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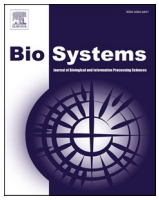
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Full Length Article



What kinds of empirical correlates for a general theory of living organization? Revisiting the (***M, R***)-system and its 'replication'

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ABSTRACT

Robert Rosen proposed in the late 1950s the metabolism-repair or the (***M, R***)-system as a general model of living organization, or any "autonomous life form." Since then, the model has persisted as a recurring subject of interest in certain areas of theoretical biology; however, beyond those specific circles, its influence on biological thought has remained minor. One likely reason for this is the difficulty of interpreting the conceptual insights of the model in concrete terms, which Rosen himself identified as the basically unresolved "realization problem." In more recent literature, attempts to do so have focused relatively strictly on the cellular or even biochemical context, and suggested changes to the model's basic nomenclature: most notably, the technical term 'replication' appearing in the model has been interpreted as something quite unrelated to replication in the usual biological meaning of the term. The aim of the present paper is to argue, firstly, that this is likely to be a deviation from Rosen's original intentions, and secondly, that quite apart from those intentions, there is a practical way of applying the (***M, R***)-system for organizing standard empirical knowledge about any living organism, multicellulars included, and furthermore in such a way that formal 'replication' directly relates to biological replication. Without supposing this new practical scheme to be perfect or beyond further refinement, it is shown to exemplify an analytical point of view that is not covered by more familiar biological theories.

1. Introduction

Robert Rosen introduced the metabolism-repair system, or the (***M***, ***R***)-system, originally in the late 1950s and developed it further throughout his career (Rosen, 1958a, 1958b, 1959, 1966, 1967, 1971, 1972, 1973, 1985/2012, pp. 195-200, 1991, 2000, pp. 254-269). Though he did discuss it mainly in the cellular context and through cellular metaphors, the technical terms of the model were deliberately chosen to be general (see below), and the actual target of this theoretical model is accordingly any "autonomous life form" (Louie, 2006; see also Rosen, 1991, p. 252 and 2000, p. 263). Its key formal feature is the *closure* condition, and the particular manner in which Rosen came to analyse closure has been recognized as "a crucial step forward in the theoretical understanding of organization" (Mossio, 2024 p. 14). In brief, closure may be thought of as arising such that the "outputs" of metabolism are the "inputs" of repair; in other words, the living being is modelled as a natural system which metabolizes and within which the metabolizing system is repaired by utilizing the products of its own metabolism.[1] This aspect of the model is biologically highly plausible and not particularly controversial. As Cornish-Bowden and Cárdenas (2020) put it, closure in this sense might be "ignored in most accounts of life chemistry," while being nonetheless an "important principle of life that is obvious once pointed out."

For instance, one may consider an enzyme that catalyses a flow from substrates to products, such that some of these products will eventually end up as membrane proteins (or parts thereof). Thus, it could be said that the enzyme catalysis participates in the "repair" of the cell membrane; sustaining, amongst other things, the ability of the latter to maintain a stable intracellular milieu. But this maintenance of the intracellular milieu by the membrane, through active and passive transport etc., is quite essential for the enzyme catalysis itself to occur, for the enzyme proteins to fold correctly, and so forth (Hofmeyr, 2021). Therefore, one could conversely say that the activities of the membrane participate in the "repair" of the catalysing enzymes. Or, in multicellular consideration, it is quite trivially so that, for example, repair of the heart (renewal of heart tissue etc.) requires gas exchange to occur in the lungs,

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[1] In the context of Rosen's own work, this is not yet the "full" closure to efficient causation, since repair remains unentailed (see the main text). Nevertheless, the coupling between metabolizing and repairing activities is already an insight in itself, and the main aspect shared by resembling models in theoretical biology. For convenience, I shall refer by the term 'closure' to their coupling throughout the paper, and discuss replication (which entails repair) separately.

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and conversely, that repair of the lungs requires a heart that pumps. Of course, things are not quite this simple, and more nuanced studies of the actual "repair" processes would require considerations of the "genetic" aspects of the respective organisms also. And indeed, in this respect it is of much current interest (see e.g. Soto et al., 2016) to observe how Rosen often uses the term 'genetic' as a synonym to 'repairing', while being explicit in his suggestion to generalize the notion of genetic such that it may include, but never be exhausted by, considerations of the molecular sequences of the DNA (see e.g. Rosen, 2000, pp. 45-55 and below). In any event, for the moment the point is merely that apparently living beings *are* circularly organized in the above fashion, and to this end some version of the closure condition is, apart from technical details, at least a legitimate point of departure in their theoretical analyses (cf. Gánti, 1971/2003; Eigen and Schuster, 1979; Maturana and Varela, 1980; Kauffman, 2000; Moreno and Mossio, 2015; for a review, Cornish-Bowden and Cárdenas, 2020).

Another central feature of the (***M, R***)-system is the so-called replication mapping, which, from a purely *formal* point of view, actually "closes" the closure (to efficient causation) by entailing the repair mapping (similarly as the repair mapping formally entails the metabolism mapping). This is the more controversial aspect of the model, and the question of what it might mean from a *biological* point of view is the key motivating question of the present study. But before addressing it in further detail, it is necessary to consider briefly how the interpretation or application problem of the (***M, R***)-system actually arises – that is, the problem of relating the formal to the biological, or what Rosen himself calls the "realization problem" of the model (e.g. in Rosen, 1971 & 1991).[2]

Thus, what Rosen regards as belonging to his "basic and deeply-held methodological views about theoretical investigations into any kinds of systems" is that "one must first see how much follows already from the weakest and most general hypotheses … before making more specific structural assumptions" (Rosen, 1971). This may strike as an idiosyncratic direction of analysis, especially in comparison to molecular biology, insofar as the *modus operandi* therein has more often been, conversely, "to try to infer biological function as a consequence of physico-chemical structure" (*ibid.*). However, it should be noted that e.g. Darwin's theory of evolution by natural selection is not based on specific structural assumptions at all, but rather on very weak and general hypotheses about variation, fitness, selection, etc., quite independently of *what* it actually is that varies, is more or less fit, selected for or against, and so on. Hence, to this end one could think of Rosen as doing in "functional biology" what Darwin did in "evolutionary biology" (in Ernst Mayr's terminology) – I intend this parallel, which I discuss more thoroughly elsewhere (Weckström, 2026), to be taken seriously, and I will return to it later below. But for now, let us merely note that in the basic construction of the (***M, R***)-system, the following weak and general hypotheses can be identified: firstly, that an arbitrary cell or organism, however constituted in material terms, can at least be studied in terms of "metabolic" activities and in terms of activities that "repair" the metabolizing activities; secondly, that the "repairing" activities will essentially utilize the outputs of "metabolizing" activities; and thirdly (as I will argue below), that the cell or the organism may also engage in "replicating" activities that may even result in a faithful re-production of its entire organization. Hence, the *formal* (***M, R***)-system is a joint expression of these – weak and general indeed – hypotheses in a systematic language. But in the thus resulting formal-inferential construct *per se*, there is

> no membrane, no nucleus, no cytoplasm, no mitosis, nothing that a histologist, or even a biochemist, would immediately recognize (Rosen, 1971),

analogously to how 'variation' is entirely abstract and nothing actually recognizable *until* it has been made to refer to, say, the variation *of* the clutch size of the bird *Larus marinus*. Therefore, the question of how a particular, given organism actually realizes its "metabolic", "repairing", and "replicating" activities becomes a separate problem, which on the one hand follows from the general hypothesis that *somehow* these activities must be realized and related to one another in any living being, and on the other, from the reluctance to make "more specific structural assumptions" while establishing the general framework. Thus, in the concrete study of concrete organisms, structural assumptions and empirical observations must be made, and these can be quite different when inspecting prokaryotes, eukaryotes, multicellulars, etc., without the original combination of hypotheses becoming thereby disqualified – *if* it had succeeded in capturing something fundamental of the reasons why we recognize those various natural systems jointly as living beings. Nonetheless, in the absence of a sufficiently clear recipe for translating the formal features of the model into concrete proposals about particular organisms ("prediction"), and vice versa ("explanation"), it is unsurprising that one may see the model as theoretically inspiring while feeling that it "still remains too abstract" (Mossio, 2024, p. 14; see also Cornish-Bowden, 2015).

After Rosen's passing away at the turn of the century, there have been several attempts to develop and apply the (***M, R***)-system. Further investigations by Aloisius Louie have arguably been the most detailed in formal terms (Louie, 2006, 2009, 2012, 2013 & 2017). John Kineman (2011) has sought to synthesize a comprehensive relational science out of the (***M, R***)-system and anticipation formalisms, epistemological considerations of complex systems, and with a particular emphasis on Rosen's concept of the modeling relation. But a more biochemically motivated line of inquiry, which is especially directly connected to the realization problem, has been pursued e.g. by Letelier et al. (2003 & 2006), Hofmeyr (2021), and Vega (2023). A notable suggestion that has arisen therein is that the basic *nomenclature* of the original model should be changed, especially when it comes to 'replication'. Indeed, according to Letelier et al. (2006), "Rosen used a number of words, such as *replication*, in ways that can only confuse readers familiar with their usual meanings in biology" (original emphasis). Similarly, Hofmeyr (2021) maintains that 'replication' was "a rather unfortunate and misleading choice of name", and also Vega (2023) believes that "in the context of the cell, it would be more appropriate to replace 'repair' and 'replication' with 'replacement' and 'organizational invariance'", respectively. Thus, these authors seem to indicate that Rosen did not in fact *mean* by 'replication' those replicating, and perhaps eventually re-producing, phenomena that actually occur in organisms, and to which the term conventionally refers. In one way or another, they seem to think that fixing this "confusion" is essential for coming to grips with the realization problem of the model.

