

Bistability without Hysteresis in Chemical Reaction Systems: A Theoretical Analysis of Irreversible Transitions between Multiple Steady States

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The coexistence between two stable steady states, referred to as bistability, is generally associated with a phenomenon of hysteresis in which a system jumps back and forth between the two branches of stable states for different, critical values of some control parameter, corresponding to two limit points. We focus here on the cases where the transitions between the two branches of stable steady states become irreversible when one of the limit points becomes inaccessible or goes to infinity; we refer to these two cases as irreversible transitions of type 1 or 2, respectively. In order to study in detail the conditions in which such irreversible transitions between multiple steady states occur in chemical systems, we analyze two models based on reversible chemical steps. The first model, due to Schlögl, has long been studied as a simple prototype for bistability. This model is shown to admit irreversible transitions of type 1 as one of the limit points associated with bistability moves into a physically inaccessible region of negative values of a control parameter. A second, original model is proposed, to illustrate the case of irreversible transitions of type 2 in which a limit point goes to infinity. Irreversible transitions of type 1 can also occur in this model, as a function of other control parameters. In both models irreversible transitions take place under nonequilibrium conditions. The analysis indicates what reaction steps need to remain reversible in the models in order to preserve the irreversible transitions.

Introduction

The coexistence between two stable steady states, referred to as bistability, has long been known to occur far from equilibrium in chemical systems governed by appropriate nonlinear kinetic laws. The phenomenon is illustrated by a large number of experimental and theoretical studies in chemical^{1–9} and biochemical^{10–18} systems. When a parameter λ is continuously increased, it is often observed (see Figure 1A) that the system jumps from one branch (say branch 1) of stable steady states to another branch (denoted 2) at a limit point associated with a critical value λ_2 ; when the parameter is then reduced, the system jumps back to branch 1 at a different limit point associated with a value λ_1 of the control parameter. Such a phenomenon of *hysteresis* is one of the most conspicuous properties generally associated with bistability.

Bistability can, however, occur in the absence of hysteresis. Theoretical studies of biochemical and combustion systems have shown that one of the limit points bounding the domain of bistability may not be accessible to the system.^{19–26} In such cases (illustrated by panels B and C in Figure 1), the system can jump from one branch of steady states to the other but cannot undergo the reverse transition when the control parameter is varied back and forth across the bistability domain. The transition is said to be irreversible.²⁰ Either the limit point to the left moves into a region of inaccessible negative values (Figure 1B), or the limit point to the right goes to infinity (Figure 1C), and thus becomes an infinite limit point (ILP). The two situations will be referred to below as irreversible transitions of type 1 and 2, respectively. The symmetrical situation may also occur: the limit point to the right may remain finite and positive but may nevertheless go into a physically inaccessible region, and the left limit point may go to $-\infty$.

It may also occur that the two limit points are out of the system's reach; then the branches of stable steady states are not connected (see Figure 1D), so that the system will not be capable of switching in any direction between these branches upon continuously varying the control parameter.^{27,28} Another case of nonconnected branches is that of isolas (Figure 1F) which originate from "mushrooms" in which two hysteresis loops are present (Figure 1E); such isolas are formed when two limit points (denoted λ_2 and λ_3 in Figure 1E) coalesce. In this case, in contrast to the situation shown in Figure 1D, the system can jump irreversibly from the stable branch of the isola to the other branch of stable steady states. Isolals have been found both experimentally and theoretically in chemical systems,⁹ and in biochemical models.¹⁸ We shall not consider here irreversible transitions associated with isolals and shall restrict our investigation to the case of irreversible transitions schematized in Figure 1, B and C.

The inaccessibility of one or two limit points in conditions where bistability occurs has been investigated experimentally in several biochemical reaction systems.^{28–32} The interest of the phenomenon lies in its possible physiological significance. Irreversible transitions between multiple steady states could indeed play a role in memory and differentiation.

Theoretical studies of the loss of one or two limit points in bistable systems have been devoted so far to models governed at least partly by irreversible kinetic laws.^{19–27} In order to see whether the phenomenon is not an artifact produced by approximations in the derivation of the evolution equations, we analyze the conditions in which bistability occurs without hysteresis in simple theoretical models for chemical systems based on fully reversible kinetic steps, for which kinetic equations are derived without resorting to any quasi-steady-state assumption.

Our aim is to analyze theoretical models that illustrate the different types of irreversible transition observed when one of the two limit points bounding a domain of bistability ceases to

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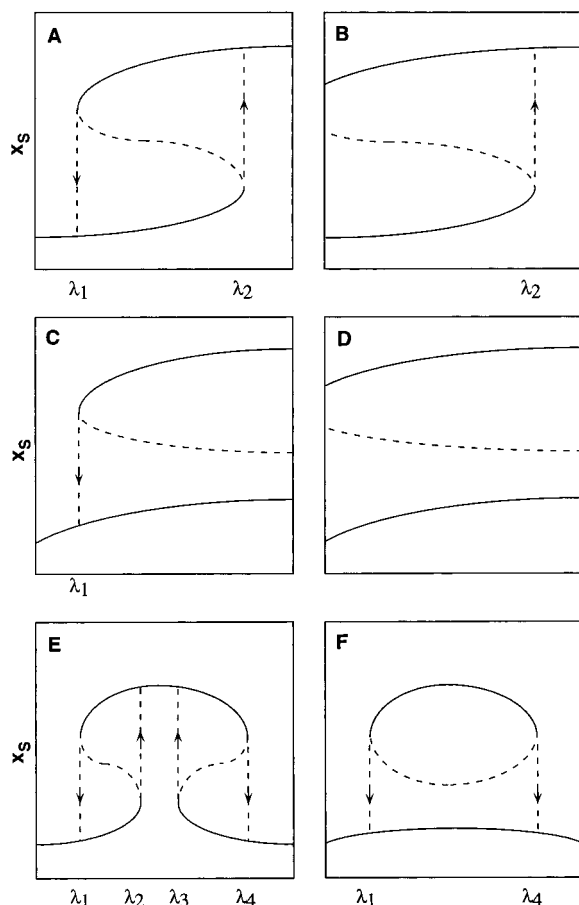


Figure 1. Different modes of bistability (see text). (A) Bistability with hysteresis. The two limit points are located in λ_1 , λ_2 . Panels B–D illustrate various cases of bistability without hysteresis. (B) Irreversible transition of type 1: the left limit point has moved toward an inaccessible domain. (C) Irreversible transition of type 2: the right limit point has moved toward infinity. (D) Nonconnected branches of steady states: the left limit point has become inaccessible, while the right limit point has gone to infinity. (E) “Mushroom” with two hysteresis loops which, upon merging, produce an isola (F) associated with irreversible transitions. Here, as in subsequent figures, dashed lines indicate unstable steady states.

be accessible to the system or disappears by going to infinity. Two models are studied to this end; the first is the well-known model for bistability proposed by Schlögl,^{1–3} for which we show how one of the limit points can become associated with a negative value of a control parameter for which only positive values correspond to physically acceptable situations—the control parameter represents, for example, the concentration of a chemical reactant or a kinetic constant. This situation corresponds to the irreversible transition of type 1 illustrated in Figure 1B. A second, original model is constructed to illustrate the case where one of the limit points goes to infinity, which corresponds to the irreversible transition shown in Figure 1C. In both models we determine the equilibrium state and show that it is located outside the region of bistability.

