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Kinetic asymmetry as a key source of functional diversity in biochemical networks

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Abstract

From the analysis of the dynamic properties of various symmetric and asymmetric kinetic schemes, the present report demonstrates that all kinetic schemes, which can be hypothetically divided into two equal halves about an axis of mirror symmetry, are endowed with structural metastability under mass-closed conditions. In mass-closed symmetric schemes, absolute symmetry in reaction conditions in two halves is essential for the occurrence of ordered dynamic behaviour. Even an infinitesimal deviation from the symmetry relations instantaneously drives such systems from limit-cycles to turbulence. Reaction schemes with no axes of symmetry may exhibit a large variety of complex, structurally stable temporal order for wide ranges of values of system parameters and variables. Kinetic asymmetry, therefore, may confer to biochemical networks the functional diversity as well as stability against environmental perturbations. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Symmetric schemes; Structural metastability; Asymmetric perturbations; Dynamic order; Turbulence

1. Introduction

The phenomena of self-organization impart to biological systems the flexibility which permit them to regulate their chemical and biological activities and thus, endow upon them the sophisticated structural/functional organization [1,2]. The non-linear kinetics of numerous biochemical reactions constitutes the major source of dynamical order that prevails in living systems. Depending on the environmental conditions, these reactions can generate a large variety of complex dynamic phenomena like complex oscillations, multiple periodicity, hard excitation or chaos [1–5]. The more complex and ordered the system dynamics is, the higher is the level of biological organization achieved.

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Mathematical models of oscillatory chemical or biochemical networks generally consider reaction schemes having feedback or autocatalytic pathways leading to symmetry-breaking instabilities [1]. One of the necessary conditions for acceptability of these models is that they must exhibit structural stability [1,6]. In other words, a kinetic system can have spatial or temporal organization only when its dynamic properties remain invariant for a finite range of initial conditions. The distinct type of structural stability for two identical coupled cyclic autocatalytic reaction networks (CCARN model) occurring in different compartments of a system has recently been reported [7]. The system exhibits ordered behaviour (limit-cycles or steady-states), when reaction conditions are exactly identical in both the compartments. Such dynamic behaviours are stable against any arbitrary 'symmetric perturbations' (even large ones). Perturbations are referred to as 'symmetric' when they are applied simultaneously in the same magnitude and direction to both the networks. However, the presence of even an infinitesimal asymmetry in initial conditions, parameter values or external perturbations causes an abrupt transition of the system from ordered, periodic behaviour to turbulence. Systems, the dynamic properties of which are stable against arbitrarily large values of symmetric perturbations, but unstable against minute asymmetric fluctuations in environmental conditions, will be referred to as 'structurally metastable'.

When a reaction scheme can be hypothetically divided into two equal halves having an axis of mirror symmetry (the membrane M in the CCARN model), the scheme will be considered 'kinetically symmetric'. When both the halves of such a symmetric scheme maintain identical reaction conditions, the two sets of rate equations become similar to one another and in effect, the number of independent dynamic variables reduces to half. A distinct feature of the CCARN model [7] was the symmetry inherent in its kinetic scheme (Fig. 1) and it is because of this kinetic symmetry that symmetric reaction conditions become imperative for displaying stable, ordered dynamic behaviour [7]. With a view to examine whether other kinetic schemes having axes of symmetry also exhibit structural metastability, the present study aims at investigating the dynamic stability of diverse types of symmetric and asymmetric reaction schemes. Results presented here show that the symmetric schemes are, in general, vulnerable to asymmetric perturbations and reaction schemes with no axes of symmetry can exhibit more complex, stable and ordered dynamic behaviour. This observation is extremely pertinent to living systems because biochemical reactions are in general asymmetric and living systems maintain a high degree of stability.

2. Symmetric and asymmetric kinetic models

The dynamical behaviours of four hypothetical reaction schemes (Fig. 2), of which two (S-I and S-II) are kinetically symmetric and the other two (A-I and A-II) do not have any axis of mirror symmetry have been analyzed. X_i $(i = 1, 2\ldots 6)$ are polyfunctional macromolecules, while Y is a cofactor.

All the reaction steps in these models are autocatalytic, so that they have a potentiality of exhibiting temporal oscillations for suitable values of system parameters [1,8,9]. For example, the actual reaction steps in the scheme S-I can be written as:

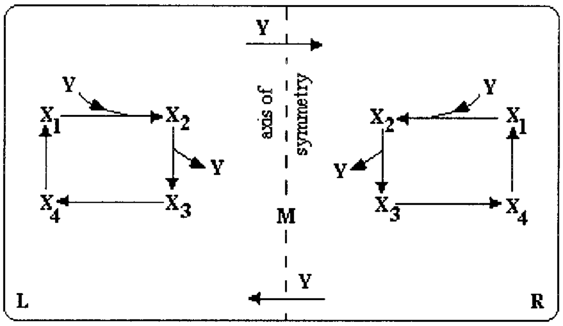

Fig. 1. Kinetic symmetry in previously reported CCARN model [7]. The hypothetical membrane M is acting like an axis of mirror symmetry dividing the system into two identical halves L and R. X_is are reacting macromolecules ($i = 1$ to 4) and Y is a co-factor. All reaction steps are autocatalytic.

