a bit and think or to be close to his natural ally – books!

"*Let's move on*," he says.

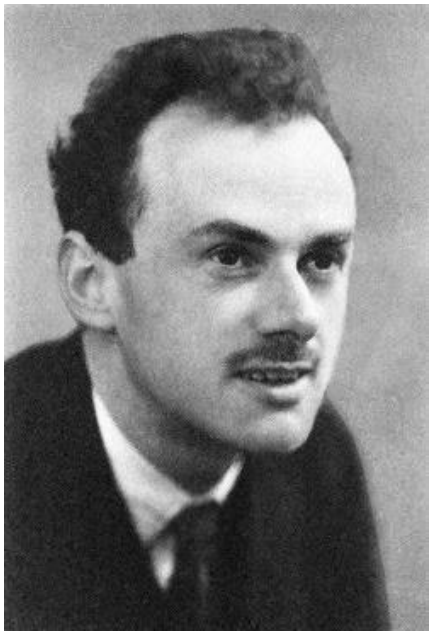
"*Before I move on to the very interesting and important topic of entropy, I'll have to tell you that all of the above might not be of much importance today, based on the advances in modern biology and biophysics. There are very small groups of individuals –of participants, let's say– in a process, which play an important role in the expression of statistical punctuality as a biological result or as information. So, it appears that they have influence and control, I'd say, over any given features, i.e., the phenotype, which become visible in our reality, say the color of someone's eyes, or the way in which certain illnesses manifest at a higher or lower level of intensity in our parents or grandparents*'. *In that way, the genetic code and the disclosure of the human genome helped reveal the value small sets of atoms (micro-atomic sets) have in the expression of information that, based on the numbers (number of atoms-participants) required by statistical physics, could not possibly have a biological role and importance that generated results in the visible world and in everyday life. So, we see that it is not only the number which is numerically necessary for the expression of a 'statistically important' physical or biological piece of information, but also the 'intensity' of the expression, which is related to the stability and the physical forces that prevail. Furthermore, in my opinion, entropic change (ΔS) in the interest of what we call 'negative entropy' –I'll explain to you later what this means– functions creatively towards the expression of the functionality and the organization of a biological system and keeps it in thermodynamic instability, which means it is stable for us, ergo functional, if it refers to the biological expression. Obviously, it is also stable for its own survival for as much time as its own energy content allows. At this stage you need to know that the change of free energy (ΔG) must be > 0 in a thermodynamically unstable system, which is a system in a non-equilibrium state. This favors biological functionality, based on the second law of thermodynamics.*"

$\Delta G = \Delta H - T\Delta S$ must be **>0**

"I get it, Grandpa. I must say that I like approaches of this kind. It would be very nice if you had some kind of example to help me better understand what we're talking about."

"Yes, of course. I'm well prepared. I have many books, and even scrolls. If you look for them, you'll find them. You'll find scriptures in scrolls, in other classical books. You'll know it's them. You'll just need to focus and pay close attention. I've been deliberately buying them for such a long time now; initially, because I was searching for theoretical and pragmatic approaches to social phenomena and conditions and later on, as I matured and grew, I sought out approaches to scientific matters. One needs to respect books. They contain such a wealth of intellectual struggle and accumulated experience. Let me tell you something to help you understand a book's value. A long time ago in times of conflict, books were burnt and destroyed, because the regime of the time feared new opinions and forms of behavior that would lead to developments that undermined their power. Why don't you go to the bookcase and fetch me Erwin Schrödinger's book What is Life? With Mind and Matter and Autobiographical Sketches [12] *? He won the Nobel Prize on December 10, 1933 for his contribution to the creation of wave physics, along with another great mind from the world of natural sciences, Paul Dirac. Would you like to read a bit?"*

[12] E. Schrodinger, "What is Life? With Mind and Matter and Autobiographical Sketches", Cambridge University Press, 1944.



Picture 6: Paul Adrien Maurice Dirac

Paul Adrien Maurice Dirac **(**8 August 1902 – 20 October 1984) was an English theoretical physicist who made fundamental contributions to the early development of both quantum mechanics and quantum electrodynamics. He was the Lucasian Professor of Mathematics at the University of Cambridge, a member of the Center for Theoretical Studies, University of Miami, and spent the last decade of his life at Florida State University. Among other discoveries, he formulated the Dirac equation which describes the behavior of fermions and predicted the existence of antimatter. Dirac shared the 1933 Nobel Prize in Physics with Erwin Schrödinger "for the discovery of new productive forms of atomic theory" (https://en.wikipedia.org/wiki/Paul_Dirac).

Picture 7: Erwin Schrödinger

Erwin Schrödinger was a Nobel Prize-winning Austrian physicist who developed a number of fundamental results in the field of quantum theory, which formed the basis of wave mechanics: he formulated the wave equation (stationary and time-dependent Schrödinger equation) and revealed the identity of his development of the formalism and matrix mechanics. Schrödinger proposed an original interpretation of the physical meaning of the wave function. In his book What Is Life? Schrödinger addressed the problems of genetics, looking at the phenomenon of life from the point of view of physics. He paid great attention to the philosophical aspects of science, ancient and oriental philosophical concepts, ethics, and religion. He also wrote on philosophy and theoretical biology. He is also known for his 'Schrödinger's cat' thought-experiment (https://en.wikipedia.org/wiki/Erwin_Schr%C3%B6dinger) **.**

"Yes, of course. I'd like to learn about this great scientist."

"He was born in Vienna in 1887. In 1926, he was asked by Max Plank to take over from him at the Institute and so he settled in Berlin. It was the same year that he published four major essays on wave mechanics, about which Born said 'There is nothing more beautiful in theoretical physics'. His theory struck a tremendous blow to the then current knowledge on classical physics and proved that an electron behaves like a wave when it is located on an atom. He used the following equation:

$$\nabla^2 \psi + 2m/\hbar^2 (E-V(x,y,z))\psi = 0, \quad \text{where} \quad \nabla^2 = \frac{P^2}{Px^2} + \frac{6^2}{6y^2} + \frac{6^2}{6z^2}$$

where m is the mass of the particle, moving under the influence of a potential V (x,y,z), ψ *the wave function, and ħ = h / 2π, where h is Plank's constant (h = 6.626 070 15 x 10 $^{-34}$ J·Hz^{-1} or as a unit of energy h = 4.135 667 696… x 10 $^{-15}$ eV·Hz^{-1}).*

The equation has a solution when the energy of the electron is a multiple of Plank's constant. It is what is called energy quantization (E = hv). Based on the above it seems that there is an 'uncertainty' in the position and momentum of the particle.

I would also like to mention another great scientist: Werner Karl Heisenberg who first formulated the 'uncertainty principle' in 1927."

Picture 8: Werner Karl Heisenberg

Werner Karl Heisenberg (5 December 1901 – 1 February 1976) was a German theoretical physicist and one of the key pioneers of quantum mechanics. He published his work in 1925 in a breakthrough paper. In the subsequent series of papers with Max Born and Pascual Jordan, during the same year, this matrix formulation of quantum mechanics was substantially elaborated. He is known for the Heisenberg uncertainty principle, which he published in 1927. Heisenberg was awarded the Nobel Prize in Physics for 1932 "for the creation of quantum mechanics". Heisenberg was president of the German Research Council, chairman of the Commission for Atomic Physics, chairman of the Nuclear Physics Working Group, and president of the Alexander von Humboldt Foundation (https://en.wikipedia.org/wiki/Werner_Heisenberg).

"In 1927 Heisenberg formulated the 'uncertainty principle', which constitutes a fundamental principle in quantum physics. The 'uncertainty principle' replaces classic physics' determinism, which is prevalent in the macroscopic interpretation of natural phenomena, with the idea of the uncertainty of the events which happen in the microcosm. According to this principle, it is not possible to calculate both the momentum and the position of any given particle at the same time. On the basis of the uncertainty principle, W. Heisenberg, E. Schrödinger and P. Dirac established the field of Quantum Physics. Quantum Physics introduced the idea of the binary nature of light (meaning it is both a particle and a wave) and expanded the uncertainty principle to cover the impossibility of predicting any given event. Albert Einstein, who opposed the unpredictability theory, said that it is not possible that 'God played dice with the universe'. According to Cornelius Castoriadis –about whom we're going to be talking again later on– this phrase shows that Einstein believed that '[...] there are logical truths and understandable sequences between things'[13]**.** *Despite all that, the 'uncertainty principle' found application in the field of quantum physics, where it stemmed from. It concerns not only calculations regarding very small objects, such as electrons, atoms and molecules, but also big ones. However, since a big object also has high inertia, the calculation barely interferes with its speed.*

I could also tell you that theology[14] *would also agree with Einstein's phrase I have just quoted. 'The natural order is the result of freedom and creation's diversity and is inseparable from its limits.' This diversity in the world's creation, which coexists in unique harmony and functionality, is nothing more than superhuman wisdom and the inherent human inability to understand and to explore every reason behind the creation of the cosmos. This inability should not lead us to conclude that the creatures of the world were randomly created. Saint Basil the Great highlighted the necessity of natural determinism and ruled out randomness, thereby offering arguments in the fight against sorcery and idolatry. W. Heisenberg, in his book <u>The Representation of Nature in Contemporary Physics</u>*[15]*, points out that 'Nature was thought of as a work of God, and for people of that time (the Middle Ages), studying the material world independently from God would make no sense'. The existence of order in the world –especially in the microcosm and the megacosm (i.e., the Universe) – extends the levels of order and*

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13 C. Castoriadis, "Φιλοσοφία και Επιστήμη. Ένας διάλογος με τον Γεώργιο Λ. Ευαγγελόπουλου" (Philosophía kai Epistími. Énas diálogos me ton Yeóryio L. Evangelópoulou / Philosophy and Science; A Conversation with Georgios L. Evangelopoulos), Eurasia publications, Athens 2010 (in Greek).

14 N. Matsouka, "Επιστήμη, Φιλοσοφία και Θεολογία στην Εξαήμερο του Μ. Βασιλείου" (Epistími, Philosophía kai Theología sto Exaimero tou M. Vasileiou/Science, Philosophy and Theology in the Six Days of St. Basil, p.200) Kyriakidis publications, 2016, Volume 7 of the series Theology and the Universe, 2016 (in Greek).

15 Heisenberg, W. "The Representation of Nature in Contemporary Physics." Daedalus, vol. 87, no. 3, 1958, pp. 95–108.

the logic of the creation of beings according to their functionality and their cooperativity in deterministic communication networks, whose structure and organization exclude the possibility of randomness.

Thus, the 'uncertainty principle' defines the human inability to study and understand the ultimate natural determinism of creation. This human inability to understand the inherent wisdom of beings and of micro- and macro-societies constitutes a driving force in the constant evolution of the human species and is indicative of the humbleness one should have faced with the magnitude of Nature's wisdom.

The cryptic code = information (see below, Entropy and life) and 'silence functionality'[16] *may contribute to this approach. Therefore, we could say that ''the concept of probability in quantum theory should be approached in a different way from the concept of possibility in statistical.*

Eugene Wigner (1902-1995), Nobel laureate in Physics in 1963, suggested that […] if Schrödinger's equation represents a reality, then the cryptic variable, which is decisive for the result of any event, could be consciousness itself.

Oh my, I got carried away. You asked me for an example to understand how 'statistically insufficient' numbers of atoms in a system –or better said, a biosystem– could influence the expression of the biosystem's function and lead it to viable functionality and functions. Take Erwin Schrödinger's [17] *book and turn to page 30.*

"*Oh, oh... yes, of course, I had made a note back when I read it*: *'But let me draw attention at this point to the fact that 300 Å is only about 100 or 150 atomic distances in a liquid or a solid, so that a gene contains certainly not more than about a million or a few million atoms. That number is much too small (from the √n point of view) to entail an orderly and lawful behaviour according to statistical physics – and that means according to physics. It is too small, even if all these atoms played the same role, as they do in a gas or in a drop of liquid. And the gene is most certainly not just a homogeneous drop of liquid. It is probably a large protein molecule, in which every atom, every radical, every heterocyclic ring plays an individual role, more or less different from that played by any of the other similar atoms, radicals or rings. This, at my rate, is the opinion of leading geneticists such as Hadane and Darlington, and we shall soon have to refer to genetic experiments which come very near to proving it.'*"

[16] C. Demetzos, "Pharmaceutical Nanotechnology. Fundamentals and Practical Applications", Springer Nature, 2016.

[17] E. Schrödinger "What is life? With Mind and Matter and Autobiographical Sketches", Cambridge University Press, 1944.

Key Point

(…) The concept of probability in quantum physics should be approached in a different way from that of statistical physics and possibility (…)

"Before we move on to understand of the concept of entropy, I'll only mention that quantum theory has revealed what is called the 'non-continuous behavior' of a system, which interprets the behavior of small systems, i.e., of the groups of atoms with a small number of participants. When phenomena are perceived on a large scale, we perceive the changes in energy, and we can easily calculate them. Take for example the movement of a pendulum. In microsystems, i.e., in systems where the number of atoms that participate is small, the system transitions from one state to another by using discrete quantities of energy (quanta) and is led to what we call 'quantum leaps'. It is these 'quantum leaps' that the small-scale system uses for its transitions, i.e., for the creation of transitional non-equilibrium phases, which have a thermodynamic behavior and change in a non-continuous way; this means they are 'quantized', which is to say they are assigned a specific, energetically allowed number of non-equilibrium states. Transition or residence time is of no importance in quantum phenomena because it is a dynamic non-equilibrium state which 'gives birth' to functional self-assembled structures that statistically influence the microsystem's functionality towards the 'purest' 'metastable phase' in thermodynamic and quantum terms, which is predominant and functional.

You see, my dear boy, nature has chosen microsystems, those systems with a limited number of atoms-participants to make 'quantum leaps', which lead to the evolution of macroscopic systems, the ones that we can perceive with our senses. Of course, we perceive those macroscopic systems to be in an equilibrium state."

"Now, you might well ask for how long this goes on. That does not matter at all, because their evolution is in a dynamic state one way or another, and any given time in the macrocosm corresponds not to a specific time in microcosm but to an unknown number of 'quantum leaps' and to the creation of 'metastable phases' in a non-equilibrium state. These 'quantum leaps' are predetermined, and these systems don't have the possibility to adopt other formations or, better said, other 'metastable phases', except for the ones that are energetically allowed. This is related to their physiochemical properties, which can lead to a certain assembly and expression. Don't get me wrong when I say, 'a certain' assembly, 'a certain'

expression, as there is not only one but an infinite number of them and the prevalent ones are expressed through the infinite string of 'non-continuous' 'metastable phases'. In this way, for example, genetic polymorphism, i.e., the change in the base sequence (from adenine to thymine for example) created a different kind of information and different production of proteins, changing the functionality map of an organism. At the level of a human organism, this can be translated into an illness or resistance to illnesses or into a different behavior in general, it could even be a social behavior. This polymorphism which, in my point of view, is lyotropic, –we'll get to that later if we're given the chance– constitutes the statistical expression of a constant dynamic process which in the microcosm manifests as the functionality or non-functionality of an organism. Quantum physics clearly plays an important role which we'll examine further later on."

"Grandpa, this is all marvelous. Maybe what you said before about 'predetermined quantum leaps' and the lack of possibility to adopt other formations or other 'metastable phases' is related to what we called free will".

"That's a very important line of inquiry indeed, but I couldn't possibly reply. I don't know what statistically 'has a will' to choose the 'energetically allowed' states. Schrödinger (I interpret and expand on what he said according to my own personal understanding) talked about the autonomy of expression of molecules, their chemical rings etc., which statistically influence the overall expression of the big system. This in turn could still be a microsystem compared to bigger ones, and all of the above in relation to human beings [18]*."*

"I feel happy and satisfied", Grandpa.

In one single sentence it seems I'd managed to formulate a line of inquiry. Grandpa accepted that I've already brought up a line of inquiry, and an important one no less. I need to write it down on my notes so, if I'm given the chance, I can start to make connections with what we'll talk about later on and with what I'm going to be studying. The puzzle is starting to take on some form, or I'd say that the framework within which I'm going to move as the conversation progresses, is being created, and that is starting to show in my Mirror. Perhaps by changing the colors and the light I could achieve a better result. Or I should probably try to analyze them in the same way as white light, by looking at the individual concepts and phenomena that appear to be homogeneous, swimming in a 'soup'. That would mean analyzing the separate colors of white light, which make up the ingredients of the 'soup'. It is hard to conduct qualitative and quantitative analysis on something with an unknown qualitative and quantitative composition. Yes, by Jove! That's it! What I need to do is perform an analysis and right after that, to

[18] E. Schrödinger, "What is Life? With Mind and Matter and Autobiographical Sketches", Cambridge University Press, 1944, p. 30.

engage in synthesis. Of course, it'll be a synthesis that suits me best, one I understand. This might even be a means to control my own thoughts. Right... right, maybe I can thus define the code for communicating with nature and with Grandpa as well.

"Grandpa! Grandpa, I actually understand not only the complexity of everything we're studying and what you're telling me, but also our inability to control all of these processes. I'm following you, reflecting and slowly acquiring a compass; a means to orientate myself. Of course, we're too weak to be able to interfere with such processes given the complexity and diversity of infinite formative non-equilibria. Perhaps for this reason the concept of disorder is connected to order itself; it's just that in our macrocosm we see disorder as something really bad and we try to live in a well-organized, non-arbitrary system. Is that so? Or could it be that the order we experience in the macrocosm is related to the creative disorder in the microcosm?"

"*Dear boy, you're talking about ideas and actions which also have social implications*", Grandpa said as if he could read my mind. "*Yes, that is correct. I should also remind you of a basic piece of knowledge that will probably be useful to you in our conversation, namely that there are four fundamental interactions. These fundamental interactions can be taken into account and then adjusted in relation to particle movement and to their dimensions. I also believe that, later on, we will have to refer to mathematics and geometry, though we won't be doing that in depth. For that reason, I should mention that the great mathematician Bernhard Riemann, whom we'll most probably talk about later on, was a firm believer of the important role of natural forces and of their implications for spatial geometry, and also of the fact that the tidal forces of gravity are connected to the curvature of space-time* [19]*. But let's return to the fundamental interactions*."

"Could you remind me what the fundamental interactions are, Grandpa? I'll study the rest by myself, based on what we've been talking about."

"*Well, they are gravitation, electromagnetic, strong nuclear interaction and weak nuclear interaction. To remind you of these four is useful, because it allows us to approach complex biosystems. Well, biosystems are complex no matter how you look at them. So, it's useful to know about these forces because they constitute necessary and sufficient 'participating laws' for the interpretation of complex systems of the biocosm (i.e., of the microcosm), as well as of the megacosm (i.e., of cosmology). However, these forces only constitute necessary, but not sufficient conditions, for the mesoscopic level. Mesoscopic space could be*

[19] Cornelius Castoriadis, "Φιλοσοφία και Επιστήμη. Ένας διάλογος με τον Γεώργιο Λ. Ευαγγελόπουλου" (Philosophía kai Epistími. Énas diálogos me ton Yeóryio L. Evangelópoulou / Philosophy and Science; A Conversation with Georgios L. Evangelopoulos), Eurasia publications, Athens 2010 (in Greek).

defined as the space in between the electron of an atom in an object in the macrocosm and the object itself. More precisely, the area between classical mechanics and quantum mechanics is considered to be a grey area. In the view of theoretical physicists, the area in between is defined as the mesoscopic area of the system, which is to say biosystems are called mesoscopic systems. Theoretical physicists define this area as the area of the nanoworld [20]*. I'm glad, dear boy, because judging by your reactions I see that you understand that disorder is an excellent way of understanding 'qualitative leaps', though through processes which are prevalent and qualitative leaps which –if we refer to society– should benefit social order and tranquility in the macrocosm, because it's there that we live and it's the one that we perceive. In order to be happy, we should experience order in the macrocosm and strive for creative and functional disorder in the microcosm, quietly and creatively."*

"That's so beautiful, Grandpa. Just like the mathematics in Edwin Schrödinger's works. It was acknowledged as 'beautiful' mathematics because through the idea of disorder, non-continuity and 'quantum leaps', happiness emerged, and people's quality of life was improved through a macroscopic system of order. And also, Edwin Schrödinger writes in his book What is Life? [21] 'How is it possible that a microscopic trace of an element, i.e., in the core of a fertilized ovary, contains a complex code which includes the entire future development of an organism', which is just what we were talking about before. 'Pick up a seed from the soil, or look up at the sky, and you'll see the same events on a different scale'. And Schrödinger [22] goes on, 'A well-ordered association of atoms, endowed with sufficient resistivity to keep its order permanently, appears to be the only conceivable material structure that offers a variety of possible (isometric) arrangements, sufficiently large to embody a complicated system of *determinations* within a small boundary. Indeed, the number of atoms in such a structure need not be very large to produce an almost unlimited number of possible arrangements. For illustrations, think of the Morse code. The two different signs of dot and dash in well-ordered groups of not more than four allow for thirty different specifications. Now, if you allowed yourself the use of a third sign, in addition to dot and dash, and used groups of not more than ten, you could form 88,572 different *letters or* with five signs and groups up to 25, the number is 372,529,029,846,191,405.'"

[20] C. Demetzos, "Pharmaceutical Nanotechnology. Fundamentals and Practical Applications", 2016, Springer Nature

[21] E. Schrodinger, "What is Life? With Mind and Matter and Autobiographical Sketches", Cambridge University Press, 1944.

[22] E. Schrodinger, "What is Life? With Mind and Matter and Autobiographical Sketches", Cambridge University Press, 1944.

Grandpa continued, "*I think that now it's time to tackle another big issue, a challenge, a difficult concept for somebody who is trying to grasp it, at least for the first time. It's the science of thermodynamics, which forms a part of physics and the natural sciences. Entropy and the second law of thermodynamics, in particular, constitute for me topics of constant study. We can study them in books, and we'll also try to understand the concepts by placing them into a framework of biological value. Let's provide you with a brief introduction based on the books, and we'll also use concepts taken from our conversation so far. What do you think? Do you agree? Alright then, your nod indicates you are in agreement, and also that you wonder whether we'll manage to succeed. So shall we try, then*?"

Grandpa wanted to push me to the limits. Perhaps he hoped that I'd give up or even that I'd become indifferent. But that was not the case at all. This poker game of knowledge with so many partners –I don't even know how many– seemed to be evolving into a tough one. I pictured myself as a traveler, like some modern-day Ulysses throwing himself into challenges, taking up invitations, heading towards unknown yet marvelous destinations, some of which might be forbidden. I knew I'd have to make choices, so as not to make mistakes, I'd have to choose the pieces of the puzzle in order to create pictures that could be understood and knew all the while there were more pictures underneath that I'd have to bring to the surface. Each picture was a knowledge challenge, and each grain of knowledge acquired a personal victory. Human history is full of struggles and sacrifices. Grandpa has always been there to air his opinion, to sing, to lead. Maybe he was Homer, or maybe Socrates or Plato, enlightened men who, over the centuries, voiced their opinions and offered their knowledge trying to attribute to the human existence its real value, the singularity of creation; the creation through the non-visible yet omnipresent in our life, primeval and timeless trajectory in the universe. They tried to offer respect to men and became pioneers of social justice by creating new directions of travel and opening up new horizons in man's trajectory on Earth and further afield. But I should curb my thoughts and get back to Grandpa.

Outside night had begun to fall and winter had already made its presence known.

"Grandpa, it's winter, if seasons mean anything important to you. Or are colors and emotions better at signaling a season?", I thought to myself. The rain and the cold, a hot beverage –drinking it slowly so that it doesn't finish– are company of some sort, besides Grandpa's company that is. The library, warm and cozy, gives you the certainty of the dawn, the perspective of the new day to come, offering you both reality and the most beautiful dreams. Dreams, ah dreams... The dreams in our everyday life and the dreams at night-time. I don't know which ones

are real, or even what we would like to dream of, or rather what we're allowed to. Perhaps what we're going to dream is predetermined and it is just influenced by our surroundings, our experiences. We dream of faces, of images... our desires take form. We 'see' situations that could not possibly exist based on natural laws; yet, we experience them as if they were real. And then, what?

Often, we experience our dreams. There are even people who interpret them: bad omens, good signs... they influence our lives. And we pass those interpretations on to our descendants, as an experiential tradition, the 'signs' of the future, of the things to come. We exorcise evil; good and evil are in perpetual conflict.

But what about nature? Could it be that tradition is part of it and participates in the spells? 'Deep down', they say, are the elves with their entropic tricks and efforts are trying to destroy the tree of the world. They are always eating away at it and, just before it bends, good emerges to offer the 'negative entropy' that life needs to exist. In a beautiful way, so beautiful, as beautiful as Schrödinger's maths. It's just two sides of the same coin.

"Grandpa, what are you talking about? Are you talking to yourself again over there in the corner of the room? Can't you just sit still, and stay where I found you when I came here? I'm asking you again, about dreams, let's see... Right... You don't look happy. Is there something you want to say? Don't tell me to do research and study dreams! That's a totally different topic. Up to now we've been discussing about precise scientific matters."

"*No, young boy, I won't tell you to read about dreams if you don't want to. But I know that traditions and beliefs influence you. I dare say you even like them*."

"Yes, it's true. Tradition and beliefs, as you say, are part of our culture. They are the microcosm of every society, and its decisions influence the macrocosm. That's the same way in which things happens in the universe, right? You said so, Grandpa. So, why shouldn't I like it? It's true that the microcosm, with its minor social conflict, produces beliefs, culture, and creates social networks, and generates structure and organization. Until some elves come to offer their positive entropy to the social network. Then, it will either be destroyed, or qualitatively better structures will be created."

"*Yes, my boy, that's exactly how it is. You think for yourself and that's important. You try to interpret reality and that's great. Tell me, my boy, what do you dream about when you're awake and what do you usually dream about when you're asleep? Is it what you want to happen in order for you to be happy? Or do you dream about what you try to avoid, again in order for you to be happy? Is happiness the point of convergence when you dream, both with your eyes open and closed? What do you reckon? Is happiness the objective? Everyone seems to*

be pursuing it and keeps seeking out the means to achieve it. Plato discussed this very topic in his dialogue entitled Euthydemus."

"Grandpa, do you think that dreams are a tool given to us by nature? Or rather, not the dreams, but let's say a brain function, through which we're able to approach goods such as happiness?"

"*I don't have an answer to that. But perhaps science – through the medium of philosophy- could give us one or more ways to approach achieve happiness.*"

"But Grandpa, dreams are scary. We often have nightmares. How could they be a tool to happiness?"

"*Yes, you're right. We don't want to have nightmares, to have bad dreams. But if we have them or we recognize the terror within them, then we might think more about the need to achieve happiness though personal transcendence and upheavals in our everyday life. They might be a mechanism to activate our defense system in order to become more useful to humanity. But I'd suggest that we look at the matter of happiness when we decide to bring our conversation to a conclusion, if we ever manage to do that. It'd be a pity if it came to an end. It would mean that we have reached final conclusions and that there's no chance to move on; something that would exclude us from the evolutionary process*."

I looked around me. The room was small, but as large as necessary to accommodate all of these conversations with Grandpa. It turns out there is enough space in this small room, in the library, and we can move around freely. At times someone would knock on the door to offer some fruit and tea or water, just like it happened now.

I heard a voice saying: "Come on, rest for a while. You'll ruin your eyes if you spend so many hours confined in here. I wish I knew what you have been studying and discussing with Grandpa. Are there really that many things that you have to learn? Have something to eat. Lie down. Leave Grandpa alone, he could go on forever if you let him. You can't tell his age, it's unfathomable."

That voice appeared to come from the Earth, I thought to myself. How could you explain to her all these things that Grandpa has to teach you.

"And why do you have to learn it all?"

It's the voice of the Earth that grounds you every time, gently trying to offer you the 'negative entropy' we all need to go on.

Life needs simple, clear, things, the Earth says.

"If you want to be helpful to society, to be honest and to do wrong to no-one, tell the truth and keep your thoughts to yourself. But when you're right, stake a claim and fight for your cause."

"Grandpa, come, quick! The Earth has come to raise some serious lines of inquiries! Let's go back to our own, simple ones, quick! Back to the entropy, to

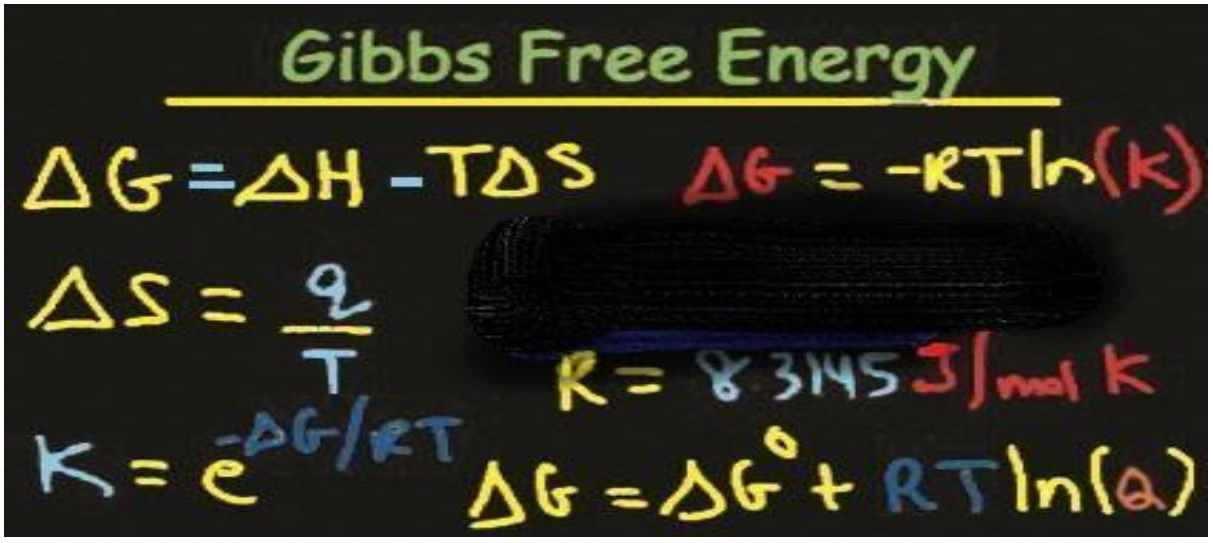
our thermodynamic approaches. The rest is serious and we're scientists... We don't understand those things... What do you think? What do you say, Grandpa? Will I be able to talk someday about such serious things? Honesty, truth, wrongdoing... No, let's not go down that path. I don't want to, at least not for the moment."

At some point it may become day and perhaps I'll still be in Grandpa's company in the library, leaving aside serious issues like the ones the Earth tried to introduce into a great conversation, one that Grandpa and I cannot have... We're still only scientists after all.

In fact, I'm still trying to be one.

PART II

A SHORT INTRODUCTION TO THERMODYNAMICS



Picture 9

The blackboard has always been the 'footprint' of our study and thought and the means to showcase our effort – perhaps even our intellectual superiority and arrogance, especially when it comes to teachers. For the rest, it represented the pains of the unanswered questions and the queries that would trouble them in the future. In general, the blackboard has been and still is a part of our lives, our evolution and our adaptation in a world where the inanimate objects have a key role to play in the behavior of animate beings.

Furthermore, the possible errors marked on a blackboard also constitute part of the learning process and of the 'conversation' between the student and the teacher. They are part of knowledge and should be acknowledged as such.

"*So, this blackboard*", Grandpa said, "*makes a small allusion to thermodynamics.*".

"*The nature of thermodynamics dictates the so-called thermodynamic principles, its subject being well-documented and reliable, just as its predictions are. Thermodynamics, as a field of the science of physics, examines the macroscopic properties of matter (bulk and observable properties), like temperature T, pressure P, volume V etc.), which are calculated in the total quantity of the material. Thermodynamics examines the system; in the case of biological systems, it examines the biosystems and their surrounding environment. When we define a biosystem or a system in general, it is important*

to define its limits so as to be able to study the transmission of energy (energy is defined as the ability to do work W or to transfer heat q) and matter from and to the system [23]. *Can you follow me, my boy*?"

"Of course, I can, Grandpa." I wonder where this blackboard picture came from, back from the university auditorium and the digital notes I took in class. Indeed, it is from back then, and this makes me glad.

But I am also thinking that Grandpa can sometimes be irritating when he keeps asking me if I am following him. Of course, I'm following you, I want to yell at him. Why else do you think I am here? I am thinking about what you are saying.

I am sometimes lost in thought, in order to absorb what you tell me and to sort out the thoughts in my mind. The 'metastable phases' in my brain must reach an equilibrium state even for a little while, to assimilate challenging concepts, perhaps keep the ones they can store and then set on their non-equilibrium journey into the new data.

Show some compassion, Grandpa, it wouldn't hurt!

So, wait until I eat some fruit, have some water at least...

Here, it's right here on the desk, come have some too, I was thinking while I was looking greedily at the fruit and the water.

We need to have a short break to be able to look each other in the eye. We may be able to see through the Mirror of knowledge without talking and without trying to understand what we are describing. We need to just look at the puzzle of small pieces and make sure a bigger picture is created, with more information.

These are complex concepts, each containing more and more, never reaching an end. What does 'thermodynamics' mean, and how can it fit into our conversation?

Of course, I am sure that it is useful if Grandpa suggests it and insists on it, but is it more useful than the contribution of fruit and water to my thermodynamic equilibrium? Is it hydration, Grandpa? I learnt about it at university.

Without food and water how am I supposed to keep the 'metastable phases' of my brain alert and absorb the challenging concepts and information? I should probably be saying that out loud, so that Grandpa can hear it and know that I am still following our conversation, even though I am thinking.

But I wouldn't want to upset him and miss the rest of our conversation. I'd say that, generally speaking, I'm patient and very obedient.

"*Come over here, come on!*", said Grandpa patiently. "*Come, taste some fruit. Here, have some water to stay hydrated. In the end you will ask to lie down*

[23] H.D. Brooke Jenkins, "Chemical Thermodynamics at a Glance", first published by Blackwell Publishing Ltd., 2008, see chapter 7.

and have me transmit to your brain all the information and our conversation. Let's get serious, my boy, our task is hard... I'll say this to you again to make it clear, heat q and work w constitute ways to transmit energy. Now, let's move on."

Grandpa shows no mercy, I thought. How much strength does one need to have to be able to keep up with him! I imagine what will happen then... I hope I will have the strength to put a period where I need in our conversation... unlikely as that may be.

Grandpa goes on, he doesn't have any biological needs, that's for sure. Where is his medicine? What about his natural needs? He does not seem to have any. What kind of man is he?, I kept thinking. How much stamina can he possibly have?. I was about to ask him, but he read my thoughts and yet went on ignoring me.

"*It is very important to know about the thermodynamics of complex systems. You see, thermodynamic equilibrium is related to thermodynamic variability. In a given thermodynamic system, the entropy could be produced by irreversible processes, i.e., thermal transfer, diffusion of matter and change of momentum etc. Very close to the thermodynamic equilibrium, the rate of entropy production is minimum; far away from it, the production of negative entropy becomes the predominant process if the system is chosen to survive. This approach could be the driving force to produce functional biosystems that can be kept alive for a given time, depending on the production of a new negative entropy which would be the new driving force for the creation of improved forms of life. This process is directly related to the evolution and adaptation of living beings to the ever-changing environment.*

A thermodynamic system, therefore, is that which can exchange heat, energy and matter with the surrounding environment. A system and of course a biosystem in a state of thermodynamic equilibrium is that which is not undergoing visible changes through time. In our approach of the equilibrium of a system or biosystem, we should take into consideration the following kinds of equilibria: thermal equilibrium, mechanical equilibrium, and chemical equilibrium. It is important to point out that it is not possible for the thermodynamics of a given system in equilibrium to tell us how fast or how slow the process is."

Grandpa stops for a while and lowers his gaze. He fixes his stare on the floor; perhaps there is a crack on the tile –time ate it away– and he is looking at it, I thought... He might be thinking that 'down there' events are still happening, and he instinctively lowers his gaze, probably out of respect for what he describes and thinks.

From time to time we should lower our gaze, out of respect for all the extraordinary events that happen around us without us seeing them, kind like a

prayer. Grandpa used to do this, especially when he was about to say something important.

"*No, my boy, I am not staring at the tiles on the floor. You see, I'm thinking about reversibility. Reversibility, young man, is of great importance in biological processes, so let me take some time to explain to you what it means*."

"I will not question Grandpa ever again; his skills and his biological stamina are impressive. He even outsmarts my smartphone", I thought.

I should follow Grandpa's thoughts and words through books. I should let him concentrate for a while, let him rest, and see what happens next through the books, the literature on thermodynamics.

This is getting hard, but I am here to face it. Grandpa is also right next to me to help me.

So, there's fruit and there's water, the most important and necessary staples for my intellectual struggle. Although I think that very soon people will be giving me bread and olive soup, as they will think I became a monk leading a reclusive life!

This is a reclusive way of life, like the life of monks in monasteries, who live in solitude and pray for man's salvation. It is the study and investigation of truth, that's what it's all about. You need to live in isolation in order to look 'deep down', just like Grandpa; to be able to see the world "up above" with magnanimity, understanding its weaknesses, with love and forgiveness, without selfishness and arrogant demands. All of us need the same amount of fruit and water to satisfy our biological needs. But it seems we differ in our attempt to satisfy our intellectual needs. It takes effort to acknowledge our intellectual deficit. Each one of us considers oneself content with what they know, with what they have provided themselves with intellectually, as a minimum gift in return for the supreme gift of their existence, thinking that the effort in the intellectual field was enough. It never is; the intellectual struggle continues until the end, until our biological end.

