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ARTICLE

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A measure for the distance from equilibrium

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Abstract Subcellular systems represented by macromolecules (enzymes, ion channels etc.) function far from equilibrium. We propose a characterization of such systems in terms of their distance from equilibrium (DFE). Standard chemical and physical approaches are not always applicable because they need too detailed kinetic and thermodynamic information. We suggest a general measure for DFE in systems described by fluxes. Each connection between subsystems corresponds to two unidirectional fluxes, f and b. These fluxes form forward and backward vectors, $\mathfrak{F}$ and $\mathfrak{B}$, respectively. The forward direction is defined by a net flux, so that $0 \leq b \leq f$. The flux vectors $\mathfrak{R} = \{\mathfrak{F}, \mathfrak{B}\}$ and $\mathfrak{U} = \{\mathfrak{F}, -\mathfrak{B}\}$ are introduced. DFE is defined as $P = (\mathfrak{R}\mathfrak{U}/\mathfrak{U}\mathfrak{U})^2 = \cos^2\alpha$, α being the angle between the $\mathfrak{R}$- and $\mathfrak{U}$-vectors, with $0 \leq \alpha \leq \pi/2$. The distance from strict irreversibility, E, is defined symmetrically: $E = \cos^2(\pi/2 - \alpha) = 1 - P$. For a single-stage reaction, parameter P is strictly equivalent to the chemical affinity. For multi-stage reactions P reflects DFE better than chemical affinity. Near equilibrium P is equivalent to excess Gibbs energy. Away from equilibrium, P scales DFE better.

Key words Kinetic systems · Unidirectional fluxes · Chemical affinity · Gibbs energy

Introduction

A characteristic feature of living systems is that they function in far from equilibrium states that are maintained by pumping internally produced entropy into the environment (Alberts et al. 1989). One of the main aims of the biological sciences is therefore to reveal the mechanisms for maintaining highly ordered nonequilibrium states at different levels of biological organization. This is one of the reasons for the persistent interest in different kinds of dissipative structures (Haken 1977; Eigen and Schuster 1979; Nicolis and Prigogine 1977; Nicolis and Prigogine 1990; Läuger 1989; Hain et al. 1991; Pastushenko and Chizmadzhev 1985). Dissipative structures typically appear far from equilibrium. However, in a recent paper Walz and Caplan (1995) report that one such structure, chemical oscillations "may occur near equilibrium" in terms of the overall chemical affinity. Without going into the merits of this paper, we would like to indicate that this work shows the need for a quantitative measure for DFE in kinetic studies.

Different measures for DFE were discussed earlier. In thermodynamics the concept "far from equilibrium" is usually understood in the sense of nonlinearity of the equations expressing the fluxes in terms of driving forces (Haken 1977; Eigen and Schuster 1979; Nicolis and Prigogine 1977, 1990). In the case of chemical reactions DFE is usually connected with the affinity of the overall system of reactions (Lefever et al. 1988; Lavenda et al. 1971). An experimental example of nonequilibrium functioning of an ion channel is given by Hamill and Sakmann (1981). These citations are all related to systems which in principle admit a thermodynamic description. However, this is frequently not possible owing to the lack of detailed kinetic and thermodynamic information. For the very same reason, application of the thermodynamic principles at the supermolecular level of biological organization is even more difficult. An example may be given by problems connected with migration in populations. At the same time, the question of nonequilibrium may still be discussed in cases where different fluxes may be measured. Therefore it is challenging to find a measure for DFE more general than the thermodynamic criteria which are based on statistical laws governing the ensembles of randomly interacting molecules. Such a new criterion should however cover the thermodynamic case.

Läuger (1983) proposed to characterize the DFE of a single-stage reaction (forward and backward fluxes f and

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b) by the ratio of "net" flux $N = |f - b|$ to "unit" flux $U = f + b$:

$$L = N/U \tag{1}$$

This definition was generalized for multistage reactions and applied for nonequilibrium characterization of induced membrane transport (Pastushenko et al. 1991, 1992) by defining N and U as norms of the net and unit flux vectors:

$$L = \|\boldsymbol{N}\| / \|\boldsymbol{U}\| \tag{2}$$

The norm of a vector is understood in the usual Euclidean sense. Nonequilibrium of membrane transport for carrier and facilitated diffusion mechanisms was characterized by a measure, there called "dissipation order parameter" (Pastushenko et al. 1991, 1992), proposed on the basis of symmetry of the flux vectors. In this paper we derive a parameter P from the unidirectional fluxes considered as mutually orthogonal components of "net" and "unit" flux vectors. Afterwards we compare P with thermodynamic measures of DFE, such as overall chemical affinity and excess Gibbs energy over its equilibrium value. In a subsequent paper (Pastushenko et al. 1998) we show the application of this parameter for characterizing DFE in a nonlinear kinetic system represented by the Brusselator.

