Proceedings of the
47th IEEE Conference on Decision and Control
Cancun, Mexico, Dec. 9-11, 2008

A kinetic mechanism inducing oscillations in simple chemical reactions networks

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Abstract— **It is known that a kinetic reaction network in which one or more secondary substrates are acting as cofactors may exhibit an oscillatory behavior. The aim of this work is to provide a description of the functional form of such a cofactor action guaranteeing the onset of oscillations in sufficiently simple reaction networks.**

I. Introduction

Apart from circadian rhythms, many biochemical networks exhibiting oscillations have been intensively studied, such as, for example, cell cycle [1], Ca^{+}-induced oscillations [8], glycolysis [15], [20], [14], yeast metabolic cycle [19], genetic oscillators [4], [18]. Given a biochemical reaction network with nonlinear rate laws, it is in general difficult to predict exactly when oscillations will arise, as this depends on the "graph" of the reaction network, on the form chosen for the kinetic equations, and on the values assigned to the parameters. In this context, systems in 2D are exceptional in the sense that for them the onset of oscillations can be described almost exhaustively, see [2], [5] for an overview. There is a number of ways in which oscillations can arise (see [17], [12] for surveys). In this work we are interested in the case in which they are due to the catalytic effect of a secondary substrate acting as a co-enzyme in a reaction. A typical example (and the inspiration for this work) is given by ATP in the glycolysis pathway [20]. ATP is a cofactor in some of the reaction steps (e.g. in the step catalyzed by Hexokinase: glucose $\longrightarrow$ glucose-6-phosphate) while a too high concentration of ATP leads to inhibition of the reaction itself. Since the net production of ATP in the glycolysis pathway is positive, this activator/inhibitor role has a regulatory action and it induces the oscillations.

Clearly the appearance of oscillations on a model of the pathway depends on the functional form chosen to describe this activation/inhibition mechanism, call it ϕ. The aim of this paper is to give explicit conditions on the form of ϕ sufficient to induce oscillations on simple reaction networks. As we are interested in analytically provable sufficient conditions (the tools we shall use are essentially Hopf bifurcation analysis and Poincaré-Bendixon theorem), our "networks" are limited to very simple chains of reactions. Nevertheless once the conditions are given, they can be applied (and verified numerically) in arbitrarily large networks.

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II. Oscillations for 2D systems - Background material

The onset of sustained oscillations on nonlinear dynamical systems is fully understood only on 2D systems, see e.g. [2], [5] for general considerations or [17], [12] for recent reviews dealing with simple reaction networks. In this section we recall some results which are used in the rest of the paper.

Let (x, y) belong to $\mathcal{R}^2_+$ (the positive orthant in $\mathcal{R}^2$), and consider the family of parameters $p \in \mathcal{R}^r_+$. In this section, we will consider the system

$$\begin{array}{l} \frac{dx}{dt} = f(x, y, p) \\ \frac{dy}{dt} = g(x, y, p), \end{array} \tag{1}$$

and, to simplify notations, we will sometimes forget to explicit the dependency on p of f and g. If the jacobian of this system at an equilibrium $(\bar{x}, \bar{y})$ is

$$J = \begin{bmatrix} f_x(\bar{x}, \bar{y}) & f_y(\bar{x}, \bar{y}) \\ g_x(\bar{x}, \bar{y}) & g_y(\bar{x}, \bar{y}) \end{bmatrix} = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix},$$

the associated characteristic polynomial is $s^2 - tr(J)s + det(J)$, where $tr(J) = a_{11} + a_{22}$ and $det(J) = a_{11}a_{22} - a_{21}a_{12}$. Its eigenvalues determine the stability of the equilibrium and we have

- If $det(J) < 0$, then there is one positive and one negative real eigenvalue, so the steady-state is unstable (saddle point).
- If $det(J) > 0$ and $tr(J) < 0$, then the steady-state is stable.
- If $det(J) > 0$ and $tr(J) > 0$, then the steady-state is unstable.

