

# Chemical Carnot cycles, Landauer’s principle, and the thermodynamics of natural selection

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An idea from computer science known as *Landauer’s principle* provides a useful way to think about relations between metabolic energy and the information in biological systems. Landauer’s principle relates the Shannon entropy in data streams to the thermal entropy of heat flows, and asserts that a reduction in the entropy in a data stream (as by a computation) can be accomplished only with the rejection of at least as much entropy to the environment, in the form of heat produced from work performed by the computer. Entropy reduction from the creation of ordered chemical ensembles by metabolism, structured by natural selection, corresponds to data entropy reduction in computer science. A formally identical Landauer principle relates the metabolically-instilled chemical information to heat rejected to the environment, and to the chemical work required to be performed by cells. The Landauer bound is attained when metabolism operates *reversibly*, an idealization that in real cells is limited by the ability of enzymes to create an infinite separation of timescales between their catalyzed and uncatalyzed reactions. Metabolism in the reversible limit can be organized around cycles isomorphic to the Carnot cycle for heat engines and refrigerators. Particles transported across different chemical potentials by metabolism take the place of entropy transported across different temperatures by a Carnot engine or refrigerator. Chemical “Carnot cycles” are the elementary computational steps of metabolism, and when their rates are structured by natural selection, Landauer’s principle relates the total work consumed to the Kullback-Leibler divergence produced in the chemical system from its Gibbsian thermodynamic equilibrium. If this argument is extended to include simple models of dissipation, a relation is obtained between the structure of the selective fitness function, the information maintained in biomass, and the metabolic work required to maintain it against dissipative degradation.

Keywords: Carnot cycle; Landauer’s principle; Thermodynamics; Natural Selection

## I. INTRODUCTION: KINETICALLY CONSTRAINED ENSEMBLES AND THE LIKELIHOOD OF LIFE

Characterizations of life in terms of information [1–3] have always been hard to interpret [4], because information is a statistical concept [5–8], and yet the paradigms that shape our thinking about statistical mechanics are severely deficient, even for describing the emergence of organization in simple chemical reactions, much less for talking about the origin of life, metabolism, or evolution. This longish introduction argues that the incorporation of kinetic constraints as corrections to equilibrium statistical mechanics is the major requirement to produce an ensemble description appropriate to living matter, and advocates a paradigm based on separation of timescales and engine-like organization of chemical reactions to capture the essence of metabolism.

The introduction summarizes all main results of the paper, which are that: 1) the natural composite transformation in terms of which to organize metabolism is a chemical analogue to the thermal Carnot cycle; 2) the chemical “states” on which metabolic cycles operate are akin to data in physical models of computation, and a relation called Landauer’s principle limits the information that can be put into a chemical state by a given amount of metabolic work; 3) the transformations of particular chemicals by metabolic pathways lead in the presence of natural selection to non-equilibrium chemical

distributions reflecting some part of the structure of the selective “fitness function”, and; 4) Landauer’s principle describes transient phenomena, and dissipation must be understood if we wish to relate the rate of ongoing metabolic work to the information maintained in evolutionary steady states. Sketches of the arguments justifying these claims are given where they are introduced, and the subsequent sections provide precise definitions and proofs. A discussion at the end returns to a number of issues that will have to be solved to use the bounds derived abstractly here, in chemically realistic and biologically relevant ensembles.

### A. Stability, entropy, and information

From the perspective of classical thermodynamics, biomass is a paradoxical state of matter [3]. It appears to have been a stable component of the earth’s chemical milieu for almost four billion years [9], and yet any calculation of the entropy of its constituents that we understand how to perform yields a number far below the entropy of the same components in a thermodynamic equilibrium [1, 2]. In statistical mechanics, the exponential of the difference between the entropy of any macrostate and the entropy at equilibrium is the approximate probability that the macrostate should occur as a large deviation within the equilibrium ensemble [10]. Thus biomass as a state of matter is predicted to be have

been highly unlikely to form [11], and correspondingly certain to have decayed as quickly as kinetic constraints permitted, should it ever have arisen by chance.

A parsimonious interpretation of the rapid emergence of life on earth (probably in less than 0.2 billion years) [9] is that there are not very large kinetic barriers between terrestrial states with and without life – certainly not large enough to preserve life as a metastable state over billions of years – and that life has persisted because the primordial *abiotic* state of earth was unstable or metastable, and the origin of life was a relaxation into a more likely state [12]. In that case the “improbability” of biomass by current calculations should be regarded as a measure of the failure of equilibrium statistical mechanics to describe the kinds of ensembles within which life is observed.

The existence of life obviously depends on non-equilibrium boundary conditions. On earth these take the form of ordinary intensive state variables with different values where they couple to different nodes in the large network of possible chemical reactions. (In an equilibrium ensemble, each intensive state variable is required to have a unique value affecting all degrees of freedom.) For instance, sunlight and the earth’s thermal microwave background are both well approximated as black-body spectra, but they have respective temperatures of 6000K and 300K, and among terrestrial molecules the biologically produced chromophores couple particularly strongly to sunlight [13]. Similarly, geothermal cycling produces sulfur and nitrogen in reduced forms, while inorganic carbon and phosphorus occur highly oxidized [14]. This difference in redox state (a kind of chemical potential for electrons) is associated with particular molecules (carbon dioxide and phosphate versus ammonia and thiols or hydrogen sulfide), and the resulting flow of electrons powers biosynthesis in chemotrophic ecosystems [15] (and is maintained by redox differences produced photosynthetically for the same purpose in phototrophs [16]).

The entropy reduction upon formation of biomass from abiotic precursors (including the emergence of life from lifeless geochemistry) thus seems to arise from quite coarsely specified boundary conditions, more like the entropy of latent heat in a phase transition than like microscopically dictated order. The challenge is to understand how the very large errors made by equilibrium statistical mechanics are related to the magnitudes of difference in the multi-valued state variables away from equilibrium.

Chemical kinetics has the potential to produce large deviations in a driven ensemble from its counterpart at equilibrium, but the roles of kinetic constraints can be so diverse that it is helpful to have an organizing paradigm within which to introduce them as refinements to equilibrium ensembles, and to estimate their consequences. For this the choices vary widely. Proponents of “dissipative structures” [17] attempt to classify the formation of biomass with such pattern forming processes as Benard convection and Belousov-Zhabotinsky chemical

oscillation, in which irreversibility and particular characteristic timescales for dissipative reactions are essential components for the formation of spatial patterns.<sup>1</sup>

A quite different proposal is that metabolism is organized similarly to the Carnot organization of heat engines [19], a paradigm in which separation of timescales serves to decouple the transformations constituting “work cycles” from those responsible for dissipation, though the work cycle transformations themselves could be approximated as reversible within some range of timescales.<sup>2</sup> 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 [20]. The separation of timescales between catalyzed and uncatalyzed reactions kinetically isolates particular reaction sequences and couples these to sources of energy (the non-equilibrium component of boundary conditions), while leaving most mechanisms for decay slow and decoupled. Moreover, the sequencing of reactions as substrates bind to first one and then another catalyst make the construction of complex composite transformations natural.

For many reasons, paradigms based on reversibility and engines are preferable to paradigms based on dissipation for describing cell physiology, which will be taken here as the primary process responsible for producing the properties of biomass. The patterns formed by dissipative structures are soft, because they arise from ensembles in which the local statistics are near equilibrium [17], and structure forms only on the scale of macroscopic diffusion across gradients. In contrast, molecules with significant free energies of reaction are often well mixed in the cytosol, but inert until acted on by an enzyme that couples their reaction very precisely to some other chemical transformation. In this sense enzymatic control of reaction pathways resembles the action of valves and linkages in engines, and it is responsible for both the great efficiency of many cellular processes, and their ability to operate across a range of rates depending on environmental conditions, and in some cases even to re-

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<sup>1</sup> Schrödinger [3] had already characterized models of the type now called “dissipative structures” as describing the formation of “order from disorder”, and argued that the principles behind such models were less relevant to addressing the failures of equilibrium statistical mechanics than principles explaining the creation of “order from order”, or the emergence of mechanistic function and stability in ostensibly microscopic ensembles. Among the more convincing roles for dissipative structure formation in biology continue to be those related to Turing mechanisms, responsible mostly for organization in intracellular and intercellular physiology during development [18].

<sup>2</sup> A difficulty with the Kauffman proposal is that it exists only as an analogy, due in part to the vague treatment afforded the notion of work [19]. One purpose of this paper is to formalize the role of chemical work in metabolism and evolution, and show in what senses it does or does not correspond to the thermal work of Carnot.

verse direction.<sup>3</sup>

Perhaps most important, paradigms that treat dissipation phenomenologically in terms of local equilibrium state variables do not produce entropy measures different from the equilibrium entropy. Though in cases the correct phenomena can be predicted with “entropy production” principles [17] (but see also Ref. [7], Ch. 14), the loss of the interpretation of entropy as a log likelihood<sup>4</sup> reflects the deeper problem that such phenomenological treatments do not correspond to well-defined kinetically constrained ensembles. It is possible to show in simple cases that the interpretation of entropy as log likelihood is not lost when driven ensembles are properly defined, but that the “entropy” function of equilibrium state variables is no longer the true entropy and uncertainty measure on macrostates [21].

Within a reversible paradigm it remains sensible to talk about the states of subsystems, their entropies and associated measures in a statistical phase space, and also how those entropies are changed as subsystems are brought into contact and transformed, much as one does in the study of engine cycles. Kinetics enters the specification of the ensemble as a constraint on which subsystems are in approximate equilibrium and which are subject to transformation, as a function of timescale and contact with each other and the non-equilibrium boundary conditions.

With the existence of well-defined subsystem states, it also becomes possible to regard reductions in subsystem entropies as measures of *information*, in the usual sense of statistical inference [7]. Thus we are led to interpret the log-“improbability” of life in equilibrium statistical mechanics as a measure of the information in the kinetic constraints separating the components of biomass and the reactions of metabolism from a background of near-equilibrium reactions, and to ask how much information there can be in living systems, what it is about, and how to model the process by which it is “written into” biomass.

The amount of information in biomass should depend on metabolic energy flux and on regularities in the action of natural selection, and two questions must be answered to predict these dependencies. The first question is how much “new” information can be written per unit flux under ideal conditions. This limit describes the creation of new domains of order, whether new cells grown from abiotic precursors or new genomes introduced into an ecosystem. In principle it is a question about lossless construction, for which the bounds on information per energy should be drawn from equilibrium thermodynam-

ics. The second question concerns how fast ordered structures decay and what fraction of metabolic flux, rather than writing “new” information, must re-write a representation of existing information as it decays, limiting the amount of information that can be metabolically maintained. To answer this question one must know something about the structure and timescales of dissipative processes. However, in this role dissipation is treated as a limiting factor in the maintenance of information, rather than a process essential to its creation.

This paper does not proceed further with a systematic construction of a kinetically constrained ensemble appropriate for describing the emergence and stability of life. Instead it derives general relations between energy flow, entropy transfer among subsystems, and the production of information, which give structure to any such ensemble, taking as given the kinds of separation of timescales typical of catalysis, and a kinetically and energetically structured environment capable of providing sources of chemical work as well as dissipation. (Some further considerations relevant to the full construction are discussed in Sec. V). The key elements in the derivation are: 1) formal organization of metabolic processes that transfer energy and entropy around the chemical counterpart to Carnot cycles, 2) relations between metabolic cycles and certain models of computation, particularly those concerning the physical limits of information production, and 3) the interplay of metabolism as a process at the individual level and natural selection as a statistical filter on the organization of ecologies.

## B. New information production and Landauer’s principle

Reasoning from dimensional analysis and the definition of temperature, in the absence of dissipation one can argue for a general relation between work, heat, and information defined as some sort of entropy reduction, of the form

$$dW = dQ = -k_B T dS \equiv k_B T d\mathcal{I}. \quad (1)$$

In Eq. (1),  $dW$  is an increment of work performed on some system,  $dQ$  an increment of heat rejected by the system to a thermal bath at temperature  $T$ ,  $-dS$  the reduction in some thermodynamic entropy of the internal state of the system (measured in nats),  $d\mathcal{I}$  the definition of this entropy reduction as some measure of information, and  $k_B$  is Boltzmann’s constant.

The dimensional argument,<sup>5</sup> which is roughly correct and will be refined in later sections, goes as follows: the entropy of a driven system can only be reduced by some amount  $-dS$  if the entropy difference is “exported” to

<sup>3</sup> The premiere example is the functioning of the ATP synthase, of which extensive use will be made in Sec. II.

<sup>4</sup> This is implied by what has been said so far. If the entropy of an ordered macrostate remains much lower than the entropy at equilibrium, but the ordered macrostate is predicted by other considerations to be the outcome instead of equilibrium, the entropy can no longer be functioning as a log likelihood.

<sup>5</sup> Dimensional analysis is only unambiguous, of course, if a single value for  $T$  characterizes the entire system and its environment.

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. Furthermore, for this 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  $dW = dQ$  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  $dU/k_B T$ ).

Morowitz [1] 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 Avogadro’s number times the dry weight of the cell, divided by an average molecular weight – about ten grams – of the cell’s constituents.) The minimum heat  $\int dQ$  required by this argument to be rejected to the environment during growth of a new bacterial colony differs surprisingly little (about a factor of 1/3) from calorimetric measurements, suggesting that bacteria under optimal growth conditions waste little metabolic energy beyond what is required for growth. The comparison is not quite proper, because 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.

While Eq. (1) is dimensionally sound and consistent with the definition of temperature, it is a non-trivial assertion that entropy can simply be transferred among system components subject only to the constraints of the intuitive argument given above, and the dimensions alone do not suggest what kind of thermodynamic structure a “driven system” must have for interesting transformations to exist. For a classical thermodynamic system with state variables pressure ( $p$ ), volume ( $V$ ), temperature ( $T$ ), such as the ideal gas commonly used to study heat engines [22], Eq. (1) describes trivial operations like isothermal compression, but since all entropy is transported as heat, there is no way to extend such simple transformations into more “lifelike” repetitive cycles if the temperature is fixed. Interesting cycles are possible if the system comprises a collection of isolated subsystems, some of which can be cooled by a Carnot refrigerator while the entropy extracted from them is rejected to an environmental heat bath, but it is not clear that such cases are directly relevant to biochemistry, which to good approximation is carried out at a fixed temperature.

Essentially the same questions as those about the organization of biomass arise in the study of the physical limits of computation, where they have led to a relation called *Landauer’s principle* [23]. A rough statement of Landauer’s principle is that an amount of heat equal to  $k_B T \log 2$ , must be rejected by an ideal computer to the environment per bit of information produced. A proper

statement of the principle defines the vague notion of “production of information” in terms of erasure of memory cells containing some bits from an input data stream, and asserts that heat  $k_B T \log 2$  must be rejected per bit erased. Computation in this context is like metabolism in being carried out at a single temperature, and requiring the transfer of entropy to a heat bath from other forms of configurational uncertainty, in this case representing “data”. The argument for Landauer’s principle is essentially the same as that just given for metabolism, with some additional steps to make terms well-defined.

Landauer’s principle for computation remains a subject of debate among some philosophers [24, 25], mostly concerning whether one should represent both data streams (where the microscopic configuration is of interest) and heat baths (where it is not) with a common ensemble description. It is therefore interesting from multiple perspectives to recognize that the problem of computation that leads to Landauer’s principle is in fact the same as the problem of creating order metabolically, and that a variant on Eq. (1) can be derived for both from first principles.