In my view, this is a misinterpretation of Rosen's writings, of his own word-use – if that is kept separate from the meaning of 'replication' in later theoretical developments by other theorists. Namely, while it is true that especially the formal elaboration of the (***M, R***)-system in *Life Itself* (Rosen, 1991, pp. 248-253) may give an impression that the replication mapping was introduced for formal or logical reasons, i.e., for the purpose of closing the closure while avoiding infinite regress, elsewhere the author is quite clear in that it was biologically motivated. If so, one may acknowledge these later developments by other authors, in which 'replication' does not mean replication, as valuable in their

[2] Rosen employs the term 'realization' in several related ways; in the present paper, it will mainly appear in association with empirical problems of this form: "… To determine whether a particular concrete biological system is in fact a *realization* of an (M, R)-system (i.e. to identify the functional components [of the formal (M, R)-system] in a real biophysical system)" (Rosen, 1971, emphasis added). Alternatively, one could understand the problem of realization as a problem of finding the relevant *encoding* of such-and-such aspects of a real biological system onto relevant aspects of the formal (M, R) system (see Weckström, 2023).

own right, as theoretical approaches, but refuse to say that *Rosen* was particularly confused or misleading while using the term. As a native English speaker and a professional theorist of biology, he probably knew the conventional meanings of 'replication', and perhaps had his reasons for choosing to use that particular term. Importantly, this is not to say that replication in his formalism should *be* the replication of conventional biological descriptions; I think Rosen was quite careful in not confusing the map with the territory in this sense (see Weckström, 2023). Yet, considering the potential value of the (***M, R***)-system for general biological thought, the possibility that 'replication' could be non-trivially *related to*, or model, biological replication is intriguing – for, arguably a model of a natural system that maintains itself alive *and* may possibly replicate the functional components of its internal organization, and eventually re-produce that organization entirely, is the model biology, for biological reasons, ultimately needs. Real living beings (also the mule) do come from other living beings like them; and if there is a reason to suspect that an insight related to this was already included in the original construction of the (***M, R***)-system, then perhaps the dominating post-Rosennean interpretation of 'replication' strictly as non-replication deserves its opponent – in the name of healthy intellectual exploration, if nothing else.

Thus, the present paper begins with a brief argument explaining why I do not believe that Rosen himself was confused when choosing to use the term 'replication' (Section 2). Subsequently, I will introduce a protocol for applying the (***M, R***)-system as a general framework for organizing concrete knowledge about particular organisms, first by considering the empirical correlates of 'metabolism' and 'repair' (Section 3), and then of 'replication' (Section 4) such that it means, or at least very interestingly relates to, replication in the usual biological sense. It should be emphasized that while Section 2 *is* concerned with Rosen's own intentions, the developments from Section 3 onwards are not. In other words, the revisiting of 'replication' in the context of Rosen's own writings contextualizes the developments from Section 3 onwards, but the aim of those developments themselves is to create a *new* manner of using and interpreting the formalism of the (***M, R***)-system. It will be different from anything Rosen himself ever said – the terms and the formalism I shall not touch, but the manners of using and interpreting them will be new. To my knowledge, the empirical protocol thus arising has not appeared elsewhere, apart from being preliminarily anticipated in Weckström (2025). Lastly, I will say a word about the relevance of the (***M, R***)-system for current debates on what could perhaps be called post-gene-centric biology (Section 5). In particular, I will propose that the key issue here is not whether the model is perfect or beyond further refinement, but about appreciating how it recognizes the living organization as a well-defined *object* of analysis (Weckström, 2026). At root, this is not too different from how Darwin's theory identified evolution by natural selection as such an object, and proposed a respective framework for its further inspection – a framework that has been subject to refinements, additions, reinterpretations, and other improvements ever since.

2. The intended meaning of 'replication'

Letelier et al. (2006) write:

> *Replication* was another unfortunate choice of term, evoking ideas of biological reproduction whereas the essential notion is *organizational invariance* … under continuous structural change (original emphasis).

Apparently, this conclusion is based on the view that the (***M, R***)-system is "an attempt to understand how a system must be organized if it is to *continue in operation indefinitely*," and that the replication mapping was added to the model for explaining "how the R_i [repair components] are replaced *while avoiding infinite regress*" (*ibid.*, my emphasis). If this were the case, one could indeed say that the replication mapping is there primarily for formal-logical, rather than conventionally biological, reasons. Vega (2023) similarly identifies the replication mapping with the activity of "replacing the repair components that disappear", and accepts the substitution of 'organizational invariance' for 'replication'. According to Letelier et al. (2006), (***M, R***)-systems "without organizational invariance would be transient entities."[3]

However, the biological situation is such that, generally speaking, organisms do *not* continue in operation indefinitely, and *are* transient entities; viz., entities that tend to undergo senescence and death. Hence, one could attach quite relevant biological meaning to the idea that while "metabolizing" activities and components are "repaired" during the lifetimes of the respective individuals, there is no overall "repair of repair" *in them* – senescence and death are irreversible processes – and the maintenance of "organizational invariance" takes place at the level of generations, through the processes of replication relating to, or entailing, the re-production of the entire organization. Rosen, as a matter of fact, was explicitly interested in the theoretical question of why this is so; that is, why individual real cells and real organisms, as complex and organized thermodynamically open natural systems,[4] apparently *must be* transient entities in this sense (see e.g. Rosen, 1985/2012, pp. 330-339). He saw that the persistence of their types of organizations can be understood on the basis of the "*rejuvenation* of the entire system" (*ibid.*, p. 339, original emphasis), and that

> It is conceivable, for example, that the function of mitosis is to effect precisely such a recalibration at the cellular level (*ibid.*).

Already this indicates, in my view quite clearly, that Rosen took mitotic cell division (which, incidentally, we already met in the above-quoted formulation of the realization problem) and phenomena associated with it as a manifestation of something rather fundamental about living beings, and while actually discussing the (***M, R***)-system elsewhere in the same book, he says that

[3] This is an interpretation that may easily arise while reading e.g. the elaborations of Rosen (1972); but it seems to me that also therein, replication is not introduced (only) as an idiosyncratic theoretical construct, but rather, and perhaps primarily, as a well-known nature's solution to a formally comprehensible problem: "In biological cells the problem is solved by making the repair components R_i (self-) *replicating*" (p. 235, original emphasis). What is essential here, in my view, is to remember the complexity of time in dynamical considerations of biology (e.g., Rosen, 1972, pp. 227-229); in other words, that replication may entail repair as a process unfolding at its own time scale, rather than "under continuous structural change" (Letelier et al., 2006).

[4] While discussing how different theories of life succeed in taking thermodynamical openness into account, Cornish-Bowden and Cárdenas (2020) say that while *they* can interpret the (***M, R***)-system such that there is an "irreversible conversion of food into waste," it is only implicit in the formalism and they "do not know whether Rosen would have recognized it," though admitting that "in his last book" Rosen mentions openness in connexion to Schrödinger. However, in my view openness (and explicit criticism of closed system reasoning) is one of the most central themes throughout his writings. In Rosen (1988), for example, he says that "Material systems whose mathematical images do not satisfy conservation laws or other special conditions of this type are collectively called open systems. In particular, biological organisms are open systems in this sense … The distinction between closed and open systems is not merely a technical matter. It touches on some of the most basic issues of system epistemology; the distinction between system and environment; between inside and outside." Such reflections belong to the main themes addressed from multiple angles in *Fundamentals of Measurement*, *Anticipatory Systems, Life Itself, Essays on Life Itself,* and in numerous journal articles.

> One of the decisive features of genetic activity in real cells pertains to the *replication* of the genetic material. Thus it would be most important to show that, already within the (M, R)-system formalism as we have defined it, and without the need for making any further *ad hoc* assumptions, a mechanism for such replication was already present. This is what we shall now proceed to show (*ibid.*, p. 197, original emphasis).

Evidently, in this passage 'replication' does not refer to a peculiar formal construct, but conversely to "One of the decisive features … in real cells" that must be *accounted for* by an apt theory, and "without the need for making any further *ad hoc* assumptions." Thus, any interpretation of the (***M, R***)-system in which 'replication' is taken *not* to mean replication will precisely face the need to make such *ad hoc* assumptions, and is to that extent at odds with these words of Rosen. Anyway, after the above passage Rosen demonstrates how the replication-mapping actually arises out of the (***M, R***)-system formalism, and concludes that "To our knowledge, this kind of result is unique; there is no other situation in which replicative capacity can be made to *follow* from repair activity without the intervention of *ad hoc* assumptions" (p. 198, original emphasis). In my view, this conclusion is sensible if, and only if, 'replicative capacity' is understood in its conventional biological meaning, rather than as a peculiar property of his own formalism – for, how could it be anything else but the "only formalism" in that case? Moreover, this is a conclusion Rosen repeats many times throughout his entire oeuvre. In earlier writing, such as in Rosen (1971), he says that "This construction [the (***M, R***)-system] has two important consequences: (a) it is the only formalism, to my knowledge, which incorporates replication of genetic components as an essential and natural consequence of metabolic activities …" Similarly, in later writing, he says that

> Under the appropriate conditions, metabolism and repair already entail replication … To my knowledge, this result still remains the only one in which replication is entailed by something – where it does not have to be posited independently. And *this is the main reason I have remained interested in them* [i.e., in the (***M, R***)-systems]. (Rosen, 2000, p. 263, emphasis added.)

