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Complex dynamics of mass-closed coupled autocatalytic systems in response to minute asymmetric perturbations

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Abstract

The role of kinetic coupling in catering to a remote-control mechanism for the onset and regulation of self-organization phenomena in a multicompartmental biochemical system has been examined. Using two cyclic autocatalytic reaction networks operating in two chambers separated by a membrane and coupled through a common cofactor, it has been demonstrated that (i) in response to asymmetric perturbations, the coupled reaction networks exhibit a variety of temporal self-organization phenomena such as bistability, multiple periodicity, hard excitation and coexistence of aperiodic oscillation with limit cycle even in mass-closed conditions; (ii) without disturbing a network directly, its dynamic behaviour can be regulated by perturbing some other network kinetically coupled to it and (iii) the dynamics of two coupled networks can be made to flip-flop between oscillatory and steady-states simply by modulating the time of application of external perturbations. The extreme sensitivity of this model to minute asymmetric fluctuations in the environment can predict how the impact of local changes in physico-chemical conditions can be transmitted from one compartment to another through coupled biochemical pathways in a living cell. © 1997 Elsevier Science B.V.

Keywords: Coupled autocatalytic reactions; Multicompartmental system; Multiple periodicity; Aperiodic oscillation; Asymmetric perturbations; Remote control mechanism

1. Introduction

In complex chemical or biological systems, reactions are, in general, coupled to one another. Analysis of self-organizational phenomena in such systems [1] might provide a better understanding of the inter-pathway regulations of such coupled reaction networks. Realizing the importance of such study, a large number of analytical [2–5] and map [6] models have been proposed to analyze the self-organizational properties of coupled reaction systems under varying environmental conditions. In all the proposed models, complex dynamics like multiple periodicity, bistability or subharmonic oscillations have been demonstrated, assuming the systems to be open to mass flow [2–7]. Besides, these models generally consider the existence of diffusional flow [3,6], imperfect mixing [8] or non-ideal interactions [6] in the system leading to highly nonlinear, complex, ordinary or partial differential rate equations that act as the source of spatial and/or temporal instabilities in the system. It would be interesting to examine

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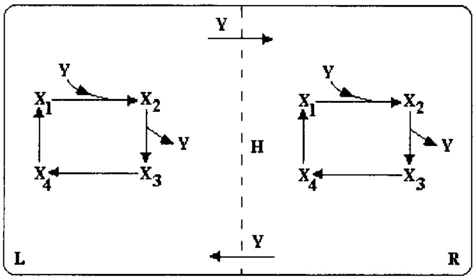
whether kinetic models with relatively simpler rate equations and environmental conditions can lead to complex dynamic phenomena observed in such models. To address this issue, the present report aims at developing a model of coupled cyclic autocatalytic reaction networks (CCARN) obeying the law of mass action in a homogeneous isotropic mass-closed system with no nonideal interaction or diffusional flow.

A major source of temporal self-organization in biochemical systems arises out of autocatalytic reaction networks [1,5,9,10]. A unique feature of a cyclic, autocatalytic reaction network is that it is capable of exhibiting stable, conservative oscillations over a wide range of parameters even in a mass-closed system [11]. In the presence of an unbuffered cofactor [12], such a mass-closed reaction network can display period-doubling bifurcations leading to chaos. It is known [4,5] that the interplay of two instability-generating mechanisms may result in a variety of new modes of dynamic behaviour of the system that are significantly different from those exhibited by these mechanisms individually. It is in this context that the present study examines whether kinetic coupling between two such autocatalytic reaction cycles can enhance the complexity of the dynamic behaviour of the coupled system. It has been shown that two identical cyclic, autocatalytic reaction networks, when coupled through a common cofactor, can exhibit a wide spectrum of temporal self-organization such as bistability, hard excitation and coexistence of limit-cycle and aperiodic oscillation for suitable values of system parameters even under mass-closed conditions.

