An applied mathematician's perspective on Rosennean Complexity

Ivo Siekmann[a]

[a]*Institute for Mathematical Stochastics, Georg-August-Universität Göttingen, Goldschmidtstraße 7, 37077 Göttingen, Germany*

Abstract

The theoretical biologist Robert Rosen developed a highly original approach for investigating the question "What is life?", the most fundamental problem of biology. Considering that Rosen made extensive use of mathematics it might seem surprising that his ideas have only rarely been implemented in mathematical models. On the one hand, Rosen propagates relational models that neglect underlying structural details of the components and focus on relationships between the elements of a biological system, according to the motto "throw away the physics, keep the organisation". Rosen's strong rejection of mechanistic models that he implicitly associates with a strong form of reductionism might have deterred mathematical modellers from adopting his ideas for their own work. On the other hand Rosen's presentation of his modelling framework, (M, R) systems, is highly abstract which makes it hard to appreciate how this approach could be applied to concrete biological problems. In this article, both the mathematics as well as those aspects of Rosen's work are analysed that relate to his philosophical ideas. It is shown that Rosen's relational models are a particular type of mechanistic model with specific underlying assumptions rather than a fundamentally different approach that excludes mechanistic models. The strengths and weaknesses of relational models are investigated by comparison with current network biology literature. Finally, it is argued that Rosen's definition of life, "organisms are closed to efficient causation", should be considered as a hypothesis to be tested and ideas how this postulate could be implemented in mathematical models are presented.

Keywords: Robert Rosen; Complexity; Network biology; mechanistic models; definition of life

*Corresponding author
Email address:* `ivo.siekmann@mathematik.uni-goettingen.de` (Ivo Siekmann)

1. Introduction

When for the first time I heard about Robert Rosen's life-long quest for the secrets of life, his theory of (M, R) systems and his approach to complexity I didn't quite know what to make of all this. There was an obviously highly original idea for investigating a question which is so hard to answer that it is, in fact, rarely asked: What is life? Also the methods that Rosen used for his work, borrowed from the highly abstract theory of categories, do not quite fit in the classical arsenal of the applied mathematician's toolbox. Could category theory, an area of mathematics so abstract that, in fact, even some of its pioneers referred to it as "abstract nonsense" be successfully applied to a fundamental real-world question "What is life?" which at the same time happens to be one of the hardest scientific questions that one may possibly ask?[1] That sounded interesting, very interesting, indeed!

So I asked two questions that I usually ask myself when I hear about something new and exciting to me in science:

1. Which of Rosen's ideas can I steal for my own work? (more about stealing later, see Section 5.3!)

2. Do I believe Rosen's answers to his research questions "What is life?" and "What is a complex system?"

I will present my answers to these questions as my personal perspective on Robert Rosen's work. The purpose of this is two-fold: First, in my opinion, Rosen's highly original work deserves more attention from the mainstream of mathematical biologists. Second, I believe that Rosen's frustration that his ideas were not more widely and openly accepted (Mikulecky, 2001) is not completely coincidental—there are important differences between Rosen's theoretical concept of a model and the understanding of modelling within the applied mathematics community. These differences are on the one hand philosophical— Rosen demands that a model accurately represents the causal relationships between the elements of the system to be modelled (see Section 4) whereas models typically built by

---

[1]Rosen's work on (M, R) systems is by no means the only application of category theory to the sciences. Best-known are perhaps applications in computer science— two examples for textbooks are Pierce (1991) and Barr and Wells (2012)—as well as mathematical physics (Coecke, 2011). A recent introduction to category theory with a view towards applications in the sciences by Spivak (2014) underlines the the fact that the trend of category-theoretic ideas in science is increasing. But Rosen's work is one of the earliest, if not the earliest application of category theory outside mathematics.

applied mathematicians can be regarded as formal representations of a *hypothesis* regarding a possible mechanism underlying the system behaviour (see Section 5). On the other hand, Rosen applies mathematical notions, in particular, category theory, in a different spirit than most applied mathematicians would. This issue—which is related to Rosen's presentation of his ideas rather than the ideas themselves—is more important than it may look at a first glance because this difference in using mathematical tools may deter an audience with a mathematical background from Rosen's ideas (Section 6.2.1). My presentation is based on the original publications Rosen (1958a,b, 1959, 1971, 1973, 1991) and Rosen (2000) but I will most often refer to Rosen (1972) because this, in my opinion, is the best summary of Rosen's early publications and to his monograph "Life Itself" (Rosen, 1991) which is the most comprehensive account of the philosophical basis of Rosen's work. Another good introduction into Rosen's thinking are his "Autobiographical Reminiscences" (Rosen, 2006).

The article is structured as follows: In Section 2 we introduce the notions of metabolism-repair systems ((M, R) systems). In Section 3 we present Rosen's proposed characterisation of life as systems that are "closed to efficient causation". We show that this concept is not—as Rosen suggests—a specific property that can be deduced from the architecture of (M, R) systems but should be regarded as a postulate, a hypothesis to be tested by implementing "closure to efficient causation" in mathematical models. Rosen's specific view of modelling which is closely related to his interpretation of category theory is presented in Section 4. I describe the conceptual basis of mechanistic models in Section 5. In particular, I will argue that Rosen's relational models can be regarded as a specific type of mechanistic models. In the Discussion (Section 6) I compare mechanistic models with Rosen's perspective on modelling and present some ideas how his concept of an organism could be investigated via mathematical models in physiology and ecology.

2. Rosen's answer to the question "What is life?"

Although most people—with or without a scientific background—seem to have a good intuition when it comes to decide if something is "alive" it is nevertheless very hard to come up with a rigorous scientific definition of life. Thus, definitions of life are usually descriptive—a list of properties that are characteristic of living systems is given such as the following appearing in Campbell (2008):

1. *Order.* Organisms are highly ordered, and other characteristics of life emerge from this complex organization.

2. *Reproduction.* Organisms reproduce; life comes only from life *(biogenesis).*

3. *Growth and Development.* Heritable programs stored in DNA direct the species-specific pattern of growth and development.

4. *Energy Utilization.* Organisms take in and transform energy to do work, including the maintenance of their ordered state.

5. *Response to Environment.* Organisms respond to stimuli from their environment.

6. *Homeostasis.* Organisms regulate their internal environment to maintain a steady-state, even in the face of a fluctuating external environment.

7. *Evolutionary Adaptation.* Life evolves in response to interactions between organisms and their environment.

But these properties are not necessarily defining: systems that are not usually considered to be living systems may have one or even several of these properties. Indeed, Campbell (2008) refers to this list as emergent properties and processes of life rather than a definition.

Instead of a descriptive definition, Rosen proposes a relational approach for distinguishing systems that are "dead" from systems that are "alive". He starts from a set of components that he explicitly refers to as black boxes i.e. he avoids making any assumptions on the internal structure of these components. Instead his focus is on the relationships between these components—he develops a highly abstract theory with the purpose of demonstrating that the way that components interact determines if a system is "complex" or "simple" and also, if a system is "alive" or "not alive". By developing an approach that intentionally ignores the properties of individual components of a system and emphasising the relationships between these components he followed a motto of his mentor Nicolai Rashevsky (cited according to Rosen (2006))—"Throw away the physics, keep the organisation".

More generally, the question of the relationship between structure (i.e., for example, the underlying physics) and function in biology has a long history. For example, the famous Cuvier-Geoffroy debate in front of the French Academy of Sciences in 1830 was ultimately about the two principles "form follows function" which was Georges Cuvier's view whereas Geoffroy Saint-Hilaire argued for the opposite position "structure determines function". In Rosen (1991), his monograph "Life itself", he strongly rejects "structure

determines function" which is currently, for example, influential in molecular biology in the theory of protein folding—because the sequence of amino acids (primary structure) to a great extent controls the three-dimensional arrangement (tertiary structure) and this 3D structure determines the function of a protein it is argued that structure determines function (Petsko and Ringe, 2008).

