Thermodynamics of natural selection I: Energy flow and the limits on organization

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Abstract

   This is the first of three papers analyzing the representation of information in the biosphere, and the energetic constraints limiting the imposition or maintenance of that information. Biological information is inherently a chemical property, but is equally an aspect of control flow and a result of processes equivalent to computation. The current paper develops the constraints on a theory of biological information capable of incorporating these three characterizations and their quantitative consequences. The paper illustrates the need for a theory linking energy and information by considering the problem of existence and reslience of the biosphere, and presents empirical evidence from growth and development at the organismal level suggesting that the theory developed will capture relevant constraints on real systems. The main result of the paper is that the *limits* on the minimal energetic cost of information flow will be tractable and universal whereas the assembly of more literal process models into a system-level description often is not. The second paper in the series then goes on to construct reversible models of energy and information flow in chemistry which achieve the idealized limits, and the third paper relates these to fundamental operations of computation.
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1. Introduction

1.1. The existence of the biosphere

   Suppose that we wish to account for the emergence and stability of the biosphere that is observed on earth. Surely this should be one of the foundational problems of biology, establishing the context within which many particularities of form and function must be understood. For a variety of reasons, it is natural to describe the emergence of life physically as a process of self-organization, and to suppose that its robustness and resilience arise from the same forces responsible for its emergence (Smith and Morowitz, 2004; Morowitz and Smith, 2007; Hoelzer et al., 2006; Smith, 2007). However, such a claim is difficult to evaluate or even to express within the current paradigms or practices of biology.

   Self-organization is inherently a system-level phenomenon, depending on the flow of energy (and sometimes

matter) from environmental sources to restrict the possible states of order for a system (Kondepudi and Prigogine, 1998; Smith, 2003). Energy and information are not treated within common paradigms within most of biology, indeed the contexts in which they appear have often been mutually exclusive.

   The two paradigms dominating biological theory are the machine-like functioning of componentry (increasingly elaborated in molecular biology) (Alberts, 2002), and the Darwinian framework for understanding the stochastic dynamics of death and reproduction (Gould, 2002; Lewontin, 1974). The representation of biological processes as machines is often by way of *models*, which represent control flow and causation, and for which the goal is to conceptually or quantitatively reproduce typical observed behaviors (mechanisms of binding, Stormo and Fields, 1998, transcription or translation, Berman et al., 2006, cell cycling, Novak et al., 2001, regulation of cell division, Tyson et al., 2002 or metabolic pathways, Holter et al., 2001, etc.). Energy naturally appears in these contexts as an input, as a quantitative constraint, or as a medium of

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control. However, models constructed for the purpose of illustrating causality often diminish the importance of the incursion of error at all levels of organization and the consequent energetic costs of systemic error correction, and so are not suited to composition into a system-level description of either emergence or stability. At the other extreme, Darwinian selection is a purely informational theory, concerned with emergence and stabilization through statistical processes. Yet, for lack of a comprehensive theory of individual function, models of the dynamics resulting from selection inevitably take for granted (Hartl and Clark, 1997) the platform of physiology, growth, development, and reproduction, decoupling the problem of information input from energetic constraints on the mechanisms by which it occurs.[1]

In the absence of traditional biological paradigms that link energy flow and the restriction of states of order, how are we to understand at an aggregate level what the biosphere is doing as it constructs and maintains itself, and what limits may exist to how well or how far it can do this? The current paper and two sequels (Smith, 2008a, b) construct one such paradigm, attempting to circumvent the difficulties inherent in models by instead studying the *limits* on the capacity of the biosphere to order itself. The motivation for this choice—explained more fully below—is that limits of self-organizing behavior are both more flexibly defined and more universal than the instances that they bound. The universality of limits renders them independent of particular models that may realize them, and allows us to make definite statements about aggregate processes whose fine structure may be variable, unknown, or beyond modeling capabilities. More important, it is possible for well-defined limits to accommodate the fact that not all possible processes are even represented in the extant biosphere. Such limits are thus consistent with the essential element of *innovation* in evolution. It is also possible to sensibly aggregate and compare the limits on such different processes as elementary cell physiology and population-level selection, for which models attempting to capture more particular detail often obscure or omit altogether those features that provide grounds for comparison.

As would be expected of a self-organizing system, the common currency paying for all biological information is energy flow (Morowitz, 1979). Not only is energy a dimensionally homogeneous quantity; the energetic boundary conditions on the earth which sustain life (geothermal chemistry and the baths of visible and thermal infrared radiation) are essentially homogeneous compared to the complexity of the biosphere. Indeed, it is this homogeneity that qualifies the biosphere as *self*-organized, rather than as a system merely imprinted with the complexity of an external constraint. The featurelessness of the few (though potent) sources of energy powering life ensures that all sources of biological information are effectively compared against one another by the biosphere itself, through its partitioning of energy flow. For the biosphere as for other physical systems, it will be natural to quantify information as the reduction in some measure of entropy (Shannon and Weaver, 1949; Brillouin, 2004; Quastler, 1964; Morowitz, 1987), though care will be required to ensure that this definition is consistent across scales. The limits on the biosphere's ability to reject disorder will then derive from limits on energy flow and limits on the *efficiency* with which energy flow can reject entropy. Whereas different biological processes may approximate their limits to differing degrees, the limits themselves derive ultimately from the second law of thermodynamics. Where the second law can be applied, it asserts that information, like entropy, is comparable among processes and across scales.

A key observation in these papers will be that the optimal efficiency in using energy to reject entropy is attained by *reversible transformations*. This result has long been known in the thermodynamics of heat engines (Fermi, 1956), where a particular reversible cyclic transformation known a the *Carnot cycle* has become the basis for a general theory of efficiency. Whereas there may be no way to predict the consequences of aggregating arbitrary irreversible transformations, the reversible Carnot cycles form a basis for an arbitrarily precise constructive approximation of *any* reversible cyclic process. Thus the thermodynamic theory of optimal efficiency is generative, in the sense that a small universal set of elementary processes may be combined to produce processes of arbitrary complexity, with the properties of the composite transformation derivable from those of the constituents.