The confusion that has been introduced into the discussion of computation, about which variables should and which should not have an ensemble description, does not arise for biochemistry, where it is understood that the ensemble description is defined by the choice of boundary conditions for the system. The clearer emphasis given by chemistry to the meaning of statistical mechanics shows that the questions leading to Landauer’s principle only make sense when data as well as configurations in the heat bath are treated statistically.<sup>6</sup> Moreover, the Legendre dual structure of chemistry makes clear that the extension of a  $(p, V, T)$  state space to include at least one more state variable pair (such as chemical potential  $\mu$  and particle number  $N$ ) is what makes interesting Landauer relations of the form (1) possible at fixed temperature. Finally, the mapping that generates parallel derivations of Landauer’s principle for metabolism and computing provides one concrete sense in which metabolism and evolution may be considered computational processes.

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<sup>6</sup> Jaynes [7] has emphasized that statistical mechanics is properly understood as the application of methods of statistical inference to physical systems in which only a subset of the dynamical degrees of freedom are explicitly controlled by boundary conditions that define the resulting ensemble of possible configurations. Jaynes emphasizes that these boundary constraints, which appear as *state variables* of the thermodynamic description, define all that is “known” about the allowed configurations. This paper will emphasize that they define all that is *controlled*. Because the data input to a computer are not determined by the computer’s design, it follows that the appropriate statistical description of computation uses an ensemble description of the data.

### C. Evolution and the maintenance of information

Individual metabolic pathways or cycles consume chemical work to reduce the entropy of small clusters of atoms or functional groups, but it is the accumulated action of diverse metabolic cycles that generates biomass as a distinctive distribution enriched in some molecules and depleted of others, relative to equilibrium. The entropy of a single molecule relative to its biosynthetic precursors is a measure of the information produced by a single pathway, but the distributional entropy reduction characteristic of biomass provides information about which pathways have acted most often to convert work to heat in the environment.<sup>7</sup> This relative rate bias among pathways, created by the energetic and chemical structure of the environment, is the lowest-level metabolic source of “fitness” discrimination by natural selection.

Adami has advocated [26, 27] interpreting the entropy reduction in a population of genomes in equilibrium under natural selection, relative to an imagined population with equal a priori probabilities, as a measure of *mutual information* about the structure of the selective environment, because of a formal similarity of the evolved distribution to a conditional distribution on an environment that happens to have a determined value. The interpretation of mutual information is intuitively appealing as a statement that not only gene sequences, but metabolites, enzymes, and cell structures are not so much special in themselves, as that they form an *anticipatory* model of the useful situations that the organism is likely to encounter in its environment, and for gene sequences it has some functionality for identifying selectively neutral loci [27]. However, the interpretation only applies in a certain degenerate sense, in that there is no variability or probability distribution assumed on environments, so one is really only comparing entropies of some random reference state (whose status as part of a living system is in itself problematic) and of the evolved state (acknowledged in Ref. [26]). This difference of entropies will appear below in relation to the work flux that produces it, though we will generalize from the case of chemically degenerate gene sequences to more heterogeneous chemical states, and the entropy difference will be generalized to a Kullback-Leibler divergence [6].

The Landauer bounds on information from energy provide a foundation for analysis, both of individual

metabolic cycles and of evolutionary regularities, and nontrivial kinds of fitness can be incorporated even in thermodynamically reversible models. Comparisons of estimated Landauer bounds to calorimetric measurements of metabolically generated heat flux [1] even suggest that in some situations these may quantitatively approximate leading constraint on the dynamics. However, the growth of bacteria into new medium (and indeed *any situation* to which the Landauer bounds can sensibly be applied) is a transient phenomenon, which gives way to different dynamics as organisms approach the carrying capacity of their environment. In the latter kinds of quasi-steady dynamical states, new biomass replaces old biomass, and what we are able to measure is the ongoing *state* of entropy reduction in relation to the *rate* of metabolic energy flux. Even with a Landauer principle as foundation, to compare a state to a rate we need a characteristic timescale, whether it be a generational timescale for cells to die and be replaced, or an evolutionary timescale for innovation or fixation.

The treatment of dissipative timescales is not the main concern of this paper, but the formal inclusion of dissipation both adds physical realism, and stabilizes certain artifacts (such as chaotic dynamics) that arise in a reversible world, and which would otherwise make assigning a steady-state entropy reduction as the outcome of natural selection impossible. Evolution is also typically thought of as having three equally important elements: replication, selection, and mutation. [28] While the first two are readily and naturally incorporated in reversible models, mutation is by nature an irreversible process, and most naturally modeled together with other sources of dissipation. The results derived below for dissipative timescales are less general than those for reversible metabolism.

### D. On the use and interpretation of models

Landauer’s principle is usually studied with highly artificial models of logic and memory devices [23], which make analysis of the statistical issues transparent, but which would be impractical to build into a computer for performing computations of any complexity. Conversely, existing computers do not approach saturating the Landauer bound, because currently practical logic and memory devices still have complex internal states and make dissipative transitions. The artificial models remain useful, though, because neither the essential features of computation nor the steps in the Landauer derivation are changed by the kinds of dissipation that occur in real computers.

This paper will use conventional idealizations in the discussion of Landauer’s principle, and adopt similar simplifications for discussing metabolism and evolution. The assembly of oligomers (RNA and DNA are the canonical model, though polypeptides also fit the general schema) from monomers, coupled to ATP hydrolysis, will be

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<sup>7</sup> We will see in Sec. III that the same distinction is natural in computation, where different observations of a data stream lead to entropy reductions that define different information measures. In particular, observations of the output of different instances of a computation, corresponding to the outputs of different metabolic cycles, are informative of the residual deviation *not* eliminated by the computation, while the entropy reduction of the output relative to the input is informative about the computational algorithm itself, corresponding in biology to the structure of the evolutionary fitness function.

adopted as a model of the basic function of metabolism. Though it accounts for only a tiny fraction of the physical entropy change from building a cell, polynucleotide assembly is the biochemical process that best separates informational state from the chemistry of biosynthesis or polymerization in real cells, and digestion and polymerization of nucleotides can usefully be idealized as reversible processes without qualitatively changing either the actual mechanism or its significance.

Similarly, the basic mechanisms of natural selection will be modeled as the biased action of a variety of metabolic cycles whose only function is to digest one polymer and re-assemble its monomers into another of the same constitution but generally differing sequence. Population-level models of this process yield conventional replicator equations, and with appropriate dependence of the rates on the concentrations of digested and synthesized polymers, single polymers admit the interpretation of Darwinian “individuals”, and catabolism and anabolism correspond respectively to death and reproduction of these individuals. The intrinsic bias that distinguishes different metabolic cycles provides a concrete notion of “fitness”, and non-metabolic transitions that interconvert polymers can be added to model mutation or other dissipative processes, and to represent any chemical non-uniformity among polymers that may cause sequence specification to deviate from an absolute measure of the “information” in an ordered population of polymers.

These models are to be understood in the same way as the idealized models of computer logic and memory (though their correspondence to processes in actual cell physiology is somewhat more literal). In many respects, they are not representative of all biochemical processes, and they need not be as long as their simplicity and the idealization of reversibility do not introduce qualitative changes of mechanism from the more general cases. For instance, the entropic cost of specifying a gene sequence does not scale (in cell size) with the Gibbs entropy reduction to synthesize the biomass of the cell it is in from abiotic precursors [29], and probably does not reflect “information” of the same kind. (Sec. V returns to questions of how these may be related.) Also, the distinction of sequence information from chemical entropies of formation, which is not a bad approximation even for real polynucleotides, does not exist for many classes of biomolecules. Finally, the neat separation between chemical “work” and entropy-changing energy exchanges in ATP-driven polymerization, which will be used below to relate metabolic cycles to Carnot cycles, does not hold for most biochemical pathways, or even for ATP synthesis through substrate-level phosphorylation. Outside of the pathways used as examples, the processes considered separately here are usually present together in each reaction step, and some of them are burdened by large dissipative losses. Yet, just as the Carnot cycle can be used to define a general covering of a thermal  $(p, V, T)$  state space with oriented cycles, and thus to predict the efficiency of any reversible engine, the metabolic cycles considered here

provide a covering for chemical state spaces with particle number as well as heat exchange, and imply Landauer’s principle for general cycles in this state space.

## E. Landauer’s principle and Carnot cycling

While the notion of thermal refrigeration is not quite the correct one to capture how entropy is transferred by metabolism out of forming biomass and into the environmental heat bath, a related concept of “chemical refrigeration” exists and can be idealized analogously to the Carnot idealization for thermal refrigeration.<sup>8</sup> Where Carnot engines and refrigerators transport entropy among reservoirs at different temperatures, “chemical Carnot cycles” can be defined, which transport molecules or functional groups among reservoirs where these have different chemical potentials. Biomass becomes ordered when particles are transferred from reservoirs at low potential to reservoirs at higher potential, just as refrigeration is accomplished by the transfer of entropy from low-temperature to high-temperature reservoirs.

The close similarity between thermal and chemical Carnot cycling explains why the same relation (1) can be used for a multi-component thermal system as for metabolism at fixed temperature. However, the chemical Carnot cycle is not the same as the thermal cycle because the former exists in a richer space of state variables. The chemical cycle is only analogous to the closed thermal Carnot cycle if one first projects onto the  $(\mu, N)$  state variables, and then maps the cycles with the formal correspondence  $(\mu, N) \leftrightarrow (S, T)$ . In the full state space including entropy the chemical “cycle” is not actually a closed path, and the difference between its starting and ending points measures the Landauer entropy transfer that necessarily accompanies “chemical Carnot cycling”.<sup>9</sup>

In a sense Landauer’s principle is dual to Carnot’s theorem. The problem addressed by the Carnot engine is the

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<sup>8</sup> Chemical refrigeration cycles, like the thermal Carnot cycle, are nothing more than convenient composite transformations obtained by judicious ordering of elementary chemical reactions. However, together with assumptions such as separation of timescales and sequential catalysis needed to motivate them (addressed in detail in Sec. II), these quite conventional constructions very nicely address Schrödinger’s call for “new physics” to describe biology. In particular, the idealization of reversibility and the way it separates the constraints on transformations from intrinsic timescales make chemical refrigeration a description of “order from order”.

<sup>9</sup> Through this derivation we can assign a concrete meaning to the “work cycles” proposed by Kauffman [19] as the basic unitary elements of metabolism. Note that this definition both limits the context in which these may be properly treated as cycles, and identifies the connection to Landauer’s principle and computation, which a purely formal analogy to thermal Carnot cycling misses.

extraction of energy from stochastic degrees of freedom. To import the energy into a system (the engine plus its load), one must also import entropy, and if the import step is to be performed repeatedly by a finite system, the entropy taken in must be rejected to some other reservoir, yielding net work only if the output reservoir has lower temperature than the input. Carnot’s theorem states that entropy flux, here acting as the “carrier” of energy flux, is conserved under idealized conditions, and that the efficiency of energy extraction is thus determined by the relative temperatures of the input and output reservoirs. The converse problem is faced by metabolism or computation, to reject entropy from a data stream or chemical system to a heat bath, for which energy is required as a “carrier”. Landauer’s principle states that, under ideal conditions, energy flux is conserved in passing from a source of work to a sink for heat, and this conservation law limits the rate of entropy rejection.

#### F. Organization of the remainder of the paper

With these statements the reader has seen in a rough form all the essential relations between metabolism, refrigeration, computation, and Landauer’s principle, and the sense in which they provide a foundation for organizing statistical ensembles structured by kinetic constraints and non-equilibrium boundary conditions. The following sections derive the results formally.

Sec. II introduces the “chemical Carnot cycle” and analyzes its thermodynamics. In particular it shows that the Kullback-Leibler divergence is the information measure altered by chemical work, which reduces to the negative entropy for chemically degenerate systems or those in which the Gibbsian equilibrium is a coarse-graining of the evolved distribution.

Sec. III reviews Landauer’s principle from the usual computational perspective, emphasizing the meaning of different information measures. It shows how the statistical assumptions that are natural in chemistry resolve the usual objections to ensemble modeling of data.

Sec. IV then attempts to relate formal models of metabolism and evolution. The relations in this section are the only explicitly model-dependent results in the paper, and are intended to illustrate how the information in biomass relates to the structure of selective fitness functions. A detailed treatment of evolution may be as complex as all of biology, and may be unapproachable until better models of development exist. However, some constraints known from allometric scaling do lead to interesting relations between growth and the Landauer bound, and between aging and dissipative processes.

Finally Sec. V returns to the issues with which we opened the discussion. It considers the actual chemical constraints on organosynthesis, as they apply both to modern organisms and possibly to the origin of life, and describes how they may produce a multi-scale statistical ensemble with the organization proposed here. It

also surveys the considerable complexity that will have to be understood to relate genomic to thermodynamic information measures.

## II. CHEMICAL CYCLES IN METABOLISM AND EVOLUTION

The most obviously informational component of biomass is the oligomers: RNA, DNA, polypeptides, and some oligosaccharides used in signaling. These are large molecules made of roughly uniform inventories [11] of a small number of monomers, for which the free energy of assembly is roughly independent of sequence. In terms of chemical or energetic cost, they are more or less combinatorially neutral under sequence permutations. Among these, the most exclusively informational are RNA, which has lost all but a few enzymatic functions it may once have had, and DNA, which probably never had such functions. If we are to choose one idealized chemical reaction to illustrate the relation of metabolism to information, we will deviate least from the literal biochemistry by considering the problem of sequence selection in a population of chemically identical oligomers. We can omit further specific assumptions about the energetics of polymerization by considering only oligomers with some fixed number  $N$  of monomers each.

To maximize the correspondence with the Carnot analysis of heat engines, it is convenient to have some source of chemical *work* coupled to permutation of the sequences of oligomers. A minimal idealization of real biochemistry accomplishes this also, if we model ATP-mediated assembly and dis-assembly of polymers within a solution of monomers, and adopt an idealized model of the ATP synthase as a source of entropy-free enthalpy in the conversion of ATP to AMP and orthophosphate. The ATP synthase – remarkably mechanical and approximately reversible in real cells – becomes the piston of the Carnot analysis, decoupling the polymerization problem of interest to us from whatever chemical engine cycles drive the synthase. It is certainly interesting that nature appears to have favored such a mechanical coupling between redox energy and the most prevalent biosynthetic reaction (phosphate-driven polymerization) so strongly that the ATP synthase has been an invariant feature of cells since the last common ancestor [30].

Therefore introduce an alphabet of  $Z$  monomers with chemical symbols  $M_z, z \in 1, \dots, Z$ , and vectors of ordered components  $\vec{\alpha} \equiv (\alpha_1, \dots, \alpha_N)$ , with  $\alpha_i \in 1, \dots, Z$  for each  $i$ , to index polymers of length  $N$  made from the monomers. Take  $\Pi_{\vec{\alpha}}$  as the chemical symbol for a polymer with sequence  $\vec{\alpha}$ .