It seems that fruit, water, and indispensable material goods do not have the same value for all of us, they are not equally respected by everyone. Intellectual effort, intellectual struggle, leads to the recognition of our simple everyday needs, of food and sleep, the same simple everyday needs we trivialize by adding volumes of unnecessary material and information which diminish and assimilate human values – values that Nature and its laws have designated as sufficient for our survival.

This is what I believe, and I think that Grandpa will agree.

Let's move on to the thermodynamics of the systems and to the non-equilibrium states. I hope that, in intellectual terms, I will also be in a similar state

of thermodynamic non-equilibrium, so that I can manage to generate productive thoughts and inquiries.

The infinitesimal changes of a thermodynamic system in a state of equilibrium, meaning changes in T or in P, will produce an infinitesimal change in the state of the biosystem. The so-called thermodynamic reversibility is due to the restoration of the reversibility of the changed variable (i.e., T or P). The reversibility of the biosystem requires that the state of the biosystem is close to equilibrium and the infinitesimal changes are carried out very slowly [24].

Moreover, thermodynamic systems can be classified as follows: open systems, which exchange both matter and energy with the environment; closed systems, which exchange energy with the environment, but not matter; isolated systems, which do not exchange energy or matter with the environment. Living beings are open systems because they exchange both matter and energy with the environment.

Artificial cell membranes [25] can be designed and produced in research laboratories and can be used as models for biophysical and thermodynamic purposes. These artificial membranes are composed of phospholipids and lipids (e.g., cholesterol) and are used to study and analyze the behavior of biological membranes. We can also correlate their behavior to biological networks (bionetworks) and create scientific technological platforms. For example, the 'system approach' is considered to be an amazing concept in therapeutics.

It is also important to underscore the importance of thermodynamic equilibrium, at the level of the macrocosm, given that it defines human actions and choices. The stability of biosystems affects their functionality and viability. It is obvious that the reversibility of a biosystem can provide us with important information on how fast or slow a process occurs and on phase transitions. The study of these phenomena is of extreme importance, especially when it comes to the evolution and adaptation of systems and biosystems to a given environment in the quest for survival. The functionality of the living cells and, consequently, of their structural components, such as the phospholipid bilayers of cell membranes, is related to their thermotropic behavior and phase transitions, also widely known as the 'metastable phases' of the cell membrane. Thus, bio-thermodynamics has emerged as a significant approach for the study of the functionality and evolution of the cell, through the study of artificial membranes. The qualitative and structural characteristics of artificial cell membranes, their complexity, and the

[24] K. A. Connors and S. Mecozzi "Thermodynamics of Pharmaceutical Systems", John Willey and Sons, Inc, 2010.
[25] C. Demetzos, 'Pharmaceutical Nanotechnology. Fundamentals and Practical Applications, Springer -Nature, 2016.

level of their self-assembly play an important role in the rational design of studies and the evaluation of the results.

I look at Grandpa who stops resting for a while and starts talking to himself, knowing of course what I am reading, since he managed to catch a glimpse of my book.

"*I am thinking*", Grandpa said, "*that the equilibrium and non-equilibrium phenomena that take place on the surface of cell membranes signal the important contribution of interfacial phenomena which affect the viability of living organisms. Moreover, the interfacial phenomena are essential to the cells' behavior and functionality. It is thus clear that the design and development of artificial biosystems which are as close as possible to the structural and functional complexity of living biosystems is an important interdisciplinary research field. The evaluation of experimental findings should be carefully carried out so that they are reliable and can be used as 'projections' of the functioning of living organism. What do you think? Do you agree*?", Grandpa asked.

"Yes Grandpa, of course I agree. May I make a comment on what you said? The 'metastable phases' that we referred to extensively in our conversation seem to constitute the substrate for cell functionality. In addition, they seem to play a key role in the integrity of living systems. My question is, how small can such a system be considered? [26] And by 'system', I mean a cell. Because whatever we cannot see we consider it to be small, isn't it so? Or is scaling another factor that affects size measurement?

Moreover, I suppose that thermal transitions that take place during the life span of a biosystem are extremely important. Their thermotropic behavior is related to dispersed properties of the biosystem into the media where it exists; this means that water and its properties, as well as its thermodynamic behavior, are influenced by the changes of the variables of the surrounding environment (i.e., temperature, ionic strength, pH)".

"*Yes, you are absolutely right, and I am delighted to hear from you such observations. Let's move on*."

"We could recognize thermodynamic and biophysical similarities regarding the behavior and functionality of the cell membranes, that are a reflection of the behavior of bio-elements such as lipids, DNA, proteins etc."

"*Exactly, young man, what you say is absolutely right, and I am really excited by your observations*."

[25] U. Lucia, *A link between Nano and Classical Thermodynamics: Dissipation Analysis. The Entropy Generation Approach in Nano-Thermodynamics*, Entropy, 1309-1328, 17, 2015

Key Point

Biosystems are non-equilibrium dispersed systems (…) and their interactions with the environment are guided by thermal fluctuations.

"*There is growing interest by the scientific community on biosystems as non-equilibrium dispersed systems*", Grandpa said, "*and it has acknowledged that they are dynamic systems with structural characteristics and morphologies, and their interactions with the environment are dominated by thermal fluctuations. Pressure in a biosystem cannot be considered isotropic and must be generally treated as a tensor. The distinction between heat and work (expressed as displacement) is hard. Properties considered in classical thermodynamics as intensive in equilibrium, like internal energy, specific enthalpy, specific entropy, specific free Gibbs energy, are not intensive anymore. This is related to the fact that chemical potential (μ) for phases depends on size (number of atoms) and on micro-environmental factors. A phase transition in small-non-extensive systems can be classified by the topological and morphological properties of the entropic surface*[27]*, according to the energy and the number of particles. According to the book Nonextensive entropy. Interdisciplinary applications, edited by M. Gell-Mann and C. Tsallis* [28]*, non-extensive statistical mechanics replace Boltzmann-Gibbs statistical mechanics in systems that are in thermal equilibrium consistent with ergodicity. Non-extensive statistical mechanics could be applied in a variety of open systems in economics, linguistics, biology and other fields.*

Phase transition and its consequences, such as the 'metastable phases' in biosystems, are dynamic quantum phenomena and processes. Static (equilibrium) nature, as it is a macroscopic phase transition, is called 'phase equilibrium', i.e., gas, liquid, solid, triple point of water.

Phases in small systems are expected to occur over bands, in a graphic way rather than only at a sharp point, as is the case in large systems."

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27 C.Tsallis '*Introduction to Nonextensive Statistical Mechanisms. Approaching a Complex World*', Springer, 2010

28 "*Nonextensive entropy. Interdisciplinary applications",* Ed. M. Gell-Mann and C. Tsallis, Santa Fe Institute, Studies in the Science of Complexity, Oxford University Press, 2004.

Key Point

The non-extensive statistical mechanics replace Boltzmann-Gibbs statistical mechanics for systems that are in thermal equilibrium consistent with ergodicity. Non-extensive statistical mechanics could be applied in open systems like economics, linguistics, biology etc.

"*It is important now to move on to the thermodynamics of small systems*", Grandpa said.

What is a small system? I think that the scaling of a system is related to what we are looking for. Moreover, the advances of technology allow us to study a system based on what we are looking for and thus define it as small or large. The next paragraphs of the book refer to small systems, so we can learn more about them. T.L Hill [29] is a pioneer in thermodynamics of small systems and his books are considered to be seminal.

THERMODYNAMICS OF SMALL SYSTEMS

According to U. Lucia "Small system is considered as a system which has a size diameter smaller than the range of the interactions of the forces acting on the system itself. Kinds of small systems are: Mesoscopic systems: Systems considered in the range size between the bulk materials and the molecules (of size of the order of 10^{-9}– 10^{-6} m); Mesoscopically, inhomogeneous systems: systems which have a mesoscopic length scale associated with spontaneous thermal fluctuations, so they are loose clusters, statistically appearing and disappearing with a definite lifetime; Soft condensed-matter materials: polymer solutions, polymer melts, microemulsions, foams, gels, colloidal dispersions, liquid crystals; Any system with long-range interactions".[30]

Moreover, T.L. Hill observes that "Thermodynamics of small systems or nanothermodynamics serve in describing the equilibrium properties of many nanosystems, since the thermodynamic functions (state or path) of a small system differ from those of a macroscopic and deviate from classical thermodynamics. The statistical small system thermodynamics is a branch of equilibrium thermodynamics and have been extended on 'metastable states' of open systems,

[29] T.L. Hill, "*Thermodynamics of small systems*. *Parts I and II"*, Dover Publications, INC, Mineola, New York.
[30] U. Lucia, "A Link between Nano- and Classical Thermodynamics:Dissipation Analysis (The Entropy Generation Approach in Nano-Thermodynamics)", Entropy, 1309-1328, 17, 2015.

though these are not strictly equilibrium" [31]. The ensemble of a small system, according to T.L. Hill, is referred to as "macroscopic thermodynamics will of course apply to large sample of a small system (e.g., a macromolecular solution), and macroscopic thermodynamic functions are well defined for such a sample" [32]. And he goes on to say, "But we wish to pursue thermodynamics on a smaller scale here: we are interested in thermodynamic functions and interrelationships for a single small system including, in general, variations in the size of the system (e.g., N, the degree of polymerization or aggregation, V, the volume etc.)"[31].

A small system is an atomic nucleus system composed of nucleons or other particles; an atom is also considered a small system comprised of electrons. Thermodynamics could be an interesting scientific approach to study the behavior of such systems, while the study of such systems under the laws of thermodynamics would be impressive. Generally speaking, the laws of thermodynamics apply to materials on all scales. At the small scale, some bio-phenomena are not visible (i.e., interfacial energy, thermal fluctuations), and should be taken into consideration when studying a small system and evaluating the relevant findings.

Consequently, a number of different approaches have been introduced and improved, i.e., non-equilibrium statistical thermodynamics, quantum thermodynamics, non-equilibrium fluids, molecular dynamics should be considered as crucial in the evaluation of experimental measurements and processes regarding biological events.

"*Let's go through the two basic laws of thermodynamics*", Grandpa proposed.

"*Alright*", Grandpa, "*they are amazing laws that are suitable for the understanding of natural phenomena and of the activities of natural objects.*"

"*So, let's start*", Granpda said, "*and let's refer to the principle of conservation of the total energy of a biosystem which is defined by the first law of thermodynamics and is expressed as*:

$$\mathbf{\Delta U = q - w}$$

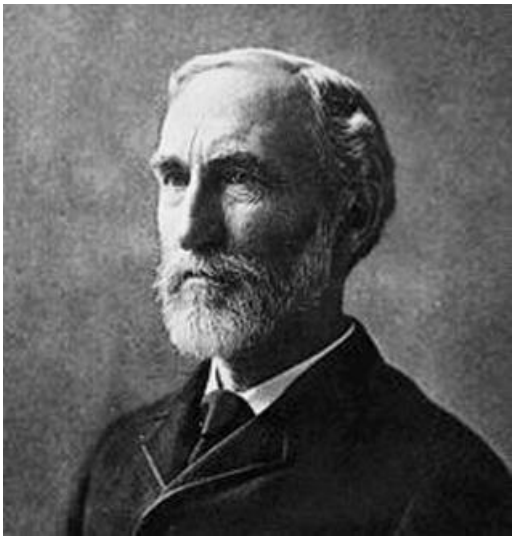
where ΔU represents the change of energy of the biosystem, q represents the input

[31] Hill, T.L., "Thermodynamics of Small Systems. Part I and II, Dover Publications", Inc.New York; Hill, TL. "Extension of Nanothermodynamics to Include a One-Dimensional Surface Excess", Nano Lett, 2001 1, 159-160; Hill, TL; Chamberlin RV, "Extension of the thermodynamics of small systems to open metastable states: An example", Proc Natl Acad. Sci USA, 1998 95 12779-12782].

[32] Hill, T.L., "Thermodynamics of Small Systems. Part I and II, Dover Publications", Inc.New York; Hill, TL. "Extension of Nanothermodynamics to Include a One-Dimensional Surface Excess", Nano Lett, 2001 1, 159-160; Hill, TL; Chamberlin RV, "Extension of the thermodynamics of small systems to open metastable states: An example", Proc Natl Acad. Sci USA, 1998 95 12779-12782].

of energy that the biosystem received as heat and w is the energy lost, because of the work that the biosystem offers to the environment.

The second law refers to entropy. We can say that entropy S is a factor which contributes to the full understanding of the change of Gibbs free energy, which is represented by ΔG. Gibbs free energy (G) constitutes an overall parameter which is incorporated in the change of enthalpy ΔH, and which indicates if a change can take place spontaneously or not."



Picture 10: Josiah Willard Gibbs

Josiah Willard Gibbs (February 11, 1839 – April 28, 1903) was an American scientist who made important theoretical contributions to physics, chemistry, and mathematics. His work on the applications of thermodynamics was instrumental in transforming physical chemistry into a rigorous inductive science. Gibbs also worked on the application of Maxwell's equations to problems in physical optics. As a mathematician, he invented modern vector calculus (independently of the British scientist Oliver Heaviside, who carried out similar work during the same period). In 1863, Yale awarded Gibbs the first American doctorate in engineering

(https://en.wikipedia.org/wiki/Josiah_Willard_Gibbs).

"*You can understand*", Grandpa continues, "*that the Gibbs free energy of a biosystem, incorporated in thermodynamic parameters such as enthalpy H, and entropy S, could be considered important in the study of biological phenomena and their spontaneous evolutionary process. Indeed, we can say that they constitute important scientific tools for understanding the behavior of living beings from a thermodynamic point of view."*

"Excellent, Grandpa. I've clearly understood the role of these parameters we discussed, and I have read the equations that are related to them."

The change of free energy of a biosystem is presented based on the following equation and is the thermodynamic criterion of a spontaneous process when the temperature (T) and the pressure (P) remain unchanged:

$$\mathbf{\Delta G = \Delta H - T\,\Delta S},$$

in other words, the Gibbs free energy is defined as:

$$\mathbf{G = H - TS}$$

It is obvious that a reduction in the Gibbs free energy (G) of a biosystem is related to its spontaneous behavior. Therefore, when:

$$\mathbf{\Delta G = 0}$$

then the biosystem is in a state of equilibrium and no change of the free energy occurs. This could be characterized as 'the thermodynamic death' of the biosystem and we could say that its evolutionary process would be terminated.

A change in the entropy of a biosystem (ΔS) is related to the increase of disorder in the molecules in a biosystem. The changes in both entropy (ΔS) and enthalpy (ΔH) must act competitively and, consequently, must have opposite signs. In the above equation, which correlates the change of Gibbs free energy with the changes in enthalpy (ΔH) and entropy (ΔS), it seems that the importance of change in entropy (ΔS) will increase as temperatures rise. It is for this reason that the product TΔS was introduced [33].

"*Let's now move on to the third law of thermodynamics*", Grandpa continued, "*which is related to the 'absolute entropy' of a given biosystem*. *It is well established that the entropy of a biosystem increases after an increase in the movement of the system's elements i.e., the biomolecules. Conversely, when the organization of matter is more ordered, the entropy of the biosystem is reduced. Therefore, at temperature T = 0 K (-273^{0}C), meaning at a temperature equal to absolute zero, in which a 'perfect' crystalline structure exists, without any structural abnormalities within the crystalline matrix, the absolute entropy of the system is zero (0).*

$$\mathbf{S^O\ (0\ K) = 0}$$

We should note at this point that any effect of change in nature is always related to the dynamic balances of the interactions between the biosystem and the environment. It is obvious that the evolution of biosystems and their adaptation to the constantly changing conditions of their micro-environment, but also of the

[33] H.D.Brooke Jenkins, "Chemical Thermodynamics at a Glance", first published by Blackwell Publishing Ltd, 2008, see chapter 13, 13.2 in the English text.

environment in general, are related to the reduction of the free energy of the system. The study of complex systems is a challenging scientific field and is currently being applied to the study of small systems. It should be noted that the most acceptable definition of complex systems based on the literature is the following: 'a system containing many interdependent constituents which interact nonlinearly' [34]**.**

The definition is still not precisely delineated, but it is generally accepted that the ideal complex systems are the biological ones. Centuries of studies and experiments try to approach the complexity of natural phenomena and to interpret them, promoting the evolution of knowledge of science, technology and human culture in general. Indeed, it is difficult to reproduce the complexity of biosystems in research laboratories and this is due to the fact that humans are unable to comprehend the greatness of physical complexity and the laws of nature. Nature created this complexity to be able to choose the most dominant biostructures and biosystems in order to maintain the possibility of evolution and reproduction based on the prevailing quality characteristics. Based on the literature, we can point out the following:

Thermodynamics of small systems is based on Hill's theory, offers a quantitative treatment of biomaterials in thermodynamic equilibrium. The biomaterials are involved in the construction process of micro and nano biosystems. These heterogeneous biosystems are affected by kinetic issues which explain the effect of perturbation on small systems, through non-equilibrium thermodynamics. The thermodynamic properties of a small biosystem are not necessarily proportional to its size.

Generally, small bio-systems present very high surface-to-volume ratios and have the characteristic that the interactions of the forces acting on the biosystem are of larger range than the size of the biosystem itself. Mesoscopic systems, such as the liquid crystalline membrane, belong to that class. The laws of thermodynamics apply, but some phenomena must be taken into account, like interfacial energy and thermal fluctuations. In addition, surface energies affect the chemical and physical properties of biosystems, and for this reason they are introduced as a contribution to the Gibbs free energy. An equation that links some biosystem's surface properties with its behavior is:

$$dU = TdS - pdV + \mu dN + \gamma dA_l$$

where U is the biosystem internal energy, T the temperature, S the entropy, p the

[34] "*Nonextensive entropy. Interdisciplinary applications"*, Ed. M. Gell-Mann and C. Tsallis, Santa Fe Institute, Studies in the Science of Complexity, Oxford University Press, 2004 p. 377.

pressure, V the volume, μ the chemical potential, N the number of particles, γ the interfacial free energy and A_l the interfacial surface [35].”

“*It is a very ambitious effort to explore such scientific fields*”, my boy. “*Are you feeling tired? Are you OK*?”, Grandpa asks, half-hiding a smile and some satisfaction that there is someone –in fact a young man– who listens to everything he carries in his soul and mind.

“*Alright, alright*”, Grandpa continues, “*I understand your passion to study more, to explore and to learn more, and the term entropy is an exciting topic that we should discuss later. I now suggest that we relax for a few hours and drink something. Then, we will move on. Are there any cookies and water here? Water is necessary for keeping us hydrates and for satisfying our senses*.”

“I guess my mother, Grandpa, has stored in a safe place everything we need for our survival but also for the satisfaction of our tastebuds. But, yes, wait a minute, yes of course; I found cookies and fruit, but also various food items. I also found some alcohol, the label on the bottle reads ‘raki’.” “What do you know”, respected Grandpa, “or better what do you think about ‘raki’.”

“*Oh dear! Of course, I know. Do you think that I have reached this age without knowing about ‘raki’? What do you think, my young man, that I spent all my time locked up in the library drinking only the juices of knowledge and renouncing the golden apples when they were offered to me. No, my dear boy, the balance that nature asks for and, let's say, sometimes imposes on the macrocosm, requires that you acquire knowledge through different opinions which you will have to process in order to arrive at specific views. These will constitute the concentrated wisdom of all the years you live on earth. It is this wisdom that you should pass on to the younger generations and rest assured that it will be the ‘vehicle’ of your creative contribution to the qualitative development of society.*

But let me see! Oh my! The content of this bottle could be hundreds of years old. If memory serves me right, my mother has been saving it to be used for massaging in case someone fell ill. In other words, rubbing, i.e., the delivery of heat, created or rather restored the functional ‘metastable phases’ of human tissues to normal function. Alcohol helped achieve this. Empirical bio-thermodynamics… What a nice definition.

So what is rubbing, young man?”

“Grandpa, I will answer using the terminology and thermodynamic logic that you taught me. Rubbing is the attempt to transfer heat through friction and topical temperature rise in the human body, for therapeutic purposes. It was –I have to admit– very effective.”

[35] De Hoff, RT. “Thermodynamics in Material Science”, 2nd Edition. Florida: Taylor & Francis; 2006.

ENTROPY AND LIFE

Classical thermodynamics is related to macroscopic observation, while statistical thermodynamics deals with a huge number of small systems and follows the suggestion that "all spontaneous processes represent changes from a less probable to a more probable state". Therefore, the probability of a biosystem reaching any given state should be clarified and established by counting all the possible distributions accessible to it. We can primarily conclude that spontaneous processes increase its entropy, as well as its probability. However, statistical thermodynamics is quantitatively related to measure changes in entropy from a less probable to a more probable state [36], playing a key role in the analysis of thermodynamic phenomena.

It is also important to refer to the 'intelligence' of biosystems based on structural polymorphism (i.e., lyotropism), which can behave as a 'metastable phase' which acts as a navigator and biosensor of the biosystem. It is obvious that biosystems do not have logic and logical decision-making mechanisms, so any 'decision-making' process is essentially selected based on the biophysics and on the thermodynamic profile of the system. According to Grainger and colleagues, "…thermodynamic criteria governing phase transitions are the mechanistic basis for their 'smartness'. There are no logic algorithms on board, no decision–making or rationalizing framework and no intellectual capacities."[37]

"*I think you would be interested in learning more about the concept of entropy, young man. You may be surprised to find that this thermodynamic parameter can be used as a tool for interpreting even social phenomena. Does that sound like a good idea to you*?"

"Of course, Grandpa, let us proceed to the understanding of this important thermodynamic parameter and the second law of thermodynamics. I'm surprised you tell me that based on entropy we can even approach social phenomena. But let me take a look at my books for a moment, so that I am more prepared to hear what you have to say."

Alright, here it is. Clausius, in 1854, was the first to introduce the concept and, in 1865 he coined the term 'entropy'. The expressions of the first and of the second law of thermodynamics are mentioned below and are milestones in the history of thermodynamics:

[36] K. A. Connors and S. Mecozzi "*Thermodynamics of Pharmaceutical Systems",* John Willey and Sons, Inc, 2010.
[37] D. Grainger Int. J. of Pharmaceutics 454, 521-524, 2013.

"Die Energie der Welt ist constant" and "Die Entropie der Welt strebt einem Maximum zu"

According to the Polish scientist J. Sestak, who wrote the monograph entitled Heat, Thermal Analysis and Society [38], "the most basic and also unlocking quantities in thermodynamics are temperature and entropy, where the latter is an artificially introduced phenomenological parameter expressed as the ratio of heat and temperature."

Contrary to temperature, which can be measured, entropy is an observable parameter based on the visible changes in the system. Entropy can be understood as the attempt of human beings to oppose the laws of nature on a macroscopic and microscopic level. Biosystems self-assemble in a complicated manner and their diversity is proportional to their functionality. Adaptation and evolutionary processes are directly related to the complexity of the biosystem and of its bionetworking processes. It is our responsibility to understand such diversity and complexity, taking into account that this is a continuous, naturally occurring dynamic effect.

Natural engines, or to phrase it better bio-engines (meaning bionetworking processes), are bio-actors producing unlimited 'biometastable phases' and conformational and structural polymorphism (i.e., lyotropism). In this way, the lyotropic state of matter of liquid crystals is prioritized, producing new and unending biostructures that are competitively involved in the bio-ecosystem. Those affect the evolution of human beings on both a macroscopic and microscopic level.

"*I think I have gone too fast, introducing terms like lyotropic liquid crystal. But do not worry, young man, I promise you that I will return to these terms and they will be fully understood. In fact, later you will be surprised to read and hear the meaning of lyotropism in social phenomena. For now, follow my thoughts and try to create the puzzle of your knowledge using what you know so far. You will see that as the discussion progresses, the images in the Mirror of your knowledge will become blurred and new images richer in information will appear. This will be proof of the evolution of knowledge*."

"Ok, Grandpa, do not worry, I follow you and note what you say. Yes, let's move on now and discuss later the terms which are unknown to me, lyotropism and liquid crystal state of matter."

"*Good then. Young man, I see that you can stand the game with the Mirror. It is of course provocative, and I have to admit that you can spend your whole life*

[38] J. Sestak, "*Heat, Thermal Analysis and Society"*, 2004 Published by Nucleus HK, Divisova 882, CZ-50003 Hradec Kralove.

looking for the 'true' image. Uncertainty and dynamic phenomena that evolve in nature, in the biosystems that interest you most, are the evolution of life. The Mirror of knowledge can even be the purgatory of your passions. You have to be careful, to know your limits, to know to what extent you can endure the evolution of truth, rejection and vindication. I think you are tenacious and passionate, and you will succeed. The entropic process is not something simple or easy. It is ambitious and it is the expectation of many generations from the past. You can refer to J. Sestak's work. Based on his book, Maxwell introduced the supernatural 'Maxwell's demon' which is nothing but, as J. Sestak suggests, 'a mental artifact to explain the concept of entropy, but not a real device' [39]**.**

It should be noted that a large number of biomaterials, mainly polymers (biopolymers) and lipid biomaterials which are components of living organisms and are biocompatible and biodegradable and based on their properties, are used to perform daily functions. and activities of living organisms. These biomaterials, as well as many others, are used after formulation even for the treatment of human pathogens. Thus, new and innovative pharmaceutical and therapeutic products are released on the market based on new scientific data with new technological applications. Thermodynamics and its laws contribute to the understanding of the function of new therapeutic products and to the development of new and effective drugs.

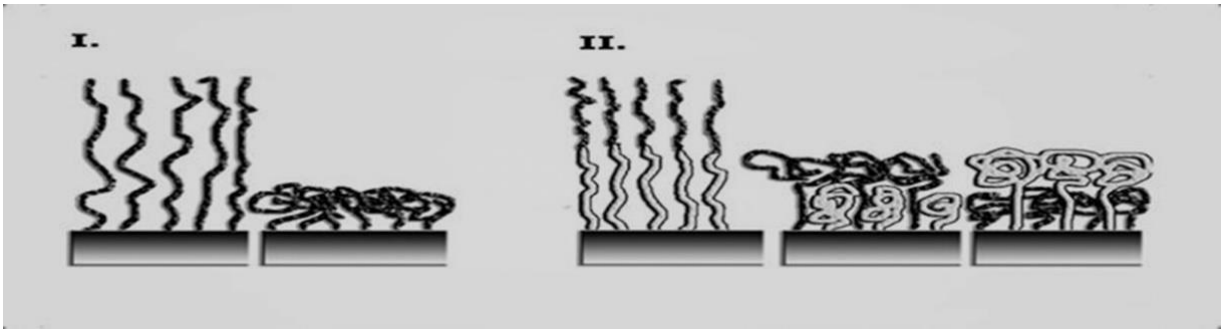
Can you see the image below?", asked Grandpa. "*This image represents a polymer (I), a diblock copolymer (II) and their conformations that are used as innovative excipients, to produce innovative medications* [40]**.** *They are able to change their conformational properties and consequently, their entropic state. Can you see their shape and their functionality? Such polymeric behavior takes place in nature through biopolymers such as proteins, peptides etc., that are stimuli responsive to the surrounding environment. It is an amazing process in nature that occurs in a dynamic and non-equilibrium way, aiming at the adaptation and the selection of the most favorable thermodynamical conformation that promotes life processes. Can you discern the differences between the conformations I and II* ?"

"Yes, Grandpa, it is a brilliant form of behavior. But what is the driving force behind these changes?"

"*In my opinion, it is their physicochemical properties that define their shape, morphology and functionality; also, their behavior in the networking process and, finally, the adaptation to the environmental changes and the*

[39] J. Sestak, "Heat, Thermal Analysis and Society", 2004 Published by Nucleus HK, Divisova 882, CZ-50003 Hradec Kralove.
[40] C. Demetzos "*Pharmaceutical nanotechnology. Fundamentals and practical applications"*, Springer Nature, 2016.

evolution to higher quality self-assembled structures. Obviously, it is vital that such bio-responsiveness occurs in biosystems, to promote their very survival."



Picture 11

Different in nature biomaterials (dark (I) and dark/grey (II) change their conformations due to an external stimulus.

I should also mention that the macroscopic forces visible are entropically driven. The statistical tendency of the biosystem as a whole seems to play a key role. Since you are familiar with cyberspace and with information-mining tools, I can give you related links for further investigation of such phenomena. You can also have a look at the article entitled 'The effect of an external field on an interface, entropic repulsion' [41]**.**

*As we mentioned earlier in our discussion, 'metastable phases' are characterized as high-quality processes and can be described as the '*cryptic *codes' that science must read and understand. If you remember, we have already mentioned in our discussion of 'cryptic variables' and 'cryptic codes' which function as information vehicles, and I believe that the mysteries of nature should be tried to be revealed. In my opinion, they are a high priority research process. Of course, many of them have been approached by science, and we have all understood their value e.g., the identification, reading and understanding of our genetic code. They are mysteries that we do not know of, but perhaps due to our already established knowledge we suspect that they exist. They are constantly revealed in front of us and surprise us with their complexity but also the high degree of difficulty in reading and understanding them.*

So can you describe the behavior of biopolymers in the image in front of you and interpret this behavior?"

"Yes, I can, Grandpa. Let me describe what I see. There are two polymeric

[41] "*The effect of an external field on an interface, entropic repulsion",* Journal of Statistical Physics Volume 46, Numbers 1-2 / January,1987] http://en.wikipedia.org/wiki/Entropic_force; http://en.wikibooks.org/wiki/Entropy_for_beginners ;http://en.wikipedia.org/wiki/Entropy

biomolecules, (dark and dark/grey) that are different in nature. Alright, so, these two polymers are mixed and there is a transition from one conformation to another. Maybe an external stimulus is responsible for this transition. That is what I see. These two conformations of polymers could influence and produce different 'metastable phases' dynamically; statistical physics should decide and promote the one that could adapt to the surrounding environment, taking into account the statistical biodata and promoting the priority of the stimulus responsiveness effect. I guess that the external stimuli (i.e., temperature, pH, magnetic or electrical changes etc.) correspond to environmental changes and could affect their behavior and response, which are expressed as the most thermodynamically favorable and consequently functional conformation. Finally, their conformational properties have been selected as energetically favorable among a huge number of properties in order to continue to transfer bio-information and life processes."

"*Oh, that's excellent, my boy, really excellent. I am very proud of you. However, two different molecules that are grafted on any biological substrate, like the polymeric compounds in the image, can behave in a very different way, promoting different 'metastable phases' that could be essential for important biological functions and phenomena. Moreover, based on this approach, we can conclude that the development of artificial substrates (such as lipidic or phospholipidic membranes that are able to host biomolecules like polymers on their surface and are composed of more than two different in nature phospholipids or lipids), mimic real biological membranes more precisely than binary systems do. These biological models can be developed in research laboratories and the studies and analyses of the phenomena that occur in them, can be 'projections' of natural biological phenomena and very important conclusions can be drawn about the behavior of living matter.* [42]

It is clear that the complexity of such artificial systems plays a major role in the conformational properties of the whole system and are considered to be similar to real membranes, actually reflecting what happens in natural phenomena. As pointed out already, nature prefers and promotes complex systems and biodiversity in the environment because of the ability of complex systems to behave more effectively in terms of natural functions. The plethora of 'metastable phases' that a biosystem can achieve due to its complexity plays a vital role in its survival.

In the same document I mentioned above, the authors state that the presence of divalent ions such as Ca^{++} *in lipid membranes composed of phosphatidylserine bilayers seems to stimulate the 'metastable phases'. But we*

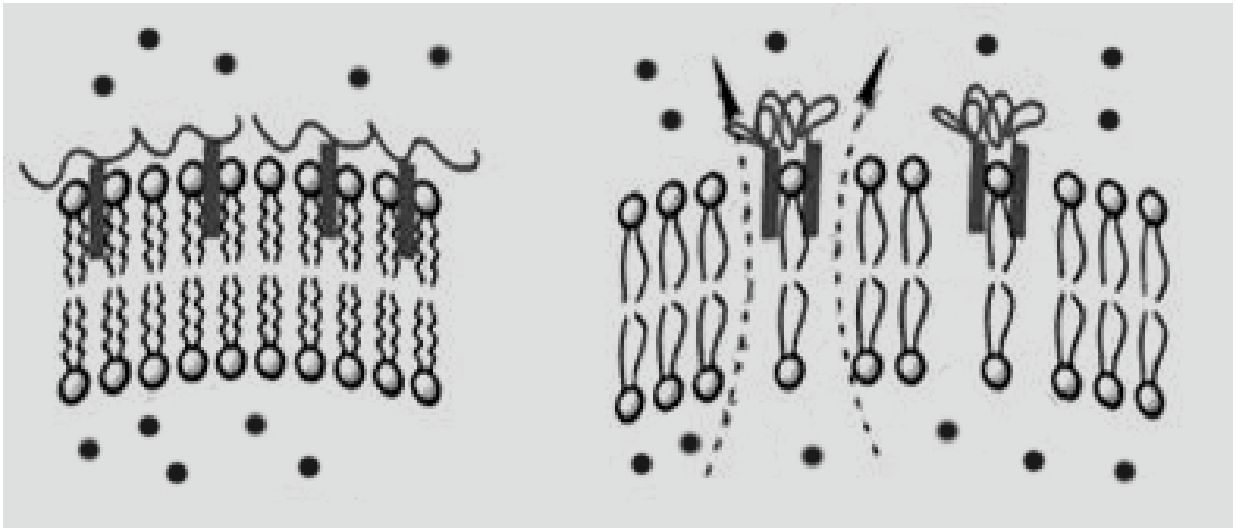
[42] W. H. Binder, V. Barragan, and F. M. Menger "*Domains and rafts in lipid membranes"* in the Journal of *Angew. Chem. Ind. Ed*, 2003, 42, 5802-5827.

have to be careful in the development of such membrane models because the concentration of the partners, i.e., polymeric guests in the mixed system, plays a crucial role in their stability. An unstable mixed artificial system is produced when the concentration of Ca^{++} *is more than 30 mM. It is clear that nature does not only select the appropriate biomolecules to produce effective biosystems and networks, but it also takes care of the concentration used. By switching the composition of the polymeric guests or their concentration, meaning that other biomolecules with different physicochemical 'memories', i.e., properties (e.g., different hydrophobicity) are promoted, it is true that the interactions -and above all the interactions with water molecules- will change. As a consequence, this affects repulsive or attractive hydration forces, according to the theory which explains the aggregation of aqueous dispersions. This theory is denoted as DLVO (named after Boris* ***D****erjaguin, Lev* ***L****andau, Evert* ***V****erwey and Theodoor* ***O****verbeek).*

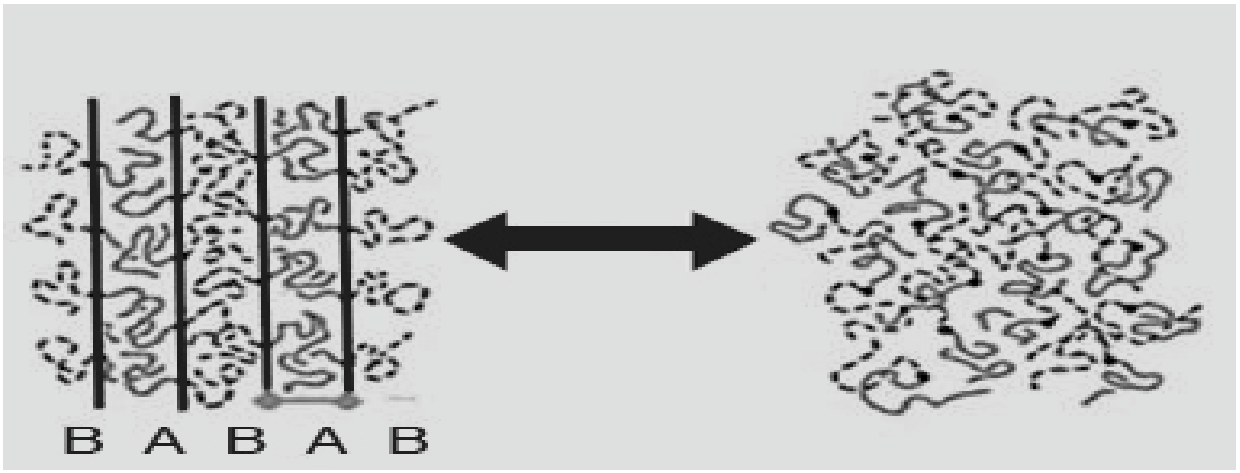
I think, my young man, we are now at an increased level of difficulty and the approaches we take to understand complex natural phenomena in biological processes, you will agree I imagine, require thermodynamic and biophysical knowledge. We need effective and reliable standards for simulating biological processes that mimic those of living systems. So, these systems are biomimetic. Do you know what biomimetic systems are?"

"Yes, Grandpa, I have read something in the books from your library. I tried at some point to comprehend the logic of designing and developing bio-mimetic drug delivery systems with increased efficiency. So, I realized that they were using biocompatible and biodegradable biomaterials and designing biomimetic systems in terms of their functionality. They then trapped drug molecules in them and by acting as 'Trojan horses' they mimicked the behavior of biological membranes. It's impressive to try to copy as much as you can nature in order to create high efficiency technology platforms e.g., in the designing of innovative therapeutic products. "*All this is extraordinary, young man. Now look at the figure in the book. Where is it? There, somewhere on the library shelf. Yes, that one. But before we discuss this figure, I want to suggest that you study the publication of by T. Lammers. For now, however, let us stick to the following comment from his publication. So, T. Lammers says: 'Most of novel nanomaterials are 'art' rather than 'smart'. This is because they generally are highly complex formulations […] difficult to synthesize and scale-up in a controllable and reproducible manner'* **[43]**.