In contrast, Rosen states that biological functions arise from the interactions between the parts of a biological system, independent of the material realisation of the components. In order to explain this idea, let us consider calcium signalling. In many cases when hormonal or electrical signals reach a cell, calcium oscillations are used for propagating these signals within the cell and control a wide range of cellular functions such as the contraction of heart cells or the transcription of particular genes. The shape of these oscillations can be very different between cell types although the Ca^{2+} signalling components involved are the same—voltage-gated Ca^{2+} channels, that allow calcium influx in response to electrical signals, intracellular channels like the inositol-trisphosphate or the ryanodyne receptor, that release large amounts of calcium from intracellular stores when stimulated, and Ca^{2+} pumps, that return Ca^{2+} released to the cytosol back to intracellular stores. How can Ca^{2+} oscillations be so different in different cell types if they are generated by similar sets of Ca^{2+} signalling components? An obvious explanation is that Ca^{2+} oscillations in particular cell types are shaped by relationships between the components that are characteristic of this cell type. This is the concept of the Ca^{2+} "toolbox" which is the basis of our current understanding of Ca^{2+} oscillations (Berridge et al., 2000). But does the fact that differences in the relationships between components are important for explaining the different shape of Ca^{2+} oscillations imply that we should restrict ourselves to investigating relationships and completely ignore structural properties of the components? We will come back to this question in more general terms in the Discussion.

From Rosen's introduction of his (M, R) systems it is quite clear that he not only wishes to apply this approach for explaining the behaviour of particular biological systems but from the outset he aims for answering the grand question "What is life?". As for many models, also for (M, R) systems the answer to his question "What is life?" is already determined to some extent by the construction of the model—this will be explained in more detail in Section 5. Here, we will demonstrate that Rosen focuses mostly on two of the aspects of life mentioned above, energy utilisation (in the following referred to as metabolism) and homeostasis.

5

The M in (M, R) systems refers to metabolism. Metabolism is formally modelled as the transformation of "input materials" to "output materials" via the action of *components*. Mathematically, components are represented as mappings

$$f : A \to B, \quad a \mapsto b = f(a) \tag{1}$$

between sets A ("input materials") and B ("output materials"). In biochemical terms, f may be interpreted as an enzyme because it catalyses the transformation of elements of A to elements of B while remaining unchanged.[2] However, in real metabolic networks, enzymes degrade so that f will eventually "disappear".[3] Thus, in order to ensure long-term stability, Rosen assumes for each component f of an (M, R) systems the existence of a component Φ that "replicates" f should it be degraded. We denote such a component Φ_f if we want to emphasise the fact that Φ_f replicates the component f. The mappings Φ are again components (called *repair components*) as defined in (1)

$$\Phi_f : C \to H(A, B), \quad c \mapsto \Phi_f(c) \tag{2}$$

but the range of Φ_f must be $H(A, B)$, the set of maps between A and B.[4] Also, it is postulated that the domain C of Φ_f contains at least one *environmental output O* i.e. there exits a subset of $O \subset C$ that does not contain the domain of any component f (Rosen, 1972).[5] With the repair components Φ (the R in (M, R) systems), Rosen adds a representation of homeostasis to his (M, R) systems—each Φ_f ensures the continuous operation of a particular component f. To give the repair components a biological interpretation similar to the enzymes f, Rosen sometimes refers to the Φ as genetic components. Thus,

---

[2]An adaptation of Rosen's terminology to biochemistry may be found in Letelier et al. (2006). Here, we keep the original terminology.

[3]The nature of this "disappearance" is not made explicit in Rosen's writings. He only states that disappearance of a component has the effect that the production of output material B stops.

[4]By using this notation, Rosen would like to imply that the maps appearing in $H(A, B)$ are "(homo)morphisms", maps that preserve mathematical structure associated with A and B rather than general maps—see Section 4 for an explanation of the category-theoretic notion of morphism via an example. But because Rosen avoids assigning a specific mathematical structure to the sets A and B this has no consequences for his model, in particular, the maps $H(A, B)$ cannot model, for example, biochemical properties of metabolism. Moreover, in many circumstances the morphisms $H(A, B)$ are still just a set even if A and B have a particular mathematical structure.

[5]By introducing Φ_f, strictly speaking, the set O fails to be an environmental output because it is now contained in the domain of Φ_f.

although this is not stated explicitly in Rosen's writings, he therefore characterises life as the combined effect of metabolism and homeostasis.[6]

Unfortunately, whereas the degradation of components f can be prevented by the repair components Φ, repairing these newly introduced components Φ would require another set of repair components. But Rosen was able to demonstrate that the infinite regress of having to add more and more repair components could be avoided—he proposed that under certain assumptions a repair component for Φ_f could be identified with an element from the range of f. Because a repair component for Φ_f (which Rosen denotes β and names *replication map*) therefore does not need to be added to the system, the infinite regress is avoided. We will discuss the construction of β in the next section, Rosen himself explains the details most clearly from a a mathematical point of view in Rosen (1972).

In summary, we observe that by suitably combining metabolic and repair components, an (M, R) systems is capable of achieving homeostasis. Although all components have a limited life time, the system is able to survive for much longer (in theory indefinitely) because components are replaced early enough before they degrade. Of course, this only refers to the components that are parts of the (M, R) systems because at least some of them depend on environmental inputs. This demonstrates that (M, R) systems are able to autonomously maintain their internal organisation, provided that an "energy source" (via environmental inputs) is available. We will explain Rosen's own formulation of this result in more detail in the next section.

3. Closure to efficient causation

In the previous section we explained that through interactions of metabolic and repair components a (M, R) system achieves some level of autonomy—it is capable of maintaining its internal components (which all have a limited life time) by drawing on an energy source from the environment. Rosen summarised this this as "organisms are closed to efficient causation". In "Life Itself" he discusses in detail how his theoretical ideas relate to the

---

[6]In Rosen's own biochemical interpretation of the components f as enzymes and Φ as genetic components, (M, R) systems can be related to the production of enzymes via gene transcription which itself depends on the activity of enzymes. But the abstract construction of (M, R) systems are general enough that the approach can be applied to different domains.

four Aristotelean causes,[7] one of which is the *efficient cause*. The efficient cause is most closely related to the modern notion of causality. In the context of (M, R) systems each of the components are the efficient causes of the transformation of elements in the domain to elements in the range, for example, in (1), f is the efficient cause for transforming A to $f(A) \subset B$. For the same example, A provides the *material cause* for the transformation of A to $f(A)$.[8]

We only consider the simplest (M, R) system,[9] consisting of one metabolic component f and one repair component Φ_f. In order to avoid degradation of the repair component Φ_f we need an additional repair component β that replaces Φ_f. Summarising (1), (2) and adding β we get

$$A \xrightarrow{f} B \xrightarrow{\Phi_f} H(A, B) \xrightarrow{\beta} H(B, H(A, B)). \tag{3}$$

Rosen develops a complicated argument why the map β in (3) can be identified with an element b of the set B. He explicitly constructs a parameterisation

$$B \ni b \mapsto \beta_b : H(A, B) \to H(B, H(A, B)) \tag{4}$$

that assigns a map β_b to each $b \in B$. Rosen's interpretation of (4) is that each β_b is, in fact, already contained in set B and needs not be explicitly added to the system. Rosen's construction of the β_b has caused a considerable amount of confusion—some authors disputed its mathematical feasibility (Landauer and Bellman, 2002) whereas others responded to this claim by explicitly constructing sets and maps as in (3) following Rosen's approach (Letelier et al., 2006).

In contrast, I will argue that from a mathematical point of view there is, in fact, nothing to show. The only restriction for β is the condition that $\beta(f) = \Phi_f$ which means in terms of (M, R) systems that β repairs Φ_f by transforming f. After choosing any map β that fulfils this condition, a parameterisation β_b as in (4) can be easily obtained—we only

---

[7]Applications of Aristotle's classification of four causes have some tradition in biology, confer Tinbergen's levels of analysis, first presented in Tinbergen (1963).

[8]Rosen also discusses the *formal cause* and the *final cause*. Although all four causes are important for Rosen's theory, the remaining two Aristotelean causes are not directly relevant to our discussion. Therefore we refer the reader to Rosen (1991).

[9]This is, in fact, not as strong a restriction as it may seem—by combining sets via Cartesian products '×' and defining maps on the products in an obvious way, several (M, R) systems with more than three components can be cast in the form (3).

need to select an arbitrary b^* that maps to $\beta_{b^*} = \beta$ and map all other elements of B to arbitrary β_b.

Rosen's difficulty arises because he insists on deriving the parameterisation β_b from evaluation maps, see Rosen (1972) where ϵ_b is denoted $\hat{b}$:

$$\epsilon_b : H(B, H(A, B)) \to H(A, B), \quad \Phi \mapsto \Phi(b). \tag{5}$$

But there is no reason for constructing the maps β_b in this way—the fact that the β_b were obtained from evaluation maps ϵ_b (5) never plays a role in Rosen's discussions of the replication map β. In summary, as Rosen postulated, it is indeed possible to construct (M, R) systems where all components are "repaired" by other components once they have surpassed their finite life time. But the realisation of the map β does not, as Rosen suggests, follow from the architecture of (M, R) systems. Instead, I propose to consider the existence of the replication map simply as a postulate regarding the structure of living systems, summarised in the statement "organisms are closed to efficient causation".

