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How can a chemical system act purposefully? Bridging between life and non-life

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One of life's most striking characteristics is its purposeful (teleonomic) character, a character already evident at the simplest level of life – a bacterial cell. But how can a bacterial cell, effectively an aqueous solution of an assembly of biomolecules and molecular aggregates within a membrane (that is itself a macromolecular aggregate), act purposefully? In this review, we discuss this fundamental question by showing that the somewhat vague concept of purpose can be given precise physicochemical characterization, and can be shown to derive directly from the powerful kinetic character of the replication reaction. At the heart of our kinetic model is the idea that the stability that governs replicating systems is a *dynamic kinetic stability*, one that is distinctly different to the thermodynamic stability that dominates the inanimate world. Accordingly, living systems constitute a *kinetic state of matter* as opposed to the thermodynamic states that dominate the inanimate world. Thus, the model is able to unite animate and inanimate within a single conceptual framework, yet is able to account for life's unique characteristics, amongst them its purposeful character. As part of that unification, it is demonstrated that key Darwinian concepts are special examples of more general chemical concepts. Implications of the model with regard to the possible synthesis of living systems are discussed. Copyright © 2008 John Wiley & Sons, Ltd.

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INTRODUCTION

Attempts to understand the relationship between animate and inanimate matter have been the goal of much philosophic and scientific thinking since ancient times. At the very heart of this issue lies the problem of the origin of life, which stubbornly remains one of the major scientific riddles still awaiting resolution. This latter problem is not merely historical in nature, namely, what was the specific path taken on the extended road from inanimate to animate, but much more fundamental: what laws of physics and chemistry are consistent with the transformation of some prebiotic inanimate system into the highly complex and dynamic system that is life? A number of secondary questions, also unresolved, derive from the primary problem. For example, given that living things are both replicative and metabolic, what characteristic emerged first?[1,2] Did some early replicator become metabolic, or did some metabolic system become replicative, or possibly, did a system that was simultaneously replicative and metabolic emerge at some point? This lack of fundamental understanding has far-reaching consequences. It means, for example, that not only are we unable to synthesize life *in practice*, but that we are even unable to offer a plausible theoretical scheme that *in principle* could lead to the synthesis of a simple living system. Whitesides[3] recently summarized the current state of understanding: '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 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'.

Of course what makes life such a special chemical system is not just its extraordinary complexity, but one particular characteristic that is unique to living systems and places them in a totally different class to inanimate systems – living systems are *purposeful*, or to use the scientific term coined by biologists, *teleonomic*.[4–6] Kauffman[7] has expressed that behavior pattern as follows: *living systems are autonomous agents – they act on their own behalf*. Thus, in contrast to non-living systems, living systems appear to operate according to some explicit agenda, rather than merely obeying established laws of physics and chemistry. Given the above comments, the problem of the emergence of life might then be reformulated as follows: what laws of physics and chemistry can explain the conversion of 'regular' chemical systems, whose behavior can be understood solely on the basis of the standard laws of physics and chemistry, into ones that of course still obey those laws, yet somehow operate on their own behalf, that seem 'to do their own thing'. As we subsequently discuss, teleonomic behavior is not just observed at the organismic level – birds, bees, camels, and humans, but is already starkly evident at the single cell level. Indeed, Monod[8] termed the existence of this purposeful behavior of all living systems, whether single-cell or multi-cellular, 'the central problem of biology'. As Monod pointed out, the essence of the scientific revolution of the 17th century was the profound realization that the laws of Nature are devoid of purpose, that the universe is *objective*. That being the case, Monod was led to ask: *how could projective (purposeful) systems have emerged from an objective universe?*

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The need to address Monod's paradox extends beyond resolving philosophic issues regarding the nature of the universe. Indeed, Monod's question can be rephrased so as to give it a more scientific focus: Can the teleonomic character associated with all living systems be explained in chemical terms, that is, in the same kinds of chemical terms that we use to explain the hardness of crystals, the electrical conductivity of metals, or the immiscibility of hexane and water? Is teleonomy a chemical characteristic of certain material forms that can be specified in advance? If living systems are characterized by their teleonomic character, it follows that if we can specify that character in chemical terms, one might obtain greater insight into the kinds of chemical transformation that would have induced inanimate matter to complexify into living systems. Just as we have today a fundamental understanding of the physicochemical relationship between solid, liquid, and gas phases, we should strive for a similar level of understanding regarding the relationship between animate and inanimate material forms. That, after all, is a major goal of all scientific endeavor – to organize diverse empirical data into 'patterns of understanding' – what we term rules, and subsequently to unify localized rules into more fundamental and more general patterns that we term laws. Clearly, then a single unifying framework encompassing both living and non-living could have far-reaching scientific implications. Its ultimate achievement – at present a distant dream – would be to offer, at least in principle, a process by which inanimate matter could be transformed into a living system, that is, the outlines of a recipe for the synthesis of life.

