

Integral Biomathics Reloaded: 2015

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1. Recap and antrorse

Many biological phenomena do not have adequate mathematical representations. This is because living systems use structures that are not yet grasped by our present conceptions of mathematics and computation. In particular they are circularly organized and they use recursions. Mathematics and computation at the present time deal only superficially with circular organization or the consequences of recursion. We just have not yet found a way to adequately deal with such matters¹!

Current approaches to complex problems rely on modelling, but one aspect of the problem is that they rely on a single form of mathematics, switching from it to another to address the next aspect, and so on. All this switching is an indication of how inadequate our mathematical tools are to date (ODE/PDE systems, stochastic models, discrete state-transition systems, topological algebra, etc.). Biological systems function at all these levels simultaneously. Yet, *the real problem is that even the simplest recursions are beyond our capacity to analyse at the present time*. It is not biology that is too messy to be modelled; it is our use of current mathematical paradigms that are not able to adequately address these biological problems (Root-Bernstein, R. S., 2012). These paradigms are keeping biology within the fixed boundaries of physics, the domain of non-living matter. Despite being the most advanced mathematics-based natural sciences discipline, physics is currently experiencing its own crisis when trying to overcome the dichotomy between its major theories (Smolin, 2006) and remains not sufficiently developed to explain living systems. Is this a chance in disguise? We believe that further advances in the sciences — physical, biological, social — require *new levels of integration across the domains*. It is a commonplace to seek a “paradigm shift” (Kuhn, 1962) to advance the frontiers of a scientific domain. Such shift can also uplift the network of interdisciplinary connections among existing research areas. However, we are seeking *more than a shift* that advances the network of the complex dynamical system of knowledge. We seek *to advance the nature of the links of this network* by encouraging the development of mathematical and computational methods *that will at once change the shapes of the nodes and the links*, thus performing a simultaneous “quantum jump” in multiple disciplines, to enable a new integration and rationalization of knowledge: *Integral Biomathics*. The major implications of this new paradigm for reinventing and re-engineering mathematics and computation address the life sciences and medicine. They encompass meanwhile also the foundations of creativity and cognitive processes in the sciences and the arts, as well as the phenomenology of consciousness in general.

¹ Recursion and computation are well defined concepts in arithmetic and set theory. The problem addressed here is related to the physical implementation of recursion (and to the question what is physics, which opens another discussion outside the scope of this paper). Louis Kauffman’s favorite example of a deep recursion — that can only illustrate how complex could be the relationship between phenome features and inherited genome mutations in the course of evolution — is the Collatz Recursion:

$N = \{0, 1, 2, 3, \dots\}$ = Natural numbers plus zero.

$F: N \longrightarrow N$ defined by

$F(n) = n/2$ if n is even,

$F(n) = 3n + 1$ if n is odd.

Start with any n and iterate F : $n, F(n), F(F(n)), \dots$

Conjecture: The sequence will eventually hit 0. This is unproved.

The conjecture has been with us since the 1940’s. There is no solution in sight yet. But Fermat’s last theorem has been also with us for around 300 years until it was proved not long ago. So, the only limitations we know are of the form: “If you restrict discussion to a particular language L , then there will be results that cannot be explained within L .” (corollary from Gödel’s theorem). When mathematicians generate very difficult to understand recursions they are using the simple language of elementary mathematics to create abstractions that are not so easy to explain with that simple language. Then they are asked to become empiricists like Laplace and see what happens (Root-Bernstein, 2012) in the temporality of the recursion. Then (these) scientists can begin developing/ inventing a more sophisticated language for describing these phenomena. But these new nested levels of organization are not going to be simple axiomatics. They are going to appear much more like observational science. This is exactly the way in which Andrée Ehresmann and Jean Paul Vanbremeersch have developed (and still develop) *Memory Evolutive Systems* out from category theory (Ehresmann and Vanbremeersch, 2007).