More interesting than the details of the mathematical investigation is Rosen's interpretation of (M, R) systems whose elements interact in a way that mutually ensures replacement of failing components. (M, R) systems with this property provide Rosen's model for organisms which he characterises as "organisms are closed to efficient causation". In order to explain this concept, Rosen (1991, chapter 10) presents a diagram that illustrates this statement (Fig. 1). The diagram shows—indicated by solid arrows—the "material" transformations between elements of the sets A, B, $H(A, B)$, $H(B, H(A, B))$ and $H(H(A, B), H(B, H(A, B)))$ (by a mapping to B) but also shows "causal" relationships—indicated by broken arrows—where components initiate a transformation by acting on elements in one of these sets. By following a broken and then a solid arrow we see that the production of each component is "caused" by another component in the system—in Rosen's own words, f "entails" β_b, β_b "entails" Φ_f and Φ_f "entails" f. Thus, the system contains a closed loop of efficient causation $f \to \beta_b \to \Phi_f \to f$, a property that Rosen denotes *closure to efficient causation.*

In summary, in this section we have explained Rosen's proposed definition of living systems, "organisms are closed to efficient causation". We have shown that "closure to efficient causation" is not a result that follows from the construction of (M, R) systems. In contrast, the ability of organisms to autonomously maintain their internal organisation should be regarded as a postulate, a hypothesis to be tested for concrete biological sys-
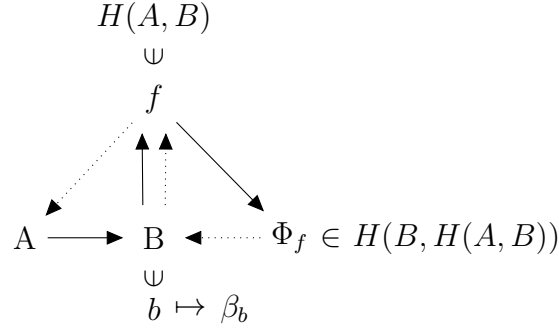
$$H(A, B)$$
$$\cup$$
$$f$$

$$A \longrightarrow B \longleftarrow \Phi_f \in H(B, H(A, B))$$
$$\cup$$
$$b \mapsto \beta_b$$

Figure 1: *Closure to efficient causation:* This diagram (adopted from Rosen (1991, chapter 10)) illustrates the different processes that the individual components of the (M, R) system in (3) are involved in. On the one hand, solid arrows show where transformations from input material to output material occur— A is transformed to B, B is, in turn used for "repairing" f whereas f is transformed in order to repair Φ_f. On the other hand, for the broken arrows, a component located at the start of an arrow indicates the initiation of a transformation located at the arrow tip—f catalyses the "metabolic" transition of A to B, Φ_f acts on B for repairing f and the replication map β_b starts the repair of Φ_f by transforming f. It is clear that each of the components f, Φ_f and β_b regulates the repair of another component. In Rosen's words, the sets A, B, $H(A, B)$ and $H(B, H(A, B))$ can be regarded as "material causes" whereas f, Φ_f and β_b are "efficient causes". Because each of the components is in turn produced by one of the other components the system is *closed to efficient causation.*

tems by developing mathematical models. We will return to this important idea in the Discussion.

4. The modelling relation

Interesting about Rosen's approach are not only (M, R) systems themselves but also how they are constructed and investigated. He uses category theory, one of the most abstract mathematical disciplines, that was developed starting from the 1940s.[10] In order to give a simple example that introduces many important aspects of category theory without requiring much mathematical background consider a planar algebraic curve.[11] Readers that are familiar with category theory may safely skip this slightly lengthy example but I

---

[10]The following introduction to category theory is intentionally informal—the point is to introduce the spirit of category theory rather than enabling the reader to start their own career as a category theorist. See the Introduction of the classical monograph by Mac Lane (1971) for a very readable exposition for the mathematically inclined reader.

[11]This is, in fact, the first example of category theory that I saw as a student. I thank Prof. Heinz Spindler (University of Osnabrück, Germany) for his beautiful lectures on algebraic geometry that gave me a lot of pleasure.

hope that it may be helpful for readers without prior knowledge of category theory. The main purpose of this section is to explain that the precise meaning of Rosen's notion of a *modelling relation* may be regarded as the *representation* of a *functor* between different categories. This has been explained more formally by Louie (2009).

4.1. Algebraic curves or: an introduction to category theory

An algebraic curve in the plane is defined by a polynomial equation in two indeterminates x and y i.e. f is an element of a polynomial ring $K[x, y]$. Examples include the parabola, $y - x^2 = 0$ or the unit circle, $x^2 + y^2 = 1$. Geometrically, the curve is the set of pairs (a, b) that fulfil the equation $f(x, y) = 0$; the (a, b) are elements of a two-dimensional vector space R^2. One of the most important aspects of modern algebraic geometry is not to be very specific about R, the interest is in general properties of algebraic sets defined by systems of polynomial equations. Whereas classical algebraic geometry investigates polynomial equations over the complex numbers $\mathbb{C}$, we may instead consider the real numbers $\mathbb{R}$, the rationals $\mathbb{Q}$ or a finite field with q elements $\mathbb{F}_q$.[12] Even more generally, we may choose an algebra R over a field K. A K-algebra is a vector space over a field K whose elements can in addition be multiplied, unlike in a general vector space which only requires addition of elements. Because, trivially, a field can be regarded as a one-dimensional K-algebra over itself, this includes the examples of different fields given above. The generality with which R can be chosen is expressed quite clearly by the following category-theoretic description of an algebraic curve. For an arbitrary non-constant polynomial $f \in K[x, y]$, the affine planar algebraic curve C over R with equation f is defined as the *functor*

$$\mathscr{C} : \mathscr{A}\ell g_K \to \mathscr{S}ets \tag{6}$$

with

$$\mathscr{C}(R) = \{(a, b) \in R^2 | f(a, b) = 0\} \tag{7}$$

for all K-algebras R. Thus, $\mathscr{C}(R)$ is the set of zeroes of f over R^2 which means that the functor $\mathscr{C}$ provides us with a set for each K-algebra. From the category-theoretical point

---

[12]A *field* K is an algebraic structure where addition and multiplication of elements are *associative*, *commutative* and *distributive* and additive and multiplicative inverses exist. This means that for each $a \in K$ we find a $b \in K$ so that $a + b = 0$ (b is denoted $-a$) and for each $c \in K$, $c \neq 0$ there is a $d \in K$ such that $c \cdot d = 1$ (d is denoted d^{-1}). Examples are the complex numbers $\mathbb{C}$, the real numbers $\mathbb{R}$, the rational numbers $\mathbb{Q}$ or finite fields $\mathbb{F}_q$ with q elements.

of view, each K-algebra R is an *object* of the category of "all" K-algebras $\mathscr{Alg}_K$ and "all" sets are the objects of the category $\mathscr{Sets}$[13]. But a category not only consists of objects but also of maps between objects that preserve the algebraic structure of the objects, so-called *morphisms*. For $\mathscr{Sets}$ the morphisms are just ordinary maps but for $\mathscr{Alg}_K$ these are K-algebra homomorphisms $\phi : R \to S$. As a map between categories, a functor not only relates objects but also morphisms. For our example, for a K-algebra homomorphism $\phi : R \to S$ between K-algebras R and S we obtain a corresponding map $\phi_* : \mathscr{C}(R) \to \mathscr{C}(S)$ between the sets $\mathscr{C}(R)$ and $\mathscr{C}(S)$ via

$$\phi_* : \mathscr{C}(R) \to \mathscr{C}(S), \quad (a,b) \mapsto (\phi(a), \phi(b)). \tag{8}$$

Because ϕ is a K-algebra homomorphism it is indeed true that if (a,b) is a zero of f (over R^2), $(\phi(a), \phi(b))$ is also a zero of f (over S^2).

