ORIGINAL PAPER

Kinetic Models of (M-R)-Systems

J. A. Prideaux

Abstract   Kinetic models using enzyme kinetics are developed for the three ways that Louie proved that Rosen's minimal (M-R)-System can be closed to efficient cause; i.e., how the "replication" component can itself be entailed from within the system. The kinetic models are developed using the techniques of *network thermodynamics*. As a demonstration, each model is simulated using a SPICE circuit simulator using arbitrarily chosen rate constants. The models are built from SPICE sub-circuits representing the key terms in the chemical rate equations. The models include the addition of an ad hoc semi-permeable membrane so the system can achieve steady state fluxes and also to illustrate the need for all the efficient cause agents to be continually replaced. Comments are made about exactly what is being simulated.

Keywords   Enzyme · Kinetic model · *Life itself* · Louie · (M,R)-systems · Realization · Relational biology · Robert Rosen · SPICE

1 Introduction

Louie's book "More Than Life Itself" (Louie 2009) is a monumental achievement laying out the groundwork for the theoretical development of relation biology. In it he develops and expands upon the mathematics behind both Rosen's and his own insights. The subject matter is difficult and the terminology sometimes inaccessible to all but the mathematically trained. This paper will concentrate on chapter 12 of

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part IV entitled "Synthesis of (M,R)-Systems" and attempt to form kinetic models of the various ways Louie shows that Rosen's minimal (M,R)-system can be closed to efficient cause. The information in this chapter also appears in the earlier papers (Louie 2006; Louie and Kercel 2007). This paper will attempt to bridge the gap between the abstract math and more common (at least to the physiologist) concepts.

In Rosen's development (Rosen 1958, 1971, 1973, 1991) Rosen starts with the mapping f: A → B and proceeds to ask entailment questions like "Why f?" where the answer needs both a material and efficient cause. f is a member of H(A, B) which is the set of items that maps A to B. The results of iterating these "why" questions a couple of times are shown in (1). The hollow arrows indicate the material cause of an effect. The filled arrows indicate the efficient cause of an effect. For example the material cause of f is X. The efficient cause of f is Φ.

$$(1)$$
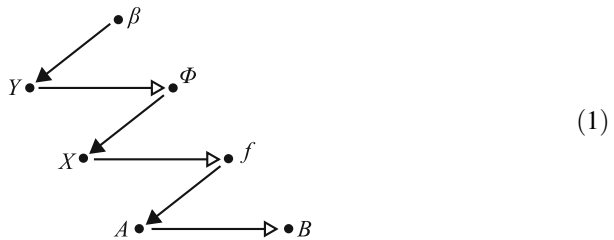
Rosen then proceeds to set $X = B$ and the diagram then can be condensed to what is shown in (2).


$$(2)$$
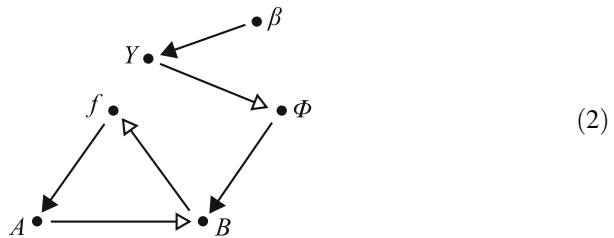
In closing the system to efficient cause, Rosen sets $Y = $ H(A, B) and shows that under certain conditions the function β could be related to the items in B. Thus, the diagram could be succinctly expressed (3) as his closed to efficient cause diagram 10C.6 from (Rosen 1991, p. 251).


$$(3)$$
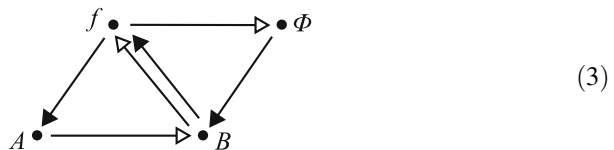
Louie, though, shows that there are other possibilities if you start from (2) with setting Y equal to other things within the diagram. For each different assignment β

would have a different definition. The interested reader can refer to the cited references for the mathematical details. To draw attention to the things that are different in his three realizations, Louie shows the arrows that were the same between each realization with dotted lines and the arrows that are different with solid lines. Rosen's original closure where $Y = H(A, B)$ is shown in (4). The function β is related to (but not the same as) b. This will be identified later in the paper by the closure definition β: $H(A, B) \rightarrow H(B, H(A, B))$.

$$\beta : H(A, B) \rightarrow H(B, H(A, B)) \tag{4}$$
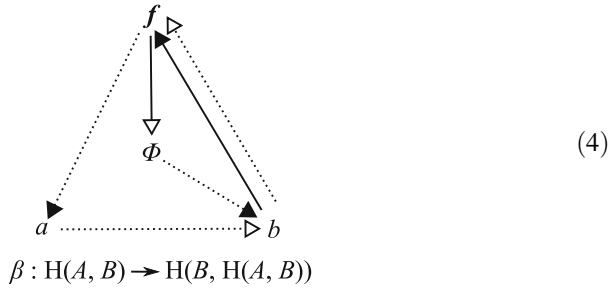
An alternative closure where $Y = B$ and β is related in a different way to items in B is shown in (5). This will be identified later in the paper by the closure definition β: $B \rightarrow H(B, H(A, B))$.

