Stepping Beyond the Newtonian Paradigm in Biology

Towards an Integrable Model of Life:
Accelerating Discovery in the Biological Foundations of Science

White Paper

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The best of science doesn't consist of mathematical models and experiments, as textbooks make it seem. Those come later. It springs fresh from a more primitive mode of thought when the hunter's mind weaves ideas from old facts and fresh metaphors and the scrambled crazy images of things recently seen. To move forward is to concoct new patterns of thought, which in turn dictate the design of models and experiments.

Edward O. Wilson, The Diversity of Life, 1992, Harvard University Press, ISBN 0-674-21298-3.

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Note: This White Paper is not a concise report on the research program we seek to elaborate in INBIOSA. It has been conceived as a 'living' document, progressively developed along the months by discussions among scientists with differing formations and states of mind. We have chosen to respect their personalities, at the risk of some lack of homogeneity and repetitions between different passages. Also, incompleteness, inconsistences and antagonisms could not be completely avoided.

This document is not intended to question the goals or the validity of Systems Biology or its approaches. However, it is necessary to clearly differentiate what our Integral Biomathics community is attempting to do from what systems biologists are already doing.

Contents

We still know little about how the world works, and these limits are acknowledged in our emergent biological systems and in the frontiers of astrophysics. A new mathematical foundation could punch through those barriers and produce completely unexpected benefits.

The reason that biology has failed to develop a viable set of mathematical methods appropriate to solving its problems is that we have relied too long on mathematics developed to model physical problems that are intrinsically different.

The goal of the INBIOSA project is to devise a long term research program for naturalistic biocomputation based on a general theory of entangled coherent complex systems, both living and non-living ones, from quantum computers to the human brain.

We focus on an integral/wholist, approach to dynamic, ordered, layered systems and on the development of their emergent properties and structure. At its core is a set of principles, "axioms of life" upon which we build a testable formal theory.

We use both, a top down and bottom-up approach, modeling natural behaviours from the simplest proteins to complex systems (bodies and societies).

Executive Summary

The INBIOSA project brings together a group of experts across many disciplines who believe that science requires a revolutionary transformative step in order to address many of the vexing challenges presented by the world. It is INBIOSA's purpose to enable the focused collaboration of an interdisciplinary community of original thinkers.

This paper sets out the case for support for this effort. The focus of the transformative research program proposal is biology-centric. We admit that biology to date has been more fact-oriented and less theoretical than physics. However, the key leverageable idea is that careful extension of the science of living systems can be more effectively applied to some of our most vexing modern problems than the prevailing scheme, derived from abstractions in physics. While these have some universal application and demonstrate computational advantages, they are not theoretically mandated for the living. A new set of mathematical abstractions derived from biology can now be similarly extended. This is made possible by leveraging new formal tools to understand abstraction and enable *computability*. [The latter has a much expanded meaning in our context from the one known and used in computer science and biology today, that is "by rote algorithmic means", since it is not known if a living system is computable in this sense (Mossio et al., 2009).] *Two major challenges* constitute the effort.

The first challenge is to design an original general system of abstractions within the biological domain. The initial issue is descriptive leading to the explanatory. There has not yet been a serious formal examination of the abstractions of the biological domain. What is used today is an amalgam; much is inherited from physics (via the bridging abstractions of chemistry) and there are many new abstractions from advances in mathematics (incentivized by the need for more capable computational analyses). Interspersed are abstractions, concepts and underlying assumptions "native" to biology and distinct from the mechanical language of physics and computation as we know them. A pressing agenda should be to single out the most concrete and at the same time the most fundamental process-units in biology and to recruit them into the descriptive domain. Therefore, the first challenge is to build a coherent formal system of abstractions and operations that is *truly native* to living systems.

The paradigm shift in biology comparable to those invoked by the theory of relativity and the quantum theory in physics has not yet been achieved.

Organisms are not machines. Life is not a specialization, but rather an expansive generalization of mechanism.

Living systems should not always be modeled as physical systems are, since the frontiers of living systems are hard to define and are changing at any time.

A living system is impredicative and self-referencing: its definition invokes the system itself, or perhaps another set which contains it. This is what makes it more than a machine.

Classical computing is based on precise algorithmic procedures which are immensely suited to model mechanisms. This quality, however, is exactly what makes it unsuitable to model impredicativity, life, since a consequence of impredicativity is the entailment of ambiguity.

Nothing will be thrown away, but many common methods will be philosophically recast, just as in physics relativity subsumed and reinterpreted Newtonian mechanics. This step is required because we need a comprehensible, formal system to apply in many domains. Emphasis should be placed on the distinction between multi-perspective analysis and synthesis and on what could be the basic terms or tools needed.

The second challenge is relatively simple: the actual application of this set of biology-centric ways and means to cross-disciplinary problems. In its early stages, this will seem to be a "new science".

This White Paper sets out the case of continuing support of Information and Communication Technology (ICT) for transformative research in biology and information processing centered on paradigm changes in the epistemological, ontological, mathematical and computational bases of the science of living systems**.** Today, curiously, living systems cannot be said to be anything more than dissipative structures organized internally by genetic information. There is not anything substantially different from abiotic systems other than the empirical nature of their robustness. We believe that there are other new and unique properties and patterns comprehensible at this *bio*-logical level. The report lays out a fundamental set of approaches to articulate these properties and patterns, and is composed as follows. **Sections 1 through 4** (preamble, introduction, motivation and major biomathematical problems) are incipient. **Section 5** describes the issues affecting Integral Biomathics and **Section 6** -- the aspects of the Grand Challenge we face with this project. **Section 7** contemplates the effort to formalize a General Theory of Living Systems (GTLS) from what we have today. The goal is to have a formal system, equivalent to that which exists in the physics community. Here we define how to perceive the role of time in biology. **Section 8** describes the initial efforts to apply this general theory of living systems in many domains, with special emphasis on cross-disciplinary problems and multiple domains spanning both "hard" and "soft" sciences. The expected result is a coherent collection of integrated mathematical techniques. **Section 9** discusses the first two test cases, project proposals, of our approach. They are designed to demonstrate the ability of our approach to address "wicked problems" which span across physics, chemistry, biology, societies and societal dynamics. The solutions require integrated measurable results at multiple levels known as "grand challenges" to existing methods. Finally, **Section 10** adheres to an appeal for action, advocating the necessity for further long-term support of the INBIOSA program.

This proposal addresses the fundamental problem in biology: how to characterize the distinction between the living and the non-living.

We aim at creating a discourse environment for exploring radical approaches to mathematics and computation within biological context with the potential for a breakthrough and paradigm shift.

The understanding of living processes has not been amenable to orthodox mathematical modeling and logic despite enormous advances in computational and experimental tools.

There could be a possible paradigm change to DEVELOPMENT, not evolution as the basic orientation of biology. The living / non-living gap can never be closed without it.

A basic perspective opposite to the 'growth ideology' of our culture could be truly a radical departure.

The report is concluded with preliminary non-exclusive list of challenging research themes to address, as well as required administrative actions.

The efforts described in the ten sections of this White Paper will proceed concurrently. Collectively, they describe a program that can be managed and measured as it progresses.

1. Preamble

Fundamental assumption: all natural objects and phenomena have representations in the language of mathematics. Biology is a subject concerned with the organization of relations. Life is not primarily characterized by its underlying physicochemical structures, but by its entailment relations – by what the physiochemical structures do, and to what end.

Organisms are not man-made machines. Life is not a specialization of engineering; it is an expansive generalization of engineering, subject to regulations of internal origin. To answer biological questions, it is therefore insufficient to follow the reductionist strategy derived entirely from the Cartesian metaphor and Newtonian mechanics. Such a 'watchmaker' approach is often limited to breaking down a complex entity into simpler pieces, to examine the pieces themselves, and then to attempt to understand the organism from a parts-only perspective.

It is necessary to revive efforts to advance science beyond such reductionism; its failure is due to the inability of a small surrogate representation to exhaust the real world's complexity. The limits of physicochemical and mechanistic dogma are specific examples of the restrictiveness of self-imposed methodologies. The resulting artificial 'limitations' on science and knowledge are due to the non-generic nature of the methods and their associated bounded microcosms. The obstruction of the advance of science beyond such limitations is not merely a problem within science; it has left societies floundering in the face of what are now called 'wicked problems', problems that cannot be dealt with by the old forms of science.

Classical computing, framed today in third person descriptions, is often based on unambiguous known algorithmic or rote procedures; it is this lack of ambiguity that makes it precisely suited to modeling mechanisms. A living system is impredicative and self-referential: this is what makes it more than a machine. We might call it a new variety of machine, perhaps a relational machine, as yet, not fully entailed. The introduction of the *self,* the *subject* in addition to the *object*, makes the participation of first person descriptions inevitable. The precision of conventional classical computing makes it unsuitable for modeling impredicativity and its natural entailment of ambiguity. Ambiguity is by no means an infamy: it is a great asset to biology in its redundancy, its ubiquitous degeneracy properties and survivability. INBIOSA will shed light not only on third person descriptions of biology, but also on first person descriptions for both organisms and machines. For computation to be a successful tool in biology, it must go far beyond any strict limitation of currently known algorithms. However several properties of living systems, including impredicativity can be computed, for instance by using typed (polymorphic) programming languages (Mossio et al., 2009). While we often speak of "mathematics" and "computation" in this INBIOSA White Paper, these terms are not intended in a narrow, classical sense[1].

2. Introduction

The goal of the INBIOSA support action is to devise a long-term research program for naturalistic biocomputation. There are two problematic areas in this enterprise: mathematical techniques, and their ability to enable reflection on biological processes. Currently available mathematical techniques appear to be insufficient to deal with the complexities of biology, and biological processes do not easily lend themselves to traditional mathematical analysis. The central target of INBIOSA is to devise ways in which these two initially independent domains may be resolved and integrated into a common framework. There are a number of different regimes within which this integration may be attempted. A major theme of INBIOSA is to critically consider each of these regimes to see where common ground may be found. It is not initially obvious how biocomputational integration must, or can take place, but the evidence of the natural world is that such integration is itself natural. While an easy starting place would be to try to extend the reductionist position to include biology, this is likely to be unsuccessful or at least incomplete, and we will almost certainly need to step beyond the Newtonian paradigm (Ulanowicz, 2009; Simeonov, 2010a/b) in search of success. One alternative approach, for example, could be based on a general theory of entangled coherent complex systems, both non-living and living, from quantum computers (e.g. Monz et. al., 2011) to the human brain (e.g. Ehresmann & Vanbremeersch, 2007). Karl Pribram (Pribram, 2001) has proposed that one kind of quasi-quantal neural processing takes place within the 'axonite mesh' between neurons. The associated presumption would be that if entangled quanta can 'calculate' by methods more powerful than Boolean algebras, then entangled nerves can also 'calculate' at a higher level than individual ones. Multicellular systems (animals, hearts, kidneys, brains, etc.) work as unified entities, and exhibit emergent effects, which are not immediately obvious from the properties of their constituent cells.

[1] In particular, computation belongs to the modern philosophical view of reality in which information assumes place of substance, and computation of the dynamics of its transformation (Collier, 2004).

Biological systems are integrated through their complementary functions and structures, so that they can only be treated *properly* as causally integrated systems. Our mistake until now in biology has been to treat them as if their causal integration matters less than their syntactic integration (as in computer programs).

To understand and explain how biological systems work is the task of Integral Biomathics (Simeonov, 2010a/b) and of the INBIOSA project. In the distinction between living and non-living systems, and the consequent generation of *meaning* (Rosen, 1991; Cottam et al, 2005; Gare, 2008; Louie, 2009), the basic questions we ask about *computation* from a revised conceptual framework are:

i) *What* is computation within the biological context?

ii) *How useful* is computation for living systems, where usefulness is considered from the viewpoint of the entity performing the computation?

iii) *To what extent* can a computation be carried out in an organism or an ecosystem with the available resources?

Returning to the quantum mechanical domain, the underlying central question, which may indeed deliver breakthrough answers, is:

> *What can serve as a cohesive factor for making biological beings as they are?* Can we take *quantum entanglement and superposition models from physics and apply them to biology and, vice versa, can we use models of integrated biological systems to model quantum entanglement and superposition? How can we relate the occurrence of a cohesive factor unique to biology to nonlocal simultaneous correlations available in physics in general and in quantum mechanics in particular?*

One associated area of investigation, which has up to now received little or no attention is the possibility that biology makes use of quantum logic without the implication of physical quantum systems (Schroeder, 2009; 2011). We will come back to this issue in sections 5.8 and 7.4.

It is not entirely beyond the bounds of reason that biological processing may rely on large-scale quasi-entanglement. In this case we could postulate that individual cells in an organism are entangled to work in a coherent way. The key question would be to understand the *meaning* of this biological computation and entanglement of the whole organism. But this and other similarly specific questions should be tackled in the context of the two initial difficulties we cited – those of mathematical viability for biology, and of biological process suitability for mathematics. We will address these two aspects in the following sections of this document. We must also come to understand how lower level quantum processes affect other biological processes unfolding on differing scales in the body, flowing up to the level of consciousness and behavior in the lived environment over time. This will be discussed in section 5.2 *Scale and Hyperscale* and in section 5.8 *Quantum Effects in Biology*.

3. Motivation

In the history of science it is noted that Laplace had a checkered career. He seemed to work on physics or astronomy for several years and then drop this and switch to studies of pure mathematics for a few years; then suddenly, he would switch back to physics or astronomy, and so forth for decades (Gillispie, 2000). Laplace was such a productive scientist and mathematician because the two fields were completely integrated in his mind. He derived his mathematical problems from his astronomical and physical researches and his astronomical and physical problems from the regions in which existing mathematical methods failed. So in practice, what Laplace did was to study a physical process, develop a model for the behaviour of the system that would, in turn, yield a set of equations describing the model. More often than not, because Laplace focused on processes that had no adequate physical explanation, he would find that it was impossible to solve the equations needed to model the system. Being a first-rate mathematician, he would therefore refocus his efforts on deriving from first principles the new methods necessary to solve the sets of equations he had invented. This effort often took him several years. Once he had satisfactorily set that new area of mathematics to rights, he would go back to his astronomical or physical studies, apply his new mathematical insights to his models, and see what kinds of new problems these revealed. This story is important in devising a new field of biomathematics: those undertaking the work should understand that, historically, both science and mathematics have provided each other with fruitful problems and methods. Laplace was not a mathematical physicist or a physical mathematician, but both, simultaneously. This integrated (or back-and-forth) view of the relation between science and mathematics is quite at odds with the dominant (and long-outmoded) Comteian positivistic philosophy of science that still predominates among scientists and mathematicians today.

Positivism explicitly posits the notion that science is founded in logic, and mathematics drives progress in the rest of science, so that it is possible to rank-order the scientific reliability of a field by the degree to which it has become mathematized. The increase in “positive knowledge” is always from mathematics through physics to the “softer” sciences.

There are two errors in this positivistic philosophy. One is that even pseudoscience[2] can be expressed in terms of equations, (making the pseudoscience no more ‘true’ than it was when expressed only in words). The other error is to mistake the purpose of mathematization as being primarily a means of validating scientific research. To the contrary, mathematics can provide novel tools for exploring scientific problems. But that said, existing mathematics does not contain all the possible tools that scientists may need. Like Laplace, present-day mathematicians are likely to find fascinating and valuable mathematical problems by learning enough biology to understand where existing mathematical tools fail. From this perspective, mathematics is useful to any given science only to the extent to which it is appropriate to addressing the problems posed by that science.

[2] Pseudosciences are often promoted by sects as true sciences with the support of mathematical modeling, thus misleading even serious researchers, including biologists.

Simply mathematizing biology using existing methods does not add anything to our understanding of biology unless the mathematics illuminates points that non-mathematical statements of the same models or theories cannot address. Unfortunately, many scientists make their models conform to existing mathematical methods rather than doing what Laplace did, which is to devise an appropriate model and then invent the mathematics to describe it. Thus, historically, “mathematical biology” has not yielded many deep insights.

The history of science suggests a second reason that mathematics has not been as useful in the biological sciences as in the physical sciences. Scientists tend to ascribe the power of physical sciences to their mathematization, but the real power has come from the ability of astronomers and physicists to define their problems accurately and precisely enough for mathematical methods to be valuable. The emphasis here is on problem finding and defining. Historically, chemists, biochemists, biologists, and social scientists have rarely been able to define their problems with the precision and accuracy of the physicist or astronomer, making the mathematical investigation of their relatively “fuzzy” problems difficult. Thus, one reason for the lack of mathematics in biology is that the lack of well-defined problems has made the field less amenable to mathematization than, say, physics. Recognizing that categories in non-physical systems are often ‘fuzzy’ is, in fact, what led Zadeh to invent his theory of ‘fuzzy sets’, a major advance for both mathematics and modeling in biological and social sciences (Zadeh, 1965). The degree to which we can define our biological problems accurately and precisely enough to intrigue mathematicians will determine whether we make progress in developing biomathematics, e.g. in working toward defining new forms of dynamic relational sets.

The third reason that biology has so far failed to benefit from mathematization to the degree that physics and astronomy have, is that the mathematics that is used to describe physics and astronomy developed hand-in-hand with those sciences but has not developed hand in hand with biological problems. Laplace is hardly unique in having had hands in both mathematics and physics simultaneously – think Descartes, Leibnitz, Lagrange, Fourier, Poincare, etc. Unfortunately, the mathematical methods developed to model physical processes do not (in general) illuminate biological problems. Biology is not chemistry, which is not physics. Simple hierarchical reasoning states that we can recognize a new level of organization when the principles, properties and models that worked for the previous level of organization can be reinterpreted and harnessed by the higher level (Weiss, 1971).

Chemistry becomes chemistry (and not physics) at the point where we can ignore the physical properties of the components carrying out the chemistry. We don’t need an understanding of nuclear physics to describe the kinetics of a chemical reaction; we don’t need to know the movements of every molecule in a gas to measure its temperature or volume; we don’t need an understanding of electron shells to explain how DNA encodes genetic information. Similarly, biology becomes biology and not chemistry when we can ignore the chemical properties of the components carrying out the biology. For example, Mendelian genetics was invented without any concept of the structure of a gene, let alone what macromolecular structure encoded genetic information. Darwinian evolution by survival of the fittest does not rely upon any chemistry at all! This is not to say that biological systems are not comprised of chemicals or to deny that they obey the laws of physics, but rather to make the point that biological systems are recognizably biological because they have organizational properties that allow them to carry out processes that cannot be accounted for purely on the basis of the physics and chemistry of their individual components. So, what we need is new mathematical notions and a new concept of computing, but also a number of new mathematical tools, that permit us to model the emergence of new properties resulting in the carrying out of novel processes as a result of innovative forms of organization within complex systems. Or, put more simply, a mathematics which will be appropriate to biology must be motivated by problems that are biological in their origins and nature, just as mathematics appropriate to physics was physical in its origin and nature.

Thus, to develop a new field of biomathematics, we would propose that we behave as a community as Laplace and his colleagues did, by going back and forth between the science and the mathematics, letting each inform the other. Biology has much to contribute to mathematics, especially to the development of new forms of mathematics appropriate to solving the kinds of problems that make biology different from physics or astronomy. And biology-inspired mathematics can be expected to return to biology the same kinds of gifts that physics-inspired mathematics returned to physics. Indeed, not until we abandon the Comteian idea that mathematics should drive science, will biology benefit, as it should from mathematics. Reversing the equation, and permitting biology to drive the mathematics (at least half of the time!) may yield us new insights as important as those generated by Laplace and the other physicist-mathematicians who founded their fields. Moreover, it may revolutionize mathematics itself, just as the focus on physical problems motivated many of the great mathematicians of the past.

But Integral Biomathics is not going to be a purely theoretical discipline. Because "simulation" is not only running a discretized differential equation on a computer, and visualization is not only graphical imaging and animation, it will also explore the creation of *new simulation and visualization paradigms* and techniques for biological phenomena. The reason behind this multi-perspective, quantitative-emergent approach is that there are certain emergent features of fundamental processes that cannot be easily described/captured by closed form, differential or any currently known mathematical object or expression. A good example can be found in molecular dynamics (MD). For instance, if we want to computationally assess a macroscopic constitutive parameter such the permeability of a cell membrane with respect to a given molecule, then much insight can be gained by simulating the dynamics of a large number of molecules of the different species involved, whereas trying to find some elegant mathematical equation that will answer the question may currently fail. The same holds for instance in astrophysics where simulation techniques such as smooth particle hydrodynamics are used to study the formation of complex astronomical objects such as a galaxy. In both these examples the emergent complexity is assessed via simulation in which the mutual interactions between the objects themselves are described by simple laws (e.g. Newton's law of gravitation and those of classical electrodynamics). Cellular automata, e.g. (von Neumann, 1966; Wolfram, 1994; Wolfram, 2002; Miller & Fredkin, 2005) are another example of how a simulation tool can produce emergent behaviour by simulating the dynamics of agents that follow simple rules.

Therefore, we consider the development of *new kinds* of biologically inspired simulation and visualization methods as part of the INBIOSA research program from which emergent features can be rigorously analyzed. They constitute part of the intermediate steps towards the discovery of new abstract mathematical tools enabling virtual experimentation, and enable with systems to study complexity and emergence.

4. Major Biomathematical Problems

What kinds of well-defined biological problems exist that seem not to be amenable to current mathematical approaches, or have simply been overlooked by mathematicians who already have the kinds of novel approaches that would open up these biological areas to formal analysis? INBIOSA's collaborators and colleagues have been struggling with *six such areas*, all of which are general enough to have broad implications both in and beyond biology and are therefore potentially worth the effort of a mathematician to explore. All of them, in one way or another, share the common feature that the systems that need to be described combine some type of continuous function with some type of discontinuous function and some add the fillips of vector/tensor, relational and geometrical aspects as well. The mathematical challenge is how to analyze biological problems that currently exist in two or more of these domains thought to be unrelated in orthodox mathematics.

The first problem concerns the modeling of a cell as a dynamic process. The cell itself is a discrete object yet the flow of materials in, out, and through a cell is continuous[3]. Moreover, if one asks at any given time what defines the cell, the details of this description will differ fro those at any other time. For example, when a cell replicates, it breaks down its Golgi apparatus, its actin fibers, and various other cell organelles, into the molecular constituents from which they are assembled. These molecular constituents are randomly distributed into the two daughter cells. Both of the resulting cells are still cells of the same species as the parent cell, yet neither has exactly the same number or even exactly the same proportion of cellular constituents as the parent cell or as each other. So clearly there is "variance" in the absolute numbers and in the proportions of the constituents of a cell within which the cell can still function as a cell. Moreover, the rates at which these constituents turn over, are replenished and excreted also vary from cell to cell and from instant to instant. Now, this variance[4] is clearly open to experimental manipulation. One can dehydrate cells and find out how little or how much water they require or can sustain and continue to live. One can destroy particular cellular constituents, or block particular receptors or transporters, and see how these modifications affect the proportions of other cellular constituents in relation to whether, and how, the cell continues to function.

So we can obtain plenty of quantitative data. But what do these data mean in terms of what the interactive variances in constituents can be within a living system? The problem becomes even more complicated when we start playing with cellular structures and macromolecules. While there are so many molecules of water or glucose or ATP in a cell that it might be acceptable to model cellular dehydration as a continuous function, one cannot vary the numbers of actin fibrils, Golgi apparatus, mitochondria, chloroplast, ribosomes, nucleoli, centrosomes, chromosomes, etc. as continuous functions. These are discrete variables, with variances that are measured in discrete units.

[3] The flow of material is actually a flow of discrete particles, but the time flow may be considered continuous. In fact, the discrete/continuous duality does not reflect a fundamental modeling necessity, but the consequence of observer's perspective, (s. section 5.4) and modeling choice.

[4] Under steady-state conditions the cell's total mass must remain constant otherwise it would increase or decrease in size (which is the case when a cell is dividing or differentiating). Barring statistical fluctuations changes over time of some cell products like hormones depend on the context (e.g. signaling from other cell types) that explains (at least partly) the variances.

The mathematical problem therefore becomes one of finding means to utilize all of this information, both continuous and discrete, in an integrated model that lets us understand what the limits of variance, and the limits of life, are for a functioning cell[5].

Secondly, posing the question of what constitutes a cell in this way has provoked interest in set theory as a possible basis of a new biological mathematics. But the current state of set theory seems inadequate in two fundamental ways. First, cells are autopoietic – they form themselves. Indeed, evolutionary theory asserts that cells evolved from primordial aggregates of self-organizing compounds built from even simpler interactive modules, back to the primordial soup. Sets, at least as they exist in mathematical forms, are not autopoietic. Existing set theories use axioms which limit the way sets are defined, for instance by limiting the expressions describing their elements to avoid self-reference, which in turn is a critical property of living systems. Development of a set theory suitable for such systems could be attempted, for example allowing sets to be defined by dynamic rules, including self-referential ones, so as not to produce paradoxes, but to permit autopoiesis[6] (Maturana & Varela, 1980). This is, in a sense, what complexity theory is about (e.g., Kauffmann, 1993), but complexity theory does not incorporate most of the useful features of set theory. Could a mathematics that described autopoietic sets through complexity-like theory exist? Might it shed light on the evolution of the “sets” we call “cellular life” by permitting us to describe continuous functions that produce rules that then limit the entry and exit of possible components of the set, and that can undergo transformations (metabolism) within the set? After all, this is what cells do. So why not develop a mathematics that describes what nature can already do? Another way in which modern set theory cannot be trivially applied to tackle biological problems is because biological sets have the variance property described above. Any given cell must have chromosomes, but their number can vary (as they do in cancers and parthenogenotes) and still be viable; they can have many or few ribosomes and mitochondria and still live; they can accumulate certain amounts of toxins or lose a certain amount of key ions and still function; etc. So in addition to inventing autopoietic sets, is it possible to invent sets that are not defined by specific numbers of constituents, but by variances within which all of these constituents must exist. A bacterial cell that becomes dehydrated may die, or it may sporulate. How can some form of set theory be devised that models the process of switching between stable states when certain variances are exceeded? What, in general, does such a state-sensitive, mathematical set look like? How does it behave? What properties does it have that sets, as currently defined in mathematics, do not? How might these new set properties inform living systems and perhaps even our understanding of social processes, supply chains, and other useful functions? Since the origin of the first protocells/autocells is imaginable, this approach appears reasonable. But since we have no idea about the origin of the genetic apparatus where does that get us?

[5] In this *First Problem* there are actually three sub-problems, where the first one is somewhat unrelated to the other two: i) combining discrete with continuous quantities, ii) explaining their variances and their interrelatedness, iii) discovering the cells’ functioning (and non-functioning) parameter ranges. Regarding the third sub-problem, dynamic systems theory, sensitivity analysis and bifurcation theory seem to provide some tools to tackle it.

[6] The mathematics necessary to cover/explain autopoiesis may *not* necessarily require “autopoietic” sets but self-referenced objects. An alternative approach could be to define an object by the transitions rules (predicates) that hold over pairs of objects. This allows under certain circumstances a (static) mathematical description of an object that would self-replicate in simulation space. However, we wish to go beyond these limits.

So one thing that is needed in our new biomathematics is a way to model self-emergent sets (origins of first cells; self-assembly of viruses, etc.) But these self-emergent sets would seem to need the ability to carry out functions (selecting/rejecting among possible components; minimizing what a physicist thinks of as free energy; etc.). One possible focus of a new biomathematics would be to invent an appropriate theory of self-emergent sets that can carry out functions within variances.

Such a theory would preferably incorporate the work that has been done on understanding hierarchical systems' emergent properties, complexity theory and so forth. Such a mathematics would therefore be extraordinarily integrative, a point to which we will return.

Thirdly, a biological problem related to set-like properties is that organization strictly limits variance through the formation of modules in a manner that requires diligent ways of using probability theory. Imagine a clueless, blind "watchmaker" of the sort that Richard Dawkins likes to put in charge of evolutionary processes. But let this watchmaker carry out a process first investigated by Herb Simon in one of his little known and under-appreciated essays on evolutionary processes (Simon, 1981). Combining Dawkins's and Simon's watchmakers produces the following scenario that exemplifies one of the critical problems that needs to be addressed in the origins and evolution of life. Imagine two watchmakers, the first of whom must randomly assemble 25 parts in order to put together a "watch". This completely ignorant watchmaker must explore every possible combination of the 25 parts he has in front of him, which is to say 25!, or about 1.55×10^{25} possibilities! If it took a single minute for each of these possibilities to be explored, our watchmaker would not succeed in making even a single watch within the lifetime of the universe! Moreover, because he's just a random assembler and cannot learn from experience, he has to explore all these possibilities each and every time he tries to build a watch! Clearly, such an entity working by such a process would, for all intents and purposes, never succeed, making *de novo* evolution of life virtually impossible.

But what Simon first recognized, and Root-Bernstein has developed (Root-Bernstein and Dillon 1997; Hunding et al., 2006), is that an equally clueless, blind and random watchmaker who uses stable modules built on the principle of molecular complementarity would succeed, and astoundingly quickly! Simon's model assumed that the watchmakers knew how to make a watch (a clearly un-biological assumption), from which he derived the following equation: the time required for the evolution of a complex form from simple elements depends critically on the number and distribution of potential intermediate stable forms. In particular, if there exists a hierarchy of potentially stable 'sub-assemblies', with about the same span, s, (i.e., the number of parts or components required to form each stable subunit) at each level of the hierarchy, then the probability that a subassembly process will be completed within any given time, T, can be expected to be about $1/(1 - p)^s$, where p is the probability that the assembly process will be interrupted during time T. Clearly the less stable each step is in the assembly (i.e., the greater p is) and the larger the number of components that must be assembled to achieve a complete assembly (s), the less probable any particular assemblage is to evolve. Conversely, the more stable each step in assembly is (i.e., the smaller p gets) and the smaller the number of components required to produce a completed assembly (s), the greater the probability an assemblage is to evolve, (Simon, 1981, p. 203).

