A Mathematical Model for Protein Oscillations in Bacteria

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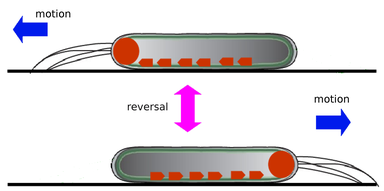
Protein oscillations in bacteria govern many fundamental processes, such as cell polarity which influences the direction of motion. Oscillatory changes in protein concentration between cell poles lead to reversals in the cell's directional movement.

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



Scheme of *M. xanthus* reversing.

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.

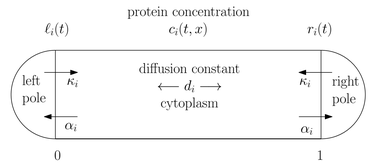
Model assumptions

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 $i = 1, \ldots, n$



Identical laws of interaction at both poles $\rightarrow$ no directional bias

Differential equations

The assumptions yield a weakly-coupled reaction-diffusion system.

$$\begin{aligned}
\frac{\partial}{\partial t} c_i(x) &= \underbrace{d_i \Delta c_i}_{\text{diffusion}}, \quad x \in [0,1] \\
\frac{1}{d_i}\frac{d}{dt}\ell_i &= \underbrace{\alpha_i(\ell) c_i(0)}_{\text{binding}} - \underbrace{\kappa_i(\ell)\ell_i}_{\text{unbinding}} \\
\frac{1}{d_i}\frac{d}{dt} r_i &= \underbrace{\alpha_i(r) c_i(1)}_{\text{binding}} - \underbrace{\kappa_i(r) r_i}_{\text{unbinding}}, \quad i = 1, \ldots, n
\end{aligned}$$

$\alpha_i, \kappa_i \geq 0, i = 1, \ldots, n$ assure positivity of concentrations at all times.

Boundary conditions

The following boundary conditions for c_i are imposed,

$$\begin{aligned}
\frac{\partial}{\partial x} c_i(0) &= \alpha_i(\ell) c_i(0) - \kappa_i(\ell)\ell_i, \\
\frac{\partial}{\partial x} c_i(1) &= -\alpha_i(r) c_i(1) + \kappa_i(r) r_i, \quad i = 1, \ldots, n,
\end{aligned}$$

so that for continuous α_i, κ_i the mass

$$m_i(t) := \ell_i(t) + \int_0^1 c_i(t,x)\, dx + r_i(t), \; i = 1, \ldots, n,$$

is constant, $m_i(t) \equiv m_i(0), i = 1, \ldots n$ 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 α_i, κ_i designed according to mathematical analysis to produce an unstable steady state.

A starting point is the homogeneous steady state $\ell_i = r_i = c_i(x) = 1, \forall i$.
Initially the case $n = 2$ is considered [4].
If $\alpha_1(1,1) = \alpha_2(1,1)$, and $d_1 = d_2$, this steady state is unstable if the matrix of partial derivatives

$$\left(\begin{array}{cc}
\frac{\alpha_{1,1}}{\alpha_1} - \frac{\kappa_{1,1}}{\kappa_1} - 1 & \frac{\alpha_{1,2}}{\alpha_1} - \frac{\kappa_{1,2}}{\kappa_1} \\
\frac{\alpha_{2,1}}{\alpha_2} - \frac{\kappa_{2,1}}{\kappa_2} & \frac{\alpha_{2,2}}{\alpha_2} - \frac{\kappa_{2,2}}{\kappa_2} - 1
\end{array} \right) \Bigg|_{(1,1)}$$

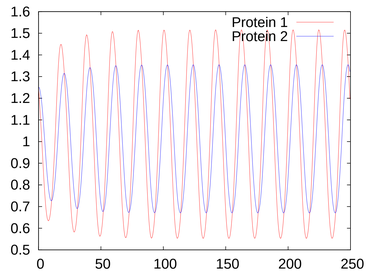
has eigenvalues with positive real part [4].
A more complex criterion exists for $n > 2$, general α_i, and $d_1 \neq d_2$.

"Stalker" scenario

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

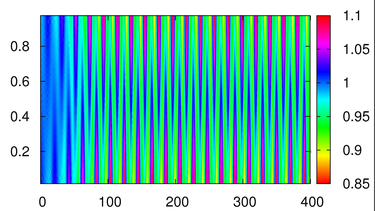
$$\begin{aligned}
d_1 = d_2 &= 1 \\
\alpha_1(x_1, x_2) &= 0.2 + 0.8 x_1^2 \\
\alpha_2(x_1, x_2) &= 0.5 + 0.5 x_1 \\
\kappa_1(x_1, x_2) &= x_2 \\
\kappa_2(x_1, x_2) &= \frac{2}{1 + x_2}
\end{aligned}$$

Concentration profile at left pole



Second protein ("stalker") is lagging on the first.

Color-plot of $c_1(t,x)$, horizontal axis t, vertical axis x



Oscillations across cytoplasm are sinusoidal.

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.

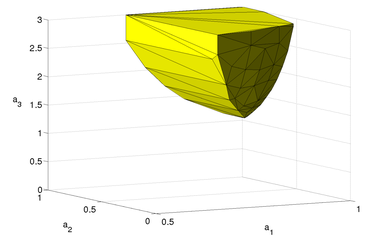
A parameter scan is undertaken to define the parameter range where the qualitative behavior of the model remains unchanged.

For the "stalker" scenario the parametrized interaction functions are

$$\begin{aligned}
\alpha_1(x_1, x_2) &= 1 - a_1 + a_1 x_1^2 \\
\alpha_2(x_1, x_2) &= 1 - a_2 + a_2 x_1 \\
\kappa_1(x_1, x_2) &= x_2 \\
\kappa_2(x_1, x_2) &= \frac{a_3}{1 + (a_3 - 1) x_2}
\end{aligned}$$

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

Numerical results



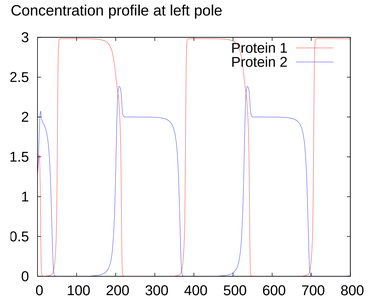
Range of $(a_i)_{i=1}^3$ where the solution is oscillatory.

"Antagonist" scenario

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

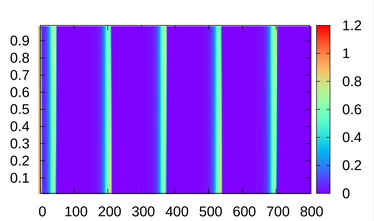
$$\begin{aligned}
d_1 = d_2 &= 1 \\
\alpha_1(x_1, x_2) &= 0.05 + 0.95 x_1^2 \\
\alpha_2(x_1, x_2) &= (0.8 + 0.2 x_1) x_2 \\
\kappa_1(x_1, x_2) &= \frac{2 x_2}{1 + x_2} \\
\kappa_2(x_1, x_2) &= \frac{4}{3 + x_2}
\end{aligned}$$

Concentration profile at left pole



Proteins display "antagonistic" pattern at the pole.

Color-plot of $c_1(t,x)$, horizontal axis t, vertical axis x



First protein remains in cytoplasm for short periods.

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*.

References

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[4] Rashkov et al. A Model of Oscillatory Protein Dynamics in Bacteria. *Bull. Math. Biol.* (2012)

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`http://www.synmikro.de`