Nanophysics and Nanoengineering for Synthetic Biology

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Abstract
The plans, history and *state-of-the-art* concerning **Synthetic Biology** are presented. Its first general formulation dates back to the 70s, and its development is now increasing, with recent great successes digging deeply into biosystem structure-function, with near-future plans and the present capital investments. Ecological and ethical problems have been raised that might delay such plans, and in spite of its successes, Synthetic Biology and its branch Synthetic Life that aims at recreating life itself, both as an *extreme engineering* effort whose enabling technologies stem from biosystem Nanophysics and Nanoengineering, lack the background for realization of their most advanced purposes: attaining the ability to nanoengineer biological members as genes, genomes, sub-cellular members, cells and tissues, up to recreating life in the lab through *ab initio* processes.
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1. Introduction

Synthetic Biology is a research and development field where attempts are made at combining biological knowledge as a fundamental scientific discipline with the eminently constructive objectives and scope of engineering branches. Accordingly, the Synthetic Biology scope is largely focused on the creation and perfection of genetic devices and small modules that can be built from such devices. For the more advanced view aiming at the realization of programmable biological cells, it will be of the essence to try and find effective strategies for assembling components, devices and modules into complex larger scale systems, better if with suitable customization for novel approaches to many practical applications like green processes for energy production, biomedical therapeutic systems, engineered human cells resisting infections, biological implementation of algorithms and unconventional computing, synthesis of a minimal cell, building of viruses from inorganic/organic compounds etc. While details of the history of such approach to biosystems and of its very recent and ever increasing development and successes are given in the following section, the subject of discussion here is whether the basic Synthetic Biology project, as involving a really extreme engineering effort, can rely as any other engineering branches on a technological background sufficiently developed as yet.

This field is quite rapidly reaching the industrial enterprise, with remarkable interest of investors and the establishment of special dedicated companies.

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All that has resulted in the raising of societal and ethical issues, discussions and hostile attitudes which will be considered in **Section 4**.

And even more and deeper problems and objections were raised against the subsection of Synthetic Biology that has been dubbed **Synthetic Life**, whose mission is the development of the ability to create life from non-living, i.e. abiotic, matter. The roots of this new intellectual adventure – recreation of life in the lab through *ab initio* processes – are to be found in the now time-honoured efforts to understand the origin and evolution of life on Earth from physicochemical principles [1 - 3]. And the attitude of Synthetic Life could certainly give substantial support to the efforts, ineffectual as yet, to simulate the origin of life by creating self-replicating, autocatalytic chemical reactions taking abiotic matter from the few hundreds of bits of information on the primeval Earth up to the 10^{10} bits of human genome.

But some crucial problems of computational and information theoretic nature will be put into evidence in **Section 5** as to such project.

The best definition of Synthetic Life has been formulated by W. Wayt Gibbs through the identification of **three major goals** that differentiates this approach from that of Synthetic Biology [4]:

"*One, learn about life by building it, rather than by tearing it apart. Two, make genetic engineering worthy of its name – a discipline that continuously improves by standardizing its previous creations and recombining them to make new and more sophisticated systems. And three, stretch the boundaries of life and machines until the two overlap to yield truly programmable organisms*".

With reference to the thumbnail sketch of the history of biological thinking up to the views in our times presented in **Section 2**, it is interesting both from the epistemological and scientific standpoint to note that, against the Cartesian view of the ***animal – automaton*** identity,

Synthetic Life distinguishes its realm as belonging to living systems that are conceived as opposed to mechanical life, the latter belonging to the field of robotics. But it is assumed that the boundaries between life and machines will overlap. Stated otherwise, the Cartesian view would not be in Nature, but it might be constructed on the basis of a deeper physics. And indeed such *synthetic* ***Cartesian*** *programmable organisms* would be the result from the merging of the field of Synthetic Life with that of Bionanotechnology.

Though a number of the present biological and chemical technologies – *DNA sequencing, fabrication of engineered genetic sequences, modeling of biomolecular interactions in transcription, translation, regulation, induction of gene regulatory networks etc.* – would be some basic tools for Synthetic Biology and Synthetic Life, ultimately the key enabling technologies for the most advanced results of such extreme engineering efforts would stem from a suitable development of Nanophysics and Nanoengineering.

The present limitations of such emerging disciplines as to the ambitious achievements of such new biological thinking are stressed in **Sections 5, 6** and **7**.