$$\beta : B \rightarrow H(B, H(A, B)) \tag{5}$$
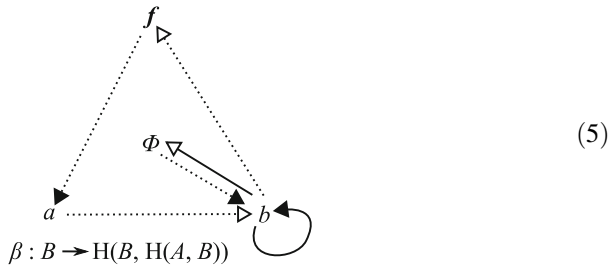
Finally, (6) shows a closure where $Y = A$ and β is related to items in A. This will be identified by its closure strategy β: $A \rightarrow H(B, H(A, B))$.
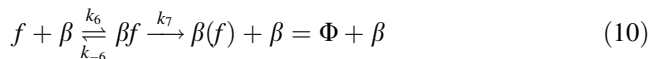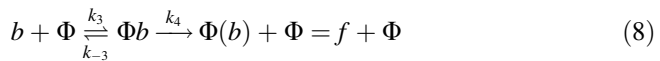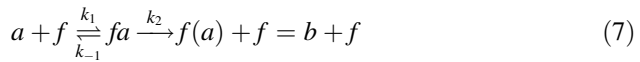
$$\beta : A \rightarrow H(B, H(A, B)) \tag{6}$$
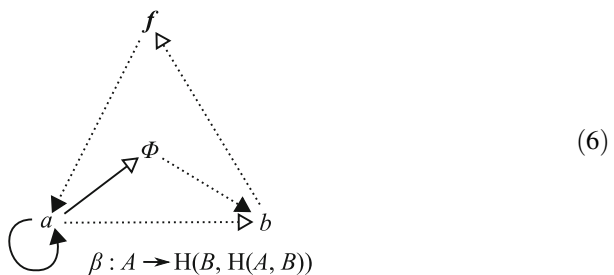
The kinetic models will now be developed. As a starting point, we will look to one of Rosen's papers from the early 1970s.
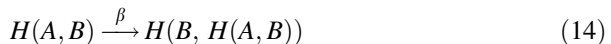
1.1 Kinetic Models

Rosen (1971) suggested three different ways to approach the realization problem:

1. A formal approach—developing the mathematical theory behind (M,R)-systems. For example category theory.
2. A dynamic approach—studying the abstract organization in concrete terms. For example kinetic models.
3. Determining whether or not known concrete systems are in fact realizations of his (M, R)-system. For example critiquing the "machine metaphor" often used in biological science and analyzing claims made in the field of "artificial life" about simulating life.

In the section describing the dynamic approach, Rosen listed a system of enzymatic Eqs.[1] 7, 8, 9, and 10 that were intended to be a crude example of how the dynamic approach could be done.

$$a + f \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} fa \xrightarrow{k_2} f(a) + f = b + f \tag{7}$$

$$b + \Phi \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \Phi b \xrightarrow{k_4} \Phi(b) + \Phi = f + \Phi \tag{8}$$

$$b \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} \beta \tag{9}$$

$$f + \beta \underset{k_{-6}}{\overset{k_6}{\rightleftharpoons}} \beta f \xrightarrow{k_7} \beta(f) + \beta = \Phi + \beta \tag{10}$$

These enzymatic equations were intended to be representative of his abstract Eqs. 11, 12, 13, and 14.

$$A \xrightarrow{f} B \tag{11}$$

$$B \xrightarrow{\Phi} H(A, B) \tag{12}$$

$$\beta = \widehat{b}^{-1} \tag{13}$$

$$H(A, B) \xrightarrow{\beta} H(B, H(A, B)) \tag{14}$$

In this paper we will take seriously those enzymatic chemical equations that Rosen published and build a phenomenological kinetic model. As such, it will be able to track the changes in concentrations over time but will not give any detail of the internal structure of the reacting molecules. These equations were also mentioned in a recent review article (Cardenas et al. 2010) to point out that β is related to b but is not b itself.

These Michaelis and Menten (1913) styled rate equations depict simple enzymatic catalyzed reactions with only a single substrate, an irreversible second

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[1] Rosen sub-divided these equations on different lines. He also used different numbers on his subscripts for the rate constants for Eqs. 9 and 10.

step, and no activators or inhibitors.[2] These equations can be viewed in one of two ways. The first way is to consider three different enzymatic reactions that happen to realize Rosen's minimal (M,R)-System. In reality, though, there is probably no such set of three enzymatic coupled reactions. One could consider it, though, as a theoretical exercise to re-express Rosen's abstract mathematics in a kinetic form. The other way they could be interpreted is that each reaction is a place-holder for a whole class of different reactions. This was probably what Rosen intended. A $\rightarrow$ B, for example, would represent all the metabolism reactions in the organism. As a crude approximation, they could be modeled by a single mono-substrate enzymatic reaction.

In any event, the changes in concentration of a, f, Φ, b, and the intermediates can be described by a set of coupled differential equations where the variables represent concentrations of the various substances. The terms that describe the changes in concentration can be determined from the *law of mass action*[3] where the reaction flow in a direction is proportional to the product of the concentrations of the participating molecules. For example, the flow of the forward reaction $a + f \rightarrow fa$ would be $k_1[a][f]$. The flow for the reverse reaction $a + f \leftarrow fa$ would be $k_{-1}[fa]$. By aggregating all the flow terms that represent a change in concentration of each compound the full set of differential equations describing the change in each concentration can be written.

As an alternative to working directly with the differential equations, a *network thermodynamic*[4] approach will be used with the formulation of an electric circuit analogy to the underlying chemical kinetic system. The analogous circuits will be simulated using one of the vendors[5] of SPICE (Simulation Program with Integrated Circuit Emphasis). Consult Mikulecky (1993) for a general reference on using SPICE in the field of *network thermodynamics*. Even though SPICE is an electrical circuit simulator, it can be used to model biochemical pathways when the appropriate analogies are developed. Forming a network of the reactions also has the advantage of clearly showing the topology of the system. The same conservation laws that apply to the flow of electrons in an electrical circuit are also applicable for the flow of materials in a chemical system.

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[2] Many other more complicated forms of enzymatic reactions are possible involving multiple active sites on the enzyme with possibilities for both activation and inhibition.

[3] Law of mass action—even though the law was originally developed for the equilibrium condition, the definition of the flow terms also has applicability when a system is not at equilibrium assuming that the reactions under consideration are sufficiently slow and close to equilibrium.

