Editorial

The idea behind this special theme journal issue was to continue the work we have started with the INBIOSA initiative (www.inbiosa.eu) and our small inter-disciplinary scientific community. The result of this EU funded project was a white paper (Simeonov et al., 2012a) defining a new direction for future research in theoretical biology we called *Integral Biomathics* and a volume (Simeonov et al., 2012b) with contributions from two workshops and our first international conference in this field in 2011. The initial impulse for this effort was given a year earlier by a publication of one of the guest editors of this issue (Simeonov, 2010) in this journal. This time we wish to provide a broader forum and more space to elaborate in detail some of the most interesting concepts we have encountered in our discussions, as well as to invite some new contributions of particular interest in the field. Another goal we had in mind was to collect and review as many provocative perspectives as possible on the same key topic we are interested before making a decision to follow a more focused notion that would lead to a funded research program.

Therefore we welcomed the generous suggestion of Professor Denis Noble, FRS, who is also editor of this journal to prepare a special theme issue entitled: "*Can biology create a profoundly new mathematics and computation?*"

It has taken a while to invite and collect the contributions. Most of them had a couple of revision cycles and adjustments after having been thoroughly discussed with colleagues, incl. the editors of this issue. We think that the result we have obtained at the end is a satisfactory one, since we succeeded to integrate a diversity of original, but sometimes controversial and mutually excluding concepts organized within chapters of a self-contained volume. The task of compiling all this was not easy at all. Despite our efforts to position the articles of different authors and themes in a way allowing their easy comprehension and relation to each other within the individual chapters, some of them still require a sort of introduction to dissolve possible ambiguities. This is what we are going to do in the following few paragraphs with the hope that the reader (and some of the authors) would excuse our failures.

1. Prologue

The prologue to this issue is written by Arran Gare. His article continues the line of thought he began with his epilogue to the 2012 INBIOSA book, developing it into a prologue to this special theme issue. Indeed, it became "a sweeping review", as one of our reviewers put it, of theoretical biology from Immanuel Kant up to Robert Rosen and still onward while putting a special emphasis on Schelling's "Naturphilosophie" concept which has influenced generations of scientists (often without their knowledge) in their pursuit of truth. The reason for putting this long historical and philosophical article in the beginning of this issue is to clearly identify the role and the purpose of the research program we are trying to put together along this old tradition.

2. Introduction

The introduction to this special theme issue is written by Marcin J. Schroeder who criticizes the status quo of practicing contemporary sciences. In his contribution "Crisis in Science: In Search for New Theoretical Foundations" he joins the growing group of sceptics, who do not believe in further development of science without fundamental changes of scientific methodology reflecting the need for taking into consideration the way human intellect is involved in the process of scientific exploration. Schroeder proposes what he calls a new alternative where scientific methodology has to be based on the study of life and of consciousness as primary domains. (Felix Hong comes back to a similar topic focused on creativity in the epilogue of this issue.) This study can be carried out in the new framework with information and its integration as fundamental concepts. He identifies the source of present methodological problems in preoccupation with the quantitative methods and disregard of the qualitative, structural approach. In order to overcome these limitations, Schroeder proposes to use a new, structural theory of information.

3. Questioning the Status

This chapter asks about the status of modern biology in science. Three articles are addressing this issue from different viewpoints.

Tschernyschkow and colleagues approach the problem of combinatorial complexity when dealing with large dynamic multi-protein complexes in living systems. Conventional modeling approaches like differential equations fail to describe the self-assembly process, due to the combinatorial explosion of the number of intermediate complexes. Tschernyschkow et al. show how to apply a novel rule-based modeling approach in space to study the formation of the inner kinetochore structure, which forms at the chromosomes and which plays a central role for chromosome segregation and cell division. These simulation experiments require unconventional mathematical and computational methods for analysis and interpretation. In particular structure clustering, information theory, phylogeny, and visualization are applied so far. Nevertheless, the challenges laid open in this article display the need for new mathematical and computational approaches tackling the combinatorial complexity of living systems in space.

Matsuno explicates the notion of internal measurement further in the context that it is practiced both in physics and in biology on a par interchangeably. Internal measurement is a local material act of distinguishing between before and after the event. Precipitation of a record after the event is decidable in the sense that the internal observer decides on setting the demarcation line separating between before and after the event. Thus, internal measurement is decidable and at the same time, its aftereffect constantly spills over into the neighborhood so as to induce further internal measurements being capable of making decisions in the latter. One advantage of internal measurement is within recognizing the material capacity of making decisions. Once the internal observers form a cycle in which each observer constantly processes the spillover of internal measurement passed over from another observer located in the immediate upstream, the cycle would come to be stabilized with probability one. Internal measurement provides both decidability and durability that biology would require for its own sake of the foundational underpinning.

