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EMERGENCE AND ITS PLACE IN NATURE: A CASE STUDY OF BIOCHEMICAL NETWORKS

ABSTRACT. We will show that there is a strong form of emergence in cell biology. Beginning with C.D. Broad's classic discussion of emergence, we distinguish two conditions sufficient for emergence. Emergence in biology must be compatible with the thought that all explanations of systemic properties are mechanistic explanations and with their sufficiency. Explanations of systemic properties are always in terms of the properties of the parts within the system. Nonetheless, systemic properties can still be emergent. If the properties of the components within the system cannot be predicted, even in principle, from the behavior of the system's parts within simpler wholes then there also will be systemic properties which cannot be predicted, even in principle, on basis of the behavior of these parts. We show in an explicit case study drawn from molecular cell physiology that biochemical networks display this kind of emergence, even though they deploy only mechanistic explanations. This illustrates emergence and its place in nature.

1. INTRODUCTION

We will show that there is a strong form of emergence in cell biology. Emergent properties have long been discussed in philosophy and in the sciences (Beckermann et al. 1992; Stephan 1999). The philosophical debate is largely inspired by metaphysical concerns. Metaphysical conceptions of emergence have metaphysical goals. So understood, the problem is the nature of the mental, or the nature of life, and whether they differ from the physical. The key questions are whether mind can be reduced to body and whether life can be mechanically explained. If some phenomenon is emergent, in the metaphysical sense, then it is somehow fundamental and irreducible. It is fundamentally different from the physical basis on which it nonetheless depends. So, for example, Kim (1999, 4) says the key idea from emergentism is supposed to be that complex systems exhibit irreducibly novel properties, and that these novel properties are neither predictable nor explainable in terms of the properties of their constituents. The goal of emergentist theories is to find an approach that avoids both the Scylla of vitalism (or dualism) and the Charybdis of reductionism (or

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materialism). Metaphysical emergence then faces a dilemma that Kim artfully exploits. Metaphysical emergentists embrace physicalism, insisting that all parts are physical constituents. They likewise insist that at least some macrofeatures could not be explained or deduced as complex microfeatures (Kim 1999, 10). Kim argues, essentially, that emergentism is an unstable position; that is, they face a dilemma. If they are consistently physicalist than they are committed to reductionism (or materialism); alternately, if they avoid reductionism then they are committed to vitalism (or dualism). So long as properties can be "functionalized", Kim claims they are reducible. He illustrates the point with chemical and biological properties:

> Consider the transparency of water: so it would seem that once this property has been functionally understood, as the capacity of a substance to transmit light beams intact, there should be no principled obstacle to formulating a microphysical explanation of why H_2O molecules have this power. The same strategy should allow microphysical explanations and predictions of biological phenomena as well, for it seems that many biological properties seem construable as second-order functional properties over physical-chemical properties. (Kim 1998, 100–101)

The same holds true for mental properties: if they are functionalizable they are reducible, and therefore not emergent. The only residual properties which elude reduction include the qualitative characters of our phenomenal experiences, and they elude reduction only because they have intrinsic properties that elude any functionalization.

Metaphysical emergence, in this *a priori* sense, has no place in the natural sciences. Emergent properties defy any naturalistic explanation. Emergence is therefore regarded as suspect in those sciences. Any appeal to emergent phenomena is seen as a sign of intellectual weakness. For emergence to have any positive role to play in a scientific setting, it must be understood differently. It must be compatible with the thought that scientific explanations are mechanistic explanations (Bechtel and Richardson 1993; Craver 2001; Craver et al. 2001; Darden and Craver 2002; Machamer et al. 2000; Glennan 2002). Ideally, emergence would be a natural consequence of physical processes. Finally, emergence should not be merely an epistemic notion, as Ernest Nagel thought it would be:

> It is clear. . . that to say of a given property that it is an 'emergent' is to attribute to it a character which the property may possess relative to one theory or body of assumptions but may not possess relative to some other theory. Accordingly, the doctrine of emergence . . . must be understood as stating certain logical facts about formal relations between statements rather than any experimental or even 'metaphysical' facts about some allegedly 'inherent' traits of *properties* of objects. (Nagel 1961, 369)

Nagel thought that 'emergence' would disappear with improved theories. According to Nagel even if some phenomenon cannot be explained or

predicted by a theory at a time this does not constitute a metaphysical fact. An improved theory at a later time might be capable of explaining the phenomenon. Nevertheless, some complex phenomena seem to be emergent, even from a thoroughly mechanistic point of view. For instance, complex systems that comprise nonlinearly-interacting components can exhibit qualitatively new behavior relative to the behavior of their parts (Westerhoff 2000). These systems are often described as emergent.

We seek an account of emergence that is not merely epistemological and yet does not suffer from the problems of *a priori* metaphysics.[1] We explore emergence and its place in nature. There are already scientists and philosophers who embrace naturalistic forms of emergence. For example, Ernst Mayr describes emergence this way:

> Systems almost always have the peculiarity that the characteristics of the whole cannot (even in theory) be deduced from the most complete knowledge of the components, taken separately or in other partial combinations. This appearance of new characteristics in wholes has been designated as *emergence*. (Mayr 1982, 63)

The quote reflects the ideas of one of the classics of British emergentism, C.D. Broad, who in 1919 offered a notion of emergence that captures all that is useful for the natural sciences. He did not base his notion of emergence merely on the abstract relationship between systemic behavior and the behavior the components exhibit within the system, as metaphysicians would have it; instead, he also based it on the contrast between the behavior the components show within the entire system and the behavior they show in isolation or in other (simpler) systems. Mayr and Broad both think of systemic properties as emergent if they cannot be deduced, even in principle, from the behavior the system's components show within simpler wholes.

We will present an explicit example from cell biology that displays emergence in the sense articulated by Broad and Mayr. In Section 2, we distinguish two conditions for emergence in the work of C.D. Broad. One is closer to the metaphysical problem. The other is more useful in natural science. It gives emergence its place in nature. In Sections 3, 4, and 5 we show that biochemical networks display this kind of emergence. Microorganisms essentially are large biochemical networks. They exhibit a variety of systemic properties, such as homeostasis, regulation, plasticity, and adaptation, that appear to transcend the physical properties of their constituent parts, including enzymes, individual pathways, organelles, and other systems smaller than the cell. It seems that it is here where life emerges from its inanimate constituent matter. Nonetheless, every phenomenon in the cell is mechanistically explainable. Emergent phenomena are mechanical effects.

2. BROAD'S EMERGENCE

Broad distinguishes between emergent and mechanistic theories in *The Mind and its Place in Nature*:

> Put in abstract terms the emergent theory asserts that there are certain wholes, composed (say) of constituents A, B, and C in a relation R to each other; that all wholes composed of constituents of the same kind as A, B, and C in relations of the same kind as R have certain characteristic properties; that A, B, and C are capable of occurring in other kinds of complex where the relation is not the same kind as R; and that the characteristic properties of the whole R(A, B, C) cannot, even in theory, be deduced from the most complete knowledge of the properties of A, B, and C in isolation or in other wholes which are not of the form R(A, B, C). The mechanistic theory rejects the last clause of this assertion. (Broad 1925, 61)

According to Broad systemic properties are nomologically dependent on the micro-structure of the system: the behavior of wholes depends on the behavior of their parts and their relations to one another. A systemic property, as Broad uses the term here, is emergent if the property cannot be "deduced from" a "complete knowledge" of the arrangement of the system's parts and the properties they have 'in isolation' or in other systems.[2]

It is important in this context to distinguish between *strong* and *weak* emergence. The weaker version of emergentism pervades "emergentist" theorizing in various scientific approaches, e.g., connectionism, artificial life, and theories of self-organization. Its three basic features – the thesis of *physical monism*, the thesis of *organizational* (or collective) properties, and the thesis of *synchronic determinism* – are compatible with mechanistic approaches without further ado. *Physical monism* is a metaphysical thesis about the *nature* of systems that have emergent properties. It says that the properties, dispositions, behaviors, and structures which are classified as emergent are instantiated by systems consisting exclusively of physical entities. The thesis denies that there are any supernatural components. In a biological setting, this precludes vitalism. *Organizational properties* are the candidates for emergent properties. These are properties that none of the systems' parts have.[3] *Synchronic determination* specifies the type of relationship that holds between a system's micro-structure and its systemic properties: there is synchronic determination if all of a system's properties and dispositions depend only on its micro-structure, that is to say, on its parts' properties and their arrangement. There can be no difference in the systemic properties without there being some differences in the properties of the system's parts or in their arrangement (Broad 1925, 61). In recent debates, the thesis of synchronic determination is sometimes stated in a weaker version as the thesis of *mereological supervenience*,

which claims that intrinsic system properties supervene on the properties of the parts and their arrangement. Again, there can be no difference in the systemic properties without some difference in the parts' properties or their arrangement. Mereological supervenience, however, is weaker than synchronic determination, as we use it, since it does not claim the *dependence* of the system's properties on its micro-structure. It only claims their *covariance*.

Weak emergentism is too weak. All organizational properties turn out to be emergent. And there are many. This shows that the notion of weak emergence is too weak to be useful. We are interested in strong emergence. The central question then is, in Broad's terms, whether there are properties of systems which cannot be "deduced" from the behavior of parts, together with a "complete knowledge" of the arrangement of the system's parts and the properties they have in isolation or in other simpler systems. Properties that are not deducible in this way we call strongly emergent properties.

