

Metabolic closure in (M,R) systems

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Abstract

The work of Robert Rosen, related to metabolic networks called (M,R) systems is reviewed and clarified. We study the algebraic formulation of (M,R) systems particularly the mapping β , which encapsulates Rosen's solution to the problem of metabolic closure and infinite regress. We construct an arithmetical example of an (M,R) system and also an (M,R) system based on a three-step minimal metabolism.

Introduction

The theories of Robert Rosen pose a scientific enigma. The core of his theory, called here *Rosen's Central Result*, is that metabolism *bootstraps* itself without the help of external agents thus keeping cellular organization invariant in spite of continuous structural change (Rosen, 1958a; Rosen, 1959; Rosen, 1972; Rosen, 1991). In theory, Rosen's insights and results should have had a profound impact in theoretical biology, especially in the field of Artificial Life as he claimed that his theory was directly relevant to the problem of *fabrication* of living systems (Rosen, 1991). But, in spite of recent attempts to use Rosen's ideas in areas like bioinformatics (Wolkenhauer, 2002) and control theory (Casti, 2002), the impact and dissemination of Rosen's ideas have been extremely small. The lack of impact is partly due to the highly abstract nature of the central result and to the surprising fact that Rosen never gave biological or mathematical examples of his ideas. Because of this, and because it is such a special result regarding its biological as well mathematical aspects, we have found it necessary to revisit and clarify it as well as to connect it to other theoretical ideas concerning metabolic closure.

Overview of (M,R) Systems

Rosen's theory centers around a model of metabolic networks he called (M,R) systems. As the study of these systems is an essential first step to understand Rosen's result, here we give an outline of them. Initially an (M,R) system looks like a simple graph-theoretic view of metabolism, but this interpretation is misleading as (M,R) systems are endowed with a richer mathematical structure.

The M Components

In an (M,R) system every biochemical reaction is interpreted as a mapping. Thus the first reaction of glycolysis, catalyzed by the enzyme glucokinase:



can be formalized as an operator M that transforms molecules a_1 and a_2 into b_1 and b_2 :

$$a_1 + a_2 \xrightarrow{M} b_1 + b_2 \quad (1)$$

The catalyst M , acts as a mathematical mapping, transforming variables (a_1, a_2) into variables (b_1, b_2) . As enzymes are not totally specific for the types of molecules that they transform, Rosen interpreted M as a mapping between two sets defined by Cartesian products, where sets A_i, B_i represent the admissible molecules that the enzyme can process.

$$\begin{aligned} M : A_1 \times A_2 &\longrightarrow B_1 \times B_2 \\ (a_1, a_2) &\mapsto M((a_1, a_2)) = (b_1, b_2) \end{aligned} \quad (2)$$

Although Rosen did not mention it, this over-reaching formalization is extreme. An enzyme can be presented *in vitro* with artificially produced molecules that are accepted and processed as substrates because of their structural resemblance to the natural substrate, and it then appears that the set A_1 is "large". However, it is radically different *in vivo* because in the organism only one (or a few) acceptable substrates exist. For example, in some bacteria the enzyme glucokinase mentioned above will not accept any natural sugar substrate other than glucose.

This mathematical framework can be extended to take account of the network of thousands of biochemical reactions that constitute a living metabolism. We can interpret the overall metabolism M_{met} as the following transformation:

$$\begin{aligned} M_{met} : A = (A_1 \times \dots \times A_p) &\longrightarrow B = (B_1 \times \dots \times B_q) \\ \mathbf{a} = (a_1, \dots, a_p) &\mapsto \mathbf{b} = (b_1, \dots, b_q) \end{aligned} \quad (3)$$

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In a very compact notation, the complete metabolism is the (huge) mapping f between the (huge) sets A and B .

$$\begin{aligned} f : A &\longrightarrow B \\ \mathbf{a} &\longmapsto f(\mathbf{a}) = \mathbf{b} \end{aligned} \quad (4)$$

As many metabolisms are theoretically possible between sets A and B , conceptually we define \mathcal{M} as the set of all possible metabolisms between A and B . Does \mathcal{M} have some sort of structure? After all, a metabolic network is much more than just a random collection of transformations between molecules. This is a crucial point that was never clarified by Rosen, who presented his arguments by assuming

$$f \in \mathcal{M} = \text{Map}(A, B) = \text{set of all mappings between sets } A \text{ and } B$$

We will see that this identification is too general, and that \mathcal{M} must be a proper subset of $\text{Map}(A, B)$, consisting only of some selected, admissible mappings from A to B . Intuitively we might think of \mathcal{M} as consisting of all mappings from A to B that preserve some sort of underlying, implicit, structure common to sets A and B as these two sets must be much alike (A represents the left-hand side of biochemical reactions and B the right-hand side). We develop this viewpoint in our arithmetical example in a section below.