A counterpart to the thermal Carnot cycle exists for chemistry—the de facto substrate of life—and will be derived and studied in the second paper of the series. The somewhat richer structure of this cycle than the thermal Carnot cycle, created by its chemical as well as thermal degrees of freedom, turns out to be not only a model for chemistry, but also a model for the elementary physical constraints on computation. The combination of chemical conversion with entropy transfer corresponds to the manipulation of data by a physical computer at nonzero temperature. The generative character of thermal Carnot cycles for the analysis of arbitrary heat engines is thereby extended to chemistry in a manner that maps to the generative character of elementary logical operations for arbitrary computation (Hopcroft and Ullman, 1979). Thus we will arrive at a map by homology, between the limits on the self-organizing capability of the biosphere and the

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[1] These characterizations are of course oversimplified: in more nuanced treatments, cellular or developmental processes which are stochastic and driven may take on elements of selection and competitive exclusion, while evolution may incorporate deterministic and even mechanical steps. The point is that the very concept of control, intended to capture the rich causality of living processes, presumes the ability of one component to restrict variation in another, while Darwinian dynamics arise when prior variation cannot be suppressed, but only evaluated after it occurs by the selective environment. This paper addresses the lack of any single coherent paradigm to integrate the informational aspects of selection with the energy flow made possible by control, when both are co-present and coupled.

physical limits on computation. The latter are known in the computer science literature as *Landauer's principle* (Landauer, 1961; Bennett, 1973, 1982), so we will refer to the "chemical Carnot cycle" as the *Landauer cycle*. The third paper in the series is devoted to the study of the Landauer cycle in its computational interpretation, which is significantly elucidated by the homology to chemistry.

Thus the willingness to study limits rather than models allows us to relate self-organization in the biosphere to computation, not by analogy but by homology of their constraints. The manner in which we can derive limits on the energetic cost of arbitrary computations, without necessarily knowing details of their internal steps and without ruling out innovation, is the manner in which we can limit energy-driven changes in the biosphere, because limits have a path-independent logic for composition which most models do not have.

1.2. Layout of the arguments

The remainder of this Introduction will fill in the argument that the biosphere should be understood as self-organized, and explain some of the difficulties of attempting to build up an informational account of life from molecular process descriptions and abstract evolutionary models. The remainder of the paper will then be devoted to the assumptions and consequences of a theory of limits. Section 2 explains how the concept of state variables both defines optimality in terms of reversibility, and renders optimal processes universal and generative in a way that general processes are not. Section 3 considers the assumptions underlying the idealization of reversibility in chemistry and biology. It shows how reversibility unifies such maximally diverse processes as core biochemistry and population-level natural selection, and then considers more abstractly how the key assumption underlying reversibility—a separation of timescales—is the defining characteristic of a proper statistical understanding of the robustness of the biosphere.

A paradigm, of course, is useless if the constraints that it captures are irrelevant to the systems it purports to describe, perhaps because other constraints become binding first. The fundamental consequence of ideal efficiency is a linear proportionality between energy flow and information gain (Eq. (1)). Section 4 reviews several results on growth and development, in which such scaling relations may be tested quantitatively. A remarkable conclusion is that, across domains of life and mechanisms of organization, the linear scaling predicted by ideal limits is respected. The coefficient of proportionality differs from the ideal, reflecting the inherent irreversibility of these processes. Yet they scale as if they are limited by a fixed cost of energy per bit of information gained. The biological interpretation is that many invariant properties of life are linked directly to increments of information, and largely unlinked from the passage of time, from temperature, and from other such "material" influences.

1.3. The relevance of self-organization

The idea that the biosphere is a self-organized structure is certainly not a universally accepted tenet of biology (Miller and Orgel, 1974). Yet most people are willing to accept arguments (Schrödinger, 1992; Brillouin, 2004; Morowitz, 1987) that life maintains its state of order by continuously "rejecting" unwanted variations (usually defined by some measure of entropy) to the physical environment.[2] The substance of a claim of self-organization, which goes beyond piecemeal acknowledgement that one or another process somehow rejects entropy, is the assertion that having a biosphere is a definite "state" for the earth, which is positively favored over alternative states devoid of life.[3] The designation of self-organization thus entails an assumption of comprehensive error-accounting: that the diverse and semi-autonomous error-correcting activities of subsystems do not result in structureless churning about an average condition of equilibrium, but rather converge on a definite and robust non-equilibrium average.

By this characterization of self-organization, the biosphere could fail to qualify as a self-organized state in two ways. One is that it could fail to qualify as a definite state by any specific criteria. We have argued elsewhere (Smith and Morowitz, 2004) that the universality of core metabolism is already enough to suggest several metabolic pathways as definitive features of all life, and also that other higher-level and more complex features, such as the capacity of cells to maintain genomic information, have many characteristics of state variables (Smith, 2007). The other failure to qualify could arise if life is so strongly contingent in all respects on very unlikely events that its definitive features are all arbitrary and not characteristic of a "state" in any statistical sense (Monod, 1971; Miller and Orgel, 1974). Fig. 1 shows the possible roles of improbable events in making a claim of self-organization correct, wrong, or useless.

To make a logical taxonomy of the roles of improbable events, we consider the possible conditions of the earth as making a topological space. Two conditions x and x' are nearby if a small deviation from x can produce x'. $p(x)$ is

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[2]On earth over long timescales, this ultimately means rejecting unwanted entropy as thermal radiation to space.

