

Some Thoughts on A. H. Louie's "More Than Life Itself: A Reflexion on Formal Systems and Biology"

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Abstract We review and discuss A. H. Louie's book "More than Life Itself: A Reflexion on Formal Systems and Biology" from an interdisciplinary viewpoint, involving both biology and mathematics, taking into account new developments and related theories.

Keywords Relational biology · Systems biology · (M,R) systems · Robert Rosen · Efficient causation · Autopoiesis · Organizational closure · Metabolism · Computability · Self-reference · Ouroborus equation

1 Introduction

Aloisius Louie's book "More than life itself: a reflection on formal systems and biology" undoubtedly constitutes a serious attempt to accomplish the most commendable task of laying the mathematical foundations of relational biology in the spirit of Robert Rosen's pioneering albeit somewhat cryptic work as exposed in Rosen (1958a, b, 1971, 1973, 1991). We discuss below how successful this attempt may be deemed to be. Our analysis will by necessity embrace two vast universes:

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Mathematics and Biology, with an unavoidable focus on Rosen's theoretical work known as (M,R) systems. Our analysis will have to encompass a wide field, because in the last 20 years many formal models of biological organization have been created, if we take as an arbitrary starting line the first Artificial Life Conference at Los Alamos in 1987. An important question, yet to be resolved, is an esoteric one: are living systems computable? Rosen, and others, have tackled this important question with unorthodox techniques (it is very difficult to define what an orthodox approach would be) and gave a resolute negative answer. This was not appreciated by everyone, especially by the large army of researchers that have identified living systems with Turing-like computers. Louie was Rosen's graduate student, and he centers his effort on giving an airtight demonstration of this remarkable conclusion. But his quest seems so narrowly focused that his analysis perpetuates the isolation of Rosen's intellectual corpus: he does not build 'gentle bridges' towards other important models of biological organization, especially the theory of autopoiesis created by Maturana and Varela (1980). Thus we feel that to give a correct vision of Louie's book we shall need to jump continuously between mathematics and biology, as he invites us to do in his subtitle.

2 A Reflection on Mathematical Formalisms in Biology

The mathematical formalization of the foundations of relational biology (one of the roots of what is nowadays called systems biology) was started by Rashevsky (1938), and installed as a discipline by Rosen (1958a, b).

The very notion of relational biology originated at the intersection of biology and mathematics. Louie states this so in his Preface (p. xv):

Thus *relational biology* is the operational description of our endeavor, the characteristic name of our approach to our subject, which is *mathematical biology*. Note that 'biology' is the noun and 'mathematics' is the adjective: the study of living organism is the subject, and the abstract deductive science that is mathematics is the tool. Stated otherwise, biology is the final cause and mathematics is the efficient cause. The two are indispensable ingredients, indeed complementary (and complimentary) halves of our subject (p. xv).

To meet this challenging task, Rosen rested on the mathematical machinery available in the mid-twentieth century and applied it to the foundations of biology. It is then no surprise that category theory, mathematical logic and computer science—flourishing new disciplines at the time—lie at the core of his approach; in fact they may be considered as the basic pillars of his mathematical toolbox.

2.1 Louie's Approach

Louie's book uses a similar approach regarding mathematical formalisms. Notice in the quotation above that the abstract deductive aspect of mathematics is emphasized in detriment of the role of visualization, representation and metaphor in

mathematics as “the art of seeing the invisible” (Lakoff and Johnson 1980; Soto-Andrade 2008). Also, Louie seems to agree with Aristotle, when he writes (p. xv):

After all, he (Rosen) was a master of *les mots justes*, and one can only rearrange a precise mathematical statement in a limited number of ways. As Aristotle said, “When a thing has been said once, it is hard to say it differently”

This shows that Aristotle was clearly not a mathematician, since it may be argued convincingly that “mathematics is the art of seeing and saying things differently....” In fact, for every mathematical concept or process several different relevant metaphors are available! It is surprising indeed that Aristotle said that, knowing well (but perhaps not so well as (Lakoff and Johnson 1980) what a metaphor is.... However, two pages later (p. xvii), Louie takes an opposite stance:

One needs to remember that the essence of a complex system is that a single description does not suffice to account for our interactions with it. Alternate descriptions are fundamental in the pursuit of truth; plurality spices life. “One world is not enough.”

