Simulation of Circadian Rhythms

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Introduction

The circadian rhythm is widely known as the mechanism that generates the 24hour cycle in living organisms. In this area of study, the cyanobacteria is currently the simplest organism recognized that exhibits such behavior (1).

It's been demonstrated that ATP and only 3 proteins: KaiA, KaiB and KaiC, are enough to produce circadian oscillation (2). The main piece of this clock is KaiC, which has phosphorylation kinetics that act in circadian manner. KaiA enhances KaiC phosphatase activity while KaiB inhibits this effect (2,3).

Recently, allosteric transition of KaiC is proposed as a determining factor to the (de)phosphorylation rhythm (1,4). KaiC molecules alternate between two states, one is likely to phosphorylate and bind to KaiC while the other tends to dephosporylate and bind more frequently with KaiB(5,4).

However, since each KaiC Hexamer reacts independently, allosteric transition is not enough to generate the oscillations (1). Thus, there should be another mechanism responsible for synchronizing KaiC individual activity.

Until now, several models have been proposed(1,5) but the synchronization of KaiC has not been completely elucidated.

Purpose

In order to find some new answers to this questions, two 'allosteric transition with monomer shuffling' models by Eguchi et. al. were used as a base (1). One is simplified and simulated in a deterministic way. The other is a stochastic full model.

The both models describe the scheme in Figure 1. In this proposal, KaiC has two states; *Tense*, in which KaiA has a higher tendency to bind to KaiC and monomer exchange is not frequent (exchange occurs with R6 only), and *Relaxed*, where KaiB has more affinity with KaiC, decreasing the catalytic effect of KaiA, letting KaiC dephosphorylate. Moreover, in this state, the hexamer structure allows monomer shuffling, generating in consequence, the synchronization of the individual KaiC molecules.

The simple deterministic model doesn't directly represent KaiA and KaiB, but the phosphorylation and dephosphorylation reactions can be associated to KaiA-B binding. Fig. 2 shows the data obtained in the simulations. When shuffling is prohibited (the shuffling rate parameter is 0), the oscillation fails. It also damps when the allosteric transition from Tense to Relaxed is accelerated. In this model, the R->T transition must be slower than the phosphorylation(as shown in experimental data (3)), allowing T6 to accumulate.

The full stochastic model is not complete yet due to its size, but it can be analyzed and compared to other models.

According to the full model, KaiB has a competitive roll with KaiA for binding to KaiC, but doesn't demonstrate any KaiC-inhibitor property, which is constantly mentioned in publications of experimental data (2,3,6).

It's also visible that, even though this model is more flexible to KaiA-B concentration changes, it still moves in a very short range.

Another mechanism that will be studied in this research is the differential affinity model proposed by Van Zon et. al.(4). In this representation, KaiC can also be found

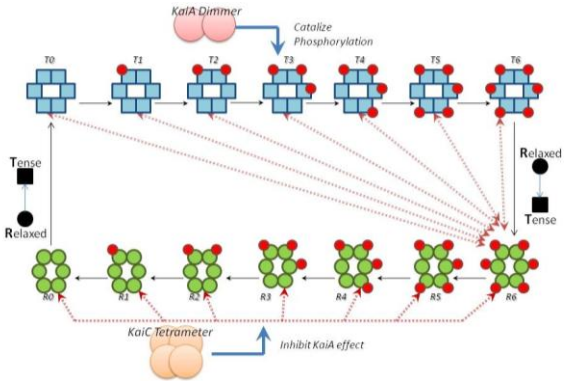

Figure 1. Circadian oscilation with allosteric transition and monomer shuffling scheme. The light blue and green structures represent Kaic hexamers. Circles stand for relaxed state and squares stand for tense stare. The red little circles symbolize that the monomer is phosphorilated. The red dotted line represents monomer shuffling. The allosteric transition only occurs in the borders, at R0=>T0 and T6=>R6 steps.

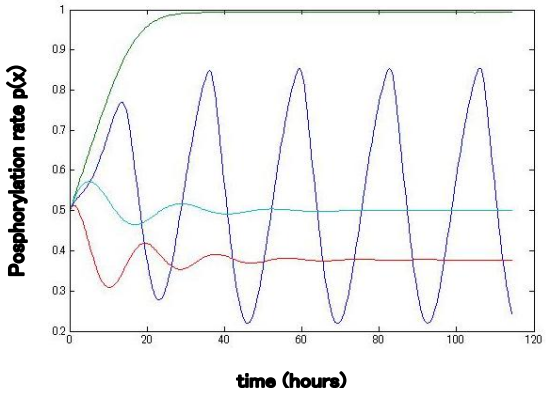

Figure 2. Simulation of the simple model. Blue line shows the regular oscillation. Green: Shuffling prohibited. Red: Rate of T6=>R6 increased. Aquamarine: Rate of T6=>R6 increased and monomer shuffling prohibited.

in two states: *Active*, when it's likely to phosphorylate, and *Inactive,* where the opposite occurs. According to this model, KaiA is supposed to have more affinity toward less phosphorylated KaiC. Even though this model produces adequate oscillation (4), it also has a problem: a molecule that absorbs KaiA in necessary (1). With greater amounts of KaiA, the affinity becomes ineffective. This condition is not satisfied in vitro experiments that produce robust oscillation(1,2).

Conclusion

After the completion of the stochastic model, direct modifications on the parameters that are biologically significant can be made.

The experimental data in this moment is very large, so the models proposed can also be further analyzed and compared.

References

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