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Uniqueness and global attractivity of glycolytic oscillations suggested by Selkov's model

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Abstract In this work, we study the qualitative properties of the model proposed by Selkov Eur J Biochem 4: 79–86 (1968) for the description of the glycolytic oscillations. First we show that the Selkov's model can be put in form of a Newton's equation, thus allowing to define a pseudo-energy. Then, we show without imposing additional conditions that the limit cycle, if it exists, it is unique and globally attractive, thus precluding the possibility of multi-rythmicity. Finally, based on energetic and geometric considerations, we investigate the global properties of the unique equilibrium (idest of the arrest of the oscillations). Some biochemical remarks on the relevance of the uniqueness of sustained oscillations end the work.

Keywords Limit cycles · Glycolysis · Energy · Global stability

1 Introduction

A fundamental step for the sustainment of the life is the transformation of glucose into energy that is available to the cell through the oxidation of glucose to carbon dioxide and water, with a net release of energy [1,2]. Glycolysis is the first step of this very complex process that involves many fundamental chemicals, among them ATP (Adenosin triphospate) and ADP (Adenosin diphospate) [1,2]. In turn, glycolysis itself is a complex process being composed of 11 enzymatic reactions [1].

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Sustained oscillations were and are being experimentally observed in glycolysis in various settings [3–7], which has triggered a vast amount of literature, also in theoretical biology (see [8,9] and references therein). Those oscillations in theoretical biology are so relevant that A. Goldbeter stressed: "Glycolytic oscillations in yeast cells provided one of the first examples of oscillatory behavior in a biochemical system. They continue to serve as a prototype for cellular rhythms" [10].

Being a complex process, it has been difficult to ascertain which sub-process is the main responsible of the onset of such oscillating behaviour. However, there are strong evidences indicating that the phosphorilation [2] of the fructose-6-phosphate to fructose-1,6-phosphate, catalyzed by the enzyme phosphofructokinase (PFK1), is the instabilizing step of the reaction chain [10,1]. Namely, the oscillations are the result of a positive feedback exerted on the PFK by ADP itself, which is a product of the enzymatic reaction [10,1].

In particular, 1968 Selkov proposed in Ref. [11] a widely influential mathematical model of this feedback of ATP on PFK. The Selkov's model is able, although with some limitations [1], to well mimic the glycolytic oscillations in yeast and it triggered a number of further studies [9].

The aim of the present work is to assess, through a mathematical analysis, the degree of robustness of glycolitic oscillations respect to large deviations of the concentrations of ATP and ADP. We address this point by showing that if the Selkov system has a limit cycle, it is unique and locally stable. Moreover, we also give a non-local attractiveness result for parametric region where the unique equilibrium state is locally and globally stable.

2 The Selkov's model

In Selkov [11] proposed a five-dimensional ODE-based model of glycolisis that, via singular perturbations, may be with excellent approximation reduced to the following bidimensional system:

$$
\begin{aligned}
\frac{dx}{d\tau} &= 1 - xy^\gamma \\
\frac{dy}{d\tau} &= \alpha(\gamma)\left(xy^\gamma - y\right)
\end{aligned}
\tag{1}
$$

where : $x(\tau)$ is the adimensional concentration of ATP at time τ; $y(\tau)$ is the adimensional concentration of ADP at time τ; $\gamma > 1$ is the stoichiometric parameter of the reaction ADP-fosfofructokinase $\gamma ADP + FF \leftrightarrow P$; the parameter α is an exponential function of γ: $\alpha(\gamma) = cb^{-\gamma}$ (or, conversely, γ logarithmically depends on α).

Selkov showed that the above bidimensional model has a unique equilibrium state $EQ = (1, 1)$, as well that some orbits may be unbounded because of the presence of two improper singular points: $O_2 = (+\infty, 0)$, $O_3 = (0, \infty)$, whose qualitative properties were studied by Selkov by means of the method of the Poincare's spheres [16]. Note, that if $y(0) = 0$ then $(x(t), y(t)) = (x(0) + \nu t, 0)$. Moreover, it exists a

strictly positive and decreasing function $h(y)$ such that it exists a real positive number $0 < a \leq +\infty$ such that $h(a) = 0$ and that all initial points (x_0, y_0) lying under this curve (i.e. such that $0 < x_0 \leq h(y_0)$) are attracted by $(+\infty, 0)$. We note here that since $y(t) \to 0+$ it has to be

$$\lim_{y \to 0+} \left(h(y) - y^{1-\gamma} \right) = 0.$$

In turn, Selkov showed that there is a heterocline orbit connecting the two improper equilibria, whose flow is from O_2 to O_3.

