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Birhythmicity, chaos, and other patterns of temporal self-organization in a multiply regulated biochemical system

(biological rhythms/oscillatory enzymes/dissipative structures/deterministic chaos/strange attractors)

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ABSTRACT **We analyze on a model biochemical system the effect of a coupling between two instability-generating mechanisms. The system considered is that of two allosteric enzymes coupled in series and activated by their respective products. In addition to simple periodic oscillations, the system can exhibit a variety of new modes of dynamic behavior: coexistence between two stable periodic regimes (birhythmicity), random oscillations (chaos), and coexistence of a stable periodic regime with a stable steady state (hard excitation) or with chaos. The relationship between these patterns of temporal self-organization is analyzed as a function of the control parameters of the model. Chaos and birhythmicity appear to be rare events in comparison with simple periodic behavior. We discuss the relevance of these results with respect to the regularity of most biological rhythms.**

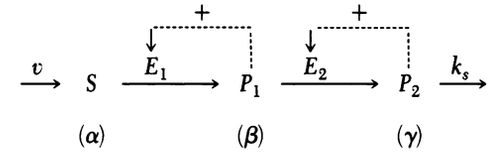
Rhythmic behavior is a property of living systems that is encountered at all levels of biological organization (1). Most biological oscillations have a stable period and amplitude. From a thermodynamic point of view, such oscillations represent temporal dissipative structures, which occur in the form of a limit cycle around a nonequilibrium unstable steady state (2). Thus, finding the mechanism of periodic behavior largely reduces to finding the mechanism producing instability. A question arises as to what happens when two such instability-generating mechanisms are operating in the same system? We show here on a model biochemical system that the variety of possible types of dynamic behavior is then greatly increased.

Among these behavioral modes, one should single out for their rareness and potential implications the coexistence under the same conditions of two stable periodic regimes and the occurrence of chaos. For other parameter values, the system shows simple or complex periodic oscillations of the limit-cycle type and coexistence of a stable limit cycle with either a stable steady state or chaos. Evolution to chaos appears to be a universal way by which periodic behavior looses its regularity and becomes impredictable, although governed by deterministic laws (3–5). The latter phenomenon occurs in physics (6) and chemistry (7) and has been associated with pathological conditions in certain physiological systems (8).

The construction of stability and bifurcation diagrams sheds light on the origin of these patterns of temporal self-organization and on the way in which they are interrelated. We obtain the conditions in which the various modes of behavior occur as a function of the control parameters of the model and discuss the likelihood of chaos in comparison with regular periodicities.

MODEL AND KINETIC EQUATIONS

Among oscillations in biology, enzymatic periodicities are those which are the best understood at the molecular level (9–11). These oscillations, which have a period of several minutes, are of interest both for their role in metabolic pathways and as general models for biological rhythms. The best known examples are glycolytic oscillations in yeast (12, 13) and muscle (14) and the periodic synthesis of cAMP during the aggregation of the slime mold *Dictyostelium discoideum* (15). The mechanism of instability that generates these periodicities is based on the positive feedback exerted by a reaction product on phosphofructokinase and adenylate cyclase, respectively (10). To investigate the new types of behavior that may result from the interplay between two instability mechanisms, we analyze a sequence of enzymatic reactions that comprises two positive feedback loops coupled in series (Eq. 1).



[1]

Substrate S is injected or synthesized at a constant rate v; its transformation is catalyzed by an allosteric enzyme E_1, which is activated by its product P_1; a second allosteric enzyme E_2 uses P_1 as substrate and is activated by its product P_2; k_s is the apparent first-order rate constant for removal of P_2. This model represents an extension of those previously studied for glycolytic (16, 17) and cAMP (18, 19) oscillations. The latter models, based on a single positive feedback, were only capable of evolving either towards a stable steady state or to a stable monoperiodic regime.