Statement of the problem

A wide class of systems in physics, chemistry, biology etc. is described by ordinary differential equations, reflecting the balance of some "substance" exchanged between different connected subsystems or states. The number of states is denoted by S, so that for any system $S \geq 2$. Two arbitrarily selected states may have zero, one or more connections with each other. Each connection is characterized by two unidirectional fluxes, f and b, which are assumed to be known. All unidirectional fluxes have the same dimensionality. For each connection, the forward direction is defined by the net flux. Thus by definition, for any connection $f \geq b$. All connections are numbered by index c: $1 \leq c \leq C$. Systems with not more than one connection for any pair of states will be called canonical. For canonical systems $1 \leq C \leq S(S-1)/2$. Noncanonical systems can have an arbitrary number of connections $C \geq 1$. In noncanonical systems, the "forward" directions for two connections between the same pair of states may even be opposite to each other ("antiparallel connections"). We shall consider the general case, including noncanonical systems. Our aim is to construct from unidirectional fluxes a parameter P which should serve as a measure for DFE.

Typically, such parameters are scaled between 0 and 1. We assume $P = 0$ in the state of detailed balance and $P = 1$ in maximum nonequilibrium (i.e. strictly irreversible) systems. Thus the range of possible P values is $0 \leq P \leq 1$. By definition, considering only finite fluxes, in "maximum nonequilibrium" systems at least one of the unidirectional fluxes in each connection is zero. If both unidirectional fluxes are identically equal to zero, then the corresponding connection may be considered as empty (absent).

A system with one connection

Unidirectional fluxes may have different nature, so that in the general case it is more reasonable to treat them as independent quantities. Therefore we shall consider these fluxes as mutually orthogonal components of a vector, or as real and imaginary parts of a complex number. In the simplest system containing only one connection, the complex formalism is most transparent. In order to be able to combine f and b into different entities without loss of their independence, we could measure either f or b in imaginary units, j (i.e. $j^2 = -1$). Both versions are equivalent, and we select the second one. The result of this operation is b/j. In analogy with the above mentioned approach we construct a complex flux N:

$$N \equiv f - b/j = f + bj \tag{3}$$

The unit for measuring this flux should be combined from the same unidirectional fluxes. Using the symmetry between positive and negative directions, we could change the sign of real or imaginary components. It will be clear later that both versions are equivalent. Thus, another combination of f and b/j leads to following definition of a "unit" flux:

$$U = f + b/j = f - bj \tag{4}$$

We define next a complex nonequilibrium parameter as the ratio of the two complex fluxes:

$$N/U = \exp(j\alpha) = \cos\alpha + j \sin\alpha \tag{5}$$

$$\alpha \equiv \arg(N) - \arg(U) \,, \quad \text{with } \ 0 \leq \alpha \leq \pi/2 \,. \tag{6}$$

In principle, the quantity $(1 - 2\alpha/\pi)$ can serve as a measure for DFE, P, and the quantity $2\alpha/\pi$ as a complementary measure for distance from strict irreversibility, E. We prefer, however, a simpler version, which follows from Eq. (5), where the real and imaginary parts of the complex parameter N/U, $\cos\alpha$ and $\sin\alpha$, have the desired properties of P and E respectively. However, any monotonic function of them, such as power functions $(\cos\alpha)^n$ and $(\sin\alpha)^n$ with arbitrary positive n would have the same properties. The special choice $n = 2$ has the advantage that the sum of the distances from equilibrium and from strict irreversibility is unity for any α. Thus we define parameters P and E as squared cosines of the angles α and $\pi/2 - \alpha$ respectively:

$$P \equiv \cos^2\alpha = \left(\frac{f^2 - b^2}{f^2 + b^2} \right)^2 \tag{7}$$

$$E \equiv \sin^2\alpha = \left(\frac{2\,fb}{f^2 + b^2} \right)^2 \tag{8}$$

The complementarity of parameters P and E is expressed as

$$E + P = 1 \tag{9}$$

A system with an arbitrary number of connections

We shall generalize the definition of P for an arbitrary subset of M connections, i.e. $1 \leq M \leq C$. One can always renumber the selected connections by $m = 1, 2, \ldots, M$. We introduce now forward and backward flux vectors, $\mathfrak{F}$ and $\mathfrak{B}$, in two mutually orthogonal M-dimensional spaces:

$$\mathfrak{F} = (f_1, f_2, \ldots, f_M) \tag{10}$$

$$\mathfrak{B} = (b_1, b_2, \ldots, b_M) \tag{11}$$

The $2M$-dimensional vectors $\mathfrak{R}$ and $\mathfrak{U}$ are introduced as:

$$\mathfrak{R} = (\mathfrak{F}, \mathfrak{B}), \quad \mathfrak{U} = (\mathfrak{F}, -\mathfrak{B}) \tag{12}$$

