# Simplified model for the mammalian circadian clock

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## Abstract

In this poster we present a mathematical model as a system of four ordinary differential equations to better understand the intrinsic mechanism of circadian oscillations inside the cell. This model is a simplified version of a model proposed by Leloup and Goldbeter [1, 2]. The four variables are the concentrations of two proteins PER and CRY and the concentration of the complex PER-CRY, first in the cytosol and then in the nucleus. The dynamic of these four variables shows a limit cycle, the period of which may be chosen equal to 24 hours for specific (and realistic) values of the parameters. The main purpose of this poster is to study the Hopf bifurcation which take place with disappearance of the limit cycle for the degradation parameter of the complex PER-CRY in the nucleus crossing some value.

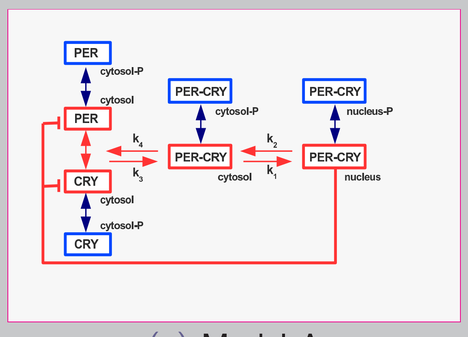
## Introduction

The continuous time model of Leloup and Goldbeter [1, 2] contains 16 differential equations. The model is based on 5 genes per, cry, bmal1, clock and rev-erb$\alpha$. They take into account the phosphorylation cycle, translocation between nucleus and cytosol, the translation of mRNA into protein, the association of PER and CRY proteins to form the complex PER-CRY. Goldbeter and Leloup [1, 2] also focus on the behavior of the concentrations over time under some light-dark alternation patterns: they compare the circadian cycle when there is no light (endogenous cycle) with the case of an alternation of light and darkness in order to model anomalous behavior of the circadian rhythm.

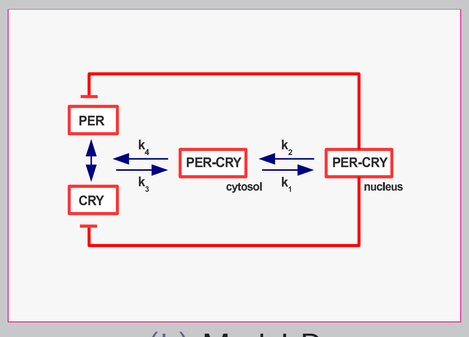
## Simplification of the biological model

To better understand the intrinsic mechanism of circadian oscillations inside the cell, we focus on the behavior of the complex PER-CRY: During the day, the proteins PER and CRY are phosphorylated by CKI$\epsilon$ (Casein-Kinase I$\epsilon$) and form complexes PER-CRY-CKI$\epsilon$ which then accumulate in the cytoplasm. During the night, below a certain concentration PER-CRY-CKI$\epsilon$ complex is degraded in the cytoplasm and above the concentration level this complex is translocated into the nucleus. It will be hyperphosphorylated by CKI$\epsilon$ before entering into the nucleus where the complex inhibit its own transcription. In focusing only on this mechanism we get a eight variables systems that may be even simplified in a four variables system.

## The mathematical model for the mammalian circadian clock




(a) Model A




(b) Model B

Figure 1: Two models for mammalian circadian oscillations:
($a$) The eight variables model $A$ involving negative feedback loop of PER-CRY complex into the nucleus on its own protein products. Other steps refer to protein synthesis, transport into the cytosol, degradation and reversible phosphorylation.
($b$) The four variables model $B$ can be seen as a simplification of model $A$ in which the phosphorylation steps are omitted.

## A four variables model of circadian cycle

The model B is similar to model $A$, except that it does not incorporate the phosphorylation of the protein. The dynamics of cytosolic PER protein ($P_C$), CRY protein ($C_C$) and cytosolic and nuclear PER-CRY complex are governed by the following system of four kinetic equations:

$$\begin{cases} \dfrac{dP_C}{dt} = \dfrac{K^n}{K^n + PC_N^n} v_1 - k_3 P_C C_C + k_4 PC_C - kd_1 P_C \\ \dfrac{dC_C}{dt} = \dfrac{K^n}{K^n + PC_N^n} v_2 - k_3 P_C C_C + k_4 PC_C - kd_2 C_C \\ \dfrac{dPC_C}{dt} = k_3 P_C C_C - k_4 PC_C - k_1 PC_C + k_2 PC_N - kd_3 PC_C \\ \dfrac{dPC_N}{dt} = k_1 PC_C - k_2 PC_N - kd_4 PC_N \end{cases} \quad (1)$$

The dynamic of this system shows a limit cycle, the period of which may be chosen equal to 24 hours.

