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Published in:
Biological Systems from a Network Perspective

Publication date:
2019

[Link to publication](#)

Citation for pulished version (HARVARD):
Laurent, N 2019, Biological Networks from the Relational Biology Perspective. in T Carletti, R Cazalis & R Cottam (eds), *Biological Systems from a Network Perspective*. Presses universitaires de Namur, Namur.

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Published in

Biological Systems from a Network Perspective, edited by Timoteo Carletti, Roland Cazalis and Ron Cottam, 2019, Namur, Presses Universitaires de Namur

ISBN: 978-2-39029-097-1

<https://www.pun.be/FR/livre/?GCOI=99993100953220>

Biological networks from the relational biology perspective.

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Abstract:

We will here defend the idea that the present situation of biology calls for a paradigm change. Several facts, particularly concerning the structure-function relationships, invite us to recognize the limits of experimental biology and its reductionist approach.

After these clarifications about the limits of the modern and structural approach in biology, owing to the dominant Newtonian paradigm, we will follow the main thesis of the mathematician and biologist Robert Rosen (1934-1998). We will thus turn towards relational biology, a theoretical approach which considers living systems as naturally formed by a network of functional components and interacting themselves to form networks.

Relational biology, as this author conceives it, supposes we become familiar with the notions of open systems, complexity, modelling relation and (M, R)-systems. We will introduce these notions and focus our attention on the Metabolism-Repair systems which formalize Rosen's answer to the question "what is life?".

1. Introduction.

As an introduction, we would like to briefly describe the present situation of biology. After little more than two centuries of existence, the science of the living appears to sit in an uncomfortable position. The need of a paradigm shift arises everywhere, and alternative approaches are proposed to drive biology in an opposite direction. But how can one be certain that this new way will be the right one?

During the second half of the 20th century, biologists hoped that genetics alone would be sufficient to explain life. Only few scientists anticipated the failure of genetic determinism caused by the announcement of the results of the Human Genome Project in February 2001. For them, this event sounded the end of the major paradigm guiding molecular biology, i.e. the biological theory that "complex" characteristics of human beings may be reduced to genetic information.

Rather than looking for an alternative program, some biologists started to envision the living as hosting nonlinear dynamics. For example, a cell can be envisioned like "regulatory networks of

proteins that sense or measure changes in the cellular environment and interpret those signals so that the cell can make an appropriate response” (Strohman, 2001). This new approach emphasizes the dynamical interaction between the living system and its environment, and the part of dynamics having to do with control of gene expression is called “epigenetic” regulation. In the same article, Richard Strohman underlines an important characteristic of these biological networks, i.e. some kind of self-organization: “The key concept here is that these dynamic-epigenetic networks have a life of their own – they follow network rules not specified by DNA.” (Strohman, 2001).

Obviously, biology experiences a radical change of paradigm since the beginning of this 21st century. Reductionism, which was until there the philosophical basis of biochemistry and molecular biology, is now leaving its place to *Systems Biology*, which focuses on the study of integrated systems at all levels: molecular, cellular, organ, organism, and population. The aim followed by such a holistic approach is to explain biological functions by means of the interactions occurring between system’s components (what is sometimes called “emergence”).

This new theoretical framework is generally justified as follow: “Nothing in biology acts alone: everything acts in conjunction, opposition, and synergy with other elements. Genes regulate each other's activity, gene products join forces or inhibit each other, cells communicate, metabolites move from tissue to tissue, and everything is interconnected. Systems biology aims to understand this complexity.” (Potters, 2010).

Among the self-organizing networks that are now studying following this approach by biologists, the brain particularly attracts attention. Each of us can directly observe and experiment what its billions of interconnected nerve cells can do thanks to its emerging properties such as openness, creativity, intentionality and limited predictability. Only systems with nonlinear and self-organizing dynamics are now envisaged to explain these properties. And of course, as Wolf Singer wisely pointed out a few years ago “we are still far from understanding the principles by which distributed processes in the brain assemble into coherent states that then act as the substrates of perception, concepts, decisions and actions” (Singer, 2007).

