# Bistability without Hysteresis in Chemical Reaction Systems: The Case of Nonconnected Branches of Coexisting Steady States

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*Received: May 27, 1998; In Final Form: July 14, 1998*

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. In a previous publication (Guidi, G.; Goldbeter, A. *J. Phys. Chem. A* **1997**, *101*, 9367) we focused on the cases where one of the limit points becomes inaccessible or goes to infinity. Under such conditions it becomes impossible to achieve the transitions between the two branches of stable steady states as a result of variation of a single parameter: bistability ceases to be associated with hysteresis. We referred to these two cases as irreversible transitions of type 1 or type 2, respectively. To study in detail the conditions under which such irreversible transitions between multiple steady states occur in chemical systems, two models based on fully reversible chemical steps were considered. The first model, due to Schlögl, was 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 was proposed to illustrate the case of irreversible transitions of type 2 in which a limit point goes to infinity. Here, by fusing these two models, we construct a hybrid model to analyze the conditions in which irreversible transitions of types 1 and 2 both occur as a function of a given control parameter. Then bistability still exists, but the branches of coexisting steady states cease to be connected so that the transitions between the two stable steady states can no longer be achieved, regardless of the direction of variation in the control parameter. Such transitions might only result from a change in some other control parameter or from chemical perturbation.

## Introduction

Besides oscillatory behavior, the coexistence between two stable steady states, referred to as bistability, is one of the most conspicuous consequences of nonlinearity in chemical kinetics. The phenomenon is illustrated by a large number of experimental and theoretical studies in chemical[1−8] and biochemical[9−18] systems. When a parameter $\lambda$ is continuously increased, it is often observed (see Figure 1A) that the system jumps from one branch of stable steady states to another branch at a limit point associated with a critical value $\lambda_2$; when the parameter is then reduced, the system jumps back to the original branch at a different limit point associated with a value $\lambda_1$ of the control parameter. Such a phenomenon of *hysteresis* is often associated with bistability.

The association of bistability with hysteresis is, however, by no means ineluctable. 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.[19−27] 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. Then 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). We have referred to these two situations as irreversible transitions of types 1 and 2, respectively.

If the two limit points are out of the system's reach, the branches of coexisting steady states cease to be connected (see Figure 1D). As a consequence, the system will not be capable of switching in any direction between these branches upon continuously varying the control parameter.[28,29] 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 $\lambda_2$ and $\lambda_3$ in Figure 1E) coalesce. In this case, however, 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. Isolas have been found both experimentally and theoretically in chemical systems[7,8] and in biochemical models.[17]

In a previous article[30] we investigated the conditions under which irreversible transitions of type 1 or type 2 occur in chemical reaction models based on fully reversible steps. Here, we focus on the occurrence of nonconnected branches of coexisting steady states in such systems. We shall not consider here the case of isolas, since irreversible transitions may occur under such conditions (since one branch of stable steady states remains connected with the unstable branch). Thus, we shall restrict our investigation to the case depicted in Figure 1D where no transition can occur upon varying the control parameter. The interest of this phenomenon lies in its possible physiological significance. As a system passes from the situation of hysteresis (Figure 1A) to a situation of nonconnected branches (Figure

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S1089-5639(98)02394-9 CCC: $15.00 
Published on Web 09/15/1998

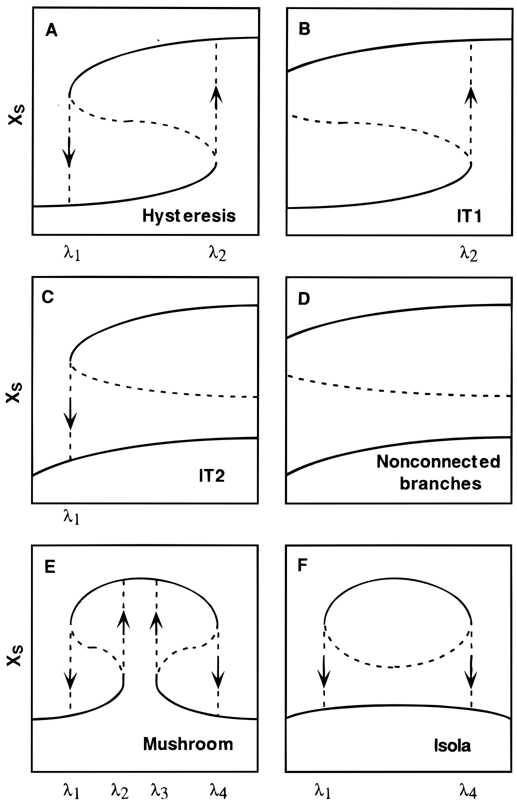


**Figure 1.** Different modes of bistability (see text). (A) Bistability with hysteresis. The two limit points are located in $\lambda_1$, $\lambda_2$. Panels B–D illustrate various cases of bistability without hysteresis. (B) Irreversible transition of type 1, in which the left limit point has moved toward an inaccessible domain. (C) Irreversible transition of type 2: the right limit point has moved toward infinity. (D) Nonconnected branches of steady states where the left limit point has become inaccessible while the right limit point has gone to infinity. Analyzing the conditions for the occurrence of such a situation is at the core of the present work. (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.

