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Ryde-Pettersson, Ulf

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On the mechanistic origin of damped oscillations in biochemical reaction systems

Ulf RYDE-PETTERSSON

Avdelningen för biokemi, Kemicentrum, Lunds universitet, Lund, Sweden

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A generalized reaction scheme for the kinetic interaction of two reactants in a metabolic pathway has been examined in order to establish what minimal mechanistic patterns are required to support a damped oscillatory transient-state kinetic behaviour of such a two-component system when operating near a steady state. All potentially oscillating sub-systems inherent in this scheme are listed and briefly characterized. The list includes several mechanistic patterns that may be frequently encountered in biological system (e.g. involving feedback inhibition, feed-forward activation, substrate inhibition or product activation), but also draw attention to some hitherto unforeseen mechanisms by which the kinetic interaction of two metabolites may trigger damped oscillations. The results can be used to identify possible sources of oscillations in metabolic pathways without detailed knowledge about the explicit rate equations that apply.

Biological reaction systems exhibiting an oscillatory behavior have been extensively studied by both experimentalists and theorists [1–4]. Particular attention has been paid to the sustained and usually non-sinusoidal oscillations that may govern the kinetics of reaction systems far from equilibrium when operating in the neighborhood of an unstable steady state. The theory of such oscillations has been thoroughly treated [3–6], and this had led to a good understanding of the mechanistic background for the sustained oscillations that have been experimentally documented to occur under certain conditions for example in the glycolytic reactions [7], in the morphogenesis of slime molds [8] and in mitochondrial ion transport [9].

Less attention has been paid to the theory of the damped and sinusoidal oscillations that may govern the kinetics of reaction systems operating near a stable steady state. This is somewhat surprising, considering that most biological systems normally would be expected to operate in, or very close to, a stable steady state. Damped oscillations may not be as conspicuous as sustained oscillations, but have nevertheless attracted the interest of many experimentalists, e.g. those working in the photosynthetic field of research [1, 3, 10–12].

A recent theoretical investigation established that damped oscillations may be a transient-state kinetic characteristic already of biological reaction systems involving a single enzyme [13]. The corresponding oscillations were found to be strongly damped, however. This indicates that weakly damped oscillations, such as those observed experimentally in the photosynthetic reaction system [11], must derive from the interaction of at least two enzymatically catalyzed reaction steps and hence from the kinetic interplay of at least two metabolites.

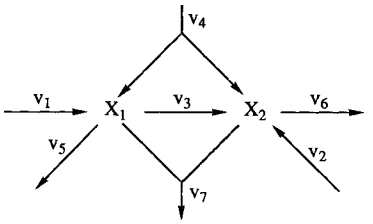
The present theoretical study examines the conditions under which the kinetic interplay of two reactants in a reaction system may lead to a damped oscillatory rate behavior. A nomenclature is proposed for the different mechanistic cases that may give rise to oscillations, and the corresponding transient-state kinetic parameters are characterized.

Correspondence to U. Ryde-Pettersson, Avdelningen för biokemi, Kemicentrum, Lunds universitet, Box 124, S-221 00 Lund, Sweden

THEORY

Generalized mechanism for the kinetic interaction of two reactants

Consider the kinetic scheme in Eqn (1):



(1)

This scheme would seem to be sufficiently generalized to account for the vast majority of stoichiometric patterns by which two reactants (X_1 and X_2) in a metabolic pathway may be stoichiometrically coupled. Denoting velocities of the individual reaction steps as in Eqn (1), the kinetics of this generalized reaction system are governed by the differential equations

$$\frac{d[X_1]}{dt} = v_1 - v_3 + v_4 - v_5 - v_7 \quad (2)$$

$$\frac{d[X_2]}{dt} = v_2 + v_3 + v_4 - v_6 - v_7. \quad (3)$$

The reaction fluxes v_i are functions of $[X_1]$ and $[X_2]$. Therefore, assuming that the reaction system operates near a steady state, the right-hand side of Eqns (2) and (3) may be expanded in a Taylor series with retention only of first-order terms to give the linear approximation (cf. [4])