Integral Biomathics involves reconceptualising what mathematics is and its role in science, granting a place to, while clarifying, the relationship between the non-mathematical concepts of philosophical biology (Sober, 2000; Griffiths, 2002; Godfrey-Smith, 2014), qualitative mathematics (Smith, 1983; Sacks, 1985; Rudolph, 2014) that provides insight but no precise predictions, analogical computation (Dampier, 2001; Kokinov and French, 2002; Gentner and Forbus, 2011) and formal models that do facilitate precise predictions. In particular, philosophical biology and philosophical anthropology are far more than descriptive and concerned with justifying the reality of life and living beings, thereby revealing how misguided are efforts to examine these only in terms of received mathematical ideas. These disciplines are indeed in a dialectic relationship with ‘mathematics for biomathics’ (Hoffman, 2013), making their own distinctive contribution but needing to be contextualized. To engage the individual disciplines with each other is the goal of Integral Biomathics. However, we should be aware that interdisciplinarity and transdisciplinarity are not enough. We have to recognise that systems can be simply defined and evolve easily, but that they are not going to be analysable at the level of the languages and descriptions at which we have produced or begun to describe them (Gödel’s insight). In fact, we are not dealing with the limitations of mathematics *per se*. We are dealing with an endless helix of creation, a *Vitruvian Evolution* of evolving and interpenetrating cognitive perspectives. When we look closely at what structures can be described or generated at a given level, new structures are enfolded and revealed like in a fractal image. These need new explorations and new levels of description, and hence imply new cycles of knowledge integration. Essentially this process comprises the search for better descriptions of living systems leading to the comprehension of their specific characteristics, including emergent properties all the way up to the higher order cognitive processes. What remains is to explain *how* this integration of multiple approaches is going to be realized in order to deliver new results and new insights about living systems.

Such a dramatic paradigm change in science has been attempted several times over the past sixty years by outstanding researchers. Now we venture to achieve the dreams of those pioneers by linking together their successors, backed by the wisdom of these forerunners. Our goal is to accelerate scientific development in the life sciences and personalized medicine through profoundly new theoretical foundations. In this quest we pursue a unified view of life that goes *over scales*. Until now, any attempt to deal with multi-scales using conventional techniques has been doomed to failure no matter how much data we collect. The problem is with their interpretation. One cannot go between adjacent scales in a real existing hierarchy by using the logic of either of the scales – the intermediate region is multiply fractal (Cottam et al., 2004a)! Local solutions require global knowledge (Cottam et al., 2013), but *mathematics, not data, remains* the key to biology. We need a return to the style of doing science in the 1970s (Justman, 2015) following bold approaches of the founders of bio-mathematics such as D’Arcy Wentworth Thompson, Alan Turing, John von Neumann, Nicolas Rashevsky, René Thom, Brian Goodwin, Conrad Hal Waddington, Michael Conrad and Robert Rosen enriched by the findings of theoretical and philosophical biologists from von Uexküll and Lorenz to Hoffmeyer and Kull. We call this new initiative for high-risk and high-impact research in Integral Biomathics *SALVE: Support Action for Living Vitruvian Evolution* to celebrate the multifaceted integrative da Vinci approach to science, engineering and the humanities. This project puts in place a cyclic discourse methodology stimulating the creation and alternation of innovative ideas for a scalable biological mathematics and computation and its validation in modelling real-life problems. The initiative organizes currently 84 experienced and enthusiastic scientists from a multidisciplinary worldwide community.

2. Research Focus (RF): Second-Order and Higher-Order Logics Mapping Self-Organized Criticalities

Reductionism reached its zenith in the third quarter of the XXth Century with the synthetic theory of evolution embracing molecular biology, cybernetics and information theory. Evolution was equated with changes in populations of genes, identified with DNA, encoding information on how to produce survival machines to reproduce themselves. Biology was reduced to chemistry, which was assumed to be explained by physics. Today theoretical biologists are intensifying their efforts to overcome reductionism in order to comprehend the reality of life. The research framework we focus on is not about developing models and engineering systems mimicking Nature based on conventional theories and automation. It is not about bioinformatics or biocomputation, understood as cellular/molecular/biochemical/DNA computing, either. The objective of a *biology-driven mathematics* pursued by Integral Biomathics is indeed an appraisal of the *second-order types of nested logic* in place of the first-order logic with which most standard mathematicians are familiar.

