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Transitions and new dynamical states induced by noise in a multiply regulated biochemical system

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Abstract

Noise-induced transitions between coexisting states, and the emergence of a new oscillatory state, are examined in a model for a multiply regulated biochemical system. For the undisturbed system, three oscillatory states, I, II, and III, coexist. It is found that noise above a critical amplitude can cause a transition between states III and II and between states III or II and state I, whereas a transition from state I to either states II or III is never observed. This indicates that the relative stability under noise perturbations is greatest for state I, and progressively less for states II and III. In addition to this transition behaviour, a purely noise-induced state is found. Under noise perturbations, the average concentration of metabolites may depend on both the time duration and amplitude of the superimposed noise. The implications of these results for understanding the in vivo behaviour of complex biochemical systems are discussed. © 1997 Elsevier Science B.V.

Keywords: Noise; Coexistence of states; Biochemical oscillations; Noise-induced transition; Noise-induced new state

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1. Introduction

Biochemical systems are governed by the kinetics of enzymatic processes which are highly nonlinear in character. Deterministic ordinary differential equations are often employed to model these systems, under the assumption that they are spatially homogeneous and are not subject to perturbations by environmental noise. Using these models, various dynamical patterns, such as oscillations, complex oscillations, chaos or coexisting states have been analysed in the context of a number of different biochemical systems (e.g., see Refs. [1–9]).

Random fluctuations are present in any real biochemical system, and are intrinsic to the observations made on that system. The interaction of noise with nonlinear systems may radically alter the dynamical behaviour ([10–15]). Therefore, the study of the effect of noise on the dynamics of biochemical systems is central to understanding in vivo behaviour, and in comparing model behaviour with experimental results.

The effect of noise on the dynamical behaviour of the systems depends on its source, and three basic types can be characterised: type-V noise, type-P noise and velocity-additive noise. Where perturbations act on the state variables of the system, e.g., the

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deviation of systems from a spatially homogeneous state, or the imperfect mixing of metabolites in experimental systems, type-V noise results. Type-P noise arises from an environmental perturbation of the system parameters, e.g., the effects of light on the photosynthesis of plants and the imperfect input control in biochemical systems. Finally, fluctuations in temperature may cause a change in reaction velocity, and this can be described as velocity-additive noise. The nature of noise inherent in biochemical systems may intermittently change, depending on the environmental conditions.

For metabolic systems, cellular metabolites and enzymes are present in different compartments in living cells. For example, in plant cells, fructose 6-P, 1-phosphotransferase (PFP) is found exclusively in the cytosolic compartment. Incomplete mixing in each compartment may induce noise in species concentrations. In addition, thermal fluctuations may induce hydrodynamic flows in living cells [16], which gives rise to noise fluctuations both in metabolite concentrations and in the input to the compartment. Furthermore, the fluctuations in environmental temperature of metabolic systems may induce noise changes in the velocity of enzymatic reactions. The noise level in metabolic systems may vary greatly, depending on the relative contribution from the above source. Previously, dynamical regimes of metabolic systems are investigated mainly in homogeneous systems, although transitions between oscillatory states have been studied by techniques involving addition or subtraction of metabolites [8]. In this work, we study how an established dynamical regime in a multiply regulated biochemical system [1–3] would be affected by noise perturbations and the physiological consequences of noise-induced phenomena. In Section 2, the model system and the details of noise superimposition are introduced. In Section 3, the transitions and new state induced by noise are analysed. Finally, the implications of these results for understanding in vivo behaviour are discussed.

2. The model and the superposition of noise

We employ the following biochemical model [1–3] to study the noise-induced phenomena and their consequences.