The R Subsystems

Rosen's crucial insight concerns the long-term stability of a metabolic network. Because components M_i represent physical objects (enzymes) they must inevitably become degraded by a wide variety of processes. If the cell is to continue operating in a steady state, every M_i must be replaced as fast as it is degraded. Rosen posited that for every M_i there must exist a subsystem R_i , made of a subnetwork of biochemical reactions, that uses metabolites, from B , to replace M_i or, in Rosen's terminology, to "repair" it (the word *repair* was a confusing choice, and in this paper we use the term *replacement*).

This insight is essential for understanding the biological relevance of Rosen's work. In contrast to a man-made machine, a living organism is a self-made machine, and all of its components must be made and, when necessary, replaced within the system by components that are themselves products of the system, are themselves degraded, and must also be replaced, again by components within the system, which are likewise degraded, and need to be replaced, and so on indefinitely. In such a system the possibility of infinite regress is obvious, and Rosen's work can be interpreted as a search for a way to escape this, or in other words a search for *closure*.

The central result is an attempt to express how a system must be organized if it is to continue in operation indefinitely. The crux of the matter is thus to understand how the

R_i are replaced and how to avoid an infinite regress. But, as we have seen, the same wear-and-tear argument that was applied to M_i applies equally well to the R_i . It is possible, of course, but not elegant or useful, to invoke a second-level repairer to replace each R_i . But this "solution" just raises the new question of how to replace the second-level repairers, and is thus no solution at all. The central result is an intuition about the systemic nature (i.e. a property that depends on the connectivity of the network) of this maintenance or "replication" function¹. Thus, in some (M, R) systems, the total network regenerates each R_i : these systems are the (M, R) systems with *organizational invariance*, and they constitute Rosen's model of living systems. Remarkably, the central result is a mathematical enunciation of this metabolic closure.

Algebraic Representation of (M, R) Systems

As we saw metabolism can be interpreted as a mapping f that transforms an instance $a \in A$ into an instance $b \in B$. But how can the collective action of subsystems R_i be represented as a mapping? The replacement mechanism is a procedure, denoted by Φ , that, starting with $b \in B$ as input, produces f according to:

$$\Phi(b) = f, \text{ with the condition } b = f(a) \text{ (for some } a \in A)$$

Because the net effect of Φ is to select from the relatively large set $\mathcal{M} \subset \text{Map}(A, B)$ the given metabolism f , we call Φ a *selector*. Thus as f represents *metabolism*, Φ represents *replacement*. As with f , Φ can also be represented by a mapping between the sets of metabolic configurations (B) and the set of possible metabolisms (\mathcal{M}). Again Rosen assumed the most general structure for the set of selectors \mathcal{S} .

$$\Phi \in \mathcal{S} = \text{Map}(B, \mathcal{M}) = \text{Map}(B, \text{Map}(A, B))$$

It is, however, trivial to find not only one but many mappings from one set to another that take a given value (f in this case) at a given point (b in this case), so that it is an essential feature of a sensible mathematical model of metabolism to ask for the set \mathcal{S} of selectors to be a *proper* subset of $\text{Map}(B, \mathcal{M})$.

Then a (M, R) system has the following algebraic structure based on mappings $f \in \mathcal{M}, \Phi \in \mathcal{S}$, acting in synergy

$$\begin{aligned} A &\xrightarrow{f} B \xrightarrow{\Phi} \mathcal{M} \subset \text{Map}(A, B) \\ a &\longmapsto f(a) = b \longmapsto \Phi(b) = f \end{aligned}$$

¹Replication was another unfortunate choice of terms, evoking ideas of reproduction whereas the essential notion is *organizational invariance* (i.e. the network maintains its connectivity) under continuous structural change.

Now, in the full language of maps, we can rephrase the closure result sought by Rosen. How can the selector map Φ be produced by the network when the system is capable of organizational invariance, without implying infinite regress?