This kind of “implicate order” (Bohm, 1980) should be also capable of capturing *acategorical elements* and other phenomenological aspects (Rosen, 2015), such as the dualistic (‘endo’ and ‘exo’) nature of time (see 3.4, KT4), which cannot be registered systematically, but only *systatically*². *The great advantage of second-order logic over first-order is within its systatic capacity*. One drawback of second-order logic is, however, that it is not decidable. Because of this weakness, most standard mathematicians still like to adhere to first-order logic, which is decidable or provable. How to make it decidable is a big issue for biology (and physics). In order to specify meaningful statements framed in second-order logic, some sort of *qualifier* needs to be used. Information, as a natural phenomenon of a layered, filtered and shared content (syntax, semantics, semiotics) is a crucial factor for making second-order logic – that is inevitably isolated on theoretical grounds – decidable, as revealed in the origins of life. The central point here is that *the phenomenology of information is intrinsically decidable if the internalist stance* (Matsuno, 1996; 2013) – that of the first person observer-participant (Vrobel, 2015) – *is adopted*. This includes the immanent decidability of complex biology-based information structures (Hankey, 2014). Our approaches target the realisation of homomorphisms within the synergetic bundle of i) higher-order multi-state switching logics (Goranson and Cardier, 2013), ii) memory evolutive systems (Ehresmann and Vanbremeersch, 2007), iii) wandering logic intelligence (Simeonov, 2002), and iv) self-organised criticalities (Hankey, 2015) in living systems. They are phenomenology-based (e.g. Simeonov, 2015; Matsuno, 2015; Hipólito, 2015; Ehresmann & Gomez-Ramirez, 2015; Goranson et al., 2015) and bio/cyber-semiotics-based (Kull, 2015; Brier, 2015; Nakajima, 2015).

Indeed, much of the problem when trying to adequately represent the organization of living systems is in the arena of *undecidability*. We need to proceed with real examples and see what can happen. Sometimes we have to work without formal models for a long time in order to find the groundings. A good example of this is the work of Humberto Maturana who understands that human communication occurs at the level of coordinations of coordinations of actions (a second order logic), and we do not have perspicuous formalisms yet for the handling of this other than ‘ordinary language’, which in its performance *IS* such *coordination of coordinations*. Yet to realize the fine-tuned scheme of such helicoid evolving modelling relations for science (Fig. 1) we need to deploy another kind of *squinted* perceptive-narrative logic recognizing the ‘difference that makes the difference’ that assigns a meaning to the overall process in the words of Gregory Bateson.

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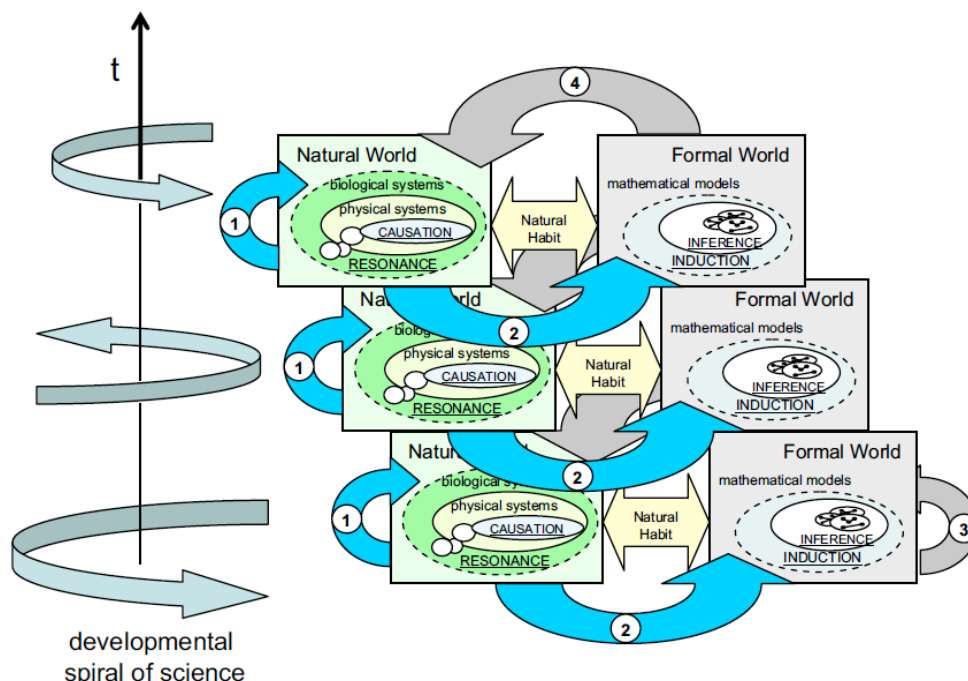


