

## **Biochemical Model with Multiple Steady States and Hysteresis**

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An analytically “simple” biochemical model with multiple steady states and a hysteresis loop is analyzed.

### **1. Introduction**

Biochemical systems with two stable steady states have been noted and used for biological modeling. Bierman (1954) was the first to demonstrate a model with two stable stationary states. Spangler & Snell (1961, 1967) then analyzed two independent enzyme reactions in which each product inhibits the other enzyme. They show that, for specific values of the parameters, in an open system, there can be two, stable, steady states and a hysteresis loop. Monod & Jacob (1961) use, amongst others, a similar model for induction and differentiation. Griffith (1968) considers the Monod and Jacob “flip-flop” as a possible mechanism for memory. Katchalsky & Spangler (1968) show that there is an analogy to two stable steady states with hysteresis, in membrane conductance.

The purpose of the present paper is to report another model, biochemical scheme which has multiple steady states and a hysteresis loop. This model consists of a single reaction system and is analytically “simple”. It is hoped that the analytical simplicity makes the scheme useful for biological modeling, although the scheme has not been biochemically demonstrated.

### **2. The Model**

Let  $a$  and  $b$  be the concentrations of the parameter chemicals A, B, to which the system is open. Let  $x$  be the concentration of an intermediate, X, and  $e$  and  $c$  be respectively the concentration of the free enzyme, E, and its complex, with X, C. The scheme (1 to 3) consists of the autocatalytic

production of X and its enzymatic degradation



The kinetic equations for the scheme are

$$\frac{dx}{dt} = k_{+1}ax - k_{-1}x^2 - k_{+2}xe + k_{-2}c \quad (4)$$

$$\frac{de}{dt} = -k_{+2}xe - k_{-3}eb + (k_{-2} + k_{+3})c. \quad (5)$$

The conservation of enzyme condition is

$$e + c = e_T \quad (6)$$

and the steady-state equations become

$$k_{-1}k_{+2}x^3 + [k_{-1}(k_{-3}b + k_{-2} + k_{+3}) - k_{+1}k_{+2}a]x^2 + [k_{+2}k_{+3}e_T - k_{+1}a(k_{-3}b + k_{-2} + k_{+3})]x - k_{-2}k_{-3}be_T = 0 \quad (7)$$

and

$$e = \frac{(k_{-2} + k_{+3})e_T}{k_{+2}x + k_{-3}b + k_{-2} + k_{+3}}. \quad (8)$$

In all that follows, and with no loss of generality, we shall put all the kinetic constants equal to one. Equations (7) and (8) become:

$$f(x) = x^3 + (2 + b - a)x^2 + (e_T - a(2 + b))x - be_T = 0 \quad (9)$$

$$e = \frac{2e_T}{x + b + 2}. \quad (10)$$

The steady-state value of  $x$  for given  $a$ ,  $b$ , and  $e_T$  is obtained from (9) by the method of Bairstow on the IBM 7040 computer, and the stability of each point is determined by the Routh-Hurwitz criteria for the secular equation (Edelstein, 1970). Figure 1 shows a region of multiple steady states and hysteresis. The steady-state values of  $x$  are plotted as a function of  $a$  for  $e_T = 30$ ,  $b = 0.2$ . The upper and lower values of  $x$  are stable. The intermediate value is unstable, with a positive real root of the secular equation.

