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Coding of Gibbs Function Flows from Nucleotide Pools

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The biochemical machinery of living systems obeys kinetic laws, but is driven by Gibbs function flows. Both the kinetic and thermodynamic aspects of Gibbs gain, transmission, and utilization are considered. An information-theoretic approach is used to find conditions under which the kinetics encodes the associated Gibbs function flow with the lowest possible error.

KEY WORDS: Living systems; Gibbs function; stationary states; gain of information; Jaynes' principle; coding.

1. INTRODUCTION

In the past few decades, information theory (IT) has been successfully used in a growing number of research fields, ranging from physical systems of particles to systems involving social relations. Thus, there are books applying the IT approach to statistical mechanics[1,2] and thermodynamics.[3,4] There are applications of IT to the liquid state[5,6] and also to predictions of the future market price of a stock.[7] Advantages of the IT approach to physical as well as nonphysical problems have been reviewed.[8] There are also papers discussing general properties of information measures,[9] leading, for instance, to a new notion of information distance.[10]

This paper presents an application of IT to a study of Gibbs function flows in living systems. In steady states, most of these systems and their subsystems operate at constant temperature and pressure; they cannot use heat as an energy source (see Ref. 11, pp. 374 and 390). It is the change of the Gibbs function of cellular fuels that predicts the direction of chemical reactions proceeding in living systems.[11] The Gibbs flows are thus indis-

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pensable for the creation and maintenance of organization in living systems, both in space and in time. A key position in the energetics of living systems belongs to so-called nucleotide pools. In the present paper we consider the problem of the degree to which kinetic quantities characterize, or encode, the associated Gibbs flow from a nucleotide pool. Exact solutions can be found by Jaynes' principle, but living systems can use only a subset of them, associated with special states only. Generally, then, approximate solutions can be found by minimizing the average error caused by the deviation from an exact code.

In the next section the problem is formulated in detail. The solutions are presented in Section 3. A brief summary and discussion form Section 4.

2. FORMULATION OF THE PROBLEM

Nucleotide pools are essential for an understanding of processes in which living systems gain, transform, and utilize the Gibbs function. Apart from the different degrees of ionization and from the formation of complexes with metal ions, a pool consists of three kinds of species: nucleoside mono-, di-, and triphosphates. A pool receives the Gibbs function from a source and distributes it to many reactions of diverse character. However, if only the nucleotides are considered, reactions splitting triphosphates into either di- or monophosphates emerge as the two most important types of processes. In terms of a communication chain, the driven processes coupled to the output of a nucleotide pool comprise a channel. The pool itself acts as a transducer, coding the output of a Gibbs function source in order to enable proper Gibbs function transmission through that channel. We define "coding" and "proper transmission" for the Gibbs function below.

Consider a system composed of N_l solvent molecules and a set of $\{N_s\}$ solute molecules. The chemical potential μ_s of any solute component is[12]

$$\frac{\mu_s}{kT} = \frac{\bar{\mu}_s}{kT} - \log \frac{V}{N} + \log \gamma_s + \log n_s \tag{1}$$

Only $\bar{\mu}_s$ does not depend on the composition of the system. The remaining three terms on the rhs do, since the n_s are molar fractions:

$$n_s = \frac{N_s}{N}, \qquad N = N_l + \sum_s N_s \tag{2a}$$

$$\sum_s n_s < 1 \tag{2b}$$

The γ_s are the activity coefficients, introduced because the system contains different ionic species of various strengths. The total volume V of the

system is a sum of molecular volumes:

$$V = N_l V_l + \sum_s N_s V_s$$

The composition dependence of V/N in (1) may often be neglected. For the nucleotides of the pool under consideration, the respective quantities will be indexed by i = M, D, T (for mono-, di-, and triphosphates, respectively).