DISCUSSION

The purposeful nature of living systems

In attempting to relate living and non-living, a sensible starting point might appear to be to seek agreement on a broad definition of life. However, as has become starkly evident over recent years, such attempts are fraught with difficulty – all definitions seem fallible in that exceptions are readily found.[9] To illustrate the problem, consider one of the most widely cited current definitions of life expounded by NASA, based on an earlier formulation by Joyce:[10] 'Life is a self-sustained chemical system capable of undergoing Darwinian evolution'. However, even putting aside minor questions regarding that particular definition, there is one key aspect of living systems that the definition overlooks, one that was strikingly obvious well before Darwin. Any one of our early ancestors, faced with an attacking predator, would have had an intuitive appreciation of what life (and death) is about without knowing what was meant by a self-sustained chemical system or having ever heard about Darwinian evolution. Similarly, a 3-year-old child already has some intuitive understanding of, say, the difference between a living dog and a toy one,[11] without knowing anything about nucleic acids, metabolism, entropy, or Darwinian selection. So, in a very real sense defining life in terms of replicating Darwinian systems seems to miss a key aspect of what life actually entails. Even the characteristic of replication (reproduction), central to most life definitions, may be less fundamental to characterizing life than is generally believed. Is a replicating molecule that undergoes mutation and Darwinian type selection, alive? We would argue it is not. No single molecule can be reasonably classified as alive just because under certain chemical conditions it can catalyze the formation of copies of itself from appropriate chemical building blocks. That reaction, like any other chemical reaction, is governed by standard and well-established chemical principles, and involves the reorganization of bonding between atoms in the reactant molecules leading to their conversion into product molecules. On the other hand, is a sterilized rabbit not alive just because it cannot replicate? Clearly, a rabbit is alive for what it is, irrespective of its fertility status. Hopefully, the above discussion makes clear that what is special about life is not merely some historic aspect revolving around replication, mutation, and selection, but a feature that is actual at any point in time – its teleonomic character. In contrast to non-living systems, the behavior of living systems can be categorized and understood in terms of the system's perceived agenda, an agenda that is empirically readily recognizable. Non-living natural systems lack that characteristic, and their behavior can only be categorized and understood through general laws of physics and chemistry.

Are simple living systems teleonomic?

One might initially attribute teleonomic behavior to highly evolved complex multi-cellular systems possessing a nervous system. But it should be made clear that teleonomic behavior is associated with even the simplest living systems, for example, a single cell bacterium. If one looks at a bacterial cell, devoid of even a nucleus, essentially each and every physicochemical process within that living cell constitutes activity associated with the cellular agenda – the multiplication of cells. Chemotaxis, the process in which cells direct their motion according to the nature of the chemicals in their environment, exemplifies the phenomenon. Thus, bacteria when placed in a glucose solution gradient 'swim' upstream to take advantage of the higher concentration of nutrient available there.[12] Or, if glucose, the cell's primary energy source, is replaced by lactose, then the cell synthesizes the enzyme necessary to break down the complex sugar into its constituent simple sugars, glucose and galactose.[13] These are just two examples out of a multitude of control and regulation factors that operate in the cell and reflect its agenda of multiplication. As Jacob[14] put it somewhat poetically – 'the dream of every cell – to become two cells'. So despite the fact that a small crystal of sugar, a micelle, and a bacterial cell are all examples of molecular aggregates of not dissimilar size, the bacterial cell compared to the sugar crystal and the micelle are fundamentally different: all physicochemical processes that the crystal and micelle undergo can be understood solely on the basis of physicochemical considerations (intermolecular forces, kinetic, and thermodynamic considerations, etc.) in striking contrast to the bacterial cell, whose behavior can be understood in terms of the cellular agenda – the replication of cells.