Moreover he showed that the local stability of the equilibrium is ruled by a threshold value $\alpha_H = (\gamma - 1)^{-1}$ for α, such that if $\alpha < \alpha_H$ the EQ is locally asymptotically stable (LAS) and if $\alpha > \alpha_H$ then EQ is unstable.

Thus, if $b \leq 1$ it exists a $\gamma^* \leq 1 + 1/c$ such that there is instability of EQ for $\gamma > \gamma^*$, and local stability for $1 < \gamma < \gamma^*$. On the contrary, in case $b > 1$ then it exist a c_a such that if $c < c_a$ then EQ is LAS, and if $c > c_a$ then there are two $1 + 1/c < \gamma_l, \gamma_h$ such that if $\gamma_l < \gamma < \gamma_h$ then EQ is unstable, otherwise EQ is locally stable.

Remark It is important to remember that Hopf theorem [16] only gives informations near the bifurcation value. In the Selkov's model, for example Selkov numerically found that for all α_H it exists a α_∞ such that for $\alpha \in (\alpha_H, \alpha_\infty)$ the orbits are limit cycles, whereas if $\alpha > \alpha_\infty$ the orbits are unbounded. Moreover, the difference $\Delta_\alpha = \alpha_\infty - \alpha_H$ seems to be a decreasing function of γ.

3 A Newton's equation topologically equivalent to Selkov's model

The temporal transformation $dt = y^\gamma(\tau)d\tau$ transforms, for $y > 0$, system (1) in the following topologically equivalent [16] system:

$$\frac{dx}{dt} = y^{-\gamma} - x \tag{2}$$

$$\frac{dy}{dt} = \alpha \left(x - y^{1-\gamma} \right) \tag{3}$$

Eq. (3) yields:

$$x(t) = y^{1-\gamma} + \frac{1}{\alpha} \frac{dy}{dt}$$

and substituting x in (2) one gets:

$$\frac{d^2 y}{dt^2} = - \left(1 - \alpha(\gamma - 1)y^{-\gamma} \right) \frac{dy}{dt} - \alpha (y - 1) y^{-\gamma}, \tag{4}$$

or equivalently:

$$\frac{dy}{dt} = v$$
$$\frac{dv}{dt} = -f(y)v - g(y)$$

(5)

System (5) is formally a Newton's system ruling, in the phase space (y, v), the dynamics of a point of mass 1, position $y(t)$ and velocity $v(t) = y'(t)$ subject to a force $\phi(y) = -g(y)$ where

$$g(y) = \alpha (y - 1) y^{-\gamma}$$

and to a position-dependent damping $\delta(y, v) = -f(y)v$, where the damping coefficient:

$$f(y) = \left(1 - \alpha(\gamma - 1)y^{-\gamma}\right)$$

(6)

is with signum-varying, being positive for $y > y_1(\gamma) = (\alpha(\gamma-1))^{1/\gamma}$, and its integral:

$$F(y) = y - y_e + \alpha \left(y^{1-\gamma} - y_e^{1-\gamma}\right)$$

is unbounded: $F(0^+) = F(+\infty) = +\infty$. In Newton's system (5), the force is antisymmetric (i.e. $y\phi(y) < 0$ for $y \neq 0$) and, as a consequence, the potential energy associated to the force $\phi(y)$ is positive:

$$G(y) = \int_1^y g(z)dz = \begin{cases} \frac{\alpha}{2-\gamma}y^{2-\gamma} + \frac{\alpha}{\gamma-1}y^{1-\gamma} + \frac{\alpha}{(\gamma-2)(\gamma-1)}, & \text{if } \gamma \in (1, 2) \cup (2, +\infty); \\ \text{Log}(y) + \frac{1}{y} - 1, & \gamma = 2. \end{cases}$$

(7)

and it is 'U-shaped'. Indeed, it is easy to show that it has a unique minimum at $y = 1$ and it is such that:

$$\lim_{y \to 0^+} G(y) = +\infty,$$

whereas:

$$\lim_{y \to \infty} G(y) = \begin{cases} +\infty, & \text{if } 1 < \gamma \leq 2; \\ \frac{\alpha}{(\gamma-2)(\gamma-1)}, & \text{if } \gamma > 2 \end{cases}$$

