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The Driving Force for Life's Emergence: Kinetic and Thermodynamic Considerations

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The principles that govern the emergence of life from non-life remain a subject of intense debate. The evolutionary paradigm built up over the last 50 years, that argues that the evolutionary driving force is the Second Law of Thermodynamics, continues to be promoted by some, while severely criticized by others. If the thermodynamic drive toward ever-increasing entropy is not what drives the evolutionary process, then what does? In this paper, we analyse this long-standing question by building on Eigen's "replication first" model for life's emergence, and propose an alternative theoretical framework for understanding life's evolutionary driving force. Its essence is that life is a *kinetic* phenomenon that derives from the kinetic consequences of autocatalysis operating on specific biopolymeric systems, and this is demonstrably true at *all* stages of life's evolution — from primal to advanced life forms. Life's unique characteristics — its complexity, energy-gathering metabolic systems, teleonomic character, as well as its abundance and diversity, derive directly from the proposition that from a chemical perspective the replication reaction is an *extreme expression of kinetic control,* one in which thermodynamic requirements have evolved to play a supporting, rather than a directing, role. The analysis leads us to propose a new sub-division within chemistry — *replicative chemistry*. A striking consequence of this kinetic approach is that Darwin's principle of natural selection: *that living things replicate, and therefore evolve*, may be phrased more generally: *that certain replicating things can evolve, and may therefore become living*. This more general formulation appears to provide a simple conceptual link between animate and inanimate matter.

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Introduction

The nature of the driving force that led to the emergence of animate matter remains a subject of continuing debate and uncertainty. What physico-chemical principles led to the emergence of biological complexity, to the formation of increasingly complex far-from-equilibrium systems exhibiting purposeful structure and behavior? And given that it is the Second Law of Thermodynamics that governs the direction that *all* spontaneous processes must necessarily follow, how do these principles relate to the Second Law? One reason for much of the confusion that has enveloped this fundamental issue derives from the fault line that continues to separate biology and physics. The "autonomy of biology" approach to science, invoked some 200 years ago by Kant (1952) with his "natural purpose" concept, and reinforced by modern biologists such as Mayr (1988), had the unintended effect of impeding attempts to provide a physical

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understanding of the evolutionary process that led to biological complexity. But the magnitude of the problem of bridging between biology and physics cannot be overstated: there is considerable inherent difficulty in applying physical principles, generally developed for model systems of limited complexity, to biological systems that are characterized by complexity of overwhelming proportion. Dawkins' (1986) opening line in *The Blind Watchmaker* says it succinctly: "We animals are the most complicated things in the known universe." Nonetheless, despite the obvious difficulties, the need to place biological reality and its emergence within a context of physical law needs to be addressed.

In discussing biology and thermodynamics, we need to distinguish between two quite different issues: (a) the relationship between the *operation* of living systems and the Second Law, a problem that was resolved a century ago, and (b), the *process* by which that complexity emerged, an issue which remains highly contentious. The first issue — the functional operation of living systems — poses no thermodynamic dilemma because the complex, far-from-equilibrium nature of living systems is maintained through the continual utilization of energy, be it solar or chemical. But how did far-from-equilibrium systems emerge in the first place? A significant advance in our ability to understand the emergence of non-equilibrium complexity took place some 50 years ago when Schrödinger (1944), Bertalanffy (1952), and then Prigogine (1978), laid down the foundations for non-equilibrium thermodynamics and the characterization of living systems as "*dissipative structures*". This base has since served as the central element in the development of what has been termed the new evolutionary paradigm (Wicken, 1985, 1989, 1998; Wiley & Brooks, 1982; Schneider and Kay, 1994; Swenson, 1997). According to this paradigm, the emergence of ordered, far-from-equilibrium, energy dissipating systems poses no thermodynamic mystery, since it is a physically allowed response of an equilibrium system reacting to some perturbing potential. However, over the period of time that these ideas have been proposed, persistent dissenting voices have also sounded (see, for example, Weber *et al*., 1988; Elitzur, 1994; Peacocke, 1989; Thaxton *et al*., 1984, pp. 151–152; Corning & Kline, 1998a). One of the responses of the scientific community to this scientific deadlock has been to widen the arena of discourse. Thus, in parallel, the debate has expanded so as to incorporate concepts from information theory (Küppers, 1990), systems analysis (Corning & Kline, 1998a; Conrad, 1997), mathematics and computer science (Kauffman, 1993, 2000), even engineering (Corning & Kline, 1998b) — sciences whose epistemological frameworks might provide additional tools for addressing the highly complex nature of living systems. However as the above-cited literature makes clear, the issue remains controversial and far from resolved.

In this paper, we address the problem of emergence from a chemical perspective, building on Eigen's (1971, 1992) kinetic approach initiated some 30 years ago, rather than on the physical perspective that characterizes much recent work. That recent work accepts the highly complex nature of living systems and the non-linear dynamics associated with that physical complexity as a given (e.g. Kauffman, 1993, 2000; Conrad, 1997; Corning & Kline, 1998b), indeed the very element that requires explanation, and therefore tackles the problem from that point of view. But as we will discuss in more detail below, by examining the evolutionary process at its earliest stages, we believe that much of the difficulty associated with this inherent complexity can be avoided. Secondly, following Eigen, we believe a *chemical* approach to be instructive simply because living systems are first and foremost *chemical* systems, whose description and governing principles should be explicable in chemical terms. It is the discipline of chemistry that bridges between biology and physics, and, with the benefit of hindsight, it is of less surprise that attempts to merge between the disciplines of biology and physics have run into the difficulties they have. Thermodynamics, though formally an integral part of physical science, does have its *chemical* aspects and orientation. Our analysis suggests that the role played by an element we term the kinetic imperative, though part of the evolutionary debate since Darwin, has not been adequately recognized. We will attempt to demonstrate that

life's unusual characteristics derive from *dynamic* rather than *thermodynamic* considerations, and that a broader perspective on the Darwinian principle may result when emergence and evolution are viewed through such a kinetic perspective.

