Synchronizing Molecular Clocks via ATP: What can we Predict?

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

Many Cells $\rightarrow$ Many oscillators $\rightarrow$ Requirement for **Synchrony**.
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)
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 Schepere Model: Describing the circadian clock

The Schepere Model is a set of delay differential equations.

**Schepere Model (X: promoting role/“mRNA”)**

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

**Schepere Model (Y: inhibitory role/“protein”)**

\[
\dot{y}(t) = r_y * x^3(t - \tau) - q_y * y(t)
\]
Initial findings

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.

\[
\begin{align*}
\frac{dx_1}{dt} &= \frac{r_x}{1 + y_1^2} - q_x x_1 \\
\frac{dy_1}{dt} &= r_y x_1^3 (t - \tau) - q_y y_1 \\
\frac{dx_2}{dt} &= \frac{r_x}{1 + y_2^2} - q_x x_2 \\
\frac{dy_2}{dt} &= r_y x_2^3 (t - \tau) - q_y y_2
\end{align*}
\]

Here, \( x_1(50) = x_1', \ y_1(50) = y_1', \ x_2(50) = x_2', \ y_2(50) = y_2' \)

\[\Delta \approx 7\]
Inferences

ATP has a promoting role in the molecular clock

Changes in Y do not lead to synchronization
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 \((\text{allo}=\text{other}, \text{steric}=\text{site})\).
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?
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: \((x_2(t), y_2(t))\)
- \(\Delta = \) Amount of ATP added
- Initial time point must be well chosen
Schepur Model with ATP addition $\Delta$

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

\[
\dot{y}(t) = r_y \ast x^3(t - \tau) - q_y \ast y(t)
\]

Deriving and Optimizing integral expression as a function of $\Delta$

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

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

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

\[
\frac{\partial \dot{y}(t)}{\partial \Delta} = 3\left[\frac{\partial x(t)}{\partial \Delta} x^2(t - \tau)\right] - \left[\frac{\partial y(t)}{\partial \Delta} \ast q_y\right]
\]
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 \( \Delta \) values for \textbf{specific} oscillators, so output is not “general.”