In this latter text, he furthermore concludes the formal developments by saying that "if an evaluation map in this case is invertible, it is precisely a replication map … And it is also easy to verify that it *must have all the biologically important properties of replication*" (*ibid.*, pp. 262-263, emphasis added). It is very difficult to see why these words would have been written if Rosen had not intended there to be a meaningful relation between replication in his own formalism, and replication in conventional biological descriptions.

On this basis, it seems to me that while Letelier et al. (2006) are arguably right in that the *formal* role of the replication mapping is to account for organizational invariance ("repair of repair"), the *biological* process responsible for this, in real cells and real organisms, is replication , which is entailed by certain kinds of outputs of the metabolic activity itself, and which in a way culminates in the re-production of the entire organization. And most importantly, I see little reason to doubt Rosen's awareness of this, or his willingness to acknowledge it as an essential fact of life. Instead, the above passages seem to indicate that it might be the very reason why Rosen decided to name the respective formal map as he did. For instance, elsewhere Rosen reflects directly on how the formal replication map relates to "currently accepted ideas on 'real' replication in biological systems" (Rosen, 1967), and says that

> the map β_b [viz., the replication map] possesses the essential property which is intuitively required for *a biologically meaningful replication* of "genetic" structure (Rosen, 1966, emphasis added).

In Rosen (1973), he furthermore describes the replication mapping as the (formal) means of going "from the 'metabolic' *mode of behaviour* … to the 'replicative' mode". Let us ask: Why to speak of distinguishable modes of behaviour in this sense? Well, on biological grounds it is, and was already then, elementary knowledge about the life cycles of real cells and real organisms that such distinguishable modes of behaviour precisely do exist, or can at least be identified and studied. Indeed, one could think of the G_0 phase of the cell cycle as a phase in which the replicative mode of behaviour is prevented from occurring, and only the metabolic mode of behaviour goes on; and in multicellulars, the difference between the two is clearer still. (Thinking of living dynamics exclusively at the timescales of biochemistry may partly conceal this; see footnote 3 above.) Besides, this text (Rosen, 1973) is another instance where the (***M, R***)-system formalism is praised due to the "fact that a mapping for the replication of the genetic [viz., repair] mapping Φ is present in the system, and need not be posited separately", which is then regarded as "One of the major items of interest in the theory of (M, R)-system" (*ibid.*). It may be noted that if *this* is indeed regarded as one of the major items of interest in the theory of (***M, R***)-system, that would appear to be an important difference to e.g. the Chemoton (Gánti, 1971/2003) and Autopoiesis (Maturana and Varela, 1980), insofar as in these frameworks, replication and reproduction perhaps must be introduced through additional theoretical structures (I will discuss this further in Section 5).

Does it not seem, then, that *dissociating* the replication of the (***M, R***)-system from replication in conventional biological descriptions – by considering 'replication' as an unfortunate and misleading name-choice from Rosen's part – is quite thoroughly at odds with all these writings, written by Rosen himself? Admittedly, a work that makes the interpretation problem somewhat more difficult is *Life Itself*, which has probably influenced the thinking of the (***M, R***)-system more than any other single publication. In it, replication is discussed purely in the formal context, indeed as the element that completes the closure to efficient causation (see footnote 1), and many readers are likely to begin *their* studies of the (***M, R***)-system from there. However, it is also true that *Life Itself* is almost exclusively a formal elaboration, and therefore not the best source, I think, for examining the extra-theoretical meanings of 'replication' or any other technical term. Also, from Rosen's own point of view, it was not the beginning but the culmination of previous inquiries. Hence, we may ask: does it seem likely that in *Life Itself*, the meaning of 'replication' has undergone a radical change, such that its relation to replication in the conventional biological sense, which in my view is evident in the above-quoted passages, no longer applies? I do not think so, for several reasons; and I shall outline some of these briefly before closing the present section.

Firstly, while introducing 'replication' in *Life Itself*, Rosen does not claim such a change of meaning to have occurred, but, instead, explicitly relies on his previous work on replication and refuses to repeat it (Rosen, 1991, p. 251). Secondly, though direct discussion of extra-theoretical meanings indeed is scarce in this book, one may, in a more indirect fashion, consider e.g. the following passage from Prolegomena, which motivates all the subsequent elaborations:

> If we give a physicist, say, a clock, his or her interest will reflexively concentrate entirely on how it works, *never on how it came to be a clock*. We shall see below that the whole formal structure of theoretical science is geared toward the former question and away from the latter (*ibid.*, p. 15, original emphasis).

Now, if the (***M, R***)-system, as an essential upshot of the book, was really intended as "an attempt to understand how a system must be organized if it is to continue in operation indefinitely" (Letelier et al., 2006) – *presuming it already exists* – then would not an (***M, R***)-system theorist still be asking only how an organism works, never how it came to be an organism? (For example, only how a mule works, not how it came to be a mule.) It is in order to recall that the subtitle of the book is … *and the Fabrication of Life*, and in Rosen's terminology, the question of how an organism comes to be an organism, basically as entailed from within another organism,[5] is a question of its fabrication. He thinks that problems of fabrication are "especially interesting when the system to be fabricated is itself an (*M, R*)-system (and in particular, a *replicating* (*M, R*)-system)" (Rosen, 1991, p. 253, emphasis added). Also, while discussing the fabrication of organisms, or the becoming of organisms, further in Rosen (2000) – that is, in a volume later than *Life Itself* – he develops the (***M, R***)-system formalism and says: "This is where the magic of *replication* comes into the picture" (Rosen, 2000, p. 265, original emphasis). Besides, that is the very same text in which he had just before stated that the replication map "must have all the biologically important properties of replication" (p. 263). It would be most absurd, in my view, to insist after this something like "However, the word 'replication' here has nothing to do with biological replication as normally understood" (recalling that the current problem is to interpret *Rosen*). And thirdly, from this point of view we may also reconsider the following iconic passage from *Life Itself*:

> To me, it is easy to conceive of life, and hence biology, without evolution. But not of evolution without life. Thus, evolution is a corollary of the living, the consequence of specialized somatic activities, and not the other way around (Rosen, 1991, p. 255).

One could ask: How could evolution be a *corollary* of the living, the *consequence* of specialized somatic activities, if those activities were incapable of *generating* generations, populations, and phylogenies? Apparently, some *ad hoc* assumptions would then be needed, but these Rosen wanted to avoid, as was observed above. E.g. Cornish-Bowden and Cárdenas (2020) interpret the above passage as consistent with the view that "Reproduction is not [the fundamental necessity], because any organism unable to stay alive long enough cannot reproduce." Yet Rosen is speaking of evolution, not reproduction, and reproduction would naturally be included in those "somatic activities" of which evolution could, under certain circumstances, be a consequence. Thus, the main insight here, on my reading, is that a theory of evolution is *not* a theory of how living organizations come from other living organizations like them (and neither is, at least in any sophisticated sense, the Central Dogma, the notion of a "genetic program", etc.; cf. Jablonka and Lamb, 2014). But a theory of evolution must *presuppose* that something like that is occurring; whether there will be evolution (especially in the sense of natural selection) *also* will depend on further factors. In Rosen's framework, one could think that for there to be evolution, there must be potentially evolving organisms, and for there to be organisms, there must be a manner for their forms of organization to come into existence, and to persist during their own lifetimes (i.e., through metabolism and repair) and beyond, in spite of senescence and death in an open world, via the "*rejuvenation* of the entire system" (Rosen, 1985/2012, p. 339, original emphasis), or via the "replicative mode of behaviour," which must be accounted for "as an essential and natural consequence of metabolic activities" (Rosen, 1971). *Then* one may come to see evolution as a corollary of the living, which can happen if there are living beings capable of generating populations and phylogenies *and* population-level variation of some traits under directional selection pressure etc. (which there need not be). Moreover, if we are given any *real* organism which, as we know, came from another real organism (also the mule), then it is essential to know how *its* existence was entailed (Rosen, 2000, pp. 235-248); how the mule came to be a mule or a bacterium a bacterium; on my reading of Rosen, this is precisely what he did not want to simply posit or leave for *ad hoc* hypotheses. Perhaps this is not the most common way of reading Rosen, but in my view it makes sense – or better, in my view reading Rosen makes sense if 'replication' is allowed to mean, or to non-trivially relate to, replication.