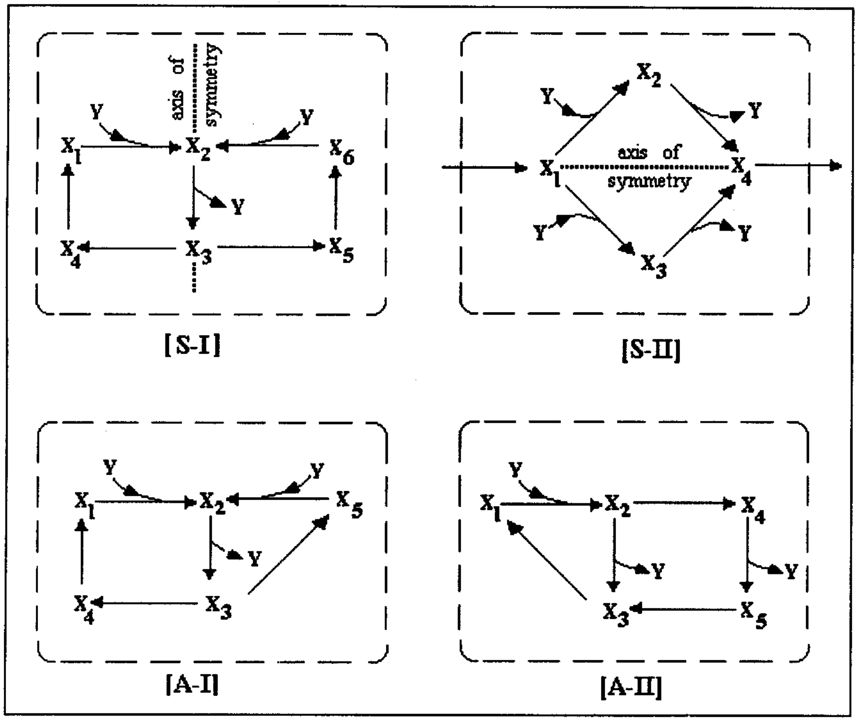

Fig. 2. Schematic representation of various kinetically symmetric (S-I, S-II) and asymmetric (A-I, A-II) reaction networks. Dotted lines define the boundaries of different reaction systems. All reaction steps are autocatalytic. X_is are reacting macromolecules ($i = 1, 2\ldots$) and Y is a co-factor. S-II is open to mass flow (arrows indicate directions of mass flow), while S-I, A-I and A-II are mass closed.

$$\begin{aligned}
&X_1 + X_2 + Y \rightarrow 2X_2\\
&\quad X_2 + X_3 \rightarrow 2X_3 + Y\\
&\quad X_3 + X_4 \rightarrow 2X_4\\
&\quad X_4 + X_1 \rightarrow 2X_1\\
&\quad X_3 + X_5 \rightarrow 2X_5\\
&\quad X_5 + X_6 \rightarrow 2X_6\\
&X_6 + X_2 + Y \rightarrow 2X_2
\end{aligned} \tag{S1}$$

The autocatalytic pathways have not been shown explicitly in Fig. 2 to avoid clumsiness. For each of the four kinetic schemes in Fig. 2, the time evolution of the system variables have been numerically simulated using the fourth-order Runga–Kutta method for wide ranges of values of the kinetic constants as well as for different sets of the initial conditions. Significant results of such simulations can be summarized as follows.

2.1. Scheme S-I

It is a cyclic, autocatalytic reaction network occurring in a homogeneous isotropic mass-closed system (Fig. 2). The rate equations are of the form,

$$\begin{aligned}
\frac{\mathrm{d}x_1}{\mathrm{d}t} &= k_4 x_4 x_1 - k_1 x_1 x_2 y\\
\frac{\mathrm{d}x_2}{\mathrm{d}t} &= k_1 x_1 x_2 y + k_7 x_6 x_2 y - k_2 x_2 x_3\\
\frac{\mathrm{d}x_3}{\mathrm{d}t} &= k_2 x_2 x_3 - k_3 x_3 x_4 - k_5 x_5 x_3\\
\frac{\mathrm{d}x_4}{\mathrm{d}t} &= k_3 x_3 x_4 - k_4 x_4 x_1\\
\frac{\mathrm{d}x_5}{\mathrm{d}t} &= k_5 x_3 x_5 - k_6 x_5 x_6\\
\frac{\mathrm{d}x_6}{\mathrm{d}t} &= k_6 x_5 x_6 - k_7 x_2 x_6 y
\end{aligned} \tag{1}$$

where x_i is the molar concentration of the species X_i and k_js are the kinetic constants of jth reaction.

