Synchronizing Molecular Clocks via ATP: What can we Predict?

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Oscillations in Biology

1. Periodic Stimuli
   - Organisms experience periodic stimuli with a consistent 24 hour period. E.g., Light-Dark cycle.

2. Molecular Clocks
   - Molecular Clocks produce output to match this stimuli by organizing biochemical processes into negative feedback patterns.

Circadian Rhythms and Synchronization

Molecular Clocks $\rightarrow$ Timekeeping $\rightarrow$ **Circadian Rhythm**.

Many Cells $\rightarrow$ Many oscillators $\rightarrow$ Requirement for **Synchrony**.

ATP Synchronizes Output in Mice Brain Cells

- The Y-axes represent extracellular [ATP] as measured among 12 separate brain cell colonies.
- The X-axes represent time.
- Extracellular [ATP] was measured every 10 minutes for a total of 72 hours
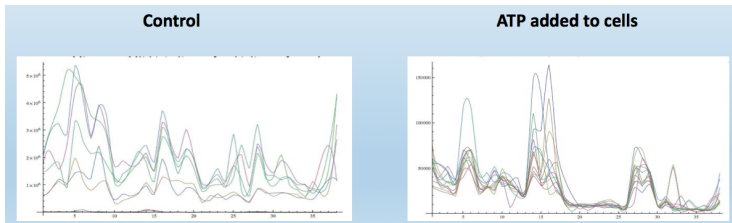
Explaining ATP's ability to Synchronize

- From a biological perspective, these findings are difficult to explain.

- ATP's biological role in clock is unknown

- ATP as a signaling molecule (exceedingly rare)

Explaining ATP's ability to Synchronize

- Hypothesis: **an effectively instantaneous, equivalent increase in a component common to multiple clocks could bring their outputs into phase.**

- The mammalian clock output may be simulated

- If simulation of Dr. Zoran's experiment yields synchronization, theoretical feasibility of the hypothesis would be demonstrable.

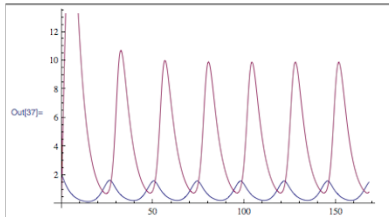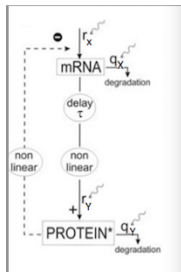# The Scheper Model: Describing the circadian clock

The Scheper Model is a set of delay differential equations.

Scheper Model (X: promoting role/"mRNA")

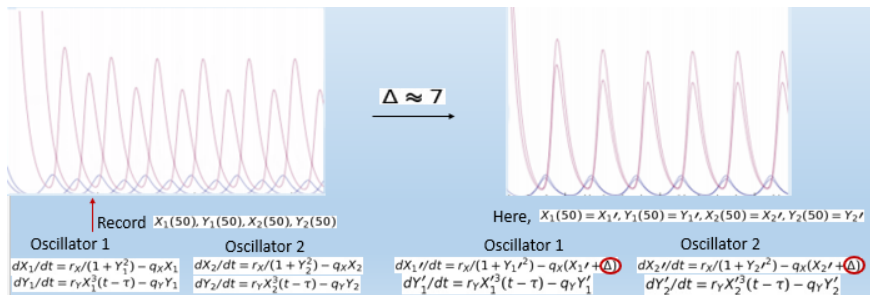$$\dot{x}(t) = \frac{r_x}{(1+y(t)^2)} - q_x * x(t)$$

Scheper Model (Y: inhibitory role/"protein")

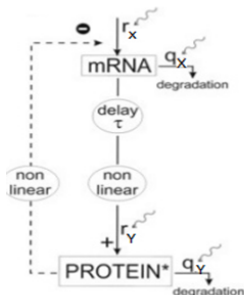$$\dot{y}(t) = r_y * x^3(t - \tau) - q_y * y(t)$$

The original hypothesis, **"An effectively instantaneous, equivalent increase in one component common to multiple clocks could bring their outputs into phase,"** was substantiated with simple trial-and-error simulations.

