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ARTICLE

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Distance of the reduced Brusselator from equilibrium

Steady-state and relaxation regimes

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Abstract The new concept of a nonequilibrium parameter *P* is applied to a reduced Brusselator, considered as a kinetic model for cellular processes. The reduction corresponds to omitting a monomolecular reaction. The deviation from equilibrium is due to a fixed nonequilibrium value of an extracellular concentration *B*, responsible for energizing and determining the steady-state value of the overall chemical affinity $\mathscr{A}$. The value of $\mathscr{A}$ is insensitive to different steady states possible for a given set of rate constants. In contrast, the parameter *P* is state dependent. In particular, it may jump together with state variables. Two limiting cases of high $\mathscr{A}$ are investigated, $B \to 0$ and $B \to 1$. In the first case *P* grows monotonically with $\mathscr{A}$. In the second case there is always a steady state solution with $P \to 0$. The physical interpretation of this effect of "equilibrium far from equilibrium" reveals the real predictive power of the parameter *P*. Relaxation regimes are investigated for a doubly reduced Brusselator. Both *P* and $\mathscr{A}$ are in general time dependent and have jumps in their time derivatives. The canonical form of *P* is compared with the noncanonical one in the context of robustness of the new concept with respect to incomplete information about the system studied. These forms of *P* are different in relaxation to a nonequilibrium state and coincide in relaxation to an equilibrium state.

Key words Nonequilibrium parameter · Irreversibility · Nonlinear kinetics

Introduction

From the point of view of physics or chemistry, life processes represent an extremely complicated system of chemical reactions, frequently coupled with each other and mostly occurring far from equilibrium (Nicolis and Prigogine 1977, 1990; Alberts et al. 1989). This explains the sustained interest in nonlinear systems, capable of demonstrating complex behavior (Lavenda et al. 1971; Lefever et al. 1988; Teorell 1959; Pastushenko et al. 1971, 1980; Drouin 1995; Pastushenko 1997). From a very general point of view, it would be of great importance to be able to characterize the distance from equilibrium (DFE) quantitatively. This question was discussed from different points of view. Thus, DFE in a system of chemical reactions is frequently identified with overall chemical affinity $\mathscr{A}$ (Lefever et al. 1988, Lavenda et al. 1971), and sometimes with entropy production (Nicolis and Prigogine 1977, 1990). We have proposed a nonequilibrium parameter *P* that is based on fluxes and scales DFE for a wide class of systems described by unidirectional fluxes (Schindler et al. 1998). The behavior of this parameter has been studied in several kinetic systems and in the case of induced membrane transport (Pastushenko et al. 1991, 1992). The systems studied were described by linear kinetic equations, i.e. the rate constants were independent of the dynamic variables. The next natural step in the development of the new approach would be its application to a nonlinear system. The main aim of this paper is to study the behavior of *P* in a specific nonlinear system.

There are different nonlinear kinetic systems. One choice could be Teorell's membrane system (Teorell 1959), capable of different kinetic regimes, including oscillations (Pastushenko 1997). We decided to select a well known example of a nonlinear system with rich kinetic possibilities, the Brusselator (Lefever et al. 1988; Lavenda et al. 1971), because it is described by ordinary differential equations and is therefore easier to handle. On the other hand, it may serve both as a kinetic model for many cellular processes with participation of coupled reactions and as a

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general model for nonlinear kinetic systems. Nonlinear systems attract special attention as models for self organization phenomena. One of the main questions discussed over the last few decades was the possibility of such phenomena near equilibrium. Walz and Caplan (1995) have studied a similar system, called the Baselator, and concluded that oscillations are possible near equilibrium. As the oscillations represent self organization in time, their conclusion is interesting from the point of view of possible ways of chemical evolution. On the other hand, such conclusions are usually dependent on how DFE is defined. For this reason the questions of DFE, and what is called "far" or "close to equilibrium" are especially important. In this paper we apply the new concept of DFE to a reduced version of the Brusselator, capable of nontrivial types of behavior.

Selection of Brusselator configuration

The Brusselator is a system of molecular reactions, developed in Brussels as a model for self organization phenomena. In this paper it will be discussed as a kinetic model for cellular processes, in which many reactions are similar to the Brusselator in the sense of coupling and nonlinearity, the latter usually due to substrate-level regulation of enzyme activity. According to Lefever et al. (1988) the Brusselator is represented by following processes:

1. A monomolecular reaction of interconversion between substances A and X:

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} X \tag{1}$$

2. A bimolecular reaction

$$X + B \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} Y + D \tag{2}$$

This reaction will be considered as two coupled monomolecular interconversions X↔Y and B↔D, proceeding simultaneously in one or the other direction.

3. A trimolecular reaction

$$Y + 2X \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} 3X \tag{3}$$

4. A monomolecular reaction of interconversion between substances X and E:

$$X \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} E \tag{4}$$

In analogy with chemical nomenclature, this system may be denoted as the 1,2,3,1-Brusselator. We shall deal with the reduced Brusselator, obtained by omitting reaction (4). This version may be denoted as the 1,2,3-Brusselator. The twice reduced, or 2,3-Brusselator, obtained by omitting the monomolecular reaction (1), will also be considered. It may be shown that the 1,2,3-Brusselator is still capable of oscillations. Here we shall consider only steady states and relaxation regimes.