At this point, we only informed ourselves about the current situation of biology, marked by a renewed interest for integrated living systems. Obviously, attention is now focused on self-organizing networks, and more specifically on their particular dynamics involving continual interactions with the environment. In the next section, we would try to better understand which degree of change this new paradigm has reached.

2. Structure-function relationships.

We will start from biology as it appears in its simplest form (in a way, its essence). At first glance, the study of the living consists in the establishment of relations between structures (for example body parts, organs, cell types, proteins, etc.), and their functions (the role they play in the overall organization). Biologists isolate and describe such structures so that they can determine their function(s). Or, based on observed functions, they attempt to identify the responsible structure(s). The central role played by structure-function relationship in biology is easy to understand. Indeed, when biologists observe living systems exhibiting autonomous behaviors, they constantly ask the question: "What will be the effect on this behavior if I eliminate, or modify, or change position, one of its parts?". Any variation between the original

behavior and the behavior following active intervention of the biologist defines the function of the altered part (structure). In doing so, the biologist discovers *a new way of describing this structure* forming part of the living system studied (a description different than that in purely physicochemical terms for example).

As they progressed since the end of 18th century, and mainly during last century, biologists have quickly realized that the organization proper to the living was far from being simply a univocal (one to one) relation between structures and functions. The following statement, posed by John von Neumann about structure-function relationships into the brain, expresses precisely what biologists observe constantly:

“It is never very simple to locate anything in the brain, because the brain has an enormous ability to reorganize. Even when you have localized a function in a particular part of it, if you remove that part, you may discover that the brain has reorganized itself, reassigned its responsibilities, and the function is again being performed.” (von Neumann, 1966, p. 49).

Indeed, localizationist theories of brain functions – so influential during 19th and 20th centuries – have become outdated and useless. As we have seen before, this situation led to a paradigm shift oriented towards utilization of networks principles and especially the consideration of *functional* networks (see for example the approach followed by the neurosurgeon Hugues Duffau in Mandonnet, Duffau, 2014).

What is true for the brain is as true for all structure-function relationships that biologists encounter (and they only meet that). We can thus generalize by distinguishing two main principles governing these relations:

Structure change principle	The same <i>function</i> is exhibited by a variety of different structures	Many-to-one relationship	<i>Degeneracy</i> (Mason et al., 2015) <i>Robustness</i> (Whitacre, 2012) <i>Bow tie architecture</i> (Csete, Doyle, 2004).
Function change principle	The same <i>structure</i> manifests a variety of different functions	One-to-many relationship	<i>Pluripotentiality</i> (Mason et al., 2015) <i>Exaptation</i> (Gould, Vrba, 1982) <i>Pleiotropy</i> (Paaby, Rockman, 2013) <i>Moonlighting</i> (Jeffery, 1999).

Given this, any explanation of a biological function in terms of structural (i.e. physicochemical) descriptions only, will prove to be insufficient. This drastic limitation of reductionist approach – which is at heart of modern science – is generally used to emphasize the “complexity” of the living.

By using the term “complexity”, we do not mean simply that things are complicated. But we are not satisfied either with this other current definition of “complex” which “designates specific

characteristics of a system comprising many individual active elements that interact in special ways” (Singer, 2007).

To better fit with the new paradigm called by biologists, we prefer to follow the approach of complexity proposed by Robert Rosen. This mathematician and biologist reformulated several times its definition of complexity, and we propose then to distinguish three main statements which appear successively in the work of Rosen:

1) Complexity: a property of system descriptions.

“This approach to complexity is novel in several ways. For one thing, it requires that complexity is not an intrinsic property of a system nor of a system description. Rather, it arises from the number of ways in which we are able to interact with the system.” (Rosen, 1985, p. 322).

“Hence, another characteristic feature of complex systems; they appear to possess a multitude of partial dynamical descriptions, which cannot be combined into one single description.” (ibid. p. 424)

2) Complexity: regards the possession of nonsimulable model.