Salthe examines the role of simulations in the framework of developmental biology. A key message is that computation as now performed would be unnatural in biology. A crucial question in this respect would be how, or if, decidability is implemented in the actual developmental process in biology. Computations conceivable in first-order logic are generally not decidable. This implies that there is no guarantee of the possibility of such an algorithm that might answer the question of the existence of an effective procedure for determining membership in a legitimate domain of discourse, or in an allowed set of formulas by means of Boolean true or false values. Salthe's paper raises the question of whether the current practice of employing simulations with the hope of applying computation in biology without examining this issue of the possibility of decidability is ill conceived. What makes a developmental process challenging from the perspective of computation is how decidability may be obtained.

4. Perspectives and Models

Chapter 4 is a collection of papers exploring six perspectives and models attempting to answer the question in the title of this theme issue.

The value of Cazalis' paper lies primarily in the original use of category theory to define the concept of the individual (biological organism) as an autonomous entity characterized with intelligence, memory, volition, self, intention, significance, desire and purpose. The author proposes new syntactic properties radically different from those we currently use to describe living beings. Indeed, category theory provides a clear syntactic base for the formulation of a new language while leaving the epistemic and the philosophical-semantic interpretations largely open. Giving semantic and semiotic values to such a conception of a living entity has to be the task of future work.

Nakajima's paper reviews recent advances in the foundations of probability theory and discusses various interpretations of the concept with regard to its suitability for understanding living systems phenomena. Then he develops an ingenious model applicable to biology at large. In particular, he recalls the cognizers-system model which he has been introducing in a series of papers since 1999 and compares this internal probability notion to Bayesian probability.

In their paper, Ramirez and Sanz focus on mathematical and statistical methodology for modeling biological systems, involving the inverse problem that system models and parameter values are determined from data obtained by measurements. By pointing out the limitations of traditional or standard statistical models, including the standard Bayesian approach, the authors introduce the truly Bayesian approach and argue for this approach as an effective tool by giving a few example in neuroscience and cell physics.

Susie Vrobel's paper undertakes a subtle use of the fractal dimension to attempt to more rigorously describe simultaneous internal experiences that can be modeled externally as being composed of nested events. She convincingly attempts here to manipulate several techniques – hierarchical structure, the internal/external perspectives dichotomy, and fractal technology – to deal with experiential complexity, using the example of anticipation, and also applies the resulting complex understanding to particular phenomena that we can ourselves intuitively experience. The paper is a 'tour de force', inviting and rewarding multiple readings.

The paper by Kitto and Kortschak is a valuable contribution to the discussion of the new paradigm for the study of biological systems. Their article begins with the statement of the problem in using Newtonian Paradigm in the study of life. The authors present examples demonstrating the difficulties in defining units of selection in biology, where this concept plays a fundamental role. They provide convincing argumentation that these difficulties are unavoidable consequences of the need for taking into consideration the context of whatever biological process is considered. This applies to the molecular level when interaction between parts of the genome needs to be considered or to a much larger scale where the genotype-phenotype interactions are important. Kitto and Kortschak identify the elements of the Newtonian Paradigm responsible for its failure to be applicable in the study of life, the concepts of *object* and *objectivity*. Next, they discuss the similarities between biological and quantum systems, arguing for the development of a similar formalism to be applied for modeling biological systems. The classic argument against a physicalistic study of life stating that living objects are open systems, whereas Newtonian Paradigm requires that systems are isolated (or if not isolated, then under controlled interaction with the outer world), is implied within the discussion of contextuality. Having said this, the authors try then to fix this problem by 'injecting' more physics into biology and focus on their concept of contextual mathematics, introduced with the discussion two key aspects of Quantum Field Theory (QFT), potentiality in terms of multiple stable ground (i.e. lowest energy) states and spontaneous symmetry breaking, and Nambu-Goldstone emergence applied to the creation of new biological objects and structures. Next, some contextual models of biological systems are discussed. Finally, the authors conclude that the quantum inspired approaches addressed in their paper will require significant extension as they are applied to biological modeling to provide new insights into a complex reality.