Fig 1. The evolving modelling relation for science (Simeonov, 2010)

² when related to combination or synthesis (systatics)

3. New Key Themes for Future Research

The following new *Key Themes (KT)* have been identified and added to our Integral Biomathics research programme (Simeonov et al., 2012; Gare, 2013; Kauffman and Gare, 2015) in the course of the JPBMB publication activities in 2013 and 2015 (Simeonov et al, 2013; Simeonov et al, 2015).

3.1 KT1: Two-sorted and multivalent logic

Structural modelling of complex biological systems relies on formalisms inherited from physics. These formalisms scale poorly when dealing with interactions involving many variables and agents operating in multi-causal biosystems that cohere at multiple overlapping layers over multiple contexts. A two-sorted logic supplements the existing formalisms to mitigate these challenges (Goranson and Cardier, 2013). The purpose of this second logic is to track how multiple contexts relate to each other, as well as to the dependent structures they inform: a situating of situations. Supervenience (Davidson, 1970; Kim 1984; 1987) could be possibly addressed with two-sorted logic. This allows for capturing the multi-layered and multi-system dynamics that have been elusive in modelling emergent systems so far. The net of co-regulators in MES (Ehresmann & Vandbremeers, 2007) realizes a multivalent logic. Future multivalent logic models will require *phenomenologies* and new kinds of abstractions to reason about interactions among contexts (as situations) as well as about facts. This advancement of current approaches will require basic research in type theory deploying phenomenological constructs for addressing the overlapping domains (Goranson et al., 2015). Of course, this focus can be only the beginning of a research on the adequate representations of dynamic structures and processes in living systems. Possible next steps could involve the investigation of the applicability of Grothendieck's extensions of abelian categories (MacLane, 1950; Murfet, 2006) for homological algebra (Grothendieck, 1957), his Topos Theory (Grothendieck, 1971; Artin et al., 1972) and other developments on this base (Lurie, 2009).

3.2 KT2: Extended and Self-Organized Criticalities

The analysis of criticality states is at the heart of regulation of complex biological systems (Thom, 1977; Rossi, 2011). A particularly interesting and relevant starting point for further investigations is related to the works on extended criticality and symmetry breakings (Longo & Montévil, 2011; Longo, Montévil & Kauffman, 2012), on self-organized criticality (Hankey, 2015) and on applying category theory to model living beings as close to criticality rhythmic pulsations between aspects of qualia and quanta (Cazalis, 2015). Criticality implies that the natural form of information processing at the loci of control of biological systems is neither digital nor limited by binary logic of the category of sets. Rather it involves *singularity-based transformations* hitherto studied in applications of renormalization group processes to complex critical phenomena (Vvedensky and Chang 1982, Chang et al., 1992). Such transformations can be shown to be relevant to elementary processing of information in all criticality based decision making processes in biology, from complex single cell behaviour (Ford, 2010), up to human information processing by manipulation of gestalts, as envisioned in (Hankey, 2015).

3.3 KT3: Hierarchy and Heterarchy

Life is hierarchically structured with complementary heterarchical (von Goldammer et al., 2003) inclusions (Cottam et al., 2005). In the brain, for example, massive information processing appears to tend towards heterarchical structures and processes, while reduction from heterarchy resulting in the sequential control of action is through hierarchical compression. But any attempt to deal with hierarchical multi-scales using conventional techniques is doomed to failure no matter how much data we collect. Generalization in a reductive world results in a small number of precise components, for example the array of physical laws. Generalization in a hierarchical living world, however, results in extreme vagueness. This makes the application of conventional mathematics to an overall view of life extremely difficult. Realizing that the one constraint on science, as on all thought, is (conventional) logic, then if we wish to go beyond it, the only possibility at present is to address vagueness, not algorithms. A possible approach to address this is the 'logic of vagueness' (Peirce, 1869; McCulloch, 1945; Brock, 1969, 1979). In addition, life is characterized by temporal evolution, whereas conventional mathematical equations are static and partially irreversible (see the example of $1+1=2$ in Cottam et al., 2004b).