If it is assumed that the system is spatially homogeneous and isolated from environmental noise, it is governed by the following ordinary differential equations [2]:

$$\frac{\mathrm{d}\alpha}{\mathrm{d}t} = \frac{\nu}{K_{m1}} - \sigma_1 \phi = f_1(\alpha,\beta,\gamma) \tag{1}$$

$$\frac{\mathrm{d}\beta}{\mathrm{d}t} = q_1 \sigma_1 \phi - \sigma_2 \eta = f_2(\alpha,\beta,\gamma) \tag{2}$$

$$\frac{\mathrm{d}\gamma}{\mathrm{d}t} = q_2 \sigma_2 \eta - \kappa_s \gamma = f_3(\alpha,\beta,\gamma) \tag{3}$$

and

$$\phi = \frac{\alpha(1+\alpha)(1+\beta)^2}{L_1 + (1+\alpha)^2(1+\beta)^2} \tag{4}$$

$$\eta = \frac{\beta(1+\gamma)^2}{L_2 + (1+\gamma)^2} \tag{5}$$

The origin and underlying assumptions of this model are fully described elsewhere [1–3] and the parameter values used in this work are taken from Ref. [2].

The effects of both type-V and velocity-additive noise on this model system will be studied. The noise is assumed to be Gaussian distributed with mean, $\langle \xi \rangle$, amplitude (standard deviation), σ. The frequency of superimposing noise, which is referred to as noise frequency in this work, is $\frac{1}{\Delta t}$. In this work, $\langle \xi \rangle = 0$, $\Delta t = 0.1$ s and we examine the effects of noise amplitude on the stability of the system. For type-V noise, perturbations are directly superimposed with frequency $1/\Delta t$ on the variables in the form,

$$\alpha^{\mathrm{fluc}} = \alpha(1 + \xi_\alpha) \tag{6}$$

$$\beta^{\mathrm{fluc}} = \beta(1 + \xi_\beta) \tag{7}$$

$$\gamma^{\mathrm{fluc}} = \gamma(1 + \xi_\gamma) \tag{8}$$

For velocity-additive noise, perturbations are superimposed on the velocity of the enzymatic reactions, i.e.,

$$\frac{\mathrm{d}\alpha}{\mathrm{d}t} = f_1(\alpha,\beta,\gamma) + \xi_\alpha \tag{9}$$

$$\frac{\mathrm{d}\beta}{\mathrm{d}t} = f_2(\alpha,\beta,\gamma) + \xi_\beta \tag{10}$$

$$\frac{\mathrm{d}\gamma}{\mathrm{d}t} = f_3(\alpha,\beta,\gamma) + \xi_\gamma \tag{11}$$

3. Results

In the absence of noise, the model system, Fig. 1, admits many types of dynamical behaviour including oscillations, complex oscillations, chaos and coexistence of attractors [1–3]. We shall focus on the case where the unperturbed system admits three coexisting stable oscillatory states and each has its own basin of attraction [2]. For the initial conditions I ($\alpha = 61.5$, $\beta = 131.0$ $\gamma = 0.250$); II ($\alpha = 61.0$, $\beta = 131.0$ $\gamma = 0.250$); and III ($\alpha = 60.5$, $\beta = 131.0$ $\gamma = 0.250$), the system settles on each of the three different states respectively [2]. In what follows, we refer to those three as states I, II and III, respectively. In order to examine the consequences of noise perturbations, the system is integrated for a sufficient time (5000 s) to allow transients to die out, i.e., until the system has settled onto either state I, II or III before noise perturbations are superimposed. The subsequent evolution was monitored for a prescribed interval of time, and the consequences of the different types of noise for the dynamical behaviour were analysed.

3.1. Noise-induced transitions and a new oscillatory state

Type-V noise was superimposed on the system in each of the three states. When the noise amplitude is below a critical value, the original states remain stable, in the sense that departures from the unperturbed behaviour are of the order of the noise amplitude. However, critical values for the noise amplitude exists, such that above these critical amplitudes, the departure from the unperturbed behaviour is of greater magnitude than the noise amplitude.