We assume that enzymes E_1 and E_2 obey the concerted transition model of Monod *et al.* (20). The time evolution of the metabolite concentrations is then governed by the three ordinary differential Eqs. 2.

$$d\alpha/dt = (v/K_{m1}) - \sigma_1\Phi$$
$$d\beta/dt = q_1\sigma_1\Phi - \sigma_2\eta$$
$$d\gamma/dt = q_2\sigma_2\eta - k_s\gamma \qquad [2]$$

with

$$\Phi = \alpha(1+\alpha)(1+\beta)^2/[L_1 + (1+\alpha)^2(1+\beta)^2]$$

and

$$\eta = \beta(1+d\beta)(1+\gamma)^2/[L_2 + (1+d\beta)^2(1+\gamma)^2]. \qquad [3]$$

Here, α, β, and γ denote the concentrations of S, P_1, and P_2 divided, respectively, by the Michaelis constant of E_1 (i.e., K_{m1}) and by the dissociation constants of P_1 for E_1, K_{P1}, and of P_2 for E_2, K_{P2}. Moreover, v denotes the constant input of sub-

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Abbreviations: LC1, LC2, and LC3, limit cycles 1, 2, and 3, respectively.

strate; σ_1 and σ_2 are the maximum activities of enzymes E_1 and E_2, divided through K_{m1} and K_{m2}, respectively; $q_1 = K_{m1}/K_{P1}$ and $q_2 = K_{P1}/K_{P2}$; k_s is the apparent first-order rate constant for removal of P_2; L_1 and L_2 are the allosteric constants of E_1 and E_2 (20); $d = K_{P1}/K_{m2}$, where K_{m2} is the Michaelis constant of E_2 for its substrate P_1.

Eqs. 3 reflect the assumption that enzymes E_1 and E_2 are both dimers, with exclusive binding of ligands to the more active conformational state (20). The kinetic Eqs. 2 have been obtained by further assuming a quasi-steady state for the various enzymatic forms (16). Finally, we restrict our analysis to the case of a spatially homogeneous system, which corresponds to the experiments on oscillations under continuous stirring in glycolysis or cAMP synthesis (12–15).

RESULTS

Eqs. 2 admit a single steady-state solution that can be stable or unstable, depending on parameter values. The variety of behavioral modes made possible by the presence of a second positive feedback is illustrated by the bifurcation diagram of Fig. 1. Here, we have plotted as a function of k_s the steady-state concentration of substrate (α_0) and the amplitude of oscillations

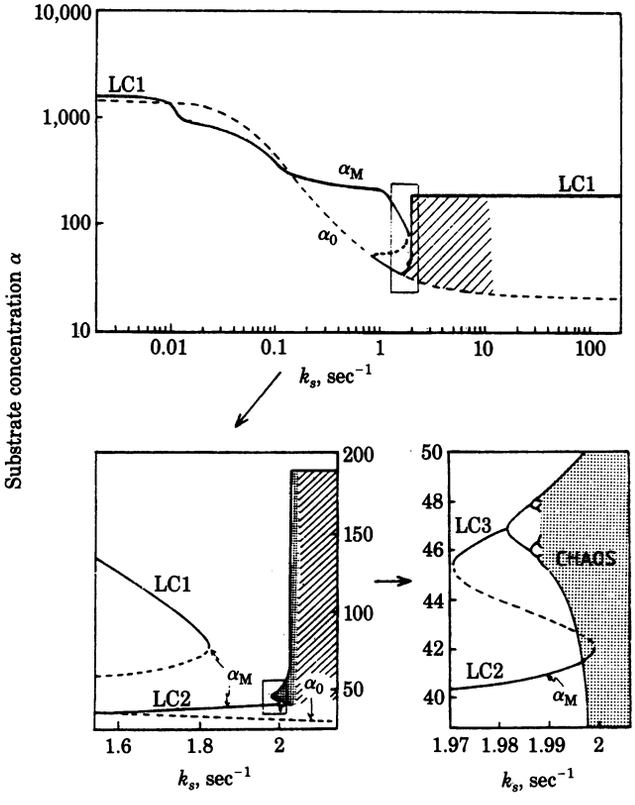

FIG. 1. (*Upper*) Bifurcation diagram as a function of the parameter k_s. The steady-state substrate concentration α_0 is shown (thin line) together with the maximum substrate value α_M during oscillations (thick line). Stable and unstable solutions are represented by solid and dashed lines, respectively; LC1, LC2, and LC3 are stable periodic solutions. The shaded area between $k_s = 1.99$ sec^{-1} and 2.034 sec^{-1} (seen more readily in lower diagrams) represents the domain of chaos. The hatched area between $k_s = 2.034$ sec^{-1} and 12.8 sec^{-1} represents a domain of complex periodic oscillations in which successive, decreasing maxima in α are observed over a period; the upper solid line bounding this domain represents the largest of these maxima. (*Lower*) Successive enlargements of the boxed domains in which hard excitation, birhythmicity, and chaos occur. Parameter values are: $v/K_{m1} = 0.45$ sec^{-1}, $\sigma_1 = \sigma_2 = 10$ sec^{-1}, $q_1 = 50$, $q_2 = 0.02$, $L_1 = 5 \times 10^8$, and $L_2 = 100$.

