

Energy Utilization, Catalysis and Evolution-Emergent Properties of Life

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Abstract: Life is fueled by available energy. In fact, life is organized around the utilization of available energy, either from photons or from chemicals. The basic architecture of life can be understood from the following propositions: catalysts are able to control the path of chemical reactions and influence their rate by transient and reversible exchange of high-grade energy between themselves and reactants, while conserving the total energy. That, in turn, enables the synthesis of essential chemicals as well as the duplication of templates. We argue in this paper that energy utilization and evolution are emergent properties in life that are based on a small number of well-established laws of physics and chemistry governing catalysis. We propose that the relevant laws constitute a framework for biology on a level intermediate between quantum chemistry and cell biology.

Keywords: Catalysis, energy partitioning, evolution, bioenergetics.

INTRODUCTION

Living organisms are capable of generating order from disordered matter. They are also capable of replicating themselves with great fidelity. The workings of living beings are intricate; they rely on molecular mechanisms that are delicate, fine-tuned yet robust to the vicissitudes of life and to their environment. Accordingly and appropriately, the bulk of textbooks and research articles are concerned with detailed description and understanding of the immensely complex workings of living organisms. Here, instead, the center of our attention will be on tracking the flow of available energy in living systems. This common thread illuminates an underlying simplicity.

Our approach may be compared with that found in well-known and respected textbooks of biology, *e.g.* [1] and of biochemistry, *e.g.* [2]. While most of the separate points in our paper can be found in those books, the centrality of energy utilization and its simplifying and organizing role is not emphasized in them, neither is it in most research papers. This paper attempts to shift the emphasis in this area.

All living systems are out of thermodynamic equilibrium with their surroundings. A necessary condition for producing, as well as for maintaining, a dynamic system out of equilibrium is to be able to access available external energy. Available energy in biology comes in several forms: photon energy, chemical energy, electrical energy, and mechanical strain are the common ones. This available energy, also called high-grade energy, has to be conserved or utilized and not completely lost as heat to the surroundings, for metabolism to function in living systems. In fact, in most metabolic processes, available energy is converted from one form to another, although never with 100% efficiency. This is the

process of energy utilization and we will call the agents that carry it out - somewhat poetically - the engines of life. From our point of view, generation of order, replication of the individual, and evolution of the species all depend on the successful utilization of external energy available to a living system. The center of our attention will be on catalysis.

It is well known that catalysts can influence the speed of a chemical reaction and select the reaction path, by a transient and reversible exchange of high-grade energy between themselves and their reactants. The selection of a reaction path gives great flexibility for channeling the reaction into a direction that produces selected and desirable products, as well as preventing available energy from being degraded into heat at once; in short, utilizing it. It is especially important when key steps in metabolism involve the reversible exchange of high-grade energy between uphill and downhill chemical processes. This flexibility enables selection of "suitable" catalysts by evolution.

Finally, proper utilization of available energy allows the synthesis of selected chemicals as well as the duplication of templates. This provides the basis for the established "central dogma" of biology: Development and replication of the individual depend on molecular memory that, in free-living organisms alive on our planet, is encoded in nucleic acids [1]. We will argue that the astonishing complexity of living organisms is an emergent property of those fundamental principles.

The paper starts with a short review of the relevant length scales and time scales and the physical - chemical principles appropriate for the scale of our description. Then the concept of emergent properties is discussed. They are applied to catalysis in biology. The framework of life is then identified. The present paper is a more systematic restatement of our earlier paper [3].

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BASIC CONCEPTS

In this section, the appropriate time scales and length scales of our description will be established. A brief statement of four physical-chemical concepts will follow in order to establish a common language and to emphasize some subtle points. They are the concepts of a thermodynamic state, spontaneous and irreversible chemical reactions, the path and speed of chemical reactions and the concept of generalized catalysis.