The implication of Simon's model is that we should therefore expect evolution to be characterized by the selection of semi-stable modules arranged in a hierarchical fashion that minimizes wasted time, effort and resources. This is precisely what we do see. But Simon's model is not an accurate portrayal of the biological problem. The problem with Simon's model is that evolutionary watchmakers do not know how to make a watch and must search randomly for stable modules. Fortunately, molecular complementarity between compounds naturally forms such stable modules, so these come into existence in just the kind of random fashion that needs to be assumed. So once again assume our modular watchmaker needs to make a watch from 25 pieces, but also assume that she makes her watches in five stable sets of five ordered parts. Stable five-element modules could be built by exploring only 5! possibilities or just 120 combinations. Then our modular watchmaker would need to explore randomly the 5! possible combinations of these five modules, or another 120 possibilities. Altogether, the modular watchmaker explores only 720 = 6! possible combinations, which, if they could be explored at one possibility per minute, would yield a watch every two hours. Quite a difference from 1.55×10^{25} minutes to explore the original 25! combinations! The impossible becomes highly likely[7] (Root-Bernstein, 2012)!

Now, obviously the advantage of modularity is not as great as just stated for a real, molecularly complementary system. Firstly, stable modules might not result from any given set of five components so that our modular watchmaker may have to explore more sets than we have assumed. Secondly, the specificity of module building is not perfect and some non-functional modules will also likely be stable, confusing final assembly. We can also assume that the proper modules will out-compete the improper ones in producing complete watches, but this may not be the case if improper modules, inefficient at assembly as they may be, so out-number the proper ones as to swamp them. Finally, there is no biological reason to assume that stable modules have five components – the number could vary from two or three to two or three dozen per module. And this is exactly the point at which current probability theory is improperly applied. How do we model the kind of system we have just proposed in which modular sets are formed in a reversible manner, may contain variable numbers of components, and compete with each other in a probabilistic scenario?

Again, such a kind of mathematics must exist, since Nature already performs these functions, but what does that mathematics look like? Perhaps it is not a matter of the non-existence of certain types of mathematics, but rather that the appropriate type of mathematics has not been applied to these questions. We do not know. What matters is that these questions are still looking for mathematical answers.

[7] However, it is necessary to pay attention to the principle of minimum of three levels of modules in hierarchy theory (Salthe, 1985): more is fine, but fewer – logically unworkable.

The importance of being able to address this modularity-probability problem is illustrated by the fact that the formation of complementary module building within complex systems can prune out huge numbers of possibilities at each step of hierarchical assembly. In general, the greater the number of pieces, and the more modular steps involved in the process, the more efficient the process becomes. Given the mathematics of these probabilities, there must be some optimal number of pieces per module, and an optimal number of modules per functional unit and an optimal stability that must be attained. All of these variables must be optimized so as to maximize the rate at which functional modules are generated while minimizing the number of possibilities that must be explored. Our assumption is that nature has already solved this problem. Analyzing naturally occurring modular hierarchies for rules of optimization might therefore have vast implications not only for understanding the evolution of life, but also, as Simon (1981) notes in his original essay, for the most efficient design of chemical, technological, and even human systems of organization.

We have already alluded above to various biological problems that require working at the interface between continuous and discontinuous functions. One might posit that most of biology consists of sets of problems that exist at this continuous-discontinuous interface. For example, chemical neurotransmitters (working continuously) release a single electrical discharge (occurring discontinuously); individual organisms can potentially interact more or less strongly with other individuals by means of chemical messages (continuously variable) that determine whether they develop as many individuals or transform themselves into a single super-organism (a biofilm). How can we mathematically handle interactions that may vary continuously but act on a small set of definable individuals? These are not amenable to modeling solely using mathematics that assumes continuous functions. We are particularly interested in these continuous-grainy problems from the perspective of complementarity. Any given species of molecule may interact more or less with any other type of molecule, so that in a very diverse mixture of molecules, a large number of weak interactions may overwhelm a small number of strong ones.

The same can be true among sets of cells or in species or social interactions that involve what Csermely has called 'weak links' (Csermely, 2006) and Root-Bernstein calls 'complementarity' (Root-Bernstein and Dillon, 1997; Root-Bernstein, 2011). There appears to be no orthodox way to model such systems mathematically, yet such systems occur at every level of biological complexity. Again, since biological systems are able to integrate units with continuous functions, surely there is a mathematics that is appropriate for modeling how biological systems do so.

A fourth set of problems relates to the key properties differentiating a living system from a non-living one. Living systems involve directional processes[8]. Their physical environment, however, is characterized by non-directional properties. In other words, we have two different models at the same level one for living and one for non-living matter. One doesn't need vectors to describe chemical reactions in a test

[8] For clarity, in what follows in this paragraph and in the next ones, we will often name by "vector" the directional properties and by "scalar" the non-directional ones, discarding that we are outside the required mathematical context in which these terms are usually defined. Thus, the use of these terms and several other ones should be understood from our context rather than from the algebraic one. Furthermore, it should be obvious when the terms refer indeed to the mathematical context.

tube, but one does need vectors to describe biochemical networks. Hence, a characteristic feature of biological systems is that some of their properties involve transformations from scalar to vector quantities. Some very interesting and important problems lie at the interfaces between the physical world and the biological one; they require mathematical means to describe how vector processes interface with scalar ones. For instance, how does random diffusion get converted into directional ion transport? We need a single integrated model, but not different ones for each domain.

We know from elementary algebra that multiplying a scalar by a scalar gives a scalar; and multiplying a scalar by a vector gives a vector; and multiplying a vector by a vector gives a scalar (V.V) or vector (VxV); but how does one get from purely scalar quantities to a vector one? Is this another kind of tensor *transformation*? How do racemic mixtures of chemicals give rise to chiral handedness in living systems? How does a chemical neurotransmitter signal (scalar diffusion) become a directional electrical signal? How does one evolve from random diffusion (scalar) to facilitated transport systems (vector)? How does one evolve from all possible reactions occurring (primordial soup, laboratory bench) to reaction pathways (vector/tensor)? In all these cases (and many more) scalar processes result in vector ones, yet mathematics generally treats *either* scalar quantities *or* vector and tensor quantities, but not the transformation of scalar to vector and vice versa. In differential geometry, scalars, vectors, tensors and matrices are considered as examples of multilinear maps, and so are graphs in the usual definition with only one arrow between 2 vertices, which is easily translated into a tensor or a matrix. Could a new operator be adapted for living systems? Or we need a new mathematical formalism for this purpose? Or should we still approach problems in differentiated way? Perhaps we may well need to apply different types of mathematics than are currently applied. Recall that the tensor concept emerged out of the necessity to have vector transformations. The issue with matrices and determinants used to solve systems of (polynomial and differential) equations is similar: they all emerged out of the necessity to solve particular problems. Mathematicians like Newton, Leibniz, Gauss and others were clever enough to discover the repeating pattern and simplify the solution. Now, we have another set of biological problems, e.g. in the domain of genetic regulatory networks, where one can trace a complex map of enactions and transitions between certain protein chains (objects) – well modeled by directed (hyper)graphs – but then at a certain point in time these objects suddenly turn into processes or entire networks of them (autopoiesis!?) revealing some hidden variable operational semantics (Bohm) that completely inverts the picture, so one has a "jump" or gap in the overall description. How to explain that? The object becomes a process, and then again the reverse situation at some point later. What we may need is a mathematics in which one assumes that every scalar quantity is actually a pair of opposite vectors (or tensors) that normally sum to the null vector (or tensor). For example, in all vector/tensor systems in biology of which we are aware, an inflow of one kind of molecule is always balanced by an outflow of another; selection for right-handed sugars occurs only where there is concomitant selection for left-handed amino acids. So is it possible that in fact the overall balance of vectors/tensors in a biological system is always conserved and that the local manifestation of one half of a vector/tensor pair (e.g., inflow) is always balanced by the expression of the opposite vector/tensor pair (outflow) in the opposing process? Is there a mathematics that can help us investigate the rules that might govern such processes by integrating vector/tensor reasoning into the kinds of set thinking postulated above so we can understand how molecules move directionally through cells as a result of metabolic processes, etc.?

The fifth type of problem involves the linkage of form and function. Biologists who deal with almost any level of biological organization have recognized that natural selection attempts to optimize forms to carry out particular functions, but since novel functions evolve from existing forms, these attempts may be seriously limited. The mathematical challenges involved in attempting to model these form-function interactions are far from trivial. Knot Theory (Manturov, 2004) allows study of the form of proteins, in particular protein folding (Kauffman and Magarshak, 1993; Taylor, 2000; Martz, 2000), but we do not have good geometrical tools that can easily model complex processes in embryological development. Fractals and other forms of mathematics that generate lovely images that look like the final products of some of these processes (e.g., the branching structure of the bronchioles in the lungs) but share nothing of the actual biological processes that give rise to these structures. But the very fact that the final outcomes of these images look similar suggests that they do share something in the functional and structural organization, even if we do not understand what it is. Our mathematical geometries generally do not illuminate the processes that give rise to biological geometries, but only their outward forms. More importantly, the interesting thing about biological forms is not their geometries per se, but the ways in which these forms are reifications of the biochemical *processes* they carry out or make possible. For example, it has become evident that the folding of chromosomes is a prerequisite to bringing together genes that would otherwise be spatially separated; and that spatial proximity permits the rapid diffusion, and control of interactive gene products that would otherwise be unable to interact in a reasonable biological time frame across an unfolded genome (Junier et al., 2011).

But what kind of mathematics would make it possible to model simultaneously the effects of geometry (spatial structure) on continuous functions such as diffusion, that in turn regulate on-off gene regulatory switches that act discontinuously or digitally? Similarly, in developmental biology, we now have excellent data concerning the sets of genes that must be turned on and when they must be activated or inactivated in order to produce proper embryological development (e.g., Carroll, 2005), yet the discrete information generated from combinations of individual genes is expressed as a continuous flow of proteins and hormones that produce gradients which must be reified as organized groupings of cells that have a specific form. So once again, embryology is stymied by the lack of mathematical approaches that can link discrete, continuous and geometrical information.

Conventional approaches to these sorts of problems rely on modeling one aspect of the problem with one form of mathematics, switching to another sort of mathematics to address the next aspect, and to a third one to describe yet another. All this switching is an indication of how difficult it is to apply our mathematical tools for addressing these problems. Biological systems function at all of these levels simultaneously, so why cannot our mathematics?

We maintain that it is not the biology that is too messy to be modeled in these cases, but the application of orthodox mathematics that is inadequate, because it is inappropriate for addressing these sorts of biological problems. This is why we need a new biomathematics! Indeed, we speculate that complementarity might be the solution to both the biological and the mathematical problems here. What we seem to need are the means to describe all of the biological problems listed above as manifestations of a single problem that can be examined using a single, (new) type of mathematics.

To summarize, our contention is that the reason that biologists have failed to develop a viable set of mathematics methods appropriate to solving biology's problems is that we have relied too long on mathematics developed to model physical problems that are intrinsically different. The assumption has been that biology can be reduced to chemistry and eventually to physics, and therefore that a physics-derived mathematics should be sufficient. But hierarchy theory suggests that reductionism can never explain how novel properties and processes emerge. Biological entities have properties that are different from chemical and physical ones and that require novel mathematics for their description.

Thus, what we need is not more detailed physical models of biological systems that can handle greater and greater amounts of detailed data from increasingly fine-grained studies of the components of systems, but ways of identifying the biological properties that are as unique to such complex conglomerations as temperature is to a set of molecules. What we have lacked, in short, is a uniquely evolutionary mathematics that deals with the emergence of organization from non-random selection among replicating variations within complex populations.

The challenge to a novel biological mathematics, or biomathematics, is to invent new mathematical tools (or to make effective use of existing ones), which are able to handle such emergent properties and organizations. This will allow the development of a biologically relevant theoretical framework integrating concepts of continuous mathematics with discrete mathematics, algebraic formalisms, abstract calculi, logics and topological/geometrical principles in a novel biologically relevant framework we call **Integral Biomathics.**

The sixth and final type of problem deals with multi-scale integration of mathematical models and the study of emergence. It is concerned with the development of a set of theories that cut across multiple spatio-temporal scales of organization. In fact, such a kind of mathematics, which is capable of unifying the different domains of mathematics, already exists: Category Theory (cf. Section 7.6.1). It allows an approach to the five types of problems mentioned above. We believe, as Charles Ehresmann noted in 1966, that mathematics "is the key for the understanding of the whole Universe, unifying all human thinking" and that "the theory of categories seems to be the most unifying trend to-day" (Ehresmann, 1966). In the past 50 years new branches of Category Theory (CT) have been further developed: monoidal categories which generalize tensor calculus and are used for instance in Categorical QM Semantics (Abramsky, 1996; Abramsky and Coecke, 2007) and Quantum Picturalism (Coecke, 2009); higher categories and sketches which Charles and Andree Ehresmann introduced and were later modified and developed by others (incl. their research students) leading to completely new sub-domains of category theory with applications in computer science and in the foundations of physics. Some of the above problems are raised in the Memory Evolutive Systems (MES; cf. Section 7.6), (Ehresmann & Vanbremeersch, 2007), which are based on a *dynamic* theory of categories incorporating time. Indeed a MES is "not" a category, but an "Evolutive System", i.e. *a family of categories indexed by time*, with transition partial functors between them modelling the changes over time, each category representing only a snapshot of the configuration of the system at a given time. The transition functors allow consideration of the dynamic aspects. Thus, Evolutive Systems can be called "changing category" with time.

What makes MES adapted for modelling living entities is not just that they are ES (it could also be the case for "mechanisms"), but their multi-agent multi-temporal self-organization, with the interplay among their agents (called Co-Regulators, CR) and its capacity of learning based on the formation of a flexible though robust and plastic memory[9]. However for MES to become a good formal methodology it needs to evolve like a living system itself, otherwise it would be a dead end. Further, it is already a living system itself, thus able to be enhanced and adapted to reflect the nature of the most recent findings in biology in order to prepare for the discovery of new ones. This will be also the case in future, for we are challenged to build Integral Biomathics on solid foundations. So, even in the best cases, MES will not remain the same in the future. We may also experience some surprises on the way. Thus, the sixth and last type of problem outlines some ideas, which give the INBIOSA incentive a push toward a real (and probably completely different) theory of living systems, cf. section 7.

We are aware that the above arguments are perhaps not sufficient to firmly underpin our position prior to discussing the above six major problems within this short 12 months project. Usually, scientific discussions of that kind take years or even decades. We will need time to systematically analyze all proven theories, postulates, facts and assumptions underlying this rough outline of a research program in order to "clearly state" (as even some of our discussants requested) the INBIOSA “roadmap”. Or the roadmap may need radically redrawn, because of new insights encountered along the way. The reader may also criticize the many overlapping issues in this section, since usually major problems of ambitious programs are defined as disjoint (although related, as e.g. in (Hilbert, 1902)) entities. But this is really entered “terra incognita” and only recently started. Thus, elaborating the details of the above six problems will be continued in a future follow-up project.

In conclusion, we feel compelled to think that **Integral Biomathics** may revolutionize mathematics itself by proposing mathematical models based on a recently developed domain of mathematics (Category Theory) that integrates (through fundamentally simple insights) disparate areas of both mathematics and the sciences. Since we have to think about biological systems in all of these ways in order to model them, and since biological processes are intrinsically carried out in these integrated ways by Nature itself, it seems logical that real and useful connections must exist within the mathematical formulations of these natural processes as well. Indeed, as we have indicated, we believe that biology is just one of many such sets of emergent properties resulting from spontaneous organization within complex

[9] The above mentioned transformation from scalar to vector could correspond to the 'jump' from process to object, and vice versa, done in MES to construct the landscape of a CR, and later realize the selected procedure. Indeed, the landscape of a CR at a given time *t* is a category which has for objects the links *f* of the system which transmit information to the CR around *t*: thus the passage from the system to the landscape of a CR transforms information processes *f* into objects. And conversely, the procedure that the CR selects is an object *Pr* (in the memory), which is realized through its commands to effectors, thus transformation of an object *Pr* into processes. Let us note that categories consider both objects and processes (as links between the objects), and, through the colimit operation, transforms patterns (= sub-networks) into higher objects. The situation is still more complex in 2-categories, where the same element can be seen either as an object or a process. A 2-category K is a category in which the sets Hom(A, B) of links from A to B are equipped with a composition law transforming them into categories (with some coherence axioms). Thus an *object g* in the category Hom(A, B) is at the same time a link from A to B in K, hence can be seen as a *process* between them. Thus, depending on how it is looked at, *g* 'jumps' from being considered as an object to a process and vice versa. However, there might be other explanations for such phenomena, e.g. the WLI’s shuttle/netbot duality principle (Simeonov, 2002), which is closely related and complementary to MES.

systems. As a consequence, the principles that are derived from our studies of biomathematics should apply to an understanding of how novel properties can emerge in complex systems of any kind, whether ecological, social, behavioural, technological or economic. Thus, just as the Scientific Revolution provided us with physics-based mathematics that made possible the investigation of whole new realms of science, so can we expect the development of a biology-based mathematics, **Integral Biomathics** (Simeonov, 2010a/b; Simeonov et al., 2011), to have equally far-reaching and revolutionary effects.

5. Issues Affecting Integral Biomathics

There are a large number of specific issues or difficulties, which impact directly or indirectly on the development of Integral Biomathics. The following list is not exhaustive, but provides an important starting point in constructing the boundary conditions within which a mathematical description can be formulated.

5.1 Complementarity

Possibly the primary defining character of biological systems is complementarity. This, in itself, is sufficient to emphasize that biology must be treated differently from physics or chemistry, where although complementarity can and does exist, it is less critical. Mathematically, complementarity will provide the biggest challenge in the conception of **Integral Biomathics**.

One sort of complementarity is methodological, enabling relational data to emerge through dialogical processes that juxtapose different mathematical approaches (both static and dynamic), as embodied within new simulation and visualization methodologies. The complexity of biological functionality necessitates the employment of a multi-perspective set of mathematical approaches. Such approaches can be realized by articulating a set of relations and interactions between the differing branches of mathematics that come into play, as well as by developing new forms of mathematics driven by the biology at hand.

Another kind of complementarity is that of investigated objects and processes. It is comparatively rare in biological settings to find a process or phenomenon, which is independent from all others and the forms in which complementarity appears are many and varied. When we observe the ways that molecules and systems interact to create complexes, whose emergent properties are unpredictable from their individual components, then complementarity resembles Escher tilings, in which each line defines two forms, and the overall design is different from the sum of the parts. Another way complementarity can appear is more like the way physicists use the term, where something can be described both as a wave and a particle. It is important to remember that Niels Bohr's position was that ideas of complementarity should not be restricted to particle-wave duality. Complementarity reminds us that we must cohesively integrate actor-centered first person descriptions and impartial third person descriptions in any overview of biology.

Any successful formulation of **Integral Biomathics** must take account of apparent dichotomies like that at the intersection of reductionism and holism. Ideally, such a formulation would be capable of re-casting this, and other dichotomies, as complementarities, thus avoiding inherent or unintended paradoxes. An important aspect of this relates to individuals, groups and evolution. Is there a way to look at natural selection from both individual and group selection perspectives that yields a new complementary model more powerful than either of them alone[10] (Fodor and Piattelli-Palmarini, 2010)? And could this lead, as it did in quantum theory, to fascinating new conundrums – such as a 'Heisenberg's uncertainty principle for biology' – in which, for example, it would only be possible to explain microevolution based on individual selection and macroevolution based on group selection, and that a population consisting of both individuals and groups would be amenable to both types of analysis, but could not be completely described by either?

5.2 Scale and Hyperscale

Confusion abounds as to the character of system *scale*. Most usually this concept is uniquely associated with its counterpart of *size*, but this often results in a complete misunderstanding of the role of scale and of its implications for system operation and function. Unfortunately, in the information sciences, the idea of scalability refers to a capacity to change the size of a system or network without running into unforeseen or undesirable situations – without any scalar effects appearing.

Unfortunately, once more, the isolated Boolean nature of purely digital systems explicitly eliminates any local-to-global effects: in their instantiation as information processors, digital systems *never* exhibit real scale, no matter how big they may become. Much is made of the possibility that a global intelligence could develop, or be developed, *within* the Internet. This is, unfortunately yet again, formally excluded for the same reasons, although it *could* be – and possibly currently *is* – a reality for the extended global system of {Internet + users}. Intelligence is a vitally important feature of any biological system. It constitutes at the very least a capacity to operationally relate the lowest organizational level of an organism to a higher organizational level, and/or levels, in support of the organism's survival. Leaving aside for the moment *how* a higher scalar level of an organism may emerge, this transition is always associated with a reduction in the available degrees of freedom, and it naturally takes place through a region of state space (or, rather, *scale space*) of great complexity[11].

[10] For instance, the Multiplicity Principle, MP (Ehresmann & Vanbremeersch, 2007) represents such a kind of complementarity: the same function can be realized by non-isomorphic complexes with the possibility of 'switches' between them. It is at the basis of the emergence of complex interactions between complexes A and B not reducible to interactions between the components of A and B. And the existence of complex links is the characteristics for the emergence of non-reducible objects of complexity order >1, i.e. complexes that have emergent properties unpredictable from their individual components but dependent on the global structure of lower levels.

[11] By 'complexity' here we refer to Rosennian complexity of real systems, and not the Kolmogorov complexity, which appears in digital information processing. However the Kolmogoroff complexity can be generalized to hierarchical systems such as biological systems to measure the 'real' constructive complexity of a component; and it has been shown that the Multiplicity Principle (formalizing the degeneracy properties of living systems) is necessary for the existence of such higher complexity (Ehresmann & Vanbremeersch 2007), which contradicts a "pure" reductionism.

Consequently, it is virtually impossible to model mathematically a *single* ('local') scale-change in an organism without also taking account of its global properties. Although the operations characterizing an organism at a single scalar level, e.g. that of biological cells, may at first sight appear intractable, the *real* challenge is to somehow model the relations between even adjacent scales. The inter-scalar 'regions' of an organism are archetypically complex, and multiply fractal. Accordingly, any approach to their understanding requires close attention to complexity theory. If we assume that individual scalar levels can be at least approximated by Newtonian representations, then the inter-scalar regions are more closely related to quantum-mechanical superposition-and-collapse: first a superposition of all the 'possible emergences' (Yardley, 2010), followed by a collapse to the most suitable one. In an information-processing context this *birational* character may be ubiquitous. Pribram has suggested a related model for the interaction of neuron groups (Pribram, 2001), where the neural dendrites and nucleus may be represented by some kind of (classical) summation of information, and where the axonite distribution of the result is transmitted to following neurons by a '(real) simulation' of quasi-wave transmission and 'collapse'. Another interesting theory of fractal space-time and scale relativity for biology was presented by Nottale and Auffray, (Nottale, 1993; Auffray & Nottale, 2008; Nottale, & Auffray, 2008).

Living systems develop into multiscalar assemblies whose organizational structure has much in common with conventional ideas of both *hierarchy* and *heterarchy*. However, where the usual concept of hierarchy imposes one of two forms – *scale hierarchy* or *specification hierarchy* – living systems appear to develop into a form which can most usefully described as a *model hierarchy* that has been described as "a specification hierarchy constructed in terms of scale"[12] (Cottam et al., 2003, 2004). Here, each level of the (quasi-)hierarchy represents the entire organism at a different scale. Whereas scale and specification hierarchies are usually referred to as *abstract* human constructions, a model hierarchy appears to successfully represent what a living system *itself constructs*. Each level of such an assembly is partially enclosed and partially in communication with its neighboring scales, and the entire assembly forms a 'self-correlating' whole of partially autonomous scaled 'sub-systems'. This type of structure not only subsumes the idea of *hierarchy*, it also subsumes *heterarchy* through the variable nature of its partial inter-scale communication and consequent variable scale autonomy. The 'traditionally' problematic aspect of hierarchy is how to represent the *emergence* of a structure's new higher scale level by 'upscaling' from a lower one. This 'transitional' upscaling in living systems appears to be a generic form of quantum error correction[13], where local system information is added to a description of the initial level to focus targeting on the higher one. Close examination of the properties and features of living systems over the last two decades has indicated that this type of Newtonian-plus-quantal 'two-stage process' characterizes *all* 'transitional' upscaling processes, whether in biotic or abiotic 'systems'[14]. This must, then, constitute a central issue in any approach to creating a mathematical scheme for biology *per se*.

[12] a citation of Stanley Salthe who also added here when reviewing this paper: "Some have proposed that diachronic processes, like evolution or development can be represented using the specification hierarchy, while any stage picked out for examination would have scale hierarchy form.

[13] a suggestion originally made by Walter Schempp

[14] Technically, all 'systems' 'include' life, and we must be careful how we refer to abiotic 'systems' within their abiotic/biotic environment.

However, as it stands this is insufficient, for it offers no advice at all about how changes in one level may impact on its lower neighbor. If we take Rosen's sole reference to scale systems as a lead, it is unclear exactly how a suitable mathematical scheme may be formulated, because to do so requires us to address how to mathematically differentiate or integrate a complementary pair! Nevertheless, more elaborate categorical tools (such as sketch theory and its application to the complexification process) can provide some answer to this question (Ehresmann & Vanbremeersch, 2007).

At the very least, any representation of a living entity, for example of a biological cell, must take account of these aspects of scale. Although many informational properties of a cell may be derived from experiments with cellular cultures, this in no way addresses the cell's internal workings, and a great deal of expertise and imagination will be required if we are to 'construct' a link between these two, even if only conceptually rather than mathematically. As seen from outside, an organism will always appear to be a set of properties which operate at a number of different scales, and although we can attempt to model these in a 'global' representation, our 'access' to internal scales will always be partial in nature and dependent on the extent to which our informing experiments disrupt the organism's 'closure' (Cottam et al., 2000).

In our daily lives we view entities in our surroundings in a similar manner – as a loose conglomeration of both 'visible' and 'imagined' multi-scale properties and processes. Here again, two decades of research have indicated that this *hyper-scale* 'picture' (Cottam et al., 2006) is not only characteristic of the way we view an entity, but that it is intimately associated with the way an entity itself builds up its very nature. Not only are the different scales of an organism only indirectly accessible from an outside platform in a 'vague' manner, their internal inter-correlation is *itself* vague – the result of 'integrating' its different scales across a number of internal levels. Thus, scale, and this difficulty of inter-scale transit, must occupy a prime position in any attempt to model biosystems. The viability of any mathematical approach must be judged by its ability to address scale issues as they unfold in time. It is far from clear that this will be possible from either a purely physics-based approach or a purely biology-based approach. Life itself appears 'automatically' within Nature, and consequently it should appear 'automatically' from any realistic model of Nature. Rather than beginning from a purely biological ground, it seems that the best route would be to first create a modeling framework, which is independent of any 'biotic or abiotic' distinction – to create a framework, which is not restricted by the constraints of either physics or biology. Such an enterprise, therefore, must encompass two quasi-independent features in relation to a specific target: first, a foundational framework within which Newtonian and quantal viewpoints, and their more local derivatives, can successfully coexist; second, a mathematical formulation which addresses features of current interest. It is most unlikely that a single general mathematical formulation will be sufficient for all purposes[15]. Instead, panoply of different techniques will need to be interlinked in **Integral Biomathics** through the foundational framework, to provide access to a useful range of system properties. In particular, defining operative sets of relational properties, drawn from the juxtaposition and future unification of differing mathematical approaches, applied across multiple scales, will become a focus of articulating methodological complementarity.

[15] Rosen has pointed out that 'real' complexity could only be accurately addressed through an infinite assembly of formal techniques.

5.3 Class Identity vs. Individual Identity

Biology is grounded on the maintenance of molecular organization *(class identity),* at the cost of constant variation in the constituent molecular subunits. Low level biological processes do not follow a rule of 'one molecule, one effect', but 'one continuation of molecular presence, one effect', where individual molecular presence is often very short-term. For instance, consider a biological organism such as a human egg cell, containing about 30,000 genes, which encode protein molecules. Roughly 3,000 genes encode specific proteins called transcription factors that regulate RNA transcriptions. These transcription factors uniquely determine when genes will be turned on, for their expression, and turned off, while at the same time orchestrating an exquisite network of transcription-sequence regulation. How is it possible for one transcription-factor molecule for every ten genes (on average) to adequately regulate the expression of each one of those ten genes in the succeeding developmental process?

A clue to the answer to this question can be found in the observation that typical genomes in cells contain extensive non-coding, regulatory regions, and that these regions can act as enhancers, silencers, insulators, and promoters of the genes. If the expression of each gene is regulated by a combination of many different transcription factors, the accompanying combinatorial control may be competent enough to form a consensus among the participating transcription factors as to whether or not the gene in the target will be expressed, and when.

The flow of time involved in the developmental process can be made explicit by referring to the input-output relationship between transcription factor concentrations and the rate of protein production from downstream genes. Although noise latent in the transcription factor molecules in the input is random and rapidly varying, due to the stochastic nature of each biochemical reaction involved, this does not imply that similar randomness and rapidity would also apply to the rate of protein production of the output downstream. A relevant experimental model indicates that fluctuations in the output level of the protein molecules are much slower than those of the input level of transcription factor molecules (Rosenfeld et al., 2005; Pedraza and van Oudenaarden, 2005). This suggests that there must be some robust scheme for generating such slower fluctuations, in which the underlying organization can serve as a standard to which the passage of time in the form of fluctuations can be referred.

The binding interaction between the transcription factors and the DNA molecule to be transcribed is rather weak (of the order of 4kJ/mol or less) due to the underlying van der Waals forces. Consequently, a transcription factor molecule can easily be detached from the DNA by thermal fluctuations at ambient temperature. If there are sufficient transcription factor molecules in the neighborhood, however, the binding site can easily be 'replenished' by another similar molecule. The functional unity of the binding site is thus effectively maintained in an uninterrupted manner, even though the individual transcription factor molecules are constantly exchanged ('touch-and-go'). This functional unity may help to suppress the rapid fluctuations associated with the frequent exchange of input transcription factor molecules.

This kind of the 'touch-and-go acrobatics' is ubiquitous in biology, making *class identity* far more relevant than the *individual identity*, which characterizes typical physics or chemistry investigation (though class identity plays a role in statistical physics and in thermodynamics). *Class identity,* corresponding to the ideas put forward by Elsasser (Elsasser, 1981) and Bateson (Bateson, 1972, 2002), must become a cornerstone of Integral Biomathics.