[3]The notion of self-organization is thus itself something of a scientific straw-man. Some observed condition is designated "organized" if, by the equilibrium conventions for computing entropy, the entropy of its constituents is lower than that of an actual equilibrium. It is "self-organized" if, despite this lower entropy, the ordered condition is statistically favored over the equilibrium, attested because it spontaneously displaces equilibrium, and remains a stable attractor under perturbations. Since entropy maximization is the general principle behind stability (Jaynes, 2003), a stable but excessively ordered state is a contradiction. The resolution of this unfortunate language is that the equilibrium entropy is no longer the relevant measure of disorder under driven conditions, so the observation of self-organization signals the need to derive a correct entropy by other means (Smith, 2005; Dewar, 2003, 2005). We will return to this point briefly in Section 3.
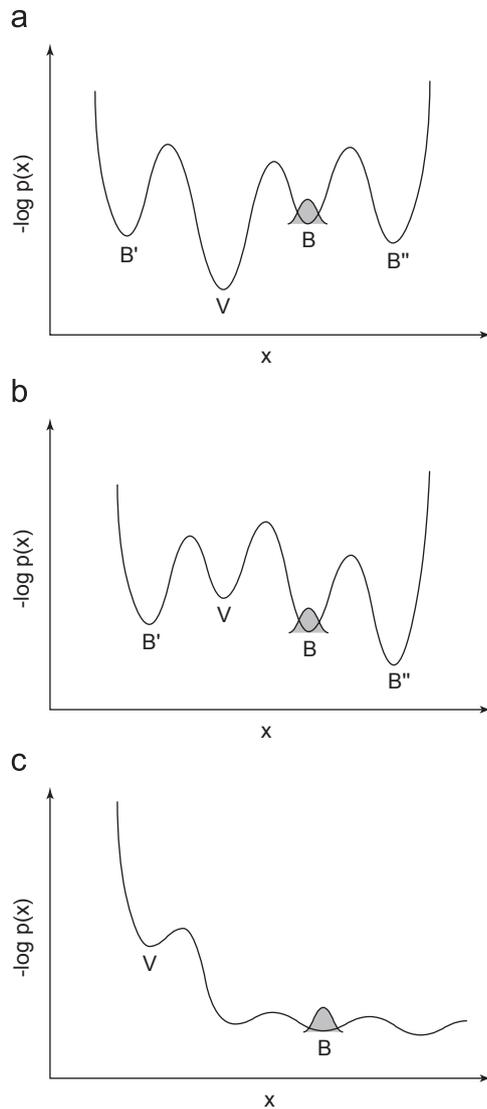
Fig. 1. The possible relations of improbable events to the state of the biosphere. x labels conditions of the earth, which may involve histories as well as instantaneous configurations, and $-\log p(x)$ is the generalization of the equilibrium concept of free energy landscape. V designates an earth persistently devoid of life, B indicates the earth with a biosphere as we know it; B' and B'' indicate states with imagined counterfactual biospheres. The interpretations of the panels are explained in the text. The shaded distribution at B represents the observed deviation in typical characteristics within the extant biosphere, in relation to the heights of possible barriers.

the probability of condition x, which may be interpreted as the likelihood of observing x in a large ensemble of repetitions of the history of the earth or geologically and astrophysically similar planets. The function $-\log p(x)$ would be a free energy landscape in equilibrium, but in general we do not suppose that x are limited to equilibrium states; they may represent historical trajectories (Dewar, 2003, 2005; Smith, 2003) or transient non-equilibrium conditions (Smith, 2005) as long as those have a statistical characterization.

Panel (a) in the figure represents the case that the assertion of self-organization is wrong. The biosphere is

not unique and not positively favored over equilibrium, but rather maintained by barriers of improbable events against collapse to equilibrium or to alternative possible states with life. The critique of this case is that the likelihood of the emergence of life is strictly lower than the likelihood of its decay (the barrier between the Void and Biosphere is more inaccessible from the Void than from the Biosphere). As life appears never to have vanished in the history of the earth, despite persistent shocks to all levels of organization[4] the inferred likelihood of its total collapse is small. For a hypothesis of self-organization to be significantly wrong, the likelihood of emergence would then have to be considerably smaller still.

Panel (b) represents the case that self-organization is a technically acceptable but useless description. The observed biosphere is statistically favored over the Void, but is not unique and is kept from exploring alternatives only by barriers to transition. Panels (a) and (b) are both versions of the "frozen accident" hypothesis for the emergence and subsequent evolution of the features of life (Crick, 1981). If they were true, they would invalidate the use of the informational limits derived in these papers, because the transition barriers and not limits on information would be the primary constraints on life. The universality of limits derived from reversible transformations is obtained at the price that all possibilities are implicitly compared, as the means to obtaining a homogeneous measure of information. While "frozen accident" hypotheses are logically admissible, their status as scientific premises is questionable (Fry, 2000). As regards the biosphere, they have always resulted from the inability to imagine probable paths to life, rather than from any strong evidence that such paths do not exist.

Panel (c) represents the case in which self-organization is both a valid and a useful description. The rapid emergence of life on earth after the end of heavy bombardment (estimated within 0.2 billion years, Fenchel, 2002) suggests that any barrier between the Void and the incipient biosphere was not very large. We need not assume that the extant biosphere is an ultimate state, for the limits on information change to be relevant constraints. It is sufficient to assume that the extant biosphere is representative of possible states, or that the waiting times between alternative states are not much longer than the energy-flow-limited transition times for the same transitions.

On the grounds that there is no predictive science of infinitely improbable events, and furthermore that many features of extant life are plausibly consistent with rapid emergence by self-organization, these papers will adopt the latter hypothesis. They will suppose that the earth containing a biosphere is a definite state under a suitable generalization of the usual sense of statistical mechanics, or at least one in a continuous progression of such states. It then becomes a quantitative question what are the limits on

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[4]These shocks are attested by extinctions large and small, and by ecological re-arrangement or collapse.

the order of this state (either in absolute magnitude or in their rates of change), and how do heterogeneous processes interact to create and to maintain order.

1.4. Subtleties of information accounting in biology

The need for a global theory of information accounting—even if it can only be achieved for idealized bounds—is illustrated by the difficulty of assigning energetic consequences to the concept of "information flow" in the central dogma of molecular biology (Lewontin, 1974). Simplifying somewhat for the sake of example,[5] and adopting an explicitly informatic language, the central dogma can be characterized as asserting (among other things) that the variation in form of some molecule class within an organism is zero if the genes coding for the synthetic pathway of that class have been specified.[6] For example, archaea synthesize particular isoprenoid ether lipids for use as their cell membrane lipids, while bacteria synthesize very different, and equally particular fatty acids to fill the same role (Lengeler et al., 1999). The entropy of bonding configurations, and most of the spatial position entropy, for a carbon atom incorporated from environmental CO_2 into a particular position in either type of molecule is essentially zero (Morowitz, 1987), given the identity of the organism performing the synthesis. In this characterization, information, or the restriction of entropy, seems to "flow" from the genes to the carbon as it is progressively restricted through core metabolic reactions.

Suppose we wish to estimate the minimal energetic requirements on natural selection to convert a heterogeneous population of bacteria and archaea to a homogeneous population of whichever type is fitter, thus realizing Gause's (1934) principle of competitive exclusion. How might we to use the idea of "information flow" to do this? We can observe, following Morowitz (1987), that the chemical entropy reduction to convert growth medium to biomatter,[7] measured in units of the natural logarithm (so factoring out Boltzmann's constant as an irrelevant conversion factor), approximately equals the *number* of synthesized atoms, multiplied by the restriction on their positions and bonding configurations. If information truly

"flowed" from genes to metabolites, we could decompose the resulting entropy reduction into two phases. First, for every atom taken in at each location occupied by an organism, the genes for the fitter organism would either not be selected (the initial heterogeneous population) or be selected (the evolved homogeneous population), specifying that atom's fate at the level of a distinction between organisms. Second, the atom would be processed by the metabolic pathways encoded in the pertinent genes, accomplishing the residual entropy reduction to form the actual population. By this argument we would correctly arrive at the physical observation that the entropy reduction to form biomatter, and also the *difference* in entropy reduction between the formation of equal biomass in a heterogeneous and in a homogeneous population of organisms, scales in proportion to the total *biomass*, not in proportion just to the total number or mass of genes.