“If, and only if, a system is simple, which means that all of its models are computable or simulable, then this set of all models becomes a reductionist paradise – otherwise, not.” (Rosen, 1999, p. 280).

“A system is simple if all its models are simulable. A system that is not simple, and that accordingly must have a nonsimulable model, is complex” (ibid., p. 292).

3) Complexity: regards the possession of impredicative loops.

“impredicativity, the hallmark of complex systems, and precisely the sort of thing which syntax alone cannot handle” (ibid., p. 271).

“I would rather, then, call a system complex if it has inherent impredicative loops in it.” (ibid., pp. 42-44:

These three formulations have to be considered as complementary facets of what Rosen designates with the term “complexity”. We will say more about some of them in following sections of this article, but before there are still things to be said about structure-function relationships.

As we have seen previously, the discrepancy between two behaviors of a given living system (one related to the native system and the other related to the same system after perturbation) defines the function of what has been perturbed into this system. We now ask this question: what is the nature of this part of the system that has been removed, modified or changed?

Modern biology is divided between two opposite ways of answering this question. The first of them consists in attributing the function to an isolable material (physicochemical) structure. This *structural approach* is based on the idea that living systems can be understood by the analysis of their simpler components, which are supposed to behave in simple, linear, and completely predictable ways. Using the reductive method of structural decomposition, scientists who follow this approach abstract the biology out of the system to investigate the remaining physicochemical problems.

On the other hand, we find a response which follow an opposite approach named “Gestalt”, “system” or “holistic”. The nature of system’s part which is responsible of the behavior change is

relational (and not material): by manipulating a part of the living system, we have perturbed the relation between this part and the whole system. This is the part-whole relation which is the function (and note the structural part alone), i.e. a unit of organization for the considered system. Such a *functional approach* is thus characteristically independent of the specific physicochemical details of the structures composing the living system.

The first approach described above is the one naturally applied by experimental biologists, mainly interested by the properties of individual living systems. Their observations and experiments always imply a total or partial decomposition of the system being studied into structural (material) parts, and this methodology represents what philosophers mean by reductionism. “This is in fact the basis for the reductionistic assertion that biology will be subsumed under physics”, writes Rosen (Rosen, 1989, p. 14).

Functional approach, for its part, is necessarily based on the construction of mathematical models, and thus on a far more theoretical and abstract methodology. Indeed, since pure relational organization comes first in the description of living systems, we need to build formalisms in order to be able to express it. Although infinitely more respectful of what life is in itself, this approach has always been the ugly duckling of modern biology.

Remember now what we said earlier about the goal of system biology, a theory that presents itself as an alternative to reductionism: its aim is to explain biological functions by means of the interactions occurring between system’s components. But if these components are the physicochemical structures that biologists handle after decomposing living systems through their analytic methods, there is no reason to hope for a paradigm shift!

Thus, if we accept the limits of this reductionist approach, it seems obvious that we had to follow the functional – and theoretical – approach. This is the choice made by Robert Rosen who continued the project initiated by Nicolas Rashevsky and named “relational biology”. Before entering this theory, we will explore a little bit more the limitation of reductionist approach.

3. The fall of reductionism.

In this section, we will show more precisely how epistemic limitations of the reductionist approach appear in the current work of biologists.

As all biologists know, The Central Dogma of Genomics (Petsko, 2000) which dominated their science over the last 50 years has been the following: “sequence determines structure which determines function”. But as they also know, one huge question remains unanswered: how can a sequence of amino acids code for one specific 3D functional protein structure? Obviously, this “protein-folding problem” has not yet been solved by computer algorithms developed within a deterministic and reductionist framework. Moreover, it is possible that the solution will never be reached by means of this structural approach.