The paper by Gabora, Scott and Kauffman suggests a novel formal approach for modeling the phenomenon of preadaptation (or exaptation) in evolutionary biology (where the current biological function performed by the adaptation was not the original one from which the adaptation evolved under earlier natural selection). Drawing on the principle of quantum potentiality, the authors develop a new mathematical framework for preadaptation that defines a state of a trait as a linear superposition of basic states, or possible forms that a trait could evolve into. These basic states are represented as mutually orthogonal weighted eigenvectors in a complex Hilbert space. The choice of possible trait changes is expressed as an adaptive function of interest, which plays the role of the observable. This model is then applied to different organization levels of biological systems as well as to cultural evolution, which depends on the human capacity to combine concepts in new ways or redefine one concept by re-examining it in the context of other concepts. The latter theme is of growing interest in science, which is also addressed by Hong in the epilogue of this special issue with his discussion on creativity.

The realization of quantum-like potentiality in evolution (Gabora et al.) in combination with other genuine ideas in this volume such as the contextuality concept of the previous article (Kitto and Kortschak), novel pro-biology probabilistic frameworks of the cognizers-system model (Nakajima) and the full Bayesian approach (Ramirez and Sanz), the formal categorization of the individual (Cazalis) and the third person expression of the internal fractalization of time (Vrobel), as well as the recursive pattern recognition practiced by creative minds in science (Hong, s. epilogue) are all consistent with and supportive of the line of thought developed in the INBIOSA project (Simeonov et. al., 2012). These approaches are not yet perfectly congruent, but we believe they provide a much-needed focus on causal dynamics, and that further exploration of them will in fact bring about a significant cultural exaptation. Specifically, our hope is that the organized publication of this series of papers under the umbrella of Integral Biomathics generates a set of potentiality states that facilitate a paradigm change in biology.

5. Computation Revisited

Chapter 5 is the kernel of this special journal issue. The three brilliant contributions here by Siegelmann, Marchal and Goranson et al. represent a small, but important part of the multiplicity of computational approaches to model biology. Each one of them is essentially different having its own merits and deficits depending on which angle it is viewed from. One may consider the selected papers controversial and mutually excluding. It is difficult to say whether the fundamental differences between them can be overcome in future. In our opinion the presented ideas – which are not the only ones – are valuable milestones (and potentialities!) on the way to new biological mathematics and computation that deserve our attention. It was our intention not to introduce or comment the selected contributions, but provide an open forum for discussing the authors' ideas. We recommend the reader to make his or her own choice and have a brief scan over chapters 6 (incl. its introduction in the next section) and 7 that would possibly explain the reasons behind our impartial decision.

6. A Conjecture About Biology

William C. Hoffman died on the 16th January 2013. This short chapter is perhaps his last paper carrying a message of his lifework, which is indeed very impressive. 'The Dialectics of Mind', referred to in his own paper, is a masterpiece of thought along the line of the Schellingian tradition, which was addressed in the prologue to this special journal issue. Therefore we decided to place this paper last to close this way the opened 'braces' with the introductory articles in the expose of this special issue.
At first sight, the paper's message is short and reads like an algorithm:

- Biology is simple
- We already have 'known biological laws and structures'
- These dynamics of biology work through manifold form
- Form in this case is equivalent to geometry
- Good enough tools exist for a 'mathematics' of these dynamics-over-form in modern Lie algebras
- Go read a certain book to learn how to address the problem that has eluded hundreds of thousands of talented biomedical scientists
- Problem solved, what's next

Well, to state that "The Mathematics is there; it just needs to be applied" is not of much help for the hopeless biologist looking for insights to biological problems in a text of pure mathematics. But what else could stand behind the brevity of this paper, which has clearly flummoxed two of our reviewers? Is that everything that the author has to tell us?

Hoffman's claim is indeed so provocative that it cannot be taken seriously at first sight. Does he suggest a naive treatise on the slipperiness of the complex problem of modeling biology? Does the author understand that we need more than a calculus, that we need a whole new set of abstractions well before we get to the machinery of biology? Does Hoffman know that we need approaches that deal at a semantic level, by definition separate from how one may think he means geometry (though Lie algebras can address topology as well)?