To establish bounds on the metabolic cost of sequence specification, we deviate slightly from literal biochemistry by supposing that polymerization is in equilibrium

with ATP hydrolysis in the reaction



( $\text{P}_i$  denotes orthophosphate.) This is really only an assumption about rates relative to diffusion and regeneration of ATP, since we need not restrict the value of the equilibrium constant to be near unity. Reaction (2) may be interpreted in terms of polymerization activated by pyrophosphate transfer from ATP (onto the other nucleoside monophosphates by nucleoside monophosphate kinases [20], p. 747), or adenylate transfer (as in polypeptide synthesis [20], p. 880, or the action of DNA ligase if the “monomeric” units are thought of as pre-formed strands of DNA [20], p. 793)<sup>10</sup>. In all such cases either the activation or polymerization step is coupled to pyrophosphate hydrolysis, and the other to release of AMP. If we denote  $\nu_z^{\vec{\alpha}} \equiv \sum_{i=1}^N \delta_{\alpha_i, z}$  (the number of occurrences of monomer  $z$  in  $\Pi_{\vec{\alpha}}$ ), we can recast Eq. (2) in canonical form



Denoting by  $[X]$  the molar concentration of any species  $X$ , and supposing that activities are proportional to concentrations for simplicity, we can write the equilibrium condition for reaction (3)

$$\left( \frac{[\text{ATP}]}{[\text{AMP}][\text{P}_i]^2} \right)^N = \frac{[\Pi_{\vec{\alpha}}]}{\prod_{z=1}^Z [\text{M}_z]^{\nu_z^{\vec{\alpha}}}} K_{\vec{\alpha}}(T). \quad (4)$$

If the polymers are chemically degenerate, all sequences are combinatorially neutral. This case corresponds to taking the equilibrium constant  $K_{\vec{\alpha}}(T)$  to be the same function of temperature for all  $\vec{\alpha}$  of length  $N$ . In general we will not need to invoke this simplification, and there is some advantage when thinking about the relation of distributional entropy to free energy of formation to treating the various  $K_{\vec{\alpha}}(T)$  as separate functions.

The ATP synthase reaction for interconverting ATP and AMP is



If we assume, by separation of timescales through catalysis, that ATP/AMP interconversion happens only through the synthase or in conjunction with polymerization/depolymerization, we need not consider reaction (5) in chemical equilibrium at any time.

We may idealize a primitive *metabolic cycle* as the combined catabolism of one polymer  $\Pi_{\vec{\beta}}$  to monomers and ATP, followed by anabolism of those monomers to some (generally different) polymer  $\Pi_{\vec{\alpha}}$ . Catabolism and anabolism correspond respectively to death and reproduction if we choose to regard the polymer produced as a molecular equivalent of an “individual”. The way in which we will endow different metabolic cycles with different relative rates below, to create a model of natural selection, respects such an interpretation but does not require it.

(Note as an aside that we need not worry too much about which polymers are interconvertible. The multinomial factor for polymer sequences  $\vec{\alpha}$  consistent with some set of constituents  $\{\nu_z^{\vec{\alpha}}\}$  give as by far the most numerous compositions those with  $\nu_z^{\vec{\alpha}} \approx N/Z, \forall z$ . Thus we could restrict the sum on  $\vec{\alpha}$  to  $\nu_z^{\vec{\alpha}} \equiv N/Z, \forall z$  from the outset, and be guaranteed interconvertibility without further restrictions on metabolic pairings, and without significantly changing the size of the configuration space of polymers considered. Everywhere below  $\sum_{\vec{\alpha}}$  may be interpreted with this convention if desired.)

### A. Serial catalysis and the metabolic cycle

Catalyst/substrate complex formation allows catalysts to act serially, so that the subset of reactions we consider to constitute a chemical equilibrium (with all other reactions forbidden) can change through time. Complex formation provides the equivalent of valves that decouple particular molecular species from the main reactions in a chemical counterpart to the classical Carnot cycle, and we may deviate from the reality of metabolism slightly to make it *reversible* by alternating coupling and decoupling with changes in the chemical potentials for ATP versus AMP in the main reaction domain.

“Biomass” in this description comprises a collection of reservoirs for the polymers of different sequences, which will be supposed here to be large enough that their concentrations and chemical potentials are not changed by the addition of finite numbers of molecules. Metabolism changes the entropy of biomass by changing individual polymer sequences and so altering the numbers of molecules and hence the entropy in different reservoirs, consuming or delivering chemical work as required to do so reversibly. An ideal cyclic metabolism preserves the total number of polymers and returns the monomer and ATP/AMP systems to their original states at the end of each cycle, so we eliminate effects of progressive energy storage in biomass from considerations of entropy change.

A single pathway in such an idealized reversible metabolism can be analyzed with the van t’Hoff reaction box [22] of Fig. 1. A reaction chamber filled with a solution of all the monomers  $\{\text{M}_z\}$  is serially coupled or uncoupled by valves from diffusive contact with reservoirs of two species of polymers  $\Pi_{\vec{\alpha}}$  and  $\Pi_{\vec{\beta}}$ . The re-

<sup>10</sup> A somewhat more complex process involving two ATP and various phosphate and adenylate transfers is involved in polysaccharide formation [16], p. 994, which would require a slightly different model reaction but not different principles.

actor is continuously in diffusive contact with reservoirs for ATP, AMP, and  $P_i$ , and these are injected with the stoichiometry of Eq. (5) by a system of pistons whose displacement is a pure work variable. The reactor and all reservoirs are kept at pressure  $p$  through the solvent, and temperature  $T$  through contact with a heat bath.

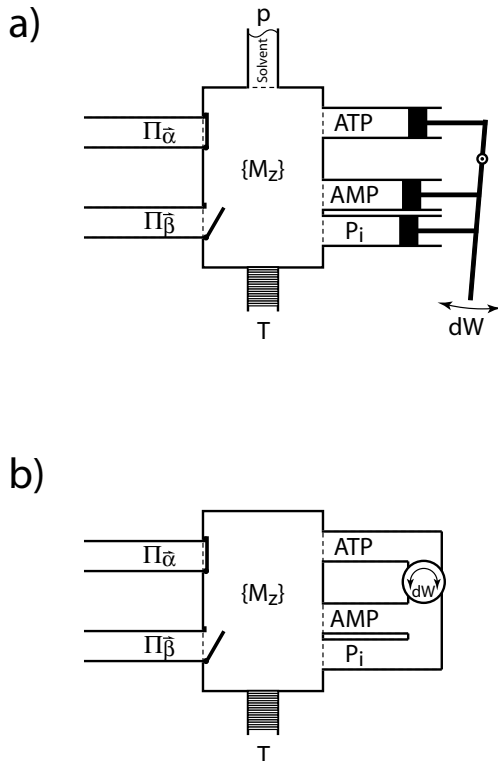


FIG. 1: a): Metabolism idealized with a van t'Hoff reaction box. Cylinders containing solutions of the indicated solutes are in diffusive contact with a reaction chamber through windows permeable only to the solvent and the solutes particular to each cylinder. Cylinders with polymers  $\Pi_{\alpha}$  and  $\Pi_{\beta}$  are infinite reservoirs, which may be decoupled from the reaction chamber by valves. The reaction chamber contains the inventory of monomers  $M_z$  and any solutes drawn from the other cylinders. The solvent reservoir is in equilibrium at a pressure  $p$ , and coupled to the reaction chamber through a window permeable only to solvent. A thermal reservoir maintains temperature  $T$  in the whole system. The action of ATP synthase is achieved in the van t'Hoff picture with some linkages that deliver concentrations of ATP, AMP, and  $P_i$  consistent with Eq. (5). b): The ATP synthase performs the transformation of Eq. (5) directly on the solutes.

A reversible metabolic cycle consuming polymer  $\Pi_{\beta}$  and producing  $\Pi_{\alpha}$  is shown in Fig. 2. It is the chemical analogue to the Carnot cycle for thermal engines or refrigerators, with particle number (in this case, ATP) taking the place of entropy and chemical potential taking the place of temperature in a Carnot state diagram. The cycle of Fig. 2 describes a chemical engine in the direction  $ADCBA$ , and a “refrigerator” in direction  $ABCD$ , if we assume the chemical potential of  $\Pi_{\alpha}$  is higher than

that of  $\Pi_{\beta}$ . The four arcs of the cycle (in the refrigerating direction) are specified as follows:

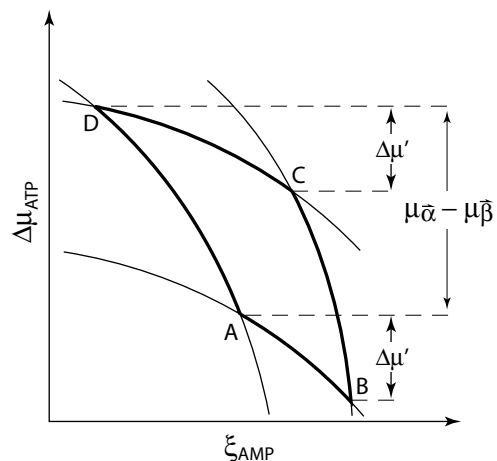


FIG. 2: A chemical refrigeration cycle  $ABCD$ A (or engine cycle  $ADCBA$ ), performed by the van t'Hoff box of Fig. 1. Individual arcs are described in the text.  $\xi_{\text{AMP}}$  is the number of moles of ATP converted to AMP by the pistons as the cycle progresses, and  $\Delta\mu_{\text{ATP}} \equiv \mu_{\text{ATP}} - \mu_{\text{AMP}} - 2\mu_{P_i}$ . If we assume chemical equivalence of  $\Pi_{\alpha}$  and  $\Pi_{\beta}$ , arcs  $AB$  and  $CD$  will lie on identical curves translated by  $\mu_{\alpha} - \mu_{\beta} = \log([\Pi_{\alpha}]/[\Pi_{\beta}])$  in the polymer reservoirs. Because the same number of monomers is generated along  $AB$  as is consumed along  $CD$ , the same change in chemical potential  $\Delta\mu'$  occurs along arc  $AB$  and arc  $DC$ . The total chemical work  $\oint dW \equiv -\oint \Delta\mu_{\text{ATP}} d\xi_{\text{AMP}}$  done on the system is the area inside the dark boundary, positive for refrigeration and negative for the engine cycle.

1. Arc  $AB$  is performed with the reservoir for polymers  $\Pi_{\beta}$  open to the reaction chamber. The concentration (hence chemical potential) of ATP is lowered with the pistons, driving reaction (3) toward the left and consuming  $\Pi_{\beta}$  to produce monomers. Because catabolism generates ATP, the pistons must remove this and more to reduce the ATP concentration.
2. Arc  $BC$  is performed with the reaction chamber isolated from both polymer reservoirs, using  $\text{AMP} \rightarrow \text{ATP}$  conversion to raise the reactor chemical potential from equilibrium with  $\mu_{\beta}$  to equilibrium with  $\mu_{\alpha}$ .
3. Arc  $CD$  is performed in contact with the reservoir for  $\Pi_{\alpha}$ . Now ATP is generated to drive reaction (3) to the right, producing  $\Pi_{\alpha}$  and returning the monomer concentration to its original value. More ATP must be produced on arc  $CD$  than was consumed on arc  $AB$ , because  $\mu_{\alpha} > \mu_{\beta}$ .
4. Finally arc  $DA$  is performed in isolation from both polymer reservoirs, using  $\text{ATP} \rightarrow \text{AMP}$  conversion to restore the chemical potential to equilibrium

with  $\mu_{\bar{X}}$ . More ATP is consumed by the pistons on arc  $DA$  than was produced on arc  $BC$ , because the average ATP concentration is higher in equilibrium with lower concentrations of monomers, and more moles are consumed to effect the same change in concentration.

### B. Heat transfer in the metabolic cycle

To analyze the entropic consequences of the cycle in Fig. 2, we consider the flows of particles, enthalpy and entropy, making use of the strict cyclicity of this model of metabolism. A few standard definitions are provided in Appendix A to establish notation, and also to present the point of view from which Legendre duality will be considered throughout the paper. Temperature will be measured in energy units,  $\tau \equiv k_B T$ , and entropy  $\sigma \equiv S_{\text{Gibbs}}/k_B$  will be measured in nats.

Since it is conventional to work with molar concentrations rather than particle numbers, for each molecular species  $X$ , we express the particle number in terms of the concentration by  $N_X = V N_A [X]$ , and the Gibbs free energy (A7) as

$$G_X = V N_A [X] \mu_X, \quad (6)$$

where  $V$  is the containing volume in liters,  $N_A$  is Avogadro's number, and  $\mu_X$  is the chemical potential of  $X$ . All species changed over whole metabolic cycles are in separate solutions in Fig. 1, and entropies of mixing in common reaction volumes will be omitted from the notation here for simplicity.

Under the simplifying assumption that we can replace activities with concentrations,  $\mu_X$  at any concentration  $[X]$  is related to its value  $\bar{\mu}_X$  at reference concentration  $[\bar{X}]$  as

$$\mu_X = \bar{\mu}_X + \tau \log \left( \frac{[X]}{[\bar{X}]} \right), \quad (7)$$

If  $[\bar{X}]$  is simply a reference scale for concentrations, independent of species, we may recognize  $\bar{\mu}_X \equiv G_X^0$ , the standard free energy of formation of species  $X$ , up to a constant that can be absorbed in the zero of chemical potential. For instance, under a thermodynamic equilibrium among the polymer species, the relative concentrations are related by

$$\mu_{\text{eq}} = G_{\Pi_{\bar{\alpha}}}^0 + \tau \log \left( \frac{[\Pi_{\bar{\alpha}}]_{\text{eq}}}{[\bar{X}]} \right), \quad (8)$$

for all  $\Pi_{\bar{\alpha}}$ . It is useful to keep the notation for  $G_{\Pi_{\bar{\alpha}}}^0$  from Eq. (8), even if the polymers are chemically equivalent, because it clarifies the role of chemical work in producing deviations of the polymer distribution from equilibrium.