Another restriction for our system is given by Bendixon's criterion:

Theorem 1 (Bendixon's criterion) *Consider the system (1). If the divergence $\frac{\partial f}{\partial x} + \frac{\partial g}{\partial y}$ is not zero on some simply connected domain $\mathcal{D}$, then no periodic orbit can lie entirely in $\mathcal{D}$.*

For the system (1), the divergence corresponds to $tr(J)$. In general, $tr(J)$ and $det(J)$ depend continuously on p. In order to have oscillations, Bendixon's criterion requires that we have a transition between stability and instability. If by varying one of the parameters (call it p_1), we can carry $tr(J)$ from negative to positive values, while keeping $det(J) > 0$, then the steady state passes through a bifurcation. As $tr(J)$ is close to 0, we have two complex conjugated eigenvalues, with real part approaching zero. At the bifurcation point ($p_1 = p_{crit}$), $tr(J) = 0$, and the eigenvalues are purely

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imaginary $s = \pm i\omega$. Close to the bifurcation point, i.e., $p_1 \approx p_{crit}$, small amplitude limit cycle solutions surround the steady state, and the period of oscillation is close to $\frac{2\pi}{\omega}$: we say that periodic solutions arise by a Hopf bifurcation at $p_1 = p_{crit}$ (see [9] for more details on Hopf bifurcations).

If, in addition, the trajectories of (1) are confined in a closed bounded set inside which the system has at most a repelling equilibrium point, then the Poincaré-Bendixon theorem can be applied.

Theorem 2 (Poincaré-Bendixon theorem) *Consider the system (1). If for $t \geqslant 0$ a trajectory of (1) is confined to a closed, bounded set $\mathcal{D}$ and does not approach any critical point in $\mathcal{D}$, then it is either a closed periodic orbit or it approaches one.*

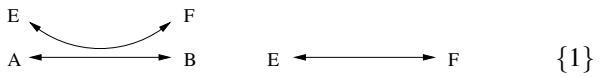
If (1) represents two chemical species, then in order to have oscillations it is required that at least one of the two reactants x and y is acting on itself with effect that varies as we change p in a neighborhood of p_{crit}. For example if on the diagonal we have just one or more degradation terms e.g. $x \to 0$ and/or $y \to 0$, then $a_{11} + a_{22} < 0$, and no oscillation can appear. Likewise if both diagonal terms are autocatalytic, $x \to \alpha x$, $\alpha > 1$, and/or $y \to \beta y$, $\beta > 1$ ($a_{11} + a_{22} > 0$ in this case). Combination of the two cases can already induce oscillations, provided that $tr(J)$ changes sign when varying some of the parameters.

The conclusion is that for 2D systems a necessary condition for the appearance of a Hopf bifurcation is that at least one of the variables involved experiences an autocatalysis for some values of the parameters but not for others. The arising of sustained oscillations is guaranteed in the case Theorem 2 is applicable. For a more thorough discussion about oscillating 2D chemical reactions see e.g. [5].

III. An elementary mechanism inducing oscillations

The context in which we are interested to investigate the appearance of oscillations is that of biochemical reaction kinetics modeled to a large extent by means of mass-action laws, with some nonlinear non mass-action terms providing the necessary autocatalytic/inhibitory mechanisms. This is a very common setting in literature, see [2], [15], [19], [20] and many others. Our attention is in particular focused on the case in which the non mass-action term involves a secondary substrate of a reaction.

In order to apply the exact 2D-results, we shall consider the simple mechanism depicted in $\{1\}$. In the graph $\{1\}$



$\{1\}$

$A \longleftrightarrow B$ represents the principal branch of the reaction and the cofactors E, F are required for the reaction to take place (e.g. through allosteric regulation). The action of E on A is non-linear and unknown. The other rate-laws are assumed to be of mass-action form, leading to the following dynamics

$$\begin{cases} \frac{dA}{dt} = -k_1^+ A\phi(E) + k_1^- BF \\ \frac{dB}{dt} = k_1^+ A\phi(E) - k_1^- BF \\ \frac{dE}{dt} = -k_1^+ A\phi(E) + k_1^- BF - k_2^+ E + k_2^- F \\ \frac{dF}{dt} = k_1^+ A\phi(E) - k_1^- BF + k_2^+ E - k_2^- F, \end{cases}$$

where ϕ is the unknown function (at least C^1) modeling the nonlinear action of E on A, $\phi(0) = 0$, $k_1^\pm$, $k_2^\pm \in \mathcal{R}_+$. Although simple, this system is e.g. non-monotone for non-monotonic choices of ϕ [7] and, by construction, not treatable by means of mass-action formalism [6]. For such system, we have two moiety conservations ($\frac{dA}{dt} + \frac{dB}{dt} = 0$ and $\frac{dE}{dt} + \frac{dF}{dt} = 0$), so by writing $A+B = M_1$ and $E+F = M_2$, it simplifies to the 2D-system:

$$\begin{cases} \frac{dA}{dt} = & -k_1^+ A\phi(E) + k_1^-(M_1 - A)(M_2 - E) \\ \frac{dE}{dt} = & -k_1^+ A\phi(E) + k_1^-(M_1 - A)(M_2 - E) \\ & -k_2^+ E + k_2^-(M_2 - E). \end{cases} \quad (2)$$