There are two independent conditions for emergence, not distinguished at this point by Broad, which we think of as "vertical" and "horizontal" (see Figure 1). A systemic property P_R of R(A, B, C) is emergent if either of these conditions is fulfilled. The first is the vertical condition: A systemic property is emergent if it is not mechanistically explainable, even in principle, from the properties of the parts, their relationships within the entire system, the relevant laws of nature and composition principles.[4] The micro-structural base in this condition (together with the laws and principles) will not be sufficient to "deduce" the systemic properties. Broad assumes that supervenience of macroscopic properties on their subvenient bases is always fulfilled. What is at issue is whether there is a mechanistic explanation for P_R given the behavior of A, B, and C in R(A, B, C). The second is the horizontal condition: A systemic property is emergent in this sense if the properties of the parts within the system cannot be deduced from their properties in isolation or in other wholes, even in principle. The properties of, say, part A in the context of system R(A, B, C) would be emergent in this sense if they were not deducible from the properties of A, B, and C in isolation or in other systems.

Broad does not explicitly distinguish the horizontal and vertical conditions for emergence; nonetheless, if either is fulfilled, then the behavior of the system's parts A, B and C in isolation or in other contexts is not sufficient to determine the systemic properties P_R. Since the two conditions are independent, there are two different possibilities for the occurrence of *emergent* properties: (a) a systemic property P_R of a system *S* is *emergent* if it does not follow, even in principle, from the properties of the parts within *S* that *S* has property P_R; and (b) a systemic property P_R of a system

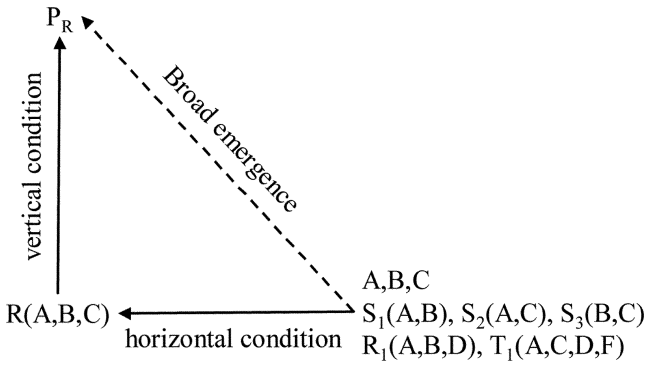


Figure 1. This is a graphic illustration of the two conditions for emergence. A, B, and C are the parts making up the system. S_1(A,B), S_2(A,C), and S_3(B,C) are simpler, binary, wholes including these parts. R_1(A,B,D) is a system with the same number of parts, and T_1(A,C,D,F) is a system with more parts than R(A, B, C). P_R is a systemic property. The diagonal arrow represents Broad's idea of emergence. The horizontal and vertical arrows capture the two conditions implicit in Broad.

S is *emergent*, if it does *not* follow, even in principle, from the properties of the parts in constellations different from S how they will behave in *S*. These two conditions are captured in Figure 1.

Broad is not wholly unambiguous what kind of "other wholes" we should be allowed to refer to when trying to deduce the parts' behavior within R(A, B, C). The key question is how rich the base for deduction is. We'll come back to this point later. The diagonal arrow in figure 1 depicts Broad's idea that a systemic property is emergent if it is not "deducible" from the properties parts exhibit in isolation or in other wholes (e.g., in S_1, S_2, S_3, R_1, R_2, R_3, T_1, T_2, T_3, ...). So Broad says, two pages earlier, that there is emergence provided

> ... the characteristic behaviour of the whole *could* not, even in theory, be deduced from the most complete knowledge of the behaviour of its components, taken separately or in other combinations, and of their proportions and arrangements in this whole. (Broad 1925, 59)

Once again, this fails to distinguish the two conditions for emergence. There are two reasons systemic properties might fail to be "deduced" from the properties of the parts. Fulfilling the vertical conditions means there would be a failure of mechanistic explanation. The properties (and behaviors) of the system would then be inexplicable in terms of the properties (and behaviors) of the parts as they function in the system. Fulfilling the horizontal condition means the properties (and behaviors) of the parts within the whole cannot be predicted from their properties (and behaviors) in other systems. In either case the systemic properties will be emergent.[5]

Let us look at and comment on the two conditions in more detail now. Broad is cautious over the question whether the *characteristic* properties of

chemical compounds and viable organisms are emergent. These properties would be emergent if the behavior of the parts in the system were not predictable from the behavior of the parts in isolation or in other wholes together with their arrangement in the whole. He does claim that secondary qualities and phenomenal qualities are emergent, because they are neither adequately characterizable in qualitatively different macroscopic terms nor by the microscopic behavior of the system's parts when embedded in the entire system, even in principle. They fail to be what Kim would call a "functionalizable" property. That a certain object is red or a chemical substance has the smell of ammonia does not mean that the corresponding parts in the system *behave* or *move* in a certain way. If being red is emergent, then redness cannot be identified with any more fundamental physical properties such as reflectances; neither can it be characterized in structural terms, though some particular shade of red might be characterizable by comparison with other shades of red or other colors.

Similarly, Broad distinguishes between (behaviorally) *analyzable* and *unanalyzable* properties by pointing to the characteristics of being alive and having a mind, respectively (Broad 1925, 612–614, 621–623). If secondary and phenomenal qualities are not analyzable, even in principle, then there is no prospect that an increase of scientific knowledge will close the gap between physical processes and secondary qualities or between physiological processes and phenomenal states of consciousness (qualia), respectively.[6] If a property is unanalyzable then the vertical condition is met: no mechanistic explanation of the property P_R in terms of the behavior of the parts in the system is possible. Notice that the appeal here is to the behavior of the parts *within the system*: emergence would entail that even a complete knowledge of how the parts function within the system must be insufficient to explain systemic behavior. It is this vertical condition many philosophers of mind are mainly interested in: the issue is whether, given complete knowledge about the neural base (or correlates) of our mental states, we can mechanistically explain the latter.

Systemic properties also will be emergent if the behavior of the parts in the system could not be predicted from their behavior in isolation or in other constellations. This is the horizontal condition. Broad thinks that such examples of emergent behavior might occur in chemical compounds and also in organisms. The parts of a genuinely novel structure, such as chemical compounds within an organism, might behave in a way that is not deducible from the behavior of the parts in other (non-organic) structures. If the behavior of any part within the system is, in principle, unpredictable on the basis of their behavior in isolation or in other wholes, then all properties that depend nomologically on the behavior of the parts in the system

are emergent. This leaves it open whether these "other wholes" include only other naturally occurring systems or any other possible systems.

Broad (1919) discusses what we here call "the horizontal condition" in his earlier article "Mechanical explanation and its alternatives" (1919). The passage differs importantly from those in *The Mind and its Place in Nature*. It is only in this earlier article that he focuses explicitly on this type of case:

> Let A, B, C be compounds in the chemical sense, i.e. first order groups. Let X be a second order group consisting of A, B, and C in certain definite proportions and positions, and with a definite structure in space. Let the atoms in A be $\alpha_1 \ldots \alpha_p$, those in B be $\beta_1 \ldots \beta_q$, those in C be $\gamma_1 \ldots \gamma_r$. Let us call the structures of A, B, and C, σ_A, σ_B, and σ_C, respectively, and the state of their surroundings S_A, S_B, and S_C, respectively. Then presumably the chemical behaviour of A is $f_A(\alpha_1 \ldots \alpha_p, \sigma_A, S_A)$, that of B is $f_B(\beta_1 \ldots \beta_q, \sigma_B, S_B)$, and that of C is $f_C(\gamma_1 \ldots \gamma_r, \sigma_C, S_C)$. What we know from ordinary chemistry is that over a very wide range of variation a change in the variables S_A, S_B, S_C, is irrelevant. Naturally, we never know that all possible changes in them are irrelevant. Now take the behaviour of the second order complex X. In the first place, we can write this as $f_X(A, B, C, \sigma_X, S_X)$ Here σ_X, refers to the structure of the second order complex in terms of the first order complexes taken as elements, and by S_X to the surroundings of the complex X taken as a whole. Now let us consider, e.g., the behaviour of A in this complex. B and C, with their structures and components, σ_X, the structure of the complex, and S_X, the surroundings of the complex, will now all be lumped together as S_A, the surroundings of A in the function $f_A(\alpha_1 \ldots \alpha_p, \sigma_A, S_A)$, which expresses A's chemical behaviour. Now all that we know from chemistry is that the value of the latter function is unaltered or alters in certain known ways over a wide range of variation of S_A; we do not know that it will remain unaltered or will alter in any of these ways if S_A be varied beyond these limits. Now in some second order complexes, such as living organisms, S_A will be very different from any of the surroundings which have been tried in ordinary chemistry, and it will not, therefore, be surprising if A should exhibit new and unexpected properties. (Broad 1919, 113 f.)

This quote is the precursor of the "classical" passage from his book we quoted above.[7] However, the abstract "case study" in the present article is far more complex and is better suited to cover real cases we encounter, e.g., in cell physiology, or in biology in general. Whereas Broad here acknowledges that we might encounter "new" and "unexpected" properties when considering a "biological environment" S_A of some compound A instead of its purely "chemical environments", he would address this issue as a possible candidate of non-deducibility in his later publication, even in the pure chemical case. For instance, in *The Mind and its Place in Nature* Broad says that,

> so far as we know at present, the characteristic behaviour of Common Salt cannot be deduced from the most complete knowledge of the properties of Sodium in isolation; or of Chlorine in isolation; or of other compounds of Sodium, such as Sodium Sulphate, and of other compounds of Chlorine, such as Silver Chloride. (Broad 1925, 59)

Notice that, here, Broad allows us to use our knowledge of the behavior of Sodium and Chlorine in structures that are *as complex* as the compound whose behavior we wish to explain. So in explaining the behavior of salt, we are allowed to appeal not only to the properties of Sodium and Chloride in isolation, but also to their behavior in compounds such as Silver Chloride (AgCl) or Sodium Sulphate (Na_2SO_4). In contrast, in his abstract model he refers to a *hierarchy* of complexity in the structures of, e.g., biological and chemical systems.

