CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200900805

Seeking the Chemical Roots of Darwinism: Bridging between Chemistry and Biology

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Dedicated to Prof. Yitzhak Apeloig on the occasion of his 65th birthday

Abstract: Chemistry and biology are intimately connected sciences yet the chemistry–biology interface remains problematic and central issues regarding the very essence of living systems remain unresolved. In this essay we build on a kinetic theory of replicating systems that encompasses the idea that there are two distinct kinds of stability in nature—thermodynamic stability, associated with "regular" chemical systems, and dynamic kinetic stability, associated with replicating systems. That fundamental distinction is utilized to bridge between chemistry and biology by demonstrating that within the parallel world of replicating systems there is a second law analogue to the second law of thermodynamics, and that Darwinian theory may, through scientific reductionism, be related to that second law analogue. Possible implications of these ideas to the origin of life problem and the relationship between chemical emergence and biological evolution are discussed.

Keywords: Darwinian theory · kinetics · molecular evolution · RNA · thermodynamics

Introduction

The extraordinary developments in molecular biology over the past half century have served to reaffirm that all biological systems are nothing more than a complex set of chemical reactions, that as van Helmont daringly proposed some 350 years ago— "All life is chemistry".[1] However, this realization, now quite uncontroversial, has not been able to resolve some fundamental difficulties at the biology–chemistry interface. As a consequence chemistry and biology do not merge smoothly, as do, say, physics and chemistry. The sub-areas of physical chemistry/chemical physics are a natural bridge linking physics and chemistry so that these two sciences may be thought of as a scientific continuum. However, with regard to chemistry and biology, despite what would seem to be a natural connection, a conceptual chasm remains. Let us explain the basis for this pointed statement.

First, despite the fact that biological systems are fundamentally chemical in their nature, the striking characteristics that distinguish animate from inanimate systems are not readily explicable in chemical terms. We are referring to their highly organized complexity expressing functional design; their homeostatic nature, an ability to maintain a dynamic far-from-equilibrium steady-state through a complex network of control and feed-back mechanisms; their metabolic capability (used in the sense of energy-gathering), an ability to tap into an external source of energy for maintaining that far-from-equilibrium steady-state, to mention some key aspects. How can one explain the very existence of such elaborate systems? The dilemma pertains to the very essence of living systems and was expressed by Kauffman[2] as follows: "*...we know many of the parts and many of the processes. But what makes a cell alive is still not clear to us. The center is still mysterious.*" Schrodinger's provocative question, "What is Life?" raised over half a century ago[3] still appears to await a more definitive answer.

Second, a fundamental understanding of life in chemical terms would entail an understanding of the physicochemical process by which life emerged on this earth. However, despite the intense interest this question has attracted, the topic remains highly contentious.[2,4] Whitesides[5] recently expressed the current state of understanding in frank terms: "*Most chemists believe, as do I, that life emerged spontaneously from mixtures of molecules in the prebiotic Earth. How? I have no idea. Perhaps it was by the spontaneous*

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emergence of "simple" autocatalytic cycles and then by their combination. On the basis of all the chemistry that I know, it seems to me astonishingly improbable." The issue being addressed here is not primarily the *historic* process by which life on earth emerged, which is likely to remain uncertain for the foreseeable future. Historic events are only as clear and unambiguous as the historic record that describes them. Rather, we are referring here to the *ahistoric* principles that would lead particular inanimate systems to undergo chemical transformations of a kind that would eventually lead to simple living systems. As Wächtershäuser[6] pointed out, chemistry is an ahistoric science, so in the first instance it is ahistoric physicochemical principles, ones that are independent of time and place, that we must seek out—principles that would explain the transformation of inanimate into animate. And it is on this most fundamental of issues that confusion and controversy stubbornly remain.

Finally, an additional demonstration of the problematic biology–chemistry interface manifests itself in our inability to cross that interface through the transformation of inanimate matter into simple life. Simply put, we are far from being able to synthesize a simple living system. As we see it, this inability does not just stem from some technical difficulties that have yet to be overcome, but from basic conceptual issues that need to be resolved. Are we able to propose a coherent synthetic pathway that would link inanimate elements to a metabolic replicating system that we could classify as living? Which, of course, leads us right back to the "origin of life" question posed earlier: if the principles by which life on earth emerged remain uncertain, then the chemical means by which we might mimic that process and synthesize a simple living system, *based on an understanding and application of those same principles*, must also remain uncertain.