[4] Network Thermodynamics—from Mikulecky (1993, p. 1) "Network Thermodynamics is a new field which arose out of the marriage of electrical network theory with the formalism of non-equilibrium thermodynamics".

[5] The program TopSpice: http://www.penzar.com was chosen because it had a free evaluation version that could be used for non-commercial purposes and also because it had a nice graphical user interface in which to develop the circuits. Additionally, both the circuit diagrams and the plotted output could be rendered in vector files that with only a small amount of editing could be (and were) used in this paper. Note, though, that there are other venders of SPICE that could also have been used.

2 Defining the Subcircuits

SPICE has a number of circuit elements that can be used in forming the analogies to the various terms in the chemical rate equations. Concentrations (moles[6] in a volume) will be represented by voltage on capacitors since capacitance can be thought of as charge in a charge container. Charge will be analogous to moles of a substance. The flow (rate constants multiplied by concentrations) can be represented in SPICE by voltage-controlled current sources that define currents based on expressions involving voltages in the circuit. The way the terms in the chemical rate equations are combined will be modeled by how the circuit is connected together.

As an aid in keeping the circuit diagrams as uncluttered as possible and not to be distracted with conventional electrical symbols, three different sub-circuits will be developed that represent the main core analogous concepts. By using these sub-circuits in different ways (different ways of wiring them up) Rosen's original and Louie's two alternative realizations of Rosen's minimal (M,R)-system can be modeled and their phenomenological concentrations and flows simulated.

In the sub-circuit definition figures to follow, the sub-circuit symbol (used in the larger circuits) will be shown on the left side of the figure and what it represents will be shown on the right within the dashed rectangle. Each sub-circuit will contain input and output pins to connect to other items in the larger circuit. The pins are the 5-sided symbols whose names start with a "P". These sub-circuits will not have any meta-knowledge of the overall circuit. They are truly reductionist parts. The sub-circuits will allow certain parameters to be provided to customize its use. Unless overridden in the circuits using the sub-circuits, the sub-circuits will use the parameter values listed in the sub-circuit definition. Some of the parameter values will include one of the following metric symbols: $T = 10^{12}$, $m = 10^{-3}$, $K = 10^3$. Since this exercise is merely a demonstration of how the phenomenological models can be simulated, the various rate constants were just chosen arbitrarily.

Each sub-circuit will be introduced with its definition, a simple usage example, and a simulation of the simple usage example. In the sub-circuits, the usage examples, and the subsequent models using the sub-circuits, crossing lines are considered touching only if there is a dot at the intersection.
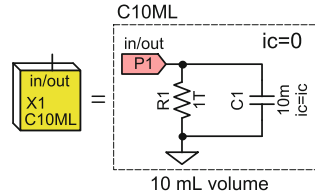
2.1 Volume and Concentration

Each of the chemical reactions will be modeled to occur in a volume of 10 ml (think of a test-tube). A volume sub-circuit (Fig. 1) will represent this volume for the purpose of tracking the concentration of a single compound. Whenever there are multiple compounds present in the same volume, multiple volume sub-circuits will be used to track the concentrations of the various substances individually. Therefore, multiple volume sub-circuits will be used to represent the same physical volume of solution when there are multiple concentrations to track.
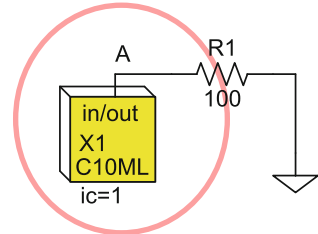
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[6] One mole is approximately 6.022×10^{23} items of something. It is defined as Avogadro's Number which is the number of particles in 12.000 g of carbon-12.

Fig. 1 Volume sub-circuit

Fig. 2 Simple usage example of the volume sub-circuit from Fig. 1

Since concentration will be analogous to the voltage on a capacitor, the volume sub-circuit contains a capacitor. The extremely high value resistor in parallel with the capacitor is there for technical requirements of SPICE and has no physiological significance. The volume sub-circuit contains one pin (in/out) to allow the flow of material in or out of the volume of solution thus changing its concentration. The volume sub-circuit can be provided with an initial concentration by specifying an "IC" parameter when appearing under the volume box. If the IC parameter is not shown, it will take the value of zero.

Perhaps the most simple, but nevertheless important, phenomenological circuit in physiology is passive diffusion across a semi-permeable membrane. This will be modeled with a resister connected to the volume sub-circuit. The concept of a membrane will be included in the upcoming models of the kinetic equations. The sub-circuit usage example in Fig. 2 represents a 10 ml volume with an initial concentration of 1 mol/l enclosed by a membrane surrounded by an infinite volume of zero concentration. The membrane is depicted here by a shaded circle going through the resistor. This shaded circle is for illustration purposes only. The triangle pointing down represents an infinite region of zero concentration (ground for the electrical circuit).

The simulation of this simple use case (Fig. 3) shows the expected exponential decrease in concentration as the concentration within the membrane approaches equilibrium with the infinite region of zero concentration outside.