However, in his book, even on the same page, Broad is ambiguous concerning the resources we can use in explaining a system's behavior. Thus, he acknowledges that "the characteristic behaviour of the whole" may be "deduced from a sufficient knowledge of how the components behave in isolation or in other wholes *of a simpler kind*" (Broad 1925, 59; our emphasis). These are what he calls "mechanistic theories". In the same vein, he refers to "laws of composition" which have "manifested itself [themselves] in *lower orders*" (Broad 1925, 78; our emphasis) when distinguishing "reducible characteristics" from the "ultimate" ones.

It is important to be careful concerning the extent of the explanatory resources that are allowed for explaining the behavior of parts within a system. We might deduce or explain the behavior of the parts in the system on the basis of systems of greater, equal or less complexity. That is, we might be allowed to consider the behavior of the parts in

(i) other systems without any restrictions, including even systems which are more complex (e.g., allow to refer to T_2(A,C,D,F) to explain A's behavior within R(A, B, C)),
(ii) other systems which may at most have the same degree of complexity (e.g., allow to refer to T_1(A,B,D) to explain A's behavior within R(A, B, C)), or
(iii) systems of a simpler kind only (e.g., allow to refer only to the parts A, B, and C in isolation, and to S_1(A,B), S_2(A,C), S_3(B,C) to explain A's behavior within R(A, B, C)).[8]

Broad does not think we can deduce the behavior of chemical complexes on the basis of the behavior of parts even when we allow for systems of the same or greater complexity.[9] Thus, he says this about water:

> Oxygen has certain properties and Hydrogen has certain other properties. They combine to form water, and the proportions in which they do this are fixed. Nothing that we know about Oxygen by itself or in its combinations with anything but Hydrogen would give us the least reason to suppose that it would combine with Hydrogen at all. Nothing that we know about Hydrogen by itself or in its combinations with anything but Oxygen would give us the least reason to expect that it would combine with Oxygen at all. . . . Here we have a clear instance of a case where, so far as we can tell, the properties of a whole composed of

two constituents could not have been predicted from a knowledge of the properties of these constituents taken separately, or from this combined with a knowledge of the properties of other wholes which contain these constituents. (Broad 1925, 62–63)

But Broad is not at all sure about the existence of emergent properties and behaviors of the components of systems typically studied by the natural sciences, as witnessed by the following citation where he turned it into an epistemological problem:[10] "Within the physical realm it always remains logically possible that the appearance of emergent laws is due to our imperfect knowledge of microscopic structure or to our mathematical incompetence" (Broad 1925, 81). He also hinted at the fact that the final proof for the existence of emergent properties due to the horizontal condition should always come from the empirical sciences: "It is not my business as a philosopher to consider detailed empirical arguments for or against mechanism [reductionism] or emergence in chemistry or biology" (Broad 1925, 81). The horizontal condition is of particular interest for natural science. In subsequent sections, we will illustrate emergence in cell biological systems, which are both functionalizable and mechanistically explainable.[11] Their properties are describable in terms of the properties and behaviors of their realizers. There is no failure of analyzability in these biological systems. There is emergence nonetheless: knowing the properties the parts exhibit "in isolation" or "in other systems" is sometimes insufficient to predict the properties and behavior they exhibit in this very system. This is the point illustrated by Broad's (1919) article. Being more precise on these matters opens the general debate on emergentism.

In order to see how we can get emergence, the question is whether we can predict the behavior of parts within a system from more limited resources. If we cannot predict the behavior of parts within a system, then we cannot predict system behavior either. Whether we can in turn predict the behavior of parts depends on the resources available. Assume we know the relevant laws of nature, we know what the structure of the system is, and we know what the constituents of the system are. Ultimately, we want to predict system behavior, and for that we need to predict the properties and the behavior the parts exhibit within it. The resources we have may be more or less inclusive. Here are four possibilities. If we are to explain the behavior (or properties) of a system S, or the behavior of the parts within S, this could be based on

(a) the behavior of the parts within systems including some which are more complex,
(b) the behavior of the parts within systems as complex but not more complex,
(c) the behavior of the parts only within less complex systems, or
(d) the behavior of the parts in isolation alone.

Only (c) is an interesting condition for emergence since condition (d) trivializes it and conditions (a) and (b) trivialize non-emergence. Let us begin with (d). The fact that the behavior of S cannot be explained in terms of the behavior of its parts in isolation alone is not sufficient for any interesting sense of emergence. We in general cannot predict even the "ordinally neutral properties" of the system containing these parts based on the properties of the parts in isolation. Relatively simple properties, such as the weight of a pile of sand can be predicted from the weight of its grains only if we know weight is additive. In other cases, such as temperature, we cannot add the temperatures of subsystems in order to predict the system temperature. So, under (d), even non-organizational properties would be emergent. If this were emergence, then everything would be emergent.[12]

Let us turn to (a) and (b). Remember the issue is whether S displays emergent properties or behaviors. Using more complex systems always guarantees that S's behavior can be explained. If you begin with a complete explanation of the behavior of a containing system in terms of its components then you already have a complete explanation of the behavior of S and its components since S is a part of the containing system. This would make emergence impossible by fiat. If we begin with a complete explanation of similarly complex systems, then some of those explanations will refer to systems that are nearly identical to S. In those systems the behavior of the components will be similar to the behavior of the components in S. If these systems are similar to S then they are sufficient to explain the behavior of S. This trivializes the non-emergent character of the behavior of S.

The key case for understanding emergence must therefore be (c), in which we attempt to explain the behavior of S or its parts on the basis of systems which are less complex than S. In short, the question is whether the behavior of S is ever emergent relative to these simpler systems or their parts in isolation.

Notice this does not make emergence epistemological. Excluding cases (a) and (b) does not limit our knowledge. We could have complete knowledge of the behavior of more complex systems or systems of equal complexity. We do not use it because it would trivialize the question whether there is emergence.

Among less complex systems included under (c) are naturally occurring systems; e.g., bacteria are typically simpler organisms than are eukaryotes. Some of these simpler systems are not natural systems. Laboratory manipulations allow us to create systems which are very different from natural ones and nonetheless still informative; e.g., knockout mutants. Some could

exist only under artificial conditions. We can explore the behavior of systems we cannot even produce in laboratory settings; e.g., reconstructed systems *in silico*. The point is that the range of systems that are "simpler" is very broad. However, there is one limitation. Consider experiments or dynamic models in which the boundary conditions of a part within a system are mimicked without reproducing the entire system. *Prima facie* the resulting systems are "simpler" wholes. Nevertheless, if we replicate the conditions of the original system relevant to the part, then we use information from the original system in order to construct the boundary conditions of the part in the "simpler system". That is to say, we use knowledge from the original system which, of course, is not a "simpler whole". We then presuppose already what we want to predict. This would render it a case like (a) or (b).

In the sections to follow, we will show that physiological properties can be fully accounted for in terms of system properties of biochemical networks and that this can be experimentally tested through precise modeling of biochemistry. These biochemical networks exhibit organizational properties, ones not manifested at the level of the parts, but which result from the interactions among the parts. Consequently, they should be explained in terms of component properties, which depend both on the properties of the parts and on the state of the entire system. Although the organizational properties we encounter in biochemistry will always be vertically reducible, there are some cases of non-deducibility if we restrict the deduction base appropriately. Thus, we are able to present cases of emergence from a horizontal perspective.

These are neither what the *a priori* metaphysicians were looking for nor are they purely epistemological. These are the conditions we laid down in Section 1 for understanding emergence and its place in nature.

3. COMPLEX SYSTEMS IN CELL BIOLOGY

The complex systems studied by the biosciences are semi-open or "metabolic" systems (Westerhoff and van Dam 1987). They are open insofar as they allow free exchange of some chemical and heat with the environment; however, exchange of other substances is limited because they have a boundary (a membrane) separating them from their environment. They are systems that selectively interact with their environment by way of mass and energy (heat and work) exchange. The mass exchange is selective. Only certain chemical compounds and ions can enter or exit the cell. The exchange is often active. It is coupled to a chemical reaction that dissipates free energy. As long as such systems are driven by an external

free energy source, they will display what is known as nonequilibrium behavior. Unless the system is at a steady state they will also show net changes in their macroscopic state and properties,[13] for instance, in net mass flow, growth or heat generation. The free energy source represents the Gibbs free energy potential[14] of imported chemicals or photons for systems at constant pressure and temperature.

The Gibbs free energy potential is the amount of energy available to do 'useful' work, for instance, the interconversion of chemical compounds, locomotion (e.g., chemotaxis), or the synthesis of complicated building blocks (fats, polysaccharides, proteins, RNA, DNA). By consuming the external Gibbs free energy potential the system can increase its own free energy and even order itself (decrease its own entropy). The free energy consuming processes pose an important demand on the organization of the cell; they require more free energy input than they can consume. These processes are not directly coupled to the catabolic processes that extract free energy in the degradation of food. Instead they are often coupled to the hydrolysis of ATP to ADP and phosphate. Rephosphorylation of ADP to produce ATP is coupled to processes of food degradation. Upon depletion of the external free energy source, the system relaxes into an equilibrium state in which useful work is no longer performed – the system no longer has the capability to order itself – and, concomitantly, no net changes are observable in its macroscopic state. The macroscopic equilibrium state is characterized by a minimal Gibbs free energy, and a maximal entropy: it represents a state of maximal 'disorder'.