Using the relation (6) that, for any species,  $V N_A [X] \mu_X = G_X = H_X - \tau \sigma_X$ , the entropy under

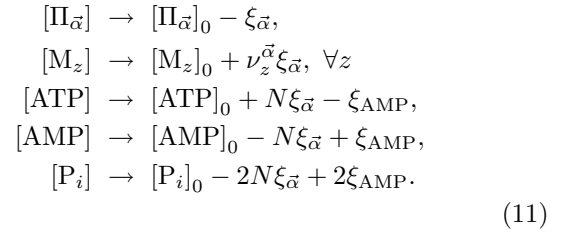
the same conditions can be written

$$\sigma_X = \frac{1}{\tau} (H_X - V N_A [X] G_X^0) - V N_A [X] \log \left( \frac{[X]}{[\bar{X}]} \right). \quad (9)$$

In Eq. (9),  $H_X/V N_A [X] - G_X^0$  is an entropy per particle for species  $X$ , including entropies of solvation and internal degrees of freedom. For polymers we may reference the entropy to a chemical equilibrium by rewriting Eq. (9) as

$$\sigma_{\Pi_{\bar{\alpha}}} = \frac{1}{\tau} (H_{\Pi_{\bar{\alpha}}} - V N_A [\Pi_{\bar{\alpha}}] \mu_{\text{eq}}) - V N_A [\Pi_{\bar{\alpha}}] \log \left( \frac{[\Pi_{\bar{\alpha}}]}{[\Pi_{\bar{\alpha}}]_{\text{eq}}} \right). \quad (10)$$

The reaction (3) (proceeding to the left) converts polymers to monomers and AMP to ATP, while the reaction (5) (proceeding to the left) consumes ATP to produce AMP and chemical work. Denote the extent of the former reaction of polymer  $\Pi_{\bar{\alpha}}$  by  $\xi_{\bar{\alpha}}$ , and the extent of the latter by  $\xi_{\text{AMP}}$ . These reactions take initial concentrations  $[X]_0$  for species  $X$  to concentrations  $[X]$  in the course of the reaction according to



The equilibrium equation (4) arises from the more general equation of chemical potentials

$$\mu_{\Pi_{\bar{\alpha}}} - \sum_{z=1}^Z \nu_z^{\bar{\alpha}} \mu_{M_z} = N (\mu_{\text{ATP}} - \mu_{\text{AMP}} - 2\mu_{P_i}) \quad (12)$$

under the assumption (7). Suppose also that the initial concentrations  $[X]_0$  are in equilibrium with each other (for consideration of a single metabolic cycle, the polymer concentrations  $[\Pi_{\bar{\alpha}}]_0$  need not be in chemical equilibrium with each other at values  $[\Pi_{\bar{\alpha}}]_{\text{eq}}$ ), and denote the chemical potential coupled to the ATP synthase (the pistons in Fig. 1) by  $\Delta\mu_{\text{ATP}} \equiv \mu_{\text{ATP}} - \mu_{\text{AMP}} - 2\mu_{P_i}$ . The chemical work done on the system, formally the sum

$$dW \equiv \sum_X dG_X = \sum_X \mu_X dN_X \quad (13)$$

over all species, reduces by Eq. (12) to

$$dW = -\Delta\mu_{\text{ATP}} d\xi_{\text{AMP}}. \quad (14)$$

which by Eq. (A6) may also be written  $dW = dH - \tau d\sigma$  for total enthalpy  $H$  and entropy  $\sigma$ . Over a complete metabolic cycle therefore

$$\oint dW = \oint dH - \oint \tau d\sigma. \quad (15)$$

If we assume that  $K_{\vec{\alpha}}(\tau)$  is the same function of  $\tau$  for all  $\vec{\alpha}$ , we will have further that

$$\oint dH = 0, \quad (16)$$

though the results below are derived more generally.

In this idealization of metabolism the internal components of the reactor return to their original conditions over complete cycles

$$\oint \left( dG_{\text{ATP}} + dG_{\text{AMP}} + dG_{\text{P}_i} + \sum_{z=1}^Z dG_{\text{M}_z} \right) = 0, \quad (17)$$

and we consume as many polymers as we produce,

$$\Delta N_{\Pi_{\vec{\alpha}}} = -\Delta N_{\Pi_{\vec{\beta}}}. \quad (18)$$

Therefore from the definition (13) of chemical work and Eq. (17), we also have

$$\begin{aligned} \oint dW &= \mu_{\Pi_{\vec{\alpha}}} \Delta N_{\Pi_{\vec{\alpha}}} + \mu_{\Pi_{\vec{\beta}}} \Delta N_{\Pi_{\vec{\beta}}} \\ &= \Delta G_{\Pi_{\vec{\alpha}}}^{CD} + \Delta G_{\Pi_{\vec{\beta}}}^{AB}, \end{aligned} \quad (19)$$

in which superscripts serve as a reminder over which arc of the cycle a given polymer number changes. With Eq. (18), we get the chemical equivalent of Carnot's theorem [22] for the cycle of Fig. 2,

$$\oint dW = \left( 1 - \frac{\mu_{\Pi_{\vec{\beta}}}}{\mu_{\Pi_{\vec{\alpha}}}} \right) \Delta G_{\Pi_{\vec{\alpha}}}^{CD}. \quad (20)$$

For a Carnot engine, the reference energy on the right-hand side would be the heat rejected to the hot reservoir. For the chemical cycle it is the change  $\Delta G_{\Pi_{\vec{\alpha}}}^{CD}$  in Gibbs free energy of the polymer reservoir at higher chemical potential. The number  $\eta_{\vec{\alpha}\vec{\beta}} \equiv \left( 1 - \mu_{\Pi_{\vec{\beta}}}/\mu_{\Pi_{\vec{\alpha}}} \right)$  is the chemical counterpart to the Carnot efficiency, and  $\gamma_{\vec{\alpha}\vec{\beta}} \equiv \eta_{\vec{\alpha}\vec{\beta}} / \left( 1 - \eta_{\vec{\alpha}\vec{\beta}} \right)$  is called the coefficient of performance when the cycle is being run as a refrigerator.

To understand the distributional consequences of work flux, introduce a probability distribution  $p$  (now for any number of polymer types), with components  $p_{\vec{\alpha}}$  that are the fractions of polymers in each sequence state  $\vec{\alpha}$ . Supposing for convenience that the volume is the same in each polymer reservoir, and denoting by  $N_{\Pi} \equiv \sum_{\vec{\alpha}} N_{\Pi_{\vec{\alpha}}}$  the total number of polymers, the probability components may be expressed also in terms of concentrations

$$p_{\vec{\alpha}} \equiv \frac{N_{\Pi_{\vec{\alpha}}}}{N_{\Pi}} = \frac{[\Pi_{\vec{\alpha}}]}{\sum_{\vec{\alpha}} [\Pi_{\vec{\alpha}}]}, \quad (21)$$

Denote by  $\pi$  the value of the distribution  $p$  when the polymers are in chemical equilibrium at concentrations  $[\Pi_{\vec{\alpha}}]_{\text{eq}}$  (recalling that always  $\sum_{\vec{\alpha}} [\Pi_{\vec{\alpha}}] = \sum_{\vec{\alpha}} [\Pi_{\vec{\alpha}}]_{\text{eq}}$  by Eq. (18)).

Then combining Eq. (15) for the chemical work with the equilibrium-referenced form (10) for the entropy

$$\begin{aligned} \oint dW &= N_{\Pi} \tau \sum_{\vec{\alpha}} \oint dp_{\vec{\alpha}} \log \frac{p_{\vec{\alpha}}}{\pi_{\vec{\alpha}}} \\ &= N_{\Pi} \tau \oint dD(p \parallel \pi), \end{aligned} \quad (22)$$

where

$$D(p \parallel \pi) \equiv \sum_{\vec{\alpha}} p_{\vec{\alpha}} \log \frac{p_{\vec{\alpha}}}{\pi_{\vec{\alpha}}} \quad (23)$$

is the Kullback-Leibler divergence [6] of the distribution  $p$  from the chemical equilibrium distribution  $\pi$  and we have used the fact that  $\sum_{\vec{\alpha}} \oint dp_{\vec{\alpha}} = 0$ . The explicit enthalpy terms cancel in Eq. (22), and the contribution to the Gibbs free energy from  $\mu_{\text{eq}}$  vanishes by conservation of polymer number, with the only remaining contribution represented in the equilibrium distribution  $\pi$ . This relation is therefore valid whether or not  $K_{\vec{\alpha}}(\tau)$  is the same function for all  $\vec{\alpha}$ .

The Kullback-Leibler divergence (23) is positive-semidefinite and vanishes only on  $p = \pi$ , and its value at any nonzero  $\oint dW$  serves as a measure of the ‘‘information written into’’ the distribution of polymers by the sequence of metabolic reactions. If metabolism has the effect of introducing new constraints on  $p$  but *respecting* all of the constraints on the equilibrium distribution, the Kullback-Leibler divergence takes on an additional interpretation as an entropy difference. Formally, the condition is that the equilibrium distribution  $\pi$  be a *coarse-graining* of the distribution  $p$  [31], in which case

$$S(\pi) - S(p) = D(p \parallel \pi). \quad (24)$$

Then any integral of the form (22), starting from the equilibrium distribution, is directly an entropy reduction, which as noted could be regarded as a degenerate case of a mutual information [26], and also as an instance of effective complexity [31]. (We will return in Eq. (45) to the terms by which the coarse-graining relation (24) may be violated, but it remains an interesting empirical question to what degree metabolism refines the energetic structure of abiotic matter but mostly respects the ordering of compounds according to free energy of formation.)

Eq. (22) is valid whether only two indices  $\vec{\alpha}$  and  $\vec{\beta}$  are affected by a single metabolic cycle, or the work flux is summed over an arbitrary collection of reversible cycles acting broadly over the entire distribution.  $D(p \parallel \pi)$  differs from the negative of the Shannon entropy

$$-S(p) \equiv \sum_{\vec{\alpha}} p_{\vec{\alpha}} \log p_{\vec{\alpha}} \quad (25)$$

only by the distribution average of the standard free energies of formation of the polymers  $\sum_{\vec{\alpha}} p_{\vec{\alpha}} \log(1/\pi_{\vec{\alpha}})$ , which takes into account the enthalpy and internal entropy contributions from the work flux, the integral of

which vanishes if the polymers are chemically identical. In such a case of symmetric particles Eq. (22) reduces to

$$\frac{1}{N_{\Pi}} \oint dW = -\tau \oint dS(p), \quad (26)$$

where  $N_{\Pi}$  now counts the total number of polymers over any collection of sequences  $\vec{\alpha}$ . Case (26) is appropriate for comparison to computation on a combinatorial data stream of physically interchangeable components, and is the appropriate form of Eq. (1) for processes decomposable into complete metabolic cycles.

From the chemical work relation (19), and the relation between work and both heat (15) (with  $\oint dH = 0$ ) and information (26), we could refer to the cycle of Fig. 2 as a *Landauer cycle* (the connection with the classical Landauer construction in computer science will be developed in Sec. III.) A Landauer cycle is any reversible cycle isomorphic to the Carnot cycle in some *other* state variable pair than  $(\tau, \sigma)$ , which for metabolism is  $(\mu, N)$ . Instead of entropy flux conservation between reservoirs as in the Carnot cycle, it conserves the other extensive quantity ( $N$ ), which identifies the coefficient of performance and the relevant free energy. Because it is reversible, however, it *also* conserves total entropy if the heat bath is taken into account. If we plot the same pathway on the simplex of constant total entropy, we obtain the non-closing plaquette of Fig. 3.

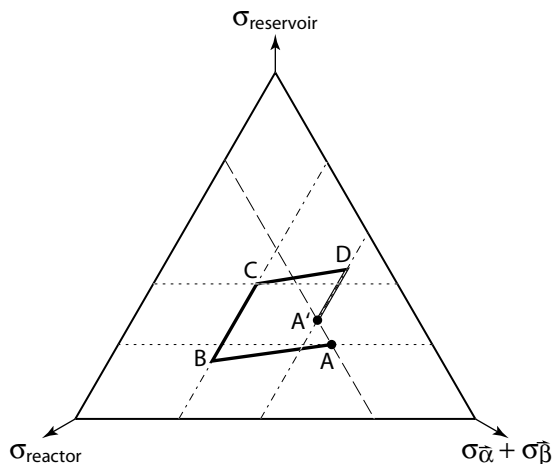


FIG. 3: The chemical refrigeration cycle on the simplex of conserved total entropy  $\sigma_{\text{reservoir}} + \sigma_{\text{reactor}} + \sigma_{\vec{\alpha}} + \sigma_{\vec{\beta}}$ , for the case of chemically identical polymers. The catabolic arc  $AB$  could be endothermic (shown) or exothermic, depending on the assumed reactions, and likewise for the inverse anabolic arc  $CD$ . Arcs  $BC$  and  $DA'$  are performed in isolation from the polymers  $\Pi_{\vec{\alpha}}$  and  $\Pi_{\vec{\beta}}$ , and exchange heat solely between reactor and reservoir. The path that is cyclic in Fig. 2 makes a non-closed plaquette here, whose net effect is to transfer an amount of entropy  $\oint dW/\tau$  from the polymer system to the reservoir.

Here  $\sigma_{\text{reservoir}}$  is the entropy only of the heat bath,  $\sigma_{\text{reactor}} \equiv \sigma_{\text{ATP}} + \sigma_{\text{AMP}} + \sigma_{\text{P}_i} + \sum_{z=1}^Z \sigma_{\text{M}_z}$  is the en-

trophy of all those components that return to their original states after each cycle, and  $\sigma_{\vec{\alpha}} + \sigma_{\vec{\beta}}$  is the entropy of the chemical system on which metabolism has acted. The input of nonzero work  $\oint dW$ , together with the assumption that the enthalpy of the chemical reservoirs has not changed, requires that an amount of entropy  $\oint dW/\tau$  be rejected to the thermal reservoir, equal to the entropy reduction in the chemical system, distinguishing the end of the pathway  $A'$  from the beginning  $A$ . Sec. III develops the argument that the transfer of entropy from some non-thermal form of ensemble uncertainty to a heat bath is the essence of computation, and the conservation law demonstrated in Fig. 3 is the familiar Landauer’s theorem for computation. Landauer entropy transfer is not the same as thermal refrigeration, in the sense that the system and heat bath are at the same temperature, and the coefficient of performance of a cycle is determined by its chemical parameters.

By repeating a Landauer cycle we can reduce the entropy of a polymer distribution arbitrarily. We achieve a particular structure in the ordered distribution if we act on it with a collection of metabolic cycles with different rates, instantiating a process of evolutionary adaptation. For reversible cycles, no further details matter about how the rates are biased or how cycles are sampled to act on the distribution.

### C. “Reversible” natural selection

The metabolic model represents only which polymer is consumed and which produced in a given cycle. We may elevate “production” to “re-production” if we imagine that the molecule produced is of the same type as some “parent” molecule in the population, which remains unaltered in the process. At the level of metabolism, the basis for natural selection is that some types of molecules (pores, enzymes, or the DNA that code for them) prepare a cell to carry out energy-yielding reactions on the species actually present in its environment, keeping it alive or allowing it to reproduce, while other molecules either provide no function or prepare the cell for situations that never arise in its actual environment, and are hence maladaptive. Where the environmental molecules also represent other individuals, metabolic competence and behavioral competence are not distinguished.

We can model an ecology of molecular species with a distribution of polymers, and consider binary interactions through metabolic cycles, whose probabilities to be sampled depend on the input and output molecules. For reversible cycles the unit of time does not matter, so by Eq. (26) we may pass directly from single-particle cycles to a representation of their action on the distribution. The lowest-order polynomial for which the rate of production of species  $\Pi_{\vec{\alpha}}$  from species  $\Pi_{\vec{\beta}}$  is proportional to the probability of binary collision between  $\Pi_{\vec{\alpha}}$  (parents)

and  $\Pi_{\bar{\beta}}$  (food) is

$$\left. \frac{dp_{\bar{\alpha}}}{dt} \right|_{\text{rev}} = \sum_{\bar{\beta}} p_{\bar{\alpha}} r_{\bar{\alpha}\bar{\beta}} p_{\bar{\beta}}. \quad (27)$$

The requirement that the total number of polymers be conserved is

$$0 = \sum_{\bar{\alpha}} \left. \frac{dp_{\bar{\alpha}}}{dt} \right|_{\text{rev}} = \sum_{\bar{\alpha}, \bar{\beta}} r_{\bar{\alpha}\bar{\beta}} p_{\bar{\alpha}} p_{\bar{\beta}}, \quad (28)$$

thus we must choose the rate matrix  $r_{\bar{\alpha}\bar{\beta}}$  antisymmetric. In the domain of reversible metabolic cycles, there is no energetic or entropic consequence to simultaneous fluxes  $\Pi_{\bar{\alpha}} \leftrightarrow \Pi_{\bar{\beta}}$ , so the antisymmetric rate matrix governing the evolution of probabilities also governs work and heat flows, per Eq. (26).

