

Incorporating the CHE-CCA1 loop in a mathematical model of the *Arabidopsis thaliana* circadian clock

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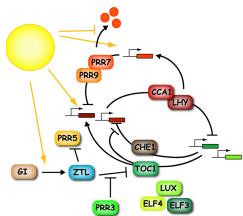
Biology

Why model circadian clocks:

Most organisms, from bacteria to humans, have an internal clock that allows them to adjust the physiological processes to the daily and seasonal changes. To maintain the anticipatory mode on constant basis, the clocks must be adjusted daily. This is achieved in part via signaling light-dark pathways to the clock. Different organisms have developed a variety of methods to keep the clock running on time. Circadian clocks are important regulators of a plant's vital functions, they are the "mastermind" behind scheduling photosynthesis and respiration hours, carbohydrate metabolism, inducing germination and hibernation, controlling growth and cell division among plethora of other processes.



Where are these clocks? Are they created by intercellular interactions or are they cell autonomous? How are they entrained by light-dark cycles and how do they control physiology? To answer these and other questions the genetic components of the circadian clocks are studied in live and simulated systems.



Farré et al. 2009

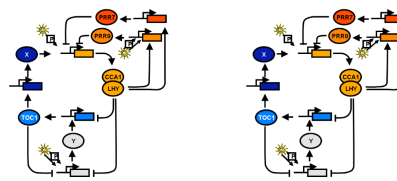


Plant's are very sensitive to the surrounding them environment and act as indicators and expermental playground for bioactive chemical agents, pharmacology, climate studies etc. The medicinal value of phytoextracts is tightly linked to the correct harvest and cultivation timing

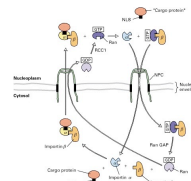
Models

Along with experimentation modeling helps to learn about genetic interactions that generate oscillations of the circadian clock. In the model plant *A. thaliana*, a botanical version of the lab rat, oscillations are thought to originate from reciprocal transcriptional regulation between TIMING OF CAB EXPRESSION (TOC1), CIRCADIAN CLOCK ASSOCIATED1 (CCA1) and LATE ELONGATED HYPOCOTYL (LHY). The mechanism of CCA1 negative regulation was an open question until a new protein was found to be responsible for the repression of CCA1 production. As described in Pruneda-Paz et al. CHE is the main factor causing repression through the TCP-binding site in CCA1 promoter. Besides introducing new states, the model of CCA1 LHY interactions was changed to reflect the three dimmer formation pathways. This gave an incentive for creating the three *Arabidopsis* circadian clock models from the existing 2006 Zeilinger and Taylor model and performing comparative analysis on them. Combining the introduced changes with two possible light inputs for each of the models, six candidate models were created.

Alternative light pathways models



Dynamics of protein interactions during trafficking across the nucleus membrane is complex. The following scheme outlines some of the possible scenarios (Lodish, Berk et al):



Models Analysis

We evaluated performance of the selected models by conducting sensitivity analysis, constructing mutant profiles, and comparing the results with the previous model and data from recent mutant studies. We optimized the models producing new parameter sets. The models are capable of reproducing the correct periods under free-running conditions in constant darkness. We computed the VRCs in the constant darkness conditions. We expect to reveal significant difference between models under light conditions comparing the cost function results.

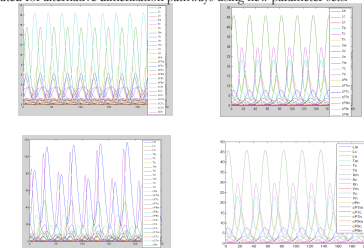
PRC

Phase Response Curve measures the phase shift induced by a short pulse of light. They provide specific information about the plant's response to light

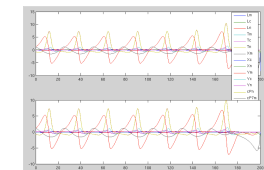
VRC

Velocity Response Curves describe changes to the clock's phase velocity. In this case, the majority of the phase shifting occurs at dawn and dusk because those are the only times the clock's velocity cannot be altered.

PRCs generated for alternative dimerization pathways using new parameter sets.



VRCs generated in dark condition are equivalent for both light pathways



References

Locke J.W.C., Millar A.J., Turner M.S. Modelling genetic network with noisy and varied experimental data : the circadian clock in *Arabidopsis thaliana*. Radio and Wireless Symposium, 2008. McClung C.R. CIRCADIAN RHYTHMS: Linking the loops. Nature, 2009 Pruneda-Paz, J., Breton, C. A Functional Genomics Approach Reveals CHE as a Component of the Arabidopsis Circadian Clock Science, 2009 Nakamichi, Kiba et al. PSEUDO-RESPONSE REGULATORS 9, 7, and 5 Are Transcriptional Repressors in the Arabidopsis Circadian Clock, Plant Cell, March 2010; Farré, E.M., and Kay, S.A. (2007). PRR7 protein levels are regulated by light and the circadian clock in Arabidopsis. Plant J 52, 548-560.