2. The CCARN model

To examine how the dynamic behaviour of a biochemical system changes after coupling, we have considered two identical cyclic autocatalytic reaction networks in a mass-closed system functioning in two compartments separated by an imaginary membrane and coupled through a common cofactor (Y), which alone can pass through the membrane (Fig. 1). The whole system is closed to mass flow, but energy flow takes place to drive the reactions. It has been assumed that the rate of diffusion of Y is much faster than the rates of reactions, so that the concentration of Y remains the same in both the compartments. This assumption allowed us to specifically examine the temporal self-organization in the system and to eliminate the diffusion terms in the rate equations that rules out the possibility of spatial instability. The rate equations of the scheme (Fig. 1, lower panel) are given by,



$$\begin{aligned} X_1^i + X_2^i + Y &\longrightarrow 2X_2^i \\ X_2^i + X_3^i &\longrightarrow 2X_3^i + Y \\ X_3^i + X_4^i &\longrightarrow 2X_4^i \qquad \cdots\cdots\cdots \quad \text{R1} \\ X_4^i + X_1^i &\longrightarrow 2X_1^i \end{aligned}$$

Fig. 1. The CCARN model. Upper panel: two identical cyclic autocatalytic reaction networks operative in two compartments (L and R) separated by a hypothetical membrane H, impermeable to the reacting macromolecules X_j. The two reaction cycles are coupled through a common cofactor Y which only can pass through the membrane. The whole system is closed to mass-flow but energy flow takes place to drive the reaction cycles. Lower panel: reaction scheme occurring in each compartment.

$$\frac{dx_1^i}{dt} = k_4^i x_4^i x_1^i - k_1^i x_1^i x_2^i y \qquad (1a)$$

$$\frac{dx_2^i}{dt} = k_1^i x_1^i x_2^i y - k_2^i x_2^i x_3^i \qquad (1b)$$

$$\frac{dx_3^i}{dt} = k_2^i x_2^i x_3^i - k_3^i x_3^i x_4^i \qquad (1c)$$

$$\frac{dx_4^i}{dt} = k_3^i x_3^i x_4^i - k_4^i x_4^i x_1^i \qquad (1d)$$

where k_r^i is the kinetic constant of rth reaction, x_j^i is the concentration of jth species in the ith

(i = L for left and R for right) compartment and y is the free cofactor concentration.

The mass-conservation equations are $\sum_{j=1}^{4} x_j^i =$ constant (say, 1 M) and, $y + x_2^L + x_2^R = m$ where m is the total concentration of the cofactor both in free and bound form in the system. At steady states,

$$\frac{\mathrm{d}x_j^i}{\mathrm{d}t} = 0 \,(\text{where, } i = \mathrm{L,R};\, j = 1 \text{ to } 4) \ldots \ldots \qquad (2)$$

The linearized rate equations around the steady-states are given by:

$$\begin{bmatrix} \delta\dot{x}_1^{\mathrm{L}} \\ \delta\dot{x}_2^{\mathrm{L}} \\ \delta\dot{x}_3^{\mathrm{L}} \\ \delta\dot{x}_1^{\mathrm{R}} \\ \delta\dot{x}_2^{\mathrm{R}} \\ \delta\dot{x}_3^{\mathrm{R}} \end{bmatrix} = \begin{bmatrix} -a^{\mathrm{L}} & -b^{\mathrm{L}} & -a^{\mathrm{L}} & 0 & c^{\mathrm{L}} & 0 \\ d^{\mathrm{L}} & -c^{\mathrm{L}} & -e^{\mathrm{L}} & 0 & -c^{\mathrm{L}} & 0 \\ a^{\mathrm{L}} & f^{\mathrm{L}} & a^{\mathrm{L}} & 0 & 0 & 0 \\ 0 & c^{\mathrm{R}} & 0 & -a^{\mathrm{R}} & -b^{\mathrm{R}} & -a^{\mathrm{R}} \\ 0 & -c^{\mathrm{R}} & 0 & d^{\mathrm{R}} & -c^{\mathrm{R}} & -e^{\mathrm{R}} \\ 0 & 0 & 0 & a^{\mathrm{R}} & f^{\mathrm{R}} & a^{\mathrm{R}} \end{bmatrix} \times \begin{bmatrix} \delta x_1^{\mathrm{L}} \\ \delta x_2^{\mathrm{L}} \\ \delta x_3^{\mathrm{L}} \\ \delta x_1^{\mathrm{R}} \\ \delta x_2^{\mathrm{R}} \\ \delta x_3^{\mathrm{R}} \end{bmatrix} \ldots \ldots \qquad (3)$$