For an equilibrium point $(\bar{A}, \bar{E})$, we have the conditions

$$\begin{cases} -k_1^+ \bar{A}\phi(\bar{E}) + k_1^-(M_1 - \bar{A})(M_2 - \bar{E}) = 0 \\ -k_1^+ \bar{A}\phi(\bar{E}) + k_1^-(M_1 - \bar{A})(M_2 - \bar{E}) \\ \qquad -k_2^+ \bar{E} + k_2^-(M_2 - \bar{E}) = 0, \end{cases}$$

which imply

$$\begin{cases} \frac{k_1^+}{k_1^-}\frac{\bar{A}}{M_1 - A}\phi(\bar{E}) = M_2 - \bar{E} \\ \bar{E} = \frac{k_2^-}{k_2^+ + k_2^-} M_2 \end{cases} \quad (3)$$

i.e.,

$$(\bar{A}, \bar{E}) = \left(\frac{M_1 M_2 k_2^+}{(k_2^+ + k_2^-)\frac{k_1^+}{k_1^-}\phi(\bar{E}) + M_2 k_2^+}, \frac{k_2^-}{k_2^+ + k_2^-} M_2 \right) \quad (4)$$

At the equilibrium, the corresponding jacobian matrix $J = (J_{ij})$ has elements

$$\begin{aligned} J_{11} &= -k_1^+\phi(\bar{E}) - k_1^+ \frac{\bar{A}}{M_1 - \bar{A}}\phi(\bar{E}), \\ J_{12} &= -k_1^+ \bar{A}\phi'(\bar{E}) - k_1^-(M_1 - \bar{A}), \\ J_{21} &= -k_1^+\phi(\bar{E}) - k_1^+ \frac{\bar{A}}{M_1 - \bar{A}}\phi(\bar{E}), \\ J_{22} &= -k_1^+ \bar{A}\phi'(\bar{E}) - k_1^-(M_1 - \bar{A}) - k_2^+ - k_2^-, \end{aligned}$$

and the associated characteristic polynomial is

$$\chi(s) = s^2 + \Delta s + \Omega,$$

where $\Delta = k_1^+\phi(\bar{E}) + k_1^+\frac{\bar{A}}{M_1 - A}\phi(\bar{E}) + k_1^+\bar{A}\phi'(\bar{E}) + k_1^-(M_1 - \bar{A}) + k_2^+ + k_2^-$ and $\Omega = k_1^+\phi(\bar{E})(1 + \frac{\bar{A}}{M_1 - A})(k_2^+ + k_2^-)$. The determinant of the jacobian is Ω, and its trace is $-\Delta$. As we have seen before, the interesting case for Hopf bifurcations is $\Omega > 0$. But $\Omega = k_1^+\phi(\bar{E})(1 + \frac{\bar{A}}{M_1 - A})(k_2^+ + k_2^-)$, so if ϕ is positive for positive entries, then $\Omega > 0$

(as $\bar{E} \neq 0$). Our aim is to make the real part of the eigenvalues evolve from negative values to positive values (or the contrary) by modifying only the parameters ($k_i^{\pm}$), thereby inducing a Hopf bifurcation. From the expression of Δ, the only term that can assume a negative sign is $k_1^+ \bar{A}\phi(\bar{E})$, meaning that ϕ must be decreasing at $\bar{E}$.

The following proposition provides conditions sufficient in order for ϕ to induce oscillations.

Proposition 1 *If the function ϕ is $\mathcal{C}^1$, positive, non identically zero, and corresponds to one of the following situations:*

- ***Activator/Inhibitor case:***
  ϕ is increasing on $[0, \alpha]$, decreasing on $[\alpha, \infty[$ for some α in $]0, \infty[$, $\phi(0) = 0$ and $\lim_{x\to\infty} \phi(x) = 0$, and fulfills the following conditions:
  1) $\alpha < M_2$,
  2) $\phi^{'}(0) > 0$,
  3) $\exists(k_i^{\pm}) \in \mathcal{R}_+^4$, $i = 1, 2$, *for which* $x_m = \bar{E}$, *and*

$$\Delta^0 = k_1^+\phi(x_m)\left(1 + \frac{k_1^-}{k_1^+}\frac{(M_2 - x_m)}{\phi(x_m)}\right) + \frac{k_1^+k_1^-M_1(M_2 - x_m)\phi^{'}_{min}}{k_1^+\phi(x_m) + k_1^-(M_2 - x_m)} + k_2^+ + k_2^- + k_1^-\left(M_1 - \frac{k_1^-M_1(M_2 - x_m)}{k_1^+\phi(x_m) + k_1^-(M_2 - x_m)}\right) < 0$$

