Bidirectional transport model of morphogen gradient formation via cytonemes

Hyunjoong Hune Kim

Department of Mathematics
University of Utah

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Morphogen Gradient

- A **morphogen** is a signaling molecule that acts directly on cells to produce specific cellular responses depending on its local concentration.

- A **morphogen gradient** is a spatially varying concentration of a morphogen.

- A morphogen gradient drives a corresponding spatial variation in gene expression through a thresholding mechanism.

- Continuous varying morphogen concentration $\Rightarrow$ discrete spatial pattern of differentiated gene expression across a cell population.
The first and popular model to explain morphogen gradient formation is diffusion-based model. It was introduced by Francis Crick and explains various pattern formations in nature. Unless you assign additional reaction, it is hard to generate various form of morphogen gradient.
Tom Kornberg, biologist, UCSF.

Kornberg observed the direct delivery of morphogens along thin cellular extensions known as cytonemes.
Mathematical Model of Morphogen Gradient Formation

Consider $N + 1$ embryo cells arranged in a line, and introduce the cell label $n = 0, 1, \cdots, N$.

Suppose that the cell $n = 0$ acts as the source cell and produces morphogens at a rate $Q$. The source cell also projects $N$ tubular cytonemes, each of which attaches to a unique downstream cell.

Morphogens are transported to the $n$th target cell via the $n$th cytoneme at an $n$-dependent rate $w_n$, $n = 1, \cdots, N$. 

Here is the first mathematical model: Compartmental model.
Mathematical Model of Morphogen Gradient Formation

- Let $C_n(t)$ denote the density of signaling molecules at the $n$th cell at time $t$. The corresponding evolution equations take the form

$$\frac{dC_0}{dt} = Q - C_0(t) \sum_n w_n,$$

$$\frac{dC_n}{dt} = w_n C_0(t) - kC_n(t).$$

- Find the steady-state solution

$$\frac{C_n}{C_0} = \frac{w_n}{k},$$

- Obtain a morphogen gradient from $w_n$. What is $w_n$?
Mathematical Model of Morphogen Gradient Formation

Better mathematical model... Bidirectional transport model!

Awesome! Let’s develop it!
Bidirectional Transport Model

- Consider a cytoneme of length $L$.
- Denote the density of anterograde ($+$) and retrograde ($-$) motor-cargo complexes at position $x$ along the cytoneme by $u_+(x, t)$ and $u_-(x, t)$.

$$\frac{dC_0}{dt} = Q - J_{in}, \quad \frac{dC_1}{dt} = J_{out} - kC_1.$$
Bidirectional Transport Model

- Transport equations are

\[
\begin{align*}
\partial_t u_+ &= -v_+ \partial_x u_+ - \beta u_+ + \alpha u_- \\
\partial_t u_- &= v_- \partial_x u_- + \beta u_+ - \alpha u_-, 
\end{align*}
\]

where \(v_\pm\) are the motor speeds and \(\alpha, \beta\) give rates of switching between the two states (and achieve by CK Eqn).
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where \( v_\pm \) are the motor speeds and \( \alpha, \beta \) give rates of switching between the two states (and achieve by CK Eqn).

- At the source end: the injection is proportional to \( C_0(t) \):

\[
u_+(0, t) = \kappa C_0(t).
\]

- At the target end: all particles are absorbed: \( u_-(L, t) = 0 \).
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- Flux at \( x \) is

\[
J(x, t) = v_+ u_+(x, t) - v_- u_-(x, t)
\]

and set \( J_{\text{in}} = J(0, t) \) and \( J_{\text{out}} = J(L, t) \).
Bidirectional Transport Model

- Solving the steady-state equation yields

\[ w(L) = \frac{kC_1}{C_0} = \frac{\kappa v_+ e^{-\gamma L}}{1 + \alpha[1 - e^{-\gamma L}]/\gamma v_-} \]

where

\[ \gamma = \frac{\beta v_- - \alpha v_+}{v_+ v_-} = -\frac{v}{v_+ v_-} \frac{\alpha + \beta}{v_+ v_-} \]
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Multiple Target Cells