2. Synthetic Biology – Life from Past to Present Conceptions

> *... ces fonctions suivant toutes naturellement in cette Machine, de la seule disposition de ses organes, ne plus ne moins que font les mouvements d'une horloge, ou autre automate, de celle de ses contrepoids et de ses roues; ...*
> ["... these functions stem in this Machine just from the arrangement of its organs, nothing but the motions of a clock, or an automaton, by those of its counterweights and wheels ... "]
> *Car ne considérant rien que l'extérieur du corps humain, nous n'avons point imaginé qu'il eut en soi assez d'organes, ou de ressorts pour se mouvoir de soi-même, en autant de diverse facons que voyons qu'il se meut.*
> ["Because considering just the outside of human body we would never had imagined that it has within itself enough organs, or springs for it to move by itself, in so many ways that we see it to change."]
> Descartes, *La description du corps humain*, AT XI 202 - AT XI 224

Let us briefly try and see the roots, in the conceptions that modeled the living being in the past centuries, of the present views about living matter inspiring the engineering-minded formulation of Synthetic Biology and some recent views as to self-organization and evolution. Our views are at the end of a chain of hypotheses and debates from Descartes to Pierre Gassendi, Baruch Spinoza, Malpighi's microstructuralism, Locke, Leibniz's concept of organism [cf. 5 – 9 respectively].

After three centuries of proposed hypotheses and debates, from the time when the very heart of Scientific Revolution began to develop, the Cartesian mechanistic view of *animal – machine*, and the recognition of the fact that the body structure is sufficiently complex for implying the action of mechanical *self-regulation* turn out again in our times and becomes the basic assumption for the Synthetic Biology project. But this eminently engineering effort is supposed to rely on Pierre Gassendi's biological project involving the gathering of the particular certainties supplied by experience, with the aim of building up an analysis of the correlated appearances, as well as the transposition of such particular evidences into the form of causal hypotheses. The latter will be used to represent the structures and the corpuscular properties underlying any complex phenomena.

Malpighi's microstructuralism with its concept of *hierarchical structures* of the living microstructured machines is also reflected in the extremist nanoscale research for investigating the physics of subcellular members, with the support of tools created by nanoengineering to operate down to the macromolecular world and explore the hard to determine nanoscale interactions. The biosystem integrated conception of Spinoza through his principle of organic order, and the Leibnizian notion of organism both prelude to the holistic notion of the present Biology, and Gassendi's theory of quality according to Aristotelean definition of the notion of quality reappears recently, in an attempt at deepening the concept of computation as applied to biosystems [10]. A dynamic capability for *self-deployment* into different motility effects is also contemplated that takes us back to Synthetic Biology.

This term has a history that starts in 1974, when the Polish geneticist Waclaw Szybalski coined it and set forth the Synthetic Biology project and formulated its scope and objectives in a clear-cut way that differentiates it from other previous biological approaches and circumscribes its methods and tools with respect to new recent approaches like Nanobiology, Nanobiotechnology and Bionanotechnology [11]: "... *Let me now comment on the question '**what next**'. Up to now we are working on the descriptive phase of molecular biology. ... But the real challenge will start when we enter the synthetic biology phase of research in our field. We will then devise new control elements and add these new modules to the existing genomes or build up wholly new genomes. This would be a field with the unlimited expansion potential and hardly any limitations to building 'new better control circuits' and ... finally other* 'synthetic' *organisms like a '**new better mouse**'. ... I am not concerned that we will run out of exciting and novel ideas, ... in synthetic biology, in general*".

The most striking success of such philosophy, at the border between the Synthetic Biology and the Synthetic Life approach, was publicly attained in 2010 by a team at the J. Craig Venter Institution. The paper published on 20th May, 2010 in the journal *Science* [12] online described the creation of Synthia, a natural cell first deprived of its original genome and capable of reproducing on insertion of a different genome obtained by **fully chemical synthesis**; i.e. a novel kind of living matter featuring a kind of synthetic biochemical life as illustrated in a more detailed way in Section **3.**

3. "To live, to err, to fall, to triumph, to recreate life out of life"

This quotation from J. Joyce's "*A Portrait of an Artist as a Young Man*" is one of the four phrases inserted as coded nucleotidic sequences in the chemically reproduced genome of *Mycoplasma mycoides* to change its original (natural) genome into an artificial genome to be inserted into a cell of *Mycoplasma capricolum*, a bacterium akin to *Mycoplasma mycoides*. After insertion of the engineered genome, with its original DNA modified in a score of positions, the *Mycoplasma capricolum* was able to reproduce, and the novel engineered cell was dubbed *Synthia*. The whole technique consisted first in placing an order for the chemical synthesis of 1078 DNA fragments, each one of 1080 base pairs, with a company specializing in the synthesis of genetic material; then, the fragments were assembled into eleven DNA blocks of 1,000,000 base pairs; third, the eleven blocks were assembled into the starting genome but modified in some positions. The other phrases inserted as "*labels*" to distinguish in the future between Synthia and the natural bacterium were the key of the alphanumeric code, the names of the scientists who realized the work, and an Internet address.