1D), the irreversible nature of the evolution would be even stronger than in the cases illustrated in part B or part C of Figure 1, where a transition between the two branches of steady states can still occur in a single direction. The situation of nonconnected branches could lead to the irreversible trapping of the system on one or the other branch of stable steady states (depending on the system's history). In a manner different from the irreversible transitions of type 1 or type 2, such a situation could play a role in memory and differentiation.

Theoretical studies of irreversible transitions in bistable systems have been devoted so far to models governed at least partly by irreversible kinetic laws.[19−27] The case of the loss of the two limit points has been considered theoretically by Hervagault and Schellenberger[28] and studied experimentally in a biochemical reaction system.[29] To see whether the phenomenon can occur in a fully reversible chemical reaction system, we analyze the conditions under which nonconnected branches of coexisting steady states occur in a simple theoretical model based on fully reversible kinetic steps, for which kinetic equations are derived without resorting to any quasi-steady-state assumption.

The model proposed for nonconnected branches of coexisting steady states is of a hybrid nature, since it is obtained by fusing the two models previously analyzed for irreversible transitions of type 1 or type 2. Thus, to the model recently constructed to illustrate the case where one of the limit points goes to infinity, which corresponds to the irreversible transition of type 2 shown in Figure 1C, we add a reaction step borrowed from the bistability model proposed by Schlögl,[1] which ensures that the same system admits an irreversible transition of type 1 depicted in Figure 1B. In such a way the two branches of stable steady states admitted by the model cease to be connected with the unstable branch. The equilibrium state in this model is located outside the region of bistability. We analyze in detail the conditions for the occurrence of nonconnected branches of coexisting steady states and also show that the model may admit more complex configurations of stable and unstable steady states, such as a succession of irreversible transitions of type 1 or type 2 as a function of a given control parameter.

## Model for Nonconnected Branches of Coexisting Steady States

Our strategy in constructing a model for nonconnected branches of coexisting steady states was to use the reversible chemical model that shows an irreversible transition of type 2 (this irreversible transition thus originates from the shifting of a limit point to infinity) and to add to this model (referred to as the *infinite limit point* or ILP model) a step capable of giving rise to an irreversible transition of type 1, in which the other limit point associated with bistability goes into a physically forbidden region of negative values of the control parameter.

In our previous analysis,[30] we had shown that irreversible transitions of type 1 can occur in the model proposed by Schlögl for bistability. This model consists of the following steps:[1]

$$A + 2X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 3X \tag{1a}$$

$$X \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} B \tag{1b}$$

where the concentrations of reactants A and B are kept constant. The ILP model considered for irreversible transitions of type 2 consisted of the following steps:[30]

$$P + X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Z \tag{2a}$$

$$Z \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} P + B \tag{2b}$$

$$Z + A + X \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} Z + 2X \tag{2c}$$

$$X \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} C \tag{2d}$$

in which the concentrations of A, B, C, and P are kept constant. We have shown[30] that irreversible transitions of type 1 can also occur in this model. We showed, however, that it is not possible to observe both types of irreversible transitions as a function of a single control parameter. Finding such a situation is precisely the purpose of the present paper.

To realize a hybrid model capable of displaying irreversible transitions of the two types as a function of a single control parameter, we add the autocatalytic step (reaction 1a) from the Schlögl model to the ILP model. The full reaction scheme for the hybrid model, therefore, is

$$\mathrm{P} + \mathrm{X} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{Z} \quad (3a)$$

$$\mathrm{Z} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathrm{P} + \mathrm{B} \quad (3b)$$

$$\mathrm{Z} + \mathrm{A} + \mathrm{X} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \mathrm{Z} + 2\mathrm{X} \quad (3c)$$

$$\mathrm{X} \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} \mathrm{C} \quad (3d)$$

$$\mathrm{D} + 2\mathrm{X} \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} 3\mathrm{X} \quad (3e)$$

The variables are $X$ and $Z$; $A$, $B$, $C$, $D$, and $P$ are concentrations that are controllable parameters. It should be noted that the second step of the Schlögl model is also present in the hybrid model in the form of step 3d, which was also part of the ILP model. As will become clear later, the strategy followed to obtain nonconnected branches of coexisting steady states in the hybrid model requires that step 3e does not involve reactant P, which is the control parameter as a function of which bistability will be determined.