The aim of this paper therefore is an attempt to narrow the chemistry–biology conceptual gap by building on a concept we have described in earlier papers—*dynamic kinetic stability*, the particular kind of stability associated with replicating systems.[7] In the present paper we will argue that this distinct and specific form of stability is a missing conceptual link that can help bridge between chemistry and biology, that the process of emergence, a long standing and unresolved chemical problem, and the central theory of biology, evolution by natural selection, can be unified into a single continuous process underpinned by a single driving force principle—the drive toward greater stability, but a stability that is inherently different to the traditional kind of stability that dominates "regular" chemistry. We will attempt to demonstrate that Darwinian theory can be generalized and shown to be part of established chemical kinetic theory, and that a kinetic stability approach to replicating systems can contribute to the theoretical basis for a systems chemistry,[8] a relatively new area of study, that examines the dynamics of autocatalytic molecular networks as potential subsets within larger supersystems, and which may be thought of as the bottom-up pendant of systems biology.

Discussion

Is biology reducible to chemistry? Central to the scientific method is the process of induction, as first formally laid down by Francis Bacon almost four centuries ago. It is the inductive method that provides the basis for the reductionist approach to scientific understanding, whose contribution to the scientific revolution of the 17th century and the establishment of modern science is now universally acknowledged. While the term reductionism can be understood in somewhat different ways, we apply the term here in the sense succinctly described by Weinberg:[9] *explanatory arrows always point downward*, suggesting that higher hierarchical level phenomena may be understood and explained in terms of lower level concepts. Chemistry has certainly greatly benefited from that reductionist approach. Our understanding of chemical phenomena is often expressed in physical terms and in that sense reflects the intimate link that binds chemistry to physics.

With a reductionist view in mind one might well argue that biology should be reducible to chemistry. After all biological systems are composed of nothing other than molecules—biomolecules, it is true, proteins, nucleic acids, lipids, and so forth, but chemical entities nonetheless. However it is also widely recognized that the reductionist approach cannot always be successfully applied. It is not always possible to explain the properties of the complex whole in terms of rules that operate on their individual parts—emergent properties are often quite unexpected. So is biology reducible to chemistry? Well, in some limited respects the answer is yes. The dramatic developments in molecular biology that began with Watson and Crick's discovery of the structure of DNA[10] prove that. We understand why grass is green, we understand many of the individual chemical process that take place in living systems—the mechanism of DNA replication, protein synthesis, key metabolic cycles, to mention central ones—but, as noted above, various emergent properties of biological systems, the global ones in particular, are less explicable in chemical terms. Consider consciousness and teleonomy as two striking examples; we are still far from being able to explain consciousness in either physical or chemical terms, and understanding the phenomenon of teleonomy was viewed by Monod as the "*central problem of biology*".[11] Adding to the difficulty with a reductionist approach to biology is the fact that biology has been considered by some biologists to follow a separate scientific philosophy compared to that of physics and chemistry. That distinction in fact led Mayr, a leading biologist of the late 20th century, to argue for the autonomy of biology,[12] thereby further accentuating the scientific discontinuity between chemistry and biology. Thus, given these inherent difficulties it is of little surprise that the all too facile manner of explaining emergent biological phenomena by sweeping them under the expansive complexity carpet has proved particularly attractive.

We now attempt to demonstrate that a reductionist approach to biology should not be dismissed out of hand; that

biology may be reducible to chemistry to a greater extent than has been generally recognized. The test of whether biology in its broader sense can be reduced to chemistry is a simple one: Can reduction be successfully applied to global biological phenomena? Can reduction provide biological insights that would otherwise be missed? Can reduction assist in bridging the perceived biology–chemistry conceptual gap? In the following sections we build on the concept of dynamic kinetic stability, a concept that is readily derived from standard chemical kinetic theory, and, in true reductionist spirit, attempt to further our goal of bridging between chemistry and biology, as well as provide new biological insights.

Nature of stability: The term *stability* means permanence, persistence, unchanging with time. In previous publications we have argued that in the natural world there are two fundamentally different kinds of stability, and it is the two kinds of stability that lead to the existence of two material worlds—chemical and biological.[7] In the regular chemical world, stability is primarily associated with lack of reactivity, and, through the framework of thermodynamics, can be quantified as the Gibbs energy. Indeed, it is this stability that dominates much of our thinking within chemistry. However, there exists another distinctly different kind of stability that is associated with things than can replicate, and this stability we have termed *dynamic kinetic stability*. This second kind of stability is a direct consequence of the fact that that things that can make more of themselves will tend to abound, thereby maintaining a physical presence. However, it is the exponential nature of the replication reaction, already appreciated by Malthus 200 years ago, that provides this physical presence with a truly profound impact. Thus after just 79 cycles of replication a single replicating molecule would become a mole of material ($2^{79}=6.10^{23}$, Avogadro's number), and a mole of replicating material, if provided with sufficient raw material, would, at least in principle, consume the entire mass of the planet after just 60 more cycles of replication![13]

