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Feedbacks, nonlinearities and nonequilibria: A thermodynamic perspective

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ABSTRACT

The feedback circuit approach to nonlinear dynamical systems pioneered by Thomas and coworkers is revisited in a thermodynamical perspective. The role of nonequilibrium conditions and of other types of constraints such as mass action kinetics or microscopic reversibility around thermodynamic equilibrium in the way positive feedback circuits are operating is analyzed. It is shown that the appearance of nontrivial steady-state and time-dependent behaviors necessitates that the strengths of the feedback loops present exceed some well-defined critical values. Illustrations are provided on prototypical systems giving rise to multiple steady states.

1. Introduction

Even since the beginnings of his ground-breaking work on the Boolean approach to biological regulatory processes (Thomas, 1973; 1979), René Thomas has been in search of a natural way to incorporate time into the logical description. Characteristic of his brilliance and creativity, he realized along the way that the target should somehow be redefined and indeed turned upside down so that, rather than introduce dynamics in a formalism that was by essence static, reformulate instead dynamics in terms of elementary feedback circuit structures similar to those that he had identified and analyzed in his earlier approach. He and his coworkers (Kaufman and Thomas, 2003; Thomas, 1991; Thomas and d'Ari, 1990; Thomas and Kaufman, 2001) carried out this reformulation systematically, showed how feedback circuits can be related to the elements of the Jacobian matrix of a dynamical system and established that the stability properties of a reference state and the onset of non-trivial behaviors depend solely on the circuits present in the system among which nuclei, i.e., circuits involving the full set of the system's variables play a prominent role.

In their quest of the connections between feedback circuits and complex dynamical behaviors Thomas and coworkers focused on generic classes of abstract dynamical systems, whatever their origin or specific mechanisms might be. On the other hand, natural systems obey to strict constraints imposed by physical laws such as mass action law in chemical kinetics, microscopic reversibility and detailed balance around the state of equilibrium, or positivity of state variables such as concentrations. Furthermore it is by now established that, in addition to appropriate nonlinearities, macroscopic-scale complex dynamical behaviors cannot emerge unless the system is driven sufficiently far from the state of thermodynamic equilibrium (Glansdorff and Prigogine, 1971). Our objective in this work is to revisit feedback circuits in this perspective and to inquire on how nonequilibrium conditions and other types of physical constraints may interfere with the way they are operating. As a corollary, a number of quantities allowing one to highlight these effects will be introduced and evaluated in prototypical systems.

A major result pioneered by Thomas and coworkers has been to establish a firm link between positive feedback circuits and the occurrence of multiple steady states. We will focus here on positive feedbacks generated by chemically reacting systems in which all reactive steps are elementary in the sense that (a), they satisfy mass action kinetics; and (b), they admit an equilibrium state in which microscopic reversibility and detailed balance are secured. This latter property entails, in turn, that forward steps coexist with their reverses. Positive feedbacks will be associated to autocat-

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alytic steps and the respective roles of such feedbacks, nonlinearities and distance from equilibrium will be assessed. We will address steady-state properties in connection with multistability as well as time-dependent behavior in connection with the transient evolution toward a particular steady state starting from an initial condition far away from this state.

The general formulation is presented in Section 2. Sections 3 and 4 are devoted to detailed studies of positive feedback circuits in their simplest forms associated, respectively, to second order and to higher order autocatalysis. The main conclusions are summarized in Section 5.

2. Kinetics and thermodynamics of a positive feedback loop

In what follows we will be interested in the role of positive feedback circuits embedded in a kinetic pathway in which an initial substance A is converted into a final product B through a sequence of intermediate steps. Let $\{x_i\}$, $i = 1, \dots n$ be the concentrations of the species involved in the sequence and $\{w_\rho\}$, $\rho = 1, \dots r$ the rates of the individual proceses. Assuming that the system is in mechanical equilibrium and maintained spatially uniform and at a constant temperature one may write the balance equations linking $\{x_i\}$ to $\{w_\rho\}$ in the form (De Groot and Mazur, 1962)

$$\frac{dx_i}{dt} = \sum_{\rho=1}^{r} \nu_{i\rho} w_\rho\left(\{x_j\}\right) \qquad i, j = 1, \dots n \tag{1}$$

where $\nu_{i\rho}$ are the stoichiometric coefficients.

As stressed in the Introduction, at the fundamental level of description all steps in Eq. (1) are reversible and expressible in terms of elementary processes according to the law of mass action. Under the additional assumption of an ideal solution this entails, in particular, that individual rates are products of integer powers of state variables. The right hand side of Eq. (1) has thus the structure of a polynomial in the x_i s.