  where $x_m = max\{x \in \mathcal{R}_+ | \phi^{'}(x) = \phi^{'}_{min}\}$, with $\phi^{'}_{min}$ the minimum of $\phi^{'}$.
- ***Inhibitor/Activator case:***
  ϕ is decreasing on $[0, \alpha]$, increasing on $[\alpha, \infty[$ for some α in $]0, \infty[$, tends to a constant when $x \to \infty$, and fulfills the following conditions:
  1) $\alpha < M_2$,
  2) $\phi(0) \leqslant \frac{k_2^-M_2}{k_1^+M_1}$,
  3) $\exists(k_i^{\pm}) \in \mathcal{R}_+^4$, $i = 1, 2$, *for which x_m (defined as above) is such that $x_m = \bar{E} \in [0, \alpha]$ and*

$$\Delta^0 = k_1^+\phi(x_m)\left(1 + \frac{k_1^-}{k_1^+}\frac{(M_2 - x_m)}{\phi(x_m)}\right) + \frac{k_1^+k_1^-M_1(M_2 - x_m)\phi^{'}(x_m)}{k_1^+\phi(x_m) + k_1^-(M_2 - x_m)} + k_2^+ + k_2^- + k_1^-\left(M_1 - \frac{k_1^-M_1(M_2 - x_m)}{k_1^+\phi(x_m) + k_1^-(M_2 - x_m)}\right) < 0,$$

then oscillations must occur in the elementary reaction network {1} obeying to (2) *for some values of the parameters $k_i^{\pm}$.*

Proof:

- **Activator/Inhibitor case:**
  Under the assumptions above, the rectangle $\mathcal{D} = [0, M_1] \times [0, M_2]$ is invariant to the flow of the system as $\forall E \in [0, M_2]$

$$\left.\frac{dA}{dt}\right|_{A=0} = k_1^-M_1(M_2 - E) \geqslant 0, \quad (5)$$

$$\left.\frac{dA}{dt}\right|_{A=M_1} = -k_1^+A\phi(E) \leqslant 0, \quad (6)$$

  and $\forall A \in [0, M_1]$

$$\left.\frac{dE}{dt}\right|_{E=0} = -k_1^+A\phi(0) + k_1^-(M_1 - A)M_2 + k_2^-M_2 \geqslant 0 \quad (7)$$

$$\left.\frac{dE}{dt}\right|_{E=M_2} = -k_1^+A\phi(M_2) - k_2^+M_2 \leqslant 0. \quad (8)$$

  In correspondence of the point in the parameter space for which:

$$x_m = \bar{E} = \frac{k_2^-}{k_2^+ + k_2^-}M_2$$

  we have

$$\Delta = k_1^+\phi(\bar{E})(1 + \frac{\bar{A}}{M_1 - \bar{A}}) + k_1^+\bar{A}\phi^{'}(\bar{E}) + k_1^-(M_1 - \bar{A}) + k_2^+ + k_2^- = \Delta^0 < 0$$

  as $\bar{A} = \frac{k_1^-M_1(M_2 - x_m)}{k_1^+\phi(x_m) + k_1^-(M_2 - x_m)}$ and $\frac{\bar{A}}{M_1 - \bar{A}} = \frac{k_1^-}{k_1^+}\frac{(M_2 - x_m)}{\phi(x_m)}$. This implies that the two eigenvalues corresponding to the equilibrium have positive real parts. We use k_2^+ as bifurcation parameter, and leave the other parameters unchanged. As from (3)

$$\begin{cases} \lim_{k_2^+\to\infty} \bar{E} = \lim_{k_2^+\to\infty} \frac{k_2^-}{k_2^+ + k_2^-}M_2 = 0 \\ \lim_{k_2^+\to\infty} M_2 - \bar{E} = \lim_{k_2^+\to\infty} \frac{k_2^+}{k_2^+ + k_2^-}M_2 = M_2 \end{cases}$$

  and also

$$\lim_{k_2^+\to\infty} \bar{A} = M_1,$$

  then as $\phi^{'}(0) > 0$, for k_2^+ large enough, $k_1^+\bar{A}\phi^{'}(\bar{E}) + k_1^-(M_1 - \bar{A}) > 0$, and consequently $\Delta > 0$, implying that the eigenvalues corresponding to the equilibrium have negative real parts.
- **Inhibitor/Activator case:**
  The invariance of the flow on $\mathcal{D}$ follows from (5)-(8). Notice in particular that from (7) the condition