Let us consider a stationary state of the living system and of the pool; the latter is characterized by the sets $\{\mu_i^{(1)}\}$ and $\{n_i^{(1)}\}$ and by the rates of the corresponding reactions. Let the system as a whole and the pool as part of it evolve to another stationary state, with $\{\mu_i^{(2)}\}$, $\{n_i^{(2)}\}$, and another set of the rates. The transition from state 1 to state 2 reflects the fact that the Gibbs function flow through the pool has been varied. Accordingly, as the rates of some (or all) chemical reactions have had to change as well, the chemical composition of the system in state 1 generally differs from that in state 2. It has already been mentioned that it is the Gibbs function source and hence the Gibbs flow that control the performance of the system. In particular, the rates of the most important processes (for example, the synthesis of certain macromolecules) should sensitively respond to the Gibbs function resources available to the system. However, the rates of processes in the system directly respond to and are regulated by concentrations; chemical potentials and hence the Gibbs function cannot be immediately involved. If the system were an ideal one, no problem would arise: the terms containing the activity coefficients [see (1)] would vanish, and there would be an unambiguous correspondence between chemical potentials and molar fractions, that is, ultimately, concentrations. The system is not ideal, however, hence there is no unique correspondence of that kind; yet the rates of processes proceeding in the system should concur with the thermodynamic conditions under which the system operates. An effective response between the kinetics and thermodynamics of the system requires the existence of a relation between concentrations and chemical potentials, to circumvent the difficulty with the activity coefficients, which cannot be directly involved in regulation. Considering the two states of the system, we therefore ask: Under what conditions do changes in rates and concentrations provide information about changes in the Gibbs function flow? Or, less strictly, to what degree is that (necessarily incomplete) information reliable? In terms of coding, we ask for the conditions under which changes in rates and concentrations encode variations in Gibbs function flow, and how good the codes are.

This problem is probably unsolvable in its full generality, but it can be solved for the Gibbs function output from a nucleotide pool. Two features make this possible: the central position of nucleotide pools in the energetics

of the system and the structure of a pool. A nucleoside triphosphate can be split in two ways, each of which offers the possibility for coupling to a large number of particular processes. Any complete reaction involving the nucleotides of the pool in question thus occurs at random; then information theory can be used to find useful extremum conditions for the performance of the pool.

Up to this point, in speaking of information provided by concentrations and reaction rates, we of course have had in mind the common meaning of this word, rather than any of the information measures used in probability theory. In fact, one of these measures will be introduced for the nucleotide concentrations by formula (1).

3. CODING

The transition from state 1 to state 2 is accompanied by a change $\Delta\mu_i = \mu_i^{(2)} - \mu_i^{(1)}$, which may be expressed in the form

$$\frac{\Delta\mu_i}{kT} = -\Delta \log \frac{V}{N} + \log \frac{\gamma_i^{(2)}}{\gamma_i^{(1)}} + \log \frac{n_i^{(2)}}{n_i^{(1)}} = \frac{\Delta_i}{kT} + \log \frac{n_i^{(2)}}{n_i^{(1)}} \tag{3}$$

We define α_i by the expression

$$\alpha_i = 1 - \Delta_i/\Delta\mu_i \tag{4}$$

so that

$$\log \frac{n_i^{(2)}}{n_i^{(1)}} = \frac{\Delta\mu_i - \Delta_i}{kT} = \alpha_i \frac{\Delta\mu_i}{kT} \tag{5}$$

Let us consider a reaction involving at least one nucleotide species from a pool, for example, the reaction

$$T_n + B \rightleftharpoons D + C \tag{6}$$

where T_n and D denote the nucleoside triphosphate and diphosphate, respectively, B denotes all substrates other than T_n, and C denotes all products other than D. Its affinity is

$$A_j = -(\mu_D + \mu_C - \mu_T - \mu_B)$$

and the associated thermodynamic entropy production is

$$\sigma_j = v_j A_j / T$$

The expression $v_j A_j$ may be regarded as a Gibbs function flow from the pool to the chemical subsystem (C, B). A transition from state 1 to state 2 corresponds to the differences ΔA_j and $\Delta\sigma_j$. If we choose as the reference

state that one in which the rate and affinity vanish, we may write

$$\frac{\Delta\sigma_j}{k} = v_j \frac{\Delta A_j}{kT} = v_j\left[\frac{\Delta\mu_T - \Delta\mu_D}{kT} - \frac{\Delta(\mu_C - \mu_B)}{kT}\right]$$

$$= v_j\left[\frac{1}{\alpha_T}\log\frac{n_T}{n_T^{(0)}} - \frac{1}{\alpha_D}\log\frac{n_D}{n_D^{(0)}}\right] - v_j\frac{\Delta A_{jr}}{kT}$$