(8)

Moreover, the total energy reads

$$\mathcal{E}(t) = \frac{v^2}{2} + G(y).$$

Finally, note that the constraint on the positiveness of the concentration $y \geq 0$ it is preserved in the equivalent Newtonian formulation. Indeed, let us define:

$$h_1(y) = \begin{cases} h(y), & \text{if } y \leq a; \\ 0, & \text{if } y > a \end{cases} \tag{9}$$

and, in the phase plane (y, v), the set:

$$\Gamma = \left\{ (y, v) \big| y > 0 \text{ AND } v \geq \alpha \left(-y^{1-\gamma} + h_1(y) \right) \right\},$$

where the constraint on v follows from

$$x = \frac{v}{\alpha} + y^{1-\gamma} \geq 0.$$

It is straightforward to show by direct inspection that Γ is positively invariant for (5).

4 Uniqueness of the self-sustained oscillations

A number of theorems exist that assess the uniqueness of limit cycle solution for (5), but the most celebrated, although giving a very strict condition, is the Zhang's theorem [12] that in a more applicable form due to Yang Kuang and Freedman [13] reads:

Proposition 4.1 [13] *Considering a Newton's canonical system with $f(y)$ and $g(y)$ continuous and differentiable in (a_1, a_2), where: $-\infty \leq a_1 < a_2 \leq +\infty$. Thus, if it exists a $y_e \in (a_1, a_2)$ such that $g(y_e) = 0$ and $(y - y_e)g(y) > 0$, and, moreover, the function*

$$\varrho(y) = \frac{f(y)}{g(y)}$$

is non-decreasing in $(a_1, y_e) \cup (y_e, a_2)$ then there is at most limit cycle in the region $a_1 < y < a_2$ and it is locally stable, if it exists.

The above theorem allows us to state the following:

Proposition 4.2 *If EQ is unstable and $\gamma > 1$ then the Selkov's model has at most a limit cycle in $(y, v) \in \Gamma$, and it is globally stable if it exists.*

Proof We preliminarily note that the unstability condition $\alpha(\gamma)(\gamma - 1) > 1$ is equivalent to say that $y_1 > 1$. Thus, the function $\varrho(y)$ here reads:

$$\varrho(y) = \frac{y^\gamma - \alpha(\gamma - 1)}{\alpha(y - 1)},$$

which is an increasing function. Indeed:

$$\varrho'(y) = \frac{\alpha(\gamma - 1) - R(y)}{\alpha(y - 1)^2},$$

where $R(y) = \gamma y^{\gamma - 1} - (\gamma - 1)y^\gamma$. As a consequence, $\varrho'(y) > 0$ since $\alpha(\gamma - 1) > 1$ and, as it is easy to verify, $\text{Max}_{y \geq 0} R(y) = 1$.

Thus, thanks to the properties of $f(y)$ and $g(y)$, from the Huang-Freedman theorem it follows that there may be at maximum a limit cycle, and it is locally asymptotically stable. Finally, if there is such as limit cycle, in Γ there cannot be orbits tending to the two improper infinite equilibria. □

Note that the function $\varrho(y)$, apart its sign, is the ratio between the damping and the force.

At the best of our knowledge, there is only another example of assessment of uniqueness of glycolitic oscillations, that, however, concerns a model involving ADP and fruktose-6-phosphate (FGP). That model, shortly studied as an example in Ref. [14], has a transfer term from ADP to FGP [15].

5 On global stability of the equilibrium point

Proposition 4.2 concerns the case of unstable EQ. In case of LAS EQ, at global level there might be forms of stable and unstable temporal self-organization. Indeed, from a geometrical point of view, the locally attractive biochemcial equilibrium state might be surrounded by an unstable limit cycle, in turn surrounded by a locally attractive limi cycle, and so on *ad libitum*.

Thus, in this section we shall investigate, via energetic and geometric methods, the properties of global attractivity of the unique equilibrium state.

We start noticing that thanks to the equivalence between the Selkov's model and the Newton system (5), the pseudo energy $\mathcal{E}$ can give useful informations on the arrest of the oscillations. Indeed, if the initial pseudo-energy is less than $G(y_1(\gamma))$ the point will remain in the zone of dissipation of energy.