$$\frac{d\Delta X_1}{dt} = a_{11}\Delta X_1 + a_{12}\Delta X_2 \quad (4)$$

$$\frac{d\Delta X_1}{dt} = a_{21}\Delta X_1 + a_{22}\Delta X_2 \quad (5)$$

where

$$\Delta X_j = [X_j] - [X_j]_\infty; \quad j = 1,2 \quad (6)$$

$$a_{11} = d_{11} - d_{31} + d_{41} - d_{51} - d_{71} \quad (7)$$

$$a_{12} = d_{12} - d_{32} + d_{42} - d_{52} - d_{72} \quad (8)$$

$$a_{21} = d_{21} + d_{31} + d_{41} - d_{61} - d_{71} \quad (9)$$

$$a_{22} = d_{22} + d_{32} + d_{42} - d_{62} - d_{72} \quad (10)$$

$$d_{ij} = \left(\frac{\partial v_i}{\partial [X_j]}\right)_{\substack{[X_1]=[X_1]_\infty \\ [X_2]=[X_2]_\infty}}; \quad i = 1,\ldots,7; \quad j = 1,2 \quad (11)$$

$[X_j]$ and $[X_j]_\infty$ denote the concentration of X_j at time t and at steady state, respectively. Eqns (4) and (5) are known [4] to have solutions of the form

$$[X_j] = [X_j]_\infty + A_{j1}\, e^{\lambda_1 t} + A_{j2}\, e^{\lambda_2 t}; \quad j = 1,2 \quad (12)$$

prescribing that the approach of $[X_j]$ to the steady state is governed by two exponential transients with amplitudes A_{j1}, A_{j2} and rate parameters λ_1, λ_2. The latter parameters represent the eigenvalues of the Jacobian matrix [a_{ij} in Eqns (7 – 10)] of the linearized system [4], and are given by

$$\lambda_{1,2} = \frac{a_{11} + a_{22} \pm \sqrt{(a_{11} - a_{22})^2 + 4 a_{12} a_{21}}}{2}. \quad (13)$$

If $4a_{12}a_{21} + (a_{11} - a_{22})^2 < 0$, the transient rate parameters will be a pair of complex-conjugated roots:

$$\lambda_1 = -a + b\sqrt{-1} \quad (14)$$

$$\lambda_2 = -a - b\sqrt{-1}. \quad (15)$$

The solution may then be written as

$$[X_j] = [X_j]_\infty + B_j e^{-at} \sin(bt + \varphi_j); \quad k = 1,2, \quad (16)$$

where a, b, B_j and φ_j denote, respectively, the damping factor, the angular frequency, the amplitude and the phase of a damped sinusoidal oscillation.

Stoichiometric patterns giving rise to oscillations

The above theory shows that the appearance of damped oscillations in a reaction system near a steady state is directly related to the existence of complex rate parameters in the transient-state kinetic solution for the linearized system. According to Eqn (13), complex rate parameters (and hence oscillations) will be at hand if, and only if

$$\begin{aligned}(d_{11} - d_{31} + d_{41} - d_{51} - d_{71} - d_{22} - d_{32} - d_{42} + d_{62} \\ + d_{72})^2 < 4(d_{21} + d_{31} + d_{41} - d_{61} - d_{71}) \\ (-d_{12} + d_{32} - d_{42} + d_{52} + d_{72}).\end{aligned} \quad (17)$$

Algebraic expansion of the right-hand side of Eqn (17) gives a sum of products of two individual d_{ij}. Eqn (17) provides the obvious inference that oscillations are possible only if at least one of these d_{ij} product terms is non-vanishing and of the appropriate sign. Depending on which term is non-vanishing, 25 possible cases that may give rise to oscillation are inherent in the generalized kinetic scheme in Eqn (1). By symmetry, only 16 of these cases are distinct. The latter cases are listed in Table 1.

Nomenclature

The terms d_{ij}, defined by Eqn (11), have a simple physical meaning. They express the change of the reaction rate v_j due to a change in the concentration of a reactant $[X_i]$. If $d_{ij} = 0$, the reaction rate v_i is independent of $[X_j]$. If $d_{ij} > 0$, X_j is a substrate or an activator of the reaction proceeding at rate v_i. If $d_{ij} < 0$ finally, X_j must be a product or an inhibitor of the reaction proceeding at rate v_i.

The kinetic structure of the oscillatory systems listed in Table 1, therefore, can be described using standard enzyme kinetic terminology. A suitable nomenclature for characterization and distinction of the different mechanistic patterns that may give rise to oscillations is proposed in Table 1.

Restrictions on the oscillations

According to Eqn (13), the damping factor of an oscillation is given by

$$a = -\frac{(a_{11} + a_{22})}{2}. \quad (18)$$

Eqns (7) and (10) provide the inference that this factor is positive in the standard case when all reaction rates increase with increasing substrate concentration and decrease with increasing product concentration. Positive damping factors ensure that the steady state is stable against perturbations, such that it will be of physiological significance.