$$\phi(0) \leqslant \frac{k_1^-(M_1 - A)M_2 + k_2^-M_2}{k_1^+A}$$

  follows from the assumption $\phi(0) \leqslant \frac{k_2^-M_2}{k_1^+M_1}$ since $0 \leqslant A \leqslant M_1$. Concerning the Hopf bifurcation, the scheme above can be followed also in this case, but with k_2^- as bifurcation parameter. Let us begin from a point in parameter space for which $x_m = \bar{E}$ and

$$\Delta = k_1^+\phi(\bar{E})(1 + \frac{\bar{A}}{M_1 - \bar{A}}) + k_1^+\bar{A}\phi^{'}(\bar{E}) + k_1^-(M_1 - \bar{A}) + k_2^+ + k_2^- = \Delta^0 < 0$$

  as $\bar{A} = \frac{k_1^-M_1(M_2 - x_m)}{k_1^+\phi(x_m) + k_1^-(M_2 - x_m)}$ and $\frac{\bar{A}}{M_1 - \bar{A}} = \frac{k_1^-}{k_1^+}\frac{(M_2 - x_m)}{\phi(x_m)}$. This implies that the two eigenvalues cor-

responding to the equilibrium have positive real parts. Since from (3)

$$\begin{cases} \lim_{k_2^- \to \infty} \bar{E} & = & \lim_{k_2^- \to \infty} \frac{k_2^-}{k_2^+ + k_2^-} M_2 = M_2 \\ \lim_{k_2^- \to \infty} M_2 - \bar{E} & = & \lim_{k_2^- \to \infty} \frac{k_2^+}{k_2^+ + k_2^-} M_2 = 0 \end{cases}$$

and also

$$\lim_{k_2^- \to \infty} \bar{A} \quad = \quad 0,$$

so, as $M_2 > \alpha$ there exists a η such that $k_2^- > \eta \Rightarrow \bar{E} > \alpha$, which means $\phi^{'}(\bar{E}) > 0 \Rightarrow \Delta > 0$ and the two eigenvalues have negative real parts.

Under the regularity assumptions, in both cases $\Delta = k_1^+ \phi(\bar{E})(1 + \frac{\bar{A}}{M_1 - \bar{A}}) + k_1^+ \bar{A} \phi^{'}(\bar{E}) + k_1^- (M_1 - \bar{A}) + k_2^+ + k_2^-$ is at least C^0 in k_2^+ (resp. k_2^-) (parametric version of the Cauchy-Lipschitz theorem). Since Δ takes both positive and negative values with the evolution of k_2^+ (resp. k_2^-), it must be zero for some intermediate value of k_2^+ (resp. k_2^-). In a sufficiently small neighborhood of this value, the eigenvalues will be complex as Δ is small whereas Ω remains positive. Then a Hopf bifurcation must occur. Since in both cases the dynamics of (2) is confined to $\mathcal{D}$ and, from (4), the unique equilibrium point in $\mathcal{D}$ is a repeller for the range of parameters for which $\Delta < 0$, the Poincaré-Bendixon Theorem is applicable, implying that $\exists\, k_i^{\pm}$ for which the system trajectories must approach a closed periodic orbit.

♢

The proof of the above Proposition emphasizes (through the parameters k_2^+ and k_2^-) the important role of the secondary reaction involving only E and F. As a matter of fact, the pathway $\{1\}$ without this secondary reaction cannot produce oscillations (the jacobian in that case has a row rank equal to 1). In fact, without the $E \longleftrightarrow F$ reaction, the nonlinear ϕ would quickly exhausts the concentration of E in the activator phase or F in the inhibitory phase.

Remark 1 *Relaxing monotonicity properties on ϕ.* In the *Activator/Inhibitor* case, the monotonicity properties required above for ϕ in the two intervals $[0, \alpha]$, $[\alpha, \infty[$ can be in part relaxed. If we assume only that ϕ is decreasing in $[\alpha, \infty[$ (the other assumptions remaining unchanged), then with $x_m = max\{x \in [\alpha, \infty[\text{ s.t. } \phi^{'}(x) = \phi^{'}_{min}\}$ and $\phi^{'}_{min}$ minimum of $\phi^{'}$ in $[\alpha, \infty[$, the previous result still holds.

Remark 2 *Relaxing a moiety constraint.* The hypothesis of the above Proposition use the explicit value of A and $\frac{A}{B}$ at the equilibrium, values linked by a moiety constraint. The same Proposition can be formulated without the hypothesis $A + B = M_1$.