where $a^i = k_4^i \bar{x}_1^i$, $b^i = \{k_4^i + k_1^i(\bar{y} - \bar{x}_2^i)\}\bar{x}_1^i$, $c^i = k_1^i \bar{x}_1^i \bar{x}_2^i$, $d^i = k_1^i \bar{x}_2^i \bar{y}$, $e^i = k_2^i \bar{x}_2^i$, $f^i = \{(k_2^i + k_3^i)/k_3^i\}k_4^i \bar{x}_1^i$(bars and dots indicate steady-state values and time derivatives of the corresponding variables)

The key dynamical features of the model are analyzed by studying the dynamics of the system for different values of the system parameters and initial conditions using 4th order Runge-Kutta method of numerical simulation.

3. Results

If the cofactor is buffered, i.e., present in large excess in the system, its activity can be considered to remain constant and hence can be included into the relevant kinetic constants. Under this condition, the two reaction cycles apparently behave like independent systems, with no coupling between them. When the cofactor is unbuffered, its concentration plays a key role in governing the system dynamics.

When the initial conditions of all the reacting species and the values of kinetic constants are identical in two compartments, the coupled networks either exhibit limit-cycle oscillation or approach to steady-state depending upon the values of system parameters. For example, when $k_1 = 10\ \mathrm{s}^{-1}$, $k_2 = k_3 = k_4 = 1\ \mathrm{s}^{-1}$ for both the networks and $m = 0.4$ M, the eigenvalues of the Jacobian matrix in Eq. (3) are given by

$$\lambda_1 = -1.094, \quad \lambda_{2,3} = 5.551 \times 10^{-17} \pm 0.458 \times i, \quad \lambda_{4,5} = 0.022 \pm 0.317 \times i, \ \lambda_6 = 1.383 \times 10^{-16} \ldots \ldots \qquad (4)$$

As the real parts of the complex conjugate eigenvalues $\lambda_{2,3}$ and $\lambda_{4,5}$ are positive, both the reaction networks in the system exhibit limit-cycle oscillations (Fig. 2a). The values of the kinetic constants and the initial concentrations of the reacting species giving the limit-cycle oscillation in Fig. 2a will be taken as the reference condition in all subsequent analysis. When m is varied, keeping all the kinetic constants same as the reference condition, the networks L and R exhibit limit-cycle oscillations for $0.35\ \mathrm{M} \leq m < 0.98$ M and approach steady-states for $m < 0.35$ M (Fig. 2b, dotted line) or $m \geq 0.98$ M, provided the initial conditions are identical in both the compartments..

The dynamic properties of the system are stable against any arbitrary perturbations (both small and large), when the same perturbation is applied simultaneously to both the networks L and R. For example, when the kinetic constants remain same as the reference condition and $m = 0.4$ M, the system exhibits the same limit-cycle oscillation as in Fig. 2a for any arbitrary set of 'symmetric' initial conditions such that $(x_j^{\mathrm{L}})_{t=0} = (x_j^{\mathrm{R}})_{t=0}$ for all values of $j = 1$ to 4. Similarly, when $m = 0.2$ M, for all values of 'symmetric' initial conditions, the system approaches to the same steady-state as in Fig. 2b (dashed line). In other words, when both the networks are perfectly synchronized and operate under identical environmental conditions, its dynamic properties become insensitive to the initial conditions, and the system can be considered to be structurally stable, as the conventional structurally unstable systems like the Lotka-Volterra model [1], in general, cannot exhibit such properties. But desynchronization of the two networks (L and R, Fig. 1) by introducing asymmetry in the reaction conditions in the two chambers such as variation in initial concentrations of reacting species, values of kinetic constants or external perturbations induces instability in the system resulting in different but distinct complex dynamic behaviour as enumerated below.