If the external free energy source is kept constant for a sufficiently long time, the system will often end up in a stationary state. These stationary states are functional states of complex systems in biology; that is, they have biological significance. The main examples of stationary states are steady states and oscillatory states. Chaotic behavior usually represents pathological functioning of physiological systems, and will not be part of our focus. Stationary states may have certain characteristic properties, e.g. being robust to internal and external fluctuations, showing memory, displaying adaptive behavior. These systemic properties do not in general manifest themselves at the level of the parts but arise out of the interactions among the parts they are therefore organizational properties. Organizational properties, therefore, are likely to be explained in terms of the dynamics of these interactions.

The molecular biosciences teach us that all the action in biological cells is at the level of (macro)molecules: biological cells are physicochemical systems composed of interacting low-molecular weight molecules (metabolites, e.g., lactate, pyruvate), macromolecules (enzymes, protein complexes,

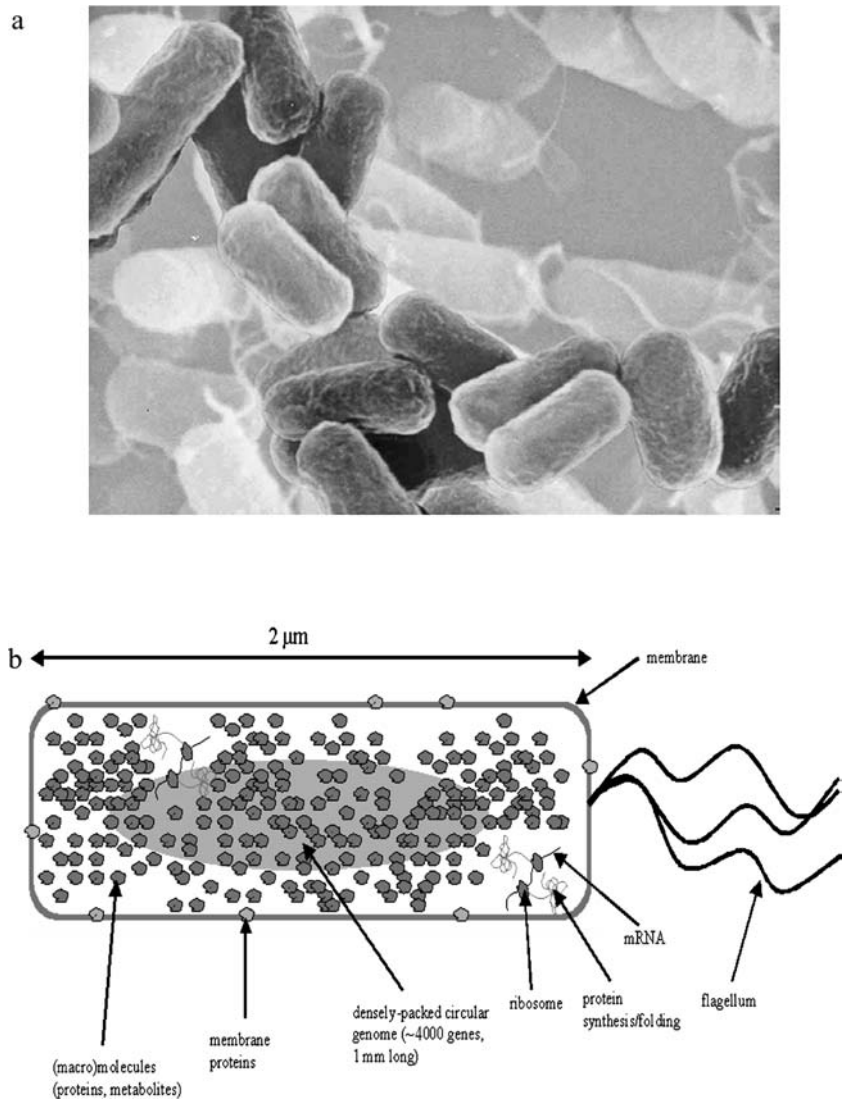


Figure 2. *Escherichia coli.* Typical dimensions are 1 by 2 μm. (a) Scanning electron-micrograph. (b) Schematic rendering. Figure 2a was reprinted with permission from D. Lundberg (www.chromosome.com).

DNA, mRNA) and larger structures thereof, all compartmentalized by semi-permeable lipid-containing membranes. Such systems can be looked upon as huge supra-processes composed of networks of interacting micro-processes. These are cells. The proteins interact either through direct physical interactions or indirectly through binding of metabolites. The amino acid sequence of the proteins is coded by structural genes on the DNA. The genes are

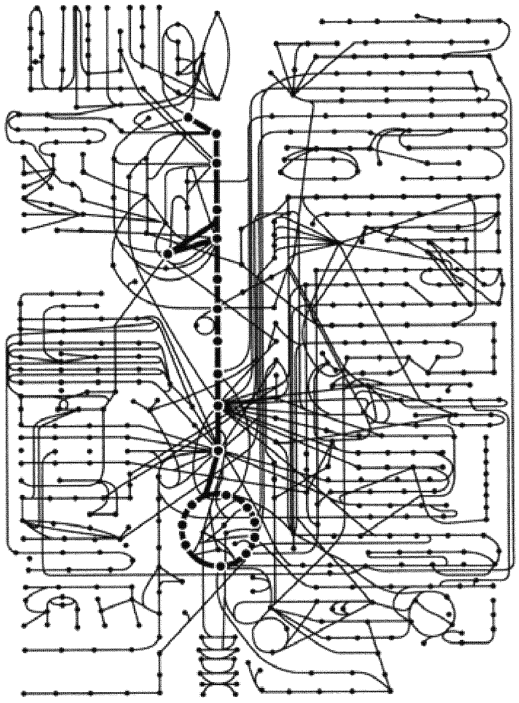


Figure 3. Metabolic networks. The nodes depict metabolites, connections depict enzyme-catalysed reactions. This metabolic network is representative for most eukaryotic organisms, except that it is very simplified. The bold circle and the pathway feeding it are Krebs cycle and glycolytic pathway, respectively. Reprinted with permission of Routledge/Taylor and Francis Books.

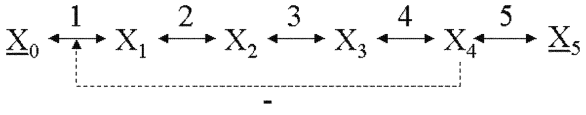
transcribed by RNA polymerases into mRNA strands under specific (tightly regulated) conditions and the transcripts, in their turn, are translated into proteins by ribosomes. Additionally, there are mechanisms that take care of the controlled degradation of mRNA strands and proteins. These properties of the (macro)molecules underlie cell behavior.

One way to investigate the effects of these (macro)molecules is by making *in silico* reconstructions of biological cells, or of subsystems, on the basis of the (macro)molecular properties. Such models incorporate experimentally determined *in vitro* properties of (macro)molecules and, relying on that knowledge, reconstruct the behavior of cells. Not all properties of enzymes are necessary for predicting cell behavior. For emergence, the only properties that matter are those that refer to the interactions between the enzymes and the other (macro)molecular (sub)system constituents. The structure, mass and composition of the (macro)molecules insofar as it does not depend on these interactions belongs to the class of non-emergent properties of both the system and its components. Biochemical

networks are similar to the linear pathway described in Box 1, but far more complex due to the occurrence of multiple branches and cycles.[15] (See Figure 3 for an illustration.) They are composed of multiple enzymes that sequentially convert different substrates into different products (mass flow). They are complicated by regulatory interactions including feedback and feedforward loops, which both can be activating and inhibiting.

The set of parameters representing all the interactions defines the topology of the network. K-values reflect affinities of metabolites for given enzymes. K values are constant for given enzymes and metabolites. A lower K value means that the enzyme binds the corresponding metabolite at lower concentrations of the latter. Metabolites include substrates, products, inhibitors and activators. Each has an associated K-value: K_S for substrates, K_P for products, K_i for inhibitors, K_a for activators. K_{EQ} is the equilibrium constant, which is defined as the ratio of products to substrate concentrations for a particular reaction in thermodynamic equilibrium.[16] The state of the biochemical network at a time is defined by the magnitudes of the variable metabolite concentrations. The rate of a particular enzyme-catalysed reaction depends non-linearly on the concentrations of the metabolites with which it interacts, on the associated K-values, on K_{EQ}, and linearly on the enzyme concentrations.

BOX 1.



Here is an example of how *in silico* modelling of biochemical pathways is carried out. The linear metabolic pathway displayed above is composed of five consecutive reversible reactions, each catalyzed by an enzyme. The enzymatic reactions are depicted by solid double-sided arrows and the respective enzymes are denoted by numbers (1 to 5). Six metabolites (X_0 to X_5) are interconverted in the pathway. Metabolite X_4 inhibits the rate of enzyme 1 as indicated by the dashed arrow and the minus sign. The underlined metabolites X_0 and X_5 are kept constant at all times by the environment. The other metabolites may vary with time and conditions.