The mass-conservation equations are given by,

$$\Sigma\, x_i = 1 \text{ (say)} \quad \text{and} \quad x_2 + y = m \tag{2}$$

where m is the total mass of the co-factor present in the system (in free and bound form). Numerical simulations of the rate equations in Eq. (1) reveals the following dynamic characteristics of the scheme:

(a) the system exhibits regular periodic behaviour only under symmetric conditions, i.e. when

$$\begin{array}{lll} k_1 = k_7 & & [x_1]_{\text{initial}} = [x_6]_{\text{initial}} \\ k_3 = k_5 & \text{and} & \\ k_4 = k_6 & & [x_4]_{\text{initial}} = [x_5]_{\text{initial}} \end{array} \tag{3}$$

where $[x_i]_{\text{initial}}$ is the initial concentrations of X_i. Under such conditions, depending on the values of kinetic constants and m, the system either evolves to a steady state or exhibits limit-cycle oscillations. For any limit-cycle oscillation, the phase-space trajectories of x_1 and x_6 are always identical, while the values of x_4 and x_5 at any instant of time are equal to one another;

(b) the evolution of the system to any particular stationary or oscillatory state depends on the parameter values and not on the initial conditions provided they are symmetric (Eq. (3)). For example, when $k_1 = k_7 = 10$ (in arbitrary units) and $k_j = 1$ $(j = 2, 3, \ldots 6)$, the system approaches to a steady state for $m = 0.1$ M (SS, Fig. 3a) and exhibits limit-cycle (LC, Fig. 3b) for $m = 0.3$ M for all sets of symmetrical initial conditions. But if there is even an infinitesimal difference between the values of $[x_1]_{\text{initial}}$ and $[x_6]_{\text{initial}}$ or between $[x_4]_{\text{initial}}$ and $[x_5]_{\text{initial}}$, the system instantaneously switches over from the regular rhythmic behaviour to aperiodic turbulence (data not shown) as also seen in case of the CCARN model [7];

(c) if a small asymmetric perturbation is applied to the system at the steady state (Fig. 3a), the system starts to exhibit slowly damped oscillation and both X_1 and X_4 exhibit 180° phase difference with their corresponding conjugates X_6 and X_5;

(d) the limit-cycle behaviour (Fig. 3b) is stable against any arbitrary perturbation applied symmetrically to both sides of the axis of symmetry in the scheme (S-I, Fig. 2). If identical perturbations are simultaneously applied to x_1 and x_6 (or to x_4 and x_5), the symmetry in the reaction conditions is retained and a rapid decay of such perturbations brings back the system to its original phase-space trajectory (the arrow in Fig. 3b indicates the point of application of a symmetric perturbation). Similarly, one-time addition of a small amount of the co-factor Y, X_2 or X_3 (i.e. any reacting species lying on the axis of symmetry (Fig. 2, S-I)) does not disturb the symmetry of the reaction condition and hence, the system can retain its original mode of behaviour in response to such perturbations (data not shown);

(e) in response to any asymmetric perturbations, even those of infinitesimal magnitudes, the system suffers an abrupt transition from regular periodic oscillation to turbulence (Fig. 3c and d). The perturbation is rapidly amplified and the pairwise synchronized time evolutions of X_1 and X_6 or of X_4 and X_5 are transformed into completely desynchronized aperiodic oscillation having no definite amplitude. Similar effects are observed also in case of small deviations from the symmetric reaction conditions (Eq. (3)), e.g. if $k_7 = k_1 + \delta$, or $x_1 = x_6 + \varepsilon$, where δ or ε represent infinitesimal variations in kinetic constants or initial concentration values across the axis of symmetry. It is worth emphasizing at this point that the transition of the system dynamics from limit-cycle to aperiodic behaviour (Fig. 3c and d) of the system does not follow any definite route like period-doubling bifurcation [9,10] and such turbulent behaviour is quite different from the conventional form of the ‘deterministic chaos’ [10];

(f) in spite of extensive searching through different regions of both phase-space as well as