The subscript 0 represents the reference state. We sum all similar equalities (assuming a common state 0 for all reactions) and obtain for the total entropy production associated with the pool output the expression

$$\frac{\Delta\sigma}{k} = \sum_i v_i'\frac{\Delta\mu_i}{kT} + v_{TD}\frac{\Delta\mu_T - \Delta\mu_D}{kT} + v_{TM}\frac{\Delta\mu_T - \Delta\mu_M}{kT}$$

$$+ v_{DM}\frac{\Delta\mu_D - \Delta\mu_M}{kT} - \sum_j v_j\frac{\Delta A_{jr}}{kT}$$

$$= v_T\frac{\Delta\mu_T}{kT} + v_D\frac{\Delta\mu_D}{kT} + v_M\frac{\Delta\mu_M}{kT} - \sum_j v_j\frac{\Delta A_{jr}}{kT}$$

$$= \frac{v_T}{\alpha_T}\log\frac{n_T}{n_T^{(0)}} + \frac{v_D}{\alpha_D}\log\frac{n_D}{n_D^{(0)}} + \frac{v_M}{\alpha_M}\log\frac{n_M}{n_M^{(0)}} - \sum_j v_j\frac{\Delta A_{jr}}{kT} \qquad (7)$$

Here the v_i' are the total rates of deletion from the pool [for reactions of this type, the lhs of (6) contains the ith nucleotide, other species do not belong to the pool], v_{XY} are the total rates of reactions with X in the lhs of (6) and Y in the opposite side, and v_i ($i = M, D, T$) are self-evident combinations of v_i' and v_{XY}.

State 0 is now defined as that in which both the rates and the affinities of all contributing reactions vanish. It therefore reflects the kinetic and thermodynamic properties of the entire system to which the pool belongs.

The molar fractions of the nucleotides represent an incomplete distribution. Then each term

$$\log(n_i/n_i^{(0)})$$

is a quantity called gain of information.[13] From (5) and (7) we see that, generally, the three separate gains of information provide no common measure of the corresponding differences $\Delta\mu_i$ and therefore only incompletely characterize that part of $\Delta\sigma$ (or of $v_j\Delta A_j$) which is related to the pool. We may say that each nucleotide has its own code, and that the pool as a whole has no common code: while an individual code of a particular nucleotide establishes a relation between $\Delta\mu_i$ and the corresponding $\log(n_i/n_i^{(0)})$, it does not convey information on analogous relations concerned with the other two kinds of nucleotides. Moreover, with respect to valid

thermodynamic conditions, the estimates provided by the individual nucleotides differ from each other. A reliable estimate would require rather sophisticated evaluation of information from all three kinds of nucleotides. Consider, however, the case when $\alpha_M = \alpha_D = \alpha_T = \alpha$. Not only is there such a common code for the pool, so that the differences

$$\log \frac{n_T}{n_T^{(0)}} - \log \frac{n_i}{n_i^{(0)}}, \qquad i = M, D$$

are proportional to $\Delta\mu_T - \Delta\mu_i$, but also [see (7)] the expression

$$\sum_i v_i \log \frac{n_i}{n_i^{(0)}} \tag{8}$$

measures one part (that related to the pool itself) of the Gibbs function flow or the associated part of the entropy production. An individual code now provides information on any of the three kinds of nucleotides. The regulating mechanisms then can have the simplest design: valid thermodynamic conditions are reflected equally well by any one of the three nucleotides. In contrast with the preceding case, a single estimate of thermodynamic conditions is sufficient. In other words, if there is a common α, the distribution $\{n_i\}$ is the least prejudiced one with respect to the set $\{\Delta\mu_i\}$ and relative to $\{n_i^{(0)}\}$. Both distributions together then define a common code for the differences $\Delta\mu_i$. We shall also denote it as an exact code.

This consideration and relation (5) suggest that the least prejudiced distribution $\{n_i\}$ satisfies Jaynes' principle.[14] Originally, this principle was formulated for problems involving a single probability distribution. Here we consider two states; we therefore have two distributions. For this reason, we use a slightly generalized form of the principle, requiring essentially the minimum of the path function

$$\sum_i n_i \log \frac{n_i}{n_i^{(0)}} \tag{9}$$

subject to the constraint that a measurable quantity is given. The constraint must express those characteristics of the system that are relevant to the problem. According to how our problem has been posed, the Gibbs function difference between the two states of the pool should be considered as given and used as the constraint.