And yet, the fact remains that the realization problem was left largely unresolved; in other words, the theoretical-empirical relationship remains anything but clear.[6] Thus, I do think that while there might be an insight behind the original term-choice that should not be given too easily up, we the later generations are, nonetheless, fully permitted to bend and twist the theory, and to try to find new ways of interpreting and using it – certainly, the purpose of the present paper is not to entertain a scholastic or dogmatic attitude on these matters. Hence, what follows next is one attempt to bend and twist the theory, when it comes to its use and interpretation; from now onwards, I will no longer restrict myself to an analysis of what *Rosen* perhaps thought. Instead, I shall try to find an entirely new way of relating the (***M, R***)-system to some basic biological observables, and 'replication' to replication.

3. Metabolism and repair

In the relational modeling scheme devised by Rosen, the elementary "building block" of any system description is the concept of a *component*. That is, components, instead of e.g. physical particles, are taken as the "the basic analytical units into which natural systems are resolved" (Rosen, 1991, p. 120). The component is an inherently "non-reductionistic" unit of analysis insofar as it necessarily invokes a non-arbitrary *outside*, or a larger system, of which the component must be part of (in the intuitive sense that e.g. enzymes can only catalyse and hearts only pump *within* organisms). In addition, while component-descriptions do seek to capture perfectly real or material processes, there needs be "no kind of 1 to 1 relationship" between these component-descriptions and the "structures which realize them" (*ibid.*, p. 280). For instance, a description of an enzyme as a material structure will contain much information that is quite irrelevant (and hence changeable) with respect to the properties of its *active site*; conversely, a given material structure, such as the endoplasmic reticulum, the cell membrane, the skin, etc., can well be "simultaneously involved in a variety of functional activities" (Louie, 2006). In this sense, a component may be seen both as an "inertial thing" to which material structures can be attributed (in a case), and a "gravitational thing" that exerts effects on other aspects of the larger system to which it belongs (see Kineman, 2011; Rosen, 2000, pp. 11-14), but a description of its structural properties is not sufficient for deducing its functional properties, and vice versa. Formally, components are represented as *mappings* of the form $f : A \rightarrow B$, or diagrammatically as in Fig. 1.

A rudimentary interpretation-example of Fig. 1 would be that an

[5] In addition, there is the separately frameable "The 'origin of life' problem [which] requires us to specify, in one way or another, how to fabricate an organism from things which are not organisms" (Rosen, 1989).

[6] It may be noted that Rosen was sceptical towards the idea the biological theories should be *verified* empirically, and especially through explicit experiments (2000, p. 274). However, this is not to say that biological theories would not need to permit better *understanding* of what is actually going on in the empirical world; quite the contrary. In *Life Itself*, he says that perhaps the problem in coming to grips with "What is life?" is not that we do not yet know enough, but rather that "we simply do not properly understand what we already know [about empirical biological phenomena]" (1991, p. 17). The developments from Section 3 onwards may be thought of in this vein; the proposed protocol yields a framework in which to make more sense of what we already know.

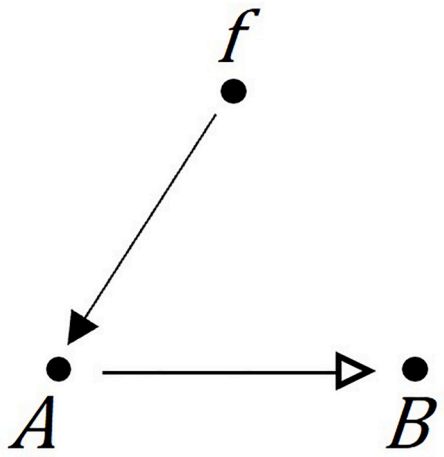


Fig. 1. A component f entails or processes (solid-headed arrow) a material flow or consequence (hollow-headed arrow) from A to B.

enzyme f catalyses a material flow from substrates A to products B; or, in a more complicated situation, that the digestive system f facilitates a material flow from food A to digested biomolecules B (after which f, A, and B could be factorized or decomposed into more detailed mappings; see Rosen, 1991, pp. 123-127). Thus, one could basically think of a component as an identifiable aspect of an organism that *does something* – and what I propose now is that this "doing" of a component, inside an organism, can be regarded as the elementary referent of the technical term 'metabolism'. Hence, on this reading, the "metabolism" of an enzyme would be its catalysis (the entailing or processing of products B out of substrates A), and the "metabolism" of the heart would be its pumping (the entailing or processing of high-pressure blood B out of low-pressure blood A).

It is true that this generalizes the conventional meaning of 'metabolism', but there are reasons, I think, to consider it a legitimate move. Firstly, the suggested meaning of 'metabolism' can be anchored to the formal diagram of Fig. 1, in which f, A, and B can be interpreted in alternative appropriate ways (e.g., in the case of the digestive system, the enzyme, and the heart), and to this end the generalization is not vague or arbitrary, but quite explicit. Secondly, if we wished to delimit the meaning of 'metabolism' to some sort of "processing of material", and considered a complex biochemical pathway that in some sense begins from active intake of the material, and in some sense ends in the use of that material, then it would really be a matter of convention (or theory) to say where metabolism ends and something else begins. Thirdly, on biological grounds we know that if f_i is identified with the heart, say, and A_i and B_i with incoming and outgoing blood, respectively, and if then the functioning of f_i is decomposed into descriptions of finer detail, these more detailed descriptions will identify processes that would more intuitively be called "metabolic", in the biochemical sense of processing something into something else. And fourthly, it is worth recalling that 'metabolism' is here only a word, a symbol, that can be changed without changing the inferential structure of the theory – thus, if it feels more comfortable to speak e.g. of 'physiology' in place of 'metabolism', especially in multicellular consideration, this can be done, and it is what Rosen sometimes does and I will do also, on some occasions below.

Therefore, let us proceed by supposing that the internal organization of *any* living being can be approached by studying its distinguishable components, and that doing so will yield a *set* of empirical descriptions $f_1, f_2, \ldots, f_n \equiv f$. This set of descriptions I propose to be interpreted as the "metabolism" of the (***M, R***)-system, which in the most composed expression can be referred to by the mapping $f : A \rightarrow B$. What is encapsulated in this expression is *one type of knowledge* we may have of the organism: accounts of some particular components f_i, each of which permits us to *infer* ($\rightarrow$) how some $b \in B$ actually comes out of some $a \in A$. It is crucial to think of this carefully – the ***M*** of the (***M, R***)-system, in the present scheme, gives us an abstract *locus* into which we can encode concrete knowledge of this *form*; knowledge whose actual content in a particular case must be obtained empirically. For example, specific knowledge of the heart permits us to infer (to reason about, to explain) how high-pressure blood actually comes out of low-pressure blood, and specific knowledge of the enzyme permits us to infer how products actually come out of substrates. Thus, intuitively the set f can be thought of as a set of mechanism-descriptions in the traditional sense (or more provocatively, the entire set f as the "proximate" scientific description of the respective organism by the lights of the late twentieth century). Now the question is, with this set of descriptions f, do we already know our organism?

If it were a machine, then perhaps, but because it is an organism, there is still a whole set of *questions* of a different *kind* that must be asked in the context of its own, internal organization. These are of the following general form: given a component f_i that does something in the organism, then what it is, inside the organism, that *does and maintains this component*? This is the question of the "repair" of f_i. Whatever is needed for addressing it, let us refer to that by the symbol Φ_i, and think of it as playing an inferential role encapsulated by the mapping $\Phi_i : C_i \rightarrow f_i$. In other words, we apply knowledge *of* Φ_i *on* something and *infer* the existence of f_i. Doing this systematically, component by component, generates another set of descriptions $\Phi_1, \Phi_2, \ldots, \Phi_n \equiv \Phi$. In the most composed presentation, knowledge contained in this new set of descriptions will be of the form $\Phi : C \rightarrow f$.

But the above question can still be raised: for, is it not possible that Φ was already included in f; in other words, that if we had faithfully described every "mechanism" of every component we could identify, then this other set had already become redundant? It is essential to think of this in the context of real biological *inquiry*. Thus, suppose f_i is an enzyme (or more precisely, its functional role as a component), and ask: How is it repaired? It is obvious that for addressing this question, knowledge of the doings of quite many other components will be needed. For example: knowledge of the components that unwind the DNA, knowledge of the components that incorporate the ribonucleotides, knowledge of all the other components that facilitate all the other aspects of transcription; knowledge of the doings of the chaperons, ribosomes, the endoplasmic reticulum, the transport system, etc.; knowledge of the cell membrane that maintains a suitable intracellular milieu and makes correct folding possible, and so forth. Hence, we need to know quite many other "mechanisms" in order to infer the existence of a mere functional enzyme. Anyway, let us suppose that we had indeed described all such mechanisms involved, and included them in our f. But then, if we really wished to give an explanation of why the given f_i is where it is, doing what it does, we would need further knowledge of how all those mechanisms, or more precisely their outputs, are actually *related* to each other in the cell. This is not the same knowledge as knowledge of how they function "in isolation" – as the history of molecular biology vividly illustrates (Matlin, 2022), knowledge of such relations is generally obtained by different means (for instance, through histological rather than biochemical inspection). Thus, what we actually always do, when we seek to explain the existence and maintenance of some f_i, is that we apply knowledge *of* such relations between various components *on* the outputs of the components or mechanisms and infer (i.e., explain) the existence of f_i.