Under “reversible” evolution, differential “fitness” results from differential rates of survival and reproduction for each type of individual. Here the net of the two effects is given by the appropriate column (or row) of  $r_{\bar{\alpha}\bar{\beta}}$ . The excess probability of death (being catabolized) over replacement per polymer  $\Pi_{\bar{\beta}}$  is  $\sum_{\bar{\alpha}} r_{\bar{\alpha}\bar{\beta}} p_{\bar{\alpha}}$ , or alternatively, the excess probability of reproduction over death per polymer  $\Pi_{\bar{\alpha}}$  is  $\sum_{\bar{\beta}} r_{\bar{\alpha}\bar{\beta}} p_{\bar{\beta}}$ .<sup>11</sup>

The well-studied replicator dynamic (27) can produce attractive fixed points (on the boundary of the probability simplex) limit cycles, or even chaotic orbits [32], depending on the dimension and the spectrum of  $r_{\bar{\alpha}\bar{\beta}}$ . In the first case a well-defined entropy of the asymptotic distribution exists; in other cases the best we may be able to do is define an average entropy over the stationary distribution on the attractor. Some amount of persistent dynamical variation in the entropy of an ecological distribution may be physical in appropriate models (where irreversible driving may be taken as a primitive of the dynamics), but within the context of these models, where we are concerned with the consumption of work to generate heat, persistent dynamics arises as an artifact of the idealization of reversibility, as will be shown below. The organism distribution in this model gains entropy by extracting heat and offering work to the environment, allowing repeated switching among types to persist indefinitely.

Differential survival and reproduction are incorporated in Eq. (27), but not the third canonical element of natural selection: mutation. It could certainly be incorporated by expanding  $r_{\bar{\alpha}\bar{\beta}}$  to a three-index matrix  $r_{\bar{\alpha}'\bar{\alpha}\bar{\beta}}$ , to produce  $\Pi_{\bar{\alpha}'}$  (offspring) from  $\Pi_{\bar{\alpha}}$  (parent) and  $\Pi_{\bar{\beta}}$

(food). However, non-forward-looking mutation in the Darwinian sense arises from error mechanisms related to those that cause decay and entropy production, and the rates of the two types of processes will generally be quantitatively related. Therefore it is more natural to incorporate mutation in whatever model we adopt for decay. These issues are addressed in Sec. IV, following the comparison to Landauer’s principle in computation for the thermodynamically reversible case.

### III. COMPUTATION AND LANDAUER’S PRINCIPLE

Though something of a surprise when it was originally proposed [33], it is now generally accepted [23] that under sensible idealizations the operations of Boolean logic can be implemented in physical hardware that neither requires the input of work nor generates heat, as long as the hardware provides additional bits from whose value the operations can be *inverted*. However, it has not been shown that a general recursively enumerable function [34] can be computed in this way with any finite number of of such extra “history bits” (as Bennett calls them), and so performed on finite-size hardware. Thus computation encounters a problem analogous to that addressed by Carnot: the need to re-use a limited-capacity device to carry out some function of indefinite extent. The solution in computation is to *erase* the history bits, and Landauer’s principle asserts that this step requires input of work and generates heat, even on idealized hardware.

Landauer’s principle, if correct, solves the problem of violation of the second law of thermodynamics by Maxwell deamons [5, 35]. These are imagined devices that, doing no work, can reduce the entropy of a physical system by anticipating its microscopic dynamics and sorting its configurations, for instance allowing all fast particles through a gate in a partition to the left side of a chamber and all slow particles through to the right. The second law is saved if such deamons, requiring *information* about the system state that they must erase after it has been used, always generate an amount of heat at least as great as  $k_B T$  times the entropy they eliminate from the physical system.

The second law of thermodynamics is not an intrinsic property of system dynamics, but rather a property of *coarse-grained* entropies introduced with statistical descriptions [31]. Operationally the coarse-graining is defined by the boundary conditions that specify the macroscopic condition of the system, and a coarse-grained entropy initially maximized subject to some set of boundary constraints cannot then decrease through subsequent interaction of the dynamics with the boundary conditions<sup>12</sup>. The second law is only precisely stated, then,

<sup>11</sup> If symmetric rate terms for  $\Pi_{\bar{\alpha}} \leftrightarrow \Pi_{\bar{\beta}}$  were added to these excesses, separate gross rates for death and reproduction could be modeled, and in terms of them the expected fecundity as the reproduction rate times the expected lifetime for a given polymer species. In  $r_{\bar{\alpha}\bar{\beta}}$  only the excess rates can be represented.

<sup>12</sup> Thus a Maxwell demon programmed with a partial specification

if an ensemble description has been put forth for both the physical system in question and the operation of any computational devices attached to it. The objections to Landauer’s principle that persist in the literature [24, 25] hinge on whether or not the possible data subject to computation should be part of the same statistical ensemble description as the microscopic configurations defining the physical computer and its heat reservoir.

In chemistry there is no such temptation to exclude particle configurations from the ensemble that also includes thermal excitations, because with an understanding of the goal of statistical mechanics, the limited specification of the boundary conditions clearly makes such separation impossible. The same is true of any description of computation for which the second law can be well formulated. A *computer* may be defined as a device capable of converting a variety of states of some *input* into (deterministically or stochastically) specified corresponding states of some *output*. The apparatus of the computer imposes boundary conditions on internal state variables that are incompletely specified in the absence of an input (and possibly in its presence), and generally automatically executes some standard changes in these boundaries as well, called its *algorithm*. Like any other thermodynamic apparatus, the computer is “re-usable” in the sense that neither the nature of the boundary conditions it imposes, nor the algorithm under which they evolve, depends on the values of its input. As argued by Rissanen [36], we must suppose that the machine is built beforehand and repeatedly applied to inputs distributed in some fashion, and we can only ask questions about the average energy input or output required by the algorithm in the course of repeated application. Such a “frequentist” description of computation is consistent with the use of changes in entropy as measures of the *average* information gained by observing the value of some variable.

In an ensemble description, the *input state* of a computer corresponds to a random variable  $X$  taking values  $x$ , and the *output state* to a random variable  $Y$  taking values  $y$ . The computer’s algorithm  $f$  makes the output a function of the input, with values  $y = f(x)$ . For an example  $f$  will be taken to be a deterministic function, though the observations about entropy and information apply equally well to a stochastically functioning algorithm, such as natural selection. The entropy of the distribution for  $Y$  any function of  $X$  cannot exceed the entropy of the distribution for  $X$  [6]. A computer that takes data repeatedly from a stream of instances of  $X$  and produces a stream of instances  $Y$  thus converts the

joint data stream  $Y \times X$  at any time<sup>13</sup> to a joint data stream of equal or lower entropy with each successive act of computation. A schematic diagram of the interaction of  $X$ ,  $f$ ,  $Y$ , physical properties work ( $W$ ) and reservoir temperature ( $T$ ) is shown in Fig. 4.

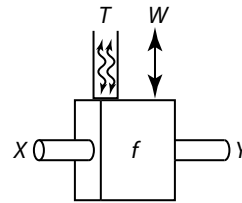


FIG. 4: Schematic diagram of a physical model of computation.  $X$  is the input random variable, and  $Y$  the output. The computer is a physical “black box” representing  $X$  and  $Y$  with variables of its internal state, and coupled also to a source of work  $W$  and heat exchanged with a thermal reservoir at temperature  $T$ . Each particular computer is associated with the algorithm  $f$  it implements.

The input and output data streams are reservoirs in this description of computation, and we may consider the important transformations of the reservoirs by supposing that inputs and outputs correspond at various stages in a computation to elements of the *internal state* of the computer itself. The question posed by Landauer is how the computer converts the distribution of the input state to that of the output.

### A. An example of computation

Consider as an example an input  $X$  comprising two binary digits  $X \equiv (X_1, X_2)$ , drawn IID  $\sim (0.5, 0.5)$ . Suppose we ask “are the digit values the same”. The function that answers this question is XOR:  $y = x_1 \oplus x_2$ . Conventionally we break the algorithm into (reversible) transformation and (irreversible) erasure stages. The reversible stage might take the two input values  $(x_1, x_2)$  and canonical states  $(0, 0)$  of two output variables, and transform the output to  $(y, x_1)$  while transforming the input to canonical values  $(0, 0)$ <sup>14</sup>. This is the step that can be done without work input or heat production.

To restore the computer to a state capable of processing another input, the algorithm must erase the value  $x_1$  in the second position and output the value  $y$ . Suppose

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of the initial microstate of a box of gas could perfectly well reduce the classical Gibbs entropy for a while without erasure and without generating heat. In such a system, though, the classical extensive state variables of the Gibbs description would not represent the true boundary constraints, because the daemon’s program would be a relevant constraint on possible ensembles.

<sup>13</sup> We thus think of a stream of  $Y$  instances as representing the past, on which computation has already acted, and the stream of  $X$  values as the future, on which it has yet to act. The present defines the reference for these two semi-infinite data streams.

<sup>14</sup> I don’t worry here about how new values are introduced for input variables, but assume that that mechanism also assumes canonical starting states.

that the output process is symmetric with the input process, so that in transferring  $y$  to the data stream the computer resets to a standard state of the first output variable. One standard model for erasure of the second output variable uses Szilard’s single-particle ideal gas [35]. A particle on the left-hand side of a two-chamber box is taken to represent value 0 and a particle in the right-hand side to represent value 1. Erasure takes place by removal of a barrier between the state-0 and state-1 sides of the box, followed by compression with a piston to reset the particle in canonical state 0 while the box is in contact with a thermal reservoir, after which the wall is re-inserted. The entropy that must be rejected to the reservoir is  $k_B \log 2$  (in logical units, “1 bit”) for an IID boolean variable, and if the reservoir is at temperature  $T$  the energy required from the piston is  $k_B T \log 2$ . Energy lost to the reservoir is heat because the reservoir degrees of freedom are not explicitly controlled by the computer apparatus, while energy input from the piston is work because the piston position is a (mechanical) boundary parameter. The input-output map and essential steps in erasure are illustrated in Fig. 5

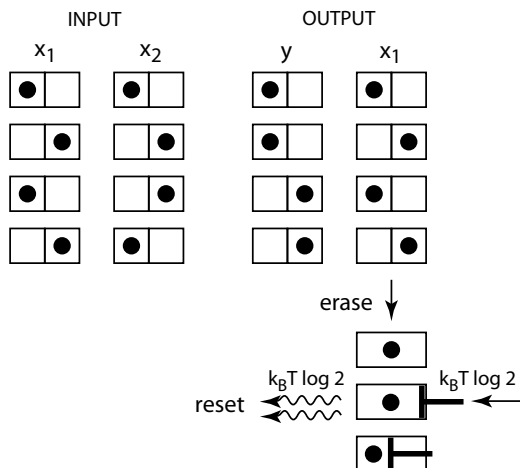


FIG. 5: States and stages in a computer that computes XOR. Two input variables ( $X_1, X_2$ ) are represented in the leftmost two columns as Szilard boxes, with the particle in the lefthand chamber of a box representing state 0 and in the righthand chamber representing state 1. Four equally probable input values are arrayed vertically. Two output variables are represented in the rightmost two columns, after the reversible transformation from inputs to outputs. Not only XOR, but the identity function on  $X_1$ , is computed at this stage. To compute only XOR, we reset the second output variable, by removing the partition and then using a piston to compress the particle into a canonical 0 state, after which the divider is replaced (not shown).

For a single particle the Shannon and Gibbs entropies are the same, and the reduction in a Shannon entropy of some distribution is the conventional formal definition of information. We may thus ask in what sense various reductions in the entropy of the states of the computer are measures of information. First, observed that the entropy

of the computer’s states is entirely driven by the entropy of its inputs, which in this example is 2 bits. The entropy of the outputs as they are shown in the right-hand column of Fig. 5, after the reversible transformation, is also 2 bits. At this stage the ensemble description of the computer admits with equal probability all input states. If we were to observe the value of the output at this stage we could reduce that entropy to 0; thus such an observation carries 2 bits of information. For a reversible computation, restricting consideration to particular values of both output variables is equivalent to specifying the input exactly.

In the transformation labeled “erase” in Fig. 5, where the wall is removed in the second output bit, the entropy of the computer’s state remains that of the input ensemble (2 bits), only now there is no way to use the coarsened boundary conditions of the output state to restrict the admitted inputs to less than 1 bit of uncertainty. The ensemble of computer states induced by the ensemble of inputs is not changed by removal of the barrier alone; only our ability to infer input values has changed. In this sense it is not Jaynes’s emphasis on what one “knows” that determines the entropy, but rather what one “controls” physically.

The transformation labeled “reset” in Fig. 5 has energetic consequences, and does change the ensemble of the engine. It leaves the  $x_1$ -valued bit of the output in a canonical state 0, while leaving the  $y$ -valued bit of the output to be specified by the inputs. The entropy of the engine state is reduced by  $k_B \log 2$  (1 bit) relative to that of the inputs, and an energy of  $k_B T \log 2$  has been required as work to carry this entropy to the reservoir as heat. Practically these values are averages over a sequence of inputs. The algorithm for wall removal and piston movement is specified before an output value is produced. For some output values no work may be required to convert the  $x_1$ -valued output bit to canonical 0, and for other values  $2k_B T \log 2$  may be required. The algorithm pays the average energy cost because it does not adapt to the data value in each instance. The generalization of this XOR example to arbitrary logical operations is Landauer’s principle.

## B. Informations

Even if every reduction in a Shannon entropy is regarded as an “information”, there are multiple informations available in the example, about different things. Landauer’s principle, to the extent that we have illustrated it here, only applies to some of them. Here we will clarify some usage that becomes important in relating computation to natural selection.

To begin, recall that a direct observation of the input  $X$  has 2 bits of information, because a definite value for  $X$  reduces the entropy of any given instance of the input from 2 bits to zero. The information in such an observable is “about” the value of  $X$ .

In informal usage it is common to refer to the “information in  $Y$ ” as the output of a computation, but any such “information” is not what Landauer’s heat generation bought in the preceding discussion. Rather, the “information in  $Y$ ” is the uncertainty about the input *not* affected by the computation. After erasure/reset, but prior to observation of the output state, the entropy of the ensemble of inputs admitted by the computer is 2 bits. If we observe  $Y$  and construct an ensemble only from those instances  $y = 0$ , the resulting ensemble has entropy 1 bit. The 1 bit of “information in  $Y$ ” is the reduction in the entropy of inputs admitted by the computational algorithm, if we also condition on the bits’s being identical. Ordinarily (if this XOR were embedded in a larger and more interesting computation) the entropy of  $Y$  would not be reduced by conditioning on value  $y = 0$ , but rather passed downstream as the calculation proceeded to act on the whole range of inputs. At this stage the entropy of  $Y$  is only the remainder of the entropy of  $X$  consistent with representation in an XOR, and the information obtained if  $Y$  is observed is that part of the information about the value of  $X$  representable in the XOR. As with any computable function, the “information” in the output is only about the category of inputs from which it could have come.

The information paid for with Landauer’s principle is  $S(X) - S(Y)$  (also equal to 1 bit in the example), which was transferred to the reservoir in resetting the second output variable, before observing  $Y$  or passing it along in the calculation. Had we observed the second variable instead of erasing it, the reduction in entropy of the inputs from conditioning on its value would have come from the knowledge of  $X$  that an XOR cannot convey. Another way to say this is that the entropy rejected as heat is “about” the fact that the remaining variable calculates XOR. The reduction in entropy of the computer’s state after erasure/reset is the “information” arising from filtering the inputs through XOR, rather than according to the value of any of the Boolean variables. It is information about *what the computed function is* rather than about the values of the inputs. When we consider natural selection as a computing process, the work required by selection to bias a population from equilibrium will be proportional to the information written into the biased distribution, about the selective environment.

