Bread Mold Can Tell Time:
A computational analysis of mold circadian clocks

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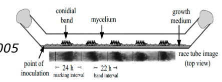
Background

Circadian clocks provide organisms with the ability to coordinate daily rhythms in their behavior.

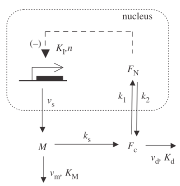
Image based on Price-Lloyd et al 2005



The daily growth pattern displayed in this image is an example of a vital process regulated by the circadian clock of *Neurospora crassa*, a red bread mold.

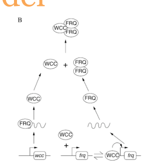
Gerard Model

- Simplest Model
- Three States
- Ten Parameters
- Nineteen Parameters
- Mass Action, Michaelis Menten, and Hill kinetics



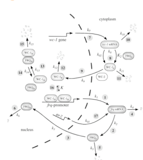
Francois Model

- More Complex Model
- Ten States
- Seventeen Parameters
- Mass Action Kinetics



Hong Model

- Most Complex Model
- Seven States
- Nineteen Parameters
- Mass Action, Michaelis Menten, and Hill kinetics.



Mathematical Models

Circadian clocks are modeled by a system of differential equations. These equations make up the Gerard Model.

Left Hand Side

The left side of the equation is the state variable.

$$\frac{dM}{dt} = v_s \frac{K_I^n}{K_I^n + F_N^n} - v_m \frac{M}{K_m + M},$$

$$\frac{dF_c}{dt} = k_s M - v_d \frac{F_c}{K_d + F_c} - k_1 F_c + k_2 F_N$$

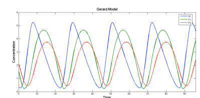
$$\frac{dF_N}{dt} = k_1 F_c - k_2 F_N.$$

Right Hand Side

The right side of the equation describes the cellular interactions affecting the state.

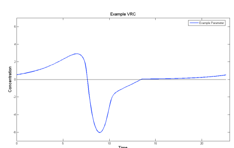
Δ Nuclear FRQ =
forward rate of nuclear transition * cytosolic FRQ
– backward rate of nuclear transition * nuclear FRQ

Solving this system over time



Methodology

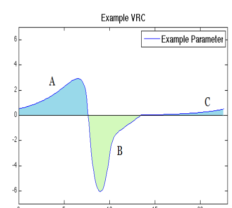
We compute a velocity response curve (VRC) in order to analyze the model's sensitivity to each kinetic parameter.



Where the VRC is positive, parameter perturbation increases the speed of the clock. Where negative, perturbation decreases clock speed.

How much can the clock's timing be affected by a given parameter?

Measure: Area Under Curve



If A + B + C for parameter 1 > A + B + C for parameter 2 then the clock is more sensitive to parameter 1.

This quantification allows us to rank parameter sensitivities.

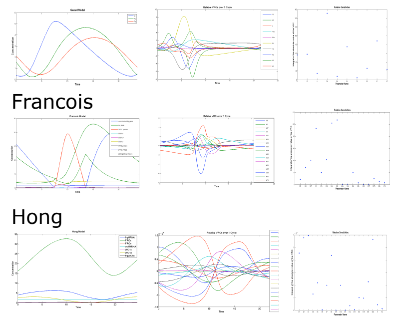
Results to Date

Clock Model → VRCs → Parameter Sensitivities

Gerard

Francois

Hong



Insight

The VRCs contain an overwhelming amount of information. Analyzing the models requires condensing the data to extract the most important information. Here we have meaningfully quantified parameter sensitivity. The three models, however, have very different parameters. In order to compare models, we must devise a method of relating model sensitivity to features common to all models.

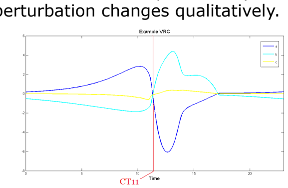
Future Research

How can we compare models which have different states and parameters?

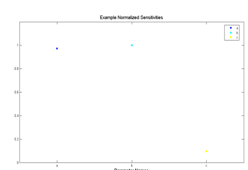
The feature common to all models is a ~24 hr period. We devise a method of relating model sensitivity to circadian time.

Critical Point Analysis

We define a critical point as a point in time at which the effect of parameter perturbation changes qualitatively.



- Here CT11 is a critical point.
- How critical is the point?
- Critical score = Sum of the normalized sensitivity values of all parameters critical at the point
  - Here CT11 has a critical score of 1 + 0.972 + 0.095 = 2.067



Critical point analysis will allow us to create a sensitivity timeline for each model. Because sensitivities are now based on overall model sensitivity and time, comparative analysis is possible.

Citations

Hong, Christian I., et al. "Simulating Dark Expressions and Interactions of frq and wc-1 in the Nuerospora Circadian Clock." Biophysical Journal 94 (2008): 1221-1232.
Gerard, Claude, Didier Gonze and Albert Goldbeter. "Dependence of the Period on the Rate of Protein Deredation in Minimal Models for Circadian Oscillations." Philosophical Transactions of the Royal Society A 367 (2009): 4665-4683
Francois, Paul et al. "A Model for the Neurospora Circadian Clock". Biophysical Journal 88 : 2369 - 2583.

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