In a subsequent paper we shall examine a model for which the two branches of stable steady states cease to be connected. The latter situation, illustrated in Figure 1D, is encountered when one limit point moves to an inaccessible domain (e.g. negative values) of the control parameter while the second limit point either goes into another domain of inaccessible values or toward infinity.

Irreversible Transitions of Type 1 in the Schlögl Model

Bistability. The model of Schlögl^{1–3,5,7,9} provides a simple prototype for bistability. Its very simplicity allows a detailed

analysis of the conditions in which multiple steady states occur. The model describes the conversion of the initial reactant A to B via an intermediate X which can catalyze its own production. The system is open to infinite reservoirs of reactants A and B, so that the concentrations of both species are kept constant within the system:



To analyze the conditions for irreversible transitions, it is necessary to recall the salient features of the model.^{1–3,5} The rate equation for the single variable X is

$$\frac{dX}{dt} = -k_{-1}X^3 + k_1AX^2 - k_2X + k_{-2}B \quad (2)$$

This equation admits an equilibrium solution, provided the conditions ensuring detailed balance of both reactions are fulfilled:

$$\begin{aligned} k_1AX^2 &= k_{-1}X^3 \\ k_2X &= k_{-2}B \end{aligned} \quad (3)$$

Thus, at equilibrium

$$\left(\frac{A}{B}\right)_{\text{eq}} = \frac{k_{-1}k_{-2}}{k_1k_2} \quad (4)$$

and

$$X_{\text{eq}} = (k_{-2}/k_2)B \quad (5)$$

Whenever the ratio (A/B) differs from the above value, the system operates under nonequilibrium conditions.

The steady-state solutions obey the equation

$$X^3 - aX^2 + kX - b = 0 \quad (6)$$

where

$$a = k_1A/k_{-1}, \quad b = k_{-2}B/k_{-1}, \quad k = k_2/k_{-1} \quad (7)$$

Equation 6 admits, for certain values of the parameters a , b , and k , three solutions, two of which are stable and one unstable (Figure 2). At equilibrium, condition 4 yields the following relation:

$$(b/a)_{\text{eq}} = k \quad (8)$$

Using eq 8, it is possible to show that multiple steady states cannot be observed at equilibrium.⁵ Indeed relation 8 cannot be satisfied together with condition 9 which ensures the existence of three real roots for eq 6:

$$P = q^3 + r^2 < 0 \quad (9)$$

where

$$q = -\frac{1}{9}a^2 + \frac{1}{3}k \quad (9a)$$

$$r = \frac{1}{27}a^3 - \frac{1}{6}ak + \frac{1}{2}b \quad (9b)$$

The same conclusion can also be reached by expressing a as a

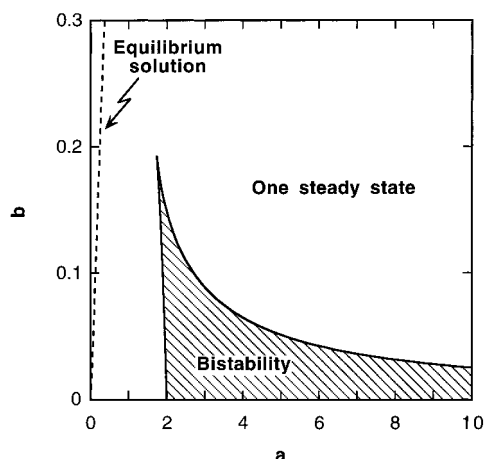


Figure 2. Domain of bistability in the Schlögl model. The domain (hatched area) is obtained as a function of parameters a and b using the program AUTO³⁴ applied to eq 6 for $k = 1$ (parameters are expressed in arbitrary concentration and time units). The dashed line indicates the unique equilibrium solution, which lies outside the domain of bistability. The equilibrium solution corresponds to eq 8.

function of b and k at equilibrium by means of eq 8 and factoring out the equilibrium solution. Then eq 6 can be written as

$$\left(X - \frac{b}{k}\right)(X^2 + k) = 0 \quad (10)$$

The only physically acceptable solution admitted by this equation, and hence by eq 6, is the equilibrium solution (5).

Irreversible Transitions of Type 1. To show the occurrence of irreversible transitions in this model, instead of studying the multivalued function yielding X as a function of parameter b , it is convenient to study the monovalued function

$$b = f(X) = X^3 - aX^2 + kX = X(X^2 - aX + k) \quad (11)$$

obtained from eq 6. Because the function $f(X)$ has a polynomial form, it does not admit any vertical asymptote. Vertical asymptotes obtained when b is plotted as a function of X are a necessary (but not sufficient) condition for the occurrence of irreversible transitions of type 2 in which a limit point goes to infinity when X is plotted as a function of b . Irreversible transitions of this type are therefore not allowed in the fully reversible Schlögl model (the effect of considering irreversible steps is discussed further below). The polynomial form of $f(X)$ nevertheless allows the occurrence of irreversible transitions of type 1 in this model. As shown by Figure 1B, such transitions occur when a limit point enters into the region of negative values of b (which plays here the role of parameter λ). In this case it will not be possible to connect the steady states of the upper and lower branches of X only by reversibly changing parameter b . To observe this situation the function $f(X)$ has to cross three times the positive part of the X -axis; i.e., $f(X)$ must have three nonnegative solutions for $b = 0$. We can readily obtain the conditions in which such a situation occurs in eq 11. Indeed, one solution is always $X = 0$, and the other two solutions are

$$X = \frac{(a \pm \sqrt{a^2 - 4k})}{2} \quad (12)$$

The latter solutions are real provided that $a > (4k)^{1/2}$, and are then always positive. Thus if the condition $a \geq (4k)^{1/2}$ is fulfilled, we have an irreversible transition of type 1. This occurs in Figure 3, established for $k = 1$, when $a \geq 2$.

Observing bistability as a function of b implies the existence of both a maximum and a minimum in b as a function of X .

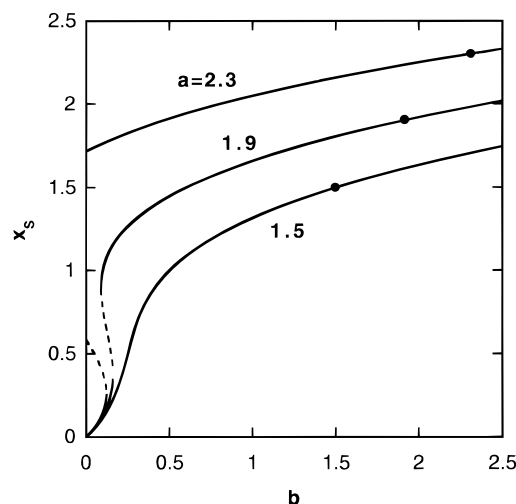


Figure 3. Bistability with or without hysteresis in the Schlögl model. For $a = 2.3$, the left limit point becomes inaccessible, giving rise to bistability without hysteresis, with an irreversible transition of type 1. For $a = 1.9$ and $a = 1.5$ the curves correspond, respectively, to bistability with hysteresis and monostability. The curves are obtained by solving numerically the steady-state eq 6 as a function of b for $k = 1$. On each curve, the equilibrium point (black dot), corresponding to $b = a$ (see eq 8), lies on the upper branch of steady states.

Studying the zeros of the first derivative of $f(X)$, equal to $3X^2 - 2aX + k$, we find that the condition for bistability is

$$a > \sqrt{3k} \quad (13)$$

Thus, as a function of b , we have monostability if $0 < a < (3k)^{1/2}$; bistability with reversible transitions (accompanied by hysteresis) if $(3k)^{1/2} < a < (4k)^{1/2}$, and bistability without hysteresis (irreversible transition of type 1) if $a \geq (4k)^{1/2}$.

