A Mathematical Model for Protein Oscillations in Bacteria

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Protein oscillations in bacteria govern many fundamental processes, such as cell polarity which influences the direction of motion. Oscillatory changes in protein concentration between cell poles lead to reversals in the cell’s directional movement.

The soil bacterium Myxococcus xanthus moves with help of two gliding motility systems regulated by the MglA-MglB protein complex [3].

Empirical evidence on MglA, MglB [1, 2, 3] shows that they
- set up correct polarity of motility proteins at the poles,
- can bind to both poles and diffuse through the cytoplasm,
- localize ‘antagonistically’ at opposite poles, whereby MglA clusters near the leading pole and MglB near lagging pole,
- interact only at localized sites at the cell poles.

Aim: develop a minimal model producing pole-to-pole oscillations under these assumptions without external triggers.

Model assumptions
Cell is modeled in 1-D as segment of length 1.
- Diffusion coefficient of each protein is assumed constant.
- Conservation of mass holds for each protein.
- Binding of the proteins to the cell poles occurs at a rate proportional to the cytoplasmic concentration near the pole.
- Unbinding of the proteins from the poles into the cytoplasm occurs at a rate proportional to their polar concentrations.
- Binding and unbinding rates depend on the concentrations of the pole-bound proteins.

Three-compartment cell model
A system of $n \geq 2$ proteins, labeled by $i = 1, \ldots, n$

A starting point is the homogeneous steady state $l_i = \xi_i = c_i(x) = \frac{1}{2}$. Initially the case $n = 2$ is considered [4]. If $\xi(1, 1) = \xi(1, 1)$, and $d_1 = d_2$, this steady state is unstable if the matrix of partial derivatives

$$\begin{bmatrix} \frac{\partial q_{11}}{\partial c_1} & \frac{\partial q_{11}}{\partial c_2} \\ \frac{\partial q_{21}}{\partial c_1} & \frac{\partial q_{21}}{\partial c_2} \end{bmatrix} \left| (1, 1) \right|$$

has eigenvalues with positive real part [4].

A more complex criterion exists for $n > 2$, general $\alpha_i$ and $d_1 \neq d_2$.

Robustness of model
To make reliable predictions, it is necessary to verify that the model dynamics is robust against small variations in parameters or initial conditions.

The model should contain as few parameters as possible.

A parameter scan is undertaken to define the parameter range where the qualitative behavior of the model remains unchanged.

For the ‘stalker’ scenario the parametrized interaction functions are

$$\begin{align*}
\alpha_1 (x_1, x_2) &= \frac{1}{2} - x_1 + x_2 \\
\alpha_2 (x_1, x_2) &= \frac{1}{2} + x_1 - x_2 \\
\kappa_1 (x_1, x_2) &= \frac{1}{2} x_1 + x_2 \\
\kappa_2 (x_1, x_2) &= \frac{1}{2} x_1 - x_2 \\
\end{align*}$$

Computations are performed under the assumption $d_1 = d_2 = 1$.

Numerical results

Range of $\alpha_i\xi_i$ where the solution is oscillatory.

References

http://www.mathematik.uni-marburg.de/~rashkov/
http://www.synmikro.de

Discussion
✓ Model produces self-sustained regular oscillations without external triggers.
✓ Dynamics of the model is robust against small variation in parameters and initial conditions.
✓ Different interaction functions produce diverse spatiotemporal concentration patterns.

Outlook
Study extensions of the model to higher number of proteins and incorporate stochastic effects in order to describe irregular oscillations characteristic of wild-type M. xanthus.

Differential equations
The following boundary conditions for $c_i$ are imposed:

$$\begin{align*}
\frac{\partial c_i}{\partial t} (0, t) &= -\alpha_i (c_i (0, t) - \kappa_i (t), \quad i = 1, \ldots, n \\
\frac{\partial c_i}{\partial t} (1, t) &= -\alpha_i (c_i (1, t) - \kappa_i (t), \quad i = 1, \ldots, n \\
\end{align*}$$

so that for continuous $\alpha_i$, $\kappa_i$ the mass

$$m_i (t) = e_i (t) + \int_0^t c_i (\tau, x) dx d\tau + x_i (t), \quad i = 1, \ldots, n.$$

is constant, $m_i (0) = m_i (t), \quad i = 1, \ldots, n$ for all $t \geq 0$.

Stability analysis
Regular oscillations can occur as stable limit cycle of nonlinear system. Design considerations:
- Linearized system at the steady state exhibits eigenvalues with positive real part.
- Nonlinear terms should limit growth of the solution and bend the trajectory into a limit cycle.
- Necessary conditions for unstable steady state based on linear stability analysis are given in [4].
- Interaction functions $\alpha_i, \kappa_i$ designed according to mathematical analysis to produce an unstable steady state.

“Stalker” scenario
Protein 1 is attracted to both poles; protein 2 follows it and repels it from the poles:

$$\begin{align*}
d_1 &= d_2 = 1 \\
\alpha_1 (x_i, x_2) &= 0.2 + 0.05 x_1 \\
\alpha_2 (x_i, x_2) &= 0.5 + 0.05 x_2 \\
\kappa_1 (x_i, x_2) &= 0 \\
\kappa_2 (x_i, x_2) &= \frac{2}{3} \frac{2}{3} x_1 + x_2 \\
\end{align*}$$

Proteins display "stalker" pattern at the pole.

"Antagonist" scenario
Both proteins cluster at opposite poles over an extended time period:

$$\begin{align*}
d_1 &= d_2 = 1 \\
\alpha_1 (x_i, x_2) &= 0.05 + 0.95 x_1 \\
\alpha_2 (x_i, x_2) &= (0.8 + 0.2) x_2 \\
\kappa_1 (x_i, x_2) &= \frac{2}{3} \frac{2}{3} x_1 + x_2 \\
\kappa_2 (x_i, x_2) &= \frac{2}{3} \frac{2}{3} x_1 - x_2 \\
\end{align*}$$

Proteins display "antagonistic" pattern at the pole.

Linearized system at the steady state exhibits eigenvalues with positive real part. The soil bacterium Myxococcus xanthus changes in protein concentration between cell poles lead to reversals in the cell’s directional movement.

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\end{align*}$$

so that for continuous $\alpha_i$, $\kappa_i$ the mass

$$m_i (t) = e_i (t) + \int_0^t c_i (\tau, x) dx d\tau + x_i (t), \quad i = 1, \ldots, n.$$