The foregoing analysis satisfies an inescapable entropy accounting, that the entropy difference between a homogeneous and a heterogenous population of organisms is proportional to the total biomass, and on the order of the number of atoms incorporated. Furthermore, it does describe a "flow" of information from gene to metabolite, in that the full restriction of the metabolite's fate in an evolved population is first accomplished as a restriction of the genes, and subsequently of the metabolite within a specific pathway. If there were an energetic cost to each step, that cost could be apportioned between the specification of the gene (accomplished by selective exclusion) and the residual specification of the metabolic reactions given the gene (the equivalent "residual" entropy rejection performed by either the bacterium or the archaeon). However, note that to produce this accounting we assumed an independent event of selection on the gene with every carbon atom that passes through metabolism. Such an assumption seems incompatible with the central dogma, which maintains that the active events of genetic selection occur upon death or reproduction, and that the molecules carrying the resulting information are metabolically inert during the lifetime in which they direct metabolism. If, instead of the foregoing argument, we had attached the costs of selection to the events of death or reproduction of genes, the required entropy reduction would have been expected to scale with gene number or gene mass per generation, but not with the biomass.

The paradox is resolved in principle—though in a manner difficult to use in practice—by recognizing that the events of death and reproduction are subordinate to whole lifetimes of independent moments of *persistence*, during which biosynthesis cumulatively occurs. Whatever information "flows" from the genome to the metabolome, it is not simply the state information gained by designating one among many possible genes for a function, but the additional cumulative information that gene has the property of persistence, as part of the larger organism. Persistence is a system as well as a molecular property, and the energy cost of ensuring persistence should somehow be

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[5]A minor industry has sprung up cataloguing "violations" of the central dogma—processes by which information flows "backward" from the phenotype to proteins, RNA, or DNA. These complicate the statement of the central dogma, but do not alter its main characterization of the direction of information flow responsible for distinguishing Darwinian from Lamarckian evolution. They are also beside the point of this paper, which is to determine what "information flow" actually stands for.

[6]More technically, the conditional information (Cover and Thomas, 1991) of the chemical configuration of the molecules is zero, given that the genes have been specified.

[7]In this and the subsequent papers, *biomatter* will be used to refer to the compositional state of the constituents of living systems. The older term *biomass* will be used only as a measure, to refer to the mass accounted for by some collection of biomatter.

counted as the cost of making the information "in the gene" continuously available during a sequence of biosynthetic events.

Thus it is not a straightforward exercise to assemble mechanical pictures of molecular function, together with the Darwinian accounting of events of death and reproduction, into a quantitative theory of information flow in natural selection and its energetic costs. Energy is continuously consumed to ensure persistence at the level of the cell or organism, by correcting errors of structure or function that occur in all components. This persistence is not merely incidental to information flow from the genome to the growth processes that underlie selection, but rather is fundamental to the scaling of the total information transferred. The costs of error correction of both component function and system organization would need to be estimated, and these would then need to be assembled into a model of the costs and consequences of system persistence for each synthetic reaction, to create a quasi-literal model of information flow from natural selection to the composition of the biosphere.

The informational cost of persistence of the gene or the organism expresses in microcosm the problem of persistence of the biosphere as a whole. It may in the future be possible for a highly developed systems biology to produce such an information accounting from calibrated models of molecular function, but new concepts as well as a wealth of new detail and very complex calculation will be required. The composition of limits is not similarly arduous, but to derive it from the second law of thermodynamics requires a way to map out the boundary of what is *just possible*, and therefore maximally efficient.

2. Reversible transformations and optimal efficiency

The problem of identifying performance limits on systems whose internal structure might not be representable was faced in the nineteenth century in engineering. The concepts leading to its solution formed the foundation first for phenomenological—and later for statistical—thermodynamics. In engineering as in biology, internal structure and dynamics might go un-represented because they are too complex to model, because they are not yet known, because they are not strictly controlled and are therefore variable even within the class of systems studied, or because they may be products of innovations not yet experienced. Understanding the performance limits on engines of arbitrary design was the problem faced by Sadie Carnot, and understanding the limits on innovation by evolution is a problem faced by evolutionary biologists in understanding the possibilities for the biosphere.

The two key concepts leading to the solution of performance limits in thermodynamics were the related notions of *equilibrium state variables* and *reversible transformations* (Fermi, 1956; Huang, 1987; Jaynes, 2003). Both shall be of importance in this analysis as well, because they are the basis for definitions of ideal efficiency.

In the traditional and most conservative definition (Huang, 1987),[8] state variables are the macroscopic properties sufficient to specify all determinable characteristics of a system that has reached equilibrium. Equilibrium is special because it is the condition with highest entropy, hence least information, of all conditions compatible with the values taken by its state variables. In an equilibrium system, there is no "hidden information" that can influence its future dynamics beyond the influence from the state variables. Reversible transformations are those that cause the system to pass only through (or arbitrarily close to) states of equilibrium at all times. Reversible transformations can never create or destroy information; they can at most redistribute it among components of a system. Because, by definition, all components constantly meet criteria for equilibrium during a reversible transformation, each component has the least information compatible with its boundary conditions (the state variables), implying that the other components all have the most. Because this is true for every component, information content is exactly controlled by the definite values of the state variables during reversible transformations. In thermodynamics one says that the entropy is a *state function* of the other state variables, and one uses the reduction in entropy as the general definition of a gain of information.

It is this state relation between information and other constraints which is lost during irreversible transformations. Since such transformations can arise, starting from (component-wise) equilibrated inputs only by the release of constraints, total information can only be lost as a result of irreversible processes (Gell-Mann and Lloyd, 1996).