as measured by the maximum in α over a cycle (α_M). The stability properties of the steady state were determined by linear stability analysis, whereas stable and unstable oscillatory regimes were obtained by numerical simulations. The different types of behavior observed upon varying k_s are summarized in Table 1, and are discussed below.

Limit-Cycle Oscillations. At both extremes—i.e., at low and high values of k_s—the system displays simple oscillations of the limit-cycle type for the particular set of parameter values considered (see Fig. 2*a*). This observation can be explained by noting that for $k_s \to 0$ (i.e., $\gamma \to \infty$) and $k_s \to \infty$ (i.e., $\gamma \to 0$), the equations for α and β, in the limit of negligible d values (which limit will be considered here), reduce to those previously studied for glycolytic oscillations (16, 17), with an apparent first-order rate constant for removal of P_1 equal to σ_2 and $\sigma_2/(L_2 + 1)$, respectively. Linear stability analysis and phase-plane analysis of the reduced (α, β) system show that the steady state is unstable for these two values of the removal constant. The bifurcation diagram of Fig. 1 shows that these two asymptotic regimes are reached rapidly, when k_s goes below 10^{-2} sec^{-1} or above 10 sec^{-1}. As both regimes have a common origin, we shall refer to them as limit cycle 1 (LC1).

Hard Excitation. When k_s is increased from a low initial value, the system reaches a critical point at which the steady state becomes stable. As LC1 keeps its stability, there occurs a phenomenon of hard excitation (21) (see Fig. 2*b*): the system, starting from the steady state, returns to it upon slight perturbation but evolves to a stable periodic regime when the perturbation exceeds a threshold.

Birhythmicity. At further increase in k_s, the steady state becomes unstable, and a new stable periodic solution appears (limit cycle 2, LC2). As the LC1 still exists (see Fig. 1), the system can now choose between two stable periodic regimes, depending on initial conditions (Fig. 3*a*). We shall refer to this unusual phenomenon as "birhythmicity." For the same parameter values, the two types of rhythmic behavior differ significantly in period and amplitude and take place around different mean substrate levels. Each stable limit cycle possesses its own basin of attraction, defined as the set of initial conditions from which the system evolves to the particular periodic solution.

Between the two stable limit cycles, there is an unstable cycle. When the system departs from an initial condition close to the separatrix of the two basins of attraction, it may stay tran-

Table 1. Dynamic behavior of the regulated enzymatic system as a function of k_s

Parameter range, sec^{-1}	Observed behavior
$k_s \leq 0.792$	One limit cycle
$0.792 < k_s \leq 1.584$	One limit cycle and one stable steady state (hard excitation)
$1.584 < k_s \leq 1.82$	Two limit cycles (birhythmicity)
$1.82 < k_s \leq 1.974$	One limit cycle
$1.974 < k_s \leq 1.99$	Two limit cycles, one of which undergoes a sequence of period doubling leading to chaos
$1.99 < k_s \leq 2.034$	Aperiodic oscillations (chaos)
$2.034 < k_s \leq 12.8$	Complex periodic oscillations (including bursting)
$k_s > 12.8$	One limit cycle

Parameter values are those of Fig. 1. Only the asymptotic regimes are indicated; this eliminates unstable periodic trajectories. The variation in k_s considered could result from a continuous change in enzyme activity; a similar increase in phosphodiesterase and adenylate cyclase activity has been associated with behavioral transitions during development of the cAMP signaling system in *D. discoideum* (19).

