Stability and accuracy analysis of the circadian clock coupled with metabolism

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***Short Abstract* — Circadian rhythms are near 24-hour oscillations, these oscillations are generated by molecular circadian clocks formed by biochemical networks with negative feedback loops. However, although the coupling has been studied, little attention has been placed on the precision of the circadian clock coupled with metabolism. In this work, the accuracy of the circadian clock coupled with metabolism in hepatocyte is studied. We developed a minimal nonlinear model. The local stability and limit cycles are studied. Our predictions suggest that the metabolism has an essential role in the performance of the daily rhythms.**

***Keywords* — Nonlinear circadian model, Systems biology, Dynamics analysis, Robustness.**

I. Introduction

Physiological rhythms are of vital importance to life. These rhythms arise from nonlinear biological mechanisms interacting with a fluctuating environment. Mathematical analysis of physiological rhythms shows that nonlinear equations are necessary to describe it [1]. They are controlled by many feedback loops that enable life. Abnormal rhythms are associated with the disease. Many of these rhythms follow day and night cycle produced by the rotation of the earth. They are called circadian rhythms. It is well known that these rhythms are controlled by a molecular clock. It is called the circadian clock, and in mammals it is in every tissue with a master clock in a region of the hypothalamus called the suprachiasmatic nucleus (SCN). The neurons in the SCN are synchronized, and experimentally it has been found that, if they are dissociated, each cell can present autonomous oscillations at slightly different periods, from 20 to 28 h [2]. The architecture of the clock network is well known, consist of transcription-translation feedback loops that oscillate the concentration of proteins every 24 hours and control a wide variety of physiological events, including metabolism. Energetic cycles are one type of physiological process that shows transcription-dependent circadian periodicity. The liver plays a central role in maintaining energy homeostasis. Accordingly, the feeding and fasting cycle is a potent zeitgeber for the liver clock than systemic cues controlled by the circadian clock in the SCN [3]. Circadian clocks have been studied with a mathematical approach. There exists a substantial body of literature regarding the molecular mechanisms of the circadian clock from mathematical point of view. Recently, it has been reported a mathematical model that links circadian rhythm with liver metabolism [4]. However, little attention has been paid to accuracy. We use mathematical modeling to address the following question: whether the accuracy of the liver clock cells coupled with metabolism is sensitive to parametric variation.

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II. Results

We considered a reduced model of six variables and two coupled oscillators. Using stability analysis, we found a stable equilibrium point from the linearization of the proposed model. Then we performed simulations of the coupled model with a forced function that represents feeding-fasting periods under the effect of parametric variation. Each parameter value was scaled by multiplying by a factor of 0.5, 2, 10, and 50, one factor at a time, while the rest of the parameters was kept without change. Then, the period was measured and the accuracy evaluated based on a criterion of ±10% around 24-hour period following [5][2]. The model was strongly sensitive to variations in parameters associated to circadian but mostly with metabolic molecules.

III. Conclusion

According to [6] organisms are subject to a series of entraining agents that promote the synchronization and resonance of different clocks in peripheral tissues. We can conclude from these facts that perturbations of the metabolic cycles affect the accuracy of the circadian clock.

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