2.2 Inter-Conversion

In order to model an inter-conversion such as b to β from Eq. 9 an inter-conversion sub-circuit will be utilized (Fig. 4). A voltage controlled current source will determine the inter-conversion rate based on the concentrations at the connecting pins and the rate constants provided. This sub-circuit models the inter-conversion of the input at P to the output at Z. The sub-circuit internally includes the storage

Fig. 3 Simulation of volume sub-circuit usage example from Fig. 2
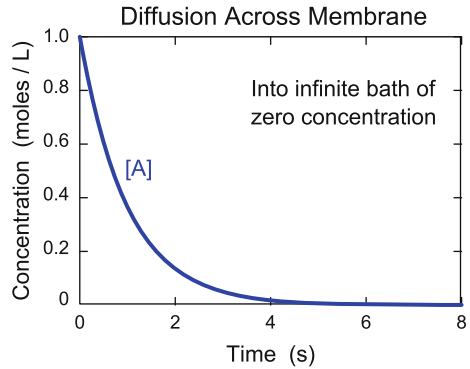
Fig. 4 Inter-conversion sub-circuit (for example the inter-conversion of *b* to *β*)
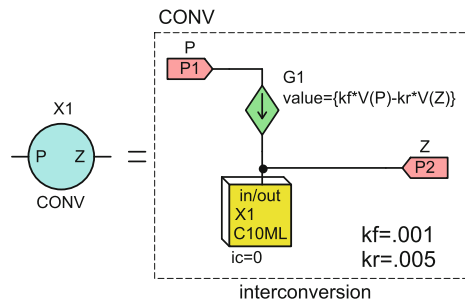
representation of the concentration of *Z*. The representation of the storage of the concentration of *P* is outside the sub-circuit. The G1 element simulates the flow from *P* to *Z*. Since the concentrations are being modeled as voltages the current source equation requires reference to the voltage at the "*P*" and "*Z*" nodes (thus V(*P*) and V(*Z*).

A simple usage example of the inter-conversion sub-circuit is shown in (Fig. 5).

A simulation of the simple usage example with the default rate constants as the system progresses towards equilibrium is shown in Fig. 6. The default rate constants were chosen to illustrate a situation where at equilibrium the concentration of "*Z*" will be less than the concentration of "*P*".

2.3 Enzyme

An enzyme sub-circuit (Fig. 7) can be constructed using a combination of volume sub-circuits (X1 and X2) and voltage controlled current sources (G1, G2, and G3) to model the terms in a basic mono-substrate enzymatic reaction such as that in (7), (8), or (10). E1 is a voltage controlled voltage source that is used merely as a sub-calculation that is referenced in G1 and G2. R1 is necessary to complete the circuit with E1. Its value can be arbitrary. The enzyme sub-circuit has 3 connecting pins (S, E, and P) representing the substrate, enzyme, and product respectively. The substrate-enzyme bound intermediary is hidden inside the sub-circuit but its concentration can be viewed if desired. The enzyme sub-circuit has volume sub-

Fig. 5 Simple usage example of the inter-conversion sub-circuit from Fig. 4
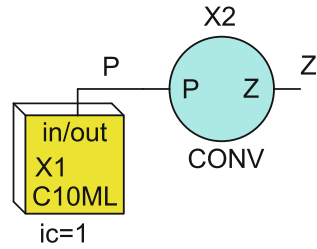

Fig. 6 Simulation of the inter-conversion sub-circuit usage example from Fig. 5
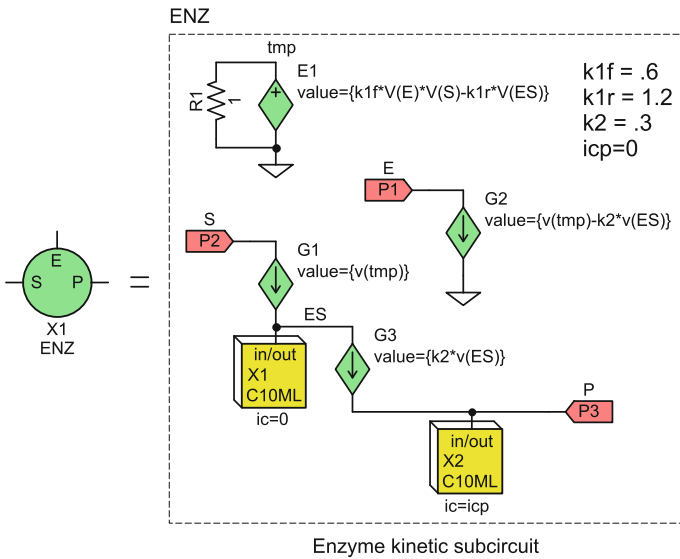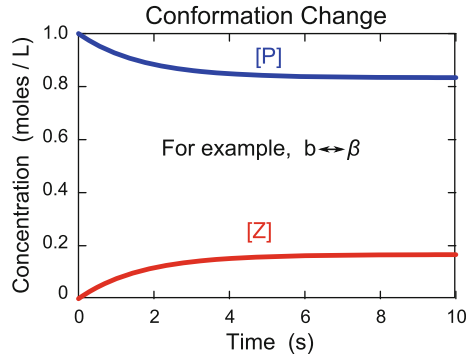
Fig. 7 Mono-substrate enzyme reaction sub-circuit

circuits internally for tracking the concentration of the enzyme-substrate binding and the product. The volume sub-circuits for the substrate and enzyme are purposefully located outside of the enzyme sub-circuit to aid in the interconnection

Fig. 8 Simple usage example of the enzyme sub-circuit from Fig. 7
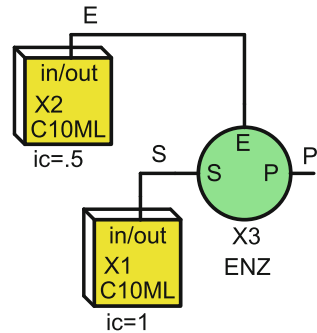
of multiple enzyme sub-circuits into a larger network. This will become evident when the subsequent models are formed.

A simple usage example of the enzyme sub-circuit is shown in Fig. 8. A minimal circuit can be crafted merely by providing the needed substrate and enzyme volume sub-circuits each with an initial concentration.

This simple enzyme usage example can be simulated as the system progresses to equilibrium as shown in Fig. 9. The plot shows the bound enzyme-substrate concentration quickly rising, then as the substrate is converted to product, the enzyme ultimately all returns to the unbound state as expected.

3 Assembling the Models

We now have all the necessary sub-circuits to assemble the various kinetic realizations of Rosen's minimal (M, R)-system. Once the first kinetic model is built, the other two will mainly involve only topological changes in the wiring.