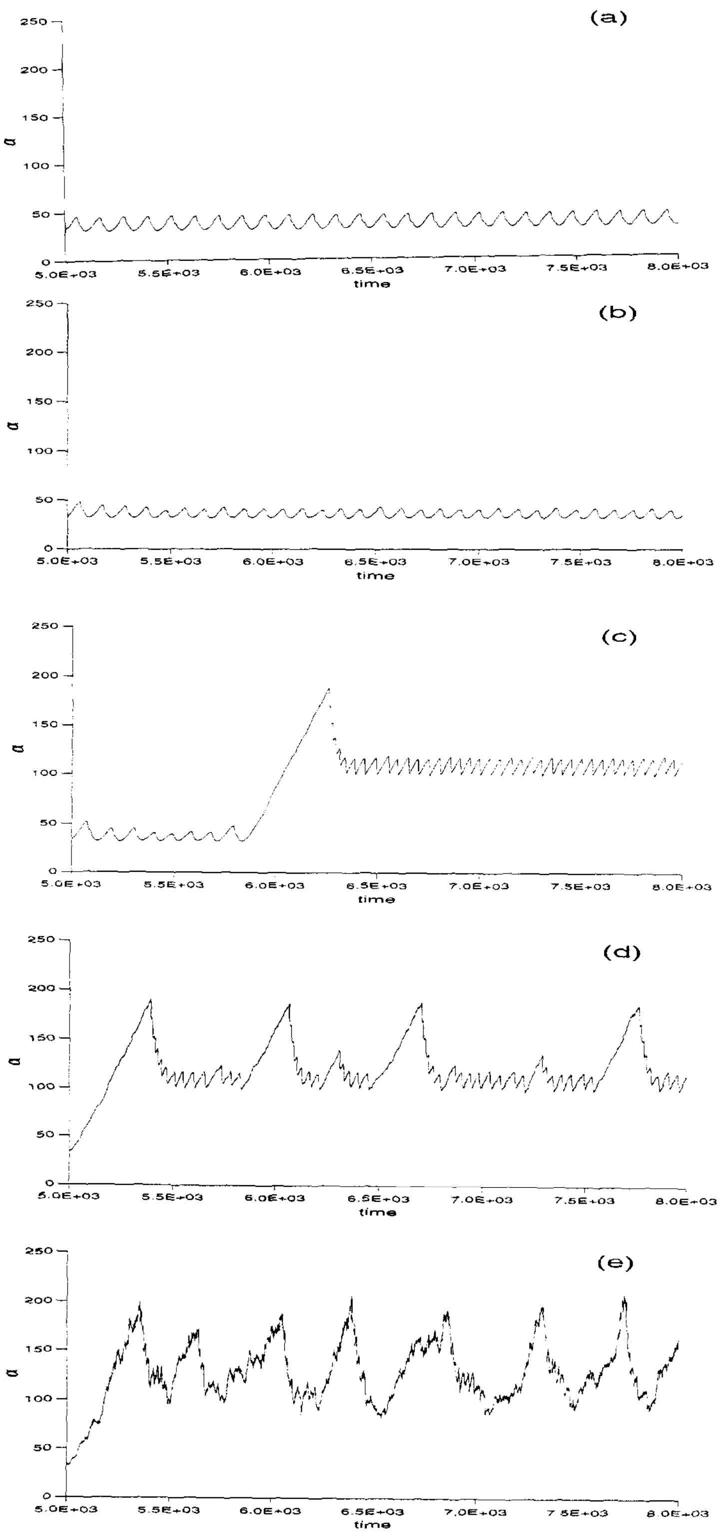
Furthermore, switching between states is observed.

For the system in state III, as noise amplitude increases to 1.0 E-4, a transition from state III, Fig. 2a, to state II, Fig. 2b, is observed. If the amplitude of the noise is three times greater (3.0E-4) the system switches from state III, Fig. 2a, to state I, Fig. 2c. For noise amplitudes greater than 5.0E-4, noisy large-amplitude bursts emerge and become persistent. The frequency of these large-amplitude bursts increases as the noise amplitude is increased (Fig. 2d and e). If the superimposed noise is subsequently removed, this large-amplitude bursting state disappears. Therefore, this state arises purely as a consequence of noise, and we refer to it in what follows as the noise-induced state. The large spikes in the noise-induced state (Fig. 2d and e) have the same form as the single large spike observed during the transition from state III to I at a lower noise amplitude (Fig. 2c). In the absence of noise, a similar peak is observed during the initial transient to state I [2]. When noise is superimposed on state II, a transition from state II to state I then to the noise-induced state is found for noise amplitudes above 3.0 E-4 and 5.0 E-4, respectively. However, a noise-induced transition from state II to state III is never observed. When noise is superimposed on state I, only the transition to the noise-induced state occurs.