Discussion

The Second Law of Thermodynamics, a fundamental tenet of physics and chemistry, requires that in an isolated system all transformations proceed irreversibly toward a state of equilibrium, that state being defined as one of maximum entropy. In living systems however, we see a thermodynamic pattern that is striking and unusual. Though of course living systems fully obey the Second Law, all living entities are far-from-equilibrium systems that constantly consume energy in order to maintain the far-from-equilibrium state so essential for life. For example, non-equilibrium ion concentration gradients, both within the cell and between the cell and its environment, are maintained by the action of ion pumps that consume considerable metabolic energy in order to pump ions against the concentration gradient. Key physiological functions, such as nerve cell transmission, crucially depend on the maintenance of such non-equilibrium concentration gradients (Bolsover *et al.*, 1997).

Of course, as already noted, living systems do not violate the Second Law since living systems exist in a situation of material and energy exchange with their environment. So just as a refrigerator, by the consumption of energy, can transfer heat from a cold region to a hotter one, against the natural thermodynamic direction, so living systems can create order from disorder, and maintain themselves in a far-from-equilibrium state, through the constant utilization of energy — from food in the case of animals, or solar energy in the case of plants.

But appreciating that living systems are functional thermodynamic entities that do not violate the laws of thermodynamics does not in itself resolve the dilemma. Indeed the starting point for the half century long debate began with the realization that the function of living beings are fully consistent with the laws of thermodynamics. Living systems still appear highly improbable and extremely surprising, as the refrigerator analogy makes clear. A refrigerator exists because it has been designed and built to function in a manner that counters the natural thermodynamic direction whereby heat flows from hot to cold. The reasons for its existence and function are inseparable. But how does one explain the emergence of a *natural* system that from a thermodynamic viewpoint seems to mimic refrigerator behavior? What general principle can explain the emergence of a highly complex system that taps into some external energy source — be it solar or chemical, in order to maintain its far-from-equilibrium state? Indeed, several of the noted physicists of the early 20th century argued that the laws of physics were inadequate for explaining biological phenomena. Schrödinger (1944) exemplifies this view when he observed in his book, *What is Life*? "that we must be ready for the fact that living matter works in a way that cannot be reduced to the usual physical laws".

There are other distinct characteristics of living systems that need to be addressed in the context of explaining life's emergence. Monod (1972), Dobzhansky *et al.* (1977), Küppers (1990) and others, have pointed out that life's direction is governed by its teleonomic character — that undeniable sense of purpose associated with the *behavior* and *organization* of living beings. As Dobzhansky (Dobzhansky *et al.*, 1977, p. 95) put it: "Purposefulness, or teleology, does not exist in nonliving nature. It is universal in the living world. It would make no sense to talk of the purpose or adaption of stars, mountains, or the laws of physics. Adaptedness of living beings is too obvious to be overlooked." Thus, life's unique teleonomic character, expressed by Jacob as the "dream" of every cell to become two cells (quoted in Monod, 1972, p. 20), seems intimately linked to life's unusual thermodynamic behavior. Indeed it is evident that the evolutionary process has equipped living entities with the ability to exploit the rules of thermodynamics to maximum advantage so as to enable them to pursue their teleonomic goals as efficiently as possible. Monod considered the very existence of this teleonomic character as a "flagrant epistemological contradiction", and

went so far as to state: "In fact the central problem of biology lies with this very contradiction, which if it is only apparent, must be resolved; or else proven to be utterly insoluble, if that should turn out to be the case." Dobzhansky expressed the same sentiment: "The origin of organic adaptedness, or internal teleology, is a fundamental, if not the most fundamental problem of biology". Given the modern view that all living beings are physico-chemical systems that are merely following the laws of physics and chemistry, this teleonomic character must have some physico-chemical rationale, whose essence needs to be identified.

THE NON-EQUILIBRIUM THERMODYNAMIC APPROACH

In the past half century, new insights into the problem of emergence of biological complexity were obtained by extending the thermodynamic domain from equilibrium systems to non-equilibrium ones (Bertalanffy, 1952; Prigogine, 1978; Peacocke, 1989; Babloyantz, 1986; for more recent treatments, see: Weber *et al.,* 1988, Schneider & Kay, 1994; Swenson, 1997). When a system at equilibrium is perturbed by some external force, small random fluctuations are induced that can amplify dramatically and lead to spontaneous self-organization and order — so-called "dissipative structures". According to this view, living beings are not unique in their highly organized non-equilibrium state. Living beings simply represent one particular class of organized complex systems far-from-equilibrium, that are able to maintain their highly ordered structure by the constant transfer of energy and matter between the system and its environment. Thus, according to this approach the emergence and existence of complex non-equilibrium biological systems poses no thermodynamic dilemma — life's unusual thermodynamic character is explained by its characterization as a dissipative structure.

While the non-equilibrium thermodynamic approach does remove some of the mystery regarding the very existence of biological complexity in its far-from-equilibrium state, there is continuing and persistent opposition to its central claim (see, for example, Peacocke, 1989; Weber *et al.*, 1988; Elitzur, 1994; Corning & Kline, 1998a; Collier, 1988; Thaxton *et al.*, 1984). Firstly, the categorization of life as a dissipative structure appears too general. Biological systems are clearly different to dissipative structures, such as heated liquids and whirlpools, with which they are compared. Dissipative structures tend to be relatively transient, generally form in response to some immediate perturbation, and are characterized by *order.* In contrast, the existence and function of each and every biological system on the planet today, be it single or multi-cell, is characterized by *organization* (rather than *order*), and is directly linked to events that took place almost four billion years ago. Thus the highly intricate and organized complexity of biological systems, one based on heritable coded information, makes biological complexity unique and quite distinct from the relatively transient and "arbitrary" order of typical non-biological dissipative structures.