3.1. Variation in initial conditions

Even a minute difference in the initial conditions (Fig. 2b,c,d) in two compartments results in transition of both the reaction cycles either from one steady-state to other steady (data not shown) or oscillatory states (Fig. 2b) or from a state of limit-cycle oscillation to aperiodic oscillation (Fig. 2c,d). For example, when the initial concentrations of x_1 and x_3 in the left compartment are changed to $x_1^L = 0.9699$ M (i.e., 0.01% decrease) and $x_3^L = 0.0101$ M, keeping all other conditions the same as the control, the dynamic behaviour of all the species of not only the left, but also the right compartment will experience a drastic change. For $m = 0.2$ M, the system exhibits hard excitation [4,5], when the species in the two networks oscillate 180° out of phase (Fig. 2b, solid lines), instead of approaching the steady-state to which the system evolves under reference condition (Fig. 2b, dotted lines). At $m \geq 0.98$, the two reaction cycles evolve to two steady-states that are different from the one obtained under

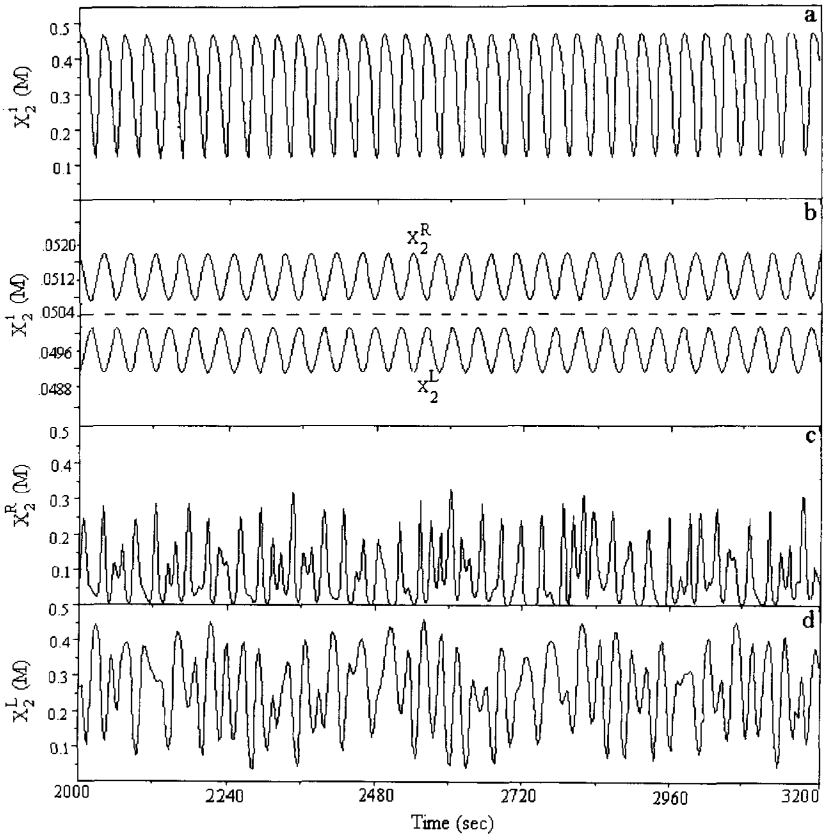


Fig. 2. Initial condition dependent changes in the dynamic behaviour of the coupled networks. The time evolution of only x_2 has been shown. The initial values $x_1 = 0.97$ M, $x_2 = x_3 = x_4 = 0.01$ M, $k_1 = 10\ \mathrm{s}^{-1}$, $k_2 = k_3 = k_4 = 1\ \mathrm{s}^{-1}$ in both compartments have been taken as the reference condition for subsequent analysis. For $m = 0.4$ M, both the networks exhibit limit-cycle oscillation (a) and for $m = 0.2$ M, both evolve to the same steady-state (b, dashed line) under reference condition. When the initial concentrations of X_1 and X_3 in the left compartment are changed to $x_1^L = 0.9699$ M and $x_3^L = 0.0101$ M, keeping all other conditions invariant, for $m = 0.2$ M, x_2^L and x_2^R evolve to twin states of oscillation in 180° out-of-phase exhibiting hard excitation (b) and for $m = 0.4$ M, both x_2^L and x_2^R switch from limit cycle to aperiodic oscillation (c,d). Transient states are not shown here.

