Computational model for the mammalian circadian clock

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Abstract

In this poster we present a simplified version of the computational model of the mammalian circadian clock proposed by (Leloup and Goldbeter, J. Theor. Biol. 2004, 230, 541-562). This simplification is based on the negative feedback loop involving the Per and Cry genes, which play a crucial role in the dynamics of the mammalian circadian rhythm : This loop results in a 24 hour oscillation in the expression of protein levels. The period gene "per" and its protein product "PER" are essential components of the negative feedback loop and the cryptochrome gene "cry" in mammals acts together with the per gene in circadian rhythm regulation. Moreover, phosphorylation by several kinases complexifies the regulation of the per gene within mammalian cells. In mammals, the suprachiasmatic nucleus in the hypothalamus is considered to be a major pacemaker for circadian rhythm phenomena, as demonstrated by many physiological studies.
We found a set of parameter values that give rise to sustained oscillations with a circadian period. After comparing the effect of these parameters, we show that the period of oscillations are generally most sensitive to parameters related to synthesis or degradation of PER and CRY protein. This study is an attempt to explore a minimum but biologically realistic prerequisite for a negative feedback loop to produce circadian oscillations.

Introduction

In the paper of Leloup and Goldbeter the circadian clock in mammals is translated into 19 differential equations. It is a continuous time model. The model is composed of genes PER, CRY, BMAL1, CLOCK and Rev-Erbα.Their scheme takes into account the cycle phosphorylation, membrane exchanges between nucleus and cytosol, the translation of mRNA into protein, the association of PER and CRY proteins to form the complex PER-CRY.The equations expressing this cycle can produce curves of circadian periods. Goldbeter and Leloup will then focus on the behavior of concentrations over time by alternating light and darkness: DD for continuous darkness and LD for an alternating light-dark of 12 hours. It is a model quite close to the biological reality, despite some simplifications. They use this model to predict anomalous behavior of the circadian rhythm.

Model for the mammalian circadian clock by Leloup and Goldbeter (2003)

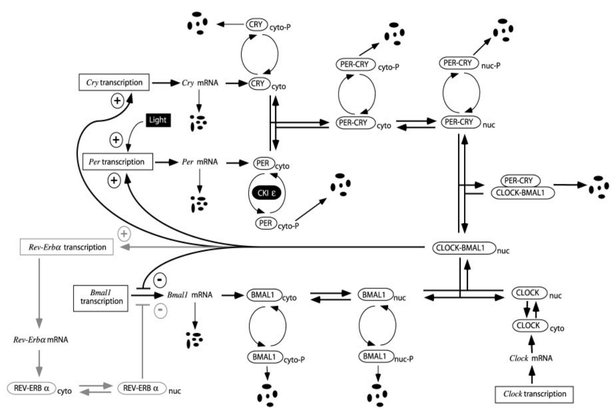

Figure: Model for circadian oscillations in mammals involving interlocked negative and positive regulations of Per, Cry, Bmal1 genes by their protein products(Leloup and Goldbeter, 2003).

Simplified model for the mammalian circadian clock

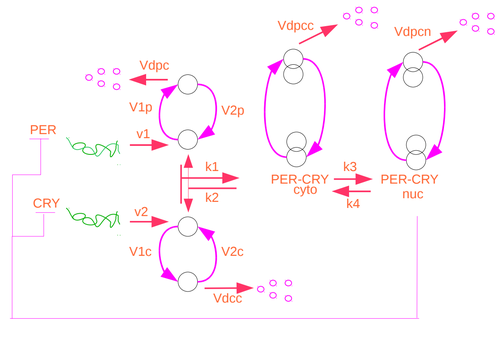

Figure: Simplified model for circadian oscillations in mammals based on a negative feedback loop involving Per, Cry genes and PER-CRY complexes only.

What happens without phosphorylation?

In the mathematical model, each interection is modelized by a Hill function, a Michaelis Menten equation or simply a linear degradation. Here is a version of the model when we neglected phosphorylation (with phosphorylation 4 additional equations are needed). We have removed CLOCK and Rev-erbα loop and decided to model it as a negative feedback control of PER-CRY complex contained in the nucleus of Per and Cry genes. We also skipped the step of mRNA from the gene directly to the protein and finally we have neglected phosphorylation. Lastly, we get a model with four differential equations.

$$\frac{dP_c}{dt} = (1 - \frac{PC_n^n}{K_1^n + PC_n^n})v_1 - k_1 P_c C_c + k_2 PC_c - kd1 P_c \quad (1)$$

$$\frac{dC_c}{dt} = (1 - \frac{PC_n^n}{K_1^n + PC_n^n})v_2 - k_1 P_c C_c + k_2 PC_c - kd2 C_c \quad (2)$$

$$\frac{dPC_c}{dt} = k_1 P_c C_c - k_2 PC_c - kd3 PC_c - k_3 PC_c + k_4 PC_n \quad (3)$$

$$\frac{dPC_N}{dt} = k_3 PC_c - k_4 PC_n - kd4 PC_n \quad (4)$$

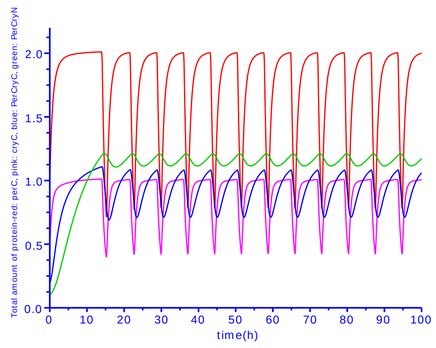

Figure: The model shows the expected periodic behavior but not of 24 hours. For example a 8 hour period of circadian oscillations with parameters kd1=0.9, Kd2=0.8, Kd3=0.2 and Kd4=0.1.

Simplified model (with phosphorylation)

When adding phosphorylation in our model, we take into account at each step that the proteins are phosphorylated, dephosphorylated and degraded and this produces a 24 hours period oscillations.

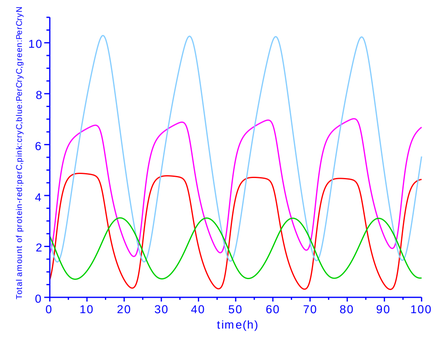

Figure: A 24 hour period of circadian oscillations with parameters kdn=0.01, Kp=0.1, Kdp=0.4 and Kd=0.1.

Conclusion

The lack of data in biology is a real problem for making mathematical models. Although we found curves with 24 hour period, these do not correspond to biological reality. In this model we have 24 parameter values and few are very sensitive, especially the one that related to synthesis or degradation of PER and CRY protein. Finally, we hope that understanding why the reduced model without phosphorylation produces too short oscillations, will allow us to understand better the role of phosphorylation in the circadian cycle.