The original question of interest in engineering was how much work could be produced (more being better) by an engine that was required to undergo a cyclic transformation, so that finite machinery might be re-used for tasks of indefinite size. The only answer given by the second law of thermodynamics was a prohibition: no process can spontaneously proceed while reducing total entropy (Huang, 1987), and this includes the function of all machinery. The prohibition of the second law was used constructively by observing that any engine could at most preserve the information within itself and its environment, producing work by exchanging information between subsystems. The maximum work produced by an information exchange is, in turn, the minimum *cost* if work is required as an input to perform that information exchange in the opposite direction. Since information can be lost by spontaneous processes but not gained (entropy can increase but cannot decrease), the transformations that produce the most work are those that lose no information (the reversible ones), and conversely the transformations of

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[8]The definition based on equilibrium will be used in the remainder of this paper and in the second paper of the series. This narrower usage is not in conflict with the characterization of the biosphere as part of a non-equilibrium "state" of the geosphere in Section 1.3, but properly defining non-equilibrium notions of state is a different problem than the one addressed in this series.

least cost to exchange information are reverses of those that produce the most work. Thus, while there are infinitely many non-equilibrium conditions and irreversible transformations that might return a system to its initial state, *all of these* have a work output that is bounded by that of a reversible transformation acting within the same environment. Conversely, if a cyclic transformation accomplishes the exchange of information (putting it into one component by removing it from others), the work cost of that cycle is always at least as great as the work cost from a reversible cycle accomplishing the same exchange. The engineering concern with cycles is obviously relevant to the evolution of the biosphere over long times, because matter on earth is ultimately conserved. For many processes within cells or within ecosystems, the approximate cycling of matter is an equivalent constraint even on short timescales (Morowitz, 1966).

From the ideal efficiency of reversible cycles (most work/ least cost) follows their *equivalence*. We need not know which reversible cycle acts within a given environment, to extract work or exchange information, in order to compute the efficiency of that process, since it is the same for all such cycles (Huang, 1987). A corollary is that reversible cycles—which may be drawn on a *state diagram*[9] because they maintain all subsystems near equilibrium—may be used as building blocks to systematically estimate bounds on *any* cyclic transformation. Even transformations involving many subsystems, and having very complex exchanges of information, may be decomposed into elementary reversible cycles acting between one pair of subsystems at a time (Fermi, 1956). The use of reversible cycles, of which the *Carnot cycle* is the original and best-known example, has become the foundation for all analysis of transformations involving energy and entropy (or information) in thermodynamics.

3. On the separation of timescales

The distinctive feature of biological systems, which can make models difficult to compose but limiting behaviors tractable, is the machine-like nature of biological control (Stryer, 1981; Alberts, 2002). The essence of mechanical control is the *separation of timescales* between the processes of change in the controlled system and those in its controller. The problem of assigning informatic costs to persistence, discussed in Section 1.4, is the problem of explaining the stability of a controller which is itself composed of stochastic components (Schneider, 1991a, b; Krishnamurthy et al., 2007). However, when it arises, this kind of persistence is what makes possible the approximation of reversible transformations considered in Section 2. The substrate on which a reversible machine acts may be kept near its equilibrium as long as the relaxation of its components is fast compared to the timescales on which the machine moves, fails, or requires replacement.

Catalysts create an ideal context for the abstraction of Carnot-like chemical cycles, whether in the first emergence of metabolism from geochemistry (Copley et al., 2007) or in the later function of cell physiology. Good catalysts can sustain reaction rates at or near the diffusion limit, while uncatalyzed reactions involving the same covalent bonds take place (routinely six or more) orders of magnitude more slowly (Stryer, 1981). The separation of timescales between catalyzed and uncatalyzed reactions kinetically isolates particular reaction sequences and couples these to sources of energy, while leaving most mechanisms for decay slow and decoupled. Moreover, the sequencing of reactions as substrates bind to first one and then another catalyst lends itself to description in terms of complex composite transformations.

The limits defined by assuming a separation of timescales can be composed *whether or not* we can account for the mechanisms by which long-lived components persist. For instance, to analyze the minimal cost for natural selection to produce a homogeneous from a heterogeneous population of organisms, we may begin by computing the limiting entropy of formation of each population from growth medium by reversible means, idealizing catalyzed metabolic processes and taking persistence of the catalysts as given. We may then construct an optimal process to convert the heterogeneous to the homogeneous population by reversibly "un-growing" the heterogeneous population back to growth medium, and then reversibly growing the homogeneous population. The resulting minimal cost of natural selection will be proportional to the biomass, as argued in Section 1.4. The means by which natural selection manipulates the combined growth and un-growth processes to alter the population does not affect the optimal cost of the conversion, just as the protocol for directing a reversible engine through its cycle does not affect the energy cost to transfer entropy between its input and output.

In this way metabolism and natural selection, which seem to be opposite poles in the description of biological phenomena, may be unified under a common framework. Superficially, metabolism is the least self-organizing of processes, the conversion of the metabolic substrate merely reflecting the order imposed by a collection of persistent catalysts external to the reactions themselves. Natural selection is the opposite, producing the intricately co-adapted biosphere from minimally structured energy sources and geochemistry. Yet in the derivation of limits, the structure of catalysts external to metabolism, and of the energetic and chemical environment which selects for the emergence of a biosphere, are treated equivalently.

It might seem that for an idealization of biology to be valid, metabolism, physiology, and natural selection should not be so symmetrically treated. After all, natural selection proceeds by the expenditure of whole organism life cycles, with the lives of the unfit variants wasted. However, the foundation of trophic ecology is the observation that much of primary organosynthesis is not reversed at death, but

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[9]A state diagram is a graph of system states and transformations in which the state variables serve as the coordinate axes.

conserved as small metabolites and cofactors serving as food. Thus, the idealization of "un-growing" an unfit population, and re-growing its replacement, may not be a qualitatively worse characterization of the life cycle than a characterization of physiology that omits signaling, RNA proofreading, or active chaperoning of molecular folds. The scaling results of the next section, though too limited to span this large scope, suggest that inefficiencies expressed through aging and inefficiencies inherent in physiology are not readily distinguishable.

3.1. The more general notion of kinetically constrained ensembles

The idea that, with the correct entropy measure, the biosphere might be recognized as the most disordered state compatible with its boundary conditions—and therefore the most stable—is not inconsistent with the use of reversible transformations and equilibrium entropy measures to characterize its informational state. The idealizations of reversible processes guided by rigid machinery are merely limits of the more general admission that the flow of energy through real non-equilibrium systems is governed by kinetic as well as energetic constraints. Whereas equilibrium is defined in part by the assumption that all kinetic barriers to internal transformation have been surpassed, and so only energetic structure determines distributions, under driving boundary conditions the kinetic structure is as primary as energetics.