Before entering into the details, we may ask at this point: What are the “good” mathematical formalisms for addressing the challenging task of building the foundations of relational biology today?

Although we have no strict answer to this question, we would have expected that the revolutionary developments that occurred in the last fifty years, since the origins of category theory and computer science, and in the golden years of mathematical logic in the second half of the twentieth century, be reflected in some way in the theory under construction.

Louie’s approach is based, however, on particular formalization approaches that essentially follow the main trends of the mid-twentieth century, that is, a classical-logic approach, in spite of the ample discussion on what should be the logic for modeling particular scientific areas; a set-theoretic framework, a view of systems as collections of things; an identification of ‘simulable’ with ‘computable’, disregarding the complexities of more sophisticated contemporary notions in the theory of computability. Each of them implies a choice of formalization, and deserves to be discussed in more detail.

First, at the most abstract level, we could ask what is the “logic of life”, that is, which is the reasoning framework best suited to discuss entailment in this domain. Classical logic is the (default) option chosen in this book. However classical logic was built to model static and finite objects (or rather, built on metaphors involving static and finite objects (Lakoff and Johnson 1980; Lakoff and Nuñez 2000), whose characteristics are clearly far away from the essence of life processes. On the other hand, the relevance of statistical approaches to reasoning, increasingly widespread, deserve at least a discussion in this context. Maxwell already in 1850 devised the problem: “The actual science of logic is conversant at present only with things, either certain, impossible. or entirely doubtful, none of which (fortunately) we have to reason on. Therefore, the true logic for this world is the calculus of Probabilities,

which takes account of the magnitude of the probability which is, or ought to be, in a reasonable man's mind" (cited in Jaynes 2003, p. 3).

Second, set-theoretical assumptions seems to permeate Louie's view of the basic objects in this domain. For instance (Part II, p. 82) when he states:

System is a basic undefined term, a primitive. It takes on the intuitive meaning of "a collection of material or immaterial things that comprises one's object of study."

But, is a system just a collection of things? It is rather a network of interrelations, as the goal of *relational* biology states. And it seems that here the *scale* (size) and complexity of the network is a non-trivial barrier to address. Here one misses the link with the machinery of networks, not in the basic graph theoretical sense of the fifties, but in the modern twenty-first century science of networks (Barabasi and Oltvai 2004; Newman et al. 2006).

Third, the notion of computable ("simulation" is the word that codes this notion in the book) is at the core of the discussion. But, should 'the computable' be at the center of researching life? Be that or no, it seems that 'the computable' is the current machinery we have to investigate life, or to say it more bluntly, it is the limit we currently have to investigate and conceptualize life (or any other phenomena) with formal systems (if one trusts the results of Gödel on the analysis of formal systems and those of Turing on the notion of procedure by 'finite means' involved in a proof). A better, though more modest, question is: what part of the phenomena of life can be captured with formal methods (i.e. what part is simulable?), what is left out? How important are the phenomena that are being left out? How can the phenomena of life be approximated with formal methods? Recall that for Louie "a *formal system* is an object in the universe of mathematics" (p. 88).

It is interesting to speculate which formalisms from mathematics would Rosen have chosen if he had been born fifty years later. In fact, at the dawn of the twenty-first century, we witness an increasing role of new methodologies that attempt to capture phenomena that are at the very basis of the problem of life: large numbers, huge dimension, complex systems, besides reflexive domains. It is no surprise that statistical methodologies are permeating computer science and logic to deal with these phenomena. We should add to this that the relational world is just opening up with what some call 'network science' the study of huge networks, that model many types of phenomena, particularly in chemistry, biology and sciences of the mind. The notions of complexity and emergent properties are at the center of this discussion, and trying to capture the phenomena from their own points of view. Here again, the discussion on the formal tools available or consistent to address these phenomena is a significant part of the challenge.

2.2 Mathematical Toolbox

That said, in this book Louie decided to rely on Rosen's toolbox, and so he devotes many pages (almost half of the book) to develop and explain these machinery to biologists. Part I consists of mathematical preliminaries, dealing with ordered sets, the lattice of relations and properties of lattices (distributivity, modularity, etc.), all

classic notions today. The choice of topics says in fact more about what is left out, and among the missing ones that would deserve discussion are the related topics Scott's continuous lattices and λ -calculus (Scott 1972; Lawvere 2006; Soto-Andrade and Varela 1984).