We first define the distributions $\{p\}$ and $\{p^{(0)}\}$ by the relations

$$p_i = \frac{n_i}{n}, \qquad \sum_i p_i = 1, \qquad i = M, D, T \tag{10a}$$

$$p_i^{(0)} = \frac{n_i^{(0)}}{n^{(0)}}, \qquad \sum_i p_i^{(0)} = 1, \qquad i = M, D, T \tag{10b}$$

We will suppose that

$$n = \sum_i n_i = \sum_i n_i^{(0)} = n^{(0)} \tag{10c}$$

Then the modified Jaynes' principle requires for $j = \mathrm{M}, \mathrm{D}, \mathrm{T}$ that

$$\frac{\partial}{\partial p_j}\left[\sum_i p_i \log \frac{p_i}{p_i^{(0)}} - \alpha\left(\sum_i p_i \frac{\Delta\mu_i}{kT} - \frac{\Delta G_n}{k}\right) - (\Omega + 1)\left(\sum_i p_i - 1\right)\right] = 0 \tag{11}$$

where ΔG_n denotes the difference of the Gibbs function per nucleotide. The solutions of (11) yield the distributions $\{p\}$ satisfying the requirement of exact coding. We shall denote these solutions as mathematically defined exact (or common) codes.

Now, from the discussion on the difference between the individual codes and a common code it is clear that exact codes correspond to special situations and therefore must be established by some mechanism. Its design may leave many (or even most) mathematically defined exact solutions unused, being capable of adjusting only a certain subset of the common codes. As a matter of fact, in living systems there exists a simple and nearly ubiquitous reaction which can be shown[15] to define sufficient conditions for exact codes to exist; they are concerned with equilibrium states of that reaction. We will suppose that this reaction serves as that mechanism necessary for the adjustment of exact codes. This assumption may seem only weakly justified; however, we will show that a meaningful extremum condition *defines* the equilibrium states of that reaction. It is this remarkable feature that supports our assumption concerning that reaction and tempts us to regard its equilibrium states as the only ones in living systems in which exact codes can be adjusted. If necessary, such codes will be denoted as the operationally defined common codes, to distinguish them as a subset of the mathematically defined ones.

To see what states then allow exact coding operationally, let us define the function

$$f = \left[\sum_i p_i\left(\log \frac{p_\mathrm{T}}{p_\mathrm{T}^{(0)}} - \log \frac{p_i}{p_i^{(0)}}\right)\right] \Big/ (2p_\mathrm{M} + p_\mathrm{D}) \tag{12}$$

For the mathematical exact codes, this function is the informational image of the quantity

$$g = \left[\sum_i p_i(\Delta\mu_\mathrm{T} - \Delta\mu_i)\right] \Big/ (2p_\mathrm{M} + p_\mathrm{D}) \tag{13}$$

It is easy to show the meaning of these functions. A diphosphate has one free site for a phosphoryl group, a monophosphate has two. Their total

fraction in the pool is $2p_M + p_D$. However, of the two sites of a monophosphate, only that next to the monophosphate moiety is a real free site, since the other cannot be filled unless the first one is occupied. Then $p_D/(2p_M + p_D)$ and $p_M/(2p_M + p_D)$ are the fractions of free sites per phosphoryl group that can be attached to the pool. Since $\Delta\mu_T - \Delta\mu_i$ are the relevant differences of chemical potentials, it is clear that g in (13) is their average per phosphoryl group; then f in (12) is the average difference of relevant information gains, again per phosphoryl group. All differences are measured with respect to the triphosphate related quantities. Let us now keep $\{p^{(0)}\}$ fixed and look for the conditions under which f is an extremum. We obtain readily

$$\delta p_D \cdot (1 - p_T) \log \frac{K}{K^{(0)}} = -\delta p_T \cdot \left(\frac{2p_M + p_D}{p_T} + p_D \log \frac{K}{K^{(0)}} \right) \tag{14}$$