- **Activator/Inhibitor case:** By writing

$$\Delta^0 = k_1^+ \phi(x_m) \left(1 + \frac{k_1^-}{k_1^+} \frac{(M_2 - x_m)}{\phi(x_m)}\right) + k_1^+ \bar{A} \phi^{'}(x_m) + k_1^- \bar{B} + k_2^+ + k_2^-$$

(with $\bar{B}$ the steady state value of B), the same Proposition holds, as at the equilibrium we still have

$$\begin{cases} \frac{k_1^+}{k_1^-} \frac{\bar{A}}{\bar{B}} \phi(\bar{E}) = M_2 - \bar{E} \\ \bar{E} = \frac{k_2^-}{k_2^+ + k_2^-} M_2 \end{cases}$$

and $\bar{B}$ goes to 0 when k_2^+ goes to $+\infty$ in the same way as $M_1 - \bar{A}$ did.

- **Inhibitor/Activator case:** The same kind of reasoning leads to replacing the former expression of Δ^0 by

$$\Delta^0 = k_1^+ \phi(x_m)(1 + \frac{k_1^-}{k_1^+} \frac{(M_2 - x_m)}{\phi(x_m)}) + k_1^+ \bar{A} \phi^{'}(x_m) + k_1^- \bar{B} + k_2^+ + k_2^-.$$

Then Proposition 1 still holds for this new system.

IV. Examples of ϕ functions

A. Activator/Inhibitor case

- The first example of ϕ function, is the one suggested by [20] for the glycolytic oscillations:

$$\phi_1(x) = \frac{x}{1 + (\frac{x}{K_s})^n}$$

with $n > 1$ (if $n = 1$, ϕ is a monotonically increasing Michaelis-Menten's law)(cf Figure 1).

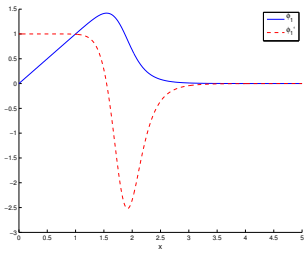


Fig. 1. Qualitative behavior of the ϕ_1 function, $K_s = 1.891$ and $n = 12$.

Such a function is increasing in $[0, K_s e^{-\frac{1}{n} ln(n-1)}]$, and decreasing in $[K_s e^{-\frac{1}{n} ln(n-1)}, \infty[$. We are in the Activator/Inhibitor case, with $\alpha = K_s e^{-\frac{1}{n} ln(n-1)} \approx 1.518$. The derivative of ϕ is:

$$\phi_1^{'}(x) = \frac{1}{1 + (\frac{x}{K_s})^n} - \frac{n(\frac{x}{K_s})^n}{(1 + (\frac{x}{K_s})^n)^2}$$

We know that $\phi^{'}$ is positive in $[0, K_s e^{-\frac{1}{n} ln(n-1)}]$ and negative in $[K_s e^{-\frac{1}{n} ln(n-1)}, \infty[$. Its minimum depends only on n

$$\phi^{'}_{min} = \frac{-(n-1)^2}{4n}$$

and is reached at the point $x_m = K_s e^{\frac{1}{n} ln \frac{n+1}{n-1}} \approx 1.929$. If we consider the reaction network $\{1\}$, then, for the

set of parameters

$$\begin{array}{ll} M_1 = 3, & M_2 = 4, \\ k_1^+ = 1, & k_1^+ = 1, \\ k_2^- = \frac{5}{12}, & K_s \approx 1.891, \\ n = 12, & k_2^+ \approx 0.425, \end{array}$$

(where k_2^+ is chosen according to the equilibrium conditions, so $M_2 > x_m = \frac{k_2^-}{k_2^+ + k_2^-} M_2 \approx 1.917$), the condition $M_2 > \alpha \approx 1.548$ is fulfilled, and we have $\Delta^0 \approx -0.597 < 0$. We also have $\phi^{'}(0) > 0$, and consequently our Proposition can be applied. Numerical simulations are shown on Figure 2:

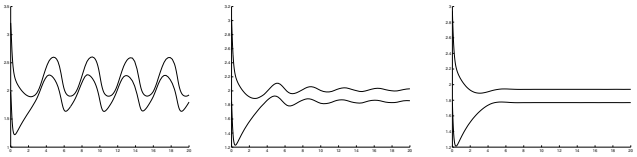


Fig. 2. Solutions for A and E, in correspondence of ϕ_1, for 3 values of the bifurcation parameter $k_2^+ = 0.42($ (left), $k_2^+ = 0.485$ (middle) and $k_2^+ = 0.525$ (right).

- Another example of function is $\phi_2(x) = Cxe^{-(x-\eta)^2}$. The shape of the function an its derivative are shown on Figure 3, and reveal that we are again in the Activator/Inhibitor case.