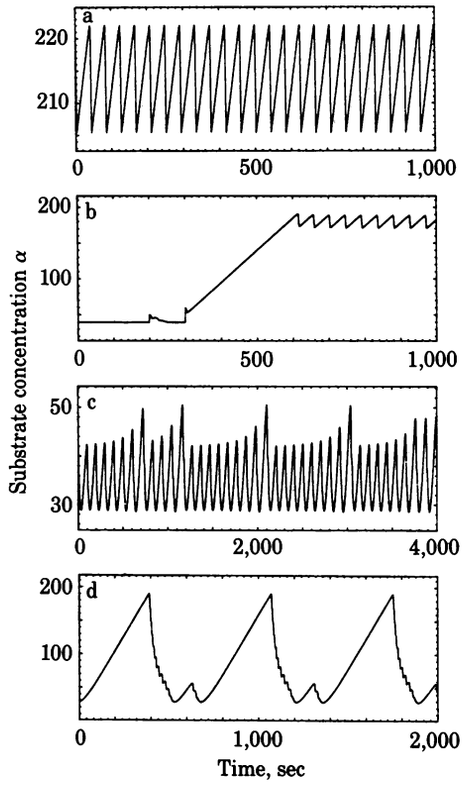

FIG. 2. Different behavioral modes of the regulated enzymatic system as a function of parameter k_s. Only the time evolution of the substrate concentration α is shown. (*a*) Simple periodic oscillations, $k_s = 0.6$ sec^{-1}. (*b*) Hard excitation, $k_s = 1.2$ sec^{-1}. (*c*) Chaos, $k_s = 2$ sec^{-1}. (*d*) Complex periodic oscillations, $k_s = 2.032$ sec^{-1}. The curves are obtained by numerical integration of Eqs. 2 for the parameter values of Fig. 1. These are physiologically acceptable values, close to those used in modeling glycolytic and cAMP oscillations (16–18).

siently on the unstable periodic trajectory and then be attracted by one of the two stable cycles as shown in Fig. 3*a*.

Period Doubling and Chaos. Upon further increase in parameter k_s, only one stable limit cycle (LC2) at first persists. Then, as shown in the enlargements in Fig. 1, there is a new hysteresis loop between two oscillatory regimes, LC2 and limit cycle 3 (LC3). LC3 appears in $k_s = 1.974$ sec^{-1}, whereas LC2 disappears in $k_s = 2$ sec^{-1}. A particularity of this birhythmic pattern is that the oscillatory regime LC3 undergoes a bifurcation beyond which the monoperiodic evolution of the substrate becomes unstable, and a period-2 oscillation, reflected by alternating higher and lower maxima, is observed. Period doubling often occurs along a sequence of successive bifurcations leading to trajectories of period 2, 4, 8, ..., and eventually to a trajectory of period 2^∞ (3, 22). The latter aperiodic oscillatory regime is referred to as "chaos" or "turbulence" (see ref. 7 for a recent account). Period doubling occurs in the present model from $k_s = 1.982$ sec^{-1} on, and chaos is reached in $k_s = 1.99$ sec^{-1} (see Fig. 2*c*). A sequence of period-doubling bifurcations is obtained for parameter v as for k_s, and preliminary results suggest that in both cases the transition to chaos obeys Feigenbaum's route to turbulence (22). That the behavior shown in Fig. 2*c* is chaotic has been established by a variety of diagnostics, such as sensitivity to initial conditions, Poincaré sections, return maps, and power-spectrum analysis. These results and the detailed transition to chaos will be discussed in a forthcoming publication.

Thus, between $k_s = 1.974$ sec^{-1} and 2 sec^{-1}, we observe the coexistence of a stable limit cycle (LC2) with, successively, a stable limit cycle of period 1, 2, 4, 8, ..., and chaos. In analogy with Fig. 3*a*, we show in Fig. 3*b* the passage from an unstable limit cycle to either chaos (upper curve) or a stable limit cycle (lower curve) for slightly different initial conditions.

Chaos is associated with the existence of a strange attractor (5, 23) in the phase space (α, β, γ) (Fig. 4*a*). The trajectory followed by the system is trapped by the attractor and wanders on it, on closely related paths, without ever passing through the same point. Hence, the elements of both randomness and periodicity which characterize this behavior.