In kinetic models, the changes in the concentrations of the variable metabolites can be described with differential equations, which consist of terms describing the consumption or production of all the metabolites. For this pathway, the set of differential equations would read as follows (in matrix format):

$$(1) \qquad \begin{bmatrix} \frac{dX_1}{dt} \\ \frac{dX_2}{dt} \\ \frac{dX_3}{dt} \\ \frac{dX_4}{dt} \end{bmatrix} = \begin{bmatrix} v_1 - v_2 \\ v_2 - v_3 \\ v_3 - v_4 \\ v_4 - v_5 \end{bmatrix}$$

v_1 to v_5 each represent the rate of the corresponding enzymatic reaction; that is, the number of product molecules formed per unit time per unit volume. As an example of a rate equation, consider enzyme 1 that catalyses the reaction $X_0 \leftrightarrow X_1$, and which is inhibited by metabolite X_4. The enzyme has two binding sites: a substrate (product) binding site for X_0 (or X_1) and an allosteric binding site for X_4. The rate of the reaction is a function of the concentrations of X_0, X_1 and X_4. For the simplest case, the net rate (v_1) of product formation can be described in terms of a (rapid-equilibrium) rate equation:

$$(2) \qquad v_1 = \frac{1}{1 + \frac{X_4}{K_{1,X_4}}} \cdot \frac{V_1^+ \cdot \frac{X_0}{K_{1,X_0}} - V_1^- \cdot \frac{X_1}{K_{1,X_1}}}{\left(1 + \frac{X_0}{K_{1,X_0}} + \frac{X_1}{K_{1,X_1}}\right)}.$$

The first term represents the inhibitory effect of X_4 on enzyme 1. The second term represents the net rate of the reaction apart from that inhibition. In the equation, each $K_{1,s}$ is an equilibrium dissociation constant (in mM) that indicates the ratio $(e_1 \cdot s)/e_1 s$ when the binding has relaxed to equilibrium (where s stands for X_0, X_1 or X_4). Here $e_1 s$ is the concentration of the enzyme-substrate complex, and $e_1 \cdot s$ is the product of the concentrations of the free enzyme e_1 and of the free substrates s. V_1^+, and V_1^- are the maximal forward and backward rates of catalysis (in mM min^{-1}), respectively. The latter rates depend linearly on the enzyme concentration (e_1 in mM); that is, $V_1^+ = k_1^+ \cdot e_1$, and $V_1^- = k_1^- \cdot e_1$, respectively, with k^+ and k^- as catalytic forward and backward rate constants (in min^{-1}). In contrast to its linear dependency on the enzyme concentration, the rate is a non-linear function of the metabolite concentrations. Importantly, all kinetic parameters can be measured *in vitro* (Segel 1993).

The net rate of the reaction varies monotonically with the extent to which the reaction is displaced from equilibrium (Westerhoff and van Dam

1987). The equilibrium constant (K_{EQ}) of the reaction is defined as the ratio of the product (X_1) and substrate (X_0) concentration in equilibrium: $K_{EQ} = (X_1/X_0)_{EQ}$. The equilibrium constant of a certain reaction is determined by the properties of the reactants and by the temperature. It does not depend on the properties of the enzyme concerned – its kinetic properties (various K's and k's) – or on its concentration. The enzyme may considerably shorten the time required to reach the equilibrium state or stationary state between the reactants, but it does not affect the equilibrium constant.

When the enzymatic reaction approaches equilibrium, i.e. when the actual ratio of product and substrates Γ ($= X_1/X_0$) becomes equal to K_{EQ}, its rate becomes zero. Thus the ratio Γ/K_{EQ} quantifies the extent to which the reaction is displaced from equilibrium. If the above equation is rewritten incorporating the last term and by using the Haldane relation ($K_{EQ} = V_1^+ K_{1,X_1}/V_1^- K_{1,X_0}$), one obtains:

$$(3) \qquad v_1 = \frac{1}{1 + \dfrac{X_4}{K_{1,X_4}}} \cdot \frac{V_1^+ \cdot \dfrac{X_0}{K_{1,X_0}} \cdot \left(1 - \dfrac{\Gamma}{K_{EQ}}\right)}{\left(1 + \dfrac{X_0}{K_{1,X_0}} + \dfrac{X_1}{K_{1,X_1}}\right)}.$$

The displacement from equilibrium is directly related to the molar Gibbs free energy difference or chemical potential differences that drives the reaction ($\Delta\mu_1$),

$$(4) \qquad \Delta\mu_1 = R \cdot T \cdot \ln \frac{\Gamma}{K_{EQ}}$$

(with R being the ideal gas constant and T the absolute temperature). This equation shows that in equilibrium the chemical potential of the reaction indeed equals zero.

Silicon cell modelling starts from the experimental (often *ex vivo*) determination of the rate equation and of the magnitude of all parameter values (K's and V's) for each reaction. This gives v_i as a unique function of all x_j. Using Equation (1), changes in x_j can be written as a vector function of x_j. Starting from initial values for the state variables x_j, Equation (1) can be integrated to calculate x_j at other times.

4. KINETIC MODELLING IN CELL BIOLOGY

There are two general approaches to modelling complex systems such as biochemical pathways (Bechtel and Richardson 1993). One approach predicts behavior of the components from information about the systemic behavior of the actual system. This is, in practice, a top-down approach. The properties of the components are retrieved from system properties. If we know that a bacterium is in a steady state, and we know the input and output together with the topology of the network, then in principle we can retrieve many of the rates at which individual enzymes convert their substrates into products. This is called *flux balance analysis*.

Another approach predicts system behavior using information about the properties of parts, independently of their systemic context. This is a bottom-up approach. We begin with the properties of the parts independent of their relations with other parts. We can, for example, measure the parameters that characterize the rates at which enzymes convert substrates directly. These for instance are the K_{1,X_1} and V_1^+ values in Box 1. Knowing these values we know the capacities of the parts. The behavior of the system is in part a function of these values. This is *kinetic modelling*. We will focus on this latter approach.

The dynamics of a system is a function of the properties of the constituents, the configuration of the system, and the external and internal conditions. The structure of the system is in turn a function of the parts, whose properties we can characterize in isolation. A bacterium includes a set of enzymes whose properties can be characterized in isolation. This is sufficient information to determine all the behavioral *capacities* of the organism. Once situated in an appropriate environment, we can capture its actual behavior. The behavioral capacities of the system include the entire range of possible dynamic behaviors, including the actual behavior. This is represented in Figure 4a.

Modelling the dynamics of a system follows an analogous pattern. There are two kinds of properties which characterize the parts: (i) *intrinsic properties*, which are completely determined by the part itself, such as its mass or the amino acid sequence of a protein; and (ii) *relational properties*, which are determined not only by the parts but also by one or more other parts. Among these properties are, for instance, the dissociation constants that characterize the dissociation of a complex into its parts. These relational properties are sufficient to determine which parts of the system interact with each other and in what manner.[17] In Box 1, they were used to describe the dependency of the rate of an enzyme on the concentrations of its substrates, products, and effectors.

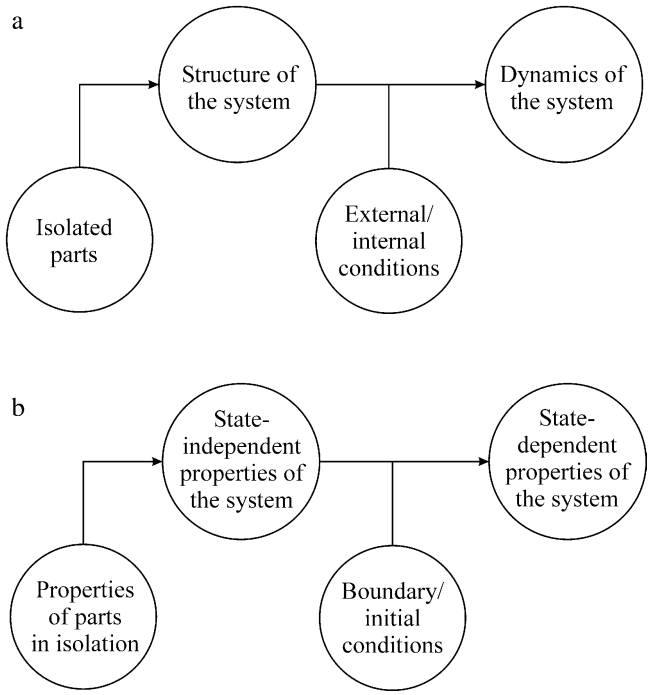


Figure 4. Kinetic modelling in complex systems: (a) System perspective: The structure of the system is determined by a set of parts subject to some composition relations and physical laws; the dynamics of the system is determined by the structure of the system together with external and internal conditions. (b) Property perspective: State-independent properties of the system result from properties of parts and their relations; state-dependent properties are determined by state-independent properties, and by boundary and initial conditions.

A model of the static system combines the relational properties of the parts, through a composition relation.[18] This composition relation amounts to the spatial organization of the cell. The application of physical laws, given this information suffices to determine the state-independent properties of the system. To a first approximation, we can treat cells as homogeneously stirred (Francke et al. 2003); that is, we assume that the constituents of the cells are randomly distributed. Introducing, for example, organelles would compartmentalize the system. Using these composition relations and the relational properties, we can then derive the state-independent properties of the system. This is represented in Figure 4b. Examples of state-independent properties would include the number of cycles or branches in a biochemical network, or what we earlier called the topology. These structural properties of the network can be retrieved from

biochemical pathways (see Figure 3). The composition relations do not generally depend on the intrinsic properties of the constituents; thus, not all the properties of the parts are necessary to reconstruct system properties. If a system is purely aggregative, all its systemic properties depend only linearly on the properties of the parts (Wimsatt 1976, 1986). In complex biochemical systems, aggregative system properties are a function only of the intrinsic properties of the parts; for example, the mass of a bacterium is simply the sum of the masses of the parts. The flux through a biochemical pathway, in contrast, depends non-linearly on the concentrations of its constituent enzymes. This is not an aggregative property.