Recall that Scott introduced continuous lattices to construct by a limiting process *reflexive domains* (structures that are isomorphic to their set of structure preserving mappings, which is a structure of the same type in a natural way) and so obtain a concrete realization of type-free lambda calculus (loc. cit). The key idea in this "calculus for self reference" is that the same object x may simultaneously play the roles of argument, operand and value, collapsing completely the Procrustean bed of the four Aristotelian causes.

Then, more than a decade ago it was suggested (Fontana and Buss 1996) that Rosen's (M,R) systems could be couched in the language of λ -calculus; this approach has been actively pursued later, by Mossio et al. (2009) among others, by looking at (M,R) systems as fixed points of a suitable operator. However no significant results concerning the construction of examples of (M,R) systems have so far been obtained in this way (see Cárdenas et al. 2010 for a more detailed discussion).

The author proceeds then to discuss more conceptual topics, like qualitative versus quantitative (p. 54), the notion of observable and the sharp statement "quantitative is a meagre subset of qualitative". Nevertheless, it seems that the author's intention is not to go deeper into these notions. As he avows, in one of his most revealing sentences on formalisms (p. 76):

For us, the features of natural systems in general and of biological systems in particular, that are of interest are precisely those that are 'unquantifiable.'

In Part II starts the presentation of biological material proper. Interestingly, here mathematical rigor gives way to biological concepts. In fact, mathematics is used as 'illustration' of the possibility of formalizing some concepts like causation, model, simulation, etc.

Part III is definitely the most interesting from a formal point of view and presents a laudable effort to apply mathematical formalism and proofs to support biological notions and intuitions. The proofs are not rigorous and sometimes not even correct (for example the proof that N has a unique largest model is based on Lemma 8.21, which is actually false). But this does not diminish the value of the concepts presented; on the contrary, highlights the intuition that the discussion at hand overflows the current mathematical formalisms and is in strong need of a new logical framework. This is by no means a simple task, and has been pursued in many directions, still without apparent success. The "mathematics of circularity and self-reference" in the spirit of (Varela 1975, 1981) can be noted among them (see also Cárdenas et al. 2010 for references).

3 (M,R) Systems and Their Biological Realization

Part IV of "More than Life itself" enters the biological realm proper, or at least seriously intends to do so. Recall that the final aim of Relational Biology, whose

standpoint we share, modest and ambitious at the same time, is to set up a theory suitable for every biological system by modeling the *relations* that need to be fulfilled for a system ‘to be a living system’. The theory of (M,R) systems, which we recall below, arises as the result of pursuing this aim.

Without regard to what we may say about (M,R) systems as a purely formal construct, at some point we want, however to bring them back to the natural world, by what Louie and Rosen call ‘decoding’. In this section we will discuss some of Louie’s (M,R) system ‘decoding’ strategies, exposed in Chaps. 11 and 12 of Part IV of “More than Life itself”.

3.1 Louie’s General Strategy

The foundational principle in Louie’s epistemology seems to be “every process is a mapping”, which means that every process can be modeled by a *one-to-one* or a *one-to-many* relation. We will explain below how this assumption, that might be found too cursory, imposes strong conditions on biological representation. For the time being, another key aspect for understanding Louie’s way of thinking is his use of the four Aristotelian causes to describe a mapping.

We will briefly explain how he undertakes this tour de force. For a given mapping, the input is identified with the *material cause*, the nature of the mapping with the *formal cause*, the mapping itself is regarded as a the *efficient cause* and the output is usually interpreted as the *final cause*. Louie in most cases identifies the *function* of a process with the output of the mapping that represents it.

We notice here that Louie has more sympathy for this Aristotelian viewpoint than most mathematicians, who would rather look on Aristotelian four causes as a Procrustean bed on which mathematical objects fit awkwardly, with no compensatory gain in understanding or insight.

Our main topic in this section is discussing how Louie pursues (M,R) -system realizations. Very likely the most characteristic point of his strategy is his belief that for finding the realization of a formal system we should look for *final causes*. Many consequences follow from Louie’s attention to *final causes*, but for now we would like to discuss a few general implications.