Bistability with Irreversible Transition of Type 2

Building up a Model with an Infinite Limit Point. We now look for a reversible chemical model which, upon variation of some control parameter, shows a type of irreversible transition that is qualitatively different from the one that occurs in the Schlögl model. There we observed the shifting of one limit point into a physically forbidden region of negative values of the control parameter. The other possibility, to be investigated below, is that the irreversible transition originates from the shifting of a limit point to infinity.

We consider, as in the Schlögl model, the inverse function $P = h(X)$ obtained from the steady-state equations, where P is a control parameter of the model (in the present case, P will denote the concentration of a chemical species) and X is a steady-state solution. To have a limit point going to infinity, the curve yielding P as a function of X must have at least two vertical asymptotes for positive X values. Thus $h(X)$ must be a rational function with at least two vertical asymptotes in the region $X > 0$. Writing $h(X)$ in the form

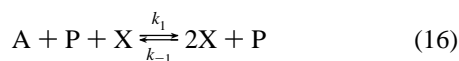
$$P = h(X) = f(X)/g(X) \quad (14)$$

we see that $g(X)$ must have at least two positive roots (the situation of a single positive root of $g(X)$ must be avoided; indeed, $h(X)$ would have a unique vertical asymptote in which it would also change sign, and P would be positive on one side of the asymptote and negative on the other side). The evolution equation yielding expression 14 at steady state will be

$$dX/dt = Pg(X) - f(X) \quad (15)$$

To have at least two strictly positive roots, $g(X)$ must be at least of the second order in X . The simplest assumption is to consider

that P is involved as a catalyst in a trimolecular, autocatalytic step producing X:



To avoid having a trivial solution of X, we need also to assume that P is involved in the transformation of X into another substance B:



The corresponding rate equation for X will be

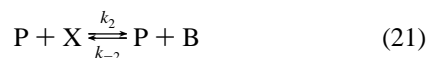
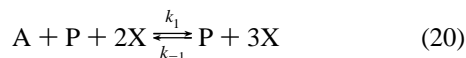
$$dX/dt = -k_{-1}X^2P + k_1APX - k_2PX + k_{-2}PB - f(X) = P(-k_{-1}X^2 + (k_1A - k_2)X + k_{-2}B) - f(X) \quad (18)$$

Therefore, in eq 15,

$$g(X) = -k_{-1}X^2 + (k_1A - k_2)X + k_{-2}B \quad (19)$$

A rapid examination of $g(X)$ leads to the conclusion that it cannot admit two positive solutions, according to the rule of Descartes for the coefficients: the term in X^2 will always be negative and the zero-order term is always positive, so that $g(X)$ admits at most a single positive real root.

Therefore, $g(X)$ must be a polynomial of at least order 3, and this means that, with only one concentration variable X (we assume that the system is open in such a manner that all other concentrations A, P, and B are kept constant), the autocatalytic reaction must be quadrimolecular:



The corresponding rate equation is

$$dX/dt = P(-k_{-1}X^3 + k_1AX^2 - k_2X + k_{-2}B) - f(X) \quad (22)$$

In this case $g(X)$ is a third-order polynomial in X:

$$g(X) = -k_{-1}X^3 + k_1AX^2 - k_2X + k_{-2}B \quad (23)$$

According to the rule of Descartes, this polynomial has either one or three real positive roots. Thus $h(X)$ given by eq 14 either has only one asymptote or three vertical asymptotes. In the first case, the system has either one stable steady state, or two stable steady states with hysteresis. In the second case, the multiplicity of vertical asymptotes gives rise to bistability with irreversible transitions of type 2.

To have the full expression for $h(X)$ we still need to define its numerator $f(X)$. Because $g(X)$ —and hence the steady-state equation for X—is already of the third degree in X, which is a necessary condition for bistability, the degree of $f(X)$ is not crucial for the occurrence of bistability or irreversible transitions. As seen from eq 15, $f(X)$ is a polynomial which is at least of first order in X and corresponds to reactions in which P is not involved. We choose the simplest case of a unimolecular reaction:



The full rate equation becomes

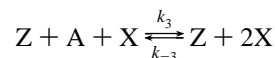
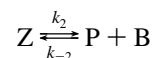
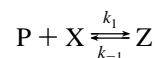
$$dX/dt = P(-k_{-1}X^3 + k_1AX^2 - k_2X + k_{-2}B) - k_3X + k_{-3}C \quad (25)$$

and $h(X)$ is

$$P = \frac{k_3X - k_{-3}C}{-k_{-1}X^3 + k_1AX^2 - k_2X + k_{-2}B} \quad (26)$$

We could carry on the detailed analysis of the model for the above mechanism including a tetramolecular step. For reasons of chemical plausibility, however, we prefer to demonstrate irreversible transitions of type 2 when we decompose the quadrimolecular step into a trimolecular step plus a bimolecular reaction and introduce to this end a second variable, Z. We will show in the following that in this way we retain the required analytic form for $h(X)$ at steady state.

The total reaction scheme for the model therefore is



The variables are X and Z; A, B, C, and P are concentrations which are controllable parameters. P can be thought of as an enzyme which transforms X into B, via the formation of complex Z; the latter, when complexed with a second molecule of X, can transform A into X.

For convenience, we shall refer to this model in the following as the *infinite limit point* (ILP) model, even if under different conditions it can also admit irreversible transitions of type 1, as shown further below.

Kinetic Equations. The rate equations governing the time evolution of the concentration variables in the model corresponding to reactions 27 are

$$\begin{aligned} dX/dt &= -k_1XP + k_{-1}Z + k_3ZAX - k_{-3}X^2Z - k_4X + k_{-4}C \\ dZ/dt &= k_1XP - (k_{-1} + k_2)Z + k_{-2}PB \end{aligned} \quad (28)$$

At equilibrium we have the following relations between the concentrations and the kinetic constants:

$$\begin{aligned} A &= \frac{k_{-3}k_{-4}}{k_3k_4} C = \frac{k_{-1}k_{-2}k_{-3}}{k_1k_2k_3} B \\ Z &= \frac{k_1k_3}{k_{-1}k_{-3}} PA \\ X &= \frac{k_3}{k_{-3}} A \end{aligned} \quad (29)$$

To simplify the analytical treatment, it is useful to rescale the

concentrations and time:

$$X = \frac{k_4}{k_1}x, \quad Z = \frac{k_4^2}{k_1 k_{-1}}z, \quad A = \frac{k_1 k_{-1}}{k_3 k_4}a, \quad B = \frac{k_4}{k_{-2}}b, \\ C = \frac{k_4^2}{k_1 k_{-4}}c, \quad P = \frac{k_4}{k_1}p, \quad t = \frac{1}{k_4}\tau \quad (30)$$

The system of eq 28 takes the form

$$\begin{aligned} dx/d\tau &= -xp + z + zax - C_1 x^2 z - x + c \\ dz/d\tau &= (xp - C_2 z + pb)C_3 \end{aligned} \quad (31)$$

where

$$C_1 = \frac{k_4^2 k_{-3}}{k_1^2 k_{-1}}, \quad C_2 = \frac{k_2}{k_{-1}} + 1, \quad C_3 = \frac{k_{-1}}{k_4}$$

The equilibrium relations (29) thus take the form

$$a = C_1 c = \frac{C_1}{C_2 - 1}b, \quad C_1 z = pa, \quad a = C_1 x \quad (32)$$

To obtain the steady-state solutions of system (31) we have to solve the following equations:

$$\begin{aligned} z &= \frac{p(x+b)}{C_2} \\ x^3 + \frac{C_1 b - a}{C_1}x^2 + \frac{p(C_2 - 1) + C_2 - pab}{pC_1}x - \frac{cC_2 + pb}{pC_1} &= 0 \end{aligned} \quad (33)$$

These equations are obviously satisfied at equilibrium where relations 32 hold. Expressing a and c as a function of b according to eq 32 and factoring out the equilibrium solution, we rewrite eq 33 as:

$$\left(x - \frac{b}{C_2 - 1}\right) \left(x^2 + bx + \frac{p(C_2 - 1) + C_2}{C_1 p}\right) = 0 \quad (34)$$

Since C_2 is always larger than unity, as shown by eq 31, we see that at equilibrium the system does not admit any other physically acceptable steady state. The phenomenon of bistability demonstrated below therefore occurs only far from thermodynamic equilibrium.