One might at this point pose the following criticism: the cell is not purposeful – the bacterium swims upstream in a glucose solution gradient because of specific biochemical mechanisms. The purposeful nature is something that we conceive in our minds, is not an observable, and so does not exist in reality. Such an argument is however unjustified and reveals some misunderstanding as to the essence of the scientific method. Without delving too deeply into this complex philosophical issue, let us briefly address the question by considering a chemical example – the reality of atoms in molecules. Most chemists would consider atoms in molecules as 'real', but Parr[15,16] recently pointed out that atoms in molecules are not well-defined physical entities, and goes as far as to characterize them as noumenons, a noumenon being defined as 'an object knowable by the mind or intellect, not by the senses; specifically (in Kantian philosophy) an object of purely intellectual intuition'. To quote Parr: '. . . the atom in a molecule is a vital, central chemical concept, yet forever elusive. Despite its utility, the atom in a molecule cannot be directly observed by experiment'. In other words while atoms in molecules might be thought of as 'real', the border separating so-called real entities from conceptual ones is actually much vaguer and less well-defined than experimental scientists would like to believe. Thus, in the same sense that chemists build on the concepts of atoms in molecules, biologists build on the concept of teleonomy. Each concept provides the particular practitioner with a conceptual framework that allows the organization of diverse phenomena – chemical or biological, and provides that practitioner with the ability to make predictions regarding relevant systems in his/her area of study. One can conclude this section therefore by stating that, despite the strengthening of the mechanistic approach to biology brought about by Darwinism, the concept of purpose in modern biology has been firmly re-established over the past half century – teleonomy is now recognized by leading biologists as a prime organizational principle in biology.[5,6] Simply, without the noumenon of teleonomy, much of functional biology ceases to mesh into a meaningful whole.

Once we accept the concept of teleonomy as one that is scientifically legitimate, we are faced with the challenge of explaining that specific biological pattern of material behavior, one that is empirically irrefutable, in more fundamental, more physical terms. How can a chemical system such as a bacterial cell, ostensibly an aqueous solution of chemicals and chemical aggregates within a membrane (itself a chemical aggregate) act on its own behalf? Can teleonomic character be reduced to physics and chemistry in the same way that Kepler's laws of planetary motion can be reduced to Newton's more general laws of gravity? There is a common view that teleonomy is an 'emergent property of complex systems'; however, a moment's consideration tells us that such an explanation (beyond its use of two currently popular buzz words), does not really provide genuine insight into the problem – complexity, as a concept, does not of itself explain biological behavior. As Weinberg noted recently:[17] 'In the study of anything . . . including the study of complexity, it is only simplicity that can be interesting'. In the following sections, we attempt to provide a physicochemical interpretation of teleonomy.

Defining purpose in chemical terms

One of the primary goals of chemistry is to explain global properties of matter based on established chemical concepts. Thus, we can explain why ice is hard, why water is soft, and, based on that understanding, we can readily convert ice into water and vice versa. In fact, the principles governing the physical characteristics of the various states of matter and the relationship between those states is a relatively well-understood area of chemistry. In a similar vein, it would be most beneficial to be able to characterize the purposeful nature of living systems in conventional chemical terms. That would hopefully enable us to specify the kinds of chemical systems that would exhibit such a characteristic, as well as allowing us to specify the *minimal* chemical requirements for a system to exhibit purposeful behavior. That, ultimately, might even suggest possible paths toward the ultimate Holy Grail – the synthesis of simple living systems.

Let us begin by pointing out that when we speak about the purposeful nature of living systems we are actually making a statement about the *chemical reactions* of such systems that, at least in their totality, exhibit purposeful character. What chemically definable aspect of this complex set of reactions has led to our classifying the reaction set as a whole as purposeful? Before addressing this issue, let us briefly remind ourselves what governs 'regular' chemical reactions – the ones we characterize as non-purposeful.

The global explanation as to why *any* chemical reaction takes place is provided by the Second Law of Thermodynamics, namely, that any spontaneous irreversible chemical process takes place because the process leads to a global increase in entropy. Thus, the chemical explanation for why gasoline can react spontaneously with oxygen to yield carbon dioxide and water is that the reaction leads to an *increase* in global entropy.