This abstract representation of a planar algebraic curve as a relationship between K-algebras and the geometric objects of interest, the sets $\mathscr{C}(R)$, has a punch line that may give some insight why category-theoretical ideas have been quite successful in some areas of mathematics but, more importantly, clarify one of Rosen's key ideas, the *modelling relation*. It can be shown that for describing algebraic curves it is sufficient to consider only one particular K-algebra, the *coordinate ring*[14]

$$A = K[x,y]/(f), \quad \text{where } (f) = fK[x,y]. \tag{9}$$

With the expression $fK[x,y]$ we denote the set of all polynomials that contain the polynomial f as a factor. The crucial point is that the the coordinate ring A alone is sufficient for finding the curves $\mathscr{C}(R)$ for *all* K-algebras R. We remind the reader that the functor $\mathscr{C}$ assigns the evaluation map $\phi_* : \mathscr{C}(A) \to \mathscr{C}(R)$ defined in (8) to each K-algebra homomorphism $\phi : A \to R$. It can be shown that we can calculate the curve $\mathscr{C}(R)$ via

$$\phi_*([x],[y]) = (\phi([x]), \phi([y])), \quad [x],[y] \in A. \tag{10}$$

by evaluating ϕ_* at the particular point $([x],[y])$.[15] In category-theoretical terms, the coordinate ring A is called a *representation* of the functor $\mathscr{C}$ via the *universal element* $([x],[y])$.

---

[13]Due to set-theoretic paradoxes, we can, in fact, not consider categories of "all" K-algebras or "all" sets.

[14]A (commutative) ring is an algebraic structure similar to a field. The difference is that multiplicative inverses are not required to exist for all elements. Note that in addition to the ring structure the coordinate ring also has the structure of a K-algebra.

[15]$[x]$, $[y]$ are equivalence classes and can be considered as those polynomials with "remainder" x or y,

Informally this means in the context of our example that some objects of the category $\mathcal{S}ets$, algebraic curves defined by f, can be understood by analysing a particular K-algebra, the coordinate ring A.

4.2. The modelling relation and simulation

We will now—still with the example of a planar algebraic curve—explain that Rosen's idea of a *model* can be understood as a functor between a natural and a formal system. Both the natural as well as the formal systems are represented as categories, in fact, shortly after the initial introduction (Rosen, 1958a), Rosen (1958b) redefined (M, R) systems using category-theoretical ideas—we will discuss Rosen's use of category theory in Section 6.2. It is instructive to observe how the representation of the "planar algebraic curve functor" $\mathcal{C}$ that assigns to a K-algebra R a curve $\mathcal{C}(R)$ is used by mathematicians working in the field of algebraic geometry.

Let us say that algebraic curves are the "natural system", graphs obtained by finding the zeroes of a polynomial equation $f(x, y) = 0$. In contrast, we regard K-algebras as a "formal system" that—according to Rosen—encodes the "causal entailments" present in the natural system. In general, causal entailment refers to the relations between objects defined by the morphisms of a category which is quite abstract. But for the specific example of algebraic curves it is quite clear what this means. From a mathematical point of view, studying a general algebraic curve over a general K-algebra R is impossible without further assumptions on the K-algebra R because sets do not have a lot of structure. In contrast, for K-algebras, arithmetical operations such as addition and multiplication are defined and mathematical theorems have been proven that give insight into how the elements behave under these operations. Thus, whereas the structure of K-algebras may be investigated with a variety of tools from commutative algebra, much less insight can be gained by simply considering the sets $\mathcal{C}(R)$ of algebraic curves over R. But the functor $\mathcal{C}$ enables us to switch between the "natural system" (sets) and the "formal system" (K-algebras) so that we can explore geometric facts using algebra. Incidentally, algebraic geometers are well aware of this and refer to this process with the motto "Think geometrically, prove algebraically!" (Alekseevskij et al., 1991).

---

respectively, when "dividing" by f—the coordinate ring is an example of a *quotient ring*. We will not go into more detail because it does not add much to the discussion and refer the interested reader to any introduction to algebra.

Each K-algebra R can be understood as a "model" of another K-algebra S because we can "translate" the algebraic curve $\mathscr{C}(R)$ over R to the algebraic curve $\mathscr{C}(S)$ over S using the functor $\mathscr{C}$ by assigning the evaluation map ϕ_* to each K-algebra homomorphism $\phi : R \to S$. Even better, because the functor $\mathscr{C}$ has a representation via the coordinate ring A (9) we may even resort to studying only *one* K-algebra, namely the coordinate ring, and translate the results to any other K-algebra via evaluating the functor at the universal element (10).

Whereas the functor $\mathscr{C}$ provides us with an example of a *model* in Rosennean terms, we may also look for an example of *simulation* in the same context. Rosen defined a simulation as a relationship that considers the natural system as a "black box" without attempting (or being able) to capture the "causal entailment" within the natural system. An example of simulation for our example is the numerical approximation of algebraic curves. Numerical methods may succeed in obtaining an approximation of an algebraic curve without any consideration of the underlying algebraic structure by iteratively approximating points of the curve from a starting value (x_0, y_0) known to lie on the curve (Gomes et al., 2009). With Rosen we might say that these numerical methods are able to "predict" the "natural system" i.e. the algebraic curve. But it is clear that this is not based on bringing the entailment structure of a formal system in congruence with the entailment structures of the natural system to be modelled. This, however, is according to Rosen the ideal that a model should live up to. [16] As I will explain in the Discussion, it is exactly this ambition that, in my opinion, separates Rosen's understanding of modelling most strongly from an applied mathematician's view on modelling which is illustrated in the next section.

---

[16]An anonymous reviewer brought to my attention that two famous articles by Alan Turing provide a good example for the difference between simulation and model. The imitation game (also known as the Turing test) was proposed by Turing (1950) in order to answer the question "Can machines think?". In order to pass the test the machine must communicate in natural language with a human evaluator and through this conversation convince the evaluator that it is human. This is a perfect example for simulation because by definition of the test it is unimportant if and to which extent the machine attempts to accurately represent human intelligence. In contrast, Turing (1952) proposes a mathematical model that exhibits inhomogeneous stationary distributions (Turing instability). This leads to a model that explains morphogenesis in terms of two interacting chemical species (an "activator" and an "inhibitor") that diffuse with different speeds.

5. Lie, cheat and steal—the applied mathematician's ways for finding the truth

I believe that there is no elaborated philosophy of modelling in applied mathematics that could be compared to Rosen's. So it might be helpful to first look at *Dynamic Models in Biology*, a highly readable introduction to mathematical biology by Ellner and Guckenheimer (2007). Near the end of the book the authors briefly introduce the "three commandments of modelling":

1. Lie
2. Cheat
3. Steal

After explaining the three commandments in a bit more detail I will provide a description of models in applied mathematics that will be compared with Rosen's modelling relationship in Section 6.

5.1. Lying

Everyone knows that models are based on assumptions. What not everyone knows is that models (at least the good ones (Ellner and Guckenheimer, 2007)) are based on *false* assumptions. As illustrations we can take nearly all mathematical models from physics. One of the most striking example is the apparently harmless notion of a mass point. Moving bodies such as cars, space ships or parachutists are described by particles without spatial extension whose mass is concentrated in a single point. In this way our model describes objects that may weigh several tonnes or more while at the same time they "are not even there" because it is assumed to have no spatial extension! The only reason that we find such an idea not completely outrageous is by the justification we get for this model after we have applied it to a natural system. We "get away" with this obviously wrong assumption, we can, for example, predict the trajectories of celestial bodies to a certain accuracy. Also, more detailed models of rigid body motion and the notion of the centre of mass give additional support for this model and insight why representing bodies as mass points worked in the first place. The most important point here is, though, that before this model was applied to a concrete problem, it was not at all clear that it would turn out to provide a useful description of a physical object. The justification of "lies" in modelling can only be given in hindsight.

5.2. Cheat

With cheating, Ellner and Guckenheimer (2007) mostly refer to a particular way of using statistics. They recommend to do things that "would make a statistician nervous" by stretching the limits within which statistical methods can be used instead of just "letting the data speak for itself". It is not easy to provide an example for "cheating" because obviously scientists will usually not describe anything they did in a study as cheating. Because I would not like to accuse colleagues of cheating either I have no choice but to give an example of "cheating" from my own work. A few years ago I was working on a model for an ion channel (Siekmann et al., 2012). My motivation was to take into account model gating, a feature that is quite common in ion channel dynamics but which has rarely been accounted for in models. Instead of continuously adjusting their activity many ion channels switch spontaneously between highly different types of behaviour (modes). I wanted to demonstrate that across all experimental conditions each of the different modes defined the same type of behaviour i.e. could be described by statistically similar models. Unfortunately, for some experimental conditions I was not able to fit a model to the segments representative for the modes because the channel was switching too fast and therefore the segments were too short in order to produce statistically conclusive results. But although I thus was not able to rigorously prove my claim I nevertheless argued that the hypothesis of modes which are unchanged across all experimental conditions was—with some positive and in the absence of contrary evidence—presumably correct.