If any reaction is substrate inhibited or product activated (as in schemes 8, 11 and 15 in Table 1), the damping factor may be arbitrarily small or even negative. A negative damping factor makes the steady state unstable and therefore physiologically unattainable. In some cases, however, the unstable steady state may be surrounded by a limit cycle that gives rise to sustained oscillations (cf. [4, 5]).

The quotient of the angular frequency (b) and the damping factor (a) provides an estimate of the damping of an oscillation. As a rule of thumb, if $b/a \approx 2n$, then about n full oscillations will occur before the oscillation has been damped to 5% of the original amplitude. In those cases where the damping factor may be arbitrarily small or negative, b/a may attain arbitrarily large values. The same is true also if any of the non-vanishing terms on the right-hand side of Eqn (17) is not present on the left-hand side. If all the non-vanishing terms on the right-hand side of Eqn (17) are present also on the left-hand side, however, b/a will have an upper boundary. For schemes 12 and 16 in Table 1, for example, one has $b/a \leqslant 1$ independently of which detailed rate equations apply. This means that the corresponding oscillation will be so strongly damped that one may have difficulty in distinguishing it from a non-oscillatory transient governed by two real transient rate parameters (cf. [13]). The existing upper boundaries of the quotient b/a are given in the last column in Table 1 in applicable cases. This column also lists other restrictions on the term d_{ij} which can be derived without knowledge of the explicit rate equations. The latter restrictions refer only to the simplest case of the schemes considered, i.e. the case with the least number of non-vanishing d_{ij}. For more complicated cases, an explicit analysis of Eqn (17) is needed in order to establish which restrictions may apply.

DISCUSSION

Coupling characteristics of oscillating systems

Oscillating reactions always involve some kind of dynamic coupling of at least two reactants in the system. In the terminology of Higgins [5], this coupling can be either stoichiometric or kinetic. The generalized reaction scheme in Eqn (1) includes two potentially oscillating sub-systems involving only stoichiometric coupling (schemes 12 and 16 in Table 1). These systems may oscillate without any feedback or feed-forward effects in the standard kinetic sense, because the stoichiometric

Table 1. *Potentially oscillating sub-systems of the generalized kinetic scheme in Eqn (1)*
The minimal reaction scheme, the characteristic pair of d_{ij} that is necessary for the oscillation with the requested sign of the product term, a proposed name and possible restrictions, are listed for each of the 16 potentially oscillatory sub-systems of the reaction scheme in Eqn (1). A curved arrow in the scheme, indicates a kinetic interaction necessary for the oscillation. The interaction depends on the sign activation (+) or inhibition (−). It is assumed that every reaction velocity is activated by the substrate. If a reaction must be reversible (i.e. inhibited by the product) this is indicated as an restriction. The pairs indicated within brackets are those that are not symmetrically distinct

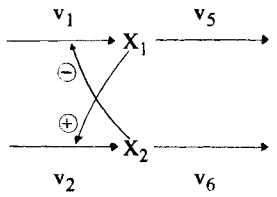
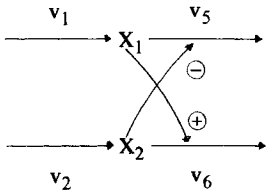
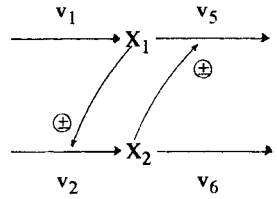
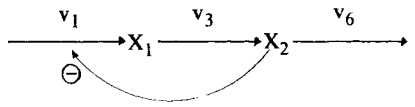
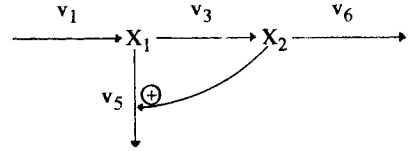
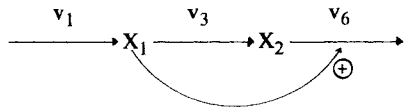
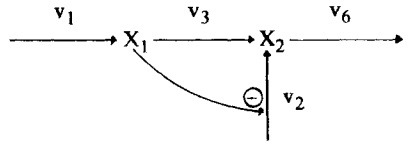
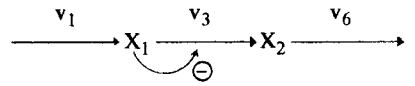
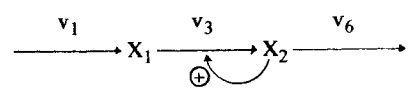
No.	Scheme	Characteristic product pair	Proposed name	Restrictions
1.		$d_{21}d_{12} < 0$	crosswise input coupling	
2.		$d_{61}d_{52} < 0$	crosswise output coupling	
3.		$d_{21}d_{52} > 0$ $(d_{61}d_{12} > 0)$	crosswise mixed coupling	
4.		$d_{31}d_{12} < 0$	feedback inhibition	
5.		$d_{31}d_{52} > 0$	branch output activation	
6.		$d_{61}d_{32} < 0$	feed-forward activation	$d_{32} < 0$ $d_{61} > d_{31}$
7.		$d_{21}d_{32} > 0$	branch input inhibition	$d_{32} < 0$ $\lvert d_{21}\rvert > d_{31}$
8a.		$d_{31}d_{32} > 0$	substrate inhibition	$d_{11}, d_{31}, d_{32} < 0$
8b.		$d_{31}d_{32} > 0$	product activation	$d_{31}, d_{32} > 0$