3.1 β: H(A, B) $\rightarrow$ H(B, H(A, B))

Figure 10 shows an initial attempt to form a kinetic phenomenological model of (3) or (4). By studying the network connections, you can see how the various kinetic equations are modeled. For instance X2 represents (7) or (11). X3 represents (8) or (12). X4 represents (10) or (14). X5 represents (9) or (13). X1, the volume sub-circuit, is the required substrate volume for enzymatic reaction X2. For the interconnected enzyme sub-circuits, the output product of one enzyme sub-circuit becomes the input for another enzyme sub-circuit. Now you can appreciate the strategy of locating certain volume sub-circuits outside the enzyme and inter-conversion sub-circuit definitions.

This model, though, is materially closed since there is no flow of material in or out of the system. As such, it will inevitably[7] progress toward equilibrium as can be seen Fig. 12. Figure 11 shows how the concentration changes over time. One definition of equilibrium is when the net flows all go to zero.

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[7] A materially closed system could avoid equilibrium with an inward flux of energy. Here, though, we are assuming that any energy would come in the form of materials (chemical energy).
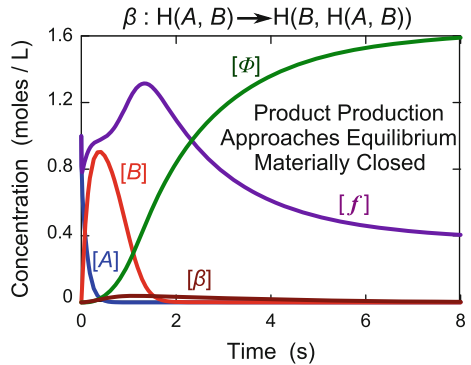
Fig. 9 Simulation of the enzyme sub-circuit from Fig. 8
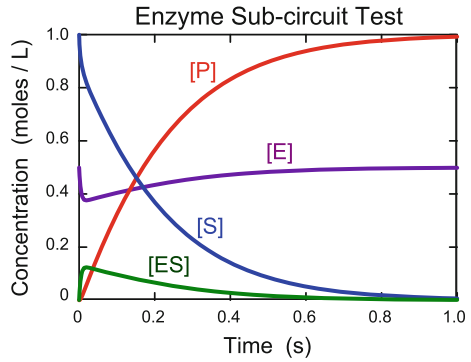
Fig. 10 Materially closed kinetic model of the enzymatic system described by Eqs. 7, 8, 9, and 10
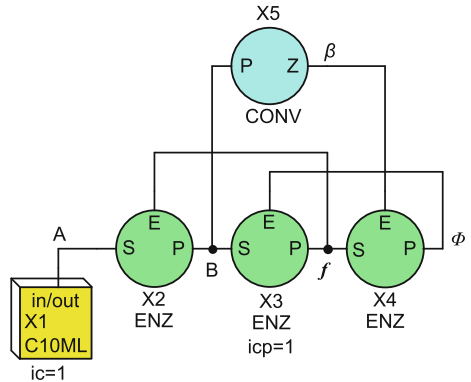

Fig. 11 Simulation showing concentrations for the materially closed kinetic model from Fig. 10 as it proceeds to equilibrium


One way to open the system up to the environment is to enclose the system with a semi-permeable membrane and allow material to flow in and out. Therefore we will make some ad-hoc additions to the basic model to add in a membrane and an unlimited ability of the environment to provide more of A and take away any other material that diffuses out of the membrane. By making the membrane semi-permeable to B, β, f, and Φ in addition to A, it will also demonstrate the ability of the system to regenerate these materials as they diffuse out of the system. For

Fig. 12 Simulation showing production flows for the materially closed kinetic model from Fig. 10 as it proceeds to equilibrium
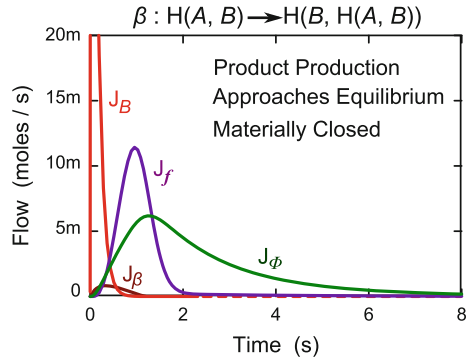
Fig. 13 Materially opening Fig. 10 to allow the possibility of achieving steady state flows. This is the kinetic model for system (3) or (4)
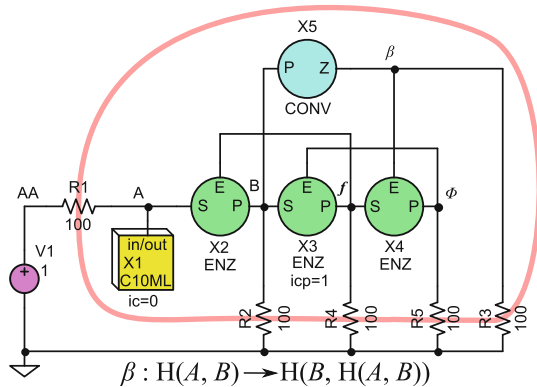
simplicity, the membrane will not be considered permeable to the substrate-enzyme bound intermediate (*f-A*, *Φ-B*, and *β-f*) represented within the enzyme sub-circuits.

Figure 13 shows the addition of the ad-hoc membrane and unlimited bath of fixed concentration of *A*. Image a vesicle immersed in a perfused solution that maintains a 1 M solution of *A* and a zero molar solution of the other compounds that can diffuse out through the membrane. The membrane is represented by the resistors. The shaded closed curve enclosing the original model is merely a visual clue to conceptualize the membrane. The fixed external concentration of A is modeled by constant voltage source V1. The ground symbol models the outside zero concentration of the other compounds that can diffuse out of the membrane. Figure 13 will be the kinetic model of (3) or (4).

