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Review

On some recent insights in Integral Biomathics

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ABSTRACT

This paper summarizes the results in Integral Biomathics obtained to this moment and provides an outlook for future research in the field.

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1. What are the challenges in formalizing biology today?

Formalization of any kind presumes the prior presence of something concrete and particular. Recognizing this in biology is not easy (Waddington, 1966, 1968–1972, 1974). Many biological phenomena do not have adequate mathematical representations. This is because living systems are deploying logic and semiotics

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beyond our conception of mathematics into the domain of computation, which is on its part much richer than the standard Turing machine paradigm. In particular, there are four areas deserving attention with broad impacts in and beyond biology (Root-Bernstein, 2012a):

1. *A theory of self-emergent objects* that can carry out functions within interactive variances of the constituents of living systems: developing models of self-emergent objects (origins of first cells; self-assembly of viruses, etc.) that carry out functions (selecting/rejecting among possible components; minimizing free energy; etc.) while utilizing both continuous and discrete information. Set theory is too abstract to handle such "objects"; they have more structure and other properties than sets and the elements of sets. Therefore self-emergent objects must be defined in a frame where their different qualities can be described. Such a theory should be able to incorporate the work that has been done on understanding hierarchical systems, emergent properties, complexity theory, etc. Its mathematics should therefore be extraordinarily integrative. A subsumptive or specification hierarchy is more general than set theory and could be the first step in this direction.

   There are two fundamental issues to be taken in consideration. First, cells are autonomous/autopoietic – they form themselves. Therefore, we need to use a frame in which we can describe self-organizing/self-emergent objects mimicking "cellular life" as evolution of such objects using specifications of the relations between them that do provide rules i) to limit the entry and exit of individual elements, and ii) allow elements to undergo transformations (e.g. metabolism) within the object. A key question to answer here is whether the *self* (the individuum with a distinct identity) is a prerequisite for or a consequence of the self-organization? Second, biological objects (cells) have the variance property.[1] We need a theory that allows the definition of objects that are not characterized by specific numbers, proportions and rates of turnover, excretion and replenishment of the object/cell constituents, but i) by (empirically determined) *variances* (number ranges) within which all of these constituents must exist in order for the living object to function as such (Zadeh, 2000; Kauffman, 2001), and ii) with the *self* being *potentially* associated with these variances.

   This "bio-affine" theory must allow the integration of continuous and "grainy"/discrete temporalities for the same "object" simultaneously: a circular relation of i) handling continuous variations of the chemical kinetics, e.g. continuous interactions/flows of elements, while ii) acting on small sets of definable/discrete elements/individuals (calculations of modular probabilities) determined by the chemical kinetics. Also, it should have operators/functions capable of defining *state-sensitive objects*, i.e. to model switching processes between stable states when certain values or variances (within them) are exceeded.
2. *A theory of complementary assembling*: biological systems build and organize themselves based on the principle of molecular complementarity to produce robust aggregates/modules. Such a theory is therefore important, because the formation of complementary (symmetric or asymmetric/chirality) modules within complex systems can prune out huge numbers of unfeasible possibilities at each step of the hierarchical modular assembly.
3. *A qualia jump*[2] *theory*: Mathematics generally treats either scalar quantities or vector quantities (statically defined), but not the transformation of scalar to vector (dynamic type transitions). However, some properties of biological systems involve transformations from pure scalar to pure vector quantities (and vice versa): e.g. a chemical neurotransmitter signal (scalar diffusion) becomes a directional electrical signal (a vector).
4. *A hidden morphology theory*: the linkage between form and function.

The mathematical challenges involved in attempting to model biological form-function interactions are far from trivial. Natural selection attempts to optimize forms to carry out particular functions, but since novel functions evolve from existing forms, these formal attempts may be seriously limited. On the one hand, we do not have geometrical tools that can easily model processes such as the complex folding of proteins or chromosomes, or detailed embryological development. Mathematical forms share little with the actual biological processes that give rise to these structures. The mathematical abstractions currently used in system biological models generally do not illuminate the processes that give rise to biological geometries, but only their outward forms despite the work of René Thom (1994). What is interesting about biological forms, however, is not their geometry per se, but the ways in which these forms are *reifications of the biochemical processes* which 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 also 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., 2010). Similarly, in human developmental biology we have now 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, 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 embryology is also stymied by the lack of mathematical approaches that can link discrete, continuous and geometrical information simultaneously. But what kind of mathematical notions 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? And how can a mathematical object obtain and maintain its identity? Also, Lewontin has stressed the *reciprocal relationships between genes, organisms and their environment*, in which all three elements act as both causes and effects (Lewontin, 2002). Therefore, we should be able to explore alternative avenues to traditional unidirectional genotype–phenotype relationships such as cyclic or helical or chaotic genotype-phenotype mappings.

[1] Any given cell must have chromosomes, but their number can vary (as they do in cancers and parthenogenesis) and still be viable; they can have many ribosomes and mitochondria or but a few and still live; they can accumulate certain amounts of toxins or lose a certain amount of key ions and still function; etc.

[2] A quale is an individual instance of subjective, conscious experience, "an unfamiliar term for something that could not be more familiar to each of us: the ways things seem to us" (Dennet, 1988).

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