Of course exponential replication is unsustainable so in practice a replicating system can only be stable if its rate of generation and decay are in approximate balance such that a steady-state population of replicators is established and maintained. A simple and widely used kinetic formulation going back to Lotka's pioneering work,[14] and which expresses this requirement for balance between rates of generation and decay, is given by Equation (1) in which X is the replicator concentration, M is the concentration of building blocks from which X is composed, and k and g are rate constants for replicator formation and decay, respectively.

$$dX/dt = kMX - gX \quad (1)$$

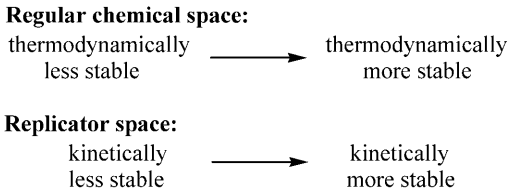
Thus the bottom line, while simple, has profound consequences: whereas systems in the regular chemical worlds are considered stable because they do not react, systems in the replicative world are perceived as stable because they do react—they react to make copies of themselves, thereby maintaining their physical presence over extended periods of times—in some cases over billions of years.

Needless to say this replicative type of stability is not applicable at the individual level, but rather at the population level. The individual entities within that population are continually being turned over, so that it is the replicator population as a whole that is perceived as stable and forms the basis of the dynamic kinetic stability concept. Importantly, the dynamic kinetic stability concept applies to replicating systems of all kinds, *regardless* of whether those systems are chemical or biological. Note also that the nature of the steady-state associated with the dynamic kinetic state is quite different to the internal steady-state generated by any chemical system at equilibrium. The replicative steady-state is associated with an open system and involves irreversible processes, while the equilibrium steady-state involves reversible processes within a closed system.

Some comment regarding the possible quantification of the dynamic kinetic stability concept is now in order. In contrast to thermodynamic stability, which for any given system is a quantifiable state function, dynamic kinetic stability is not a state function, since it necessarily applies to open systems, and therefore cannot be formally quantified. Simply, the dynamic kinetic stability of any system depends not only on the system itself, but on its surroundings. It is the surroundings that provide the system with the energetic and material resources to maintain the replicative steady-state, and thereby its stability. Nonetheless two crude measures of dynamic kinetic stability that do offer some *qualitative* insight into the stability of the system can be proposed. First, the *period of time* the system has managed to survive offers a practical measure of the system's stability. On that basis, for example, one could safely conclude that cyanobacteria, having survived continuously for some 3.5 billion years, are highly stable. A second, though less reliable indication of a system's dynamic kinetic stability, may be provided by the system's *population size*—the larger the steady-state population of replicators at any given point in time, the more stable it is likely to be. To give a simple biological example, mosquitoes and cockroaches, being abundant, would be predicted to exhibit greater dynamic kinetic stability than pandas, which are relative scarce. However this instantaneous measure of dynamic kinetic stability should only be considered indicative, rather than definitive.

Having now characterized the two kinds of stability that can be found in nature, we can utilize that concept to consider the nature of changes that will take place in each of the two worlds. Since the concept of stability is a fundamental one—things that are stable persist over time—nature's basic selection rule is the same in both worlds and is strikingly simple: *Systems tend to be transformed from less stable to more stable.* In fact that rule has elements that are axiomatic. Once we accept on empirical grounds that chemical transformations in nature do take place, that matter is not immutable, it is then axiomatic that transformations would take place from less stable to more stable; the validity of

that statement is inherent within the very definition of stability. However, because there are *two* kinds of stability, one based on reactivity, the other based on lack of reactivity, the selection rules that govern the respective transformations in the two spaces, replicative and "regular", must reflect that difference. The different selection rules have been discussed previously and are summarized in Scheme 1.[7] Thus, in the



Scheme 1. Selection rules in "regular" and replicative spaces.

regular chemical world the selection rule is the well-known second law, that is, the transformation of regular chemical systems takes place from thermodynamically less stable to thermodynamically more stable (with kinetic factors playing a secondary role), while in the replicative world the selection rule is generally from kinetically less stable to kinetically more stable. As we have discussed previously, once a replicating system has incorporated a metabolic (energy-gathering) capability at some particular point along the evolutionary path (by kinetic selection), kinetic selection is largely freed from thermodynamic constraints, thereby relegating thermodynamic factors to a secondary role.[7] The recent comment by Eschenmoser: "*...exemplifying on the chemical level one of biology's major lessons, namely, that replication can substitute for thermodynamic stability when continuance is at stake",* also captures aspects of this idea.[15] Let us now use these two kinds of stability and their corresponding selection rules to relate chemical and biological changes.

Conceptual tools for understanding chemical and biological transformations: As noted above, a central focus of chemical theory is the set of rules or laws that govern chemical transformations. Of those laws the second law of thermodynamics is of primary importance, since ultimately it is this law that determines whether a chemical reaction, or set of coupled chemical reactions, can take place. Of course the role of kinetics cannot be ignored. A reaction that is allowed by the second law may or may not proceed since kinetic factors do play a role, though one that is of secondary importance.