Rosen’s Central Result in a Nutshell

Rosen’s solution to avoid infinite regress, encapsulated in his central result, was to posit that, for a suitable b , for any metabolism $f \in \mathcal{M}$ there should exist *one and only one* selector $\Phi \in \mathcal{S}$ such that $\Phi(b) = f$. He called β the assignment $f \mapsto \Phi$. Thus, on purely formal grounds, Rosen’s β is a mapping from \mathcal{M} to \mathcal{S} which is none other than the inverse mapping to the the mapping for evaluation at b , map $ev_b : \Phi \mapsto \Phi(b)$ from \mathcal{S} to \mathcal{M} . Admittedly, the invertibility of an evaluation map ev_b is unusual, but Rosen, besides making this demanding hypothesis, never produced a clear-cut mathematical description or an algorithm to construct such an invertible evaluation and its inverse β . He only showed that it was logically possible (Rosen, 1959; Rosen, 1972; Rosen, 1991), and sometimes he admitted that the existence of β was mathematically difficult (Rosen, 2000, pages 261-265). The beauty of the concept of β is that Rosen introduced it as the inverse of the evaluation mapping ev_b , so that in some sense β simplifies to some b . This prompted Rosen to say that β was equivalent to an element $b \in B$, thus closing the loop and avoiding infinite regress.

The operation of an organizational invariant (M,R) system can therefore be viewed as (just) three mappings (f, Φ, β) acting in synergy

$$\begin{aligned}
 A &\xrightarrow{f} B \xrightarrow{\Phi} \mathcal{M} \xrightarrow{\beta} \mathcal{S} & (5) \\
 f(a) &= b \\
 \Phi(b) &= f \\
 \beta(f) &= \Phi, \text{ with } \beta = (ev_b)^{-1}
 \end{aligned}$$

In this brief presentation, as in all Rosen’s writings, the precise description of conditions that would entail the invertibility of the evaluation at b , and so the existence of β , are left open.

Also, Rosen’s claim that the existence of β enables us to avoid infinite regress deserves further discussion. Indeed, we might legitimately ask whether a mapping $\gamma : \mathcal{S} \rightarrow H(\mathcal{M}, \mathcal{S})$ is not needed, which would reconstruct β as a product of the metabolism as well, i.e. $\gamma(\Phi) = \beta$. Following Rosen’s insight, we could assume that since β is equivalent to b , then γ should be equivalent to something that produces b , namely f , since $f(a) = b$. In more precise terms then, a natural idea is to take γ to be the inverse of the evaluation at f , if possible. This requires that β must be the only mapping in $H(\mathcal{M}, \mathcal{S})$ which transforms f into Φ , in other words, the equation $\beta(f) = \Phi$, in β , has exactly one solution, namely $\beta = ev_b^{-1}$. However, natural as it may be, this property is, in general, not entailed by the assumption that ev_b is invertible, and needs to be stated as a supplementary assumption.

As β encapsulates the notion of metabolic closure we intend to clarify its nature in the next section.

(M,R) Systems with Organizational Invariance and the Notion of β

Consider the relations defining an organizationally invariant (M,R) system

$$A \xrightarrow{f} B \xrightarrow{\Phi} [\mathcal{M} = \text{Map}(A, B)] \xrightarrow{\beta} [\mathcal{S} = \text{Map}(B, \mathcal{M})]$$

Recall that β stands for the inverse of the evaluation map at b , denoted $ev_b : \Psi \mapsto \Psi(b)$, for any mapping $\Psi \in \mathcal{S}$. Now we can express the central result mathematically:

For β to exist, the functional equation in Φ , $\Phi(b) = f$ must have *one and only one* solution, where f and $b = f(a)$ are given.

We see then that the mapping $\Phi \in \mathcal{S}$ must have the quality of being completely determined by its value at a single element b . This is admittedly a rather unusual property for everyday mappings from one set to another, even for continuous mappings. Intuitively this property means that Φ somehow has a rigid behaviour.

