

# Extending the concept of kinetic stability: toward a paradigm for life

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**ABSTRACT:** The physico-chemical relationship between living and non-living systems remains a question of intense debate. This paper introduces the concept of *dynamic kinetic stability* as a means of incorporating living systems within a conventional physico-chemical framework. Its essence, all replicating systems, both animate and inanimate, represent elements of a replicator space. In contrast to the world of non-replicating systems (all inanimate), where selection is fundamentally *thermodynamic*, selection within replicator space is effectively *kinetic*. Driven by mutagenic autocatalysis selection in replicator space leads from kinetically *less* stable systems to kinetically *more* stable systems. Our kinetic approach suggests that all living systems may be thought of as manifesting a *kinetic state of matter* (as opposed to the traditional thermodynamic states), and allows the translation of key Darwinian concepts, such as fitness and natural selection, into traditional physico-chemical terms that are applicable at the molecular level. Copyright © 2004 John Wiley & Sons, Ltd.

**KEYWORDS:** kinetic stability; kinetic selection; natural selection; steady state; emergence of life

## INTRODUCTION

Although it is now universally agreed (at least amongst scientists) that both biological and non-biological systems follow the same laws of chemistry and physics, the striking physico-chemical pattern manifested in biological systems, and the manner in which that pattern derives from the laws of physics and chemistry, continue to be debated. Hence although Darwinian natural selection constituted the enormous intellectual leap that has dominated the biological arena for the past 150 years, the need to strengthen the link between that *biologically* oriented idea and established *physico-chemical* concepts remains.

One long-standing approach that has been used to address the problem has been a kinetic one.<sup>1,2</sup> After all, even the simplest living system is but a complex network of chemical reactions, and many biological features such as control and regulation seem to be governed by kinetic rather than thermodynamic factors. Indeed, beginning with Lotka's pioneering work<sup>3</sup> at the beginning of the 20th century, considerable effort has been dedicated to providing a kinetic perspective on the emergence and function of biological systems. Yet despite this effort, a widely accepted conceptual framework, within which the function and character of both biological and non-biological systems can be readily accommodated, still appears lacking. Dawkins has written: 'Darwin's

'survival of the fittest' is really a special case of a more general law of *survival of the most stable*.'<sup>4</sup> But what is meant by the term 'most stable'? Certainly in a thermodynamic sense living systems are actually *unstable*, having constantly to consume energy in order to maintain their far-from-equilibrium state. What, then, is the physico-chemical relationship between *fitness*, a biological term, and *stability*, a physical term? In this paper we wish to address this issue by building on the established kinetic approach to living systems and to introduce the concept of *dynamic kinetic stability*. Our goal is to relate better the nature of chemical transformations in biological as opposed to non-biological systems.

## DISCUSSION

As noted above, Dawkins alluded to a fundamental universal law that leads to the survival of the most stable. The term 'stable' in non-scientific usage merely means that the object in question is persistent—that it remains (relatively) unchanged with time. However, within a physico-chemical context, the term 'stable' has a more precise meaning, normally referring to a *thermodynamic stability*, although Dawkins certainly did not intend to imply that living systems are thermodynamically stable. In fact, as we well know, the reverse is true—living systems are thermodynamically *unstable*, continually tapping into some external energy source (chemical or photochemical) in order to maintain the far-from-equilibrium state so

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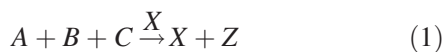
essential to life. Living systems appear stable in some *non-thermodynamic* sense, in that they maintain their structural and functional integrity over extended periods of time. How, then, can we classify the non-thermodynamic stability associated with living systems within physico-chemical orthodoxy? In order to do so, we now extend the concept of *kinetic stability* and apply it to living systems.

### Static and dynamic kinetic stability

The term *kinetic stability* is an established one in chemical thinking and refers to a chemical system, often thermodynamically unstable, whose free energy of activation is such that its rate of reaction into some relatively stable thermodynamic product is slow. Thus a mixture of hydrogen and oxygen at standard temperature and pressure exemplifies a kinetically stable system in that the thermodynamically favored transformation into water does not take place at a measurable rate without some form of activation. This form of kinetic stability, however, is a *static* one and we now extend the term to one that is *dynamic* in nature, one that may be usefully applied to living systems.