Length Scales and Time Scales

Living matter, on a large scale, has a well-defined temperature, pressure, density and chemical composition. In short, it is in a thermodynamic state. Although there are statistical fluctuations, they are negligibly small. In contrast, isolated single molecules have to be described by the laws of classical or quantum mechanics. Most of our descriptions in this paper are on an intermediate scale of length and time, that can be called, lacking a better name, mesoscopic scale. The length scales are those of a single large molecule or an organelle and the time scales are long compared to elementary molecular processes, *e.g.* vibrations or electron transfers. The mesoscopic scale, as applied here, can be roughly measured by the product of the volume and time of interest; it should be $\approx 10 \text{ nm} \times 10 \text{ nm} \times 10 \text{ nm} \times 10^{-10} \text{ sec} \approx 3 \times 10^{-7} \text{ nm}^3 \text{ sec}$ to within three orders of magnitude. The mesoscopic description is applicable to a small collection of single molecules in a solvent or even to a single molecule on a time scale longer than a few tens of picoseconds. It should be noted that at biologically interesting temperatures all such systems transfer heat to and from their surroundings, so the equality of time and ensemble averages, the so-called ergodic property, is never in question. Note however, that in a volume as big as a mitochondrion at pH 8 there is only a single proton present on the average. The transfer of a single proton across the membrane, therefore, changes pH appreciably. This highlights the fact that all thermodynamic properties of such small systems undergo appreciable fluctuations in space and time. Although not at all obvious, it can be shown that the concepts of thermodynamics and statistical mechanics are applicable even on this scale. All our descriptions will be on such mesoscopic length and time scales, not on the usual scale of thermodynamics. This is the relevant scale for biological catalysis. The systems will be called, for short, the "system of interest".

A Thermodynamic State

Thermodynamic states of matter are fully described by a small number of thermodynamic variables: the total volume, temperature, pressure, density, chemical composition and concentrations of the chemical components. It is implied that the microscopic states of the molecules therein are as disordered as possible, given the constraints set by those macroscopic quantities. Such a description is valid when changes in the macroscopic quantities are slow compared to changes in the microscopic states of the molecules. Under such conditions microscopic fluctuations have time to attain their equilibrium values; the local values of thermodynamic quantities are then well defined. When such a description is adequate for the states in living matter, we call it local equilibrium.

The fundamental thermodynamic variables that characterize the system of interest can be combined to form thermodynamic functions: the energy, U , the enthalpy, $H = U + PV$, the Helmholtz free energy, $A = U - TS$, and the Gibbs free energy, $G = U - TS + PV$, where P is the pressure, V is the volume, T is the absolute temperature and S is the entropy of the system. When chemical or other changes connect two thermodynamic states, the thermodynamic functions, A and G , change by well-defined amounts. In fact, in biology, the two changes are almost equal, $\Delta A \approx \Delta G$, because volume changes are usually negligible. Indeed, these quantities are often used interchangeably in biological textbooks. Thermodynamic functions are defined and discussed in [4-6]. All the thermodynamic functions are "state functions": they are independent of the way the state was formed. During chemical reactions the reactants and their immediate environment can be far from any equilibrium state. The reaction paths and the reaction rates can be calculated only from a detailed, microscopic knowledge of the reactants and of their environment [7].

A local equilibrium state under constant temperature and pressure is one with a local minimum of the Gibbs free energy, $G(T, P, N)$, where N denotes the local concentrations of all chemical components. The principles of statistical mechanics imply that, even in local equilibrium, the microscopic states fluctuate on small scales and in short times. In fact those fluctuations and their magnitudes are a direct consequence of the thermodynamic description and can be calculated from it [6]. Note that, in a small system, all state variables fluctuate in time; the thermodynamic variables should always be understood as averages. The above properties are usually assumed without stating them explicitly. Being out of equilibrium means that the local value of G is greater than the absolute minimum for the atomic constituents. When a chemical reaction occurs, G changes by a well-defined amount. The amount, ΔG , depends on the kind of reaction, the temperature, the pressure and the local concentrations of the components. Complex structures in biology are able to alter local conditions. They evolved precisely for the purpose of establishing the local thermodynamic conditions to carry out specific reactions. Similarly, we postulate that all processes produce another thermodynamic state.

Reversible and Irreversible Processes

Next, consider the fundamental concepts of available energy and maximum amount of work. The available energy of one thermodynamic state, with respect to another thermodynamic state [4-6], is the maximum amount of reversible work that can be extracted from it under any circumstances¹. It is equal to the difference in their Helmholtz free energies, ΔA . The change in the Gibbs free energy ΔG is, similarly, the maximum amount of non-expansion work that can be extracted. Although ΔA is independent of the details of the reaction, the maximum amount of work can be extracted only when the change of states proceeds through fully reversible steps.

