

# Periodic solutions of catalysed models with generalized mass-action law

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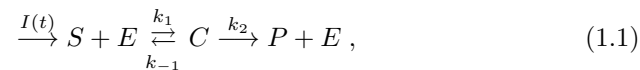
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**Abstract.** In this work, we prove the existence of periodic solutions for some enzyme catalyzed reaction models with periodic input and power-law. Numerical simulations are performed using specific substrate functions to illustrate our analytical findings.

**Key words:** *Cooperative systems, enzyme kinetics, Michaelis-Menten equation, periodic orbits*

## 1. Introduction

Mathematical models have become important tools in analyzing chemical reactions, of special interest are enzymatic reactions in biochemical systems. Enzymes are important in regulating biological processes acting as activators or inhibitors in a reaction. A basic scheme for a catalyzed reaction is based into the Michaelis-Menten equation which is fundamental for enzyme kinetics. It can be described by the following kinetic mechanism:



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where  $E$  denotes enzyme,  $S$  denotes substrate,  $P$  denotes product and  $C$  denotes enzyme substrate complex.  $I(t)$  is the rate of input of the substrate into the system. Letting  $[A]$  denote concentration of a chemical specie  $A$ . The law of mass action is well studied. It assumes that the rate of a reaction is proportional to the concentrations of its reactants; however in the most common models for chemical concentrations the reactions occur at mixed or crowded concentrations in intracellular environment. So for to account these aspects we consider a generalized mass-action law where the rate of a reaction is proportional to the powers of the concentrations of its reactants see Regensburger (2012). The generalized mass-action law leads to the system of following non-linear reaction equations

$$\begin{aligned}\frac{d[S]}{dt} &= I(t) - k_1[S]^\alpha[E]^\beta + k_{-1}[C]^\gamma, \\ \frac{d[E]}{dt} &= -k_1[S]^\alpha[E]^\beta + (k_{-1} + k_2)[C]^\gamma, \\ \frac{d[C]}{dt} &= k_1[S]^\alpha[E]^\beta - (k_{-1} + k_2)[C]^\gamma, \\ \frac{d[P]}{dt} &= k_2[C]^\gamma.\end{aligned}\tag{1.2}$$

All of the parameters are positive constants. Since the scheme (1.2) is reversible then by adding the second and third equations in the system (1.2) we have  $([E] + [C])' = 0$ , therefore  $[E] + [C] = K$  for all time  $t$  for some positive constant  $K$ , using this relation and since the last equation in system (1.2) decouples from the other equations we can reduce model (1.2) to a two-dimensional system in terms of  $[S]$  and  $[C]$  as follows:

$$\begin{aligned}\frac{d[S]}{dt} &= I(t) - k_1(K - [C])^\beta[S]^\alpha + k_{-1}[C]^\gamma, \\ \frac{d[C]}{dt} &= k_1(K - [C])^\beta[S]^\alpha - (k_{-1} + k_2)[C]^\gamma.\end{aligned}\tag{1.3}$$

In chemical engineering is common that the nutrients are supplied at periodic form. In the biological context frequently the rate of input of the substrate  $I$  fluctuates in periodic way, due to intrinsic oscillations in living organisms, see glycolytic oscillations in Stoleriu et al. (2005). Thus, due to the interest of the chemical industry or for biological reasons, we can assume that  $I$  is a non negative, non constant continuous  $T$ -periodic function

$$I(t + T) = I(t) \text{ and } I(t) \geq 0, \forall t \in \mathbb{R}.$$

In addition, we consider a controlled situation where the enzyme is entering the process at a time-dependent oscillatory consumption rate, with an equal amount of extraction of the compound. Thus, we add the arrows  $\xrightarrow{J(t)} E, C \xrightarrow{J(t)}$ , in (1.1). Because of mass conservation, the non negative, non constant continuous  $T$ -periodic function,  $J(t)$ , need to be subtracted of the rate of compound  $[C]$ . Hence get the system

$$\begin{aligned} \frac{d[S]}{dt} &= I(t) - k_1(K - [C])^\beta [S]^\alpha + k_{-1}[C]^\gamma, \\ \frac{d[C]}{dt} &= -J(t) + k_1(K - [C])^\beta [S]^\alpha - (k_{-1} + k_2)[C]^\gamma. \end{aligned} \tag{1.4}$$

This kind of model may be useful for the analysis of biochemical reactors where the enzyme degradation with time is periodically regenerated by replacing exhausted enzyme by fresh active enzyme, see for instance NIIR Board (2004).

