Comparison of *Drosophila* Circadian Clock Models Through Oscillator-specific Phase Sensitivity Analysis

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Drosophila Circadian Clock

How can a cell tell time?

Cells in certain tissues in the head of the fruit fly, *Drosophila melanogaster,* maintain the organism's daily rhythms by expressing different genes at different times of day. In these cells, the concentrations of mRNAs and proteins from certain clock-specific genes oscillate in regular daily cycles.

Autoregulation leads to oscillations

Some proteins or complexes of proteins regulate expression of genes. In *Drosophila*, a dimer consisting of the proteins PER and TIM inhibits expression of the *per* and *tim* genes that produced the proteins. The structure of this loop and its built-in delays cause PER and TIM levels to oscillate even in constant darkness (DD cycles).

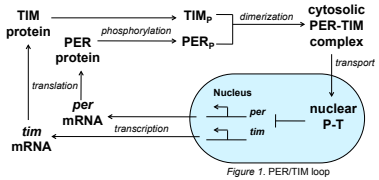


Figure 1. PER/TIM loop

Interlocking loops

All of our models include the PER/TIM loop. The more recent models incorporate another, interlocked loop with CLK, CYC, VRI, and PDP proteins. Biologists continue to discover more clock components.

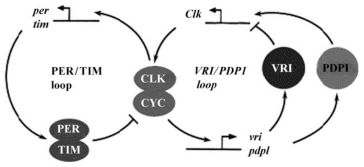


Figure 2. Interlocking feedback loops. (Xie, et. al.)

Phase and Entrainment

Some processes in the clock are sensitive to light, enabling the clock to entrain, or sync its internal rhythms with external cycles of light and darkness (LD cycles). Under normal LD conditions the oscillator is at the same phase of its cycle at the same time every day.

Hour of day (0 = dawn)	Event
0 - 4	Peak *clk* mRNA, trough of PER and TIM mRNAs
11 - 15	Peak *per* and *tim* mRNA
12	Peak *vri* mRNA
15 - 17	Peak VRI, PER, and TIM proteins
18	Peak PDP1 mRNA and protein
23 - 24	Peak of *clk* protein

Table 1. Known events in the daily circadian rhythms of *Drosophila*

Modeling the Clock

Parameters:
- Known constants
- Example: rate at which PER-TIM is degraded

States:
- Concentrations of clock components and their trajectories as they change over time
- Examples: *per* mRNA, PER protein in cytosol

The rate of change of each state is described by an ordinary differential equation (ODE). The models use mass action, Michaelis-Mentin, and Hill kinetics to model various processes. We use Matlab to solve the system of ODEs numerically.

We analyze four models, which can be distinguished by the feedback loops they include:

MODEL 1: PER loop

MODEL 2: PER/TIM loop

MODEL 3: PER/TIM loop and **CLK/CYC** loop

MODEL 4: PER/TIM loop and **VRI/PDP1/CLK/CYC** loop

Phase Sensitivity Analysis

Robustness and sensitivity

To maintain internal rhythms, the oscillator must be robust to random noise in its environmental conditions. To entrain to external stimuli, it must also be sensitive to changes in its environment. A sensitivity analysis measures the model's response to perturbations in its parameters or states.

Velocity response curve

Given internal clock time Φ (the phase of the oscillator), external time t, parameter index j, and some signal z(t), the rate of the clock's time (or "phase velocity") may be expressed as:

$$d\Phi/dt = 1 + VRC_j(\Phi) * z(t)$$

…where VRC is the velocity response curve of each parameter, and is affected by the parameters of the system:

$$VRC_j = (d/dp_j) * d\Phi/dt$$

A change in system parameters can thus cause a change in one of the state speeds which affects the phase.

What's a VRC?

The velocity response curve describes continuous adjustments to a clock's speed.

The magnitude of a VRC for a parameter *P* predicts how much a perturbation of *P* at any time will change the model's phase, and thus, the relative importance of that parameter over time.

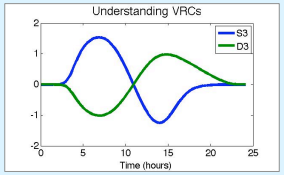
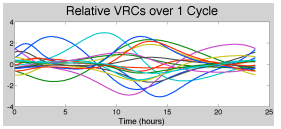


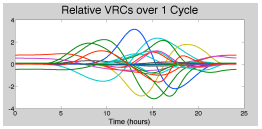
Figure 3. VRCs for two parameters: transcription (S3) and degradation (D3) of *tim* mRNA.

Results

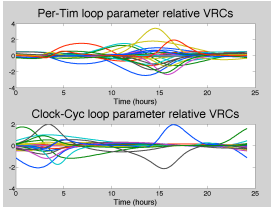
All models appear to accurately represent the importance of the different clock processes that take place during the day (refer to Table 1).



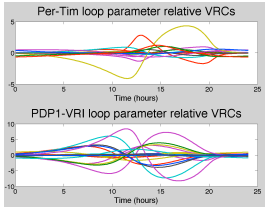
Model 1: Goldbeter, Proc. R. Soc. Lond. B, 1995



Model 2: Leloup & Goldbeter, JBR, 1998



Model 3: Ueda et al., JTB, 2001



Model 4: Xie & Kulasiri, JTB, 2007

Figure 4. Relative VRCs for the four models. Every line represents a the relative VRC of a parameter over the course of a day. These parameters vary in terms of their relative VRC magnitude, and therefore, how important they are to the model at the time. All graphs approximately match with the actual biological events.

Discussion

To conclude, we have shown that:

- Phase-sensitivity analysis can help us simplify complex biological models
- Phase-sensitivity analysis is thus a helpful tool to compare models of biological systems, and
- The four models generally agree in terms of the biological clock events.

Future Work

We hope to:

- Continue analysis of current four models, and
- Incorporate two more models into our analysis. The sixth model will include DBT and the CWO loop (see Table 1).

Further Questions:

- Do we observe the same patterns for different parameterizations of the same model?
- Do we find analogous patterns in all our models?

References

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Acknowledgements: We extend special acknowledgements and thanks to Stephanie Taylor for her guidance as a mentor and advisor, and to the Colby Computer Science Department for its invaluable support.