The interplay between the circadian clock and the cell cycle

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***Abstract*—The cyanobacterial clock is remarkable: it consists of only three proteins which generate a 24-hour rhythm in the phosphorylation state of one of them. This clock is very stable against changes in the environment and variability in growth rates. We show, using a very generic model for a biological oscillator, that the period of the clock is altered by effects induced by the cell cycle. This raises the question of how the clock can be robust against variations in the growth rate. We discuss possible mechanisms which stabilize the clock's period against disruption by the cell cycle.**

***Keywords*—Kai, circadian oscillator, clock stability, period disruption**

I. Introduction

Circadian clocks are 24 hour biochemical oscillators that coordinate the metabolism and behavior of an organism with the day-night cycle. Essential to their design is that they maintain their 24 hour period while subjected to daily changes in temperature and variability in protein expression levels. The periods of growth and division the cell go's through, called the cell cycle, could disturb the clock's period. Until now, the effects of the cell cycle on the clock have not been considered. Using mathematical modeling, we investigate to what extend the cell cycle changes the period of the circadian clock. Furthermore, we give design principles for a circadian clockwork that dampen the effects of the cell cycle.

To address these issues, we will study one of the simplest version of a circadian clock, which exists in the cyanobacterium Synechococcus elongatus. The core of the oscillator consists of only three proteins -KaiA, KaiB and KaiC- which together generate a 24 hour period in the phosphorylation state of KaiC [1]. Since the Kai proteins are continuously diluted in growing cells, new Kai monomers need to be produced. As a continuous influx of new KaiC would disturb the rhythm, the clock regulates the production of KaiC such that it is only expressed at a certain time in the day [2], [3].

Over the course of its cell cycle, the cyanobacterium duplicates its multiple chromosomes asynchronously, and divides them over the daughter cell at cell division [4]. Recent work shows that this can have a considerable influence on the production of new proteins [5]. Thus, the cell cycle introduces another oscillation into the problem: next to the 24 hour period of the circadian clock, there is change in the production rate with the periodicity of the division time. We hypothesize that this influences the clock such that the length of its period is drawn towards (or locked to) the cell cycle period.

Current models of the Kai system do not take into account the periodic changes induced by the cell cycle. Here we include it to the model, and study the effect on the robustness of the circadian clock.

II. Methods

We use a recent model for the Kai circadian oscillator to study the effects of the cell cycle. Using ordinary differential equations (ODE), this model describes the phosphorylation cycle of the protein interactions, and the transcription-translation cycle of the production of new Kai proteins. In the original model the maximal possible production of new KaiC proteins is set by a constant rate. We replace it with a rate that depends on the phase of the cell cycle.

We run the model for a wide range of biologically relevant division times ranging between 6 hours up to several days. In each run, we check how much the clock's period is altered by the cell cycle.

III. Results & Conclusion

We find that the periodic changes in the production rate significantly alters the period of both the protein concentration and the phosphorylation ratio. Particularly at values where the division time is close to 24 hours, the clock period is changed the most. Here, the deviation of the period of the clock can be as high as 20 percent. Our results show that current models of the Kai circadian clock are very sensitive to the cell cycle. Since these large effects have not been observed in experiments, we look into mechanisms the cell might use to prevent the disruption of the clock's period.

References

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