In the study of enzymatic models the analysis of periodic solutions is seen as an important goal as this periodicity reveals the recurrence of biochemical rhythms of living organisms. Hence, determining existence of such solutions under different parameter configurations and input functions is crucial. In this work, using the theory of cooperative systems, we give sufficient conditions for the existence of periodic orbits for the above system.

## 2. Results

We first review the cooperative systems this material is included for completeness and to fix some of the notation, for a brief introduction to cooperative systems see (Smith, 1995). For two points  $u, v \in \mathbb{R}^n$  denote the partial order  $u \leq v$  if  $u_i \leq v_i$  for each  $i$ , also denote  $u < v$  if  $u \leq v$  and  $u \neq v$ . Consider a system

$$\begin{aligned} \dot{x} &= f(t, x(t), y(t)) \\ \dot{y} &= g(t, x(t), y(t)), \end{aligned} \tag{2.5}$$

where  $f, g$  are  $C^1$  in an open  $D \subset \mathbb{R}^2$  and continuous  $T$ -periodic functions on  $t$ , recall that (2.5) is said a *cooperative system* in  $\mathbb{R} \times D$  if

$$f_y(t, x, y) \geq 0, \text{ and } g_x(t, x, y) \geq 0, \forall t \in \mathbb{R}, (x, y) \in D. \tag{2.6}$$

The cooperative systems have very important properties for example: the monotonicity of the local flow generated by (2.5).

We say that a pair of  $T$ -periodic differentiable functions  $(a(t), b(t))$  is a *subsolution pair* of (2.5) if

$$\begin{aligned} \dot{a} &\leq f(t, a(t), b(t)) \\ \dot{b} &\leq g(t, a(t), b(t)), \text{ for all } t, \end{aligned} \quad (2.7)$$

analogously a pair of  $T$ -periodic differentiable functions  $(A(t), B(t))$  is a *super-solution pair* if

$$\begin{aligned} \dot{A} &\geq f(t, A(t), B(t)) \\ \dot{B} &\geq g(t, A(t), B(t)), \text{ for all } t. \end{aligned} \quad (2.8)$$

We say that sub and supersolution pairs are ordered if for all  $t$  we have  $a(t) < A(t)$  and  $b(t) < B(t)$ .

An important feature for cooperative system (2.5) about periodic orbits was established in Korman (2016), Theorem 2.1. More precisely, the following result holds

**Theorem 2.1** *Assume that the system (2.5) is cooperative and has ordered sub- and super- solution pairs  $(a(t), b(t))$  and  $(A(t), B(t))$ . Then the system has a  $T$ -periodic solution  $(x(t), y(t))$ , satisfying  $a(t) < x(t) < A(t), b(t) < y(t) < B(t), \forall t$ .*

For a  $T$  periodic continuous function  $M : [0, T] \rightarrow \mathbb{R}$ , we set

$$M^* := \max_{t \in [0, T]} M(t) \text{ and } M_* := \min_{t \in [0, T]} M(t). \quad (2.9)$$

Now we state our main result

**Theorem 2.2** *Assume  $\alpha, \beta, \gamma, k_1, k_2, k_{-1}, K$  are positive constant and  $I(t), J(t)$  are non constant continuous  $T$ -periodic functions. If*

$$I^* < k_2 K \text{ and } I_* - J^* \geq 0, \quad (2.10)$$

*then there is at least one  $T$ -periodic solution  $[S(t)], [C(t)]$  of (1.4) whose components are positive.*

*Proof:* By straightforward calculation for the system (1.4) condition (2.6) is verified,

$$k_1\beta(K - [C])^{\beta-1} + \gamma k_{-1}[C]^{\gamma-1} \geq 0, \quad \alpha k_1(K - [C])^\beta [S]^{\alpha-1} \geq 0.$$

Therefore (1.4) is a cooperative system.

So, to establish the existence of periodic solutions of at least one periodic solution of (1.4) via the Theorem 2.1 we need to construct ordered sub- and super-solution pairs.