where

$$K = p_T p_M / {p_D}^2 \tag{15}$$

and similarly for $K^{(0)}$. Relation (14) implies that $K = K^{(0)}$ is equivalent to $\delta p_T = 0$. This defines the point of minimum p_T on the curve $f = \text{const}$. Also, if we look for an extremum of f at fixed p_T, we obtain maximum f for $K = K^{(0)}$. Provided that exact coding applies, that is, by (5) and (10),

$$\log (p_i/p_i^{(0)}) = \alpha \, \Delta\mu_i/kT \tag{16}$$

the condition $K = K^{(0)}$ also means

$$\Delta\mu_T + \Delta\mu_M - 2\Delta\mu_D = 0 \tag{17}$$

Extremum points of the function f (and, since we assume exact coding, also of g) thus coincide with equilibrium states of the reaction

$$2D \rightleftharpoons T_n + M \tag{18}$$

where M, D, and T_n denote the nucleoside mono-, di-, and triphosphate, respectively. Reaction (18) is just what we had in mind when speaking of the mechanism capable of adjusting exact codes, including the fact that (17) and $K = K^{(0)}$ are sufficient conditions[15] for a subset of exact codes to exist.

For other states, then, operationally defined exact solutions of (11) do not exist. In practice, however, approximate solutions may suffice. Of course, they introduce some error; it can be expected that in exacting situations it is desirable or even necessary to keep this error as low as possible. In the following, we suggest an appropriate approximation and investigate the error introduced.

If for a distribution exact codes are defined operationally, we shall denote it as $\{p^{(1)}\}$ and the state itself as state 1. Therefore we may write

the condition of operationally defined exact coding in the form

$$\log(p_i^{(1)}/p_i^{(0)}) = \alpha^{(1\text{-}0)}\,\Delta\mu_i^{(1\text{-}0)}/kT \tag{19}$$

For distributions $\{p\}$ different from $\{p^{(1)}\}$, no relation like (19) is defined operationally; perhaps the simplest approximation is to require that a similar relation be valid in the mean:

$$I = \sum_i p_i \log \frac{p_i}{p_i^{(0)}} = \alpha \sum_i p_i \frac{\Delta\mu_i}{kT} \tag{20}$$

Note that the overall information gain I has been used in the minimizing condition (11). We use (19) to define

$$I^{(1\text{-}0)} = \sum_i p_i^{(1)} \log \frac{p_i^{(1)}}{p_i^{(0)}} \tag{21}$$

We also introduce the function $I^{(1)}$:

$$I^{(1)} = \sum_i p_i \log \frac{p_i}{p_i^{(1)}} \tag{22}$$

This information measure depends on the actual distribution $\{p\}$ involved in the approximation (20), and on $\{p^{(1)}\}$ involved in exact coding. It therefore measures the error introduced by that approximation; however, this statement needs additional explanation. In fact, $I - I^{(1\text{-}0)}$ generally is not equal to $I^{(1)}$, since we obtain

$$I - I^{(1\text{-}0)} = I^{(1)} + \sum_i (p_i - p_i^{(1)}) \log \frac{p_i^{(1)}}{p_i^{(0)}} \tag{23}$$

In this form, the difference $I - I^{(1\text{-}0)}$ does not measure the error, because it has not been specified which of the states 1 should be used; without a precise specification, the expression (23) even can be negative, in contrast to the essential nonnegativity of any error measure. The requirement $I = I^{(1\text{-}0)}$ seems to be the optimum case, but it is not: it introduces a functional dependence among the three distributions, calling thus for an adjusting mechanism and restricting the choice of admissible actual states. Fortunately, it is possible to avoid these difficulties by setting the second term on the rhs of (23) equal to zero. The condition (19) for exact coding and the equilibrium condition (17) then yield the relation

$$2E = 2p_{\mathrm{T}} + p_{\mathrm{D}} = 2p_{\mathrm{T}}^{(1)} + p_{\mathrm{D}}^{(1)} = 2E^{(1)} \tag{24}$$

where the first and last equalities are definitions of the quantities E and $E^{(1)}$ (often used in biology to characterize the status of the system under