Irreversible Transitions of Type 2. For simplicity we consider, without loss of generality, the case where all kinetic constants are equal to unity. Then $C_1 = 1$ and $C_2 = 2$ and the steady-state equations (33) become

$$z = p(x+b)/2 \quad (35)$$

$$x^3 + (b-a)x^2 + \frac{p+2-pab}{p}x - \frac{2c+pb}{p} = 0 \quad (36)$$

As a function of a and b , for different values of p , the region of bistability $\Gamma(p, c)$ is determined by the conditions ensuring the existence of three real positive roots to eq 36:

$$b < a < \frac{p+2}{pb}, \quad q_1^3 + r_1^2 < 0 \quad (37)$$

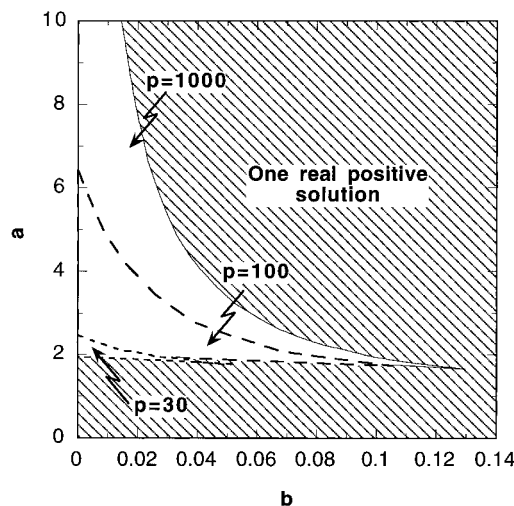


Figure 4. Domain of bistability in the infinite limit point (ILP) model. The domain (white region) was determined as a function of parameters a and b , for three values of p , using the program AUTO³⁴ applied to eq 36. Parameter c is equal to 2. In this and subsequent figures, all parameters and variables are dimensionless.

where q_1 and r_1 are given by the expressions

$$\begin{aligned} q_1 &= -\frac{1}{9}(b-a)^2 + \frac{1}{3}\frac{p+2-pab}{p} \\ r_1 &= \frac{1}{6}\frac{(b-a)(p+2-pab)}{p} + \frac{1}{2}\frac{2c+pb}{p} - \frac{1}{27}(b-a)^3 \end{aligned}$$

The domain of bistability is shown in Figure 4 for different values of p .

To determine the conditions in which bistability is accompanied by irreversible transitions of type 2, we express p as a function of x :

$$p = \frac{2(x-c)}{-x^3 + (a-b)x^2 - (1-ab)x + b} \quad (38)$$

This function will have three vertical asymptotes if its third-degree denominator has three positive real roots. This will occur when

$$b < a < 1/b, \quad q_2^3 + r_2^2 < 0 \quad (39)$$

where

$$\begin{aligned} q_2 &= -\frac{1}{9}(b-a)^2 + \frac{1}{3} - \frac{1}{3}ab \\ r_2 &= \frac{1}{6}(b-a)(1-ab) + \frac{1}{2}b - \frac{1}{27}(b-a)^3 \end{aligned}$$

The two conditions 39 are satisfied in the region shown in Figure 5 as a function of a and b . In this domain (referred to below as TI) we have irreversible transitions of type 2. This region is included as a subset in the union of all the regions $\Gamma(p, c)$ of bistability (see Figure 4) obtained under the variation of p and c :

$$TI \subset \bigcup_{p, c} \Gamma(p, c)$$

Furthermore, it can be proved that

$$TI = \lim_{p \rightarrow \infty} \Gamma(p, c)$$

Indeed, conditions 37 become, in the limit of $p \rightarrow \infty$, equivalent

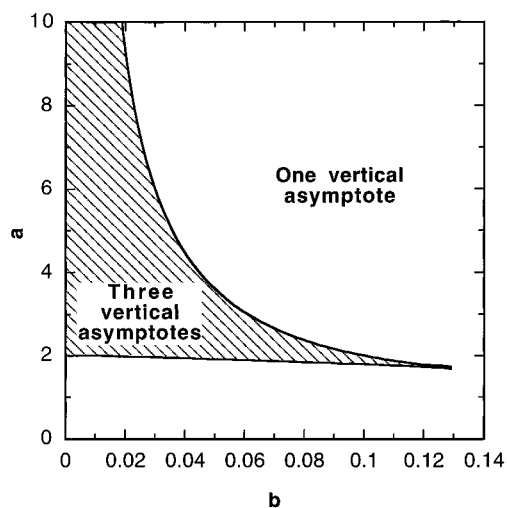


Figure 5. Domain of existence of three vertical asymptotes for function 38 (the existence of three such asymptotes ensures the existence of an infinite limit point). The domain was determined as a function of parameters a and b using conditions 39.

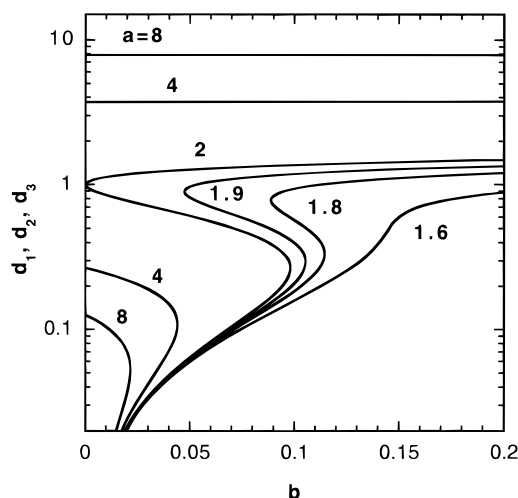


Figure 6. Roots of the denominator of function 38 determined as a function of parameters a and b by means of the program AUTO³⁴ applied to the denominator of eq 38. Each root corresponds to a vertical asymptote for function 38. The existence of three vertical asymptotes ensures the occurrence of an irreversible transition of type 2.

to conditions 39:

$$\lim_{p \rightarrow \infty} \frac{p+2}{pb} = \frac{1}{b}$$

$$\lim_{p \rightarrow \infty} (q_1^3 + r_1^2) = (q_2^3 + r_2^2) \quad (40)$$

Therefore, for $p \rightarrow \infty$, the fulfillment of conditions 37 for the existence of bistability ensures that the phenomenon is associated with an irreversible transition of type 2.