The fact that kinetic constraints occupy a *spectrum* is what allows a subsystem to be treated as quasi-equilibrated—all of its internal transitions being available—while the larger system within which it exists is treated as a quasi-rigid machine. To identify an entropy principle for the biosphere as a whole requires coupling the whole kinetically constrained ensemble to its driving boundary conditions (Smith, 2005). Meanwhile, the internal structure of states and processes at the subsystem level within that ensemble may be analyzed with equilibrium variables if the separation of timescales between the relevant levels is sufficiently large.

4. Information in growth, development, and aging

The distinguishing feature of the bound developed in this and the next two papers is that the limit on the amount of information that can be put into a biological system is determined by the cumulative work done on the system and by its temperature as an energy scale, but not on the time taken to do the work, on thermal effects of degradation, or on any other "material" aspect of the system or its transformations. This dependence of information solely on work and energy scale is a necessary consequence of any bound derived from reversible transformations.

The most obvious test of the relevance of such bounds to real systems is a comparison between their cumulative energy used for metabolic work and the entropy of the biomatter produced. Living systems have generation times ranging from minutes to hundreds of years, and life cycles ranging in complexity from the indefinitely repeated division of prokaryotic cells, to the highly stereotyped birth, maturation, and death of animals. The remarkable observation reviewed in this section is that the cumulative metabolic energy required for a wide variety of processes is predicted at leading order by the biomass formed, and is approximately independent of other factors. The coefficient of proportionality is different for real systems than for their reversible idealizations, but is again not strongly dependent on which observation is considered, or on timescale or aggregate level of complexity. Thus it appears as if the active constraints on growth, development, and aging take the form of a limiting work required per bit of information gained, with a fixed factor of inefficiency relative to idealized processes.

4.1. The second-law relation between work and information

To establish notation for the remainder of this and the subsequent papers, we introduce the fundamental scaling relation which includes the second law of thermodynamics, Landauer's principle, and the thermodynamic limits on natural selection. All expressions for the minimal energy cost to reject entropy may be understood as a joint consequence of dimensional analysis and the definition of temperature. The differences among the forms that characterize heat engines, chemistry, or computation involve only which values of temperature enter, and which measures of energy or information are used.

To avoid later re-formulation, the bound will be denoted from the outset as it arises in the context of computation (Landauer, 1961; Bennett, 1982)

$$dW = dQ = -k_B T \, dS \equiv k_B T \, d\mathscr{I}. \tag{1}$$

In this general class of relations, dW is an increment of work performed on the system by its environment, dQ an increment of heat rejected by the system to a thermal bath at temperature T, $-dS$ the reduction in entropy of the system's internal state (measured in units of the natural logarithm, referred to as "nats"), and $d\mathscr{I}$ the definition of minus the entropy reduction as an increase in information. k_B is Boltzmann's constant, with dimensions of energy per temperature.

In computation, where data are carried by physically identical degrees of freedom, it is natural to define $d\mathscr{I}$ as the reduction in entropy upon converting an input to an output data stream, and dW as the total energy (delivered as mechanical work) to run the computer. In the analysis of physiological transformations performed in the second paper (Smith, 2008a), where information can be carried on molecular degrees of freedom with different energy costs, the computer-science convention can still be used, but alternatively it is sometimes convenient to define $d\mathscr{I}$ as a measure containing free energies of formation, and dW as a chemical work excluding internal free energy changes.

The interpretations are consistent and inter-convertible, and in this paper $d\mathscr{I}$ will stand strictly for the reduction in chemical entropy of formation. As an aside, we note that the assumption of a single temperature T would be inadequate for the analysis of heat engines, which involve multiple temperatures, but it is acceptable for both biochemistry and idealized models of computation.

The second-law reasoning behind Eq. (1) is this: The entropy of a driven system can only be reduced by some amount $-dS$ if the entropy difference is "exported" to the environment in the form of heat. Yet to reject entropy $-dS$ as heat to a bath at temperature T requires an amount of energy $dQ = -k_B T \, dS$, by definition of temperature, as the energy-per-unit-entropy in a heat flow. Furthermore, for all of this amount of energy to have been available to carry away entropy as heat, it must have come to the system in some entropy-free form, in other words as work in an amount $dW = dQ$ carried on some non-stochastic degree of freedom. If energy is imported on stochastic degrees of freedom, an amount $dU > dQ$ will be required, to export the entropy on which dU enters as well as $-dS$ (obviously, this is only possible if the entropy brought in with dU is less than $dU/k_B T$). In biochemistry the entropy rejected by growth and development comes jointly from the entropic terms in the free energies of formation of biomolecules, and from the distributional entropy of phase separation, whereby cellular material becomes a concentrate of "improbable" molecules, while higher-entropy wastes are rejected to the extracellular (or extra-organismal) environment.

4.2. New growth, metazoan development, and aging

Morowitz (1955) proposed the relation (1) in 1955, with $\int dS$ for de novo formation of a cell being the Gibbs entropy reduction to fully specify the spatial position and bond distribution for all atoms in the cell, relative to a random ensemble. (Thus $\int dS$ is on the order of Avagadro's number times the dry weight of the cell, divided by an average gram-molecular weight—about $10\,g$—of the cell's constituent elements.) The minimum heat $\int dQ$ required by Eq. (1) to be rejected to the environment during growth of a new bacterial colony differs surprisingly little (about a factor of $\frac{1}{3}$) from calorimetric measurements, suggesting that bacteria under optimal growth conditions waste little metabolic energy beyond what is required for growth. The simplicity of this entropy estimate fails to take into account the fact that at least part of the entropy reduction to make new cells has already been performed in selecting the molecules in the growth medium, but to order of magnitude the agreement probably remains valid. The physiological entropy reduction associated with new growth is on the order of the number of atoms (or functional groups) fixed by biosynthesis. (For comparison, the conventional bioinformatic information to completely specify a gene sequence is on the order of megabits for bacteria and at most hundreds of megabits for the most complex eukaryotes, vanishingly less than the chemical entropy.)

The scaling of bacterial heat of metabolism in proportion to synthesized biomass is only moderately suggestive of a fixed energetic cost per bit of chemical information secured. Bacteria growing into new medium do not systematically die, and growth is a self-similar process of cell expansion and division, so any per-cell cost of maintenance will generally scale in proportion to the per-cell cost of creation, making it difficult to disentangle the relative importance of the two as constraints.