Faced to the problem of relating a formal construct (for example a mapping f) with a natural process, one possible approach is to look for a process that performs an operation analogous to f . In this case we are focused on *how* the process happens, or in Louie’s terminology we are looking at *efficient causes*. On the other hand, by focusing our attention on *final causes* we find ourselves trying to answer *why* the process happens or in Louie’s terminology “what is its *function*?”.

Note that from a computational viewpoint, there is a big difference between simulating (we are using the term as in computer science) a phenomenon or process, that is, writing a piece of code that performs the same function (input/output), and studying its properties: for example, does the process finish for every input? Do the outputs of the process have some property? As the famous theorem of Rice states, “almost all properties of a function are not computable” (Rice 1953).

It follows from this last approach that if we are searching for the realization of given a mapping f and we know what its output b represents, we should look for

a natural process such that its *function* can be (uniquely?) related to the realization of *b*.

Now, believing that knowing the output *b* of a mapping *f* we can find its realization, is indeed surprising. In mathematics, if we take the number 16 and we ask ourselves “which mapping has 16 as output?”, we can find infinitely many mappings that perform this task. However, if we ask ourselves “which mapping takes 4 and returns 16?”, the square function arises as a natural answer, albeit still not the only one, for sure. But of course mathematics and natural phenomena are two different domains and nothing prevents us from assuming that natural phenomena are constrained in a way that this belief might turn true. Louie makes efforts to provide biological principles that support his approach. Nevertheless, as we will discuss in subsequent sections, his assumptions related to biological phenomena are too restrictive to provide a general biological application.

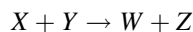
The concept of teleology is inherent to arguments based on *function*. The use of teleology in biology is definitely controversial (Bedau 1992), but Louie remarks something that is certainly true: biology (and science in general) is full of teleological arguments such as optimization, parsimony, or even fitness in ecology. In most cases, teleology is used when our arguments are based on principles that can not be proved or when their details remains unknown, and therefore they should be regarded very carefully. Louie’s identification of the *function* of a process with its products, makes his use of teleology more operational, however defining the product(s) of a process not as unique as it may appear.

Any process has a large number of products and by-products (or side-effects), probably as many as the observer may wish to count. Within Louie’s perspective is not clear how to trim this multiplicity, and we can only deduce what is his true intention. One may argue that only those that may play the role of input for other processes in the system can be related to its function or *final cause*. But this would introduce an endless loop because for knowing the function of one process we would need to know the inputs of every process in the system. Again in Louie’s defense, one may say that research by itself is an endless loop, or in other words, that by knowing more about one process we would gain more knowledge of the *function* of every other process in the system. This dynamic perspective of research and knowledge might be one of the things that we miss the most in Louie’s analysis.

3.2 A Brief Description of (M,R) Systems

Before proceeding any further, a brief explanation of (M,R) systems is needed (for further details, refer to Letelier et al. 2006; Cárdenas et al. 2010). Robert Rosen developed (M,R) systems as a model for living systems, thus every aspect of his model is based upon his definition of life: a living system is a “system closed to *efficient causation*” (Rosen 1991).

For explaining how a (M,R) system is constructed, let us first introduce the following generic chemical reaction



Our first step will be to represent this reaction as a mapping (f_1) between the reaction reactants (the left hand side of the arrow) and products (the right hand side of the arrow).

$$f_1(X, Y) = (W, Z)$$

For generality, for any mapping f_i let us name the reactant set as a_i and the product set as b_i . A typical organism may perform thousands of chemical reactions, and using the previous terminology we can represent them as a list

$$f_1(a_1) = (b_1)$$

$$f_2(a_2) = (b_2)$$

...

This setup, together with the remark that biochemical reactions concatenate in a natural way, suggests strongly that we should formalize our system as a *category*, of a special type, a ‘metabolic category’ we could say, whose objects are reactants and products (metabolites, in general) and whose arrows are the reactions themselves, regarded as transformations, as Rosen does. Rosen however claims at his point to encapsulate the whole metabolic category in just one single (multi-component) mapping f such that

$$f(a) = b$$

where a stands for all the reactant sets a_i and b for all the product sets b_i (or rather their disjoint union). So Rosen’s f , the first component of an (M, R) system, appears as an abstraction of an organism metabolism. There are several ways to interpret this mathematical construct. Somehow f is intended to capture the family of all particular mappings f_i , and at the same time the operationality of them all. From a computational point of view, however, this juggling encapsulation hides the inherent complexities of concurrency in networks of processes (cf. Petri Nets Petri and Reisig 2008) in favor of a less fruitful abstraction.