The kinetic equations governing the time evolution of variables $X$ and $Z$ are

$$\frac{\mathrm{d}X}{\mathrm{d}t} = -k_1XP + k_{-1}Z + k_3ZAX - k_{-3}X^2Z - k_4X + k_{-4}C + k_5DX^2 - k_{-5}X^3 \quad (4a)$$

$$\frac{\mathrm{d}Z}{\mathrm{d}t} = k_1XP - (k_{-1} + k_2)Z + k_{-2}PB \quad (4b)$$

With the scaling,

$$X = \frac{k_4}{k_1}x; \quad Z = \frac{k_4^{\,2}}{k_1k_{-1}}z; \quad A = \frac{k_1k_{-1}}{k_3k_4}a; \quad B = \frac{k_4}{k_{-2}}b; \quad C = \frac{k_4^{\,2}}{k_1k_{-4}}c; \quad D = \frac{k_1}{k_5}d; \quad P = \frac{k_4}{k_1}p; \quad t = \frac{1}{k_4}\tau \quad (5)$$

where all lower case letters denote dimensionless quantities, and by introduction of the dimensionless parameters,

$$C_1 = \frac{k_4^{\,2}k_{-3}}{k_1^{\,2}k_{-1}}; \quad C_2 = \frac{k_2}{k_{-1}} + 1; \quad C_3 = \frac{k_{-1}}{k_4}; \quad C_4 = \frac{k_{-5}k_4}{k_1^{\,2}} \quad (6)$$

kinetic eqs 4a and 4b become

$$\frac{\mathrm{d}x}{\mathrm{d}\tau} = -xp + z + zax - C_1x^2z - x + c + dx^2 - C_4x^3$$

$$\frac{\mathrm{d}z}{\mathrm{d}\tau} = C_3(xp - C_2z + pb) \quad (7)$$

As shown in the appendix section, at thermodynamic equilibrium, the system admits a unique solution.

## Irreversible Transitions of Types 1 and 2 and the Origin of Nonconnected Branches of Coexisting Steady States

**Steady-State Equations for the Hybrid Model.** At steady state the following relations hold:

$$z = \frac{p(x + b)}{C_2}$$

$$x^3 + \frac{C_1pb - pa - C_2d}{C_2C_4 + C_1p}x^2 + \frac{p(C_2 - 1) + C_2 - pab}{C_2C_4 + C_1p}x - \frac{cC_2 + pb}{C_2C_4 + C_1p} = 0 \quad (8)$$

For simplicity we consider, without loss of generality, the case where all kinetic constants are equal to unity. Then $C_1 = 1$, $C_2 = 2$, $C_3 = 1$, $C_4 = 1$, and the steady-state equations become

$$z = \frac{p(x + b)}{2}$$

$$x^3 + \frac{pb - pa - 2d}{2 + p}x^2 + \frac{p + 2 - pab}{2 + p}x - \frac{2c + pb}{2 + p} = 0 \quad (9)$$

It will be convenient to express the last equation in the form of a function $p(x)$:

$$p = \frac{2(x^3 - dx^2 + x - c)}{-x^3 + (a - b)x^2 - (1 - ab)x + b} \quad (10)$$

This function will have three vertical asymptotes if its third-degree denominator has three positive real roots. This will allow for the occurrence of an irreversible transition of type 2. To obtain an irreversible transition of type 1, the numerator of this function must have three positive real roots, since this will ensure that the limit point that bounds the bistable domain on the left goes to negative values. Combining the conditions for an irreversible transition of type 1 with those corresponding to an irreversible transition of type 2 allows the occurrence of three nonconnected branches of steady states.

**From Bistability with Hysteresis to Nonconnected Branches of Steady States.** We first wish to show how the situation of nonconnected branches of steady states arises in the hybrid model, starting from a situation where bistability is accompanied by full hysteresis. In Figure 2, the top panels correspond to such a situation. The left panel shows the loci of the limit points LP1 and LP2 in the $p-c$ parameter plane. These loci are determined by imposing the mathematical conditions on $p$ and $c$ for which the third-degree polynomial (eq 8) in $x$ admits three real, positive roots. In the region between the two loci, three steady states occur, two of which are stable. The dashed horizontal line in the $p-c$ plane illustrates the behavior, shown in the right panel, at a fixed value of $b = 0.045$ and of $c = 0.198$, as a function of $p$. The fact that the horizontal line intersects with the loci of LP1 and LP2 means that the two limit points exist for this value of $c$ so that a full hysteresis is then observed as a function of $p$.

In the middle panels, obtained for the same value of $b$ but for $c = 0.129$, the horizontal line in the $p-c$ parameter plane intersects only with the locus of LP2. As shown in the corresponding right panel, the disappearance of LP1 is associated with a situation that allows an irreversible transition of type 1. If the value of $b$ is then changed to 0.08, without changing the value of $c$ (this change in $b$ affects the position of the loci of LP1 and LP2), the horizontal line does not intersect anymore with either the locus of LP1 or with that of LP2 (lower left panel). This situation introduces an irreversible transition of type 2, in addition to the transition of type 1 noted in the previous case, so that the two branches of stable steady states are not connected anymore with the unstable branch (lower right panel).