A more interesting and diverse test of the scaling of energy cost with information comes from growth and aging of metazoans. For these the apparent allocations of energy to new cell formation and existing cell maintenance vary strongly with body size, as does organism developmental time and lifetime. Yet when the complementary variations in all these characteristics have been combined, it will turn out that metazoans demonstrate the same overall scaling as bacteria, with modestly different constants of proportionality describing their inefficiency.

It is known that a variety of strong allometric scaling regularities across a huge range of organism sizes (West et al., 2002), governing both post-embryonic and pre-embryonic development trajectories (West et al., 2001, 2004; Gillooly et al., 2001, 2002), are captured in a simple energy-conservation equation of the form

$$B_0 m^{3/4} = \frac{B_c}{m_c} m + \frac{E_c}{m_c} \frac{dm}{dt}. \tag{2}$$

Here B_0 is a measure of the metabolic rate of supply in a metazoan, with dimensions of (power × mass$^{-3/4}$), which can be predicted in some cases from models of vascular or respiratory perfusion (West and Brown, 2005). B_0 has Arrhenius dependence on temperature (Gillooly et al., 2002) $B_0(T) \approx e^{-\bar{E}(1/k_B T - 1/k_B T_0)} B_0(T_0)$ relative to an arbitrary reference temperature T_0, with a characteristic activation energy $\bar{E} \approx 0.6\,\text{eV}$, and $B_0(T_0)$ a nearly taxon-independent constant. E_c/m_c is a characteristic energy per unit mass required to produce a new cell from growth medium, with a weak dependence on aspects of cell composition such as carbon to phosphate (C:P) ratio (Gillooly et al., 2002). This parameter plays the same role as the cost of cell growth for bacteria, and can be seen to depend primarily on the free energies of formation of cell constituents, not only within the metazoa but even comparing major divisions of life such as oxidizing and reducing organisms (McCollom and Amend, 2005).

B_c/m_c is the metabolic power per unit mass described by West et al. (2001) as being "needed to sustain the organism", but it has no universal value. Rather, it appears to be established in embryogenesis and held approximately constant throughout development, and its value determines the adult body mass of the organism as the value at which dm/dt can no longer exceed zero because all metabolic power is used for sustenance. I would argue that the natural empirical interpretation of B_c/m_c is that of the *regulatory* parameter used by the genome to control adult body mass (e.g., in response to selection pressures), while

maintaining a universal and scale-independent growth algorithm (leading to $B_0 m^{3/4}$) and a scale-independent regulation (through B_c/m_c), in both ontogeny and phylogeny.

Eq. (2) may be converted to a non-dimensional form expressing the growth of the fraction m/M of adult body mass in terms of a "metabolic age" $\tau \equiv t/t_C$ as

$$\frac{d}{d\tau}\left(\frac{m}{M}\right)^{1/4} = 1 - \left(\frac{m}{M}\right)^{1/4}. \tag{3}$$

Here the adult body mass $M = (m_c B_0/B_c)^4$ and the characteristic timescale $t_C = 4E_c/B_c = M^{1/4}(4E_c/m_c B_0)$. t_C inherits the temperature dependence of B_0, and scales with adult body mass as $M^{1/4}$. The solution to equation (3) may be written relative to an appropriate zero of time as

$$\left(\frac{m}{M}\right)^{1/4} = 1 - e^{-\tau} \tag{4}$$

and provides good fits to the growth curves for a variety of vertebrates (West et al., 2001), with up to 75% of the variation in development time accounted for by temperature and body-mass dependence, and 67% of residual variation in growth rates with C:P ratio, demonstrated for zooplankton (Gillooly et al., 2002).

Many stages of development are linked to fractions of adult body size rather than to absolute size—for instance onset of adulthood at $m/M \approx 0.5-0.9$ (Gillooly et al., 2002)—and thereby to characteristic values of τ. For any such stage i we may write the metabolic energy consumed between fertilization and physical age t_i as the integral

$$E(0, t_i) \equiv \int_0^{t_i} B_0 m^{3/4} = M\frac{E_c}{m_c}\int_0^{\tau_i} d\tau(1 - e^{-\tau})^3, \tag{5}$$

in which it has been approximated that embryogenesis begins at $t = 0$ to the accuracy of these equations.

In particular, the "metabolic age" at death (denoted τ_D here) for a variety of aquatic invertebrates and fish may be obtained from the fits in West et al. (2001) and Gillooly et al. (2002), up to the scale of E_c/m_c (not provided). The value of E_c/m_c for fish may be estimated by comparing fits for B_0 in Gillooly et al. (2002) to the parameter a in West et al. (2001), using values of temperature and adult body mass[10] from Froese and Pauly (2006) (source www.fishbase.org). (The estimated value $E_c/m_c \approx 2750\,\text{J/g}$ is smaller by a factor of 2.5 than the value $7\,\text{kJ/g}$ quoted for mammals in West et al. (2001)).[11] Assuming this value is typical of both fish and aquatic invertebrates yields estimates $\tau_D \approx 1.94$ for the invertebrates and $\tau_D \approx 2.8$ for fish at a median value $T = 294\,\text{K}$ for the data in Gillooly et al. (2002). Lifespan estimates for fish from Froese and Pauly (2006) together with the timescale estimates from Gillooly et al. (2001), yield shorter but comparable values

$\tau_D \sim 2.3$, and Ernest (2003) for mammals yields slightly larger values $\tau_D \sim 10$, compatible with lifespan data in West et al. (2001).[12] The metabolic energy consumed over a lifetime is thus related to the adult body mass by a taxon-dependent but roughly body-size independent integral

$$\frac{E_{lifetime}}{M} = \frac{E_c}{m_c}\int_0^{\tau_D} d\tau(1 - e^{-\tau})^3. \tag{6}$$

Thus we note that, although the maintenance rate B_c/m_c per unit *time* varies over four orders of magnitude between zooplankton and large fish or large mammals, it is roughly invariant per unit *biomass* grown. Developmental times and lifetime scale inversely to maintenance rate so that physical time factors out of Eq. (6).