At the points of (9) where

$$\frac{dx}{da} = \frac{\frac{\partial f}{\partial a}}{\frac{\partial f}{\partial x}} \rightarrow \infty \quad (11)$$

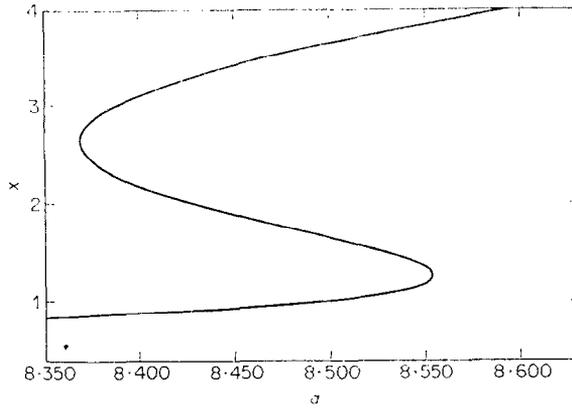


FIG. 1. Multiple-steady-states and hysteresis of  $x$  as a function of  $a$  for  $b = 0.2$ ,  $e_T = 30$ .

there is the coalescence of two roots of (9), with a non-oscillatory marginal state of stability. In Fig. 1 these are the extreme points of the hysteresis loop, with vertical tangents.

If there is only one point with a vertical tangent, this curve is the transition between systems with and without hysteresis. Analytically, the requirement is

$$\frac{\partial f}{\partial x} = 0 \quad (12)$$

has a double root satisfying (9). The transition from a region of a single steady state to that of multiple steady states occurs as  $e_T$  increases (Fig. 2) or as  $b$  decreases (Fig. 3). These can be mechanisms (with different time constants) for fixation after a transition of states.

As can be seen from (9) and Descartes' rule of signs for positive roots of a polynomial, the critical requirement for multiple roots is that the total enzyme concentration be greater than that of A and B. The concentrations for multiple steady states are not physically unreasonable, and may become biologically realistic with  $k$ 's  $\approx 1$  (7).

The simplicity of the model allows an investigation of the thermodynamics of the hysteresis loop. The thermodynamics of multiple stationary states has been studied by Lavenda (1970).

Figure 4 is a three-dimensional graph of the steady-state values of  $x$  against both  $a$  and  $b$ , for the same hysteresis loop as in Fig. 1. It demonstrates that each stable branch of the hysteresis loop can be a continuous extension of a different equilibrium point. Equilibrium for the system

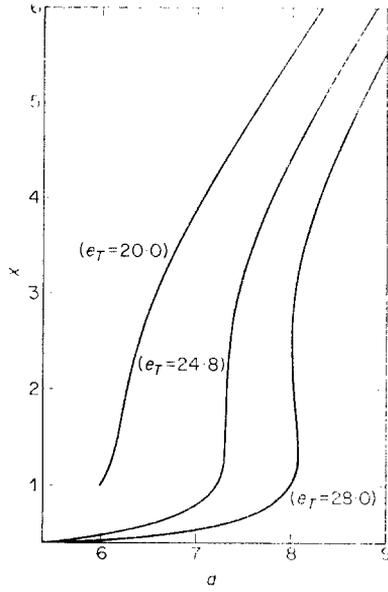


FIG. 2. Steady states of  $x$  as a function of  $a$  for  $b = 0.2$  and  $e_T = 20.0, 24.8$  and  $28.0$ . These curves show the transition from a unique steady-state situation to a multiple-steady-state situation as  $e_T$  is increased.

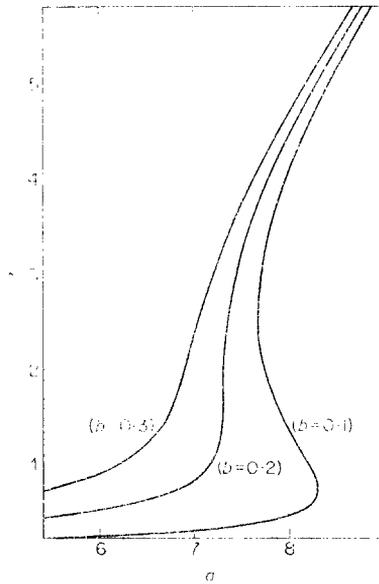


FIG. 3. Steady states of  $x$  as a function of  $a$  for  $e_T = 24.8$  and  $b = 0.1, 0.2$  and  $0.3$ . These curves show the transition from a unique steady-state situation to a multiple-steady-state situation as  $b$  is decreased.