Chemical, mechanical and electrical energies can *in principle* be fully converted into one another by reversible processes. For simplicity, therefore, chemical, mechanical and

¹The term "exergy" is sometimes used for available energy.

electrical energies will be called high-grade energy, and heat will be labeled low-grade energy. Unfortunately, the categories are more complicated. Heat can be converted into high-grade energy in a heat engine (Carnot cycle) and some changes in entropy are reversible. One example is a difference in ion concentration across a membrane that produces an electrochemical potential. Part of the potential stems from a “high-grade” $T \Delta S$. Nevertheless, the reader is reminded and reassured that G *always* gives a correct account for the high-grade energy available. It is an important fact that once high-grade energy is degraded into heat, it is not recovered by living systems².

The change in G determines whether a reaction occurs spontaneously or not. Negative $\Delta G = G_{\text{after}} - G_{\text{before}}$ is the spontaneous direction. ΔG of a reaction depends on the concentrations of the reactants and of the products according to the formula

$$\Delta G = \Delta G_0 + kT \ln \left\{ \frac{[D][E]}{[B][C]} \right\}, \quad (1)$$

where k is the Boltzmann constant and T is the absolute temperature. The equation was written in units of energy per molecule. The equation describes the dependence of G on the concentrations of the reactants and products in a reaction, $B + C \rightleftharpoons D + E$. As usual, the letter B denotes a chemical species and $[B]$ denotes its concentration - actually its fugacity, to be pedantic. The standard free energy of the reaction is denoted by ΔG_0 . It occurs when the concentration of the reactants and the products are equal. Chemical equilibrium occurs when $\Delta G = 0$. The second term in Eq (1) comes from reversible entropy differences. For example, across some biological membranes there are concentration differences and there are differences in electrostatic potential; they are both high-grade energy.

When a chemical reaction is irreversible, the actual work extracted is less than ΔA ; a fraction of the available energy, or even all of it, is dissipated. This is the case for most spontaneous reactions. In irreversible, spontaneous reactions ΔG is negative and it is completely dissipated as heat, *i.e.* it generates irreversible entropy [7]. We make the plausible assumption that if a large enough part of the reactants and their environment is included in the description, it is possible to describe the chemical processes of life in such a way that the change in free energy, ΔG , is completely converted into heat. This is clearly possible if the *reversible* exchange of energy is limited to a few molecules in the close environment of the reactants. By including all parts of the reacting system that exchange reversible energy in our system of interest, it can be achieved in practice.

The Path and Speed of Chemical Reactions

The detailed evolution of a reaction has a complex dependence on its environment. Here it will be referred to simply as the reaction path. Within a given environment, whatever the path, ΔG depends only on the reactants and the products. Given ΔG , the ratio of the forward and reverse reaction rates is $\exp[-\Delta G/kT]$.

The speed of a chemical reaction depends on its detailed path. In ordinary reactions, a great simplification results from postulating a transition state that constitutes the bottleneck for the reaction. In this approximation, the transition state is produced by local, microscopic fluctuations within the thermodynamic state. The reaction rate can then be obtained from the probability of getting to the transition state by local fluctuations, multiplied by the crossing probability of passing beyond the transition state [7].

Given a set of reactants, usually many reaction paths are possible. Among those, the one with the fastest rate predominates. A crucial observation is that the reaction rate is determined by the “activation” free energy of the transition state, ΔG^\ddagger , and not by the final ΔG of the reaction. In particular, some reaction paths can generate a large amount of heat, *i.e.* have a very large negative ΔG , while some other reaction path with a much smaller negative ΔG and different reaction products can be a faster reaction. That is the case when the transition state energy ΔG^\ddagger of the second reaction is lower, and/or its crossing probability is larger than those for the first one. A similar argument can be given for generalized reactions if a bottleneck for the reaction can be identified.

Catalysis in its General Form

We will define catalysis in the broadest possible way, very much in accordance with the original definition of Berzelius³. We will include any change in the reaction path caused by the catalyst. That encompasses the change of speed of a given reaction, but includes changes in the products. A prerequisite for the catalyst to be able to influence a chemical reaction is that high-grade energy be exchanged among the catalyst and the reactants; or, expressed even more starkly, the catalyst has to interact with the reactants in order to influence the reaction. As mentioned above, quantitative predictions can be obtained only by solving the microscopic equations of classical or quantum mechanics respectively.