Turning now to biology, there can be no doubt that the central conceptual tool of that science is Darwin's theory of evolution. As Dobzhansky noted: "*Nothing in biology makes sense except in the light of evolution.*"[16] In fact evolutionary theory has led to the science of biology being effectively divided into two general areas—functional biology, which deals with the operation and interaction of elements within living organisms, and evolutionary biology, which deals with all aspects of the process by which early life on earth evolved once it emerged. Of course it is through the key Darwinian concepts of natural selection and survival of the fittest that evolutionary transformations within a species, or between species, can be explained.

However, given that biological systems are ultimately chemical systems—complex chemical systems it is true, but chemical systems nonetheless—leads us to ask whether the central principles of chemistry and biology may be in some way related? Can the central theory of biology, Darwinian theory, and the central law of chemistry, the second law of thermodynamics, be related in some fashion?

Darwinian theory as part of chemical kinetic theory: Some indication as to how Darwinian theory and the second law may be related can be ascertained by considering the chemical patterns of simple replicating molecules. A particularly striking set of experiments conducted by Spiegelman and Orgel several decades ago was based on the test-tube replication of Qβ viral RNA.[17] In these classic experiments it was discovered that imperfect replication of the extended RNA strands led to the formation of increasingly shorter strands, exhibiting significantly higher replication rates, a result that was interpreted as illustrating the operation of key Darwinian concepts—mutation, natural selection, and evolution—at the molecular level. Indeed, extension and application of these central Darwinian ideas to the molecular level, and so into chemistry, led Eigen to offer an illuminating conceptual bridge between the sciences of chemistry and biology.[4a]

However, there is a fundamental difficulty with explaining what is strictly a chemical phenomenon using terms borrowed from biology. Over several centuries chemistry has developed its own conceptual framework and terms such as natural selection, survival of the fittest, and evolution are not part of that framework. Recalling Weinberg's comment of explanatory arrows always pointing downward, suggests that a proper application of the scientific method would entail explaining biological concepts in chemical terms, and not chemical concepts in biological terms. Borrowing concepts and terminology from a higher hierarchical level science could be taken to imply that chemistry is unable to explain the observed phenomena in chemical terms, but this is not the case. Chemical theory *can* explain the phenomenon utilizing standard kinetic theory. The observed effect in which some replicating entity has been transformed into another is simply one in which a process of kinetic selection has led to the formation of the kinetically more stable replicator.

A simple example that illustrates the kinetic selection rule in replicator space was pointed out by Lifson several years ago.[18] For the case in which two replicating molecules, X_1 and X_2, each following the general kinetic scheme of Equation (1), as shown in Equation (2) and (3), and competing for the same building blocks, *M*.

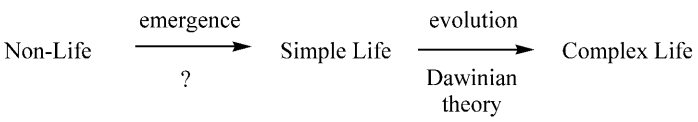
$$dX_1/dt = k_1MX_1 - g_1X_1 \quad (2)$$

$$dX_2/dt = k_2MX_2 - g_2X \quad (3)$$

The solution of the two equations is that the steady-state concentration of one of the replicators, say X_1, drops to 0, while that of the other replicator, X_2, reaches a limiting value of s/k_2M (in which s is the rate of supply of building blocks, M). In other words one of the replicators, the kinetically more stable one, out-replicates the kinetically less stable one until the latter is totally eliminated from solution. Of course the above kinetic scheme is a simplistic one and unlikely to accurately mirror the kinetic pattern of a real replicating system. Yet even that simplest of kinetic models captures the essence of dynamic kinetic stability in the replicator world; namely, when a sustained replicating system is allowed to undergo a continuing process of replication, it will, through a natural process of structural variation (mutation), tend to be transformed into kinetically more stable variants; that is, the more stable replicators will tend to replace the less stable ones.

Is the above discussion, in which we prefer a chemical explanation (based on chemical kinetics) for the chemical outcome of competing molecular replicators, rather than a biological one (expressed in Darwinian terms) merely one of semantics? Does it matter whether we describe the competitive outcome in chemical or biological terms? The answer, emphatically, is yes, it does! By describing chemical behavior in biological rather than chemical terms we are effectively dismissing an opportunity to help reduce biology to chemistry. If the behavior of simple replicating systems can be explained in chemical terms, and if that pattern is also found to apply to complex replicating systems, that is, biological systems, we have effectively found a *chemical* link between biology and chemistry, one that can be usefully exploited. In the present case the reductionist process enables us to uncover the roots of Darwinian theory within chemical kinetic theory, thereby helping to incorporate a central theme of biology within a general chemical framework. Benefits of such a reductionist approach can be readily demonstrated.