From $k_s = 2.026$ sec^{-1}, the system undergoes large excursions in the phase space (Fig. 4*b*), corresponding to increased maxima in α during oscillations (Fig. 2*d*), with superimposed bursts in β and γ. Between $k_s = 2.026$ sec^{-1} and $k_s = 2.034$ sec^{-1}, the trajectory associated with the large excursions passes once or several times through a small loop, which is a vestige of the strange attractor of Fig. 4*a*. The trajectory may then be periodic (as in Fig. 4*b*) or chaotic, depending on the value of

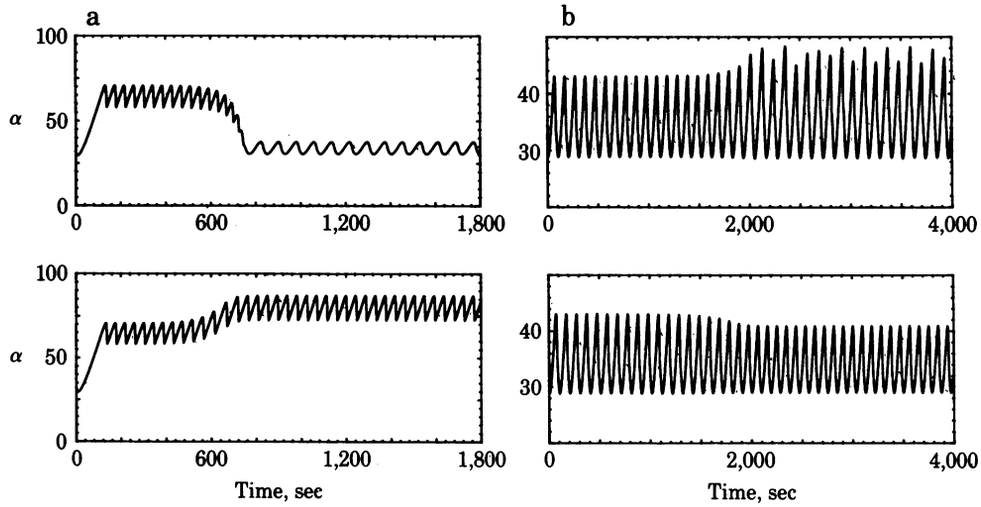

FIG. 3. Coexistence, for the same set of parameter values, of two stable periodic regimes (birhythmicity) (*a*) and of a stable periodic regime and chaos (*b*). The curves are obtained for the parameter values of Fig. 1, with $k_s = 1.8$ sec^{-1} for *a* and 1.99 sec^{-1} for *b*. In both cases, an unstable periodic trajectory is followed transiently by the system as it evolves towards either one of the asymptotic regimes. Initial conditions in *a* are: $\beta = 250$, $\gamma = 0.25$, upper-curve, $\alpha = 32.02223$, and lower-curve $\alpha = 32.02222$; initial conditions in *b* are: $\beta = 188.8$, $\gamma = 0.3367$, upper curve $\alpha = 29.19988$, and lower curve $\alpha = 29.19989$. The periods of the two stable periodic regimes in *a* are 79 sec and 44 sec, respectively.