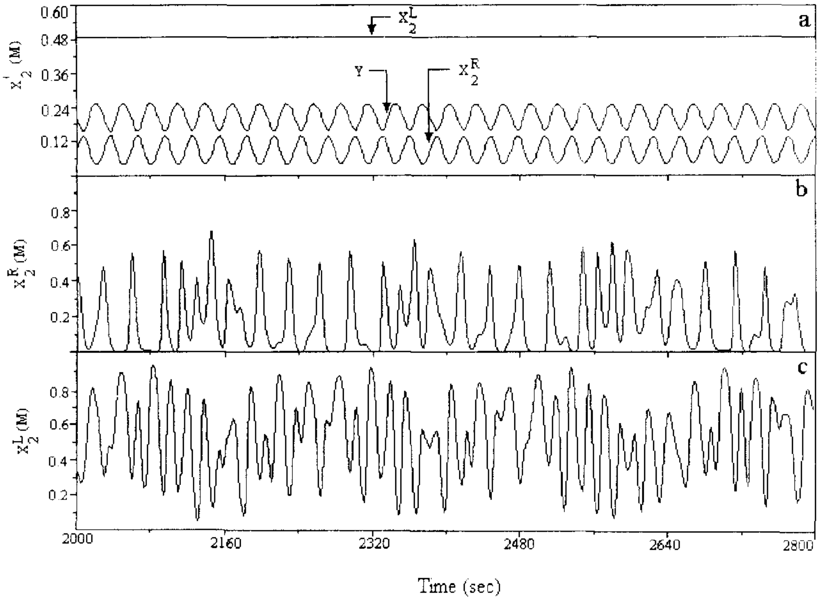


Fig. 3. Response of the system to minute asymmetric variations in kinetic constants k_i^L for different values of m. When one of the kinetic constants, say k_3^L, is changed from 1 s^{-1} to 1.0001 s^{-1}, keeping all other kinetic constants and initial conditions same as the reference condition, for $m = 0.8$ M, the right reaction cycle, along with the cofactor Y, exhibits small-amplitude oscillation, while the left cycle evolves to a steady state (a) and for $m = 0.4$ M, both the reaction cycles exhibit aperiodic oscillation (b,c). Transient states are not shown.

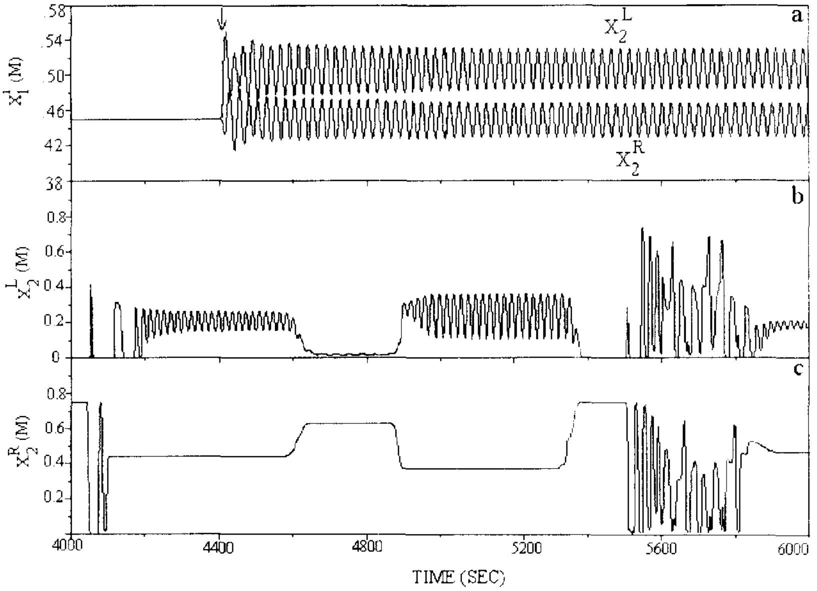


Fig. 4. Response of the coupled networks to one-time addition of X_3 (say) only in the left compartment for different values of m. For $m = 0.2$ M, x_1^L and x_1^R move away from the steady-state to exhibit slowly damping coupled oscillations 180° out-of-phase (hard excitation). The arrow indicates the time of addition of 0.1 M of x_3^L (a). For $m = 0.75$ M, x_2^L shows irregular transitions between steady-states and random oscillation (b) and x_2^R switches from one transient stationary state to another (c) for a long time ($>$ 4500 s) in response to one-time addition of 0.001 M of x_3^L. Finally, the reaction networks evolve to either a pair of steady-states (soft excitation) or a combination of steady and oscillatory states. Initial and final states are not shown here.