Catalysts provide a local environment to the reaction. As long as the reactants are in their macroscopic, thermodynamic states this is a valid and useful description. The reactants are then in local equilibrium before the reaction: they have a local G , a local pH and some chemical groups have locally varying pK. Most catalysts provide a specific environment for a specific reaction. Similarly, the products are in local equilibrium after the reaction with a different local G , etc. Note that at this intermediate stage ΔG of the reaction depends on the catalyst. This apparent contradiction is resolved if ΔG of binding the reactants and of unbinding the products is properly added. The resulting total ΔG is independent of the catalyst, as it should be.

The importance of catalysis for biology is that catalysts can influence the pathway of the reaction in order to accomplish a biological task. For example, catalysts are able to change the path of a reaction in such a way that available energy is sequestered during the reaction and, possibly,

²Insofar as $P \Delta V$ work can be ignored. The jet of a bombardier beetle is expelled by local heating. It is, indeed, high-grade energy produced by a heat (Carnot) engine.

³The original Greek word “catalysis” means dissolution, destruction, ruin, decomposition. Berzelius defined catalysis in chemistry as the effect produced in facilitating a chemical reaction, by the presence of a substance, which itself undergoes no permanent change [Berzelius, JJ. Edin. New Phil. Jnl. XXI. 1836; 223].

channeled into new products. By selecting a reaction path, catalysts can change the fraction of the available energy, G , in each of the steps, while keeping the sum of ΔG constant for all steps in the sequence. In such reactions, even when a catalyst does not change the dissipated fraction of G , it can alter the path of the reaction in such a way that it temporarily holds some of the available energy during one part of the reaction, releasing it in a later part of the reaction⁴. The fundamental mechanism of coupled reactions, ubiquitous in metabolism, is the exchange of high-grade energy between the exoergic and the endoergic components. We can state quite generally that the channeling of a reaction along a pathway of low heat loss, by enzymes, is the most important way high-grade energy is utilized in biology.

EMERGENCE

It is accepted wisdom that properties of living systems are based on well-established laws of physics and chemistry [1-3]. Nevertheless, the rules that govern complex systems in general and biological systems in particular cannot be directly deduced from those laws. In fact, they have to be described and understood on several distinct layers or levels. On each level a set of rules, appropriate to that level, has to be established. These properties have been called emergent behavior. Emergent laws of biology must not contradict the laws of physics and chemistry but they have to be established in addition to them [9]. Some of these ideas have been present in biological thinking for many years, witness Monod's book, *Chance and Necessity* [10]. Recent papers of Laughlin and Pines [9], Woese [11] and Noller [12] as well as the classic works of Dawkins [13, 14] and Eigen [15], [16] illuminate the subject.

Since our main interest is in the utilization of available energy by living systems, as the driving force of life, we divide the description into only three layers, or levels: macroscopic, mesoscopic and microscopic. At the macroscopic level, thermodynamics is valid and fluctuations are negligible. In particular, the concepts of free energy and of reversible and irreversible processes are well defined. The mesoscopic level is used here to explore the energetics of the basic metabolic processes. It is intermediate between quantum chemistry and cell biology. At the microscopic level, that is the level of quantum chemistry, the equations of motion are reversible and thermodynamic concepts lose meaning. In the section below we attempt to describe energy utilization - on the mesoscopic level - in a physically, chemically and biologically meaningful way.

EMERGENCE IN BIOLOGY: BIOENERGETICS AND METABOLISM

Metabolism represents the set of chemical and physical changes that take place within an organism and enable its continued growth and functioning. Living organisms exchange material and energy with their surroundings; and, from a thermodynamic point of view, they are open systems. The engines of life that keep metabolism going are fueled by available energy; this is the most general expression of the principles of bioenergetics [17].

Almost every reaction in metabolism is catalyzed. This is true even for generalized reactions in living systems, such as motion or protein folding. A very cursory outline of functions and mechanisms of biological catalysis will be given below, centered on the utilization of available energy.