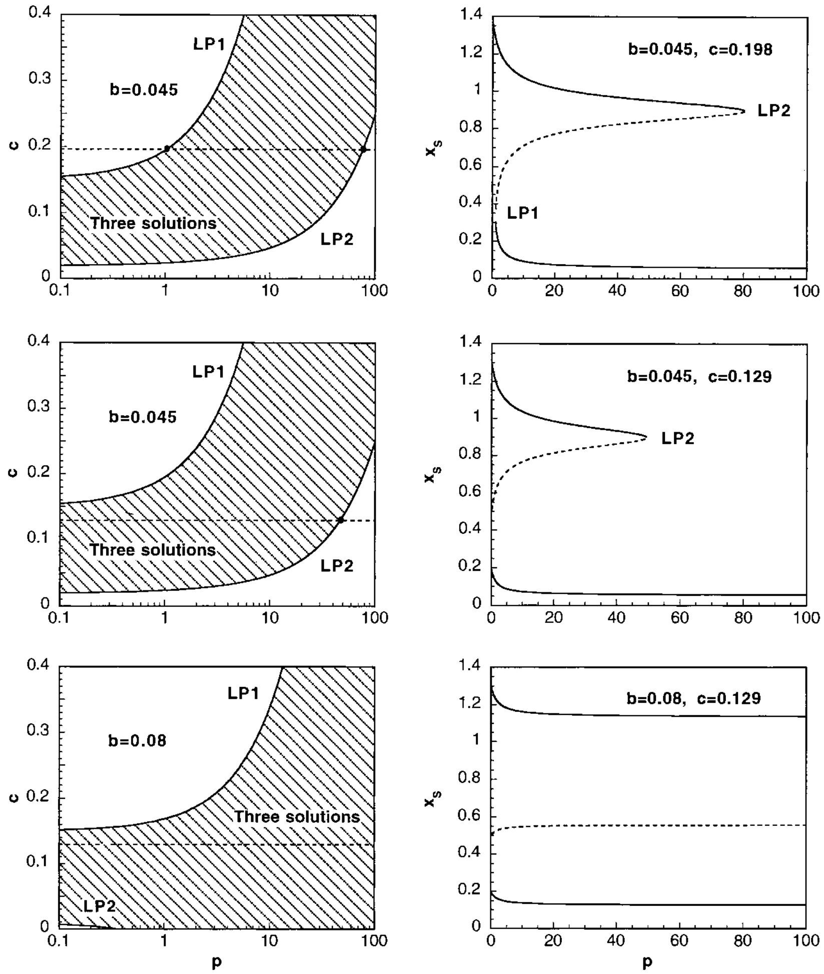


**Figure 2.** From bistability with hysteresis (upper panels) to nonconnected branches of coexisting steady states (lower panels) via an irreversible transition of type 1 (middle panels). Left columns show the loci of limit points LP1 and LP2. These limit points bound the domain of bistability (hatched area) in which eq 9 admits three steady-state solutions, two of which are stable and the third one unstable. The transition from top to bottom is obtained by first lowering the value of *c* at constant *b* and then by increasing *b* at constant *c* (this path is marked by the two arrows in the diagram of Figure 4). The values of *b* and *c* are indicated in each panel. The dashed horizontal lines in the left panels refer to the values of *c* considered in the corresponding right panels. The limit point LP1 (LP2) exists only if the horizontal line intersects with the LP1 (LP2) locus. Thus, LP1 and LP2 both exist in the right upper panel; only LP2 exists in the middle right panel, whereas neither LP1 nor LP2 exist in the lower right panel. Other parameter values are $a = 1.9$, $d = 1.9801$.

**Detailed Analysis of the Conditions Leading to Nonconnected Branches of Coexisting Steady States.** To explore in more detail the occurrence of three nonconnected branches of coexisting steady states, it is useful to carry a comparative analysis of the conditions in which irreversible transitions of type 1 type or 2 arise in this hybrid model. The condition for an irreversible transition of type 2 is that the denominator of function $p(x)$ given by eq 8 admits three real, positive roots. This will occur in the hatched area of the diagram established in Figure 3A as a function of parameters *a* and *b*. This diagram is identical to that established for the infinite limit point (ILP) model studied in our previous publication. Similarly, the condition for an irreversible transition of type 1 is that the numerator of function $p(x)$ given by eq 8 admits three real, positive roots. This will occur in the hatched area of the diagram established in Figure 3B as a function of parameters *c* and *d*. The latter diagram is the same as the diagram previously established for the existence of three real solutions in the Schlögl model.

As will be illustrated below by specific examples, if the values of *a* and *b* correspond to a point of the hatched domain in Figure 3A while the values of *c* and *d* correspond to a point of the hatched domain in Figure 3B, we will observe either nonconnected branches of steady states or more complex situations involving multiple irreversible transitions. If *a* and *b* belong to the hatched domain in Figure 3A while *c* and *d* lie outside the hatched domain in Figure 3B, an irreversible transition of type 2 will occur. If *a* and *b* lie outside the hatched domain in Figure 3A while *c* and *d* correspond to a point in the hatched domain in Figure 3B, an irreversible transition of type 1 will occur. If both pairs (*a*, *b*) and (*c*, *d*) correspond to points outside the hatched domains in Figure 3A,B, either bistability with hysteresis or monostability will be encountered.