Proposition 5.1 *The equilibrium state* $(1, 0)$ *is globally asymptotic stable in*

$$\Omega_\gamma = \left\{ (y, v) \in \Gamma \Big| \frac{v^2}{2} + G(y) < \text{Min} \left(G(y_1(\gamma)), G(+\infty) \right) \right\}.$$

Proof First we note that by construction, in Ω_γ the level curves of the energy $\mathcal{E}(y, v)$ are closed and lying in the region $y > y_1$. Second, noticing that: in Ω_γ:

$$\mathcal{E}' = -f(y(t))(v(t))^2$$

from the LaSalle's invariance theorem [16] we easily see that Ω_γ is a positively invariant set for our system and, applying the LaSalle's theorem with Liapunov's function $\mathcal{E}$, that the equilibrium state is globally attractive in Ω_γ. □

Remark We shortly note that the case where $\gamma \leq 1$ is not biochemically meaningful [11]. Any case it does not allow for temporal self-organization. Indeed, in such a case $G(y)$ is U-shaped and the damping coefficient $f(y)$, defined in (6), is positive. Thus the derivative of the energy is negative: $\mathcal{E}' = -f(y(t))(v(t))^2 < 0$, implying that the equilibrium is GAS.

From a geometrical point of view, recently in [14] it has been defined a powerful extension of the dulac's criterion for the nonexistence of closed orbits:

Proposition 5.2 [14] *Considering a Newton's system endowed with a unique equilibrium point y_e where it is $g'(y_e) > 0$. If there exist $a, b \in \mathbb{R}$ such that:*

$$f(y) + ag(y) + bg(y)F(y) \geq 0 \text{ on } (r_1, r_2), \tag{10}$$

where $y_e \in (r_1, r_2)$, has no closed orbits in (r_1, r_2).

The above criterion allows to show that:

Proposition 5.3 *Denoting with $m^*(\gamma)$ the slope of the straight line passing for $(1, 0)$ and tangent to the curve z^γ. If it is $\alpha(\gamma)(\gamma - 1) < 1$ and:*

$$\alpha(\gamma)\gamma^\gamma(\gamma - 1)^{2-\gamma} \leq m^* \tag{11}$$

then the system has no closed orbits, and the equilibrium state is globally asymptotically stable.

Proof Applying condition (10) with $b = 0$ the constraint

$$y^\gamma + \alpha a y + \alpha(1 - \gamma - a) \geq 0 \tag{12}$$

is obtained. By setting $a = -q < -(\gamma - 1) < 0$ and $y = z(q + 1 - \gamma)/q$ one may rewrite (12) as follows:

$$z^\gamma \geq \alpha(\gamma)K(q)(z - 1), \tag{13}$$

where: $K(q) = q^\gamma(q + 1 - \gamma)^{1-\gamma}$, whose minimum is $\gamma^\gamma(\gamma - 1)^{2-\gamma}$. As a consequence, if (11) holds then, thanks to Proposition 5.2, there are no limit cycles. Finally, from the local asymptotic stability of the equilibrium, it must also be globally stable.   □

6 Concluding remarks

In this work we proposed an analytical study of the Selkov's model for describing the glycolytic process. Our starting point was to transform the original model in a topologically equivalent Newton's system, thus allowing to define a pseudo-energy associated to the system. That equation is such that the direct application of the Kuang-Freedman-Zhang theorem allows to infer the uniqueness (and local stability) of the limit cycle, if it exists, and also its global attractivity.

We want to stress here that the uniqueness of the Selkovian oscillations is an interesting biochemical result since it means that the system when cycling, after large perturbations, will not only recover the original period, but also the concentrations will follow the original dynamical law. Thus, this implies that Selkov's model predicts that the dynamical features of the self-sustained oscillations of glycolysis only depend

on the stoichiometric parameter γ (the rate parameter α depends in turn by γ), since the behaviour is independent of the initial conditions. However, we must stress that this uniqueness result is biologically sound exclusively in the range of validity of the Selkov's model. More complete models have been proposed [9], whose analytical study, if possible, might confirm or not this result in a more general biochemical setting.

Moreover, based on energetic considerations, we gave, at the best of our knowledge, first non-local results for the global attractiveness of the equilibrium state.

Finally, we hope that this study might trigger some investigation on the biochemical meaning of the pseudo-energy $\mathcal{E}$ we defined in this work.

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