Fig. 1. A multiply regulated biochemical system [1,2]. This system admits three coexisting periodic states for suitable values of parameters.

The above results indicate that state I is the most stable state, and that stability decreases from state II to state III. It has been previously shown [17,18] that the main determinant of the stability of coexisting states subject to noise perturbations is the relative size of the corresponding basins of attraction. Therefore, we speculate that the areas of the basins of attraction increase from state III, to states II and I, respectively; although we are currently unable to verify this for the present system.

The emergence of the noise-induced state suggests a threshold phenomenon is operating in the system. In the first instance, the time series of α in the noise-induced state does not include segments corresponding to the time series of states II or III, and the value for α remains significantly higher than in these states. This suggests that the noise-induced state is not simply a consequence of a phase-space trajectory which is perturbed between the attractors of the three coexisting states. Secondly, Fig. 3a and b show the consequences of removing noise at two different points in the time series of the state. State I can be recovered by two ways: one is via a large amplitude excursion, Fig. 3a; the other is rapid relaxation onto the unperturbed attractor, Fig. 3b. The


(a)
(b)
(c)
(d)
(e)
a
250
200
150
100
50
0
5.0E+03
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6.0E+03
6.5E+03
7.0E+03
7.5E+03
8.0E+03
time

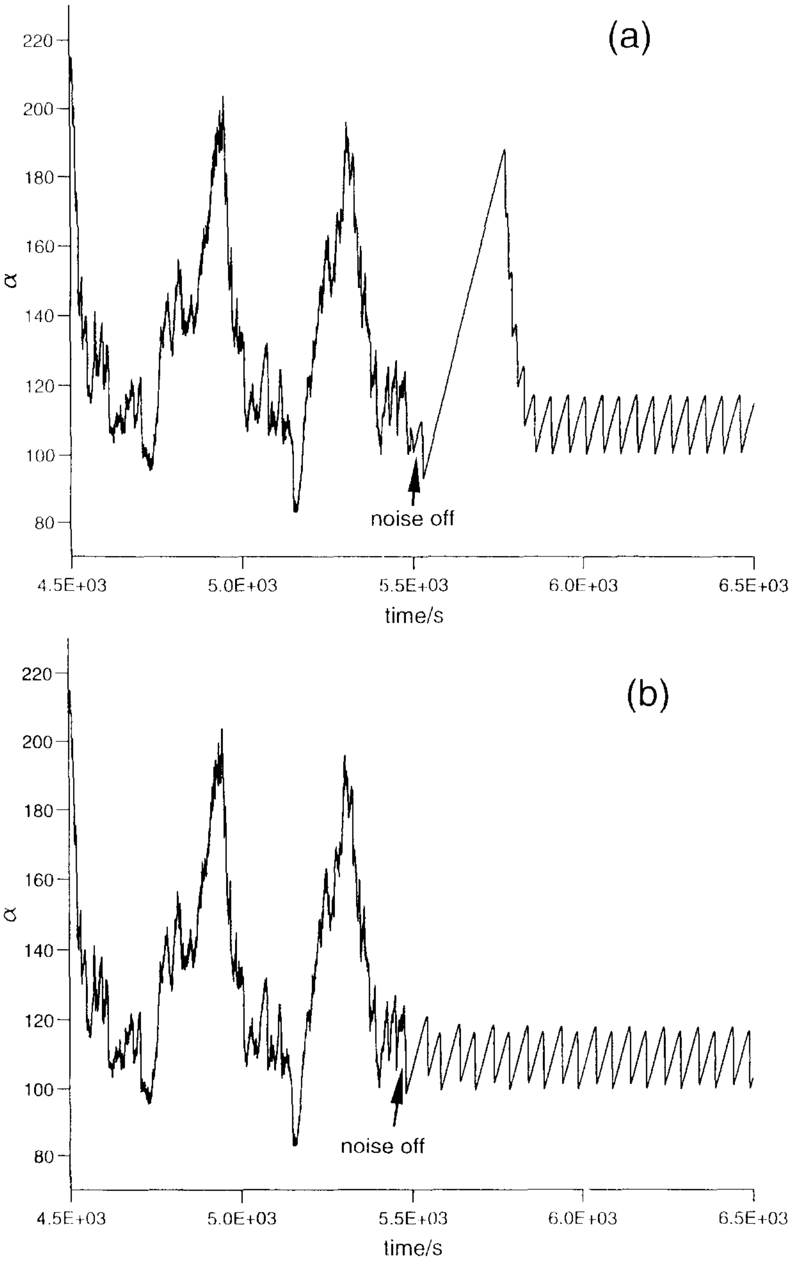

Fig. 3. Two different ways of recovering state I after noise is removed. Noise amplitude is fixed at 5.0 E-3, and frequency at 10 s^{-1}. Noise is removed at (a): 5500 s, and (b) 5480 s. Comparison between (a) and (b) shows that the noise-induced state is due to the excitability forced by noise perturbations through a threshold.

Fig. 2. Dependence of the dynamical behaviour of state III (see Section 3.1 for explanation) on the amplitude of noise. The noise frequency is fixed at 10 s^{-1}. Noise amplitude: (a): 0.0; (b): 1.0 E-4; (c): 3.0 E-4; (d): 1.0 E-3, (e): 5.0 E-3.

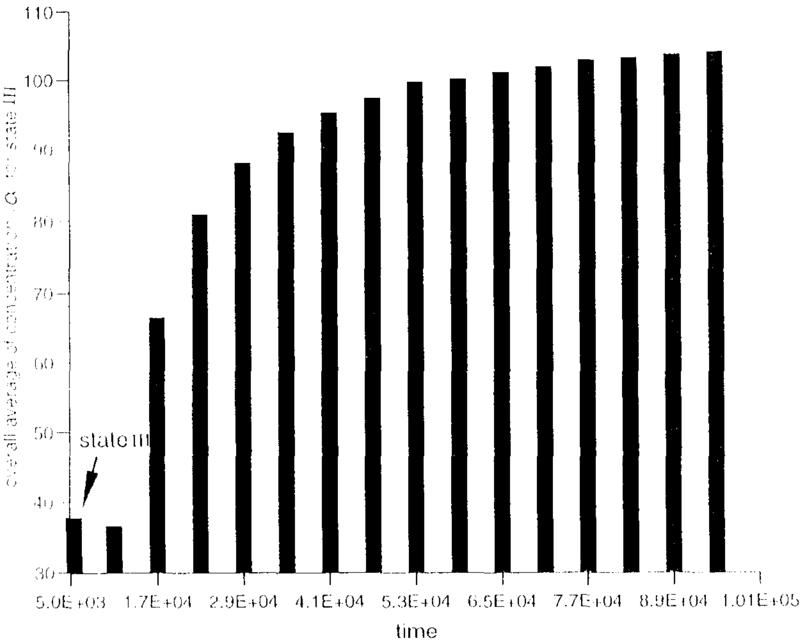

Fig. 4. Dependence of overall average concentration of α for state III on the averaging time interval. Noise amplitude is fixed at 3.0 E-4, and frequency at 10 s^{-1}. Superimposition of noise starts at 5000 s, and the average concentration of α is plotted against averaging interval in increments of 6000 s.