To discuss the behavior of the model as a function of only two control parameters (say, *b* and *c*, as previously considered in Figure 2), let us fix the values of *a* and *d* as in Figure 2. These values of *a* and *d* allow *b* and *c* to take values corresponding to points located in the hatched areas in Figure 3A,B (see the dashed lines in the two panels of Figure 3). Shown in Figure 4 are the different domains encountered in the $b-c$ parameter plane for these values of *a* and *d*. The domain of nonconnected branches corresponds to the central, rectangular region of this diagram in which the values of both *b* and *c* are such that the two pairs (*a*, *b*) and (*c*, *d*) correspond to points inside the hatched domains in Figure 3A,B. The other domains around this central region correspond to regions in which irreversible transitions of type 1 or type 2 occur, to regions of monostability, or to bistability associated with hysteresis.

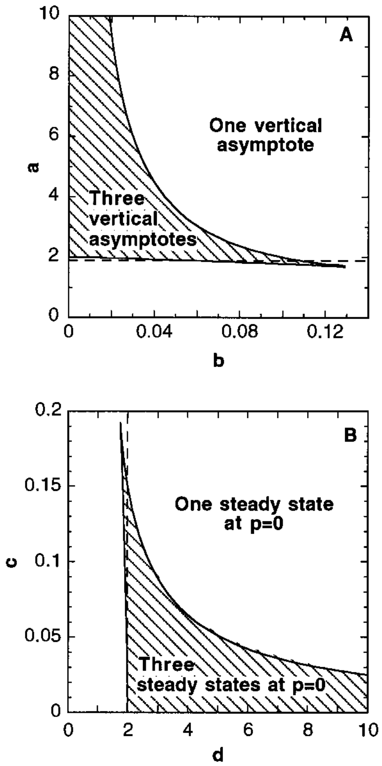


**Figure 3.** Domains (hatched areas) in which (A) the denominator or (B) the numerator of function $p(x)$ defined by eq 10 admits three real, positive roots. When the denominator admits three such roots (upper panel), the curve yielding the steady state $x_s$ as a function of $p$ will admit three distinct horizontal asymptotes. This situation corresponds to an irreversible transition of type 2 and is also a necessary but not sufficient condition to observe nonconnected branches of coexisting steady states. When the numerator admits three real positive roots for $p = 0$ (lower panel), the system admits three distinct steady states $x_s$ in $p = 0$. This condition corresponds to an irreversible transition of type 1 and is also a necessary but not sufficient condition to observe nonconnected branches of coexisting steady states. The situation of nonconnected branches of coexisting steady states occurs when the pairs of values ($a$, $b$) and ($c$, $d$) correspond to points located in the hatched domains of panels A and B, respectively (see also Figure 4). The dashed lines in panels A and B refer to the values of $a$ and $d$ considered in Figure 4.

The horizontal and vertical arrows in the right part of Figure 4 correspond to the path followed in Figure 2 for switching successively from bistability with hysteresis to an irreversible transition of type 1 (upon decreasing $c$) and then to the situation of nonconnected branches of steady states (upon increasing $b$).

It is possible to understand in further detail the transitions sketched in the diagram of Figure 4 by plotting the roots of the numerator and denominator of function $p(x)$ as a function of $c$ and $b$, respectively. This is done in Figure 5, where $a$ and $d$ have been fixed at the values considered in Figures 2 and 4. As can be expected from the above discussion, both the numerator and the denominator of $p(x)$ can display one or three roots as parameters $c$ or $b$ vary. The type of pattern of steady states observed for $x$ as a function of parameter $p$ will depend not only on the number of roots admitted by the numerator and denominator of $p(x)$ but also on the relative positions of these roots.

To allow the occurrence of nonconnected branches, consider the case illustrated in Figure 5 in which we fix $c$ at the value 0.08 (this value corresponds to the dashed vertical line in Figure 4). The three roots of the numerator of $p(x)$ corresponding to this value of $c$ are marked by black dots in Figure 5. We then progressively increase parameter $b$ from a low initial value. The

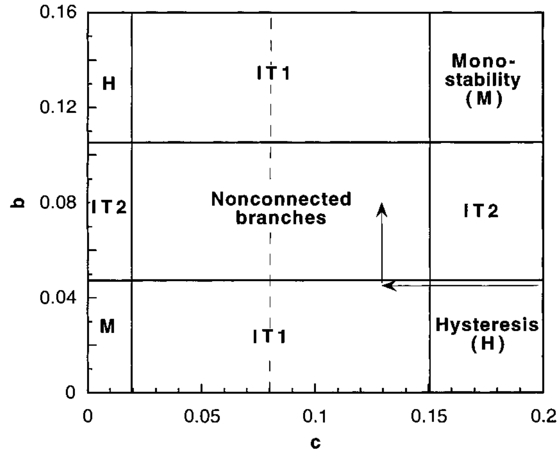


**Figure 4.** Diagram showing the domain of nonconnected branches of coexisting steady states as a function of parameters $b$ and $c$. Also indicated are the domains of monostability (M), bistability with hysteresis (H), and bistability with an irreversible transition of type 1 (IT1) or type 2 (IT2). The diagram is established for $a = 1.9$, $d = 1.9801$. As indicated by the dashed lines in Figure 3, these values allow the multiplicity of roots of the numerator and denominator of function $p(x)$. The two arrows in the diagram refer to the path followed in Figure 2 to illustrate the transition from bistability with hysteresis to the situation of nonconnected branches of coexisting steady states. The vertical dashed line refers to the value of $c$ considered in Figure 6 below (the three roots of the numerator of $p(x)$ marked by black dots in Figure 5 are also obtained for this particular value of $c$).