For almost twenty years, some biologists have shown that many functional proteins lack stable tertiary and/or secondary structure either entirely or at their significant parts. “Such intrinsically disordered proteins (IDPs) and hybrid proteins containing ordered domains and functional IDP regions (IDPRs) are highly abundant in nature, and many of them are associated with various human diseases”, explains Vladimir N. Uversky (Uversky, 2014). This specialist of protein folding gives some great characteristics of disordered proteins:

“As a result, a typical IDP/IDPR contains a multitude of potentially foldable, partially foldable, differently foldable or not foldable structural segments. This distribution of conformers is constantly changing in time, where a given segment of a protein molecule has different structures at different time points. The distribution is also constantly changing in response to changes in the environment. This mosaic structural organization is crucial for their functions and many IDPs are engaged in biological functions that rely on high conformational flexibility and that are not accessible to proteins with unique and fixed structures.”

This surprising discovery reminds us how *open* a living system is. The conception of biological organisms as open systems has been advanced by Ludwig von Bertalanffy since 1932. While physics and physical chemistry have been concerned almost exclusively with processes in closed reaction systems, leading to chemical equilibria, it became more and more obvious that a living entity as a whole could not be understood following the same way of thinking.

With great efforts, von Bertalanffy defended the idea that “the theory of open systems opens a new field in physics” (von Bertalanffy, 1950). For him, “the nature of the open system is at the basis of fundamental life phenomena, and this conception seems to point the direction and pave the way for biology to become an exact science.” (von Bertalanffy, 1950).

Despite it being obvious that living systems maintain themselves in exchange of materials with environment, and that openness is the necessary condition for the continuous working capacity of organisms (continuous building up and breaking down of their components), the science of open systems is still waiting. In its « Autobiographical reminiscences », Robert Rosen (2006) did not hesitate to write:

“I would say that, today, there is still no satisfactory ‘physics’ of open systems, primarily because people persist in thinking of closed systems as fundamental, and of open ones as simply closed ones canonically perturbed.” (p. 9)

The strategy of considering the natural systems as closed is pursued for methodological reasons. Indeed, how could a biologist work if he did not control a maximum of parameters in its experiments? Given the nature of its structural and reductionist approach, it is clear that any experimenter starts by (at least partially) closing the system he wants to examine. If he doesn't do that, it will be impossible for him to reproduce some results. No objective knowledge can be reached about how a system works if he does not choose some parameters to observe, and if he does not fix the influence of the environment on it.

Yet the living reveals through its intimate specificities and its natural functioning that it is, in the strong sense of the term, an open system. What we need to understand life, thus, is a biology that can do without experiences, that is to say a science whose point of departure is not structural but relational.

4. Relational biology.

Let Robert Rosen himself make the transition with the above: “the first step in conducting any structural study of a biological system is to abstract away the organizational properties of the system, leaving behind a purely structural residue to be studied entirely in structural (that is, physicochemical) terms” (Rosen, 1972, p. 219).

To overcome this radical limitation of the mechanistic approach of living systems, Nicolas Rashevsky (1899-1972) proposed in the 1950s a new path for biology. He called “relational

biology” this approach of biological systems in which one seeks to understand the organization of relations in an organism. This means that the properties of these systems are understood in terms of a decomposition into *functional* components, rather than into structural components as is commonly done following the Newtonian paradigm of modern biology. Such approach seems a most natural way of comprehending the types of organization manifested by life.

Robert Rosen, who joined Rashevsky’s group in University of Chicago to perform his PhD work in the late 50s, completely adopted this way of thinking. He developed further relational biology with help of “category theory”, a mathematical theory introduced in the 1940s by Samuel Eilenberg and Saunders MacLane. Luckily, Eilenberg was Rosen’s teacher at Columbia University, and MacLane was part of the University of Chicago. Rosen took this opportunity to continue his training, and rapidly found that category theory is “the natural habitat” for its own theory of cellular system – which was the subject of its doctoral work. This is what he said about it:

“I became intrigued by the historical roots of the theory, which had grown out of the attempt to make algebraic "models" of geometric objects in order to discriminate between them. It expressed in a purely mathematical realm the patterns of relations, between objects and models, and between one model and another, which I was trying to find in the realm of the living.” (Rosen, 2006).