40 million USDs were invested in the project of the Craig Venter Institution. The interest of investors in high technologies is now increasing, as products fit for commercialization are envisageable. Mammalian cells can be treated in ways similar to bacterial cells; the latter can be "*trained*" to work as swarms of intelligent mechanical robots to get fuels, drugs, to treat wastewaters, and for many other processes of great importance to humans. The concept of "*synthetic microbial consortia*" is promising for performing these and other more complicated functions.

Anyway, oppositions have been raised against Synthetic Biology. Calls for a global moratorium on developments in that field and for no synthetic organisms to be released from the lab [13]. Other groups opposing the development of Synthetic Biology include: *Friends of Earth, Alliance for Humane Biotechnology, International Center for Technology Assessment, Centro Ecologico (Portugal).* Oppositions are mainly based on issues concerning safety, security, societal and ethical issues. Public perception has also been addressed as a problem [14]. Many a people indeed think that all that means for mankind to start (much dangerously and even ruinously disrespectfully) *playing God.*

4. Let Us Play God

STUDENT (reads out the dedication that Mephisto under the guise of a university professor has written
on his workbook): ***Eritis sicut Deus, scientes Bonum et Malum****
[* *You will be like God, aware of Good and Evil*]
MEPHISTO (mutters to himself while the Student thanks him, bows and exits):
Please follow the old saying of my uncle The Serpent. The day will come that your being similar to God will scare you to death.

Goethe, *Faus*t I, 2048 - 2050

Life not only is an intellectual intriguing adventure for human thinking. It is also felt emotionally as a fascinating, mysterious and sacred phenomenon that, for the largest part of mankind, is fully and must be fully in the hands of God. Moreover, *knowledge* quite often in the history of human societies has been felt as something in which evil and sin would be lurking and as a definitely serious menace for Man. So, obviously many people feel as scaring any scientific approach to life, intelligence, consciousness.

But really a problem is the fact that while modern Man is by and large above the intellectual and technological level of his stone age ancestor, from the ethical standpoint there's not much difference. Hence the worry for a malicious use of knowledge. Moreover, a risk with breakthrough advances in Science is that we might be driven to act much more as the *"sorcerer's apprentice"* set to music by Paul A. Dukas in Walt Disney's *Fantasia* than as scientists.

5. From Synthia to Andromeda?

Metaphors are a way to help our minds process the unprocessable.
The problems arise when we begin to believe literally in them.

D.Brown, *The Da Vinci Code*

Synthia actually is not a fully artificial cell. Its realization does not mean the synthesis of life from scratch. It comes from a very refined technique for copying something made by Nature, and without the possibility of predicting the results (hence, the four phrases used as labels, and a door opened for some sorcerer's apprentice to come in). Its cytoplasm with all its subcellular members is natural, and the present knowledge and misconceptions in Nanophysics and Nanoengineering prevent deeper insights.

Indeed, living matter, as *"matter that chooses"* (Lyn Margoulis) involves much more the notion of *information* – too vague a notion indeed as yet – than energy. Mastering this notion will be of the essence if, as it is the project of Synthetic Life, we want to go from *Synthia* to an extreme future realization like *Andromeda* of the famous science fiction novel "*A for Andromeda*" by the prominent British cosmologist Fred Hoyle: the artificial woman built on Earth in a laboratory by a group of scientists who detect a radio signal from a distant galaxy that contains coded instructions for the design of an advanced computer. When the computer is built it gives the scientists instructions for the creation of a living organism, named Andromeda. And one of Andromeda's creators, John Fleming, fears that her purpose is to subjugate humanity.

There's a mistake in this conception of a computer that can be programmed to build a living organism. Such misconception also involves entropy and Shannon information, all of them stemming from *metaphors* taken literally; they prevent Nanobiology and Nanoengineering from achieving deeper insights into living matter (points **1.** and **2.**). And other thought-blocking attitudes are discussed in **3. – 5.**

1. *Information as negentropy*: even a second-year student of Physics knows that entropy is a state function, i.e. it is definite just for systems in equilibrium, described from the statistical mechanical standpoint by Maxwell-Boltzmann distribution. A physical meaning for a "*bit*" of information can be set forth under these conditions. But in the case of living systems, as *far-from-equilibrium* systems, and maybe even of *non-thermodynamic* character, the Maxwell-Boltzmann distribution is to be kissed good-bye. The notion of entropy loses any physical meaning, and so information as negentropy.