A characterization of the system in terms of state-independent properties is not sufficient by itself to determine the dynamic properties of the system. For this we need, in addition, to impose boundary conditions and initial conditions. For a bacterium, this would include concentrations of nutrients, enzymes, metabolites, mRNA, as well as physical conditions such as temperature and pressure. The external environment as defined by the boundary conditions provides the free energy source for the system to function. The initial conditions are the starting state for the system. The result is a set of state-dependent properties of the system at a particular moment in time. These include rates of free energy dissipation, rates of heat liberation, nutrient uptake fluxes, and growth rate. The state-dependent properties differ from state-independent properties in a number of ways. The former are associated with the dynamics of the system, and the latter with the structure of the system. State-independent properties do not change with time: they do not depend on dissipation of free energy through the system. In the case of state-dependent properties, the system consumes free energy to perform work. This displaces the system from the state of minimum free energy. The parts constituting the system now display what we call *component properties*. These properties are determined in part by the relational properties of the parts, and in part by the state of the entire system. Examples of component properties would be the enzymatic rates of metabolite conversion, the sensitivity of these rates to changes in metabolite concentrations, the saturation level of enzymes, and their displacement from equilibrium. Experimentally, we can recreate component properties provided that we can recreate the appropriate systemic context *in vitro* or *in silico*; for example, we can measure the rate of a particular enzyme *in vitro* if we supply substrates and products at concentrations matching those *in vivo*. (See Box 2 for an explicit example.)

BOX 2.

The sensitivity of the rate of the enzymatic reaction to a substrate concentration is a component property. We will illustrate this for the enzyme treated in Box 1. The sensitivity of this enzyme to its substrate X_0 is described by an elasticity coefficient ($\epsilon_{X_0}^{v_1}$). This is a component property of the enzyme, because its magnitude depends both on the concentrations of the metabolites it communicates with and on the relational properties of the enzyme. An elasticity coefficient quantifies the fractional change in the rate of an enzymatic reaction ($\partial v_1/v_1$) upon a fractional change in the concentration of any of its substrates ($\partial X_0/X_0$), products, or effectors. For $\epsilon_{X_0}^{v_1}$ this would read:

$$(5) \qquad \epsilon_{X_0}^{v_1} = \frac{\partial v_1}{\partial X_0} \cdot \frac{X_0}{v_1} = \frac{1}{1 - \frac{X_1}{X_0} \Big/ K_{EQ}} - \frac{\frac{X_0}{K_{X_0}}}{1 + \frac{X_0}{K_{X_0}} + \frac{X_1}{K_{X_1}}}.$$

The first term expresses how sensitivity changes when approaching thermodynamic equilibrium. The second term expresses how sensitivity changes as the amount of substrate-bound enzyme increases. The elasticity coefficient is a function of the state of the biochemical pathway; in this case, it depends on the concentrations of X_0, and X_1. The elasticity coefficient is also a function of the relational properties of the enzyme and the reactants; in this case K_{X_0}, and K_{X_1}, and K_{EQ}, respectively. These K values are state-independent and relational properties of the parts. The elasticity coefficient is also affected by the displacement from equilibrium; in this case, by the term $X_1/(X_0 \cdot K_{EQ})$. At equilibrium this value is 1. Upon displacement from equilibrium the first (thermodynamic) term in the equation for $\epsilon_{X_0}^{v_1}$ becomes smaller; as the reaction approaches equilibrium, this value approaches infinity. If we increase X_0 the right (kinetic) term becomes larger. The properties of the enzyme (K_{X_0} and K_{X_1}) are important for determining the sensitivity of the enzyme to X_0 only if the enzyme operates at nonequilibrium states. There are similar elasticity coefficients for all enzymes with respect to their substrates, and products.

To explain systemic properties mechanistically, it is essential to turn to component properties. This can be exemplified with metabolic control analysis. Suppose we change the concentration of the first enzyme (e_1) in the metabolic pathway shown in Box 1 and study the resulting change in the steady-state flux (J) through the pathway. The rate of the first enzyme reaction depends linearly on the concentration of the enzyme and nonlinearly on the concentrations of metabolites X_0, X_1, and X_4. This was illustrated

in Box 1. An increase in e_1 initially increases the rate of conversion of metabolites X_0 to X_1 linearly. This will affect the other enzymes in the system: the change propagates through the network and ultimately affects the rate catalyzed by e_1 nonlinearly.

Formally, the fractional change in the steady-state rate through the pathway (J) upon a fractional change in e_1 is given by (Kacser and Burns 1973; Heinrich and Rapoport 1974; Westerhoff and van Dam 1987):

$$(6)\qquad \frac{d\ln J}{d\ln e_1} = \frac{d\ln v_1}{d\ln e_1} = \frac{\partial \ln v_1}{\partial \ln e_1} + \frac{\partial \ln v_1}{\partial \ln X_1}\cdot\frac{d\ln X_1}{d\ln e_1} + \frac{\partial \ln v_1}{\partial \ln X_4}\cdot\frac{d\ln X_4}{d\ln e_1} = 1 + \epsilon^{v_1}_{X_1}\cdot C_1^{X_1} + \epsilon^{v_1}_{X_4}\cdot C_1^{X_4}.$$

The term $d\ln J/d\ln e_1$ describes the effect the change in the concentration of e_1 has on its own rate after the entire system has responded and a new steady state has been attained. This relationship shows that the immediate effect of the enzyme on its own rate ($\epsilon^{v_1}_{e_1} = \partial \ln v_1/\partial \ln e_1 = 1$) is affected by the remainder of the system through the other two terms, which represent the effects of X_1 on v_1 and of X_4 on v_1 ($\epsilon^{v_1}_{X_1}\cdot C_1^{X_1}$ and $\epsilon^{v_1}_{X_4}\cdot C_1^{X_4}$). Changes propagate through the system.

The concentration control coefficients (C_i) can be expressed in terms of elasticities through utilization of so-called summation and connectivity theorems (Westerhoff and Kell 1987; Bruggeman et al. 2002a). As a consequence mechanistic explanations of changes in the steady-state properties of complex systems should ultimately be expressed in terms of changes in component properties.

5. COMPONENT PROPERTIES AND MECHANICAL EXPLANATION

The component properties described in this paper are reminiscent of the roles played by parts – subcapacities – in a mechanical explanation of a complex capacity of the containing system (Cummins 1975; Bechtel and Richardson 1993; Wouters 1999; Craver 2001). Robert Cummins (1975) defended a "functional" analysis of systemic phenomena; that is, a top-down analysis in which systemic properties are explained as the effects of functionally defined components. Cummins' was exclusively a top-down analysis. Cummins saw that these functional or mechanical explanations are interesting only if the analyzing subcapacities are 'less sophisticated' than and 'different in type' from the analyzed capacity; furthermore, they must show a 'complex organization'. In addition to the

top-down constraints emphasized by Cummins, an adequate mechanical explanation requires independent information concerning the capacities of the realizing mechanisms. In what Bechtel and Richardson (1993) call a strategy of "decomposition and localization", in addition to the analysis or decomposition of capacities, localization requires identifying the physical components and identifying their capacities. Peter Machamer, Lindley Darden, and Carl Craver, among others, have more recently insisted on the importance of these mechanistic explanations, though the models they appeal to are largely qualitative (Machamer et al. 2000; Craver 2001). The case we described emphasizes the importance of the properties of the parts within the system (component properties), as well as the significance of a rigorous and precise mathematical quantification of mechanical explanations. We combine the roles played by the parts in a mathematical model to yield a description and explanation of the systemic behavior; that is, we describe a mechanical explanation of the systemic phenomenon in mathematical terms. This is a mathematical equivalent of what Stuart Glennan introduced as a mechanical model (Glennan 2002). Having a precise mathematical description allows for a more exact examination of the properties exhibited by the system.

6. EMERGENCE IN MODULAR SYSTEMS

Modular organization introduces an intermediate level of complexity: systems may be composed of modules which in turn are composed of multiple parts. This is analogous to Broad's description of a system in terms of subsystems. Modules, like their constituents, have intrinsic properties, relational properties, and component properties. System behavior depends on the component properties of modules. The behavior of modules depends in turn on the component properties of their parts. Suppose we have a complex system A that includes n variable factors $\mathbf{X} = \{X_1 \ldots X_n\}$. These might be metabolites that are interconverted by enzymes. If A is a dynamic system, it is displaced from thermodynamic equilibrium by a fixed external Gibbs free-energy potential. When the external conditions and internal parameter values are time independent, the state of system A at time t can be defined as,[19]

$$A(t) : \{\mathrm{d}\mathbf{X}(t, \mathbf{p})/\mathrm{d}t = \mathbf{F}(\mathbf{X}(t, \mathbf{p}), \mathbf{p}) \mid \mathbf{X}(0, \mathbf{p}) = \mathbf{x_0}, \mathbf{p} = \{\mathbf{p_K}, \mathbf{p_{BC}}\}\}$$

$\mathbf{X}(t, \mathbf{p})$ is the state of system A, and is a vector composed of the concentrations of all the individual species X_i at time t. The state changes as a function of time as a result of the processes (enzyme-catalyzed reactions)

that mediate the changes in the concentrations of the components of A. The vector $\mathbf{F}(\mathbf{X}(t, \mathbf{p}), \mathbf{p})$ is sufficient to determine the state-independent properties of the system. It is the structure of the system. The state of A at a particular time t depends on the initial conditions of A and on $\mathbf{F}$. The former are given as the concentrations X_i at $t = 0$ (denoted by $\mathbf{X}(0, \mathbf{p})$). The state of A also depends on two sets of parameters: (i) the kinetic parameters ($\mathbf{p}_K$) that define the relational properties of the enzymes and (ii) the boundary conditions ($\mathbf{p}_{BC}$) that define the relationship of A with the environment. This is illustrated in Figures 4a and b.