This way of using statistical methods emphasises that experimental data is only one of many sources of knowledge that are synthesised in a mathematical model, thus, the fate of a model should not depend solely on the success or failure of a particular statistical method.

5.3. Steal

Although it may sound even worse than lying and cheating, in scientific terms, stealing might actually be the most acceptable of the three commandments. It simply means reusing ideas of models that have previously appeared in the literature by, for example, applying them to new systems. A famous example is the well-known Lotka-Volterra model which can be seen as the beginning of predator-prey modelling. Volterra (1926) simply reinterpreted the law of mass action kinetics where the rate of a chemical reaction is assumed proportional to the product of the concentrations of the two reactants as the catch rate of a predator

feeding on a prey. The reason that terms characteristic of chemical models were often "stolen" by ecologists and epidemiologists is because the law of mass action and enzyme kinetics can, from a more abstract point of view, be interpreted as contact rates between two populations (Siekmann, 2009).

We briefly mention one danger of stealing—in comparison to the original domain of application, a "stolen" model may increase the amount of lying and cheating—on the one hand the assumptions of the original model may be less valid and on the other hand experimental validation of the original model may not be available in the new context.

5.4. What is a mechanistic model?

In order to compare the approach followed in typical models in applied mathematics with Rosen's modelling relation I will give a brief description of models in applied mathematics. I will refer to these as "mechanistic" in the following because Rosen presumably means similar models when he refers to mechanistic models. However, I will argue in the Discussion that at least some of his objections only arise when mechanistic models are interpreted in a reductionistic sense.

The aim of a mechanistic model is to provide insight into a natural system by synthesising different sources of knowledge. This is achieved by defining a formal system that transparently captures how the elements of the system interact with each other and how these interactions are parameterised with experimental data. A mechanistic model is also strongly determined by a purpose which means that already the architecture and not just the interpretation of the model results is defined by the question that the model should answer.

Building a mechanistic model starts with the formulation of a set of assumptions that summarise what is known about a system, extended by some hypotheses regarding details of the natural system that are currently unknown. Which aspects of our knowledge are represented in how much detail depends on the model purpose. Based on the underlying assumptions a model structure is constructed that is meant to represent the assumptions as well as possible. This model can then be simulated in order to produce results. The results obtained from the model are then interpreted in comparison with the natural system and in the light of the assumptions made in the beginning which leads to conclusions that are drawn from the modelling study.

To give an example, I will refer to recent work in mathematical ecology that I con-

tributed to. A series of papers, starting with Bengfort et al. (2016a) and Siekmann and Malchow (2016), primarily had two purposes. The aim of Bengfort et al. (2016a) was to investigate alternatives to the classical model of population dispersal based on the common model for diffusion due to Fick (Fick, 1855). Siekmann and Malchow (2016) considered alternatives to the classical model for environmental fluctuations based on stochastic terms that scale linearly in the population densities. Bengfort et al. (2016b) studied the combined effect of Fokker-Planck diffusion (Fokker, 1914; Planck, 1917), an alternative to Fickian diffusion, and linear noise terms whereas Siekmann et al. (2017) combine Fokker-Planck diffusion with a nonlinear noise term proposed in Siekmann and Malchow (2016). Consistent with the model purpose, the authors primarily consider a very simple model for the interactions of populations, the Lotka-Volterra competition model. Also, a special parameter set is considered where in the deterministic, non-spatial version of the model, the population with the higher initial population always outcompetes its competitor. In order to investigate spatial and stochastic effects, the parameter of the diffusion model and the noise model are varied. The models demonstrate that stochastic fluctuations enhance the success of invading species that invade the habitat of a resident population but may also enable resident and invader to coexist which is impossible in the deterministic non-spatial version of the model.

At this point it is important to note that the definition of a mechanistic model presented here by no means excludes relational models favoured by Rosen—in the terms developed here, an important underlying assumption of a relational model simply is that the internal structure of the individual system elements is not represented in detail. The most important difference to Rosen's interpretation of models is that no suggestion is made that a mechanistic model accurately captures the causal relationships of the system to be modelled—there is no modelling relationship that in a theoretical sense provides the modeller with access to the structure of the natural system. The reason for this is scepticism—a large proportion of applied mathematicians would presumably be highly pessimistic that achieving congruence between a formal system and a natural system as envisaged by Rosen was possible and even if it could be achieved that this could be verified. Thus, from the outset, the motivation of a mechanistic model is much more modest. The aim of modelling is to provide insight into an *aspect* of a natural system that is defined by the *purpose* of the model. Obtaining a complete understanding is, in principle, out of reach due to the simplifying assumptions made when the model was built. Also, mechanistic models can

only provide *possible explanations* of phenomena observed in the natural system. If the results obtained from the model contradict the behaviour of the natural system one concludes that the underlying assumptions of the model are either incorrect or incomplete. But if the results are consistent with the system to be modelled we cannot conclude that the explanation provided by the model is correct because we cannot exclude the possibility that alternative models with completely different underlying assumptions produce similar results. Instead of regarding a mechanistic model as a mathematical representation of some "truth" it is therefore more accurate to think of a model as an argument for a particular *hypothesis* explaining the observed behaviour of a natural system.

Finally, it is widely accepted among applied mathematicians that not the development of individual models but the comparison of several competing models of the same system that are based on different assumptions provides most insight. Modelling is therefore not so far from studying a system via experiments—with the important advantage described by the mathematician Vladimir Arnold with the words "mathematics is the natural science where experiments are cheap". This is very well illustrated by several monographs on mathematical biology for which we give a few examples—the general introductions by Murray (2002, 2003), Edelstein-Keshet (2005) and Ellner and Guckenheimer (2007) mentioned above, also we refer to more specific books on ecology (Okubo and Levin, 2001; Malchow et al., 2008) or physiology (Keener and Sneyd, 2009a,b).

6. Discussion

6.1. Rosen's answer to his question "What is Life?"

As explained above, Robert Rosen looked for an answer to the question "What is life?" in a way that was different to the commonly used modelling approaches at his time. Following the motto "throw away the physics, keep the organisation" he proposed to investigate relationships between "components" without associating these abstract entities themselves with any structure.

Looking at this idea from the point of view of an applied mathematician, we observe that Rosen's model starts with the "lie", in the sense of Section 5.1, that the physics of components that make up a biological organism is mostly irrelevant for understanding its functioning. A problem with this is that we can only learn in hindsight, once this model has been applied to a real biological organism, if this assumption has been able

to provide new insights. But because Rosen himself was more interested in developing his formal framework and developing the theoretical ideas he drew from those studies, his publications contain at most hints to possible applications.

The idea of a relational approach to biology has, in the last two decades, become quite influential under the name of "network science"—we refer to the recent textbook by Barabási (2016), one of the most influential figures of the discipline, as an introduction to the large body of literature. Papers in network science often follow statistical approaches for inferring networks from data and the resulting networks are analysed by computational techniques developed with methods from graph theory and statistical mechanics.

Studies in the area of network science clearly illustrate the challenges with "throwing away the physics and keeping the organisation". For example, once a large-scale biological network has been inferred from data, the question of its interpretation might not be easy to answer, precisely because only minimal assumptions are made regarding the properties of individual nodes. Is it most important that a network has certain global properties such as being scale-free (Watts and Strogatz, 1998; Barabási and Albert, 1999), to which extent the network can be controlled (Liu et al., 2011; Ruths and Ruths, 2014) or that certain "network motifs" are more prevalent than expected by chance (Milo et al., 2002; Alon, 2007)? If we consider, more specifically, gene regulatory networks, another problem becomes apparent. Rosen always assumes that relationships between the components of his (M, R) systems are known. Unfortunately, inferring the interactions within biochemical networks such as the highly complicated large networks of genes and their transcripts is often quite challenging and might not lead to conclusive results. This motivated, for example, Oates et al. (2014) to include a more detailed model of the underlying reactions in order to obtain more accurate results on the interactions between the components of the biochemical network. Also, as far as the impact of the conclusions is concerned, one might argue that combining network models with at least some description of the underlying "physics" of the components has been more promising than studies that are restricted to networks whose nodes without considering their underlying structure. As an example I refer to Colizza et al. (2006) who investigated the global spread of epidemics along the airline traffic network using the example of the 2002 outbreak of severe acute respiratory syndrome (SARS).