To give an example of *rigidity*, think of a mapping Φ on the set \mathbb{Z} of the integers into itself, which has the property of being *additive*, i.e. $\Phi(m+n) = \Phi(m) + \Phi(n)$. Then, if you know its value $\Phi(1)$ at 1, you can deduce its value at any positive integer n . Indeed, since $n = 1 + 1 + \dots + 1$, n times, we must have $\Phi(n) = \Phi(1 + \dots + 1) = \Phi(1) + \dots + \Phi(1) = n\Phi(1)$. Moreover, since $\Phi(0) = \Phi(0+0) = \Phi(0) + \Phi(0)$, we see that $\Phi(0)$ must necessarily be 0. Then, since $0 = \Phi(0) = \Phi(1 + (-1)) = \Phi(1) + \Phi(-1)$, we realize that $\Phi(-1)$ is forced to coincide with $-\Phi(1)$. It follows that for any negative integer $-n = (-1) + \dots + (-1)$, n times, we must have $\Phi(-n) = \Phi((-1) + \dots + (-1)) = \Phi(-1) + \dots + \Phi(-1) = -n\Phi(1)$.

So the global behaviour of the additive mapping Φ is completely determined by its value $\Phi(1)$ at 1. We will develop this into an arithmetical example of a metabolism in the style of Rosen.

\mathcal{M} Must be a Proper Subset of $\text{Map}(A, B)$: $\mathcal{M} = H(A, B) \subseteq \text{Map}(A, B)$

For the central result to hold, the mappings involved must be restricted *a priori* to a special type, i.e. f must belong to a strict subset of $\text{Map}(A, B)$, called here $H(A, B)$, and Φ must belong to strict subset of $\text{Map}(B, \text{Map}(A, B))$, called here $H(B, H(A, B))$. Note than in this notation $\mathcal{M} = H(A, B)$ and $\mathcal{S} = H(B, H(A, B))$.

Rosen’s initial formulation: $H(A, B) = \text{Map}(A, B)$ and $H(B, H(A, B)) = \text{Map}(B, H(A, B))$, is definitely too general since there will be then many choices of Φ such that $\Phi(b) = f$. Of course, if the set $H(B, H(A, B))$ were too small, there

might be no Φ such that $\Phi(b) = f$. Thus in order to work, Rosen's scheme requires a subtle balance in the size of the sets $H(A, B)$, $H(B, H(A, B))$, to achieve both existence and unicity for Φ . Intuitively, the set $H(A, B)$, for instance, must be strictly smaller than $Map(A, B)$ because it should consist only of those admissible mappings from A to B that preserve some sort of underlying or implicit structure on A and B . Thus an organizational invariant (M, R) system, should be represented as:

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

and can be interpreted as two coupled (M, R) systems acting in conjunction:

$$\begin{aligned} (M, R)_{\text{internal}} &: A \xrightarrow{f} B \xrightarrow{\Phi} \mathcal{M} \\ (M, R)_{\text{external}} &: B \xrightarrow{\Phi} \mathcal{M} \xrightarrow{\beta} \mathcal{S} \end{aligned}$$

The following properties must be emphasized:

- In these two coupled (M, R) systems Φ is the replacement function for one and the metabolic function for the second.
- Φ must be reconstructible from its value at a single point.
- Rosen's formulation, which appears to indicate $\mathcal{M} = Map(A, B)$ and $\mathcal{S} = Map(B, Map(A, B))$, is incorrect because \mathcal{M} and \mathcal{S} are too big.

Examples of (M, R) Systems

One problem in Rosen's work is the lack of examples of the theoretical notions (like Φ and β). To partially overcome this difficulty we introduce two examples of (M, R) systems. One is an arithmetical construction and the other uses a minimal and ideal metabolic network.

An Arithmetical Example of an (M, R) System

Let $A = B = \mathbb{Z}_{12}$, the integers $(mod 12)$. So our metabolic states (a and b) are parameterized by the integers $(mod 12)$. Since integers $(mod 12)$ can be added, for example $9 + 7 = 16 = 4(mod 12)$ our set of metabolic states is endowed with an additive structure. We posit that the mappings f representing metabolisms are to be additive mappings from A to B , i.e. from \mathbb{Z}_{12} to itself. These mappings are necessarily of the form

$$f_c : n \mapsto f_c(n) = c \cdot n \pmod{12}$$

For example, the metabolism f_7 transforms the metabolic state $a = 5$ into the state $b = 11$, as $f_7(5) = 7 \cdot 5 = 11(mod 12)$.

So, in terms of our previous notations, $\mathcal{M} = H(A, A) = \{f_c | c \in A\}$.