- Let $u^n_\pm$ denote subpopulations along cytoneme interacting with $n$-th target cell.
- Introduce injection distribution rate $f_n$ with $\sum_n f_n = 1$ and change the boundary condition $u^n_+(0, t) = \kappa f_n P_0(t)$. 
Bidirectional transport model can establish various forms of morphogen gradient!
Accumulation Time

- What if it takes a lot of time to reach the steady-state?
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- Measure the formation time of $P_n(t)$ to $P_n^*$ by

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\tau_n = \int_0^\infty t \frac{d}{dt} \left( \frac{P_n(t)}{P_n^*} \right) dt
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- Performing Laplace transform to the equation gives...

$$
\tau_n = \frac{1}{k} + 2\kappa v^2 \sum_{m=1}^{N} \tilde{w}_m \cdot e^{-\gamma L_n/2} \frac{f_n}{\tilde{w}_n} \cdot \frac{d}{ds} \frac{e^{s \delta L_n} f(s)}{a_n(s)q(s)} \bigg|_{s=0}.
$$
- Depict in case of single target cell

![Graphs showing concentration over time and accumulation time vs. cytoneme length with different values of \( \gamma \).]
Depict in case of single target cell

(a)

\[ \text{Concentration} \]

\[ P_1(t) \]

\[ \tau_1 \]

Time \( t \)

(b)

\[ \text{Accumulation time} \]

\[ \tau_t \]

Cytokine length \( L \) [\( \mu m \)]

Depict in case of multiple target cells
Accumulation Time

One can rewrite the accumulation time as

$$\tau_n = T_n(0) + \frac{\int_0^{L_n} u_+(x, \infty) + u_-(x, \infty) \, dx}{J_n^*} + \frac{1}{k}$$

where $T_n(0)$ is the accumulation time of $J_n(0, t)$, $J_n^*$ is the stationary flux along $n$-th cytoneme and $k$ is the degradation rate of target cells.
Denote $y_c$ is threshold position corresponding to threshold concentration $P_c$.

Measure the robustness as the change of threshold position with respect to production rate $\frac{dy}{dQ}|_{y=y_c}$.
Robustness of Morphogen Gradient

- Denote $y_c$ is threshold position corresponding to threshold concentration $P_c$.
- Measure the robustness as the change of threshold position with respect to production rate $dy/dQ|_{y=y_c}$.
- Continuate model equations by substituting $n \rightarrow y$ and compute steady-state solution of $P^*(y)$.

$$P^*(y) = \frac{Q}{k} \cdot \frac{f(y)w(y)}{\int_0^L f(y)w(y)dy}.$$
Robustness of Morphogen Gradient

- Calculate $dy/dQ\big|_{y=y_c}$ at the threshold $P_c$

$$
\frac{Q}{k} \cdot \frac{f(y_c)w(y_c)}{\int_0^L f(y)w(y)dy} = \frac{Q + dQ}{k} \cdot \frac{f(y_c + dy)w(y_c + dy)}{\int_0^L f(y)w(y)dy}.
$$
Robustness of Morphogen Gradient

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Depict with varying $\gamma$
Robustness of Morphogen Gradient

- Depict with varying injection distribution $f(y)$
Summary

- Identified transport rate $w_n$

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w(L) = \frac{\kappa v_+ e^{-\gamma L}}{1 + \alpha [1 - e^{-\gamma L}] / \gamma v_-}.
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- With varying injection distribution, we explains various morphogen gradient (may loose robustness).
Summary

- Identified transport rate $w_n$

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- With varying injection distribution, we explain various morphogen gradient (may lose robustness).

- Properties of morphogen gradient (accumulation time, robustness) via cytoneme depends on the sign of mean speed $\bar{v}$ (or $\gamma$):
  - mean speed $> 0 \implies$ small accumulation time,
  - mean speed $< 0 \implies$ bounded robustness, similar with diffusion.
Future Work

- Cytoneme tip interaction with target cell: switching or synaptic interactions
Questions?
References