In summary, by considering the example of "network science" which is the area of science that is probably most closely related to Rosen's idea of a relational biology, the

benefit of Rosen's proposal of throwing away the physics and keeping the organisation are not entirely clear. But this has to be considered in a situation where applications of his ideas are still in relatively early stages because Rosen himself did not work towards applying his theory to concrete biological problems.

6.2. Rosen's relational biology and category theory

As mentioned several times above, a strong view of Rosen's is the motto "throw away the physics and keep the organisation". For this reason he deliberately defines the components of his (M, R) systems as "black boxes". Rather than describing the structure of components that form a system, his relational biology focuses on their interactions with other components. Consistently, he primarily uses category theory for describing interactions between objects; that the objects are members of categories with certain underlying mathematical structures hardly plays any role.

This use of category theory is likely to disappoint most readers of Rosen's works with a mathematical background. In the preface of her recent textbook "Category Theory in Context" Emily Riehl introduces category theory like this (Riehl, 2016):

> Atiyah[17] described mathematics as the "science of analogy." In this vein, the purview of category theory is *mathematical analogy*. Category theory provides a cross-disciplinary language for mathematics designed to delineate general phenomena, which enables the transfer of ideas from one area of study to another.

A strong motivation for the development of category theory and one of the main reasons for its success as a mathematical discipline is the formalisation of links between different areas of mathematics. When category theory was originally formulated by Eilenberg and MacLane (1945) the new notions of category theory facilitated understanding the connections between topological spaces and algebraic objects such as groups or vector spaces that can be associated to them. The ability for finding such mathematical analogies (between topological and algebraic objects in the case of algebraic topology) crucially depends both on relations between objects from particular categories (such as topological spaces

---

[17]Sir Michael Atiyah (*1929), British mathematician, one of the most distinguished mathematicians of the 20th century. Apart from many other awards and honours he won the Fields medal (1966) and the Abel Prize (2004).

or groups) but also on the underlying mathematical structures of these objects that are preserved by morphisms.

6.2.1. Rosen's treatment of category theory as an incremental extension of graph theory

But, as already mentioned, Rosen explicitly avoids assigning structure to the components of his (M, R) systems. From the introduction of (Rosen, 1958b) it becomes clear that Rosen regards category theory as an incremental extension of graph theory that enables him to more flexibly describe relations between "black boxes". Unfortunately, this prevents him from taking much advantage from the main strength of category theory, namely, relating the structure of mathematical objects appearing in different disciplines of mathematics.

The negative impact of this use of category theory on an audience of applied mathematicians must not be underestimated. A strong motivation in mathematics itself as well as in the community of applied mathematicians is to use mathematical notions as efficiently as possible. By failing to take full advantage of the ability of category theory to relate mathematical structures Rosen does not only miss the chance to capture properties of a biological system that might be encoded in such structures. Even worse, an audience from a mathematical background might even be deterred from Rosen's ideas, not because of the ideas themselves but due to the perceived shortcomings in their mathematical presentation. In summary, one might go as far as saying that instead of being a strength of Rosen's theories, category theory is one of the most important obstacles for their acceptance. Nevertheless one shall not be overly critical of Rosen's approach of using category theory for his research—after all he was a pioneer in applying a novel, quite difficult mathematical discipline at a time when even the foundations of this discipline were still under development.

6.2.2. An alternative perspective on relational biology

Does the preceding section imply that category theory is not an appropriate tool for investigating biological systems? One reviewer of an earlier version of this manuscript kindly directed me to work from the group of mathematical physicist John Baez who have most recently applied category theory to open reaction networks (Baez and Pollard, 2017). It is worthwhile to compare this emerging research with (M, R) systems which were inspired by networks of metabolic reactions. Rather than abstracting reaction networks to a network of input-output relationships, Baez and co-workers go the opposite way—they develop

specific categories **RNet** and **RxNet** in order to formalise Petri Nets, a diagrammatic representation of chemical reactions. By constructing a functor to the category **Dynam** of open dynamical systems they can relate a given Petri net to a system of ordinary differential equations, the rate equations associated with this particular Petri net. A functor from **Dynam** to the category of relations **Rel** maps dynamical systems to their steady states. Of course, the ambition of Baez and co-workers is presumably not to answer questions like "What is life?" but their "compositional framework" allows them to build reaction networks from simpler components via composition of morphisms and relate the structural properties of reaction networks to similar models such as electrical circuits (Baez and Fong, 2016), signal-flow diagrams (Erbele, 2016) and Markov processes (Baez et al., 2015) which are all formalised in a similar way as described above using the language of category theory. It seems clear that although this work is not less "relational" than Rosen's (M, R) systems or the network science approaches mentioned in Section 6.1, the publications from Baez's group clearly take advantage of category theory for relating the different mathematical structures characteristic of different modelling approaches.

6.3. Rosen's modelling relation and mechanistic models in applied mathematics

In "Life Itself", Rosen (1991) repeatedly proposes relational models as alternatives to mechanistic models. But, first of all, according to the view explained in Section 5.4, mechanistic models should not be considered as the opposite of relational models, in fact, relational models can be regarded as a particular type of mechanistic model. Second, many of Rosen's objections arise because he implicitly assumes that mechanistic models necessarily have to be interpreted in a reductionistic way. But building a mechanistic model does not mean that the natural system necessarily must be "reduced" to the mechanism represented by the model—in fact, this is just a specific interpretation. In contrast, in Section 5.4 we propose an alternative perspective on mechanistic models—according to this view the "mechanism" represented in a mechanistic model only provides an explanation of a particular aspect of the system behaviour which is defined by the underlying assumptions of the model. If additional aspects of the system behaviour are to be considered this requires refining the assumptions of the model, as a result the new model will represent a more detailed mechanism that provides a more comprehensive (but still partial) explanation of the system behaviour.

6.4. Rosennean complexity and mechanistic models

The difference between Rosen's view on modelling and the view I outlined in Section 5.4 is most obvious when considering his definition of complex systems:

> A system is simple if all its models are simulable. A system that is not simple, and that accordingly must have at least one non-simulable model, is complex.

Rosen's concept of complexity is a direct consequence of his modelling relationship. With his modelling relationship he outlines an approach that enables us to directly relate a natural system to a formal system, the model. Thus, it might seem that modelling is, at least conceptually, trivial. Indeed, for our example of an algebraic curve $\mathscr{C}$ (Section 4.1), the representation of the functor $\mathscr{C}$ by the coordinate ring A (9) provides us with a "model" for the algebraic curve over arbitrary K-algebras. But according to Rosen's definition, the fact that the coordinate ring A exists as a model for arbitrary K-algebras makes algebraic curves a "simple" system. For a "complex" system, an analogue of the coordinate ring A might still exist but it is "non-simulable" which Rosen defines as not Turing-computable. Although such a model would still perfectly describe the natural system, the required calculations formalised by a Turing machine might not terminate in finite time.

Most striking about Rosen's definition of a complex system is how the relationship of a system and "its" models is described. According to Section 5.4 and in contrast to Rosen's concept of the modelling relation a system does not "have" models—models cannot be objectively associated with a system via the modelling relationship but rather are subjectively attributed to the system by the modeller. A model will—due to the requirement of making simplifying assumptions—necessarily always remain incomplete, the case of a "simple" system in Rosennean terms, where a perfect formal representation of a natural system can be found, does not exist. Mechanistic models serve a specific purpose by efficiently representing a set of underlying assumptions that are consistent with the purpose of the model. As explained in Section 5.4, rather than being a formal representation of a particular "truth" about a natural system, the aim of mechanistic models is to explore scientific hypotheses that are represented in the assumptions of the model. Therefore, consideration of competing models based on alternative assumptions is an important part of scientific discussion in the literature.

6.5. Rosennean complexity in the toolbox of mathematical biologists

The most important aspect of Rosen's theories is his postulate that "organisms are closed to efficient causation". In order to to assess how well this notion is able to describe living systems one has to go beyond theoretical considerations. From the perspective of a modeller it is therefore the most important shortcoming that so far there are very few examples of mathematical models implementing Rosen's postulate in the context of concrete biological systems.

In the field of modelling biochemical reactions, this issue is being addressed by the group of Cárdenas and Cornish-Bowden. In a series of papers, Letelier et al. (2006); Cornish-Bowden et al. (2007); Cárdenas and Cornish-Bowden (2007) developed a simple (M, R) system representing a simple biochemical reaction network that was later implemented in a mathematical model and investigated by simulation (Piedrafita et al., 2010, 2012a,b; Cornish-Bowden et al., 2013).