Consider scheme 2 which illustrates the on-going origin of life dilemma. The conversion of non-life to complex life is widely considered as having taken place in two stages: the first stage, commonly termed emergence, is the one in which inanimate matter somehow complexified into a simple life form. The second stage, the Darwinian stage, is the one in which that simple life form, once formed, evolved and diversified. While a basic understanding of the Darwinian phase was provided some150 years ago, the first stage remains a source of confusion and controversy. Darwinian principles, broadly speaking, govern the second phase, but what general principles would govern the first phase, the conversion of inanimate matter into simple life? As mentioned earlier, this issue continues to be an unending source of controversy and



Scheme 2.

confusion,[2,4] despite Eigen's proposal that Darwinian thinking may be extended to that prebiotic phase.[4a] Let us now attempt to reassess the chemistry–biology relationship through a reductionist approach.

Replicator space second law analogue: Our previous discussion has revealed that the driving force for the transformation of both simple chemical replicators (as illustrated by the Spiegelman and Orgel experiments[17]) as well as complex replicators (as expressed by Darwinian theory) is actually identical—*the drive toward greater kinetic stability.* The fact that the same physicochemical driving force principle is seen to be operative at both the molecular level and the biological level suggests that the two stages *can be considered as one continuous process governed by a single driving force.* By reducing Darwinian theory to its chemical equivalent we discover what appears to be a fundamental principle linking animate to inanimate and underlying the emergence of life on earth: once some simple replicating entity (the precise nature of which will likely remain forever uncertain), emerged through prebiotic chemical processes and exhibited minimal dynamic kinetic stability, that is, it was able to maintain its structural integrity over some time, the drive toward greater kinetic stability would have led that primordial system to stabilize through a process of complexification eventually leading to the highly complex and diverse kinetically stable replicating systems that we term life. Thus the process of complexification is just the response of that primordial replicating system, to the drive toward greater kinetic stability.

We have recently illustrated the complexification principle using as a model the mechanism of phage action.[19] The phage, simplistically viewed as a two-molecule assembly (nucleic acid + protein), is a highly effective replicator. In contrast, each of the two individual components when separate, are unable to replicate in the same (biotic) environment. Complexification, whereby two molecular entities have aggregated, has provided the molecular assembly with a kinetic stability that was absent in its separate components. Thus the phage is effectively an integrated cross-catalytic system in which each component cross catalyses the replication of the other component, resulting in the establishment of a holistic and highly efficient replicating system. Other examples demonstrating this same idea can be provided. Thus Lincoln and Joyce[20] have recently reported the first self-sustained RNA replication of a pair of RNA enzymes (in the absence of any protein enzyme), the high replicative capability of which was also based on a cross-catalytic scheme. By comparison, single RNA enzyme self-replication was found to be inefficient and displayed limited exponential growth.[20] The significant role of cross-catalysis within autocatalytic molecular networks has recently been described.[21]

Significantly, the same complexification principle that is operational at the molecular level can be seen to also apply at the biological level. The origin of eukaryotic cells, for example, is attributed to a primordial endosymbiotic event

that involved the engulfment of one bacterial cell by another, and key eukaryotic organelles, mitochondria and chloroplasts, are also thought to have come about through endosymbiotic capture.[22] Thus, despite the uncertainty regarding the precise kinds of those merging bacterial cells, it seems evident that the greater complexity of that primal eukaryotic cell, as brought about through an endosymbiotic event, endowed it with biological advantages that ensured its survival, that is, high kinetic stability, which then allowed for further evolutionary development. Accordingly, both chemical and biological complexification constitute two manifestations of the same operational principle, lending further support to the view that emergence and evolution constitute two phases of the one continuous process. *Thus the entire process of chemical complexification (emergence) followed by biological complexification (evolution) can be understood as the response of some primordial replicating chemical system to a single driving force principle,* one that has both a theoretical basis in chemical kinetic theory as well as empirical support at both molecular and biological levels. Indeed, the above discussion points to the existence of a replicative analogue to the second law of thermodynamics. Whereas the second law requires all chemical systems to be directed toward their most stable state (lowest Gibbs energy state), the replicative second law—the second law analogue in replicator space—directs all sustainable replicative systems toward those structures that exhibit high dynamic kinetic stability. Both the second law and the second law analogue govern the nature of transformations that chemical systems will tend to undergo in their respective spaces - "regular" or replicative.

