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On the mechanistic origin of damped oscillations in biochemical reaction systems

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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 systems (e.g. involving feedback inhibition, feed-forward activation, substrate inhibition or product activation), but also draws 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 has 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.
\[ a_{12} = d_{12} - d_{32} + d_{42} - d_{52} - d_{72} \]  
\[ a_{21} = d_{21} + d_{31} + d_{41} - d_{61} - d_{71} \]  
\[ a_{22} = d_{22} + d_{32} + d_{42} - d_{62} - d_{72} \]  
\[ d_{ij} = \left( \frac{\partial x_i}{\partial [X_j]} \right) \]  
\[ [X_i] = [X_i]_0; \quad i = 1, \ldots, 7; \quad j = 1, 2 \]  
\[ \lambda_1, \lambda_2 = \lambda_{1,2} \pm \frac{\sqrt{(a_{11}-a_{22})^2 + 4a_{12}a_{21}}}{2} \]  
\[ \lambda_1 = -a + b \sqrt{-1} \]  
\[ \lambda_2 = -a - b \sqrt{-1} \]  
\[ [X_j] = [X_j]_0 + A_{j1}e^{\lambda_1 t} + A_{j2}e^{\lambda_2 t}; \quad j = 1, 2 \]  
\[ \lambda_{1,2} = \frac{a_{11} + a_{22} \pm \sqrt{(a_{11}-a_{22})^2 + 4a_{12}a_{21}}}{2} \]  
\[ \frac{\partial x_i}{\partial [X_j]} = d_{ij} \]  
\[ a = -\frac{(a_{11} + a_{22})}{2} \]  

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

\[ a = -\frac{(a_{11} + a_{22})}{2} \]  

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 \( b/a \approx 2 \), 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 \( b/a \leq 1 \) 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.

<table>
<thead>
<tr>
<th>No.</th>
<th>Scheme</th>
<th>Characteristic product pair</th>
<th>Proposed name</th>
<th>Restrictions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><img src="image1" alt="Scheme 1" /></td>
<td>$d_{21}d_{12} &lt; 0$</td>
<td>crosswise input coupling</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td><img src="image2" alt="Scheme 2" /></td>
<td>$d_{01}d_{12} &lt; 0$</td>
<td>crosswise output coupling</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td><img src="image3" alt="Scheme 3" /></td>
<td>$d_{23}d_{32} &gt; 0$ (or $d_{01}d_{12} &gt; 0$)</td>
<td>crosswise mixed coupling</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td><img src="image4" alt="Scheme 4" /></td>
<td>$d_{31}d_{32} &lt; 0$</td>
<td>feedback activation</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td><img src="image5" alt="Scheme 5" /></td>
<td>$d_{31}d_{32} &gt; 0$</td>
<td>branch output activation</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td><img src="image6" alt="Scheme 6" /></td>
<td>$d_{41}d_{32} &lt; 0$</td>
<td>feed-forward activation</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td><img src="image7" alt="Scheme 7" /></td>
<td>$d_{51}d_{32} &gt; 0$</td>
<td>branch input inhibition</td>
<td></td>
</tr>
<tr>
<td>8a.</td>
<td><img src="image8a" alt="Scheme 8a" /></td>
<td>$d_{51}d_{32} &gt; 0$</td>
<td>substrate inhibition</td>
<td></td>
</tr>
<tr>
<td>8b.</td>
<td><img src="image8b" alt="Scheme 8b" /></td>
<td>$d_{51}d_{32} &gt; 0$</td>
<td>product activation</td>
<td></td>
</tr>
<tr>
<td>No.</td>
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<tr>
<td>9.</td>
<td><img src="image" alt="Scheme 9" /></td>
<td>(d_{61}d_{43} &gt; 0) ((d_{41}d_{22} &gt; 0))</td>
<td>bimolecular output inhibition</td>
<td>(d_{42} &lt; 0) (</td>
</tr>
<tr>
<td>10.</td>
<td><img src="image" alt="Scheme 10" /></td>
<td>(d_{51}d_{42} &lt; 0) ((d_{61}d_{12} &lt; 0))</td>
<td>bimolecular branch input inhibition</td>
<td>(d_{42} &lt; 0) (d_{31} &gt;</td>
</tr>
<tr>
<td>11.</td>
<td><img src="image" alt="Scheme 11" /></td>
<td>(d_{53}d_{42} &lt; 0) ((d_{43}d_{32} &gt; 0))</td>
<td>bimolecular input cycle</td>
<td>(b/a \leq 1) (d_{42} &lt; 0)</td>
</tr>
<tr>
<td>12.</td>
<td><img src="image" alt="Scheme 12" /></td>
<td>(d_{31}d_{22} &gt; 0) ((d_{11}d_{12} &gt; 0))</td>
<td>bimolecular input activation</td>
<td>(d_{21} &gt; d_{71})</td>
</tr>
<tr>
<td>13.</td>
<td><img src="image" alt="Scheme 13" /></td>
<td>(d_{61}d_{52} &lt; 0) ((d_{61}d_{52} &lt; 0))</td>
<td>bimolecular branch output inhibition</td>
<td>(</td>
</tr>
</tbody>
</table>
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-

<table>
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</thead>
<tbody>
<tr>
<td>15.</td>
<td><img src="image1" alt="Scheme 15" /></td>
<td>$d_{11}d_{72} &lt; 0$</td>
<td>bimolecular substrate inhibition</td>
<td>$d_{11}, d_{71} &lt; 0$</td>
</tr>
</tbody>
</table>
| 16. | ![Scheme 16](image2) | $d_{11}d_{72} > 0$  
$ (d_{11}d_{32} < 0)$ | bimolecular output cycle | $b/a \leq 1$ |
avour, 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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REFERENCES