Whereas organisms are postulated to be closed to efficient causation, they must be open to "material causes" as explained in Section 3 or, in more familiar terms, flows of matter and energy. A mathematical model that realises Rosen's concept of an organism should therefore also appropriately account for the exchange of matter and energy with the environment. The bond graph methodology (Borutzky, 2010) is an established approach from the engineering literature for building models of complex systems with energy flows between multiple domains (electrical, chemical etc.). Bond graphs were recently applied to biochemical reactions (Gawthrop and Crampin, 2014; Gawthrop et al., 2015) and subsequently to more complex physiological systems (Gawthrop and Crampin, 2016; Gawthrop et al., 2017). Also, in mathematical ecology there are several examples of energy-based models ranging from the early (E, M) framework developed by Smerage (1976) to the more recent studies by Cropp and Norbury (2012) and Bates et al. (2015). Extending these frameworks by modelling approaches that realise closure to efficient causation will enable us to investigate the significance of Rosennean Complexity for ecosystems.

In all implementations of Rosen's principle of closure to efficient causation an obvious difficulty is to identify "efficient causes" and distinguish them from "material causes"— Rosen's own publications provide relatively little guidance due to the mostly formal presentation with very few specific biological examples. In this regard, the recent paper Mossio et al. (2016) is highly relevant: the authors develop a theory of biological organisation that comprises Rosen's views but draws from the much longer tradition of organicism.

Organicism is a perspective on biology which states that "organisms are the main object of biological science because [...] they cannot be reduced to more fundamental biological entities (such as the genes or other inert components of the organism)" (Mossio et al., 2016). Organicism implies that the individual parts that the organism consists of can only be understood by taking into account their relationships and interactions with other parts. But crucially, in contrast to the approach that Rosen takes with his (M, R) systems, Mossio et al. (2016) avoid reducing the parts of an organism to "black boxes" without underlying structure. Instead, they identify specific parts of biological systems as *constraints* which control processes without themselves being altered by them—they give the role that enzymes play in reaction networks and the influence of the vascular system on the flow of oxygen in the body as examples. Biological organisation according to Mossio et al. (2016) is realised via "closure of constraints" which shows that constraints are a closely related concept to Rosen's "efficient causes". This idea of biological organisation is one of three theoretical principles for biology proposed in the highly readable special issue "From the century of the genome to the century of the organism: New theoretical approaches" published in *Progress in Biophysics and Molecular Biology*—the others are variation (Montévil et al., 2016) and a postulated biological "default state" (Soto et al., 2016). The articles from this special issue provide valuable guidance to modellers who wish to construct models which represent Rosen's idea of an organism or, indeed, stand in the much longer tradition of organicism.

Although it seems clear that the task of building such mathematical models that provide a better representation of organisms will not be an easy one, it seems equally clear that this will bring us another step further towards answering the grand question "What is Life?".

Acknowledgements

Alekseevskij, D. V., Vinogradov, A. M., Lychagin, V. V., 1991. Basic Ideas and Concepts of Differential Geometry. Vol. 28 of Encyclopedia of Mathematical Sciences. Springer, Berlin, Heidelberg.

Alon, U., 2007. Network motifs: theory and experimental approaches. Nature Reviews Genetics 8 (6), 450–461.

Baez, J. C., Fong, B., 2016. A compositional framework for passive linear networks, unpublished.
URL https://arxiv.org/abs/1504.05625

Baez, J. C., Fong, B., Pollard, B. S., 2015. A compositional framework for Markov processes. Journal of Mathematical Physics 57, 033301.
URL https://arxiv.org/abs/1508.06448

Baez, J. C., Pollard, B. S., 2017. A compositional framework for reaction networks, unpublished.
URL https://arxiv.org/abs/1704.02051v2

Barabási, A.-L., July 2016. Network Science, 1st Edition. Cambridge University Press, Cambridge, United Kingdom.

Barabási, A.-L., Albert, R., October 15 1999. Emergence of scaling in random networks. Science 286, 509–512.

Barr, M., Wells, C., 2012. Category theory for computing science. Reprints in Theory and Applications of Categories 22, 1–538.

Bates, M. L., Nash, S. M. B., Hawker, D. W., Norbury, J., Stark, J. S., Cropp, R. A., 2015. Construction of a trophically complex near-shore Antarctic food web model using the Conservative Normal framework with structural coexistence. Journal of Marine Systems 145, 1 – 14.
URL http://www.sciencedirect.com/science/article/pii/S0924796314003327

Bengfort, M., Malchow, H., Hilker, F. M., 2016a. The Fokker–Planck law of diffusion and pattern formation in heterogeneous environments. Journal of Mathematical Biology 73 (3), 683–704.
URL http://dx.doi.org/10.1007/s00285-016-0966-8

Bengfort, M., Siekmann, I., Malchow, H., 2016b. Invasive competition with Fokker-Planck diffusion and noise, under review at Ecological Complexity.
URL https://arxiv.org/abs/1611.10091

Berridge, M. J., Lipp, P., Bootman, M. D., 2000. The versatility and universality of calcium signalling. Nature Reviews Molecular Cell Biology 1 (1), 11–21.

Borutzky, W., 2010. Bond Graph Methodology—Development and Analysis of Multidisciplinary Dynamic System Models. Springer, London.

Campbell, N. A., 2008. Biology, 8th Edition. Pearson/Cummings, San Francisco, CA, USA.

Cárdenas, M. L., Cornish-Bowden, A., 2007. Organizational invariance in (m, r)-systems. Chemical Biodiversity 4, 2396–2406.

Coecke, B. (Ed.), 2011. New Structures for Physics. Vol. 813 of Lecture Notes in Physics. Springer, Berlin Heidelberg.

Colizza, V., Barrat, A., Barthélemy, M., Vespignani, A., 2006. The role of the airline transportation network in the prediction and predictability of global epidemics. Proceedings of the National Academy of Sciences of the United States of America 103 (7), 2015–2020. URL http://www.pnas.org/content/103/7/2015.abstract

Cornish-Bowden, A., Cárdenas, M. L., Letelier, J.-C., Soto-Andrade, J., 2007. Beyond reductionism: metabolic circularity as a guiding vision for a real biology of systems. Proteomics 585 (15), 2138–2145.

Cornish-Bowden, A., Piedrafita, G., Morán, F., Cárdenas, M. L., Montero, F., 2013. Simulating a model of metabolic closure. Biological Theory 8, 383–390.

Cropp, R., Norbury, J., 2012. Constructing ecologies. Journal of Theoretical Biology 294, 1–8.

Edelstein-Keshet, L., 2005. Mathematical models in biology. Vol. 46 of Classics in Applied Mathematics. The Society for Industrial and Applied Mathematics, Philadelphia.

Eilenberg, S., MacLane, S., 1945. General theory of natural equivalences. Transactions of the American Mathematical Society 58, 231–294.

Ellner, S. P., Guckenheimer, J., 2007. Dynamic Models in Biology, 1st Edition. Princeton University Press, Princeton, New Jersey.

Erbele, J. M., December 2016. Categories in control: Applied PROPs. Ph.D. thesis, University of California, Riverside.
URL `https://arxiv.org/abs/1611.07591`

Fick, A., 1855. Über Diffusion. Poggendorffs Annalen der Physik 94, 59–86.

Fokker, A. D., 1914. Die mittlere Energie rotierender elektrischer Dipole im Strahlungsfeld. Annalen der Physik 348 (5), 810–820 (in German).

Gawthrop, P., Siekmann, I., Kameneva, T., Saha, S., Ibbotson, M. R., Crampin, E. J., May 2017. Bond graph modelling of chemoelectrical energy transduction. IET Systems Biology.
URL `https://arxiv.org/abs/1512.00956`

Gawthrop, P. J., Crampin, E. J., 2014. Energy-based analysis of biochemical cycles using bond graphs. Proceedings of the Royal Society of London A: Mathematical, Physical and Engineering Sciences 470 (2171).

Gawthrop, P. J., Crampin, E. J., 2016. Modular bond-graph modelling and analysis of biomolecular systems. IET Systems Biology 10 (5), 187–201.

Gawthrop, P. J., Cursons, J., Crampin, E. J., 2015. Hierarchical bond graph modelling of biochemical networks. Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences 471 (2184)), 1–23.

Gomes, A., Voiculescu, I., Jorge, J., Wyvill, B., Galbraith, C., 2009. Implicit Curves and Surfaces: Mathematics, Data Structures and Algorithms, 1st Edition. Springer Publishing Company, Incorporated.