Implications of a unified emergence–evolution process toward life: We believe that the proposed unification of emergence and evolution through the kinetic stability concept may assist in a narrowing of the chemistry–biology conceptual gap. In particular it may throw additional light on the "origin of life" issue through an assessment of the various mechanistic possibilities that have been raised and their compatibility with that underlying concept. First, while the following statement might be considered uncontroversial and widely accepted, we make it for completeness: a replicative capability was central to the process of emergence (of simple life) in the same way that it is central to the process of evolution. Just as it is clear that there would be no evolution without biological replication/reproduction, we would say there would be no emergence without chemical replication. The very essence of a stability type that we have termed "dynamic kinetic" depends on the existence of such a capability.

Once there is general agreement that emergence began with the appearance of some primal replicating entity, a second and more problematic question involves a more precise characterization of that primal entity. While we believe the uncovering of evidence that would explicitly identify that primal replicator (likely transient in nature) several billion years after the event is highly improbable, questions regarding its general characteristics can be addressed; for example, would it have been metabolic (i.e., based on some unidentified autocatalytic reaction cycle) or genomic (i.e., based on some unidentified polymeric structure of variable sequence)? This particular question has been a focus of intense debate in recent years and remains controversial,[2,23,24] though more recent considerations have suggested that a sharp demarcation between the two views may not be entirely warranted.[25] Let us now address this issue in the light of the above discussion.

In previous publications it has been argued that available evidence, both experimental and theoretical, points to a primal genomic rather than a primal metabolic replicator.[23] First, there is abundant empirical evidence for the existence of simple molecular (genomic) replicators that can undergo structural change leading to kinetically more stable replicators, while the existence of stable autocatalytic metabolic cycles has yet to be demonstrated, and their physicochemical feasibility has been theoretically questioned.[18,23] A second difficulty with the metabolism-first view is the lack of either empirical or theoretical evidence, which would support the idea that such a metabolic cycle, even if it did exist, would be capable of evolving. Evolvability is of course central to any Darwinian-type process and without that capability, such an entity could not have continued along the path toward a primal living system. However, notwithstanding the above arguments, and in the context of a continuous emergence–evolution process as proposed in this paper, the argument in support of a genomic emergence can be further strengthened.

Biological evolution has been a subject of intense study for over one hundred years, and considerable empirical data on that topic has accumulated over time. Accordingly, if we accept the idea of a continuous emergence–evolution process, it stands to reason that the general understanding of evolution obtained from that extended period of study may well provide mechanistic insights into the poorly understood earlier period of emergence. An example that illustrates and lends support to this way of thinking can be provided. It is a generally accepted principle of ecology that two different species following a similar way of life will not be able to coexist—one of the species will drive the other into extinction.[26] It is striking therefore that at the chemical level precisely the same pattern is observed. Lifson's simple kinetic analysis regarding competing molecular replicators that feed off the same molecular building blocks, leads to an identical result—kinetic selection does not permit the coexistence of two competing molecular replicators constructed from the same molecular building blocks.[18] Of course, the experimental data of Spiegelman and Orgel[17] merely serve to reaffirm this general conclusion, lending empirical support to our suggestion *that evolutionary patterns gleaned from evolutionary biology may provide insights into the chemistry of emergence.* Let us now consider possible applications of this way of reasoning.

Modern Darwinian thinking rests on two key elements. First, all living systems, whether cyanobacteria, believed to

have existed on earth for some 3.5 billion years, or more recent life forms such as we humans, utilize the same basic nucleic acid genomic system. Second, evolution is considered to have taken place by small incremental steps, which in molecular terms is attributed to genomic sequence mutation. If we now build on our hypothesis that emergence and evolution constitute a single extended process, thereby utilizing the pattern observed in evolution as a likely model for describing the process of emergence, we are led to several conclusions. First, both the universality and the stability of the sequence-based genomic system of information storage over the billions of years during which life on earth evolved suggest that the mode of information storage in the prebiotic phase would have been similar in kind, rather than one based on some alternative system. That way of thinking in itself lends support to the RNA-world view in which the emergence of an oligomeric (genomic) replicator led to the emergence of life.[27] However this argument in support of a genomic origin may be taken a step further.