5.4 First Person Perspective

Classical science is based entirely on a third-person perspective of Nature. This is the basis of its objectivity, as a way of developing representations of reality, which are both independent of human observer and reproducible. This is arguably the central strength of *science* and of its child *technology*, and it depends on the central assumption that the entities or processes which it studies are incapable of initiating action, that they are unconscious and to that extent inert.

The picture obviously changes when we move to the examination of human affairs, where we assume that 'free will' based on first person perspective is extant (or at least there is something which from outside resembles 'free will'). This is a major problem, which faces practitioners of the social sciences, that although reliable data may be obtained for populations, this is not the case for individuals. Here again, *class identity* is of overriding importance.

The question which now faces us is whether, in developing an **Integral Biomathics**, we should permit the inclusion of first person perspectives or not? Historically, the study of biology has taken the same line as physics and chemistry, in insisting that third person perspective alone should be taken into account. Philosophically, this has corresponded with the view that mankind is unique in its 'free will', and that consequently the non-human first person perspective could be ignored. We can permit ourselves no similar luxury. Clearly we should include first person perspective at the level of complete organisms: but at the level of biochemicals? Integral Biomathics will need a well thought out internal framework to take account of differences in the importance of first person perspective right across the multiple scales of biology. The example of clock-control by *cyanobactrium Synechococcus* cited below suggests that care must be exercised even at low levels of organization.

Why do we need a First Person perspective?

Probability theory is a branch of mathematics concerned with assigning a numerical value (a probability) to a possible event. There are two main approaches to this problem, on the one hand, the frequentist view in which studies probabilities as frequencies i.e. the ratio of the times the event occurs over a test series, and on the other hand, the Bayesian view, in which probability is a measure of the degree of belief that an event will occur (Jaynes, 2003). While the first approach is externalist, it measures a "hard fact", frequency, which is "out there in the world", the Bayesian approach to probability is inherently internalist (mental) because the probability of an event is always conditioned by the prior knowledge we have in the moment we make the prediction. Thus, the Bayesian or mental approach to probability is on the basis of both the information we have (degree of belief) and the information we lack (uncertainty), rather than as the outcome of a repeated series of experiments. The frequentist view of probability can work in those situations in which everyone has the same information, for example when we are told that the probability of flipping a coin and have head is 50%, it is possible to perform that experiment a number of times and arrive to the conclusion that 50% is the limit value, so the more times one flips the coin, the closer will be the outcome to the 50%. But for statements like “the probability of rain tomorrow is 50%” the frequentist approach objectivist point of view is ill suited because it cannot be tested. There is only one “tomorrow”, so we cannot make ensembles of tomorrows in order to find the limit value of the outcome. This kind of probability relies on prior beliefs already present in the forecaster’s mind. To put it simply, when the “game” cannot be repeated, the probability of an outcome reflects the fraction of paths leading to this outcome. Our capacity to understand the dynamics and the sensitivity to the initial conditions of what is encoded in the internalist approach to probability (Sornette, 2000) is limited. To sum up, Bayesian (internalist, subjectivist or classical) probability is not restricted, as the frequentist or objectivist view is, to situations in which the repetition of large numbers of equiprobable events is viable. It must be said that while a purely Bayesian approach may pose computational problems for large models it may always be used as an insightful guiding principle, that can result in explicit ways to model internal knowledge in, for example, neural systems. In this line, the paper of Fiorillo provides a new perspective to information processing in neural systems that relies on first-person Bayesian approach, (Fiorillo, 2012). In addition, Gomez-Ramirez and Sanz formally define “The Internal Model Principle” and postulate it as a guide for investigating how much knowledge a biological system has of itself, (Gomez- Ramirez & Sanz, 2012).

5.5 Biological Time

The Flow of Time

There are two quite different versions of the flow of time. One is the flow of time exclusively in the present tense, which Newton took as a serious matter as demonstrated in his propositions made in the present tense in *Principia*. Another one is the flow of time crossing different tenses, say from past to present to future, which has been the main concern of philosophers including Aristotle and McTaggart.

The idea of the uniformity of the flow of time can be applied to Newtonian time because of the ubiquity of the presumed homogenous fluxionum in the present tense. Nonetheless, the uniformity has already equipped itself with the arrow of time implicitly since the flow has originally been conceived of based on the constant rotation of the Earth that is totally empirical.

Yet, at the quantum level micro-time reversals are also at play. Rössler in his discussion of *Endophysics* suggests that “there is a macro dynamics (the coarse-grained responses of the dissipative structure called the ‘observer’), and there is an underlying, much faster microdynamics”. Even the most rapid macro change in the observer lasts several orders of magnitude longer than a micro time slice does. The micro time slices therefore are necessarily “integrated over” from the macro point of view, (Rössler, 1998).

Physical laws remain invariant under the inversion of time. However, it would be next to impossible to properly comprehend how the flow of time conceived in the present tense alone could be reversed without referring to past and future. If both past and future are referred to when the direction of the flow is addressed, it will not be the flow of time unique to the present tense. Hence, a challenging question is how to conceive of the flow of time crossing different tenses. In other words, time itself is already dynamic in its capacity of integrating different tenses. Physics has unwittingly dismissed the presence of such question. Thus we also need to address mathematical approaches to hyper-scale issues, where the lowest level has different properties to other scales. Alternately the nature of biological change over a human lifetime needs to be enfolded. An additional time-related factor is the Libet's delay and how it impacts cognition and environmental response.

How should we study time in biology? The nature of *biological* time is of fundamental importance to the formulation of **Integral Biomathics**. As usual, whether for time or any other parameter, to measure differences we need an invariant reference. In the scheme of classical mechanics, Newton, following Ptolemy, conceived of the invariant "clockwork" of celestial bodies as a reliable reference, and posited the flow of time based on repeated cycles of the celestial clockwork motion. The flow of time derived in this way has been treated as being specific to the physicist instead of to the clockwork itself. A serious question now arises: is it only human beings that experience the flow of time in nature?

A Lesson from Cyanobacteria

One empirical response is the circadian oscillation observed in *cyanobactrium Synechococcus elongatus* – the most primitive photosynthetic bacterium (Kageyama et al., 2006). Cyanobacteria can move and read the circadian clocks they carry. The essence of the circadian oscillation is in a monomer shuffling of the protein called KaiC hexamer. The experimental background of the monomer shuffling is of a predecessor hexamer K-K-K-K-K-K being alternated by the successor K*-K-K-K-K-K, then by K*-K*-K-K-K-K . . . and so on, where K is a monomeric KaiC unphosphorylated subunit and K* is the similar phosphorylated subunit in the presence of ATP as the phosphate source. When the hexamer reaches K*-K*-K*-K*-K*-K*, it starts dephosphorylation back to K-K-K-K-K-K. What is peculiar here is that although the KaiC hexamer does not undergo the monomer shuffling during the phase of dephosphorylation (from K*-K*-K*-K*-K*-K* to K-K-K-K-K-K), the phosphorylation phase (from K-K-K-K-K-K to K*-K*-K*-K*-K*-K*) *does* require the monomer shuffling in the sense that the hexamer recruits the monomers to be phosphorylated from the outside and lets the unphosphorylated ones disperse. This has been experimentally confirmed (Kageyama et al., 2006). The KaiC hexamer remains as it is, even though the monomeric KaiC subunits are constantly exchanged. This means that the KaiC hexamer sets itself to be an invariant reference to specify time constantly passing away, in sharp contrast to Newtonian time.
Although Newton could not move celestial bodies, the KaiC hexamers in cynanobacteria can both read and move its clock. The *class identity* of the hexamer outlives the individual identity of each monomeric subunit within that hexamer, as an invariant reference.

Alternatively, if we focus upon the *individual identities* of the monomeric KaiC subunits both entering and leaving, these can be associated with the flow of time. The agent responsible for implementing the flow here is cyanobacteria themselves, instead of the physicist as in the case of Newtonian time.

Integrating Mathematical Symbolism and Physical Internalism

Once the flow of time is naturalized, the material substrate supporting its carrier will become a *sign*, that is, something having the causal capacity of relating itself to something else. Rudimentary types of sign have already been available in physics, but have so far failed to receive due attention. A case in point is found in thermodynamics.

Consider, for example, Boyle-Charles law of the ideal gas in the form of the equation PV=RT, in which P is pressure, V is volume, T is temperature and R is the gas constant. The equation by itself is under-complete, in that if any one of the three variables is fixed, there is ambiguity in specifying the values of the remaining two variables. The situation is different, however, if all three variables in whatever natural settings are fixed in the course of time. Although the physicist may say that the three variables are determinable as a matter of principle once thermodynamics is grounded upon statistical mechanics, the minimal specification of thermodynamics as a fundamental ingredient of empirical sciences remains independent of statistical mechanics. But even at the minimal specification level, each variable is 'competent enough to determine its own value' in relation to the two others to fulfill the Boyle-Charles law. Each thermodynamic variable has the capacity of detecting the others *internally* and specifying its own value accordingly. This is equivalent to saying that a thermodynamic variable is a *sign* on its own – always referring to the activity of something relating itself to something else.

The likelihood of the action of *signs* in the empirical world now opens up a novel vista within which mathematical expertise could be extended to meet the challenge of how signs could be symbolized.

Summarizing, we conclude the following:

i) biological systems have internal clocks, and processes synchronize with them, and

ii) physical variables affect each other – particularly in a complex way within (or among) living things – so we can refer to them as *signs*, for they have a deeper meaning for an individual organism, and their understanding demands better interpretation schemes.

Underlying this perception is the appraisal of first person descriptions. The presence of an internal clock in each biological system lends it a self-supporting temporal identity, and a self is unquestionably related to first person descriptions, which we cannot then avoid. Physical variables which affect each other, like the three thermodynamic variables of the Boyle-Charles law, are not mechanistically controlled from outside, but from inside through the agential activity of detecting and fulfilling the law. Such an agential capacity can be approached through relation to first-person experience.

A crucial question here would be how to accommodate signs perceivable in first person descriptions with third person descriptions, the latter of which are inevitable to any explanatory model. One prerequisite when entering the symbolization of a sign is to specify the sign's concrete material nature.

A relevant example here is the synthesis of meta-stable products in chemical evolution as attempted in the laboratory. A meta-stable product (as the material partial carrier of the preceding reaction) is a material embodiment of past memory, and at the same time it directs the succeeding reaction to a limited extent. Such a meta-stable product is nothing but a sign, which relates the preceding reaction to the succeeding one. The action of signs is already operative in the successive synthesis of meta-stable products, unless it is methodologically eliminated by integrating each individual action in the statistical ensemble of the similar individual actions, as is often attempted in statistical mechanics. *In this sense, meta-stable products may serve as a mediator between non-life and life*. Meta-stable products themselves are already the material embodiment of history and memory. The relevant question at this point would be to evaluate how rich the individual action of a sign could be in its content.

5.6 Memory

The functioning and survival of living systems necessitates a kind of long term "memory", which can be purely innate or may develop over time for better adaptation. For instance, bacteria engage in metabolic activity, reproduce and repair damaged DNA. All these activities are autonomously controlled by their genetic 'program', which serves as a memory of the organism's ancestry. An animal with a rudimentary nervous system, such as a fish or a lizard, receives information/stimuli about its environment and its internal states (e.g., hunger or pain), and may remember them for later recognition; it has some innate behaviours, but is also able to learn new skills and behaviours, and to evaluate them. More highly developed animals (mammals, birds, octopi) are capable of developing a semantics, which may modulate their actions according to their circumstances and allow for communication.

An organism's memory plays an essential role in the dynamics of the system, by allowing it to recognize objects and events which were met previously, and to select procedures that were already used, while taking into account previous results. Such a memory is not rigid like a computer memory, but it is robust (meaning that it maintains its contents in spite of disturbances), and plastic enough to adapt to the context. Its 'records' can be innate or they can be formed, for example, when triggered by an event to remember features of the environment.

Other triggers may take the form of internal configurations, or situations the system does not recognize, along with the procedures it develops to react to a situation in an adaptive manner. These 'memory' records can be more or less complex, and their internal organization may vary to facilitate adaptation to more or less approximate situations.

5.7 Vagueness

We create models of the world, which are as fully explicit as possible, but the real world that they represent – or our perception of it – is always to some extent vague. Models can capture very well any generic or coarse aspects of a phenomenon, but do not capture the details so well. Some of these details, however, may be very important, and may even trigger emergent behaviour. Observed systems will be vague when they can be affected by small-scale events which occur during experimental observation, and which can be obscured by historical contingencies, where these are not embodied in the models' boundary conditions. This means that we must be very aware of the scale of our observations with regard to that of an observed system and of how that may be impacted by events at other scales. Our observational frame is imposed upon an observed system, and this makes the interaction less than objective; our observations may deform the observed system, marking it. How should this be taken into account, most specifically in the case of biological systems? In addition, the observed system may be in the process of changing at a scale which is greater than that of our observational time-frame, in which case we may well carefully and accurately measure aspects of the observed system that are ultimately of little relevance, even though these measurements provide values for variables in our model.

Biological phenomena in particular will be vague with respect to our models of them because they are affected by history and because they will usually be changing at time-scales both smaller and larger than our observational timeframe. Models are limited generally; they cannot be constructed so as to maximize accuracy, precision and generality. In particular, "models proposed by those who enter biology by way of physics often sacrifice realism to generality and precision", (Levins, 1968). Thus, any aspect of the system being modeled that is not in the focus will remain *vague* in the view of that model. This especially applies to complex systems, which are subject to many different sorts of modeling.

5.8 Quantum Effects in Biology

The grounding of any embodiment of a biological system lies within Quantum Mechanics (QM) (Ball, 2011). At first sight we might expect that quantum effects and biology would occupy completely different worlds. We cannot, however, blindly eliminate quantum effects from our investigations of biology without good reason. Here again, the question is primarily one of scale. It would be fatuous to investigate the biochemical basis of life without even *considering* the relevance of QM, but should this also apply to descriptions of the ways in which organs or complete organisms operate? A first consideration is clearly the size of the entity we are thinking about: it would be natural to assume that it is only small things that are influenced by QM, even though some evidence of large scale entanglement has been published (Ghosh et al., 2003). A second consideration is the nature of the processes we are considering. If inorganic chemical reactions can be described without recourse to QM, why would organic chemical reactions be any different? But, are interactions involving enzyme catalyzation as simple as inorganic reactions? The principle of macromolecular self-assembly was first used by Michael Conrad to construct a quantum molecular computing model (Conrad, 1992).

Suspicions of the influences of QM in biology abound, but it is difficult to obtain conclusive hard data. Many birds navigate by using the Earth's magnetic field to direct their migrations. It is known that their magnetic sensors are affected by the incidence of light on their retinas, and the suggestion has been made that the result is an entangled pair of electrons (Ritz et al., 2004) with a coherent lifetime of tens of microseconds (Gauger et al., 2011). More prosaically, QM effects in biomaterials are now of great significance to the electronics industry, where nature-inspired organic semiconductors are of growing importance (Smits et al., 2008; Glowacki et al., 2011). Prime examples of the links between quantum coherence and entanglement with photosynthesis at the biophysical and biochemical level, providing a base for 'green' quantum computing and 'green' photovoltaics, can be found in (Engel et al., 2007; Lee et al., 2007; Sension, 2007; Scholes, 2009; Sarovar et al., 2010; Panitchayangkoon et al., 2010; Collini et al., 2010).

However, a central question concerns the extent to which mathematical descriptions must themselves be based on QM. The difficulties in finding mechanisms responsible for the phenomenal experience of consciousness based on classical mechanics, in particular its unity, attracted many researchers to the possibility of quantum mechanical explanation. Several authors proposed quantum mechanical explanation of consciousness or cognitive functions of the brain in the 1970's (Pribram et al., 1974; Hameroff, 1974; Frohlich, 1975). The attempts to apply quantum mechanics have been hampered by the relatively large size of the functional units of the brain, so long as this role was given to the neurons. Hameroff's idea was to identify as units much smaller microtubules, and this raised hope of applicability of quantum descriptions. In cooperation with Penrose, whose writing for the general audience greatly contributed to popularization of this approach (Penrose, 1994), Hameroff developed a model of consciousness based on such description (Hameroff & Penrose, 1996; Hameroff, 1998). The main obstacle to becoming acceptable for the majority of those interested in consciousness studies, was the difficulty of justifying physically unrealistic assumption of maintaining quantum coherence for sufficiently long period of time at realistic temperatures. More than a decade later, only sporadically has the issue of coherence and the model returned to discussion.

However, more recently the relationship with QM has been examined from a different perspective. Schroeder (2009) proposed considering a model of information integration[16] in the brain based on the assumption that the mechanism is exhibiting the formal characteristics of coherence expressed in the mathematical structures used in QM, but without the assumption that the brain or its functional units are quantum mechanical systems. This formal characteristic (direct product irreducibility) is a common property of the structures describing geometric, as well as many other systems, which do not have any relationship with QM. Moreover, in this perspective it is not the brain, which exhibits quantum-mechanical properties, but quantum mechanical description which reflects the cognitive functions of the brain.

[16] Information integration has become the central theme of Tononi's concept of consciousness. However, all that he and his collaborators contributed so far were either very general statements referring to phenomenal experience of unity of consciousness (Edelman & Tononi, 2001), or to identifying the integration with statistical synchrony of neural firings in terms of entropy, (Laureys & Tononi, 2008). There were some recent efforts in investigating the theoretical and empirical evidence of information integration (Seth et al., 2011; Barett & Seth, 2011), but neither they, nor Tononi, or anyone else, incl. (Sloman & Chirsley, 2004) provided any model of integration or any idea of how it can be implemented.

There are also other possible ways of developing new perspectives on the relationship between QM and biology. In particular, in a categorical model such as MES (Ehresmann & Vanbremeersch, 2007; cf. Section 7.6) quantum entanglement can be modeled as a special form of categorical colimit. Such colimits impose constraints on the lower logics (up to the molecular level), where they play an important role. At the higher levels, entanglement can play a role only through lower order processes; indeed, during the interplay of the logics, there is a risk of decoherence because of the variety of higher constraints.

At these higher levels, what is important for living systems is the existence of multiform components, which can operate through two non-connected decompositions (this "degeneracy" property is formalized in the Multiplicity Principle). MP allows for the emergence of structures and processes of increasing complexity order in MES and provides flexibility and robustness to the system (cf. Section 7.6). Now, MP is itself a consequence of QM (Ehresmann & Vanbremeersch, 2002). Indeed QM implies that MP is satisfied at the lower particle-atom level, from which higher levels have evolved by iterated complexification processes. As complexification preserves MP, it is also satisfied at higher levels, hence in living systems. It explains how quantum properties (entanglement, non-localization) allow, through the MP, for the emergence of higher and higher processes up to consciousness

To conclude, entanglement has its role at the lower levels, but the characteristics of life depend more on the (somewhat 'opposite') degeneracy/multiplicity principle, which is itself deduced from QM properties at the lower level. However if there is any evidence implying constraints on the higher levels that realize entanglement through higher order processes, we should take it into account in our model. Our general point of view must be an open one, permitting investigation of QM relevance at every level of mathematical representation.

5.9 Biotic vs. Abiotic Systems

If we wish to move beyond the issues raised by Salthe, who noted that "Today, curiously, living systems cannot be said to be anything more than dissipative structures informed internally by genetic information. There is not really anything substantially different from abiotic systems in them other than greater stability due to this internal information.", we need to decide on a level at which to start. If we think in terms of independent living entities (ignoring viruses, prions) then what these have in common is that they are based on the cell. Thus we become interested in characterising the living cell. Cells stand at a particular level: they are omnipresent in animals and plants (from the single celled amoeba to all plants to all classes of animals): indeed they are just about *all* that is omnipresent, and they are constituents of multicellular animals. So our first actual suggestion for a biomathics is that it should reflect this. But what does that actually imply?

We can characterize a cell by its boundary, B. This provides a division of space: we have in(B) and out(B), and we have B itself. We have mechanisms for crossing this boundary both from in(B) to out(B) and from out(B) to in(B). We then need to consider the nature of B, in(B), out(B), crossings from in(B) to out(B) and out(B) to in(B) might usefully be: as matters stand, it is difficult to imagine anything simpler (as it stands, it's quite like Spencer-Brown's *Laws of Form* (1972), which implies that it can be used a basis for logic). The system needs much in addition (at least): events, time, mechanisms for examining what's happening inside the cell (which might well be based on the same abstraction), mechanisms governing movement and transfer across the cell membrane, and mechanisms for putting cells together. In this area, the work of Cardelli (2005, 2008) provides one possible way forward, although it is more oriented towards a purely computational approach. At a lower level, there are internals that can cope with (e.g.) protein/protein interactions in the style of Hong (2005a/b), as well as abstractions that can stand in for diffusible chemicals, concentration gradients, perhaps gravity, and other physical issues, and at higher levels there are multi-cellular organisms. Inside the cell, we have protein interactions, as well as influences from enegry chnages (etc.) from outside the cell. These are unlikely to be precisely defined or replicatable: protein interactions rely on reactive surfaces being brought into close proximity with each other, while they are moving in aqueous solution, and having their shapes influenced by local electric fields caused by other proteins and external forces.

One can argue that cells perform information processing as well (deciding to move, or to engulf a particle, or create a protein), however, it is not necessarily possible to separate out that the cell does in order to survive and live, and what it does from an information processing view: we need to be careful not to enforce our own narrow interpretations of their activity too strongly.

Thus, there is a whole level (or indeed several levels) inside the cell that we could conceivably put together to determine the activity of a cell. Yet while the cell lives, its behaviour appears to possess a unity that (in some sense) belongs to the cell, and not to its numerous constituents. At a higher level, the same is true for multicellular organisms: they possess a unity thet belongs to the organism, and not the its constituent cells, or their constituent elements. At death, this ceases to be true. Cells appear to have a more purposeful behaviour than, say, a protein. Whatever the cell is doing, its behaviour is always subordinate to its main goal: survival. This holds for all higher levels of cellular organization up to communities, societies and nations. Clarifying/rendering a "crisper" notion of purposeful behaviour is part of the early research agenda of INBIOSA.

6. The Grand Challenge

This section addresses three major questions or grand challenge issues in the sciences of complexity that underlie biology and the related study of living entities. The first issue is the relevance of a more complete understanding of biological complexity and the increasing complexity of artificial (engineered) systems to the progress of science. The second question is why a paradigmatically radical shift in methodology is critical to progress in biology. The third issue is the potential impact of a revolutionary advance in biology on all sciences and technologies involving life-like or life-enabled complexity. A discussion of these issues is followed by a recommendation for a new strategic collaboration *framework* to support the advancement, articulation and development of new theoretical and computational foundations for biology.

6.1 The Relevance of Complexity to the Problems of Science

We begin by examining the historical trajectory of science and how that changed dramatically with the invention of mathematical physics. Next we examine the current impasse in the progress of biology and other sciences involving life-like complexity or life-enabled complexity. We then conclude with the role of mathematics in the development of complexity sciences.

6.1.1 The Trajectory of Science: the Transformation of Methodological Paradigms from Descriptive to Mathematical

The following scheme is a sequential model of science:

Observation of new phenomena → **speculative concepts/ hypotheses/ theories → new mathematical formalisms → predictive conjecture** → empirical demonstration and verification → theoretical foundation for practical applications

The schematic trajectory of science presented above is a simplification of much more complex system. A more complete model of science, as a highly complex system of thought, a noetic system in itself, would illustrate how the process is simultaneously cyclic, recursive and unpredictable in the sense of generating novel emergent structures (predicting new phenomena) from its own mathematical grammars. The power of mathematics (mathematical language and its grammars) to transform the methodological paradigm of physics was first demonstrated by James Clerk Maxwell with his revolutionary use of the differential equations that effectively *described* electromagnetic field phenomena to *predict the existence* of electromagnetic waves and the electromagnetic nature of light, both phenomena then unknown to experimental physics (Arianhod, 2006). The subsequent experimental observation of radio waves enabled the modern world of telecommunications and the concept of the radiation of light led to the science of quantum physics. The paradigm shift in physics from concrete models to mathematical imagination created the methodology of modern mathematical physics.

The science of biology awaits a similar transformation. Biology needs a new mathematics allowing for a new form of computing that will permit us to model the emergence of new structures carrying out novel processes as a result of innovative forms of organization within complex systems. At that point, we will be on the verge of a transformation in biology as profound as that in physics. In other words, the transformative paradigm shift in biology requires the development of mathematics appropriate to biology that is motivated by problems that are biological in their origins and nature, just as the mathematics appropriate to physics was physical in its origin and nature (Root-Bernstein, 2012).

6.1.2 The Impasse in Biology and the Need for Convergent Theoretical Synthesis

Much progress has been made in biology. The last fifty years have generated a huge amount of information on life processes. DNA, the genome and systems biology have had huge success in extending our understanding of many of the basic processes in living cells and tissues. But in recent years, research seems to have concentrated on more and more detailed molecular understanding of these processes, without managing to pull these together across scales of space and time, without increasing our overall understanding of the nature of these processes, or of how they make living organisms actually live. Developing a set of theories that cut across these levels aims to fill that space.

The sciences of living systems are stalled at the most basic stages of observation and speculative ontologies/hypotheses/theories. The energetic and optimistic application of the highly successful Newtonian and von Neumann paradigms of physics and computation have not really enabled a breakthrough in the understanding of living systems as *distinct* from non-living matter. Mechanistic models are still dominating biology and science. To make new inroads into biological study we must move to new forms of dynamic relational models that enfold multiple mathematical approaches.

Funded research is producing ever more detailed reductionist descriptions of biological systems, but failing to produce the understanding and insight that would be necessary for real progress. The central idea behind our proposal is therefore to develop theoretical foundations that can bring together the huge range of biological (genetic. molecular, protein-based) knowledge by developing theories that cross boundaries. Mainstream research appears to be about building up more and more knowledge in the hope that one day it might be altogether made sense of. In Physics, there is a strong belief in clear underlying principles that drives fundamental research. In Biology, such principles seem to be more difficult to find, and are often seen as less important, if only because clinical work has different aspirations from pure science.

6.1.3 The Evolution of Mathematics in the Development of Science

There are many scientific problems a new mathematics of biology (biomathematics) would have to address. How to model self-emergent sets (origins of first cells; self-assembly of viruses, etc.) How to have such self-emergent sets carry out functions selecting/rejecting among possible components; minimizing what a physicist thinks of as free energy. How to create a mathematics that can simultaneously deal with continuous variations in chemical kinetics yet yield information about modular probabilities within complex systems to prune out huge numbers of possibilities at each step of hierarchical assembly. The new mathematics would preferably incorporate the work that has been done on understanding hierarchical systems, emergent properties and complexity theory.

Current approaches to these sorts of problems rely on modeling one aspect of the problem with one form of mathematics, switching to another sort of mathematics to address the next aspect, and to a third to describe yet another. Such switching is an indication of how inadequate our mathematical tools are for addressing these problems. Biological systems function at all of these levels simultaneously, and so must our mathematics. A new mathematics would therefore be integrative.

In a nutshell, mathematics will be required to expand its descriptive capability. The traditional mathematical disciplines have been well versed with monologic discourses and formalization in an unsurpassed manner, while the real processes operating in biology are dialogic in maneuvering a wide variety of resource explorations and exploitations among the participating material agencies. A major theme of the upcoming biomathematics we call **Integral Biomathics**, should be how to reach monologic discourses, starting from the dialogic dynamics anchored upon the real material world without being entrapped by easy static or statistical artifacts. One breakthrough that might be expected is extending the scope of category theory as a mediator integrating the primitive nascent categories in the dialogic dynamic domain into the full-blown formal categories in the monologic descriptive enterprises.

6.2 The Radical Paradigm

We suggest a new collaborative pathway in this section – convergent theoretical synthesis – as a paradigm shift and an alternative to the current heavy emphasis on empirical research in order to accelerate progress in these sciences. The envisioned research program is not an extension of the existing paradigm in which the principles underlying the successful models, philosophical assumptions and computational approaches of physics are assumed to apply as the foundations of biology. It is not that we are suggesting that the laws of Physics do not apply to biology! However, we propose that there are additional deep laws that apply to biological systems *as well*. The current paradigm has failed in substantial ways to advance life sciences. The understanding of living processes has not been amenable to orthodox mathematical modeling and logic despite enormous advances in computational and experimental tools. Von Neumann computing is practically unable to address the complexity of interactions involved in even the simplest molecular expressions. Therefore, INBIOSA focuses on challenging the central reductive and simplification assumptions of classical science.

6.2.1 A New Trajectory: Towards Theoretical Foundations for Biology

This concept is best expressed as a transposition of the modeling assumptions that enabled the emergence of the Newtonian paradigm, which forms the base of biological theories today:

Non-living systems (Newton):
Apparent *complexity* of observable phenomena →
Modeled effectively by *simplistic* minimalist formalisms
Living systems (Darwin):
Apparent *simplicity* of observable behaviour and development →
Require modeling of ultra *complex interacting structures*

Nevertheless the physical sciences have lead to the development of new observational, analytical and computational tools applicable to modern experimental biology. This has in turn enabled the collection of a vast highly detailed new repository of data at all levels of complex living systems.

Observation of new phenomena → speculative concepts/ hypotheses/ theories → new mathematical formalisms → predictive conjecture → empirical demonstration and verification → theoretical foundation for practical applications

These technologies have in turn enabled the evolution of many disciplines and sub-disciplines of biology founded upon a wide variety of paradigms, hypotheses and theories based upon on specific (narrow) evidential bases. There is great need for convergent theoretical syntheses (Kant, 1999) to reduce the number of plausible theories and to synthesize across paradigms. **Such tests of convergence have been the pillar of scientific advance in astronomy, geology and biology** (Donald, 2004). In biology theoretical integration and synthesis will enable more precise conceptual models for the newly observed key processes of complex systems.

Observation of new phenomena → **convergent theoretical synthesis** → new mathematical formalisms → predictive conjecture → empirical demonstration and verification → theoretical foundation for practical applications

These new conceptual models in turn will enable new mathematical formalisms will be the developed for each process with a possible integrated mathematics from which all processes can be derived (Root-Bernstein, 2012). Thus, computation can be part of convergent theoretical synthesis.