On that basis, the reverse reaction cannot take place spontaneously because it would lead to a *decrease* in global entropy. Expressed in terms of an isolated system, we state that a physicochemical system is driven toward its lowest Gibbs energy (equilibrium) state. In other words, reactions that are explained by the thermodynamic directive are considered *non-purposeful*. Naturally, kinetic factors also affect chemical reactivity, but the influence of those factors is *secondary*. If a chemical reaction is *disallowed* thermodynamically, no combination of kinetic factors will enable that reaction to proceed. The bottom line: *chemical reactions are governed by both thermodynamic and kinetic directives, but the thermodynamic directives are primary, while the kinetic directives are secondary*.

Let us now consider the archetypal purposeful set of chemical reactions – those involved in cell replication. Needless to say for that reaction set the Second Law is fully obeyed. But as Schrodinger already pointed out in his classic book,[18] 'What is life?', there is something very puzzling about that reaction set. Living systems do not tend toward equilibrium (death), but rather maintain a far-from-equilibrium state. Furthermore, they can maintain that far-from-equilibrium state without disobeying the Second Law by the continuing exploitation of some external energy source. In fact, that unusual thermodynamic behavior is the *reason* we characterize that chemical system as purposeful – because our understanding of *why* those reactions are taking place is not based on the traditional thermodynamic explanation, but rather on the cell's agenda of multiplication. To exemplify, if we ask why a bacterial cell swims upstream in a glucose solution gradient, our initial answer is couched in teleonomic language (seeking food for itself), rather than in thermodynamic terms. In other words the Second Law, though applicable to all cell reactions, often provides little or no direct insight into the basis for cell behavior. Categorizing and generalizing cell behavior is more effective *when it is based on teleonomic considerations, rather than thermodynamic ones*.

Having said that, scientific inquiry requires us to seek understanding at its most fundamental level. So given the evident teleonomic character that is associated with all living systems, and which implies the operation of some directive that is *non-thermodynamic* in nature, can that directive be identified and understood in conventional physicochemical terms. As we now discuss, closer examination of the set of chemical processes that take place within a replicating cell can in fact reveal the nature of that non-thermodynamic directive.[19]

A small sample of *Escherichia coli* bacteria, when placed in a glucose solution with added salts, results in the rapid generation of billions of additional bacterial cells. That is the biological perspective. In chemical terms, however, the view is quite different. In chemical terms what has transpired is a series of chemical reactions of glucose. Approximately 40% of the glucose has been converted to (living) cellular material, the thermodynamically less stable but kinetically preferred product, while the remaining 60% of the glucose has been oxidized to carbon dioxide and water, the thermodynamically more stable product.[20] At first sight, this product bifurcation might seem to signify competition between kinetically and thermodynamically controlled reaction pathways of the glucose reactant, in that both kinetic and thermodynamic products are formed. But this is not the case. In reality, the process is strictly controlled by the kinetic pathway and the two pathways are *not* in competition with one another, but are actually coupled. The exergonic energy producing process of glucose oxidation to carbon dioxide is coupled to the endergonic process of cellular material production enabling that latter, thermodynamically unfavored process to take place. Thus, the biological process of cell multiplication involves chemical processes in which *just sufficient oxidation of glucose to carbon dioxide occurs to cover the free energy requirements of the complex process of cellular material synthesis*. In other words, for the process of cell multiplication, the primary directive is *kinetic* rather than *thermodynamic*; the thermodynamic component of the reaction pathway (carbon dioxide formation) is secondary, *and is present in just the right amount to power the energetic requirements of the kinetic* (*replicative*) *pathway*. Thus, in contrast to what one finds for regular (non-teleonomic) chemical reactions, the relative importance of the kinetic and thermodynamic directives appears to have *inverted*.[19] Whereas in regular chemical processes, the thermodynamic directive is the primary one with kinetic directives playing a secondary role, for cell replication it is the *kinetic* directive that is primary, with the thermodynamic directive now playing the secondary and supportive role. In some manner that we will subsequently discuss, the process of emergence that led from some simple prebiotic chemical system to the complex chemical aggregates we term life, has inverted the relative importance of the two physicochemical directives – kinetic and thermodynamic. Note however *that it is this inversion of kinetic and thermodynamic directives that has induced the pattern in cell behavior that we term purposeful*. Thus, we believe we have identified the non-thermodynamic directive in cell chemistry that has led to the pattern of behavior we term purposeful – it is the *kinetic* directive.

So how could a system, whose primary directive was thermodynamic, become transformed into one whose primary directive is now kinetic? In order address this key question, we now need to consider the concept of stability in chemistry, and in particular, to note that in the context of a chemical system there are *two* distinct types of stability.