Notice that $\mathcal{M} = H(A, A)$ may be identified with A , via the one-to-one correspondence $f_c \longleftrightarrow c$. Under this identification the operation of addition of mappings in $H(A, A)$ corresponds to addition of numbers $(mod 12)$ in A , i.e. $f_c + f_d = f_{c+d}$. Thus the first part of this (M, R) system is represented by:

$$A \xrightarrow{f_c} A \longrightarrow [\mathcal{M} = H(A, A)]$$

We need to specify the set $\mathcal{S} = H(A, \mathcal{M})$ of the selectors $\Phi : A \longrightarrow H(A, A) = \mathcal{M}$. As we have essentially the same additive structure on A and \mathcal{M} , as explained above, the mappings Φ in \mathcal{S} must preserve this common additive structure on A and \mathcal{M} , i. e. to satisfy

$$\Phi(c + d) = \Phi(c) + \Phi(d)$$

for all $c, d \in A$. It follows that any mapping Φ in \mathcal{S} will be completely determined by its value at 1, which must be an $f \in \mathcal{M}$. But we already know that any such f must be of the form f_k , for some $k \in A$. If we write for convenience $\Phi = \Phi_k$, we then have

$$\begin{aligned} \Phi_k(1) &= f_k \\ \Phi_k(b) &= b\Phi_k(1) = bf_k = f_{bk} \end{aligned}$$

We consider three examples to illustrate the various possibilities for Φ .

Example 1. Let us choose $a = 4$, $f = f_5$. Then $b = f(a) = f_5(4) = 5 \cdot 4 = 20 = 8(mod 12)$. Let us look for $\Phi = \Phi_k$ such that $\Phi_k(b) = f$, i.e. $\Phi_k(8) = f_5$. Since $\Phi_k(b) = f_{bk}$, this simplifies to $f_{8k} = f_5$, i.e. to the equation $8k = 5$, which has no solution in A .

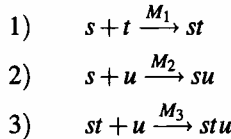
Example 2. Let us choose $a = 5$, $f = f_3$. Then $b = f(a) = f_3(5) = 3 \cdot 5 = 15 = 3(mod 12)$. Let us look for $\Phi = \Phi_k$ such that $\Phi_k(b) = f$, i.e. $\Phi_k(3) = f_3$. Since $\Phi_k(b) = f_{bk}$, this simplifies to $f_{3k} = f_3$, i.e. to the equation $3k = 3$ in A , which has solutions $k = 1, 5$ and $9(mod 12)$. We see that in this case there are three mappings Φ (Φ_1 , Φ_5 and Φ_9) such that $\Phi_k(b) = f$.

Example 3. Let us choose $a = 5$, $f = f_7$. Then $b = f(a) = f_7(5) = 7 \cdot 5 = 35 = 11(mod 12)$. Let us look for $\Phi = \Phi_k$ such that $\Phi_k(b) = f$, i.e. $\Phi_k(11) = f_7$. Since $\Phi_k(b) = f_{bk}$, this simplifies to $f_{11k} = f_7$, i.e. to the equation $11k = 7$ in A , which has the unique solution $k = 5(mod 12)$. Thus in this case, as an organization invariant (M, R) system demands, there is only one Φ (Φ_5) such that $\Phi(b) = f$. We see now that, for $b = 11$, in fact for every $f = f_c$, we can find a unique Φ such that $\Phi_k(11) = f_c$, where k is the only solution of the equation $11k = c$ in A , i. e. $k = 11c$. So we realize

that for this happy choice of b , the core of Rosen's central result, i.e the invertibility of the evaluation at b , is fulfilled. Following Rosen's terminology, we then have $\beta(f_c) = \Phi_{11c}$, for all $f_c \in \mathcal{M}$.

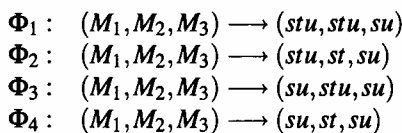
A Metabolic Example of an (M,R) System

An example with a more biological flavor can be constructed from simplified rules representing idealized metabolisms. Consider the following three reactions, without specifying the nature of the catalysts M_1 , M_2 , and M_3 , that represent a minimal metabolism

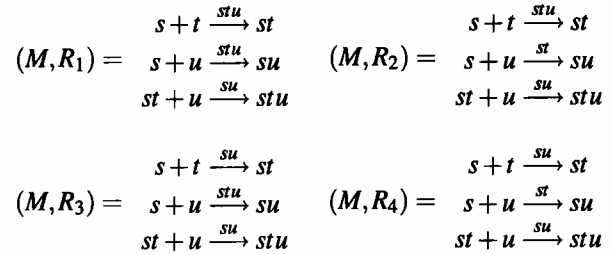


These three equations specify a particular instance of a metabolism M between the sets $A = \{a\} = \{(s, t, u, st)\}$ and $B = \{b\} = \{(st, su, stu)\}$. Here the set \mathcal{M} is simply one transformation f such that $f((s, t, u, st)) = (st, su, stu)$, i.e. $f(a) = b$.