Dynamic equations for the 1,2,3-Brusselator

As is clear from Eqs. (1–3), in general the 1,2,3-Brusselator represents a system of five dynamic variables, *A*, *X*, *Y* and *B*, *D*. In the context of applications to cellular processes, the substances B and D may be considered as extracellular, and substances A, X, Y as intracellular, so that the coupling between transformations B → D and X → Y is mediated by some membrane enzyme. The nonlinearity of the Brusselator may formally be considered as an analog of substrate level enzyme regulation by X. To simplify the formulas, we adopt the cellular volume v as a unit, v = 1. We also introduce the volume of extracellular space *V*, which will be typically assumed to be large, $V \gg 1$. Denoting different concentrations by italic letters, the dynamic equations for intracellular variables under isothermal conditions may be written as:

$$dA/dt = -k_1 A + k_{-1} X \tag{5}$$

$$dX/dt = k_1 A - k_{-1} X - k_2 BX + k_{-2} DY + k_3 X^2 Y - k_{-3} X^3 \tag{6}$$

$$dY/dt = k_2 BX - k_{-2} DY - k_3 X^2 Y + k_{-3} X^3 \tag{7}$$

The equations for extracellular concentrations may have different forms. Consider first the case when the Brusselator represents an isolated system, where no matter and energy exchange with the surrounding medium occurs. The isothermal conditions may be provided by the assumption of high thermal capacitance (Lefever et al. 1988). Thus, under the conditions of an isolated system the extracellular concentrations are governed by

$$V\,dB/dt = -k_2 BX + k_{-2} DY \tag{8}$$

$$V\,dD/dt = k_2 BX - k_{-2} DY \tag{9}$$

Equations (5–9) will be used to find the equilibrium state of the 1,2,3-Brusselator. More interesting results will be found for nonequilibrium steady states. The deviation from equilibrium will be realized by keeping extracellular concentrations *B*, *D* constant and different from their equilibrium values B_e, D_e. There are two main physical possibilities for how this may be realized. One is connected with the analysis at not very long times in the case where $V \gg 1$. Owing to slow variations of *B* and *D*, these concentrations may be considered as constant. The second possibility, corresponding to strict stationarity, assumes the existence of some mechanism responsible for maintaining *B* and *D* at constant levels. In any case, if *B* and *D* are constant, the Brusselator is essentially represented only by the dynamic variables *A*, *X*, *Y*, the parameters *B*, *D* playing the role of external conditions. Therefore, in nonequilibrium states only Eqs. (5–7) will be solved using given constant values of *B* and *D*. To simplify the formalism, we now introduce normalized variables and parameters.

Normalization of time, concentrations and rate constants

Two conservation laws follow from Eqs. (5–9), in analogy with the paper by Lefever et al. (1988)

$$B + D = N_{\mathrm{out}} = \mathrm{const} \tag{10}$$

$$A + X + Y = N_{\mathrm{in}} = \mathrm{const} \tag{11}$$

Here N_{out} is the total concentration of extracellular substances in forms B or D, and N_{in} is the total concentration of intracellular substances in any form. These quantities represent natural units for measuring corresponding concentrations. Equations (5–9) are invariant with respect to transformation

$$\begin{aligned} t &\to k_{-1}\, t \\ (k_1, k_{-1}) &\to (k_1, k_{-1})/k_{-1} \\ (k_2, k_{-2}) &\to (k_2, k_{-2})\, N_{\mathrm{out}}/k_{-1} \\ (k_3, k_{-3}) &\to (k_3, k_{-3})\, N_{\mathrm{in}}^2/k_{-1} \\ (B, D) &\to (B, D)/N_{\mathrm{out}} \\ (A, X, Y) &\to (A, X, Y)/N_{\mathrm{in}} \end{aligned}$$

The combinations to the right of the arrows will be used as normalized parameters and variables, and they could be denoted differently from those to the left of the arrows. However, because we shall subsequently deal only with normalized quantities, we shall retain the same notations. Thus, the conservation laws will be written as

$$B + D = 1 \tag{12}$$

$$A + X + Y = 1 \tag{13}$$

Equation (12) may replace one of Eqs. (8–9), and Eq. (13) – one of Eqs. (5–7). In terms of normalized quantities, only Eq. (5) changes its appearance:

$$dA/dt = -k_1 A + X \tag{14}$$

Together with Eqs. (6) and (8), where now normalized quantities are considered, Eqs. (12–14) will be used for the analysis.

Equilibrium state

This state is uniquely defined by detailed balance, where in each reaction forward and backward fluxes are equal to each other. By definition, both $\mathscr{A}$ and $P = \cos^2(\alpha)$, defined in Schindler et al. (1998), are equal to zero in this state. As follows from detailed balance,

$$k_1 A_{\mathrm{e}} = X_{\mathrm{e}} \tag{15}$$

$$\gamma_2 B_{\mathrm{e}} X_{\mathrm{e}} = Y_{\mathrm{e}} D_{\mathrm{e}} \tag{16}$$

$$\gamma Y_{\mathrm{e}} = X_{\mathrm{e}} \tag{17}$$

Here we have supplied equilibrium values of different concentrations by index "e" and introduced notations for partial equilibrium constants,

$$\gamma_2 = k_2/k_{-2}; \quad \gamma = k_3/k_{-3} \tag{18}$$

For reaction (1), the role of the partial equilibrium constant is played by the normalized rate constant k_1. Introducing a parameter ν, we find

$$\nu = 1 + 1/k_1 \tag{19}$$

$$A_{\mathrm{e}} = \frac{\gamma}{k_1 (1 + \nu\gamma)} \tag{20}$$

$$X_{\mathrm{e}} = \frac{\gamma}{1 + \nu\gamma} \tag{21}$$

$$Y_{\mathrm{e}} = \frac{1}{1 + \nu\gamma} \tag{22}$$

$$B_{\mathrm{e}} = 1/(1 + \gamma_2\, \gamma) \tag{23}$$

$$D_{\mathrm{e}} = \gamma_2\, \gamma/(1 + \gamma_2\, \gamma) \tag{24}$$

The expressions for equilibrium intracellular concentrations of the 2,3-Brusselator follow from Eqs. (21, 22) at $\nu = 1$. The equilibrium extracellular concentrations are the same in both cases. It follows from Eq. (23), that both γ_2 and γ influence the value of B_{e} in the same way. For instance, if $\gamma \gg 1$, then, for not very small γ_2

$$B_{\mathrm{e}} \ll 1\,, \quad D_{\mathrm{e}} \cong 1 \tag{25}$$

Nonequilibrium steady states

To study the dependence of nonequilibrium parameter $P = \cos^2(\alpha)$ on B, it is convenient to consider two nonequilibrium intervals, $B < B_{\mathrm{e}}$ and $B > B_{\mathrm{e}}$ separately. We begin with the more interesting case

$$B_{\mathrm{e}} < B < 1 \tag{26}$$

In this interval, denoting reactions (1–3) by index $i = 1, 2, 3$, we have forward and backward fluxes f_i and b_i as:

$$f_1 = k_1 A\,, \quad f_2 = k_2 B X\,, \quad f_3 = k_3 Y X^2 \tag{27}$$

$$b_1 = X\,, \quad b_2 = k_{-2} D Y\,, \quad b_3 = k_{-3} X^3 \tag{28}$$

Partial values of $\cos(\alpha_i)$ are defined as

$$\cos(\alpha_i) = \frac{f_i^2 - b_i^2}{f_i^2 + b_i^2}\,, \quad i = 1, 2, 3 \tag{29}$$