In the realm of life, relations come first: that’s the core idea of relational biology initiated by Nicolas Rashevsky and pursued by Robert Rosen. Since then, this biology cannot adopt the experimental methods. By abstracting away the structure (i.e. the physics and chemistry), this functional approach starts from purely theoretical terms. If we proceed in this way “we can obtain new insights and results of a generality not easily possible with purely structural studies” (Rosen, 1972).

Concretely, Rosen took as point of departure general input-output systems, i.e. black boxes or components “which can accept a certain family of inputs from its environment, and convert these into a corresponding family of outputs which are discharged back into the environment” (Rosen, 1972, p. 220). Then, given a family of such *functional* components, he began to string them together into networks, where some of the output elements produced by black boxes are accepted as input elements by one or more other components. This *block diagram* became an *abstract block diagram* when Rosen translated it into the language of the category theory. This description of input-output behaviors of very general systems uses the terms of set theoretic mappings: “every component of such a system could be represented by a mapping the domain of which was the set of inputs to the component and the range of which was its set of outputs” (Rosen, 1972, p. 236).

To better evaluate the implications of this purely functional approach of the living, we will now compare it again with the structural approach. This time we are going to use the modelling relation proposed par Robert Rosen, which is a very instructive commutative diagram.

5. Structural and functional biology formalized.

Modelling relation is a relation between a class of phenomena, i.e. a natural system characterized by causal relations (or “causal entailment”), and a formalism describing this class of phenomena, i.e. a formal system characterized by inferential relations (or “inferential entailment”). Figure 1 illustrates this relation which is central in any scientific enterprise.

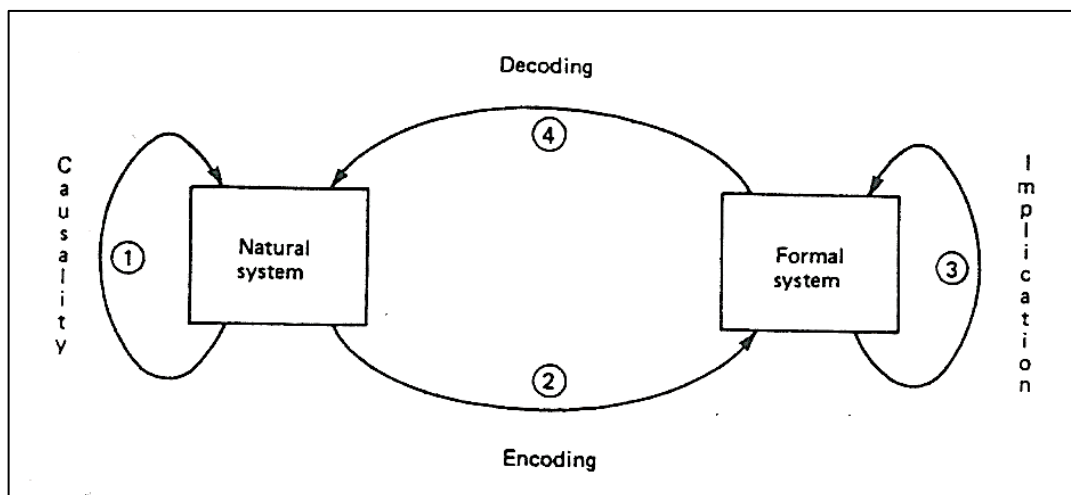


Figure 1: Commutative diagram expressing a modelling relation between a natural system and a formalism describing this system (Rosen, 1989).

In his book *Anticipatory Systems*, and on many occasions afterwards, Rosen has asserted that “Natural Law consists essentially of belief that the two great realms of entailment or necessity can be brought into some kind of congruence” (Rosen, 1989, p. 16). If you look at the figure 1, such a congruence translates into the following commutativity:

arrow 1 (“causal entailment”) = arrows 2 (“encoding”) + 3 (inferential entailment) + 4 (“decoding”)

In other terms, “we get the same answer whether we simply watch the sequence of events unfolding in the external world, or whether we encode into our formalism, employ its inferential structure to prove theorems, and decode these theorems to make predictions about events in the external world” (Rosen, 1989). And Rosen continues his reasoning as follows: “If commutativity holds, we can then say that our formalism is a *model* of the phenomena occurring in the external world, or equivalently that the events themselves constitute a *realization* of the formalism.” (Rosen, 1989, pp. 16-17).