Observation of new phenomena → convergent theoretical synthesis → **new mathematical formalisms** → predictive conjecture → empirical demonstration and verification → theoretical foundation for practical applications

In particular, there could be a possible paradigm change to development, not evolution as the basic orientation of biology. The groundwork was laid by A. I. Zotin in the 1960's in Russia (Zlotin, 1972). It is thought of (if at all) as a 'dismal science', as it is based in thermodynamics and focuses on the processes of senescence (Salthe, 1993) and complexity (Salthe, 2005a). Developmental Biology is not informed by this possible theoretical basis, and has, indeed, no theoretical basis of its own. This approach is grounded in a basic perspective opposite to the 'growth ideology' of our culture, and it would be truly a radical departure.

Actually, developmental and evolutionary biology represent a complementary pair. Development is the process underpinned by genetics. It is genetics that determines the response to an event, at a certain level, since it determines what the protein structures will be, that will detect the changes that constitute events, as well as determining the reaction cascades that eventually result in action after an event.

6.2.2 The Entailments of Complexity

The traditional aim of science and the technological tools and processes that it enables, is the increase in our control over matter. This power rests entirely in the predictability entailments of the sciences, as we know them today. An understanding is scientific according to its power of predictability. Our historic understandings of the world around us (including our more recent understandings of human language, thought, consciousness and foresight) are based on the canon of predictability. That canon together with the mathematical innovations that enabled precision in predictability have been highly effective as we advanced our understandings in the traditional domains of physics, chemistry, biology, neuroscience, economics and in the varied technological and engineering domains that are derived from those sciences and upon which our material, economic and social progress have depended.

We are entering a new era, however, in which we seek to make even further interventions in the ways of nature and expand the potential for yet further material and social progress in the man-made world. What we have discovered is that we now have to address real complexity rather than an apparent complexity that can be reduced to simpler manageable and hence predictable entities. We are not surprised that nature presents such challenges, but we are realizing now that the pervasive and information-intensive infrastructure of our built worlds (at all scales) is exhibiting the same features: **unpredictable** interaction between components and sub-systems of exceedingly complicated systems.

The extraordinary capacity of all living entities to restructure themselves in order to address both internal and external stresses in ways that evade understanding is based on the canon of predictability. Biology as the study of living entities is the science that has faced the complexity phenomenon from its outset. Physics took somewhat longer to confront irreducible and irresolvable complexity in its formulations of non-equilibrium thermodynamics to account for its theories of the emergence of matter from energy and of life from matter, (Chaisson, 2002).

The problems in biology and other fields of life-enabled complexity are not about the energy-budgets of structured matter, as physics might be concerned with but about the complex of processes that enable life and its continuing evolution in human culture and technology.

The bottom line is that even understanding complexity will not allow us to avoid the emergence of unpredictable properties or the illusion that we can manage the outcomes of emergence.

How essential it is then to understand the conditions, under which emergence of new properties occurs in biological systems (natural and synthetic) and in technologically complex engineered systems. Our challenges will be how to manage emergence and to perhaps to shape the envelope of possibilities. The canon of predictability (the old sciences) will not apply. We have entered a new era in science.

6.2.3 Bridging the Complexity-based Disciplines

The theoretical syntheses and mathematics that are derived from transdisciplinary studies of the above five grand scientific challenges have the potential to be applied to an understanding of how novel properties can emerge in complex systems of any kind, whether ecological, social, behavioural, technological or economic (Root-Bernstein, 2012). There are therefore many opportunities to advance understanding simultaneously by transferring new insights from a simpler kind of complexity to advance research in higher complexity regimes. We give our highest priority therefore to research spanning and integrating the insights to be gained from both engineered and natural systems of complexity.

INBIOSA proposes the development of bridges with EU Future and Emerging technology (FET) programs addressing the design of complex interacting engineered systems. Adoption of the INBIOSA institutionalization agenda (summarized below) can greatly assist FET programs that are beginning to address the problems of emergence of undesirable properties in what may be considered extremely complex engineered systems.[17] These efforts would benefit from the innovative perspectives of those who have articulated theories for a wide variety of emergent phenomena in biology, which involve much greater complexity than those in human-designed technologies. Mapping a new generation of bio-inspired emergence theories to complexity issues in engineered systems would accelerate design solutions as rapidly as new mathematical formalisms were developed and tested. Conversely, **adoption of an internalist perspective** involving our reflection upon the process of creating and operating a vast network of human-intelligence driven self-organizing engineered systems might give us some insight into how biological complexity in nature works.

The salient aspect of this argument was captured by Simeonov's Flagship Proposal (Simeonov, 2010a):

> "… we cannot truly rely on these machines to autonomously discover and explore new worlds which are impenetrable for us. They simply lack the ability to grow, develop and evolve under the two other fundamental capabilities that living systems possess: effectiveness and innate adaptability/learning (**without any human intervention**). "

However if we include the capabilities of effectiveness and innate adaptability/learning available through human intervention we might have much to learn from such biosynthetic complexity. Take for example telecommunications networks. We have entered an engineering era distinguished by an entirely new systems phenomenon: exceedingly complex interactive networks of computers and communicating devices. Such complex systems provide a new observational platform enabling the opportunity to explore, **from the inside out**, how exceedingly complex systems develop new properties.

[17] The FET consultation on evolvability raised further concerns that FET research projects pursuing advancements in collective adaptive systems are failing to address deeper fundamental issues in complexity engineering involving: the long-term controllability of autonomous artificial systems; artificial chemistries that may have the ability to re-write the operating system, or control system in which it is embodied; the need to understand emerging complexity in modern-world systems at the level of interaction between artificial systems; and ways of controlling emergence in artificial systems, (Kernbach et al., 2009).

While not natural emergence as in the case of living systems, it is observable engineered emergence, the manipulation or re-configuration of technological capabilities towards an overt human purpose. Pioneering research on "recommendation architecture" has challenged von Neumann computer architecture as the way towards higher-performance global telecommunications infrastructures and at the same time provided theoretical insights into neural cognitive processes otherwise unavailable to experimental biology. INBIOSA believes that the time has come to discover universal "emergence" principles in the interaction between the human mind and its engineering goals for complex systems of all kinds through the new observational platforms being offered by complex engineered systems at many scales.

6.3 Institutionalizing the Lessons of the First Scientific Revolution

We believe that convergent theoretical synthesis and innovative mathematics hold the keys to transformative progress in biology and the other sciences and technologies of complexity. How then do we propose to create the conditions for focusing resources and talent upon these processes in the context of extreme disciplinary specialization and the massive commitment of resources to observational, clinical and experimental methodologies? The first principle that we propose as a foundation for transformative research is that of universality: that there is a commonality, a transdisciplinarity, an integrative view of what can be perceived by human intelligence that must assimilate the knowledge gained from research in all disciplines. Hence, our proposals recognize the variety and theoretical complementarity of complex systems, i.e. there are many kinds of complex systems, from relatively simple ones to ultra-complex ones. What they have in common is the ability to develop novel (i.e. unanticipated) properties from their own self-organizing capabilities. We can currently identify at least seven distinct kinds of complex self-organizing systems based on their distinct forms of semiosis, i.e. classes of communicating meaning with signs, (Logan, 2007):

Kind of Self-organizing System/Discipline	**Form of Semiosis (communicating meaning through signs)**
molecular biology	digital transmission of information by DNA
cellular biology and ecology	process by which receptors of prokaryotes interpret signals from the environment
developmental biology	epigenesis of the phenotype from the DNA influenced by signals from the environment
neurocognitive science	biosemiosis of learning by virtue of the emergence of a central nervous system in animals
cognitive evolution	transition from percept-based thought to concept-based symbolic thought that emerged contemporaneously with human speech
distributed cognitive evolution and sociology	human culture, a symbolic thought based phenomenon
Semiotics	science, mathematics, technologies and economies, as products of the human mind generated through signs both spoken and notated

Focusing on biology, INBIOSA has identified five principal phenomena in biology towards which efforts at theoretical convergence and the development of an innovative mathematics should be focused in the immediate future:

1. the autopoiesis (self-construction) of cellular life;
2. the emergence of modules of hierarchy in all complex systems;
3. the varieties of modalities of communication within and between hierarchical levels of living systems;
4. the transformations of information processes from scalar to vector/tensor quantities; and
5. integrated mathematical approaches that can link discrete, continuous and geometrical information simultaneously.

6.4 A New Strategic Collaboration Framework

INBIOSA is the first formal attempt to provide a collaboration *framework* to support the advancement, articulation and development of new theoretical foundations for biology. We have drawn together a community of researchers to provide guidance on both the scientific and institutional steps required for a continuing scientific deliberation of paradigm shifting alternatives.

It is clear however, that the disciplinary structure, vocabularies and inertial belief patterns of academic research invite premature closure to cross-disciplinary debate and paradigm-transforming challenges. INBIOSA therefore proposes that FET continue to provide an institutional setting conducive to the research agenda we have proposed to address fundamental questions relevant to the broader field of complexity sciences. The FET program itself recognizes the acute need for a continuing process enabling scientific deliberation of paradigm shifting theoretical research. The EC report on the Future Internet[18] makes the extra-ordinary and rarely recognized point about the contingency of future progress at the economic enterprise level on "*new scientific foundations to produce Enterprise Systems offerings that are rested on and subject to the rigour of science*"**:**

> *"More fundamentally, a science base is required for the development of the next-generation Internet-based Enterprise Systems able to cope with a new set of complex issues and requirements, while at the same time ensuring reliability, flexibility, scalability and other qualities that have made the Internet such an indispensable tool for businesses and society."*

The existence of such a process will help to overcome a historic weakness in enabling challenges to orthodoxies, strengthening the climate for new paradigms and enabling new cross-disciplinary and inter-disciplinary syntheses in support of convergent paradigms. A first step in this direction was made in the panel discussions during the iBioMath 2011 workshops in San Jose (California) and Paris and the ACIB-11 research forum in Stirling, UK. The broad range of disciplinary response to these workshops demonstrates the latent interest of a wide range of research communities involved with theoretical and practical development of complex systems of all levels.

[18] Future Internet Enterprise Systems (FInES). Position Paper on Orientations for FP8. Final Version. 18 March 2011.

INBIOSA therefore proposes an expanded program of consultations and collaboration with relevant scientific and engineering communities focused on three objectives:

1. Identifying the scientific challenges in biological and artificial systems information processing;
2. Confirming support for the relevance of INBIOSA Grand Challenge Goals to the research objectives their expert communities;
3. Commitment to joint development of an integrated research agenda.

INBIOSA suggests consideration of a conceptual model for such an institutional framework based on the concept of emergent complex systems itself. In other words, to mimic in the larger world, the thought processes and structures that enable the emergence of new ideas in the human mind. The table below lists potential fields of research addressing complexity issues. The institutional challenge is to recreate the individual thought process of performing the necessary convergent synthesis of theory underlying the complexity of living systems at the scale of the total societal effort in the relevant sciences. In other words, the co-ordination (but not the control) of the many modules of thought that could be, but are not being brought together into a more coherent model of life itself.

This would involve co-coordinating efforts through FET programs and academic interdisciplinary collaborations guided by the principle of synthesis. Implementing such co-ordination is the institutional challenge. The form of structure and communication that would most benefit this process is not known yet. What is known is that existing processes of collaboration and disciplinary integration and co-ordination do not support such synthesis and mathematical innovation.

The following table summarizes the fields to be engaged, the problems identified for joint activity and the focus of specific research proposals.

The Reflective Collective Intellect: A preliminary schematic framework for enabling the emergence of a new scientific discipline of the complexity of natural and engineered systems – Integral Biomathics

Discipline/Organization	Knowledge Problems	Required Interdisciplinary Science Research Activity
Theoretical biology	Understanding how different levels interact (molecular, genomic, intracellular, extracellular, multicellular, organ level, whole organism level, ecosystems)	Development of multi-level/multi-temporal modelling synthesizing all levels and time scales
Biosemiotics	Understanding the different nature of all levels of abiotic, biotic and symbolic communications relevant to self-organizing entities	Process-based modeling (Mathematical, computational).
Mathematics	How to formalize biological problems that currently exist in two or more essentially unrelated domains of mathematics	a) Develop mathematics beyond autopoetic sets along the line of category theory and MES theory, using recent domains able to unify probability theory, hierarchy theory, network theory, vector/tensor calculus, logic, topology and others. b) Invent new mathematical methods and tools beyond a)
Health sciences	The lack of theoretical advances, the adoption of a naive immune inspired approach and the limited application of Artificial Immune Systems have limited immune systems research. Devise multi-scale models of pathologies and human anatomy/physiology accelerating therapeutic research; discovery of new pharmaceuticals and medical devices fostering an integrative approach to health care.	Similar to theoretical biology, but with an emphasis on pathogenesis and the means to eradicate/reverse the degeneration processes with minimal side effects while mobilizing and enforcing natural resources such as the immune system.
Systems engineering	Potential instability of highly complex systems as they increase in scale and complexity	How do biological systems integrate across multiple levels to produce long-living robust systems with clear goals?
Telecommunications engineering	Reconfiguration approaches to meet increasing flexibility in demand patterns and system reliability	As above
Cognitive science	How could the self emerge? What could be the material requirement for the emergence of the most primitive cognitive unit?	How could consciousness be related to cognition? Is cognition equivalent to measurement?
Synthetic biology	Knowing how to build synthetic biology systems; Understanding how to control a synthetic biological system in order to take advantage of its capabilities	Using the Mathematics and semiotics to help create systems for controlling (programming) these systems.
FET Projects	Unpredictability of self-replicating, high plasticity and self-healing and programming functionalities Complex Systems Unconventional Computing	New studies of heterogeneous systems. Studies of information processing in living systems: re-interpretation of biological computing.
Other (economy, finances, other complex technology disciplines.	Reducing dialogic movement to monologic discourse	Constantly transforming temporal categories

7. Towards a General Theory of Living Systems (GTLS)

This section describes the effort to formalize a general theory of living systems from what we have today. The eventual result will be a formal system, equivalent to that which exists in the physics community.

7.1 Objective

We focus on *evolving integral* models of life as an integration of both descriptive and explanatory models. An advantage of recruiting descriptive models amenable to first-person experience is to go beyond being entrapped by easy syntactic integrations unique to explanatory models limited to third-person descriptions, i.e. non-reductionist and both endo- and exophysical approaches to the emergence and development of dynamic, ordered hierarchical systems. These are facets of biological systems that no one can model at present.

The elements we want to address have applications to "intelligent systems" of all kinds, including AI/ALife systems and emergent ecologies, etc. All these systems can be demonstrated to have similar features and functions (albeit at different levels of organization).

To address these issues, we postulate the development of a 'dynamic model' of the entangled system 'in the making', trying to size up the successive specifications of its logic and semantics over time (Ehresmann & Vanbremeersch, 2007). At each time, we assume the overall ('global') logic of the system to result from the interplay among a hierarchy of 'local' logics and process event driven non-local crossovers, each with its own temporality, complexity and multiform components. Furthermore, this interplay is reckoned to become flexible through 'switches' between different decompositions of multiform components, allowing for a kind of fitness selection between them to preserve as much as possible of the local logics. While the local logics resort to 'classical' computations, the real challenge is to deal with their interplay, in particular how to handle switches between different possible decompositions of a multiform component, and with their non-local 'quantum' entanglements (Ehresmann & Vanbremeersch, 2002, s. Appendix A2).

The INBIOSA initiative suggests a radical approach to theoretical biology, biomathematics and bio-computation in the long term that can be supported by a transitional strategy in the short and middle term by addressing looming problems in complex interacting artificial systems that deserve attention according to the FET program (Kernbach et al., 2011).

7.2 Background

This section explores the reasons why the core question stated in the previous section has long been dismissed in the traditional scheme.

The history of science is a constant tension between those who would understand the world by examining its pieces (Democritus) and those who would understand it by studying its processes (Heraclitus). Erwin Chargaff wrote a very insightful (and unpopular) book about this conflict as it applies to molecular biology called *Heraclitean Fire* (Chargaff, 1978). The importance of making this distinction is that this book at present reads as if molecular biologists are studying cascades of molecular processes/changes, but in fact they are not, because these are only a small, low level part of the organism, and they ought to be examining the whole system. At least they have moved beyond simply looking at specific molecules, but they still make the often-repeated error of thinking that if they can isolate parts of the system that participate in the processes, the processes themselves will become clear. This is the epitome of the reductionist fallacy. The individual pieces of a clock do not predict or explain its "clockness", which resides instead in the way its organization permits it to carry out a specific process. The importance of making this distinction is that the mathematics used to model most biological processes have likewise developed from reductionist approaches, having been developed to model a Newtonian "clockwork universe". Reading the clock is irrelevant to a Newtonian universe since every inhabitant in the universe is no more than part of the single gigantic clock available there.

Despite the unquestioned success of the "omics" revolutions the paradigm shift in biology comparable to those invoked by the theory of relativity and the quantum theory in physics has not yet been achieved. Addressing the issues of parts of a clock, clockness and reading clocks discussed earlier may provide a key to engineering such a change in view.

How can we describe the synchronization of two adjacent clocks without relying upon Newtonian time? Just as physics has adopted novel forms of mathematical modeling that explicitly reject mechanistic reductionism, so must biology if it is to deal with similarly complex systems comprised of components that have multiple states and vary constantly in number and composition through time.

Another point that needs to be made explicitly is the necessity of taking into account hierarchies of organization. Biology is not chemistry, which is not physics. Chemistry becomes chemistry and not physics at the point where we can ignore the physical properties of the components carrying out the chemistry. Biology becomes biology and not chemistry when we can ignore the chemical properties of the components carrying out the biology. Yet, this is not reductionism. Simple hierarchical reasoning leads us to conclude that we can recognize a new level of organization when the principles and properties and models that worked for the previous level of organization can be ignored[19]. This is not to say that biological systems are not comprised of chemicals that obey the laws of physics, but to say that biological systems are *recognizably biological* because they have organizational properties and patterns that allow them to carry out processes that cannot be accounted purely on the basis of the physics and chemistry of their individual components. Here we often have interspersed interactions from higher layers of organization.

[19] We don't need an understanding of nuclear physics to describe the kinetics of a chemical reaction; we don't need to know the movements of every molecule in a gas to measure its temperature; we don't need an understanding of electron shells to explain how DNA encodes genetic information, but sometimes we need to invoke reasoning based on lower levels.

Consequently, what we need to describe and explain this "native biology" is the application of areas of mathematics not previously applied to it and the development of new ones, as well as of new forms of computing that permit us to model the emergence of new biological properties and patterns resulting in the carrying out of novel processes as a result of innovative forms of organization within complex systems. This kind of mathematical formalism is expected to enable us to answer the question: "What exactly is so typical and unique for living systems that does not occur in non-living ones?" We do however recognize that attacking this question should proceed under the constraint of the impredicativity. That is equivalent to practicing whatever theoretical synthesis is to be framed in third person descriptions without forgetting about inevitable interferences from first person descriptions.

The reason that biology has failed to develop a viable set of mathematical theories is therefore a result of having attempted to treat its universal, hierarchically-unique, organizationally-derived processes in terms of reductionistic principles derived from studying the chemical particles upon/from which these processes emerged. Additional confusion comes from the usage of wrong and mixed-up definitions. We wish to know how the reaction cycle could emerge.

In fact, the reaction cycle, as a higher level organization compared to the constituent individual molecules, raises a serious question of how the identity of the higher level can come to outlive the identity of each constituent molecule in the lower level. Once it emerges, what kinds of problem would remain? Hierarchy theory suggests that reductionism can never explain how novel properties and processes emerge[20].

What we need is not more detailed models that can handle greater and greater amounts of detailed data from increasingly fine-grained studies of the components of systems, but ways of identifying properties that are as unique to such complex conglomerations as temperature is to a set of molecules. In short, what we lack is a uniquely developmental mathematics that deals with the emergence of organization from non-random selection among replicating variations within complex populations of living entities. Could it be possible to have a type of mathematics that may support the robust transformation from non-cyclic to cyclic reaction network (Yardley, 2010) in a sense approachable empirically? What then would the mathematics of emergent properties and organization look like? Biology is only one case of such emergent properties resulting from spontaneous organization within complex systems. Political and economic systems are two others.

Josephson's emergence approach suggests how to join mathematics and biology using signs/symbols (semiosis), along the same path that the fundamental concepts of natural numbers, Euclidean geometry, algebra and logic were developed: "By retreating into symbolism one escapes inconvenient facts about the world and is able to create a system that has a certain resemblance to the world even though there is no exact correspondence." (Josephson, 2012)

[20] They still have underlying causes; however, looking at them may obscure their higher-level important properties.

The principles that are derived from our studies should apply to an understanding of how novel properties can emerge in complex systems of any kind[21], whether ecological, social, behavioural, and possibly even technological.

Among other things, we would conjecture that such a new mathematics would not be related to digital computation. Biological systems invariably involve weak interactions and complementarity between molecules and systems that are in dynamic motion. Such systems have characteristics shared with analogue systems as well as digital ones in the light of appreciating a novel source of cohesion. The analogue side of computing, while not entirely novel, has largely been ignored since the digital revolution. We will not make progress in modeling and understanding complex, emergent *living* systems until we have computational systems that are based on similar principles.

Again, many systems besides biological ones are analogue[22]. Most functions describing weather, economic indicators, etc. are also analog. It might therefore be possible to create a revolution in modeling across many disciplines by focusing on developing analogue modeling tools for biological systems.

However, the replacement of digital by analog might not provide the ultimate solution for biology. INBIOSA is in favor of integrative approaches combining the benefits of both worlds, but we need to turn our attention to analog computation and its derivatives, which appear to be more adequate for explaining biological phenomena. Yet, we should not forget that analog modes of operation can be also reductionist. So, a major question on the way to answer is: *Where is the border between reductionism and holism?* How can we find out whether a model entails all necessary variables and constraints?

How could we evaluate the roles of indefiniteness or potentiality and transform the indefiniteness? Perhaps we should make sure that such a model is capable of evolving and include more components approaching the real world situation in a series of iterations.

7.3 The Road Ahead

One possible breakthrough for cultivating the central task of INBIOSA research further may be in sight once we pay attention to the exchange of material, (ubiquitous in biology), as a demonstration of the interplay between first and third person descriptions. A helpful example is the monetary economy. A unique property of the monetary economy is the occurrence of something called *paper money* as an institutional means capable of paying for any kind of debt. To be sure, the paper money is by itself of no value as a physical body and cannot serve even as a substitute for a soft facial tissue, while some interesting figures are printed on its surface in many cases. Nonetheless, paper money used in the process of exchanging its ownership does serve as a means of being exchanged for whatever goods or services of equal value are printed on the paper.

[21] including future Internet infrastructures, virtual communities and extra-terrestrial life

[22] In fact, everything is analogue at a Newtonian level. At a lower level systems may be grainy (discrete), but one needs to realize what advantage have accrued by using digital systems with very small discrete graduations.

The paper money keeping its designated value right in the process of exchanging its ownership is a prerequisite to the operation of the monetary economy, and the monetary stock in the hand of each economic subject is merely a consequential derivative from the process (Matsuno, 1978). When one tries to address the monetary economy computationally or from the perspective of experiencing the monetary transactions internally, we need to pay attention to the dynamics of the monetary flow in the exchange. Furthermore, since no one except the central bank sanctioned by a nation state or a sovereign union can issue and destroy the paper money, each economic subject other than the central banks is under the inevitable constraint of fulfilling monetary flow continuity from each participatory perspective. Fulfilling monetary flow continuity is the computational task each economic agent must assume. What upholds the computational task is the identity of the body facilitating the exchange of the monetary ownership, rather than the identity of the paper money itself. Thus, the basic dynamic predicate coping with the monetary economy computationally must be the monetary flow rather than the monetary stock, the latter of which may be regarded as merely an instantaneous snapshot of the flow variable to be recorded. The appraisal of the priority of monetary flow necessitates the involvement of first person descriptions, since referring to the active agency (assuming first-person status) maneuvering the monetary flow from within is required there. Each economic subject is always busy with and serious about how to maintain monetary flow continuity by any means.

In essence, the keeper of a retail store is busy in managing his day-to-day business so as to clear the draft to be expired by the end of month, while a certified public accountant (CPA) is quietly vigilant in observing whether the double-entry bookkeeping to be prepared by the storekeeper by the end of month would actually let both the ends literally meet. Here, the storekeeper's activity is in first person descriptions, whereas the CPA's observation of the bookkeeping is in third person descriptions.

Both of them are involved in computation in one form or another. Above all, the computation specific to the storekeeper is definitely in first person descriptions.

Once it is properly perceived, the monetary economy in the making should be accessible in first person descriptions, while the record is also legitimately approachable in third person descriptions. Despite that, third person descriptions alone cannot be good enough for appreciating the priority of the flow variables since the simultaneous participation of the stock variables would also be made inevitable there. Computation in terms of flow variables as the most fundamental predicates thus makes the distinction between first and third person descriptions indispensible.

What is concretely at stake is computation underlying the implementation of empirical flow continuity processing various flows as the most fundamental dynamic predicates. The occurrence of the exchange of material in the empirical world is a necessary condition for the likelihood of letting the flow variables be irreducibly fundamental. This perception suggests to us that such computation in terms of the flow variables accessible exclusively in first person descriptions could have been operative even ever since the verge of the origin of life on Earth because of the ubiquity of the exchange of material. The remaining problem may be how to implement the scheme in an explicit manner as reminding us of the distinction between first and third person descriptions.

We are all economic agents; all of us participate, in some way or another, in trading, producing or consuming goods and services. It goes without saying that this poses an unprecedented problem in terms of dimensionality and complexity in modeling of systems such as national economies.

The mechanistic view of economy assumes that agents and the economy performed by them can be separated. In this classical view, the economy, for example the market economy, pursues a natural course towards equilibrium. The equilibrium hypothesis is needed in order to be able to obtain the analytical solutions to the complicated models formulated in ordinary or partial differential equations.

This approach, by emphasizing idealistic conditions (perfect competition, perfect knowledge of all agents etc.) in order to make the modeling problem tractable, sacrifices a more realistic account of how complex systems, like consumers, banks or institutions, adapt and react to the dynamic patterns that they create through their interactions.

This is one of the reasons why economic science has a layer of complexity that natural science does not have: agents elaborate purposive actions and strategies that try to cope with potential outcomes of their own actions, as they interact with other agents. For example, when an agent e.g. Goldman Sachs, predicts patterns in stock prices, that prediction is drastically modifying the pattern itself because other agents will try to adapt to the potential outcome of that action. It is known that herding behaviours like panic or euphoria may produce qualitative changes of regime in the systems that seem to be related with financial booms and busts. With this example we want to suggest that Economic Science, as any other social science that wants to model behaviour of complex systems (humans), is in sorely need of a new methodology.

Therefore, we need a **complex organic approach** able to revisit and elaborate, inside a new theoretical framework grounded in empirical data, concepts such as meta-stability/meta-instability, catastrophes and bifurcations.

7.4 The Junctions

7.4.1 Back to Aristotle?

The forerunners who recognized the significance of irreversibility latent in time include Heraclitus and Aristotle. In particular, Aristotle made a remark on irreversibility when stating “The now in one sense is the same, but not the same in another” or “While passing away constantly, time remains as time” according to Heidegger’s translation. This statement may look contradictory in the light of the principle of contradiction whose significance Aristotle certainly recognized. The principle says that one cannot both affirm and deny the same thing in the same respect at the same time. The remedy Aristotle came up with was the infamous entelecheia or telos at which when reached all of the likely contradictions would disappear in a wholesale manner. Although Aristotelian physics based upon entelecheia has lost its influence since the advent of Galilean physics, this does not mean that the irreversibility itself, noted by Aristotle, would also lose its significance. Quite the contrary, Aristotle’s remark on subjective irreversibility sets a critical criterion on explicating how our conception of time in the first place.

7.4.2 Back to Plato?

When searching for new mathematical formalisms in biology it might be beneficial to take into account the paradigm change imposed by the discovery of the universal machine and the mathematics associated with it so far: that is, recursion theory and theoretical computer science. This might be useful independently of the mechanist hypothesis in the sciences of life and/or mind. If the mechanist thesis is correct, we can assume that the formalism we are searching for is already part of the very rich mathematics of computer science taking the word in a broad sense. If the mechanist thesis is refuted, then a good understanding of machines and their limitations can only help in developing another, better formalism for non-mechanically emulable processes. Indeed, the larger part of computability theory is already a study of the infinite ladder of non-computable functions, and the study of degrees of non-algorithmic solubility. In fact, "computability theory" is really the study of the non-computable functions and processes, and the very existence of the notion of universality is made possible conceptually by the fact that programmable processes have intrinsically non-computable effects, as Turing's non-halting machine problem already illustrates. The study of computer science leads by itself, for this reason, to the study of *partial* computability [23], and degrees on non-computability and non-machine 'emulability'. Marchal shows in a direct way that IF we are machines (whatever "we" might means, as far as "we" have consciousness), then the physical laws cannot be computable or Turing emulable (Marchal, 1998). Despite this, it is also obvious that many biological phenomena are mechanical in their nature, for instance the reproduction process, self-regeneration and embryogenesis. The conceptual problems of reproduction and self-regeneration were not solved either by Descartes, despite his many attempts, nor by the embryologist Driesch who concluded on the presence of some unknown vitalist force. But those problems have been solved in the humble opinion of the present authors both in theory and practice (Case, 1971; Marchal, 1992). The basic idea is very simple, and has many very deep consequences, including eventually the possible refutability of mechanism or of the Aristotelian conception of reality. In a nutshell, the solution for self-duplication or for any more general formal self-transformation T is given by the idea to apply a duplicator operator of 'itself'. If Dx gives xx (or T(xx)), that is if DA gives AA (or T(AA)) and DB gives BB (or T(BB)), then what is it that will give DD? Obviously DD will give DD. And this solves the problem of self-reproduction. Or it will give in the general case T(DD), which gives in turn a general solution for arbitrary computable self-transformations. This technique has been used to implement "amoeba" (a self-reproducing program) and "planarian", a program that can be cut in pieces such that each piece regenerates the missing parts. It presupposes the existence of discretely standardized cellular components.

The same kind of "diagonalization" (going from x to xx, and applying the result to itself) is the basis of a whole field of self-reference theory, and it has been shown that machines are able to introspect and even to discover what the laws of physics have to be, in case that the mechanistic hypothesis is correct. This leads to a total reversal of the Aristotelian paradigm and shows that the Platonist conception of reality is closer to the mechanist consequences than the Aristotelian. Somehow the physical reality is no longer primary but appears to be the border of a Universal Mind, which can be seen as the mathematical structure describing the highly structured potentiality of a universal machine.