Keener, J. P., Sneyd, J., 2009a. Mathematical Physiology I: Cellular physiology, 2nd Edition. Vol. 8/1 of Interdisciplinary Applied Mathematics. Springer, New York.

Keener, J. P., Sneyd, J., 2009b. Mathematical Physiology II: Systems Physiology, 2nd Edition. Vol. 8/2 of Interdisciplinary Applied Mathematics. Springer, New York.

Landauer, C., Bellman, K. L., 2002. Theoretical Biology: Organisms and Mechanisms. AIP Conference Proceedings 627.

Letelier, J.-C., Soto-Andrade, J., Abarzúa, F. G., Cornish-Bowden, A., Cárdenas, M. L., 2006. Organizational invariance and metabolic closure: Analysis in terms of systems. Journal of Theoretical Biology 238 (4), 949 – 961.
URL http://www.sciencedirect.com/science/article/pii/S0022519305003073

Liu, Y.-Y., Slotine, J.-J., Barabási, A.-L., 2011. Controllability of complex networks. Nature 473, 167–173.

Louie, A. H., 2009. More Than Life Itself. Vol. 1 of Categories. ontos Verlag, de Gruyter, Heusenstamm, Germany.

Mac Lane, S., 1971. Categories for the Working Mathematician, 1st Edition. Graduate Texts in Mathematics. Springer, New York, USA.

Malchow, H., Petrovskii, S. V., Venturino, E., 2008. Spatiotemporal Patterns in Ecology and Epidemiology – Theory, Models, and Simulation. Mathematical and Computational Biology Series. Chapman & Hall / CRC, Boca Raton.

Mikulecky, D. C., 2001. Robert Rosen (1934–1998): a snapshot of biology's Newton. Computers and Chemistry 25, 317–327.

Milo, R., Shen-Orr, S., Itzkovitz, S., Kashtan, N., Chklovskii, D., Alon, U., 2002. Network Motifs: Simple Building Blocks of Complex Networks. Science 298, 824–827.
URL http://dx.doi.org/10.1126/science.298.5594.824

Montévil, M., Mossio, M., Pocheville, A., Longo, G., 2016. Theoretical principles for biology: Variation. Progress in Biophysics and Molecular Biology 122 (1), 36 – 50, from the Century of the Genome to the Century of the Organism: New Theoretical Approaches.
URL http://www.sciencedirect.com/science/article/pii/S0079610716300967

Mossio, M., Montévil, M., Longo, G., 2016. Theoretical principles for biology: Organization. Progress in Biophysics and Molecular Biology 122 (1), 24 – 35, from the Century of the Genome to the Century of the Organism: New Theoretical Approaches.
URL http://www.sciencedirect.com/science/article/pii/S007961071630089X

Murray, J. D., 2002. Mathematical biology. I. An introduction. Vol. 17 of Interdisciplinary Applied Matthematics. Springer, Berlin.

Murray, J. D., 2003. Mathematical biology. II. Spatial models and biomedical applications. Vol. 18 of Interdisciplinary Applied Matthematics. Springer, Berlin.

Oates, C. J., Dondelinger, F., Bayani, N., Korkola, J., Gray, J. W., Mukherjee, S., 2014. Causal network inference using biochemical kinetics. Bioinformatics 30, i468–i474.

Okubo, A., Levin, S., 2001. Diffusion and ecological problems: Modern perspectives. Vol. 14 of Interdisciplinary Applied Mathematics. Springer, New York.

Petsko, G., Ringe, D., 2008. Protein Structure and Function. Primers in Biology. Oxford University Press, Oxford University Press.

Piedrafita, G., Cornish-Bowden, A., Morán, F., Montero, F., 2012a. Size matters: influence of stochasticity on the self-maintenance of a simple model of metabolic closure. Journal of Theoretical Biology 300, 143–151.

Piedrafita, G., Montero, F., Morán, F., Cárdenas, M. L., Cornish-Bowden, A., 2010. A simple self-maintaining metabolic system: Robustness, autocatalysis, bistability. PLoS Computational Biology 6 (8), e1000872.

Piedrafita, G., Ruiz-Mirazo, K., Monnard, P.-A., Cornish-Bowden, A., Montero, F., 06 2012b. Viability conditions for a compartmentalized protometabolic system: A semi-empirical approach. PLOS ONE 7 (6), 1–12.
URL https://doi.org/10.1371/journal.pone.0039480

Pierce, B. C., 1991. Basic Category Theory for Computer Scientists. MIT Press, Cambridge, Massachusetts.

Planck, M., 1917. Über einen Satz der statistischen Dynamik und seine Erweiterung in der Quantentheorie. Sitzungsberichte der Königlich Preussischen Akademie der Wissenschaften XXIV, 324–341 (in German).

Riehl, E., 2016. Category Theory in Context. Aurora, Dover Modern Math Originals. Dover Publications, Mineola, New York.

Rosen, R., 1958a. A relational theory of biological systems. Bulletin of Mathematical Biophysics 20, 245–260.

Rosen, R., 1958b. The representation of biological systems from the standpoint of the theory of categories. Bulletin of Mathematical Biophysics 20, 317–341.

Rosen, R., 1959. A relational theory of biological systems II. Bulletin of Mathematical Biophysics 21, 109–128.

Rosen, R., 1971. Some realizations of (m, r) systems and their interpretation. Bulletin of Mathematical Biophysics 33, 303–319.

Rosen, R., 1972. Some relational cell models: the metabolism-repair system. In: Rosen, R. (Ed.), Foundations of Mathematical Biology. Vol. 2: Cellular Systems. Academic Press, New York, Ch. 4, pp. 217–253.

Rosen, R., 1973. On the dynamical realization of (m, r)-systems. Bulletin of Mathematical Biophysics 35, 1–9.

Rosen, R., 1991. Life Itself, 1st Edition. Vol. 1 of Complexity in Ecological Systems. Columbia University Press, New York, USA.

Rosen, R., 2000. Essays on Life Itself, 1st Edition. Vol. 6. Columbia University Press, New York, USA.

Rosen, R., 2006. Autobiographical reminiscences of Robert Rosen. Axiomathes 16, 1–23.

Ruths, J., Ruths, D., 2014. Control profiles of complex networks. Science 343, 1373–1376.

Siekmann, I., 2009. Mathematical modelling of pathogen-prey-predator interactions. Dissertation, Fachbereich Mathematik/Informatik, Universität Osnabrück.
URL https://www.researchgate.net/publication/261178558_Mathematical_modelling_of_pathogen-prey-predator_interactions

Siekmann, I., Bengfort, M., Malchow, H., 2017. Coexistence of competitors mediated by nonlinear noise. The European Physics Journal–Special Topics 226 (9), 2157–2170.
URL https://doi.org/10.1140/epjst/e2017-70038-6

Siekmann, I., Malchow, H., 2016. Fighting enemies and noise: Competition of residents and invaders in a stochastically fluctuating environment. Mathematical Modelling of Natural Phenomena 11 (5), 120–140.

Siekmann, I., Wagner II, L. E., Yule, D., Crampin, E. J., Sneyd, J., 2012. A kinetic model of type I and type II IP$_3$R accounting for mode changes. Biophysical Journal 103 (4), 658–668.
URL `http://dx.doi.org/10.1016/j.bpj.2012.07.016`

Smerage, G. H., 1976. Matter and energy flows in biological and ecological systems. Journal of Theoretical Biology 57, 203–223.

Soto, A. M., Longo, G., Montévil, M., Sonnenschein, C., 2016. The biological default state of cell proliferation with variation and motility, a fundamental principle for a theory of organisms. Progress in Biophysics and Molecular Biology 122 (1), 16 – 23, from the Century of the Genome to the Century of the Organism: New Theoretical Approaches.
URL `http://www.sciencedirect.com/science/article/pii/S0079610716300785`

Spivak, D. I., 2014. Category Theory for the Sciences. MIT Press, Cambridge, Massachusetts.

Tinbergen, N., 1963. On aims and methods of ethology. Zeitschrift für Tierpsychologie 20 (4), 410–433.
URL `http://dx.doi.org/10.1111/j.1439-0310.1963.tb01161.x`

Turing, A., 1950. Computing machinery and intelligence. Mind 59 (236), 433–460.

Turing, A. M., 1952. On the chemical basis of morphogenesis. Philosophical Transactions of the Royal Society of London B 237, 37–72.

Volterra, V., 1926. Fluctuations in the abundance of a species considered mathematically. Nature 118, 558–560.

Watts, D. J., Strogatz, S. H., 1998. Collective dynamics of 'small-world' networks. Nature 393 (6684), 440–442.