Biological Catalysts - Enzymes

The fundamental mechanism of enzyme action is a transient, *reversible* exchange of high-grade energy between the enzyme and the reactants. In classic terms, the enzyme exchanges high-grade energy with a reactant reversibly; both the reactant and the catalyst are distorted when they bind. The change in free energy, ΔG , of the *unbound* reactants and the products in a specific reaction does *not* depend on the presence of the catalyst. Nevertheless, when the reactants and the products are bound to a catalyst, the local values of G of the reactants and the products depend strongly on the local environment provided by the enzyme. A reaction is speeded up when the bound reactant "approaches" the transition state.

The most widely recognized property of enzymes is that they can speed up spontaneous reactions by binding to the transition state more strongly than they bind to the reactants. That lowers the relative free energy of the transition state ΔG^\ddagger . Note that we do not differentiate among the various ways this is accomplished: by lowering the transition state, unbinding the reactants and "pre-organizing" the enzyme itself.

It is especially important that key steps in bioenergetics involve the reversible exchange of high-grade energy between uphill and downhill chemical processes. Such "coupled reactions" are the backbone of biosynthesis.

At this point it is convenient to extend the definition of catalysis to a situation when the exoergic and the endoergic reactions are carried out consecutively. The exoergic reaction then "charges" the enzyme with high-grade energy and the endoergic reaction is driven by the energized enzyme. Only the net difference between the two ΔG 's is dissipated as heat and, at the end of the cycle, the enzyme is reusable. In order to make each step spontaneous, ΔG has to be negative at each step separately.

The great flexibility enables selection of "suitable" catalysts by evolution. We note that many biochemical cycles, *e.g.* the citric acid cycle and the Calvin cycle are now included in our definition. Also, that different enzymes have different efficiencies for the same reactions [18, 19].

Heat generated during metabolism is not reconverted into available energy by living beings today⁵.

A FRAMEWORK OF LIFE

Here we assemble key components of our discussion into a framework for catalytic energy utilization. We propose that it is the simplest set of rules that explains the functioning of living matter. These rules are emergent, in the sense that they

⁴Obviously, in such cases all molecules that exchange high-grade energy have to be included in the system of interest.

⁵Some organisms benefit from the generation of heat. There are many great examples: (i) Flowers have hot plates to evaporate attractants. (ii) Insects (*e.g.* the bumble bee) produce heat in futile cycles so that they can take off in the cold. (iii) Bears waking from hibernation heat up their body by uncoupling electron transport.

are compatible with the basic laws of physics but they cannot be derived from them. We propose that they provide the link between biology on one side and physics and chemistry on the other.

- (i) Dynamic systems require an input of external energy to move away from thermodynamic equilibrium and a continuous input of external energy to maintain a position away from equilibrium.
- (ii) Dynamic, changing and evolving systems can stay out of equilibrium only if they do not degrade all of the available energy into heat during chemical changes. In order to achieve that, the fastest chemical reactions have to proceed on paths that have a relatively small negative ΔG .
- (iii) A catalyst interacting with its reactants can exchange high-grade energy with the reactants and thereby alter the fastest path of the reaction. The sign of this transient energy exchange can be either positive or negative with respect to the catalyst, and when it is positive, the catalyst gets transiently energized. In the simplest coupled reactions, the energy is transmitted to another reactant and the net result is an activated molecule. The conserved high-grade energy from this step is then available to the organism for other uses. In more complex - and more common - coupled reactions, the temporarily stored high-grade energy in the catalyst becomes available to drive another reaction up-hill. This ability is a "built in" feature of catalysis, and follows from the transient exchange of high grade energy between catalyst and reactants, as discussed here.
- (iv) Catalysts provide a very large range of possibilities for selecting and varying chemical reactions. An enzyme with less than perfect specificity allows evolution to work; actually, it is the prime vehicle of evolution. As a consequence, in living systems, evolution selects catalysts that are best suited for a specific task.

We conclude that replication and evolution are consequences of this relatively simple framework, and as such they are also emergent properties of biological systems.

In closing, we declare that "there is nothing new" in this paper, except a concise and systematic exposition of the framework of life, bringing the temporary energy exchange between catalyst and reactants to center stage. A far-reaching conclusion is that no "fundamental" new discoveries are needed to understand the workings of life.

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