[23] For a recent discussion of incomputability in biology and physics please refer to (Longo, 2010).

This insight is helpful to (re-)formulate the classic old "mind-body" problem in a mathematical way, and many promising results have already been obtained here. It shows, notably, that being a machine necessarily entails that physics cannot be entirely computational. And this in turn can be extended to life processes – despite the mechanist initial assumptions. Paradoxically, this makes mechanism a very general vaccine *against* reductionist thought in general. Thus, Universal Machines already defeat all reductionist theories concerning their *behaviour* and *thought processes*.

The "physics of machines" is thus offered in two parts: a provable part and an unprovable part of the machine. And this motivates a theory of qualia as an implicit addition as it were extending the theory of quanta (or talia in Latin), which is the one we use to test mechanism, and also to measure our degree of non-Turing emulability in case that mechanism has been shown to be wrong. All of this exemplifies also that the difference between natural and artificial is an artificial one, and thus is natural for any creature developing a self-centered conception of its surroundings. Just as Jacques Lafitte already foresaw in 1911 and published in 1932, that machines are natural collateral extensions of life, and biology cannot really be separated from engineering and computer science studies (Lafitte, 1932).

We have by now isolated and implemented eight modal logics which are variants of the Gödelian type of self-reference, which makes it possible to handle the two notions of first person and third person point of view for machines with or without oracles[24] (Marchal, 1998; Chaitin, 2011). Further research here would consist in developing a flexible categorical semantics, based on linear logic and sketches theory, allowing some "fuzzification" of those logics, and allowing the ideal case of correct self-referencing logics to be extended to machines capable of self-revision and self-updating. We thus have found an interesting link between the logic of first person knowledge and time-duration, which makes such an extension naturally embeddable into the Integral Biomathics of the INBIOSA project. We anticipate fruitful consequences for anchoring Integral Biomathics as a major bridge across engineering, biology, computer science, mathematical logic and category theory.

We expect also some deep clarification on more philosophical issues related to Fredkin's Digital Philosophy[25] (Fredkin 1990; Fredkin 1992), Chaitin's Omega Theory (Chaitin, 2006) and a possible shift from an Aristotelian towards a more Platonist or Neoplatonist conception of reality, which would lead to a very important new emphasis on fundamental biology on the part of physics.

[24] An oracle is a machine that computes a single arbitrary (non-recursive) function from naturals to naturals (Turing, 1939). In other words, is just another name for non-trivial meta-level heuristics that lies outside an object-level theory. In Integral Biomathics, we regard "oracles" truly lying beyond the object-level (scientific and/or mathematical) theories such as group theory and QM. In other words, an oracle is anything that *is* or *can lead to* a true statement that cannot be reached within a formalized (syntactic) system of the said theory. Oracles are part of all human knowledge that cannot be proven within any of the *currently known* formal systems; i.e. they contain "true" statements that cannot be proven in the Gödelian sense. All our theories will remain incomplete, but as they become richer, what once lied outside a given theory will become part of the (still incomplete) new theory.

[25] Fredkin's Finite Nature Hypothesis states that ultimately all quantities of physics, including space and time, are discrete and finite (Fredkin 1990; Fredkin 1992). It suggests that all measurable physical quantities arise from some Planck scale substrate for multiverse information processing. Also, the amount of information in any small volume of space-time continuum is supposed to be finite and equal to a small number of possibilities.

7.4.3 Back to Kant?

Although the critical thought of Kant was intended as a restoration of Newtonian paradigm of certainty questioned by Hume and in consequence led to conclusions limiting our access to knowledge of the world as it is – which may go beyond interests of this study – his greatest and most universal achievement was the *recognition of conditions for the acquisition of knowledge*. The pessimistic conclusions of Kant have been based on the assumption that the necessity of the intervention of the Twelve Categories of Understanding shaping or forming Sensibilities (or we could say perceptions) obstruct the access to things as they are. However, it may be reinterpreted simply as self-referential character of knowing. To know something, we have to employ our knowledge, considered by Kant as a priori to avoid problem of circularity. For us, it should not be a surprise, as it is yet another expression of autopoiesis, a characteristic of all living systems. We can attempt to change our perspective and instead of escaping, engage in resolving the issue of self-reference, for instance by investigating the mechanisms in the brain responsible for these categories, but in terms transcending classical conceptual framework. Such a framework can be found in the study of information, which gives a more general view of living systems, but includes cognition as one of many functions of the higher organized forms.

Kant believed that the statements of Euclidean geometry are synthetic, but a priori, and that they condition in a necessary way our understanding of the spatial relations. Non-Euclidean geometries have shown that we can go beyond these. It is true that our scientific analysis in science is guided by Boolean form of logic, which seemed necessary, but quantum mechanics shows that logic of events in the micro-world is non-Boolean, which does not preclude their comprehension. Thus, if we can go beyond the limits of the categories of understanding, there is no reason to believe that we cannot reach the level of perspective in which we can understand understanding. Moreover, we can expect that in an autopoietic process this may allow us to make our understanding essentially deeper. Conditions for transcending limits of the mechanisms of understanding consist in formulation of a conceptual framework in which living systems are both subjects and objects of inquiry. The concept of information is present in the study of such systems at every level of organization, and therefore it is a natural candidate for this conceptual framework. Schroeder (2009) considered also a secondary concept of *information integration*, which allows the introduction of quantum logics into the study of consciousness, thus extending classical, Boolean logic without the necessity to involve quantum mechanical description of the system. The work includes a theoretical mechanism of processing information at this extended level.

This leads to another generalization, which allows the consideration of a wider class of theoretical processing devices corresponding to geometric, topological and other relations. This conceptual framework opens the way for studies of all varieties of categories of understanding in terms of theoretical brain mechanisms. However, understanding of the implementation of such theoretical mechanisms in the brain will probably be impossible without resolving the more fundamental problem of the description of a living system in terms of information and its processing, where the autopoietic essence of the mechanisms will have to be considered.

No matter what solutions are proposed, it is necessary to recognize the importance of the lesson from the great synthesis of Kant, and from its errors. Our comprehension of the world is conditioned and shaped by the fact that we are living systems, which are creating their (our) own tools for this comprehension and at the same time participating in the world. Thus, development of our knowledge is a subject of an autopoietic process.

What we know cannot be separated from how we know. From this point of view, biology has the potential to inform and guide other disciplines, in particular those considered more fundamental. Maybe better understanding of our understanding can bring solutions to the problems studied by physics and mathematics.

7.5 What Can We Do Now?

It is essential for this review that we recognize both perspectives taken on science, that of Plato and that of Aristotle. While empiricism has been dominating science ever since Galileo and Newton, the idealistic view was abandoned for a very long time. Now in the age of logic, computation, immersive reality and virtual worlds, Neoplatonism can have a renaissance. Instead of Plato vs. Aristotle, both viewpoints are suddenly legitimate and arguable under Kant. But we also recognize both their unity and antagonism with Hegel and Schelling. The issue of "assumed objectivity" becomes disputable again – and taboos such as the suggestion that the way of natural sciences is the only one that can be taken seriously are being questioned again (Fasching, 1996). We welcome the return of scientific disputes, for it is indeed dangerous to have a "thinking monoculture." After many years of research, we still do not know what reality is (Fasching, 2000; 2003). Therefore, there will be no taboo questions on the INBIOSA path. Note also that the position stated cautiously in section 7.4.2 above is only that, IF mechanism is true, THEN we are in a Platonist arithmetical video game. But it does NOT say that mechanism is true.

When questioning the foundations of biology, we are going to leave no stone unturned, including those on which we stand and will step on in future. Dogmas will not be accepted. We will also consider the implications of modern physics for this work. In particular, we realize the likely relevance of quantum theory (QT) to biology and the chance for a fruitful dialogue between physicists and biologists, specifically about quantum entanglement and quantum coherence which are considered by some to be the key to life and consciousness, despite the unsettled state of physics in this area. On the one hand, it could greatly benefit biology to take note of QT in accounting for living processes (Schrödinger, 1945; McFadden, 2002; Ho, 2008). On the other hand, biology could help explaining QT (Pattee, 1971; Josephson, 2012), an argument, which is relevant to Salthe's Hierarchy Theory (Salthe, 1985). Yet, it is Hierarchy Theory that erects the main problem to QM effects at above the microscopic scale[26]. If there are three levels separated by scale, such as [biological cell [macromolecule [atom]]] and there are occasional effects on atoms by QM fluctuons (in Conrad's terminology), this might have fleeting effects on several out of thousands of macromolecules.

[26] Any level constructs an interpretation of lower level effects (which do not penetrate as such to a higher level), while being governed by boundary conditions imposed by higher levels. The levels are screened off from each other dynamically; otherwise there would be no levels!

But the question is what would be the likelihood of significant effects on one cell? It is not easy to resolve this conflict between Hierarchy Theory and most QM interpretations.

An interesting example in this respect is an unorthodox theory related to a key concept in quantum mechanics, – entanglement and the EPR paradox (Einstein, Podolski & Rosen, 1935). One interpretation of this entanglement is known as the "Everettian heresy", (Osnaghi et al., 2009). In 1957, Hugh Everett, III, proposed a new interpretation of quantum mechanics questioning the orthodox view of the Copenhagen school, proposing a "relative state" formulation (Everett, 1957a/b; Everett, 1973), denying the existence of a separate classical realm from the QM one and asserting a state vector for the whole Universe. According to this theory, known as the theory of universal wave function, the state vector never collapses, and hence reality as a whole is scale-free and rigorously deterministic. Everett's idea correlates to Hierarchy Theory because it is higher levels that govern the lower ones by imposing boundary conditions constraining them.

This reality, which is described jointly by the dynamical variables and the state vector, is not the reality we customarily think of, but is a reality composed of many worlds[27] as a source of potential splitting to come in the development of time. By virtue of the temporal development of the dynamical variables the state vector decomposes naturally into orthogonal vectors, reflecting a continual splitting of the universe into a multitude of mutually unobservable but equally real worlds in retrospect, in each of which every good measurement has yielded a definite result with the aid of the environmental decoherence and in most of which the familiar statistical quantum laws hold[28]. Should we dare to question the foundations of modern science? Yes, because this makes it science. And it is our job to ask questions. Everett's theory is interesting for biologists because it has the potential to solve the riddle of entanglement in a rational (humanoid) manner without invoking laws except for those specific to QM, dispensing with the demarcation line separating the quantum and the classical. The "relative state" vector implies that the two measurements in the EPR experiment are each simultaneously connected (or even integrated!), by their very definition, with the observer, and hence automatically correlated**.** In other words, the fact that an observed object state (psi-object) is a function of BOTH the capital wave function of the whole universe (Psi-universe) AND the observer's own to himself unknown state (psi-obs) in the formalism of quantum mechanics was the solution, (Rössler, 2011).

Perhaps the "many worlds" theory is only a (first person) subjective reality incompatible with (third person) objective physics? But isn't that another explanation for the information integration that Schroeder speaks about in his "quantum logic/coherence without quantum mechanics" (Schroeder, 2009), cf. sections 5.8 and 7.4.3?

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[27] The phrase "many-worlds" is due to Bryce DeWitt, who was responsible for the wider popularization of Everett's theory.

[28] Note that Everett's theory is only one of a number of alternative interpretations of quantum theory dealing with the measurement paradox. Roger Penrose listed six types of interpretation in his book "The Road to Reality" (Penrose, 2005, p.786), the last of which, calling for further theorizing about the nature of reality, has a number of variations. The list includes the many worlds interpretation of Everett-Wheeler, which Penrose lists as second. The only reason for selecting Everett in this example is that entanglement is connected with the observer as a living system and the state vector, which unifies the classical and the quantum world. A unifying theory is a clear objective of Integral Biomathics. But there might be better arguments than the option/choice of having multiple worlds that motivate this goal. We don't know yet.

This question shows how we are going to attack the riddles of biology: by being open to and discussing any good idea. This holds particularly for the enigma of life, the genetic system, enabling the preservation of historical events.

The interpersonal (de)coherences in our INBIOSA discussion circle could be exemplified metaphorically by the following citation of one of our members about another one[29]:

> "Matsuno takes chemical reactions generally to be mediated by QM coherence with the end products falling into decoherence. This signals an escape from externalist 'statistical mechanics' into a QM 'internalist' mode of seeing the physical world. Matsuno argues that achieving QM coherence of chemical reactants can be seen as a process of mutual internal measurement -- which we will note, would be a semiotic process -- one which antedates the origin of life." (Salthe, 2008, p. 145)

In short, we have discovered an interesting theoretical co-relation between such ideas in biology as internalism (Matsuno, 1989, 1996, 2003; Rössler, 1998; Salthe, 2001), quantum coherence (Matsuno, 2000; Schroeder, 2009), emergence and self-organization (Salthe & Matsuno, 1995), development and evolution (Salthe, 1993; Salthe, 2010), perception/semiosis (Salthe, 2005b), cognition, consciousness, first person descriptions (Matsuno, 2003), information, information integration and the way we use it[30] when we actively participate in structuring the universe (Schroeder, 2011), making science and so on: all this within the framework of Integral Biomathics. But isn't that a perpetual interaction and circulation of Plato, Aristotle, Kant, Hegel, Schelling and others?

Which are the major challenges on the three junctions described in the previous sections?

Aristotle: A new challenge awaiting us will be: how to appreciate the class identity that can outlive the individual identities in our current practice of the empirical sciences? In physics, it has been common practice to conceive of the class identity of the atoms or molecules of the same kind only in terms of their individual indistinguishability. However, once we enter the biological realm, the situation becomes drastically changed. Even if the physicist cannot distinguish this from the outside, there arises the not unlikely possibility that a material body may maintain its identity through a constant exchange of its constituent material subunits.

A partial list of challenging questions, which can be addressed, reads as follows:

[29] Everett's theory is contrasted with decoherence interpretations (listed third by Penrose, although he considers it a pragmatic, and now most common interpretation) that Matsuno is drawing upon. We often have disjoint and even rival views presented in INBIOSA (which is also the intention of the project). The important issue is, however, the consent that quantum entanglement is likely to be relevant in biology, and it could be that through biology it will be possible to get a clearer insight into which of these interpretations is best for living systems, or whether some new interpretation will emerge.

[30] being 'mechanisms' of information integration in our brains, which create what we experience as *mind*

1. Does the exchange of materials assume an irreducibly fundamental significance, even without prior participation of possible cellular structures? (This question is related to another basic question seen e.g. by Putnam of whether the exchange of materials could be as fundamental a property as (in the context of the material body referred to in isolation) its inertia.)
2. What could the principal characteristic of a material body, whose class identity can outlive the individual identities of the constituent material subunits, be?
3. How does the flow of time unique to cyanobacteria differ from a similar flow of time so obvious to the physicist (except for Boltzmann)? (The question is how cyanobacteria experience what the physicist calls time, rather than how the physicist reads time into what cyanobacteria are doing.)
4. How influential could the likely existing network of the various biological clocks be on the distinction between the class identity and the individual identities? (Even in cynanobacteria, the clockwork of the KaiC protein requires ATP as the phosphate source, and this again requires a different kind of clocks for its own synthesis. The activity of signs also requires an attribute of time, e.g. an activity through some sort of medium. The same applies to action, reaction, synchronization and the like. The question is: from where can we recruit what is eventually called time that could apply to whatever material agencies?)
5. How can we describe[31] the synchronization of various clocks of material origin without relying upon the equation of motion? (If we employ a form of the equation of motion for describing the possible scheme of synchronization, this would turn out to be self-defeating in the sense that it has already assumed the flow of time equated to the displacements of the state variables – unless time does not flow in physics as Boltzmann claimed.)
6. How can we estimate the robustness of a complex network of various clocks operating upon the distinction between the class identities and the individual identities[32]? (An answer to this question may be relevant to how and to what extent each biological species including ours can remain robust in the whole network. Addressing this kind of problem is possible in the framework of the present methodology since the flow of time is here tentatively attributed to each material body's capability of making a distinction between the class identity and the individual identities.)

[31] Note: Here is a deep confusion that is inevitable for all of us who can speak. All of us are inclined to think that time is irreducibly fundamental unless asked otherwise. However, this strange stipulation simply does not apply to biological organisms other than our human beings. Time for us is a representation of something enigmatic. All of the other biological organisms experience that "something" directly without using the tag "time" as we do. The underlying question is: how can we distinguish time as a representation from the original object to be represented eventually as time by us.

[32] For instance, individual dogs are always "dog-like", even if the internal clocks vary from one dog to another. A dog is "dog-like" in the human frame of mind, not in the dog's mind. In a sense dog-like-ness is a timeless abstraction. But, *individual* dogs are different (Elsasser, 1981). How different? In particular, their bodies are constantly exchanging their constituent material elements. The individual identity of each carbon atom entering their bodies is traceable only over half a year at most. When we say that the major ingredients of dogs bodies are carbon atoms, what we refer to by the tag "carbon atoms" are not the carbon atoms to be distinguished individually, but the class property of the carbon atoms that can be maintained in their bodies even if each one of them is replaced by another one of the same kind (as implied in physics). Metabolism in biology makes any organism as a material manifestation of the class identity when viewed from the perspective of the participating atoms. Each atom in the material world has both the individual and the class identity. The question is about how can we distinguish between these two?

Plato: From a logician's perspective, Everett's "interpretation" is the literal (technically, the free or Herbrand model) of quantum mechanics without collapse (Everett, 1957a/b, 1973). Everett only applies the wave equation to the couple made of the physicists and the observed particle. The work of Marchal (2001; 2004; 2005) is very similar, in the context of digital mechanics. Starting from a well defined distinction between first person and third person in the mechanist frame, Marchal discovers that physics becomes reduced to an internal many worlds, or probably better "many dreams" statistics on semi-decidable arithmetical relations (computations), where a dream is defined by a computation seen in some precisely defined first person perspective. These works accomplish a reduction of physics to the biology (or psychology, or theology[33]) of numbers (or digital machines).

It shows that Everett's way of embedding the subject (physicists) in the object (the quantum wave) *necessarily* has to be extended into an embedding of the subject (mathematician, biologist, theologian) into arithmetic, and that this leads directly to an arithmetical quantum logic justifying why, from the points of view of 'number', physics seems linear, symmetrical and having many branches interfering statistically. It is the only precise theory, which provides a *testable* explanation of where the laws of physics come from, and which exploits the incompleteness phenomenon to distinguish a mathematically precise theory of quanta from a more general theory of qualia. The quanta appear to be first person plural sharable qualia. Marchal argues that the gap between proof and truth that machines can infer when introspecting themselves (a possibility already seen by Gödel), justifies the use of the term "number's theology" instead of biology or psychology. It shows also that Rössler's endophysics (1987; 1990; 1998) is naturally extended into an endoarithmetic once we assume digital mechanism.

A key question to answer on the way is: how could we save the best of the Platonic world in the wild if the phenomenon called time is not an illusion?

Kant: Kant (2003) based his synthesis on the distinction and opposition of the understanding, structured by categories and the sensibilities reflecting external structural characteristics of reality. The former basically defined the idea of an object (thing) in general; the latter identified its instances. They were related by means of schemata such as time or space without which there could be no explanation about how categories can function to organize sensibilities. It is clear that Kant's idea of schemata, although extremely obscure, served as the uniting element of his philosophy of knowing. The choice of time and space as schemata can be interpreted as a reflection of the mechanistic view of the reality influenced by the success of Newtonian paradigm. It implies that objects are assembled by schemata into an organized whole, which can be studied in a mechanistic way.

[33] Marchal defines the theology of a machine by the arithmetical truth *about* it, or involving it (in third and/or first person views) minus what the machine can prove about itself. He sums it up often by saying that theology is Tarski's truth minus Gödel's provability. This gives a "toy" theology of the ideally self-referentially correct machine. It provides a theology close to early Platonist theologies, which include physics as a sub-branch. Indeed, he proposed a complete and testable arithmetical interpretation of Plotinus's neoplatonist theology (Marchal, 2007), including his "two matters" theory (sensible and intelligible matter).

Our task is to review both the categories of understanding and the idea of schemata, to prevent the bias of the mechanistic view of the world. To some extent the initial steps in this direction have been taken by Humberto Maturana and Francisco Varela (1980), who focused their study of the foundations for the comprehension of living systems on the relationship between concepts of structure and function, with the autopoietic process as a uniting element. However, this framework is too narrow to provide a comprehensive vision of reality. Also, their explanation of the concept of autopoietic machine includes references to the spatial separation from the world outside and to the temporal aspects of perpetuation. Therefore, although autopoiesis remains an important concept characterizing living systems, it lacks generality and independence from more fundamental referents, which are necessary to initiate building of a new synthesis. For instance, the transition from the traditional focus on substantial aspects to organizational (relational) ones is, in the case of living systems necessary, but it is not obvious and very doubtful that the category of substance can be left without any counterpart.

The work on such tasks should proceed from beginnings in Aristotelian categories through Kant's more elaborate, but much less clear system of categories, sensibilities and schemata, to a system all of whose elements are clearly justified. In addition, it is important to analyze the mutual relations of these elements, in particular relationships between the categories, or whatever would take their place. If we want to retain the framework of Kant's synthesis, one key question we have to answer on the way is: how could we naturalize the Kantian schemata for space and time in the face of the latest version(s) of quantum mechanics at the turn of the 21st century? In other words, do we need to revise Kant's synthesis?

Conclusion: Everett's interpretation is not the only choice among all other alternative theories of QM. In particular, it is based on concepts of the old, original wave function formalism which does not require mathematical elaboration and remains very useful in practical applications, but, because of the involvement of accidental, only historically justified elements and the lack of generality is of less value for understanding QM[34]. However, theories such as Everett's also have some merits: in provoking the established methodology of thinking, in the virtue of Aristotle's potentiality principle, in the conception of gedanken-experiments and in the scientific discussions that precede adequate choice and (if necessary) development of the mathematical apparatus. This is what really counts, but is usually neglected, when planning and doing science. Most of the time is used for thinking, which cannot be measured in physical, let alone, monetary units. Therefore, the Integral Biomathics approach aims to minimize presuppositions and consider all possible interpretations of physical theories for assessing their value in explaining life. It is interesting to note that very different approaches as those of Everett's, Marchal's and Schroeder's lead to some similar conclusions by involving the observer in the equation. This correlation must mean something. To answer what we need to do more research.

Nevertheless, theoretical advances in QT and its impact on biology are one issue, and their empirical evidence is a different one. Theoretically, QM effects might affect a macromolecule[35], but such events

[34] In particular, this formalism cannot accommodate superselection rules, which show that actual physical systems considered as quantum ones are partially quantum and partially classical.
[35] Salthe places them in the chemical realm on the basis of scale compared with the size of the cell (Salthe, 1985).

would be individual. The question is: how do they accumulate in order to have an effect on the cell? There are differing opinions:

> "Neurobiologists and most physicists believe that on the cellular level, the interaction of neurons is governed by classical physics. A small minority, however, maintains that quantum mechanics is important for understanding higher brain functions, e.g. for the generation of voluntary movements (free will), for high-level perception and for consciousness. Arguments from biophysics and computational neuroscience make this unlikely." (Koch & Hepp, 2007)

The quest continues, e.g. (Georgiev, 2011).

7.6 A Unifying Formal Framework

In biology, classical models (mostly based on non-linear differential equations, dynamic systems, graph theory, stochastic processes or information theory) are well adapted to study local problems, but it is impossible to extrapolate global properties of a system from its local features. For example, in a cellular system, the molecules that make up the cells follow different laws from those at the level of cells, even though both molecules and cells are part of the same whole. Moreover, each part operates on its own time scale, and these temporal variations play an essential part in the evolution of a system. So we need to develop another frame in which both local and global problems can be analyzed. Category Theory is a good candidate for providing the unifying formal framework for **Integral Biomathics,** in particular to propose solutions to some of the problems indicated in the preceding sections.

7.6.1 Why Categories?

Category Theory (CT) is strongly related to graph theory. A category is a (directed hyper) graph[36] plus an internal composition of directed arcs. Conversely, a graph generates the category of its paths, obtained just by adding its paths as new edges (with convolution as composition). Eilenberg and MacLane introduced Category Theory in the early 1940’s; it has a unique status, at the border between mathematics, logic, and meta-mathematics. It was introduced to relate algebraic and topological constructs, and later its foundational role in mathematics and logic was emphasized by several authors, for example, in the theory of *topos* developed by Lawvere and Tierney, and in the *sketch theory* developed by Ehresmann. In particular it provides a single setting unifying many domains of mathematics and makes a general concept of structure possible. Categorical logic is now a well-defined field based on type theory for intuitionistic logics, with applications in functional programming and domain theory, where a Cartesian closed category is taken as a non-syntactic description of a lambda calculus (Church, 1940; Lambek, 1986).

Category Theory, seen as an analysis of the main operations of the "working mathematician", reflects some of the prototypical operations that man does for making sense of his world.

[36] Here we restrict ourselves to 'small' categories whose objects form a set. In general, 'large' categories are also accepted. Lawvere has shown how Category Theory can serve as an alternative to axiomatic set theory (Lawvere, 1966).

Among these operations are formation, dissolution, comparison, and combination of relations between objects (morphisms and their composition in a category); synthesis of complex objects from more elementary ones ("colimit" operation); analysis (decomposition of complex objects); optimization processes (universal constructions); formation of hierarchies of objects ("complexification"); classification of objects into invariance classes (formation of concepts as projective limits).

As these operations are at the basis of science, it explains the interest of applying Category Theory in other scientific domains. For instance, categories propose new perspectives on the foundations of physics (e.g., using higher order categories and "higher symmetries") for studying quantum field theories, quantum gravitation, string and D-branes theory (cf. Baez, Coecke, etc.). In the late fifties, Robert Rosen introduced categories to develop a relational biology.

A 'dynamic' Category Theory (incorporating time and durations) is at the basis of the Memory Evolutive Systems (Ehresmann & Vanbremeersch, 1987, 2007), which give a frame for hierarchical natural systems with a multi-agent, multi-temporal self-organization, such as biological systems, cognitive systems or social systems. MES simultaneously cover the local, global, evolutionary and temporal aspects, in particular analyzing how the interplay among the possibly conflicting local logics of the co-regulator agents can lead to a 'less disruptive' global logic merging most of them into a higher synthesis. Among the categorical tools used in MES figure the (co)limit operation to model the hierarchy.

Goguen, a well-known computer scientist (who died in 2006), one of the first to use categories, had proposed to use this operation already to this end in 1970 (Goguen 1970). However even in his later works (e.g., Goguen, 1992), he does not contemplate the main problems studied in MES. For instance in their first 1987 paper on hierarchical evolutive systems, Andrée Ehresmann & J.-P. Vanbremeersch already apply colimits in a more elaborate manner to develop a theory of emergence and complexity and to construct the "complexification process" (which relies on previous works of Andrée and Charles Ehresmann (A. Bastiani-Ehresmann & C. Ehresmann, 1970-1972). And there is nothing in Goguen's work (e.g. Goguen, 1992, based on sheaf theory) that relates to the 'dynamic' aspect of MES with its multi-temporal self-organization as developed in (Ehresmann & Vanbremeersch, 1990, 2007).

7.6.2 The Memory Evolutive Systems (MES)

The Memory Evolutive Systems (MES) provide a mathematical model for autonomous evolutionary systems of higher complexity, such as biological, neuro-cognitive or social systems. Such systems have a tangled hierarchy of interconnected components varying over time; their self-organization is directed by a net of mutually entailed functional regulatory subsystems, the "Co-Regulators" (CRs), each operating with its local logic at its own complexity level, with a specific timescale and a differential access to a central flexible *memory*; where successive experiences can be stored and later retrieved for better adaptation.

The model developed by A. Ehresmann and J.-P. Vanbremeersch since 1987, (Ehresmann & Vanbremeersch, 2007; for a summary, cf. (Ehresmann and Simeonov, 2012)) is based on a 'dynamical' theory of categories which provides a frame for studying the following problems:

(i) The *Binding Problem*: how do simple objects bind together to form a complex object forming "a whole that is greater than the sum of its parts"? (The "whole" C is represented by the 'colimit' (Kan, 1958) of the pattern P formed by the interconnected simple "parts", explaining how the class identity (or complex identity of C) can be preserved while the "individual identity" of the components of P varies? And what are the simple and complex interactions arising between complex objects? The simple links just bind clusters of links between lower level components. However it is proven that "complex links" can emerge when the system satisfies the "Multiplicity Principle" (MP), a kind of "degeneracy" (in Edelman's sense, 1987), ensuring the existence of 'multiform' objects admitting functionally equivalent, but non-connected, lower order realizations. These complex links compose simple links binding non-adjacent clusters, and they reflect global properties of the lower levels not observable locally at these lower levels.

(ii) The *Emergence Problem*: how to measure the 'real' complexity order of an object and to characterize the property allowing for the formation of objects and processes of increasing complexity orders through successive "complexification processes" over time? The complexification process explains how new categories can 'emerge' and gives an explicit description of them. A major result proves that MP is the necessary condition for the emergence of objects and processes of increasing complexity order through iterated complexifications; for instance the emergence of complex organisms, or of higher cognitive processes (as explained in MENS, cf. Section 8.1.3). And MP clarifies the difference between "mechanisms" and "organisms" (in Rosen's terminology).

(iii) *Multi-scale self-organization*: how is the dynamic of the system generated internally, through the competition/cooperation between its net of coregulators, each operating as a hybrid system, at its own rhythm and with its own logic? Each coregulator selects a procedure on its "landscape", but their various procedures may conflict, requiring a global equilibration process, the interplay among coregulators, a kind of selection process among them, to which the Multiplicity Principle provides more flexibility. This process must respect the temporal constraints expressed by the "synchronicity laws". It leads to the global logic which will be implemented, possibly causing loops of dysfunction/repairs between the coregulators.

The MES model leads to several applications, for instance:

(a) Efficient *methods for ubiquitous complex events processing*, in particular leading to a *Theory of aging* for an organism (cf. Section 8.4).

(b) Model *MENS* for a neuro-cognitive system (cf. Section 8.3). It is a MES obtained by successive complexifications of the evolutive system modeling the neural system of an animal.