But even if we accept the theoretical basis for the thermodynamic paradigm, a serious difficulty remains. Modeling living systems on dissipative structures fails to provide insights into the nature of biological function, and, in particular, into the specific processes by which that function emerged. As Collier (1988, p. 231–232) has pointed out, there is no evidence that the laws of non-equilibrium thermodynamics apply to biological systems in a *non-trivial* fashion. Also it should be noted that the other striking life characteristic discussed earlier — teleonomy — finds no resolution within the dissipative structure approach. Corning & Kline (1998a), for example, have recently pointed out that life's teleonomic character is not derivable from the Second Law nor from any of its thermodynamic parameters.

In the last two decades, attempts have been made to overcome the above-mentioned deficiencies of the non-equilibrium approach by focussing on features that characterize biological systems specifically — in particular *information*, and incorporating them into a thermodynamic description (Wiley & Brooks, 1982). However, the thermodynamic problem was greatly magnified by the introduction of information into the physically grounded discourse. The concept of entropy had now to accommodate, not just an

energetic and statistical aspect, but an informational one as well. As a result, attempts to merge these various concepts seem to have led to even greater confusion. Thus argument regarding the distinction between *order* and *organization*, the various definitions of entropy — some mutually contradictory, and the conflicting thermodynamic treatments of information, have all conspired to create a thermodynamic paradigm whose derivation and particulars remain uncertain. The problem may be summarized as follows: attempts to apply rigorously defined physical parameters, derived from well-defined physical systems, to the broad sweep of highly complex biological systems, where the corresponding parameters are not readily quantifiable, and in some cases are not even definable, remain theoretically controversial. These sentiments are reflected in Corning and Kline's (1998a) detailed critique of the thermodynamic paradigm that concludes: "Monolithic thermodynamic theories of evolution are fundamentally flawed…" Interestingly, using insights from cosmology, Layzer (1988) has also concluded that the Second Law is not the driving force responsible for life's emergence, though his analysis does lead him to support the Wiley and Brooks view that entropy and information do indeed grow together. We would conclude therefore by saying that the non-equilibrium thermodynamic framework, while able to resolve the apparent paradox inherent in the very existence of non-equilibrium biological systems, fails to provide fundamental insights into the evolutionary process by which biological complexity emerged.

In an attempt to provide some alternative description of the evolutionary driving force, there is one additional characteristic of life beings that needs to be mentioned. We are referring to the diversity and widespread nature of living beings. As one looks over the planet, it is evident that life in one form or another has overwhelmed it — a fact that Darwin was already well aware of over 150 years ago. We are not referring here to just plant, animal and marine life that may be found on most parts of the planet, but in particular to microbial life. As pointed out by Gould (1996), life is extraordinarily abundant. A small sample of garden soil might contain billions of microbes belonging to thousands of different species, a square centimeter of our skin might house some 10^5 microbes, and it has been estimated that fully 10% of a human body's dried weight consists of bacteria, many of which we cannot survive without. The growing awareness of the existence of a class of bacteria termed extremophiles that survive without difficulty in extreme environmental conditions, such as high salinity, high pressure, high and low temperatures, etc. are further evidence for life's extraordinary adaptability. Indeed, in a memorable comment Gold (1992) has stated: "Microbial life exists in all the locations where microbes can survive." Simply put, at least with respect to our planet, life is almost everywhere. Thus, the unusual thermodynamic characteristics of living beings mentioned earlier, manifest themselves within one of the most widespread set of chemical reactions on the face of the earth — the metabolic reactions of life. So given the increasingly widespread view that the emergence of biological complexity is *not* a direct manifestation of the Second Law, what *is* the physical principle or principles that can be considered responsible for the emergence and maintenance of biological complexity? Can we identify some *non-thermodynamic* factor that is operational, one that drives the evolutionary process in a way that is *consistent* with the Second Law without actually being *directed* by it.

THE POWER OF REPLICATION

Living systems are no more than a manifestation of a set of complex coordinated chemical reactions, and, as such, are governed by the rules of kinetics and thermodynamics, just as for any set of chemical reactions. The Second Law tells us that any isolated chemical systems will tend toward a state of equilibrium, though the *rate* at which this equilibrium may be attained will be governed by kinetic (i.e. non-thermodynamic) factors. Accordingly, both kinetic *and* thermodynamic factors affect chemical reactivity and in many cases compete with one another. It is therefore not uncommon for thermodynamically less stable products to be formed preferentially over thermodynamically more stable ones — at

least in the short (defined liberally) term. Thus we speak of chemical reactions as proceeding under either *kinetic* or *thermodynamic* control, though clearly even in the case of kinetic control, it is still the thermodynamic directive that drives the reaction forward. Hence given the importance of kinetic considerations in determining what chemical processes will actually take place, can we identify some *kinetic* characteristic of the prebiotic reaction(s) that might have encouraged the early chemical processes that led to life's emergence.

Some 30 years ago Eigen (1971, 1992) proposed that the first step toward life began with the appearance of a replicating molecule, which then evolved by a process of *imperfect replication* and *chemical selection* into early life forms. Eigen's ideas have served as the basis for the "replication first" school of thought that holds that a simple molecular replication reaction was the first step on the long road to life. Now if, as Eigen has suggested, the first step along the road to life indeed began with a primal replicating molecule, then inspection of its characteristics may provide insights as to what is unique about the *entire* set of life reactions. Indeed, Eigen (1992), Lifson (1997) and others have pointed out that the replication reaction, being autocatalytic, has unique kinetic properties and constitutes the ultimate example of a kinetically driven reaction. Lifson (1997) has provided a numerical example that makes the point vividly. Consider the two reactions:

$$A + B \xrightarrow{X} C, \tag{1}$$

$$A + B \xrightarrow{X} X. \tag{2}$$

Reaction (1) is just a general representation of *any* chemical process — reactants A and B are converted into C through the catalytic effect of X. By contrast, reaction (2) — the molecular replication reaction, is an *autocatalytic* reaction, in which the catalyst X converts A and B into more of itself. For reaction (1), if we assume a single molecule of catalyst X and an arbitrary reaction rate of 10^{-6} s/molecule, a period of 6×10^{17} s (derived from $6 \times 10^{23} \times 10^{-6}$ s) or 20 *billion years* would be required in order to generate a mole of product, C. On the other hand for reaction (2), due to the enormous kinetic power of replication, *it would take just a tiny fraction of a second for a mole of product, X, to be generated!* The mathematics of replication is such that a single replicating molecule undergoing some 79 acts of replication becomes a mole ($6 \times 10^{23} \approx 2^{79}$), so in the above example it would take just 79×10^{-6} s for a molecule to become a mole. The relative magnitude of these two figures, 20 *billion years* for catalytic reactivity and 79 μs for autocatalytic reactivity, though dependent on the particular reaction parameters that are chosen, is striking and makes it clear that the enormous kinetic potential associated with the replication reaction places it in a unique kinetic category. Thus the *kinetic* pathway leading to molecular replication is likely to be favored over any competing pathway, even if the rate of replication is many orders of magnitude *slower* than the rates of the competing routes. The autocatalytic replication reaction, by its very nature, is an extreme expression of kinetic control, and will tend to overwhelm any competing reaction, thermodynamically preferred or not. Note that the above analysis does not require us to *identify* that early replicating entity — only to characterize it as one capable of undergoing that replication reaction.

Of course, the remarkable kinetic power of replication is not just applicable to replicating molecular species. A single bacterium placed in a suitable medium will also replicate and make billions of copies of itself very quickly. And if we consider multi-cell systems, the underlying mathematics is exactly the same, as Malthus already noted two centuries ago with respect to the earth's human population. In other words, once any form of matter, present in either microscopic or macroscopic quantities, and capable of replication (or reproduction) begins to do so, we are entering a kinetic world of awesome power, one that is in a unique class of its own. Recent kinetic analyses of the replication reaction, which consider sub- and super-exponential growth, in addition to regular exponential growth (Lifson & Lifson, 1999; Szathmary & Maynard Smith, 1997) do not significantly change the qualitative picture.

In practice, of course, visible manifestation of the unique kinetic power of replication, is not

always apparent, and can frequently lie dormant. Any replication reaction cannot and does not follow the exponential kinetic course for very long — resources will be exhausted very quickly. In that sense it differs from other processes, such as nuclear fission and crystallization from a supersaturated solution, which follow the same "explosive" kinetics. The replication reaction may be thought of as a "controlled explosion", and hence its effects are frequently less obvious. With respect to simple life forms, the control arises primarily from the finite amount of reactants available at a given time. For advanced life forms the control is much more complex, involving social as well as material constraints. Thus the *actual* kinetics of the replication reaction are not always readily quantifiable. In some circumstances, the replication reaction may slow dramatically or cease altogether, only to burst forth at a later stage when appropriate conditions have re-emerged.

We argued above that in chemical terms the *primal* replication reaction is subject to kinetic control. But can the same statement be made regarding an *evolved* biological system — the *entire* set of chemical reactions that together constitute a particular living system, say a unicell bacterium? Establishing that the chemical processes associated with living beings are also kinetically controlled would help strengthen the causal link between the simple primal and complex evolved systems. In fact, the validity of the proposal is readily verified by examining the thermodynamics of replication of an *actual* biological system.

Placing a small sample of *Escherichia coli* bacteria in a solution of glucose and essential mineral salts leads within 36 hr to the production of *billions* of copies of the bacterium. In chemical terms, the reaction that has taken place is one in which some of the glucose, about 40%, has been converted to (living) cellular material, while the remaining 60% has been oxidized to carbon dioxide and water (Monod, 1972, p. 19). In this case, *the product distribution itself indicates that the overall process is one of kinetic control.* The *globally thermodynamically* favored course for the above reactants would be one in which *all* the glucose would be oxidized to the thermodynamically stable products, carbon dioxide and water, without *any* cell replication taking place. But, of course, under the biological reaction conditions this is not what occurs; only *part* of the glucose is oxidized to carbon dioxide. From a biological perspective this pattern is perfectly normal, but from a chemical one it is actually quite remarkable. As an evolutionary entity, the cell has developed metabolic pathways that allow glucose to be fully oxidized to carbon dioxide and water, thereby following the thermodynamically preferred pathway. However that capability has not emerged as an independent one, but one that is linked to the concomitant formation of *less* stable cellular material — a *kinetically* preferred pathway. Moreover the two pathways are not in competition with one another, as is often observed in a chemical system. Within a biological system the thermodynamic component of the reaction pathway has evolved for one reason alone — *to power the energetic requirements of the kinetic* (*replicative*) *pathway*. Glucose oxidation to carbon dioxide only occurs to cover the free energy requirements of the complex process of cell replication. The bottom line: evolution of the living cell has created a chemical system that is clearly directed along the *kinetic* teleonomic pathway of cell replication, not the *thermodynamically* preferred path of glucose oxidation to carbon dioxide. In this sense, both the complex process of biological replication and the relatively simple primal replicating reaction share a fundamental chemical link — *both constitute examples of the extreme kinetic control associated with the replication reaction.*

A key distinction between the set of reactions associated with living systems and "regular" chemical reactions can now be pointed out. Wicken (1985) has argued that a deeper understanding of causation requires a two-tier approach — an answer to both "how" and "why" questions. In addressing the *cause* of some phenomenon the "how" question requires a *mechanism* for its answer, while the "why" question seeks out a *driving force*. When we ask the cause of a chemical reaction, the mechanistic "how" specifies the reaction pathway — the individual steps along that pathway, but does not of itself specify *directionality*. It is the answer to the "why" question that addresses

the direction the reaction takes, and for chemical reactions this is invariably expressed in thermodynamic terms — the *direction* of a chemical reaction is the one for which $\Delta G<0$. Paradoxically however, the above discussion suggests that the answer to life's "why" question is *not* the usual thermodynamic one, but rather a kinetic one — *the kinetic power of autocatalysis*, though formally of course it is still thermodynamics that determines the replicating reaction's direction as well. The kinetic power of autocatalysis effectively transcends thermodynamics, not through negation of the Second Law, *but by steering a kinetically driven and directed autocatalytic pathway that at all times remains fully consistent with the Second Law*. Thus we can consider this kinetic phenomenon as an enormously powerful driving force, *the driving force responsible for the emergence and evolution of life.* This force operates at every stage along the evolutionary road — from the primal replicating reaction stage through to the single-cell stage and on to the multi-cell stage.