Our next operation should be the measurement of $\mathfrak{R}$ in units of $\mathfrak{U}$, i.e. division $\mathfrak{R}/\mathfrak{U}$. For vectors, such a division is not defined. However, it can be made meaningful if we multiply this ratio by an apparent unity, represented by the ratio $\mathfrak{U}/\mathfrak{U}$. Fulfilling multiplication first in the obtained expression, we find the cosine of the angle between both vectors, α, due to $\|\mathfrak{U}\| = \|\mathfrak{R}\|$:

$$\cos\alpha = (\mathfrak{R}\mathfrak{U})/(\mathfrak{U}\mathfrak{U}) \tag{13}$$

Thus we obtain the expressions for P and E:

$$\begin{aligned} P = \cos^2\alpha &= [(\mathfrak{R}\mathfrak{U})/(\mathfrak{U}\mathfrak{U})]^2 \\ &= [\|\mathfrak{F}\|^2 - \|\mathfrak{B}\|^2]^2/[\|\mathfrak{F}\|^2 + \|\mathfrak{B}\|^2]^2 \end{aligned} \tag{14}$$

$$E = \sin^2\alpha = [2\|\mathfrak{F}\|\,\|\mathfrak{B}\|]^2/[\|\mathfrak{F}\|^2 + \|\mathfrak{B}\|^2]^2 \tag{15}$$

To illustrate the properties of parameters P and L in systems of practical interest, we use several linear kinetic systems, exemplified by chemical reactions.

Parameters P and L in linear kinetic systems

In this section we consider several examples of kinetic processes formally analogous to monomolecular reactions. To find a compromise between a reasonably complete overview and minimum number of examples, we shall assume the following three rules:

1. The number of different states will not exceed 3.
2. The system is initially in only one state (shown by filled circles in Fig. 1).
3. Nonzero rate constants will be all set to 1.

The results of such calculations of topologically different combinations are shown in Fig. 1, A through N. Parameter P is shown by the solid line, the second power of Läuger's parameter L by the dashed line. Owing to rule 2, common to all pictures and curves is that both P and L start from the value 1. For this initial condition the initial slope of P is always zero. The initial slope of L is zero only if the initial state is connected to other states by strictly irreversible connections, such as in cases D and H. Both P and L can have local minima and maxima, as in cases F and G. This is not, however, the exclusive property of these parameters: the energy dissipated in an explosion or in some other autocatalytic process also has a maximum in dependence on time.