To further visualize the region of bistability with irreversible transitions of type 2, we show in Figure 6 the root(s) denoted d_i ($i = 1-3$) of the third-degree denominator of eq 38 as a function of b for different values of a . The system admits irreversible transitions when three solutions are present for a given value of b . This occurs when b is less than a critical value (see Figure 6 for $a > 2$) or comprised in a range bounded by two critical values (see for example the curve for $a = 1.8$).

Depending on the value of parameter c relative to the values of the three roots (d_1, d_2, d_3) of the denominator of eq 38, we obtain different possible shapes of p as a function of x , as illustrated in Figure 7A–D in which $d_1 = 0.126$, $d_2 = 0.559$, $d_3 = 1.135$ for $a = 1.9$ and $b = 0.08$. Shown successively in

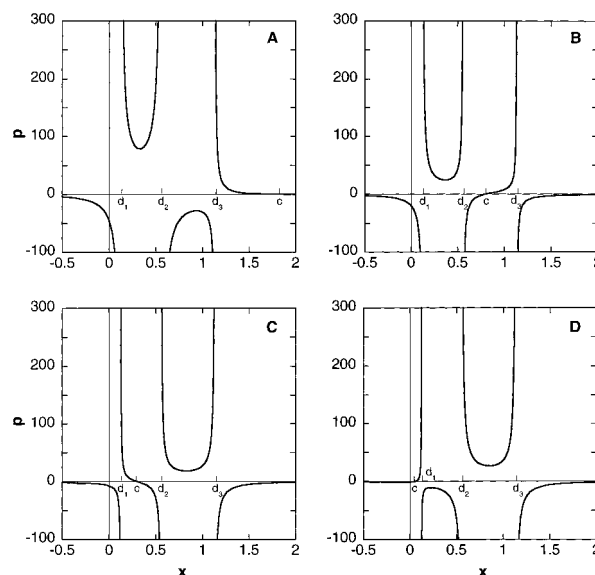


Figure 7. Different cases illustrating how function p given by eq 38 varies as a function of x , depending on the value of parameter c relative to the three roots d_1, d_2 , and d_3 of the denominator of the same function. The value of c is 1.8, 0.8, 0.3, and 0.06 for panels A to D, respectively. Moreover, $a = 1.9$ and $b = 0.08$. The corresponding modes of irreversible transition of type 2 are shown in Figure 8.

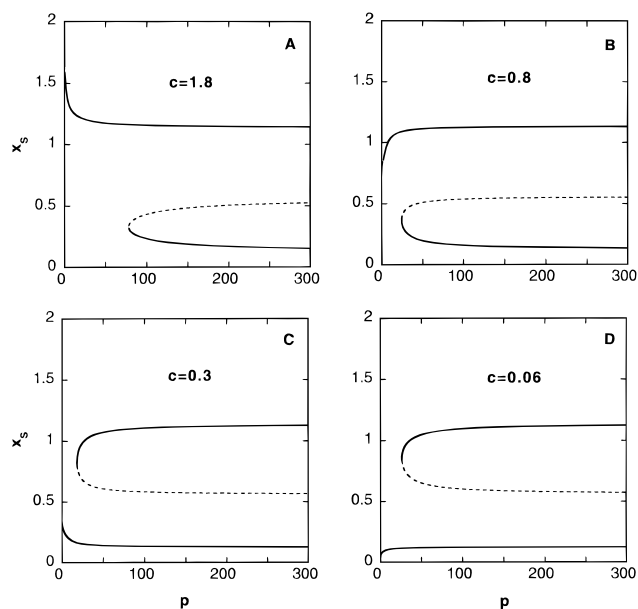


Figure 8. Different modes of irreversible transition of type 2 in the ILP model. The diagrams show the steady-state level of x as a function of parameter p in the different cases illustrated in Figure 7. The equilibrium state cannot be reached here since conditions 32 cannot be satisfied, given that $a \neq b$.

this figure are the cases $d_3 < c$ (Figure 7A), $d_2 < c < d_3$ (Figure 7B), $d_1 < c < d_2$ (Figure 7C), $c < d_1$ (Figure 7D). In Figure 8A–D, we show the corresponding variation of the steady-state concentration of x (denoted x_s) as a function of p . The four cases considered illustrate the different sorts of irreversible transition of type 2 observed in this system.

By decreasing c continuously from a sufficiently large initial value, we pass through the intermediate situations in which c becomes equal to one of the three roots d_3, d_2 , and d_1 . The bifurcation diagrams which correspond to these special situations are shown in Figure 9A–C. Particularly interesting is the case shown in Figure 9B for $c = d_2$; this case corresponds to a pitchfork bifurcation. Therefore, the situations intermediate between those shown in Figures 8, B and C, can be seen as perturbations of the pitchfork bifurcation, in terms of the

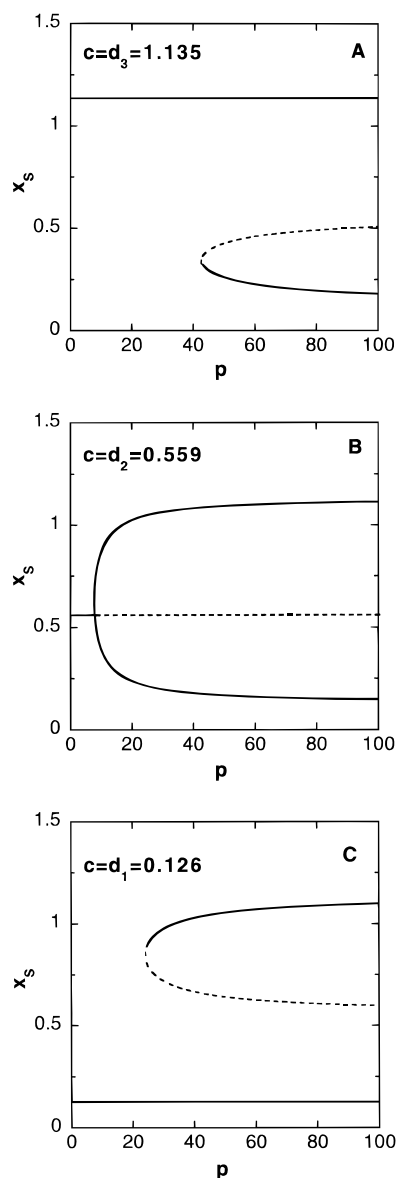


Figure 9. Steady-state level of x as a function of p when c is equal to one of the three roots (d_1 , d_2 , d_3) of the denominator of function 38. The case shown in (B) corresponds to a pitchfork bifurcation. The situation considered is that of Figure 7.

parameter $\epsilon = c - d_2$. This is illustrated in Figure 10 where the pitchfork bifurcation obtained for $\epsilon = 0$ is shown (Figure 10B), together with the bifurcation diagrams obtained for slightly positive (Figure 10A) or negative (Figure 10C) values of ϵ .

Transitions between Monostability and Different Modes of Bistability. So far we have studied the behavior of the model as a function of parameter c for values of a and b such that function $p(x)$ given by eq 38 admits three vertical asymptotes. This situation corresponds to bistability without hysteresis, with an irreversible transition of type 2. It is possible to vary one parameter of the model (e.g. a or b) to pass from such a situation to a situation in which the denominator of $p(x)$ in eq 38 admits a single positive real root, which corresponds to monostability, or bistability with hysteresis. Such transitions are illustrated in Figure 11A–D (established for $a = 1.9$ and $c = 1.2$) where, in agreement with the results of Figure 6 (see curve for $a = 1.9$) on the number of roots of the denominator of $p(x)$ in eq 38, we successively observe as a function of b monostability, bistability with hysteresis, bistability without hysteresis, and monostability again as parameter b is increased progressively.