Table 1. (Continuation)

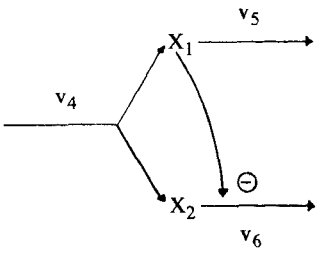
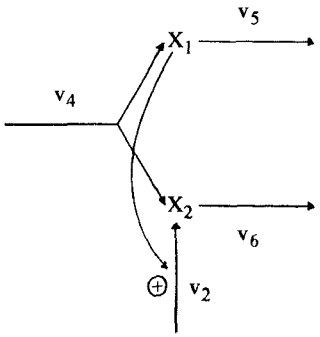
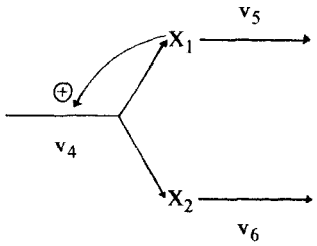
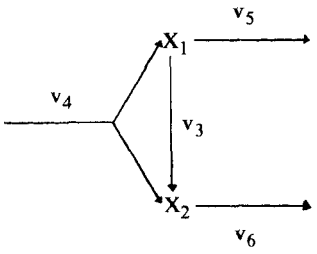
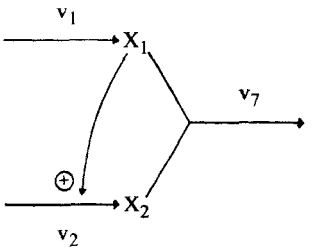
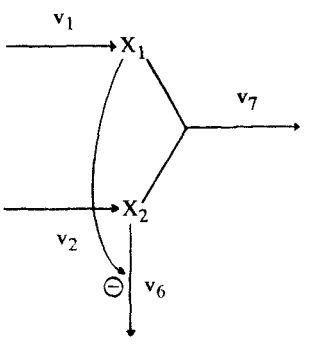
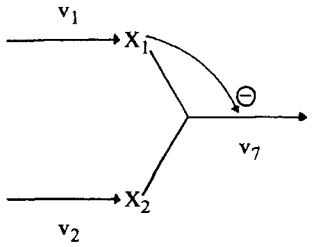
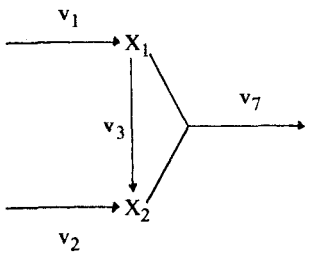
No.	Scheme	Characteristic product pair	Proposed name	Restrictions
9.		$d_{61}d_{42} > 0$ $(d_{41}d_{52} > 0)$	bimolecular output inhibition	$d_{42} < 0$ $\lvert d_{61}\rvert > \lvert d_{41}\rvert$
10.		$d_{21}d_{42} < 0$ $(d_{41}d_{12} < 0)$	bimolecular branch input inhibition	$d_{42} < 0$ $d_{21} > \lvert d_{41}\rvert$
11.		$d_{41}d_{42} < 0$	bimolecular product activation	$d_{41} > 0$ $d_{42} < 0$
12.		$d_{31}d_{42} < 0$ $(d_{41}d_{32} > 0)$	bimolecular input cycle	$b/a \leq 1$ $d_{42} < 0$
13.		$d_{21}d_{72} > 0$ $(d_{71}d_{12} > 0)$	bimolecular input activation	$d_{21} > d_{71}$
14.		$d_{61}d_{72} < 0$ $(d_{71}d_{52} < 0)$	bimolecular branch output inhibition	$\lvert d_{61}\rvert > d_{71}$