Note that by beginning our thermodynamic analysis with the primal replication reaction, we have circumvented the need to explain life's unusual direction using the notions of irreversible thermodynamics or complexity theories in general. At the earliest phase of life's emergence — at the simple molecular stage — the evolutionary pathway can be understood in terms of a coherent step-by-step process of replication and mutation, and consequently we would argue that the same fundamental principles may well apply at all levels of complexity, even if the precise nature of those intermediate stages remains unknown. Replication, by definition, is autocatalytic and the kinetic power of autocatalysis would apply at all levels of complexity along the evolutionary path from molecule to cell.

THE EMERGENCE OF COMPLEXITY

The question at the heart of the evolutionary debate concerns the nature of the organizing principle responsible for the emergence of biological complexity — structural, organizational and informational. We, therefore, now need to ask whether a *kinetic* perspective on life's evolutionary path can provide insight into reasons for the emergence of this complexity. Is there some physical principle that would anticipate a process in which a replicating entity becomes increasingly complex and metabolic? And what is the thermodynamic framework in which this occurs? Dyson (1985) has pointed out that the condition for homeostasis, the ability to maintain a steady chemical balance within the cell, requires a minimum level of complexity. But the reason for the evolutionary trend toward increasing complexity seems to be more fundamental. Before addressing this question, let us briefly mention the current view on the evolutionary process that has transformed relatively simple single-cell life forms into highly complex multi-cell beings such as plants and animals. This description will turn out to be relevant since, as we will subsequently argue, nature's ploys and techniques appear to be remarkably invariant and apply equally at the various stages of the evolutionary process.

Gould (1996) has argued that despite common perception to the contrary, examination of the planet's phylogeny reveals *no* evolutionary trend toward complexity, at least not in a directed sense. Using the well-known drunken walk analogy, he claims that the evolution of complex life forms is just an asymmetric expansion of diversity from a minimal level of complexity below which life cannot exist. Life emerged in its simplest functional form close to the "left wall" of minimal complexity, and as a consequence, any change in complexity — as part of a random walk — could only take place by an arbitrary movement to the right, away from the minimum complexity wall. Thus genetic drift will on occasion lead to greater complexity — an expansion into what Gould terms "complexity space". Gould's view has much in common with Wiley and Brooks' informational approach to the problem when the latter is removed from its thermodynamic setting. Wiley and Brooks point out that the genome of biological systems can continually increase with time. Accordingly, the total phylogeny would be characterized by an *ever-increasing genetic phase space*. In this view, growing evolutionary complexity merely reflects a persistent exploration and occupation of new elements of that increasing genetic phase space.

The point is that the mechanism of evolution is not restricted solely to one of natural selection, but also includes stochastic processes — *a random walk that results in a continual increase in genome size*. These ideas resonate well with Kimura's (1983) neutral theory of evolution that also emphasizes the role of genetic drift. Let us now consider these ideas within the context of the primal replicating molecule.

According to the Eigen (1992) model for the emergence of life, the mechanism by which the simple replicating molecule evolved into complex cellular systems is through the effect of chemical selection — in effect natural selection at the molecular level. It is argued that imperfect replication and kinetic selection together lead to a process of molecular evolution. But according to this model, the beginnings of the evolution of complexity are not immediately apparent. Is there inherent reason to believe that a longer and therefore more complex replicating entity would have a selective advantage? Spiegelman's (1967) classical experiments with the Q_β virus, though somewhat contrived, might in fact argue to the contrary. In that case an extended RNA sequence actually evolved by chemical selection into a much *shorter* sequence, dubbed Spiegelman's monster, due to its relatively high replicative prowess, though the reasons for this chain shortening were specific and related to the artificial constraints imposed on the system. If, however, we now apply the random walk argument to the simple primal replicator as an *adjunct* to chemical selection, we may obtain insight into a fundamental complexification principle that may already be functional at the molecular level.

If we consider the primal replicating molecule to be some biopolymer of limited length - say 10 units long, its process of imperfect replication might randomly lead to 9- unit and 11-unit sequences, in addition to 10-unit entities. Now, if we arbitrarily assume that the shortest sequence length capable of replication is 10 units, then this would mean that the 9-unit sequence plays no further role, other than to provide a source of building blocks for active replicators. Thus the 10-unit replicator represents the minimum complexity wall in the Gould metaphor. If we now consider the possible reactions of the 11-unit replicator, formed by genetic drift from the 10-unit one, we could by further acts of imperfect replication lead to the formation of both 10- and 12-unit sequences. In similar fashion the 12 unit moiety could lead to the formation of a 13unit moiety, and so on. The trend is clear — just as there appears to be *asymmetric genetic drift* from simple life forms to complex ones, as described by Gould, so a *simple* molecular replicator would also respond to asymmetric genetic drift, and therefore evolve over time toward *longer* and hence inherently more *complex* replicating entities. Recent computer modeling of the evolutionary process at the genomic level does indeed support the idea that the amount of coded information (presumed to reflect phenotype complexity) within a given sequence length continually *increases* with time (Adami *et al.,* 2000).