ATP has a promoting role in the molecular clock

Changes in Y do not lead to synchronization

Inferences

ATP promotes clock gene transcription

Gene transcription, which is catalyzed by enzymes, is the fundamental promoting process in a mammalian molecular clock. ATP allosterically activates many enzymes, which means it binds to a peripheral site on the enzyme to cause activation (*allo=other, steric=site*).
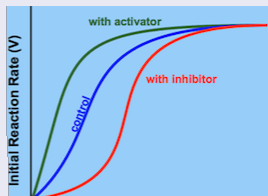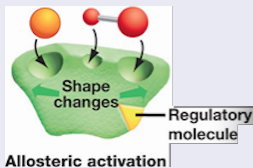
Predictive Power

Trial-and-error and observing specific cases are easy, but predictions and generalizations are more useful.

- How much ATP is optimal for synchronization?
- Does ATP desynchronize in any case?
- Does synchronization process depend on time of ATP addition?
- Do initial parameters affect synchronization?

Predictive Power

Quantifying Synchrony between two oscillators

$$F(\Delta) = \int_a^b [(x_1(t) - x_2(t))^2 + (y_1(t) - y_2(t))^2] dt$$

- a=initial time point, b=final time point
- Oscillator 1: $(x_1(t), y_1(t))$
- Oscillator 2: $(x_2(t), y_2(t))$
- Δ = Amount of ATP added
- Initial time point must be well chosen

Predictive Power
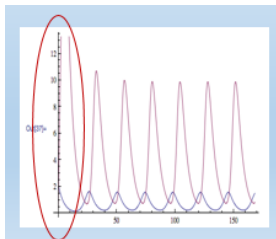
Scheper Model with ATP addition Δ

$\dot{x}(t) = \frac{r_x}{(1+y(t)^2)} - q_x * (x(t) + \Delta)$

$\dot{y}(t) = r_y * x^3(t - \tau) - q_y * y(t)$

Deriving and Optimizing integral expression as a function of Δ

$F(\Delta) = \int_a^b [(x_1(t) - x_2(t))^2 + (y_1(t) - y_2(t))^2] dt$
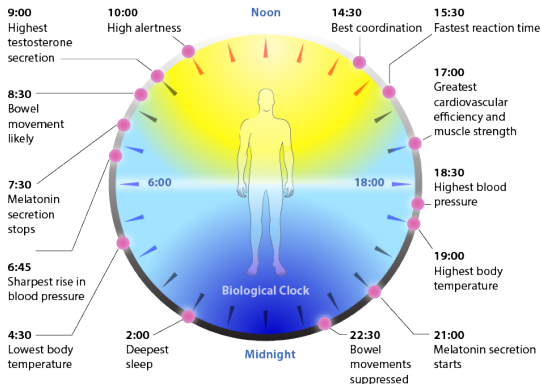
$F'(\Delta) = \int_a^b 2(\frac{\partial x_1(t)}{\partial \Delta} - \frac{\partial x_2(t)}{\partial \Delta})((x_1(t) - x_2(t)) dt + \int_a^b 2(\frac{\partial y_1(t)}{\partial \Delta} - \frac{\partial y_2(t)}{\partial \Delta})((y_1(t) - y_2(t)) dt$

$\frac{\partial \dot{x}(t)}{\partial \Delta} = -[\frac{\partial x(t)}{\partial \Delta} q_x] - [\frac{\partial y(t)}{\partial \Delta} * \frac{2y(t)r_x}{(1+y(t)^2)^2}]$

$\frac{\partial \dot{y}(t)}{\partial \Delta} = 3[\frac{\partial x(t)}{\partial \Delta} x^2(t - \tau)] - [\frac{\partial y(t)}{\partial \Delta} * q_y]$

Real World Application

Predicting the behavior of molecular clocks and manipulating their synchrony would allow us to regulate and strengthen our circadian rhythm output.

Limitations and Challenges

Main Potential Limitations

- Scheper Model
- Grouping of processes
- Instantaneous addition and uniform mixing of ATP.

Limitations with the Predictive Methods

- $F(\Delta) = \int_a^b [(x_1(t) - x_2(t))^2 + (y_1(t) - y_2(t))^2] dt$ requires input of two reference oscillators.
- $F(\Delta)$ only provides Δ values for **specific** oscillators, so output is not "general."