[43] T. Lammers 'Smart drug delivery systems: back to the future vs. clinical reality', Int. J. of Pharmaceutics 454, 527-529, 2013.



a



b

Structure in order **Disordered structure**

Picture 12

In other words, T. Lammers states that natural processes are so beautiful that they could be considered art rather than an 'intelligent' achievement of science that mimics biological processes. Indeed, it is. The beauty of nature and its processes are the highest art form due to the complexity of the natural processes that lead to beauty, just like the beauty of E. Schrödinger's mathematics. The 'intelligence' of artificial biomimetic systems for the study of biological phenomena is due to their unique physicochemical properties, especially when new ones are created, due to their mixing and the creation of new biomaterials, as we discussed above. Thus, self-assembly, the 'metastable states' created in research laboratories, are important achievements of human endeavor to get as close as possible to the biosystems and functionality of living organisms. It seems that perhaps the art of nature precedes the 'intelligence' of biomimetic systems, and the scientific community should understand that if we cannot discern the beauty of natural phenomena, we will not be able to develop new scientific

and technological tools, thus advancing the natural sciences."

"Let us now try to describe what the figure shows in the book", I said, looking into my Grandpa's large, clear eyes. When I look at him, I have the impression that I am lost in time and in the light of infinite knowledge and emerging questions. What is this Grandpa after all? Is he the tale of our lives that hides truths we need to reveal? Is he our selfish gene that wants to be expressed, but has to 'discuss' with its natural ancestors, to know the present and the uncertainty of the future, and decide if it is strong enough or if it must obey acquired commands? Grandpa with the 'metastable phases' imprinted on his forehead, is sure of the orders he gives, which are orders for the direction I should follow; not for the choices I should make. Is my freedom in fact my choices? Is it the perspective I give to the perpetual dance of events in the microcosm, to create the macroscopic natural phenomena we see in the macrocosm? I want to know this, I want to see the usefulness of my presence, of my participation on our planet or even in the world. Why should I be useful or why not? What is the need for my creation in a cosmic space where events seem to ignore me.

"I'm coming, Grandpa. I got a little absorbed in my thoughts and I got lost… The first figure (a) [Picture 12] shows different biomaterials (dark and grey) which are self-assembled based on their thermodynamic and biophysical 'memory', due to their physicochemical properties. They are structurally organized in bilayers – like our cell membranes– and if their building blocks are phospholipids or cholesterol, then they are structurally close to our cell membranes. It appears from the figure that changing their morphology requires the existence of an external stimulus; I do not know which one. However, an external physicochemical stimulus creates the need in this system to change its morphology, i.e., its morphological polymorphism, in order to survive thermodynamically and reduce its entropic 'mood'. This external stimulus influences, perhaps, one of the two biomaterials. If this happens, then the affected bio-material changes morphology and indirectly affects that of the other biomaterial and they are eventually led to a thermodynamic 'agreement' for their survival, as we said before. The entropy of the system is certainly affected and creates the macroscopic changes which can – I would probably say– affect its functionality. For example, if this system acts as a transporter of a drug molecule, then the release of the drug molecule from this system will be different before the external stimulus and of course different after the occurrence of the stimulus. And this may be related to the therapeutic value of the whole system which will affect the therapeutic effect.

We can say that similar types of biosystems –we call them biosystems because they have been created with biocompatible and biodegradable materials so that they are not toxic to humans and the environment– are designed and

developed in research laboratories and used as technological platforms for the study of natural and biological processes. In other words, we can study phenomena that occur in living organisms such as: states of non-equilibrium, self-assembly, modulatory changes, physicochemical stability, functionality, interaction with neighboring or distant biosystems, responsiveness to external stimuli, etc."

"What do you say", Grandpa? "Am I doing well? Are your eyes bigger or do I see bigger images in the Mirror of your eyes?"

I'm probably doing well, because I see you're not talking. Your smile shows satisfaction; yes, I know you do not want to interfere with the magic of interpreting the complex phenomena that you make me decipher. That's why you don't talk. But I want it, I want it very much, I have to understand what is happening, what are all these incomprehensible things that are happening around me, day and night, incessantly. How can I bear to constantly see in front of me images in a Mirror which collapse and are reappear as something better, which create a new desire in me to conquer them? And as soon as this happens after a lot of effort, here comes a new image. The magic of the Mirror of knowledge and the alternations of life and death, of positive and negative entropy. This constant alternation will never end.

Let me now move on, escaping my thoughts for a minute.

"The image from the book is still here. So, figure (b) [Picture 12] shows changes in the organization of biomolecules from an ordered structure (B A B A B) into a disordered one because of an external stimulus (e.g. change of temperature); this change is due to the supply of heat to the biosystem and therefore to the increase of its temperature and this leads to a non-order (disordered) state. This means that the biosystem was fed with positive entropy, i.e., with an increase in its enthalpy due to the increase in heat as an external stimulus. Its response is due to the fact that the temperature level reached is greater than its temperature 'memory' associated with changing its morphology from one temperature level upwards. If the temperature change was below its temperature 'memory', then there would be no change in the order of the biosystem. This could be considered a reversible phenomenon. But, as we have already mentioned in our discussion, the system will never be able to get to where it started, due to the entropic process. At the macroscopic level, we will find absolute reversibility, only this is not true due to the second law of thermodynamics, and of course entropy. In the following we will see some equations concerning the relation of thermodynamic parameters. Enthalpy is defined as follows based on the first law of thermodynamics:

$$\mathbf{\Delta U = q - w}$$
$$\mathbf{q = \Delta U + w \quad and \quad w = P\Delta V \quad and}$$
$$\mathbf{q = \Delta U + P\Delta V}$$

The variables U, P and V are all state functions. Enthalpy could be defined as:

$$\mathbf{H = U + PV}$$

and consequently

$$\mathbf{q = \Delta H}$$

ΔH is equal to the heat that the biosystem received and stored or the heat that the biosystem lost, assuming pressure remains constant.
Therefore, we can claim that the change in enthalpy of the biosystem is:

$$\mathbf{\Delta H = \Delta U + P\Delta V}$$

Because in biological processes the change in the volume of the ΔV biosystem is considered negligible, then:

$$\mathbf{\Delta H = \Delta U}$$

"*Oh, that's an excellent overview, and the equations are well presented. I did not believe that you were able to provide such explanations! But what about your smartphone? Are you connected to the Internet? Really, my boy, I cannot quite believe how impressive your knowledge is… Tell me now how you managed to collect such information to be able to explain all these difficult scenarios. You probably try a lot, you work a lot, I see it, we are always together, for years now, ever since you went to school. You have been consistent and diligent*".

"Grandpa, I am trying with ambition, I would say, perhaps, and with vanity to conquer your thought, to understand the 'metastable phases' of your brain, i.e., your knowledge, which is 'engraved' on your wrinkles and invite me to travel to Ithaca which will not disappoint me."

"*Alright, so you're a really brilliant young scientist. Now, move on, move on,"* Grandpa said. *"Let's find out what is going on with the entropy and the 'metastable phases', as you mentioned. But let me tell you* [44] *that the polymers that you proposed previously as guests in the artificial lipid bilayers for the study*

[44] W. H. Binder, V. Barragan, and F. M. Menger, "*Domains and rafts in lipid membranes"* in the Journal of *Angew. Chem. Ind. Ed*, 2003, 42, 5802-5827.

of biological phenomena can lead to clustering effects which, from a biological point of view, are considered high quality processes when the phenomena take place within the lipid bilayer of the cell membrane. Think that this clustering process promotes the signaling transduction and information regarding the network formation. It is important to point out that the artificial membrane bilayer could consist of polymeric compounds, forming, for example, the so-called polymerosomes (i.e., polymers with such conformational properties that they could be able to curve to a bilayer). The type of structure to be formed depends on the amphiphilicity of the molecules, and consequently of the hydrophilic/lipophilic balance, their molecular mass, as well as of the solvent properties, meaning the properties of water (i.e., pH, ionic strength etc.). So, we can conclude that a huge number of 'metastable phases' could take place in nature, and they can select biomolecules based on their physicochemical and structural properties. The environmental properties of each changing environment play a key role in the formation process and in the functionality of each structure. A thermodynamic parameter, such as enthalpy H and entropy S, is important, as it manages the stability of the biostructures formed."

"Let's talk a bit more about entropy. Let's talk about how it relates to the equilibrium and non-equilibrium state of a biosystem. What do you say, Grandpa?"

"*Alright. What is the main characteristic required in order to classify a biosystem as 'alive', in the sense of it being functional*?"

"I suppose the movement of biomaterials, Grandpa. In the case of a living cell, the well-known mechanism is the exchange of vital compounds with the surrounding environment, i.e., metabolism. Am I right?"

"*Yes, you are. This 'immobility' of a system, a zero change in the chemical potential or the absence of chemical interactions between bio-elements results in a non-functional system, with entropy being predominant. This is called 'maximum entropy of the system'. In reality, a system never reaches maximum entropy, but it always approaches it. This process might take a significant amount of time, or even centuries, and this may not be visible within the lifespan of a human being. What do you say, is that clear*?"

"And how does a living organism avoid the entropic process?"

"*The entropic process is pushed away, but not for long, in the living organism's attempt through their metabolism to produce what is known as 'negative entropy', thus gaining time to survive... but the organism will not survive forever. 'Negative entropy' could be the driving force in supplying effective 'structural information' for a biosystem and, as Brillouin states, 'negative*

entropy' is the so-called 'negentropy' [45]*, but as a term it is not that well known* [46]*.*

It is important to bear in mind that a biosystem has a better organizational profile that drives it to a level of less chaos and less disorder when it is offered some kind of task to perform. In other words, an organized biosystem needs a structural input to offer it better organization. However, the input of energy increases the organization of the biosystem and promotes the self-assembly process, offering as added value to the whole biosystem a more improbable thermodynamic state.

A living organism, a biosystem, increases its entropy, meaning 'positive entropy', and this is not an acceptable situation in order to stay alive. The real 'food' for any living organism is 'negative entropy'. The living organism is obliged to remove the entropy produced in order to remain functional and alive. An essential point that we should stress is that at absolute zero (-273 ^{o}C), the entropy of a given 'structural well defined' system is considered to be zero. The mathematical expression of entropy according to Schrodinger [47] *is given by the following equation:*

$$\boldsymbol{S = k_B \log D}$$

S= entropy; k_B = Boltzmann constant (= 1,381 x 10^{-23} JK^{-1}); D = reflects the quantity measure of the non-order (disorder) of a given system. So, if D expresses the level of non-order (disorder) of a system, the level of order of a system can be defined on the basis of the aforementioned equation (1 / D). In this way, the formula for negative entropy could be as follows:

$$\boldsymbol{-S = k_B \log (1/D)}$$

And we can also accept that this equation, i.e., negative entropy, expresses the order of a system, and as such is related to life and its functions.
Boltzmann proposed a general description of entropy, which we could say is its statistical definition [48]*.*
Would you like me to give you an example so you can see the mathematical expression of the equation of entropy?"

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[45] J. F. Brillouin, "Science and Information Theory", 1956.

[46] J. Sestak, "*Heat, Thermal Analysis and Society"*, 2004 Published by Nucleus HK, Divisova 882, CZ-50003 Hradec Kralove.

[47] J. Sestak, "*Heat, Thermal Analysis and Society"*, 2004 Published by Nucleus HK, Divisova 882, CZ-50003 Hradec Kralove.

[48] H.D.Brooke Jenkins "*Chemical Thermodynamics at a Glance"*, first published by Blackwell Publishing Ltd, 2008, see chapter 17 in the English text.

Picture 13: Ludwig Eduard Boltzmann

Ludwig Eduard Boltzmann (February 20, 1844 – September 5, 1906), was an Austrian physicist and philosopher whose greatest achievement was in the development of statistical mechanics, which explains and predicts how the properties of atoms (such as mass, charge and structure) determine the physical properties of matter (such as viscosity, thermal conductivity and diffusion**)**

(https://en.wikipedia.org/wiki/Ludwig_Boltzmann).

"Yes, of course, Grandpa. I am waiting for you to talk to me – not about lines of inquiry and centipedes, but about something I can understand. Well, I have to admit everything we have talked about so far is amazing and you haven't made a single allusion to centipedes, and I appreciate that a lot. So, let's see."

"*Drawing on H.D. Brooke Jenkins' book that we mentioned above, suppose we have a basin of water at a constant temperature, which is not influenced by the surrounding environment in any other way. If we pour a drop of dye into one corner of the basin, what do you think we will observe*?"

"We will see that the dye will slowly spread to the whole basin, without any turbulence or external stimulus."

"*That's right, that's exactly what we will observe. Do you think the opposite could also happen? I mean, if dye was spread into the water in a basin, could it start accumulating in the corner of a basin without any external intervention? Would that make sense?*"

"No, of course not. As far as I know such a phenomenon has never been recorded."

"*Boltzmann observed that for any possible molecular movement of the molecules of water (regular behavior) there is an equal possibility that any other molecular movement could occur. Furthermore, out of all the possible movements that may be described, the 'statistical majority' of them will promote movement allowing the dye to spread to the whole basin and for the molecules of the dye to disperse from the initial position. The driving force for such phenomena is entropy S and in the aforementioned description this is related to the probability of the most favourable dispersion process of the dye molecules into the water.*

Thus, the mathematical expression of the above statement is:

$$S = k_B \ln W = (R / N_A) \ln W$$

where S = entropy; k_B = Boltzmann constant (= 1,381 x 10^{-23} JK^{-1}); R = gas constant (= 8,314 $JK^{-1}mol^{-1}$); N_A the Avogadro constant (6,023 x 10^{23} mol^{-1}):

$$k_B = (R / N_A)$$

and W is the number of independent probable positions of the molecules.

The beauty of the Boltzmann equation is that it links the macrocosm (S) with the microcosm (W) in a straightforward manner.

The so-called universality classes of systems, according to the remarks Tsallis makes in Chapter 1 of his monograph Introduction to non-extensive statistical mechanics. Approaching a complex world [49] *'[...] share the same functional connection between the entropy and the set of probabilities of their microscopic states. The most known such universality class is that which we shall refer to as the Boltzmann-Gibbs (BG) one. Its associated entropy is given (for a set of W discrete states) by*

$$S_{BG} = -k_B \sum_{i=1}^{W} p_i \ln p_i$$

this equation is considered to be a landmark in Boltzmann-Gibbs statistical mechanics and is successfully used in physics, chemistry, mathematics, as well as computer sciences [50] *'.*

Where pi is the probability that a system will be in state ***i***

with $\sum_{i=1}^{W} p_i = 1$

For the case of equivalent probabilities (i.e., $p_i = 1/W, \forall_i$), the above equation becomes

$$S_{BG} = k_B \ln W$$

Tsallis, in his monograph, believes that '[...] they need to be modified (generalized) in other settings, in particular in most of the so-called complex

[49] Tsallis C., "*Introduction to nonextensive statistical mechanics. Approaching a complex world"*, Springer 2010.
[50] Tsallis C., "*Introduction to nonextensive statistical mechanics. Approaching a complex world"*, Springer 2010.

systems'.

Drawing on his beliefs and inspired by the scaling properties of multifractals, Tsallis proposed a generalization of entropy extending the well-known statistical mechanics and thermodynamics. The form of entropy is given below:

$$S_q(p_i) = \frac{k}{q-1}\left(1 - \sum_i p_i^q\right),$$

where k is a positive constant and q € R, p_i is the probability of the system in the quantum state i, and q is the 'entropic index'. The well-known Boltzmann-Gibbs entropy is recovered at the limit of q →1.

This equation can be applied to nano-non-extensive systems, while preserving the fundamental properties of entropy in the Second Law of Thermodynamics.

Entropy is considered to be an extensive property, i.e., its value depends on the amount of material present. Tsallis has proposed a non-extensive kind of entropy (Tsallis entropy) as an extension of traditional Boltzmann–Gibbs entropy.

However, the statistical approach by Tsallis have been applied in a huge number of systems underlying non-extensivity, such as systems with long-range interactions (gravitational; Coulomb forces), and systems in thermodynamic equilibrium (long range correlations)."

"What you are telling me and reading to me is not easy to grasp, Grandpa. I guess you would agree. How can we understand complex mathematical equations which have been formed through mathematical calculations and theorems that only experts in the subject know about?"

"*You're right, this is not an easy topic. I would like to suggest that you do not delve deep into these matters, that you go only until the point that you intuitively feel you understand it and that it connects to your previous knowledge or to the needs of your scientific field. You could also try to find an application for these laws and principles in your own scientific field. Another good approach would be if you could confirm the usefulness of these laws and principles in your everyday practice. That would be great, because in that way you could have proof of their application and usefulness. But, let me ask you a question, my boy. To relax a bit. Do you remember when you went to school? I still remember it, because I was there, no matter how strange that might sound to you*."

"Really, Grandpa? Were you there? Do you remember my school years, when I went to primary school for example?"

"Of course, I remember them. What kind of Grandpa would I be if I didn't? Do you remember that little boy, Mimis, in the elementary school textbook?

Wasn't there also a Grandpa on the page you used to read, and a girl called Anna? Try to remember. You don't remember it, or you only do so when you see the images or when someone describes it to you, like I'm doing right now. These memories have been recorded as 'invisible' images, let's say, which influence your everyday life. They have created 'populations' – perhaps the ***w*** *in the mathematical formulas above, I don't know! These populations participate in the statistical result of your choices without you perceiving it. That is what sparks your interest when it comes to learning, what provokes your interest in art, in culture, and how your very personality is shaped in the end. Without you perceiving it, it is certain that this past participates without these memories being 'visible'. There are some moments like shadows in our brain, when for example we see an object from the past. Even a smell can bring to our mind a forgotten image, and we can see ourselves in a moment from our childhood which we had forgotten completely. All of this is related to the entropic process and the 'metastable phases' we have been talking about. Personality is what remains and is visible to other people and to ourselves when what we experienced or learned in our education at school and our family is 'forgotten'... basically, it is our education. What do you say, do you think this is valid?"*

"Of course, Grandpa what you say is true. Yes, it should be. The primary school textbook, the teacher's perfume, the principal's strictness… how could I not understand their value then, Grandpa? These were really great moments; personality, yes, you are right as you define it. It's all that we learned in school and that we often considered 'useless' because we did not have the big picture of society and the quests that put them in the right place and completed the puzzle of our needs, expectations and ambitions. I should probably stop reminiscing about the past now and see what lies ahead, Grandpa."

Key Point

Personality is what remains and is visible to other people and to us when what we experienced or learned in our education at school and in our family is "forgotten". Basically, it is our education.

THE RELATION BETWEEN INFORMATION AND ENTROPY

It is pitch dark outside and I can't hear a thing. This silence is strange, it scares me because it makes me expect the unexpected... But it is also a deep breath away from the hustle and bustle, the colorless sounds, it gives me the chance to be by myself and think, to let some cells which also need relaxation time to gain the 'negative entropy' they need for their survival.

"Come, Grandpa, stop sleeping! Just try... There's a long way to go."

"*Hey, my boy, here I am, I was looking at a picture from my childhood... I have grown up and matured but yes, you are right, there's a long way to go. So, let's go. I would like you to understand that entropy is related to information. This is a very important point that we should take into account and work on, as far as it is of concern to us, of course. There is a very good presentation of the theory of information by Shannon* [51]*. I will tell you this, before we move on to the relation between entropy and information.*

Chaotic systems (limited number of variables with nonlinear correlation in-between them), constitute another category of systems, apart from determined systems (limited number of variables with linear correlations) and stochastic systems (very large number of variables with nonlinear correlations). They refer exclusively to nonlinear dynamical systems. The time evolution of a chaotic system is unpredictable or more precisely it is predictable for a short time period due to sensitivity to initial conditions.

Within the framework of chaotic systems, I can provide with the following important points."

"Grandpa, before we proceed to the points you want to talk to me about, would you like to tell me a little bit more about chaotic systems and about the concept of chaos in general?"

"*Yes, of course, why not? Just a moment, I will check some notes and books and I will be ready shortly. In any event, I will proceed with... chaotic observations. ... Well, well, the concept of chaos is mentioned in the Orphic Cosmogony and in Aristophanes' Birds* [52]*: "There was chaos at first"... In Hesiod's Theogony* [53]*, we read "Chaos was first of all"... Moreover, the concept of chaos has been used to describe states of disorder, but it actually refers to a system which presents a change in its evolution, which is not proportionate with one of the changes in its initial states of function. Chaotic systems are ones whose evolution is susceptible to change in their initial states of function. In dynamic*

[51] C.E. Shannon, Bell System Tech. J. 27, 379, 1948.
[52] Aristophanes, "The Birds", translated by George Gilbert Aimé Murray, London: George Allen and Unwin, 1950.
[53] Hesiod, "Cosmogony", translated by Dorothea Wender, Penguin, 1976.

systems there are losses of energy and obviously the laws of thermodynamics apply. Therefore, these systems present chaotic behavior, which means they present sensitivity to initial states. I should also mention that these systems present the phenomenon of self-similarity, i.e., a repetition of their morphological characteristics. As a result, their geometry is described as fractal, i.e., they have fractal dimensions. It is important to mention that fractal geometry is not a geometry within the three-dimensional Euclidean space, it adds to Euclidean geometry, and it functions in the Euclidean space.

It is a very important point to understand not the shape, but rather the morphology of natural objects, but also of artificial objects that are produced by human activities. You will understand that beauty and virtue (kallos; κάλλος) –in the classical sense of the word– are provided by the morphology of an object and not by its shape according to Euclidean geometry. So, this is a very important point. But let's see the directions of a chaotic system. That's where we were, weren't we going to talk a bit about chaotic systems?"

"Yes, Grandpa... So, let's go on."

"*In every chaotic system there are directions which divert exponentially and also directions which might have been distant in the beginning, but which converge exponentially. So, if for example our chaotic system, on the basis of the quantum rationale of statistics is 'sampled', it is evident that the diverging directions have a lower possibility to be 'selected', always when it comes to sampling. In this way, the uncertainty of the system increases in relation to the diverging direction, and the biosystem can be characterised as entropic. But in the case that the directions of the chaotic system converge, then it is evident that, when it comes to sampling, they will have higher chances to be selected, in this way, the system functions as a source of information. Now you understand the relationship between entropy and information in chaotic systems such as biosystems, and how the term 'information' functions when it comes to the communication between biosystems and the creation and functionality of complex systems. Furthermore, it is rather obvious that organization in biosystems is due to information and not to entropic processes, and that information is produced at a higher rate. Let's take an example from modern experimental scientific observation. Look at this picture... yes, the one in this book I'm holding now. It was taken with an electron microscopy. The scientists took two biomaterials and mixed them, changing their molecular ratio, i.e., changing the concentration of the first and maintaining the concentration of the second biomaterial stable. Then, they examined them in an electron microscope, through which we can see structures in the nanometer range, which is one billionth of the meter. Well, they observed that different self-assembled structures are produced depending on the*

concentration of the biomaterials used. There is a hierarchy in the selection of biostructures that have priority to 'survive'. But notice something and I will not go any further because we will discuss it later. There is a hierarchy of choices in society, in each of us in our daily lives. How is the selection made? But of course, on the basis of the usefulness, functionality and efficiency that our choice may have.

According to the aforementioned theory of information and entropy, information overall is the prevalent statistical direction. However, there is a hierarchy as to which biostructure is considered to be necessary for survival. By changing the concentration, the hierarchy of the biostructures also changes. The self-assembly process is directly linked to the lyotropism of liquid crystalline structures that are created and the entropy alternates with the information. This alternation depends on the concentration of the biomaterials.

The question is, what is the quality of information, which is to say, what information is effective and how is it selected? Of course, there is more to study, but the subject becomes extremely specialized and raises many questions concerning topology and about the existence of biological memory, etc.

Clearly, I believe that all of those behaviors of biosystems are related to the production of 'metastable phases', which could be considered as biological attractors.

You should read more on this subject because we will spend much more time than we had planned talking about it in our long conversation. A very important thing is that the concept [54] *is based on activities that take place in the microcosm. The changes in entropy may be driven by the need for re-structural organization processes in subcellular micro-biosystems. These changes in the entropy transition between micro-biosystems and in their 'metastable phases' that incorporate all the variables necessary for the effective behavior and survival of the biosystem could be related to information transferring processes between living organisms, which consequently have an effect on the sustainability of the natural laws or create new ones.*

There is one more observation that in my opinion could be interesting in this field. Is entropy responsible for the 'missing information' in the self-assembly process and the evolution of nature? If so, why does the second law of thermodynamics still exist and why has it not been discarded? Why is it that entropic behavior does not destroy itself? I do not have an answer to that, my boy.

There is only one thing that could be obvious from all of the above, that information is related to the organization and self-assembly of biosystems and of

54 C.E. Shannon, "*Bell System Tech"*. J. 27, 379, 1948.

living organisms.

On the other hand, entropy is the level of organization of each bio-organism, of biosystems and of the behavior of life. It is logical to say, according to the experiments that were carried out by Szilard, that 'additional information about a system can lead to a decrease in its entropy' [55, 56]. We can therefore say that information refers to the coding of the processes of a biosystem, while entropy to complexion, while the relationship between them is given by the following equation [57]:

$$\mathbf{JK^{-1} = 10^{23}\ bits} \text{ or } \mathbf{1bit = 10^{-23}\ JK^{-1}}$$

It is finally useful to say that, just as energy exists in different forms (such as mechanical, chemical, electrical, heat), information also exists in many different forms, and both can be transferred from one system to another and have similar behavior.

It was back in 1877 that Ludwig Boltzmann referred to the relationship between information and energy in his publication [58]. In 1929, Leo Szilard in his publication On the decrease of entropy in a thermodynamic system by the intervention of intelligent beings [59], studied the relationship between entropy and information through experiments that are referred to today as 'Szilard's engine'. His goal was to understand the so-called 'Maxwell's demon', so this was all about 'thought experiments'. The 'demon' refers exactly to those 'thought experiments' which are presented in the course of natural sciences as engines with special capabilities which can pose difficult intellectual challenges. As we already mentioned before in our conversation, Maxwell proposed the supernatural demon known as 'Maxwell's demon', which is a 'mental artifact to explain the concept of entropy, but not a real device' [60]. Maxwell's demon is a thought experiment James Clerk Maxwell created in 1867, when he mentioned it in a letter, he wrote to Peter Guthrie Tait, before he published it in his book Theory of Heat in 1872 [61]. Maxwell's intention was to use the demon to prove that the second law of

[55] L. Szilard, Z. Physik, 53, 905, 1929.
[56] J. Sestak, "*Heat, Thermal Analysis and Society"*, 2004 Published by Nucleus HK, Divisova 882, CZ-50003 Hradec Kralove.
[57] J. Sestak, "*Heat, Thermal Analysis and Society"*, 2004 Published by Nucleus HK, Divisova 882, CZ-50003 Hradec Kralove.
[58] L. Boltzmann, in "*Archives for History of Exact Sciences"*, 27, IX, 1990; 41: 1-40.
[59] Translated from the original work "*Uber die Entropieverminderung in einem thermodynamischen System bei Eingriffen intelligenter Wesen", Zeitschrift fur Physik*, 1929, 53, 840-856, translated by Anatol Rapoport and Mechihilde Knoller.
[60] J. Sestak, "*Heat, Thermal Analysis and Society"*, 2004 Published by Nucleus HK, Divisova 882, CZ-50003 Hradec Kralove.
[61] Leff Harvey S, Rex Andrew F., editor. "*Maxwell's demon 2: Entropy, classical and quantum information, computing"*: Boca Raton: CRC Press, 2002.

thermodynamics, which is related to entropy, only has statistical certainty. It was recently that Chan and Linni [62] *published the two-way relationship between information and energy as:*

$$\Sigma I \leftrightarrow \Sigma E$$

Based on Szilard's thoughts we saw above, Leon Nicolas Brillouin studied the relationship between entropy and information and proposed the following relationship:

$$S = k_B \ln 2 \ (J/K)$$

This relationship shows that 1 bit of information leads the system to reduction and to a quantity of entropy with the value k_B ln2 (J/K), where k_B = 1.380649 X 10^{-23} (J/K) is Boltzmann's constant.

It is clear, my boy, that the 'demon of science' also calls for a philosophical approach, as we will see later on. More importantly, an in-depth literature review is necessary to understand challenging concepts that these illustrious minds have provided us with. Of course, I should also point out that information cannot be created or destroyed, only transferred or transformed, according to the principle of the preservation of information [63].

The changes in the energetic content of a material or of an event may change the quality or the content of the information it transfers. So, we can say that the total information of a system, a material or an event, could be equal to the total information flowing into it minus the total information flowing out. So, we can understand that these changes are related to the entropy of information. Boltzmann's and Shannon's equations, as we saw above, draw a parallel between entropy and information. This is a unique direction for the development of new applications and products in the market. Of course, it is evident that the 'metastable phases' we have already discussed and are going to discuss more, are information and entropy traps and the balance between those two defines the macroscopic behavior and also the end picture of a system or an event.

To conclude this in-depth reference I made to the relationship between entropy and information, as well as to the 'scientific demons', I will also mention that the great Polish physicist Marian Smoluchowski (1872-1917), who worked in the Polish territories of the Austro-Hungarian Empire and was a pioneer of statistical physics wrote that 'As far as we know today, there is no automatic, permanently effective perpetual motion machine, in spite of the molecular fluctuations, but such a device might, perhaps, function regularly if it were

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[62] CC.Chan, J. Linni, "*Correlation Between Energy and Information"*, *Journal of Asian Electric Vesicles*, 11: 1625-1634, 2013.

[63] C.C. Chan, F.C. Chan, D. Tu, "*Energy and information correlation : towards sustainable energy"*, in : *J. of International Council on Electrical Engineering*, 5:1, 29-33, DOI: 10.1080/22348972.2015.1050773, http:// www.tandfonline.com/loi/tjee20

appropriately [designed] by intelligent beings […]'.

I think that the concept of entropy is now clear enough, as well as its relationship to the functionality of living organisms and, consequently, with life, and all of this without having to resort to hardcore mathematics.

The 'metastable phases', as you must have realized by now young man, are considered to be a very brilliant and amazing type of behavior, not only in living organisms and biosystems, but also contributing to numerous other processes of matter. The 'metastable phases' are kinetically trapped and the modulation process is a function of the kinetics of the biosystem and of the flexibility of the lipidic bilayer in the case where we are exploring the outer surface of a living cell. By simulating the membranes of living cells by means of artificial ones, we can draw a picture of the biophysical behavior of a biosystem. Physical phenomena such as the stability of a biosystem, aggregation phenomena, and the fusion of biological objects, are related to the barriers regarding the quality of biosystems. The biophysical performance of the artificial biomembranes includes physicochemical issues like morphology and shape that are important and predominant concerns for living organisms. However, the biophysics of living cells is important in order to study and to evaluate the behavior of those cells. It is obvious from the above remarks that thermodynamics and biophysics are important elements [64].

We have to look carefully at how we can interfere with biosystems, depending on their biophysical properties; these can influence their structural and morphological properties and changes can produce 'metastable phases' that have an effect on their behavior."

"*Oh dear*!" Grandpa exclaimed, terrified by what he said. "*Don't go yet,"* he said, *"now I'll talk to you about more understandable things. I'd suggest that you take some notes on your smartphone. I understand that what we say and read about is not easily accessible via our conventional and finite brain functions. I imagine that you know, my boy, that by working passionately on a subject and by pursuing your objectives, you basically increase the 'negative entropy', which helps you be strong, healthy and creative. Passion and focus on success, on your goals, are like hermeticism. You need consistency, focus and endless attempts to narrow down the distribution of possibilities and to become more effective in order to achieve positive results. So, what do you think, shall we move on*?"

"Of course, of course", I murmured. In order not to wrong my grandfather, everything I learn I do not learn overnight; it is a process that evolves, it does not

[64] C. Demetzos, "Thermodynamics and biophysics as the building blocks' AAPS PharmSci Tech, 2015, 16(3):491-5

stop. I do not know when it started, maybe before I was born, maybe it was my destiny to meet him. He has been with me forever. I mostly find him in the library, but even outside, Grandpa escapes and follows me.

"Yes, of course", I replied, without being too sure. I had started to perceive the complexity of systems and biosystems. "Also, Grandpa, I understand that thermodynamics, and especially bio-thermodynamics of small systems, completes or constitutes a prerequisite for the understanding of their behavior, according to what we discussed at the beginning of our conversation, regarding the importance of small systems. Their 'decisions' appear as the natural laws that we can observe macroscopically in our objective world. I think that the 'quantum leaps' we talked about, as well as the non-arbitrary behavior of small systems that are comprised of a small number of participating atoms, are influenced not only by their structural characteristics as molecules, but also by their thermodynamic behavior, which functions as the basis for the changes of 'negative entropy', allowing their survival. If we could see the variability of complex systems, based on 'quantum leaps' and on 'metastable phases', as we said before, we would perceive a constant dynamic and chaotic behavior which would perhaps make us sad based on our 'empirical' nature. We would 'see' another world, a world of light and shadows, a 'soup' of atoms and changes, without any images, but only the terrifying truth of our nature. Grandpa, nobody would like to see something like that. Imagine if we could see the movements of the atoms of an object, without perceiving its form! We would live, as I said, in a 'soup' of atoms and colors, without being able to define objects... life would not be the same. What do you think, Grandpa?"

"*I absolutely agree, my boy*."

"But I insist, Grandpa. How does nature choose the changes we have talked about on a macro-scale? How do they manifest in the macrocosm, our objective world, while the tools –the natural laws– are essentially produced in the microcosm? What is going on there? What is the force that leads to these changes, what drives it, how did it first begin? How are the most 'prevalent' 'metastable phases' our cells have selected, despite their thermodynamic and biophysical demands? The 'metastable phases' are responsible for the functionality of our cells and consequently of our tissues and of all the organisms. They contribute to all life's functions and are responsible for health, diseases [65] and, finally, death."

"*My boy, I cannot possibly reply to all of these things. But I can just add a nuance, based on the relevant bibliographical references we have mentioned, by way of an attempt to address the aforementioned questions, that could also be classed as lines of inquiry to be pursued. According to the Hexaemeron* [66]**,** *there*

[65] W. H. Binder, V. Barragan, and F. M. Menger in the Journal of *Angew. Chem. Ind. Ed*, 2003, 42, 5802-5827.
[66] Saint Basil the Great, 'Ομιλίαι εις την Εξαήμερον'' (Lectures in the Exaimeron / Hexaemeron) p. 29, 113A, (in

is no perception of automatic genesis and randomness. In the Hexaemeron by Saint Basil the Great, we read that: 'Nothing happens without a reason; nor automatically; in all things there is some secret wisdom' (ουδέν αναίτιον · ουδέν από ταυτομάτου · πάντα έχει τινά σοφίαν απόρρητον)[67]*.This means that the creation of all things contains a secret wisdom, a supreme wisdom that coexists with Creation, according to theological thought*."

"Yes, Grandpa, I understand, but you did not really give me an answer. Where did that wisdom come from, the one that coexists with 'creation' (*ktisma; κτίσμα*), if I am to use the theological terminology?"

"*According to the reference works we read, with which I share the same opinion, the human mind has limited capacity to fully comprehend the wisdom of animate and inanimate creation. Perhaps this –as I see it and on the basis of our approach regarding the 'metastable phases' of the human brain– might be the obstacle to understanding the inner wisdom of Creation in the world (in the micro-, macro- and the megacosm), i.e., the origin and the logic behind it. It is as if we try to understand Creation itself, to understand the complexity of its structure and functionality and of the communication network that binds it. There are inherent limitations in our own mental approach, as Saint Basil the Great describes (see above), and we can only have limited knowledge of –or rather, an opinion about– the changes in nature, natural laws and their evolution. So, we need philosophical and theological tools. In my opinion, you should study in-depth similar texts, which will enable you to provide interpretations that, in a way, will reassure you when it comes to the big, real inquiries that concern you. But let's move on with some philosophical observations and let's try to understand the philosophical dimension of classical texts and authors. The scriptures of the Church Fathers, along with theological approaches, as we mentioned at the beginning of our conversation, will filter into our conversation where and when needed, without us delving too deep in them... perhaps we will do that in the future, after we try to talk through the line of inquiry we have introduced into our conversation. There's no doubt that theological approaches intersect with philosophy and science and can coexist dialectically in a harmonious way."*

Greek), reference from N. Matsouka's book, "Επιστήμη, Φιλοσοφία και Θεολογία στην Εξαήμερο του Μ. Βασιλείου", [Epistími, Philosophía kai Theoloyía stin Exaímero tou M. Vasilíou / Science, Philosophy and Theology in Saint Basil's the Great Hexaemeron] p. 200, Kyriakidis publications, 2016, vol. 7, "Θεολογία και Οικουμένη" (Theoloyía kai Ikouméni) series, 2016 (in Greek), 2016.

[67] Translator's Note: our translation.