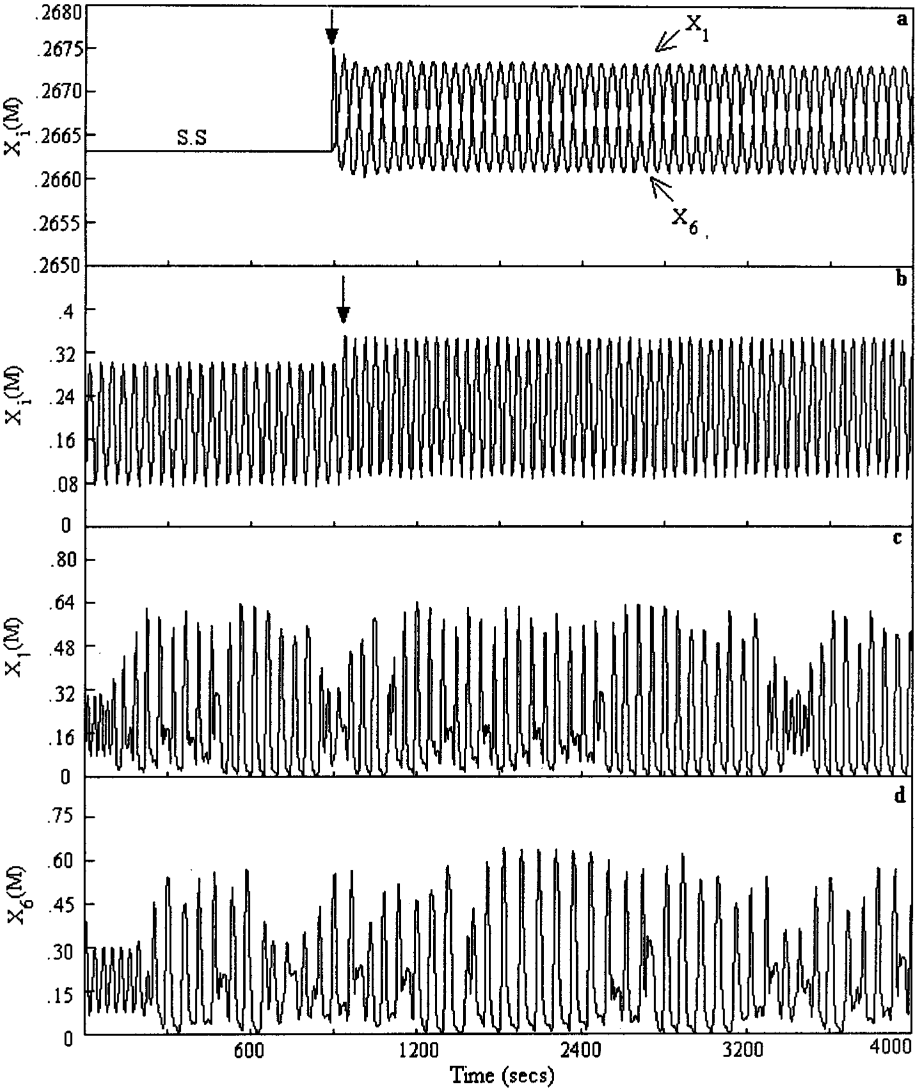

Fig. 3. Dynamic behaviour of x_i ($i = 1$ or 6) in scheme S-I for $k_1 = k_7 = 10$ and $k_j = 1$ (in arbitrary units), ($j = 2$ to 6) and at $t = 0$, $x_1 = x_6 = 0.45$ M, $x_2 = x_3 = x_4 = x_5 = 0.025$ M. (a) Under identical conditions in both halves of S-I, both x_1 and x_6 evolve to identical steady state (SS) for $m = 0.15$ M, but in response to one-time addition of 0.02 M of X_1 to the system, they exhibit small-amplitude oscillations having 180° phase difference. (b) For $m = 0.35$ M, x_1 and x_6 exhibit identical limit-cycle oscillations. In response to one-time addition of 0.02 M of X_2, the system continues to exhibit limit-cycle of slightly greater amplitude. (c) and (d) One-time addition of 0.02 M of X_1 to the system in (b), desynchronizes the time-evolution of x_1 and x_6 and drives the system from limit cycle to turbulence.

parameter-space, occurrence of any dynamic behaviour that would be stable against both symmetric and asymmetric fluctuations in the reaction conditions could not be demonstrated so far.

2.2. Schemes A-I and A-II

While the symmetric schemes S-I or S-II fail to exhibit any stable dynamics, the mass-closed schemes like A-I or A-II, being devoid of any axis of mirror symmetry, display a wide variety of complex phenomena of self-organization which are structurally stable. The rate equations of scheme A-I are

$$\frac{dx_1}{dt} = k_4x_1x_4 - k_1x_1x_2y$$
$$\frac{dx_2}{dt} = k_1x_1x_2y + k_6x_5x_2y - k_2x_2x_3$$
$$\frac{dx_3}{dt} = k_2x_2x_3 - k_3x_3x_4 - k_5x_3x_5$$
$$\frac{dx_4}{dt} = k_3x_3x_4 - k_4x_1x_4$$
$$\frac{dx_5}{dt} = k_5x_3x_5 - k_6x_5x_2y \qquad (4)$$

and the mass-conservation equations are the same as in Eq. (2).