The nature of stability

In general usage, the term ‘stability’ means ‘persistent, unchanging with time’, but from a chemical perspective there are two kinds of stability which can give rise to persistent character.[21] In the inanimate world, the stability we generally refer to is *thermodynamic stability*. In that world, all chemical systems are driven toward their thermodynamic sink, and their reactivity is related to that type of stability – the more stable the system, the less likely the system is to react. Of course, once a system has reached its thermodynamic sink it will cease to react – it has reached its lowest Gibbs energy state.

However, as we have described previously, the stability of replicating systems is of a distinctly different kind, one we would term a *dynamic kinetic stability*.[21] Replicating systems are stable, not because they do not react, rather because they do! They react to make more of themselves and at a rate that may be exponential. Thus, one single molecule that undergoes just 79 acts of replication would become a mole of material ($2^{79} \sim 6.10^{23}$). Of course, given this extreme kinetic driving force, unchecked replication is unsustainable and, at best, the replicating system at some point reaches a steady state, that is, a dynamic state where the rate of generation and the rate of decay more or less balance out.[22] A long-standing simple kinetic Scheme [23] that describes that steady state situation is illustrated:

$$\frac{dX}{dt} = kMX - gX \qquad (1)$$

where X is the replicator concentration, M is the concentration of molecular building blocks from which X can be built up, 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 $dX/dt = 0$). So the stability of replicating entities is also one of persistent presence, but one that is *dynamic*, not static, much like a water fountain that is persistently present (stable), but in which the constituent water is constantly being turned over. Accordingly, replicator stability applies in a *population* sense, rather than in an *individual* sense. Note that dynamic kinetic stability can be readily quantified – the larger the steady state population of replicators, the greater their kinetic stability. The size of the replicator population is thus a simple but effective measure of its kinetic stability, at least at any given point in time.[21]

Remarkably, dynamic kinetic stability, despite its dynamic nature, can be high, and may easily surpass the static thermodynamic stability of supposedly stable non-replicating systems. Consider Mt Everest, for example. We might be inclined to think that a mountain is a highly stable entity. Well, given that Mt. Everest is thought to be some 60 million years old that view would seem to be confirmed. But consider an ancient life form, such as cyanobacteria. Cyanobacteria are believed to have existed on earth for some 3.5 billion years with little change having taken place in the species over that enormous period of time.[24] Thus, one would have to conclude that the stability of cyanobacteria is actually orders of magnitude *greater* than that of Mt. Everest, as measured by the time these two entities have existed. The conclusion is clear – dynamic kinetic stability, though quite distinct in its nature to (static) thermodynamic stability, is an important kind of stability and is therefore likely to govern the nature of observable chemical entities. Eschenmoser *et al*.[25] recently expressed the same basic idea: ‘Thermodynamic functional selection (by base pairing) would appear as a forerunner of kinetic functional selection (by replication), exemplifying on the chemical level one of biology’s major lessons, namely, that replication can substitute for thermodynamic stability when continuance is at stake’. It is no wonder then that when we look around us we see as many examples of kinetically stable entities (life) as we do thermodynamically stable ones (non-life). Based on this view, we can characterize life as a *kinetic state of matter*, in contrast to the thermodynamic states that dominate the inanimate world. We believe this characterization to be of value in that it helps clarify what it is that unites these two worlds, as well as what separates and distinguishes them. As we now discuss, such characterization has dramatic chemical consequences.

Selection rules for chemical change

We have noted above that the nature of stability for 'regular' chemical systems compared with replicating systems is fundamentally distinct. What that means however is that the *selection rules* that govern chemical transformations for the two kinds of systems in their respective spaces are also different.[26] In regular chemical space, that is, the space that includes all inanimate systems, the selection rule is familiar – from thermodynamically less stable to thermodynamically more stable, in accordance with the Second Law. But the selection rule in replicator space, the space that includes all replicating systems, is based on kinetic stability, that is, *transformations in replicator space tend to be from kinetically less stable to kinetically more stable*. The role of thermodynamics in such processes cannot, of course, be ignored and will be discussed subsequently, but let us just say at this point that it has been delegated to a secondary role.