One key feature of living systems is their ability to replicate. Indeed, a common view suggests that life began with a replicating molecule<sup>5</sup> leading to an RNA world,<sup>6</sup> and that the kinetic power of replication is the driving force for both evolution and emergence.<sup>2,7,8</sup> We will therefore attempt to understand the physico-chemical pattern manifest in complex biological systems by using as a model the much simpler pattern that can be established by simple molecular replicators. The inherent assumption here is that the kinetic patterns associated with simple molecular replicators and living systems (i.e. complex replicators) share key basic attributes.

All replicating systems, whether molecular or complex assemblies, are necessarily autocatalytic. Thus in a general autocatalytic reaction depicted by



$X$  might be a polynucleotide,  $A$ ,  $B$  and  $C$  activated nucleotides and  $Z$  pyrophosphate ion; or  $X$  could be a pair of rabbits,  $A$ ,  $B$  and  $C$  carrots, water, and oxygen, and  $Z$  rabbit waste and carbon dioxide. However, replication, like all autocatalytic processes, is unsustainable. A single replicating molecule undergoing 79 acts of replication generates a mole of material ( $2^{79} \sim 6 \times 10^{23}$ ), and if that mole were to undergo another 83 replication steps, it would, in principle (given sufficient resources), generate a mass about that of the Earth! Clearly, unchecked replication *must* at some point run into the brick wall of resource limitation.

One possible kinetic resolution of unsustainable autocatalytic replicator formation is the establishment of a

steady-state replicator population. This involves a process whereby at some point in time the rate of replicator formation on the one hand, and the rate of replicator degradation on the other, are roughly in balance. A widely used kinetic formulation that has been employed over the years to describe the net rate of accumulation of a molecular replicator (for example, see Ref. 9), one whose roots go back to Lotka's pioneering work,<sup>3</sup> is given by

$$dX/dt = kMX - gX \quad (2)$$

where  $X$  is the replicator concentration,  $M$  is monomer concentration and  $k$  and  $g$  are the rate constants for replicator formation and decay, respectively. The key feature of this equation (and others of its kind) is that the replicator is undergoing competing processes of formation (the  $kMX$  term) and decay (the  $gX$  term), with a steady state being achieved if and when those two rates are equal (i.e. when  $dX/dt = 0$ ). Replicators capable of maintaining a significant steady-state population under a particular set of conditions could, by definition, be classified as *kinetically stable* in that a seemingly permanent population of replicators is present, even though the individual molecular identities of that system are undergoing constant change.

This chemical example of replicator kinetic stability is akin to the physical example of a large flowing river. A river may be classified as a stable entity in the sense that it persists over extended periods of time; however, that stability is also *kinetic* rather than *thermodynamic* in nature. A river's appearance when it remains constant over time reflects a *physical* steady state—the water that constitutes the river is continually being replaced, with the rate of water flow into the river from its sources equaling the rate of flow out into the lake or sea.

Having extended the term kinetic stability to replicating systems, we can now take the concept a step further by quantifying it. A simple measure of the dynamic kinetic stability of a replicating system would be the *size* of the equilibrium population of replicators that is established. The larger that population, the greater is the ability of that replicator to survive any perturbation of the steady-state conditions which might lead to a reduction in population number. Accordingly, the greater is its kinetic stability. Thus a replicating system that (i) can only maintain a *small* equilibrium population or (ii) one that *cannot* maintain a steady-state population at all (owing to its tendency to degrade more rapidly than it can replace itself through replication) would be classified as *kinetically unstable*. At some point in time its population number may fall away to zero. On this basis, most biological species that populate the Earth (although not all) would be characterized as kinetically stable. Note that the quantification of dynamic kinetic stability can also be illustrated with our flowing river example. Thus, large rivers would tend to be more stable than small rivers. A rain-free period, for example, might lead to a

small stream drying up, whereas a large river normally flows independently of normal climatic changes.

Of course, kinetic stability (static or dynamic), in contrast to thermodynamic stability, is not an intrinsic function of the system alone but, as intimated earlier, is also dependent on its surroundings. So whereas thermodynamic stability is *inherent*, kinetic stability is *circumstantial*. A hydrogen–oxygen mixture in a glass container is kinetically stable, although that same mixture in the presence of a platinum catalyst becomes kinetically unstable. Dynamic kinetic stability, as reflected in replicating systems, follows the same pattern. A particular bacterial population in a pool of water might be kinetically stable, whereas that same population in a chlorinated pool would be unstable. Clearly, changes in circumstance may dramatically affect the kinetic stability of physical, chemical and biological, systems. So with regard to this feature, kinetic stability and thermodynamic stability are fundamentally distinct. *Thermodynamic stability*, being a state function, is inherent to the system itself, whereas *kinetic stability* is necessarily dependent on factors extraneous to the system.