MES allow incorporating typical biological properties, and also physical ones, for the first time in a formal mathematical framework. However they do not tell the whole story of living systems.

7.6.3 Open Problems

Up to now, the MES theory comprises the following characteristics:

- **Advantages**: The MES theory offers a model, which simultaneously takes account of the hierarchy, complexity and dynamic multi-agent multi-temporal self-organization (beyond autopoiesis). Its main result is the singling out of the Multiplicity Principle (MP) at the basis of emergence of higher structures and processes, providing the only explanation of emergence we know at this moment.

- **Weaknesses**: Theoretically, MES cannot solve the difficult problem of interplay among CRs; we point to the temporal constraints given by the synchronicity laws, but there are many other constraints, which should be taken into account. Besides, we need to answer the question of how to deduce a global logic from more or less conflicting local logics, each with multiple instantiations. Practically, the above issues are not easily amenable to computations of any kind to this moment. A possible approach for a more dynamic computing/communications approach to these problems could be through the *Wandering Logic Intelligence* (Simeonov, 2002a/c). This is what Ehresmann and Simeonov propose in (Ehresmann & Simeonov, 2012).

Another problem is to take account of the fact that living systems exhibit supplementary structures. To account for them, (the configuration categories of) a MES can be "enriched" with these structures. It is easy with topologies or higher categories. It is more difficult to introduce the kind of randomness natural phenomena exhibit (for instance the firing of a neuron when the depolarisation is above threshold generally occurs only with some probability). An important step in this respect would be to introduce a notion of "stochastic" category in which the composite only exists with some probability.

7.7 Conclusions and Outlook

The new paradigm of **Integral Biomathics** distinguishes physical structures from functional structures, the former being defined in physical terms while the latter are defined in terms of their behaviour. In physics there is little difference between the two in that structure or constitution tends to determine behaviour while given some observed behaviour one is often able to determine the structure that is responsible. In biology, on the other hand, there may be no specific structure associated with a given function; instead there are many ways to achieve a given goal: the functionality acts a filter determining which structures are possible.

Functionality is not entirely straightforward either, as it is typically achieved through a number of components working together. Thus, an important aspect of functionality consists in components *learning to play their part* in a larger system, consisting of two or more components. In some cases this involves systems learning to recognize *signs* and responding appropriately. In other cases a function is developed by a less constrained process, which can be characterized as play. These processes all go towards making a biosystem behave as a unitary whole, with a particular perspective of its own.

This tendency to create "wholes" extends to the environment of a biosystem, as each particular unit finds *niches* in which it can function effectively. In an even subtler mode, *signs* may find niches where they are effective, as in our use of language.

Another unique aspect of biological systems is that as they evolve, they create new *signs* and new niches. Niche creation is a relatively new and rapidly growing field of study, mainly in ecology (Ulanowicz, 1986; 1997), but it is a concept that applies to all levels of organization. One of the most intriguing aspects of niche creation is that it is often the excreta of one organism that creates the niche for another (classic examples being oxygen, which poisons anaerobes but created a new niche for aerobic organisms, and dung and the evolution of dung beetles).

Furthermore, the concepts of selective retention of some components and the selective elimination of others also seem to be unique to biology. A further twist is provided by the idea of complementarity (s. section 5.1). Complementarity relates to the ambiguity of reality in our perception of it. The fact that we may view, for example a situation or thing as one entity or alternatively as another entity, or even choose between the two to fit our purposes, reveals Nature, as it were, offering us options.

The usual ways of characterizing Nature loses these subtleties, treating Nature in objective terms, assuming we can master it cognitively and say definitely what is there. With the concepts discussed above we can start to consider the question 'what is really going on', in the new light of **Integral Biomathics**.

8. Initial GTLS Application Domains

This section describes the efforts to apply this general theory in many domains, with special emphasis on cross-disciplinary problems and multiple domains spanning both "hard" and "soft" sciences. The result will be a coherent collection of computationally hostable analytical techniques.

The following sections present a non-exclusive list of applications in Brain/Mind Science using Category Theory as major tool.

8.1 Fusing the Different Levels of Brain/Mind Modeling

At the synaptic and neuronal level, since Hodgkin-Huxley's seminal work in the early 50's, we have accurate biophysical models of single neuronal dynamics. Sophisticated computational models have been produced since then, but neuroscience itself has remained fragmented at the different levels of organization in the brain. These are the microscopic level of neurons, the mesoscopic level of networks of neurons, and finally the macroscopic level of whole brain areas in which cognitive function arise. Thus, we have a whole host of mathematical structures and frameworks to fuse together. Each one of them has to be evaluated regarding its effectiveness in order to decide how it could be developed further into a larger framework for which we are searching. The use of mathematical tools, such as Category Theory combined with stochastic continuum neural field theory and related dynamical systems analyses, will give a common underlying framework to obtain variables relating the different levels of description (micro, meso, macro) for studying these mechanisms, and for explaining how they may lead to the emergence of higher cognitive processes. Computational models of the hippocampus (Burgess, 1994; Arleo, 2000) state that the sum of a set of elements (grid cells) directly produces another element, a place cell. In doing so, these models take for granted that the properties of the sum are directly reducible to those of its components. This strict form of reductionism is at odds with the nature of complex systems. Gomez-Ramirez (2010) has used Category Theory for modeling the formation of place cells from grid cells in the hippocampus in a non-reductionist way. The cooperation of the grid fields gives rise to a colimit, which is a place field.

8.2 Scale-free Dynamics

An object that presents invariance over changes of scale of observation is scale invariant. This is a symmetric property of paramount importance in mathematics and natural science. Simply stated, scale invariance means that the object reproduces itself on different time or spatial scales[37]. For example, it presents self-similarity in a geometrical context. Scale free dynamics refers here to the invariance of the equations that describe the dynamics of the system. Thus, given an observable O i.e. an equation, which depends on the parameter x, we say that is scale invariant under the change of x by αx, if exists a number, $\phi(\alpha)$, such that $O(x) = \phi(O(\alpha x))$. For a more in depth characterization of scale invariance, and other related phenomena like self-organized criticality or fractality, see for example (Sornette, 2000; Embrechts 2002).

Studies on scale invariance in the brain are being spurred thanks to the progressive increase in spatial and temporal resolution of recording techniques. It has been recently demonstrated (Expert et al., 2010) that even fMRI data when appropriately analyzed, exhibits self-similarity and hierarchical structure at all length scales. Indeed, the apparent heterogeneity of various parts of the brain hides some general mechanisms at the basis of its functioning. In particular, it is well known that mental operations depend on the activation of synchronous neuronal groups, different such neural groups having the same role. We explore the concept of meaningful patterns, which is similar to the term “cognit” coined by the neurobiologist J. Fuster (Fuster, 2005) and with the concept of “neurocognitive networks” conceived by S. Bressler (Bressler, 2007). The neural populations at the mesoscopic level in the olfactory bulb studied by W. Freeman (Freeman, 2000) are also similar to our meaningful patterns.

However, the identification of meaningful networks or patterns that express those cognitive functions, which are what this theory promises, is, as is recognized by its own proponents, simply daunting.

[37] In a topological context, it is interesting to note that a scale-free network is one that does not have a specific scale of the size of connection e.g. power law distribution is scale-free (Barabási, 1999)

Indeed, when dealing with broadly distributed connections of a large number of components, highly coupled with non linear dynamics, the resulting behaviour of the neurocognitive networks are, in many cases, impossible to control and predict. The problem is as follows: assuming that we know how to describe the dynamics that neurons would exhibit in isolation, and assuming that the dynamics of the temporal patterns of those isolated neurons have a well-known long-term behaviour, like for example stable fixed points or chaotic attractors; if we couple those systems together the global behaviour is still missing.

This is the essence of Complexity Science: understand the global dynamics of complex systems, consisting of a number of elements, strongly coupled and with highly non-linear dynamics. We believe that i) by acknowledging scale free dynamics hypothesis, and ii) by using mathematics like Category Theory combined with other methodologies of complexity sciences such as Network Theory, a more effective and fruitful approach in the unveiling of meaningful patterns in the brain will be possible.

Scale-free dynamics of neocortex are characterized by hierarchical self-similarities of patterns of synaptic connectivity and spatiotemporal neural activity (Freeman, 2007). We are going to develop a novel framework to investigate the structure of complex brain networks, based on Category Theory, combined with statistical mechanics to model high-dimensional complex data.

8.3 The Model MENS

MENS (Ehresmann & Vanbremeersch, 1990, 2007, 2009) is an application of MES (cf. Section 7.6) to a neuro-cognitive system. This hierarchical model has the neural system at its base with its neurons and synaptic paths between them. The components of higher levels, called category-neurons, represent increasingly complex mental objects or processes obtained as the colimit of each synchronous neural (hyper-)assembly which they activate. Such category-neurons are obtained from the neural level by iterated complexification processes, and they have multiple physical realizabilities into neural 'pyramids'. The model accounts for the formation of a flexible internal model of the Self, the Archetypal Core, and explains how it is at the root of the emergence of higher mental or cognitive processes, up to consciousness (Ehresmann & Vanbremeersch, 2002, 2009). For a more precise discussion, please refer to (Ehresmann, 2012).

8.4 Application to Complex Event Processing. A Theory of Aging

Organisms such as living systems have a multi-agent multi-temporal self-organization. In MES the agents are the coregulators (CRs). Each CR operates locally stepwise with its own rhythm, logic and partial information. However, their commands to effectors must be coordinated through 'interplay' among CRs, which, as said in Section 7.6.2, causes dysfunctions (fracture, dyschrony or even the need for re-synchronisation) to the CRs whose commands cannot be realized. In particular the temporal constrains of each CR must be respected, and hence the synchronicity laws relating the period of a CR to the stability span of the intervening components and the transmission delays between them; these laws are indicated by (Ehresmann & Simeonov, 2012).

Failure to respect these laws may lead to loops

fracture → repair → fracture…

between CRs of different levels, possibly leading to a re-synchronisation of some CRs.

One application is an Aging Theory for an organism, through a cascade of re-synchronisations for physiological co-regulators of increasing levels (Ehresmann & Vanbremeersch, 1993). This theory agrees and unifies most known physiological theories. On the other hand, Zlotin's work (Zlotin, 1972) forms the physical basis of a theory of aging, which applies to all dissipative systems (Salthe, 1993).

Other applications of this process have been developed for complex event processing for various organisms (Ehresmann & Vanbremeersch, 2011), leading to a methodology for anticipation using complex switches between different realizations of multiform objects to generate complex scenarios.

9. The GTLS Test Cases

This section describes the theory's test cases. These are designed to demonstrate, prove and communicate the results. The problem is one that spans physics, chemistry, biology, societies and societal dynamics. It requires integrated measurable results at many levels, and it is in a general area known to present "grand challenges" to existing methods.

A key aspect of understanding the brain and other complex systems is to appreciate the logic in relatively small and simple sets of information. The goal should not be complexity per se, but design systems that provide complex functions, without structural complexity. Thus the goal is to eliminate complexity from the design side. If we can do that we can understand complexity in biological systems. This can only be done by grasping the underlying principles, such us robustness, stability etc. We need to go small for doing that, e.g. to start with small complex systems like the e. coli.

In the following we propose three projects as test cases.

9.1 WLIMES

Living systems are systems with a tangled hierarchy of interconnected components varying over time, with a multi-scale self-organization. As explained in section 7.6, the *Memory Evolutive Systems, MES* (Ehresmann, A. C., Vanbremeersch, 2007) provide a mathematical model based on a 'dynamic' category theory for such multi-scale complex systems. However MES are not yet amenable to some kind of "computation".

The Wandering Logic Intelligence, WLI (Simeonov, 1999-2002a/c), is an open, hierarchical and dynamically structured model for communication systems. It enables the design of a special class of ad-hoc mobile active networks, Wandering Networks (WN), defined by the following characteristics:

- flexible, multi-modal specialization of network nodes as virtual subnetworks;
- mobility and virtualization of the net functions as hardware und software;
- self-organization as multi-feedback-based topology-on-demand.

Network elements can contain several exchangeable modules capable of executing diverse network functions in parallel. They can be invoked, transported to or generated in the nodes upon delivery of mobile code about the node's behaviour. For this purpose, both the processing nodes (ships/netbots) and the information packets (shuttles) are active (i.e. executable), exchangeable, re-configurable and programmable. The WN elements are of temporal character; they can be created, configured and removed. Functions can change their hosts, wander and settle down in other hosts.

WLI is a technical concept taken from the domain of biology, i.e. a "bio-inspired" mechanism with the goal of solving problems of growing complexity in communication networks. It combines the issues of information processing, exchange, storage and virtualization into a robust operational engineering framework. The solutions are distributed "human-designed" self-organization algorithms such as WARAAN (Simeonov, 2002b) and HiPeer (Wepiwé & Simeonov, 2006) implemented as conventional Turing Machine computation. They are artificial constructs and run essentially as any other communication protocol or resource discovery scheme. The only distinction is their inherent growing behavioural complexity achieved by "memorizing" and distributing navigation and structural information about the evolving environment "locally" in the genetic code of the shuttles when traversing the netbots.

Now, WLI as an extracted-from-Nature model can be applied back to biological systems in a series of iterations to ensure its verification. The most characteristic concept is the one of fractal virtualization of resources and its continuous multiplication in terms of "software chunks" over time, which does not really have analogs in biology and physiology.

Therefore, one of the intended projects is to combine the two approaches WLI and MES into a novel theoretical model framework, WLIMES, the Wandering LIMES, the suitability of which has to be verified against real world biological systems. In particular this frame could approach the computational problems raised by MES. The idea is that the CRs of MES and the *netbots* of WLI play similar roles. What of the shuttles? In MES a link is 'active' at *t* if some information passes through it. This information of various kinds (physical, chemical, code, etc.) could be carried by *shuttles,* which activate several consecutive links on their way.

One of the main problems for making MES amenable to computation is the 'interplay' among the CRs. Indeed the commands sent to effectors by the various CRs at a given time can be conflicting. In terms of WLI it means that there are competitive shuttles. Can WLI methods be extended to solve this problem? We will try to answer this question.

9.2 Hyper-B

The importance of scale to biological systems makes it imperative that one of our test cases should face this issue head on. Our second project addresses the properties and operation of a multiscale complex computational hierarchy, as briefly described earlier.

Following the description of Section 5.2 of this document ('Scale and Hyperscale') such a computational hierarchy will consist of alternating levels of logical 'normality' and logical 'complexity'. The former will be provided by *InfoMax*, a currently successful cortical processing model, (Cottam et al., 2000), while the latter will be modeled using Schroeder's (2009) informational integration 'quantum logic without quantum systems'. In many ways this project is parallel to WLIMES, but its grounding philosophy and integrated mechanisms are very different. This follows from the Integral Biomathics approach of testing different approaches to the same target – that of modeling biosystems.

Hyper-B will start by establishing a single computational scaling model – where data at one level becomes contextualized to information at another. The following phase will be to couple more than one of these computational schemes together to represent the multiscale nature of biology. In doing so, the information created at one level becomes the data for the next, as the context itself will be scaled. As indicated in Section 5.2, inter-level transit appears to resemble quantum error-correction techniques, and this will be simulated by the collection of contextual ecosystemic information at one level to facilitate transit to a higher one.

This kind of scheme is neither bottom-up, nor top-down in character: propagation in both of these directions is necessary to instill the required cross-scalar correlations, which will lead to the generation of a global systemic identity.

We envisage two different ways in which the resulting computational assembly will be accessed by considering applications. The first corresponds to a scheme, which was put forward in 1991 (Cottam et al.) to provide computational responses to threats within a limited time-window. This kind of *survival computation* envisages access to a hierarchical assembly by propagating a (threatening) stimulus internally from the highest hierarchical level towards the lowest. Each successive level takes more and more processing time, but results in progressively greater accuracy of response. Waiting as long as possible during the available window of time then yields the 'best' response possible.

The second way in which we envisage access is through a separately computed *hyperscale* representation of the multiple scales. This hyperscale representation will be created in a manner similar to that integrated the multiple scales themselves – by a combination of *quantum logic without quantum systems* and *InfoMax*. In this case, all of the scales will be simultaneously accessible, but only with a reduced precision (as the scales themselves are partially enclosed when viewed from outside). The net result here will be a systemic identity which takes account of the degrees to which individual scales are enclosed (and therefore partially inaccessible), and which delivers a systemic image which is biased towards the naturally most open, and therefore most representative scales.

9.3 Morphogenesis

A third test case could be the realization of a computational framework dedicated to the generation of multi-scale models of living tissues and organs. The framework would be founded upon the self-organizing principles of morphogenesis. One of the most spectacular and fascinating manifestations of self-organization in living systems is embryogenesis and the morphogenesis of organs during the developmental phase of the embryo. It is during this phase that the exceedingly complex and interwoven structures of tissues and organs are grown out of a "disordered" mesenchyme. Only morphogenetic-based methods will be able to produce realistic multi-scale 3D models of tissues and cells. Manual modeling can only produce a stereotyped organization by concatenating parametric "template" elements. Today's modern imaging systems (RMI, scanners) can provide gross anatomical features but are a far cry from "showing" the intricate capillary and lymphatic networks and nerve structures around, say, a small group of cells. Yet, if building models of living tissues and organs is the goal, we need to model all the dynamics that occurs around and within its most important unit: the single living cell. The structures involved are individually complex, interwoven, and anisotropic in their physico-chemical properties. The challenge then is to devise self-constructing models that can simulate the self-organizing processes that underlie embryogenesis, growth and adult-life adaptation.

Living tissues are highly complex and intertwined. They perform functions like mass transport. And any attempt to model such functions requires shape information at all levels of detail before setting the boundary conditions across each interface (e.g. flux, partial-flux or no-flux across boundaries for a given chemical species). Thus an important part of modeling life-like tissues lies in producing realistic multi-scale 3D morphologies, boundary conditions and incorporating the anisotropic properties of the system under study. This is particularly true when modeling living organisms. Understanding the morphogenesis of tissues and organs from a single cell will open the window to Nature's secret of generating forms of tremendous complexity from the initial egg structure. Despite this complexity, fundamental research in developmental biology seem to confirm that morphogenesis results from coordinated cell behaviour such as signaling motion and aggregation, division, differentiation and apoptosis (Dressler, 2006). The process is initiated by inductor cells and coordination is mediated by short-range direct cell-cell and cell-extra-cellular matrix interactions as well as medium to long-range interactions mediated by chemical and electrical morphogenetic fields. It is the spatiotemporal organization of these interactions that determine the final structure.

This test case addresses many issues of the INBIOSA research program. Indeed, the following points could be studied:

- multi-scale structural generation;
- multi-modal, short, medium and long range interactions;
- simultaneous co-dependencies between these interactions and the global form/geometry of the structure being generated;
- combination of discrete structures (e.g. cells) with "continuous" quantities such as morphogenetic chemical and electric fields.

In addition, descriptive knowledge (predicates) could also be included in the framework in order to inform the latter about the agents and entities involved in morphogenesis. This would open the door to other INBIOSA issues, such as:

- addressing entailment and relational biology
- incorporating Category Theory / MES
- developing introspectively articulated systems.

10. Call to Action

In the following sections we summarize the major conclusions of this report.

10.1 The Case for Transformative Research in Biology

This section summarizes the argument in this paper seeking FET support for a continuance into Phase 2 of the transformative, i.e. high risk, high payoff research proposed by the INBIOSA group of researchers. The proposals are organized around the broader theme of the sciences of complexity rather being narrowly focused on biology as a complex science *per se*. However there is a central focus on biology because of the many advances contributing to the new sciences of complexity achieved from the massive societal investment in health and related sciences research over the past 50 years. Our proposals are organized around two fundamental themes that we believe are essential to the transformation of modern science:

- the need for convergent theoretical syntheses which will crystallize the theoretical challenges and
- the need for innovative mathematical concepts to effectively articulate these new syntheses into a verifiable theoretical foundation for practical applications.

Lastly, we provide proposals for institutionalizing these transformations into future FET funded research.

We believe that our research proposals meet the criteria for qualification as scientific grand challenges and are worthy of further investment as the spearhead of a new renaissance in science. The proposals are critically relevant to scientific progress because they address the issue of systems (real and artificial) of increasing complexity; they are paradigmatically radical because they call for convergent theoretical synthesis of a magnitude not seen in biology since Darwin; and they will have a radical impact on all sciences of complexity because they will offer new metaphors and mathematical innovation. We recognize that such language may appear to be overly and insupportably ambitious. Indeed, we do not know if among the world scientific community, there exists the genius to address the problem statements we have put forward.

What we do know is that is has happened before – a methodological revolution in the physical sciences: the transformation of physics into a dual discipline of experimental and theoretical physics – that brought forth the modern world.

That revolution was founded on the discovery that the apparent complexity of the world could be addressed by rigorous experimental methods and the development of mathematical languages and grammars that stunned our own beliefs in the power of human thought (Wigner, 1960).

But now we face a new intellectual challenge, not of apparent complexity but of *genuine irreducible* complexity in our quest for a more fundamental understanding of living entities and the complex institutions and technologies enabled by our scientific culture. The rigor and fundamental paradigms of physics advanced all sciences across a very wide field of knowledge bringing new observational tools and computational capabilities to bear on the new quest. That quest is beleaguered by the intransigence of living systems to submit to the assumptions of simplification and computation of the physical sciences. The dynamic complexity of all living entities appears to be irreducible and totally confounding.

Our ability to describe the biological world in all its manifestations has reached the point where we can track neurons and chemical transactions in the brain simultaneously; at the higher levels of the organization of life we have terabytes of data describing our social, ecological, technological and economic systems. We have reached this condition of information overload in the sciences of living systems because our theoretical understanding greatly lags our observational capabilities. We are confounded with an excess of incommensurable observation and theory in much the same way that the astronomers of old were confounded with what appeared to be irresolvable inconsistencies in their observations of the stars and Ptolemaic theory until the Copernican Revolution. Because biology has proliferated too many theories and paradigms, all too narrowly focused, there is the need for convergent theoretical synthesis ultimately synthesizing a simpler theory (canon of parsimony) that encompasses the subordinate ones. The implicit response of mainstream science is to wait for the Copernicus of the modern era and for the generations of genius that will inevitably follow him. But we have reasons not to wait.

10.2 The Threat to the Certainities of Continuing Progress

The first reason why we cannot wait and why we must attempt to accelerate the progress of science is that the growing complexity of the modern world – the product of first scientific revolution – is becoming increasingly evident to all. We are many now. We are massive consumers of the earth's energy resources. Our information technologies support industries, economies, education and financial systems from the global to the individual level. Our medical and biochemical technologies enable bodily interventions of unparalleled complexities in an ever more costly effort to manage the diseases of modernity. Our industrial technologies demand equally intensive and complex interventions in all the natural ecologies that support life on this Earth. But all is not well. Despite the undeniable progress in human welfare the complexities of modernity are growing and threatening the certainties of our continuing progress as a society and species.

What makes these threats extremely problematic is that we have a world universally entrained in complex systems and interventions where we know scarcely anything of their potential interaction and failure rates and forms[38]. The risk is therefore of catastrophic failure because of this universal deployment and extreme dependence. In some areas, such as national security, where our security is based on engineered systems of complexity, we take steps to limit catastrophic failure by pursuing the development of systems of even higher complexity (e.g. countermeasures utilizing quantum computing as the shield against computer hacking or subversion).

However the availability of opportunities in most areas of natural complexity is very limited because we do not understand how Nature develops complexity in the first instance.

10.3 The Intellectual Challenge of the Complexity Complexity

There is a second reason not to wait. Frustration with the inadequacy of conventional scientific approaches in addressing societally supported research objectives and the unquenchable thirst for understanding that drives human existence invites intellectual risk-taking. Some of that risk-taking is paying off. We are painstakingly learning how to conduct the many sciences of complexity[39]. For science itself is a complex system of human creation[40]. We now understand science as a highly complex hierarchical system of thought, a noetic system in itself, whose careful reasoning and open-ended insight processes are irrepressibly capable of generating novel theories. We can have a new confidence in embarking on a journey of intentionally challenging ourselves to explore the complexity of living entities because we have begun to learn from the history of science how to advance science itself. The lessons are twofold: first, there is a need for theoretical convergence of the many working theories and hypotheses that arise across the many narrow subdomains of complex fields; secondly that it is essential to develop mathematical formalisms derived specifically from and for the fields in which complexity reigns. *If we adopt these overarching principles of scientific innovation we will have new tools to apply to the methodological challenges in biology and complex systems generally.*

[38] Notably, an earlier EC expert consultation has reported: "… that the number of digital systems and artifacts is increasingly exponentially, such that we are approaching a point where digital entities have ceased to be just technical systems and have become part of the socio-technical fabric of society. This plethora of semi-autonomous, 'cyberphysical systems' – which all rely on embedded ICT and are connected to the information ether – will constitute a new kind of physical intelligence…For our societies to function effectively, we have to learn to identify and give meaning to interactions within these highly complex, cooperative and dynamic systems. This poses severe challenges from both technological and societal perspectives." *FET Consultation on Collective Adaptive Systems,* November 2009.

[39] "Semiosis and self-organization are co-extensional - there are as many different basic types of semiotic processes as there are basic types of systemic self-organizing processes." (Hofkirchner, 2002)

[40] "Human language, culture, science, technology, systems of governance and economies are all examples of human symbolic systems that propagate their organization. They occupy a special place in the biosphere. They are products of human conceptual thought and represent emergent phenomena. They differ from the materially based information in biological systems in that they are abstract and symbolic and not materially instantiated as such with the exception of technology. In the case of technology it is the concepts and organization that goes into the creation of the physical tools that propagates." **(**Kauffman et al., 2008)

10.4 Programmatic Advance in Theoretical Research

While history is replete with stories grand and (sometimes) failed of intentional efforts to develop technologies for extremely ambitious human undertakings (e.g., the Manhattan Project, the Man on the Moon Project, the (Japanese) Fifth Generation Computing Project, The Human Genome Project, The Blue Brain Project, etc.) there is no history of programmatic advance in theoretical science, the essential foundation for all scientific and technological advance. It took two thousand years for the world to be persuaded of the importance of theory to the establishment of heliocentrism, but only four hundred years more to await the discovery of the power of mathematical abstraction to advance theoretical science. Perhaps within a generation we will extend our grasp of the dynamics of living systems and their sister technologies. Let us assume that there may indeed be genius in our midst with the imagination required to unlock this most complex of mysteries. How should we accelerate engagement with this challenge among our best and brightest?

We have no answer to this question but offer three considerations:

1. The first is that the modern world is unique in history in that it is rapidly proliferating complex technologies of production and intervention on a global scale and it does so without full and responsible knowledge of the consequences of continued complexification of these technologies; that is a risk no one has measured or considered; the need to understand is great; never has the project of scientific advance worked under such conditions.

2. The second consideration is that of the possibilities of the complexity sciences enabling a second revolution in the re-shaping of the world towards human needs, security and sustainability. Advances in disease management, ecological stabilization, resource efficiencies, and social justice are potential outcomes of greater understanding of basic life processes and the cultural edifices and artifacts enabled by cumulative human creativity and collaboration.

3. The third, and even more encouraging consideration, is that we have a much greater potential in terms of human resources and its new-found connectivity to bring to bear the human intellect required to address the challenge – if we want; we lack only the institutional frameworks to do it. The challenge is to invent and create the necessary institutional settings required to foster specific methodologies for the advance of critical areas in science.

INBIOSA suggests consideration of a conceptual model for such an institutional framework based on the concept of emergent complex systems itself: in other words to mimic, in the larger world, the thought processes and structures that enable the emergence of new ideas in the human mind. The list in the next section is a reformulation of the previous table in section 6.4 listing potential fields of research addressing complexity issues. The reformulation as a (tentative) hierarchy of theoretical orientation is a first-cut schematic for implementing the central scientific challenge of performing the necessary convergent synthesis of theory underlying the complexity of living systems. The institutional challenge is to recreate that thought process at the scale of the total societal effort in the relevant sciences.

In other words, the co-ordination – but not the control – of the many modules of thought that could, but are not being brought together into a more coherent model of life itself. This would involve co-coordinating efforts through FET for academic and private interdisciplinary collaborators guided by the principle of synthesis. Implementing such co-ordination is the institutional challenge. The form of structure and communication that would most benefit the process is not yet known. What is known is that existing processes of collaboration and disciplinary integration and co-ordination do not support such synthesis and mathematical innovation. There is a great deal to explore ahead of us.

Despite revealing more detail, natural sciences have not provided a complete theory of reality yet. Modern culture and science constrain us (Pickering, 2011). For instance, mind and intelligence have been investigated in a very limited way in Artificial Intelligence, (Ray, 2011). There are natural phenomena such as sentience (Clarck, 2000) and emotion (Damasio, 2005) that do not have measurable characteristics (quanta). The nature of Nature is its incompleteness, (Deacon, 2011). Integral Biomathics accepts that and tries to discover the missing links and fill the gaps by putting/developing mathematical theory and computation into/ out of biology. A part of the broad perspective that lies in the future of Biocomputing and **Integral Biomathics** is shown in (Seaman & Rössler, 2011) and (Josephson, 2012).

10.5 A New Framework for Mathematics and Computation

In what follows, we present a (non-exhaustive) list of key themes for research in Integral Biomathics. It is far from Hilbert's famous list of challenging problems in mathematics (Hilbert, 1902). We do not believe in reviving the idea of an axiomatic system of science. We consider INBIOSA, as a developing project, a permanent "building site" with concepts and ideas in permanent movement. "The future is easier to predict with hindsight". So, this list should be considered to be a preliminary one. We will continue working on it in a follow-up project.

The following two activity fields comprise our research framework.

Living Systems Modeling

- Develop new realistic mathematical models tailored for living systems, obtained by integration and development of different domains of mathematics: algebraic topology and geometry, cohomological algebra, functional analysis and differential equations, differential geometry and fibred spaces, statistics and probability, different kinds of logic, and so on.

- Develop new simulation, visualization and creativity support techniques and tools for these novel mathematical models of the living.

Steps towards a "New Integral Science"

The essence of typical questions to be addressed is how to take account of the (possibly fuzzy) interactions between discrete and continuous phenomena, leading to the emergence of complexity.