The value of $\cos(\alpha)$ for 1,2,3-Brusselator is defined as the weighted average of the partial values of $\cos(\alpha_i)$:

$$\cos(\alpha) = \sum_{i=1}^{3} q_i \cos(\alpha_i) \tag{30}$$

Here statistical weights q_i are defined as

$$q_i = \frac{f_i^2 + b_i^2}{\sum_{i=1}^{3} (f_i^2 + b_i^2)} \tag{31}$$

For the 2,3-Brusselator the summation is made only over $i = 2,3$. For a given steady-state value of X, the steady-state values of A and Y are:

$$A = X/k_1 \tag{32}$$

$$Y = 1 - \nu X \tag{33}$$

The equation connecting the values of X with those of B is obtained by equating total fluxes in reactions 2 and 3:

$$f_2 - b_2 = f_3 - b_3 \tag{34}$$

Solving this equation for D, we get for the 1,2,3-Brusselator:

$$D = X\,\frac{(\nu k_3 + k_{-3})X^2 - k_3 X + k_2}{(k_2 - \nu k_{-2})X + k_{-2}} \tag{35}$$

The value of B is then defined by Eq. (12). In the case of the 2,3-Brusselator it is sufficient to set $\nu = 1$ in Eqs. (33) and (35). The calculations are now straightforward, and we shall illustrate some typical and interesting situations, beginning with the 2,3-Brusselator. Figure 1 shows the values of P, X and $P_3 = \cos^2(\alpha_3)$, the latter characterizing the degree of nonequilibrium of the trimolecular reaction. The equilibrium point B_e is in this figure shifted to the right in the order A, B, C, D owing to the decreasing k_2-value, which is the only variable parameter here. Different types of $X(B)$ curves are presented.

In Fig. 1A the variable X tends to zero monotonically and continuously with $B \to 1$. In Figs. 1B, C a jump in X occurs, so that at the back movement of B from 1 to 0 there may be a hysteresis. In Fig. 1D the jump of X occurs only at the back movement of B from 1 to 0, if $X = 0$ at $B = 1$.

In the region of B where three solutions exist, we denote the highest one as basic (continuously evolving from equilibrium), the lowest one as the zero-solution, and the intermediate one as the unstable one (this will be shown later). The instability of the intermediate solution is clear intuitively, because at growing B one expects physically decreasing X which is not the case for the intermediate solution. In Figs. 1B, C the jump from basic to zero solution occurs, but in one case P grows before the jump, forming a characteristic loop. In case D one may not reach the zero solution from the basic one only by increasing B; some additional factor is necessary for that.

In all four cases $\cos(\alpha_3) \to 1$ at $B \to 1$. Monotonic growth of P with B is observed only for the basic solution in Fig. 1D. In contrast, in Figs. 1A, B, C the value of P tends to zero at $B \to 1$. This effect represents our most interesting finding. Indeed, the situation seems rather paradoxical: by increasing the value of B, we try to "pull" the system away from equilibrium, but the parameter P, which is expected to characterize DFE, grows only at the beginning, and then decreases. The force "pulling" the system from equilibrium may be characterized by the overall chemical affinity:

$$\mathscr{A} = \sum_{i=1}^{3} |\ln(f_i/b_i)| \tag{36}$$

In steady-state regimes this gives a time-independent expression (time independence in steady-state sounds peculiar, but it is a frequent belief that the overall chemical affinity is always constant), the same for 1,2,3- and 2,3-Brusselators:

$$\mathscr{A} = |\ln(\gamma_2\,\gamma B/D)| \tag{37}$$

We now consider the case $B > B_e$, so that the sign of the absolute value may be omitted. As $B \to 1$, the value of $\mathscr{A}$ grows indefinitely, but $P \to 0$. We discuss the mechanism and explanation for this phenomenon later, and our position is that in this limiting case parameter P characterizes the equilibrium state of the system more logically than $\mathscr{A}$.

Let us see some more examples. Figure 2 presents an analogous sequence of situations for the 2,3-Brusselator as in Fig. 1. In spite of the apparent similarity with Fig. 1, there is a major difference: the equilibrium point is now shifted to the left owing to consequently growing values of k_3 (the only variable parameter in this figure). It is not very clear what happens with parameter P_3 in the vicinity of 1 in both figures. For this reason we show in Fig. 3 the values of $1 - P$ and $1 - P_3$ on a logarithmic scale, P and P_3 are the same as in Fig. 2. One may see from Figs. 3B, C that when a jump from the basic to the zero solution occurs, P_3 jumps closer to 1 by two or four orders of magnitude, respectively.

Figure 4 demonstrates analogous results for the 1,2,3-Brusselator at $k_1 = 1$, showing no big difference from the

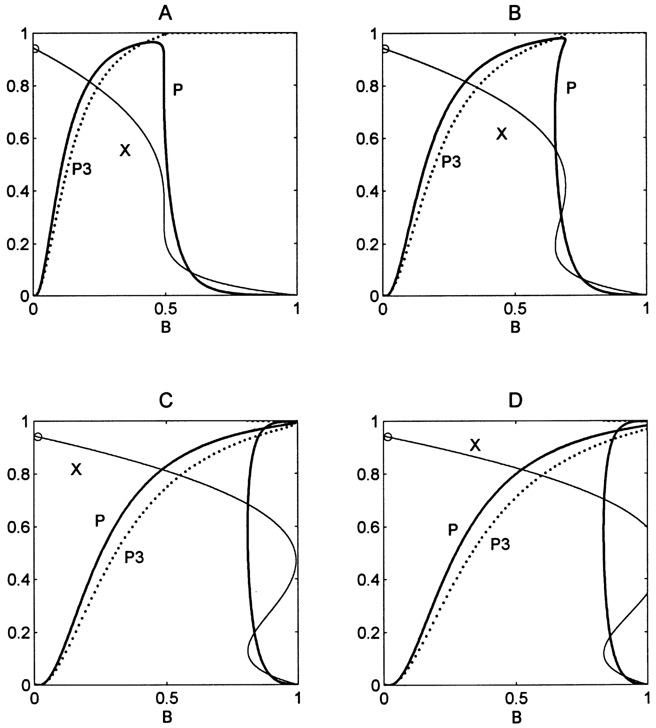

Fig. 1 A–D The nonequilibrium parameter for steady states of the 2,3-Brusselator (P, *thick line*) and for the trimolecular reaction separately (P_3, *dots*) as a function of B. The steady-state values of X are shown by a thin line. Rate constants: $k_{-2} = k_{-3} = 1$, $k_3 = 16$. Values of k_2: **A** 9, **B** 6, **C** 3.8, **D** 3.5