A simple illustration described by Lifson some years ago exemplifies the kinetic stability selection rule.[27] Lifson pointed out that two molecular replicators, X_1 and X_2, competing for the same building blocks M, and each following the kinetic scheme of Eqn (1) cannot co-exist – the value of either X_1 or X_2 drops to zero, that is, *the kinetically more stable replicator drives the second replicator – the kinetically less stable one, into extinction*. This pattern whereby the kinetically more stable replicator drives the less stable one into extinction is, of course, just the biological process of natural selection at the chemical level. It suggests that Darwinian 'survival of the fittest' is just the biological expression of a more general chemical principle: *when a number of replicating systems – chemical or biological – compete for the same limited resources, there will be a general tendency for kinetically more stable replicators to replace kinetically less stable ones*. Thus, the biological term *less fit to more fit*, when translated into physicochemical terminology, becomes *kinetically less stable to kinetically more stable*. Furthermore, Darwinian natural selection is just a specific form of chemical selection – kinetic selection. Thus, biology can be viewed as a specialized area of chemistry – replicative chemistry, whose detailed chemistry is only now beginning to be explored.

Let us now clarify the special kinetic-thermodynamic interplay as it applies to replicating systems, since kinetically directed processes must necessarily take place under the watchful eye of the Second Law. For molecular replication, the directive for the reaction, as for any other individual chemical reaction, is *thermodynamic*, meaning that a replicating molecule when mixed with its building blocks will only replicate as long as the reaction is thermodynamically allowed. Once equilibrium concentrations of replicating molecule and its building block components are reached, the reaction ceases. Thus, being under thermodynamic control we would necessarily classify molecular replication as non-purposeful. Both the reason that the molecular begins to replicate, and the reason it ceases to replicate, are expressed in thermodynamic terms.

In contrast, when we consider a cellular replicator we see a system that is indeed highly kinetically stable through its prodigious ability to make copies of itself. However, despite its high kinetic stability, that particular chemical system is far from equilibrium and hence *thermodynamically* unstable – without an external source of energy it cannot maintain that far-from-equilibrium state and would therefore rapidly decay (die). The distinction then between the molecular replicator and the cellular replicator is that the former follows the thermodynamic directive, while the latter, being metabolic, and therefore less constrained by thermodynamic factors, does not. By possessing an energy-gathering capability, that replicating cell can 'circumvent' thermodynamic constraints. What this boils down to is that the incorporation of a metabolic capability into a non-metabolic replicating entity *would convert it from being thermodynamically directed to kinetically directed, from being non-purposeful to being purposeful*, at least as we have defined it.[19] What we believe this means is, therefore, that teleonomic (non-thermodynamic) behavior would have likely commenced the moment a metabolic capability was incorporated into a non-teleonomic (thermodynamic) replicator. But if indeed life emerged through the transformation of a non-metabolic replicator (lacking purpose) into a metabolic one (that acts purposefully), how would such a transformation have come about? By what chemical principles could such a transformation be explained? Being a historic event, we may never know the actual historic process that transformed a thermodynamic replicator into a purposeful kinetic one (if that is indeed what happened – see Reference [1]). But a model process that would illustrate that transformation can be outlined, and in particular, can reveal why in a general Darwinian scheme such a process could be expected to occur.

Consider a molecular replicator X_P formed by mutation from X that also happens to possess photoacceptor properties ($P = $ photoacceptor). X_P being both replicative *and* possessing an energy-gathering capability, would be less bound by thermodynamic constraints than X, a simple replicator. To the extent that the replication reaction of X_P would be assisted by energy input, its structure would enable the necessary energy to be gathered through photochemical excitation. In other words, X_P could be expected to be a more effective replicator, that is, kinetically more stable than X due to its energy-gathering capability. *Accordingly, the transition from a pre-metabolic X to a (mutated) metabolic X_P would be expected to be kinetically selected for* – a favorable transition in replicator space leading to the emergence of a kinetically directed system from a thermodynamically directed one. But that particular structure, being one that is kinetically, rather than thermodynamically directed, *is one we would now classify as teleonomic*. It would no longer be the thermodynamic factor that controls the reaction path of that particular system. The significance of this crucial step cannot be overstated: *It would be through the incorporation of a metabolic capability, whether chemical or photochemical, that would enable thermodynamic impediments on replicative capability to be largely circumvented, and would lead from an objective replicator to a purposeful one*. Importantly, since such a transformation would lead to an increase in kinetic stability, it would be selected for. In fact, once a replicating entity would have incorporated an energy-gathering capability of whatever kind, the door to an entire new region of replicator space would have opened up. Given that the far-from-equilibrium regime of replicator space is where the kinetically most stable replicators happen to be located, access to that region of replicator space would lead to an enormously wide range of successful, purposeful replicators – what we term life.