3.4 KT4: Biological and Phenomenological Temporality

The internalist manifestations of time in biology as a process awareness of internal and external changes (Matsuno, 1998; Matsuno and Salthe, 2002; Matsuno, 2012) and as *time-consciousness* (Husserl, 1991; Heidegger, 1996; Varela, 1999; Kortooms, 2002; Vrobel, 2013; 2015) are characteristic for living systems. “Time is obviously a phenomenon at the interface between (human) mind and the physical world.” (Simeonov, 2015). Therefore this is going to be another key theme for the Integral Biomathics programme in future.

3.5 KT5: Naturalistic Computation

Many biological phenomena do not have adequate mathematical representations. This is because living systems are deploying logic and semiotics beyond our conception of mathematics into the domain of computation, which is on its part much richer than the standard Turing machine paradigm. Hypercomputation has probably the best chances today to develop into a form of *naturalistic/naturalized computation*, i.e. information processing based on its realization in living systems (Simeonov, 2010; Schroeder, 2013a/b; Schroeder, 2014). This is one of the greatest challenges, but also best opportunity in computation theory. Therefore, the results of KT1, KT2, KT3 and KT4 can directly flow into the SALVE research track on naturalizing computation. The most important goal of KT5 is to investigate the opportunities of a Turing Oracle Machine (TOM) implementation and two-sorted logic (KT1), capable of delivering complementary first and third person system descriptions³, incl. their hierarchy/heterarchy (KT3) and temporality (KT4), thus bridging the gap between the formal and informal/narrative/visual modelling systems. Of course, such a system description addressing a challenging question like understanding the movements of viruses within the host organism (Zaichick et al., 2013) also implies a context (Kitto and Kortschak, 2013). The latter needs to be considered from a much broader perspective⁴ (Gabora et al., 2013; Gare, 2013) of interest for further research.

3.6 KT6: AI & Advanced Visual Analytics

A good example of the significance of our proposal for the biomathematics of the future is the recent upheaval of weak artificial intelligence in almost any field of life today after decades of stagnation and deadlocks (Bostrom, 2014). Also, advanced data visualization techniques (Mazza, 2009; Signer et al., 2011; Zhang et al., 2011; Dill et al., 2012; Ware, 2013) often provide *the key of the qualifier* to decrypt ambiguous second order logic in biological phenomena such as the recognition and learning of cancer cells in virtual microscopy with the help of human experts in observation as practiced in digital pathology (Randell et al., 2014; Higgins, 2015). We regard advanced visual representation and analytics as adequate supplements to formal machineries of mathematics and computation. All the other key themes of KT1-KT5 are going to be addressed in KT6.

4. Outlook

There are basically two guideline themes motivating the relevancy of Integral Biomathics for science:

1. internal modelling problems in biology due, in part, to circularity and recursion, and
2. a need for wider and more sensitive interdisciplinary work.

They are separate but related parts of a whole that needs further exploration. A specific research goal of the SALVE project will be the creation of an exemplary model comprising a strategy to address these themes and exhibiting some of the proposed new key themes for research in this context. As a first practical step towards the realization of this vision, we propose to devise a moderate, but integrative and extensible methodology. This includes the development of a unified research framework in biomathematics and biocomputation to explore the relationship between morphogenesis and the development, evolution and degeneration of brain functions across multiple layers, domains and perspectives. This focus is interesting for investigation because networks of neurons are known to mimic arbitrarily complex catastrophes (Thom, 1977). Therefore, they must be uniquely qualified to model and control genetic networks (Hankey, 2014, p.245), which contain critical instabilities and operate at ‘The Edge of Chaos’ (Kauffman, 1996). If we succeed in testing this hypothesis in silico, then a holistic approach to treating neuroblastoma and cancer in general might be derived.

³ agent-based simulations could be held to be first person.

⁴ incl. evolution, ecology, society and the researcher engaging in scientific inquiry, theorizing, measuring and communicating results as part of the context being investigated

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