In scheme A-II, the kinetic rate equations can be written as

$$\frac{dx_1}{dt} = k_3x_1x_3 - k_1x_1x_2y$$
$$\frac{dx_2}{dt} = k_1x_1x_2y - k_2x_2x_3 - k_4x_2x_4$$
$$\frac{dx_3}{dt} = k_2x_2x_3 - k_6x_3x_5 - k_3x_1x_3$$
$$\frac{dx_4}{dt} = k_4x_2x_4 - k_5x_4x_5$$
$$\frac{dx_5}{dt} = k_5x_4x_5 - k_6x_3x_5 \qquad (5)$$

while the mass-conservation equation for the co-factor is $x_2 + x_4 + y = m$.

Such asymmetric schemes exhibit, in general, various types of complex dynamic phenomena that are much more robust against environmental perturbations than those observed in case of the symmetric schemes. Major differences between the stability properties of the schemes A-I (or A-II) with S-I (or CCARN) are as follows.

1. The asymmetric schemes exhibit limit-cycle oscillations for large, continuous ranges of parameter values. For a particular set of kinetic constants and m, one and only one limit-cycle is approached from all sets of initial conditions lying within its basin of attraction (Fig. 4a). In contrast to the oscillations exhibited by scheme S-I, no symmetry condition is required to generate regular rhythmic behaviour in A-I or in A-II.
2. Response of the systems to any perturbation depends on the absolute value of its magnitude as well as direction and not on its symmetry or time of application. The dynamic behaviours of the systems are, in general, stable against the external perturbations so long as their magnitudes do not exceed some threshold values.
3. In response to the perturbations beyond the threshold values, or small changes in the parameter-values (e.g. an increase in the total co-factor concentration m due to one-time addition of Y in the system), schemes A-I or A-II may exhibit complex but ordered dynamic behaviour such as hard or soft excitations, birhythmicity etc. [2]. For example, in Fig. 4b, the scheme A-I suffers a transition from an oscillatory state to a stationary state (soft excitation) in response to one time addition of X_2 by 0.05 M at point P. On the other hand, additions of the co-factor Y to the system at two discrete time-points P_1 and P_2 (Fig. 4c) result in transitions between different modes of complex oscillations marked as O_1, O_2 and O_3. Similarly, the scheme A-II exhibits hard excitation [2] (Fig. 5a) and birhythmicity (Fig. 5b) in response to small perturbations in x_1. It is worth mentioning at this point that the perturbations applied to the asymmetric schemes A-I or A-II need not follow any symmetry relation to induce new levels of dynamic order to the system, as required in case of symmetric scheme S-I. In other words, the schemes A-I or A-II are endowed with a potential of exhibiting complex, yet ordered phenomena of self-organization for wide ranges of values of parameters and variables.