Table 1. (Continuation)

No.	Scheme	Characteristic product pair	Proposed name	Restrictions
15.		$d_{71}d_{72} < 0$	bimolecular substrate inhibition	$d_{11}, d_{71} < 0$
16.		$d_{31}d_{72} > 0$ $(d_{71}d_{32} < 0)$	bimolecular output cycle	$b/a \leq 1$

structure itself provides the appropriate coupling. In both cases, however, the oscillations will be strongly damped and may, hence, be difficult to detect experimentally.

All other sub-systems listed in Table 1 involve kinetic coupling, in the sense that one reactant acts as an inhibitor or activator of the reaction steps through which the second reactant is produced or consumed. Most of these cases represent mechanisms where standard feedback or feed-forward effects operate and need not be discussed in detail.

Attention should rather be drawn to schemes 1 – 3 in Table 1, which point to a hitherto unforeseen possible source of oscillations in biological systems. The two reactants that are kinetically coupled need not be stoichiometrically interconnected, but may appear in distinct metabolic pathways. In that case, the coupling must be based on two cross-wise interactions of specific nature. For example, oscillations may be triggered if reactant X_1 in one pathway activates the production of X_2 in a second pathway, at the same time as X_2 inhibits the production of X_1. Such cross-wise interactions may not have been frequently described in the literature, but must nevertheless be considered as an important potential source of metabolic oscillations. In complex metabolic networks, there are a very large number of possibly interacting pairs of reactants that have to be checked before the existence of cross-coupling effects can be ruled out.

In the reaction scheme in Eqn (1), it is assumed that all the stoichiometric coefficients are equal to unity, i.e. that one molecule (of each species) is consumed and one molecule produced in every reaction. With a different stoichiometry there is no qualitative change; all systems that may oscillate with one stoichiometry may also oscillate with another. Quantitatively, however, there may be appreciable changes.

Biological occurrence of potential sources of oscillations

The list of potentially oscillating systems presented here includes several mechanistic patterns that are frequently encountered in biological reaction systems. Feedback inhibition (scheme 4 in Table 1) is a well-known characteristic of virtually all metabolic pathways and is usually held as one of the most important factors contributing to the regulation of metabolic flux [6]. Substrate inhibition and product activation (scheme 8), similarly, represent frequently observed phenomena that have been previously discussed as possible sources of metabolic oscillations [2, 5, 14].

Less attention has been paid to the kinetic coupling that may exist between the two reactants in bimolecular reaction steps, despite the fact that most enzymes act on two substrates and/or catalyse reactions yielding two products. The present investigation shows that such systems also may represent important possible sources of oscillations in systems where two reactants are produced (scheme 9 – 12), as well as in systems where two reactants are consumed (scheme 13 – 15).

The results presented here, therefore, might seem to suggest that damped oscillations should be more frequently observed in transient-state kinetic studies of biochemical reaction systems than they actually have been. This is not the case for two main reasons. First, Table 1 lists only the minimal mechanistic patterns that are required to obtain oscillations. In most of these cases, additional conditions have to be fulfilled in order to ensure that oscillations do occur. These conditions can be expressed only by consideration of the explicit rate equations that govern the kinetics of the system and will not be discussed here. It may suffice to point out that, for some cases listed in Table 1, the actual functional character of the rate equations may well be such that the system cannot oscillate at all or will oscillate only over restricted ranges of reactant concentrations or values of kinetic parameters in the rate equations.

Secondly, even if oscillations do occur in a reaction system, they may not have such kinetic characteristics (damping factor, frequency or amplitude) that they can be experimentally observed. The damping factor, for example, defines the time scale of the transient and must correspond to the time scale of the experiments; like ordinary exponential transients, oscillations may well be too rapid or of too low amplitude to be readily detected.

Results in Table 1 can be used to decide whether or not a specific reaction system may exhibit an oscillatory rate behav-

iour, as well as to identify possible mechanistic sources of experimentally observed oscillations. Such analysis only requires knowledge about the stoichiometric structure and the kinetic couplings of the reaction system; the explicit rate equations are not needed. Decisions as to the actual existence of detectable oscillations in a postulated reaction system (or calculations of the kinetic parameter values characterizing the oscillations), however, requires a more thorough mathematical analysis based on detailed knowledge of the rate equations that apply.

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