We can summarize this analysis with a conservation law between input and output entropies and rejected heat:

$$S(X) = S(Y) + Q/T, \quad (29)$$

where  $Q$  is the rejected heat from erasure. If we had a computation that could reduce  $Y$  to a definite value, the “information” so written into the computer’s state, from the original distribution on  $X$ , would be balanced by rejected heat equal to  $TS(X)$ .

### C. Logical versus thermal reversibility

Confusion about Landauer’s principle arises from its statistical treatment of a data stream together with a heat bath, in which the particular data values are of interest from a computational point of view, while those of the bath are not. Ordinarily in the modeling of a Hamiltonian dynamical system, a choice is made either to treat all degrees of freedom microscopically and reversibly (even for systems where statistical mechanics would normally be used [37]), or to treat the values of all non-state variables as stochastic. Analysis of the physical substrate of deterministic computation happens to be a domain that falls in between, where determinism of the computation is a property of a subset of the microscopic degrees of freedom, but not one implied by the weaker requirement of thermodynamic reversibility, in which entropy is preserved through a transformation but the mapping of microscopic configurations need not be.

The erasure/reset step in computation is *logically* irreversible, but *thermodynamically* reversible. In substituting an output variable with some erased bits for an input variable in a data stream, we transfer entropy from the data stream to the heat bath. The physical operations of the computer during this transformation can certainly be reversed: we could add energy and entropy from the heat bath to a canonically set 1-bit variable while extracting the piston to remove the energy as work, and insert a wall to obtain a standard randomized variable with one bit of entropy. Combining this introduced variable with  $Y$  and inverting the reversible XOR, we would obtain a data stream with the same entropy as  $X$ , though not the same sequence of data values.

For conventional thermodynamic examples, including the above analysis of metabolism, the failure of microscopic reversibility is unremarkable. The fact that deterministic computation is also not reversible should not obscure the fact that the path in the space of state variables, shown in Fig. 6, is essentially the same as that of Fig. 3.

### D. Computation and compression

The combination of logical irreversibility with thermodynamic reversibility reflects those reasons we compute at all, which do not concern the distribution of inputs. They are illustrated by the relation between computation and data compression.

As operations on probability distributions, reversible computation and lossless compression are both trivial, as they amount to ways of re-labeling the atoms on which a probability distribution is defined. Data compression alters the resources consumed in representing the atoms by changing the lengths of labels, while computation creates labels in which the answers to particular questions occupy a small number of pre-specified bits, allowing us to re-order them. Lossy compression selectively further

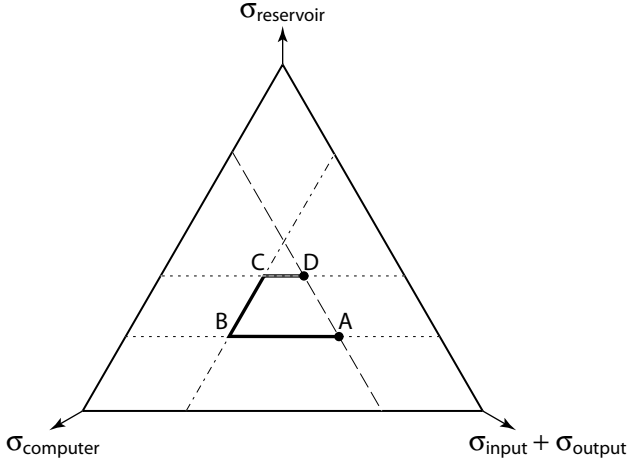


FIG. 6: The canonical Landauer path corresponding to the computation model of Fig. 5. Arc  $AB$  increases entropy in the computer by accepting data from the input, and arc  $CD$  sends data to the output. Only the erasure/reset arc  $BC$  is canonically assumed to be performed in contact with the thermal reservoir. There is no arc corresponding to  $DA'$  of Fig. 3 because we have ignored possible conditions for the computer to be in “equilibrium” with the different input and output data streams. On real hardware (such as a chemical system) the diagram 3 may be more realistic.

reduces resource consumption relative to ideal lossless compression, by eliminating the need to represent certain atoms at all. Similarly, irreversible computation shortens lables to their salient bits, and could be seen as a form of lossy compression optimized for ordering rather than length. Lossy compression clearly obeys the same Landauer relation between heat and data entropy as irreversible computation, so it is not surprising that the thermodynamics should fail to capture other logical criteria particular to one or the other.

#### IV. IRREVERSIBILITY

Suppose we now extend Eq. (27) for “reversible” evolution to incorporate decay as well. This can be done in a principled way by taking the lowest-order polynomial, which for decay is simpler than the polynomial for reproduction:

$$\left. \frac{dp_{\vec{\alpha}}}{dt} \right|_{\text{rev}} = \sum_{\vec{\beta}} \left( d_{\vec{\alpha}\vec{\beta}} + p_{\vec{\alpha}} r_{\vec{\alpha}\vec{\beta}} \right) p_{\vec{\beta}} \equiv f_{\vec{\alpha}}(p). \quad (30)$$

The only mathematical requirement on the matrix  $d$  is probability conservation, ensured if  $\sum_{\vec{\alpha}} d_{\vec{\alpha}\vec{\beta}} = 0, \forall \vec{\beta}$ . Physically, if we suppose that all consequences of driving are treated with the reversible bound represented in  $r$ , the remaining dissipative process must have the equilibrium distribution  $\pi$  as the stationary  $r \equiv 0$  solution. Thus  $\sum_{\vec{\beta}} d_{\vec{\alpha}\vec{\beta}} \pi_{\vec{\beta}} = 0, \forall \vec{\alpha}$ . The stationary solution

is stable if  $d_{\vec{\alpha}\vec{\beta}} \geq 0$  for  $\vec{\alpha} \neq \vec{\beta}$ , and it describes a microscopically reversible process if detailed balance holds:  $d_{\vec{\alpha}\vec{\beta}} \pi_{\vec{\beta}} = d_{\vec{\beta}\vec{\alpha}} \pi_{\vec{\alpha}}$ , for all pairs  $\vec{\alpha}, \vec{\beta}$ .

We may thus define a matrix  $\hat{d}$  with components  $\hat{d}_{\vec{\alpha}\vec{\beta}} \equiv d_{\vec{\alpha}\vec{\beta}} \pi_{\vec{\beta}}$ , which is symmetric and has the vector of all ones as its (left or right) null eigenvector.  $\hat{d}_{\vec{\alpha}\vec{\beta}}$  gives the (equal and opposite) current leaving  $\vec{\alpha}$  and  $\vec{\beta}$  respectively, along link  $\vec{\alpha}\vec{\beta}$  in the equilibrium state.

Under these assumptions it is not hard to show that as long as all off-diagonal  $d_{\vec{\alpha}\vec{\beta}} > 0$ , boundary solutions are ruled out, and that if there is an interior fixed point of Eq. (30), it is a stable attractor. To prove the first claim, suppose that there is a boundary solution with component  $p_{\vec{\alpha}} = 0$ . The driven current out of index  $\vec{\alpha}$  is proportional to  $p_{\vec{\alpha}}$ , thus zero, while the inward current equals  $\sum_{\vec{\beta}} d_{\vec{\alpha}\vec{\beta}} \pi_{\vec{\beta}} > 0$ . Hence  $p_{\vec{\alpha}} = 0$  cannot characterize a steady state.

To prove the second claim, note that  $f_{\vec{\alpha}}(p) = 0$  implies  $\sum_{\vec{\beta}} r_{\vec{\alpha}\vec{\beta}} p_{\vec{\beta}} = -(1/p_{\vec{\alpha}}) \sum_{\vec{\beta}} d_{\vec{\alpha}\vec{\beta}} p_{\vec{\beta}} = -d_{\vec{\alpha}\vec{\alpha}} - (1/p_{\vec{\alpha}}) \sum_{\vec{\beta} \neq \vec{\alpha}} d_{\vec{\alpha}\vec{\beta}} p_{\vec{\beta}}$ , as long as we can divide by  $p_{\vec{\alpha}}$  (interior assumption). But for  $r_{\vec{\alpha}\vec{\alpha}} = 0, \forall \vec{\alpha}$  (implied if  $r$  is antisymmetric),  $\partial f_{\vec{\alpha}}(p) / \partial p_{\vec{\alpha}} = d_{\vec{\alpha}\vec{\alpha}} + \sum_{\vec{\beta}} r_{\vec{\alpha}\vec{\beta}} p_{\vec{\beta}} = -\sum_{\vec{\beta} \neq \vec{\alpha}} d_{\vec{\alpha}\vec{\beta}} \left( p_{\vec{\beta}} / p_{\vec{\alpha}} \right) \leq 0$  for each  $\vec{\alpha}$ , by the assumption that all  $d_{\vec{\alpha}\vec{\beta}}$  in the sum are non-negative. Thus  $\text{Div}(f) \leq 0$ , with strict inequality unless the matrix  $d \equiv 0$ . In the generic case any polymer will be subject to decay, so that within this simplified model of decay as sequence permutation, each component  $\partial f_{\vec{\alpha}}(p) / \partial p_{\vec{\alpha}} < 0$  independently. Then there cannot be interior saddle points, and any interior fixed point must be unique and have the whole probability simplex as its basin of attraction.

#### A. Work fluxes

Stationary solutions to Eq. (30) satisfy

$$\begin{aligned} p_{\vec{\alpha}} &= \frac{\sum_{\vec{\beta} \neq \vec{\alpha}} d_{\vec{\alpha}\vec{\beta}} p_{\vec{\beta}}}{(-d_{\vec{\alpha}\vec{\alpha}}) - \sum_{\vec{\beta}} r_{\vec{\alpha}\vec{\beta}} p_{\vec{\beta}}} \\ &= \frac{\sum_{\vec{\beta} \neq \vec{\alpha}} d_{\vec{\alpha}\vec{\beta}} p_{\vec{\beta}}}{(-d_{\vec{\alpha}\vec{\alpha}}) - (r \cdot p)_{\vec{\alpha}}} \end{aligned} \quad (31)$$

At a stationary solution, the particle flux driven into any index  $\vec{\alpha}$  by metabolic consumption of work,  $p_{\vec{\alpha}} \sum_{\vec{\beta}} r_{\vec{\alpha}\vec{\beta}} p_{\vec{\beta}}$ , equals the dissipative particle flux out,  $-\sum_{\vec{\beta}} d_{\vec{\alpha}\vec{\beta}} p_{\vec{\beta}} = \sum_{\vec{\beta} \neq \vec{\alpha}} \left( d_{\vec{\beta}\vec{\alpha}} p_{\vec{\alpha}} - d_{\vec{\alpha}\vec{\beta}} p_{\vec{\beta}} \right)$ , where we have used  $\sum_{\vec{\alpha}} d_{\vec{\alpha}\vec{\beta}} = 0$ .

The metabolic work flux that maintains steady state against dissipation is not distinguished from a work flux that changes a distribution in a dissipationless world, so we may express the work flux  $\bar{W}$  (defined as an average over times longer than the cycle time) from Eq. (22),

using only the metabolic component of  $dp_{\vec{\alpha}}/dt$  (which in steady state equals the dissipative component),

$$\frac{\dot{W}}{N_{\Pi}\tau} = \sum_{\vec{\alpha}, \vec{\beta}} \left( d_{\vec{\beta}\vec{\alpha}} p_{\vec{\alpha}} - d_{\vec{\alpha}\vec{\beta}} p_{\vec{\beta}} \right) \log \frac{p_{\vec{\alpha}}}{\pi_{\vec{\alpha}}}. \quad (32)$$

Equations (31) and (32) can be clarified by working with the matrix  $\hat{d}$ , and similarly defining a matrix  $\hat{r}$  of rates of metabolism evaluated at the equilibrium state, with components  $\hat{r}_{\vec{\alpha}\vec{\beta}} \equiv \pi_{\vec{\alpha}} r_{\vec{\alpha}\vec{\beta}} \pi_{\vec{\beta}}$ , and similarly working with the probability relative to equilibrium, defined as  $\hat{p}_{\vec{\alpha}} \equiv p_{\vec{\alpha}}/\pi_{\vec{\alpha}}$ .

Then Eq. (31) becomes

$$\hat{p}_{\vec{\alpha}} = \frac{\sum_{\vec{\beta} \neq \vec{\alpha}} \hat{d}_{\vec{\alpha}\vec{\beta}} \hat{p}_{\vec{\beta}}}{\left( -\hat{d}_{\vec{\alpha}\vec{\alpha}} \right) - \left( \hat{r} \cdot \hat{p} \right)_{\vec{\alpha}}}, \quad (33)$$

and Eq (32) becomes

$$\begin{aligned} \frac{\dot{W}}{N_{\Pi}\tau} &= \sum_{\vec{\alpha}, \vec{\beta}} \left( \hat{d}_{\vec{\beta}\vec{\alpha}} \hat{p}_{\vec{\alpha}} - \hat{d}_{\vec{\alpha}\vec{\beta}} \hat{p}_{\vec{\beta}} \right) \log \hat{p}_{\vec{\alpha}} \\ &= \frac{1}{2} \sum_{\vec{\alpha}, \vec{\beta}} \hat{d}_{\vec{\alpha}\vec{\beta}} \left( \hat{p}_{\vec{\alpha}} - \hat{p}_{\vec{\beta}} \right) \log \frac{\hat{p}_{\vec{\alpha}}}{\hat{p}_{\vec{\beta}}}, \end{aligned} \quad (34)$$

where we have used symmetry of  $\hat{d}$  in the second line.

For each pair  $(\vec{\alpha}, \vec{\beta})$  in Eq. (34) the product  $(\hat{p}_{\vec{\alpha}} - \hat{p}_{\vec{\beta}}) \log(\hat{p}_{\vec{\alpha}}/\hat{p}_{\vec{\beta}})$  is non-negative and symmetric under exchange of  $\vec{\alpha}$  and  $\vec{\beta}$ , and vanishes only when  $\hat{p}_{\vec{\alpha}} = \hat{p}_{\vec{\beta}}$ . As all  $\hat{d}_{\vec{\alpha}\vec{\beta}}$  contributing to the sum are non-negative,  $\dot{W} = 0$  only if  $\hat{p}_{\vec{\alpha}} = \hat{p}_{\vec{\beta}}$  for all nonzero  $\hat{d}_{\vec{\alpha}\vec{\beta}}$ . In other words,  $\dot{W} = 0$  only if the distribution  $\hat{p}$  is uniform on all components connected by decay processes (which may effectively depend on timescale). Since both the  $\pi_{\vec{\alpha}}$  the  $p_{\vec{\alpha}} \equiv \hat{p}_{\vec{\alpha}} \pi_{\vec{\alpha}}$  sum to unity, uniform  $\hat{p}_{\vec{\alpha}}$  over all  $\vec{\alpha}$  is possible only at equilibrium,  $p = \pi$ .

Steady-state flux balance (34) is part of a more general relation for the evolution from the uniform distribution at time 0 to  $p$  at any later time,

$$\int_0^t dt \frac{\dot{W}}{N_{\Pi}\tau} = D(p \parallel \pi) + \frac{1}{2} \sum_{\vec{\alpha}, \vec{\beta}} \hat{d}_{\vec{\alpha}\vec{\beta}} \int_0^t dt \left( \hat{p}_{\vec{\alpha}} - \hat{p}_{\vec{\beta}} \right) \log \frac{\hat{p}_{\vec{\alpha}}}{\hat{p}_{\vec{\beta}}}, \quad (35)$$

wherein both integrals diverge as  $t \rightarrow \infty$  while the difference converges to  $D(p \parallel \pi)$  at the steady (evolved) state.