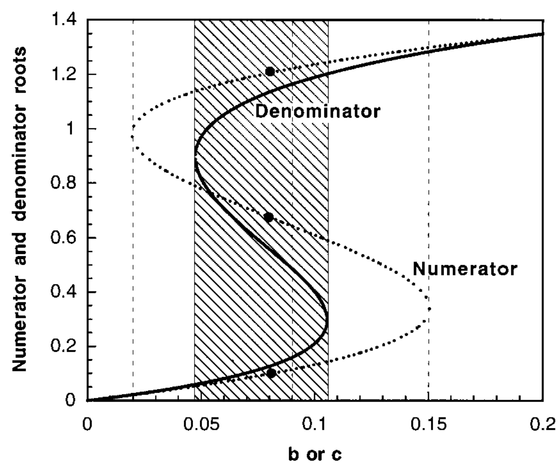


**Figure 5.** Roots of the denominator (solid curve) and of the numerator (dotted curve) of $p(x)$ as a function of parameters $b$ and $c$, respectively. In the hatched area, the denominator admits three real positive roots. For the value of $c = 0.08$ considered, the numerator also possesses three such roots, which are marked by black dots. To observe nonconnected branches of coexisting steady states, the value of $b$ must be in the range corresponding to the hatched domain. The vertical dashed lines relate to the three values of $b$ considered in Figure 6. Parameters $a$ and $d$ are as in Figure 4.

increasing values of $b$ correspond to the vertical dashed lines in Figure 5. The intersections of these lines with the S-shaped curve yielding the roots of the denominator of $p(x)$ as a function of $b$ yield the position of the asymptotes of $x$ as a function of $p$.

The different patterns obtained in this case are shown in Figure 6 where the steady-state value of $x$ is plotted as a function of $p$ for the three values of parameter $b$ considered in Figure 5. We start with an irreversible transition of type 1, with the lower branch of stable steady states approaching the unique asymptote. At the largest value of $b$, we still observe an irreversible transition of type 1, but now it is the upper branch of stable steady states that approaches the unique asymptote. Between

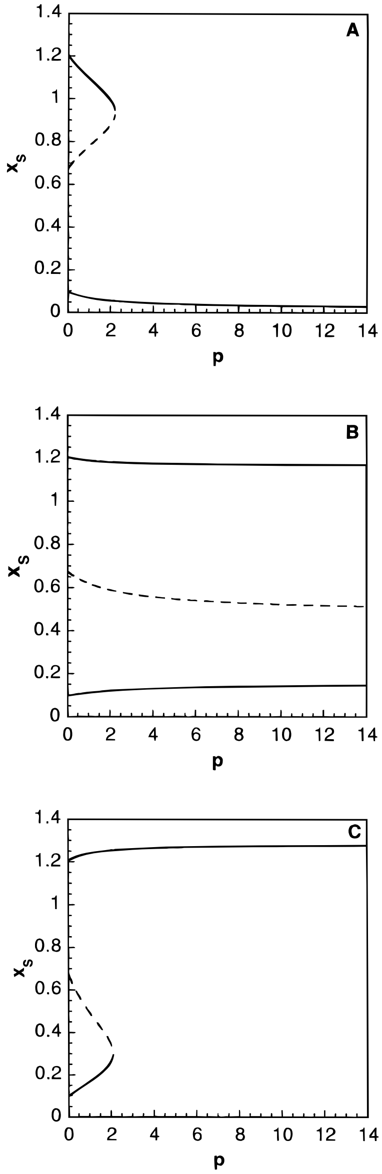


**Figure 6.** Passage through the domain of nonconnected branches of coexisting steady states, starting from and returning to bistability with irreversible transition of type 1. The path followed corresponds to an increase in parameter *b* along the vertical dashed line shown in Figure 4. Thus, $b = 0.02$ for (A), 0.09 for (B), and 0.15 for (C). These values correspond to the three vertical dashed lines in Figure 5, which permits us to determine the locations of the horizontal asymptote(s) with respect to the steady states $x_s$ in $p = 0$ (black dots). Parameters *a* and *d* are as in Figure 4.

these two extreme cases, we observe nonconnected branches. The relative positions of the three branches of stable (or unstable) steady states with respect to their associated asymptotes depend on the value of *b*.