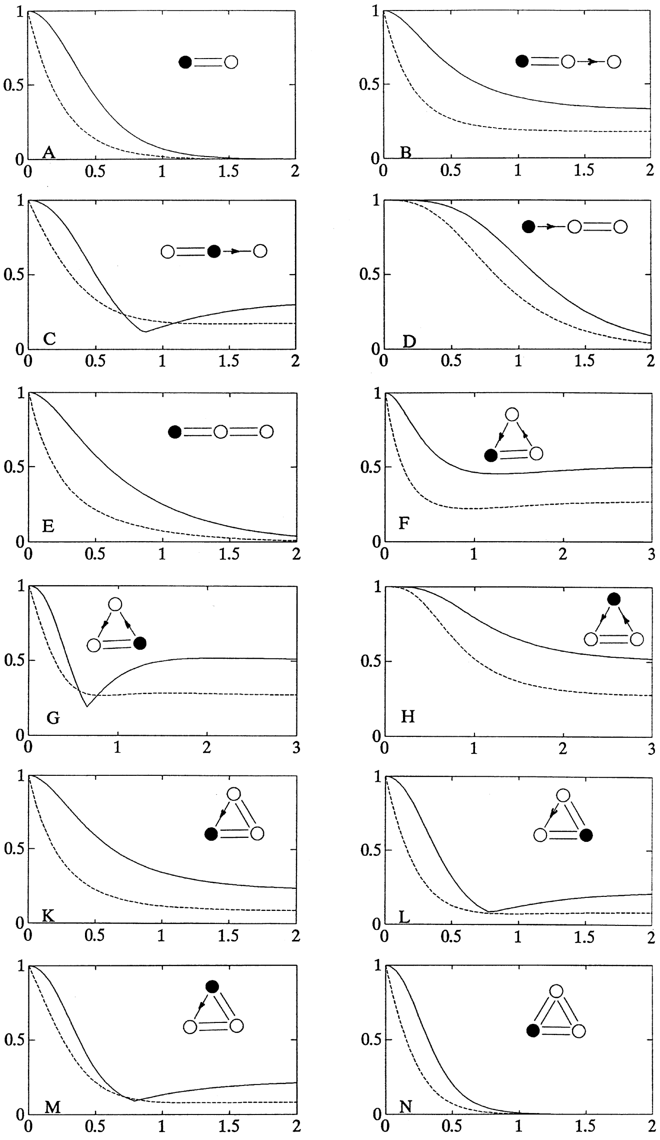

Fig. 1 Nonequilibrium parameter, P (*solid*) and generalized Läuger's measure for nonequilibrium, L^2 (*dashed*) as functions of time for different kinetic systems, represented by corresponding schemes. *Filled circles* indicate initially populated states

Both parameters can have nonzero asymptotic values, as in cases F through M. A circular kinetic scheme is not a necessary condition for nonzero asymptotics, cf. Figs. B and C. However, this feature for noncircular schemes is specific only for an intermediate level of description which allows for strictly irreversible stages as an approximation to reality. In this sense parameters P and L do not differ from the usual criteria.

Parameter P can have discontinuities in its first derivative. Such points correspond to reversals of the "forward" direction, indicating local equilibrium. The time derivative of L is a continuous function of time. This fact could be considered as an argument in favor of P, because the singularities in P make this parameter more sensitive to details of the process considered.

Comparison with thermodynamic criteria

We shall compare parameters P and L with thermodynamic criteria, such as chemical affinity or excess Gibbs energy for reactions proceeding at constant pressure and temperature.

1. Chemical affinity. Consider an arbitrary one-stage conversion of reactants R_i, $i=1, 2, \ldots, M_R$ into products P_j, $j=1, 2, \ldots, M_P$ with rate constants k_1 and k_2 according to equation

$$\sum_{i=1}^{M_R} m_i\, R_i \underset{k_2}{\overset{k_1}{\rightleftarrows}} \sum_{j=1}^{M_P} n_j\, P_j \tag{16}$$

If we select the number of moles of reactants equal to corresponding stoichiometric numbers m_i, then the numbers of moles of corresponding products will be equal to n_j. Using the standard expression for Gibbs energy, we can write

$$G_R = \sum_{i=1}^{M_R} m_i\, \mu_i\,; \quad G_P = \sum_{j=1}^{M_P} n_j\, \mu_j \tag{17}$$

We shall measure both Gibbs energies G and chemical potentials μ in RT units. In the ideal case where chemical potentials are defined via standard chemical potentials μ^0 and concentrations x,

$$\mu_i = \mu_i^0 + \ln x_i\,; \quad \mu_j = \mu_j^0 + \ln x_j \tag{18}$$

chemical affinity $\mathscr{A} \geq 0$ is defined as

$$\mathscr{A} = G_R - G_P = \mathscr{A}^0 + \sum_{i=1}^{M_R} m_i \ln x_i - \sum_{j=1}^{M_P} n_j \ln x_j \tag{19}$$

Here $\mathscr{A}^0$ is minus the change of the standard Gibbs energy (in RT-units), connected with the equilibrium constant $K=k_1/k_2$ as

$$\mathscr{A}^0 = \ln K \tag{20}$$

The expressions for forward and backward fluxes are defined by the law of mass action:

$$f = k_1 \prod_{i=1}^{M_R} x_i^{m_i}\,; \quad b = k_2 \prod_{j=1}^{M_P} x_j^{n_j} \tag{21}$$

It follows from Eqs. (19)–(21) that the chemical affinity $\mathscr{A}$ is expressed in terms of the fluxes ratio:

$$\mathscr{A} = \ln(f/b)\,, \quad (f \geq b) \tag{22}$$

Owing to the fact that parameters P and L are also functions of the ratio of the fluxes, one can find their connection with $\mathscr{A}$:

$$P = \tanh^2 \mathscr{A}\,; \quad L = \tanh(\mathscr{A}/2) \tag{23}$$

Thus, parameters P and L are single-valued functions of $\mathscr{A}$. Therefore, for single reactions both P and L are strictly equivalent to chemical affinity. The main difference is only in scaling: whereas $\mathscr{A}$ changes in the interval $0 \leq \mathscr{A} < \infty$, the interval for P is $0 \leq P \leq 1$. In the vicinity of equilibirum parameter P has a continuous derivative over x. In contrast, in the point $\mathscr{A}=0$ parameter L has a nonanalytical behavior (jump in the derivative). This is not reflected in the time derivatives of L, because the system never crosses the equilibrium point.