CONCLUDING REMARKS

This review has attempted to demonstrate that living and non-living systems can be more readily accommodated within a single unifying framework through a physicochemical analysis of 'purpose'. By classifying living systems as dynamic kinetic states of matter, we have attempted to show that a clearly defined physicochemical relationship between animate and inanimate can be established. Thus for inanimate systems, structural and reactivity characteristics are primarily governed by thermodynamic considerations, while the structural and reactivity characteristics of animate systems are governed primarily by kinetic considerations. The purposeful nature of all living systems can be shown to derive directly from this fundamental difference. Thus just as chemistry can explain the hardness, softness or shininess of a substance, we suggest that the purposeful character of living things can also be understood in standard chemical terms.

Key elements in our analysis may be summarized as follows:

(a) Due to the unique kinetic character of the replication reaction (capable of exhibiting exponential growth rates), transformations of replicating systems are likely to follow different selection rules compared to transformations of 'regular', non-replicative systems. The predominant selection rule in replicator space, being kinetic rather than thermodynamic, results in a number of distinct characteristics of replicating systems. Of those various characteristics, purposeful character is the most striking.

(b) The dynamic nature of the kinetic stability that is associated with replicating systems explains a number of the special characteristics of living things. In particular, why is the conversion of a living system to a non-living one so facile, while reversing the process (i.e., synthesizing life) is so deep within the realms of the unknown? Some initial thoughts on this conundrum can be offered. Life cannot be synthesized by simply mixing the chemical ingredients from which life is composed. Simple mixing of life's molecular ingredients will only create a *thermodynamic* aggregate (non-living), whereas life is a *dynamic kinetic* aggregate and therefore quite distinct. The distinction may be made clearer with a physical analogy. What is the difference between a juggler juggling several balls (a metaphor for life) and a juggler merely standing next to those balls (a metaphor for non-life)? Compositionally, the two systems are identical, but reflect two very different states of the one system. How does one convert the non-juggling state to the juggling state and vice versa? Needless to say, converting the juggling state to the non-juggling state is easy – a hefty push is all that is required. But the reverse process is more complicated. One cannot create a juggler juggling several balls by just giving all the balls to the juggler (the equivalent of mixing). The juggling state in which all balls are juggled simultaneously needs to be accessed in *a precise, step-wise manner*. First, two balls are juggled, a third is then added in a suitable manner, then a fourth, etc., until all balls are in dynamic play. In order to achieve the dynamic juggling state, that state has to be accessed in a deliberate, step-wise, and controlled manner. Of course, at any point in time, the low energy non-juggling state can be readily re-accessed – the fragile and finely balanced juggling state is susceptible to degradation to the non-juggling state at each and every step. Accordingly, we suggest that any proposal for the synthesis of the simplest living system will need to be based on the above considerations, that is, on *a step-wise process of kinetic aggregation* beginning with some simple replicator, from which more complex ones would then be formed in a step-wise manner, with a key step being the incorporation of a metabolic capability, either chemical or photochemical, into the replicating entity. Given the fragility of dynamic kinetic states in general, it is evident that the difficulties in the synthesis of life, on this score alone, will be formidable! The general role of complexity in governing replicator kinetic stability was discussed in an earlier publication.[28]

(c) Given the difficulties in defining life, the question at what point in time life began is clearly one that cannot be answered with any precision. But considering the centrality of purpose to the characterization of living systems, we would propose a practical working description of minimal life based on the teleonomy concept. Once a replicator that we would classify as non-purposeful was transformed into a purposeful one, we would venture to say that a non-living system was transformed into a living one. On the basis of the foregoing discussion, that transformation can be outlined in chemical terms. The moment some thermodynamic replicator would have acquired, through a process of kinetic selection, an energy-gathering capability, it would have become 'alive'. At that point, a system that was capable of circumventing thermodynamic constraints in order to further the 'dream', would have been generated. That was the point in time in which the replicating system, whose historic structure we may never know, began to operate according to a perceived agenda – the agenda of replication.