It is odd, however, that Rosen, who was well acquainted with the language of category theory, did not use a category to represent metabolism instead of just a single mapping. One reason for that may be that his intuition of categories was rather algebraic than geometric.

Notice that a (geometric) graph theoretical approach to metabolism has indeed developed during these last decades, (Barabasi and Oltvai 2004; Newman et al. 2006) which could be further developed in terms of the path category of the corresponding graph, to combine in a more fruitful way “the angel of geometry and the devil of algebra” (Connes 2005).

A consequence of Rosen’s definition of life is the assumption that the conditions that make the chemical reactions happen (such as enzymes) are produced by the system itself. Thus, there should exist ways to relate the metabolism products b with the components that ‘perform’ those chemical reactions (i.e. f in (M, R) system terminology). This idea is contained in the following equation that introduces a new mapping Φ

$$\Phi(b) = f$$

So, in addition to the ‘Metabolism’ component f , the ‘Replication’ component Φ is introduced. To avoid confusion with the term ‘replication’ and its more accepted biological meaning (referring to DNA repair, for example), we will use the terminology introduced by Letelier et al. (2006) and name Φ as the ‘Replacement’ component.

Rosen first presented this construction using a model close to what we call now *hypergraphs*, where the individual mappings were represented by black boxes and the relation they entailed, by an arrow. Based on the later representation, Louie decided to name the construction of the Metabolism and Replication components as an (M,R) network.

As the concept of closure is the key to his definition of life, we can ask ourselves: given the mapping f what determines the process Φ that ‘replaces’ it? To answer this question, a new mapping β is introduced, such that

$$\beta(f) = \Phi$$

This procedure would lead us however to recursively introduce a chain of infinitely many new mappings, opening in this way the Pandora box of ‘infinite regress’. To avoid this, Rosen found an ingenious but at the same time troublesome solution. To close the loop, so to say, he took the mapping β to be just the inverse of the ‘evaluation at b mapping’, that he assumed to be one-to-one. In simpler words, he assumed that, b being given, there is only one admissible mapping Φ such that $\Phi(b) = f$. Then we can associate one well defined Φ to each given f , and this association is the mapping β , which is then no longer coming from nowhere. Of course, this assumption, which says that the admissible mappings Φ are wholly determined by their sole value at b is a most unusual one in everyday life, and mathematics, where you have in general many (graphs of) mappings going through the same point. It may make sense however in the case where only a rather rigid class of mappings Φ is relevant, say something like a family of elementary growth curves. Intuitively, in living system, metabolism f “knows” exactly how to repair itself, i.e. ‘knows’ which Φ to choose.

Since the mapping β is so closely related to the output b , being just then the ‘reverse’ of the evaluation at b , Rosen suggested that we could *identify* β with b . We notice anyhow that identifying objects does not mean than we can substitute one object in place of the other in an unthinking way. For instance, there is a one-to-one correspondence between non-zero real numbers and their inverses, but we cannot usually replace a number by its inverse in a calculation. The operational meaning of this identification is discussed in Letelier et al. (2006) and also in Cárdenas et al. (2010), where it is pointed out that in concrete toy examples of (M,R) systems, the mapping β appears to be identifiable with the inverse b^{-1} of the output b , when this makes sense, rather than with b itself. This is actually a major pitfall in perfunctory applications of λ calculus to the description of (M,R) , since λ calculus *per se* does not allow us to handle inverses, in the arithmetical, algebraic or functional sense (Cárdenas et al. 2010).

However, nothing stops us from identifying β with some other ingredient already present in our setup, i.e. ‘closing the loop’ otherwise. Louie in his book explores some of the consequences of this last remark. He decided, moreover, to use the term (M,R) systems only for those where such identification can be performed (in contrast to the more general (M,R) network). Rosen used to call them ‘replicative (M,R) systems’ instead.