But this brings us directly to the closure condition between metabolism and repair, in the sense discussed in Introduction (see footnote 1). Namely, if we know how the nucleus, the endoplasmic reticulum, the ribosomes, the transport vesicles, the cell membrane, etc. are related to one another in a cell, and if we apply *this* knowledge *on* the effects or outputs of their "doings", then we may be able to infer or explain the existence of f_i. Thus, we remain entirely consistent by saying that Φ refers to this sort of relational-organizational knowledge (sometimes obtained e.g. by microscoping rather than by biochemical analysis), and

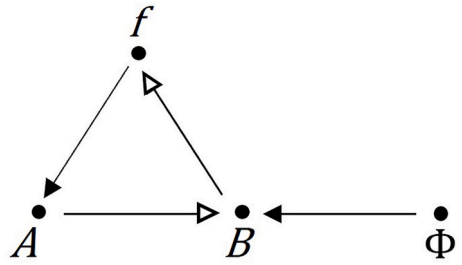


Fig. 2. The formal (***M, R***)-system without replication.

considering its domain, we can in fact maintain, on the basis of the foregoing, that $C = B$. In other words, what we always do is that we apply this kind of relational-organizational knowledge not on anything, but on specific outputs of the functional components f_i of the organization, that is, to the elements of B. Consequently, in the most composed presentation, we can refer to our knowledge of repair by the mapping $\Phi : B \rightarrow f$, and adding it to the diagram of Fig. 1 yields the new diagram of Fig. 2.

The diagram of Fig. 2 is the formal (***M, R***)-system without replication. Biologically, it is an explicit framework for reasoning about the internal organization of any organism which is alive, but not engaged in the "replicative mode of behaviour" (or, which is alive but whose existence as such an organized being we still must only suppose, or take for granted). The framework can be applied as follows. Given an arbitrary organism, living at any specific moment of the evolutionary history, the internal organization of this organism can be supposed to be inspectable in terms of empirically identifiable components f_i, each of which may be subjected to the following three empirical considerations (see Weckström, 2025). Firstly, one must ask,

i. What does the component f_i *do* (viz., what is its "metabolism")?

This is a rather "normal" question to be asked; addressing it in the case of the heart would yield a description of the "mechanism" of its pumping, in the case of an enzyme a description of the mechanism of catalysis, etc. Secondly, one must ask.

ii. What Φ_i *does* the *component* f_i (viz., how is it "repaired")?

This is a more difficult problem to be addressed empirically. The reason is that while we can in an important sense *decide* to focus on, say, the functioning of the heart or the enzyme as the component f_i, we cannot similarly delimit ourselves (by the procedures of abstraction, experimentation, etc.) when accounting for its repair Φ_i. What is relevant here depends less on our research interests, and more on the actual organization of the being in question. Hence, Φ_i must be inspected with a more "open mind". Consequently, it must be accepted that the question of how much of the studied organization should actually be included in a specific Φ_i may, in practice, remain vague (at limit, it could be the whole Φ). Nevertheless, it is undeniable that knowledge *of this sort* is absolutely crucial for understanding any component f_i, and that starting from f_i, and trying to comprehend its repair Φ_i, is always a legitimate and inherently an empirical thing to do, when practicing biology.

In the scope of the present paper, I will leave more precise formal character of Φ_i open, though some heuristic reflections will be made in Section 5 below. However, let it be quickly mentioned that since Φ_i must, from a phenomenal point of view, be at least able to *prevent* the deterioration of f_i, etc., the technical language developed in Rosen's *Anticipatory Systems* (1985/2012) might be quite useful for developing it in further formal detail (see also Louie, 2012; Kineman, 2011). This might also yield an approach to addressing, in the formal realm, the problem with "missing" *regulation* as identified by Cornish-Bowden and Cárdenas (2020). But for the moment, suffice it to say that whatever knowledge about the organization of components and processes is needed for inferring or explaining a given f_i, this knowledge, which usually comes in the form of a set of empirical descriptions, can be interpreted as the empirical correlate of Φ_i. Also, it may be stressed that while Φ_i is formally expressed as a mapping like f_i, its interpretation in material-structural terms is still less 1 to 1, because Φ_i can always be expected to be a complex organization of material processes. These same considerations apply also to the third and the final question of the proposed scheme:

iii. What does the *doing of* f_i *do* (viz., how does the "metabolism" of f_i contribute to the "repair" of other components)?

This question follows from the closure condition. It is about ascertaining how, say, enzyme catalysis participates in the repair of the cell membrane; how the selective flow of chemical species facilitated by the membrane participates in the repair of enzyme catalysis; how the pumping of blood by the heart participates in the repair of the lungs; how the gas exchange facilitated by the lungs participates in the repair of the heart. There is no need to require that every identifiable component of a living organism should make such essential or "vital" contributions to the existence of the system – rather, the study of which do may be used for clarifying what is in fact meant by a "vital component." Accordingly, sets of empirical descriptions arising in response to (ii) and (iii), out of which a systematic description of an *organization* of components inevitably emerges, can be employed in focused reasoning about the various ways in which a given organism may develop pathologies and die (Weckström, 2025). Conversely, they may permit a focused consideration of what it is for that particular organism to be "healthy" and alive.

Lastly, let us note that in the above elaborations, I have not singled out the DNA as the distinct "secret of life", and in particular, not associated it exclusively with the repair activity Φ – why? It may seem reasonable to think that in the repair of any essential component f_i, reading of the DNA must be involved. But even if this is true, it is quite equally true that in every instance of DNA reading, there must be other components, and indeed quite much of the rest of the living organization, operating. Thus, it is not so that organization "flows out" from the DNA; rather, the DNA is part of an organization that may construct itself and maintain itself. Accordingly, its functional role(s) as a component can be subjected to the very same analytical-empirical protocol (i–iii) that applies to components in general. In particular, one must inspect (i) what the DNA "does" when it participates e.g. in the functional activity of transcription, in which the DNA, like a catalysing enzyme, remains itself structurally unchanged; one must also inspect (ii) how the DNA is and must be continuously repaired, by processes quite different from transcription, and facilitated by other components such as DNA glycosylases etc.; finally, of course, one must inspect (iii) the many direct and indirect ways in which transcription (etc.) participates in the repair of many (if not all) other components of the system. From this point of view, it may be argued that perhaps the "secret of life" is more in the closure-organization between metabolism and repair, in the above sense, though clearly the DNA plays an important role in its realization at least here on Earth. Or, that if we wish to think beyond gene-centrism, we need to embed our knowledge of DNA-RNA-protein flows, in the sense of the Central Dogma, within a larger theoretical conceptualization of organization. Indeed, that is what may replace, at a general-fundamental level, the somewhat naïve image of a flow from DNA to traits by an account of how such flows themselves are entailed. An embedding of the Central Dogma within the formal (***M, R***)-system, with an alternative interpretation of the formalism but essentially with this same result (and also including replication in the sense of replication), has been developed by Abir Igamberdiev (2023a; see also 2023b).

For more philosophically inclined readers, it may be mentioned that when the (***M, R***)-system theory is put to use in this manner, the relationship between the theoretical and the empirical in fact aligns rather

well with Hasok Chang's (2022, p. 112) view that "Any meaningful correspondence we can actually work with is between two things that reside in the Kantian phenomenal world, not between our conceptions and bits of the noumenal world." This is because instead of explaining life by postulating noumenal or unobservable entities (or by borrowing candidates for such from physics), we are making sense of it by establishing meaningful relations between such aspects of living organisms that can be separately *described* (i.e., as Kantian phenomena). The purpose of theory is to give a framework for doing this, and above, I developed the concepts of metabolism and repair as general loci into which distinct types of descriptive knowledge can be encoded. Thus, what we obtain is, indeed, a third-way-biology: it is neither "mechanism" that essentially denies life as a phenomenon, considering it as a biased conception or an "appearance"; nor is it "vitalism" that accepts the phenomenon but postulates a noumenal vital force. On my reading, Rosen's epistemology is quite compatible with seeing the function of theory in this light (Weckström, 2023). What theory gives us are relevant *questions* to be asked of a given living organism, or analytical probes. And to me, it seems that the questions (i-iii) from above indeed are quite relevant probes in the examination of any component of any living organism, and that an examination in terms of them does yield an account of a living organization that may, amongst other things, die, and be to that extent regarded as being alive (see Weckström, 2025 & 2026 and below).

4. Replication

Humberto Maturana and Francisco Varela (1987, pp. 55-70) make an elementary but crucial observation about replication, or rather about reproduction,[7] that applies independently of the material details of the reproducing unity. It is that reproductive replication, if going to occur through a division by a fracture, can only happen if the original unity is organized in a *distributed*, or *non-compartmentalized* manner. Otherwise division cannot yield two new unities of the original type. For instance, dividing a radio in two would not yield two radios but two parts of a broken radio; in contrast, dividing a bunch of grapes or a piece of chalk in two would yield two bunches of grapes or two pieces of chalk, respectively (*ibid.*). Similarly, dividing a non-modular multicellular organism in two would yield two parts of a dead organism, and dividing an eukaryotic cell at a wrong moment of the cell cycle would not re-produce the organized cell, but would, instead, produce two non-functional organizations in which the nucleus and the endoplasmic reticulum, for example, might end up in one daughter unity but not in the other. Therefore, from an organizational point of view, those activities which we tend to associate with the "replicative mode of behaviour" can, quite generally, be regarded as *de-compartmentalizing activities* – a sort of an inverse of compartmentalization, differentiation, and development. Familiar examples would be the duplication of chromosomes, the breakdown of the nuclear envelope, the increase in the number of mitochondria and other cell organelles resulting in their distribution, etc. It is only after such preparations that cytokinesis can actually re-produce the *organization* in question.