(d) Despite recent attempts to argue that biology cannot be reduced to physics and chemistry, that biology is an autonomous science that rests on a separate philosophy of biology,[5] the ultimate goal of unifying the sciences remains. Just as we continually seek to reduce chemistry to physics, there must be the parallel drive to reduce biology to chemistry, that ultimately biology must be an extension of chemistry. In that light, it is satisfying to note that our analysis indicates that teleonomy, the most fundamental of all living characteristics, can be given clear physicochemical expression. Moreover, all the fundamental Darwinian concepts that lie at the heart of modern biology can be seen to derive directly from basic chemical principles. Thus, Darwinian *fitness* when translated into chemical terms is just *dynamic kinetic stability*, *survival of the fittest* is just the drive toward *greater kinetic stability*, and *natural selection* is just *kinetic selection*. In a fundamental sense then, biology can indeed be viewed as an extension of chemistry – a complex form of *replicative chemistry*. One of the current challenges in chemistry is to map out this relatively unknown area of chemistry, to delineate the rules governing simple replicating systems beyond the single molecule, by which we mean small replicating aggregates and minimal replicating networks. It is precisely a detailed understanding of these minimally complex replicating systems that may help bridge the yawning conceptual chasm that still separates the living from the non-living.

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REFERENCES

[1] For a recent discussion on the replication first – metabolism first issue, see: A. Pross, *Origins Life Evol. Bios.* **2004**, *34*, 307–321.
[2] For an alternative view, see: R. Shapiro, *Quart. Rev. Biol.* **2006**, *81*, 105–125.
[3] G. M. Whitesides, *Chem. Eng. News* **2007**, *85*, 12–17.
[4] C. S. Pittendrigh, in (Eds: A. Roe, G. G. Simpson), *Behavior and Evolution*, Yale University Press, New Haven, **1958**, pp. 390–416.
[5] E. Mayr, *Toward a New Philosophy of Biology*, Harvard University Press, Cambridge, **1988**.
[6] T. Dobzhansky, F. J. Ayala, G. L. Stebbins, J. W. Valentine, *Evolution*, Freeman, San Francisco, **1977**.
[7] S. A. Kauffman, *Investigations*, Oxford University Press, Oxford, **2000**.
[8] J. Monod, *Chance and Necessity*, Random, New York, **1972**.
[9] For a discussion on life definitions, see, for example, C. E. Cleland, C. F. Chyba, *Orig. Life Evol. Biosp.* **2000**, *32*, 387–393.
[10] J. Joyce, in (Eds: D. W. Deamer, G. R. Fleischaker), *In the foreword of 'Origins of Life: The Central Concepts*, Jones & Bartlett, Boston, **1994**.
[11] *Noa Pross, private communication.*
[12] S. R. Bolsover, J. S. Hyams, S. Jones, E. A. Shephard, H. A. White, *From Genes to Cells*, Wiley, NY, **1997**.
[13] D. Freifelder, *Molecular Biology*, Jones & Bartlett, Boston, **1983**, p. 18.
[14] *Cited in Reference [8], p. 20.*
[15] R. G. Parr, *J. Phys. Chem. A* **2005**, *109*, 3957–3959.
[16] See also: R. G. Woolley, *J. Amer. Chem. Soc.* **1978**, *100*, 1073–1078.
[17] S. Weinberg, *NY Review Books*, **2002**, *49*(16), NYREV Inc., NY.
[18] E. Schrodinger, *What is Life? The Physical Aspects of the Living Cell*, Cambridge University Press, Cambridge, **1944**.
[19] A. Pross, *Orig. Life Evol. Biosph.* **2005**, *35*, 383–394.
[20] *Reference [8], p. 19.*
[21] A. Pross, *Pure Appl. Chem.* **2005**, *77*, 1905–1921.
[22] A. Pross, *J. Theor. Biol.* **2003**, *220*, 393–406.
[23] A. J. Lotka, *J. Phys. Chem.* **1910**, *14*, 271.
[24] L. Margulis, *Symbiosis in Cell Evolution*, Yale University Press, New Haven, **1981**.
[25] K-U. Schoning, P. Scholz, S. Guntha, X. Wu, R. Krishnamurthy, A. Eschenmoser, *Science* **2000**, *290*, 1347–1351, Reference [26].
[26] A. Pross, V. Khodorkovsky, *J. Phys. Org. Chem.* **2004**, *17*, 312–316.
[27] S. Lifson, *J. Mol. Evol.* **1997**, *44*, 1–8.
[28] A. Pross, *Orig. Life Evol. Biosph.* **2005**, *35*, 151–166.