Mathematical Model of Phospholipid Dynamics in Gradient Sensing

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Based on Narang et al., Annals Biomed. Eng., 29, 677, 2001

Properties of Gradient Sensing Mechanism

Chemoattractant gradient is mild, but actin polymerization is localized

↓

External signal must be amplified

Amplification occurs only for sufficiently large gradients

↓

There must be a threshold for amplification
**Response to Non-Uniform Chemoattractant Gradient**

In the presence of the gradient induced by a micropipette, the PI localization appears and disappears

In neutrophils, the localization of PH-Akt-GFP is 6 times the chemoattractant gradient

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**Response to Uniform Chemoattractant Stimulus**

In neutrophils

- $\text{PH}_{\text{Akt}}$ -GFP accumulates uniformly along the membrane within 10 secs
- But $\text{PH}_{\text{Akt}}$ -GFP localizes ultimately and remains so for up to 8 minutes
**Response to Uniform Chemoattractant Stimulus**

*In Dictyostelium*

- GFP-PH immediately migrates to cell periphery, reverts to cytosol within 2 minutes, then develops a polarization.

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**Switch in direction of the gradient:** *Shallow Gradient*

- Shallow Gradient:
  - A gradient whose influence is felt all the way to pre-existing leading edge.

- New pseudopod (or Arp3 localization) does not form at the new location. Instead, existing pseudopod swivels to the new location.
Switch in direction of the gradient: Steep Gradient

- Old pseudopod (PI localization) retracts and new pseudopod (PI localization) forms at the new location

The Model

Model consists of two interacting species

<table>
<thead>
<tr>
<th>Activator</th>
<th>Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Synthesized</td>
<td>• Inhibits the activator</td>
</tr>
<tr>
<td>autokatalytically</td>
<td>• Diffuses rapidly</td>
</tr>
<tr>
<td>• Diffuses slowly</td>
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Wish to account for two experimental observations:

1. *Localization of PIs* in response to non-uniform and uniform chemoattractant gradients
2. *Movement of pre-existing PI localization* in response to changes in direction of chemoattractant gradient
**PI Cycle: Intuitive explanation for PI localization**

- Receptor activation activates PI3K.
- ↑ in PIP$_3$ ⇒ Recruitment of PI5K via Rac
- Leads to autocatalytic synthesis of PIP$_2$ and PIP$_3$. Feedback is further reinforced by PA.

The net effect is:
1. Membrane PI’s builds up at the expense of PI’s in ER
2. PI cycle turns faster

**Leading Edge**

- Synthesis of $P$ is *autocatalytic* and *cooperative* at small $p$ and *self-limiting* at large $p$.
- Receptor activation increases $k^+$ and “lifts” the synthesis curve.
- New steady state has higher $p$ and higher turnover rate.
**Intuitive explanation for PI peak stabilization**

- Receptor activation causes autocatalytic build up of PI’s at the leading edge which results in localized inositol formation.
- Inositol diffuses away from the stimulus site and transfers PI from the membrane to the ER, thus preventing the peak from spreading.

**Trailing Edge**

- $i$ increases at the trailing edge.
- Slope of removal curve increases.
- Steady state $p$ decreases and turnover rate is little slower.
Role of PLCγ in movement of fibroblasts and neutrophils

“Both the PLC and motility responses [in fibroblasts] were decreased by expression of a dominant-negative PLC gamma-1 fragment in EGF-responsive infectant lines.” – Alan Wells et al., 1994

“… cell motility [in neutrophils] is [Ca2+]i dependent when the cells are examined on physiological substrates such as fibronectin or vitronectin. Calcium-buffered cells appear to make repeated attempts to move but are unable to detach from a fibronectin or vitronectin substrate” – Hendey et al., 1993

Mathematical Model

2-D disk of radius $R$

$p$ : Activator

$i$ : Inhibitor

Model Variables

• $p$ Slow-diffusing membrane phosphoinositides

• $i$ Fast-diffusing cytosolic inositol phosphates

• $p_s$ Slow-diffusing phosphoinositides in ER
Model Equations

\[
\frac{\partial r^*}{\partial t} = k_{d1} r^* + k_{d2} \theta^2 - D_p \frac{\partial^2 r^*}{\partial \theta^2}
\]

\[
\frac{\partial p}{\partial t} = k_r r^*(\theta) p^2 - k_p p + c_p k_p p + D_p \frac{\partial^2 p}{\partial \theta^2}
\]

\[
\frac{\partial i}{\partial t} = s[k_r r^*(\theta) p^2 - k_i i] - c_i k_i i + D_i \frac{\partial^2 i}{\partial \theta^2}
\]

\[
p_i = \frac{1}{2\pi R} \int_0^{2\pi} (p + p_s) \, Rd\theta
\]

Periodic Boundary Conditions

- Concentrations of \( p \) and \( i \) are equal at \( \theta = 0, 2\pi \)
- Fluxes of \( p \) and \( i \) are equal at \( \theta = 0, 2\pi \)

Initial Conditions

- At \( t<0 \), cell is in a uniform steady state corresponding to a uniform concentration of active receptors
- At \( t=0 \), a non-uniform profile imposed on the concentration of the active receptors
Response to chemoattractant gradient

- Non-uniform SS develops in 120 secs
- Inhibitory effect can be seen at the back of the cell
- \( i \) has a nearly flat profile

Response To Uniform Chemoattractant Stimulus

- Chemoattractant concentration may be macroscopically uniform
- But there might be significant random fluctuations in receptor-ligand binding

Simulating receptor-ligand binding fluctuations

- Cell membrane was partitioned into ten equal arcs.
- In each arc, fluctuations in active receptor concentrations were simulated by a stochastic model describing receptor-ligand interactions.
- Noise in the stochastic model is simulated by a Wiener process.
- Active receptors (\( r^* \)) have a 1% deviation from the mean value.
Response to Uniform Stimulus

- Cells initially accumulate PI uniformly
- This is followed by the formation of a PI peak

Switch in direction of the gradient: Shallow Gradient

Weiner et al., 1999
**Switch in direction of the gradient**: Steep Gradient

Switch to direction of steep gradient. Initial localization develops at locations of both sources. Finally, the larger source “wins” and a single localization forms at the site of highest chemoattractant concentration.
Two peaks can form only if the difference between the two chemoattractant maxima is very small relative to the magnitude of the maxima.

Variation of peak width with rate constants

\[ k_f = \text{Rate of PI formation} \]

- Width of the steady state peak increases with \( k_f \)
- PI is synthesized so fast that peak spreads before inositol phosphates can contain them
- Similar results if \( k_r \) is decreased.
Variation of steady states with $k_f$:

- Both uniform and non-uniform SS exist over a range of $k_f$
- Gradient makes system jump from uniform to non-uniform SS
- At large and small $k_f$, non-uniform SS merges with uniform SS

Conclusions:

A reaction-diffusion model predicts the following:

- PI’s localize in response to uniform and non-uniform chemoattractant gradient

- PI’s move in response to changes in direction of chemoattractant gradient
  
  *Shallow Gradient*: Existing peak moves to the new location
  
  *Sharp Gradient*: New peak forms as existing peak goes down

- Width of PI localization changes when reactions are activated or inhibited.

- Unique peak develops even in response to multiple chemoattractant sources.
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Response to Non-Uniform Chemoattractant Gradient

Observation
- Within 10 secs, GFP-PH (PIP$_2$ /PIP$_3$ marker) migrates toward highest concentration and remains there