To specify the corresponding R part, the subsystem of metabolic reactions producing each R_i must be specified. In this simplified network this specification is simply to identify one of the outputs $\{st, su, stu\}$ with one of the M_i ; thus we are specifying the production mechanism by which a given R_i is continuously generated. A great number of assignments are possible, in total 3^3 , but this number is decreased substantially by excluding autocatalytic assignments such as $M_1 = st$, or $M_3 = stu$, in which the product of a reaction catalyzes the same reaction that produces it. Although the point is arguable, and others may arrive at a different conclusion, we think that autocatalysis of this kind should be avoided in the theory of (M,R) systems as we are seeking systems in which the circularity is a property of the global connectivity in the entire network and not a property of a single reaction. This restriction requires, for example, the only valid assignment for $st + u \xrightarrow{M_3} stu$ to be $M_3 = su$, as su is neither a substrate nor a product of reaction 3. This kind of argument decreases the initial 27 possibilities to the following four valid assignments for Φ :



Each one of these selectors generates a different (M,R) system, where the M part is similar:



Thus from the 27 choices for Φ that are theoretically compatible with this simple metabolism f we have discarded 23, leaving only four as valid assignments, and the set of selectors is reduced to $\mathcal{S} = \{\Phi_1, \Phi_2, \Phi_3, \Phi_4\}$.

The procedure outlined here, which starts with the information provided by f and serves to define the set of possible selectors Φ is an explicit embodiment of the function β , which turns out here to be a multivalued function:

$$\beta(f) = \{\Phi_1, \Phi_2, \Phi_3, \Phi_4\}$$

The fact that $\beta(f)$ is not single-valued (as any honest function should be) shows that the condition of invertibility, which is the symptomatic property of (M,R) systems with organizational invariance, fails for this simple metabolic network. Thus although this metabolic network is an (M,R) system—and also an autocatalytic network (Kauffman, 1993)—it cannot be construed as an (M,R) system with organizational invariance because the rule to assign Φ starting from f gives more than one result. This example is also interesting as it shows that an autocatalytic set, such as the one represented by (M, R_1) , is not necessarily an (M,R) system with organizational invariance. The two ideas, although related, are different in a fundamental way.

Discussion

The main objective of this paper has been to clarify some central aspects of Rosen's ideas. His central result refers to something most biologists will find extremely esoteric: an attempt to prove (from purely logical grounds) the necessity for a circular organization of metabolic networks. Furthermore the mathematical fact used to introduce this notion, the invertibility of certain evaluation maps, is unusual enough to make it very difficult to explain the context of the result even to mathematicians. Rosen himself never explained the mathematical context where his central result could hold true and provided neither mathematical nor biological examples.

As may be surmised, we have adopted the point of view that Rosen had a powerful intuition on the nature of metabolic networks and the necessary (but otherwise ignored) requirement of circularity. However, his intuition is

far from being workable and ready to apply to current network analysis without major efforts, both to clarify the circumstances in which his central result applies, and to explain its meaning in biological terms. An intriguing possibility could be to combine Rosen's analysis with the notion of autopoietic systems, another theory that posits metabolic closure as the core of biological organization (Maturana and Varela, 1980; Letelier et al., 2003). This paper is intended as a step in the proper direction, as we have isolated from Rosen's extensive work what we think is its core, and we have clarified concepts like f , Φ , and β . We have explained the mathematical intuition behind the idea of organizational invariance as embodied in the operator β , a crucial concept as essentially it acts as a *generator* of the complete formal structure of an (M,R) system. In effect it is possible to reformulate the very definition of an organizational invariant (M,R) system as the kind of system where for some b the equation $\Phi(b) = f$ has exactly one solution Φ , for any given f , giving rise to the operator β , which sends any f to its associated Φ and implicitly generates the structure of the whole system.

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