- Design an original general system of abstractions within the biological domain that can be relationally examined. It should support multiple complementary mathematical approaches to phenomena that can be brought into dialogical juxtaposition.

- Define ways of identifying the biological properties that are as unique to such complex conglomerations as 'temperature' is to a set of molecules, or the 'flexible redundancy' property ubiquitous in biological systems, called degeneracy or multiplicity. What we seek to articulate is an evolutionary mathematics that deals with the emergence of organization from non-random selection among replicating variations within complex populations of processes.

We are looking here not only for space-time scale invariant properties of living organisms, but also for *cardinal* properties that may *differ* across the space-time scales, which are still inherently "biological". Our view of emergence includes both the emergence of more complex objects as aggregates of patterns of interacting lower level objects, and the emergence of complex interactions between them, which emerge at the higher level from the global structure of the lower levels but cannot be locally observable via lower level components. Also we understand emergence as a product of a system functioning over time falling in relation to the unfolding of its larger environment.

10.5.1 Approach: Constructivist Innovative Mathematical Cross-Disciplinary Models

The main activities that need to be addressed here are:

- Develop dynamic models of biochemical and biophysical systems accounting for multiple scales and time frames as they relate to new forms of dynamic modeling and physical mapping/scanning systems. Analyze how scales themselves can be of emergent character.

- Develop convergent theoretical syntheses of adequate mathematical concepts and methods, bringing them into dynamic relation with each other. Such a relational mathematics is expected to model both the dynamics of the system in a local neighborhood with its specific temporality, and at the global level of the system emerging from the possibly conflicting relations between these local dynamics, through a kind of communication and negotiation between near and far neighborhoods.

- Construct models of "hybrid" systems presenting a combination/juxtaposition of continuous as well as discrete time changes accounting for their relational, statistical and geometrical aspects as well. To analyze biological problems, the mathematical challenge is how to combine these different domains, which are generally studied separately in orthodox mathematics.

As Category Theory unifies many mathematical domains and is also at the frontier with logic and computer science, it should be used in models formally describing natural phenomena, as well as more orthodox domains such as partial differential equations and chaos theory, topology and cohomology, dynamical systems, geometry and field theory, fuzzy sets and probability, and so on.

Category Theory should itself be enriched and made more flexible by addition of more structure, for instance by introducing statistical categories. Categorical models are well equipped to analyze the problem of emergence, going further than Rosen's notion of entailment, up to the emergence of higher cognitive processes, perhaps allowing the incorporation of first person approaches (Topological Psychology). They can also provide multiple perspectives related to the problem of "class identity" and material space/time flow.

The working "algorithm" to realize this approach might be defined as follows:

1. Investigate phenomena in living systems by trying to describe them using the above (integrated) formal toolset to deliver an evolving model.

2. At the point where the model does not match the experimental results, develop new formal means to reflect and explain these peculiarities, thus advancing the model to a next stage.

3. Focus on both objects and processes and on their interactions.

This method should not be understood as strictly formal. In other words, the "match" with experimental results could be verified by means of computer programs, or only require pencil and paper. On the other hand, there are also *negative* mathematical proofs (limitation results), e.g. by logical deduction, predicate calculus, or even gedanken-experiments involving visualization tools (geometry, animation).

10.5.2 Focus and Implementation: Integral Biomathics

Integral Biomathics (Simeonov, 2010a/b) is a cross-disciplinary meta-theory, involving both internalist and externalist mathematical biology and biological mathematics based on advanced mathematics formalisms, such as e.g. the Memory Evolutive Systems (Ehresmann & Vanbremeersch, 2007), an evolutionary dynamic category theory aimed at integrating (halting)[41] oracle machines (Turing, 1939) and other related mathematical and computational theories and abstractions, as well as heuristics and a broad range of simulation, visualization and other creative support techniques capable of dealing with phenomena and data that cannot be handled by formalisms alone. It allows interrogation marks/interfaces between its constituents and builds bridges to other disciplines.

[41] The halting problem is indeed among the most famous ones in computer science. The question here is: should we restrict ourselves to *halting* oracles only? Indeed, any meta-heuristics that lies outside an (object-level) theory is an oracle *with respect to the object-level*. For instance, an agent (natural or artificial) that decides to include group theory as a means to tackle quantum mechanics takes an "oracle"-like decision with respect to both (object-level) group theory and QM. The questions/goals that arise then are: (i) how to model such an agent for biology?; and (ii) can we later devise a more general theory that would substitute the oracle and where the decision would naturally fall *within* the theory? So, we pursue the replacement of oracles in general, but as a short and middle term goal we have to focus on the halting problem. Therefore, we decided to use the term "halting" in braces henceforth to capture both the short and long-term INBIOSA objectives.

The operative framework of Integral Biomathics is defined as a multi-perspective approach to knowledge production: observation of new phenomena / incorporation of new forms of entailment-generating-technology (e.g. scanning methodologies) as well as modeling approaches → articulate convergent theoretical synthesis across divergent fields → integrate multiple mathematical formalisms under one relational umbrella → *develop integrated mathematical models accounting for multi-scale structures and multi-temporal dynamics* → study the dynamic relation between emergent phenomena and predictive phenomena → justify initial theoretical approaches via computational modeling → develop empirical demonstration and verification → articulate a falsifiable theoretical foundation for practical applications.

This gives us a panoramic view of the system with all its structures, dynamics and functionality:

- Enable the use of information from different areas of discourse to examine how low level processes "percolate up" and relate to higher levels, and how human scale behavioural processes may enable first and third person comparative relations.
- Define concrete approaches to discrete computational methodologies (functioning at different scales) to capture change over time from a series of different multi-modal observational perspectives. Define systems that can also present coherent integrated high-level processes that relate to the lower level processes. This is about the integration of the computational aspect and its material underpinning.

A first step towards realizing this goal is a follow-up project of the INBIOSA initiative that will devise a research framework combining object-level mechanisms with Turing oracles[42] (Chaitin, 2011). This is going to be a step stone towards a "unified theory" of living systems, both "natural" and "artificial" ones. Therefore, our longer-range objective will be to step-wise replace the oracles by a more general theory of life. The question is how to proceed from here? Scientific approaches are often guided by heuristics. It applies to any organism.

We distinguish between 4 classes of heuristics:

1. The meta-heuristics unique to a mathematician is anthropocentric.
2. Heuristics in foresight is a risk-taking endeavor (no analogue in the Platonic world).
3. Heuristics in hindsight is a success story.
4. Evolution and development are about heuristics in the making.

The second option is not amenable to formalization. The fourth option reflects what happens in Nature.

[42] We have to take oracles into account, because they are characteristic for biological phenomena. For instance, the evolutionary transition from dinosaurs to mammals can be modeled by halting oracles, although they do not entail local changes in the probability of histories. A reference paper about the role that oracles play in problem solving in the case of a random oracle is (Kurtz, 1983).

Evolution is just unplanned change[43]. Development, however, from the computational point of view, is a 'scripted change', with preservation of the results of the changes[44]. While evolutionary computation (Fogel, 1966) and genetic algorithms (Holland, 1975) are well known in AI and system design engineering today, development is also a promising model for computation, which is closer to the third class of heuristics.

What remains are only two opposite options/postulates, one and three, to choose from and one corollary:

1. In Nature, meta-level heuristics (i.e. mathematical heuristics of the first class) do co-exist with, and are distinct from, mechanisms. This brings the following questions:
    - how different are/what distinguishes the heuristics from the mechanisms?
    - what kind of ("Maxwell daemon"- like) intelligent agents are carrying-out the heuristics?
2. The meta-level heuristics and mechanisms are in fact one (i.e. heuristics in hindsight of the 3rd class). Their distinction is circumstantial (e.g. with reference to a given problem to solve or to a given perspective). Within the frame of this postulate, Nature and its Platonic counterpart are inherently self-referential. If this is the case then, objects, structures and operators related to self-reference should be a central part of the "unified theory".
3. Corollary to postulate (2): life is characterized by both artificial and natural objects.

We believe that these questions and the attempts to answer them are the core issues that radically distinguish the INBIOSA quest from Systems Biology, and from the EC FP7 Flagship proposals Human Brain Project (HBP) and Virtual Human Project (VPH).

Systems Biology and its cousin Bioinformatics are centered on multi-scale biological processes and making sense out of huge amounts of biological data respectively. These research programs are physics-based and data-driven. Our approach is mathematics-based and biology-driven. Further, we are dealing with life that includes artificial artifacts with self-reference (i.e. first person vs. third person) as key issues, the development of self* software is the high-yield intellectual, practical and economical reward of this high-risk program. Following results stemming from Systems Biology, AI researchers may want to extrapolate and use the life-metaphor to build systems capable of general intelligence and autonomy. But General AI in itself is *not* the concern of Systems Biology. **INBIOSA addresses life in general (both natural and artificial). Our program treats both subjects at the same time. Systems Biology and other related disciplines (Biological Computation, Computational Biology, etc.) address specific problems in biology, which are of considerable practical interest, but are not fundamental biology problems in the sense defined by the INBIOSA project[45]. The same holds for the recent efforts to apply Quantum**

[43] Any random generator, either alone or with chaotic structure guidance, will deliver evolutionary output, if the results are preserved. The results of the changes would be preserved, and further changes would be built upon these. No pattern would be expected to accrue.

[44] Most generally, aside from whatever script might be involved, changes would at first be large and happening rapidly, gradually slowing down with smaller and smaller changes resulting. The changes would all in effect be refinements of the results of the original changes. The result is a gradually stabilizing form, (Salthe, 1993).

[45] Recently, some authors began speaking of "integrative" systems biology realizing that orthodox systems biology does not address fundamental issues (Auffray & Nottale, 2008; Nottale & Auffray, 2008).

Physics for explaining biological phenomena in the same style as for the emergence of classicality from the quantum. Each one of them is based on a certain interpretation of QM taken as a base, but not on a systematic review and analysis of the appropriate theoretical models (and perhaps the creation of new ones) from the viewpoint of biology.

The INBIOSA focus is on looking for new ideas. In particular, contemporary biology and physics do *not* address the following questions/goals:

1. Are the currently existing scientific/mathematical/computational theories sufficient, such that meta-level Turing oracles could be replaced by models within these existing theories, and given that we have more data available?
2. Are the current theories insufficient in the sense that no amount of additional data is going to replace some of the oracles in our models?
3. Can we postulate/conjecture that even if (2) holds, a theory (or a set of compatible and/or complementary theories) able to replace oracles by models can be conceived/unveiled? In other words, can we imply that decision making and judgments lie *within* the theory?
4. What is missing on the way to creating a Unified Theory of Life and Consciousness?
5. How to create a "Tree of Life" (or perhaps a universe of multiple and simultaneous worlds), a living ontology of facts, axioms, propositions and theories, in biology, physics and science as a whole guiding the evolution of science?
6. Can biology be associated with the emergence of decoherence in quantum mechanics? How could the Turing's oracles be naturalized in the framework of quantum physics?

Integral Biomathics can be regarded as a new branch of Theoretical Biology. If the intended Theoretical Biology has an empirical relevance as it should do, it must be also anchored on solid material or physical grounds. Therefore, we aim to devise a research program on a global scale in a follow-up project with the following foci:

1. development of a theoretical and computational framework that incorporates both oracles and mechanisms whereby real-life complexity can be captured to an extent that other contemporary approaches (e.g. systems biology) do not;
2. stepwise elimination of oracles by the generalizing the theory (or theories) underlying the framework; i.e. the oracles will gradually be replaced by statements/models that lie within the mathematical and computational theories being generalized;
3. clear definition of milestones that include the following:
   a. conceptualization and elaboration of the computational framework that includes, but also separates meta-level oracles from mechanisms;
   b. construction of experimental and validation protocols to verify the legitimacy of the oracles (or classes thereof) and their interactions with the modeled mechanisms;
   c. search of statements/models within existing theories that will eventually replace a subset (if not all) of the oracles;
   d. discover/unveil new/neglected theories in an attempt to obtain a single "unified theory".
   e. physical or hardware implementations of oracles.

Life and mind have escaped all effective complete theories up to this moment. Therefore, we require that Integral Biomathics be an incomplete theoretical and computational framework. It uses oracle machines, but it remains always incomplete and extendible. Our goal is to replace oracles by statements within the sub-theories being developed, but we cannot keep the promise that all oracles in their overall arithmetical hierarchy will be systematically eliminated for the simple reason that each solution/replacement generates a new more powerful (halting) oracle at the next stage, which defines a harder (halting) problem. This is how life, mind and science evolve. Oracle machines are usually thought of as infinite information objects supposed to make theories complete, but paradoxically even this infinite information cannot usually lead to completeness, (Marchal, 1992). Without (halting) oracles, theories can only be "more incomplete". With (halting) oracles we obtain a research program hyper-computer or super-Turing machine (Siegelmann, 1995).

Current theories about life, such as systems biology and related computational frameworks (Wolfram's Science, DNA/cellular computing, etc.), do not use oracle machines to model living systems in their full complexity. By involving oracles in our Integral Biomathics research framework we create a methodology, which leads us stepwise closer to reality.

We have recognized that quantum mechanics is now entering the second revolutionary stage particularly from the perspective of practicing biology. That is the resurrection of the time-honored issue of causality under a rejuvenated guise. The act of measurement comes to be internalized within quantum mechanics. In essence, our main focus will be in how to implement the role of the oracles within the proper framework of quantum mechanics.

10.5.3 Summary and Prospects

Every level of a living system is partially enclosed and partially in communication with its neighboring scales, and the entire system forms a 'self-correlating' whole of partially autonomous scaled 'sub-systems', each with its logic and temporality. The global logic and dynamic is modulated by their cooperative or conflicting interactions. **Scales of time and space emerge through this sort of communication. This is the real strength of the Integral Biomathics approach.** The problem with both systems biology and molecular genetics is that they make use of standard reductionist approaches which visualise organisms as machines[46]. There are aspects of living systems that can be described in this way, and so we are trying to pass beyond this into uncharted territory. Biology is not simply about *such* automata.

We believe that phenomena in living systems can be explained using a robust mathematical theory.

[46] pre-Gödelian (almost clockwork) notion of machine

There are a few options related to mathematical and/vs. computational approaches:

1. extending an existing scientific theory that is mathematized, such as QM, GR, String Theory, etc. to life;

2. using new mathematical specialties/tools *independent* of, although applied by, science; new advances within known mathematical domains or entirely new subdomains;

3. developing a scientific theory of life that is mathematized *and* supported by computation (barring the non-computable parts);

4. developing new mathematical specialties/tools *independent* of, although applied by, science *and* supported by computation (barring the non-computable parts);

5. developing a new theory in computer science;

6. making a radical computational shift but without either a new scientific theory or new mathematics (e.g. Wolfram's Science (Wolfram, 2002), quantum computing, DNA/cellular computing, etc.);

7. all of the above?

We actually vote for the last option and wish to go even beyond it, assuming also other options, not listed above and reaching far into the fields of the arts and humanities. These are the new concepts related to mathematics and computation we often use interchangeably throughout this White Paper, demonstrating the true essence of the adjective *Integral* before *Biomathics.*

The following actions are expected to take place on the way to realizing this goal.

<u>Action 1</u>

Define a mathematical ecology that can bring the following dynamic processes in relation to:

a. autopoiesis (self-construction) and self-organization of biological systems;
b. emergence of modules of hierarchy [and potential dynamic heterarchies/bifurcations] in all complex systems;
c. variation of communication modalities within/between multiple hierarchical levels in living systems;
d. transformations of information processes from scalar to vector/tensor quantities and vice versa (see discussion in section 4: the fourth major problem) ;
e. integration of mathematical approaches that can link discrete, continuous, fuzzy/vague, probabilistic and geometrical information simultaneously; and
f. formal treatment of heuristics[47], e.g. (Chaitin, 2011).

[47] To our knowledge, there is no current theory, computational framework, or applied field such as systems biology where oracles or meta-level decision rules are used to model living systems in their full complexity.

Action 2

1. Define an n-dimensional visualization that runs in dynamic parallel form.
2. Articulate relational definitions of biological functions and their boundary conditions.
3. Articulate a set of theories that cross boundaries between traditionally distinct domains:
    a. time scales, spatial scales, adjacencies/material proximities: related to neighborhoods;
    b. new mathematical analysis of emergence;
    c. mathematics of vague/fuzzy spatial-temporal boundaries;
    d. contextual boundaries: boundaries between processes functioning at different scales of time and space; boundaries that describe the relationship between, and nature of fragmentation of, the entities they separate;
    e. subject ←→ object relation; this is about first vs. third person issues: how they are separate, yet also unified.
4. Define form and function — model the following form-function interactions:
    a. exploring mathematical viability for biology and biological process suitability for mathematics;
    b. developing of new *biology-driven* mathematical branches;
    c. maturing **Integral Biomathics**: integration of mathematical theories under a common umbrella for *biology-driven* mathematics and computation which goes far beyond what we know today as Computational Biology (Russe, 2009) and Biological Computation (Lamm & Unger, 2011).

The central questions to explore within this action plan for Integral Biomathics are:

i) *What* is computation within the biological context?

This question is about the relationship between the Church-Turing thesis and Turing's oracle machine. In short, the role of the (halting) oracle machine in the naturalized empirical setting is first on the agenda of the INBIOSA initiative.

ii) *How useful* is computation for living systems, where usefulness is considered from the viewpoint of the entity performing the computation?

This question is about the possibility for naturalizing the oracle machine. *How*? The strength of INBIOSA is in raising such a question.

iii) *To what extent* can a computation be carried out in an organism or an ecosystem with the available resources?

The computation cannot be separated from the matter of resource intake. This is another strong point of INBIOSA.

Finally, we have to articulate a program that can be managed and measured as it progresses.

Acknowledgement

This is all what we were able to write within this small and short project. If we had more time and money, we could do better. We believe that if the decision makers in the EC follow our recommendations on how we might better understand complexity, they would be better able to solve some of the most urgent problems in future.

We wish to thank all INBIOSA colleagues for the exciting discussions and valuable contributions and comments during this project that led to this White Paper. The members of INBIOSA also gratefully acknowledge the vision and support provided to this activity by the EC FET program and its staff. This report does not address itself to the considerable resistance to the transformation of science created by the institutional structures and prejudices of the academy and in the research funding priorities of most public agencies.

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Appendix: Answers to the INBIOSA Questionnaire

In the following we provide a compilation of the answers of the INBIOSA members to the questionnaire that was created and distributed by the coordinator, Dr. Simeonov, in the beginning of the project. Note that not all questions were answered by all members; individual answers are separated by new lines.

PART I: GENERAL

1: What global changes will occur in the next 20-50 years with regards to human technology needs?

In M-R (metabolism – repair) terms, our hominid species fascination and desire for more powerful and situation specific tools will continue to increase its focus of investment in the sciences and technologies that promise increase in individual health and wellbeing. We have exceeded the comfortable long-term carrying capacity of the earth by about an order of magnitude. The most urgent need is to find a way of reducing the human population.

Human technology needs fossil energy extraction. The reason is possible climate change. Two factors need to be considered: unusual solar activity and radiation contamination.

Summary: We need to increase the individual health and wellbeing, to reduce the human population, to fossil energy extraction and climate change.

a. Which positive outcomes can be brought about by the use of technology?

Sustainable energy production. Bio-technology. We can live healthier and longer. However, any such analysis must include an equally serious discussion of negative outcomes. It will be positive if we used it positively. It will be destructive if we use it negatively. Practical use will be the mix of both uses. We can improve efficiency by use of technology, which will not address the core problem.

Under the condition that there is plenty of clean and inexpensive energy, many existing environments which are degraded and polluted could be restored and improved in order to higher the quality of life for people globally.

Summary: We can achieve higher quality of the life for people globally, greener environment and clean energy by use of technology.

b. What are the really hard problems?

The competition between opposing interests.

Currently we have a monocausal explanation of the world.

We don't know how the human body and mind work.

Our hardest real problems today are environmental ones. What can be expected is that energy needs will continue to grow in spite of energy saving efforts. We do not have clean and safe energy. If robotic and nano-technology fulfill their promise we will need even more energy – both for production and for re-cycling of things, taking care of pollution, environmental restoration and similar. If cheap and clean energy is available then all the rest of technology is possible and their use justified. So the basic thing is to find good energy sources. Besides hard problems of energy, right now we have several scientific fields which seem to be on the edge of revolution. Physics seems to have troubles in explaining of what is going on in the universe. Matter that we believed was all the universe consists of turned to be just about 4%. So something is very wrong and that must be corrected. Possibly based on informational approach which could connect physics with cognition and helps us better understand how actually knowledge is produced (physics is knowledge) and on what grounds it is justified. Perhaps better formalisms for physics can simplify biology as well. Complexity is yet another hard-problems field which hopefully might be simplified by more informationalist formulation of physics.

Social and economic structures favoring the fragmentation of knowledge. Increase of population is unavoidable for a long. Thus, more buildings, more cultivated fields, less natural areas, more garbage. That cannot be stopped. At best, it can be slightly slowed down. Notice that most political parties suggest the expanding the economy activities is the solution of most problems.

Communicating the importance of reducing family size to the mass of humanity.

How to extract oil and gas without totally disrupting the local and human habitation.

Presently, the progress in science is halted due to powerful group interests. They strongly influence the fundamental research in direction that serves their interests by the funding policy and international collaboration.

Summary: The competition between opposing interests; monocausal explanation of the world; how the human body and mind work; environmental problems – energy, pollution; to find good energy sources; increase of population, reducing family size; how to extract oil and gas without totally disrupting the local and human habitation.

Presently, the progress in science is halted due to powerful group interests. They strongly influence the fundamental research in direction that serves their interests by the funding policy and international collaboration.

c. How can we tackle these problems together today and tomorrow?

By teaching children about the legitimacy of alternatives
As in physics there is a need for recognizing the limitations of orthodoxy and to strongly support the search for and development of alternative paradigms.

One good strategy is to include more people globally in the knowledge production. We need new ways of thinking and fresh impulses from groups that traditionally were excluded. It is also not clear in advance where the solutions can come from. They may come laterally from some currently peripheral field.

Specific value should be given to the value of transdisciplinarity and generalist approaches. Please convey this question to those who are elected and/or paid to find solutions: their job is to find solutions.

First we need to get past the cultural prohibition on discussing the population problem. We need to find the courage to put the matter on the table.

I presume via technological improvements. This type of directed research leads and will lead to global disasters.

2. What is The Grand Challenge in science today?

To bring together specialists of remote domains to collaborate, without exclusion.
Understanding THAT a unified field theory exists.

Making peace between science and the bulk of humanity.

The origin of life.

Lack of democracy in science and particularly the problem in fundamental basis of contemporary Physics. The CONCEPT OF SPACE IS WRONG but revision or even discussion is strongly suppressed. The suppression is in university teaching, peer reviewed journals, conferences and government projects.

a. Which challenges do we face in biology and computation today?

To develop new kinds of 'computations' able to account for the degeneracy property of biological systems and to deal with more or less conflicting logics with multiple realizabilities.

We have today two different kinds of logic and rationality: the “real”, technical logic and the “mysterious”, “biological”, “natural” logic which we do not understand yet.

Computational foundations of biology should be worked out. In the process, biological structures and processes are used as inspiration for constructing new computational devices, like in Organic Computing.

Epidemies are good candidates. Few peoplei take care about the genocid due to AIDS in some African countries. If the H1N1 flu was able to kill as surely as the Ebola virus, we would face to the greatest possible catastrophes, worst than what happened in Europe in 1347-1348. But this may be not related the "challenge", in the sense of the questionnaire.

The challenge in computation is partly algorithmic. E.g., increasing the speed of the computers by 10 led to treat problems of size 10 times larger only when the algorithms are linear. But alas many algorithms are quadratic, cubic, etc., and often exponential, so that the need to treat larger and larger datasets cannot be solved only with the increase of computer power.

Making computers with heart and soul. Understanding the human heart, mind, and soul.

How to model semiosis.

The wrong space concept strongly affects the biology.

b. Which are the highest priority themes we should turn our attention to?

As above rational explanation of biology (specifically in genetics).

Understanding life, its genesis and evolution, its processes, structures and mechanisms must be discussed. Understanding the affective domain in humans, and introducing the affective domain into computation.

A total revision of the concept of space – physical vacuum adopted 100 years ago.

c. Which are the key problems we have to solve?

To harmonize conflicting logics and interests.

The interdependence between sequenced and non-sequenced information carriers.

Re-phrasing of sciences in terms of information and computation.

We must face to an enormous increase of data. In the meanwhile, we have few more people to extract knowledge from these data. Worse: the increase of knowledge is global, but in fact it tends to be lost in the vast amount (and much increasing) of documents to be read. This is aggravated by the "publish or perish" system and the way that academic activities are evaluated: bibliometric indicators, counting papers, citations, h-factor. What is really useful in papers is what is useful after many years, not what is many times cited within two years. Too much books, papers, conferences, etc. Retrieving documents is a full science now. Think to the poor readers (and we all are readers...)!

We need to communicate between different ways of knowing (e.g. reason and feeling).

3. Is life on Earth endangered through human technology?

Man is not powerful enough to endanger life, though he could be a nuisance, in particular to his own species.

No.

In as much as technology allows the population to grow beyond a reasonable level.

Absolutely. The incorrect concept of space does not permit to understand the real danger.

a. Can life on Earth extinguish in a worst-case technological disaster scenario?

Not very possible since it has survived through so many disasters.

No.

We do not know. But it is obvious that we do not fully understand the implications of the unrestrained exploitation of the science that we have. We are experimenting with life as we know it.

Yes, definitely.

A full extinction due to technology is improbable, but major catastrophes will probably occur, such as the nuclear ones. I am afraid that nuclear energy is unavoidable, at least because in some countries it is believed so.

I believe we could extinguish life on Earth if we make the choice (consciously or not) to use nuclear energy to allow the population to continue to grow.

No. Microbial life will continue in almost any scenario.

Yes, the life could be extinguished. In the first hand – a nuclear war, in the second hand increased radiation level from nuclear disasters. This includes contamination from nuclear plant catastrophes after earthquakes or from the 200,000 tons radioactive wast accumulated from the era of nuclear energy and weapons.

b. How can science and technology prevent such a human-made technological disaster?

By more responsibility.

By smaller entities. (e.g. local production and delivery of energy)

It can only be prevented where we make greater effort to consider consequences. However the phenomenon of complexity (real and artificial) increases the difficulties of constructive anticipation.

By honestly looking at the technology and its possible consequences. Nuclear energy is the field we can learn a lot from – about what not to do. Very expensive technology which cannot be tested in a lab for all possible scenarios. And in the first place possible scenarios must be seriously analyzed instead of basing safety on faith and hope that nothing unexpected will happen.

They cannot.

Impossible to prevent. Humans (scientists and other) are convinced to set the risks to very low values. But see catastrophs with boats (Titanic and others), planes, trains, chemical factories, nuclear energy production, etc. Each time, smart people explained us that all was controlled, very low risk, and so on. But each time, there was a serie of unpredicted causes, partly due to money problems and greedy people, and this latter cause is impossible to eliminate.

The extinction scenario (as I stated it in 3a) can be prevented by controlling population and not abusing nuclear energy.

INBIOSA

By study of new type of energy alternative the nuclear one. It is referred as: vacuum energy, zero point energy, space energy, free energy and so on. It is a hidden space energy of non EM type but connected to the mass. It is a primary source of the nuclear energy. It could be accessed by specific technology not involving nuclear reactions and radioactive waist. The wrong space concept (physical vacuum) adopted 100 years ago does not allow to envision, understand and research this type of energy that is a primary source of the nuclear energy.

c. Which technological solutions are possible today?

Focused hearing, viewing.

In what sense? I would say that to prevent technological disasters many non-technological components must be involved. Like acceptance of the costs for risk management, preparedness for accidental situations etc. Society as an environment in which technology is implemented has no knowledge or understanding of all the risks of technology they have. Not many visitors of New York and even citizens are aware of the risks of Indian Point nuclear power station. Everybody hopes nothing bad will happen.

No technological solutions are possible, only philosophical and political ones.

Experts should know.

The solution that I propose is to forgo certain technologies (e.g. nuclear).

It maybe possible to begin slowly to disengage from the capitalist growth economy. I think we need to begin to value the senescent state, and begin to try to understand stasis better. Only a prolonged senescent period could be 'sustainable'.

One of the technology is the cold fusion. Other technologies based on direct EM processes are not yet developed. Only scattered success of some individuals are sporadically reported, but without funding of scientific research they are not technologically ready. Also this new energy may have a biological effect so a serious parallel research is needed and development of means for shielding from unwanted scalar (longitudinal waves).

d. Can science and technology change their one-way avail policy into a balanced avail-adversity appraisal when introducing and using new technologies?

Some responsibility is necessary to be exercised by politicians and scientists, but too strict "principes de précaution" could paralyze science and impede any progress.

Yes, by offering solutions that are acceptable to all parties because of their rationality.

Not until we fully understand complexity (real and artificial).

If I understand the question correctly, when using and introducing new technologies, science is important. Both as a basis for new technology and then as an instrument of assessment of its functioning and also for its improvements. Maybe this step is not so common today. Usually technology based on science (like nuclear technology) continues to live its own independent life. It seems to me good to connect with science even as one goes on with technology.

On the other hand, science traditionally uses high-tech – from computers to measurement instruments and similar.

They cannot change by themselves: only a new philosophical approach, grounded in science, can make the balance you indicated attractive enough to be implemented.

I don't understand this question.

e. What is the impact of the cultural and political imprint of an information society in this process of changing priorities in technological development towards maintaining living processes of interaction?

An information society speaks with too many discordant voices competing for scarce material resources to be able to develop a straightforward program.

Maybe for 100 years nothing visible

The information society enables a valuable exchange of data, information and knowledge. However the massive proliferation of electronic self-publication of low quality research and thought undermines the process of evaluation and debate which is critical to the advance of science. It does this by assuming that all perspectives are equally worthy and more importantly fails to provide platforms for structured debate (eg through target papers, evidence-based medicine)

Cultural and political impact is of course fundamental for what gets prioritized. It would be interesting to have some statistics about differences between countries globally in what they invest in sciences.

It is not a technological problem. It is a problem of education, culture, politics, etc.