The successive transformations of the bifurcation diagram as a function of b shown in Figure 11 are not general, however,

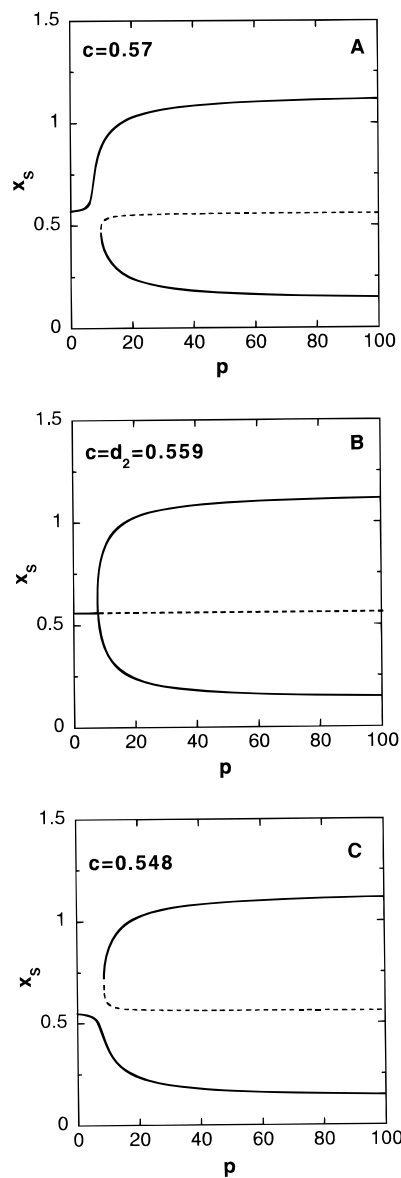


Figure 10. Perturbation of the pitchfork bifurcation obtained for $c = d_2$ (B), when c is slightly larger (A) or less (C) than d_2 . The situation is that of Figure 7.

as they depend also on the values of parameters a and c . For the value $a = 4$, for example, the denominator of eq 38 has three real positive roots for sufficiently small values of b , in contrast to the situation observed for $a = 1.9$ for which a single root exists at low values of b (see Figure 6): for $a = 4$, upon increasing b , we start from situation of Figure 11C (bistability with irreversible transition of type 2) and can only pass to the situation of Figure 11D (monostability), but we cannot have bistability with hysteresis, which can occur for $a = 1.9$ as shown in Figure 11B.

The influence of parameter c has been discussed above for values of a and b such that $p(x)$ admits three vertical asymptotes (see Figures 7–9). For other values of the latter parameters, the value of c will affect the possibility to pass from bistability with hysteresis to monostability. Thus for $c = 2$, it can be shown that the system cannot pass from bistability with hysteresis as in Figure 11B to monostability as in Figure 11A as a function of p by lowering b : the system can show monostability over the whole range of p values only for high values of b .

Irreversible Transitions of Type 1 in the ILP Model. So far we have investigated the occurrence of bistability with irreversible transitions of type 2 in the infinite limit point model.

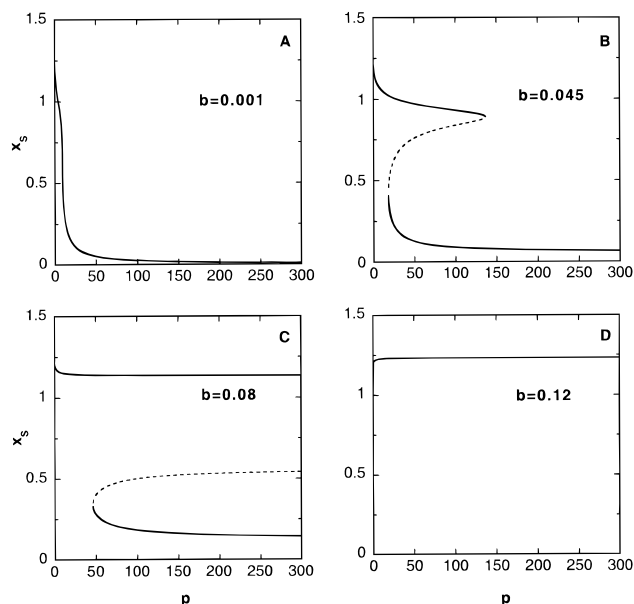


Figure 11. Steady-state level of x as a function of parameter p in the ILP model for increasing values of b . The diagrams show the passage from monostability (A) to bistability with (B) or without (C) hysteresis, and finally to monostability (D). The situation in C corresponds to an irreversible transition of type 2. Parameter values are $a = 1.9$, $c = 1.2$.

Irreversible transitions of type 1 can also occur in this model, when the lower limit value of a control parameter goes into an inaccessible domain of negative values.

To observe irreversible transitions of this type as a function of parameter p would require that three real positive values of x correspond to the value $p = 0$ in eq 38 for $p(x)$. We see from that equation that this is never possible, because a single positive value ($x = c$) corresponds to $p = 0$. Irreversible transitions of type 1 can nevertheless occur as a function of other parameters of the model. To see this, let us express a , b , and c as a function of x at steady state, from eq 36:

$$a = \frac{px^3 + pbx^2 + (p+2)x - (pb+2c)}{p(x^2+xb)} \quad (41a)$$

$$b = \frac{px^3 - pax^2 + (p+2)x - 2c}{p(-x^2+ax+1)} \quad (41b)$$

$$c = [px^3 + p(b-a)x^2 + (p+2-pab)x - pb]/2 \quad (41c)$$

Again, to observe the phenomenon as a function of one of these three parameters we need to obtain three real positive roots of x when the corresponding parameter becomes nil. Application of the rule of Descartes shows that this will never be possible as a function of parameter a . In contrast, the possibility of an irreversible transition of type 1 exists as a function of both parameters b and c . The occurrence of irreversible transitions with a negative limit point is illustrated as a function of b and c in Figures 12 and 13, respectively. The position of the left limit point in Figure 12 can be brought from negative to positive values by changing parameter a , while a similar effect can be brought about by variation of parameter p in Figure 13.

It is not possible to combine in this model the two types of irreversible transition. Equations 41a–41c show indeed that none of the curves yielding a or b or c as a function of x can admit three distinct asymptotes.

Effect of Irreversible Chemical Steps. Having analyzed the occurrence of irreversible transitions in the two models when all the chemical steps are reversible, the question arises as to what the behavior of the systems becomes when all or part of

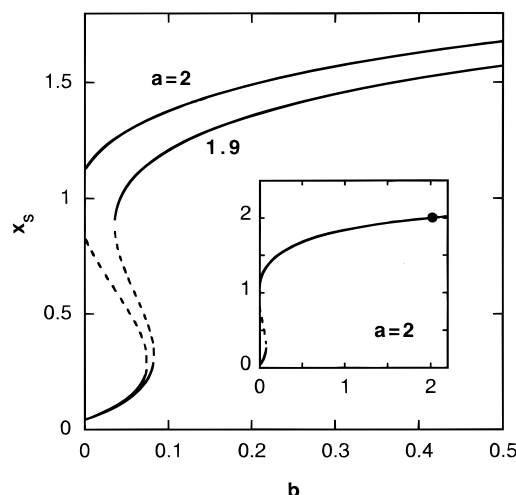


Figure 12. Bistability with or without hysteresis in the ILP model, as a function of parameter b . An irreversible transition of type 1 is shown for $a = 2$. Parameter values are $c = 2$, $p = 100$. The equilibrium state for $a = 2$ corresponds to $b = 2$ since at equilibrium $a = b = c = x$ (see eqs 32); thus the equilibrium point (shown by a black dot in the inset) lies on the upper branch of steady states on this curve. The equilibrium state cannot be shown for $a = 1.9$ since $a \neq c$.