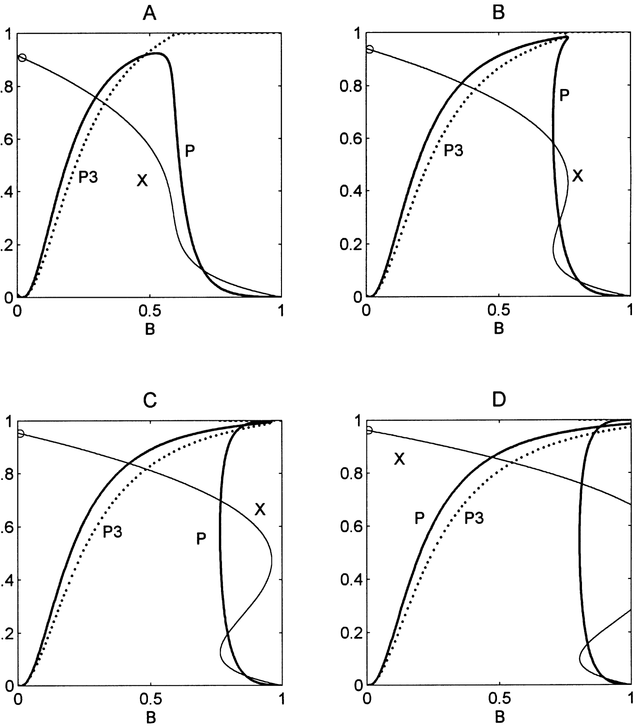

Fig. 2 A–D The same as Fig. 1 but for rate constants $k_2 = 5$, $k_{-2} = k_{-3} = 1$. Values of k_3: **A** 10, **B** 15, **C** 20, **D** 25

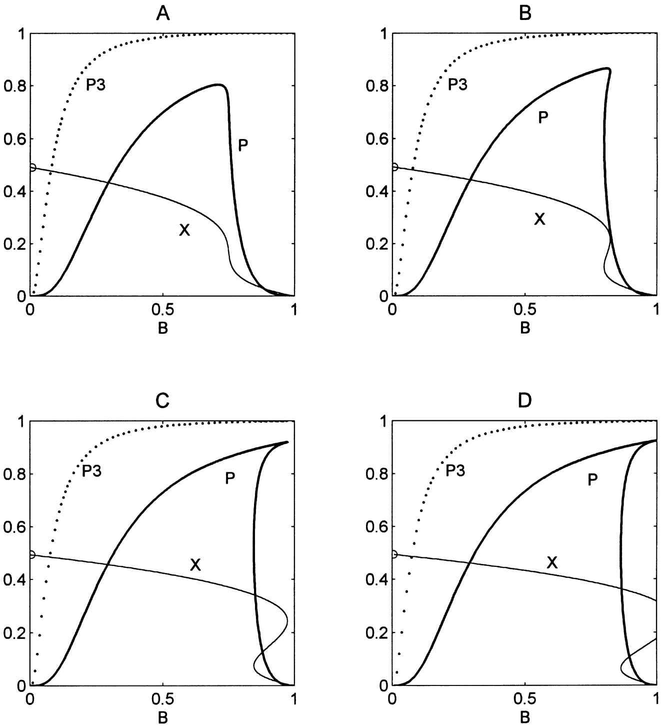

Fig. 4 A–D The parameters P and P_3 for the 1,2,3-Brusselator as a function of B. Rate constants: $k_1 = 1$, $k_2 = 5$, $k_{-2} = k_{-3} = 1$. Values of k_3: **A** 25, **B** 30, **C** 39, **D** 44

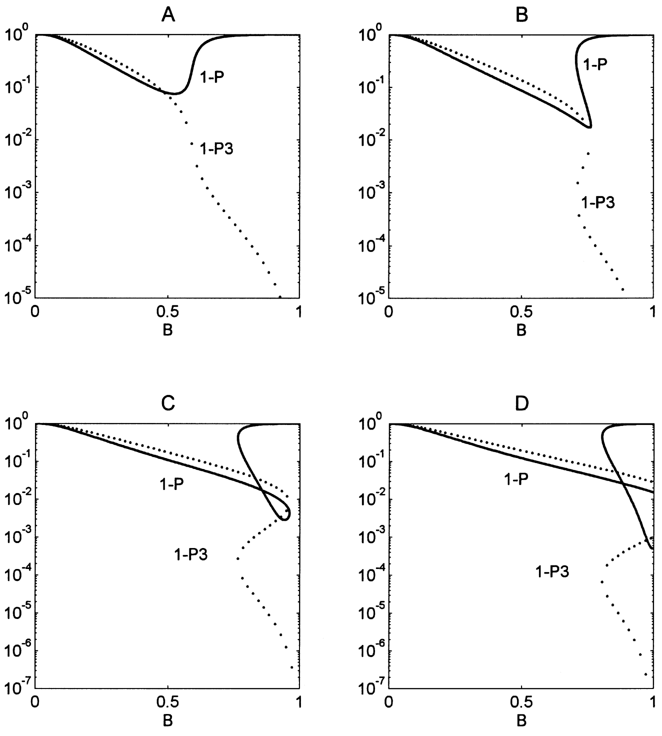

Fig. 3 A–D Semilogarithmic presentation of the data in Fig. 2

2,3-Brusselator. Again, only the k_3-values are varied. As one may see from Fig. 4B, C, the curve $P(B)$ does not make a loop, as was the case in Figs. 1–3. The values of k_3 and k_2 are now higher than earlier. If we had not changed them, the values of P would have been smaller. The main effect of k_1 is decreasing the amplitude of P with decreasing k_1, for other rate constants fixed. For this reason we return back to the 2,3-Brusselator, as the simpler system with essentially analogous properties of steady states.

