# Simulation of Circadian Rhythms

**NAME: GONZALEZ, Glebys**
**Academic Advisor: NAKAO, Mitsuyuki**
**Department of Information and Intelligent Systems**

## Introduction

The circadian rhythm is a mechanism that generates the 24 hour cycle in organisms. It is an internal clock that adapts external stimuli (such as light and darkness), but it can self-sustain even when the organism is completely isolated from them. In humans, hunger and sleepiness times are dependent of this rhythm.

The cyanobacteria is the simplest organism that's capable of producing circadian rhythms. For this reason, it has been well used by researchers for elucidating how this cycle is generated [Kageyama et al., 2002].

As showed in fig1, the circadian rhythm of cyanobacteria is mainly generated by the interaction of three proteins: KaiA, KaiB and KaiC; being the last one, the main coordinator of the cycle [Kageyama et al., 2002].

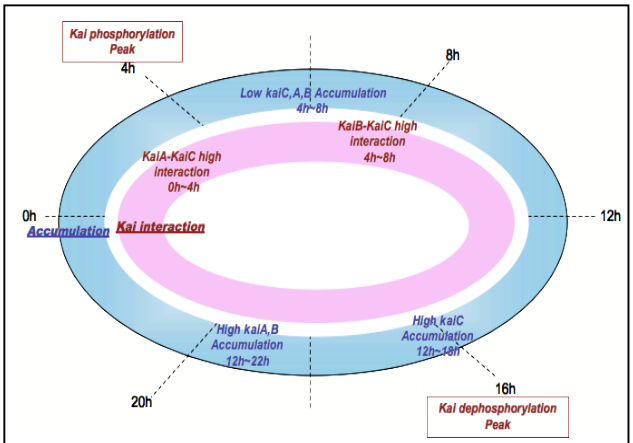


Fig1. **Basic scheme of circadian cycle**: KaiA enhances KaiC phosphorylation while kaiC hinders kaiA effect. In the day, kai molecules have a low accumulation, contrasting with night, when the opposite happens

ATP plays a crucial role in the 24h oscillation. The phosphorylation of KaiC occurs in circadian manner and it controls genomewide expression. Only KaiC and ATP are enough to produce the most basic form of circadian rhythm [Tomita et al., 2005]. Although it is not proved, KaiC might be in a negative feedback loop with KaiBC expression [Tomita et al., 2005; Kageyama et al., 2002].

In addition to the uncertainty about the role of KaiBC expression, it is still unknown how KaiC molecules achieve synchronization to phosphorylate and dephosphorylate. Since the reactions occur at random times, there has to be a mechanism underneath that's organizing all the individual KaiC Hexamer –ATP interaction [Eguchi et al., 2008].

Because of the lack of experimental evidence to clarify the previous doubts, simulation has proven to be useful in this area. Through a mathematical model, a proposition of the circadian mechanics is made, and then, through simulation, comparison to the experimental data can be done.

## Purpose

In order to bring newer information about the processes occurring in cianobacterial circadian rythms, differently oriented models have been generated. In this research, we've been focusing in a monomer shuffling and allosteric transition based model [Eguchi et al., 2008]. For comparison purposes, a differential affinity based model [van Zon et al., 2007], is used.

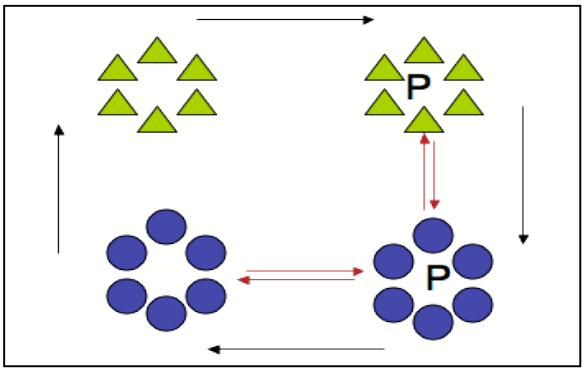


Fig2**. Allosteric scheme**. Monomer shuffling, is a process that occurs between a pair of KaiC Hexamers, in which any number of monomers is exchanged. The triangles symbolize tense state while the circles represent relaxed state. Red arrows indicate frequent monomer shuffling. "P" represents phosphorylated KaiC.

The allosteric model (see fig2) suggests that KaiC Hexamers can be present in two states: Tense and Relaxed. In the first one, KaiC binds to KaiA, enhancing the phosporylation of KaiC. In the other one, KaiC binds to KaiB, which inhibits KaiA action, allowing KaiC to dephosphorylate [Kageyama et al., 2006].

Given that monomer shuffling occurs in a lower rate between molecules in tense states, the allosteric model proposes that monomer shuffling participates in the enhancing of the structural change from tense to relaxed [Eguchi et al., 2008], witch is related, as previously explained, with KaiC dephosphorylation.

Even though this model is robust against change in the volume of the system [Eguchi et al., 2008], it still seems to be a little inflexible against change in concentration (even though it is very flexible in comparison to other models [Eguchi et al., 2008; van Zon et al., 2007]).

In this research, the allosteric model will be used as a base, that will go through a loop of modification and simulation, with the purpose of making it more tolerant to concentration changes. It would also be helpful, to test it against experimental data that hasn't been used for comparison with this model yet.

For the simulations, C++ is being used, since it allows to create high-level objects that make it easy to change from one numerical method to another. It is also more efficient than working directly with a tool like Matlab. This enviroment is only used for plotting the results into graphical figures.

As for the numerical methods, Runge-Kutta and Bulirsch-Stoer routines are used. The model is solved with more than one algorithm to allow comparison.

## Conclusion

The allosteric model still needs to be tested against experimental data (changes in temperature, for example) and to be more tolerant of concentration variation.

Routines that are used in stochastic simulations will be implemented, since they are necessary for simulating the models in a more realistic way.

With this aim, further research will be done.