reference condition (bistability). For $m = 0.4$ M, both x_2^L and x_2^R switch from limit-cycle to aperiodic oscillation (Fig. 2c,d). It is worth mentioning at this point that such transitions from limit cycle oscillations to aperiodic oscillations do not occur through the cascade of period doubling bifurcations as seen in the case of deterministic chaos. However, the aperiodic oscillations, although reproducible for the same set of initial conditions, are highly sensitive to minute variation in such conditions. Interestingly, if the initial concentrations of x_1^R and x_3^R are also changed along with x_1^L and x_3^L by the same amount, the system dynamics becomes identical with that under reference condition (Fig. 2a or Fig. 2b (dotted line)) for corresponding values of m. The occurrence of birhythmicity and a route to turbulence through the fusion of two limit cycles in a mass-closed autocatalytic system have been demonstrated earlier by Mori and Di Cera [13]. However, in the present model, birhythmicity and aperiodic oscillations occur whenever there is even a minute asymmetry in the environmental conditions in the two compartments of the system.

3.2. Variation in kinetic constants

A small change in the value of any of the kinetic constants of one reaction cycle causes a dramatic change in the dynamic behaviour of both the reaction cycles (Fig. 3). To demonstrate this, for different values of m, k_4^L has been increased from 1 to 1.0001 s^{-1} keeping all other kinetic constants including k_4^R the same as the reference condition. For $m = 0.8$ M, the reaction cycle in the right compartment as well as the cofactor exhibit small-amplitude oscillation, while that in the left compartment evolves to a steady-state (Fig. 3a) that is different from the original steady-state for $k_4^L = k_4^R = 1.0$ s^{-1}. For $m = 0.4$ M, both the reaction-cycles switch from limit-cycle to aperiodic oscillation (Fig. 3b,c), while for $m = 0.2$ M, they evolve to different steady-states, close to one another (data not shown).

3.3. Asymmetric external perturbations

The system is, in general, stable to small external perturbations, such as mid-course one-time addition of one or more species, when they are simultaneously applied to both the compartments in the same magnitude and direction. However, any asymmetry in the perturbations (e.g., if applied only to one compartment or to both the compartments in same magnitude but having a little time delay between the two), will get amplified giving rise to a variety of complex dynamic phenomena. The total concentration of the cofactor regulates the response of the system to asymmetric external perturbations. For example, in response to the addition of 0.1 M of x_3 only to the left compartment at low values of m, the system exhibits hard excitation [4,13] from a stable steady-state to twin states of oscillation of the species in the two compartments (Fig. 4a). The amplitude of oscillation depends on the magnitude of perturbation.