Assuming a modular organization, the properties of the system A can be predicted in terms of the properties of its subsystems in the systemic context. The result is a decrease in complexity, and this may help in understanding the system (Kahn and Westerhoff 1990). Suppose our organism includes an organelle. The functioning of the organelle can be understood in nearly the way we have described above, assuming its environment is constant. Since it is embedded in a dynamic system (the rest of the organism), its boundary conditions change with time. We then have two modules, in a nested hierarchy. One provides the boundary conditions for the other, which in turn provides part of the boundary conditions for the first. Each has different variables defining their states. Together, their states define the state of the entire system. Changes in the state of one module can affect the state of the other, and can be affected by the state of the other module (Bruggeman et al. 2002b). In such cases, we can mechanistically explain the behavior of the entire system in terms of the component properties of the modules.[20]

The system shown in Box 1 will serve as an example. The complete metabolic pathway would then constitute system A, which can be decomposed into two subsystems: A_1 containing enzymes 1 and 2 and subsystem A_2 containing enzymes 2, 3, 4, and 5. The state of A_1 is defined by the concentration of metabolite X_1 and, similarly, the state of A_2 by the concentrations of X_2, X_3, and X_4. The boundary conditions for A are X_0 and X_5, for A_1, X_0 and X_2, and for A_2, X_1 and X_5.

Beginning with the subsystems (A_1 and A_2), the dynamics of the entire system can be explained in terms of the properties of the modules; however, this requires an appeal to the component properties of the modules. This is exactly parallel to the case we explored in the last section, except at a higher level of organization. Experimentally, the behavior of the subsystems can be investigated *in vitro* – by reconstitution of A_1 or A_2 in the test tube – or *in silico* using mathematical models.[21] These subsystems interact dynamically in A. This means that the strengths of their interactions generally depend on the state of the subsystems and on time. Hence, to approach

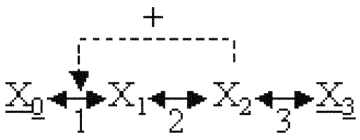
reality the interactions between the components of A_2 and A_1 somehow have to be mimicked if A_1, is studied in isolation without adding back all the components of A_2. The reverse holds for the study on A_2 in isolation. Generally, the behavior of a particular subsystem of A is approximated *in vitro* by artificially reproducing the conditions of the systemic context, so that the concentration values external to the subsystem are representative of the concentration values in A under typical conditions: for subsystem A_1, the amount of X_2 added at least would have to be representative of its value in A.[22] This means that we recreate the component properties. This does not allow us to predict or explain the component properties, for the reason that aside from already knowing the systemic context there is no principled reason for selecting one value of X rather than another. Without a determinate X value the component property is indeterminate. Moreover, precise mimicking of boundary conditions of the subsystem *in vitro* is not a base for prediction or explanation, but for reconstruction.

If the interactions between a subset of the components of A_2 and some of the components of A_1 are mimicked for subsystem A_1 in isolation by incorporating them in the boundary conditions of A_1, then in most cases the dynamic behavior of $A1$ will only change quantitatively. That is, the behavior of A_1 is only quantitatively different *in vitro* from its behavior *in vivo*. This is because we have artificially substituted a static boundary condition for a dynamic interaction.

Remarkably, we can also get *qualitatively* different systemic behavior in the two contexts. (This is shown in detail in Box 3.) This sometimes fulfills the horizontal condition. This could then include oscillatory, or chaotic states that are not present in simpler systems. The behavior of A_1, in isolation is sometimes qualitatively different from the behavior of A_1 in A, and therefore, since the behavior of A is a function of A_1, understood as a component, the behavior of A cannot generally be derived from studies on simpler subsystems of A. In general, the (dynamic) behavior of A is not simply the superposition of the (dynamic) behaviors of its subsystems studied in isolation. Dynamic interactions can bring about qualitatively new behavior in complex systems. This is precisely where prediction of system behavior on the basis of simpler subsystems fails. We cannot predict the behavior of the components within the entire system and so cannot predict systemic behavior. This is emergence, with novel system behavior that cannot be predicted on the basis of the behavior of simpler subsystems.

BOX 3.

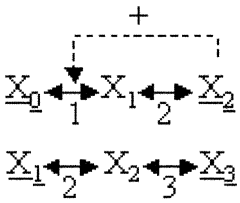
Instability can occur in a system composed of interacting subsystems that are both dynamically stable in isolation. We will illustrate this with a simple metabolic pathway. The pathway consists of three enzymes (1, 2, and 3), two variable metabolites (X_1 and X_2), and the constant metabolites X_0 and X_3. The latter metabolites constitute the boundary conditions that keep the system removed from thermodynamic equilibrium.



where v_i is the rate equation of enzyme i (cf. Box 1), the system dynamics is obtained through integration of these differential equations:

$$\begin{bmatrix} \frac{dX_1}{dt} \\ \frac{dX_2}{dt} \end{bmatrix} = \begin{bmatrix} v_1 - v_2 \\ v_2 - v_3 \end{bmatrix} \tag{7}$$

We can decompose the network into two subsystems, whose behavior can be described in isolation:



We get the first subsystem by holding X_2 constant, and the second by fixing X_1. If the entire system is at steady state dX_1/dt and dX_2/dt equal zero. If the system is stable, then any small change in X_1 and X_2 is corrected by the system. It returns to its initial state. Assume that the two subsystems above are stable in isolation. The enzymes in these subsystems have component properties, such as the sensitivity of each enzyme to the metabolites it interacts with within the relevant subsystem. Stability of the two subsystems assumes that the following relationships hold among component properties of the enzymes in the subsystems:

$$(8) \qquad \frac{\partial v_1}{\partial X_1} - \frac{\partial v_2}{\partial X_1} < 0 \quad \text{and} \quad \frac{\partial v_2}{\partial X_2} - \frac{\partial v_3}{\partial X_2} < 0$$

The first conjunct tells us that the sensitivity of enzyme 1 to X_1 is less than the sensitivity of enzyme 2 to X_1. The second conjunct tells us that the sensitivity of enzyme 2 to X_2 is less than the sensitivity of enzyme 3 to X_2. These component properties (expressed by differentials) quantify the sensitivity of a rate to a metabolite and are known as *unscaled elasticities* (cf. Box 2). The entire system is stable if both of the following relations hold (Murray 1989, 148):

$$(9) \qquad \frac{\partial v_1}{\partial X_1} - \frac{\partial v_2}{\partial X_1} + \frac{\partial v_2}{\partial X_2} - \frac{\partial v_3}{\partial X_2} < 0 \quad \text{and}$$

$$\left(\frac{\partial v_1}{\partial X_1} - \frac{\partial v_2}{\partial X_1}\right)\left(\frac{\partial v_2}{\partial X_2} - \frac{\partial v_3}{\partial X_2}\right) - \left(\frac{\partial v_1}{\partial X_2} - \frac{\partial v_2}{\partial X_2}\right)\left(\frac{\partial v_2}{\partial X_1}\right) > 0.$$

The first condition is always met if the subsystems are stable, as we are assuming. The second condition is violated if;

$$(10) \qquad \left(\underbrace{\frac{\partial v_1}{\partial X_2}}_{>0} - \underbrace{\frac{\partial v_2}{\partial X_2}}_{<0}\right)\left(\underbrace{\frac{\partial v_2}{\partial X_1}}_{>0}\right) \geq \underbrace{\left(\frac{\partial v_1}{\partial X_1} - \frac{\partial v_2}{\partial X_1}\right)}_{<0}\ \underbrace{\left(\frac{\partial v_2}{\partial X_2} - \frac{\partial v_3}{\partial X_2}\right)}_{<0}$$

The left hand term captures the interactions between the two component subsystems. The right hand term captures the interactions within each component subsystem. (The positive and negative signs of the differentials $\partial v_2/\partial X_1$ and $\partial v_2/\partial X_2$ respectively, would hold in most real cases.) So what this tells us is that, even with stable subsystems, the system can be unstable if the interactions among subsystems are more significant than the interactions within them. Thus, it is possible to have an unstable system even under the assumption that subsystems are stable in isolation. In other words, the enzymatic parameters and boundary conditions can be chosen such that systemic instability occurs. This particular phenomenon is called a saddle-node bifurcation.

Under slightly different circumstances, oscillations appear if the first condition is violated. This, however, is impossible with subsystems containing only one variable metabolite that are dynamically stable in isolation. The simplest system to display oscillations and having dynamically subsystems in isolation is when one subsystem contains two variable metabolites and the other one variable metabolite. Additionally, these

conditions show that instability is impossible with two dynamically stable subsystems if the influence is one-directional. They must mutually affect each other, as in the case above (Bruggeman et al. 2002a).
This example also illustrates the importance of nonlinearity. The unscaled elasticities are constant for a linear system and therefore result in the same behavior: if a linear system is stable it will remain stable with changed boundary conditions, and if it is unstable it will remain unstable. With nonlinearity the values of the elasticities depend on the system state, which changes with changes in the boundary conditions. This can lead to a transition from a stable to an unstable system. This is known as symmetry breaking or bifurcation. As a result, nonlinearity is necessary for the emergence of new behaviors.