Of course, the emergence of more complex replicators would not be kinetically sustainable if the added complexity were unable to provide some kinetic advantage — *complexity must provide some existential advantage*. It now seems clear that the kinetic advantage that longer sequences could provide would not have stemmed from any inherently greater replicating ability associated with the longer sequences (Spiegelman's experiment demonstrated that), but, rather, through a variety of catalytic effects that some particular sequences might have afforded. Such catalytic effects could be of a *direct* kind, such as those displayed by ribozymes, whereby certain RNA sequences display enzymatic capabilities, or of an *indirect* kind through the catalytic generation of other compounds (e.g. oligopeptides) that would themselves display catalytic capabilities (the beginnings of protein expression). The catalytic effects of such induced materials could manifest in various ways, for example by acting as simple replicases, or by undergoing self-assembly with the replicating molecule. This latter point is important given that the physical process of *self-assembly* is a most important degree of freedom open to replicating entities in their exploration of enhanced replicating capability. The crucial importance of self-assembly to the replicating activity becomes evident when it is pointed out that a virus, or

even a bacterium, is in a sense nothing more than a supramolecular self-assembly characterized by a particularly effective replicating capability. In sum, genomic variability, directed by kinetic selection, transforms *replicating molecules* into *replicating assemblies*. Thus it is the combined directive powers of kinetic selection and genetic drift that together explore genetic phase space for optimal molecular replicators, leading to the concomitant exploration of "replicative complexity space" and the emergence of increasingly complex and successful replicating assemblies.

The trend toward increasing complexity is likely however to have *unfavorable* thermodynamic consequences — to lead to a growing entropic impediment and to an increasingly *less* thermodynamically favored process. Thus, if evolution toward greater replicating ability based on complexification is to proceed, some mechanism for dealing with the growing thermodynamic impediment associated with this complexity must be incorporated. And that is where kinetic selection comes in once again. The process of kinetic selection discovers that the way to facilitate increasing complexification within a permissible thermodynamic framework is through *the incorporation of an energy gathering facility*. Thus the powerful kinetic control of the replicating reaction manages to overcome growing thermodynamic constraints *by finding and exploiting some external energy source.* To illustrate, self-assembly of the replicating entity with some molecule exhibiting photoreceptor characteristics could provide a source of solar energy, which might then improve the thermodynamics of replication. It would be this initial coupling step of the replicating reaction to some energy source — chemical or photochemical, that would constitute the first step toward the evolution of a metabolic system and the biochemical energy cycles from which metabolic systems are built up. The technique of coupling thermodynamically unfavorable reactions to thermodynamically favorable ones in order to make the former proceed more effectively is of course a standard metabolic technique. Thus through the setting up of complex metabolic cycles, nature has found a way to drive thermodynamically *unfavorable* reactions — by converting them into thermodynamically *favorable* ones. Most importantly however, the entire process is driven by the kinetic imperative. It is the kinetic driving force of replication that enables chemical selection to overcome the various thermodynamic constraints that arise, whether these derive from increasing complexity or from any other source. In the context of the evolutionary process, the result is significant: the thermodynamic impediment associated with increased complexity and thermodynamically unfavorable reactions no longer needs to inhibit the process of complexification. Complexity that provides a replicative advantage is allowed *provided* an external energy source is available to pay the necessary thermodynamic price. Thus the thermodynamic door leading from simple replicators to complex life forms has been opened.

Finally, it is interesting to consider how the relationship between kinetic and thermodynamic controlled pathways changes along the evolutionary road from replicating molecules to simple life forms. The evolutionary effect of increasing complexity and the incorporation of metabolism into the replication scheme would be to continually enhance *the kinetic reaction channel* so that it increasingly diverges from the competing thermodynamic channel. Thus the primal replicating reaction, under kinetic rather than thermodynamic control, evolves over time (due to genetic drift and chemical selection) into a complex metabolic system of reactions that becomes increasingly locked into a kinetically directed channel — a kinetic channel whose only thermodynamic constraint is that the laws of thermodynamics cannot be disobeyed. The result of this extended evolutionary process is the emergence of entities, whose chemical predisposition remains entirely replicative (e.g., bacteria such as *E. coli*), and whose thermodynamic behavior plays a secondary role — a role that is constraining in one sense (in that the laws of thermodynamics must be obeyed), though supportive in another (in that chemical selection has guided the system toward thermodynamically allowed pathways). The above discussion however has wider implications, and leads us to a more general formulation of the selection principle.

REPLICATION AND DARWIN'S SELECTION PRINCIPLE

The power of replication was of course clearly understood by Darwin. Indeed it seems that it was his reading of Malthus' *Essay on the principle of population* that actually triggered Darwin's understanding and led to the formulation of his famous selection principle. Darwin's thesis simply stated is that because living things replicate exponentially (and imperfectly), natural selection will lead to evolution. However, by focusing on the power of replication and its centrality to the evolutionary process from the earliest stages of life's emergence, we believe the selection principle can be extended in a way that encompasses both animate and inanimate matter. If the Darwinian principle can be expressed as: "living things replicate, and therefore evolve", then a more general formulation might read: "certain replicating things can evolve, and may therefore become living (if they are not so already)". If in the traditional Darwinian view *replication is a manifestation of life,* then as part of a more general chemical view, *life is a manifestation of replication*.

Despite the superficial similarity between the two formulations, their logical consequences are quite different. As Darwin himself made clear, his principle of natural selection was not intended to address the question of life's emergence. Accordingly, *replication as a manifestation of life* leaves open the questions of *how* life emerged, *why* life emerged (in a driving force sense), or indeed *what* is life. It is no surprise therefore that despite the enormity of the Darwinian contribution, the arguments on life's emergence remain as intense 140 years later. A more general chemical selection principle — that certain replicating things can evolve, and may therefore become living, seems able to clarify some of these issues. By tracing the evolutionary pathway right back to its chemical roots, it provides a bridge between animate and inanimate worlds. Thus it addresses the questions: how, why, what, though it is clear that a simply stated principle, such as the one proposed above, does not pretend to provide a detailed answer to these questions, only an *in principle* outline. A more detailed treatment of these issues will be the subject of future work.