study). For fixed $\{p\}$ and $\{p^{(0)}\}$, condition (24) and

$$K^{(1)} = K^{(0)} \tag{25}$$

define $\{p^{(1)}\}$ uniquely [we recall that (25) appeared in the extremizing condition (14) for the function f]. The rhs of (23) now consists only of $I^{(1)}$ and measures the error. It can be shown that the special choice (24) implies that $I^{(1)}$ is a minimum, the corresponding condition being satisfied trivially. In fact, varying $\{\mathrm{p}^{(1)}\}$ along the line $K^{(1)} = \text{const}$, we obtain from

$$\delta^{(1)} I^{(1)} = -\sum_i p_i \, \delta(\log p_i^{(1)}) \tag{26}$$

the relation

$$\delta^{(1)} I^{(1)} = (2p_{\mathrm{M}} + p_{\mathrm{D}}) \, \delta(\log p_{\mathrm{M}}^{(1)}) + (2p_{\mathrm{T}} + p_{\mathrm{D}}) \, \delta(\log p_{\mathrm{T}}^{(1)}) \tag{27}$$

On substituting from (24), we can rearrange (27) to the form

$$\sum_i p_i^{(1)} \, \delta(\log p_i^{(1)}) = \sum_i \delta p_i^{(1)} = 0 \tag{28}$$

which is true trivially. It is easily seen that the extremum of $I^{(1)}$ is a minimum. Inversely, requiring that (27) vanish trivially, as in (28), we should have to choose $\{p^{(1)}\}$ so as to satisfy (24); then the second term on the rhs of (23) would vanish. In this sense we may say that the condition (24) selects that distribution $\{p^{(1)}\}$ out of those allowing exact coding which is naturally (i.e., trivially) the "nearest" (because of minimum $I^{(1)}$) to the actual distribution $\{p\}$.

As a result, we have for I in (23)

$$I = I^{(1\text{-}0)} + I^{(1)} \tag{29}$$

where $I^{(1)}$ is minimum for a given actual state and $I^{(1\text{-}0)}$ refers to the "nearest" exact code.

4. SUMMARY AND DISCUSSION

The starting premise of this study is that living systems cannot "read" thermodynamic quantities, but need as exact information on them as possible. The present investigation is confined to the Gibbs function output from a nucleotide pool. If the concentrations of the three types of nucleotides in a pool convey equal amounts of information on the corresponding Gibbs function differences, we say that the differences are exactly encoded. Such a situation must be adjusted by some mechanism selecting, by its design, a special subset of exact codes—the operationally defined exact codes. In living systems, equilibrium states of a particular reaction [see (17) and (18)] are

sufficient for such codes to exist. In the other states, then, only approximate codes are defined operationally, (20). The error associated with them can be simplified and minimized. A functional dependence between the approximate and exact codes is thus avoided; it would restrict the "number of degrees of freedom" of the entire system and, moreover, an additional adjusting mechanism would be needed.

In short, the coding relations essentially substitute for thermodynamic expressions like (1): since the kinetic response cannot "read" chemical potentials directly (being sensitive to concentrations only), the thermodynamic quantities must be introduced indirectly, by coding conditions. It is the reaction (18) and the equilibrium condition (17) that allow the circumvention of the incompleteness of information conveyed by concentrations. Once the Gibbs function differences are encoded, the Gibbs function output from the pool and the associated part of entropy production are encoded as well.

It will be shown elsewhere[15] that the theory predicts preferable values of the equilibrium constant $K^{(1)}$ and of the ratio K [see (15) and (25)] if E and $K/K^{(1)}$ are given. The quantities $K^{(1)}$ and E have often been determined experimentally; it turns out that the calculated values of $K^{(1)}$ and of K agree closely with those found in real living systems. Also, the calculations show that the error measure $I^{(1)}$ tends to zero as E tends to unity (the maximum possible value). This behavior explains the well-known fact that in highly active living systems (in growing ones, for example) higher values of E are found ($E \approx 0.8$), whereas in less active systems E has a value of about 0.6–0.7 or even lower. The theory can explain this on the basis of the assumption that highly active systems are very exacting as to the sensitivity and accuracy of regulation as well as of the overall kinetic response. With respect to the nucleotide pools, these requirements claim very good codes. Such codes, in turn, are accompanied by low values of $I^{(1)}$ and can exist only at higher values of E.

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