See above. The main obstacle is the psychology of opposition to the change in the scientific community, the interest of some powerful economic groups and interest of bureaucratic groups.

f. What are the global and social consequences of such decisions?

Too many rules might endanger creativity.

Massively wasteful expenditures on low-grade research (as has been characteristic of much biomedical research in the past 30 years.)

Of course consequences are important. In Germany political opinion is against nuclear power and it has practical consequences. Such decisions must be based on informed consent. People must know what technological risks they are taking.

They will determine how severely we will damage the planet, and how much of the biodiversity we will lose.

No more growth of anything. Ascendency of currently powerful groups -- no more 'American dream' of getting rich.

A new technological revolution.

g. How can we better integrate scientific discovery and technological progress in the natural circulation processes and interactions of living systems on Earth?

I doubt man can have a deep influence on Nature except on a local plan.

By understanding it.

Reduce the number of PhDs. Introduce a new degree; uberPhD; anything to emphasize the need to know when you do not know.
That is an interesting question. We do not know at present about how those processes on Earth actually work. And we do not understand exactly what the result of our impact is. We should apply precautionary principle and at least in those cases which are obvious prioritize value of clean environment before mass production of cheap things that end as garbage in short time. Less things and more fee space would be good for many people who possess innumerable pieces of clothes, and other things that they hardly ever use.

By limiting certain destructive technologies.

The correct space concept is indispensable for such integration.

h. Can we expect a natural circulation and interaction of computation and technology on a global scale?

It seems difficult because of the conflicting interests and logics (as said earlier).

Yes.

Probably. But only by chance will we limit the products to positive outcomes.

Yes it is necessary. Idea of everything is on a global scale today.

Only if our system is largely mechanized, which I think would be a mistake,.

i. How can we achieve that?

By developing encompassing theories at the basis of computation and technology.

By using the internet, e.g.

Increase the varieties of computation and technology and the desire for their interaction in laboratory situations.

I am not quite sure what is meant by "circulation and interaction of computation and technology" but at least when it comes to technology, information technology has much higher spreading than any older technologies. Even in the poorest countries with no electricity people have mobile phones.

Communication technologies are very easily accepted globally.

4. **How does our social and cultural background define, i.e. limit (lat.), our scientific horizon?**

Heavily. We have largely lost the affective ways of knowing, and thus tend to see the world narrowly through reason and intellect. The impairs our ability to truly understand the world, and make wise judgments.

We have a capitalist, Darwinian growth ideology.
The scientific horizon is limited by the current status quo in Physics, again due to the wrong space concept.

a. **How can we expand it by overcoming these limits?**

New ideas, especially if they are really creative and/or opposite to established paradigms, are difficult to be diffused because they impose thought revisions possibly reverting the power scale.

By observing processes of senso-motoric patterns (what we perceive depends on our organs: watch the functioning of the organs and counterbalance their neurological artefacts).

Reduce the tendency to narrowing the creativity of individuals by introducing meta-, trans- and multi-disciplinary education.

When we understand info-computational mechanisms of knowledge production, this becomes obvious. See answer to (c)

Hard to do. A way could be through teaching and through TV broadcasts: this is useful philosophy. But I'm afraid that other priorities exist.

We must rekindle our affective domain.

It should be gradually disengaged from by adopting a new model of the physical vacuum, carefully verified by the experiments and observation accumulated during the past 100 years.

b. What is the role of human/machine logic and natural philosophy in this process?

Natural philosophy (in a 'large' meaning) could have more influence than classic logic for discovering new approaches.

Not hindering it.

The rejection of obvious error.

See answer to (c).

The first step is to recognize the categorial separation between human and machine logic. Existing "human" logics (epistemic, doxastic, *etc.*) have all been linguistic, truth-functional and context-independent. These are incapable of supporting a natural philosophy useful for the foundation of science, including information. Logic in Reality purports to fill this gap.

Outside of the pure hard sciences and mathematics, such as in the area of philosophy, a blend of affect and reason is required.

Need to understand the senescent condition. Need to try to understand how to discard information.

The human logic and natural philosophy should have a priority in Physics in respect to mathematical logic.

c. Which changes do we need to make in the foundations of science to better understand Nature and life?

Open the way to more imagination, in particular by giving transdisciplinary experience to young research students.

Understand that the human's sensory organs imprint an a-priori pattern on the perception and the organisation of the impulses perceived.

Introduce and demonstrate the value of meta-, trans- and multi-disciplinary higher education in the progress of science.

The synthesis of informationalism and computationalism is the best approach.

The worlds of feeling and reason need to recognize one another, reconcile, learn mutual respect, and merge, because only then can we truly be whole.

Valuing the study of senescence, not as a problem, but as a desired state.

In first place: revision of the concept of space (physical vacuum).

5. Can we engineer and maintain a balanced ecosystem of natural and artificial organisms?

Yes.

We don't know until we achieve Alife. See answer to 3.b above.

Not at current population levels.

Artificial organisms will likely be naturally senescent. Natural organisms will be needed to repair the artificial ones.

a. What kinds of conflicts have natural and artificial forms of life?

Are there conflicts?

Natural forms do not follow rules made up by humans

Many applications of AI/Alife are likely to be very beneficial in the beginning because we will design them and their decision-making capabilities for these advantageous purposes. As we go higher up the hierarchical ladder the self-maintenance of the A systems and their capacity to create their own goals (from nano to meso biological levels) would create much conflict with extant molecular, cellular, organic and human decision-making.
I have no clue. Could artificial organisms integrate in the eco-system? Can they radically change ecosystems?

Same as between natural forms of life.

Competition for finite resources.

b. Can systems theory help disentangling the hazard of exterminating natural live forms on Earth?

Systems theory (whatever it means) is formal, it can help better understanding the world around us, but I doubt it can have a serious influence on policy decisions able to have deep consequences on nature itself.

No.

Not yet. About as valuable as Archimedes principle: Give me a place to stand and with a *lever* I will *move* the whole *world.*

In any event systems theory is best suited for the purpose.

Systems theory is just a small part of math modeling tools we have.

So, any tool we have could help.

Only if it can help us address the core problem, being the need to reduce human family size.

Systems theory, as it is now, is too mechanistic. We need vaguer, fuzzier understandings

c. If not, what else can help?

More responsibility at all the levels.

Rearm with clubs, arrows and stone axes.

Also system theory operates under assumptions about what is the case, what structures and mechanisms there are. So those are also important. Even complexity theory. If systems theory covers horizontal interactions among systems, complexity theory covers vertical.

Systems theory is just a small part of math modeling tools we have.

So, any tool we have could help.

6. What needs to be developed?

Elementary school textbooks.

a. What kind of ontologies and theories should be developed?

If we knew the answer, we would already have developed them.

Rationality.

For what exactly?

Logic in Reality includes a novel categorial ontology that emphasizes *non*-separability of the interactive elements of real processes.

I would rather say that we should first discard inadequate theories.

Before that, we must realize that the main requirement is to enhance the education systems, for all people, at any level, anywhere.

Concept of space that leads to deeper understanding of Nature and universe.

b. What kind of tools and methods do we need indeed?

A collaboration between theory and applications, so that the theoretician takes account of the constraints imposed by experimental data, and the experimentalist becomes able to evaluate new ideas and possibly use them to search for more data. The problem is that most scientists have only be trained in one domain. What would be important in the future is to develop more transdisciplinary cursus for young students to acquaint them with both theory and applications and thus close the gap between them.

Learning to count more precisely.

I would rather say that we should first discard inadequate theories.

Before that, we must realize that the main requirement is to enhance the education systems, for all people, at any level, anywhere.

Fuzzy, vague logics; less focused models.

7. **Which were the pitfalls in previous attempts to create a new paradigm shift and how can we avoid them in future?**

We wish that 3+4=2+5 and decree that it is so, even though we see that the two expressions are distinct. We live in a world we dreamed up according to our wishes. But this is not the world we actually live in.

There still appears to be no general acceptance of the limitations of the "Promethean" technological paradigm. The difficulties I experience in trying to get the answers or the software I want on the Internet are not artifacts of the system; they are an inherent, essential characteristic of it.

Any attempt that avoids the revision of the main issue – the concept of space is doom to fail.

a. **What had we learned from the "OMICS" revolution (proteomics, genomics, etc.)?**

Collecting data is interesting but it remains ineffective without some theory to relate and explain them.

That there must be a clever and self-evident explanation behind the "mystery" of life have used this information to discover the human mental organs, and the diversity of ways of knowing that they represent.

More details.

b. What had we learned from progress in other disciplines?

Theory and applications should go hand in hand rather than be at odds.

From sociology and history: that there are equally legitimate, radically different social orders; that the more a systems touts its infallibility, the dumber it is

The human logic never fails in contrary to the claims of Quantum Mechanics. This is proved by computer science. The Computer science, for example, could achieve the present advances without relying on a correct fundamental base – the bulean algebra. In a similar way, all fields of the Natural science could not achieve significant progress without relying on a correct space concept.

8. WHAT IS THE STATUS OF THE "UNITY OF SCIENCES" PROGRAM?

It is difficult to be realized because of the strict specializations depending on conflicting logics, making communication difficult between specialists of different domains. And there is also a fierce competition for scarce resources.

Don't know.

The concept of the Unity of Sciences, without qualification, is part of the problem, not the solution. We should be aiming not at some abstract "unity", but for a dynamic, transdisciplinary interaction between the sciences in which none lose their specific methodology, *etc.*

I hope that this does not refer to the Moon Sect programme.

Poorly understood.

9. WHAT IS THE STATUS OF THE "UNITY OF KNOWLEDGE" PROGRAM? (intended to bridge the gap between science and humanities)

Still more difficult.

Is there any such?

The advocacy has generally failed in the universities for the usual reason of the closed-mindedness of the disciplines. It will take external pressure from public research funding agencies to force universities to address, debate and advocate the integration issue as a step towards the restoration of public confidence in the social responsibility of science and the restoration of social regard for university ideals.

One of the goals of the Nicolescu acceptation of transdisciplinarity is the Unity of Knowledge, but this must be an open system to avoid dogma and fundamentalism.

There is a continuum between sciences and humanities. The gap is only in the head of some people.

I believe that this has been dramatically advanced by Tom Ray's work in discovering the human mental organs and the diversity of ways of knowing that they endow us with.

I think it is rudimentary.

10. HOW CAN WE REALIZE THE VISION OF A RESPONSEABLE GLOBAL SCIENTIFIC COMMUNITY?

Is it not a dream?

By being responsible each one as an individual

Invite EC to debate the responsibility and accountability of the scientific community, starting with the climate science controversy as a very immediate example. How to debate the science is the ultimate problem when there is no common forum, only individual disciplinary courts.

There should be both a well functioning scientific communities and they should be interconnected and well connected to the society globally. I guess we are building this through networking and communication, openness and availability of popular information and willingness to interact with public/society (CERN web page is exemplary) and also interest in other scientific communities – collaboration across the disciplinary borders. Ethical aspects are also important. Scientists should get ethics courses.

A global scientific community cannot be separated from a global community *tout court*, but one in which values and meaning are not lost as they are currently being in the social media, despite the positive features of the latter. But this in turn requires the difficult task of finding a scientific basis for value. Modern philosophy has failed due to the absence of grounding of morality in science, including information science. I see information science (supported by my LIR) as one of the few new ways to go.

By cultivating our affective sides, so that we are not cold hollow, heartless creatures of pure logic and reason, like Spock of Star Trek.

PART II: SPECIFIC

1. **What is “fragwürdig” (ger.), i.e. what deserves to be asked about?**

How the information content in a sequenced form is equivalent with the information content in a 3-dim (4-dim, etc.) form.

Why the speed of light is constant? Is the mass equivalent to matter?

a. What should be explored?

The development of an Integral Biomathics necessitates a better apprehension of the interactions between levels with different complexities, temporalities and multiple realizabilities.

The difference between 6+7 and 5+8

Cognition, intelligence, foundations of life. The first two in order to better understand how to learn effectively and produce knowledge.

Everything.

Fuzziness, vagueness / senescence

The “not null” effect of ether drift experiment, the Cosmic microwave background anisotropy, the clock corrections in geostationary satellites and other enigmatic problems.

b. What kind of research is interesting and possible today?

No frontier should be raised; it is while doing research that new ideas emerge.

Basic research, philosophy. Once we understand what to produce, we are technically first-class. Presently, there is a lack of orientation

I would personally be interested in the research in natural intelligence and cognition, origins and evolution of life and connections between inorganic and organic matter. All of that may be done within info-computational framework.

A research on the new space energy alternative to the nuclear one, a research on a new kind of propulsion mechanism based on a gravity field control (around a spacecraft) for traveling to other planets or their satellites.

c. Who is interested to fund such kind of novel fundamental research?

Research organisms and associations who can dispose of funds which could lead to important results, but also be lost in non fructuous attempts.

Who should be interested in funding basic research? The King, Meacenas, etc.

One may expect that each of existing funding bodies should be supporting even this kind of fundamental research. The sad fact is that many of them do not dare to take risk supporting an emerging research field. In that category it must be something promising practical applications within a few years to be supported.

I would like, but I can't.

Our civilization

d. Which ideas can be funded?

The problem is that It is difficult to evaluate the interest of an idea before it has been developed.

I don't know.

Those ideas which can help to make sense of this enormous amount of knowledge and information that we have now. Producing even more information and knowledge without common system makes things even worse for a human to grasp.

That's highly polemical.

Possibly fuzziness, vagueness, off-focus.

Gravito-inertial effect for a new type of propulsion system for interplanetary travels.

Heterodyne Resonance Mechanism for accessing the hidden space energy and development of technique alternative to the nuclear energy.

e. Which solutions were suggested in the past and which results came out of them?

A lot of data have been collected, but have not been correctly analyzed nor exploited because of too much specialization and too little encompassing theory.

Many interesting models have been developed, but they are essentially of a local nature, or impose non-realistic hypotheses without any regard for the known experimental results.

There was an effort to solve the logical problems of theoretical genetics, but they were failed.

In what field? What types of solutions?

The best and the worst was done.

in the past the research on a new propulsion mechanism was classified and on an alternative energy was suppressed. In both cases there was a lack of serious physical theory (the need of an alternative concept of space have not been envisioned).

f. Which paradigms do we have at hand in biology and computation today?

They are essentially specific to a small domain and more or less reductionist.

That we pretend that our way of thinking is rational (although it is not).

In biology, we have evolution theory. It is not accepted by all people, and I am not sure that most of those who claim to accept it face to all its deep consequences. About "computation" theories, may I cite the one of Bruno Marchal, that I heard about recently, and which deserves attention due to its deep implication in biology (and in some other fields, too).

Fuzzy computation.

In Biology and particularly in living organism there is an important energy issue that could not be explained by the currently adopted space concept.

g. Do we need a transposition or an integration of existing paradigms from other disciplines into biology?

A fusion of several disciplinary approaches particularly tailored to be of use in biology and in interpreting the host of data.

No, rather the other way around: if it works in biology, it is as rational as mechanics or thermodynamics. The paradigm is not new “biology is rational”, but we have to think its implications through.

I would say so, computational paradigm is suitable for biology too, but computation is generalized from Turing Machine to Natural Computation.

Since the definitions of many paradigms cannot be fully unambiguous,
this question cannot be answered exactly.

h. Do we need an entirely new biological paradigm (What is life? … Life itself … More than life itself)? If yes, how can we develop it?

We need to erase the frontiers between different specialties, and also between theoreticians and experimentalists. However this is almost impossible…

Biology has as much with life to do as the relationship between monkeys and humans with the Holy Bible and God's works. There are countless forms on the boundary between "life" and "non-life". If yes, how can we develop it? By revisitring our elementary school textbooks and discover what nonsense we have been taught.

The word I contest here is "entirely": to expect that something will be better if it is "entirely" new is an expression of the paradigm that needs to be changed.

Yes we need. The problem is that defining life have in common with defining a cloud, that, viewed from far, it seems to be obvious what it is, but bounding it exactly is impossible. More seriously, there are two extrema: no difference between living systems and, say, a stone, and at the opposite, the restriction to some groups of humans, based on religion (which one, I do not know, religions do not agree between themselves). In the past, life was located in the human heart. Now we know that it is erroneous. Being "conscious" to be "alive", some people deduce various things: difference between living entities and non living entities, existence of the soul, special role of the human specy, etc. Would somebody claim that all that is void, the reply would be: can't you realize that you differ from a stone ? (i.e. obviously you should realize that). But would we admit that, just as the stone, we cannot understand ourself, that the apparent problem above vanishes: it is normal that we cannot explain our apparent difference with a stone or anything we like, just for the same reason that a stone can't. Personnally, I have no proposal to define life. I may just notice that very old theories (still in vigor for the vast majority of people), contain so much obvious defects that they should be discarded. Alas, they are not, and the crimes and wars they provoke are disasters since millenaries.

Start with basics = thermodynamics. Living things are dissipative structures.

The new paradigm will be delivered by the new concept about space.

i. (How) can we make biology as "good" and "serious" science as physics?

By developing adequate encompassing dynamic models rather than restricting to local phenomena.

By educating people to see the world as is and not as decreed by...

How can we make physics as "good" and "serious" topic as biology? I am a physicist, but I do not think that physics is the paradigm of science anymore. Instead, computing is the paradigm. http://www.springerlink.com/content/g14t483510156726/

Biologists must integrate the aspects of physics that are most appropriate and at the same time the most difficult, such as new conceptions of the absence of background space-time, determinism rather than randomness and non-computability (see below).

Those who rank biology as less good or serious than physics are just idiots. I hope there are no such guys. Both fields are good and serious.

As a biologist I find this question insulting. Biology is much richer and more complex than physics, thus you might want to reverse the question and ask how we could make physics as good and serious as biology.

By linking the two through thermodynamics.

j. What kind of mathematics do we need to help this scientific (r)evolution?

All domains can be adequate to solve some problems. The difficulty is to make a junction between multiple local approaches, each one of them well adapted to some particular situation (complexity level, material composition, temporal constraints, etc.), and a global apprehension.

Computing is a new sort of formal tool able to behave in time and in space (in physical world, like in robotics). So we need computing for future sciences, and that is exactly what is being developed. And we need much more and especially more intelligent and cognitive computing.

The mathematical constructs are available, they only need to be applied.

k. Is mathematics really an abstract science?

Mathematics may seem abstract if you read mathematical publications because the real underlying ideas are often hidden. However the research in mathematics, especially when it is novative, is mostly generated by 'concrete' problems and/or existential questions.

Yes.

Yes.

Yes. Even the natural numbers are a construct in our head. An other name for mathematical sciences could be "modeling".

Mathematics is abstract science. It could lead to better understanding the quantitative relations if the assumptions are correct, but it could also lead to a false image if some assumptions are wrong.

l. How can we build or discover biological mathematics?

There are already good models, their development, diffusion and testing should be helped so that their defaults can be corrected to lead to more practical applications.

By gopind back to the basics like a+b=c. What is important and relevant on "a+b=c"

Again, future is about computing tools not in the first place mathematical ones. They will get subsumed under computing.

No difference between mathematics and biological mathematics. All that are just constructed structures in our head. Fortunately, we are most time (but not always) successful to build math concepts the same way for any of us. That's much more difficult with non math concepts, due to the differences of culture and language.

Try a semiotics of math in conjunction with (Peircean) semiotics of life.

Relying on correct space concept and correct image on the microworld including the particle physics, atoms, molecules. Understanding the Quantum mechanical phenomena by classical models based on the correct space consept.

m. Can we capture, comprehend, measure, realize ("erfassen", ger.) life with a (digital) computer?

'Digital' computation could be effective at the local level. However the global logic of life relies on the interplay among a hierarchy of local logics, each with its own temporality and multiple realizabilities. This interplay needs more innovative kinds of computation than digital.

Yes.

Yes, we can model, better than with any other tool.

Computer just calculate what we programme. No programme, no computation.

Understanding the affective ways of knowing, and cracking the hard problem (how do joy, compassion, comfort, reason, logic, and consciousness emerge from biology?) would help to answer this question.

n. What kind of computer has to be the one that captures/models life? (cf. Feynman's argument about quantum computing).

I think it has not yet been discovered because, as long as I know, the problem exposed above has not yet been raised in computer science.

New computational models are being developed based on organic computing. So we might expect those new approaches improve our capabilities to properly model organic systems

In my view, *no* computer can capture life. A computer cannot model life but only an abstraction of it that represents an enormous reduction.

When quantum computers will be able to output the decimals of pi with many digits, I shall look at them closer.

One that realizes that energy is in shortage.

o. What is the use of computing and Internet in biology?

They play a large role to collect and analyze a great number of important data, but more theoretical studies should be done to approach the real characteristics of life. For instance the Wandering Logic Intelligence (Plamen Simeonov) opens the way for a more dynamic computing/Internet approach. It seems to have means for studying the problem raised in (m) above since "The intelligence of a wandering network at a certain point of time is an aggregation of its logics and their interplay". In fact, MES and WLI have comparable organizations, if we compare a "netbot" to a CR and a "shuttle" to the selection and transmission of a procedure (hence a logic), and the "Intelligence" to the interplay among the CR logics.

People can talk, talk, talk.

Bioinformatics is all about computing. Internet is important for communication.

Neural networks, genetic algorithms, etc., are just optimization methods with names evoking biology. No more. Until now, I did not investigate more about relations between biology, computing, and internet.

p. What is the use of biology in computing and Internet? Has it a use in computing?

Discovering supernumerary sets, discovering unified field theory, applying interdependences between “where”, “what kind” and “how many”

Biology is the source of inspiration for computing (including Internet).

q. What can computing and Internet learn from biology?

A better understanding of biological organization and natural selection could give ideas for developing a more performing Internet.

That sequences and commutative collections are two different concepts that we produce in our brain and visualise (hallucinate) ont the picture before us

Learn how to effectively cope with complexity.

r. What can biology learn from computing and Internet?

Computing and Internet can help put some order into the host of biological data.

Not much.

Use them as tools for modeling, computation and communication.

s. What are the unique characteristics of living that distinguish it from non-living (recall the recent discovery of the Mono lake bacteria) and from machines?

Two necessary characteristics: (i) the existence of multiform components (our "Multiplicity Principle") which ensures the formation of components of increasing complexity order, with possibility of swiches between their non-connected lower order decompositions; (ii) the different temporalities of functional subsystems which impose drastic temporal constraints on those subsystems. Both play a role in the interplay among conflicting logics (cf. answer to question (j) above).

"Life" (just a wild shot of a definition on the spot) is the bijective congruence between one-´, two- and threedimensional arrangements.

A set of self-* properties. (But people are starting to build self-* machines).

A key unique characteristic is non-computability and higher ethical value of living systems than inert matter-energy, although, as Floridi has pointed out, the latter is also deserving of *respect*, as a component of existence. I will change this view if and when you tell me how respect for existence can be programmed…

Internally informed by the genome so as to be able to self-heal.

The living is a sophisticating programing-like algorithm that constantly use and interact with the zero point energy of space in everlasting process. The non-iving process is not everlasting. It is externally invoked and then terminates.

t. Which are the boundary forms and procedures of natural and artificial life?

I suppose artificial life is not (yet?) endowed with as much multiplicity (complexity, temporality, multiform objects) as biological systems.

There is no artificial life and we have no agreement what we mean under the word "life"

Natural life relies not only on chemical but also on zeropoint energy at Quantum mechanical level. Arificial life does not rely on zeropoint energy.

u. Which states and modes has a living organism compared to a computer (an artificial one) today?

Multiform components, several local temporalities and interplay among a hierarchy of multi-scale local logics.

Nonsequenced, moredimensional as opposed to the mechanical which negates the folding-unfolding gain/loss between 1, 2, 3 and moredimensional bodies.

Those self-*

Multiple simultaneous projects, flexibly allowing temporary focusing.

v. What kind of energy and resources needs a living organism compared to a computer (an artificial one) today?

Both need energy, but under different varieties.

Entirely different basic concept.

No electricity, no computer.

Living has multiple possible sources, computer only one.

w. What kind of exchange with the external environment has a living organism compared to a computer (an artificial one) today?

The great variety of Its sensory and receptor organs allow for a multitude of specialized exchanges and communication.

There is no such thing as “a” living organism, as opposed to there being a unique computing apparatus. Living is always a multitude.

A living system has metabolism, unlike computers.

The computer does nothing as long as there is no running programme: a human product.
Multiple contacts with complex environment

x. What defines liveness, intelligence and consciousness in organisms and machines?

The development of a memory containing a kind of flexible internal model (what we have called an Archetypal Core). AC is formed by higher order multiform components relating to essential memories connected by loops of strong and fast links allowing that an activation of some of them extends to a larger part of AC, is self-maintained for a long time, and is largely diffused to lower levels (through decompositions and switches between different decompositions of multiform objects.

What are these words? Do you really think machines have conscience?

Aliveness is not really a term used for computers other than metaphorically. Intelligence in computers tries to mimic human intelligence, but it is far beyond. Partly because GOAI defined intelligence as symbol manipulation. Machines have no consciousness and we don’t even know what it would be for a machine to be conscious.

What defines the indicated phenomena is that they are indefinable in the sense intended.

Recognition that not everything can be defined, except to a certain extent as a process, would be a start on the "new paradigm".

Internal drive, flexible partial focusing

y. How to determine the physical scales and operational modes manifesting these properties?

In the human brain, the neural support of the AC is the Neural Structural Core, discovered by Hagmann et al. (PLoS Biology 6-7, 2008).

by learning to think a bit more exactly one can generate the tools needed for this task. Hierarchy theory might help.

z. (How) can we model the above characteristics adequately with the available tools and methods at hand today?

A dynamic category theory is at the basis of the ME(N)S dynamic model. In particular it helps explaining the binding problem and the emergence of higher complexity, up to higher cognitive processes and consciousness. However it remains the main problem: to find means to 'compute' the switches between non-connected decompositions of multiform components, essential in the interplay of the multi-scale logics; I think WLI could probably help.

By not ignoring the difference between 3+3 and 2+4 (even if Teacher has told us that this difference is of no importance and relevance.)

2. Which paradoxes and unsolved questions do we have in biology, computing and Internet today?

To develop other kinds of "computation" able to solve the above mentioned problem.

How does a sequence translate into a commutative collection and back

The biggest unsolved questions are origins and mechanisms of life, structures and functions of the brain.

Origin of the genetic system.

3. Which are the basic principles (beliefs, axioms) of life?

Cf. above.

That sequences (time is also a sequence) are a one-dimensional picture of an n-dimensional assembly. That a living organism is an n-dimensional unfolding of a sequence.

Those are info-computational.

Stability in the face of unexpected insults

4. What are machines and computers from the viewpoint of biology?

For the moment, they probably have a much less intricate organization, with no interplay of multi-scale local logics. But it might change with further developments.

Finite automata.

Programmes are of interest, not computers. When the power is turned on, a programme is immediatly loaded. When the computer apparently does nothing, e.g. when waiting for a mouse clic, there is in fact a programme currently running. Computer technology accelerates what we can do "by hand".

Explicit, crisp, as opposed to vague

5. How to define computation in biology? Is "biocomputing" different in kind from "classical computing"?

Cf. above

Matching place (spot in time) to extents and qualities Is "biocomputing" different in kind from "classical computing" – yes

Yes, biocomputing is a developing field, which changes as we learn about biology.

No.
I suspect not yet.

6. What is computable (predicative) in biology, and what is noncomputable (impredicative) in biology? Since it has been contended that not everything is computable under the current definition of computability by algorithmic means (Rosen[1], Louie[2]), do we need to expand the current definition of computability in order to make living systems computable?

Local models are computable. What seems non-computable is:
(i) To determine if 2 non-connected patterns can be functionally equivalent, thus giving two decompositions of the same multiform component, with possibility of a switch between them; indeed it would require to examine a too large number of situations in a too short lapse of time.
(ii) To find out the result of the interplay among local logics, taking account of the freedom degrees given by the possibility of such switches.
(iii) To 'compute' the cascade of temporal and/or structural changes which can be induced by complex events processing.

Genetic mutation -> surjective map commutative->sequenced (writing the DNA)
Genetic variation-> surjective map sequenced->commutative (reading the DNA)

Since it has been contended that not everything is computable under the current definition of computability by algorithmic means (Rosen1, Louie2), do we need to expand the current definition of computability in order to make living systems computable?

Do. Just apply it.

Count that what has traditionally been neglected, the difference between 4+5 and 1+8, e.g.

Absolutely. As they actually solve their computational problems in a satisfactory way.

As you will have understood from the above, I respectfully disagree with the formulations of these points. If living systems are not computable, expanding the definition of computability is a false problem. If computability is not the key issue in biology (and I believe it is not), the approach of bringing in concepts from the indicated disciplines is not as important as an overall compassionate philosophical and logical (in my expanded sense of logic) framework that addresses issues in all of them. This means paying attention to weaknesses in such widely accepted theories as those of Wheeler and Tegmark in cosmology; Maturana and Varela in systems and biology; and Peirce and his followers in philosophy and (still standard) logic.

This is a matter of convention. We can do formal calculus with the axioms we like. As soon as we can do it, we can store it on computers with appropriate conventions of representations, then we can programme calculations on them. Again, we should not focus on computers: we should focus on the mathematical models we need for various purposes. Once the model defined in our head, why shouldn't it not stored in a computer, then give raise to calculation programmes ?

Again, the affective domain and the affective ways of knowing may fall outside of the computational domain. We can’t really know until we understanding the affective ways of knowing, and crack the hard problem: how do joy, compassion, comfort, reason, logic, and consciousness emerge from biology?

Flexible reactions in response to insults.

I would rather imagine making computation more like the living.

7. What would be the contributions of in a new definition of computability for biology?

Classical mathematics such as mathematical biology, systems theory, information theory and chaos theory are important to develop good 'local' models. A dynamic category theory allows to describe a dynamic model such as ME(N)S which makes apparent the main characteristics at the basis of the global dynamic. A mixture of MES and WLI could perhaps lead to develop a new kind of "computation" adapted to make the global logic 'computable' in an adequate sense.

That one understands the theory behind the workings of genetics.

Those are the fundamental disciplines which constitute the foundations of a new definition of computability for biology

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All contributions are welcome. The future will tell us what are the most fruitful.

These areas need to grock affect and the affective ways of knowing.

They are all excessively mechanistic.