LIFE'S TELEONOMIC CHARACTER

The above analysis seems able to provide physico-chemical insight into the source of the teleonomic character of living beings (see also, Lifson, 1987). As discussed earlier, life scientists such as Monod (1972) and Dobzhansky *et al.* (1977) labeled life's teleonomic nature as a "mystery", a "flagrant epistemological contradiction", a "fundamental, if not the most fundamental problem of biology". Jacob's poetic description of this teleonomic character — the "dream" of every cell to become two cells — however contains within it a hint to a resolution of the problem. Whereas for a cell the process of replication with its overwhelming complexity and organization seems to create "a flagrant epistemological contradiction", with molecular replication there is no corresponding mystery — *the process is just chemistry*. Certain biomolecules, particularly polynucleotides, under appropriate conditions possess the chemical characteristic of being able to replicate. Chemical replication and evolution in a test-tube were demonstrated by the elegant experiments of Spiegelman (1967), Orgel (1979) and others. The mechanism is template replication, and its autocatalytic nature can lead to exponential kinetics. So effectively the first hint of life's teleonomic nature would already be discernible within that primal replicating molecule. Its "purposeful organization" is manifest in its molecular structure — a structure that enables the replication reaction to occur, and its "purposeful behavior" is manifest in its reactivity — its ability to replicate at kinetically significant rates. Both a replicating molecule and an *E. coli* cell when placed in their appropriate environments will replicate at an exponential rate. In both cases, a single entity is rapidly transformed into billions of copies. As the replicating system further proceeds along the evolutionary pathway, this teleonomic character intensifies and takes on more definite expression. Initially, at the stage of simple molecular replication, that teleonomic character is rudimentary, reflected only in the "desire" to replicate. But as kinetic selection takes its course creating increasingly complex structures, purposeful organization and behavior are enhanced,

both dedicated to ensuring replicating efficacy. At the cell level that character remains entirely replicative, as Jacob's "dream" comment makes clear. And proceeding further along the evolutionary path, the teleonomic character further intensifies, taking on the vast array of manifestations so typical of more highly evolved multi-cell beings. But, when all is said and done, *all* entities along that entire route, from replicating molecule through to human beings, in essence share the same "dream" — to replicate! Ultimately, much (though happily, not all) of life's behavior, organization and purpose are directed toward just this end.

Concluding Remarks

Thermodynamics is the science of the possible, and as such governs the behavior of chemical processes, both in living and non-living systems. Accordingly, a thermodynamic perspective can help bridge between these two chemical worlds that are so strikingly different, and help identify what it is that distinguishes between them. Our analysis leads us to suggest that living systems exhibit their unusual thermodynamic characteristics because in chemical terms life's processes represent an extreme expression of *kinetic control*. The emergence of life's most striking characteristics: complexity, metabolism, teleonomy, abundance and diversity, and especially their far-from-equilibrium state, are considered to all derive directly from the extreme kinetic character of the replicating reaction — a character present in *all* entities along the evolutionary pathway from primal replicator through to complex living systems. Hence, remarkably, though life itself is *complex*, the life principle may well be *simple*. Our view is diametrically opposed to an existing evolutionary paradigm that argues that it is the Second Law that drives the evolutionary process. We hold that life is driven by *dynamic*, not thermodynamic forces, though of course, as we have repeatedly emphasized, life's processes are fully consistent with the Second Law.

Our kinetic perspective on life seems to lead to some interesting conclusions. The kinetic power that we say brought about the emergence of biological complexity would in our view justify the classification of replicative chemistry as a sub-division within chemistry. Replicative chemistry would include all replication reactions, as well as the vast network of chemical processes that derive from such reactions, and are directly associated with them. Whereas *all* chemical reactions are controlled by a combination of kinetic and thermodynamic factors, the enhanced importance of the kinetic factor within the class of reactions we label replicative chemistry, leads to a qualitatively different pattern of chemical behavior. The concept of replicative chemistry suggests that the Darwinian selection principle may be extended to encompass both living and non-living entities. As pointed out earlier, we would claim that life is a manifestation of replication, rather than the other way around.

If indeed life is a particular manifestation of replicative chemistry, it also follows that life chemistry need not necessarily be built around just nucleic acid replication. It seems reasonable to believe that other efficient molecular replicators might well exist, and not just the one that natural selection happened to "discover". Such replicators might derive from alternative carbon-based systems, or even non-carbon ones. First tentative steps in seeking out model replicators, both natural and unnatural, have already taken place (Eigen, 1992; Orgel, 1992; Joyce, 1994; Sievers & von Kiedrowski, 1994; Rebek, 1994; Robertson *et al*., 2000). Clearly, the implications of future research into replicative chemistry, and the essence of life defined in a more general way, may prove to be profound.

Of course many of the above arguments depend on the primacy of molecular replication in initiating the process of life's emergence for which there is no direct evidence. What is significant however is that building on that assumption leads to a coherent and internally consistent picture, one that allows the formulation of a hypothesis which places animate and inanimate matter within a single conceptual framework. We believe that in itself lends some (indirect) support for the assumption and the "replication first" school of thought, as opposed to the "metabolism first" school, as pioneered by Oparin (1957) in the earlier part of the 20th century. Our approach contrasts with alternative

ones in which the role of complexity is assumed to be central (Dyson, 1985; Kauffman, 1993, 2000). At the present time, this latter approach appears to leave many of the fundamental life questions unresolved and the nature of the relationship between animate and inanimate unclear.

Finally, the principles we have suggested here are sweeping and general in nature. No attempt has been made to discuss the particular evolutionary stages from simple replicating molecules to complex biostructures, for example, the identity of that primal replicator, or the transient intermediate structures that must have linked between the primal replicator and simplest life forms. Indeed, as part of the emergence of life debate, there has been a widespread tendency to speculate on the detailed steps of life's emergence, a process that is, in large part historical, rather than scientifically immutable. We would suggest, however, that a fuller mechanistic understanding must necessarily depend on an improved understanding of the governing principles that underlie that transformation. The main goal of this paper has been to take some steps in clarifying the nature of those principles.

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REFERENCES

Adami, C., Ofria, C. & Collier, T. C. (2000). Evolution of biological complexity. *Proc. Natl Acad. Sci. U.S.A.* **97,** 4463–4468.