In the present practical interpretation of the (***M, R***)-system, knowledge of such activities is to be included in the replication mapping β, which in the formalism is "internalized" such that it is taken to be a specific element (or a set of elements) in the set of metabolic outputs; $\beta \in B$. Thus, β is something which is produced by metabolic activity and which "catalyses", or triggers and facilitates, replication by acting on the metabolic machinery f itself – and the output of its action will be a new repair organization Φ. Hence, the formal image of this is $\beta : f \rightarrow \Phi$, and incorporating it into the diagram of Fig. 2 yields the full, original (***M, R***)-system as presented in Fig. 3.

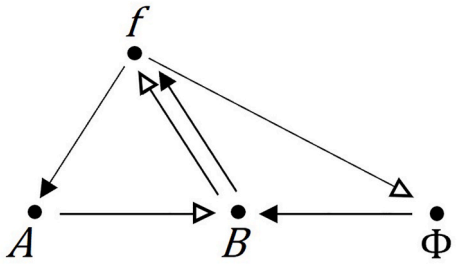


Fig. 3. The full (***M, R***)-system, in which a set of elements $\beta \epsilon B$ acts on the metabolizing system f (solid-headed arrow), and entails or processes (the replication of) the repair organization Φ (hollow-headed arrow).

Thus, in the diagram of Fig. 3, the existence of the repair organization Φ is no longer taken for granted, as it was in Fig. 2, but is rather accounted for by the replicative activity $\beta : f \rightarrow \Phi$, which in a way generalizes the phrase *omnis cellula e cellula*. The mathematics behind β are complicated, and will not be further inspected here. Instead, I shall proceed more empirically, and consider whether we can identify in real organisms entities that, firstly, act as components, in the sense of triggering or facilitating events; secondly, are produced by metabolic activity in the above sense; and thirdly, do not repair the metabolizing system, but act *on* the metabolizing components and *change* them such that de-compartmentalization, and eventual replication, may ensue. If such entities could be identified, they would seem to play, in our empirical descriptions of organisms, the inferential role encapsulated by $\beta : f \rightarrow \Phi$. As always, we may expect β to be decomposable into a set of more detailed descriptions $\beta_1, \beta_2, \ldots, \beta_m$.

Thus, suppose we have identified the following three objects of interest, in three different cells, and started to analyse each as a component according to the protocol (i–iii). These are: firstly, the "replication machine" which comprises DNA polymerases, DNA helicase, etc., and functions in duplicating the DNA of an *E. coli* bacterium (Alberts et al., 2015, p. 249); secondly, the cell-cycle control system (CCCS) of an eukaryotic cell, which "triggers the events of the cell cycle" (*ibid.*, p. 967); and thirdly, the contractile ring which facilitates cytokinesis in the final stage of mitotic division (*ibid.*, pp. 996-1000). Let us refer to these as $\beta_A, \beta_B,$ and β_C, respectively, and subject each to the three questions (i–iii):

i. What do $\beta_A, \beta_B, \beta_C$ do?

Appropriate answers can be read from any basic textbook on cell biology (*ibid.*, for instance). What is thus learned is that each does act, or can be described as acting, as a component: the replication machine facilitates DNA duplication while remaining, like a catalysing enzyme, itself intact in *this* process; the CCCS operates through a "series of biochemical switches, each of which initiates a specific cell-cycle event" while being itself largely "independent of the events it controls" (*ibid.*, p. 967); and the contractile ring generates "the force that divides the cytoplasm in two" (*ibid.*, p. 997). To this end, each can indeed be described as a component processing some "output". We may hence proceed to the next question.

ii. What does $\beta_A, \beta_B, \beta_C$?

It is obvious that the processes responsible for the existence of $\beta_A, \beta_B,$ β_C must be cellular processes: the elements of the replication machine are protein sub-units, the elements of the CCCS are cyclin-dependent

[7] These authors are strict in not using 'replication' as a synonym to 'reproduction', but since Rosen does not, as far as I can tell, restrict the uses of these terms similarly, I shall not confuse the present discussion by this. In the present context, we could e.g. say that the *replication* of DNA is an essential part of the *reproduction* of an organism, or that *concrete reproduction* may in such-and-such ways be modelled by the *abstract replication* of an organizational pattern, and so forth.

protein kinases, and the contractile ring consists in accumulated actin and myosin filaments (*ibid.*). But the key technical question is: Why to think of them as outputs of metabolic activity in the sense of $f_i : A_i \rightarrow \beta_i$, and not as products of repair in the sense of $\Phi_i : B_i \rightarrow \beta_i$? A more detailed analysis than what can be provided here would perhaps be in order (which may suggest some refinements of the language employed), but let us, for the moment, only outline the following brief argument. Above, Φ was defined as that organization which repairs the "metabolic" activity when the "replicative mode of behaviour" is *not* occurring. And when a cell is not undergoing replication, the functional activities of β_A, β_B, β_C would clearly be detrimental – thus, it may be both expected and observed that instead of being repaired, such activities are normally *prevented* from occurring. Hence, there is an empirical reason *not* to regard them formally as "outputs" of Φ. Nonetheless, regarding them as *specific* outputs of cellular, metabolic activity does make sense. Therefore, the last question:

iii. What do the doings of $\beta_A, \beta_B, \beta_C$ do?

Here, we must indeed conclude that each of $\beta_A, \beta_B, \beta_C$ does act on some f_i such that the outcome of this activity is to *change* f_i, and furthermore in such a way that this change belongs to a sequence of events that de-compartmentalizes the cell and eventually re-produces the respective organization. Considering β_A, we apply knowledge *of* the "replication machine" *on* the DNA and infer its duplication; considering β_B, we apply knowledge *of* the CCCS *on* e.g. the nuclear envelope and infer its breakdown; considering β_C, we apply knowledge *of* the contractile ring *on* the cell membrane and infer its division through the appearance of a cleavage furrow. Consequently, each can be seen as belonging to a sequence of events that is reasoned about through an inference of the form $\beta : f \rightarrow \Phi$. Therefore, via such "anomalous" answers to (ii) and (iii), entities like $\beta_A, \beta_B, \beta_C$ can be systematically identified as components to be associated with the replicative activity, or the replicative mode of behaviour, when applying the empirical protocol (i–iii).

In the re-production of non-modular multicellular organizations, which due to the requirement of non-compartmentalization normally proceeds through a single-cell stage and within a quasi-separate germline, analogous observations can be made. For example, one functional description of human semen could identify it as a component β_i which, firstly, acts on the components of the egg, notably on the cell membrane, and triggers its first divisions (in the sense of $\beta_i : f \rightarrow \Phi$); secondly, is produced by the metabolism or the physiology of male reproductive organs (in the sense of $f_j : A \rightarrow \beta_i$); and thirdly, makes no contribution to the repair of the male itself. Also, once the initiation of divisions is triggered in the egg, which had been delivered by the physiology of female reproductive organs as already non-compartmentalized (apart from awaiting for the other half of chromosomal material), drastic changes in the metabolizing or physiological components of the female will ensue – in other words, triggered changes on f will entail a change of the repair organization Φ. From an organizational point of view, these changes distribute the essential physiological functions between the mother and the developing child, allowing the bodies of the two to first co-exist and then separate, such that both may, in successful cases, remain alive. And thus, while knowledge of material-structural details is always to be obtained empirically, the (***M, R***)-system does seem to suggest a basically applicable framework for interpreting and reflecting on such knowledge – also in the case of a multicellular human being, when considered an "autonomous life form" amongst others. That this is so is neither miraculous nor trivial. As to the former, it is only a consequence of the fact that the human being, too, does satisfy the weak and general hypotheses upon which the formal (***M, R***)-system is constructed. As to the latter, not all natural systems, and neither machines, do satisfy them, which is one of the many reasons for biology to self-think its theoretical foundations (see e.g. Boogerd et al., 2007; Weckström, 2025). Amongst other things, those foundations should permit to explicitly avoid conflating a mechanical description of f_i with an (organizational) understanding of f_i; in other words, to resist the instinct that in an analysis of a natural system, one may rest content with a set of descriptions f. This instinct, it seems to me, is perhaps the essence of the "machine metaphor." A radio, for example, can be understood relatively well through a set f of descriptions of those functional components that constitute it, and the reason for this is that the components do not repair, let alone fabricate, each other, which in practice means that one can dispense with questions (ii) and (iii) almost entirely. Or, insofar as closure is "ignored in most accounts of life chemistry" (Cornish-Bowden and Cárdenas, 2020), one could think of those accounts, in general terms, as approximations under the hypothesis that organisms are like radios.