Rosen devoted a great deal of thought to the examination of this belief in a possible harmony between causal and inferential entailments (a harmony that would be supposed to reflect what happens in the external world). In short, Rosen is convinced that this congruence is rather weak in physics. He more precisely asserts that the Newtonian paradigm, which dominates the landscape of all modern science, cannot suffice to account for the relational richness of life.

What interests Rosen, and what we would like to emphasize here, is “the escape from entailment” (Rosen, 1989, p. 17) which characterizes the modelling relation. Let’s start by identifying all that is not determined by relations belonging to the commutative diagram (i.e. to the modelling relation between a natural system and a formal system).

Firstly, the arrows 2 and 4, which are labelled “encoding” and “decoding”, are themselves not entailed by anything present in either the formalism (the model) or the external realization of that formalism. The relation between the two systems (natural and formal) thus inherently involves something outside. Rosen says that it involves art and he refers to “a *creative act*, resulting in a

new kind of formal object, namely, the modeling relation itself” (Rosen, 1991, p. 54). He also asserts that the category theory is the formalism suitable to formalize this creative act: “Category Theory comprises in fact the general theory of formal modeling, the comparison of different modes of inferential or entailment structures” (Rosen, 1991, p. 54).

Secondly, the arrow 1 has been dominated by the Newtonian paradigm for which a system is something radically separated from everything else, i.e. from environment. According to this image of the world, “what is system (...) is described by phases or states; environment is not, and cannot, be represented in such terms” (Rosen, 1991, p. 19). So, “the realm of causality becomes bound irrevocably to what happens in system alone; and what happens in system alone is the state-transition sequence” (Rosen, 1991, p. 19). Environment becomes *acausal*: nothing, within it, is entailed in the conventional sense (what happens in it is entirely unpredictable), “because there is nothing in its description which even allows a concept of entailment in the first place” (ibid.). So, as Rosen explains, Newtonian mechanics is limited to the study of closed, conservative, and even dissipative systems.

Thirdly, the arrow 3 represents syntactic entailments inherent in the formal system which are also limited as was shown by Gödel:

“In a precise sense, Gödel’s Theorem asserts that a formalization, in which all entailment is syntactic entailment, is too impoverished in entailment to be congruent to Number Theory, no matter how we try to establish such a congruence. (...) It would thus require, at best, an infinite number of distinct formalizations to capture all the qualities, and hence, all the entailments of Number Theory, in terms of syntax alone.” (Rosen, 1991, pp. 8-9).

For all these reasons we are invited to consider a new form of science, namely a science of open systems, and thus a science of complexity (with the three facets we have seen about it).

I will now explore the formalism Rosen has developed and which can be envisioned as the first step into the field of this new science (or the first result of it). Of course, such a formalism takes us out of the realm of Newtonian paradigm (the world of simplicity characterized by very limited causal relationships).

6. Life’s minimal architecture: the abstract network of (M, R)-system.

In the second volume of the *Foundations of Mathematical Biology*, Rosen clearly states the basic idea which allowed him to develop such a relational model (Rosen, 1972).

Examining the internal activity of a cell (considered as the minimal unit of life), he was struck by three major characteristics of this living natural system:

- 1) *Although all components of a cell have a limited life time, the system is able to survive for much longer.* Rosen wondered how this could be possible.
- 2) He then observed that the cell can be subdivided into two main regions and that the components of the first of them (the cytoplasm) are replaced early enough before they degrade thanks to what happens in the second region (the nucleus). Following what biologists have discovered before him, he interpreted this compartmentation as follows: “the cytoplasmic part of the cell is mainly concerned with what we customarily call the metabolic activity of the cell, while one of the basic nuclear functions is concerned with repair” (Rosen, 1972, p. 229). *So, cells are continually repairing themselves.*

- 3) The repairing activity located in the nucleus is thus associated with the function of genome (DNA) from which the continual synthesis of basic units of metabolic processing (enzymes) occurs. The third characteristic highlighted by Rosen is that *this repair utilize as inputs materials provided by the metabolic activity itself*.