2.3. Scheme S-II

Under mass-closed condition, the symmetric

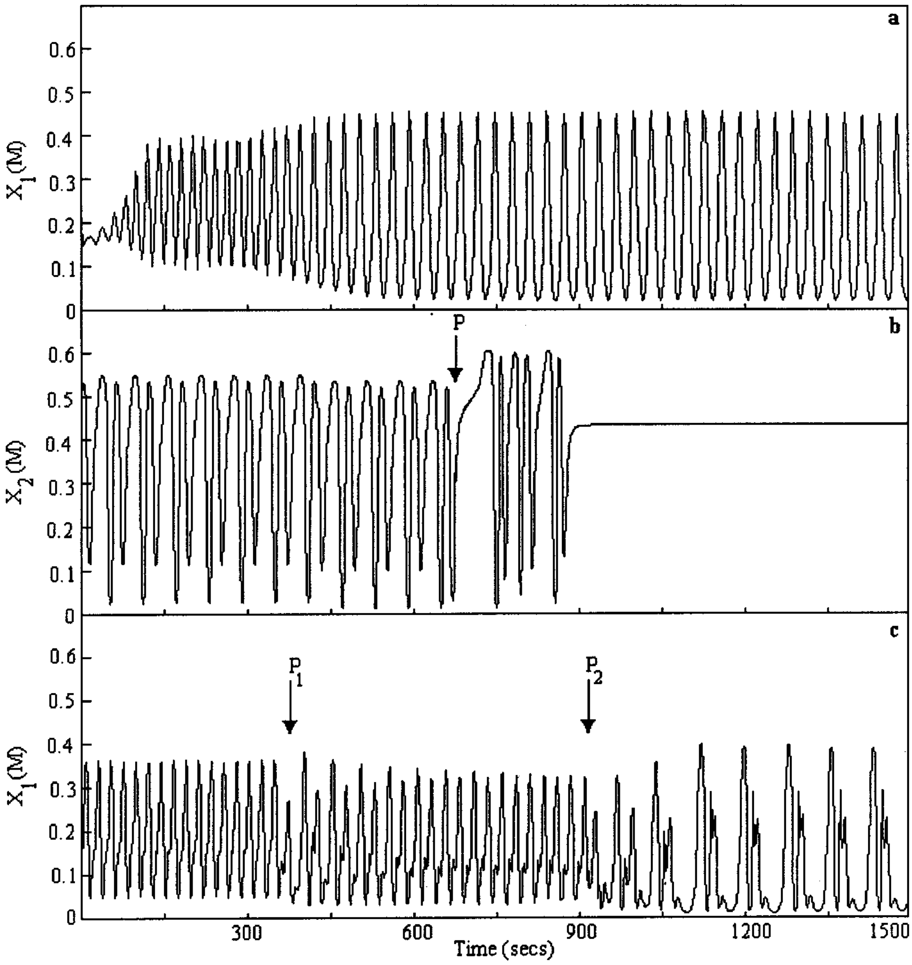

Fig. 4. Time evolution of different reacting species in the scheme A-I. (a) Limit cycle oscillation of X_1 for arbitrary initial conditions for $m = 0.4$ M. (b) Soft excitation of X_2 that exhibits complex oscillation for $m = 0.55$ M and switches over to a steady state in response to one-time addition of 0.05 M of X_2 at the point P. (c) Transition of X_1 from one mode of complex oscillation to another in response to additions of 0.05 M of co-factor Y at the points P_1 and P_2. In all cases, $k_1 = k_6 = 10$ and $k_j = 1$ (in arbitrary units), where $j = 2, 3, 4, 5$. Initial transients have not been shown.

schemes S-I (Fig. 2) or CCARN (Fig. 1) fail to exhibit any dynamic order having true structural stability, i.e. stability against the symmetric as well as asymmetric fluctuations in the environment. However, in living systems, the reacting species undergoing chemical or biochemical reactions continuously exchange mass with their surroundings [1]. It is, therefore, intriguing to examine if a symmetric chemical/biochemical network can sustain small asymmetric environmental fluctuations in an open system having continuous mass flow across its boundaries.

In Fig. 2, S-II represents a model symmetric scheme occurring in an open system. It has been assumed that X_1 enters the system at a constant rate α and X_4 leaves the system at a rate βx_4, where α and β are constants and x_4 is the molar concentration of the product X_4. All four reactions are autocatalytic like the reactions in the other three schemes of Fig. 2. The rate equations

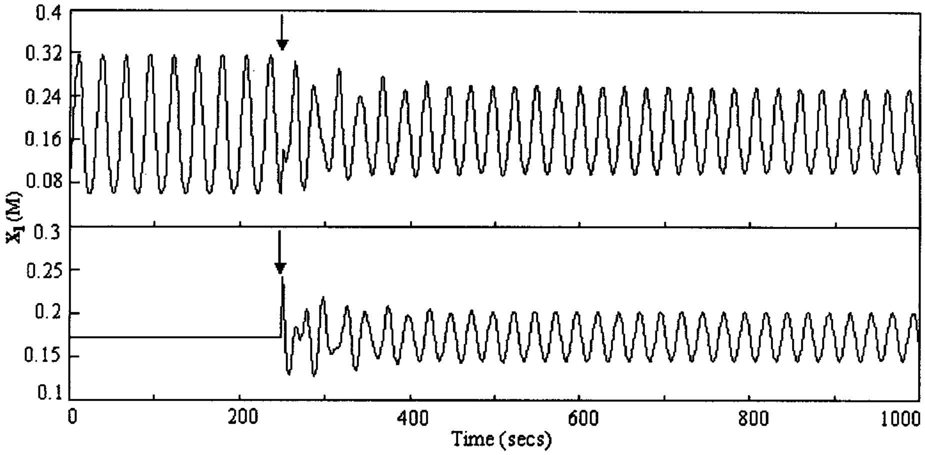

Fig. 5. (a) Birhythmicity and (b) hard excitation in X_1 in the scheme A-II in response to the addition of 0.01 M X_1 to the system at time-points P_1 and P_2, respectively. In both cases, $k_j = 1$ for $j = 1, 3, 4, 5, 6$ and $m = 1.83$. In (a), $k_2 = 0.001$, and initial conditions are $x_i = 0.1$ M for $i = 1, 2, 3, 4$; $x_5 = 0.6$ M. In (b), $k_2 = 0.01$ and initial conditions are $x_1 = x_2 = x_5 = 0.172$ M and $x_3 = x_4 = 0.242$ M. Transients have not been shown.