5. Discussion

5.1. Life as the opposite of death

The (***M, R***)-system is not an alternative to any widely accepted theory or conceptual framework in modern biology. Instead, it identifies an *object of scientific analysis* (or synthesis) which "standard biology" does not identify: the living organization, whose general features can be detached from specific evolutionary-historical circumstances (Weckström, 2026). One way of seeing this is to consider death, as the general and empirically observable endpoint of being alive. Namely, while "standard biology" says nothing general and explicit about death, the (***M, R***)-system immediately suggests to think of it as the breakdown of closure – if metabolism fails to metabolize, then repair will fail to repair, and conversely (Weckström, 2025). In the interpretative scheme developed above, this general idea translates to specific instances via specific responses to (i–iii) in the study of particular organisms. A simple example: suppose we had described, firstly, (i) the heart as entailing high-pressure blood out of low-pressure blood; secondly, (ii) its continuing functioning as being thus-and-so dependent upon the doings of other components, including gas exchange facilitated by the lungs; and thirdly, (iii) also the ways in which the doings of other components are dependent upon the heart's pumping. Then we would already have a framework, or an organized system of pieces of empirical information, within which to address the question of *why* a sufficiently severe failure of the heart *or* the lungs will result in empirically observable death. (In other words, we could then *encode* our knowledge of this organism into the closure formalism and *infer* such-and-such possible deaths, which might happen to *decode* into empirically sensible claims about the actual fate of the organism.) Accordingly, we would already have a basic framework in which to propose what death, as the opposite of life, in this case "is". And since the protocol (i–iii) is thoroughly general (not based on any specific structural assumptions), the same could be done with basically any organism, studied through considerations and descriptions of *its* components. On this basis, one could suggest that perhaps thinking more clearly about life may not, after all, require overly fancy new observations, or postulations of exotic new entities, but first of all a framework in which to "properly understand what we already know" (Rosen, 1991, p. 17).

5.2. Living organization and evolution

On the basis of the foregoing, it really is, in my view, instructive to compare the introduction of the (***M, R***)-system to Darwin's introduction of the theory of evolution. Evolution had been discussed long before Darwin and his ideas certainly were not the final word on how to understand it, but there is a non-trivial sense in which Darwin's theory, in particular, rendered evolution an object of explicit theoretical thought *and* empirical analysis. Simplifying a bit but not unduly, Darwin's insight permits us to approach any instance of evolutionary change by attaching concrete, case-specific meaning to the abstract, technical terms 'variation' and 'fitness' – which, in turn, will give concrete and case-specific

meaning to the further abstract and technical term 'selection'. Thus, what Darwin gave us was not so much a fixed image or explanation of evolution, but rather an inferential system of semantically open *loci*, in terms of which to analyse any instance of evolutionary change: What is varying in this case; how are those variations related to fitness? While theorizing, we can examine variation, fitness, and selection in abstract terms, debate on which "level" should concern us most, how fitness should be thought of and quantified, etc., and in empirical biology, we can try to see – to use Rosen's terminology – how variation and fitness might be "realized" in a case. On the basis of *both* kinds of activities, our thinking of evolution may *improve*; it may become more nuanced, less naïve, more realistic, etc.; new elements such as drift can be added, and so on. This resembles the relation between theory and practice in physics, and it is a productive relation.

Hence the question becomes, can we render living organization an *object* of study in the same sense? At least in the present interpretation of the (***M, R***)-system, the situation is rather analogous because also here, we have the basic abstract, technical terms 'metabolism' and 'repair', which, like 'variation' and 'fitness', can be applied at least as the first probes in the analysis of *any* component of *any* living organization: What is the metabolism of this component; how is it repaired within the organization? Furthermore, just like the inferential coupling of 'variation' to 'fitness' is what we call 'selection', here the inferential coupling of 'metabolism' to 'repair' is called 'closure', and as selection "accounts for" observed evolutionary phenomena, closure "accounts for" observed lives as the opposites of death. If we can give concrete, case-specific meaning to 'metabolism' and 'repair', then we have simultaneously given concrete, case-specific meaning to 'closure'. And this, it seems to me, is obviously something that can be further inspected both empirically and theoretically.

Moreover, the result of Section 4 was that by applying this *same* analytical protocol we may be able to identify, through "anomalous" answers to (ii) and (iii), such entailed processes that tend to eventually replicate the entire living organization, which is essential first of all because that is how we all living organisms, mules and monks included, come into existence (the origin-problem can be considered separately; see footnote 5). Thus, instead of braking a lance on whether an organism must "first" be alive before it can replicate and reproduce, we may acknowledge that organisms both stay alive and emerge with their living organizations from other living organizations; and we may apply the general (***M, R***)-system framework for organizing empirical knowledge about both aspects of this chicken-and-egg complex. (One could say: we have to *accept* the impredicativity, and try to model it as such.)[8]

In sum, therefore, it does seem to me that living organization can be made a definite object of study, and that doing so yields a form of understanding that is different from, and complementary to, our understanding of evolution. Thinking properly of organisms requires, on my opinion, both forms of understanding (and a bit more; see Weckström, 2026).

Historically, one should not forget that it took time, a lot of time, and e.g. the recovery from "the eclipse of Darwinism", before Darwin's insight could really become widely and systematically implemented into biological practice (Bowler, 2003). Moreover, further research has shown the original Darwinian insight to be both too limited (e.g., by lacking an account of drift), and in relation to many phenomena of historical change, perhaps even the wrong approach (Jablonka and Lamb, 2014). But what is important is that later improvements were only possible because the original proposal was sufficiently insightful, contained a sufficiently important kernel of truth, and was sufficiently systematically constructed. In a way, it was the "rest" of scientific thinking and scientific communities that needed time for becoming able to make use of the core insight, and this was perhaps even more prominently so in Mendel's case (Bowler, 2003).

5.3. The (*M, R*)-system and current biology

Thus, as more than half a century has passed since the introduction of the (***M, R***)-system, let us ask: has the intellectual climate changed meanwhile; might biological practice now be better prepared for making use of its insights? At least there are now many kinds of attempts to move beyond "the century of the genome" (Soto et al., 2016), which is also one aspect of recent discussions about the "extended evolutionary synthesis" (see e.g. Laland et al., 2015; Futuyma, 2017; Müller, 2017 and references therein). In relation to such conceptual concerns, what is particularly interesting in the (***M, R***)-system, at least in the above interpretation, is the formal entity Φ_i. For, on the one hand it accounts for the repair of some component f_i, and on the other, is always and explicitly taken to be something more than a molecular sequence of the DNA. Indeed, in a very precise sense, Φ_i is something that can never be detached from the organized living process itself, insofar as it by definition depends on the "metabolisms" or "physiologies" of several components. It is conceivable that this could permit the (***M, R***)-system analysis to "fuse" with contemporary currents in biology (in the sense of providing something new on which to work) better than a theory of life which posits a more static and traditional, structurally at least partly pre-figured image of information-storing nucleic acids (cf. Cornish--Bowden and Cárdenas, 2020).

As it stands, Φ_i is an abstract entity, but conversely it could be argued that perhaps the gene, if thought of as a molecular sequence, is "too concrete" for fulfilling the general task assigned to it in the received thinking. In other words, Φ_i might actually be *abstract enough*, such that whatever genetic, epigenetic, pleiotropic, polygenetic, interactive, etc. descriptions must be included when accounting for a trait or a phenomenon, they can in fact be included – and yet discussed, at some level at least, in a systematic language. Moreover, on the basis of the foregoing we could say that Φ_i is abstract only *until* the concrete, biological questions it implies have been asked, when considering a case (hence, abstract in the same sense as 'variation' and 'fitness' are). That is, one must ask: what is the Φ_i of *this* epigenetically adjusted trait; what is the Φ_i related to *this* multifactorial disease (Noble and Noble, 2025); what is the Φ_i of *this* especially rarely mutating region of the DNA (Zhang, 2022; Monroe et al., 2023)? There is nothing unjustifiably abstract in *answers* to such questions, and the function of the symbol Φ_i is only to pull those answers into an inferential structure (theory). Also, referring to an organization of processes in the sense of Φ_i would arguably be, in perhaps the majority of cases, a better way of answering such questions than trying to insist, "because gene(s) X".

In the same vein, development may be thought of as a living process in which temporary organizations Φ "repair with modification" the respective sets of components f which, by definition, will modify Φ itself (insofar as it *is* an organization of the components it repairs). The mature adult organization could be thought of as a "stable", fully re-compartmentalized organization Φ, in which the effect of repair is only to maintain. If so, the basic question about development would be something like: What is the Φ_i of this f_i, in this developmental stage? Answers to such questions would have to include (as they generally do in the empirical realm) accounts of active and passive genomic regions, *and more*. A theorist could, by building more formal structure (e.g., anticipation – see Kineman, 2011) into Φ and in dialogue with empirical cases, try to distinguish in general terms between situations in which Φ either "repairs with modification" (development), or "only repairs" (maintenance); hence, try to answer more explicitly what it means, from an organizational point of view, to be an adult. Plasticity, robustness, and related matters could be conceptualized in terms of Φ_i-Φ_j and Φ_i-environment interactions (see e.g. Uller et al., 2024; West-Eberhard, 2003).

[8] I see here some resemblance to Wittgenstein saying in *Remarks on the Philosophy of Psychology* that "Not to explain, but to *accept* the psychological phenomenon—that is what is so difficult."