Rosen thought that it was more intuitive to tackle this ‘recursive’ problems within the theory of categories (Rosen 1958b). However, we believe that exploring the connection between (M,R) system theory and other mathematical theories may provide new insights to this theory.

Based on the similarities between (M,R) systems and autopoietic systems (see Letelier et al. 2003) these systems are also called “ (M,R) system with organizational invariance” (Letelier et al. 2006).

3.3 (M,R) Systems and the Ouroborus Equation $f(f) = f$

Rosen tried to close the Pandora’s box of infinite regress by making the odd and unusual hypothesis that there is only one Φ such that $\Phi(b) = f$, i.e. that the operator that evaluates each mapping Φ at the output b is one-to-one (and hence invertible on an appropriate range). If we do not shun infinite regress, instead, we may construct stepwise a sequence of maps, f, Φ, β , etc., where β is no longer assumed to be the reverse of the “evaluation at b ” operator (Letelier et al. 2006). This sequence, that could be denoted more uniformly Φ_n , with $\Phi_0 = f, \Phi_1 = \Phi, \Phi_2 = \beta$, etc, tends to a limit Φ_∞ , in a sense to be made precise, and this limit satisfies Ouroborus equation: $\Phi_\infty(\Phi_\infty) = \Phi_\infty$.

It is remarkable, that Rosen’s insight, that metabolism is just a mapping $f : A \rightarrow B$, which may be too cursory for a biologist, turns out to show us the way to construct recursively, by a limiting process, solutions of the self-referential Ouroborus equation $f(f) = f$, for an unknown function f , a way that mathematicians had not imagined before Rosen (see Letelier et al. 2006 for more details).

We notice that Louie hints at Ouroborus equation in Sect. 5.12, but he neither gets a precise formulation of the fully self-referential equation $f(f) = f$ nor a down to earth biological interpretation.

3.4 Realization of the ‘Metabolism’ Mapping f

As Rosen himself proposed, Louie relates the ‘metabolism’ component of an (M,R) system to the set of enzymes in a biological system. This correlation has been made on the notion that enzymes (as catalysts) allow chemical transformation to be feasible under physiological conditions. It is worth noting that given a set of substrates, one may find that many alternative products are produced and enzymes, by kinetic control, serve to direct the reactions into particular sets of products.

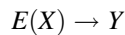
Another observation worth making is that for a given chemical reaction, other aspects besides enzymes determine its occurrence. Imagine the following trivial example. If we have a solution with an enzyme and its reactants, and we lower the temperature, we will get to a point where we will not be able to observe any

products. This means that conditions such as temperature, pH and salt concentrations should be part of the *efficient cause* of the chemical reaction. This last remark does not contradict Rosen's definition of life, because most of these conditions are maintained by the physiology of the organism.

The 'Metabolism' mapping f presents a good opportunity to discuss Louie's belief that "every process is a mapping". It is not evident by itself that it would be possible to capture all metabolic processes in one or more mappings (a discussion about of this subject, although using *genetic regulation* was made by Cottam et al. (2007). To present our concerns, we will use a simple example of how enzymes can be regulated. Metabolites and chemical compounds in general, can have a variety of effects over enzymes altering some of their properties. This effects can vary from modification on kinetic properties of enzymes to preventing the enzyme to catalyze its corresponding reaction at all (Cornish-Bowden 1995). To illustrate our point let us define a hypothetical enzyme E that catalyzes the following reaction.



It is clear that in (M,R) system formalism this reaction would be represented by the following mapping



Now, let us introduce a molecule m that binds to the catalytic site of E , having the effect that after this binding E can no longer catalyze its reaction. One approach to represent the effect of m over E , would be the introduction of the following transformation into our model



where E_m represents the inactive form of E .

Rosen was aware that enzymes are degraded constantly, and that is one of his motivations for introducing the Replacement mapping Φ , but the regulation of enzymes by metabolites is more subtle. The mapping m introduced above hardly captures this process, mainly because the factors that determine the outcome of a system where X , E and m are present are outside of our model; in particular, kinetic parameters such as kinetic constants, and variables such as the relative concentration of X , E and m (Cornish-Bowden 1995). Furthermore, we have to consider that in living systems different metabolites can regulate a given enzyme in many ways.