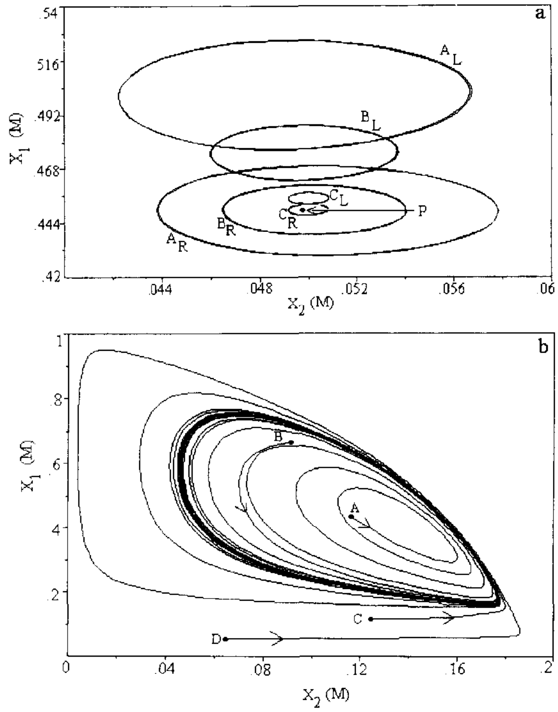


Fig. 5. Phase-space trajectories (x_2 vs. x_1) of the coupled cycles for different reaction conditions. (a) A_i, B_i and C_i represent the trajectories of x_2 vs. x_1 in ith compartment (i = L,R) in response to one-time addition of x_3 only to the left compartment by 0.1, 0.05 and 0.01 M, respectively, when $m = 0.2$ M. P represents the initial steady-state of both the reaction cycles. (b) Limit-cycle oscillation of both the reaction cycles under the reference condition (same as in Fig. 2a). For different symmetric initial conditions represented by A, B, C and D, the trajectories of x_2 vs. x_1 approach the same closed loop.

In other words, such oscillations represent centre (Fig. 5) in contrast to the limit cycle oscillations observed in the reference condition (Fig. 5b), where from different symmetric initial conditions, the system approaches to the same closed loop in the phase space. For high values of m (≥ 0.98 M), following such asymmetric perturbations, the system goes from one steady-state to another. For 0.62 M $< m < 0.772$ M, the system exhibits limit-cycle oscillations under identical reaction conditions in two compartments. Upon a minute perturbation to x_3^{L} and/or x_4^{L}, the system exhibits irregular abrupt transitions between steady-states and the states of damped or aperiodic oscillations for a long time (Fig. 4b,c), before it comes to a state where x_2^{L} and y exhibit a stable oscillation, but x_2^{R} evolves to a steady-state or both x_2^{L} and x_2^{R} along with y attain steady-states (data not shown). These irregular dynamics are extremely sensitive to the magnitude, direction and time of application of external perturbations. It is intriguing to see if such sensitivity can be used to drive the reaction-cycles to desired states by switching them between different behaviours similar to control/anti-control of chaos [14,15].

For 0.772 M $< m \leq 0.8$ M, no such long-lasting irregular temporal behaviour could be observed in response to external perturbations. Instead, following asymmetric perturbation, one network evolves to a steady-state and the other exhibits stable oscillation (Fig. 6). The phase of the reactions at the time of perturbation determines which of the two reaction-cycles will oscillate, and which one will reach the steady-state. For example, for $m = 0.8$ M, under symmetric environmental conditions in two chambers, both the networks exhibit stable two-cycle oscillation (Fig. 6, A). A small perturbation at any point during the uphill journey of x_3^{L} from minima to maxima (e.g., points 1 or 2, Fig. 6, inset) (keeping x_3^{R} invariant), drives the reaction networks in the left compartment to the oscillatory states (B_1 or C_1, Fig. 6) and that in the right compartment to the steady-states (B_2 or C_2, Fig. 6), while a perturbation in x_3^{L} at any point during its downhill journey results (points 3 or 4, inset, Fig. 6) in an opposite behaviour (i.e., the right network goes to the oscillatory and the left to the steady-state). This indicates that the dynamics of the two reaction cycles can be made to flip-flop between oscillatory and steady-states by setting the time of inducting the perturbation. The results presented here indicate that without disturbing the reaction network in the right chamber directly, its dynamic behaviour can be regulated through proper modulation of the perturbation applied to the reaction cycle in the left chamber. The extreme sensitiv-