**Complex Patterns of Bistability.** The possibility of observing more complex patterns of transitions between multiple stable steady states is illustrated by the diagram of Figure 7 established as a function of parameters *b* and *c* for the same value of *a* as in Figure 4 but for the higher value $d = 4.19$. The diagram shows the same regions as in Figure 4, but besides the region of nonconnected branches, we observe a domain of complex configurations of steady states. The latter configurations are illustrated in Figure 8 where different patterns observed are shown. The origin of such complex patterns of multiple steady states can be understood by resorting to a graphical representation of the roots of the numerator and denominator of $p(x)$, as

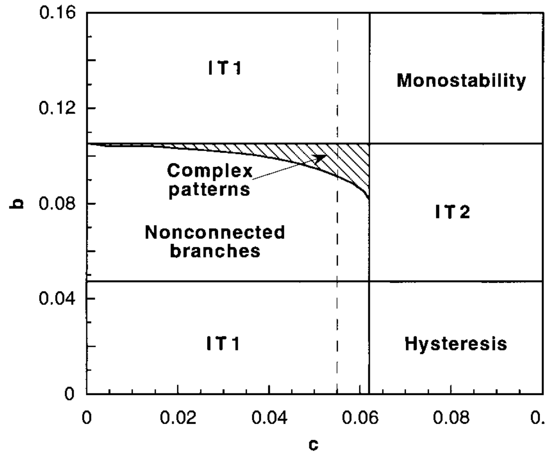


**Figure 7.** Diagram showing the domains of nonconnected branches of coexisting steady states and of more complex patterns of bistability (shown in Figure 8) as a function of parameters *b* and *c*. The diagram is established for $d = 4.19$. The value of *a* is as in Figure 4. The occurrence of complex patterns of bistability associated with the existence of two or more limit points (see Figure 8) is determined, as for hysteresis, by finding the domain where $p(x)$ admits multiple positive extrema. The vertical dashed line refers to the value of *c* considered in panel A of Figure 8.

done in Figure 5 for the patterns of Figure 6. Of particular interest is the pattern shown in panel C of Figure 8, where an irreversible transition of type 1 is followed by bistability with hysteresis and by an irreversible transition of type 2 as the parameter *p* increases.

## Discussion

Bistability denotes the coexistence of two stable steady states in a reaction system subjected to the same experimental conditions. The phenomenon is commonly associated with the capability of the system to switch back and forth between the two distinct branches of stable steady states (connected by a branch of unstable steady states) upon the reversible variation of a control parameter in a range bounded by two limit points. A phenomenon of 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 generally different.

In a previous publication[30] 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 transition between the two branches of stable steady states has become irreversible.[20] Here, we extended this analysis by proposing a model for the case where the two limit points bounding the domain of bistability have both become inaccessible. Under such conditions, the three branches (two stable and one unstable) of steady states cease to be connected so that no transition between the stable branches can occur upon continuously varying the control parameter. Bistability still exists, but the system may remain irreversibly trapped in any one of the two stable states if only the selected control parameter can change. Even when the branches of steady states are not connected, however, the transitions between the stable steady states can still be achieved by applying suprathreshold perturbations in the concentrations of chemical intermediates.

Several models showing irreversible transitions between two stable steady states 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. To clarify the

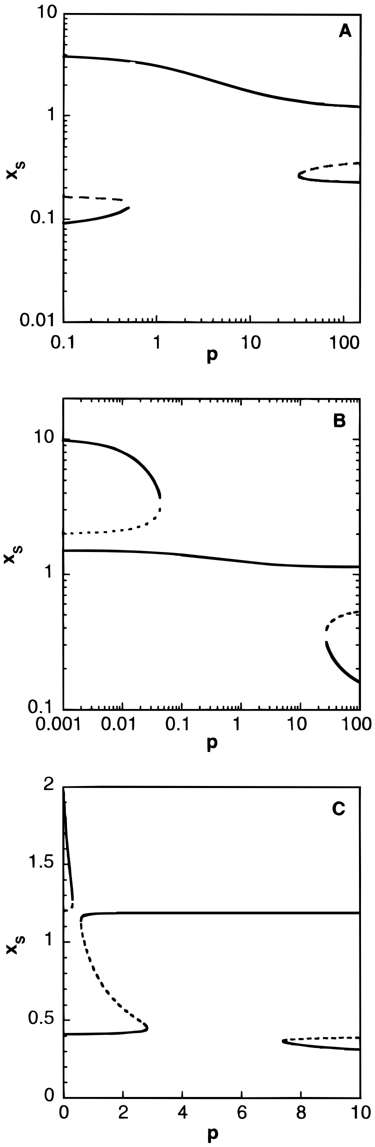


**Figure 8.** Various types of complex patterns of bistability obtained in the model. In (A) and (B), an irreversible transition of type 1 is followed by an irreversible transition of type 2 as parameter $p$ increases. In (C), a full hysteresis loop separates two irreversible transitions of types 1 and 2, respectively. For (A), parameters $a$ and $d$ are as in Figure 7; $b = 0.102$, $c = 0.055$. Although (A) and all previous figures were obtained for $C_4 = 1$ in eq 7, this parameter is equal to 0.0263 in (B) and 0.2693 in (C). Other parameter values are the following: (B) $a = 1.9$, $b = 0.08$, $c = 0.789$, $d = 0.355$; (C) $a = 1.9$, $b = 0.1$, $c = 0.265$, $d = 0.973$.

conditions under which irreversible transitions occur when one of the limit points of a bistable chemical system disappears, we examined in our previous publication[30] two theoretical models admitting a coexistence between two stable steady states. The two models, described by polynomial kinetics, are based on a sequence of reversible chemical reactions. This analysis led us to suggest a classification of irreversible transitions between two types, 1 and 2 (see Introduction). In the first model, proposed by Schlögl,[1] 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 the ILP (infinite limit point) model,[30] irreversible transitions of type 2 (but also of type 1 upon varying another parameter) are obtained.