The equivalence between the parameter P and chemical affinity, demonstrated here for a single-stage reaction of general type, does not hold for multistage reactions. In the latter case instead of chemical affinity one has to use the overall chemical affinity (obtained by summing up chemical affinities for each stage) as an indicator of nonequilibrium. For instance, if the system shown in Fig. 1E is treated as a conversion of the left state into the right state and is initially concentrated in the intermediate state, its chemical affinity, equal to the difference of chemical potentials of the left and right states, is zero. For such a system, the behavior of P is analogous to that shown in Fig. 1A. Although the scalings of DFE by the parameter P and by the overall affinity are different, both are valid indicators of nonequilibrium for the system in Fig. 1E. The use of the parameter P as the property of the whole kinetic system automatically excludes confusions connected with the misuse of the chemical affinity instead of the overall affinity, although for experts in thermodynamics this advantage of P might seem insignificant. In the next paper (Pastushenko et al. 1998) we shall study a more important difference between these two measures for the distance from equilibrium.

2. Excess Gibbs energy over its equilibrium value, called also exergy (Haywood 1980) is another thermodynamic measure for DFE. We illustrate it with the reaction (24) describing transitions of some substance between forms A and B:

$$\mathrm{A} \underset{k_2}{\overset{k_1}{\rightleftarrows}} \mathrm{B} \tag{24}$$

Consider a system containing 1 mole of such a substance. Let $x<1$ be the number of moles of B, $1-x$ the number of moles of A. The Gibbs energy of such a system in an ideal case is:

$$\begin{aligned} G &= (1-x)\,\mu_A + x\,\mu_B \\ &= \mu_A^0 + (1-x)\ln(1-x) + x(\mu_B^0 - \mu_A^0 + \ln x) \end{aligned} \tag{25}$$

Minimum of G takes place at

$$x = x_0 = K/(K+1) \tag{26}$$

$$K = \exp(\mathscr{A}^0)\,; \quad \mathscr{A}^0 = \mu_A^0 - \mu_B^0 \tag{27}$$

We can subtract from G its equilibrium value $G(x_0)$, which does not change the quality of G as a thermodynamic potential. For this reason we shall keep the same notation for excess Gibbs energy:

$$G = (1-x)\ln(1-x) + x(\ln x - \ln K) + \ln(K+1) \tag{28}$$

As expected, this function is invariant with respect to the transformation ($x \to 1-x$, $K \to 1/K$). Figure 2 shows $G(x)$

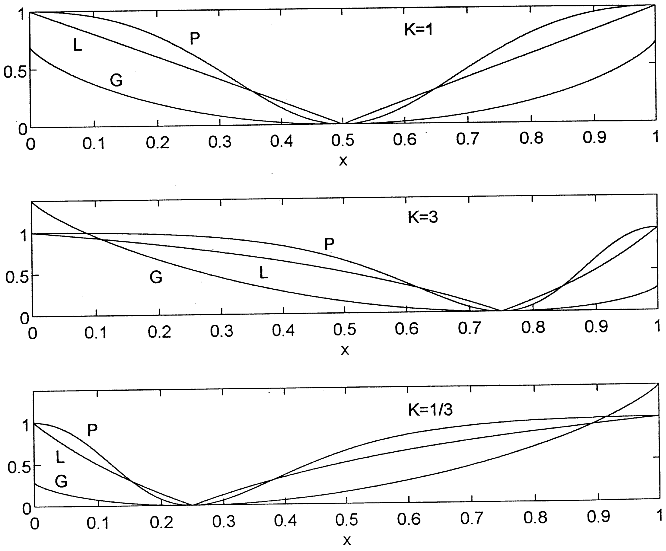

Fig. 2 Comparison of the three measures for distance from equilibrium: parameter *P*, Läugers parameter *L*, and excess Gibbs energy *G* for chemical reaction (Eq. (24)). The values of equilibrium constant: *top* $K=1$; *middle* $K=3$; *bottom* $K=1/3$. Note that $G(0)\neq G(1)$ for $K\neq 1$, although for both $x=0$ and $x=1$ the system is in the state of strict irreversibility