5.4. The pedagogical problem of biology

A word also deserves to be said of how the (***M, R***)-system as developed in the present paper relates to the basic *pedagogical* challenge of biology, which is to deliver general lessons without distorting and mispresenting the characteristic diversity of the biosphere. In the past century, the basic approach was to say that however different organisms are from one another, they can always be reasoned about, individually and collectively, "in the light of evolution" (Dobzhansky, 1973). But on the basis of the foregoing, it could be said that organisms can, in addition, be reasoned about in the light of their basic manner of organization; this is what is captured by the weak and general hypotheses of the (***M, R***)-system. It seems that an *E. coli* bacterium as much as a *H. sapiens* could be used for exemplifying those hypotheses in a pedagogical act, e.g. through the protocol (i–iii) – that is, each could be considered an example of an "autonomous life form." If so, the balance between the systematicity of thought on the one hand, and the appreciation of natural diversity on the other, would remain quite acceptable also with this approach on the menu, I think.

5.5. Biology, physics, and the scientific worldview

In the present study, I have focused on the practical application and interpretation of the (***M, R***)-system, without paying much attention to its wider philosophical and interdisciplinary consequences. However, one should not expect that a foundational and general conceptualization of living organization could simply be "added" to the body of existing ideas. I have studied the epistemological aspects of Rosen's system more thoroughly in Weckström (2023), and the physics-biology relation in Weckström (2025). In brief, "adding" a general conceptualization of living organization changes the philosophical-fundamental view of *every* material event inside an organism: what previously happened "because" of such-and-such laws of physics and chemistry and some past selection that had acted on the molecular sequences of the DNAs, happens now (also in general technical formalisms, and not only in thus devised philosophy) "because" the organization entails that entailment to happen. Thus, "mechanistic" knowledge of the form f no longer needs to be seen as the most fundamental form of knowledge because it is *always* dependent on "organizational" knowledge of the form Φ, but in order to get freed of the tacit assumption of algorithmic state-transition sequences "underneath everything," a separate argument may be needed (Weckström, 2025). As Cortês et al. (2024) succinctly put it, "We cannot hope to answer questions in biology by integrating the equations of motion" (see also Kauffman and Roli, 2023; Patra and Kauffman, 2025) – and in fact, it would not be entirely incorrect to say that integrating the equations of motion is a worthwhile strategy if and only if there is no complex Φ to be considered. Consequently, the "old" physical intuition and modes of analysis tend to lead astray (if applied beyond specifically tailored experimental circumstances) when considering material events that happen inside organisms, which clearly is a major theoretical challenge for *both* physics and biology. The embedding of the essentially biochemical-biophysical inference from DNA to RNA to protein (i.e., the Central Dogma) in an organizational, entailing context (Igamberdiev, 2023a) is an example of confronting one aspect of this challenge; the other concerns more explicit articulation of the general limits of received physical thinking. The implications of such considerations are, of course, far-reaching.

5.6. The (*M, R*)-system and other theories of life

Lastly, I may briefly comment on the relationship of the (***M, R***)-system to other theories of life, especially to Gánti's Chemoton, Maturana's and Varela's Autopoiesis, and to the more recent account of Biological Autonomy in terms of Closure of Constraints (Moreno and Mossio, 2015). The (***M, R***)-system, as I see it, is first of all an inferential framework, rather than a representative "image" of life or a list of properties to be associated with the living state.[9] By emphasizing this, I am certainly not claiming that the other theories should be seen as such constructs, but I do think that Rosen, due to his extensive examinations into the epistemology of science, rethought the role of theorizing in these directions most thoroughly. The consequence is that his theory perhaps appears to be more "abstract" than the others, but as I have tried to argue throughout the paper, being abstract in this sense can be quite different from being a useless theory (if one knows how to use it). The comparison to Darwin's theory was intended to further illuminate this point.

Indeed, by starting neither from a list nor from an "image" of life, but (much like Darwin) from "weak and general hypotheses" and their formal expression, the (***M, R***)-system is minimal in prefiguring (Chang, 2022) anything about the organism to be examined; the "facts" are not inbuilt into theory (which serves as an inferential device), but are rather to be learned from the real organism itself. The purpose of the theory is, on the one hand, to generate general insights that do not depend on any structural details, and on the other, to serve as a frame into which particular facts of particular organisms can be mapped. Moreno and Mossio (2015, p. 27) ask explicitly why Rosen developed his closure at a higher level of description than they, namely, "between very general classes of functions, not just between individual constraints"; I hope the considerations of the present study to provide at least a partial answer or approach to this question. Also Letelier et al. (2003) acknowledge the higher level of generality as a characteristic of the (***M, R***)-system, since they propose to think of autopoietic systems as a subset of the set of (***M, R***)-systems.

Considering the case of structural boundary may provide some further insight. In particular, let us ask: Should a general theory of life include it explicitly – as the (***M, R***)-system apparently does not, while both the Chemoton and (the later version of) Autopoiesis do (Cornish-Bowden and Cárdenas, 2020)? It is a known fact of known organisms that they are enclosed by a structural boundary, but the question is how to conceptualize it in an inferentially effective manner. Arguably, any attempt at being more specific about the boundary will be restricted on the one hand by the *material diversity* of real boundaries, and on the other by their *functional complexity*. As to the former, it is evident that the structural boundaries of amoebas are rather different from the structural boundaries of dinoflagellates, which in turn are quite different from the skins of humans; therefore, even though e.g. the boundary of the Chemoton is represented in relatively abstract terms, it is still likely to please more a biochemist than a human physiologist. As to the latter, if we prefigure the complex boundary as a subsystem, then *we* are pre-imposing this system-subsystem partitioning to the organism

[9] Cornish-Bowden and Cárdenas (2020) claim that Rosen "doubted whether a useful checklist had ever been produced, but he still regarded it as necessary for defining life." Then they quote Rosen (2000, p. 2) saying that "Without such a list, Schrödinger's question, and biology itself, become unanswerable at best, meaningless at worst." This is where the quote ends. However, immediately the next sentence would have been: "So we must probe more deeply into what the quest for such a list actually connotes," and shortly thereafter Rosen continues: "I take seriously the possibility that there is no list, no algorithm, no decision procedure, that finds us the organisms in a presumptively larger universe of inorganic systems" (p. 3). A moment later still: "Rather than an organism being just a standard material system plus a list of special conditions, an organism is a repository of meanings and impredicativities" (p. 4); that is, a complex natural system we can try to systematically understand, but whose character we cannot definitely pre-state and pre-figure in theory (see the main text). Thus, it seems to me that Rosen's opinion was quite the opposite of what is claimed, which might be good to take into account when comparing the (***M, R***)-system to other theories of life on the basis of how they relate to, or fulfil, a list of specific properties (Table 5 in Cornish-Bowden and Cárdenas, 2020). See the main text about the properties taken to be missing from the (***M, R***)-system (viz., structural closure, information coding, controlled growth, reproduction, and evolvability); and concerning thermodynamical openness, see footnote 4.

we study (see Weckström, 2023), and the question becomes: Where does the "boundary subsystem" begin and end, and are its limits objective? In my opinion, these are far from trivial problems, and if a theory is in fact used for making sense of an organism, the way in which the theory is used (how various aspects of the organism encode into theory) is essentially and directly dependent on solutions to these sorts of problems. Boundaries are complex entities both in terms of what they "do", and in terms of the processes that "do them"; they are not mere structures.

Thus, what is especially interesting in the (***M, R***)-system is the extent to which it can avoid prefiguration of this kind; that is, the manner in which it lets the *organisms* tell us the relevant facts of their boundaries. Namely, if we simply regard boundaries as identifiable components amongst others, and inspect them through the questions (i-iii), then we can study them with high systematicity in *all* of their material diversity and functional complexity. *As* we study them, the vital roles of the boundaries will be accounted for (i.e., through the question (iii) of the scheme). Also, in this way our knowledge of a particular boundary becomes immediately integrated with other knowledge of the respective living organization, i.e. with that knowledge from which we may e.g. infer death, and without a prefigured subsystem partitioning. The above considerations about the DNA, and especially about including it in theory as something that *participates* in complex repair organizations Φ instead of representing it in pre-figured structural terms, relate closely to this. To some extent, what one prefers and expects from a theory might be a matter of taste and focus, but the *generality* of the (***M, R***)-system is, in my view, undeniable.

Be that as it may; by consulting Rosen's own writings (Section 2), it would seem important to emphasize, in a comparison of the (***M, R***)-system to other theories, the incorporation of (biological) replication without invoking further *ad hoc* hypotheses. As was noted above, this means, in the interpretative scheme developed in the present paper, that studying replication does not require us to posit an additional theoretical structure, but can, instead, be studied within the framework of the basic questions (i-iii). Furthermore, it seems that also here, the situation then becomes such that instead of the theory prefiguring an answer of the form "Replication *is* this," the scheme rather suggests a systematic way of inspecting the question "How may replication come about in *this* case?" In other words, the theory invites us to study the organism itself, in order to learn how the existence of its Φ was entailed. In a sense, all the theory presupposes is that Φ was entailed (did not just "appear"), and that it was entailed from within the somatic activities of a living organization, which would seem to be weak and general, and therefore not easily resistible, hypotheses indeed.

Statements and declarations

The author has no competing interests to declare that are relevant to the content of this article.

Declaration of competing interest

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