Within (M,R) system terminology, our concerns can be formulated as: "What would be the *efficient cause* of a given metabolic reaction?" We have mentioned how many variables converge to determine the occurrence of a chemical transformation in living organisms. This suggest that just one or more mappings might be too naive an approach, to model more complex properties of metabolism.

We mentioned previously that Rosen first imagined biological processes as some kind of chart or graph. To some extent, those early metaphors shaped his way of representing biological knowledge. For example, it is not intuitive how to incorporate the concept of time in (M,R) system framework, which is crucial for understanding

regulatory processes. Some of his last papers about (M,R) system (Rosen 1971, 1973) present some alternatives for a more dynamical interpretation of his theory (we will not discuss here how successful they might be), but they have received little attention, even from Louie.

The main challenge here is that if we want to model a biological system, the perspective by which we identify dichotomously which components are related with each other and which are not, will usually be too narrow. It is just as important “how strong” or “how likely” is the relation between them. We envision that assigning weights or probabilities to the relations, and incorporating statistical models, may help to get (M,R) system theory closer to a more dynamical perspective of living organisms.

3.5 Realization of the ‘Replacement’ Mappings Φ

The construction of (M,R) system requires that it should be possible to uniquely relate the products of the ‘Metabolism’ component b and the ‘Metabolism’ mapping f . As Louie is focused on *final causes* for reaching the realization of Φ , he is looking for a biological process such that its *function* can be uniquely related to the realization of f , in other words the enzymes. Louie’s answer are the genes: “... a gene ‘repairs’ the metabolism function” by creating “new copies of the enzyme” (p. 264). Louie takes one step further and adds: the “Repair [Replacement] mapping” could be interpreted as an “abstract version of the *one-gene-one-enzyme hypothesis*” (p. 270).

First of all, the term ‘gene’ by itself is very difficult to define in a non ambiguous way (Gayon 2007; Portin 2009). Louie’s mention to the *one-gene-one-enzyme hypothesis* suggests that he intended to use its classical meaning (a sequence of DNA that codifies for a protein or RNA that performs a certain biological *function*). However, here is where Louie’s assumptions prove to be very limited for a general application. For example, in nature we can find proteins that can catalyze more than one class of reaction. Also we can find more sophisticated cases, where genes can be associated with multiple proteins as a consequence of multiple splicing of primary translated RNA and possible post-translational modification (see the classical textbook (Lodish et al. 2007 for instance).

We have no other choice than to realize that “one-gene-many-enzymes” relations are part of living organisms. In addition, it is possible to find the opposite situation of “many-genes-one-enzyme” relations. Some enzymes are a composition of more than one peptide chain, usually called polymeric enzymes or protein complexes. The interactions between the components of those peptide complexes play an important role to stabilize their structure and sometimes, the interactions are even required to perform their catalytic activity (Nooren and Thornton 2003).

The multiplicity of relations between genes and enzymes is not so surprising if we realize that ‘genes’ are not operationally independent units within an organism. More and more, the scientific community is realizing that for understanding genetic expression, ‘genes’ and cellular context can not be treated independently; to the extent that it has been proposed that what we usually refer as ‘gene’, should be

interpreted as a ‘process’, in contrast to a molecular instance (Gayon 2007; Portin 2009; Sapp 2009).

3.6 The Identification between b and β

We also want to find a realization for the assumption that in an (M,R) system, a set of metabolites b determines the ‘Replacement’ component Φ itself, such that b can be identified with the mapping β . As Louie is looking for *final causes*, he argues that “a metabolic product in fact determines the enzyme required in the biochemical reaction that produces it” (the principle that covers this notion is the one of “enzyme specificity”). Then “the *one-gene-one-enzyme hypothesis* ... completes the entailment path to the gene Φ ” (p. 288).

Of course, Louie’s argument rests on the realizations for the ‘Replacement’ and ‘Metabolism’ components, and we have pointed out how each one of them presents its own challenges. But before concluding this section, let us bring back our previous discussion about teleology. It is implicit in Louie’s argument, that for an enzyme to be required, the products of the reaction it catalyzes must be needed. The question “needed for what?” seems unavoidable, but Louie provides no clarification. The most general interpretation, and apparently his intention, it is to understand “metabolic requirement” as related to the survival of the organism. However, it is important to notice that under different contexts the set of metabolites required for survival is not always the same. Thus, to some extent, the “realization” of the mapping β would be dynamically changing depending on the situation that the organism is in. This last statement has the major consequence that instead of closing “the path of *efficient causation*”, we are introducing a new component (the organism surroundings) to determine the relation between b and β .