To finish the presentation of steady states, we consider the case of "opposite" rotation of the Brusselator, which occurs in the interval $B < B_e$. The equilibrium point may be shifted to the right by increasing the rate constants k_{-2} or k_{-3}, or by decreasing the rate constants k_2 or k_3. Some of these possibilities are illustrated in Fig. 5, corresponding to the 2,3-Brusselator. One may move the equilibrium point arbitrarily strongly to the right, the picture remains essentially the same: both P and P_3 grow monotonically with $B \to 0$, and both remain less than 1, although one might expect full irreversibility in this limit, because of the infinite growth of $\mathscr{A}$. The mechanism of this phenomenon is somewhat different from, but still similar to that of the main effect.

Let us consider in more detail the vicinity of the point $B = 1$ for the 1,2,3-Brusselator. The behavior of the system in this vicinity is interesting both from the point of view of the interpretation of the main result, and as a preparative step for further analysis. If all three solutions exist at

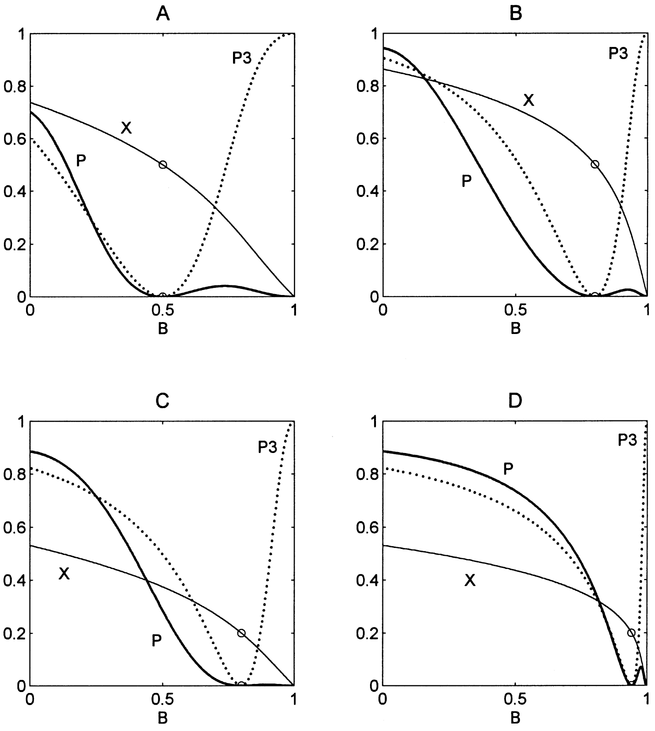

Fig. 5 A–D The dependencies of P, P_3 and X on B for 2,3-Brusselator in the interval $B < B_e$. Rate constants in the sequence (k_2, k_{-2}, k_3, k_{-3}): **A** (1, 1, 1, 1), **B** (1, 4, 1, 1), **C** (1, 1, 1, 4), **D** (1/4, 1, 1,4)

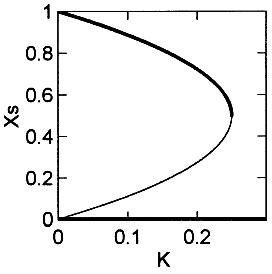

Fig. 6 Steady states of an "irreversible" configuration of the 2,3-Brusselator as a function of $K = k_2/k_3$.

B close to 1, their main terms are expressed as:

$$X_0 = D/\gamma_2\,, \quad X_{1,2} = \frac{\gamma \pm \sqrt{\gamma^2 - 4\gamma K(1+\nu\gamma)}}{2(1+\nu\gamma)} \tag{38}$$

Here $X_1 > X_2$, and K is

$$K = k_2/k_3 > 0 \tag{39}$$

The root X_1 corresponds to the last point of the basic solution, and the root X_2 to the unstable solution. For B close to 1, the root X_0 is close to 0. As is clear from Eq. (38), the basic solution is separated from the nonstable one, if

$$K < \frac{\gamma}{4(1+\nu\gamma)} \tag{40}$$

The expressions for $X_{1,2}$ are especially simple for the case of the "irreversible" configuration of 2,3-Brusselator, obtained from Eq. (38) at $\nu = 1$ and $\gamma \gg 1$:

$$X_{1,2} = 0.5\,(1 \pm \sqrt{1-4K})\,, \quad (\gamma \gg 1) \tag{41}$$

These states are illustrated in Fig. 6, where thick lines correspond to stable solutions, as shown in the next section.

Relaxation regimes of the 2,3-Brusselator

(i) Canonical view of the "irreversible" configuration

Aiming to demonstrate major results with the simplest means possible, we consider relaxation regimes for the 2,3-Brusselator. We shall first analyze its "irreversible" configuration, defined by selecting $B = 1$ and $\gamma \gg 1$. The dynamic equation for the "irreversible" configuration of the 2,3-Brusselator is:

$$dX/dt = k_3 X^2\,(1-X) - k_2 X \tag{42}$$

The steady state solutions of this equation are $X_0 = 0$, and $X_{1,2}$ described by Eq. (41). Let us first consider the stability of these solutions.

In the vicinity of a steady state $s = 0, 1, 2$, the dynamic variable X may be represented in terms of a small deviation x from the steady-state value X_s:

$$X = X_s + x \tag{43}$$

Linearizing Eq. (42), one obtains the equation for x:

$$dx/dt = (2k_3 X_s Y_s - k_2 - k_3 X_s^2)\,x \tag{44}$$

For the zero solution, the expression in parentheses becomes $-k_2 < 0$, indicating stability of this solution. For X_s with $s = 1, 2$ Eq. (44) is transformed as

$$dx/dt = x\,(k_2 - k_3\,X_s^2) \tag{45}$$

Substituting X_1 or X_2 in this equation, one finds that for any $K > 0$ the expression in parentheses of Eq. (45) is positive for X_2 and negative for X_1. Thus X_1 and X_2 are stable and nonstable solutions respectively.