PART III

PHILOSOPHICAL OBSERVATIONS

"I would say," *Grandpa went on, "that one way to tackle such lines of inquiry is by turning to philosophy. We can approach it as a world view, as the way each person perceives the world and, most importantly, how the world changes. So, we could say that every person has their own world view, a perception of the events that take place in their environment and an opinion on what has taken place and what is going to take place. I should also mention here that, according to the book Philosophy and Science by C. Castoriadis* [68]*, philosophy and science arose simultaneously in Ancient Greece, without an absolute dividing line being drawn between them. According to C. Castoriadis, we can perceive a distinction in Aristotle's works between physics and philosophy, while it is only after Kant that there emerged a truly clear distinction between science and philosophy. But let us have a look, my dear boy, at some challenging approaches to help you understand the importance of what we are going to discuss later. There is the concept of 'beginning' (arxi; αρχή), which is, to my mind, a philosophical starting point, a piece of tinder to get a conversation going. And the concept of 'beginning' is only the 'starting point' of everything. This is, my dear boy, an important line of inquiry worth exploring since we start our conversation by examining the degree to which philosophy and science, while separate and individual, also cooperate in resolving both the problems of physics and philosophy. According to Aristotle, there are four causes and principles which determine the existence of the universe and of life. These are: the first cause/principle, out of which came the very first movement; the second principle is the material out of which something is made and formed; the third one is the art of its making while the fourth is the aim or purpose for which something is done."*

"These causes, meaning these principles of creation, are very important, Grandpa. Could we say that this 'principle' constitutes the cause of the very first movement?"

"That's brilliant, my child. Yes, of course, this 'principle' as a philosophical concept is the cause of what we would call a 'beginning'. You see that by using words and by placing them in another context, you can talk about topics without a 'starting point', as we will see later on. For example, the

[68] Cornelius Castoriadis, "Φιλοσοφία και Επιστήμη. Ένας διάλογος με τον Γεώργιο Λ. Ευαγγελόπουλου" (Philosophía kai Epistími. Énas diálogos me ton Yeóryio L. Evangelópoulou / Philosophy and Science; A Conversation with Georgios L. Evangelopoulos), Eurasia publications, Athens 2010 (in Greek).

expression 'In the beginning' (en arxi; εν αρχή) that we read in the book of Genesis, constitutes a point of sublime theological, philosophical and scientific convergence. The concept of creation, taking into consideration the multidimensional meaning of the 'beginning', gains its timeless dimension, since time doesn't actually have a starting point, because then the beginning of time would not be time. To help you understand, my boy, you could not say 'the beginning of the road', because its 'beginning' is not a road yet. The same applies to time; it cannot have a 'beginning', because its 'beginning' is not time.

Saint Basil the Great says in his book the Hexaemeron that: 'Perhaps the phrase 'in the beginning' was said because creation occurred immediately, without time passing by; and the beginning cannot be divided and has no dimensions"[69,70]*. In this way, the orderly is distinguished from the disorderly; the Aristotelian 'principles' are categorized and are applied in the field in which the 'beginning' does not exist. However, this field can only be the creator of beings with energy, which is timeless as far as its principle is concerned, i.e., the timeless 'in the beginning', the 'ab initio'. So, we see that the concept 'ab initio'/'in the beginning' constitutes a complex theological-philosophical approach which gives rise to the need for scientific inquiry into the principle of everything and into the 'ab initio' creation of the natural world. Philosophy and science shift through these approaches and nobody can claim that this dimension of mutual movement along with the advances in theology by the illustrious Fathers of the Church does not contribute to our understanding of the world and to the creation of new knowledge. So, the created reality surrounding us has to do with science. It is related to the concept of time and to the timeless 'ab initio' natural order of this reality, which philosophy and theology both concern themselves with. They are both related to the non-created (aktisti; άκτιστη) reality, constituting key aspects of the constant fertile dialectic search for truth through the medium of knowledge. And since we are on the topic of knowledge, the ancient philosophers understood and accepted the difficulty in attaining knowledge. They also knew the limits within which the human mind could acquire it. But let's stop here, because we will have to study specialized philosophical and theological texts and we can do that at a later time. You should bear in mind, in any case, that the efforts you've been making using this challenging approach have been nothing more than an attempt to get closer to the truth".*

"Do you mean, the truth of what's taking place 'deep down', Grandpa?" I asked.

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69 Translator's Note: our translation from the Ancient Greek.

70 Dimitrios T. Tsamis, "Η πρωτολογία του Μεγάλου Βασιλείου" (I protoloyía tou Megálou Vasilíou / Saint Basil the Great's Protology), Thessaloniki 1970, pp. 33-35, (in Greek).

"*I could say yes. I mean that this approach which highlights the role of philosophy is not an irrelevant approach and it is at this point that the various philosophical currents and the various philosophical schools enter; as a result, an enormous amount of knowledge to process and discuss has been accumulated over the passage of time. I have in mind two major philosophical currents which are interesting for us and for the human intellect: 'materialism' and 'idealism'. I should mention here that the relationship between philosophical schools of thought and social orders influenced their expression and either empowered them or weakened them. As a result, social needs presented a philosophical view of the world as prevalent or created one or more views as a counterbalance, as long as that was what the social and economic conditions of each age required. The fundamental difference between idealism and materialism is as follows: idealism argues that nature is the product of intellect and it considers that intellect, i.e., consciousness, ideas, is the foundation of all material things on earth, while the foundation of the materialist philosophy is the acceptance that matter exists in the world independently of human consciousness. Under the light of the advances in physical sciences and the attempt to unify various theories on the genesis of the universe, the way it was created constitutes one 'unified' line of inquiry, the acceptance of which does not accommodate dualistic approaches and, in a sense, 'useless' references related to the dualism between matter and intellect. W. Heisenberg* [71] *raises the question of whether intellect is connected to the 'material' brain in human beings, because if it is then we should accept it and develop the dualism of intellect and matter, or we should explain why the structural elements of the material world that are the same everywhere else, such as carbon, hydrogen, oxygen, nitrogen and phosphorus, are different in the human brain. I've tried to convey to you the passage as I understand it, to familiarise you with it.*

Shall I elaborate a bit more on this topic, on the philosophical approach to the objective truth?"

"Of course, Grandpa, that would be interesting. As far as I know, in academia the most distinguished academic title, i.e., the Ph.D. stands for Doctor of Philosophy. Furthermore, as far as I know, a philosophical approach is also necessary when it comes to problems and inquiries which could be considered materialistic, based on calculations and recorded and proven natural laws. It is in this way that one can be accepted in academia as a professor and specialist in a field of knowledge."

[71] N. Matsouka "Επιστήμη, Φιλοσοφία και Θεολογία στην Εξαήμερο του Μ. Βασιλείου", [Epistími, Philosophía kai Theoloyía stin Exaímero tou M. Vasilíou / Science, Philosophy and Theology in Saint Basil's the Great, Hexaemeron] p. 200, Kyriakidis publications, 2016, vol. 7, "Θεολογία και Οικουμένη" (Theoloyía kai Ikouméni) series, 2016 (in Greek).

"*Of course, you are absolutely right. So, look. What could be the driving force or forces of evolution from a philosophical point of view in order for us to understand the scale of the inquiry and then delve into the natural causes and phenomena which could lead to answers? Many books mention dialectics* [72]*, a word which derives from the Ancient Greek pronoun 'diá'(διά), which we could say expresses the mutuality or the exchange of words or logical schemes in a conversation, and from the verb 'légein' (λέγειν), which means 'to say'. The noun 'dialectics' (διαλεκτική), the art of conversation, derives from the adjective 'dialectic'. Historically, according to Diogenes Laertius, Aristotle ascribed dialectics to Zeno of Elea, who was Parmenides' disciple. You can learn a lot about dialectics and its first principles if you study the pre-Socratic philosophers. What is important, in my point of view, is 'dialectic opposition'* [73]*. When one reads the word 'opposition', one understands that the assumption behind an event or object is the opposite of that behind another assumption. But this is related to the logic of opposition, i.e., 'logical opposition'. For example, we can't say that it is day and night simultaneously, or that the sun shines and doesn't shine at the same time. However, in 'dialectic opposition' things are different. It refers to the 'opposition' inherent in the objects themselves, i.e., in my opinion, we are referring to the constant evolutionary process at work in the microcosm – 'deep down', as we said. This process is dialectic, i.e., it will lead through the 'conflicts' of 'opposites' to distributions which will statistically define the result that we see in the macrocosm. Through dialectics, these antitheses create qualitatively better forms of organization of matter which depict in the macrocosm the 'fingerprint' of the 'quantum leaps' taking place in the microcosm. Furthermore, the 'dialectics of opposites' functions in the macrocosm as well, allowing us to interpret the results. For example, according to astronomers there are numerous suns. Science has also unveiled various states which act 'in opposition' to each other, so to speak. Gravity, which draws in objects and bodies, is countered by the pressure of radiation which pushes those self-same bodies outwards. The dialectics of opposition creates balance in the system. Therefore, the most stable situation –which is functional and is the one we can see– is chosen.*"

[72] Paul Foulquié, "Η διαλεκτική", (I dialektiki / La dialectique), Greek translation: M. Foteinou, I.N. Zacharopoulos publications, 1964.

[73] Rombert Staigervalnt – "Μαρξιστική Φιλοσοφία. Βασικές έννοιες και αρχές" [Marxist Philosophy, Basic Concepts and Principles], Synchroni Epochi publications in Greek, translated from the original in German "Marxistische Philosophie Einfuhrung fur die Jugend', Ed. Verlag Marxistische Blatter, Franfurt, 1979.

Key Point

(…) The constant evolutionary process in the microcosm is dialectic. It leads, through the 'conflicts' of 'opposites', to distributions which will statistically define the result that we see in the macrocosm (…)

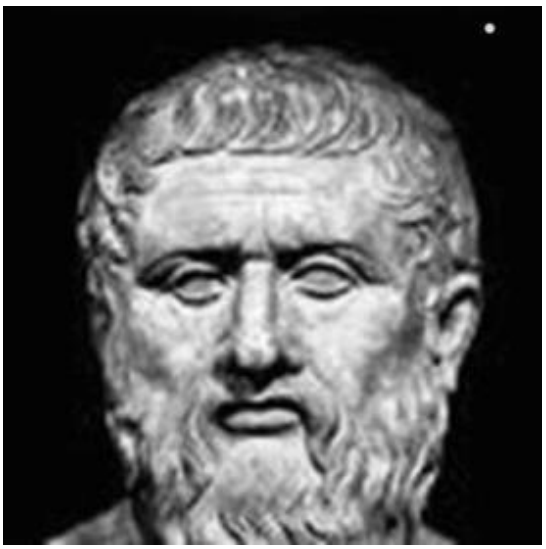
"*In Faust, Goethe says: 'Two souls, alas! reside within my breast; And each withdraws from and repels its brother* [74]*'. These oppositions are present here in all of their poetic form. These antitheses describe the whole world and all objects. In order to be able to discern these antitheses, we really ought to look at evolution, when we examine objects or events–including social ones too of course– as they evolve. Then we are talking about 'dialectic materialism'. Movement, as part of the evolutionary process through the conflict of opposing ends, is only kindled as evolution of the initial movement which, according to Thomas Aquinas (13th cent. AD), is nothing other than the existence of God.*

So, we see that the dialectics of opposition concerns us as a philosophical tool which can lead us to experimental paths to understanding of the evolutionary process which takes place in the world we can't see and whose function constitutes a philosophical inquiry.

But I see that you are interested in learning more... Here, look at the garden from the window. In antiquity there was the 'academy' (akadimia; ακαδημία), the 'lyceum' (lykeion; λύκειο) and finally the 'garden' (kipos; κήπος). There was Plato, Aristotle, Epicurus and even before them, the pre-Socratic philosophers, Anaximander, Thales, Democritus, Leucippus, etc. No, we are not going to talk about philosophy, but we need to think in a philosophical way in order to pose the right questions. People can have an opinion but not necessarily knowledge, because, according to Xenophanes' Cosmogony (570 BC – 470 BC), what people say is mere common beliefs or doxa, i.e., something that is considered probable and resembles the truth. According to Xenophanes, no man will ever acquire a clear knowledge of the Gods. Man cannot obtain this knowledge, only 'doxa' (δόξα, δοξασία). In excerpt 16 (1-2), Xenophanes says that 'the Gods didn't reveal everything from the beginning, but humans, through inquiry, may discover it).[75]

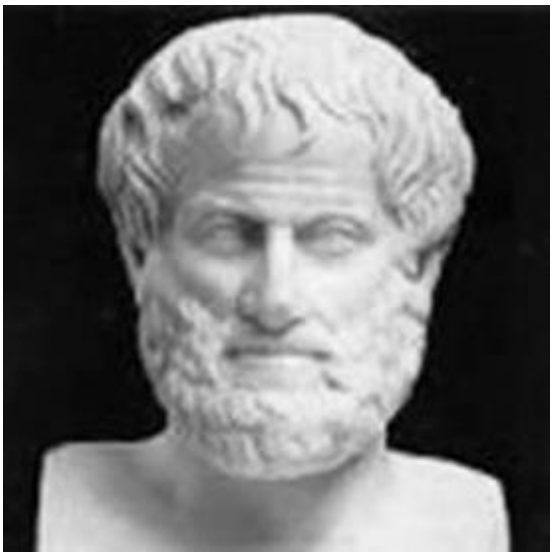
[74] Goethe JW, "Faust; A Tragedy". Translation by Bayard Taylor, published by London Ward, 1890.

[75] Translator's note: our translation from Ancient Greek.



Picture 14: Plato

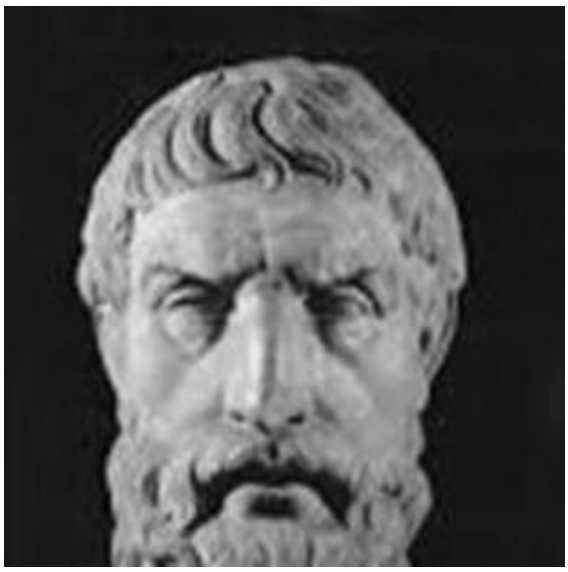
Plato holds that our one and only and finite world is created from and consisting of body and soul. The soul consists of the mixture of intermediate existence, sameness and difference[76] and its body consists of the four elements, introduced by Empedocles. Each element is associated with a component of geometric texture: earth is associated with the cube, fire with the tetrahedron, water with icosahedron, and air with the octahedron (these are the famous Platonic solids).



Picture 15: Aristotle

Aristotle believes that our one and only and finite world is uncreated and is divided into two regions: the sublunar and the superlunar. The sublunar region consists of the four known elements, but without any correlation to the four Platonic solids. The celestial bodies consist of a fifth element, the ether. He is the founder of Logic and the originator of the theory of the Unmoved Mover: He proposed that the heavens were literally composed of 55 concentric, crystalline spheres to which the celestial objects were attached and which rotated at different velocities (but the angular velocity was constant for a given sphere), with the Earth at the center. The Sun, Moon, and visible planets were attached to the spheres. There were additional "buffering" spheres that lay between the spheres. Finally, in the Aristotelian conception there was an outermost sphere that was the domain of the 'Prime Mover'. The Prime Mover caused the outermost sphere to rotate at constant angular velocity, and this motion was imparted from sphere to sphere, thus causing the whole thing to rotate.[77] His astronomical model is not mathematical, but purely mechanical, in his attempt to explain the interactions of the orbits of the planets and the eclipsing stars.

[76] Plato, "Timaeus", translated by Benjamin Jowett , http://classics.mit.edu/Plato/timaeus.html.
[77] Aristotle, "Metaphysics", translated by W.D. Ross, Book XII, http://classics.mit.edu/Aristotle/metaphysics.html



Picture 16*: *Epicurus

Epicurus holds that the infinite universe is multiverse and uncreated and that it consists only of atoms and vacuum. The atoms mostly fall vertically, but some deviate and collide with others, forming the composite bodies. The criteria of truth are four: senses, emotions and especially pain and pleasure, τηε concepts and the imaginative affections of the intellect, which are independent of the senses. Our every perception and every opinion is subject to scrutiny for confirmation or disconfirmation. Ethics is based on physics. The purpose of our life is the 'abstinence' of the body and the 'disorder' of the soul.

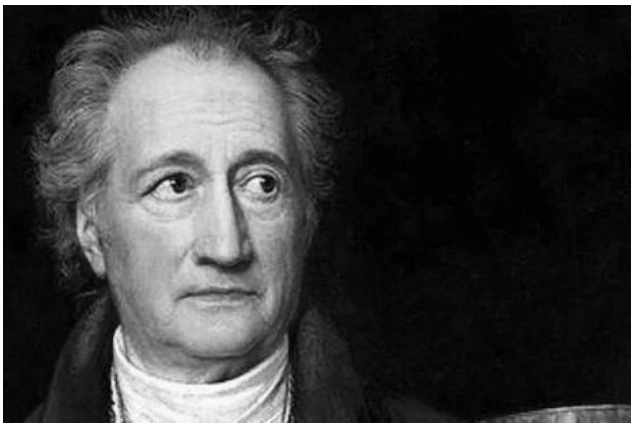
If they were alive today, in all likelihood Plato would be a great cosmologist, Aristotle an excellent neurobiologist with multiple scientific interests, and Epicurus a modern philosopher who would ground ethics on natural science and would say:

"Don't fear God,
Don't worry about death;
What is good is easy to get, and
What is terrible is easy to endure."[78]

He also claimed that: "The science of nature does not create people who are arrogant and empty-headed, nor does it create people who show off knowledge sought after by many. On the contrary, it creates people who are serious and self-sufficient, proud of the goods of their own personality and not of their possessions."[79]

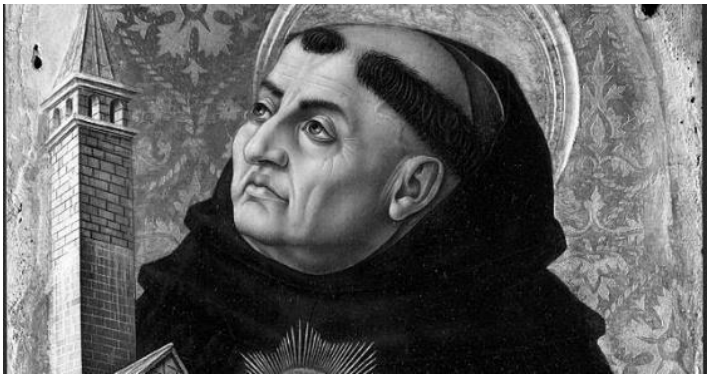
[78] Herculaneum Papyrus 1005

[79] Epicurus, Vatican Sayings, XLV.



Picture 17: Johann Wolfgang Goethe

Johann Wolfgang Goethe (Frankfurt, August 28, 1749 – Weimer, March 22, 1832), was a German writer, novelist, playwright, art theorist and scientist of international eminence. As a philhellene he dedicated many of his works to Greek Antiquity. One of Goethe's most important works is the Italian Journey, which he wrote while staying in Southern Italy. Until 1805, he maintained close contact and friendship with Schiller and a close friendship bound the two men together. In 1806, he married Christiane Vulpius, with whom he already had had a son in 1789. Faust, his lifelong creation, saw its second volume concluded one year before his death, in 1832 in Weimer. His last words were: 'Light, more light!' (in German, 'Mehr Licht!')
(https://www.google.com/search?client=firefox-b-q=Johann+Wolfgang+Goethe)

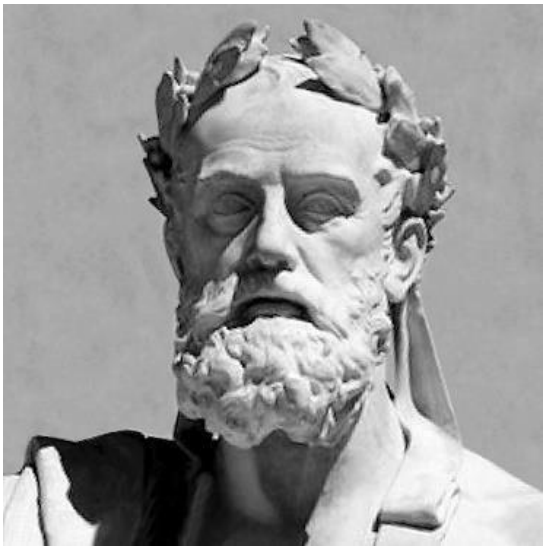


Picture 18: Saint Thomas Aquinas

Saint Thomas Aquinas (Italian: *Tommaso d'Aquino*, lat: Thomas Aquinas; 1225 – 7 March 1274), also known as St. Thomas of Aquin, Thomas of Aquino, Doctor Angelicus and Doctor Universalis, was an Italian Dominican friar of the Roman Catholic Church and an influential philosopher, theologian, and jurist in the tradition of scholasticism. His influence in Western thought is significant, as he was one of the thinkers who helped ensure Aristotle's thought was embraced by Christian Europe, synthesizing it with the Aristotelian philosophy in what is called 'Christian Aristotelianism'. In the Catholic Church, he is regarded as the model teacher for those studying for the priesthood
(https://www.google.com/search?client=firefox-b-d&q=Saint+Thomas+Aquinas+)

Key Point

(…) The dialectics of oppositions concerns us as a philosophical tool which can lead us to experimental approaches for understanding of the evolutionary process (…)



Picture 19: Xenophanes of Colophon

Xenophanes of Colophon (570 – 475 BC) was a philosopher and poet. He was born in Colophon, Asia Minor, and lived in various parts of the Ancient Greek world. He is remembered in history for his criticism of religious anthropomorphism, the boost his thinking gave to monotheism and certain innovative ideas in various fields of knowledge. Many authors were perhaps influenced by two minor allusions to Xenophanes in Plato (Sophist 242c-d) and Aristotle (Metaphysics 986b18-27), which defined him as the founder of the eleatic philosophy (https://www.google.com/search?client=firefox-b-d&q=Xenophanes+of+Colophon+).

"*Brace yourself, my boy, to embrace and delve into challenging scientific paths in order to pose the right questions in the future, and also to understand, or better to comprehend, the physical and perhaps the natural advancements – that is to say, to have an opinion*."

I thought to myself whether this could be the hologram of Grandpa's thoughts that I tried to capture on my smartphone using a not-so-effective *app*. Could it be that my personal effort, my own in-depth study and my conversation with Grandpa constitute elements of a form of communication that technological development cannot reproduce, cannot read? How could a technologically 'smart' device ever replace the complexity and the inherent variability that life has provided to our planet, through the struggles for the survival of the fittest, i.e., the most adaptable in the changing environment around us? Probably we are too little, too powerless to reproduce the emotions we are capable of experiencing, or even the prior conversation we had, using mere holograms that capture a single

momentary process without any memories from the past. If someone was looking at us from 'deep down', like Grandpa says, i.e., from the micro- and the nanoworld, the world of the subatomic particles, he would most probably be laughing at our inability to create advanced technology.

Despite all that, human existence has taken giant steps, sometimes even leaps forward, managing to approach natural phenomena and trying to understand the dynamic and primordial variables which even to this day function silently and preserve life in a thermodynamic instability, testing our faith and endurance.

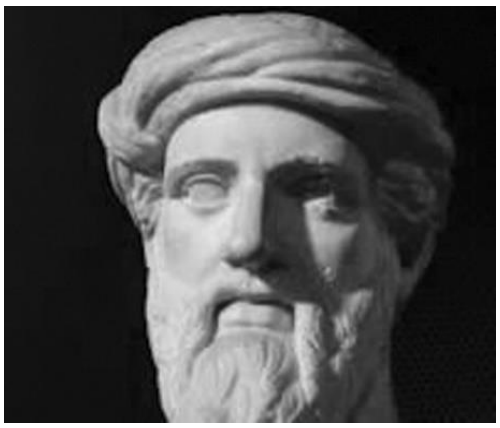
"So, let's carry on with the journey into the world 'deep down', as you yourself would say, Grandpa. I hope I will learn more later, through biophysics and bio-thermodynamics and the other objectively challenging scientific concepts. But now I understand that I also have the philosophical approach available to me as a tool for getting potential answers or formulating future lines of inquiry. That's great... it means that each time I'm having a hard time, I will turn to philosophy... What do you think, Grandpa?"

"*Of course, but you must weave your logic according to objective truths and objective lines of inquiry. I'm happy, in any event, because you are on the right track. You're bound to benefit from that...*"

So, I thought to myself that what I've been trying to understand are the 'textures' of the challenging web of knowledge and of the labyrinth of theoretical approaches, which require philosophy and perhaps imagination.

Here, I brought more books from your library, to fill the gaps of what you may not remember. I also brought some philosophical texts I found in the library. This is the first volume on pre-Socratic philosophers [80]. Perhaps it will help us find the 'primordial' truth through the philosophical thought of pre-Socratic philosophers. I should also mention here that I found some notes in the library from P. Mitropetros' classes (in fact time is no longer a concept familiar to me, and I would say that I'm not even interested in it anymore, perhaps influenced by Grandpa). His notes refer to Pythagoras and to other pre-Socratic philosophers.

[80] P. Mitropetros and D. Dialektou '*Approaches to the pre-Socratic*', Aigiis Press (Αιγηίς), 2015.



Picture 20: Pythagoras of Samos Pythagoras of Samos (Ancient Greek: Πυθαγόρας ὁ Σάμιος, translit. Pythagóras ho Sámios, lit. 'Pythagoras the Samian', or simply Πυθαγόρας; Πυθαγόρης in Ionian Greek; c. 570 – c. 495 BC) was an Ionian Greek philosopher and the eponymous founder of the Pythagorean movement. He is often revered as a great mathematician and scientist and is best known for the Pythagorean theorem (https://en.wikipedia.org/wiki/Pythagoras).

Pythagoras was born in Samos circa 570 BC – this is how texts date his presence on Earth. To me, this is not of much interest; it is only a point we can use to define the sequence of events. In 530 BC, he moved to Croton, Magna Grecia, where he stayed for the rest of his life. There, he founded a fraternity, a philosophical and theological school, where the students who attended his classes acquired knowledge 'through a process of revelation' and kept his teachings secret. It was a powerful political group, and its members were aristocratic and ultra-conservative. Pythagoras did not leave any teachings in written form. We know, though, that they focused on the fundamental difference between good and evil, the different between body and soul and between finite (i.e., order) and infinite (i.e., disorder, chaos and uncertainty). Here we read that Pythagoras talked about and was interested in concepts which are considered nowadays of extreme importance, because they concern our understanding of natural phenomena and our world. Since you asked me at the beginning of our conversation what God is, I should mention, Grandpa, that I found in the very same notes in your library information on Xenophanes the Eleatic, who is basically considered the first scientist-theologist, and whose ideas were the starting point for many scientists who sought to answer questions about God from the antiquity right up to the present day. He was a monotheist. Xenophanes' God is only one, who is probably at the centre of the earth and organises everything from there. "Grandpa, is it possible that you suggest the world 'deep down', where you said that natural laws are created, because of this? However, Xenophanes did not overlook the existence of other Gods, although he considered one God to be supreme. What did he mean? The entirety of natural forces, the networks of self-assemblies and of the huge number of 'metastable phases' that contribute to the development of the natural laws? Xenophanes said, "Only one God is the greatest between Gods and men"

(*Εις θεός εν τε θεοίσι και ανθρώποισι μέγιστος*)." [81]

"At this point, it is necessary", Grandpa says, *"to note that the aforementioned Greek pre-Socratic philosophers introduced new concepts such as order and non-order as forms of organization on earth, an idea introduced by Pythagoras, or such as the God who is at the centre of the earth, an idea introduced by Xenophanes. According to Xenophanes, more Gods were involved in the overall evolution of life in its various manifestations, but the main action unfolds at the centre of the earth, guided by the one and only major God."*

This pre-Socratic philosopher –says Grandpa– understood that at the center of the world, i.e., in the microcosm or even in the macrocosm, events occur which we as a human race cannot comprehend. And, also, that all these events have been created with absolute wisdom, which we as a human species will be able to comprehend only through lifelong learning and through the effort to overcome our inherent weaknesses.

"Do you think, Grandpa, that I'll be able to come anywhere close to that astounding wisdom and those human accomplishments by studying science and technology, and by exploring the philosophical thinking of the great men of Greek antiquity? Or will I be too overwhelmed to go on?"

"*Listen, young man. Nothing is easy; everything has some level of difficulty. This depends on the choices that each one of us makes. You will choose the path you want to follow in your quest to get answers to primordial questions using philosophical and scientific tools. And you will bear the cross. Small or big, it will be yours and you will bear it on your shoulders. But rest assured that you will come to love it, you will become better and you will pass on feelings and experiences to your fellow human beings who will be forever grateful to you. You will learn to think, to distinguish the significant from the insignificant, and above all to distinguish and appreciate those who try to ask questions because "the art of asking the right questions in mathematics is more important than the art of solving them", as Cantor said* [82]."

"OK, Grandpa. I understand what you mean. I have come to realize the significance of the questions and I wonder how nature generates inquiries? Are they inquiries just to us? Are they simply creations for nature? Do they constitute its eternal evolution in the timeless cosmic space?"

[81] Translator's Note: our translation from the Ancient Greek.

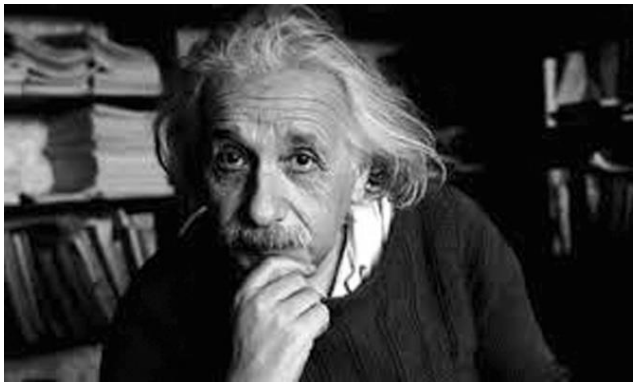
[82] https://en.wikiquote.org/wiki/Georg_Cantor

PART IV

THE SCIENTIFIC READING OF 'SILENT' NATURE. LYOTROPISM, ONE STEP AHEAD

Grandpa is lying on the couch enjoying the satisfaction that his long-term effort in creating his 'perennial' and constantly evolving library has given him. However, I believe that he also feels satisfied with my progress. The window is large, overlooking a garden with trees and flowers. Grandpa has always enjoyed the garden, the 'participants' in the natural heaven as he used to say, in heaven on earth. He turned his face and the 'metastable phases' on his forehead became even more pronounced, as if his every move wanted to indicate the continuation of a course that has begun without knowing where it will end. It was as if his inner world, his worries, his memories and his anxieties were projected on his face. How many events and feelings can fit in one movement, in one facial twitch. Lying on the couch of time, he is shaping it, in a space that embraces him sometimes tenderly and sometimes violently.

Grandpa went on to say, *"Issues and questions regarding who we are, where we are heading to and why we exist are considered as emerging inquiries among the majority of those who work in academia or who participate in the evolution of thought forging new and revolutionary paths towards a better understanding of where we come from. Any approach such a complex issue is bound to be superficial, but science demands that there is no reason for research if we know what we are looking for. As Einstein said, '[…] we are often blind trying to understand our nature.'"*



Picture 21: Albert Einstein

Albert Einstein (14 March 1879 – 18 April 1955) was a German-born theoretical physicist who developed the theory of relativity, one of the two pillars of modern physics (alongside quantum mechanics). His work is also known for its influence on the philosophy of science. He is best known to the general public for his mass – energy equivalence formula E = mc2, which has been dubbed "the world's most famous equation". He received the 1921 Nobel Prize in Physics "for his services to theoretical physics, and especially for his discovery of the law of the

photoelectric effect", a pivotal step in the development of quantum theory (https://en.wikipedia.org/wiki/Albert_Einstein) .

Yet, we should go on. It is well known that nature does not give us detailed information about the building blocks from which it has been composed. Heraclitus of Ephesus was a pre-Socratic philosopher and state that "nature likes to hide".

Picture 22: Heraclitus of Ephesus

Heraclitus of Ephesus (/ˌhɛrəˈklaɪtəs/;[1] Greek: Ἡράκλειτος ὁ Ἐφέσιος, translit. *Hērákleitos ho Ephésios*, pronounced [hɛː.rá.kleː.tos ho e.pʰé.si.os]; c. 535 – c. 475 BC, fl. 500 BC) was an Ancient Greek, pre-Socratic, Ionian philosopher and a native of the city of Ephesus, which was then part of the Persian Empire. Heraclitus believed the world is in accordance with *Logos* (literally, "word", "reason", or "account") and is ultimately made of fire. He also believed in a unity of opposites and harmony in the world. He was most famous for his insistence on ever-present change—known in philosophy as "flux" or "becoming"—as the characteristic feature of the world; an idea he expressed in the saying, "No man ever steps in the same river twice", or with *panta rhei* ("everything flows"). This aspect of his philosophy is contrasted with that of Parmenides, who believed in "being" and in the static nature of the universe. Both Heraclitus and Parmenides had an influence on Plato, who went on to influence all of Western philosophy (https://en.wikipedia.org/wiki/Heraclitus).

More often than not, in scientific research nature gives 'hints' of the information in a complicate bionetwork in which quantum effects and topological constraints are predominant. However, more efforts are needed to address the technological difficulties so that we better understand the so-called 'cryptic and silenced life-code', by using quantum physics, statistical mechanisms or Monte Carlo simulations in order to overcome the challenges and to easily disclose nature's code.

Heisenberg, a pioneer of quantum physics, said that *"*the world thus appears as a complicated tissue of events in which connections of different kinds alternate or overlap or combine and thereby determine the texture of the whole" [83].

However, it is a challenge to translate and to explain the scientific principles and the natural laws that affect the principles of the organization of life. It is more than logical to simplify fundamental questions about life's processes into more conventional turns of phrase, such as, 'How did life begin?' or 'How does life work?' instead of asking 'Why does life exist?'. Looking at these inquiries from a theological point of view, it's important to mention that in the first chapter of *Genesis*, where the cosmogony is depicted as a non-idolatrous manner, we see that the story of the cosmogony mainly refers to 'who' created the world, rather than to 'how' the world was created [84].

I don't know what is more important. What seems to be the most effective way is to build a comprehensive framework for understanding the behavior and functionality of living organisms. Such a framework could be divided into two steps: the first one is to study the structure and the bionetworks, while the second is to understand their communicated paths based on their 'metastable phases' and also based on their conformational and structural polymorphism, which all then need to be translated into functionality. Understanding this structural process of nature, from biomolecules to bio-organelles and biosystems, which are the regulators and key elements to evolution, will help bring us closer to the inquiry of 'how' creations were created in the world.

The Polish scientist J. Sestak, who is an expert in thermodynamics and calorimetric studies, wrote in his monograph that: "By the end of the nineteenth century, there were available two different mathematical tools to model natural phenomena: exact, deterministic equations of motion and the equations used in thermal physics based on statistical analysis of average quantities. Whenever any non-linearity appeared, it was put in linear regimes" [85].

We have to bear in mind that the already existing scientific tools follow Newtonian and Euclidean orderliness which is already familiar to us, in an attempt to gain understanding of the physical laws and the geometry of nature, respectively. But this is not the only way of doing this. That is because non-linearity and the non-Euclidian geometry of the processes and the shapes of natural objects already exist in real environmental conditions, but in the

[83] https://www.fritjofcapra.net/werner-heisenberg-explorer-of-the-limits-of-human-imagination/

[84] N. Matsouka, "Επιστήμη, Φιλοσοφία και Θεολογία στην Εξαήμερο του Μ. Βασιλείου", [Epistími, Philosophía kai Theoloyía stin Exaímero tou M. Vasilíou / Science, Philosophy and Theology in Saint Basil's the Great, Hexaemeron] p. 200, Kyriakidis publications, 2016, vol. 7, "Θεολογία και Οικουμένη" (Theoloyía kai Ikouméni) series, 2016 (in Greek).

[85] J. Sestak, "*Heat, Thermal Analysis and Society"*, 2004 published by Nucleus HK, Divisova 882, CZ-50003 Hradec Kralove.

environment not visible to us. The '*Big Bang'* theory serves as a paradigm describing the expansion and cooling of the universe, leading to the creation of galaxies and other objects that are found in the surrounding universe and is a very attractive way of narrating how the universe was born.

There is no sense in trying to answer the inquiry "What existed before the Big Bang?" All we can do to get more information is to search deeper in nature and to seek to find the meaning of natural phenomena, trying to read the 'cryptic code' in the evolutionary processes. This approach is offering us what Ulysses gained from his journey to Ithaca: not the destination itself, but the knowledge, the experience, the passion to stay alive, the creativity and the feelings that are disclosed from the dysfunctional domains that exist within the human brain. Finally, it is a challenge to understand what matters, what the priorities in life are.

After all, it seems that understanding natural and biological processes is a great challenge, it is life itself. We have to participate in this evolutionary process, keeping in mind that this is not an easy path to follow. One needs to fight against positive entropy; but that is also the driving force for gaining experience and becoming better human beings.

And because science has the responsibility to create the technological platforms and tools for revealing the laws of nature and the biological pathways of communication between biosystems, we must study the basic state of matter especially in biological systems, that is, the liquid crystal state of matter.