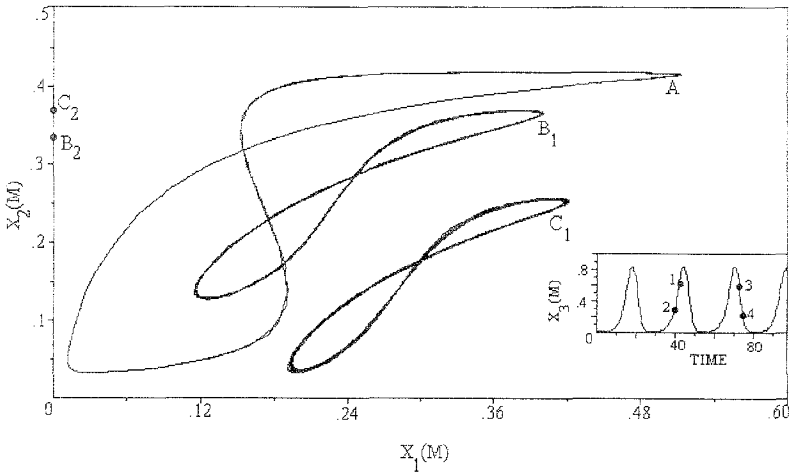


Fig. 6. Changes in trajectories in the phase–space (x_1, x_2) in response to addition of 0.001 M of x_3 only to the left chamber at different phases of oscillation (inset) for $m = 0.8$ M. Before addition of x_3, both networks exhibit identical two-cycle oscillation (A). Upon addition of x_3^{L} at points 1 and 2 (inset), the left reaction network oscillates (C_1 and B_1, respectively), but the right network evolves to steady-states (C_2 and B_2). Upon perturbations at points 3 and 4, the right network follows the trajectories C_1 and B_1, respectively, representing two-cycle oscillations, while the left network goes to the steady-states C_2 and B_2.

ity of the system to minute asymmetric environmental conditions, therefore, may provide a means of remote control of the system dynamics through selective application of perturbations. In other words, the kinetic coupling between different networks imparts to the system new modes of interpathway regulation of its temporal performance, as often observed in living cells.

4. Discussion

The present report describes a multicompartmental kinetic model (CCARN), which demonstrates the switching between the attractors or coexistence of aperiodic oscillation with limit cycle in response to minute asymmetry in the environmental conditions. Considering a homogeneous isotropic reaction system obeying the law of mass-action and ideal-solution approximation, the present model demonstrates that mere kinetic coupling can lead to complex self-organizational processes such as multiple periodicity or hard excitation under mass-closed condition. Some of the salient features of the proposed model are as follows: (i) when two identical cyclic networks of autocatalytic reactions occurring in two chambers are coupled through a common cofactor, a minute variation in the environmental conditions in one chamber can induce in both the chambers a wide variety of self-organizational phenomena such as hard excitation, bistability and the coexistence of periodic and aperiodic regimes even under mass-closed conditions; (ii) without disturbing a reaction network directly, its self-organizational properties can be adjusted by perturbing some other reaction network(s) kinetically coupled to it; and (iii) the kinetic coupling between networks might provide a remote-control mechanism for fine-tuning the dynamic behaviour of the system.

These features are extremely useful in interpreting the high level of complexity and self-organization in living cells, which are achieved through the interplay of different instability-generating mechanisms [1]. It is possible to have a better understanding of the physiological regulations of living systems by coupling suitable sources of oscillatory phenomena, as it allows to examine how the system switches from one periodic regime to another after even mild perturbations. It has already been suggested that when two enzymatic reactions having positive feedback loops are coupled in series [4] or in parallel [5], wide varieties of complex dynamic phenomena including hard excitation and birythmicity may be generated. However, in those studies, no attempts had been made to demonstrate the inter-network remote control of the reaction dynamics described in the present analysis.

To develop CCARN, two assumptions have been made: (i) all the reacting species are subjected to conservation of mass; and (ii) the rates of diffusion of the cofactor across the membrane is much faster than the rates of reactions in the system. The first assumption allows the evaluation of the complexity of the self-organizational process in coupled reactions even when there is no exchange of mass with the environment. The second assumption has been made to rule out the possibility of spatial instability so that the temporal self-organization in the system can be studied exclusively. However, these assumptions do not restrict the use of CCARN only for mass-closed systems. The dynamic behaviour of coupled reactions in open systems can also be examined using this model by incorporating the input/output terms in the rate Eqs. (1a), (1b), (1c) and (1d). For systems in which the rate of diffusion of the cofactor is slow, diffusional factors need to be considered in the rate equations. However, the conclusions drawn from the analysis presented here will remain valid in open systems with slower diffusion fluxes. Under such conditions, the system will display more complex spatio-temporal organization than that predicted by the model described here.

Although CCARN deals with autocatalytic reaction networks following the law of mass action, it has been observed that the conclusions derived by the model do not depend explicitly on any particular kinetics, and hence are valid for other types of instability generating mechanisms such as the presence of feedback loops, cooperative interactions, or other types of complex kinetics.

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