are given by

$$\frac{dx_1}{dt} = \alpha - k_1x_1x_2y - k_2x_1x_3y$$

$$\frac{dx_2}{dt} = k_1x_1x_2y - k_3x_2x_4$$

$$\frac{dx_3}{dt} = k_2x_1x_3y - k_4x_3x_4$$

$$\frac{dx_4}{dt} = k_3x_2x_4 + k_4x_3x_4 - \beta x_4 \tag{6}$$

Like other symmetric schemes, this system also exhibit ordered behaviour for symmetric reaction conditions across the axis of symmetry. Such symmetry conditions can be written as

$$k_1 = k_2,\ k_3 = k_4 \quad \text{and} \quad [x_2]_{\text{initial}} = [x_3]_{\text{initial}} \tag{7}$$

Under such symmetric conditions, the system either exhibits limit-cycle oscillation (Fig. 6a) or evolves to a steady state (data not shown). In both cases, the time evolution of x_2 and x_3 will be exactly identical.

As seen in other symmetric schemes, for the same set of parameter values, the same limit-cycle (Fig. 6a) is approached from all possible initial conditions obeying the symmetry relation (7). But if the initial conditions for x_2 and x_3 be slightly different from one another so that the symmetry relation (7) is no longer valid, the synchronization in their time-evolution is lost and instead of exhibiting identical limit-cycles, one of them (having a greater value of initial concentration) starts to exhibit an oscillation of gradually increasing amplitude (Fig. 6b), while the other one displays damped oscillation having the same time period (Fig. 6c). A little difference between the values of k_1 and k_3 or between those of k_2 and k_4 also induces a similar effect of desynchronization between the temporal behaviours of the conjugate pairs X_2 and X_3. This demonstrates that S-II is also structurally metastable like S-I or CCARN, but a major difference between the stability properties of the symmetric schemes occurring in an open system (e.g. S-II) and those occurring under mass-closed conditions is that the former are able to exhibit dynamic order (in the form of limit-cycles) even when the reaction conditions are not exactly identical across the axes of symmetry, which was not possible for the latter.

The limit-cycle behaviour in Fig. 6a is stable against all perturbations that are symmetrically and simultaneously applied across the line of symmetry. But in response to one-time addition of 0.2 M of X_2 to the system, which creates a