The term 'lyotropism' –which was mentioned earlier– denotes the different conformational polymorphisms and ordering organization of self-assemblies depending on their physicochemical characteristics and on the liquid crystalline state of cell membranes. Another element to be taken into account is the density of the cell membranes, as well as variables such as diversity, variability and quantum effects, that affect the geometry of the membranes and of the biosystem, leading to different curvatures and rates of change in their morphology.

The concept and the phenomenon of lyotropism is of great importance for the stability of inanimate systems and the survival of animate beings. The complexity of nature results not only in the constant 'transformation' of biomaterials in new chemical structures, but also in the change of their structural characteristics, i.e., of the structural polymorphism of the self-assembled structures, which aims at thermodynamic and biophysical sufficiency for their own stability or adaptation to an ever-changing environment. Lyotropism concerns the structural polymorphism of the liquid crystal state of the self-assembled structures and one might even say that it constitutes a higher level 'decision-making' for the survival and adaptation of highly functional systems and biological networks. The possibility of biomaterials being organized in a

different way or, to put it better, architecture of those biomaterials, i.e., the structure, as well as the orientation and arrangement of the biological objects and bionetworks in the time-space continuum, creates the sculpture of their morphology, all of which can be conveyed by the term ‘lyotropism’.

Lyotropism can also be correlated to the concept of the positive entropy of a biosystem, which is organized in such a way that it gradually leads to its own extinction and to the emergence of new qualitatively better structures, more adapted to any new environment which come to prevail. This means that we can label the lyotropism of liquid crystals in biosystems as a promoter or a retarder in their evolution and adaptation or, finally, as a modulator of their evolutionary process. Of course, it is evident that lyotropism does not depend solely on changes in the physical and chemical variables of a system, but also on the concentration of the biomaterials which participate in the organization of the biostructures and the bionetworks. Through the process of complexity of biostructures and bionetworks, nature functions in a hierarchical fashion, prioritizing biostructures with an architecture and sculpture that allows them to survive and adapt. Changes in the concentration of the biomaterials out of which biostructures are comprised result in changes in the hierarchy in a harmonious bio-society which observes and respects natural laws.

In the case of cosmology, ‘membrane–time’ is curved and the variability of the curvature corresponds to thermotropic behavior, to the unknown forces and consequently to the functionality, survival and adaptation of biomembranes in the midst of a continuously changing environment. Proof of this theory is not perceptible, unless we look deeper into the quantum-cosmos, into applied quantum mechanics and by using Monte Carlo simulations. The thermodynamics of the biosystem, i.e., bio-thermodynamics in a changing world, play a key role and should be taken into consideration. We could say that the concept of polymorphism and lyotropism participate in the aforementioned process, considering the hierarchy in how architectural structures and their sculptures are organized; these are related to their morphology and as a result, to their functionality.

It is important to point out that the natural laws that influence the organization and the functionality of biosystems are closely related to the statistical behavior of a huge number of atoms which are self-assembled into self-organized aggregates. The precision of the laws of statistics becomes more efficient the higher the number of atoms producing self-organized aggregates.

According to E. Schrödinger in his amazing book *What’s life. With Mind and Matter and Autobiographical Sketches*, all functional natural laws that have an effect on the organization of life belong to statistical self-organized aggregates,

which are composed of a huge number of atoms (individuals). This direction overcomes the thermal behavior of atoms and consequently reveals or creates effective natural laws. Therefore: "The statistical thermodynamics is a scientific field which is directly related with the work of the pioneers of science Ludwig Boltzmann and Willard Gibbs. It asserts that an external stimulus such as magnetic field or the diffusion process could overcome the thermal motion of atoms depending on the rate and on the quantity of the applied external stimuli." [86] To elucidate this further, the large number of atoms offers a 'statistical advantage' to the behavior of the self-assembled aggregates and it influences their functionality, leading them in a direction which achieves what is known as 'saturation'. This result is achieved due to the large number of atoms that participate in this process.

"So, what do you think, my young scientist? I believe we managed to achieve what we set out to do. Do you know the etymology of the word 'seminar'? The word 'seminar' comes from the Latin words 'semen' which means seed. This seed contains all the information that an organism needs to grow. A plant's seed contains all the necessary information that is related to its development process. And this is amazing and beautiful. It is extremely difficult to reproduce such processes in scientific laboratories. As you remember, my boy, we talked about a small population of atoms that exist in a limited space and are capable of producing exceptional functions of high quality, like the growth process that takes place in a plant or an organism."

"Grandpa, I agree and I'm optimistic about the process of our conversation. I'm delighted that I am having this chat with you. It seems that it's better by far to have a face-to-face conversation, instead of using technological applications to hack your thoughts..."

The biological organelles and their membranes are composed of different biomaterials in nature that are all involved in cell functions. The segregation process, due to the multicomponents and multicompartmental environment, in the living cell promotes phase transitions and produces metastable phases, known as 'rafts. These 'rafts', based on physicochemical, biophysical and thermodynamical laws, might be responsible for evolution and for the survival of a biosystem. Considering that the adaptation of the biosystem to environmental conditions is a dynamic process which depends on the physicochemical properties of its components, the self-assembly process which influences the structural morphology, and conformational behavior, we can conclude that there is an unpredictable and uncontrollable driving force which determines the evolution of biosystems. For example, 'rafts' have been found into biological membranes rich

86 E. Schrödinger, *What's life. With Mind and Matter and Autobiographical Sketches*, Cambridge University Press. First published in 1944.

in cholesterol and sphingolipids, and they have been involved in signaling transduction process as well as in membrane trafficking pathways [87].

LIQUID CRYSTALS IN BIOLOGICAL SYSTEMS

"So we referred to the liquid crystal state of matter. It is of course known that there are other known states of matter, such as solids, liquids and gases, but even others, such as plasma. I would prefer not to discuss the other states. I think the state of matter, which is between liquid and solid, is interesting. It is the state of matter where the phenomena of lyotropism, phase transitions, structural polymorphism and in general the changes that take place within the liquid crystal state itself, are the driving forces for the functional expression of biostructures and living organisms."

"Grandpa, I have learnt at school the three known states of matter to which you referred. Yes, I also learned about the crystal state at the University, but its applications and role in the life sciences did not impress me very well.

"Before I reply, let's see what the relevant literature says. Here, take Cornelius Castoriadis' book, Philosophy and Science; A Conversation with Georgios L. Evangelopoulos [88]. He says that the inquiry into why the states of matter you just mentioned exist is yet to be answered. Castoriadis says that 'in the framework of quantum statistical mechanics, even the very phrasing of the line of inquiry, let alone its solution, is extremely challenging. Should we attempt to simplify the problem and phrase it in the context of classical statistical mechanics, we end up with an integral, the simplest sub-case of which constitutes the problem of the 'structure of the densest arrangement of the spheres.' The first one to put this forward was Kepler [89] and according to mathematicians such as Dimitris Christodoulou, a mathematical proof for it has yet to be found [90].

But let's get back to answering your question. Yes, your answer about the three usual states of matter was correct, but there are more than the ones you mentioned. They are distinguished by pressure and temperature. During the transition of these two variables, other forms of matter emerge. Some of the low-energy states of matter are the Bose-Einstein condensate, superfluids, and super solids, which can be divided in amorphous and crystalline solids, – as well as the

[87] R.G.W.Anderson, K. Jacobson. Science, 2002, 296, 1821-1825; W. H. Binder, V. Barragan, and F. M. Menger in the Journal of *Angew. Chem. Ind. Ed*, 2003, 42, 5802-5827.
[88] Cornelius Castoriadis, "Φιλοσοφία και Επιστήμη. Ένας διάλογος με τον Γεώργιο Λ. Ευαγγελόπουλου" (Philosophía kai Epistími. Énas diálogos me ton Yeóryio L. Evangelópoulou / Philosophy and Science; A Conversation with Georgios L. Evangelopoulos), Eurasia publications, Athens 2010 (in Greek).
[89] George G. Szpiro, "*Kepler's Conjecture"*, John Wiley and Sons, Inc., New Jersey, 2003.
[90] NdT: our translation.

liquid crystal state. As far as the categories of high-energy states of matter are concerned, we can identify quark-gluon plasma, weakly symmetric matter and strongly symmetric matter. I suggest that we focus our conversation on the liquid crystal state of matter due to its ability to produce an unlimited number of polymorphisms, i.e., metastable phases that reflect in functionality. Furthermore, it is very close to the biological state of matter."

"Yes, Grandpa, I agree. It's obvious that it would be interesting to look deeper into the state of matter related to biological phenomena. Are you confident that we can talk about the state of matter, especially about transformation related to life? I guess that's what you intend to do."

Grandpa started to talk without making any comment.

"It is going to be quite difficult to approach a topic like this, but the reward, if we manage to tackle it, will be great. It is difficult to talk about the state of matter of structures and their components that produce self-assemblies directly relevant to the organization of life.

Studies on the liquid crystalline state of matter are directly related to the biophysics of the artificial lipidic membrane. Liquid crystals correspond to matter with physical properties between the liquid and crystalline state.

Liquid crystalline materials have properties between those of a conventional liquid and of a solid crystal. They combine order (crystal) and mobility (liquid). It has been reported that 5% of organic molecules could actually exist as liquid crystals [91]*. Liquid crystalline matter could flow more or less like a liquid, but the molecules that comprise it are so arranged into a molecular network that they behave like crystals. There are many types of liquid crystals depending on the organization of their molecules and their orientation in a matrix. They have different physical properties, such as different optical properties which emerge under the microscope using polarized light, or have different textures. In addition, the dynamic functional liquid crystals are known to respond to external fields (such as electric and magnetic fields) and to interact with surfaces, thereby influencing their structure and properties. As a result of the liquid crystals' intrinsic orientation towards order together with their molecular motion, they are recognized in bioscience as model systems for cell membranes* [92]*. Studies on liquid crystals are directly related to the biophysics of the artificial lipidic membrane. Based on this state of matter, which is related to phase separation, metastable phases and thermodynamical effects, in the same way the cell membranes behave*

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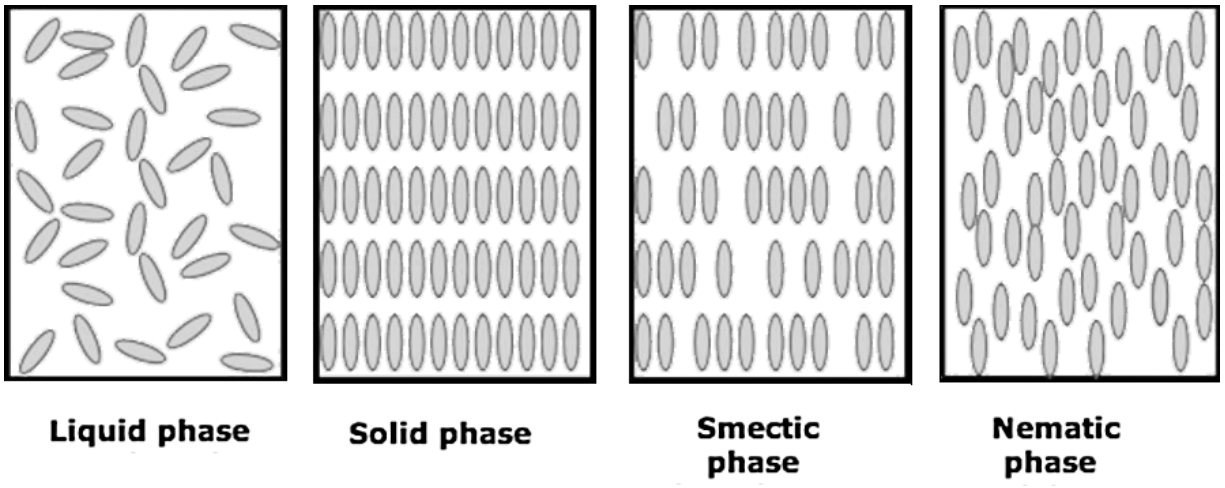
91 Y. Perrie and T. Rades in '*Pharmaceutics-Drug delivery and Targeting'*, published by Royal Pharmaceutical Society of Great Britain, 2nd ed., 2012.

92 *Synthesis and Alignment of Nanostructured Materials Using Liquid Crystals* by I. Amar-Yuli, A. Aserin, and N. Garti, in *Self-assembled supramolecular architectures, Lyotropic liquid crystals*, ed. N. Garti, P. Somasundaran, R. Mezzenga, Wiley A John Wiley and Sons, Inc., 2012.

like this, we can develop an artificial technological model to study biological phenomena. This is an amazing development, especially for getting information about interfacial phenomena and the role of metastable phases as a non-equilibrium state of matter in biological or physicochemical stimuli.

The appropriate orientation, or the thermodynamic favorable polymorphism, of the phospholipids within the lipidic fluid mosaic or liquid crystalline state is of great importance. Depending on their concentration as well as on their temperature, they form lipid bilayers. The liquid crystalline state of matter and its transitions from one order to another, due to the changes in the orientation of the structural components within the phospholipid bilayer, are considered to be the basic instrument for understanding the phenomena of life. Liquid crystals are classified as either thermotropic or lyotropic.

The behavior of thermotropic liquid crystals depends on temperature, while the lyotropic liquid crystalline state occurs by changing not only the temperature but also the concentration in the medium in which they are found. It is obvious from this that biomolecules and biostructures dispersed in water, which is the medium where life exists, could be organized by a self-assembly process depending on their concentration in water. Moreover, their structural uniformity depends on the 'kind' of water they encounter. This means that the network of water molecules, due to the dissolved ions different in nature and charge, is essential and acts as the driving force to produce functional biostructures and consequently bionetworks and bio-societies."



Picture 23: Two (nematic and smectic) out of many classes of liquid crystals.

"Can you see this figure? It represents liquid crystals of different categories such as nematic and smectic, as well as their orientation (molecular order). The liquid crystalline state of matter has its own unicity. The orientation

of the molecules involved in this state of matter plays a key role in the behavior and the functionality of the system. As far as a biosystem is concerned, the ordering and the non-ordering organization process has an effect on its functionality. Do you remember how the complexity of a system becomes the driving force for its functionality, survival and reproducibility?"

"Yes, Grandpa, I do. We have discussed complex systems a lot and highlighted the extreme importance of revealing the relation between the complexity of a system and its behavior.

However, some 'unknown force' –possibly natural laws– drives the liquid crystalline state of matter and not solids, gases or liquids to embrace vital biomolecules that are essential to life. All the essential biopolymers such as genetic material, i.e., DNA, RNA, proteins, peptides, polysaccharides etc. are in a liquid crystalline state of matter and their consequences –i.e., bio-organelles, interactions etc.– are self-organized and produce self-assemblies in which this exact state of matter is predominant. The huge and unpredictable number of metastable phases, the polymorphic and conformational structures that could be achieved through liquid crystals, are an amazing template on which nature can paint the activities of life."

"In my view, and according to the relevant literature, this state of matter, the morphological constraints, the 'metastable phases' and the physicochemical and thermodynamic balance, all constitute the background on which bio-building blocks construct living organisms."

"And what about life, Grandpa? What is it?"

"I don't know what life is. The basic bioblocks of the bio-elements and the natural laws are sufficient for the creation of living organisms and consequently for the activities and functionalities that are shuttled on those substrates… But I don't know what life is… I shall move on.

Maybe we will find some important papers on the topic later on, which will give us the information we need to better grasp these difficult matters. It is my belief that life, its functions and its organization are completely different topics and should be approached in a different way. Perhaps philosophy is the most adequate tool to supplement scientific approaches. Let's move on.

Lyotropic liquid crystals are composed of lipids whose structure consists of a polar and a non-polar group. They are categorized as surfactants due to their chemistry. It is worth noting that not all surfactants form lyotropic liquid crystals. The cell membrane of living organisms falls under the liquid crystalline state of matter. The term 'harmony', from the Greek word 'αρμονία', is the reason why molecular orientation, as dictated by the natural laws for the functions of life, coexists with and is balanced against the fluidity of the natural 'soup', which is

composed of essential bio-elements, their physicochemical properties, thermodynamics and biophysics. These, in turn, contribute to the harmony necessary for the functionality of life, giving to the cell membrane superior properties, that are directly related to what we call the organization process of life."

"Yes, yes, Grandpa, you are absolutely right. Harmony, how far our ancient ancestors had gone with their thinking, in what absolute way, I dare say, they rendered the concepts and events of nature, with philosophy, poetry, the arts. The logic of harmony in the study of natural and especially biological phenomena, contributes significantly to the understanding with scientific tools of the decisions and thinking of natural processes.

Scientific concepts, such as the stability of biosystems and lyotropic liquid crystals, their functionality, diffusion phenomena and so many others that have been scientifically recognized and studied, enable us to understand the organization and processes of life. The lyotropism of biological membranes, therefore, transmits information and drives their expression, through signal transduction networks, maintaining homeostasis and the harmonious function of the biosystem. Natural processes such as the movement of biomaterials in the order of nanoseconds and the diffusion of biomaterials into the 'soup' of biological events have been described as 'flip-flop and lateral diffusion processes, and the harmony of these dynamic events affects the operation of the whole system. The laws of nature are the orchestrator and controller of these complex processes who are constantly proposing greater complexity in the biosystem. Protein receptors, biological channels and bio-communication networks cooperate harmoniously to create the dominant statistical result in a perpetual and ever-changing dynamic creation. We could refer to a continuous 'entropic life-style', that is, a constant 'struggle' in the process of dominating information over entropy. This constant 'struggle' is preselected, due to the need to preserve life. Thus, the lyotropism of the liquid crystals that nature has chosen for the transfer of information, opposing its entropic mood, i.e., the second law of thermodynamics, is the ultimate process and the way of organization of life of the microcosm, for the preservation of life itself. It should also be noted that the kinetic trapping process is a dominant process in nature to protect sensitive information transferring biomolecules, such as genes.

Their structural integrity and their structural polymorphism through the corrections of point mutations (point polymorphism) that may occur e.g., change of nucleotide bases, due to possible changes in their micro-environment, require protection mechanisms and traps.

The concept also of saturation, due to the uncontrolled concentration of biomolecules e.g., saturation of lipids in the lipid bilayers of cell membranes causes problems in the diffusion and functional lyotropism of the liquid crystal state of the cell membrane resulting in biophysical abnormalities, which can cause endogenous and endogenous pathogens and trigger disease."

Key Point

(…) The concept of harmony, from Ancient Greece, is the key point in all efforts in nature, to maintain physicochemical/thermodynamic balance. (…) (…) Nature's main concern is to maintain the physicochemical and thermodynamic balance in a non–equilibrium state, promoting the entropic life-style process. (…)

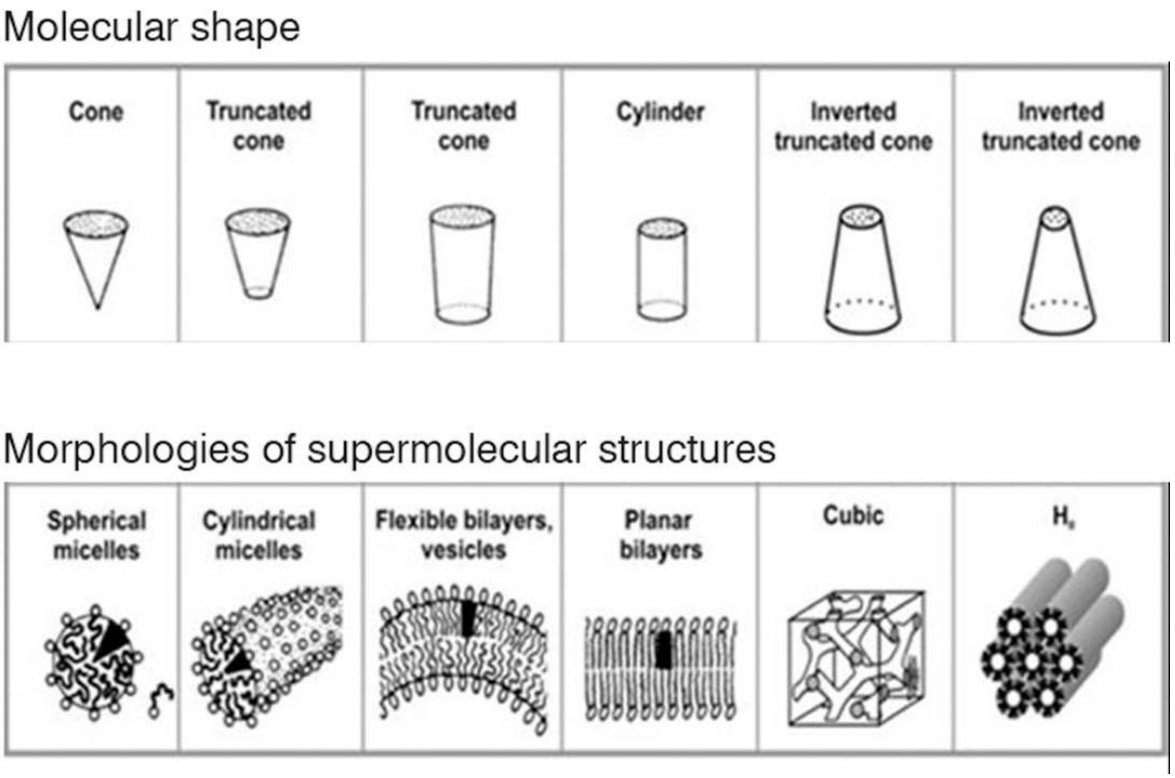
SELF-ASSEMBLED BIOSTRUCTURES AND BIONETWORKS OF LYOTROPIC LIQUID CRYSTALS

Self-assembly is a process which is considered to operate autonomously in biomaterials. It produces structures and it is very common in nature. The science of the lyotropic liquid crystalline state of matter helps one better understand the principles of self-assembly, using critical packing parameter (CPP) [93] and sophisticated thermodynamics, such as self-consistent field theory, which can be efficiently used to minimize the total free energy of a molecule-water system and identify stable metastable phases. Lyotropic liquid crystals are molecular structural components that are self-assembled in an ordered fluid phase. Moreover, they are phase-separated mixtures with an order degree which depends on their concentration.[94] They have been used as reactors for regioselective reactions due to the environment which was constituted by a very large lipid-water interfacial area.[95]

It is obvious that the above statement has to do with the role of the *lyotropism* effect that biosystems, which are composed of bio-elements, provide to living organisms. However, the lyotropic effect is involved in the functions of

[93] C. Demetzos C., "*Pharmaceutical nanotechnology. Fundamentals and Practical Applications"*, Springer Nature, 2016.
[94] D. l. Gin, C.S. Pecinovsky, J.E. Bara, R.L. Kerr, "*Functional lyotropic liquid crystal materials"*, in *Struct. Bond* DOI 10.1007/430_2007_064; 2007.
[95] "*Physics of self-assembly of lyotropic liquid crystals* by R. Mezzenga in *Synthesis and Alignment of Nanostructured Materials Using Liquid Crystals",* by I. Amar-Yuli, A. Aserin, and N. Garti, in *Self-assembled supramolecular architectures, Lyotropic liquid crystals*, ed. N. Garti, P. Somasundaran, R. Mezzenga, Wiley A John Wiley and Sons, Inc,, 2012.

living cells and consequently, in life. A better understanding of the organization and stability of biolyotropic segments that construct biosystems is helping us better grasp natural laws and we might even envisage new natural law platforms on which new forms of evolution could take place. Maybe the bio-lyotropic segments could act as bioreactors to catalyze bioreactions essential for the production of biomolecules such as amino acids, which are essential for the creation of life and the organization of living cells.



Picture 24: Different molecular and supramolecular self-assembled liquid crystal structures

The favorable thermodynamic arrangement of biomaterials (such as fatty acids), the promotion of the hydrophobic interactions and the minimization of the system's free energy (G) determine the thermotropic behavior of the system. When phospholipids are dissolved in aqueous media, they present very distinct polymorphic states that can be primarily characterized as $\mathbf{L}_{\alpha}$, $\mathbf{L}_{\beta}$ and $\mathbf{L}_{\beta'}$.

The capital letter (**L**) corresponds to the characterization of the structure-organization of the system (**L**amellar structure) (long order), while the letter of the Greek alphabet in subscript, corresponds to the characterization of the structural geometrical orientation/organization of the system (β corresponds to the structural units of the system that are organized at a specific angle) (short order). The $\mathbf{L}_{\beta}$ phospholipid structure corresponds to the gel phase in zero angle structural units (phospholipids). The $\mathbf{L}_{\alpha}$ transition corresponds to the liquid crystalline

phase. The phospholipids have the ability to re-orient how they are organized by changing their conformational properties based on the environmental/physical conditions of their hydrophobic and hydrophilic parts, and to transit from the gel phase to the liquid crystalline phase, doing so when there is a rise in temperature rise. In this case, the phospholipid molecules move at greater speed, increasing lateral motion and diffusion and *flip-flop* motion and diffusion between one and other, while the intermolecular movement around the C-C bonds increases, forming knocks.

Human cells are composed of a variety of biostructures and biomolecules, like proteins, lipids, genetic material, polysaccharides, etc. The cell membrane is an important part of the cell structure and the functionality and cooperativity of its components affect cell organization, biophysical and thermodynamic behavior and consequently survival. The cell membrane is composed of phospholipids which are different in nature: the outer side of its surface is mostly composed of ionic and polar groups that interact with the surrounding biomaterials, which are soluble in water; the inner part of the phospholipidic bilayer is the hydrophobic one and is composed of hydrocarbon chains that interact through *van der Waals* interactions. By stimulating the cell membrane with an artificial phospholipid bilayer, a polymorphic 2D structure is obtained and can be described as a dynamic fluid mosaic.

In reality, as far as the dynamic liquid crystalline state of matter is concerned, through phase transitions and the biophysical and thermodynamic processes which take place, it is important to design and develop appropriate artificial cell membrane models. Phase separation and the production of biophysical domains through the changes of the free energy of the biosystem (ΔG) are considered to be the biophysical and thermodynamical processes that affect cell functionality. The physicocehemical behavior of biological membranes has been found to be similar to that of colloidal systems. Their behavior is influenced if physicochemical variables of the surrounding environment (such as pH, ionic strength, temperature etc.) are altered. For this reason, we can produce artificial membrane structures that could be used as technological platforms for the study of biological phenomena, such as the role of metastable phases which occur on the surface of biomembranes.

The orientation of the structural components of the phospholipid bilayer (the order as well as the non-ordered phases we mentioned before) are called ‘metastable phases’, depending on the physicochemical conditions of their environment. These ‘metastable phases’ are responsible for the variability of parameters in biosystems, which causes biophysical and thermodynamic abnormalities (i.e., ‘metastable phases’) that could be defined as ‘biophysical

disease factors', as mentioned in the published monograph by Demetzos[96]. The article *Domains and Rafts in lipid membranes* [97], states that "Domains and rafts are shown in the present review to play an important role in this amazing behavior of lipid membranes. Topics touched upon include the experimental detection of domains, their composition, domain induction, properties of rafts (a special form of domain), and the relationship of rafts to human diseases". This is very close to what we are trying to prove here; the functionality of the metastable phases of cell membranes is not only responsible for the dysfunctions of the membrane, meaning diseases, but also constitute the driving force for the adaptation and evolution of living organisms and even for life itself. This is a very difficult scientific path to go down, and the experimental design here is obviously quite complicated, because of the huge diversity and variability of the order i.e., lyotropism of the biomolecules of membranes in living cells.

It is also interesting to mention that the father of the term Fluid-Mosaic Membrane Model (F-MMM), G. L. Nicolson [98], in his published review entitled *The Fluid-Mosaic Membrane Model of membrane structure: still relevant to understanding the structure, function and dynamics of biological membranes after more than 40 years*, published in the scientific *Journal Biochimica et Biophysica Acta* [99], emphasized that "Disruption of the normal membrane asymmetry is generally associated with cell activation (activation of cell adhesion, aggregation, apoptosis, recognition by phagocytic cells, etc.), and it can also be associated with pathogenic conditions". This statement perfectly fits with and supports our belief that the metastability process is the driving force that manages the functions of life. To be more specific, human diseases are driven by such mechanisms. The integration of the asymmetry of membranes and the need for functionality depends on membrane curvature, which is an essential factor that influences life's evolutionary process.

In order to better study their behavior, scientists have investigated biomolecules like phospholipids to form artificial cell membranes by means of the self-assembly process. Evidence regarding the 'rafts' in cell membranes has been collected through the use of human and hamster fibroblasts [100]. Such domains, rich in fibroblasts composed of glycosphingolipids, but insoluble in the cold non-ionic detergent Triton X-100, have been identified. A large number of studies

[96] C. Demetzos "*Pharmaceutical nanotechnology. Fundamentals and Practical applications",* Springer, Nature 2016.
[97] W. H. Binder, V. Barragan, and F. M. Menger in the Journal of *Angew. Chem. Ind. Ed*, 2003, 42, 5802-5827.
[98] S. T. Singer and G. L. Nicolson, "*The Fluid Mosaic Model of the Structure of Cell Membranes", Science, New Series*, 175 (4023), 720-731, 1972.
[99] G. L. Nicolson, BBA, 1838, 1451-1466 (2014).
[100] W. H. Binder, V. Barragan, and F. M. Menger in the Journal of *Angew. Chem. Ind. Ed*, 2003, 42, 5802-5827.

underlining the essential role of such metastable phases in biological activities have been carried out. Proteins also have been detected as being associated with such metastable phases i.e., 'rafts' whose importance in signal transduction, protein and lipid sorting, cell adhesion, mobility is acknowledged, and which are found to be related to disease. It is important to mention a class of such lipid domains, called 'caveolae', as a subset of 'rafts', with the predominant ones being lipid cholesterol, glycosphingolipids, sphingomyelin, and lipid-anchored membrane proteins. The morphology of caveolae can change in non-invaginated structures as a consequence of their activity and consequently domains can be found in cells that cannot be only invaginations of the plasma membrane, but also flat or tubular domains within the membrane. Cells that don't express caveolin, domains of molecular and structural composition similar to caveolae, have also been identified. Such domains are called '*non-caveolae rafts'*.

Key Point

(…) the functionality of the metastable phases of cell membranes is not only responsible for the dysfunctions of the membrane, meaning diseases, but also constitute the driving force for the adaptation and evolution of living organisms and even of life itself.

Cholesterol is an essential biomolecule for the organization and fluidity of cell membranes, as far as their structural polymorphism is concerned. At the beginning of the 20th century, A. Windaus and H. Wieland published preliminary results on the structure of cholesterol, while its final structure was elucidated in 1932, and biosynthesis became possible in 1956. Cholesterol affects phospholipidic bilayer behavior and temperature affects its partnership within biological membranes. When the temperature of the cell environment is higher than the transition temperature (i.e., the temperature at which a polymorphism concerning the crystallinity of the biosystem takes place, moving from a higher-order organization to a lower-order one) of the phospholipids of a particular cell membrane, the effect of cholesterol on the fluidity of the membrane and on its functionality is affected. However, cholesterol is the modulator of fluidity in cell membranes; it affects the process of how phospholipids and the other components of biomembranes are organized, by changing the biophysical and thermodynamic properties of the biosystem. Finally, it also influences the permeability of cell

membranes through essential bio-elements and consequently affects the metabolic paths of the cell."

"But let's get back to the caveole as essential 'rafts' that are involved in the functions of the bio-organism", Grandpa suggested.

"A low concentration of cholesterol influences the number of caveolae, which decreases. Moreover, a low concentration of cholesterol compromises the functionality of caveolae rafts and influences cell functions. 'Rafts and human diseases which are domains (like metastable phases from a biophysical point of view) in membranes containing caveolae and caveolin, are implicated in the molecular pathology of numerous diseases, such as cancers, atherosclerosis, neurodegenerative diseases and AIDS. On the basis of the above statement, Binder et al. come to the following conclusion: 'Future progress in biology will depend upon scientists of all types, including chemists, continuing to address membrane structures, dynamics, and function where domains and rafts play a key role. Even now it can be assumed that new strategies for fighting viral infections, lipid storage disease, cancer and other persistent illnesses of mankind will arise through the understanding of 'rafts'" [101].

"That's excellent, Grandpa. It fits perfectly with the '*biophysical disease factor'*, meaning the metastable phases. This may even become an alternative structural epitope for the targeting process in injuries of tissue, using the biophysical properties of novel therapeutic products to treat human diseases."

"This is an amazing development. The scientific community working on medical diseases need to hear this message. We have said a lot but the topic we are discussing here is endless. However, it's time to go one step further and discuss the casting process which is a hyper-realistic form of behavior for selecting appropriate biomaterials for the production of functional and stable bio-assemblies, using the statistically most prevalent lyotropic structure", Grandpa said.

"But why do you use such a term to describe biological or biophysical phenomena? Is there a 'casting process' in nature?" I asked him.

"The 'casting process' stems from the demands of natural laws, and involves identifying efficient biomaterials that are able to produce stable biosystems and biostructures. These biosystems and biostructures are the building blocks which produce living and sustainable networks that are able to communicate and to replicate themselves.

A method of 'direct templating of biostructure and bioself-assemblies', which is performed one a laboratory scale as a 'casting process', produces close-to-perfect replicas of the template as we can read in the following publication

[101] W. H. Binder, V. Barragan, and F. M. Menger in the Journal of *Angew. Chem. Ind. Ed*, 2003, 42, 5802-5827.

[102]:'By starting from lyotropic liquid crystalline phase, then the liquid phase is solidified using electrochemical or chemical reactions. It is important that the lyotropic liquid crystalline phase is to direct template of another material with new functionality'. It becomes clear that such approaches could be achieved on a biological level, and biosystems as lyotropic liquid crystalline materials could produce templates for the organization of other materials with innovative and functional properties which are involved in the adaptation and evolutionary process of life. It is obvious that scientists have discovered the properties of soft matter and reported on achievements that explain the cryptic code and the silence functionality of biomaterials in an effort to organize more functional and thermodynamically stable biosystems. Lyotropism, as mentioned before, is an excellent example which presents the behavior of bio-elements and biosystems so as to use the metastable phases of biological membranes to replicate close-to perfect copies of the template but with new properties. This is an example of how nature works in the microcosm and in the micro-environment [103].

In order for life to sustain biological functions, nature uses primordial physical laws, selecting molecular assemblies and interfaces capable of providing specific functions and structures. During the adaptation and evolutionary process, self-assembly is the basis for producing new emerging forms of organization and new functions in living organisms, through the use of bio-elements and biomaterials. New interfaces combining molecules which are different in nature are selected and produce biological platforms and substrates that are used to develop effective and sustainable living organisms. It is important to highlight that self-assembly is a common process in multicomponents and multi-compartmental biosystems that could be capable of producing bio-multifunctional networks in a dynamic manner."

"According to the literature [104]" Grandpa said, *"we have two main categories of self-assembly. The first one is static self-assembly and the second one is dynamic self-assembly. These two assembly processes differ when it comes to the dissipation of energy. Static self-assembly refers to systems in local equilibrium that don't dissipate energy, while dynamic self-assembly produces structures that dissipate energy. In the static self-assembly process, energy is the driving force for organization; the benefit of such systems is stability. Living cells know 'by default' the hierarchy of the self-assembly processes. We need to know that in the self-assembly process the driving force which produces biostructures*

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[102] D.L.Gin, C.S.Pecinovsky, J.E.Bara, R.L. Kerr, "*Functional Lyotropic liquid crystal materials"*, Struct Bond DOI 10.1007/430_2007_064 Springer-Verlag Berlin Heidelberg.

[103] D.L.Gin, C.S.Pecinovsky, J.E.Bara, R.L. Kerr, "*Functional Lyotropic liquid crystal materials"*, Struct Bond DOI 10.1007/430_2007_064 Springer-Verlag Berlin Heidelberg.

[104] G.M.Whitesides, B. Grzybowski, "*Self-assembly at all scales"*, Science 295, 2002.

is the hydrophobic effect. The hydrophobic effect is, in general, an entropic effect. This is a serious thermodynamic effect, because the water molecules that could interact with the hydrophobic acyl chains of phospholipids (which are the main building blocks of biomembranes) do so by minimizing entropy and organizing the system in a more ordered structure. Such approaches are quite difficult to grasp, even for scientists who are involved in such scientific fields."

"It's really amazing, Grandpa, how the scientific community built such knowledge long time ago by combining different scientific disciplines. I guess that the organization of life is inextricably linked to the physicochemical characteristics of the natural elements that have been selected over the course of billions of years to create living organelles and consequently living organisms. Am I right, Grandpa?"

"Yes, this is a good step towards understanding the value of scientific achievements in their efforts to reveal natural codes", Grandpa said. *"It is known that 2,500 to 3,000 years ago, the philosophers known to us as the 'pre-Socratics' dealt with all these unexplored scientific fields, thanks to their brilliant minds and their ability to conceive things, their 'noesis' (νόησις). 'Noesis, according to Plato (4th century BC), is the 'idea of things'. This tool remains exceptional even today and Greek philosophers provided unparalleled examples of how to separate the wheat from the chaff, so to speak. The term 'krísis', (κρίσις) meaning 'decision by logic', was considered to be a predominant feature in human beings, serving as a navigator, a guide to what we have to take into consideration as important and what not. But let's continue our journey into scientific utopia.*

Biomaterials are considered to be the basic elements that survived a competitive process in a changing environment by means of nature's evolutionary process over the course of billions of years. The selection of biomaterials that are involved in the production of coded information – such as shape, charge, surface properties of the assemblies or physical properties – depends on their nature, meaning that their physicochemical properties are responsible for their 'behavior' and drive their self-assembly process. The biomaterials were selected not 'by default' by existing natural laws, but rather were considered as the 'selected' bio-elements to produce micro- and macro-biosystems. These biosystems encompass the basic bio-elements and 'decided' which one would be more useful and act as the leading chemical structure to produce bionetworks, bio-organisms and consequently bio-societies. The first concern that emerged dealt with the question of what 'driving force' could guide such bioprocesses. The second one is the substrate on which bio-elements will construct bionetworks.