For a sub-solution pair; we consider

$$\begin{aligned} a(t) &:= S_1, \\ b(t) &:= 0, \end{aligned} \tag{2.11}$$

with  $S_1$  a positive constant to be chosen. Calling  $f(t, x, y)$  and  $g(t, x, y)$  the right sides in equation (1.4). By the condition of subsolution pair (2.7) we need to verify

$$\begin{aligned} f(t, S_1, 0) &\geq 0, \\ g(t, S_1, 0) &\geq 0. \end{aligned}$$

So, we take

$$g = -J(t) + k_1 K^\beta [S_1]^\alpha \geq -J^* + k_1 K^\beta [S_1]^\alpha, \tag{2.12}$$

therefore doing

$$[S_1] = \left( \frac{J^*}{k_1 K^\beta} \right)^{\frac{1}{\alpha}},$$

We obtain  $g \geq 0$ . Now replacing this  $[S_1]$  in  $f(t, S_1, 0)$  and using (2.10), we get

$$f = I(t) - k_1 K^\beta \frac{J^*}{k_1 K^\beta} = I(t) - J^* \geq I_* - J^* \geq 0. \tag{2.13}$$

Thus considering (2.12) and (2.13), we satisfy both inequalities in (2.7). Therefore they constitute a sub-solution pair.

For constructing a super-solution pair, we propose

$$\begin{aligned} A(t) &:= S_2, \\ B(t) &:= C_2. \end{aligned}$$

with  $S_2, C_2$  two constants to be determined. By the condition of subsolution pair (2.8) we need to verify

$$\begin{aligned} f(t, S_2, C_2) &\leq 0, \\ g(t, S_2, C_2) &\leq 0. \end{aligned} \tag{2.14}$$

Substituting in the first equation of the previous system, we have

$$f(t, S_2, C_2) = I(t) - k_1(K - C_2)^\beta S_2^\alpha + k_{-1}C_2^\gamma \leq I^* - k_1(K - C_2)^\beta S_2^\alpha + k_{-1}C_2^\gamma = 0. \quad (2.15)$$

So, we need take

$$[S_2] = \left( \frac{I^* + k_{-1}C_2^\gamma}{k_1(K - C_2)^\beta} \right)^{\frac{1}{\alpha}}.$$

Substituting this  $[S_2]$  in the second equation in (2.14) and taking  $C_2^\gamma$  such that  $I^* \leq k_2C_2^\gamma < k_2K$ , we get

$$\begin{aligned} g(t, S_2, C_2) &= -J(t) + k_1(K - C_2)^\beta \frac{I^* + k_{-1}C_2^\gamma}{k_1(K - C_2)^\beta} - (k_{-1} + k_2)C_2^\gamma \\ &= -J(t) + I^* - k_2C_2^\gamma \leq I^* - k_2C_2^\gamma \leq I^* - k_2K, \end{aligned} \quad (2.16)$$

using (2.10), then  $g(t, S_2, C_2) \leq 0$ .

Thus considering (2.15) and (2.16), we satisfy both inequalities in (2.8). Consequently,  $(A(t), B(t))$  form a super-solution pair.

Therefore Theorem 2.1 applies, so there exists at least one  $T$ -periodic solution for system (1.4), which proves the result.  $\square$

Theorem 2.2, gives a generalization of previous results. In the particular case of the law of mass action,  $\alpha = \beta = \gamma = 1$ , without subtraction,  $J \equiv 0$ , Katriel (2007) proved the existence of periodic orbits of (1.4), by using Leray-Schauder degree theory. Stoleriu et al. (2005) proved the existence of periodic solutions when the input rate is  $I := I_0(1 + \epsilon \sin(\omega t))$  for  $0 \leq \epsilon \leq 1$ , using Brouwer's fixed-point theorem.

## 2.1. Examples

In the previous section we established analytically the existence of periodic solutions for system (1.2) of enzymatic reactions. We now provide numerical evidence of the existence of periodic solutions. To do so, we numerically solve these equations using a 4th order accurate Runge-Kutta integrator which we program in FORTRAN 95.

**Example 1.** Consider the system

$$\begin{aligned} \frac{d[S]}{dt} &= I(t) - k_1(K - [C])^\beta [S]^\alpha + k_{-1}[C]^\gamma, \\ \frac{d[C]}{dt} &= -J(t) + k_1(K - [C])^\beta [S]^\alpha - (k_{-1} + k_2)[C]^\gamma. \end{aligned} \quad (2.17)$$

where parameters are determined by  $\alpha = \beta = \gamma = 1$ ,  $k_1 = 2$ ,  $k_{-1} = 1$ ,  $k_2 = 1.5$ , and  $K = 3$ . The substrate input function is determined by  $I(t) = 1 + 0.3 \sin(2\pi t)$  and the subtraction function is given by  $J(t) = 0.3 + 0.25 \cos(2\pi t)$ , note that  $I_* - J_* = 0.15$  and  $0 < I_* < (3)(1.5) = 4.5$ . Numerical simulations are shown in the next figures 1 and 2, which exhibit an oscillatory behavior according to the Theorem 2.2.