The presence of positive feedback circuit in this setting will be signaled by the specific structure of some of the functions w_ρ, in which the presence of a species i or of a sequence $i \to j \to k \cdots \to i$ thereof enhances the overall rate of its/their own production. We will be interested here in the repercussions of such circuits and, in particular, in the phenomenon of multistability in its simplest manifestation, in which a steady state solution of Eq. (1) prevailing in some range of values of parameters such as rate constants or concentrations of pool chemical species gives rise under certain conditions to new branches of steady-state solutions, which merge with the reference state at some critical parameter value but remain otherwise distinct. A fundamental point for our purposes is that in the vicinity of such bifurcation points of steady-state solutions the dynamics as described by the full set of Eq. (1) reduces to a single equation satisfied by a suitable combination of the initial variables, to which we refer as order parameter, and which has one of the following three universal forms (Nicolis, 1995)

$$\tfrac{dz}{dt} = (\lambda - \lambda_c)z - uz^2 \qquad \text{(transcritical bifurcation)} \tag{2a}$$

$$\tfrac{dz}{dt} = (\lambda - \lambda_c)z - uz^3 \qquad \text{(pitchfork bifurcation)} \tag{2b}$$

$$\tfrac{dz}{dt} = (\lambda - \lambda_c) - uz^2 \qquad \text{(limit point bifurcation)} \tag{2c}$$

Here λ is the bifurcation parameter, λ_c its critical value and u an additional parameter determining the direction along which the emerging solution branches will be directed.

Drawing on these results it appears legitimate to assert that the essence of multistability and of the role of positive feedbacks can be captured by systems involving a single intermediate chemical species X beyond the initial and final species A and B and a single circuit in the form of a positive feedback loop, provided that the kinetics accounts fully for the nonlinearities present in the canonical forms of Eq. (2a)–(2c). In this work we focus on two prototypical kinetic schemes satisfying these requirements (Schlögl, 1972):

(i) A second order autocatalytic scheme

$$A + X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 2X \qquad X \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} B \tag{3}$$

(ii) A higher order autocatalytic scheme

$$A + 2X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 3X \qquad X \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} B \tag{4}$$

Here X is the intermediate species of concentration x and k_i, $i = \pm 1, \pm 2$ are rate constants. A and B denote the initial and final products whose concentrations a and b are supposed to be maintained at constant levels . In a closed system this constitutes a satisfactory approximation if A and B are initially much more abundant than X, entailing that their relative variations can be neglected compared to that of X (pool chemical approximation). Alternatively, in an open system, constancy of a and b appeals to a limit where A and B are pumped into the reactor from two external reservoirs at a fast rate, counteracting their consumption by the chemical reactions. The autocatalytic steps in (3) and (4) constitute the positive feedback loops. If acting alone, they are bound to drive the system to thermodynamic equilibrium in which $x_{eq} = k_1 a / k_{-1}$ would be the unique steady state available and the positive feedbacks would eventually become ineffective. The presence of a second step allows for maintaining the system out of equilibrium as long as the overall forward reaction rate remains different from the backward one,

$$\frac{k_1 k_2 a}{k_{-1} k_{-2} b} \neq 1 \tag{5}$$

The questions we will address are, how under such nonequilibrium conditions the feedback loops are activated to produce complex behavior, including multistability; and how can one quantify the response of the system and in particular its sensitivity to the constraints present. If on the contrary the equality sign prevails in Eq. (5), each of the individual steps in schemes (3) and (4) will settle to equilibrium (detailed balance property), with

$$x_{eq} = \frac{k_1 a}{k_{-1}} = \frac{k_{-2} b}{k_2} \tag{6}$$

and, eventually, the feedback loops will be ineffective.

In addition to steady states, be they equilibrium or nonequilibrium like, transient behavior is also of great importance. For the class of one-variable systems considered here the rate equation to which Eq. (1) are reduced and which accounts for both steady-state and time-dependent properties can be written as

$$\frac{dx}{dt} = w_1(a, x) - w_{-1}(x) - w_2(x) + w_{-2}(b) \tag{7a}$$

with

$$w_1 = k_1 a x^n, \quad w_{-1} = k_{-1} x^{n+1}, \quad w_2 = k_2 x, \quad w_{-2} = k_{-2} b \tag{7b}$$

and $n = 1$ or 2 for schemes (3) and (4), respectively.

A first signature of time-dependent behavior concerns stability. Let $\bar{x}$ be a reference (typically time-independent) state. The condition under which this state will remain robust against small perturbations is that the derivative of the right hand side of (7) evaluated at $\bar{x}$ be negative,

$$\frac{d}{dx}\left[w_1\left(a, x\right) - w_{-1}(x) - w_2(x)\right]_{\bar{x}} < 0 \tag{8}$$