for three different values of K: $K=1$ (top), $K=3$ (middle) and $K=1/3$ (bottom). For comparison, parameters P and L are shown. At the equilibrium point, all three parameters are equal to zero; parameter L has a nonanalytical behavior. All three criteria grow monotonically with the deviation from the equilibrium point $x=x_0$ in both directions, as one would expect from a measure for DFE. In the vicinity of $x=x_0$, parameters P and G are proportional to $(x-x_0)^2$, and therefore they are proportional to each other. Thus near the equilibrium P is equivalent to G within a constant scaling factor. The (excess) Gibbs energy remains finite even under extreme conditions $x=0$ or $x=1$. For $K\neq 1$ all three curves are asymmetric. However, this asymmetry is different: whereas $L=P=1$ at both limits $x=0$ and $x=1$, G has different limiting values, $G(0)=\ln(K+1)$; $G(1)=\ln(1+1/K)$. The assumption of G as a measure for DFE leads to a thermodynamic paradox. For instance if $K\gg 1$ then $G(1)\approx 1/K$. Thus, for very high values of K, according to the G-value, the system at $x=1$ is very close to equilibrium. At the same time, according to the $\mathcal{A}$-value, for any value of K the system at $x=1$ is in a strictly irreversible state, because one of the unidirectional fluxes in Eq. (22) is zero. The fact that the limiting value of G is smaller at that limit which is closer to the equilibrium point, reflects the smaller work necessary to bring the system into that limiting state, but not the asymmetry in unidirectional fluxes. Clearly, the chemical affinity reflects the nonequilibrium of the system better than the excess Gibbs energy. Comparing limiting values of P and G, one can conclude that parameter P gives logically better scaling of DFE in comparison with G.

Discussion

Although in thermodynamics the concept of equilibrium does not always imply detailed balance (Van Kampen 1981), the exceptions, such as systems in magnetic fields or rotating systems, are not considered in this paper, and we use the detailed balance as a criterion for equilibrium. A formulation based on unidirectional fluxes seems to be most independent of the nature of the system. Therefore, a construction of a special parameter P from unidirectional fluxes seems to be an attractive approach to a quantitative description of DFE. It reflects nonequilibrium better even for those systems which may be characterized thermodynamically. At the same time it gives a more general measure for DFE, because not all the biological processes can be characterized by thermodynamic criteria. An example may be given by a migration process, where the fluxes can be measured, but analogs of thermodynamic driving forces are not known. The basis for a more general character of parameter P is that it uses less detailed characterization of a system than one has in the case of chemical reactions or other well characterized physical systems.

It is interesting to compare the behavior of P in different regimes with that of entropy production or energy dissipation (Haken 1977; Eigen and Schuster 1979; Nicolis and Prigogine1977; Hoffman et al. 1989). In far from equilibrium systems, the parameter P can reach its steady-state value by either decreasing or increasing in time, as shown in Fig. 1, B, C and F. At the same time at least in systems with constant phenomenological coefficients, entropy production is a minimum at stable steady-states (de Groot and Mazur 1984). Therefore, in such states entropy production tends to its steady-state value from above. If the steady state is close to equilibrium, the parameter P is analogous to entropy production, approaching its limiting value from above. A parallelism between P and entropy production was shown in a wider range for induced ionic transport (Pastushenko et al. 1991, 1992).

One of the important applications of the new measure for DFE is connected with a possible coupling between the nonequilibrium environment of an ion channel in a cell membrane and the functioning mode of the channel which is frequently represented by a kinetic scheme with loops. To prove or disprove such a coupling, one has to recover the full set of rate constants characterizing the kinetic scheme of the ion channel, without any equilibrium assumption. As a proof for such a coupling, a statistically reliable demonstration that $P>0$ schould be accepted.

Comparing parameters P and L, we have seen that P can have a discontinuous time derivative at some points, reflecting local reversals of the "forward" directions. This makes P particularly appropriate for characterizing systems in which points of local equilibrium are physically significant. An example of such a local equilibrium can be given by the carbon balance in plants on the time scale of a year: in summer synthesis prevails, whereas in autumn the plants mainly lose carbon together with falling leaves.

With the exception of the points of local equilibria, better indicated by parameter P, the quantitative behavior of parameters L and P is, so far, analogous. The main difference between these parameters lies in their derivation. Thus, whereas the net flux for each connection has a clear physical meaning, it is not clear which unit flux, f or $f+b$ should be selected. On the contrary, in the derivation of parameter P we did not construct even a net flux vector: both vectors, $\mathfrak{R}$ and $\mathfrak{U}$, represent symmetrical versions of the same set of unidirectional fluxes. It is clear then that parameter P is a more straightforward property of the flux vector. For this reason we prefer using parameter P as a more consistent approach. A further, logical argument in favor of P is that it allows one to consider the distance from equilibrium and from strict irreversibility as the same function ($\cos^2$) of the angle between two symmetric flux vectors and of its complement to the maximum possible value, respectively.