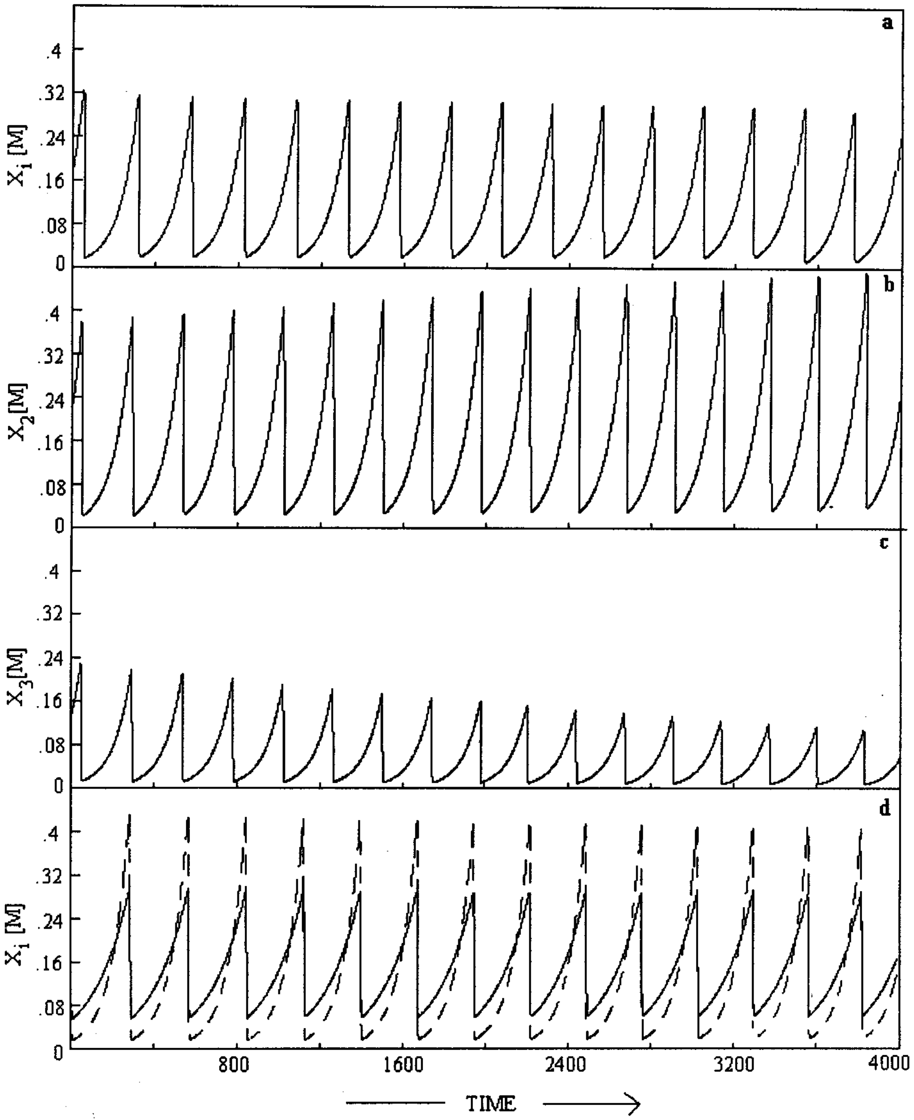

Fig. 6. (a) Identical limit cycles exhibited by X_i ($i = 2$ or 3) in the scheme S-II, when $k_1 = k_2 = 1$, $k_3 = k_4 = 2$, $\alpha = 0.5$ M/time unit, $\beta = 0.08$ and at $t = 0$, $x_i = 0.2$ M. (b) Amplified oscillation of X_2 and (c) damped oscillation of X_3, when the initial concentration of X_2 is increased by 0.01 M, keeping all other parameters and variables invariant. (d) Limit-cycle oscillations of X_2 (solid lines) and X_3 (dotted lines) having identical time-period but different amplitudes, when $k_1 = 1.1$ and values of other parameters are the same as in (a).

difference between x_2 and x_3, the system continues to exhibit limit-cycles of the same time period but having significant differences between the amplitudes of oscillation of X_2 and X_3 (Fig. 6d). Thus, in the presence of mass-flow across the boundary, any minute disbalance in the reaction conditions across the axis of symmetry does not necessarily induce an abrupt transition from limit-cycle to turbulence, as seen in the case of mass-closed systems. However, large asymmetric perturbations (beyond some critical value), completely destabilize the system leading to the onset of aperiodic oscillation (data not shown).

3. Discussion

A distinct feature of the CCARN model [7] is that the response of two coupled cyclic autocatalytic reactions occurring in a bi-compartmental system to changes in the reaction conditions is not governed by the absolute magnitudes of the individual perturbations applied to the two compartments, but by their relative values. If identical conditions prevail in both the compartments, the system exhibits an ordered dynamic phenomena like limit-cycle or steady-state. But any tiny difference in the conditions leads to a drastic change in the overall temporal organization of the system. From the analysis of the dynamic properties of different symmetric and asymmetric reaction pathways, the present report delineates that the metastable character is not unique for the CCARN model and that all kinetic schemes having an axis of mirror symmetry are endowed with such structural metastability under mass-closed conditions. For symmetric schemes, even an infinitesimal deviation from the symmetry relations instantaneously drives the closed system from an ordered temporal behaviour to turbulence (Fig. 3). In open systems, the mass-flow across the boundaries of the system might buffer the effect of small asymmetries in the reaction environment and in response to small asymmetric perturbations (of magnitudes below a threshold value), the symmetric scheme may display new modes of simple limit-cycle behaviour (Fig. 6). However, beyond the threshold value, asymmetric perturbations may drive the system to turbulence, even in the presence of mass-flow.

Absolute symmetry in reaction conditions, essential for regular temporal behaviour in mass-closed symmetric reaction schemes, can only be achieved in an idealized condition and may never be accomplished in practice. In fact, asymmetric fluctuations are bound to occur in living systems and the presence of symmetric chemical or biochemical pathways, that are unable to maintain a stable, dynamic order against such asymmetric perturbations, will pose a serious problem on the onset and maintenance of functions and/or structural order in such systems. It is, therefore, quite expected that living systems would try to elude the biochemical pathways having axes of symmetry.

In spite of an extensive search over wide ranges in both phase and parameter-space, the occurrence of complex dynamic phenomena like hard excitation or birythmicity could not be demonstrated so far in S-I or S-II. The asymmetric schemes like A-I or A-II, on the other hand, are structurally stable and are capable of exhibiting a wide variety of complex, yet ordered, dynamic phenomena in response to external perturbations. They can spontaneously give rise to increasingly complex temporal orders emerging through a succession of instabilities (Fig. 6) and thus, may confer to living systems an added plasticity, which is cardinal for such systems to achieve, maintain and regulate different biochemical functions. Under adverse environmental conditions, kinetic asymmetry presumably enhances the functional stability as well as the diversity of biochemical networks in a living cell.

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