### Transitions in replicator space

Let us now consider the process in which one replicator mutates, by whatever mechanism, into a structurally different replicator (for a recent review on molecular replicators, see Ref. 10). Can we make some generalizations regarding the preferred *direction* of the mutation process? In Darwinian terminology, we say that mutations that lead to increasingly fit replicators are favored through natural selection, but can we consider this process in chemical rather than biological terms? In order to attempt this, let us consider molecular replicators, where the mutation process is simpler and can be quantified to a degree.

Consider the mutation of some molecular replicator  $X_1$  into some other molecular replicator  $X_2$  (either through a process of imperfect replication or as a result of some secondary chemical process). We may then ask: what is the kinetic outcome when these *two* molecular replicators compete for the same molecular building blocks? Lifson<sup>7</sup> has recently pointed out that the kinetic solution for two molecular replicators  $X_1$  and  $X_2$  each following the kinetic scheme of Eqn (2) [depicted in Eqns (3) and (4)]:

$$dX_1/dt = k_1MX_1 - g_1X_1 \quad (3)$$

$$dX_2/dt = k_2MX_2 - g_2X_2 \quad (4)$$

is one in which the steady-state concentration of one of the replicators, say  $X_1$ , tends toward a limiting concentration:

$$X_1 = s/k_1M \quad (5)$$

where  $s$  is the rate of supply of monomers  $M$ , while the concentration of the second replicator drops to zero:

$$X_2 = 0 \quad (6)$$

In other words, two molecular replicators obeying the kinetic scheme of Eqn (2) cannot co-exist; one of the replicators (the one we would define as kinetically more stable) drives the second replicator (the kinetically less stable one) into extinction. [Formally, the case in which both replicators are of precisely the same kinetic stability (defined as  $k_1/g_1 = k_2/g_2$ ) would allow co-existence, but this result is highly improbable and represents a special case.<sup>7</sup>]

This kinetic result, if it were to apply to replicating systems generally, would lead to some far-reaching consequences. Let us consider all replicating entities as elements of a *replicator space*. Any mutation, leading to the conversion of one particular replicator into some other replicator, would be considered a transition in replicator space. Taking Eqn (2) as a kinetic model for replicator formation and decay would mean that successful transitions in replicator space would only be those that lead to the formation of replicators of *higher* kinetic stability. Should some mutation lead to the formation of a kinetically *less* stable replicator, then, given the kinetic result described above, it would simply decay and disappear with time. Thus the transition between two connected elements in replicator space would effectively take place in just one direction: the direction based on kinetic selection. Transitions leading to the formation of kinetically more stable replicators would be selected for, whereas transitions that lead to the formation of kinetically less stable replicators would be selected against.

Of course, this all or nothing result described above for molecular replicators derives from the kinetic formulation we have employed [Eqns(2)–(4)] and a different result could arise for different formulations. For example, two competing oligonucleotide replicators that establish a ‘predator–prey’ relationship (in that the shorter replicator becomes raw material for the replication of the longer one), could display different kinetic characteristics, and might lead to an oscillating pattern rather than to an all-or-nothing steady state.<sup>1</sup> A further possible kinetic outcome is one that leads to the co-existence of competing replicators.<sup>11</sup> This was the observed experimental result for enzyme-free oligonucleotide replication<sup>12</sup> and is explained by rate-limiting duplex dissociation which changes the kinetic response and leads to parabolic (rather than exponential) growth.<sup>13</sup> Certainly for the biological world of highly stable replicators, co-existence is a clearly established fact. The enormous range of widely varying species—eukaryotes, prokaryotes and archae—that co-exist in a single biosphere is evidence for that. Given these comments, it is clear, therefore, that the kinetic model expressed by Eqn (2) is simplistic and does not reflect biological reality. Nonetheless, we

believe it does serve to illustrate our basic point—the dynamic equilibrium that is established between different replicators, whether molecular or complex, is inherently fragile. The process of mutation necessarily leads to a variation in replicator (kinetic) stability, and once a number of replicating systems emerge, all competing (directly or indirectly) for the same limited resources, there will be a general tendency for *kinetically more stable replicators to displace kinetically less stable ones*. Thus the biological term *less fit to more fit*, when translated into physico-chemical terminology, becomes *kinetically less stable to kinetically more stable*.