1.1 *So, what is information and where is it contained? What is it that flows according to physical theories of life and cosmos?* Going through many books on information one can find the definition of *amount of information*, not of *information*. A good starting point out of this situation might be a remark by G. Bateson [15]: *Information is any difference which gives rise to a difference.* A development of this assert can be attained by arguing that we have first to distinguish an observed and an observing system. It is necessary for any *mark* (the first *difference*) existing *per se* in the observed system to become information that there is an observer *interpreting* that mark through interaction with the observed system, so creating the second difference. Thus that mark actually becomes physical information as an *emergent property* from conjugation (convolution, compression, simulation and anticipation, and thus *abstraction* as formation of collective properties *through reduction of degrees of freedom*) of external signals with the internal activity of the receptor. It is such emergence that *flows* through the parts of a nanostructured living being. Information is not contained in the "*source*", which is a misleading term for what contains just that *per se* "*mark*": this is an image that can work as a *metaphor* in the case of thermodynamic systems at equilibrium. "*Disequilibrium*" is the stumbling block of Shannon information taken from the *abstract symbol* transmission in telecommunication to the physical world.

2. *Information so conceived not only is syntactic information, but also semantic information.* It has been shown [16] that a syntactic computer, independently of its computing power (its number of "*flops*", even the exaflops envisaged for the near future, or the syntactic computer designed by a superior mind in a far galaxy as in Hoyle's novel) is hopeless in decrypting or synthesizing any semantic computing system like a living being, even the simplest macromolecular system (e.g., haemoglobin). The unsolved problem of predicting protein folding is a practical proof of this. Indeed, decrypting e.g. a haemoglobin macromolecule that acts as a physicochemical lab through spontaneous motion *not of thermal noise* origin is a kind of dialogue between the same and an observing system, in which the latter tries to break the code – to find the *meaning* in the chain of **sensing ⇔ information processing ⇔ actuating** – of the observed system. The mere *"number crunching"* paradigm cannot work for biosystems. The analogy of cells working as *logical sequential machines* through programs written in their DNA is a misleading *metaphor* of no value if we want to decipher the *dissipative* nanoscale orchestration occurring through *highly nonlinear* dynamics that takes a cell to mitosis through the prophase, anaphase and telophase [17] Any designer of VLSI chips for a *logical* (i.e. *not dissipative*) syntactic computer has to do every effort to avoid nonlinearities in the circuits. *Logical computing* can be carried out reversibly in principle: dissipation of free energy into entropy per logically reversible operation can be made arbitrarily close to zero. This is the condition for the output uniquely specify the input.

3. *Descartes' mechanistic mistake*. It comes from the *metaphor* "***animal inner and exterior motion the same as clocks inner motions (wheels) and exterior motions (counterweights, pendulum)***": the *holistic* character of biosystems, in which structure and function are just *one and the same thing*, has nothing to do with a fully dismountable mechanical system (cf. [15]). In physical terms, in biosystems the mechanical degrees of freedom and the electronic degrees of freedom are inseparable. Monsieur Descartes would be hopeless in *jouer à Dieu* on his own principles.

4. The "*great puzzle of biosystems*": this is often neglected and consists in the fact that biosystems, as dissipative systems (***input energy flow = output energy flow***) do not show any consumption of energy though their inner processes generate a dynamic order. This cannot be explained by classical physics, and is a strong indication that biosystems are essentially macroscopic quantum systems with information generated *on the nanolevel* that goes up to the macroscopic level. A Thermal Quantum Field Theoretic approach [18] based on collective *massless modes* condensation into the ground state energy could supply the solution, as such modes, being massless, would give no contribution to the (dynamically ordered) ground state.

5. *Considering modern science as the triumph of the category of quantity*: this is a misconception indeed. Actually, modern science is the triumph of *quantifiable qualities* [10]; e.g., the notion of mass ultimately is a quantifiable quality. *Quality*, i.e. meaning, is the category that should be introduced in our study of life, e.g. by geometrizing any complex dynamic problem, as Geometry and Topology are both quantity and quality. They could be the *energy-free* computing way followed *heuristically* by biosystems as *nanostructured computers* to overcome any non-computability and insolvability occurring in a dynamic description of hierarchical levels with large inter-level energy gaps, hence of very different relaxation times. Biological codes are based both on frequency-depending and *spatial arrangement*-depending interactions. Nature does not work as an engineer. She works *extralogically* and mainly dissipatively as a tinker.