## Hopf bifurcation analysis on four variables system

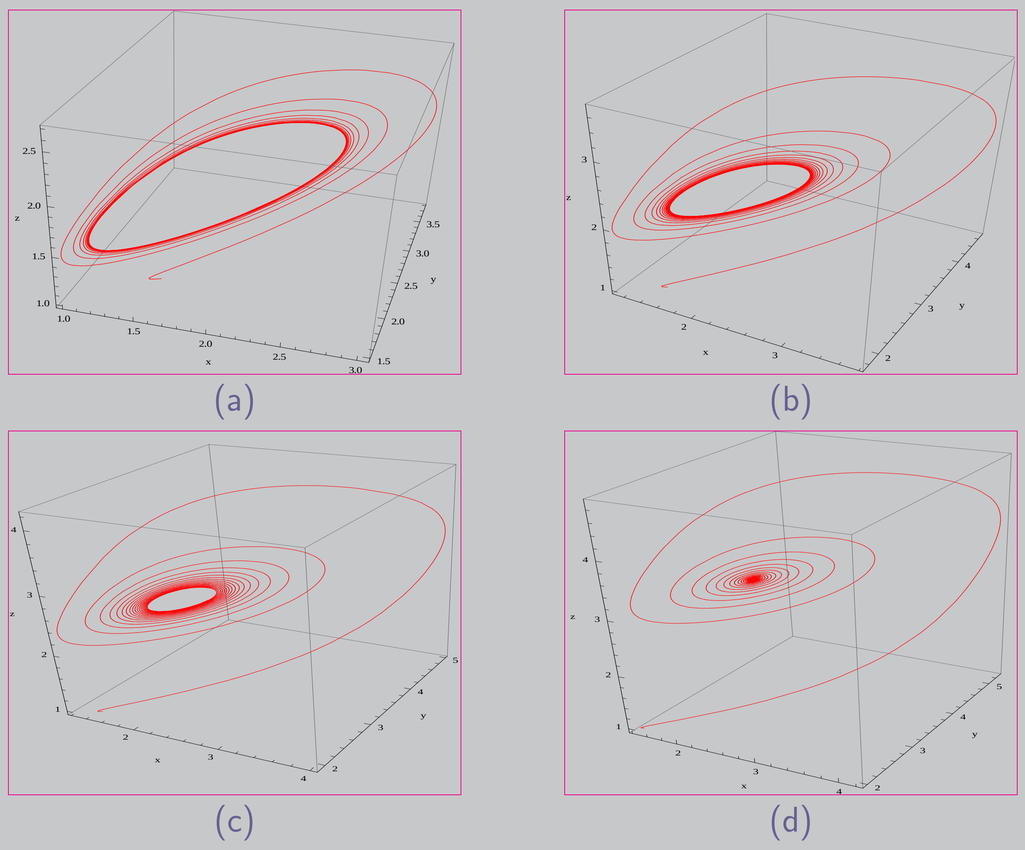



Figure 2: 3D projections of some trajectories of system (1) for $K = 0.4$, $n = 15$, $v_1 = 2$, $v_2 = 2.2$, $k_1 = 0.08$, $k_2 = 0.06$, $k_3 = 0.08$, $k_4 = 0.06$, $kd_1 = 0.05$, $kd_2 = 0.05$, $kd_3 = 0.05$ and $kd_4 = 0.25, 0.35, 0.42$ for Figure (2a), (2b), and (2c) respectively (presence of a stable limit cycle) and $kd_4 = 0.55$ (absence of a limit cycle) for Figure (2d), with initial condition $(1.5, 2, 1, 0.5)$.

## Conclusion

We observed that a Hopf bifurcation takes place with disappearance of the limit cycle for the degradation rate of the complex PER-CRY in the nucleus $kd_4$, crossing some value. This implies that for $kd_4$ smaller than 0.42 there exists one limit cycle. The same bifurcation may be observed for $kd_3$ crossing around the value 0.39. It appears that the oscillations are produced by the presence of a negative feedback loop and a delay (time needed by the complex PER-CRY to enter into the nucleus). Thus it is possible to over simplified the 8 variables model in a 3 variables model (considering either per or cry gene), but then it would be "minimal" as Gérard, Gonze and Goldbeter in [3].

## References

[1] Leloup J.-C. and Goldbeter A., (2003) Toward a detailed computational model for the mammalian circadian clock. *Proc. Natl. Acad. Sci. USA* **100**: 7051-7056.

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[3] Gérard C., Gonze D. and Goldbeter A., (2009) Dependence of the period on the rate of protein degradation in minimal models for circadian oscillations. *Phil. Trans. R. Soc. A* **367**: 4665-4683.