Several general points can now be made. First, it is apparent that our use of the term *kinetic stability* is somewhat different to the conventional chemical one, whereby a system is considered kinetically stable (of the static kind) if it is separated from possible reaction products by a large activation barrier. In the context of replicating systems, kinetically stable systems (of the dynamic kind) would include those replicators that can maintain a large equilibrium population, i.e. those that are characterized initially by either high rates of formation and/or low rates of decomposition. Second, the *kinetic* stability of a replicator is unrelated to its *thermodynamic* stability (in fact, kinetically stable replicators are almost invariably thermodynamically *unstable*, as is evident from the far-from-equilibrium state that living systems always maintain). Third, just as a thermodynamic force drives ‘regular’ chemical systems from higher free energy states toward lower ones ( $\Delta G < 0$ ), i.e. from thermodynamically less stable to thermodynamically more stable, in the parallel world of kinetically driven replication, the kinetic power of mutagenic autocatalysis would tend to drive modular replicators from ones that are *kinetically less stable* to ones that are *kinetically more stable*. Our general point, therefore, is that there is a basic similarity in the pattern of chemical behavior observed in the two parallel chemical worlds of kinetic and thermodynamic selection—in *each of these worlds chemical systems are driven from less stable to more stable*.

One further point regarding the differences between kinetic and thermodynamic selection needs to be noted. Whereas transitions in regular chemical space (thermodynamic selection) are *convergent* in character, those in replicator space (kinetic selection) are *divergent*. For example, in regular chemical space all hydrocarbon–oxygen mixtures are driven toward the same thermodynamic sink, carbon dioxide and water. In replicator space, however, transitions leading to increased kinetic stability are *not* directed towards any particular target system of maximal kinetic stability. As noted earlier, kinetic stability, in contrast to thermodynamic stability, is not a state function. Accordingly, the process of kinetic selection leads to the *divergent* exploration of replicator space utilizing all available degrees of freedom—material, spatial, even temporal—in a process in which an

ever-increasing number of kinetically stable replicators are generated through kinetic selection. Biological evolution is just the more common term for this divergent process of kinetic selection.

Finally, we suggest that the above concept of dynamic kinetic stability may help provide a physico-chemical bridge between animate and inanimate systems. On the one hand, all living systems follow the same laws of physics and chemistry that non-living systems follow, yet the physico-chemical pattern associated with living systems is uniquely distinct—a pattern that involves highly complex reaction networks with elaborate control and feedback mechanisms, maintained in a far-from-equilibrium state through some energy harvesting mechanism. Our point is that although both kinetic and thermodynamic factors play a role in *all* chemical systems, animate and inanimate, the relative importance of these two factors appears to invert in these two distinctly different worlds. Within the inanimate world, chemical transformations are primarily controlled by thermodynamic factors, whereas within the replicative world, owing to the enormous kinetic power of replication,<sup>8</sup> transitions are effectively controlled by kinetic factors, although, of course, each and every transition within replicator space fully obeys the laws of thermodynamics and, specifically, the second law. In the replicative world, mutagenic transformations supported by kinetic selection led to an evolutionary process and the emergence of energy-harvesting systems (chemical, photochemical), which in turn opened up the feasibility of a range of thermodynamically unconstrained structural and dynamic pathways. The result was *complex, kinetically stable, thermodynamically unstable replicators*. The implication we might draw from the above argument is that the physico-chemical aggregate represented by any living system may be classified as a *kinetic state of matter*, as opposed to the traditional thermodynamic states, solid, liquid, gas, with which we are all familiar. Simply put, matter under appropriate conditions can complexify into kinetic and not just thermodynamic states.

In closing, we would suggest that the above simple conceptual framework for relating living and non-living systems may have relevance to a number of current biological questions. Let us consider two examples. First, it may impact on the long-simmering origin of life question by redirecting the focus of that study from the highly problematic *historic* questions on which that research tends to dwell, questions such as where life began, what the conditions were on the prebiotic Earth and what the early replicative systems from which life evolved were, to the more fundamental *ahistoric* question of what physico-chemical principles led to the process of biological complexification and the emergence of life on Earth.<sup>14</sup> Second, it seems to us that the concepts of dynamic kinetic stability and the existence of kinetic states may provide a basis for explaining several of the unique properties of living systems—their extraordinary



degree of complexification, their far-from-equilibrium character and, in particular, their so-called purposeful structure and behavior. Further work along these lines is currently in progress.

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