In the present study devoted to the case of nonconnected branches of steady states, we aimed at combining the occurrence of irreversible transitions of types 1 and 2 as a function of a single parameter. To this end, we constructed a hybrid, two-variable model by fusing the ILP model with the Schlögl model previously studied for bistability associated with hysteresis. Besides nonconnected branches of steady states, this model can display a wide variety of steady-state behavior, including monostability, bistability with hysteresis, and irreversible transitions of type 1 or type 2. More complex configurations involving a succession of irreversible transitions as a control parameter is varied can also be observed in this model.

We have analyzed the conditions under which the situation of nonconnected branches of steady states arises in this model as a function of one of the main control parameters. Our study establishes that this phenomenon can occur in fully reversible chemical reaction systems and is therefore not an artifact due to the irreversible nature of the kinetic scheme considered. Thermodynamic equilibrium corresponds to a point located outside the domain of bistability. Thus, much as irreversible transitions, the phenomenon of nonconnected branches is possible in fully reversible chemical systems under nonequilibrium conditions.

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[1−8] and biochemical[9−18] 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] who focused on cyclical enzymatic systems governed by (partially) irreversible kinetic laws and who investigated experimentally the disappearance of limit points in such bistable systems. With the exception of studies devoted to a cyclical enzymatic system subjected to feedback regulation,[28,29] even less attention has been paid so far to the situation of nonconnected branches of steady states. Further experimental studies of bistability with irreversible transitions or nonconnected branches are clearly needed in chemical and biochemical systems to better characterize the phenomenon and the conditions under which it occurs.

Bistability without hysteresis could be of deep physiological significance for the dynamics of biological systems, particularly with respect to memory and differentiation. Once a system has reached a certain steady state as a result of a change in a given control parameter, it remains trapped in this state regardless of any further change in the parameter value. Such irreversible transitions between multiple steady states have been found in a model for the $Ca^{2+}$-induced self-activation of calmodulin kinase through autophosphorylation,[22] as well as in a model for the immune response.[23] In the latter case, the authors thus could describe the system's evolution toward a "paralyzed" state. The situation of bistability with nonconnected branches of steady states might be of further interest, since it allows a system to be trapped in any of two possible steady states and not just one of these states as in the case of irreversible transitions of type 1 or type 2.

The finding that bistability without hysteresis arises in models[18,22,24,25,31] and experiments[27−29] involving cyclical enzymatic systems suggests that a large class of biochemical processes might in principle give rise to the phenomenon. Many key cellular processes are indeed regulated by the reversible covalent modification of proteins, e.g., phosphorylation by a protein kinase and dephosphorylation by a phosphatase. Bistability may readily occur in such cyclical enzymatic systems when one of the modifying enzymes is controlled by positive or negative feedback. The possibility therefore exists that irreversible transitions between multiple steady states, as well as nonconnected branches of coexisting steady states, could play a role in a variety of cellular regulatory processes.

**Acknowledgment.** This work was supported by the Programme "Actions de Recherche Concertée" (Convention 94/99-180) launched by the Division of Science and Higher Education, French Community of Belgium.

## Appendix: Unicity of the Equilibrium State for the Scheme Depicted by Reactions 3a−3e

At equilibrium we have

$$A = \frac{k_{-1}k_{-2}k_{-3}}{k_1 k_2 k_3}B = \frac{k_{-3}k_{-4}}{k_3 k_4}C = \frac{k_{-3}k_5}{k_3 k_{-5}}D$$

$$X = \frac{k_3}{k_{-3}}A$$

$$Z = \frac{k_1 k_3}{k_{-1}k_{-3}}PA \quad \text{(A1)}$$

With the definitions given in eqs 5 and 6, the equilibrium conditions take the form

$$a = \frac{C_1}{C_2 - 1}b = C_1 c = \frac{C_1}{C_4}d = C_1 x; \quad C_1 z = pa \quad \text{(A2)}$$

Substituting the values of the concentrations at equilibrium as given by eq A2 in the steady-state equations (eq 8), we obtain the eq A3:

$$\left(x - \frac{b}{C_2 - 1}\right)\left(x^2 + \frac{C_1 bp}{C_2 C_4 + pC_1}x + \frac{C_2 + p(C_2 - 1)}{C_2 C_4 + pC_1}\right) = 0 \quad \text{(A3)}$$

It is evident that the second factor cannot have real positive solutions. Thus, at equilibrium we have only the single equilibrium solution.

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