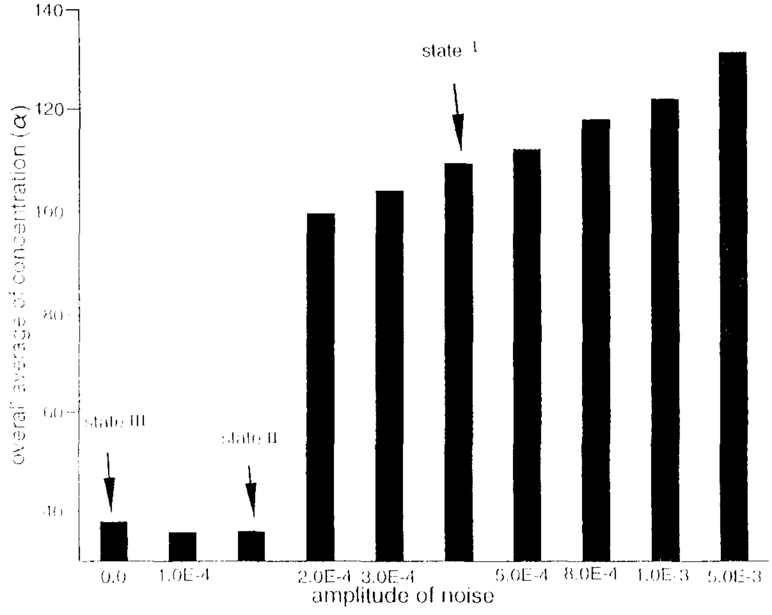

Fig. 5. Dependence of the concentration of α averaged over 200000 s for state III on noise amplitude. The average concentration of α for the unperturbed states I and II is also included for comparison.

form of recovery is the same if the unperturbed system is initiated using the values of α, β and γ corresponding to those at each point where noise was removed (results not shown). This suggests that noise above a critical amplitude applied to the system in state I moves the trajectory across a threshold which results in a large excursion in the phase space before returning to the vicinity of the attractor.