6. The Devil in the Chair of Logic

> ... *Maybe you didn't think that I was logical.*
>
> Dante's Inferno, xxvii, 61-129
>
> MEPHISTOPHELES: *Tell me, before we continue speaking, what Faculty are you going to choose.*
>
> STUDENT: *I should like to become well learned, and I willingly should span all in sky, earth and Nature that my mind could understand.*
>
> MEPHISTOPHELES: *Then you are on the right way, ... but don't let yourself be distracted. My dear friend, first I advise you to matriculate in the Collegium Logicum*.* [*Logic College]
>
> Goethe, Faust I. 1896 – 1911

The first one of such quotations concerns Devil's success by logically arguing very subtly in proving that the soul of friar Guido da Montefeltro had to be condemned to hell in spite of God's forgiveness for his sins; in the second one, the Devil dressed in gown and wig of a university professor advises an enthusiastic student to study logic first. Logic appears as a Devil's creation indeed, allowing to catch even God in fault, so forcing believers to faith in an unshaken truth. And now Devil's logic goes on stage again and strikes hard with devastating remarks as to self-organization and cognition.

I had just finished working out a possible description of an evolutionary chain in terms of self-organization, cognition and abstraction (cf. **1.1** in Section **5**) based on highly nonlinear nanochaotic differential equations, when somebody, dressed in an old-fashioned way, wearing gown and wig of an 18th century university professor, knocked at the door and came in gently (or ... did I happen to doze?) – *Can I see your notes? I am so interested in your research on evolutionary processes on the nanoscale ...* – Yes please, here you are. – *Thanks.* He sits down and reads; then – *Er ...there's something here that I do not understand ...Or better, needs some deepening from the logical standpoint ... You say that a chain of increasing abstractions can be attained through dissipative compression to n-dimensional nanochaotic dynamic spaces and formation of categories through the separatrices of basins of attraction in the phase space. But is there any maximum in this chain?* – No; there would be no limit to evolution. – *No problem; but what about the minimum level? Where does your chain begin? Or, is there a minimum level of abstraction? If Gödel's incompleteness theorems are true, then it is impossible to think of a minimal hierarchical level, i.e. the lowest irreducible cognitive level throughout the whole chain of levels of abstractions; or, stated otherwise, a system of* ***self-consistent and complete axioms****. The hierarchy would be bottomless,* ***a logically and physically unattainable depth.*** *If these theorems are not valid, then there would be a hierarchical level of "minimal abstraction", that might look like leading to paradoxes* *which could be shown illusory: indeed, the level structure in the* ***logic space*** *could be described by some corresponding physical processes in the* ***phase space*** *and rooted in the ultimate physics of the Universe ... Do you realize all that? It has something to do with your paper in [16] ...* – Er ... I realize that I have formulated in physical terms what was a problem of Scholastic Philosophy in the Middle Ages: ... William of Ockam, Duns Scotus, Anselm of Canterbury and ***his five proofs of the existence of God*** ... just that longed for **set of self-consistent and complete axioms!** ... ...

The strange figure vanished, carrying with itself my beliefs in having grasped firmly the physical meanings of self-organization, cognition and evolution: creation of really *novel*, soundly anti-entropic information, or just a rearrangement of information written in the primeval fabric of the Universe doomed to run down to entropy? This would depend on the thermodynamic state of the Universe at its very beginning... in equilibrium or far from equilibrium? The meaning of life would appear actually as closely connected with the fundamental cosmological problem.

7. Conclusion

Raffiniert ist der Herrgott, aber boshaft ist Er nicht. *
[**Subtle is the Lord, but malicious He is not*]

Albert Einstein during his first visit to Princeton University April 1921).

I have second thoughts. Maybe God is malicious.

Albert Einstein to Vladimir Bargmann, as quoted in *Einstein in America* (1985) by Jamies Sayen, indicating that God leads people to believe they understand things that they actually are far from understanding.

Subtle is the Lord, and the Devil too, alas! Nanophysics and Nanoengineering must become much subtler for enabling Synthetic Biology and Synthetic Life, i.e. for playing God **safely**. Will they actually develop tools and concepts for full control – *decrypting* by dialoguing – of biosystems? Maybe evolution will take our cognitive levels to so upper ranks of abstraction as to compress semantics (physics) and syntax (logic) to the very gist of energy, matter and information, so causing us to be able to work as tinkers, not as engineers.

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