Key Point

The 'casting process' is related to the adaptation and evolution of the functions of life and provides efficient biomaterials that are able to produce stable biosystems and biostructures. (...)
The term 'nóisis' (νόησις) and 'krísis' (κρίσις) refer to the concept of thought and the logic behind the decisions respectively and constitute pillars of science and civilization.

According to several scientists, it was in the very beginning of life on Earth, when natural laws were emerging that a dynamic process occurred. An invisible 'force' had to be there to manage and to organize the environmental diversity in some compressive and autologous manner, demanding the creation of natural laws. This issue was important and, if one were to take this approach, we have to bear in mind that we have to determine what this invisible 'force' is, taking into account that the existing natural laws are very complicated and 'energy-consuming'. We have to bear in mind too that time-consuming and energy-consuming processes were predominant and affected the survival of living matter.

The difficulties in the creation of natural systems and the societies that would arise involved the requirement for the dispersion and diversity of the 'characteristics and the 'events' that evolved in them, the composition of the systems from many different materials which would have the 'logic' of cooperation between them and also the multi-compartmentalized organization and the development of effective communication networks. The multifunctionality of first-class biomolecules and biosystems has been the result of the complexity and interoperability of primary biomaterials, a process that has not stopped to this day, as creation has not stopped, based on the infinite wisdom and harmony of the evolution of the world. As Whitesides and Grzybowski point out in their article *Self-assembly at all scales* [105], "We understand that the living cell is a sack that contains a number of reacting chemicals, is studded with environmental sensors, and allows heat and certain chemicals to pass across its walls. We also understand that the cell is a structure that is enclosed, self-replicating, energy dissipating and adaptive."

Grandpa looked at me for a moment and stroked his chair.

[105] G.M.Whitesides, B. Grzybowski, "Self-assembly at all scales", Science 295, 2002.

Silence seemed to be the answer for both of us at that moment, I would say a way out. Maybe we wanted to choose the words based on the 'casting process', to continue our discussion. It seems that the discussion evolved almost exclusively into questioning and understanding difficult concepts. It was a painful process and the Mirror shone in the natural light that got in through the crack in the window.

Was it dawn or dusk?

I chose not to see.

It was the meeting of day and night, the coming of spring that succeeds winter; I did not want to know. Creation, natural laws, and 'interviews' in biomaterials and biomolecules, were running through my mind.

I was thinking, and my Mirror, I think smiled at me.

"You are doing well", I read through the blur and rust of the years. "Do not go back, you will only see gray colors. You can, you have to reach the end, your own end, for others to continue.

***

"The literature", cried Grandpa suddenly, looking at me.

"Can you understand what is the question that Whitesides and Grzybowski raise in their article How does life emerge from a system of chemical reactions? It is obvious that the question covers all processes of life, such as mitosis, cell operation and other complex communication processes within the cell. The elegant organization of supra-molecular structures, like cell membranes or the cytoskeleton, can change through self-reassembly after the insertion of a natural object, like a virus or a microbe, or by changing the structure of already existing proteins due to external stimuli. This approach affects the normal behavior of the cell's biomembrane, alters the functional self-assembly status and generates functional abnormalities that are characterized as 'biophysical disease factors. Peptides and proteins that are composed of amino acids have properties that are driven by the physicochemical characteristics of the amino acids they are composed of but, more importantly, by the conformational properties of the polypeptide chains. However, the biophysical disease factor relating to the conformational integrity of proteins is a multitasking one and is influenced by the order of complexity of those proteins, namely a primary, secondary, tertiary or quaternary conformational structure. A particular conformational structure is important for their functionality and is influenced by a huge number of other factors and by their hydration process, as far as hydration energy and forces are concerned. The hydration rate and the balance between hydrophobic/hydrophilic

pockets of proteins that are produced during their development process, are the 'rational' design protocol for the development of a multitasking bionetwork.

The self-assembly behavior of biomaterials (i.e., amino acids, also called 'the building blocks of proteins') is a continuing biodynamic process and it is not synonymous with the term 'formation'. At this point, it's only fitting to clarify the difference in meaning of the terms 'self-assembly' and 'self-organization'. Self-assembly describes the autonomous organization of structural elements into structures, without external intervention; it can be observed on all size scales. For example, the molecular order in molecular systems of liquid crystals is the result of self-assembly. The term 'self-organization' describes the overall behavior of structural elements / structural units, as a result of interactions between them. One example of self-organization is homeostasis, which is the ability of a biological system to regulate its interior environment so as to maintain it in a stable state through multiple dynamic balance adaptations which are controlled by interrelated self-regulation mechanisms. It is worth mentioning that biomaterials which are different in nature and concentration can create different morphologies.

The self-assembly of amphiphilic molecules into discrete biostructures, and consequently into organisms, is a fundamental and interesting aspect of the processes of life; it requires primitive and dispersant biotechnologies that, in my view, were developed in situ. This in situ approach requires a process of bio-organization based on the self-assembly approach.

Let's move now to an important scientific field that combines two sciences: physics and biology. There are two processes at work as far as the term 'life' is concerned. The first one is the stochastic process at a microscopic level and the second one is the deterministic process at a macroscopic level."

BIOPHYSICAL PROCESSES THAT INFLUENCE THE ADAPTATION AND EVOLUTION OF LIVING ORGANISMS

"We need to point out two basic axes which efficiently contribute to the evolutionary processes of life. The first one is biophysics and the second one is bio-thermodynamics. An important topic that should be mentioned is 'structural polymorphism', which is known as 'mesophase' or 'metastable phases' or 'rafts'[106], and contributes to the balance of the energy within the system.

[106] W.H. Binder, V. Barragan, F. M. Menger, "*Domains and Rafts in Lipid Membranes"*, Angewandte Chemie Int Ed., 2003, 5802-5827.

The term ‘metastable phase’ is used to describe the non-equilibrium phenomena of a bio-structure that change the properties of its surface. In classical thermodynamics, there are no visible ‘metastable phases’ because of the irreversibility of the system, given that time is infinite. However, in strictly infinite systems, such as macroscopic ones, which, the identification of ‘metastable phases’ is no easy process. We can take measurements in such macrosystems using thermodynamic variables to study their thermodynamic evolution, but we have to know that a macroscopic system consists of a huge number of small systems. The dilution of such a macroscopic system protects the individuals (small systems) from interactions which, if they become favorable by producing aggregates, will lead the system to become a real macroscopic system and we will not able to study its thermodynamic details. These details are crucial for keeping biophysical phenomena alive and are fundamental for the evolution of the biosystem. It is clear that dilution and hydration forces should also be taken into account in the study of biological phenomena.”

“Excellent”, Grandpa said. *“Later on we will see the role of hydration forces in the biological stability of biosystems based on their physicochemical properties and on the interactions of their components with water molecules.*

For a better understanding of self-assemblies and of the laws that govern their behavior, we should be aware of biophysics, a scientific field where physics and biology combine. Biophysics is considered to play an important role in a number of other scientific fields such as chemistry, biosciences, applied mathematics, and micro- and nano-engineering. It deals with physical and biological phenomena that are all involved in the structural and morphological changes that occur in living organisms. Behind those changes, due to the chemical reactions and biological cascades, thermodynamics is becoming an essential scientific approach that could be appropriate for the analysis and evaluation of evolution, change and the irreversibility of life.

Going back to biophysics, I should remind you that it is a scientific tool to help us better understand the various self-assembled organization levels of life”, Grandpa said.

Biophysics is the field of natural sciences which studies natural phenomena related to the structure, organization and function of biological systems, as well as the phenomena of life, and the biological results of the impact that natural factors have on animate matter. The complexity and diversity of living organisms on different qualitative levels determine the subject matter of biophysics and of related scientific fields. Biomolecules are molecules involved in biological processes, and they are characterized by stability and variability in different surroundings. These properties of biomolecules are essential in them being

selected as functional and structural building blocks of complicated biological organelles. The figure below depicts a 3D representation of myoglobin, one of the most studied biomolecules.

Key Point

(…) Dilution and hydration forces should be taken into consideration in the study of biological phenomena. (…)

It is well established that the role of interfacial phenomena in bio-organisms may relate to biophysical behavior, as well as to the thermotropic changes of their membranes (i.e., 'flip-flopping' and 'metastable phases'). The 'metagraphic code', which is also called 'silence functionality', is a term that was first introduced in the published monograph by Demetzos entitled *Pharmaceutical Nanotechnology. Fundamentals and Practical Applications* [107]. It could be used as the living organisms were encoded by metastable phases and combined both biophysical and thermotropical behavior.

From a scientific point of view, it is important to create an artificial 'living system' that simulates the main phenomena of life in a very simple form. Model phospholipid bilayers have been well-documented as a cell membrane model, given their biophysical and thermotropic behavior, and are well investigated using thermo-analytical and physical techniques. It should be noted that most 'metastable phases' are 'kinetically trapped' in a stable macroscopic fingerprint. In reality, at a macroscopic level on Earth, everything is moving and changing very slowly. Variability, in most cases, is an invisible phenomenon. However, we have to look deep down using scientific techniques and instruments to have the sense of the real word and of the importance of metastable phases and of their value in the functionality, adaptation and evolutionary process of living organisms; and consequently, of their value in life. We can promote the role of the 'metastable phases' that act as modulators, promoters, or retarders of physical phenomena that can be observed macroscopically [108]. The real world, as we

[107] C. Demetzos, "*Pharmaceutical Nanotechnology. Fundamentals and Practical Applications",* Springer Nature 2016.
[108] C. Demetzos 'Biophysics and Thermodynamics. The scientific building blocks for bioinspired drug delivery systems' AAPS PharmSci Tech, 2015, 16(3):491-5.

mentioned above, is beyond the level of what our senses perceive. Democritus asserted that there two types of knowledge. Knowledge obtained through the senses and knowledge obtained through mental effort. Of those, the latter is dubbed 'legitimate', and the reliability of that knowledge is associated with veracity. Knowledge obtained through the senses is dubbed 'bastard' knowledge; knowledge lacking in certainty; lacking in truth[109].

"You know, my boy, since we are talking about biological membranes, artificial biological membranes, metastable phases of membranes and so on, it would be good for you to have an idea about what they are composed of."

"I already know the fundamentals, Grandpa. Don't forget that I've a University degree in natural and life sciences. I do have an idea on this subject."

"Sure, I'm sorry, you're right. But let's take a look anyway. More often than not, there are new things to learn."

Key Point

Most 'metastable phases' are "kinetically trapped" in macroscopic systems and in the world. In reality, at a macroscopic level on Earth, everything is moving and changing very slowly. Variability is an invisible phenomenon.

CELL MEMBRANES: FUNDAMENTAL ISSUES

Phospholipids are the main biomolecules in biological membranes; other biomolecules include cholesterol, lipids, etc. The main lipids composing cells are phospholipids. The hydrophobic part of phospholipids is composed of long fatty acid chains, while the polar head group consists of a moiety of phosphatidyl-amine.

Artificial membranes are composed of materials very common in nature, contributing to the bioself assembled process: they are used in scientific laboratories to simulate biological membranes and to simplify investigations into their organization and functionality. Through model membranes composed of phospholipids and lipids as biological substrates, we can study the behavior of the bio-elements of which they are composed. Thus, we can have a complete picture of the biophysical behavior of those substrates, which enables us to investigate natural laws on a macroscopic scale. There is a huge number of phenomena taking

[109] Democritus, Fragment 11, https://en.wikipedia.org/wiki/Democritus#Fr

place every second within our living 'soup'. One of the predominant phenomena is characterized by the aggregation process, which is considered a common entropic form of behavior in nature. This phenomenon is essential for the survival or death of a biosystem, and it occurs due to the emerging thermotropic abnormalities of the biosystem; namely those take place in the interfacial region between the membrane and its surrounding. These abnormalities are the well-known metastable phases or 'rafts. Their presence is not favorable to the biological processes and not acceptable as far as the thermodynamic payload is concerned. In the picture below, we can see the metastable phases of self-assembled structures.

In the phospholipid bilayer of natural biomembranes or in artificial lipidic membranes, lateral and vertical motion takes place and metastable phases are created spontaneously or by the triggering of an external stimulus (such as changes in pH, temperature, ionic strength etc.). These phase separations – or metastable phases –, along with the creation of new order in the structural components of the bilayer – i.e., lipids, proteins, hydrocarbons etc. –, result in changes in the functions of the membranes, influencing the signaling process, diffusion rate, permeability and functions vital for the survival of the biosystem. It is important to point out that the above-mentioned stimuli are not the only ones capable of influencing biomembranes; divalent ions have also been studied to explore such phenomena. Such investigations have been carried out using phosphatidylserine (PS) or binary mixed DOPE/DOPS with concentrations of Ca^{2+} between 40 and 80 mol % Ca^{2+} ions. The 'liquid/cochleate' phase was observed by freeze-fracture electron microscopy. However, both the hexagonal phase of DOPE and the cochleated phase of DOPS were observed in a 1:1 molar ratio binary mixture of the lipids in the presence of Ca^{2+}. This is considered to be an important observation and can be used to explain the promotion of structural polymorphism, i.e., lyotropism of soft matter for the production of unique lyotropic liquid crystals. These are able to remain stable in existing environmental conditions, offering new functions to the biosystem. Better understanding the structural polymorphism of phospholipids (the main components of natural membranes) could help us produce new structures with new functions or even more sustainable organisms. This might even be a preliminary explanation for the evolution of life from a physichochemical point of view [110]. Moreover, the spontaneous forces or the external stimulus that is involved and influences such phenomena, are considered to be two sides of the same coin. The difference is that

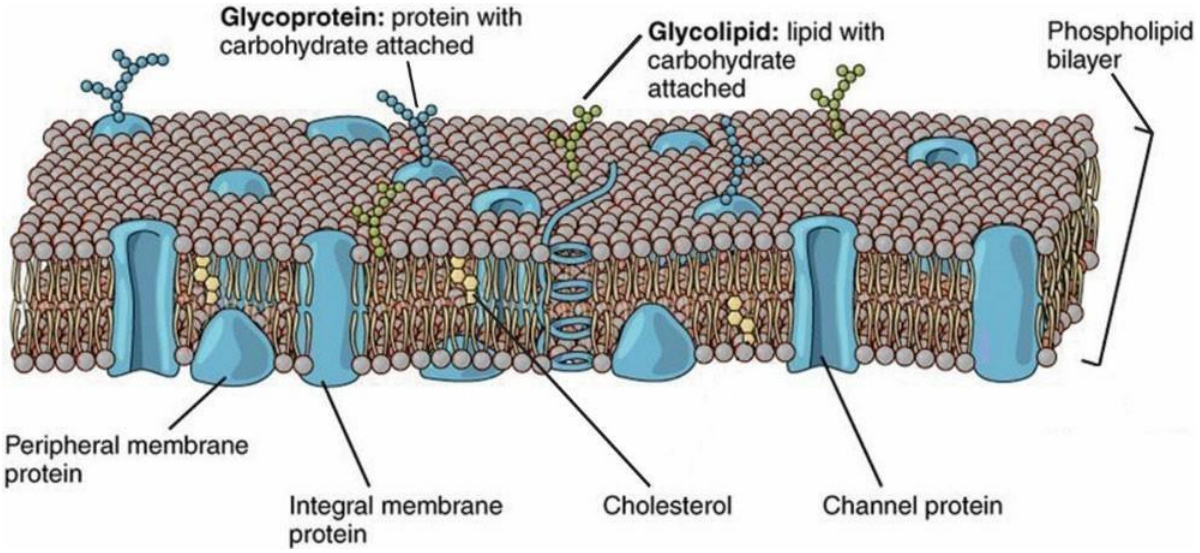
[110] W.Knoll, G. Schmidt, H.Rotzer, T. Henkel, W. Pfeiffer, E. Sackman, S. Mittler-Neher, J. Sprinke, Chem. Phys. Lipids, 1991, 57, 363-374; W. H. Binder, V. Barragan, and F. M. Menger in the Journal of *Angew. Chem. Ind. Ed*, 2003, 42, 5802-5827.

one side of the coin can be easily perceived (and can be measured), while the other side has no visible figure (and cannot be measured). However, the result is the same. The value of the coin rises and falls in the same way shares do on a stock market, affecting the evolution of life.

It is worth mentioning that because of their chemical and physical properties, large molecular entities produced through the process of polymerization, like proteins or other macromolecules, are capable of inducing phase segregation phenomena and consequently membrane 'abnormalities', i.e., domains, or caveolae. Such *clustering effects* within membranes might be necessary for the production of self-assembly processes in order to protect organelles or macromolecules which are important for living cells. These so-called *block* bio-copolymers are amphiphilic molecules. Their hydrophilic/hydrophobic balance and molecular mass are critical factors and driving forces for the production of appropriate vesicles that are able to remain stable and to embrace biomacromolecules and processes essential for life. Such approaches are not only beneficial for living organisms, but also for the physicochemical forces which are induced, which is to say the appropriate curvature of the self-assemblies, are considered essential for clustering and consequently for the production of active and functional domains – meaning 'metastable phases' or 'rafts'[111]**.** The kind of curvature is 'energy-consuming' and nature carefully designs the rate of curvature of the vesicle produced in order for it to be functional.

The figure below represents a cell membrane which is considered to be a highly complex system with an amazing degree of functionality. This biosystem is not capable of reproducing itself.

[111] W. H. Binder, V. Barragan, and F. M. Menger in the Journal of *Angew. Chem. Ind. Ed*, 2003, 42, 5802-5827.



Picture 25: A model of biomembrane

Key Point

Nature promotes complex systems as "living systems." This concept promotes a plethora of metastable phases and clustering effects which are processes of high quality (i.e., signalling transduction) that take place within the lipid bilayers of cell membranes101.

"I suppose that you have plenty of questions or remarks on what I've been talking about", Grandpa said. *"Let's take a break and have a short discussion about these matters."*

"Yes, as a matter of fact, you're right, Grandpa. I need to think for a while, sort out in my mind what you said. It is very interesting indeed, though somewhat challenging. Scientific approaches, especially in topics where the scientific terminology is complex, require peace of mind and focus. It is not only food that needs to be digested. An intellectual supper also calls for some good wine, wouldn't you agree? Which wine would you suggest we drink, to make our supper more appealing, Grandpa?"

"My dear boy, I'm glad to see you're asking for more than what you already have. The wine is the 'spirit' accompanying any meal; it can release emotions … cause biochemical and biophysical cascades. In this way, you can see and feel things you hadn't previously seen or felt. But it takes self-consciousness and modesty to enjoy them."

"What do you mean by saying that biochemical and biophysical cascades are released?"

"Well, well, look how you keep pushing our conversation forward. You are now opening a new chapter, which once again concerns the 'metastable phases' in the 'rafting' of our cell membranes. Changes in these structures of the cell membranes can easily take place when external stimuli are present, like wine (or spirit) in our case."

"What does the wine help with Grandpa?"

"It contributes to the acquisition of even an higher degree of 'rafting', which means 'metastable phases' that will lead to a different functionality. This means that, while we might feel reserved when it comes to dancing, with wine and spirits new rafts are created. Those release isolated neurotransmitters through the changes in the organization of the cell membrane platform and changes in the liquid crystalline phase. This has an instant impact on emotions. However, the biochemical cascade starts because we threw a biophysical switch. For a while, you become a different person, as people say. What is really happening is that, basically, changes of the ordering of biomaterials like phospholipids and of other composites of our biological membranes produce effective and functional lyotropism."

"So wine is the driving force that helps reveal what otherwise concealed biochemical substances can do. Am I right?"

"Absolutely right, my boy."

After taking some time to relax and have a glass of wine or two, I dreamt of the world 'deep down'. Everything was colorful, full of sound. I could not make out the shapes and the morphology of the objects well. Slowly, figures started to appear, but they did not look like human silhouettes or objects I knew... What I already knew, I could not recall, as if I was suffering from some kind of amnesia. I tried to recall what I had learned in the past... but there was no past to be found either.

After a while, –I don't remember how much time passed– I lost all sense of time; what does 'much' even mean? There is no such thing as 'much'; there is simply something. I saw shades of deep purple, through shapes which looked like buildings with pillars of supreme beauty. It was as if something was trying to wake me up... Light entered inside me and everything became clearer. Then, I saw people, but not in their familiar form. Rather, they looked like human beings, like animals, on roads made of soil, hundreds of people working, their heads bent, never stopping. Why? I asked myself.

And then something that looked like a building, like a built structure, appeared. I looked at its interior, and it was full of scrolls, thousands of them, who

knows how many... I began to worry. Where was I? I could see that I was one of the people who had entered the building containing the scrolls; one of the people who sat down, opened the books and read... Yes, I was one of them, which made me happy. But this feeling of happiness was not a familiar one. Even though I couldn't put my finger on it, I didn't want to leave...

Then a noise woke me up from my deep sleep. I could not tell for how long I'd slept, perhaps for hours. I had a dream that reminded me of Grandpa, yes, Grandpa was there himself. How is it possible for a single person to carry within them all the things I had seen? Culture, ancient culture, everything we knew from written testimonies, and from the time before that. I can't even tell from when. This sense of happiness was nothing more than an understanding of the world, the macrocosm which was being developed thanks to the work in the microcosm; the microcosm I could not see yet whose color and light I could still sense.

I turned my head and began talking to him. Yes, it was Grandpa indeed. I recognized him. His hand was resting on my head.

Key Point

The aggregation process is an entropic phenomenon which is common in nature. This phenomenon is essential for the survival or death of a biosystem. The metastable phases can contribute to producing abnormalities on the membrane or the boundaries of the system with its surrounding environment, which act as an "entropic island" that promotes its behavior – i.e., functionality or death.

"Wake up!" he said. "*We don't need any more wine. The classical Greek principle on which Western civilization is based, was moderation ('métron' (μέτρον), meaning the 'knowledge of one's own limits'). Such knowledge places human beings in the centre of the world and makes them responsible for their own decisions and for their behavior. It is something internal that controls and balances our behavior and decisions. So, 'moderation' means the point at which something becomes enough."*

"I got it, Grandpa. It's time to move on and maybe the wine that we had helped us understand these difficult scientific topics, as well as the thinking that lies behind them. But let's move on. I'll be delighted to explore the next set of issues along this journey. In my dreams I recognized shapes and morphologies that were intertangled, but I'm not sure what they represented. Probably different

features of biological objects. Do you have any idea about what nature tries to promote through the shape of biological objects or their morphology? I'm confused about that. Is this a biophysical and thermodynamic issue or is geometry involved in natural evolution as another player in biological organization, self-assembly and the process of producing stable biosystems and bionetworks?"

MORPHOLOGY *VS*. SHAPE IN BIOLOGICAL OBJECTS

"Two important and fundamental matters to be taken into account and to clarify are the terms 'shape' and 'morphology'. They constitute completely different ways to describe an object or, more importantly, a biosystem."

The conversation with Grandpa started up again. My electronic calendar played time on fast forward... I could not tell the date or time, even though there was no reason for it not to show me those temporal variables. I was impressed at how full of experience and knowledge I felt. It was as if a magic wand had changed everything, even time. But how could this be? I decided I really ought to focus on Grandpa and our conversation again.

"Can you tell the difference between shape and morphology?" he asked.

"No, I can't. They appear to be similar, but I guess there are differences… I think I dreamt of shapes and morphologies, although the lights and colors were all mixed up. Any way, it will be good to learn more about this topic."

"Shape has to do with the geometrical characteristics of a natural object or a biological element and is calculated by means of Euclidean geometry. On the other hand, morphology describes the real scheme of the object and is calculated by means of fractal geometry [112]*. They are both considered fundamental in the study of natural objects. It is important to take into consideration that the principles of cell behavior, such as stability and diversity, are influenced by the measurements of what we need to describe. This means they are influenced by shape or morphology* [113]**.** *As we've mentioned, 'metastable phases' play a key role in the functionality of living organisms by regulating the 'switching on and off" of processes (such as transmembrane communication). According to Lasic (1990)* [114]**,** *the 'metastable phases' of artificial phospholipid membranes could be characterized as 'kinetically trapped'* [115]**.** *Additionally, there is a strong link*

[112] N. Pippa, 'Pharmaceutical nanotechnology. Studies on the morphology of chimeric DDnSs', Ph.D Thesis 2016.
[113] N. Pippa, A. Docometzidis, C. Demetzos, P. Macheras, '*On the ubiquitous presence of fractals and fractal concept in Pharmaceutical Sciences : A Review*', *Int. J. of Pharm*., 456, 340-352, 2013
[114] D.D. Lasic, 'Liposome: from Physics to applications', Elsevier Science Publishers B.V., 1993.
[115] C. Demetzos '*Biophysics and Thermodynamics. The scientific building blocks of bio-inspired drug delivery nanosystems*' AAPS PharmSci Tech, 2015, 16(3):491-5.

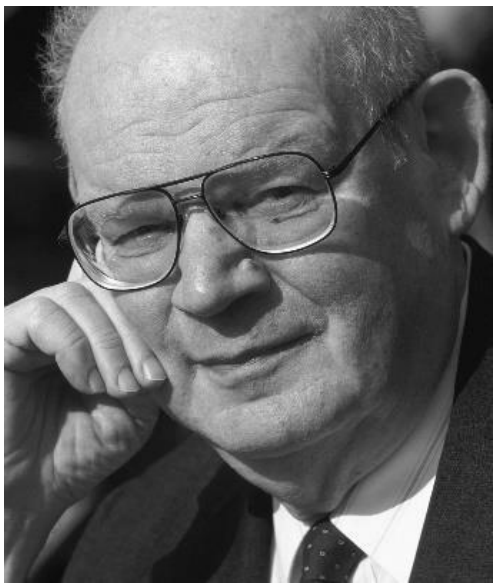
between metastable phases and the mechanistic explanation of the biophysical behavior of living organisms. However, the morphology of a biological object includes all the information reflected in what we call 'beauty'. It is very difficult to produce artificial morphologies for the purpose of studying their behavior and to compare them with the morphology of biological objects (such as proteins, antibodies, etc.). This is a very difficult task because it is not easy to reproduce their dynamic properties, without having the biological cryptic natural code available. Of course, that code is very complicated indeed."

"Grandpa, you mentioned the fractal dimension of objects. I've heard of them, but would you like to talk a bit about this kind of geometry. As far as I know, it constitutes an extension of Euclidean geometry. Is that right? What's your take on it?"

"Yes, it is exactly as you said. But let's get back to our books, to be sure of what we're learning and what we're talking about. Fractal sets, fractal dimensions. Look, here's something. Let's have a read. The first one to introduce the term 'fractal' in 1977, was Benoît Mandelbrot in his book Fractals: Form, Chance and Dimension. In that book, he unfolded his thoughts on what we call 'fractal sets geometry'.

The word 'fractus' means 'broken' in Latin, while 'fragere' means 'to break' or 'to produce misshapen forms. In his 1982 book The Fractal Geometry of Nature, Mandelbrot says: 'Clouds are not spheres, mountains are not cones, coastlines are not circles, and bark is not smooth, nor does lightning travel in a straight line' **[116]**. *He revealed that the geometry of nature does not follow Euclidean logic. Rather, what appears to be a morphology, is only an illusion of Euclidean shapes. Based on Euclidean geometry, we can calculate the dimensions we see, to make measurements. Fractal geometry is extremely popular and is based on a deeper understanding of chaotic and non-arranged systems, which constitute a 'projection' of their real forms."*

[116] B. B. Mandelbrot, 'The Fractal Geometry of Nature', San Francisco: W.H. Freeman, 1982.



Picture 26: Benoit B. Mandelbrot, the father of fractal geometry

Benoit B. Mandelbrot (20 November 1924 – 14 October 2010) was a Polish-born, French and American mathematician with broad interests in the practical sciences, especially regarding what he labeled as 'the art of roughness' of physical phenomena and 'the uncontrolled element in life.' He referred to himself as a 'fractalist' He is recognized for his contribution to the field of fractal geometry. During his career, he received over 15 honorary doctorates and served on many science journals, along with winning numerous awards. His autobiography, *The Fractalist: Memoir of a Scientific Maverick*, was published in 2012 (https://en.wikipedia.org/wiki/Benoit_Mandelbrot).

"Mandelbrot's fractal sets reveal an infinite number of identical forms within a larger shape, which is in turn enclosed in an even larger one, and so on and so forth. An important characteristic of fractal sets is scaling and dilatational symmetry. The very same level of details appears at all scales in its fractal dimension. In this way, when we look deep into the interior of the form of an object, its fractal image does not become simplified.

Another characteristic of fractal object is self-similarity. The shape of an object, which appears at a certain scale of a given fractal dimension, looks like the shapes that appear on all the other scales. In this way, no matter how many times a certain area of the fractal shape is amplified, its self-similarity remains unchanged. This is called the 'scale invariance principle'.

It is evident that it is hard to understand the concept and the practical application of fractal dimensions since we live in a three-dimensional Euclidean space and all of our calculations and references are carried out according to Euclidean geometry. But it is also clear that it is necessary to understand fractal geometry."

"Why is that, Grandpa?"

"Let's keep on reading for a while. Most probably, that will allow us to find some examples to explain why it is vital to understand fractal geometry."

"We read that fractal sets geometry is nothing but the mathematical formalism of chaos theory. The most important scientists in this field are none other than Poincaré and Lorenz. These two great scientists helped us understand natural laws through the prism of chaos theory. Chaotic systems are inherently

unpredictable as time passes since they are sensitive to their initial conditions. An important characteristic of chaotic systems is order without periodicity, which means that they present a 'disorderly' behavior. A chaotic system functions according to certain rules, but constant feedback, time delays and infinitesimal changes make it behave in a non-repeatable way. When chaotic data are displayed in the three dimensions of Euclidean space, patterns emerge, shapes which are called 'strange attractors'."

"I see, my boy. Hold on there. We need specialized books and long years of dedication on this topic. I should say though that human physiology is nothing but an endless fractal set. The human brain, the nervous system, even the morphology of our cells, are nothing but fractal sets with fractal dimensions. It is there where their functionality and uniqueness lie. I'll give you some examples so you can understand and I think that, after that, we'll bring this topic to a close, at least for the time being.

The examples are our respiratory tree, mentioned by Mandelbrot himself, which shows self-similarity; the arterial network in the human body has a fractal arrangement of 2.7, and lastly, the connection between antigone-antibody follows the principles of fractal sets."

"Let's take a break here, Grandpa. I need time to study and process all of that. I understood, at any rate, that the study and understanding of the geometry of natural objects as well as of human physiology, does not follow Euclidean geometry. It is true that Euclidean geometry is a tool for measuring objects in the macrocosm; it is an important tool for communication. But maybe that 'other' geometry might be the real one, in the sense of measuring the form of objects rather than their shapes. It seems to me it is closer to natural truth, but I bet there will be other ways of approaching this topic as well."

Picture 27: Friedrich Bernhard Riemann

Friedrich Bernhard Riemann (1826 –1866) was a German mathematician who made contributions to analysis, number theory, and differential geometry. In the field of real analysis, he is mostly known for the first rigorous formulation of the integral, the Riemann integral, and his work on Fourier series. Through his pioneering contributions to differential geometry, Bernhard Riemann laid the foundations of the mathematics of general relativity (https://en.wikipedia.org/wiki/Bernhard_Riemann).

"B. Riemann mentions in his book Uber die Hypothesen welche der Geometrie zugrunde liegen [117]*, which was his habilitation thesis, that natural forces are the ones that influence and also shape the geometry of space. Of course, today we know that the mathematization of nature, which began with Galileo and continued with Descartes and Newton, as well as the postulation of differential calculus and the emergence of a new kind of physics and the laws of physics, have influenced the evolution of natural sciences as a whole thus far. It is true that an understanding of geometrical space through Riemann geometry came years later, given that mathematical science preceded physics and physicists did not know Riemann geometry. There are also cases where physics comes first and mathematics last, such as the case of the 'unsolved nature' of spins, due to the inability of present-day mathematics to mathematize spinning phenomenon. But let's leave this complex yet extremely interesting matter aside."*

"I see you agree. Let's not dive deeper. In any case, thanks for clearing up the difference between the shape and the form of an object."

"*Look at a statue, or think of a statue,"* Grandpa said, not wanting to close the conversation. *"Tell me what you see in it. What provokes positive feelings in you? Is it its shape in the Euclidean sense? It is rather hard to explain. Or is it its form, its curves, the movement of the hands and the twist in the hair? You see, classical sculpture, with its beauty and virtue can only be described by form, not shape."*

"You are right, Grandpa. I hadn't thought about it this way. You're right."

"We could say that the architecture of biostructures is nature's primordial attempt to create a 'functional and aesthetically pleasing' culture which is presented to us at a macroscopic level. Biomaterials and their organization, based on natural laws, create architectural shapes and networks of information transmission, contributing to their macroscopic thermodynamic stability. On the other hand, though, the sculpture of biostructures in nature might spark biochemical paths and cascades of bioreactions, due to their morphologically unique, initial properties, which may lead to the macroscopic depiction of results which are called human feelings. In this way, its morphological depiction of the sense of beauty - might influence aesthetics and culture, society, and the human race."

[117] B. Riemann B, 'Über die Hypothesen, welche der Geometrie zu Grunde liegen', Berlin: Springer, 2013.

THE MORPHOLOGY OF SELF-ASSEMBLIES

"The morphological characteristics of self-assemblies and their curvature properties could be associated with their functionality and they also prevail over other morphological structures. As Bowick and Sknepnek proposed, flat surfaces, like facets, might be easier to functionalize than curved ones, when the aim is to facilitate biochemical reactions between drug delivery nanosystems and their targets. More recently there has been a study on the importance of the synaptic vesicle membrane phase state on the binding of α-synuclein presynaptic protein. This indicated that a negatively charged membrane in phase transition range or in liquid-crystalline state promotes that kind of binding and thus, boosts its own stability in the presynaptic gap. This could be relevant to neurodegenerative diseases, like Parkinson's, where it is suspected that the aggregation of α-synuclein has a role to play. Finally, protein insertion on polymer-lipid membranes was found to depend on the molar ratio of the two biomaterials, where control of topology and phase separation leads to selective protein distribution and provides specific spatial functionality [118].

These 'metastable phases' are predominant features and should be carefully evaluated. To control the structure morphology, one must take them into consideration first. Spontaneous self-assembly mechanisms also occur. They appear due to the nature of biomolecules or due to the mixing cooperativity of biomolecules that are different in nature. The concentration of each biomolecule contributes to its morphology, while the higher the number of biomolecules involved in the biosystem, the higher the non-isotropic effect, the higher the lyotropism and, consequently, the higher the probability of their survival. The self-assembly of biomaterials which differ both in their nature and in their physicochemical properties leads to the creation of novel shapes, meaning novel Euclidean structures like tubes, hexagonal structures, bilayers, worms etc., as a result of intermixture and the intramembrane asymmetric and non-isotropic distribution of amphiphiles, thereby producing high levels of spontaneous curvature. The driving force for the production of novel curvatures, and consequently novel structures and morphologies, is the physicochemical and structural properties of individuals, as well as the energetic cost involved in the production of the final structure.

In this way, tubular vesicular morphologies, for example, stem from the non-ideal mixing of amphiphiles, such as phospholipids and amphiphilic block copolymers, or corresponding biological molecules, because of their different

[118] M. J. Bowick, R. Sknepnek, *Soft Matter* 2013, 9, 8088.K. Pirc, N. P. Ulrih, *Biochim. Biophys. Acta* 2015, 1848, 2002; J. Kowal, D. Wu, V. Mikhalevich, C. G. Palivan, W. Meier, *Langmuir*, 2015, 31, 4868.

elastic properties, bending rigidities etc., thereby causing self-assembly to deviate from spherical vesicles. This is an amazing explanation of how natural laws work and how they influence not only structure (meaning Euclidean geometry and shape), but also self-assembly itself (meaning morphology, 'metastable phases', 'rafts' and, consequently, biological interactions and the survival of biological objects).

It is good to point out here that biological objects can be responsive to external stimuli, such as changes of the physiochemical variables of their environment (such as pH, temperature, electric or magnetic fields, etc.), and thus they act accordingly in order to survive. This stimuli responsiveness of biological objects is, in our point of view, the cryptic and silence functionality, because it is expressed when an external stimulus appears and influences their 'everyday' behavior. This could be called 'smartness'. It would be impressive to develop artificial self-assemblies for research purposes with surface properties able to 'sniff out' environmental, physicochemical and thermodynamic changes and control their functions accordingly.

Are you familiar with the term 'smart'? Is it a term which refers solely to human beings or can it also be used for materials?" Grandpa asked.

"Yes, Grandpa, I've heard that the term 'smart' used to describe non-living objects… smartphones for example. I know it's used to describe the behavior of a self-assembled biosystem. I've also read some papers on this subject and my opinion is that a 'smart' biological object is one that has incorporated the primordial physicochemical properties of its component parts but also has 'memories' from the past. These properties characterize the biological object from a scaling biological point of view. I suppose that all biological objects can be considered to be 'smart'. The difference between them is determined by the 'smartness' of the bio-object, biosystem or bionetwork. The differences arise from one biophysical and thermodynamical priority being promoted over another, depending on the requirements of the 'biological market'. The shape, morphological characteristics, metastable phases, stability as well as the biological effectiveness of each biological structure are considered to be the total added value they bring to the structure, which accounts for its survival and for its contribution to the evolutionary process of life."