Equation (42) has a simple analytical solution. We give it for the most interesting case of $K < 1/4$, when all three solutions exist. Introducing notations

$$\beta_1 = \frac{1-X_1}{\sqrt{1-4K}}\,, \quad \beta_2 = \frac{1-X_2}{\sqrt{1-4K}}\,, \tag{46}$$

the integral of Eq. (42) may be expressed as

$$k_2 t = \beta_2 \ln(|X - X_2|) - \ln X - \beta_1 \ln(|X - X_1|) + \text{const} \tag{47}$$

The constant term is defined by the initial value of X (at $t = 0$). Equation (47) describes the monotonic relaxation of X to that stable value, X_0 or X_1, which lies on the same side of the unstable solution as the initial value. Thus, if the initial state is above X_2, then X may either increase or decrease in time. In the case of an initial state below X_2, the value of X only decreases, approaching zero in time. The dependencies $X(t)$ for different initial conditions and values of K are shown in Fig. 7 by thin lines.

What is the value of P for the irreversible 2,3-Brusselator? Both bi- and trimolecular reactions, except for the case $X = 0$, are irreversible: the trimolecular reaction owing to the assumption $\gamma \gg 1$ and the bimolecular reaction owing to the assumption $B = 1$. Therefore even without dynamic equations one may conclude that $P = 1$. This is correct if we consider the Brusselator as a noncanonical system, i.e. within the framework of its molecular interpretation. We want to demonstrate that our concept of nonequilibrium is more general than those existing in thermodynamics. Imagine that we can only measure the total fluxes X → Y and Y → X, and nothing is known about the mechanisms of these fluxes. Such a situation is quite common even in molecular studies with labeled compounds, when no intermediate products are registered. If some molecular system under investigation were to have the same kinetic scheme as the Brusselator, this would lead to a fundamental problem: using labeled substances X and Y and studying corresponding fluxes one can only measure the sums $f_2 + b_3$ and $f_3 + b_2$, but not each partial flux separately. And, as we mentioned already, if the system can not be characterized thermodynamically (for instance, X and Y may represent populations of two cities, or whatever else) but the fluxes are still measurable, the thermodynamic criteria are not applicable any more, unlike the parameter P. The "irreversible" configuration of the 2,3-Brusselator is especially advantageous for discussing the canonical P-value, because in this case only f_2 and f_3 have nonzero values. According to the canonical view of the 2,3-Brusselator, bi- and trimolecular reactions are considered as one combined process characterized by two fluxes. For the irreversible configuration this leads to

$$P = \left(\frac{(f_2^2 - f_3^2)}{(f_2^2 + f_3^2)} \right)^2 \qquad (48)$$

The curves $P(t)$, calculated according to this equation, are shown in Fig. 7 by thick lines. For X close to steady states X_1 or X_2, P is close to zero. This is true for any steady-state of any system described by a kinetic scheme without loops. In transition from the noncanonical to the canonical view of the Brusselator the only nonequilibrium loop was removed, which explains the tendency of the canonical P to zero near steady-states.

Let us now discuss the cases of P close to 1, shown in Fig. 7. In Figs. 7A, E, F the initial value of P is close to 1 because initially only state X was populated, and therefore the initial value of $f_3 = k_3 X^2 Y$ was zero. More interesting is the case when $P \to 1$ at $X \to 0$. This result is in apparent contradiction with the previous section where we have shown that $P \to 0$ at $X \to 0$. It is basically explained by the different order of taking limits: in steady-states we first consider large times, and then vary B, whereas in the given case we have first put $B = 1$. This question is explained in the next section in more detail.

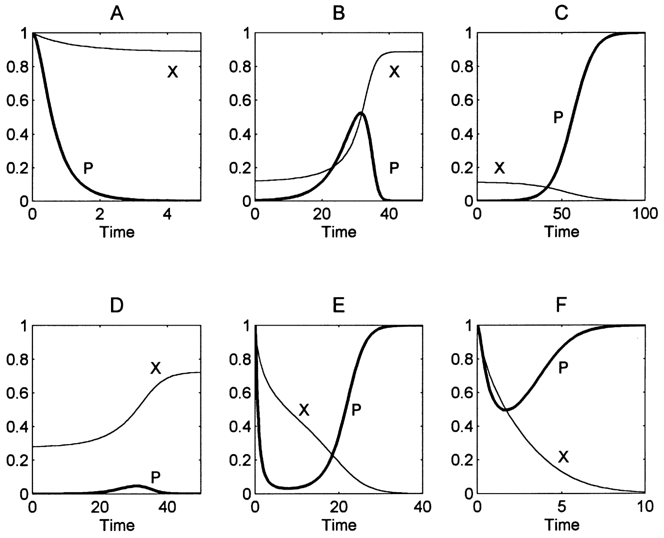

Fig. 7 A–F Dependencies of X (*thin line*) and of the canonical value of P (*thick line*) for an "irreversible" configuration of the 2,3-Brusselator. Initial values of X are slightly above the nonstable steady-state value in cases **B**, **D**, and slightly below in case **C**. **A**, **B**, **D** – relaxations to the stable nonzero solution. **C**, **E**, **F** – relaxations to the zero solution. Values of K: **A**, **B**, **C** 0.1; **D** 0.2; **E** 0.3; **F** 0.6

(ii) Canonical and noncanonical views of a "reversible" configuration

To decide, to what extent the information about nonequilibrium is reflected by the canonical value of P, it is informative to compare both canonical and noncanonical forms for the "reversible" configuration, where the assumptions $\gamma \gg 1$ and $B = 1$ are not made. This configuration may be made arbitrarily close to the "irreversible" one by increasing the values of γ and B.