## B. Cycle-free driving

Both the Kullback-Leibler measure (23) of information (and possibly internal free energy) in the ordered distribution, and the work (34) required to maintain it, depend only on the  $n-1$  independent components of  $p$ , in relation

to the probabilities  $\pi$  and diffusion barriers  $\hat{d}$  of the equilibrium distribution. Thus the  $n(n-1)/2$  independent real components of  $\hat{r}$  are  $(n/2)$ -fold degenerate.

To understand the degeneracy, introduce the current over a link:

$$j_{\vec{\alpha}\vec{\beta}} \equiv \hat{p}_{\vec{\alpha}} \hat{r}_{\vec{\alpha}\vec{\beta}} \hat{p}_{\vec{\beta}} - \hat{d}_{\vec{\alpha}\vec{\beta}} \left( \hat{p}_{\vec{\alpha}} - \hat{p}_{\vec{\beta}} \right) \equiv j_{\vec{\alpha}\vec{\beta}}^M - j_{\vec{\alpha}\vec{\beta}}^D, \quad (36)$$

in which the  $\hat{r}$  and  $\hat{d}$  components are labeled *Metabolic* and *Dissipative* respectively. By antisymmetry there is no definition of a current from a node to itself ( $j_{\vec{\alpha}\vec{\alpha}} \equiv 0$ ). Stationarity under Eq. (30) is simply the statement

$$\sum_{\vec{\beta}} j_{\vec{\alpha}\vec{\beta}} = 0, \forall \vec{\alpha}. \quad (37)$$

We may write any  $\hat{r}$  giving Eq. (37) at a given  $\hat{p}$  as a sum of terms  $\hat{r}_{\vec{\alpha}\vec{\beta}} \equiv \hat{r}_{\vec{\alpha}\vec{\beta}}^{(d)} + \delta \hat{r}_{\vec{\alpha}\vec{\beta}}$ , where the current arising from the particular ( $\hat{d}$ -dependent) solution  $\hat{r}_{\vec{\alpha}\vec{\beta}}^{(d)}$  satisfies  $j_{\vec{\alpha}\vec{\beta}} = 0$  independently on every link, and the remainder  $\delta \hat{r}_{\vec{\alpha}\vec{\beta}}$  produces link currents at the distribution  $\hat{p}$  that can be written as sums of cyclic currents around elementary plaquettes  $\vec{\alpha}\vec{\beta}\vec{\gamma}$ . The particular solution is immediately

$$\hat{r}_{\vec{\alpha}\vec{\beta}}^{(d)} = \hat{d}_{\vec{\alpha}\vec{\beta}} \left( \frac{1}{\hat{p}_{\vec{\beta}}} - \frac{1}{\hat{p}_{\vec{\alpha}}} \right), \quad (38)$$

The sum of cyclic currents created by  $\delta \hat{r}$  is free because it automatically satisfies stationarity under Eq. (30), but has no effect on the work flux.  $\log \hat{p}_{\vec{\alpha}}$  is a potential function on the positions  $\vec{\alpha}$ , so

$$\sum_{\vec{\alpha}\vec{\beta} \in \partial \mathcal{P}} j^{\mathcal{P}} \left( \log \hat{p}_{\vec{\alpha}} - \log \hat{p}_{\vec{\beta}} \right) \equiv 0, \quad (39)$$

where the sum is over directed links  $\vec{\alpha}\vec{\beta}$  in the oriented boundary  $\partial \mathcal{P}$  of some plaquette  $\mathcal{P}$ , and  $j^{\mathcal{P}}$  is the contribution to the link current  $j_{\vec{\alpha}\vec{\beta}}$  associated with cycling around that plaquette.

The form (38) for  $\hat{r}_{\vec{\alpha}\vec{\beta}}^{(d)}$  is equivalent to a requirement of path-independence,

$$\frac{\hat{r}_{\vec{\alpha}\vec{\beta}}^{(d)}}{\hat{d}_{\vec{\alpha}\vec{\beta}}} + \frac{\hat{r}_{\vec{\beta}\vec{\gamma}}^{(d)}}{\hat{d}_{\vec{\beta}\vec{\gamma}}} = \frac{\hat{r}_{\vec{\alpha}\vec{\gamma}}^{(d)}}{\hat{d}_{\vec{\alpha}\vec{\gamma}}} \quad (40)$$

together with the condition of no self-driving  $\hat{r}_{\vec{\alpha}\vec{\alpha}}^{(d)} \equiv 0$ . For  $\vec{\alpha} = \vec{\gamma}$  these imply antisymmetry,

$$\frac{\hat{r}_{\vec{\alpha}\vec{\beta}}^{(d)}}{\hat{d}_{\vec{\alpha}\vec{\beta}}} + \frac{\hat{r}_{\vec{\beta}\vec{\alpha}}^{(d)}}{\hat{d}_{\vec{\beta}\vec{\alpha}}} = 0, \quad (41)$$

and they imply closure around elementary plaquettes

$$\frac{\hat{r}_{\vec{\alpha}\vec{\beta}}^{(d)}}{\hat{d}_{\vec{\alpha}\vec{\beta}}} + \frac{\hat{r}_{\vec{\beta}\vec{\gamma}}^{(d)}}{\hat{d}_{\vec{\beta}\vec{\gamma}}} + \frac{\hat{r}_{\vec{\gamma}\vec{\alpha}}^{(d)}}{\hat{d}_{\vec{\gamma}\vec{\alpha}}} = 0. \quad (42)$$

An additional normalization requirement for  $\hat{p}$  comes from  $\pi$  via  $\pi \cdot \hat{p} = 1$ .

A basis for the cyclic terms is  $1/\hat{p}_{\vec{\alpha}}\hat{p}_{\vec{\beta}}$ , so that general  $\delta\hat{r}$  may be written

$$\delta\hat{r}_{\vec{\alpha}\vec{\beta}} = \frac{1}{\hat{p}_{\vec{\alpha}}\hat{p}_{\vec{\beta}}} \sum_{\mathcal{P}} j^{\mathcal{P}} \sigma_{\vec{\alpha}\vec{\beta}}^{\mathcal{P}} \quad (43)$$

where  $\sum_{\mathcal{P}}$  is over plaquettes,  $j^{\mathcal{P}}$  is the cycle current associated with plaquette  $\mathcal{P}$ , and  $\sigma_{\vec{\alpha}\vec{\beta}}^{\mathcal{P}} = 1$  if link  $\vec{\alpha}\vec{\beta}$  appears with positive sense in the boundary of  $\mathcal{P}$ ,  $\sigma_{\vec{\alpha}\vec{\beta}}^{\mathcal{P}} = -1$  if it appears with negative sense, and  $\sigma_{\vec{\alpha}\vec{\beta}}^{\mathcal{P}} = 0$  if the link is not in the boundary of  $\mathcal{P}$ .

### C. Ergodic decay

We can gain some understanding of the work flux (34), and consider an interesting special case, by noting that the Shannon entropy (25) for any distribution  $p$  can be rotated into a component along the distribution  $\pi$ , and the orthogonal remainder, as

$$-S(p) = \sum_{\vec{\alpha}} \pi_{\vec{\alpha}} \log p_{\vec{\alpha}} + \frac{1}{2} \sum_{\vec{\alpha}, \vec{\beta}} \left( p_{\vec{\alpha}}\pi_{\vec{\beta}} - p_{\vec{\beta}}\pi_{\vec{\alpha}} \right) \log \frac{p_{\vec{\alpha}}}{p_{\vec{\beta}}}. \quad (44)$$

Eq. (44) and a symmetric expression for  $S(\pi)$  then allow us to write

$$\begin{aligned} S(\pi) - S(p) &= D(p \parallel \pi) + \frac{1}{2} \sum_{\vec{\alpha}, \vec{\beta}} \pi_{\vec{\alpha}}\pi_{\vec{\beta}} \left( \hat{p}_{\vec{\alpha}} - \hat{p}_{\vec{\beta}} \right) \log \frac{\pi_{\vec{\alpha}}}{\pi_{\vec{\beta}}} \\ &= -D(\pi \parallel p) + \frac{1}{2} \sum_{\vec{\alpha}, \vec{\beta}} \pi_{\vec{\alpha}}\pi_{\vec{\beta}} \left( \hat{p}_{\vec{\alpha}} - \hat{p}_{\vec{\beta}} \right) \log \frac{p_{\vec{\alpha}}}{p_{\vec{\beta}}}, \end{aligned} \quad (45)$$

here we have made use of the definition (23) for the Kullback-Leibler divergences. From Eq. (45) we identify

$$D(p \parallel \pi) + D(\pi \parallel p) = \frac{1}{2} \sum_{\vec{\alpha}, \vec{\beta}} \pi_{\vec{\alpha}}\pi_{\vec{\beta}} \left( \hat{p}_{\vec{\alpha}} - \hat{p}_{\vec{\beta}} \right) \log \frac{\hat{p}_{\vec{\alpha}}}{\hat{p}_{\vec{\beta}}}. \quad (46)$$

The sum of Kullback-Leibler divergences is a symmetric (under exchange of  $p$  and  $\pi$ ), positive-semidefinite function vanishing only on  $p = \pi$ . Each term in the right-hand side of Eq. (46) is symmetric under exchange of both  $p$  with  $\pi$ , and  $\vec{\alpha}$  with  $\vec{\beta}$ . Moreover, the terms in  $\hat{p}$  in the right-hand sum are those appearing in the work flux (34).

Now note that there is a matrix  $d^{(0)}$  for which

$$\begin{aligned} \hat{d}_{\vec{\alpha}\vec{\beta}}^{(0)} &\equiv \pi_{\vec{\alpha}}\pi_{\vec{\beta}} - \delta_{\vec{\alpha}\vec{\beta}}\pi_{\vec{\beta}} \\ &= \left( \pi_{\vec{\alpha}} - \delta_{\vec{\alpha}\vec{\beta}} \right) \pi_{\vec{\beta}} \equiv d_{\vec{\alpha}\vec{\beta}}^{(0)}\pi_{\vec{\beta}}. \end{aligned} \quad (47)$$

$d^{(0)}$  has  $\pi$  as its null eigenvector, and the off-diagonal elements of  $\hat{d}^{(0)}$  are exactly  $\pi_{\vec{\alpha}}\pi_{\vec{\beta}}$ . For a large number of

indices  $\vec{\alpha}$  and small values of any single  $\pi_{\vec{\alpha}}$ , all the diagonal elements  $\hat{d}_{\vec{\alpha}\vec{\alpha}}^{(0)} \approx -1$ .  $d^{(0)}$  is a ‘‘canonical’’ dissipation matrix consistent with the chemical equilibrium distribution, with roughly equal probability to decay *from* any  $\vec{\beta}$ , and a probability per unit time to decay *into* any  $\vec{\alpha}$  equal to its occupancy at equilibrium. Decay under  $d^{(0)}$  is thus ergodic in some fairly strong sense.

If we happen to have  $d = \gamma d^{(0)}$ , then Eq. (33) reduces to

$$p_{\vec{\alpha}} = \pi_{\vec{\alpha}} \frac{\gamma}{\gamma - (r \cdot p)_{\vec{\alpha}}}, \quad (48)$$

and we can combine Eq. (46) with Eq. (34) as

$$D(p \parallel \pi) + D(\pi \parallel p) = \frac{\dot{W}}{\gamma N_{\Pi} \tau}. \quad (49)$$

The associated cycle-free rate matrix is then given by

$$r_{\vec{\alpha}\vec{\beta}}^{(\gamma)} = \gamma \left( \frac{\pi_{\vec{\beta}}}{p_{\vec{\beta}}} - \frac{\pi_{\vec{\alpha}}}{p_{\vec{\alpha}}} \right). \quad (50)$$

It is appealing (and may be correct) to think that some universal rate constant associated with dissipation establishes a limit like Eq. (49), between work flux and the information it can maintain in a distribution of molecules. Given the wide range of energy barriers that exist for organic reactions, such an idea at first seems implausible, but if we are trying to relate the entire entropy of biomass to the aggregate metabolic flux on earth, we should somehow average over all possible processes, including the evolution of catalysts by organisms to digest molecules in other organisms. Whether an aggregate process approximating ergodic decay arises in such an average, and what would set the resulting timescale  $\gamma$ , are left as open questions.

### D. Some empirical constraints from allometric scaling

The models of metabolism and evolution presented here are too simple to admit any literal comparison to the multi-scale processes in cells, which include basal metabolism, growth, reproduction and death, ecological division of labor, and genetic drift and selection. However, it is possible to place some constraints on the most basic division, between the Landauer bound on the idealized heat of growth, and the roles and magnitudes of dissipative processes.

For this, we use the remarkable observation that despite the many differences among organism structures and ways of life, a large number of fundamental developmental processes and timescales can be collapsed onto universal *allometric scaling curves* indexed ultimately by adult organism body mass and an Arrhenius factor for temperature [38, 39]. A premise that accounts for many observed allometric scaling exponents is that diffusion

is a less efficient mechanism for delivering nutrients in space than active transport networks. However, the latter are limited by their topology in their abilities to fill space, resulting in less efficient perfusion of respiratory structures in larger cells and organisms than in smaller ones. Essentially the same constraints appear to apply at scales from sub-cellular transport networks to ecologies, suggesting that the Darwinian individual is not a salient allometric unit.<sup>15</sup>

To begin, recall from the introduction that the simplest equilibrium estimate for the entropy reduction upon producing a cell from atomic precursors [1] can be put in the form<sup>16</sup>

$$-\Delta S_{\text{Gibbs, cell}} \approx k_B N_A \times \frac{M_{\text{Dry, cell}}}{10g}, \quad (51)$$

where  $M_{\text{Dry, cell}}$  is the mass of the cell excluding water. Eq. (51) provides a reference for the scaling with mass of material “information” relative to the Gibbs equilibrium, which applies equally to multicellular organisms.