Figure 14 shows a simulation of the concentrations changing as they approach steady state. Figure 15 shows the production of the products in the three enzyme sub-circuits along with the formation of *β*. Unlike in the equilibrium case, none of these production flows go to zero. Having all the flows approach non-zero constant values is a definition of a system approaching steady state.

The flows for J_B, J_f, and J_Φ are different at steady state because of the inclusion of the resistors to provide a path out of the system for these substances. If resistors R2,

Fig. 14 Simulation showing concentrations as the system show in Fig. 13 proceeds to steady state
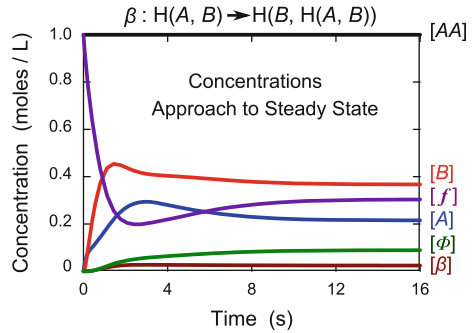

Fig. 15 Simulation showing enzymatic product formation from the system in Fig. 13 as it proceeds to steady state
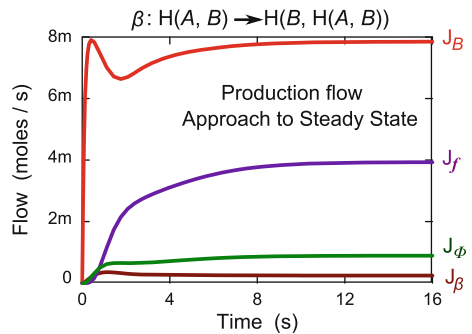
R3, and R4 were removed, leaving only R5, then these three flows would settle into the same value.

3.2 β: $B \rightarrow H(B, H(A, B))$

Louie's second realization (5) can be modeled by constructing a model of a similar set of chemical enzymatic rate equations but with substituting (15) for (10) above.

$$b + \beta \underset{k_{-6}}{\overset{k_6}{\rightleftharpoons}} \beta b \xrightarrow{k_7} \beta(b) + \beta = \Phi + \beta \tag{15}$$
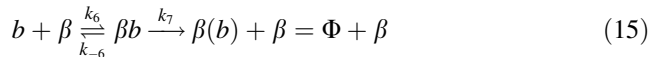
A SPICE model can be constructed as shown in Fig. 16 using the same[8] set of sub-circuits but wired up differently.

This circuit can be simulated as shown in Figs. 17 and 18 showing the concentrations and production flows respectively as the system approaches steady state.

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[8] Note that since these simulations are meant only as demonstrations, we didn't bother to change the rate constants for the different realizations. In general, though, each different realization would be expected to have different rate constants which could be passed to the sub-circuits. Additionally, each enzyme sub-circuit within a particular realization would really be expected to have different rate constants than the other two. In these simulations, though, we simply reuse the same enzyme sub-circuit with the same default rate constants. We do, though, change the initial product concentration through the IC parameter.
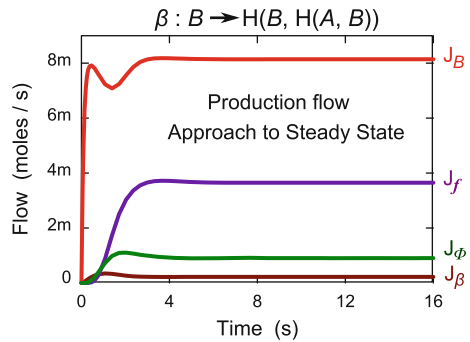
Fig. 16 Materially open kinetic model for system (5)
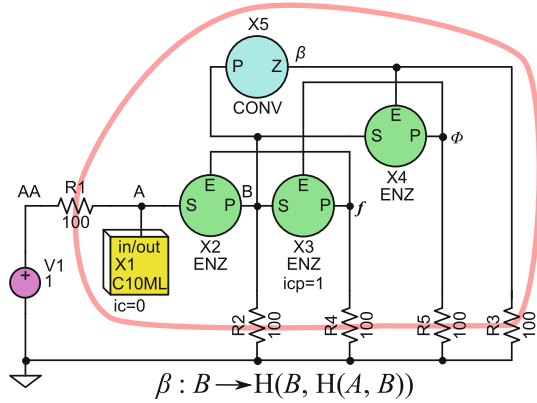
$$\beta : B \longrightarrow H(B, H(A, B))$$

Fig. 17 Simulation showing concentration as the system in Fig. 16 proceeds to steady state
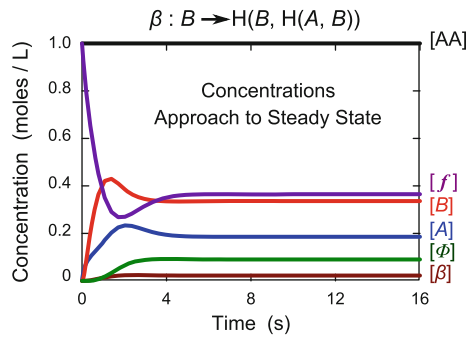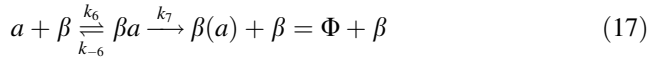

Fig. 18 Simulation showing enzymatic product production as the system in Fig. 16 proceeds to steady state

3.3 β: $A \rightarrow H(B, H(A, B))$

Louie's third realization (6) can be modeled by substituting equations (16) and (17) for equations (9) and (10) in the original set.
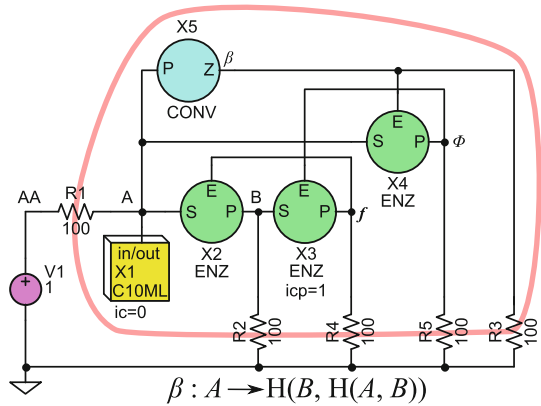
$$a \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} \beta \tag{16}$$

$$a + \beta \underset{k_{-6}}{\overset{k_6}{\rightleftharpoons}} \beta a \overset{k_7}{\longrightarrow} \beta(a) + \beta = \Phi + \beta \qquad (17)$$

A SPICE model can then readily be constructed as shown in Fig. 19.