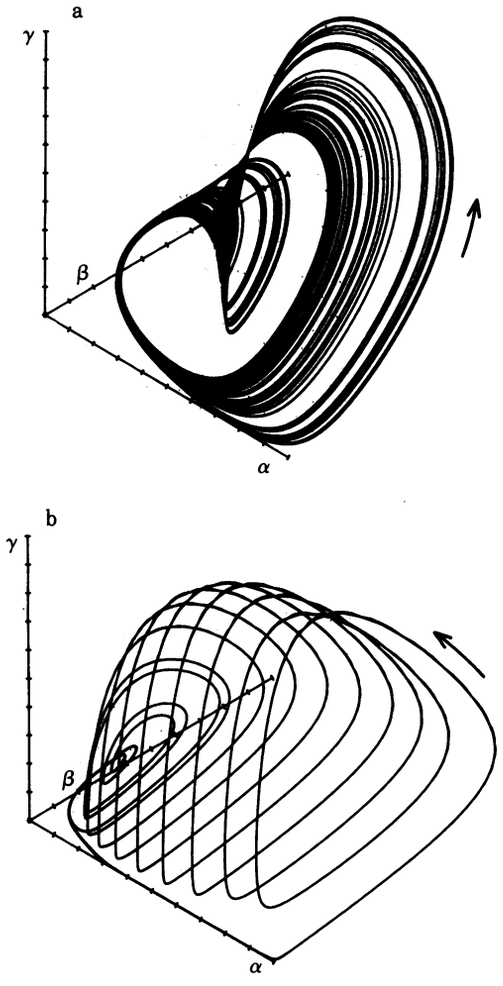

FIG. 4. Trajectories in the phase space (α, β, γ) associated with chaos (a) and with complex periodic behavior (b). The curves correspond to the substrate evolution depicted in Fig. 2 c and d, respectively, and have been obtained by integration of the kinetic equations from t = 0–5,000 sec. The ranges of variation of α, β, and γ in a are α = 28.44–50.6, β = 50.05–351.1, and γ = 0.05–2.28 and in b are α = 28.18–190.5, β = 0.14–604.0, and γ = 0.00014–8.8.

k_s. In the latter case, the data suggest a phenomenon of intermittency (24).

Complex Periodic Oscillations. As k_s increases beyond 2.034 sec^{-1}, the trajectory does not pass anymore through the small loop and remains periodic, although the oscillations exhibit several bursts in β and γ over a period. Bursts become less and less noticeable as k_s approaches 12 sec^{-1}; finally, a simple periodic regime of oscillations is restored in k_s = 12.8 sec^{-1}. The large-amplitude oscillations that end the domain of chaos abruptly reach a plateau in the maximum of α (see Fig. 1). It is intriguing that this plateau in the amplitude of LC3 seems to extrapolate to the amplitude of LC1 for k_s = 1 sec^{-1}. That LC1 is recovered upon cessation of bursting, at large values of k_s, has been demonstrated above.

Behavior in the v–k_s Parameter Space. To gain further insight on the relative occurrence of each of the above phenomena, we have determined the behavior of the system in the parameter space v–k_s (Fig. 5). Three main conclusions emerge from this study. (*i*) The bifurcation sequence of Fig. 1 is obtained in a restricted range of v values. Some behavioral modes disappear when v moves outside this range. (*ii*) The domain of chaos is located near the domains of hard excitation and birhythmicity and follows a sequence of period-doubling bifurcations. Moreover, it precedes a domain of large-amplitude, complex periodic oscillations. (*iii*) As to the frequencies of occurrence of the different behavioral modes, the data of Fig. 5 indicate that chaos and birhythmicity are relatively rare events in comparison with complex periodic oscillations and hard excitation, which are themselves much less frequent than simple periodic oscillations.

DISCUSSION

The present results show that when two instability-generating mechanisms are coupled in series, the continuous variation in a parameter can give rise to a sequence of widely different self-organization phenomena such as simple and complex periodic oscillations of the limit-cycle type, random oscillations (chaos), and coexistence of one stable limit cycle with either a stable steady state (hard excitation), a second stable limit cycle (birhythmicity), or chaos.

Although in principle most (if not all) of the above behavioral modes can be obtained with a single instability-generating mechanism, the analysis of models based on a single feedback loop suggests that this is not a typical situation. Indeed, the models previously studied for glycolytic and cAMP oscillations only showed the existence of simple periodic behavior or multiple steady states (16–19). Hard excitation, birhythmicity,

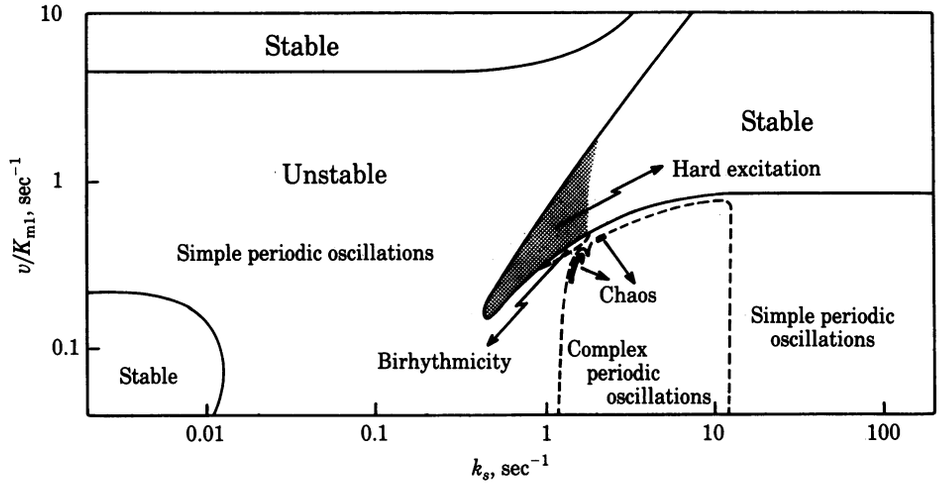

FIG. 5. Behavioral domains in the v–k_s parameter space. Stable and unstable refer to the steady state. The various behavioral domains have been determined by numerical simulations.