Babloyantz, A. (1986). *Molecules, Dynamics, and Life*. New York: Wiley.

Bertalanffy, L. von (1952). *Problems of Life.* London: Watts.

Bolsover, S. R., Hyams, J. S., Jones, S., Shephard, E. A. & White, H. A. (1997). *From Genes to Cells*. New York: Wiley.

Collier, J. (1988). *Entropy, Information, and Evolution* (Weber, B. H., Depew, D. J. & Smith, J. D. eds), pp. 227–242. Cambridge, MA: MIT Press.

Conrad, M. (1997). Origin of life and the underlying physics of the universe. *BioSystem* **42,** 177–190.

Corning, P. A. & Kline, J. K. (1998a). Thermodynamics, information, and life revisited, Part 1: to be or entropy. *Syst. Res.* **15,** 273–295.

Corning, P. A. & Kline, J. K. (1998b). Thermodynamics, information, and life revisited, Part 2: thermoeconomics and control information. *Syst. Res.* **15,** 453–482.

Dawkins, R. (1986). *The Blind Watchmaker*. New York: Norton.

Dobzhansky, T., Ayala, F. J., Stebbins, G. L. & Valentine, J. W. (1977). *Evolution*. San Francisco, CA: Freeman.

Dyson, F. (1985). *Origins of Life.* Cambridge: Cambridge University Press.

Eigen, M. (1971). Self organization of matter and the evolution of biological macromolecules. *Naturwissenschaften,* **58,** 465–523.

Eigen, M. (1992). *Steps Toward Life: a Perspective on Evolution*. Oxford: Oxford University Press.

Elitzur, A. C. (1994). Let there be life. *J. theor. Biol.* **168,** 429–459.

Gold, T. (1992). The deep, hot, biosphere, *Proc. Natl. Acad. Sci. U.S.A.* **89,** 6045.

Gould, S. J. (1996). *Life's Grandeur*. New York: Random.

Joyce, G. F. (1994). In vitro evolution of nucleic acids. *Curr Opin. Struct. Biol.* **4,** 331–336.

Kant, I. (1952). In: *Critique of Judgement* (Hutchins, R., ed.) Chapter 65. Chicago: Encyclopedia Brittanica Inc.

Kauffman, S. A. (1993). *The Origins of Order. Self-organization and Selection in Evolution*. Oxford: Oxford University Press.

Kauffman, S. A. (2000). *Investigations.* Oxford: Oxford University Press.

Kimura, M. (1983). *The Neutral Theory of Molecular Evolution*. Cambridge: Cambridge University Press.

Küppers, B.-O. (1990). *Information and the Origin of Life*. Cambridge, MA: MIT Press.

Layzer, D. (1988). *Entropy, Information, and Evolution* (Weber, B. H., Depew, D. J. & Smith, J. D. eds), pp. 23–39, Cambridge, MA: MIT Press.

Lifson, S. (1987). Chemical selection, diversity, teleonomy and the second law of thermodynamics. *Biophys. Chem.* **26,** 303–311.

Lifson, S. (1997). On the crucial stages in the origin of animate matter. *J. Mol. Evol.* **44,** 1–8.

Lifson, S. & Lifson, H. A. (1999). A model of prebiotic replication: survival of the fittest versus extinction of the unfittest. *J. theor. Biol.* **199,** 425–433.

Mayr, E. (1988). *Toward a New Philosophy of Biology*. Cambridge: MA: Harvard University Press.

Monod, J. (1972). *Chance and Necessity*. New York: Random.

Oparin, A. I. (1957). *The Origin of Life on Earth*. 3rd edn. Edinburgh: Oliver & Boyd.

Orgel, L. E. (1979). Selection in vitro. *Proc. R. Soc. London* B **205,** 435–432.

Orgel, L. E. (1992). Molecular replication. *Nature* **358,** 203–9.

Peacocke, A. R. (1989). An *Introduction to the Physical Chemistry of Biological Organization*. Oxford: Oxford University Press.

Prigogine, I. (1978). Time, structure, and fluctuations. *Science* **201,** 777–785.

Rebek, J., Jr. (1994). A template for life, *Chem. Ber.* **30,** 286–90.

Robertson, A., Sinclair, A. J. & Philp, D. (2000). Minimal self-replicating systems. *Chem. Soc. Rev.* **29,** 141–152.

Schneider, E. D. & Kay, J. J. (1994). Life as a manifestation of the second law of thermodynamics. *Math. Comput Model.* **19,** 25–48.

Schrödinger, E. (1944). *What is life*? Cambridge: Cambridge University Press.

Sievers, D. & von Kiedrowski, G. (1994). Self–replication of complimentary nucleotide-based oligomers. *Nature* **369,** 221–224.

Spiegelman, S. (1967). An in vitro analysis of a replicating molecule. *Am. Sci.* **55,** 63–8.

Swenson, R. (1997). Thermodynamics, evolution, and behavior. In: *The Encyclopedia of Comparative Psychology*, (Greenberg, G. & Haraway, M. eds), pp. 217–227. New York: Garland.

Szathmary, E. & Maynard Smith, J. (1997). From replicators to reproducers: the first major transitions leading to life. *J. theor. Biol.* **187,** 555–571.

Thaxton, C. B., Bradley, W. L. & Olsen, R. L. (1984). *The Mystery of Life's Origin: Reassessing Current Theories*. New York: Philosophical Library.

Weber, B. H., Depew, D. J. & Smith, J. D. (1988). *Entropy, Information, and Evolution*. Cambridge, MA: MIT Press.

Wicken, J. S. (1985). Thermodynamics and the conceptual structure of evolutionary theory. *J. theor. Biol.* **117,** 363–383.

Wicken, J. S. (1989, 1998). Evolution and thermodynamics. The new paradigm. *Syst. Res.* **6,** 181–186; **15,** 365–372. (Duplicate publication)

Wiley, E. O. & Brooks, D. R. (1982). Victims of history — a nonequilibrium approach to evolution. *Syst. Zool.* **31,** 1–24.