7. CONCLUDING REMARKS

We have identified two independent conditions, each sufficient for Broad's (diagonal) emergence to occur, which we represented as vertical and horizontal components. Metaphysicians such as Kim are right that there are microphysical and mechanistic explanations of biological phenomena. There are no inexplicable phenomena in the systems we have described: every systemic phenomenon is completely explicable in principle, or calculable, in terms of the component properties of the parts; that is, in terms of the behavior of parts embedded within the systemic context (Bechtel and Richardson 1993). They are mechanistically explainable. Nonetheless, we argue that there is emergence in cell biology, and that this derives from the horizontal condition. This emergence is not weak emergence.

Three conditions for weak emergence are: (i) physical monism, (ii) organizational or systemic properties and (iii) synchronic determination (Stephan 1998). We associate Broad's emergence with a strong notion of emergence on the basis of a similar reasoning as Stephan (1998). Stephan distinguished strong notions of emergence by adding either the irreducibility or diachronic unpredictability of these systemic properties to the notion of weak emergence. What we have identified is an additional condition for strong emergence; namely synchronic unpredictability. In the form we have identified and described, synchronic unpredictability means that a systemic property is not predictable, even in principle, from the properties of subsystems in isolation.

From a methodological point of view, if we attack a biological problem experimentally or theoretically, beginning with the constituents of cells treated in isolation, then the lack of a systemic context can be an impediment to scientific research. With some systemic effects, decomposition

may reveal mechanistic explanations, but this depends critically on understanding the behavior of parts as components. Beginning with the behavior of parts in radically different contexts, or in much simpler contexts, will sometimes fail to reveal their contributions to system behavior. Sometimes it will succeed. Sometimes it does not (Boogerd et al. 2002). In these cases, systemic behavior cannot be extrapolated from the behavior of parts in simpler systems, rendering them emergent. We think that this is a general phenomenon for other complex systems.

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NOTES

[1] We make use of notions like 'prediction', 'knowledge' and 'explanation' to define emergence. However, this does not turn emergence into an epistemic notion. If a person or a group of scientists is ignorant of some causal factors then a system's behavior might appear emergent. If increased knowledge of the relevant causal factors would make the behavior explainable then this is only an epistemological form of emergence. If a person or a group of scientists knows all the causal factors but lacks a theory to explain the system behavior, this behavior might still appear emergent. Once again this is merely epistemic if another theory would make the system behavior explainable. Since we allow complete knowledge of all causal factors and theories, this is an absolute notion of emergence that is not epistemological. For more detail see Stephan (1999, chapter 11).

[2] We use "property" in a generous way, to include both static properties (for example, shape), dynamic properties (for example, movement), and behaviors (for example, reproduction); we also include relational properties (for example, being a parent). If what is at issue is explaining dynamical behavior then we need to specify the initial and boundary conditions. We will return to this later.

[3] We use the term "organizational property" to cover what Stephan called a "systemic property" (Stephan 1998, 641, 1999, 16–22). In our context, "systemic property" is used in a broader sense, meaning any properties we can ascribe to a system including those it shares with its parts, such as having a weight. Properties of a system which some of its parts have are called "ordinally neutral properties" by Broad (1925, 78).

[4] The "relevant" laws in this case are the principles governing the behavior of the components of the system; that is, these describe the behavior of constituents as parts of the whole. *Mechanistic explanation* is reserved for this special case.

[5] We use prediction and explanation interchangeably. There are uses of prediction that are weak, insofar as they base prediction merely on correlations. Prediction and explanation in our sense require mechanical models. We sometimes echo Broad in speaking of "deduction" as a shorthand for explanation or prediction. What we argue for does not depend on any particular theory of explanation.

[6] Broad's position is common in recent philosophy of mind. Particularly, Jaegwon Kim (1999) and Joseph Levine (1983, 1993) focus on failures of reductive (i.e., mechanistic) explanations, assuming a (vertical) "explanatory gap" in the case of phenomenal states or the qualia they exhibit (Beckermann 2000; Stephan 2002).

[7] The "σ_X" in the article denotes the same as "R(A, B, C)" in the book. The function "f_X(A, B, C, σ_X, S_X)" is a macroscopic property corresponding to the "P_R" above.

[8] Here, T_1(A,C,D,F) stands for any system that is more complex than R(A, B, C), R_1(A,B,D) for one that has the same degree of complexity, and S_2(A,C) for one that is simpler. Of course, complexity does not depend on the number of components, but on the structure and mutual interactions of the parts. Therefore, a system with fewer components could be more complex than one with more components. However, we have to indicate differences of complexity somehow, and we do it here by the number of parts.

[9] Today, however, it is widely believed that the power of quantum theory suffices to explain chemical bonding and also the systemic properties of chemical compounds; cf., e.g., Brian McLaughlin's 'The rise and fall of British Emergentism" (McLaughlin 1992, 53–57, 89–90).

[10] He is only convinced that "this method of avoiding emergent laws is not logically possible for trans-physical processes" (Broad 1925, 81), with which he refers to both the secondary and the phenomenal qualities. Both are behaviorally unanalyzable (not "functionalizable") and thus mechanically inexplicable.

[11] Qualia are the only example of properties which cannot be functionalized.

[12] Once again, we do not distinguish between prediction and explanation. We assume there is complete information concerning components and their properties, and that explanation is not limited by computational resources. See footnote 5.

[13] In general terms, the state of a homogeneous system is defined in thermodynamic terms: the volume (V) of the system, temperature (T) and pressure (P), the number of molecular species (n_i), and their concentrations. Any change in these values brings about a change in the state of the system and thereby the macroscopic properties, e.g. Gibbs free energy, energy, enthalpy, entropy, heat flow, mass flow, etc. The systems we will discuss are "semi-open" and have constant T and P.

[14] The change in Gibbs free energy (G) is a function of changes in the total energy (U) corrected for expansion work (p.V) and entropic energy dissipation (T.S): dG = d(U + p.V–T.S).

[15] The boxes provide more detailed examinations of material described more informally in the text.

[16] In more complex cases in which there are multiple substrates and products for each reaction, more complicated definitions for K-values and for K_{EQ} are necessary. We omit the details.

[17] It is not always entirely clear whether a specific property is intrinsic or relational. For instance, the specific three dimensional structure of proteins is certainly in part a function

of their amino acid sequence. If this tertiary structure were determined entirely by the primary structure, this would make the three dimensional structure intrinsic. The environment would then exert minimal effect on the tertiary structure. However, for some proteins, their three dimensional structure also depends on other proteins, called "chaperones" (Langer et al. 1992). The effect is to select one out of many tertiary structures, all of which are, naturally, consistent with the primary structure. In such cases, the tertiary structure is not intrinsic, but relational (Bechtel 1988, 95).

[18] In describing the "ideal of pure mechanism", Broad speaks of a "principle of composition, according to which the behaviour of any aggregate of particles, or the influence of any one aggregate on any other, follows in a uniform way from the mutual influences of the constituent particles taken by pairs" (Broad 1925, 45). Sometimes he calls these "laws of composition" (Broad 1925, 62). We do not limit ourselves to pairwise comparisons, though we do limit ourselves to proper parts.

[19] Here we assume that the system is homogeneous, i.e. that there are no significant concentration gradients. This is a realistic assumption given the diffusional properties of (macro)molecules in microorganisms and the sizes of most microorganisms.

[20] If we do not have a nested hierarchy, then we can decompose A into two subsystems A_1 and A_2 that consist of the components $\mathbf{X_1}$ and $\mathbf{X_2}$, respectively;

$$A_1(t) : \{\mathrm{d}\mathbf{X_1}(t, \mathbf{p_1})/\mathrm{d}t = \mathbf{F_1}(\mathbf{X_1}(t, \mathbf{p_1}),$$

$$\mathbf{X_2}(t), \mathbf{p_1}) \mid \mathbf{X_1}(0, \mathbf{p_1}) = \mathbf{X}_{1,0}, \mathbf{p_1} = \{\mathbf{p}_{1,\mathbf{K}}, \mathbf{p}_{1,\mathbf{BC}}\}\},$$

$$A_2(t) : \{\mathrm{d}\mathbf{X_2}(t, \mathbf{p_2})/\mathrm{d}t = \mathbf{F_2}(\mathbf{X_2}(t, \mathbf{p_2}),$$

$$\mathbf{X_1}(t), \mathbf{p_2}) \mid \mathbf{X_2}(0, \mathbf{p_2}) = \mathbf{X}_{2,0}, \mathbf{p_2} = \{\mathbf{p}_{2,\mathbf{K}}, \mathbf{p}_{2,\mathbf{BC}}\}\},$$

A is defined in terms of its subsystems as:

$$A(t) : \{A_1(t) \cup A_2(t) \mid \mathbf{X_1}(t) \cap \mathbf{X_2}(t) = \emptyset \mid \mathbf{X_1}(t) \cup \mathbf{X_2}(t) = \mathbf{X}(t),$$

$$\mathbf{p}_K = \{\mathbf{p}_{1,K} \cup \mathbf{p}_{2,K} \mid \mathbf{p}_{1,K} \cap \mathbf{p}_{2,K} \neq \emptyset\},$$

$$\mathbf{p}_{\mathrm{BC}} = \{\mathbf{p}_{1,\mathrm{BC}} \cup \mathbf{p}_{2,\mathrm{BC}} \mid \mathbf{p}_{1,\mathrm{BC}} \cap \mathbf{p}_{2,\mathrm{BC}} \neq \emptyset\}\}.$$

[21] *In vitro* reconstitution is a general experimental tool that is used in biochemistry to study the properties of subsystems of living systems. For readers who are interested in *in silico* kinetic models of metabolism, there are some realistic kinetic models available at www.jjj.bio.vu.nl.

[22] It is important that we include only those factors which actually affect the behavior of the component. To include more would be to include what is irrelevant.

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