The skeptic reader who is familiar with Leyton's ideas on morphology[1] (Leyton, 1999, 2001) may consider that an adequate descriptive *representation* (not causal model) of what happens in biology could be built in terms of group theory using e.g. a mix of inner and outer products. Group theory indeed would be the first recourse if an understanding of form necessarily led to an understanding of the laws of form aspired by d'Arcy Thompson (Thompson, 1992). Indeed, Leyton suggested a process grammar for morphology recently (Leyton, 2012) based on his Symmetry-Curvature Duality Theorem (Leyton, 1987) (which he defines as the fundamental theorem of biological morphology) and process-inference rules which provide powerful causal explanations to morphological transitions. But there might be also other promising algebraic approaches such as Spencer-Brown's "primary algebra" or "calculus of indications", an elegant minimalist notation for the two-element Boolean algebra (Spencer-Brown, 1967) and Grassmann's "Ausdehnungslehre" (Extension Theory), a set of linear algebras which provided the foundations for a number of geometric and directional calculi (Grassmann, 1995). Such theories could be enhanced by diverse rule based logical systems involving operations over nonlinear vector spaces and other complex abstractions to accommodate complex transitions in the living space. Yet, is that all the mathematics we need to deal with in biology? This is the question.

Therefore we will introduce Hoffman's paper in such a way as to contextualize it and indicate where he thought the potential lays for future developments. The curious reader may wish to take into account instead the "Dialectics of Mind" (Hoffman, 2012), and this itself should be enough to serve as an introduction of his paper. If read in conjunction with the contribution that Hoffman submitted for publication here, the above paper suggests that the discovery of Felix's book (Felix et al., 2008) came as a revelation and a solution to finding a mathematical basis for the riddle of life he had been longing. We think that William Hoffman simply used the opportunity he was given in this special issue to flag the potential of algebraic models in geometry or 'rational homotopy theory'. In his brief closing article, he develops on the idea that form follows function. Life processes, in order to be properly understood, need to account for the interaction between form and function. The expression $G \times M \rightarrow M$ encapsulates this relationship between structure and function, and it is left to the biologists to "provide the particular structure of the parameter group G involved in each biological phenomenon." How this can be done is not explained in the paper. Thus, as with the six gentlemen from Hindustan, all pair partly right and all are partly wrong.

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[1] which can be represented in terms of group symmetries and group extensions using Lie algebras

It all comes down to the semantics of how we understand this paper. If we regard mathematics as *pure* mathematics in the traditional distinction between pure and applied mathematics, in G x M → M, G can be anything from graphs to categories, and M, anything from a module to a category. Given the tremendous variation that biology offers certain choices must be made in the application to particular biological phenomena. The author sees algebraic geometry as essential to understand the structure-function map in biology, and the textbook by Felix et al. is proposed as a sort of guidebook that will unveil the secrets of modern biology. Unfortunately, Hoffman only suggests what should be done.

His original approach based on algebraic geometry goes in the opposite direction of the present-day mainstream data-driven science paradigm towards a more hypothesis driven approach (which biology is badly lacking today). It could become a potentially powerful toolkit for future generations of scientists.

While algebraic geometry may represent a very fruitful, alas neglected, approach to understand biology, those interested in exploring this avenue will surely need a hands-on approach that complements the original methodology proposed here. Therefore, Hoffman postulates that "Algebraic Models in Geometry" is a conjecture that this is a route for the pure mathematics involved in Integral Biomathics. But it is only that - a conjecture, an unproved statement. Its proof remains for the generations to come.

7. Epilogue

The epilogue of this special issue is written by Felix T. Hong. In his very extensive, elaborate and eloquent study, the author develops Herbert A. Simon's idea of considering scientific inquiry a form of pattern recognition. Hong recognizes the need for a very general concept of patterns and for this purpose he adopts L. A. Coward's definition of a pattern as something that repeats in time or space in a way that allows hierarchic complexity. Also, he is well aware of the fact, that in order to give Simon's idea an authentic methodological character it is necessary to provide criteria for the recognition of patterns and to examine ontological and epistemological status of patterns. Here is where creativity comes to work and exactly this association is what makes Hong's approach to scientific discovery very innovative. It is all about the way we took when compiling this special journal issue. Progress in science is a creative, collective idea exchange process in which results of the inquiry are invented and engineered together with two main criteria for success: explanatory power and predictive power, with the former of higher precedence over the latter. Hong's major tribute with this paper is his distinction between two types of pattern recognition, the digital one, which he associates with traditional science, and the analog one, which has its new role in overcoming the limitations of complexity. It is this analog type of pattern recognition, which he believes can be mathematized with the new mathematics of parallel processing.

The whole field of creativity is of immense interest for science today. If we take as reference point the historically oriented philosophy of science, what we find are distinctions and ideas being looked at from a slightly different angle, and this is what makes Hong's paper so interesting. As a reworking of ideas on creativity from a different perspective, it also serves to provide further support for such ideas. This epilogue should provide a good anchor for our next special issue on Integral

Biomathics. We decided to conclude this final chapter with an updated survey of the field since 2010 while focusing on some promising themes for future research.

7. February, 2013

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