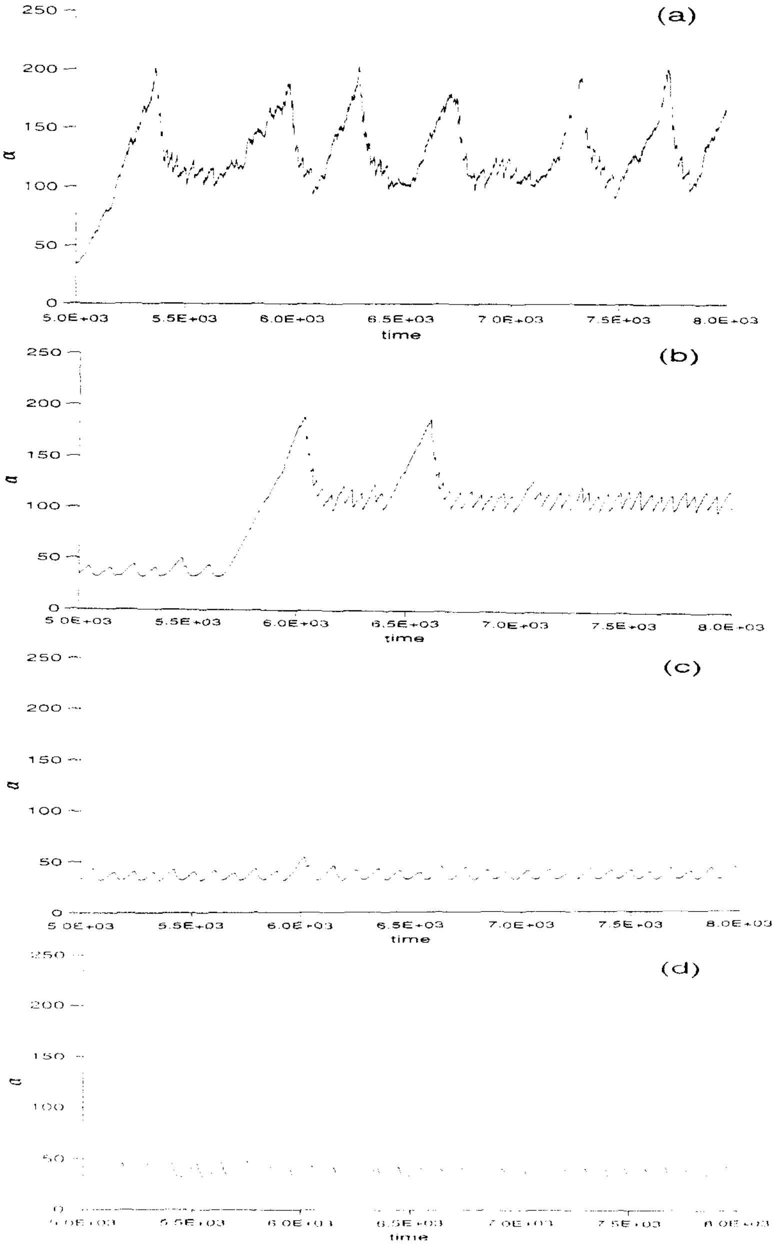

Fig. 6. Effects of noise frequency on the dynamical behaviour of state III with noise amplitude equal to 3.0 E-3. Noise frequency: (a): 10 s^{-1}; (b): 1 s^{-1}; (c): 0.1 s^{-1}, and (d): 0.01 s^{-1}.

3.2. Consequences of noise-induced phenomena

Because noise can dramatically affect the dynamical regime of the system, it can also change physiological conditions such as the average concentrations of species or the energetic efficiency of pathways [19–21]. The average concentrations of metabolites arise as a direct consequence of the oscillatory behaviour of the system, while the rate of energy dissipation, free energy change and net flux, are functions of concentrations. In this work, we employ the time-averaged concentration of substrate S, $\langle \alpha \rangle$, as a generic indicator of the physiological status of the system.

In the absence of noise perturbations, states I, II and III are period-1 oscillations, and $\langle \alpha \rangle$ can be determined by averaging over a single period. In the presence of noise, the oscillatory modes depart from simple oscillations, and therefore the value of $\langle \alpha \rangle$ can depend on the time interval of averaging, τ_{av}. Fig. 4 shows an example of the dependence of $\langle \alpha \rangle$ on τ_{av} for noise amplitude equal to 3.0 E-4. It is clear that noise perturbations may change $\langle \alpha \rangle$ dramatically. Averaging over timescales of 6000 s, 12000 s, 18000 s, and 90000 s, $\langle \alpha \rangle$ increases by −3%, 76%, 144%, and 175%, respectively. When the concentration is averaged over timescales in excess of 100000 s, $\langle \alpha \rangle$ approaches an asymptotic value, indicating the existence of a characteristic timescale in the dynamical response to applied noise.

Fig. 5 shows the dependence of $\langle \alpha \rangle$ on noise amplitude in state III averaged over 200000 s. Averaged over this timescale, the values for $\langle \alpha \rangle$ are approximately independent of the averaging time interval. For comparison, $\langle \alpha \rangle$ values for the unperturbed states II and I are also included in the figure. As shown in Fig. 5, the value of $\langle \alpha \rangle$ is sensitive to the amplitude of noise. For example, for amplitudes of 1.0 E-4, 3.0 E-4, 5.0 E-4, 5.0 E-3, $\langle \alpha \rangle$ increases by −6%, 176%, 196%, 247%, respectively. For an amplitude of 1.0 E-4, the value of $\langle \alpha \rangle$ is similar to the unperturbed value for the system in state II, indicating the transition from state III to II. Similarly, for amplitudes in the range 3.0 E-4 to 5.0 E-4, the value of $\langle \alpha \rangle$ is close to that of state I, indicating the transition from state III to I. For amplitudes greater than 5.0 E-4, the emergence of the noise-induced state results in further increases in $\langle \alpha \rangle$. However, for amplitudes above 5.0 E-3, any further increase does not significantly change the value of $\langle \alpha \rangle$. It should be noticed that this value for $\langle \alpha \rangle$ is much higher than that for either state I, II or III. From this figure it is clear that state I is most stable to noise, and perturbation to the noise-induced state still results in an increase in the value of $\langle \alpha \rangle$ of 21%.