We will not follow here all the formal developments given by Rosen in this text, but only highlight some important points. At the same time, we would like to show how the mathematic construction of Metabolism, Repair systems (called “(M, R)-systems”) is concerned by the modelling relation we have seen before.

In all cases we can start from the prototypic syntactic inferential process which finds its mathematical form in the evaluation of a mapping:

$$a \Rightarrow b = f(a)$$

Where a can represent a natural system, b a formal system and $f(a)$ the encoding relation between them (measurement). Or you can consider a as the formal system, b as the natural system and $f(a)$ as the decoding relation between them (realization). But it is also possible to consider this mapping as representing a causal relation inside the natural system, or an inferential relation inside the formal system. Rosen finds more exact to write this implication into the following form:

$$f \Rightarrow (a \Rightarrow b = f(a))$$

which means that the inferential rule f entails that a entails $b = f(a)$. He prefers this expression more suitable for situations where there is more than one inferential rule available (Rosen, 1989).

It is important to notice that the implication symbol “ \Rightarrow ” takes two different senses:

- In “ $a \Rightarrow b$ ”, “ \Rightarrow ” relates the material cause a to the effect b .
- In “ $f \Rightarrow (a \Rightarrow b = f(a))$ ”, “ \Rightarrow ” relates the efficient cause f to its effect b .

In a (M, R)-system, this mapping first appears to be equivalent to the metabolism of the cell (M): a represents reagents coming from the environment, b is the product of reactions catalyzed by f .

If we want to know what entails the operator f , we need to enlarge our system with additional inferential rules. From here, we can consider two ways of developing our reasoning. One possibility is to reduce it, what means disassemble it into parts. The parts then become the substrate of a new operator (Rosen calls it ϕ) which serves to entail f . Experimental biologists think they can do that without loss of information. They use another level of more elementary structures which interact together and give rise to new *emergent* functions. In this reductionist approach, these are the structures that determine the functions. We stay then in the Newtonian paradigm for which causes (only material and efficient ones) always come from outside the present level of organization (from the environment or other more basic levels of material organization).

An alternative way of finding additional inferential rules is proposed by Rosen in the frame of relational biology. This approach consists in exploiting all causal relations already present in the network of the actual living system. In fact, Rosen simply uses the characteristics he had observed by regarding a metabolizing cell (see above) and finds that another causal category is needed to understand such a living organization, i.e. final causation or *telos*. The formalism of (M, R)-systems

is the expression of this enlarged picture of causation which, at the same time, introduces us to a new paradigm: a formal system with the inferential structure we have seen above, which contains *within itself* a means of entailing the operator f . Our initial implication then becomes:

$$a \Rightarrow b = f(a) \Rightarrow f = \phi(b)$$

Or, in the language of category theory:

$$A \xrightarrow{f} B \xrightarrow{\Phi} H(A, B)$$

Where “ $H(A, B)$ ” represents all mappings between A and B (included f).

It should be noted that what had exclusively the status of effect in the initial mapping (i.e. b or $f(a)$) becomes now material cause on which acts the new operator ϕ . The system is repairing itself and this repair function (R) utilizes as inputs materials provided by its metabolic activity (M).

We recognize here the chicken-and-egg paradox which characterizes the problem of the origin of life (but which is also present everywhere in our descriptions of phenomena of life). In fact, the model contains now enough entailments to do biology, which implies the introduction of *circularity* into the formalism (f causes b which causes f). During the period following the publication of *Life Itself*, Rosen insisted on the importance of *impredicativity* to consider seriously the foundation of a new science of complex systems, and among them of life. The causal circularity that we have just introduced into the formalism is the hallmark of this impredicativity, and thus of complexity (see above more details about this Rosennean definition of complexity).