Let us begin by assuming that some autocatalytic metabolic system, rather than a sequence-based genomic system, did emerge prebiotically, and let us also assume (despite the lack of theoretical or experimental evidence) that such a system would be capable of undergoing Darwinian-type evolution. However, even accepting those far-reaching and questionable assumptions, it is difficult to see how a prebiotic *non-genomic* system would have been able to undergo a series of incremental changes that would have lead to a structurally quite distinct *genomic* system, while able to maintain its replicative capability during the transformation. Maynard Smith's classic model of protein evolution exemplifies the point.[28] In his model Maynard Smith made clear that the unitary mutation steps in the amino acid sequence during the evolutionary transformation of protein structure cannot pass through non-functional intermediates. Using similar reasoning we conclude that the transformation of a non-genomic replicating system into a genomic one would have required that each and every step in that transformation also pass through functional intermediates (functional here signifying the possession of a replicative capability) and it is far from clear that such a condition can be satisfied. Just how would an evolutionary process, step-wise and incremental in nature, transform a replicating system based on an autocatalytic metabolic cycle, such as the reverse citric acid cycle, into a structurally quite distinct genomic replicator, while maintaining a replicative capability at each step? After all, the replicative modalities are quite distinct; metabolic autocatalysis is typically based on autocatalytic cycle closure (termed by Eschenmoser, *circuit catalysis*[25]), while sequence-based oligomer autocatalysis is based on *reaction catalysis*[25] through template-directed fragment binding. Accordingly, it is difficult to see the physicochemical basis for the smooth interconversion of one replicative type into the other (though it should be noted that recent work is increasingly emphasizing the importance of reaction networks, not just in metabolic cycles, but in genomic replicating systems as well[20,21b]). Thus even assuming the unlikely emergence of some alternatively structured (non-sequence-based) replicative chemical system, its step-wise conversion into a sequence-based genomic system would seem chemically implausible. Even if a non-sequence-based system did happen to have emerged at some prebiotic stage, and even if it were capable of undergoing an evolutionary process (two highly questionable propositions), it would have most likely found itself in an evolutionary dead-end, so its formation would not be directly relevant to the emergence of life process. Thus our proposal for a continuous emergence–evolution process, when considered together with a Darwinian model based on the centrality of a genomic system, we believe, reaffirms the pre-eminence of some kind of genomic system in the prebiotic phase as well. The suggestion of a peptide–nucleic acid (PNA) oligomer as a possible carrier of pre-RNA genetic information exemplifies this way of thinking,[29] though definitive evidence for any particular pre-RNA entity has yet to be established.

Conclusions

We have attempted to demonstrate that a conceptual bridge between the sciences of chemistry and biology can be strengthened by relating the primary law governing all chemical reactions, the second law of thermodynamics, and the primary principle that governs all biological thinking, Darwinian theory. Our message in succinct terms is that Darwinian theory may, through scientific reductionism, be reduced to chemical kinetic theory, and that just as "regular" chemical reactivity is fundamentally related to thermodynamic stability (as expressed by the second law of thermodynamics), so replicative reactivity can be related to a different stability—dynamic kinetic stability, thereby implying the existence within replicator space of a second law analogue; that is, the drive toward greater dynamic kinetic stability. While the concept of dynamic kinetic stability is not precisely quantifiable, and is therefore "softer" in comparison to the parallel concept of thermodynamic stability, the qualitative understanding that the relationship provides is nonetheless of value in strengthening our general understanding of global biological phenomena and their incorporation within a broader chemical context. An immediate benefit of our approach is, we believe, added insights into the origin of life problem, through the conceptual merging of emergence and evolution as a continuous physicochemical process governed by a single driving force. Our recent physicochemical explanation for teleonomy, that most striking of global biological phenomena, further illustrates the utility of the approach.[7c] However, given the fundamental chemical basis on which all of biology rests, other benefits are likely to manifest themselves. Thus we believe that the current goal of synthesizing a minimal cell will necessarily benefit from a deeper understanding of the animate–inanimate relationship. Further work on addressing these kinds of questions is currently under way.

Acknowledgements

The author is indebted to Dr. Ilana Agmon, Prof. Jan Engberts, Prof. Albert Eschenmoser, and Prof. Robert Pascal for helpful comments on earlier versions of the manuscript.