Next, denote by  $\dot{W}_{\text{Org}}$  the metabolic rate of a whole organism, which may be unicellular or multicellular, and by  $\dot{W}_{\text{Cell}}$  the rate of a one of its cells cultured for a few generations in vitro at the same temperature in a medium without nutrient limitations.<sup>17</sup> In keeping with previous sections total ATP syntheses in the organism or unicell will be regarded as the measure of metabolic flux, and thus also as the rate of chemical work. Other measures do not differ to order of magnitude. West et. al. [39] (and ref’s therein) predict from first principles the observed relation that, for a large range of multicellular eukaryotes,

$$\dot{W}_{\text{Org}} \approx \dot{W}_{\text{Cell}} \left( \frac{M_{\text{Org}}}{M_{\text{Cell}}} \right)^{3/4}, \quad (52)$$

where  $M_{\text{Org}}/M_{\text{Cell}}$  is the ratio of masses of the organism and the cell. From the same argument, the lifetime  $\mathcal{T}_{\text{Org}}$  of the organism is predicted (and observed) to scale relative to the lifetime of its corresponding cell in vitro as

$$\mathcal{T}_{\text{Org}} \approx \mathcal{T}_{\text{Cell}} \left( \frac{M_{\text{Org}}}{M_{\text{Cell}}} \right)^{1/4}, \quad (53)$$

where  $\mathcal{T}_{\text{Cell}}$  (on the order of an hour) is an intercept obtained by extrapolating lifetime to  $M_{\text{Org}}/M_{\text{Cell}} \rightarrow 1$  along the power law. From these the total energy consumed in the lifetime of the organism scales as<sup>18, 19</sup>

$$\frac{\dot{W}_{\text{Org}} \mathcal{T}_{\text{Org}}}{M_{\text{Org}}} \approx \frac{\dot{W}_{\text{Cell}} \mathcal{T}_{\text{Cell}}}{M_{\text{Cell}}}. \quad (54)$$

Eq. (54) also relates unicells of different masses, and can be extended apparently as far down in scale as the mitochondrial respiratory complex in the organisms studied.<sup>20</sup>

To the extent that the dry weight of cells is a roughly constant fraction of their total weight, from Eq. (51) it follows that

$$\frac{\dot{W}_{\text{Org}} \mathcal{T}_{\text{Org}}}{\Delta S_{\text{Gibbs, Org}}} \approx \frac{\dot{W}_{\text{Cell}} \mathcal{T}_{\text{Cell}}}{\Delta S_{\text{Gibbs, Cell}}} \approx \text{const.} \quad (55)$$

Thus to leading order *all* organisms consume an amount of chemical work during their lifetimes that is a roughly constant multiplier of the Landauer estimate for the entropy rejected to create their biomass from single atoms. This finding is consistent with the ability to construct universal development curves [39], by scaling time to measure ATP syntheses rather than calendar time. It also suggests that the most important dissipative mechanisms in biochemistry scale with net growth.

Because the ratio of work flux to Gibbs entropy reduction in Eq. (55) scales inversely with organism lifetime, hence with organism mass to the -1/4 power, larger organisms seem to maintain more information per rate of metabolic work, precluding a universal relation of the form (48) deducible directly from chemical properties. However, the strong assumptions used to derive the Gibbs measure of Ref. [1] may make it an inappropriate entropy from which to relate work flux directly to constraints from chemical reactions. Multicellular organisms and even complex cells do not grow from single atoms or even from simple inorganic precursors. They form from low-entropy molecules, either exchanged within the ecology as food or generated at photosynthetic centers

<sup>15</sup> The existence of allometric constraints and the reason for their existence – structured spatial as well as chemical kinetic limitations – introduces yet another complication into a principled construction of an ensemble for biomass.

<sup>16</sup> Eq. (51) essentially measures the number of atoms in organic compounds in the cell, because other factors associated with the possible bond configurations given a physical arrangement do not differ significantly from unity. The factor 10g is a proxy for the average molar weights of H, C, N, and O (the major organic constituents), rounded to the nearest factor of 10.

<sup>17</sup> In advanced multicellular organisms, some cells scale as the quarter power of the whole-organism size, while others do not scale at all. Here I will assume  $\dot{W}_{\text{Cell}}$  refers to a somatic cell typical of the organism’s clade, which does not scale with body size. Such cells typically constitute the majority of the mass of the whole organism.

<sup>18</sup> For multicellular organisms the rate of work is a non-constant function of developmental age, in which case the product  $\dot{W}_{\text{Org}} \mathcal{T}_{\text{Org}}$  in Eq. (54) must be replaced with an integral  $\int \dot{W}_{\text{Org}} d\mathcal{T}_{\text{Org}}$ . The same relation holds [38] for the integral as for the simple product, however, because the developmental trajectories among organisms can all be collapsed onto a single dimensionless curve.

<sup>19</sup> An additional temperature correction from an Arrhenius factor may be added to Eq. (52) and Eq. (53), which cancels to recover Eq. (54).

<sup>20</sup> A factor of  $\sim 100$  separates endotherm (mammal and bird) cells in vivo from typical unicell metabolic rates [39] along their respective allometric curves, apparently associated with losses specific to endotherm transport networks. This is also the factor separating the lifetime energy estimate  $\sim 40\text{kJ/g}$  of Ref. [38] (for birds) from the estimate  $\sim 0.4\text{kJ/g}$  from Ref. [1] for bacteria at the same temperature (corrected to wet mass).

on surfaces within the organism. Allometric scaling results from dilution of these energy-rich precursors, and it is with respect to these that a Gibbs entropy reduction should presumably be computed, which is related to the work flux.

For purposes of this section, we simply observe that *given* the spatially-induced constraints of allometric scaling, the Landauer bound approximates a universal constraint on the growth of organisms, whether they are expanding into fresh medium or replacing existing organisms that have died – in itself rather a surprising regularity. Dissipation appears here only implicitly, in the mechanisms responsible for aging and death, and the spectrum of lifetimes within the ecology (itself allometrically constrained [40]) then relates the Landauer information to the average metabolic flux required for maintenance of an ecology-wide steady state.

## V. DISCUSSION

We have used an engine-like organization of metabolism as the foundation for a stochastic process model of evolution, for which the equations of motion lead to a non-equilibrium distribution in the late-time steady state. At this level such a model is not in principle different from a dissipative-structure model, in which phenomenological equations of motion predict non-equilibrium outcomes without addressing the real failures in the ensemble definition of equilibrium statistical mechanics. The foregoing models provide a somewhat more principled decomposition of the relations among information, work flux, and dissipation, but they have not been derived from a single comprehensive ensemble description, or even proved to follow from one. We now return to the (much more complicated) question of how a kinetically constrained ensemble description of driven chemical reactions might lead to an organization something like the one put forth above. Of central concern will be how kinetic constraints change the calculation of the whole-ensemble entropy, so that kinetically inaccessible molecules never contribute in “statistical equilibrium” and thus do not appear as anomalous “entropy reductions” in the characterization of biomass.

### A. Source constraints in organosynthesis

Carbon anabolism is essentially a process of transferring reductant onto  $\text{CO}_2$  to produce C-C bonds and other functional groups. Both in phototrophs (through the Calvin-Benson cycle [16]) and in chemotrophs (through the reductive citric acid cycle or the Wood-Ljungdahl pathway [15])  $\text{CO}_2$  is the exclusive inorganic carbon source, and Aldol and Claisen condensations are the two reactions through which C-C chains are extended [15], while closely related reactions provide the initial attack

on the  $\text{CO}_2$  carbon (frequently in the form of bicarbonate ion). The extant metabolic pathways can be seen as solutions to the problem of repeatedly using these two kinds of reactions in different chemical environments, not only as they appear today with modern enzymes, but also in a pre-enzymatic world containing only small molecules and inorganic catalysts [41, 42]. The carbon source effect from  $\text{CO}_2$  and the energy source effect from reductant should somehow be reflected in the kinetically constrained ensemble description, for the same reasons they are reflected in the structure of modern organosynthesis.

Aldol- or Claisen-like condensations of  $\text{CO}_2$  naturally yield carboxyl and  $\alpha$ - or  $\beta$ -ketone groups as carbon chains are extended [12]. These groups are thus prevalent in biosynthetic precursors like the citric-acid cycle intermediates, not because they are selected among all isomers in molecules with the same average reduction states for carbon (at a cost of “information”), but because they are the only groups formed by short reaction sequences from  $\text{CO}_2$ . If the reduction from  $\text{CO}_2$  to methane can be accomplished quickly by a metabolic pathway (as it is in the methanogens [15]), the narrow class of molecules with easily formed functional groups defines a separate “branch” for the short-time ensemble coupled to the carbon source (oxidized) and sink (reduced), against the background of the Gibbs equilibrium, and it is within this branch that biomass is found. A related though more complex catalytic argument may explain the selection of the biologically employed amino acids [43], and it will be surprising if other such arguments do not apply to the nucleic acid, sugar, and fatty acid inventories common among cells. For each of these molecule classes, most of biomass is formed by “sequestering” the readily formed functional groups as they travel from inorganic sources of carbon or nitrogen, to a final low-energy waste state.

The reactions within the fast-timescale ensemble have a structure resembling the engine organization of Sec. II. For cycles like the reductive citric acid cycle, both the energetic and the network-catalytic correspondence can be drawn quite literally [12].

The fact that modern metabolic enzymes reflect many of the same kinetic constraints as uncatalyzed small-molecule reaction networks also allows us to connect the problem of the entropic stability of modern life to the problem of life’s origin, which is necessary but which until now we have avoided mentioning. While Sec. II makes use of many highly optimized features of modern cells to motivate an ideal organization of metabolism, the same organization may apply in cruder form to the small-molecule ensemble from which metabolism first emerged on the Hadean earth.

If the earliest forms of life were reducing and chemotrophic, as seems likely [42], they would have had limited need to couple energy “capture” to biosynthesis, since the major biosynthetic reactions are exergonic in reducing environments. Then the statistical equilibrium in the fast-timescale branch of the driven ensemble essentially describes the formation of stable chan-

nels through which to allow environmental free energy to relax. In simple examples [21], omitting catalysis and even any literal representation of chemistry, it is possible to construct well-defined entropy functions in the presence of dissipative coupling to a source and sink, and even to build a generalization of the Gibbs free energy parametrized by the non-equilibrium intensive state variables. Within such ensembles the maximum-entropy macrostate describes spontaneously formed currents that function as such relaxation channels, providing a minimal mathematical model of a “likely” foundation for metabolism.

The overall picture for phototrophy is similar but much more complex, and it is not clear whether ordered phototrophic ensembles existed in a pre-enzymatic world.<sup>21</sup> If not, that is if they required the prior existence of fully developed cellular life to form, then the notion of restrictions on kinetic accessibility applies also to much longer-timescale components of the ensemble, describing evolutionary innovation in a world of enzymes and genes.

## B. Genome and biomass

The hazard of using a polymer-sequence model to discuss the information in biomass is that it invites a specious interpretation: that the information in the genome should be conflated with the information in biomass. It is likely that such an identification is wrong for two reasons, but as in the discussion of the chemistry of organosynthesis, it is a subtle question just how wrong it is.

The first caution is the empirical observation that the genome lengths of bacteria scale as the  $1/4$  power of cell volume [29], while the mass of metabolically produced organic compounds is proportional to cell volume. The naive measures of Shannon information to specify a single sequence from random nucleotide strings of the same length, and Gibbs entropy to synthesize biomass, thus scale differently. This difference is likely to persist even if the naive information measures are refined, because genome and the bulk of biomass are of functionally different characters. Second, as noted above, the Gibbs entropy reduction in biomass is extensive in the number of cells, while the Shannon information to specify a gene sequence would seem to be the same for a clonal population as for a single cell.<sup>22</sup> If we understood how

the cost of maintaining these two information measures relate, we would likely also be able to predict genome scaling from metabolic rate, which is currently an unsolved problem. However, we can see that the relation among the two measures shares some features with the kinetic constraints of small-molecule chemistry.

Enzymatic catalysts are reaction-specific and long-lived, while genes are catalyst-specific and long-lived. Given these two elements, a very short-timescale ensemble for biomass admits only the observed metabolites, and there is no entropy paradox to metabolic composition. In that sense the genes and enzymes appear to contain all information in metabolism not present at equilibrium, and even to redundantly encode some of the information that may have been present already from small-molecule kinetics. However, catalysts and genes do not live forever, and because of their greater complexity, they would appear generally to admit a larger number of perturbations, and of these a larger fraction that are non-functional. Thus the information to specify the catalysts may exceed that to specify the underlying substrates, despite their longer lifetimes.

Nominally natural selection is responsible for choosing and refining catalysts, but the foundation of selection is ultimately differential growth and competitive exclusion under resource constraints, causing the ensemble specification for catalysts to circle back to the engines at work in metabolism, with the complications of development and the genotype-phenotype map interposed. Thus, some of the kinetic information apparently “redundantly” specified by the genome has probably actually been specified by chemistry all along, and the kinetic constraints on genotype and phenotype arise in some complex way from their ability to deviate minimally from chemically simple mechanisms that respect the structure of the driving sources of material and energy. The problem faced by statistical mechanics in understanding life is a kind of “closure”, across a wide range of processes and timescales, and it is the ability to predict the limits on the complexity of such self-referential processes for which an ensemble description is most needed, because piecemeal descriptions at individual levels are by nature incomplete.

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<sup>21</sup> Certainly in the modern world, phototrophic metabolisms contain reducing anabolic networks essentially identical to those of reducing chemotrophs. Photosynthesis appears to have arisen as a prosthetic for autonomous production of reductant, and oxidizing metabolism as a yet later prosthetic resulting from what were initially waste products of oxygenic photosynthesis.

<sup>22</sup> Bennett [23] provides a useful framework for thinking about this identity, by considering sequence copying in a reversible world, and regarding non-random sequences as a potential source of

chemical work. Given  $J$  copies of a sequence of  $N$  bases,  $J - 1$  of them can be randomized relative to the last copy, which serves as reference, yielding  $2k_B T (J - 1) N$  of work for a four-letter alphabet. Only the last copy remains apparently random if we do not know the algorithm that gives it a short description.

collaboration within which it was performed. I am particularly indebted to my colleagues Harold Morowitz and Shelley Copley, who have shaped my thinking about metabolism, bioenergetics, and the omnipresence and importance of kinetics, and to Duncan Foley and David Krakauer for discussion and references about Landauer's principle.

## APPENDIX A: NOTATION AND LEGENDRE DUALITY

The basic measurable extensive state variables for any component of the reactor are  $U$  (internal energy),  $V$  (system volume), and  $N$  (particle number of the solute). The extensive entropy function of these variables  $\sigma(U, V, N)$  defines the surface of state for a classical thermodynamic system.

Intensive state variables are most symmetrically defined as the derivatives of the entropy by its extensive arguments. Temperature

$$\left. \frac{\partial \sigma}{\partial U} \right|_{V, N} = \frac{1}{\tau}, \quad (\text{A1})$$

pressure relative to temperature

$$\left. \frac{\partial \sigma}{\partial V} \right|_{U, N} = \frac{p}{\tau}, \quad (\text{A2})$$

and chemical potential relative to temperature

$$\left. \frac{\partial \sigma}{\partial N} \right|_{U, V} = -\frac{\mu}{\tau}. \quad (\text{A3})$$

The equation for conservation of energy within the surface of state is then a definition:

$$dU = -pdV + \mu dN + \tau d\sigma. \quad (\text{A4})$$

The Gibbs potential  $G$  off the surface of state is a function of the extensive variables *parametrized* by the intensive variables, which are regarded as properties of the system boundaries. Written as the Legendre dual to the entropy,

$$\frac{1}{\tau} G \equiv \frac{1}{\tau} U + \frac{p}{\tau} V - \sigma. \quad (\text{A5})$$

$G$  is minimized at  $U$  and  $V$  for which the derivatives of the entropy (A1,A2) equal the imposed boundary conditions ( $1/\tau$ ,  $p/\tau$ ). Within the resulting surface of state as a function of  $p$ ,  $\tau$ , we have from Eq. (A4) both that

$$dG = \mu dN = dH - \tau d\sigma, \quad (\text{A6})$$

where  $H \equiv U + pV$  is the enthalpy, and by integration (as  $N$  is the only remaining extensive argument of  $G$ ), that

$$G = \mu N, \quad (\text{A7})$$

where  $\mu(p, \tau)$  is a function only of pressure and temperature. We also recover the more usual energetic-dual definition of the chemical potential

$$\left. \frac{\partial G}{\partial N} \right|_{p, \tau} = \mu. \quad (\text{A8})$$

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