This circuit can similarly be simulated with SPICE as is shown in Figs. 20 and 21 which show the concentrations and product production as the system approaches steady state.
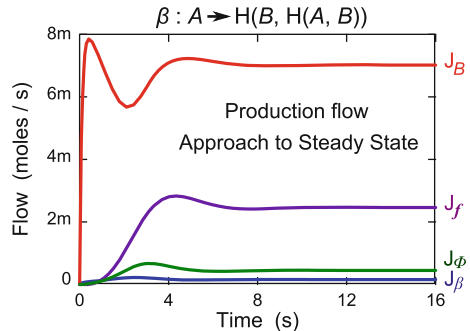
Fig. 19 Material open kinetic model for system (6)

Fig. 20 Simulation showing concentration as the system in Fig. 19 proceeds to steady state
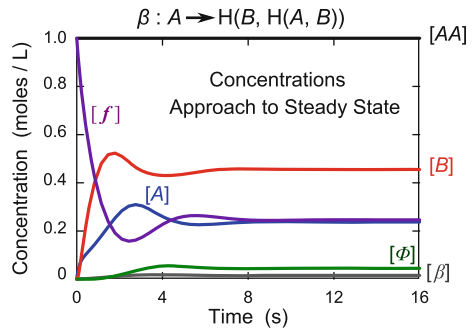
Fig. 21 Simulation showing enzymatic product production as the system in Fig. 19 proceeds to steady state

4 Is it Really Closed to Efficient Cause?

An answer to this question will depend on how rigidly efficient cause is defined and also on exactly what "it" refers to. The astute reader will have noticed that the system did not in fact generate all of the enzymes historically used. There needed to be an initial "seeding" of some quantity of f as a member of H(A, B) to get the system started. Note ICP = 1 for the enzyme sub-circuit labeled X3 in Figs. 13, 16, and 19. Once f and A where inside the membrane, the system could proceed to generate the other materials needed along with more of H(A, B). Over time, since the system assumes steady state production of all the enzymes, the historic percentage of the enzymes produced within the system approaches 100%. If a scientist only became familiar with such a system after it had achieved steady state and did not know about its early history, they might easily conclude that it was absolutely closed to efficient cause. In general it is convenient to uncouple our study of physiology from our study of abiogenesis or biopoesis.

Next we must define "it". We argue here that "it" must refer to the physical chemical system which we are modeling. "It" would definitely not be the SPICE program. One epistemological stance is that the model of the chemical system only exists in the mind of the modeler (and all others the model can be communicated with). In any extent, the SPICE simulation is not itself the model and is not itself closed to efficient cause. The SPICE program is merely a simple (in Rosen's sense) system that performs calculations. The simulation itself could be modeled by a simple function f: Input → Output. The SPICE program itself is not regenerating itself. It is only keeping track of the regeneration of the chemical quantities it is simulating.

One may ask that since the SPICE program is an electrical circuit simulator, would actual analog electrical circuits realizing these phenomenological kinetic models be closed to efficient cause? Well no. As in the simulation, an actual analog electrical circuit would only be manifesting voltages analogous to the concentrations in the chemical system. The physical analog electrical circuit would not actually be regenerating any of its own hardware parts. Therefore, an analogous analog electrical circuit would not be closed to efficient cause either.

Another legitimate concern is the ad-hoc addition of an un-entailed membrane to the model. The membrane performs a function but is not itself explicitly produced by anything in this particular chemical system. It could be rationalized, though, that the system takes advantage of an environmentally provided membrane similarly as the hermit crab takes advantage of a shell it finds. Perhaps it could also be argued that the membrane is produced as part of the family of reactions of $A \rightarrow B$. Ideally, though, a concept as important as a membrane would have some specific explicit entailment from within the system. See Cornish-Bowden and Cardenas (2007), Olasagasti et al. (2007), and Zaretzky and Letelier (2002) for models and discussions where the system produces it own border or membrane.

5 Comparisons and Optimizations

It is beyond the scope of this paper to perform a sensitivity analysis[9] of the kinetics comparing the simulation results shown in Figs. 14, 17, and 20 (or in Figs. 15, 18, 21). The kinetic responses of the simulations have a large dependence on the values of the rate constants chosen. Differently chosen rate constants would lead to very different kinetics of the systems. A sensitivity analysis, though, would be useful in determining which of the ways to close Rosen's penultimate diagram (2) was the most stable and robust. Some general comments, though, can be made in comparing the systems.

It would be expected that system (6) with closure property $\beta: A \rightarrow H(B, H(A, B))$ would have the greatest dependence on the environmental input. This is because a simple conversion of the environmental input is used as the enzyme (β from Fig. 19) to generate Φ from the environmental input. Therefore, the environmental input completely entails Φ. If the environment failed to provide the correct input, the system would fail to sustain itself. In the other two systems, the environmental input goes through a "metabolism" step by component f before the products are converted and used as enzymes. This provides an additional degree of separation from the environment.

Similarly, in system (5) Φ is entailed solely by b. A simple conversion of b is used as the enzyme (β from Fig. 16) to generate Φ from b. System (4) on the other hand has each component operating on the output of a different component which provides a degree of separation within the system. It would be interesting to further study the ramifications of having these degrees of separation within the system. The figures introduced in the closing thoughts of this paper have even more degrees of separation within the system.