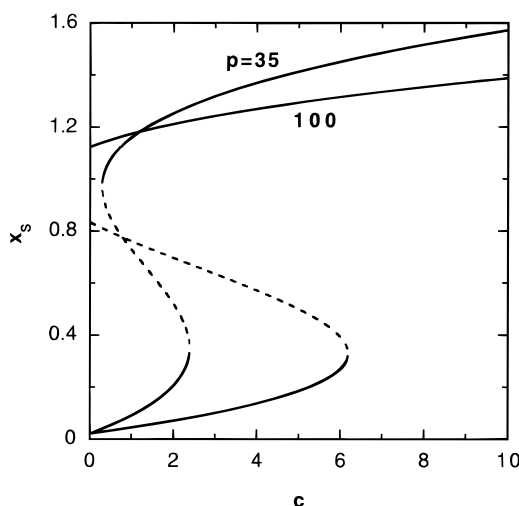


Figure 13. Bistability with or without hysteresis in the ILP model, as a function of parameter c . The curve for $p = 100$ shows an irreversible transition of type 1. Parameter values are $a = 2$, $b = 0.02$. In contrast to the situation in Figure 12, the equilibrium point cannot be shown here since $a \neq b$ (see legend to Figure 12).

the reverse kinetic constants are taken equal to zero. In the Schlögl model, irreversible transitions of type 1 disappear when $k_{-1} = 0$ since the right-hand part of eq 2 is then only of the second degree. When $k_{-2} = 0$, the irreversible transition of type 1 is not observed. The lower steady state is then always null and the right limit point goes to infinity as a function of parameter a which depends on k_{-1} (see eqs 6 and 7). Thus, for this particular value of k_{-2} , the middle (unstable) steady-state tends toward the lower, null steady state as a increases, giving rise to a particular transition of type 2.

In the ILP model, examination of eq 28 shows that in order to have the possibility of bistable behavior, it is necessary that k_{-3} be different from zero: otherwise the resulting steady-state equation for X will be of the second order. Thus when all the chemical steps are irreversible, the model does not retain the nonlinearities in the kinetic equations necessary to display bistability. If all the reverse kinetic constants, except k_{-3} , are null, we can observe bistability and irreversible transitions of type 2, but one of the stable steady-state solutions is always zero (here, in contrast to what is observed for the Schlögl model,

the middle branch of steady states possesses an asymptote which differs from the abscissa axis). In fact, we have the same situation if only k_{-1} and k_{-4} , or k_{-2} and k_{-4} are equal to zero with $k_{-3} \neq 0$. In all the other cases we have bistability and irreversible transitions of type 2 with all the steady-state solutions different from zero.

For the occurrence of irreversible transitions of type 1, it is again required that k_{-3} be different from zero, for the same reasons explained above. Moreover, the parameters b or c will be present in the kinetic eqs 28 if k_{-2} and k_{-4} are different from zero, respectively. When k_{-2} and k_{-3} are different from zero, the ILP model still exhibits, as a function of b , irreversible transitions of type 1, but one steady state solution is always nil. When k_{-4} and k_{-3} are different from zero, we have irreversible transitions of type 1 as a function of c , with the low branch of steady-state passing through $x = 0$ in $c = 0$.

Discussion

Bistability is often associated with the capability of a system to switch back and forth between two distinct branches of stable steady states upon the reversible variation of a control parameter in a range bounded by two limit points. Hysteresis results from the fact that the values of the control parameter at which the transitions occur, which correspond to the two limit points, are different. Here we focused on the situations in which one of the limit points becomes inaccessible to the system. In such cases, the system is capable of jumping from one branch of steady states to the other, without being able to undergo the reverse transition. The unique transition between the two branches of stable steady states has thus become irreversible.²⁰ Such a phenomenon could be of importance for the control of chemical reactors as well as for the dynamics of biological systems (see below). Several models showing such irreversible transitions have been proposed,^{19–26} but the kinetics of these systems is of a nonpolynomial nature and is based on the assumption of irreversible chemical steps. Therefore, the question arises as to whether irreversible transitions may occur in chemical systems consisting of a sequence of fully reversible steps described by polynomial kinetics.

In order to clarify the conditions in which irreversible transitions occur when one of the limit points of a bistable chemical system disappears, we have examined two theoretical models admitting a coexistence between two stable steady states. The two models are based on a sequence of reversible chemical reactions. This analysis leads us to suggest a classification of irreversible transitions between two types, depending on whether a limit point goes into a region of finite values not accessible to the system (irreversible transition of type 1) or to infinity (irreversible transition of type 2). In the first model, proposed by Schlögl,^{1–3,5} we showed that irreversible transitions of type 1 but not of type 2 are possible. In the second model, constructed to illustrate the phenomenon and referred to as ILP (infinite limit point) model, irreversible transitions of type 2 but also of type 1 are obtained.

To display an irreversible transition of type 1, the model of Schlögl, which contains two steps, including an autocatalytic trimolecular one, was not modified. This model was previously studied for bistability associated with hysteresis. We showed here that bistability without hysteresis can occur in this model and obtained the conditions on the parameters for which one of the limit points goes into a region of negative values corresponding to a physically inaccessible range of the control parameters.

The second model is made up of four steps. It also contains a trimolecular step for the autocatalytic production of an intermediate X, as well as the formation of a bimolecular

complex containing X, which is also involved in the trimolecular step. The coupling of these two processes further reinforces the global autocatalytic nature of this system. We showed that in this model one of the two limit points can go to infinity. The other type of irreversible transition due to the passage of a limit point into a range of finite but inaccessible values can also be observed. Thus this model can display a wide range of behavior, including monostability, bistability with hysteresis, and bistability without hysteresis due to the occurrence of an irreversible transition of either type 1 or 2.

In both models thermodynamic equilibrium corresponds to a point located outside the domain of bistability. Thus the phenomenon of irreversible transitions is possible in fully reversible chemical systems, under nonequilibrium conditions. The question arises as to how the system can evolve to equilibrium if it starts from a branch of steady states (apparently) separated from the branch containing the equilibrium state by the absence of a limit point that would allow the transition between the two branches as a function of a control parameter. In other words, the equilibrium state should be connected to any steady state by continuously varying the control parameter(s). When the equilibrium and steady-state branches are disconnected due to an irreversible transition of type 1 or 2, such a continuous passage requires the concomitant variation of more than one control parameter.

To our knowledge, the present study is the first to address the occurrence of irreversible transitions in fully reversible chemical reaction models. This allows us not only to determine the location of the equilibrium state with respect to the range in which such transitions occur, but it also permits us to determine the effect of the reverse reactions on the occurrence of the phenomenon. As indicated in the preceding section, neglecting some of the reverse steps in the two models suppresses the irreversible transitions, while neglecting some other reverse steps has no effect in this regard. The present study appears to validate the results obtained in models based on partially irreversible kinetic schemes.^{19–27} We have not investigated whether the quasi-steady-state hypotheses which were often made in these studies to reduce the number of variables influence the occurrence of irreversible transitions. The fact that the phenomenon is obtained here in the absence of such hypotheses nevertheless indicates that it is probably not a result of this simplifying procedure.