chaos, and complex periodic oscillations clearly originate here from the interplay between the two positive feedback processes, which are both potential sources of oscillatory behavior. How the two instability-generating mechanisms precisely cooperate to induce the above phenomena remains to be determined. Another question to be investigated is whether or not similar phenomena can arise from the coupling between positive and negative feedback processes—a situation which is more probable from a physiological point of view.

Some of the behavioral modes described above have been experimentally observed. Simple and complex periodic oscillations and chaos have been reported for peroxidase (25) and for the Belousov–Zhabotinsky reaction (26, 27). The related Briggs–Rausscher reaction exhibits hard excitation (28). Complex modes of oscillatory behavior have been observed in the yeast glycolytic system (12, 13), for which evidence for hard excitation also has been reported (1). The present study suggests that models comprising more than one regulatory feedback may provide a unifying mechanism for explaining these phenomena. Such models also would account automatically for the fact that simple periodic oscillations are the rhythm most commonly observed in glycolysis because this behavior is also the type of oscillation most frequently found in the present model.

The phenomenon of birhythmicity, to our knowledge, has not yet been observed in biological or chemical systems. This phenomenon would be demonstrated if an oscillatory system, upon some suprathreshold perturbation, would evolve to a new oscillatory regime with different period and amplitude. Naturally this demonstration would be of value only if the perturbation needed for the switching would not affect the system's parameters. The transition to chaos in the Belousov–Zhabotinsky reaction accompanies, as in the present model, the rapid passage from a small- to a large-amplitude limit cycle upon variation of a single parameter (27, 29). As birhythmicity here precedes this abrupt transition, the above results suggest a search for multiple limit cycles in the chemical reaction in the immediate neighborhood of the chaotic domain.

From a theoretical point of view, the coexistence of two stable periodic regimes has been reported in the modeling of a sequence of exothermic reactions (30) and of a complex genetic regulatory circuit (31) and in a problem of nonlinear optics (32). Tyson, in his study on the coupling in series of two oscillatory models (33) did not observe birhythmicity but found complex periodic oscillations. He noted the apparently random character of some of the solutions, but no attempt was made at the time to relate them to chaos. As to biochemical systems, we have recently become aware of a work by Schulmeister and Sel'kov (34) who obtained complex periodic oscillations in a model of an oscillating enzyme reaction involving inhibition by a cofactor and reversible deposition of substrate. The trajectories associated with these periodicities in the phase plane were referred to as "folded" limit cycles. The authors reported the coexistence of two stable limit cycles, simple or folded, in a narrow range of substrate deposition rates. Birhythmicity and chaos also were reported for a three-variable, modified Lotka model (35). However, a detailed characterization of the birhythmic or chaotic domains in parameter space has not been carried out in these models.

Birhythmicity requires stringent conditions both on the kinetics and on the parameter values. Thus, it is probably less frequent than its well-known stationary counterpart, bistability, in which two stable steady states coexist for a given set of experimental conditions, as demonstrated for several biochemical systems such as the peroxidase reaction (36). Birhythmicity provides a new mode of physiological regulation as it allows for a switch between two periodic regimes upon suitable perturbation. It would be of interest to search for this phenomenon not only in chemical or metabolic oscillatory systems but also in the many rhythmic processes occurring in the brain, which arise precisely from multiple regulatory interactions between neurons.

The remarkable property of chaos is the emergence of random behavior in a system subjected to a constant input and governed by deterministic laws. The present study throws light on the stringent regulatory prerequisites for the occurrence of this phenomenon in biological systems. That chaos occurs in a rather small domain of the parameter space and is much less frequent than periodic oscillations is satisfactory, in view of the regularity of most biological rhythms.

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