6 Realizations in Nature

Of Louie's three realizations (4), (5), and (6), are there any real world realizations in the natural world? All three of these systems have a "metabolism" component where $f: a \rightarrow b$. They each have a "repair" component where $\Phi: b \rightarrow f$. They each also have a "repair of repair" component that in turn entails Φ. They differ only in the entailment of the "repair of repair" component. Undoubtedly organisms in the natural world have a metabolism component. Organisms also produce their own enzymes responsible for metabolism. Organisms also regenerate their own ability to regenerate their own enzymes. In a broad brush, each of these systems (or a combination) could be considered candidates for models of real-world organisms. It should also be noted that for purposes of mathematical elegance, the systems proposed by both Rosen and Louie are the simplest possible systems able to express the closure concept in any meaningful way. They are not intended to be any kind of final (or largest) model describing the microbiology.

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[9] Sensitivity analysis—the study of how the output of a model is affected by variations in the input (or parameters) of the model.

7 Final Comments

There appears to be no logical contradiction in performing simulations of kinetic phenomenological representations of these (M,R)-systems as long as one is careful to remember what is actually being modeled. The simulation is not the model and the simulation itself is not closed to efficient cause. In this case we are simulating a phenomenological model (of concentrations and flows) which can be thought of as a meta-description of the system. As such, the meta-description is not itself closed to efficient cause and can be simulated as a purely reductionist system with the appropriate analogies to electrical circuit theory.

The "dynamic approach" is one of the three ways Rosen identified for the study of the realization problem. Each approach has its own contributions and limitations. Each approach can also serve as a check and balance to the other approaches. For example, the dynamic approach is useful in visualizing a (M, R)-system. There is a risk, though, of unwittingly forming erroneous kinetic models that nevertheless can be simulated. In such cases, the other approaches can serve as a check on the dynamic approach.

As a closing thought, this paper refers to Rosen's minimal (M, R)-system which has three components. Minimal means the smallest system that can manifest the intended relationships. It was shown that larger systems may be possible where the reactions could be segregated into their own reaction chambers without other products forming (Prideaux 2007). The minimal (M, R)-system with this property was shown to have 7 components. One such minimal system with seven compartments is shown in Fig. 22.

One thing that paper did not address is that if the reactions are considered irreversible then an even smaller system with only 6 components is possible where the reactions can be segregated as shown in Fig. 23.

To dynamically model such systems, it would be convenient to develop a "reaction chamber" sub-circuit such as shown in Fig. 24. Here only the non-
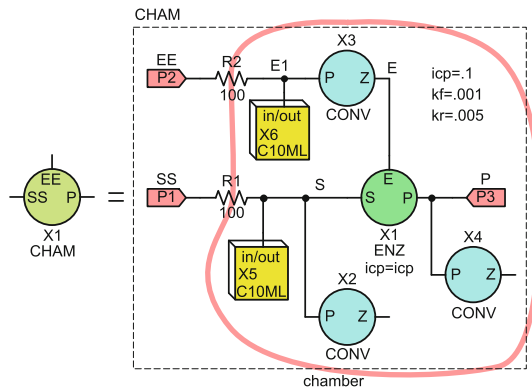

Fig. 22 Seven component system where each enzymatic reaction can be segregated into its own "reaction chamber"
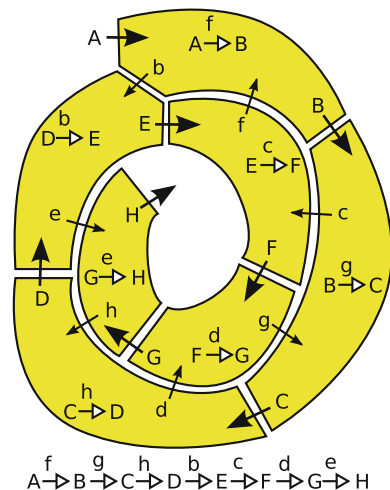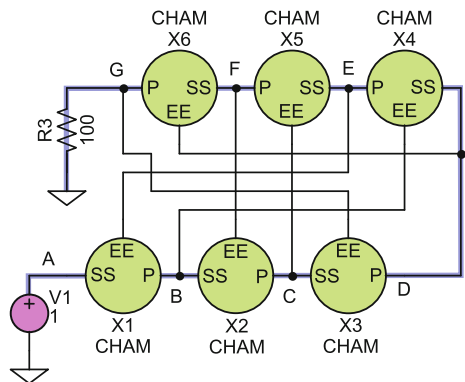
Fig. 23 Six component system where each enzymatic reaction can be segregated into its own reaction chamber
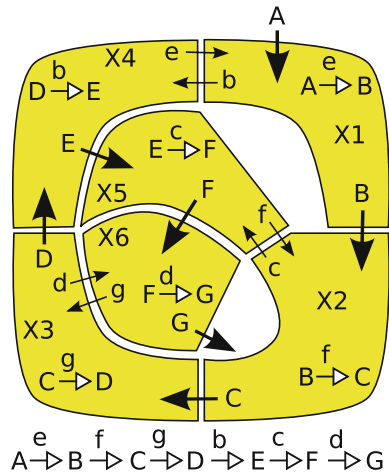
Fig. 24 Reaction chamber sub-circuit under development

Fig. 25 Model of the 6-component system from Fig. 23

converted products will be able to pass through the touching chamber membranes. Resistors to ground could also be added to the sub-circuit for leakage out of the system.

This chamber sub-circuit, or one similar to it, would allow for the assembly of models such as what is shown in Fig. 25 representing the 6-component system from Fig. 23.

It would be interesting to see a formal mathematical derivation, if possible, of the closure of one of these larger systems. More details about these larger systems will have to wait for a future paper.

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