Irreversible transitions between multiple steady states are not limited to chemical reaction systems. Thus an "incomplete hysteresis phenomenon" associated with an irreversible transition of type 2 corresponding to an infinite limit point has been described in a two-parameter, one-dimensional map obtained from a nonlinear model proposed for an optical bistable device.³³

To demonstrate experimentally irreversible transitions of type 1 as a function of a particular control parameter λ , a transition from one branch of steady state to another branch should first be demonstrated when the value of λ exceeds (goes below) a critical value. Then, the value of λ should be decreased (increased). If the system returns to the original branch of steady states at a different critical value of λ a hysteresis cycle is obtained (see Figure 1A). However, if the value of the control parameter cannot be changed any further for some physical reason (for example, positivity of rate constants or chemical concentrations) before the transition has occurred, then the system is blocked in that branch of steady states and an irreversible transition of type 1 is demonstrated (Figure 1B). However, the original state can be recovered by changing the value of some other control parameter of the system or by applying a suprathreshold perturbation in the concentration of a chemical intermediate (e.g. the addition of a certain amount

of variable x in Figure 1B). The threshold corresponds to the intermediate, unstable steady state at the given value of λ .

A similar procedure should be followed to reveal the occurrence of an irreversible transition of type 2. Here, it is impossible to reach one of the limit points because it has gone to infinity (Figure 1C). To distinguish such a situation from a true hysteresis cycle with a limit point far away (but not displaced to infinity), one could determine the critical perturbation needed to induce the passage from the lower to the upper branch of steady states. While in the case of a full hysteresis cycle this threshold should decrease as parameter λ approaches the limit point (see Figure 1A), in the case of an irreversible transition of type 2 the threshold should reach a finite, constant value or should increase as λ increases, because the middle and lower branches of steady states possess distinct asymptotes (Figure 1C).

Bistability phenomena are by now a well-known manifestation of nonlinear kinetics in chemical systems. Hysteresis behavior associated with bistability has been described in a number of theoretical or experimental studies, both in chemical^{1–9} and biochemical^{10–18} systems. Less attention has been devoted to the occurrence of irreversible transitions resulting in bistability without hysteresis. The phenomenon has been studied in detail by Gray et al.²⁶ in combustion systems, and by Hervagault et al.^{24,25,27–31} who focused on cyclical enzymatic systems governed by (partially) irreversible kinetic laws and investigated experimentally the disappearance of limit points in such bistable systems. Also based on partially irreversible kinetics, other theoretical models of biological interest which display irreversible transitions have been proposed for genetic regulation,¹⁹ membrane permeability changes coupled to biochemical reactions,²⁰ a glycolytic enzyme system,^{21,32} the isocitrate dehydrogenase reaction,³⁵ autophosphorylation of protein kinases,²² cellular dynamics involving receptor desensitization (Schepers, H.; Goldbeter, A., manuscript in preparation), and immune response.²³ It therefore appears that the phenomenon of bistability without hysteresis might be of deep physiological significance in view of its potential role in differentiation and in the storage of information in a variety of biological contexts.

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References and Notes

- (1) Schlögl, F. *Z. Phys.* **1971**, *248*, 446.
- (2) Schlögl, F. *Z. Phys.* **1972**, *253*, 147.
- (3) Schlögl, F. In *Cooperative Phenomena in Multi-Component Systems*; Haken, H., Ed.; B. G. Teubner: Stuttgart, 1973; p 21.
- (4) Geiseler, W.; Föllner, H. H. *Biophys. Chem.* **1977**, *6*, 107.
- (5) Nicolis, G.; Prigogine, I. *Self-Organization in Nonequilibrium Systems*; Wiley-Interscience: New York, 1977.
- (6) Orbán, M.; Dateo, C.; De Kepper, P.; Epstein, I. R. *J. Am. Chem. Soc.* **1982**, *104*, 5911.
- (7) Escher, C.; Ross, J. *J. Chem. Phys.* **1983**, *79*, 3773.
- (8) Epstein, I. R. In *Chemical Instabilities*; Nicolis, G., Baras, F., Eds.; D. Reidel: Dordrecht, 1984; p 3.
- (9) (a) Ganapathisubramanian, N.; Showalter, K. *J. Chem. Phys.* **1984**, *80*, 4177. (b) Gray, P.; Scott, S. K. *Chemical Oscillations and Instabilities*; Clarendon Press: Oxford, UK, 1994.
- (10) Degn, H. *Nature* **1968**, *217*, 1047.
- (11) Edelstein, B. B. *J. Theor. Biol.* **1970**, *29*, 57.
- (12) Naparstek, A.; Romette, J. L.; Kernevez, J. P.; Thomas, D. *Nature* **1974**, *249*, 490.
- (13) Eschrich, K.; Schellenberger, W.; Hofmann, E. *Arch. Biochem. Biophys.* **1980**, *205*, 114.
- (14) Tyson, J. J.; Novak, B.; Chen, K.; Val, J. In *Progress in Cell Cycle Research*; Meijer, L., Guidet, S., Tung, H. J. L., Eds.; Plenum Press: New York, 1995; Vol. 1, p 1.
- (15) Thron, C. D. *Biophys. Chem.* **1996**, *57*, 239.
- (16) Laurent, M. *Biochem. J.* **1996**, *318*, 35.
- (17) Kacser, H.; Small, J. R. *J. Theor. Biol.* **1996**, *182*, 209.
- (18) Goldbeter, A. *Biochemical Oscillations and Cellular Rhythms: The Molecular Bases of Periodic and Chaotic Behaviour*; Cambridge University Press: Cambridge, UK, 1996.
- (19) Babloyantz, A.; Nicolis, G. *J. Theor. Biol.* **1972**, *34*, 185.
- (20) Hahn, H.-S.; Ortoleva, P. J.; Ross, J. *J. Theor. Biol.* **1973**, *41*, 503.
- (21) Rapoport, T. A.; Heinrich, R. *BioSystems* **1975**, *7*, 120.
- (22) Lisman, J. E. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 3055.
- (23) Kaufman, M.; Thomas, R. *J. Theor. Biol.* **1987**, *129*, 141.
- (24) Hervagault, J. F.; Canu, S. *J. Theor. Biol.* **1987**, *127*, 439.
- (25) Hervagault, J. F.; Cimino, A. *J. Theor. Biol.* **1989**, *140*, 399.
- (26) Gray, B. F.; Merkin, J. H.; Wake, G. C. *Math. Comput. Modeling* **1991**, *15*, 25.
- (27) Hervagault, J. F.; Schellenberger, W. *J. Biol. Syst.* **1993**, *1*, 375.
- (28) Coevoet, M. A.; Hervagault, J. F. *J. Biol. Syst.*, in press.
- (29) Cimino, A.; Hervagault, J. F. *FEBS Lett.* **1990**, *263*, 199.
- (30) Schellenberger, W.; Hervagault, J. F. *Eur. J. Biochem.* **1991**, *195*, 109.
- (31) Coevoet, M. A.; Hervagault, J. F. *Biochem. Biophys. Res. Commun.* **1997**, *234*, 162.
- (32) Frenzel, J.; Schellenberger, W.; Eschrich, K. *Biol. Chem. Hoppe-Seyler* **1995**, *376*, 17.
- (33) Mandel, P.; Kapral, R. *Opt. Comm.* **1983**, *47*, 151.
- (34) Doedel, E. J. *Congr. Num.* **1981**, *30*, 265.
- (35) Guidi, G. M.; Carlier, M. F.; Goldbeter, A. *Biophys. J.*, in press.