'Smart' biosystems are defined as those with the ability to use conformational polymorphism or, put more simply, they can use how their biomolecules are organized and ordered as the 'smart domain' or as a bionavigator of their biostructure. Yet, keep in mind here the liquid crystalline phase of matter and the metastable phases. This is very ambitious, because the biosystem tries to

translate its 'smartness' into a function. It's obvious that objects and biosystems have no logic or decision-making of their own. So, how do they become 'smart'?

According to Grainger et al., "thermodynamic criteria governing phase transitions are the mechanistic basis for their 'smartness'. There are no logic algorithms on board, no decision–making or rationalizing framework and no intellectual capacities" [119].

We have to take into consideration that the biomolecules out of which smart biosystems are composed have some important properties, such as the ability to transit from one conformation-organizational level to another, due to the origin of their building blocks (such as phospholipids, cholesterol, lipids, etc.). This can be combined with mobility and consequently with the ordering process of the components in the biological membranes. This phenomenon is characterized as either lateral diffusion, flip-flop mobility, intra-chain motion or fast axial rotation.

These modes of action of the components of an artificial lipid bilayer, such as a phospholipidic bilayer, are – due to the continuous rearrangement – based on biophysical and thermodynamic arguments. The science of interfacial phenomena has contributed to the scientific explanation of such physicochemical phenomena, behavior and functionality. This functionality is directly linked to the liquid crystalline state. Also, the phase transitions of membranes –meaning the metastable phases– contribute to the positive energy balance (energy accepted *vs* energy offered) and are also linked to their functionality.

THE STABILITY OF SELF-ASSEMBLIES

"Before we move on to explore the stability of the biological objects and its relation to their morphology, we have to clarify what the term 'stability' actually means. In our case, we are interested in learning about biological stability and in describing how it could be achieved by biosystems."

"It's very interesting to be discussing this and to look for more information about biological stability. I'd be glad to learn more on this important topic."

"As far as I know, a 'biologically stable' object denotes a functional biological object and a functional biosystem. This is a key point because, if there is no effective functionality in the biosystem, there is no reason for it to exist according to the laws of thermodynamics, especially given the entropic payload and the evolutionary process demanded by existing natural laws. I think that this is directly linked to 'metastable phases', lyotropism and the physicochemical

[119] D. Grainger *Int. J. of Pharmaceutics* 454, 521-524, 2013.

properties of each biomolecule and of biosystems. As far as I know, it's clear that a thermodynamically stable biosystem is a biosystem in a state of equilibrium at the macroscopic level, the level that we can observe and that we can describe.

But this is not the truth. The number of micro-biosystems out of which a macro-biosystem is composed are all invisible to us and are in a non-equilibrium state. Classical thermodynamics cannot be so effective, and its application is not absolute. In reality, the biosystem accepts 'in-house effects' from the number of micro-biosystems that comprise it, i.e., the thermodynamic effect which affects the macro-bioproperties of the biosystem. Consequently, the stability of the macro-biosystem, meaning its biological functionality, is related to demands that influence the stability of the micro-biosystems from which it is composed. Come here, my boy, let's have a look at the relevant literature."

Biosystems are thermodynamically unstable. Under specific conditions, they have a tendency to form aggregates due to their high surface energy. It's important to mention DLVO (**D**erjaguin, **L**andau, **V**erwey, **O**verbeek) theory, which is directly linked to the stability of dispersed colloidal systems. The stability of self-assemblies in a changing environment is of great importance because their physicochemical characteristics, which were built up during the process of adaptation and evolution over billions of years, contribute to the creation of natural laws, according to biophysics and thermodynamics. A biosystem's stability is tied into entropy, which is considered the payroll by nature to the biosystem and corresponds to its survival process.

However, the term 'stability' corresponds to the struggle of a biosystem to retain its functionality, to keep on reproducing and even replicating itself. In order to become functional, biomaterials and consequently biosystems should be stable and responsive to stimuli. A biosystem's responsiveness to stimuli such as pH, temperature, ionic strength etc. is a vital factor in its functionality. The principles that govern such behavior are natural laws which, in the very beginning of the process of life, were confronted by a huge number of invisible forces.

The main aspects that are mentioned below could help us understand the term stability from a scientific point of view.

Natural objects are thermodynamically unstable. Under specific conditions, they have a tendency to form aggregates (i.e., more thermodynamically stable biostructures from the natural point of view, yet more unstable biostructures as far as the survival process is concerned) and matrix organizations, because of their high surface energy. The forces that appear in a living dispersion biosystem are: *van der Waals* force; attractive forces; electrostatic forces (repulsive forces); Born forces, mostly low range (repulsive forces); Steric forces (repulsive forces), due

to absorbed molecules (especially macromolecules) on the particles surface; and Solvation-Hydration forces.

Derjaguin **L**andau **V**erwey **O**verbeek, (DLVO) theory

The stability of a biosystem is related to the density of the dispersed particles (ρ_1) and the dispersion media (ρ_2). It is also related to the particle size (α) and to viscosity (n). Stoke's Law describes the rate of aggregation of a sphere in a liquid medium, with viscosity n.

$$v = \frac{2g\alpha^2(\rho_1 - \rho_2)}{9n}$$

α: represents the radius of the sphere, ρ_1: the density of the sphere, ρ_2: the density of the medium and g: the gravity standard.

In 1941, Derjaguin and Landau presented a theory which contributed to and explained the physical stability of a dispersion system. Biological systems are considered to be colloidal dispersed systems of liquid crystals with thermodynamic instability. This theory is well-established due to strong but short-range *van der Waals* attractive (A) forces. Verwey and Overbeek, who worked separately, managed to arrive at the same conclusion. The theory regarding the stability of colloidal dispersed systems was named after all of them and is commonly referred to as DLVO theory (Derjaguin-Landau-Verwey-Overbeek). Classic DLVO theory deals with the forces between charged objects which are a specific distance apart. These forces have been described as attractive (A) and repulsive (R) electrostatic interactions. The attractive forces correspond to the total *van der Waals* forces, while the repulsive ones correspond to electrostatic interactions. After this attractive theory was outlined, it was realized that some important physicochemical features were not explained by classical DLVO theory. Therefore, it became vital to extend this theory, and as a consequence extended DLVO theory came to deal with the hydration forces between the dispersed objects. Depending on the shape of the particles (based on their Euclidean geometry and the relevant calculations), the attractive potential (V_A) ($_A$: Attractive) is calculated using the equation below:

$$V_A = -\frac{Ar}{12x}$$

(V_A: *van der Waals* attracting interactions). The equation above corresponds to objects spherical in shape: A: Hamaker constant, r: radius of the sphere and x: distance between spheres.

$$\boldsymbol{A = \pi^2 C \rho_1 \rho_2}$$

Hamaker constant; π: 3.14; ρ_1 and ρ_2 are the number densities of the two interacting kinds of particles, and *C* is the London coefficient in the particle – particle pair interaction.

$$V_A = -\frac{A}{12\pi x^2}$$

(V_A: *van der Waals* attracting interactions). The equation above corresponds to flat-shaped objects: A: Hamaker constant, r: radius of the sphere, x: distance between spheres and π=3.14.

Repulsive forces (V_R) ($_R$: Repulsive) arise in biodispersed systems in which the objects are charged (ζ-potential). Physicochemical variables, such as ionic strength (I), the pH of the dispersed medium and its dielectric properties, affect the total repulsive electrostatic forces and they also affect the strength of those forces. It is well documented that repulsive electrostatic forces prevent the aggregation process, and this is given by the equation below:

$$V_R = \frac{8K_B^2 T^2 \varepsilon r \alpha}{e^2 z^2} e^{-\kappa x} \left[\frac{e^{\frac{ze\psi}{zK_B T}} - 1}{e^{\frac{ze\psi}{zK_B T}} + 1} \right]^2$$

This equation corresponds to spheres, where κ: Debye constant, r: radius of the sphere, K_B: Boltzmann's constant, T: absolute temperature, ε: electric constant, ψ: surface potential, z: the chemical potential of the counterion, α: chemical constant, n: viscosity in electrolyte solution and x: distance between spheres[120].

$$V_R = \frac{64 n K_B T}{\kappa} e^{-\kappa x}$$

[120] C. Demetzos, "*Pharmaceutical Nanotechnology. Fundamentals and Practical Applications",* Springer Nature, 2016.

Particles with a lamellar shape follow the equation above, in which: κ: Debye constant, T: absolute temperature, K_B: Boltzmann's constant, n: viscosity in electrolyte solution and x: distance between lamellar-shaped objects.

To calculate the total (T: total) potential of the biosystem, the equation below can be used:

$$V_T = V_A + V_R$$

According to this theory, two cases emerge regarding the kind of forces between biosystems in a dispersed medium, meaning the biological 'soup' in which bio-objects can be found.

- $V_A > V_R$: attractive forces are predominant in biosystems, causing the death of the system by increasing its entropy.

All these approaches are entropic-favorable and the survival of the system is considered limited. The adaptation process and the evolution of the biosystem is not obvious and the energetic penalty is more favorable. However, death is an inevitable outcome due to thermodynamic instability.

At this point, we need to clarify the term 'thermodynamic instability'. A system is characterized as thermodynamically unstable from the human point of view when there is a favorable entropic capacity. This is favorable for nature, which prefers the thermodynamic instability of systems, meaning high entropic capacity, and consequently death. On the other hand, the system is characterized as thermodynamically stable from the human point of view when the entropic capacity is unfavorable. This is unfavorable for nature, which does not prefer the thermodynamic stability of systems, which means low entropic capacity, and consequently survival.

- $V_R > V_A$: repulsive forces are predominant. The bio-objects and biosystems are far from each other, resulting in thermodynamical stability and therefore, biostability of the bionetwork.

As far as the observation of effects which can't be explained by classical DLVO theory is concerned, scientific efforts have contributed to the discovery and the measurement of forces that arise within the organization of a bio-colloidal dispersed system. Hydration forces and hydrophobic interactions are essential for

the stability of bio-colloidal systems. Another disadvantage of the DLVO theory is its inability to describe the behavior of biosystems whose surface is not charged. Hydration forces act at a distance of 1nm and the majority of biosystems in nature consist of water. It is known that more than 70% of the human body is comprised of water. So, it is obvious that hydration forces which are relevant to the stability, and consequently the functionality, of biosystems, are considered vital. We already mentioned that these interactive energies can be classified into two different categories: attractive and repulsive ones. However, in the case of hydration forces, there are also two categories of energy:

- repulsive hydration energy (V_{Hyd}^{R}). It is generally strong but short-range repulsive energy when the surface of the bio-object is hydrophilic. Hydration energy in this case is necessary for the water molecules to move across these hydrophilic surfaces. The force gradually weakens depending on the interfacial distance, taking into consideration a small depreciation constant of 1.7-2.5A.
- attractive hydration energy (V_{hyd}^{A}). Hydration forces cause attraction due to water realignment on the surface of the biosystems. At this point, we should mention that the hydrophobic properties of a surface with negative charge, increase when multivalent cations are added to the biodispersed system and attach to the biosystem surface. As the biosystem's surface consists of hydrophobic and hydrophilic surfaces, the total hydration interaction energy should be calculated. The equation below represents the total hydration potential:

  (*Hyd*=hydration)

$$V_{Hyd} = V_{Hyd}^{R} + V_{Hyd}^{A}$$

However, the total potential capacity of a bio-dispersed system like a human being, is given by the equation below [121]:

$$V_T = V_A + V_R + V_{Hyd}$$

[121] D. Attwood, and A.T.Florence. "*Physical Pharmacy"*, Published by Pharmaceutical Press, Fast Track series, Royal Pharmaceutical Society, Great Britain, 2012.

So ...

I felt as if Grandpa was looking at me. He said:

"Is everything alright?"

"Yes, absolutely. I've now got a general idea about stability and the forces that are involved. This has been a great lesson for me."

At that point Grandpa said, *"it's very important to mention the vital role water plays in our life, due to its ability to contribute to the stability of biomolecules and biosystems. As we mentioned before, the hydration forces involved in the stability process are extremely important for the functionality of biomolecules and biosystems. Also, as you know, when it comes to quantity, water is the number one biomaterial in our body, accounting for up to 70% of it, and it's also the number one material on Earth as well. So, its role in the evolution and maintenance of life is of paramount importance.*

It's also worth mentioning that the most important issue regarding water uptake by living organisms is the rate of uptake, not the amount of water consumed. The reason is that the morphological constraints of cells – meaning their outer surface properties – the metastable phases and their composition are crucial parameters for the rate of water uptake and affect the hydration process, which should be efficient for the living organism in order for it to achieve stability.

There is a strong link between water, biophysics and bio-thermodynamics as key components of the functionality and stability of biosystems.[122] *Because biopolymers are of great importance in biological phenomena, they owe their stereochemical stability to the hydrophilic domain of biopolymer which is hydrated. The aggregation process of biopolymers is prevented when water molecules are eliminated, which in turn is responsible for the enthalpic phenomenon; consequently, the biosystem gains energy and becomes stable. The hydration forces are important and contribute to the sustainability of biosystems, promoting their functionality and evolution. It is well known that living organisms, and humans in particular, are composed of water to a very high degree, and that the hydration forces between bioself-assemblies are important for their survival.*[123]

Water is the most abundant biomolecule in living organisms. The human body is approximately 70% water and the average percentage of water in cells is between 55% and 90%. In low temperatures, water forms ice, which has a crystalline form. The structure of ice is a consequence of the creation of hydrogen

[122] T. Heimburg, "*Thermal Biophysics of Membranes"*, 2007, Wiley-VHC.

[123] Y. Perrie and T. Rades in "*Pharmaceutics-Drug delivery and Targeting"*, published by the Royal Pharmaceutical Society of Great Britain, 2nd ed., 2012.

bonds, which basically are interactions that prevail due to the bipolar nature of water. Whereas ice has a perfect hydrogonic matrix, water in the form of steam is a gas and does not form hydrogen bonds. The in-between state is water in liquid form."

PART V

SOCIETY AND SCIENCE

SUMMING UP

"*Let's have a break so we can relax and discuss the main ideas we've seen so far*", Grandpa said.

"Yes, I'd love to. How about I summarize the main terms and concepts I found most interesting?"

"*Sure, we can do that*."

Much time passed, full of thoughts and glimpsing into the Mirror. Light took the shape of an image, which was blurred, with quite familiar faces forming on its surface; faces which I could nonetheless not discern. There were times I even saw fairy tales in picture form, like I was seeing them through old view-masters. The truth is I had learnt a lot; but not everything.

Everything! If Grandpa could hear me say that, he'd probably have called me arrogant and ungrateful. "*No, you shouldn't learn it all*", he'd say. "*How could you go on, if you knew everything? You've just read or heard a few opinions and some knowledge*."

That's what he'd say. In any case, I couldn't complain.

The Mirror and Grandpa were looking at me, as if waiting for me to raise some prism through which I'd make white light disperse into different colours, and then pick some of them and draw a picture, or even numerous pictures depicting the world.

"I taught you so much. Now put together the most important colours to create an image!" the Mirror pleaded while somewhere in the library Grandpa, sitting again on his armchair, was watching.

"Yes, I'll start right now. My knowledge, everything that I've learnt, is like a prism that can be used to scatter the light that you're asking me about. Using that prism, I'll gather the most important data to present to you, and then... after that, I'll turn it into vivid colours for the Mirror. I'll try to see images in the Mirror, perhaps even my own reflection as well. I think I'll definitely manage to do that."

"Alright", Grandpa said. "The prism to disperse your data is the knowledge you gained from our long conversation, and also from your experiences. That's a good sign for the future."

"Complex and challenging concepts which create complex conceptual networks," I thought to myself.

Each one of us tries to have our own reading of things and to define ourselves. To define how we behave, first as our own selves and then as social beings. Later on, we learn to follow our personal principles and values. If these coincide with already existing principles and values, then personal 'order' and balance is taken for granted. If not, this is where personal struggle and conflicts start as well as your attempt along with other people to contribute to a 'statistically prevalent' result, which will give an impetus to or will change the already existing condition or thought so that it takes on some different quality; that will then be preserved until the next 'statistically prevalent' changes at a personal and social level. This is something I've come to understand very well.

I also understand that personal struggle, meaning the struggle and attempt within my own microcosm, is not a lost cause, even though it might not be visible at a social/macroscopic level. But it is certain that, the completer and more proven it is, the more the potential it has and the more it will influence the 'statistically prevalent' result over the course of time. It is a result I might not even be able to experience myself, due to the biological limits imposed by my short time on Earth. However, my attempt will have been recorded as a 'transcription' in the evolutionary code, even if it is just a small one.

Thoughts like those ran through my head as I tried to gather together the basic ideas explored during my conversation with Grandpa and from the 'game' with the Mirror, and formulate some sort of preliminary conclusions.

It was the Mirror that Grandpa used to place in front of me. Every time he'd pick a different angle and light, and ask me in his own way, so many times to get into a position that would make the image I saw clearer. I learned to play with the light and the dispersion of white light, which was my guide to analytical and compositional thinking. White light was like a veil before my eyes, containing all the information combined, and I was being called upon to select the right 'dispersion prisms' so that I could more clearly make out the images.

So, I kept sitting in the armchair and looking at the garden, lost in thought. It was still winter, or perhaps the age of thought and my time as a hermit was coming to an end. I thought that we'd studied the relevant literature enough and that some preliminary conclusions needed to be drawn. During the conversation with Grandpa we had not had any disagreements, so why disagree now?

But even so, disagreement is a door one walks through on the journey to creativity. Any kind of disagreement, I thought, should be interpreted, backed up and proven. This is important, a non-aggressive way of doing things, not like the 'eristic' form of argumentation the Sophists developed in classical Greece, turning dialectics into an art of conversing using astuteness. For the Sophists, dialectics as a tool was nothing more than rhetoric and argumentation; they were not

interested in the Socratic method which is designed to draw out the truth through a series of questions.

I believe my conversation with Grandpa was honest, and was aimed at finding the truth. But what truth?

Our goal was to study some of the natural laws which eminent scientist have painstakingly managed to uncover over the years. I wonder whether we came close to the truth by examining all of these natural laws or whether our discussion was rhetorical or even eristic. Actually, I think there was no disagreement.

We chose to discuss about natural laws and natural phenomena both in the microcosm and macrocosm and we basically confirmed that the processes of life take place in a dynamic and 'arbitrary' way. It does not follow the logic of phenomena in the macrocosm, which are studied in an equilibrium state, and constitute the predominant processes in the evolution of life.

This is how we arrived at today. When we got here and what today means, I do not know. I don't know if every new day that breaks, every new moment that passes, is the same or different. And this is a silly statement! Of course, they are different.

The question is where does the difference lie and how does it manifest? How much more 'negative entropy' was provided in order to enable phenomena to assemble in the right way moments before, or the previous day, leading them to greater organization and functionality? Each year we look back at the previous one trying to predict how the events of the previous year will be the driving force for new qualitative leaps forward and success, and we also do the same thing when it comes to the personal and the social level.

I understand that the driving force for future personal, family and social success are attempts and contributions each individual makes to influence the whole. And it's obvious that this single contribution that is -and should be- made in our microcosm influences at some different point in time the degree of adaptation and the evolution of the macrocosm, the laws and conditions... It may not be visible over the course of a limited human lifespan, as history teaches us. But over a longer span of time, the results of course will be visible.

I got carried away by my thoughts. I should probably have a look at the key words. It's almost time to meet Grandpa. There he is, full of surprises, coming out of his library. Or is he coming from behind it? Where exactly is he coming from? I must be feeling dizzy from all that studying...

"*Come closer*", he said, and his warm hand touched mine again and held it tight. '*We will not lose touch. We have powerful tools to keep us here. We will try to become the microcosm of a society that suffers without knowing it. I have a library; you have a treasure. And you also have the responsibility of making good*

use of it, of passing on what you know when you too become a grandfather. You must put mechanisms in place to produce 'negative entropy'. These will supply you with the organization and order you need to survive in the macrocosm.

But be careful! Never forget your own personal microcosm! It's 'deep down' there that the great events which will make you better and more useful to society will take place. You will always need to supply your microcosm with questions and queries, to think and promote your 'dialectical oppositions', the ones that nature constantly offers to you. These are of great importance. You shouldn't ignore them, but rather recognize them and be present at all stages of evolution. You should enjoy any developments in the macrocosm, when they are the result of long-term efforts in the microcosm and are scientifically revealed to you. I think you understand this, don't you?"

"How important is it to be a grandfather?", I asked him.

"*It's not age that matters, nor the respect others have towards you, but the respect you have towards the path you followed all those years... How many years, I wonder? Knowledge and effort know no age; they can't be measured in the traditional way we measure time, but only through the soul and the wrinkles on your face. These might be the only 'metastable phases' visible to other people. How much do you respect your own efforts? Do you respect them enough to consider them worthy and to take responsibility for passing on what you have learned to the younger generation? If so, you're an important 'grandpa' figure'. I've had important grandpas myself in my own life*."

"I'm ready, Grandpa. We can start writing down the basic concepts, words or key sentences revealed during our conversation. To be fair, I think that I'll need to study some concepts in more depth, by consulting more references, so as to understand them fully. It's only in that way that I'll be able to incorporate them to the dispersion and refraction of white light in the game with the Mirror, and thus be able to create visible images.

So, I believe that the self-assembly process of biomaterials, of biosystems and of all biological objects regardless of their dimension, is something of great importance. It's the one that promotes all biological morphologies that are involved in the evolutionary process of living organisms. Also, terms such as 'metastable phases' or 'rafts' and 'metastability' were the key issue that we kept in mind; that were a priority. Moreover, the liquid crystalline state of matter, lyotropism, and lyotropic liquid crystals, also kept us busy for a long time in our conversation.

I also think that entropy is of major importance too because it characterizes all the activities in the microcosm and the macrocosm and it affects all the functions in living organisms. It's obvious that thermodynamics and the

thermodynamics of small systems in particular are considered to be the top level of understanding when it comes to the functionality of living organisms.

I should note that terms such as ‘cryptic code’ or information, biophysical metagraphic code and silence functionality, as well as biophysical disease factor were major issues we discussed and are important in the biophysical profile of biosystems and living organisms. All the above scientific terms and variables that we kept in mind are directly related to the behaviour of cell membranes, resulting in the functionality and survival of biosystems. In order to efficiently study the functionality and behaviour of the membranes of living cells, we found that artificial mixed/chimeric technological platforms could be designed and developed – to investigate biological phenomena.”

“Excellent”, Grandpa exclaimed. *“Please, go on!”*

“Another key issue in our conversation was the behaviour of macroscopic systems and how it influences micro-biosystems, when it comes to the thermodynamic understanding of small systems as well as statistical physics. Conformational polymorphism, as well as structural polymorphism of biosystems and of their building blocks, such as elementary biomolecules, provide innovative biological platforms with biophysical and thermodynamic benefits and were key points we discussed. To this list of exciting topics, I should also add two more: shape and morphology that incorporate the geometric characteristics of biological objects, terms that help us to perceive our world within the Euclidean space, but studying it in a fractal dimension.

Grandpa, do you think that the evolutionary process in nature and creation is a ‘bio-project’ that is based on the theory of dialectics, as pointed out earlier? Is it reasonable to assume that conflicts between biomolecules, the competition for self-assembly which exists between a huge number of bio-morphologies, into higher self-organised structures and into the information that the biosystems carry in their biophysical and thermodynamical fingerprint are the driving force pushing evolution towards more qualitative bio-assemblies with superior functions compared to the ones that already exist?

Is the ‘memory’ that is endogenously present in biomolecules and is constantly transcribed as a 'fingerprint' through the evolutionary process key to the quality characteristics and functionality of organisms?”

“*Well done, my boy. I can see you moved to a deeper level of questions and thought. I believe that. Let me go back to the concept of ‘negentropy’, which promotes the evolution process through current and functional ‘metastable phases’ which have trapped it endogenously as a requirement for new, more demanding biological situations. These ‘metastable phases’ and ‘rafts’ include ‘negation’ internally, because of the evolutionary process which demands a new*

form of bio-behaviour with new properties. Here, of course, young man, I recognize the concepts we have discussed, such as the code for the creation of natural laws, which we will have to reveal –if this ever happens– in order to participate in the great and daily revolution of evolution and adaptation of biological systems to constantly superior quality functions.

Of course, you know the philosopher Heraclitus and his saying, 'everything flows' (Πάντα χωρεῖ καὶ οὐδὲν μένει [124]*). This unique saying of the philosopher leaves no room for hope for a static expression of natural facts and laws. The* only thing we can hope for is nothing more than the momentary capturing of facts. Yet, by the time we understand them or design models for understanding them, they are already obsolete.

Key Point

(…) information is linked to the organization of a biosystem, while entropy to the level of organization of the biosystem. The balance between these two pillars is crucial in order for the system to survive and live or die. (…)
Our attempts are not in vain. They contribute to the code of the evolutionary process as 'transcriptions'.

"And where does the uniqueness of biosystems, of human beings stem from, Grandpa?"

"From the fact that nature needs complexity and multiplicity. This is valid not only in the microcosm where, as we said, the big conflicts and the changes of natural laws –or, to phrase it better– the evolution and adaptation of the physiochemical and thermodynamical features of the biosystems, self-assembly and their organization in functional biosystems take place. Nature demands multiplicity, complexity, diversity/biodiversity in the macrocosm as well, in order to be able to choose which biosystems are stable at the macroscopic level; perhaps it can also proceed to improvements or changes."

"And how does that take place?"

"*Oh, I think you have forgotten the concept of polymorphism and lyotropism*."

"What are the differences between the two?"

"*Look, polymorphism in science, and especially in chemistry, means exactly what the world implies: many forms. Depending on the changes in the*

[124] Heraclitus, Fragmentum 6.

surrounding environment of a physicochemical or biological system, biosystems and their elements, i.e., biomolecules, take on different forms in space. This is how stereoisomers, like the ones you have already studied in chemistry, are formed, as well as the polymorphic structures or polymorphisms, which are developed through the process of re-self-assembly of organized biosystems. In chemistry, when it comes to atoms this phenomenon of polymorphism is called 'allotropy'. Take the example of carbon, which has several states of allotropy, such as coal, graphite, diamond..."

"Did you say 'diamond'? Yes, that does ring a bell. I'm only realizing this now. This means that the diamond is only an allotropic form of what we call coal."

"*As a matter of fact, yes*."

"And why is it so expensive? Because it doesn't smear?"

"*Well, no. I imagine that one explanation could be that, in order for the atoms of carbon to have a specific structural organization and maintain it in a stable way so as to form a diamond, nature required a high energy cost. This resulted in the minimum entropic income of the system. It's also important to know that if a diamond is cut into small, very small pieces, no matter how small, it will maintain its natural, optical and mechanical properties in each of these pieces, i.e., it will retain its hardness. But in any case, it's also expensive because we may be paying for its qualitative features and for the aesthetics of the mode of organization that nature managed to achieve through such an energy-costly decision*"

Key Point

(…) The lyotropic liquid crystalline state of a biosystem in nature incorporates a 'cryptic code' – in other words, an information toolkit – that influences how it is organized. Lyotropism relates to the evolutionary process of nature. The question of how existing natural laws apply to biosystems, depending on the lyotropic changes of living matter, is a continuing debate (…)

"So, on the one hand polymorphism and allotropy are scientific concepts, but they are simply words used to describe primordial natural processes, at a molecular and at an atomic respectively."

"*Exactly, my boy*."

“And what about lyotropism, Grandpa? Is this a concept relevant to the two previous ones? I guess so! Just wait, Grandpa. I think that I can explain it, given it’s an ancient Greek word.

We all know that the Greek language constitutes the basis of scientific terminology, because it does not describe an object based on its visible characteristics, but rather it describes concepts. Based on the concept, you can form an image not only of a single object, but of a number of objects and describe them. This is an important and unique feature. The Greek language and civilization created the scientific tools for the spread of international intellectual though.

Why are you smiling, Grandpa? Oh, I know. You’re wondering what the term ‘ancient’ Greek word means, or how ‘ancient’ the time span I’m talking about actually is. What does ‘3000 years ago’ mean time-wise, as you would say? It's a drop in the ocean, just a few years before today.

So, lyotropism. Let’s see. It is a port-manteau word that derives from the Ancient Greek verb λύω (lúō, ’to ‘loosen, to dissolve’) + the adjective τροπικός (tropikós, ‘of or pertaining to a turn or change; or the solstice; or a trope or figure; tropic; tropical; etc.’). The latter stems from τροπή (tropḗ,’turn; solstice; trope’)’. So, a free translation would be the transition from one morphology to another, upon heating or cooling or generally disrupting the energetic balance of a self-assembled biosystem.”

“*Very good, my boy. You’ve obviously managed to clarify the concepts in your own head, and you explain them very well. But why do you believe they will be useful to you? What would you like to gain by having this knowledge? Do you understand that if you’re interested in these subjects –and it’s a good, a very good thing that you are– you should also be careful and make sure you don’t start talking about them more than necessary? It would make you a social pariah. You could be talking to girls or to your friend all the while thinking when you’ll get the chance to change the subject to lyotropism and entropic change. You should also think about the emotional denial that some event or a person could bring up within you: you could translate it as very positive, given the anticipated qualitative leap your theoretical formation will dictate. On the other hand, the entropic process in its ‘negative’ expression may help you achieve new, qualitatively better human relationships, or upgrade your relationships to a qualitatively higher level. What do you think*?”

“Grandpa, I know what you mean. It has been bothering me, too. I believe that I’ll manage not to let my thoughts and my microcosm take over. I have to be present in the macrocosm of my everyday life as well.”

Key Point

Nature needs complexity not only in microcosm (…) but in the macrocosm as well, in order to choose which biosystems are stable, and to make choices so as to be lead to new, more stable and functional qualities…

Winter is still at our door. Perhaps the coming spring will lead us to more optimistic thoughts; the reality of our macrocosm is for me what purges away all my concerns. I need to fight for a day-to-day life where I have a sense of responsibility towards other people. I'll keep my personal concerns and effort to myself, 'deep down'. This is how it must be. Living the life of a hermit isn't something that can be done in public; it's something humble and personal. The concepts in the microcosm, the world 'deep down', don't bear the same importance and value as those in the macrocosm, the world 'up there'. For that very reason, one needs to pay attention.

"What about feelings, Grandpa? Don't they form a part of the *lyotropism* of biosystems, the 'metastable phases', or even the hippocampus in the brain, from what I recall from Human Physiology which I studied when I was younger? Does it mean that I should always aim at conflict in order to achieve qualitative leaps that will change the quality of my relationships? Is that what I should always be after? Could it be that in doing so I'll be missing the bliss of ordinary life where 'ignorance' of such important knowledge would allow me to enjoy myself?"

"*No, not at all. This is not what I'm talking about. That's not the case. You need to have self-control; to find a balance; to define in your own way your own presence in an ever-changing surrounding environment; to choose what you want to do. You have intellect; you have opinions; you strive to gain knowledge. You're a free man. You have free will and you can direct your own personal and social developments by silently working inside your own microcosm. You shouldn't always wait for direct and visible results. You must bear in mind that inside you there is a seed which allows for eternal survival and your own personal contribution to evolution, and you must struggle to ensure it survives. This is what will throw you in a constant flurry of pursuits, of concerns, questions and maybe... why not, even what many people strive for: happiness. Look at monks. All over the world, they are shut away in hermit cells, isolated from the world. Do they feel happy? Yes, by all means. They have more feelings than most of us. Perhaps they experience truth in their own way; their own choices. It's a form of enlightenment they themselves experience and transmit to society, by being absent from it. Their*

microcosm has the power to transmit the transitions of events to the macrocosm. Take a look at the evolution of religions. In all of time, who has managed in a single human lifespan to see –or even imagine– the changes and evolutions that have taken place? But those changes did in fact take place: we experience them, we study them, we live with them, they constitute our everyday life and they influence us. They influence entire societies all around the world. Love, Eros (έρως, έρωτας), emotions. These are great concepts, which cannot be grasped solely through lyotropism and the polymorphism of cell membranes. You also need philosophy, transcendental thinking, the use of philosophical tools... But we'll have a chance to talk about those things later."

"Let's make some coffee, Grandpa. I'm tired of studying and having my mind filled with concerns. I'll let positive entropy overtake me. Let me age while enjoying a cup of warm coffee. Would you like some?"

I heard a discreet knock on the library door, as if to say "May I come in?". The Earth appeared in front of me once again, holding a warm cup of coffee and some pieces of fruit with a fork sticking out of one of them.

Why not two forks? I wondered. Could it be because, when in the library, Grandpa usually hides away when the Earth appears? He can't stand answers to queries that were never posed or responding to everyday questions, like 'Aren't you asleep yet? I saw the light on and made some coffee... I don't know what time it is, but it must be so late'. Late? How late? I wonder. In our everyday lives, time does matter, while in the world 'deep down' it most assuredly does not. What should I say to the Earth, while I find myself in some part of the time continuum where nature has opted for the real evolution of 'events' not to be counted?

"Let's go make some coffee together", Grandpa said.

I guess he hadn't noticed that we already had coffee and fruit on the desk or pretended not to notice.

"Ah, what's this?" he said finally. *"The 'Earth' stayed up late, making coffee, didn't she? Is this annoying you or making you happy, my boy? Is your nervous system functioning well? Or have you been suppressing it with all this reading?"*

"Would you like some sugar, Grandpa?"

"*No, no sugar for me, my boy. What was I talking about? Ah, right, so, what about your personal life? Are you having fun? Do you have friends? Let's talk for a while and have some coffee and fruit*."

"Yes, of course I've got friends. They will come visit today. I don't know what we will talk about, perhaps we'll go to the cinema. Will you stay here, Grandpa? Look, I'm not one for partying. It's not that I don't have friends, but I prefer to work alone until I find something in the books, or a line of inquiry that

has been bothering me clears itself up in my head. I used to think that I'd find the answers. In any case, after all of this time I've spent with you... Can you even tell me how long we've been talking together? So, during all this time I've spent talking with you, I've understood that I need to try to identify important lines of inquiry, thereby supplying the 'negative entropy' of my knowledge and constantly keeping myself in good shape, mentally speaking. This process has been going on for many years now, I can't specifically say when it started. Maybe even in my childhood, without me even realizing it."

"*What are you thinking about? I suspect that, apart from the strictly scientific topics we've discussed so far, you're also interested in social developments, in how they are created, what causes them and what their driving force is... Aren't I right*?"

"Yes, of course you are, Grandpa. Doesn't it make sense? I don't constantly live in a library or with a library and a Grandpa. I do also go out. I observe and experience the social and political developments taking place around me and they do make me think.

Often, I think that organised social events, for example, or big demonstrations, social upheavals, contain the answer, the result within them. There's a theory about a society without class differences, a society where everyone would be equal or enjoy the goods that are produced based on their participation in the production process. But should everyone really be equal? Does nature promote equality or homogeneity? Or does it promote complexity, differences, and the survival of organisms by virtue of how each one of them can absorb 'negative energy', produce information of higher quality, and participate in different levels of quality and of organisation of the materials or the systems, what you might call society or even the bio-society? At the level of the microcosm, nature gives all events equal odds and it's up to the potential and to the numerical prevalence of the individuals and of the groups, respectively, to make any given result visible macroscopically."

You know, Grandpa –I wanted to tell him–, I want to have control over my own thoughts, not to crystallize my thoughts and opinions. I'd rather identify the tools that will each time constitute the means for producing better lines of inquiry on a higher level, so that the previous lines of inquiry I explored look like answers by comparison, downgraded into simple questions and not considered lines of inquiry anymore.

"I'll stay right here, Grandpa. I don't know for how long, it doesn't matter. I'll study some books and tidy up some old and interesting ideas concerning the evolution of society; how it was viewed in the past by theorists of philosophy and sociology. I know that some of them couldn't cope with important queries they

posed for themselves, or the plot twists to which there were no answers and committed suicide. Just like Nikos Poulantzas did. Others fought back and left us their books as a legacy, like Cornelius Castoriadis with his *Imaginary Institution of Society*, to name just one."

I paused for a while, looked down and thought to myself. What am I talking about, what is happening in my mind! What is the light that contains all the truths we are struggling to understand? Where does it come from? How many have seen it? What if it's not hermitism but rather asceticism, that mental and corporeal endeavour that cleanses the soul and leads one to the true path of happiness, true happiness; which is something far removed from the constant pursuit of happiness we see in today's society.

"I should read all of these philosophers I've mentioned, Grandpa, and many more as well. Perhaps even philosophers I don't know of. Perhaps in that way I'll be able to better understand natural and social laws, and evolution based not only on biophysics and scientific data.

Nikos Poulantzas and Cornelius Castoriadis come to my mind like memories from my youth, back when I wondered whether there were contemporary Greek philosophers with a transcendental mindset ready to stand against the ideological manifestos that tantalized the thought and behaviour of the youth of the day. And the answer was yes, they did exist. And they weren't alone; there were others too: philosophers and protagonists of social evolution, pioneers in transcending well-known theoretical patterns, which though established in our consciousness are in fact now obsolete. These people tried to look through the prism of a society oriented towards humanism and justice and freedom of the human race. They worked in the microcosm, the world 'deep down' and revealed dialectic conflicts as the main ideology of qualitative leaps that are not trapped in prefixed patterns and ideologies; rather they sought out every-day personal subversion in order to make our society better. They lived by making personal subversions and asking others to do so, and they came into conflict with theories and opinions that had a clear social orientation.