[1] J. B. van Helmont in *Ortus Medicinae*, Amsterdam, **1648**, pp. 108–109; Translated in *Great Experiments in Biology* (Eds.: M. L. Gabriel, S. Fogel), Prentice Hall, Englewood Cliffs, **1960**, p. 155.
[2] S. A. Kauffman, *Investigations*, Oxford University Press, Oxford, **2000**.
[3] E. Schrodinger, *What is life? The Physical Aspects of the Living Cell*, Cambridge University Press, Cambridge, **1944**.
[4] For reviews on the origin of life, see: a) M. Eigen, *Steps Toward Life: A Perspective on Evolution*, Oxford University Press, Oxford, **1992**; b) I. Fry, *The Emergence of Life on Earth* Rutgers University Press, New Brunswick, **2000**; c) P. L. Luisi, *The Emergence of Life: From Chemical Origins to Synthetic Biology*, Cambridge University Press, Cambridge, **2006**; d) J. Maynard Smith, E. Szathmary, *The Origins of Life*, Oxford University Press, Oxford, **1999**.
[5] G. M. Whitesides, *Chem. Eng. News* **2007**, *85*, 12–17.
[6] G. Wächtershäuser, *J. Theor. Biol.* **1997**, *187*, 483–494.
[7] a) A. Pross, *Pure Appl. Chem.* **2005**, *77*, 1905–1921; b) A. Pross, V. Khodorkovsky, *J. Phys. Org. Chem.* **2004**, *17*, 312–316; c) A. Pross, *J. Phys. Org. Chem.* **2008**, *21*, 724–730.
[8] G. von Kiedrowski, *ChemBioChem* **2001**, *2*, 597–598; J. Stankiewicz, L. H. Eckhardt, *Angew. Chem.* **2006**, *118*, 350–352; *Angew. Chem. Int. Ed.* **2006**, *45*, 342–344; R. F. Ludlow, S. Otto, *Chem. Soc. Rev.* **2008**, *37*, 101–108.
[9] S. Weinberg, *Dreams of a Final Theory*, Pantheon, New York, **1992**.
[10] J. D. Watson, F. H. C. Crick, *Nature* **1953**, *171*, 737–738.
[11] J. Monod, *Chance and Necessity*, Random, New York, **1972**, p. 22.
[12] E. Mayr, *Toward a New Philosophy of Biology*, Harvard University Press, Cambridge, **1988**.
[13] A. Pross, *J. Theor. Biol.* **2003**, *220*, 393–406.
[14] A. J. Lotka, *J. Phys. Chem.* **1910**, *14*, 271.
[15] K-U. Schoning, P. Sholz, S. Guntha, X. Wu, R. Krishnamurthy, A. Eschenmoser, *Science* **2000**, *290*, 1347–1351, reference [26].
[16] T. Dobzhansky, *Am. Biol. Teacher* **1973**, *35*, 125–129.
[17] a) D. R. Mills, R. L. Peterson, S. Spiegelman, *Proc. Nat. Acad. Sci. USA* **1967**, *58*, 217–224; b) R. Saffhill, H. Schneider-Bernloehr, L. E. Orgel, S. Spiegelman, *J. Mol. Biol.* **1970**, *51*, 531–539; c) L. E. Orgel, *Proc. R. Soc. London* **1979**, *205*, 435–442.
[18] S. Lifson, *J. Mol. Evol.* **1997**, *44*, 1–8.
[19] A. Pross, *Origins Life Evol. Biosphere* **2005**, *35*, 151–166.
[20] T. A. Lincoln, G. F. Joyce, *Science* **2009**, *323*, 1229–1232.
[21] a) K. Severin, D. H. Lee, A. J. Kennan, M. R. Ghadiri, *Nature* **1997**, *389*, 706–709; b) Z. Dadon, N. Wagner, G. Ashkenasy, *Angew. Chem.* **2008**, *120*, 6221–6230; *Angew. Chem. Int. Ed.* **2008**, *47*, 6128–6136.
[22] a) A. Poole, D. Penny, *Nature* **2007**, *447*, 913; b) R. S. Gupta, G. B. Golding, *Trends Biochem. Sci.* **1996**, *21*, 166–171; c) L. Margulis, *Symbiosis in Cell Evolution*, Yale University Press, New Haven, **1981**.
[23] a) L. E. Orgel, *PLoS Biol.* **2008**, *6*, 5–13; b) L. E. Orgel, *Proc. Nat. Acad. Sci. USA* **2000**, *97*, 12503–12507; c) A. Pross, *Origins Life Evol. Biosphere* **2004**, *34*, 307–321; d) A. Lazcano, S. L. Miller, *J. Mol. Evol.* **1999**, *49*, 424–431.
[24] a) R. Shapiro, *Q. Rev. Biol.* **2006**, *81*, 105–125; b) D. Segre, D. Ben-Eli, D. Lancet, *Proc. Nat. Acad. Sci. USA* **2000**, *97*, 4112–4117; c) G. Wächtershäuser, *Microbiol. Rev.* **1988**, *52*, 452–484; d) H. J. Morowitz, J. D. Kostelnik, J. Yang, G. D. Cody, *Proc. Nat. Acad. Sci. USA* **2000**, *97*, 7704–7708; e) E. Smith, H. J. Morowitz, *Proc. Nat. Acad. Sci. USA* **2004**, *101*, 13168–13173.
[25] A. Eschenmoser, *Origins Life Evol. Biosphere* **2007**, *37*, 309–314.
[26] R. Dawkins, *The Blind Watchmaker*, Norton, New York, **1996**, p. 239.
[27] a) G. F. Joyce, *Nature* **2002**, *418*, 214–221; b) *The RNA World* (Eds.: R. F. Gesteland, T. R. Cech, J. F. Atkins) Cold Spring Harbor Laboratory Press, New York, **1999**.
[28] J. Maynard Smith, *Nature* **1970**, *225*, 563–564.
[29] P. E. Nielsen, *Origins Life Evol. Biosphere* **1993**, *23*, 323–327.

Published online: July 16, 2009