The entropy reduction ΔS_M to form a body of mass M, by the very rough estimates of Morowitz, is given approximately by

$$-\Delta S_M \sim \frac{M}{10\,\text{g}}N_A, \tag{7}$$

where N_A is Avagadro's number, and the minimal energy expected by Eq. (1) is then

$$E_M \sim k_B T \frac{M}{10\,\text{g}}N_A. \tag{8}$$

The lifetime energy consumption thus relates to the minimal energy to create the adult reversibly as

$$\frac{E_{lifetime}}{E_M} = \frac{E_c}{k_B T N_A}\frac{10\,\text{g}}{m_c}\int_0^{\tau_D} d\tau(1 - e^{-\tau})^3. \tag{9}$$

4.3. Observations about metazoan scaling

The prefactor appearing in Eq. (9) is a modestly taxon-dependent, but body-size-, and temperature-independent constant. For mammals the estimate $E_c/m_c \approx 7\,\text{kJ/g}$ in West et al. (2001) gives

$$\frac{E_c}{k_B T N_A}\frac{10\,\text{g}}{m_c} \approx 30. \tag{10}$$

The remaining dimensionless integral in Eq. (9) has a modestly taxon-dependent value $\sim 10^{0.5}-10^2$ determined by τ_D. The roughly constant magnitude of Eq. (10)—varying only by factors of about 3 in the wide range of data collected on metazoan allometry (West et al., 2002)—confirms that, for metazoans as for bacteria, the metabolic energy required for new growth is an essentially constant multiple of the minimum bound set by reversibility. Body mass varies by 14 orders of magnitude, and body temperature by 35 °C within the data set, while organizational complexity spans the range from zooplankton to mammals and birds. Across all these ranges, growth

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[10]$T = 281\,\text{K}$ for cod and $T = 288\,\text{K}$ for salmon.

[11]Note that the same comparison with fitted values of a for mammals from the cow to the rat in West et al. (2001), and the metabolic fit parameter for mammals and birds in Gillooly et al. (2002), gives $E_c/m_c \approx 5900\,\text{J/g}$, very close to an updated estimate for juvenile but non-embryonic mammals by these investigators (J. Brown, pers. comm.).

[12]Informal surveys of lifespans for birds, compared to the corresponding timescales from West et al. (2001), can yield values as large as $\tau_D \sim 100$.

appears to be constrained by a fixed energy cost per bit of information gained by the organism's biomatter.

A similar but weaker observation may be made about the dimensionless integral, which describes the more complex balance of growth and maintenance costs in metazoans and has implications for theories of aging. The energy integral (5) up to any developmental stage depends only on E_c/m_c and the body mass for that stage through τ_i. Thus developmental stages linked to fraction of adult body mass are also indexed by fixed multiples of the energy to reversibly form that mass, independent of physical time or temperature.

This statement applies also to senescence, to the extent that it is linked to other mass-dependent stages of life, such as age at first reproduction. Scaling that respects Eq. (9) with roughly constant τ_D implies that death occurs whenever an amount of metabolic energy has been consumed equal to that required to "re-write" the fundamental information in biomatter a fixed number of times (on the order of a few hundreds to thousands). Any other explicit time or temperature dependence would appear as a violation of either the fit to the universal growth curve (4) or the characteristic metabolic age at death τ_D. The fact that within a taxon where τ_D is roughly constant across a wide range of body sizes and temporal lifetimes (the mammals, for instance, or the birds), senescence is associated with a *mass-specific* ratio $E_{lifetime}/E_M \approx constant$, would seem consistent with theories of aging such as those based on mitochondrially generated radical oxidizing species (Harman, 1956, 1972).[13]

Note that one need not take a position on the theoretical explanations for these allometric relations by West et al. to accept the empirical regularities presented here. The fit of the growth equation (2) to the temporal trajectory of ontogenetic growth (West et al., 2001), together with the dimensionality of the terms in the equation, leads to the energy integral (9) as an equivalent representation of the data.

Finally, we note that the independent constancy and comparable magnitude of the prefactor and aging integral in Eq. (9) suggest no qualitative distinction between irreversible effects associated with "inefficiency" of growth and those associated with maintenance. The coefficient (10) nominally includes thermodynamically irreversible effects such as pyrophosphate hydrolysis that drives metabolic and biosynthetic reactions forward at a high rate, irrespective of organism complexity. The dimensionless integral, in contrast, describes costs of "maintenance" during the complex metazoan growth trajectory, including costs of signaling or hydrolysis and replacement of proteins and RNA during normal cell function, as well as cell degradation and replacement. There is no reason *a priori* to suppose that the inefficiencies in the coefficient (10) are qualitatively different from those in the integral, or that natural selection has not optimized finite-rate physiology against molecule or cell turnover. Each independently indicates a fixed factor in the energy cost per bit of information accumulated during the lifecourse.

5. Conclusions and segue

This paper has argued that to answer relevant biological questions—such as why a biosphere has emerged and persisted on earth—require a paradigm for joint treatment of energy and information across multiple scales of time and structural complexity. It has also illustrated the difficulty of assembling such descriptions from small-scale molecular or other models, brought about by the fact that subtle system-level effects such as persistence of the organized state are essential to the correct informatic analysis of the components.

The main assertion of the paper has been that limits on the energetic cost of information have a universality and aggregatability across scales that models of non-optimal processes lack, and that reversible processes are appropriate devices for the analysis of such limits. This assertion will be demonstrated by construction in the next paper, where a specific reversible cycle will be shown to reject chemical entropy at a minimal cost in chemical work. The importance of the universality of limiting cases is that the model in the next paper will not need to be in strict correspondence to all cellular processes to derive the correct limits on their efficiencies. This will be especially important in aggregation across scales from the smallest and most restricted processes of physiology to models of limits on natural selection.

The third paper will then flesh out the interpretation of chemical entropy rejection as information gain by mapping the chemical cycle of Paper II onto Landauer's standard model for optimally efficient computation. A question raised in this paper—how one understands information flow from control machinery to controlled substrate—will be reconsidered there in explicitly computational terms. In that context it will be possible to separate the several information measures involved in any reversible reaction or computation, and to identify which are limited by energy flows.

Acknowledgment

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[13]Note, however, that they may be consistent with theories of positive selection for senescence as well. As long as lifespan scales as $M^{1/4}$, the return of core metabolites to the environment by death of the adult organism occurs at a lifetime average rate scaling as $M/M^{1/4} = M^{3/4}$. At this rate, which has the same scaling as the ongoing rate of uptake of nutrients during the course of life, adult mass is decoupled from the conditions for stoichiometric flux balance within the ecosystem. In other words, these scaling relations cannot be used to argue against the hypothesis that, as soon as the adult has reproduced, selection favors that it die to make resources available for the next generation.

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