And it's not only the well-known ones. There are also unknown teachers, men and women, who struggled for years to pass on the light of education through their teaching. They tried, at schools, to move beyond their own biological needs by investing in actions in the microcosm, the world 'deep down'. Grandpa, teachers from Fourni (a small village in Crete) and from Kastelli Fournis which lies on the Merambello coast in the Prefecture of Lasithi on Crete, come to my mind. You know them for sure, don't you, Grandpa? In these small villages, and in many more, they created hubs of knowledge and humanity, their sole weapon

being to subvert the present each and every day in order to create a better tomorrow.

These people, Grandpa, did not know about lyotropism and thermodynamics, but they knew something deeper. They knew a society's drive to move forward, searching for truth through education; they knew about the constant and ceaseless vigilance of the mind. By observing nature and the change of seasons, the animals and the plants, the mind can obtain control over thoughts and decisions. The changes in their macrocosm led to the need to learn why and how events in nature and society evolve. And they had to study these things themselves, and persuade their children to study too, in order to subvert the things needed to become better and more useful to society."

I looked up again, looking for Grandpa. I saw him standing behind me. He was on his feet, looking huge like Nikos Kazantzakis' Zorbas. I thought he resembled that character. He was smiling. He touched my shoulder, as if he wanted to reward me for my thoughts. I wondered, can it be that Grandpa can 'hear' my thoughts?

"You forgot, young boy, that the game with the Mirror you chose to play comes with surprises. Perhaps this is one of them: me, looking like Kazantzakis' Zorbas. That's who I am!"

So, I was right. He did read my mind!

"What you thought was true... You said it all. Thought, just like life, knows no limits. Enjoy it until the end and dance with it; you're not a spectator. Dance in the primordial 'soup' of changes, evolution and conflicts at a pace which does not count breaths, but only emotions. The emotions come like the ripe fruit of autumn, like the wind of spring, changing the colours in the Mirror of nature itself. These are the colours you should look for in the white light; the ones you should consider as a 'projection' of the events of the world 'deep down'."

Picture 28: Nikos Poulantzas

Nikos Poulantzas (Greek: Νίκος Πουλαντζάς; 21 September 1936 - 3 October 1979) was a Greek-French/Marxist political sociologist. He is most well-known for his theoretical work on the state, but he also offered Marxist contributions to the analysis of fascism, social class in the contemporary world, and the collapse of dictatorships in Southern Europe in the 1970s (e.g., Franco's rule in Spain, Salazar's in Portugal, and Papadopoulos' in Greece) (https://en.wikipedia.org/wiki/Nicos_Poulantzas).

Picture 29: Cornelius Castoriadis

Cornelius Castoriadis (Greek: Κορνήλιος Καστοριάδης; 11 March 1922 – 26 December 1997) was a Greek-French philosopher, social critic, economist, psychoanalyst, author of *The Imaginary Institution of Society*, and co-founder of the *Socialisme ou Barbarie* group (https://en.wikipedia.org/wiki/Cornelius_Castoriadis)

Picture 30: Nikos Kazantzakis

Nikos Kazantzakis (Greek: Νίκος Καζαντζάκης [ˈnikos kazanˈd͡zacis]; 18 February 1883 – 26 October 1957) was a Greek writer. Widely considered a giant of modern Greek literature, he was nominated for the Nobel Prize in Literature in nine different years. Kazantzakis' novels included Zorba the Greek (published 1946 as Life and Times of Alexis Zorbas), Christ Recrucified (1948), Captain Michalis (1950, translated Freedom or Death), and The Last Temptation of Christ (1955). He also wrote plays, travel books, memoirs and philosophical essays such as The Saviors of God: Spiritual Exercises. His fame spread in the English-speaking world due to cinematic adaptations of Zorba the Greek (1964) and The Last Temptation of Christ (1988) (https://en.wikipedia.org/wiki/Nikos_Kazantzakis).

And then there was silence!

It was a long silence. Perhaps we didn't want to talk. We were exhausted from the weight of the effort of reading the images in the Mirror. I needed some fruit again, and some water.

“So, Grandpa, what do you say? Can we still continue our efforts and resume our conversation?”

I looked again out of the window. A harmonica had started to chime a happy melody I hadn't heard before. I opened the drawer and the melody became louder.

So, move on, what are you staying still for? The Mirror is not clear yet, can't you see?

Listen, listen up! That melody was the theme from Zorba the Greek. Follow that song.

"So, Grandpa, how can 'social lyotropism', i.e., the deterministic dialectic unity of oppositions in social evolution, be combined with scientific research? Could it be a tool to describe the process of evolution in society? Are the new philosophical approaches related to the natural sciences? Are they a contribution to social laws? Are they influenced by social entropy? Well, I'll go get some fresh air with some friends and... You can ponder the matter and let me know what you come up with."

"*Ha-ha, nicely put, my boy. I've already studied it. Be careful not to start conversations with your friends like the ones we've been having. But don't forget to tell them about Poulantzas and Castoriadis, they might know them. It will be interesting to share your opinions with them, to know if today people like that have any worth in a value system which is developed and maintained on the web, through social media, artificial intelligence, and smart devices used in day-to-day activities. Those people, and many more, known and unknown, had a vision for society. Without knowing it, they used social conflicts as a means to develop very intense lines of inquiries, just like the microcosm uses the same template to achieve better qualities in biosystems. What is vision in the microcosm? Which choice is best and why? You could talk about topics like that, what do you think*?"

"*Social lyotropism, not a bad idea"*, Grandpa thought. "*Yes, I like that. My young interlocutor is describing social phase transitions, the changes related to socio-economic variables, following the logic of statistical physics. To put it better, they could be related to the thermodynamics of small systems, where variability and probability are predominant."*

We try to achieve the transition of society for the benefit of our weaker neighbours, trying to preserve a non-arbitrary and non-equilibrium process, which is equal to the effective and positive changes in society. Each and every one of us at a personal level should create energy which creates and contributes to the 'negative entropic' process as a whole, maintaining our society at a higher qualitative level. Each one of us should constitute a small component in their own microcosm, in order for changes to appear in the macrocosm, in our society. We might never know if we will see those changes, given that the time span over which they appear and their action might be longer than our own life spans.

The concept of lyotropism might be a process of inner conflict between events leading to the prevalence of the most 'powerful' event, which may happen at a local scale, without concerning society as a whole, albeit it may end up influencing it. Let's say for example that the needs and the pressures experienced by people in the countryside are – as they are, indeed –, different from those

experienced by people in urban settings. In this way, the demand for ‘ideological conflicts’ arises, which in turn creates quantitative and, as a result, qualitative changes. These, in turn, influence the macroscopic equilibrium state in urban areas. This influence leads them to lyotropism, i.e., to a change in their morphological characteristics, meaning a change in social tissue. This lyotropism might be called the exterior lyotropism of a social system, where the concepts ‘inside’ and ‘outside’ don’t apply. But it’s identified as such by the different areas in which ideas and events accumulate. So, at a social level we can have an ‘accumulation’ of ideas in different areas and this might be called ‘social lyotropism’, influencing the evolution of the social system.

There are people who give their lives for the aforementioned process without knowing about these matters, which are obviously ideas that need further discussion. In this way, they benefit the macrocosm, our society, by offering ‘negative entropy’, since they might even end up dying, which is maximum level disorder and maximum personal entropy for them.

Try to explain all of these things that are happening to a young boy who is passionately trying to sort out a chaotic and non-linear process. It’s hard for anyone to vocalise opinions of this sort, but even so there should be a continuity in these matters. Young scientists should keep on raising lines of inquiry that need to be explored, even though not every proof and evidence for scientific and social matters is available.

It's still winter outside, and life goes on, smiling with the smile we put on its face.

A long time passed.

****

“Grandpa, Grandpa! I’m here! Open the door! I got bored talking and trying to convince myself that I’ve come up with some important lines of inquiry. I had some thoughts and I don't want to forget them. Quick, I need to look through some books, jot down notes.”

“*What's up, my boy? Did you fall in love? Is that why you’re chasing after the answers? Did you meet your friends? Did you make enemies? Don't they like you? Are you feeling disappointed? Are you feeling lonely or were you rewarded for your efforts? Were you praised? Were you acknowledged? Were you honoured? Which of all of those things*?

“Nothing, Grandpa. This is personal. I think it’s me. I should pay homage to everyone and everything that helps me better understand what is happening

around me, both with scientific tools and with feelings, and to identify myself in my everyday life both at a social and a scientific level. Grandpa, I knew you would like to turn the conversation to sociology with ‘social rafting’ and ‘social lyotropism’.

I feel that after all this time I’ve spent with you I've grown old, even in biological terms. How do I look like? How is my reflection in the Mirror? There are some white hairs on my head. and I can see ‘rafts’ on my forehead, metastable phases or new self-assemblies that are changing the morphology of my face. Everything you say to me seems to be depicted on my face and my body... If it goes on like this, it won't be long before I turn into a Grandpa myself.

Let me look into the Mirror. Oh well, you should see that. There are signs left from the passage of time. I look different as well, but the eyes are the same … the eyes don't change. Or is it the way they look to me that remains the same? For sure, the way I look at events now has changed.

Where are you, Grandpa? Did you go away again? I know that you’re in the library, along with your centipedes. We've left them behind as well. See, I haven't mentioned them in quite a while. Should I start talking about centipedes myself now?

Look, Grandpa, I’ve several inquiries myself to pursue as well. Perhaps I've mentioned some of them in the past but now I'm starting to understand that they constitute great lines of inquiry. Don't worry, I'll tell you. We’ve time or, to be honest, I’ve time to dedicate to you and to tell you all my concerns. I’ve time to paint on the scientific ‘canvas’ you taught me, to explore this important scientific framework we discussed.”

I can't tell how much time we had been talking. I learned a lot. More importantly, I understood a lot. The puzzle with my scattered pieces often took form over the years of my conversation with Grandpa. Some images formed, revealing observations, interpretations of our conversation. But there were also many questions I did not dare to raise. I thought it was too early and I was right. They were premature inquiries and my thoughts about those matters had not properly crystallised. Linear composition is the same, more or less, when you’re trying to describe some line of inquiry, isn't it, Grandpa? What do you think? What differentiates mature from immature lines of inquiry is how they reveal the internal ‘dialectical oppositions’ which surpass the ‘logical oppositions’ and give the line of inquiry the future qualitative dimension and any given interpretation it may have. But mainly they reveal the evolutionary dimension and the universal usefulness and application of the new form, which is the result of the interpretation or of the approach to understanding it.

“You know what, Grandpa? I’ve understood that those inquiries with a social dimension to them, and the ones which have been troubling the human race ever since it appeared on Earth, are still prevalent. I don't think I’m wrong. What do you say?”

“You’re absolutely right and I think that a conversation on the subject you’re putting forward, i.e., the approach to primordial lines of inquiry and how they are dealt with through the lens of science, could be considered an important personal achievement.”

“You know, Grandpa, ever since I was a child, I’ve always tried to understand how the evolutionary process takes place. I mean, how events evolve following one another, how day follows night, how we started from the radio era and ended up with televisions, the Internet and the current revolutionary technological applications we now have and ever-increasing speeds. I know we’ve mentioned this subject but I’d like to talk about it more calmly, give examples and talk about social evolution from the perspective of everything we’ve mentioned, based on science and the scientific data we have accumulated so far, on our scientific records. These are simple matters, not complex ones. After all, we are scientists.”

“*Alright, alright, let's take this matter as you present it. looked outside; it’s winter and the trees have the form that ‘Old Winter’ had, like in the fairy tale you used to read when you were young. Wasn't he weird? Old Winter, with his beard and his frozen look*?”

“How do I know about this fairy tale?”

“*Did you forget? We used to read it together, you used to ask me if you would get cold at night and if Old Winter would come visit and bring snow into your room. Look, you see how distant that now seems? What do you remember from back then, when you went to school, were free from concerns, or the time when you played? If you could try to remember details, you would not manage to do so. The cinema, the fairy tales, and your childhood games might be like distant memories. What did they offer? You may well wonder, given that you don't remember the*.”

“Grandpa, I don't know what such non-recallable memories offer me. Why do we insist on learning music, without becoming musicians, dance without becoming dancers and so many other things we forget later that only remain like memories?”

“*The conflicts, the oppositions my dear boy, inside you shape your personality without you always realizing it, just like you don't remember details from your past and especially back from when you were a baby or a toddler. It’s the conflicts which lead to different qualities. All the qualitative characteristics*

you acquire are used to lead you internally to the most efficient choices and qualitative leaps which will lead you to a better understanding of the social and everyday phenomena of our life. And you never know, you might be chosen, depending on your qualitative characteristics, to do something much greater, something you might not currently even think you could do. So, you understand that the evolution of events is a deterministic process which has as its driving force the 'dialectics of oppositions' from radio to television and now to the Internet. A long trajectory of 'dialectic oppositions', qualitative and quantitative changes we perceive in the macrocosm."

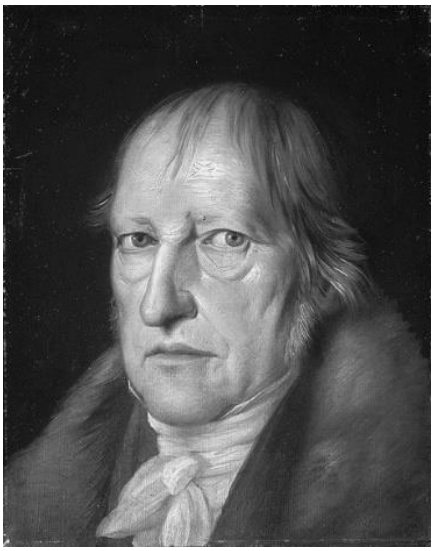
"Yes, I do believe in what you're saying, Grandpa. And it's now that I understand why we should improve what we call 'skills', so that for statistical analysis purposes there is an effective population who can take the qualitative leaps that will lead not only to quantitative but also to qualitative changes at a personal and social level. And of course, I don't remember what we used to say every day at primary school, I can't remember every single day. However, every single day that passed had a uniqueness in and of itself; it was special. It became a struggle at an everyday level, even though I don't remember the details at all right now. But I'm certain that the characteristics of every day played their role and helped in maximizing my total 'negative entropy', allowing me to become a better person and stronger personality. Of course, people who either didn't claim or were not given the chance to claim their own qualitative leaps are of necessity different, both in their quantitative and in their qualitative traits. These traits are internal and are combined with one another. I read what Hegel writes about what he calls 'external quantitative traits.'"

"*Is that so, my dear boy? Please, do tell me, I can't wait to hear*."

"Well, Hegel mentions that quantitative changes, i.e., the external characteristics of an object, might occur, but the quality of the object might not change instantly. This happens gradually, it takes time, enough time for the efficient qualitative characteristics of the object to be chosen, as well as the limits within which the quantitative characteristics are 'preserved'. May I remind you, Grandpa, that nothing is permanent, nothing is constant. As Grandpa Heraclitus said, "everything flows." We mentioned him before, do you remember? But, just to recapitulate, the characteristics are maintained within certain limits chosen by nature.

For example, water maintains its quantitative characteristics within a certain range of temperatures and the quantity of water remains the same for a certain time. But if I surpass the temperature limits, then I'll be led to qualitative changes. It takes only one degree Celsius above the maximum water temperature, i.e., 101^{o}C, for liquid water to start turning into steam, into another qualitative

state, with a simultaneous change in the quantity of its liquid state. What do you think?"



Picture 31: Georg Wilhelm Friedrich Hegel

Georg Wilhelm Friedrich Hegel (August 27, 1770-November 14, 1831) was a German philosopher and an important figure of German idealism. His philosophy of spirit conceptually integrates psychology, the state, history, art, religion and philosophy. Hegel has influenced many thinkers and writers whose own positions vary widely. (https://en.wikipedia.org/wiki/Georg_Wilhelm_Friedrich_Hegel).

"*Yes, of course I agree, you're absolutely right. But please, go on. I'm sure that at some point you will touch upon social matters too, qualitative and quantitative social changes. And then, I want to incorporate social lyotropism, as we talked about. I really like this approach*."

"Yes, Grandpa, I'll do that, you have already sensed my intentions. I'll take some old children's books I saw in the library to accompany these thoughts. I appreciate them a lot, I don't think they are naive. They have made their own contribution to the 'metastable phases' of my brain cells and I value them a lot. Perhaps for this reason, without being aware of it, I still hold on to them. I never looked down on them and they've always held an important position in my library."

Children's books lead you into your childhood dreams, they are something like 'dream and thought guides' to make feel safe. You can't dream of something you don't have an image of. Once you have the image, you can dream of it and can build your own wants and desires. Children's books give allow you to safely navigate, as well as showing you possible safe destinations.

And at night, they let you dream of witches and elves to teach you how to tackle your fears and appreciate the embrace of your mother and the safety of your family.

But let me go on reading from those books and I'll try to convey what is written in them.

An important observation to make about the process of evolution is that there's a deterministic process of human evolution from child to adult. This

process is considered to be very slow within the limits of the human life span and the changes are not visible, especially when we live with the same people on a day-to-day basis. It's evident that these changes concern external characteristics.[125]

But this entropic process, i.e., the process of degeneration, concerns all of the organs and the cells of the human body; it simply is not visible though. So, let's call these 'external characteristics', which are slowly transformed and say that most of them are not visible to other human beings. They are the characteristics of the macrocosm and the world 'up there' we've already discussed, Grandpa. Now we will see, based on the relevant literature, that the entropic/thermodynamic changes that appear as visible characteristics in the macrocosm with a very small rate of change, are directly linked to the very rapid changes that are taking place in the microcosm, i.e., 'deep down', as we've talked about. The changes in the macrocosm, like changes in the 'external characteristics', along with the changes in microcosm, constitute a whole process and the observable result is due to the unity of these two processes.

It's evident that this process does not only take place in the human species, but in every species and genus in our animate world. The very same process, on the basis of the evolutionary process, also takes place at a social level.

"Here we are, Grandpa, let's talk about society, as you said. But let's see the correlations based on the scientific tools we already possess and those we have developed in our conversation. But let's pay attention, because the processes at a social level also call for sacrifices, transcendence of human nature and of human weaknesses... We are talking about heroic attempts that really go beyond the limits that science has posed as insurmountable for human skills at a biological and intellectual level. And this is very important. This is how our civilization was created and developed: through human transcendence and conquests that go beyond even the known natural rules of human behaviour".

The concept of the social system is a dynamic state –and here, we could mention the concept of 'social lyotropism'; it's constantly changing depending on the social changes which are not visible in everyday life. It usually takes a very small change for a change in qualitative characteristics to occur and a new social system to arise, which in turn constitutes a system under revision, depending on the social developments and changes. This goes on and has been going on ever since the human species first appeared on our planet. These changes are performed by means of 'leaps'; they are the 'quantum leaps' in the bio-microcosm we've

[125] Rombert Staigervalnt – "Μαρξιστική Φιλοσοφία. Βασικές έννοιες και αρχές" (Marxist Philosophy, Basic Concepts and Principles), Synchroni Epochi publications in Greek, translated from the original in German "Marxistische Philosophie Einfuhrung fur die Jugend', Ed. Verlag Marxistische Blatter, Franfurt, 1979.

already mentioned. 'Social leaps' are nothing more than the result of the intense conflict between opposites, achieved through the prevalent/predominant social opinion holding sway and leading to social transmutation. As is evident, both in nature and at a social level, qualitative changes in evolution are prepared only when there are the quantitative changes in objects, but these take place at a very slow pace. The qualitative change does not constitute the end, i.e., an entropic process which has been concluded. This would be destructive. At the same time as the qualitative change, the new quantitative change is also prepared, which will lead to new qualitative leaps and qualitative changes."

"*Very good, my boy. I agree with what you're reading and with your own comments and thoughts on the books you've read. But I'd like to ask what is the starting point in the process of evolution? What was the driving force at a social level, the primordial 'first kick'*?"

"The driving force, the 'first kick' should have been 'in motion', i.e., it should contain the process of evolution internally to itself, and not stagnation, because how can a stagnant thing give a kick-start to something that is not stagnant? I mean, it does not know the process of movement, since it's stagnant itself. If we accept the above approach, which is movement through stillness, dialectics as we've mentioned it and incorporated it into the process of evolution is discarded. Therefore, we should incorporate another philosophical system, which could give the answers to such questions. In this way, the unity of the oppositions emerges as prevalent in the process of evolution, both scientific and social evolution.

We should always mention that the processes at a social level are, in our opinion, the result of internal mechanisms of evolution, i.e., of the conflict of oppositions within the social system itself. They don't stem from decisions of social groups or from people at any given time, without having sustained the deterministic conflict of oppositions. It's only when the internal process of conflicts of oppositions exists, e.g., of opposite opinions/world views, that social groups can contribute to qualitative changes through the quiet and silent process of evolution. Therefore, change comes from the social effort of individuals to create something better, i.e., a statistically prevalent social result which will later be expressed as a 'social leap', as a 'quantum leap' in the bio-microcosm, sparking social change that will become visible in the macrocosm, in society. And it will go on and on, in a deterministic way. What do you have to say about that, Grandpa?"

"*This is an excellent approach. Based on the relevant literature, it provides me with the necessary link between science and society. In this way, contemporary societies are created through personal effort and personal conflicts with our*

human weaknesses. This is expressed as the result of similar human attempts and ends up as a qualitative leap through the quantitative social changes."

"Should I go on, Grandpa, by asking the question why is all this happening since the entropic process is taking place through its own conflicts and qualitative changes into higher entropic levels, and will eventually be the prevalent tendency? So, why do we make all of these efforts for social evolution? What do you say, Grandpa? Is there any space in our conversation for this inquiry? Because I think it's an inquiry, not just a simple question."

"*I absolutely agree with you and I think it's time to introduce some 'valuable' and intellectually costly concepts into our conversation which will open up new lines of inquiry. Do you think that all people pursue happiness*?"

"Yes, this makes sense. But what is happiness, Grandpa?"

"*Right. Now, this is getting hard. We should study these lines of inquiry based on philosophy exclusively, otherwise they are not countable concepts from the viewpoint of scientific data. Years before, when our conversation started, I don't even know how many decades ago it was, we mentioned Plato and his dialogues.*

Back then, I mentioned his dialogue Euthydemus. In this dialogue, two brothers, Euthydemus and Dionysodorus, both of them sophists try to convince the fine Athenian youth, Cleinias, "that he should cultivate philosophy and virtue" (ως χρή φιλοσοφείν και αρετής επιμελείσθαι) [126] [127]**.** *Socrates' intervention is a catalyst to the conversation, because his discussion with the adolescent Cleinias leads to the conclusion that the only real goods are 'phrónisis' (φρόνηση) (prudence; σύνεση) and 'sophía' (σοφία) (wisdom). Therefore, it's necessary and sufficient to become as wise as possible, and this is possible because 'wisdom' can be taught. So, it's necessary to cultivate philosophy in order to acquire these goods and attain happiness. I should also mention that, according to this dialogue, dialectics emerges as the prevalent philosophical view, winning out against the sophist method of the two sophists and also demonstrating that the eristic art is ludicrous, according to the literature cited above. It's important that I go on a little bit more and, based on this dialogue, I'd like to say that Socrates and young Cleinias also show that philosophy is 'belongs to science'. Therefore, the inquiry that emerges is, which kind of science is beneficial*?"

"Grandpa, I think we are exaggerating a little. You wanted to talk about the evolution of society and you moved way too far. It's almost day. Winter is almost

[126] "Πλατωνος Ευθύδημος", (Platonos Efthídimos / Plato's Euthydemus) translated into Modern Greek by B.N. Tatakis, I.N. Zacharopoulos publications, Athens, 1956.
[127] Translator's Note: our translation.

over. Look for yourself. You made me go on a meandering trip through science, on an endless journey, one without a harbour in sight. I should also let you know, Grandpa, that as a student I've learnt a little something about Plato and his dialogues. I could take some time to find the relevant literature. For sure it will be somewhere in the library.

I don't dare to suggest something to talk about with him, we start off smoothly and well to get to a point, but he always pushes at the limits to my endurance, impelling me forward. Oh, here it's, the 'royal art' of politics... Plato must mean here 'dialectics', yes, we can find what he means in a footnote in this book.

"Grandpa, come, don't rest now. I've just found what you'd been trying to tell me."

"*Is that so? Well done, I just thought I'd take some rest on my familiar armchair... The soil smells nice, I can smell it from the open window... Open it a little bit more... Winter is almost over, spring is coming, with colours and smells of nature… childhood memories from Easter. So, tell me, before dawn cracks and the fairies and witches are gone...*"

"What are you talking about, Grandpa? Are you alright? Is your time coming to an end? If so, let me hurry, I want to know... Is happiness 'phronisis' (prudence; *φρόνησις*) and 'sophia' (wisdom; *σοφία*)? How is science directly linked to philosophy? Am I on the right track? This jigsaw puzzle, the image I want to see, is slowly falling into place."

Yes, spring has come and Grandpa is still brave and happy, combining philosophy and science. And I'm proud like Grandpa, when he used to boast and talk to me, long ago, about the composition of objects, of concepts, of 'noesis' (*νόησης*). I think that I'm starting to grasp the logic of Grandpa's thought, in any case I'll be a Grandpa myself in a while.

"*No, my child, my time is not up. Philosophy and science go hand in hand, you're right. There are dead ends, such as the inquiry into whether the 'royal art' makes people' 'wise and virtuous' which was tackled and answered by Plato. In his work The Republic, he says that only the philosopher is a virtuous politician. You should also know that in platonic thought practical reasoning is prevalent, and the advice to cultivate philosophy is nothing more than the advice to be 'well educated', which is only guaranteed through philosophy.*

This dialogue closes with Socrates' advice to the adolescent Cleinias, and I think it's useful to all of us:

'As far as philosophy is concerned, don't judge it bearing in mind the ones who engage in it; for they might be evil, as in all human endeavours and activities.

Examine the same thing from every angle, and then you will form the right opinion on it'" [128] [129].

So, philosophy, even though the simple reference we made above, seems to be inextricably linked to science, to the Socratic method with its exhortation to 'know thyself' (*γνώθι σαυτόν*) and to dialectics with deep self-control. Perhaps science and verified scientific concepts seem like an exaggeration in our everyday practice. But it's not like that. We need time and effort and personal sacrifices to manage, through self-control, to conquer and control our own spirit, our thoughts and to 'know ourselves'. I think it's worth the effort.

Key Point

(…) the constant feedback of the inherent conflicts of our dialectical contradictions based on knowledge and wisdom lead social groups through the quiet and silent process of evolution and can contribute to the process of social evolution (…)
It is necessary and sufficient to become wiser. This is possible because wisdom can be taught. So, it is necessary to cultivate a philosophical mindset in order to acquire goods and attain happiness

Grandpa fell asleep, tired after this conversation. The concepts of science and philosophy were challenging indeed. Dawn broke. It was impressive. The sun shining through April's clouds and the colours of the flowers confirmed the value of our effort. At the very least we tried, I thought, and that was great. We moved on in the struggle of our lives, and we kept on struggling. Knowledge was not given to us; rather, we had to conquer it for ourselves. Yes, personal conquest can bring great joy and relief.

I'll not exaggerate. I'm aware of the struggles and the efforts made throughout human history, man-to-man struggles, social condemnation and the sidelining of young and innovative ideas which could have changed the world. These people were born right at the moment when quantitative changes were starting to become visible, and they were a part of qualitative change. It's hard to experience it, yet some people do. The rest who will live in the years to come, or

[128] "*Οσο για την φιλοσοφία, μην την κρίνεις έχοντας υπόψη σου εκείνους που την ασκούν. Αυτοί μπορεί να είναι καλοί, μπορεί να είναι και κακοί, πράγμα που συμβαίνει με όλες τις ανθρώπινες επιδόσεις και ασχολίες. Να βασανίσεις από κάθε άποψη το ίδιο πράγμα και τότε θα μορφώσεις ορθή γνώμη γιαυτό',* "Πλάτωνος Ευθύδημος", (Platonos Efthídimos / Plato's Euthydemus) translated into Modern Greek by B.N. Tatakis, I.N. Zacharopoulos publications, Athens, 1956.
[129] Translator's Note: our translation.

who lived before, had to to prepare these changes, so that the next generation could implement them. Each one of us bears their own cross, either small or big, depending on the period during which they lived. And we also carry the obligation to contribute to the process of evolution, by making our own contribution to the process of the conflict of oppositions.

The sun had risen, the colours were gone from the sky and the clear blue hue with a few clouds showed that the day was moving on, 'heedless to our melancholy', just as some university student had written once on the University walls. Back then, students tried to depict their own social struggle, without knowing perhaps that they should study nature first, and the choices it makes, and then classical Greek and international literature, in order to create some framework for their own social behaviour. I might be wrong, I might be unfair to them... I wish we could go back to those years and explain, talk about the social and scientific changes we have been dreaming of. Perhaps the deterministic process through which events express themselves surpasses our own desires.

I looked outside the window: everyday people coming and going, the neighbourhood getting self-assembled through the known and accepted codes of everyday life which had been changing day by day, without affecting us, or so we thought. I would look outside the window, observing the coming of spring, of summer, of autumn, each season bringing its own set of scents, and colours. How much of an effort does it take 'deep down', Grandpa, for me to enjoy this morning, and each day that comes. We should be for every day that has been given to us, and enjoy the outcome of the primordial struggle of natural laws, the qualitative changes and quantitative changes which create emotions, happiness or unhappiness, poetry, art, civilization, life itself.

"Are we too, am I too, a part of the cosmic, unique evolutionary process?", I shouted at Grandpa. "Or am I just a simple unimportant observer of an evolution which just allowed me to be present?"

I must not disappoint him, I must not disappoint Grandpa.

THE MORAL OF THE STORY

Here I am again, wandering around the library. Sometimes I look for books from my childhood, to find my childhood friends, Mimis, Anna, Grandpa or an old textbook from primary school. And then, *Uncle Tom's Cabin*, Jules Vernes' books. One would normally have these kinds of books, as well as the *Encyclopaedia of Youth*. It was in that encyclopaedia that I read the biographies of great Greek poets and authors, I learned about their lives and dreamt how they

wrote, how they lived their everyday lives without paying attention to time, to dates. Back then, dates were numbers with three and four-digit figures. My eyes were different, full of childhood innocence. And of course, there was that book, *Alexander the Great* given to me as a prize for 'exceeding expectations' in second grade of primary school, as the headmistress wrote. It was an important prize, the first reward for my efforts. Back then, I used to think that every effort was rewarded. But I was wrong. Society has its own priorities, which are very often different from our own, and they come as an 'unpredictable surprise', as we like to call it.

And it's full of surprises, every day 'unpredictable situations', a constant and arduous struggle to conquer knowledge, to finish the jigsaw puzzle and see the big picture.

Grandpa has always been present, either through the textbook in primary school or through *Uncle Tom's Cabin*, or in the form of Jules Vernes himself, or even as the bearded captain, in *In Search of Castaways*.

But why was that? Why was he there? What did he want? What was he looking for? Perhaps he was trying as best as he could to see the big picture of life.

He had collected numerous large and small images of events, natural phenomena and laws, accumulating knowledge, photographs, experience, without ever completing the big picture of life. But he knows it. I'm sure he knows that the big picture of life and the world will never be completed. It would be naive to expect something like that; then entropy would be all prevalent. The puzzle with the big picture must never be completed. But he knows, he 'knows himself' and he knows he needs to struggle to complete small images that will give rise to new 'missing pieces' to be completed, in an incessant attempt to conquer new small worlds and to satisfy his own internal curiosity. What else is there? The more I know, the more I get closer to seeing the big picture, the more I approach the unknown, the transcendent that lies beyond.

Grandpa knows that very well – and I'm sure that's what he has really been trying to tell me, in his own way with his centipedes and with the scientific conversations we had. Not particularly great things, as he'd say. "We only construct small images, my boy, which are of no importance when compared to the big picture", he'd say.

This was a painstaking effort to continuously conquer or, to put it better, acquire a well-documented opinion about the hereafter. I have to say, though, that I cannot know whether it was really well-documented, or whether the effort was in vain. Was it indeed all in vain? No, of course not, attempts like these are not pointless, lacking any purpose. On the contrary, it's attempts like these that keep

us alive, making us better people, and more intelligent beings. This is the biggest conquest that humankind can achieve.

The attempts made by scientists, philosophers, intellectuals, virtuous men and women in any field of life, contribute to and participate in the dialectic conflicts leading to qualitative leaps in science and society and to the complete offering our Grandpas make to their children, their grandchildren, as a legacy that drives the evolution of human race on our planet.

I look at the library.

The books have remained the same for many years now. Of course, new additions have been made, mainly scientific books. The library per se, though, does not change, even the position of the books looks unwilling to change. Semiotically speaking, they require order, they don't like to be messed with. Perhaps they long for eternity as well, against the entropic process they know so well, and which is recorded in their pages. I was wandering around the library, between the books, and I knew that I had grown with them and they had grown with me. I thought that every time I would read a book, that reading was different from the previous one, and for sure different from the very first one. There's no doubt that maturity, i.e., the qualitative transitions between the phases of my cell membranes that help me evolve me towards a more qualitative organisation and processing of information and consequently towards higher levels of organisation, as well as the many metastable phases in my cells, have created more potential for alternative readings. The previous readings disappeared after each new reading of the text.

I could identify this evolutionary process and dialectic relation between what I had read and what I was reading. Even though the text was the same, the meanings I would extract were substantially higher in quality. I thought that this approach was like looking at a painting: each person would interpret it in a different way, depending on their culture, their experiences, their education and, in general, on the 'metastable phases' that had been created, and one could even go so far as to say that they had to translate their microcosm into an everyday life code in the macrocosm we live in.

I was lost in my own thoughts and had forgotten about Grandpa. But I was sure that he'd have fallen asleep again, in the armchair or on the couch. When I finally got away from the embrace of the books, I looked around to see where he was and what he was up to.

But he wasn't there. How come? When did he leave? I wondered to myself. He might have gone somewhere. But how? Grandpa would never leave the library. I thought for a second that he was never there, on the couch or in the armchair. But he had always been by my side; I'd felt him in my every effort to understand

the content of my books, guiding me and advising me even about the simple choices I had to make. I talked with him about many topics. He knew that my decisions could influence my life and he felt responsible for that. I felt he was something like a shield made of light with all the advice he would offer, showing me the way to self-awareness and to the social contribution I could make, even if it was a very small one. We talked about challenging scientific concepts and we tried make important revelations by constantly posing queries that were without an answer. And this was satisfying to us. We knew that we had worked on something important, it was clear to us and had reached the highest level of queries. "The first queries need to be posed first to ourselves", Grandpa would say, "The first student must be our own selves. We shouldn't be under the illusion that we know it all, all the lines of inquiry which exist, and that we are ready to teach other people."

That's perhaps because he was always by my side. Sometimes I would even startle myself at the questions I posed on the scientific matters I was exploring. Perhaps I am Grandpa now. It's very likely now with all the wrinkles on my face.

Perhaps –I'm thinking to myself– it's the culture we carry inside, our very soul that constitute the driving force behind our choices. To me, Grandpa's company was a choice. I don't know how old I am and I don't know if I'm already a Grandpa. As Grandpa says, "our biological clock has an infinite amount of time and we don't know what time the clock is showing at any given moment."

"How old am I", Grandpa? I really don't know. But I do know where I can meet up with Grandpa for him to tell me what time is, to tell me it's time to listen to the world 'deep down', the world where small, big and real evolutions take place.

I don't know how old I am, but I do know that at some point I'll meet Grandpa and everyone else and I'll join them on the long journey towards real truth in this small great world.

"This small great world", as Odysseus Elytis wrote in his poem The Axion Esti[130], after having seen it through the eyes of a poet. He was a poet truly gifted with the 'metastable phases' of his brain cells and which are blessed with the ability to project images as they appear in the microcosm; images that we can't see.

A poet who saw so much truth in the sea, so many colours and so much music!

[130] Odysseus, Elytis (1974) The Axion Esti, translated by Edmund Keeley and George Savidis, Pittsburgh, University of Pittsburgh Press.

Picture 32

Grandpa was a scientist, and for that reason he was interested in simple – not great– things, as he used to say.

And all his teachings were simple; the great ones lie ahead, still waiting to be discovered.

…to be continued

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Costas Demetzos is Professor of Pharmaceutical Nanotechnology at the National & Kapodistrian University of Athens. He received his degree in Pharmaceutical Sciences from the National & Kapodistrian University of Athens and continued his Ph.D studies at the same Institution. During his Ph.D research he collaborated with the University René Descartes, Paris V (France) where he finalized his Ph.D thesis in 1990.

After the completion of his Ph.D, Prof. Demetzos continued as a postdoctoral researcher at the Cancer Research Institute of the University of California in San Francisco (UCSF), working in the group led by Dimitrios Papahadjopoulos, where he was trained on the field of Pharmaceutical Nanotechnology and Nanomedicine. Currently, Prof. Demetzos serves as Director of the Laboratory of Pharmaceutical Technology and since 2008 he serves as President of the Hellenic Pharmaceutical Society (HPS). His research interests lie primarily on Pharmaceutical Nanotechnology (lipidic, polymeric and mixed drug delivery nano systems, and smart nano devises), Physical Pharmacy, Nanomedicine,

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In 2021, Prof. Demetzos has been elected Ordinary member in Class IV-Natural Sciences of the *European Academy of Sciences and Arts* (*Academia Scientiarium et Artium Europaea*).