As Rosen also discovered, this relational system is even rich enough to entail the operator ϕ : the system becomes then an (M, R)-system with *replication*, which means that the genetic part of the system (the operator ϕ or repairing function) is entailed from the system itself (Rosen, 1959, 1972).

In a very interesting article published in 1973 (Rosen, 1973), Rosen introduced a new manner of representing the class of these abstract cell models, i.e. a new approach to the dynamical realization of the (M, R)-systems. This general method allows “a variety of purely mathematical realizations of any particular (M, R)-system” and each of these realizations “can then be studied further with regard to its physical realizability”.

It is important to remember that we are dealing here with the *realization problem* which refers to the arrow labelled 4 in the modelling relation diagram we have commented above. In a nutshell, we ask how to realize a singular natural system from its purely formal model. We thus follow the inverse pathway comparing to the empirical scientific procedure which starts from encoding (measurements) and for which such a realization only means making predictions.

Rosen (1973) affirms that the construction of a natural system, for which the replication map is also realizable, “amounts to the creation of an autonomous life form”. Moreover, the dynamical representation of (M, R)-systems allows him to conclude that “the same genotype can give rise to a variety of different phenotypes as a function of the environmental circumstances”. In fact, this approach allows to introduce an evolutionary significant variability into the theory. Indeed, he explains at the end of this article that “perturbations arising from interactions with other systems in the environment will possibly generate totally new dynamical behaviors”.

7. Conclusions

Previous developments have allowed us to point some important limits of the paradigm which dominates contemporary biology. By following the alternative way introduced by Rashevsky and Rosen, named relational biology, we escaped this narrow picture unable to account for the essential properties of life.

The main idea behind relational biology is that we need a physics that fits much better with the causal richness of life. The spirit of this new biology only keeps “an abstract pattern of functional organization, which has properties of its own, independent of any particular way it might be materially *realized*” (Rosen, 2006). As we have seen, Rosen looks for a science of open systems, i.e. a science able to deal with complexity.

At the *epistemological* level, experimental biology taught us that a living system can always be observed in different ways (first facet of complexity). Indeed, choices made during the phase of measurement (encoding) are not absolute. This is a first important conclusion brought by Rosen:

“As Einstein kept insisting, science involves a free creative act of their intellect; ultimately, it involves wisdom. It involves the ability to select what is important about a problem from what is irrelevant or incidental, and to follow that. There is no algorithm for this, just as there is no algorithm for making a model.” (Rosen, 1991, p.280)

Thus, the models of living systems developed by experimental methods correspond only partially to the real organization of life.

At the *phenomenological* level, we have seen that principles of function change and of structure change govern the observable (measurable) organization of living systems. Thus, there will always exist at least one non simulable (non computable) model of these systems (second facet of complexity).

At the *ontological* level, the impredicativity inherent in the universal formalism of (M, R)-systems (third facet of complexity), in its dynamical version, points to the necessary singularity of the realizations that can be recognized at their base. The functional organization these formal systems describes is what remains invariant in the class of all material realizations we consider as being living. But these singular material realizations in themselves *are* unpredictable.

At the end of our journey, we find that such a theoretical approach of life is particularly in agreement with a network perspective about biological systems. More precisely, the class of (M, R)-systems described by Robert Rosen gives us a formal picture of an autonomous life form composed of a relational network between functional components. Necessarily, the realization of such a universal formalism of life gives rise to a diversity of interacting natural systems.

If novelty (singularity) is an essential characteristic of living systems we can observe, we understand why their complete knowledge is inaccessible for an experimental and reductionist approach as is the modern structural biology. As Rosen (1989) noticed, “to show that a given material system realizes an (M, R)-system is a matter of verification, not fabrication.” In other words, we cannot reproduce or simulate living systems from which we have abstracted formal models.

8. Bibliography

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