Figure 8 shows four different relaxation regimes in the "reversible" 2,3-Brusselator from the initial state $X = 1$. Figure 8A describes relaxation to the equilibrium state, i.e. at $B = B_e = 0.077$. The value of B_e corresponds to rate constants listed in the legend. The canonical value of P is shown by a thin line, the noncanonical P is shown by a thick line. The relaxation to equilibrium is particularly interesting in the sense that both versions of P for the 2,3-Brusselator coincide exactly, independent of the choice of rate constants. For this reason, relaxation to equilibrium is a unique situation where canonization does not mean a loss of information about the degree of nonequilibrium. The values of $\mathscr{A}$ are shown by dots in all four cases. In the initial state $\mathscr{A} = \infty$. For this reason it is presented as $\tanh^2(\mathscr{A})$, and, for better scaling, we calculate $\mathscr{A}$ according to Eq. (37) but using $\log_{1000}$ instead of natural logarithms. Thus, like P, the quantity $\mathscr{A}$ is in principle time-dependent, and its time derivative may also undergo jumps.

Figure 8B corresponds to the same set of rate constants as Fig. 8A, but the value of $B = 0.9$ is different from B_e. There is a certain parallelism between canonical and noncanonical versions of P: both start from the same initial

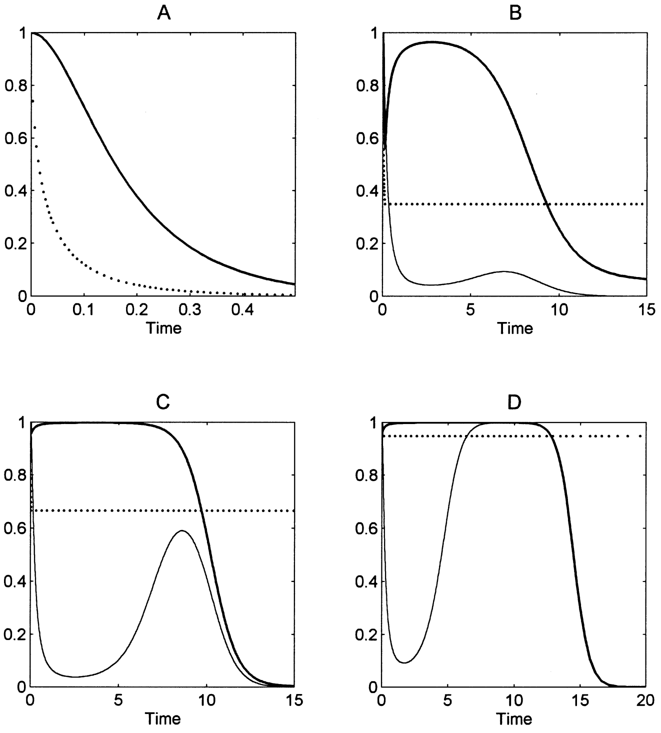

Fig. 8 A–D Different forms of P (noncanonical: *thick line*, canonical: *thin line*) and overall chemical affinity $\mathcal{A}$ (*dots*) in dependence of time for the "reversible" 2,3-Brusselator. Rate constants in the sequence (k_2, k_{-2}, k_3, k_{-3}) and concentrations B: **A** (1, 0.5, 3, 0.5), $B = B_e = .077$. **B** (1, 0.5, 3, 0.5), $B = 0.9$; **C** (1, 0.1, 3, 0.1), $B = 0.9$; **D** (1, 0.1, 3, 0.1), $B = 0.9999$. Note that in the regime of relaxation to the equilibrium state both forms of P coincide. The value of $\mathcal{A}$ varies in time and, if $B \neq B_e$, its time derivative shows jump. Figures **B**, **C**, **D** illustrate the approach to an "irreversible" configuration: the interval where the canonical P is close to 1 becomes wider with $B \to 1$

value 1, both have two intermediate extrema, and both decrease at high times. The principal difference is that while the noncanonical P tends to some positive value, the canonical value tends to zero. In general, the canonization of the connections between two given states leads to a zero value of partial cos(α) only if the net flux between these two states is equal to zero, as is the net flux from X to Y in steady-state.

Figures 8C, D differ only in the values of B: it is 0.9 for Fig. 8C and 0.9999 for Fig. 8D. At the same time, the values of γ_2 and γ are five times greater than in the two previous pictures. These two figures, together with Fig. 8B, illustrate the consecutive approach to the case of an "irreversible" configuration, analyzed in the previous section. One may see that the duration of the plateau grows for noncanonical P, and, sufficiently close to $B = 1$, a plateau for the canonical P arises. At this plateau and after it both forms of P are close to each other, demonstrating the robustness of the canonical form. Although in the initial stage of the relaxation the difference between canonical and noncanonical P-values is appreciable, it is not as important as near steady-states. Moreover, as $B \to 1$, both values indicate the same status of the system: first strong deviation from equilibrium, and then relaxation to the state characterized by $P = 0$. These considerations show that for any value $D > 0$ the canonical value of P tends to zero with growing time, but the closer to 1 the value of B is, the later this transition occurs, and in the limit of $B = 1$ this transition occurs at infinitely large times. This explains the apparent contradiction mentioned at the end of the previous section.

Discussion

We shall first discuss the mechanism of the phenomenon of "equilibrium far from equilibrium", presented above. Then we shall explain why the parameter P reflects the properties of the system better than $\mathcal{A}$. Some remarks about the importance of the canonical view will also be made.

To understand the mechanism and physical meaning of the main effect, we have to look at partial fluxes, treating D as an infinitely small parameter. Let us first consider the steady states of the 1,2,3-Brusselator. Equations (32), (33) and (38) show that in this limit $A, X \sim D$ (i.e. A and X are small parameters of the same order as D), whereas $Y \approx 1$. Therefore, assuming that all rate constants are fixed and finite,

$$f_1,\, b_1 \sim D,\; f_2 \approx k_2 X \approx k_2 D/\gamma_2 \approx k_{-2} D \approx b_2,\; f_3 \sim D^2,\; b_3 \sim D^3 .$$

This shows that $b_3/f_3 \sim D$, i.e. the trimolecular reaction is totally irreversible. In contrast, $f_2 \approx b_2$, i.e. the bimolecular reaction tends to equilibrium. In steady-states, the monomolecular reaction is at equilibrium at any value of B. For this reason (cf. Eq. 30), the value of $\cos(\alpha)$ for all three reactions is determined by the coefficients q_1, $q_2 \sim 1$ and $q_3 \sim D^2$. Thus the contribution of the totally irreversible trimolecular reaction to $\cos(\alpha)$ vanishes as D^2 with $D \to 0$. At the same time the contribution of the bimolecular reaction is

$$\cos(\alpha_2) = (f_2 - b_2)\,(f_2 + b_2)(f_2^2 + b_2^2) \sim f_3/D \sim D .$$

Thus, the reason why $\cos(\alpha) \to 0$ is that the main contribution to $\cos(\alpha)$ is from the bimolecular reaction which tends to equilibrium.