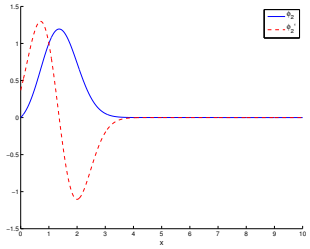


Fig. 3. Qualitative behavior of ϕ_2 and its derivative, $C = 1$, $\eta = 1$.

The derivative is $\phi_2^{'}(x) = C(-2x^2 + 2\eta x + 1)e^{-(x-\eta)^2}$. The point x_m in which $\phi^{'}$ reaches its minimum (for positive entries) is in the interval $[\frac{\eta}{2} + \frac{\sqrt{\eta^2+2}}{2}, \infty[$. Hence we must have $M_2 > x_m + \frac{\eta}{2} + \frac{\sqrt{\eta^2+2}}{2}$ (which implies $M_2 > \eta + \sqrt{\eta^2+2}$ as $x_m > \frac{\eta}{2} + \frac{\sqrt{\eta^2+2}}{2}$). For $\{1\}$ with the parameters:

$$\begin{array}{ll} M_2 = 4, & M_1 = 7, \\ k_1^+ = 1, & k_1^- = 1, \\ k_2^+ = 0.516, & k_2^- = 0.416, \\ \eta = 1, & \end{array}$$

we obtain $x_m \approx 2 < M_2$, and $\alpha \approx 1.367 < M_2$. For $k_2^+ \approx 0.416$, the equilibrium value of E corresponds to the minimum of $\phi^{'}$, and $\Delta^0 \approx -0.197 < 0$. The hypotheses of Proposition 1 are satisfied, and we obtain the results shown on Figure 4.

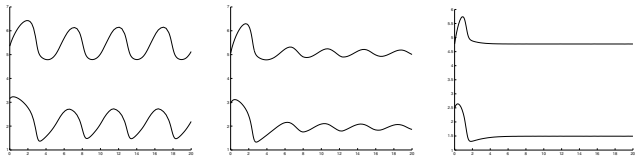


Fig. 4. Solutions for A and E, in correspondence of ϕ_2, for 3 values of the bifurcation parameter $k_2^+ = 0.356$ (left), $k_2^+ = 0.436$ (middle) and $k_2^+ = 0.7$ (right)

B. Inhibitor/Activator case

As an example of the Inhibitor/Activator case, consider $\phi_3(x) = \frac{n-1}{n} K_s e^{-\frac{ln(n-1)}{n}} - \frac{x}{1+(\frac{x}{K_s})^n}$. The behavior of this function is shown on Figure 5.

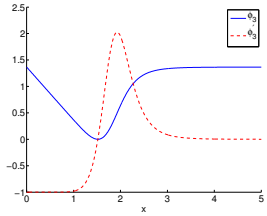


Fig. 5. Qualitative behavior of the ϕ_3 function, $K_s \approx 1.89$, $n = 10$.

Considering again $\{1\}$ with the parameters:

$$\begin{array}{ll} M_1 = 2, & M_2 = 6, \\ k_1^+ = 10, & k_1^+ = 1, \\ k_2^- \approx 0.083, & K_s \approx 1.79, \\ n = 4, & k_2^+ = \frac{5}{12}, \end{array}$$

we have $x_m \approx 1$, $\Delta_0 \approx -2.70$, and $\alpha \approx 1.36 < M_2$. Hence such a function fulfills the assumptions of Proposition 1. The results of a simulation for these values of the parameters is shown on Figure 6.

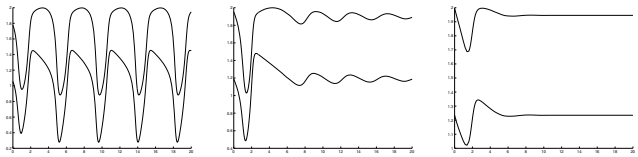
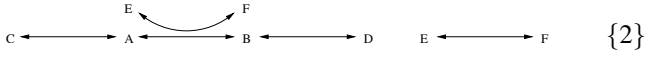


Fig. 6. Solutions for A and E, in correspondence of ϕ_3, for 3 values of the bifurcation parameter $k_2^- = 0.089$ (left), $k_2^- = 0.103$ (middle) and $k_2^- = 0.108$ (right)

V. A FEW EXTENSIONS TREATABLE ANALYTICALLY

A. Adding reactions to the elementary kinetic network

Typically, the extension of the scheme of Proposition 1 to higher dimensional systems cannot be treated analytically. Consider for example the linear pathway in $\{2\}$ with the following dynamics:



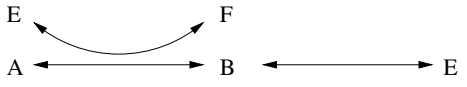
$\{2\}$

$$\begin{cases} \frac{dC}{dt} = -k_3^+ C + k_3^- A \\ \frac{dA}{dt} = -k_1^+ A\phi(E) + k_1^- B(M_2 - E) + k_3^+ C - k_3^- A \\ \frac{dB}{dt} = k_1^+ A\phi(E) - k_1^- B(M_2 - E) - k_4^+ B + k_4^- D \\ \frac{dE}{dt} = -k_1^+ A\phi(E) + k_1^- B(M_2 - E) - k_2^+ E \\ \qquad\qquad + k_2^-(M_2 - E) \\ \frac{dD}{dt} = k_4^+ B - k_4^- D. \end{cases} \tag{9}$$

Even taking into account the conservation of $A+B+C+D$, the characteristic equation associated to the equilibrium of the system is of order 4, and consequently too complicated to be treated analytically in general. However, if instead of $\{2\}$ we consider the extra reactions as irreversible, we get the same dynamics (9) but with $k_3^- = 0$ and $k_4^+ = 0$. Then using Remark 2, a sufficient condition for the oscillations to appear can be provided. Looking again at the complete system $\{2\}$, if the reaction constants of the two "outflows" $C \xleftarrow{k_3^-} A$ and $B \xrightarrow{k_4^+} D$ are small, the complete jacobian can be seen as a perturbation of the jacobian arising in the irreversible case, and consequently, for small enough coefficients k_3^- and k_4^+, we can again use the sufficient condition given in Proposition 1. Under this "small coefficients" assumption, the argument can be extended to arbitrarily long (linear) chains. In the general case, however, one must resort to numerical simulation.

B. A further coupling mechanism

A further elementary reaction scheme, of the same complexity as $\{1\}$, is shown in $\{3\}$. *In nuce*, this scheme is



$\{3\}$

inspired by the model of the sulfur assimilation pathway of [19] in which the final product, cysteine, at high concentrations has a negative feedback effect on the initial sulfate uptake. Using the same tools as above, we can first see that the reaction graph $\{3\}$ is such that $A + F = M_1$ and $B + E = M_2$. Hence the system has two free variables only, A and E, and we have

$$\begin{cases} \frac{dA}{dt} = -k_1^+ A\phi(E) + k_1^-(M_2 - E)\phi(M_1 - A) \\ \frac{dE}{dt} = -k_1^+ A\phi(E) + k_1^-(M_2 - E)\phi(M_1 - A) \\ \qquad\qquad -k_2^+ E + k_2^-(M_2 - E) \end{cases} \tag{10}$$

for which the equilibrium conditions are

$$\begin{cases} \bar{E} = \frac{k_2^-}{k_2^+ + k_2^-} M_2 \\ M_1 - \bar{A} = \frac{k_1^+(k_2^+ + k_2^-)}{k_1^- k_2^+} \frac{\bar{A}}{M_2} \phi(\bar{E}). \end{cases} \tag{11}$$

The characteristic equation is consequently:

$$s^2 + \hat{\Delta} s + \hat{\Omega} = 0$$

where $\hat{\Delta} = k_1^+\phi(\bar{E}) + k_1^-(M_1 - \bar{A}) + k_1^+\bar{A}\phi'(\bar{E}) + k_1^-(M_2 - \bar{E}) + k_2^+ + k_2^-$ and $\hat{\Omega} = (k_1^+\phi(\bar{E}) + k_1^-(M_2 - \bar{E})(M_1 - \bar{A}))(k_2^+ + k_2^-)$. The equations are very similar to those of section III. Equation (11) also shows that one of the two equilibrium constraints is modified. In the *Activator/Inhibitor* case, with $\hat{\Delta}^0 = k_1^+\phi(\bar{E})(1 + \frac{k_1^+(k_2^+ + k_2^-)}{k_2^+}\frac{\bar{A}}{M_2}) + k_1^+\bar{A}\phi'(x_m) + k_1^-(M_1 - \bar{A}) + k_2^+ + k_2^-$ as a new value for Δ^0, the same result will still hold.

VI. Conclusion

The aim of this paper is to provide a set of sufficient conditions for an allosteric cofactor action to induce sustained oscillations in a simple reaction network. Although analytically provable mechanisms inducing oscillations can be found only in low dimensional reaction networks, their study is important also for the understanding of (more realistic) higher dimensional systems, as the oscillatory behavior is typically observed also for these last.

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