From these results, it is obvious that the interaction of noise with the coexisting states of the system can have physiological implications.

3.3. Effects of noise frequency

In the foregoing calculations, we examined the effects of increasing noise amplitude on various oscillatory states, with the frequency of the noise fixed at 10 s^{-1}. Holding the amplitude constant, and changing the frequency of the noise, it was found that the effects of a high-frequency and low-amplitude noise is qualitatively similar to those of a low-frequency and higher-amplitude noise. Fig. 6 shows the effects of changing frequency from 10 s^{-1} to 0.01 s^{-1} and for fixing noise amplitude at 3.0E-3. Clearly, higher-frequency noise affects the dynamics of the system more dramatically for a fixed-noise amplitude.

3.4. Comparison of effects of type-V and velocity-additive noise

The effects of velocity-additive noise on the dynamics of the system have also been examined. Critical amplitudes for inducing transitions and a noise-induced state can be identified analogously to the type-V noise case. In general, critical amplitudes for velocity-additive noise are higher than those for type-V noise. For example, the critical amplitude of velocity-additive noise for the transition from state III to I is 8.0E-3, which is much higher than that for type-V noise (3.0E-4). However, for both types of noise, the qualitative effects on dynamical behaviour are the same.

4. Discussion

The theoretical results reveal that for the multiply regulated system, noise perturbations may lead to transitions between coexisting states, and may also induce a new oscillatory state. Consequently, there are physiological implications for the system.

For a glycolytic model system subject to periodic substrate addition, Markus and Hess [8] have observed that mutual transitions between oscillatory modes can be induced by techniques involving addition or subtraction of metabolites to the system. Such techniques may generate new initial conditions for the differential equations describing the system, and different initial conditions may lead to different oscillatory modes. Therefore, mutual transitions are possible. For coexisting states in the present, and other systems [13,17,18], the relative stability of each state can be characterised in the presence of Gaussian-distributed noise perturbations. It is found that noise above a critical amplitude may only induce transitions from less stable states to more states, and the inverse transitions cannot be observed. Such transitions may depend on both noise amplitudes and noise frequencies. Because all real biochemical systems are persistently subject to perturbations due to intermittent noise, it is interesting to consider from an evolutionary point of view whether the most stable state is selected. In addition, the physiological impact depends on both the amplitude and frequency of the superimposed noise. Should the nature of the noise change, the physiological conditions in the associated biochemical system such as (average) concentrations of metabolite species may be affected. The consequences of such noise-induced physiological changes in the coordination of large-scale biochemical systems should be fully explored.

Threshold phenomena are present in many biochemical systems (see, e.g., Refs. [22–25]). The new state demonstrated in the present work is induced by noise perturbations through a threshold. The generality of existence of such states in excitable biochemical systems subject to noise perturbations is clearly of both theoretical and experimental interest. For biological systems subject to fluctuations in applied electromagnetic fields, threshold phenomena have also been studied (see, e.g., Refs. [26,27]).

After noise is removed, or its amplitude is reduced, which of the multiple coexisting states is recovered depends on the relationship between a noisy dynamical state and the basin of attraction of coexisting states. For the present system, the basin of attraction cannot be fully quantified. A study of the relative probability of recovery for coexisting states of noise-perturbed systems is currently underway using alternative model systems.

Enzyme activities, which may be manipulated by genetic engineering, are one of main factors determining the stability of biochemical systems. As enzyme activities are modified, the stability will change. Therefore, the consequences of modification of enzyme activities in transgenics for both dynamical as well as physiological conditions should be considered.

For the present metabolic system, the coexisting oscillatory states may not be distinguished in the presence of noise. For example, when the amplitude of type-V noise is over 1.0 E-3, only a new noisy oscillatory state can be observed. This implies that the coexisting states found in model systems may not be observed in experimental systems with noisy fluctuations. Therefore, when comparison of experimental observations of metabolic systems with theoretical analysis is made, appropriate noise perturbations should be included in the model systems.

Acknowledgements

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