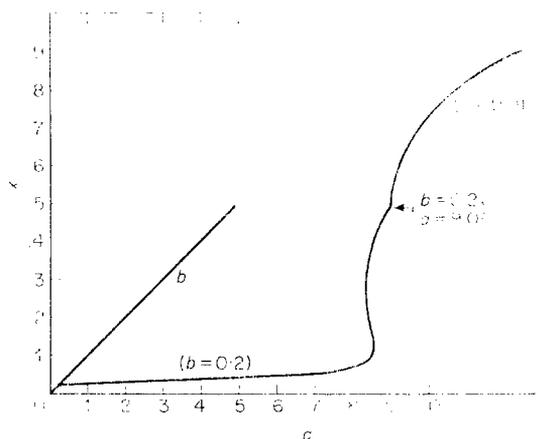


FIG. 4. Steady state of  $x$  for  $e_T = 30$ .  $a$  varies between 0.2 and 9.0 for  $b = 0.2$ .  $b$  varies between 0.2 and 9.0 for  $a = 9.0$ . The curves meet at  $a = 9.0$ ,  $b = 0.2$ . This three-dimensional graph shows that each stable branch of the hysteresis loop is a continuous extension of a different equilibrium solution.

(1 to 3), with all kinetic constants equal to one, is  $a = b$ . The lower branch in Fig. 4 runs along the plane  $b = 0.2$  from the equilibrium point  $a = 0.2$ , and contains the lower branch of the hysteresis loop. The upper branch, which contains the upper branch of the hysteresis loop, begins at the equilibrium point  $a = b = 9.0$ .  $b$  then decreases to 0.2 in the plane  $a = 9.0$ .  $a$  then decreases from 9.0 in the plane  $b = 0.2$ .

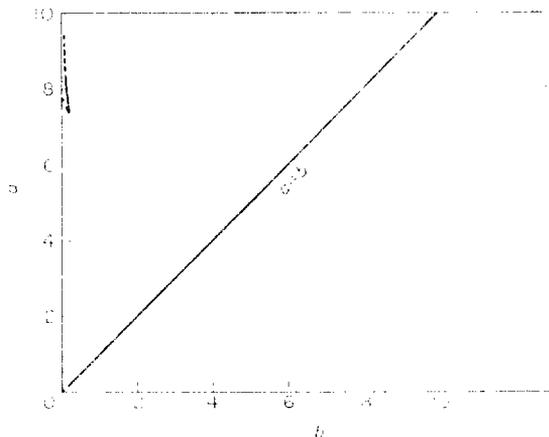


FIG. 5. The plane of the parameter chemicals, A and B. Equilibrium is the line  $a = b$ . The wedge is the region of values of  $a$  and  $b$  in which  $x$  can have multiple-steady-states, for  $e_T = 24.8$ . The dotted lines are extrapolations.

Figure 5 demonstrates the thermodynamics in the plane of the parameter chemicals. The line  $a = b$  is the equilibrium line. The wedge boundary is made up of the points of marginal stability of a steady state solution of  $x$ , for fixed  $e_T$ .  $x$  is perpendicular to the plane of the paper, and inside the wedge is the region of multiple values of  $x$  (hysteresis). The vertex of the wedge is the point of merging of the double roots. When the wedge is entered, it is either on the upper or lower branch of  $x$ , depending on the path. We then stay on that branch until reaching the further border of the wedge, where we jump to the other branch of  $x$ . This other branch of  $x$  is clearly reached from equilibrium without undergoing a transition of states. This is a distinct contrast from previous examples of instabilities (Prigogine, 1969) where it is necessary to pass through an instability to reach the subsequent state.

The model analyzed has two properties which may give criteria for its applicability to multi-steady-state phenomena. There is no thermodynamic reason for preferring either steady state; history alone determines the state of the system. Moreover, there is a reversible mechanism for the fixation of either stationary state.

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