Perhaps the metabolic products b are not the most appropriate set to be identified with β , and Louie’s efforts to explore other identifications may prove to be an alternative solution to clarify this elusive mapping.

4 (M,R) Systems and Autopoietic Systems

Rosen’s attempt, in 1958, to produce a conceptual framework for the organization of living systems was one in a string of models/theories that continues until today: autopoiesis (Varela and Maturana 1972), the ‘chemoton’ (Gánti 1975, 2003), RNA worlds, autocatalytic sets (Kauffman 1986, 1993), the artificial life movement (Langton 1987), systems biology, RAF systems (Steel 2000). In this small set, the (M,R) systems formalism stands out for its rigor, the centrality of metabolic circularity and its implied new epistemology, but it is not unique in touching these aspects. In this respect Louie’s book does a disfavor to Rosen’s work by not making any attempt to relate (M,R) formalism with similar theories. This is specially surprising in the case of autopoiesis, a model that has already been connected with (M,R) systems (see Letelier et al. 2003) and which has been, perhaps not “successful”, but well received in many areas of science, including sociology (Luhmann 1995) (see Luisi 2003 for a review). It is true that in autopoiesis

metabolic closure is not deduced, but rather demanded as *the* principal characteristics of living systems. Thus we would expect to find in a comprehensive book concerned with biological organization, at least one page trying to analyze how Rosen's β maps relate with the dual concepts of organization and structure as used by Maturana and Varela. This also applies to other formalisms like Varela's effort embodied in his book (Varela 1979) to use indicational calculus (a mathematical tool created by Spencer Brown) as a stepping stone for a mathematical framework for self-referential systems. It is true that Spencer Brown's indicational calculus is radically different from the analysis of Rosen and Louie, but it would have been commendable to address, even briefly, the similarities and differences between these two competing and complementary theories about living organization. A similar aloofness exists in the book with respect to recent theoretical models such as RAF sets, a formalism that undoubtedly could be used to clarify some fuzzy concepts in Rosen's original formalism (see Jaramillo et al. 2010). Biologists today are looking for working theoretical models (the very recent history of systems biology is an example) but the complexity of biology requires a multifaceted approach. It is naive to think that a single formalism, which never addresses the messy details of experimental biology, could do the required job. Thus Louie, by omitting the discussion of other models does relational biology a disfavor. At the end of the day we must realize that the quest for formal systems to comprehend biology is not a contest, with winners and losers, but rather an intellectual search for a new science of organization, and this search will demand a variety of tools in our toolbox.

5 Conclusion

After more than 50 years from Robert Rosen first papers about (M,R) system (Rosen 1958a, b), his arguments definitely remain controversial (Cárdenas et al. 2010). Understanding how (M,R) system mappings and assumptions can be related to actual biological processes may clarify the possible meanings and interpretations of the theory.

The choices made by Louie to provide 'realizations' for (M,R) system assumptions as discussed here, leave many loose ends. The construction of (M,R) systems is based on several mappings used in a 'recursive' manner, thus imposing unique relations among (M,R) system components. How to integrate the multiplicity and variety of biological processes into unique relations is indeed a big challenge to meet. Any contribution to this discussion is valuable, and so is Louie's book, in spite of the problems and omissions we have discussed in depth. Indeed, Louie's efforts undoubtedly deserve recognition, as few have his deep knowledge of Rosen's work. However, we believe that, as in other disciplines, "theory networking" is needed, between the theory of (M,R) systems and the various theories of the living that have arisen in the last decades, concerning their mathematical as well as biological aspects. Moreover dialog is urgently needed between theoretical models, direct experience, and experimentally derived concepts that any theory as ambitious as relational biology requires in order to be successful. We believe that efforts to bring closer (M,R) system theory, other relational biology

theories and the concepts and methods of “wet biology” should bring great benefits to all parts.

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