The question is: why does the bimolecular reaction tend to equilibrium whereas $\mathcal{A}$ grows infinitely (cf. Eq. (36)) and, apparently, tries to increase its degree of irreversibility? The answer lies in the nonlinearity of the trimolecular reaction. With growing $\mathcal{A}$, the state X is exhausted ($X \to 0$), and the state Y is saturated ($Y \to 1$). For this reason the flux f_2 grows only near $B = B_e$, and both fluxes, f_2 and b_2 decrease at $D \to 0$. Owing to the conservation law, the only chance to make these two fluxes different is to transmit their difference to the trimolecular reaction. However, this is not possible, because in conditions of exhausted X the total flux in the trimolecular reaction ($f_3 \sim D^2$) vanishes even faster. Thus, owing to nonlinearity of the trimolecular reaction, with growing A the deviation of the bimolecular reaction from equilibrium first slows down and then decreases at even higher values of $\mathcal{A}$.

The fact that the fluxes in the trimolecular reaction vanish much faster than in the bimolecular reaction with increasing B means that for extremely small values of D the trimolecular reaction virtually disappears, i.e. it becomes an empty element of the kinetic scheme. It is then reasonable to test the invariance of both criteria, P and $\mathcal{A}$, with respect to "zero perturbation" corresponding to cutting off the empty element, i.e. the trimolecular reaction. It is easy to see that parameter P "survives" such a zero perturbation, i.e. it preserves its value. At the same time, the value of $\mathcal{A}$ changes in jump from infinity to zero. For this reason P is a more invariant property of the system and is therefore to be preferred.

Now it is easy to understand the physics of the "unusual" behavior of P. Owing to efficient cutting-off of the trimolecular reaction in the limit $B \to 1$, the Brusselator (in any form, full or reduced) converts into an equilibrium system. This is easy to check by considering reactions (1, 2, 4). This equilibrium is established at any value of B, which can not vary arbitrarily in the absence of the trimolecular reaction (at $V \gg 1$), and therefore an external device for maintaining B constant is not necessary. It is this equilibrium which is indicated by the zero value of the parameter P. Now, if we compare once more the criteria P and $\mathcal{A}$ from the point of view of their predictive power, we have to conclude that P did predict this equilibrium, whereas $\mathcal{A}$ was "silent". Thus, the real predictive power of P represents a serious advantage in comparison with $\mathcal{A}$.

The question may arise of whether the effect discussed is not merely a reflection of the interplay between statistical weights q_i. What will happen to P when we relax the weight of the different reactions, or choose all weights to be equal? This may be done within the same concept of nonequilibrium by normalization of partial fluxes to unity before combining flux vectors out of partial fluxes. Because such a normalization does not change ratios of partial fluxes, one then obtains for $\cos(\alpha)$ an equation similar to Eq. (30) but with $q_i = 1/3$ for the 1,2,3-Brusselator and $q_i = 1/2$ for the 2,3-Brusselator. For this reason, the P-value in the limit $D \to 0$ will tend to 1/9 for the 1,2,3- and to 1/4 for the 2,3-Brusselator. This is exactly what happens (we omit the corresponding figures which are very much like those already demonstrated). However, this does not change the situation in principle, because P still decreases when $B \to 1$. In other words, the effect of decreasing P with growing overall affinity is robust with respect to such a normalization, reflecting the inner tendency of the system towards equilibrium. This tendency may also be interpreted as a demonstration of the Le Chatelier principle: the stronger we pull the system from equilibrium, the higher the tendency of the system to equilibrium is. Of course, one should not forget that the principle of Le Chatelier itself is a reflection of tendency to equilibrium. Nevertheless, it is interesting that this principle is in accordance with the behavior of parameter P.

One may ask further, whether the "unusual" behavior of P is not an artifact, connected with the normalization of the rate constants k_2 and k_{-2} and the concentrations B and D. The answer is "no", because the ratios of fluxes expressed in terms of normalized and "raw" quantities remain the same.

We see some analogy between decreasing P with growing $\mathcal{A}$ and the unusual behavior of dissipation in Teorell's membrane system (Teorell 1959), where, in certain conditions, resistance can quickly vary in some interval of the applied voltage. On the basis of experience with ohmic resistors one could expect that the dissipation should grow with the voltage, which is not always the case in Teorell's system. Within this analogy, the parameter P is similar to the dissipation, and $\mathcal{A}$ is similar to the voltage. It is clear again, that the voltage is more an external condition than a property of the resistor.

We should like to discuss somewhat more the physical meaning of the canonical view. As is frequently the case, detailed information about fluxes may not be available. In research, this is the rule rather than the exception, because a researcher typically deals with unknown mechanisms. It is then of importance, to know to what extent the new concept is robust with respect to lack of information about the system (say, about the reaction mechanism). This situation is well simulated by canonization, where all the fluxes between two connected states are replaced by two unidirectional fluxes, obtained by summation of partial fluxes with the same direction. Thus, canonization certainly corresponds to a loss of information. However, there are several general properties of canonization which show that the possibilities to detect nonequilibrium are lost only in certain specific cases.

1) For any noncanonical equilibrium system the corresponding canonical form will be in equilibrium.

2) Equilibrium of a canonical form does not necessarily mean equilibrium of the corresponding noncanonical form.

3) Nonequilibrium of the canonical form always indicates nonequilibrium of the corresponding noncanonical from (consequence of the statement 1).

4) Canonization of connections between two substates leads to zero partial P-value only if the total flux between these states is zero.

5) If the total flux is nonzero, the partial canonical P-value may be either higher or lower than the partial noncanonical P.

These properties show that the use of the parameter P for the characterization of the degree of nonequilibrium may be reasonable even under conditions of incomplete information. Thus, to demonstrate nonequilibrium of a noncanonical system, it is sufficient to show that its canonical form is not in equilibrium.

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