Flexibility and invariance of parameter P

A special advantage of P as a measure for DFE is its flexibility. As an example we consider a carbon cycle in a steady-state, i.e. on the time scale of many years. A simplified kinetic scheme for the carbon cycle, retaining only details important for our aim, is shown in Fig. 3 (more detailed schemes are given by Alberts et al. (1989) on p. 61, and on p. 64 in the first edition). We do not show carbon exchange between atmosphere, aquasphere, sediments, humus in soil, etc., combining all these media into a common state with the conventional name "atmosphere", and collecting the photosynthetic organisms into a common state under the name "plants", and nonphotosynthetic organisms into a state under the conventional name "animals". Strictly speaking, some plants such as Drosera, Venus's-flytrap or monkey-cup can also be considered as animals because of their ability to obtain carbon from insects which they eat. With these small exceptions, the class of animals obtains carbon from plants and returns it to "atmosphere", so that carbon exchange in animals is extremely irreversible. Figure 3A shows exchange between "atmosphere", "plants" and "animals". For this scheme the value of P is relatively high (conventionally, $P \sim 1$). If we are only interested in carbon exchange between living and nonliving matter, we combine "plants" and "animals" into a class of living organisms (Fig. 3B), which leads to $P \sim 0$. Thus, parameter P is a flexible means of reflecting the nonequilibrium state of different parts of the system. The decrease of the P-value caused by redefining the system is partly due to direct elimination of the irreversible connection between "plants" and "animals", and partly due to the resulting conversion of formerly incomparable (i.e. belonging to different connections) fluxes into comparable ones. As we shall see shortly, the value of P can also be increased, if the system is modified by elimination of reversible connections.

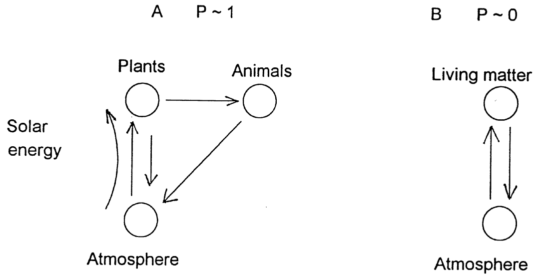

Fig. 3A, B A simplified scheme for carbon cycle in biosphere. The values of P are different in dependence on level of description. **A** "fine grained", distinguishing between "plants" and "animals"; **B** "coarse grained", combining all living organisms

These considerations put forward a more general question: to what extent is the new measure for DFE a system property, i.e. is invariant on the level of description. The invariance of this parameter as a system property should be expected at least in those situations when the level of description may be changed without losing kinetic information. We shall discuss this question in the application to linear kinetic systems with widely different rate constants.

The relaxation time τ_{ij} for a connection between states i and j is:

$$\tau_{ij} = (k_i + k_j)^{-1} \tag{29}$$

This is not the same as the relaxation time for the state variables x_i and x_j. Suppose for simplicity that there are two widely separated relaxation times, τ_f (fast) and τ_s (slow) such that $\tau_f \ll \tau_s$, and all relaxation times fall into two classes: $\tau_{ij} \le \tau_f$ and $\tau_{ij} \ge \tau_s$. At intermediate times t such that $\tau_f \ll t \ll \tau_s$ the kinetic description of the system may be reduced by taking into account local equilibria established in fast connections. In such a way one comes to a coarse grained description, based on lesser dynamic variables. The question is, whether parameter P is invariant relative to a change of description level. We shall consider two different kinds of possible coarse grained description.

Coarse grained I. If we are interested only in the values of equilibrated state variables, we can neglect the slow connections, retaining only the fast ones. The kinetic scheme then transforms into separated islands of states connected by fast connections. For each island we get then $P \sim 0$.

Coarse grained II. If we are interested in slow changes of the state variables, we can not neglect slow connections. We first combine each island of states connected by fast connections into a single state. Consider one such island consisting of n fine grained states, numbered as $i = 1, 2, \dots, n$. The new, coarse grained state (replacing the whole island) is characterized by

$$x = \sum_{i=1}^{n} x_i \tag{30}$$

The slow rate constant k_{ij} is replaced by coarse grained rate constants k_{IJ}, I and J are the numbers of coarse grained states, containing fine grained states i and j:

$$k_{IJ} = k_{ij} x_i / x \; ; \quad i \in I \, , \; j \in J \tag{31}$$

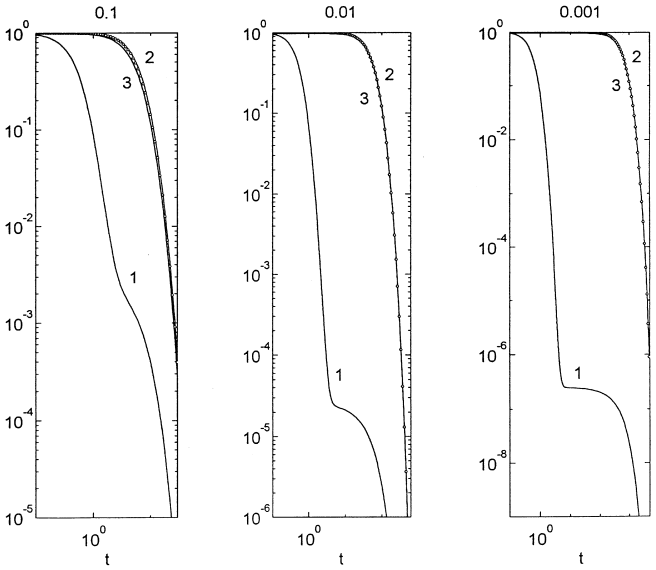

Fig. 4 Comparison of chemical affinity plotted as $\tanh^2\mathscr{A}$ and P at different levels of description for the system as in Fig. 1E, but $k_{23}=k_{32}=\nu \ll 1$; the values of ν are shown above each graph. The global fine grained value of P (*curves 1*) better reflects the details of the relaxation process in the system. *Solid curves 2* and *3* correspond to chemical affinity and coarse grained II value of P respectively. Points show the fine grained values of P for slow connection. Note that coarse grained II value of P and $\tanh^2\mathscr{A}$ practically coincide with P for slow connection at sufficiently small values of ν, therefore failing to reflect the fast relaxation

If the system was initially concentrated only in one such island, then for this type of coarse grained description at intermediate times we obtain $P \sim 1$.

The fine grained description assumes that all the states are taken into account explicitly. According to two different possibilities of our preferences at intermediate times, we can consider the analogs of two different coarse grained descriptions by selecting two subsets of connections, fast and slow respectively. For both subsets we then obtain two different values of P, a very small one for fast connections and a very large one for slow connections. Thus both versions of coarse grained description are contained in the fine grained description. To check the invariance of parameter P with respect to the level of description, we have to compare the fine grained value of P for slow reactions with the coarse grained II value of P. Without canonization, both values of P practically coincide. The reason for this is the invariance of slow fluxes in switching to the coarse grained II level of description. The canonization redefines the system, so that the invariance of P is not to be expected in this case. Thus the invariance of P holds if we do not modify the system by canonization. This conclusion illustrates the objective character of P.

To illustrate these general considerations, we select the system of the type shown in Fig. 1E, with rate constants $k_{12}=k_{21}=1$ and $k_{23}=k_{32}=\nu \ll 1$. Figure 4 shows the values of P, obtained at different levels of description, and $\tanh^2\mathscr{A}$. The overall chemical affinity for this system is

$$\mathscr{A} = \ln(f_{12}\, f_{23}) - \ln(f_{32}\, f_{21}) \tag{32}$$

which gives

$$\mathscr{A} = \ln(x_1/x_3) \tag{33}$$

The concentrations in all three states, x_i, $i=1, 2, 3$ are expressed in terms of quantities r and p_j, $j=1, 2$, defined as

$$r = (1-\nu+\nu^2)^{1/2}\,; \quad p_1 = 1+\nu+r\,; \quad p_2 = 1+\nu-r \tag{34}$$

These expressions are:

$$x_i = 1/3 + (1/6r) \sum_{j=1}^{2} (-1)^j\, a_{ij}\, \exp(-p_j\, t)\,, \quad i=1,2,3 \tag{35}$$

$$a_{1j}=1+4\nu-2p_j\,;\ a_{2j}=p_j+1-2\nu\,;\ a_{3j}=p_j-2-2\nu \tag{36}$$

The values of ν are shown in Fig. 4 above each graph. Different curves are numbered as: 1 – fine grained global value of P; 2 – $\tanh^2(\mathscr{A})$, 3 – the value of P obtained at the coarse grained II level, and points correspond to the fine grained P for slow connection. Intermediate times correspond to the second quasi-plateau in curves 1, which is more pronounced for wider separation of relaxation times. Small differences between $\tanh^2\mathscr{A}$, coarse grained II and fine grained P for slow connection can be seen only for $\nu=0.1$ (left). This illustrates the invariance of the fine grained value of P with respect to switching to the coarse grained II level of description. In contrast to these three curves, the global value of P clearly reflects both relaxation processes, corresponding to $t<1$ and $t>1$. The sensitivity of the global parameter P to details of the relaxation process shows its advantage as a system characteristic in comparison with $\mathscr{A}$.

Conclusion

We have demonstrated the advantages of parameter P proposed as a measure for DFE in comparison with other possible criteria including major thermodynamic measures. These advantages are based on a more general nature of P. It is a flexible tool for characterizing DFE in kinetic systems, especially useful in biological systems with certain unidirectional fluxes in the absence of information on thermodynamic driving forces.

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