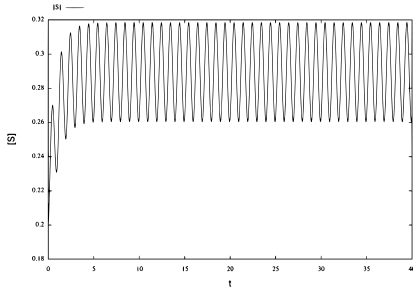


Figure 1: Time plots for enzymatic model (2.17). We consider the initial conditions  $S_0 = 0.2$  and  $C_0 = 0.2$ .

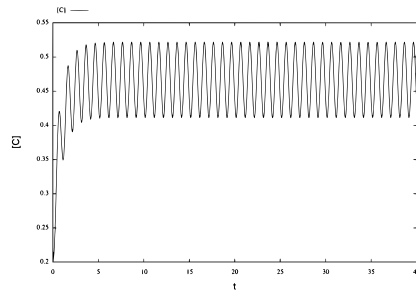


Figure 2: The solutions converge to the corresponding numerical approximation of the periodic orbit.

**Example 2.** Consider the system

$$\begin{aligned} \frac{d[S]}{dt} &= I(t) - k_1(K - [C])^\beta [S]^\alpha + k_{-1}[C]^\gamma, \\ \frac{d[C]}{dt} &= -J(t) + k_1(K - [C])^\beta [S]^\alpha - (k_{-1} + k_2)[C]^\gamma. \end{aligned} \tag{2.18}$$

where parameters are determined by  $\alpha = 5$ ,  $\beta = 2$ ,  $\gamma = 3$ ,  $k_1 = 3.5$ ,  $k_{-1} = 0.4$ ,  $k_2 = 1.9$  and  $K = 0.8$ . The substrate input function is determined by  $I(t) = 1 + 0.5 \sin^2(t)$  and the subtraction function is given by  $J(t) = 0.3 + 0.2 \cos^2(t)$ , note that  $I_* - J_* = 0.5$  and  $0 < I_* < (1.9)(0.8) = 1.52$ . Numerical simulations are shown in the next figures 3 and 4, which exhibit an oscillatory behavior according to the Theorem 2.2.

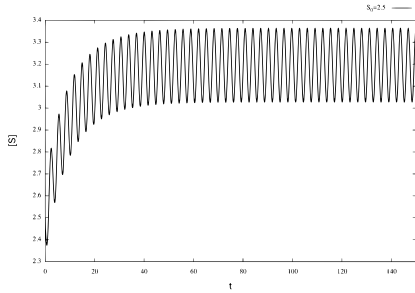


Figure 3: Time plots for enzymatic model (2.18). We consider the initial conditions  $S_0 = 2.5$  and  $C_0 = 0.7$ .

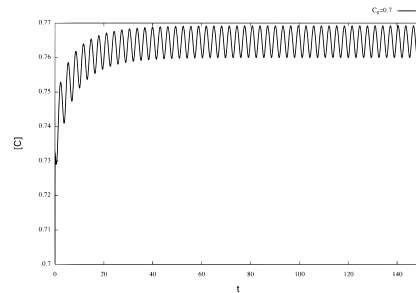


Figure 4: The solutions converge to the corresponding numerical approximation of the periodic orbit.

### 3. Discussion

For applications the analysis of Michaelis-Menten equations require the localization of fixed points. Under the conditions of periodic substrate and enzyme supply for a given reaction, applications require the existence of periodic solutions. Our analysis give some description of conditions that warranty the existence of such limit cycles. This models may be useful for biochemical reactors. Such applicability remains to be explores. We also may extend this analysis based on cooperative systems to competitive systems with applications in other more detailed enzyme reactions.

### Acknowledgment

We would like to thank the anonymous referee for the careful reading of our manuscript and for providing us with constructive comments, which helped to improve the manuscript.

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