Alternative views on gradient sensing:

- Postma and van Haastert. ‘A diffusion-translocation model for gradient sensing by chemotactic cells.’ Biophys. J. **81**, 1314 (2001).
- Levchenko and Iglesias. ‘Models of eukaryotic gradient sensing: applications to chemotaxis of amoeba and neutrophils’ *Biophys. J.* ***82***, 50 (2002).

Main point: - how to prevent cells to polarize ‘inreversibly’?

$$\frac{dm}{dt} = D_m \frac{\partial^2 m}{\partial x^2} - k_{-1} m + P$$

$D_m \sim 1\ \mu m^2 s^{-1}$
(membrane protein. lipid)
$D_m \sim 100\ \mu m^2 s^{-1}$
(cytosolic small molecule)

Images removed due to copyright considerations.
See Postma, M., and P. J. Van Haastert.
"A diffusion-translocation model for gradient sensing by chemotactic cells." *Biophys J.* 81, no. 3 (Sep, 2001): 1314-23.

For a second messenger to establish and maintain a gradient the dispersion range λ should be smaller than cell size

$$\lambda = \sqrt{\frac{D_m}{k_{-1}}}$$

$$k_{-1} = 1 s^{-1}$$

$$L = 10 \mu m$$

Second mesenger production in a gradient

$D_m \sim 1\ \mu m^2 s^{-1}$ (membrane protein. lipid)
$D_m \sim 100\ \mu m^2 s^{-1}$
(cytosolic small molecule)

$$\frac{dm}{dt} = D_m \frac{\partial^2 m}{\partial x^2} - k_{-1} m + P(x)$$

$$P(x) = k_R \left(\overline{R}^* - \Delta R^* \frac{x}{r} \right)$$

Diffusion flattens internal gradient

Gain is < 1 (the larger D_m the smaller the gain)

How to amplify ?

Amplification by positive feedback

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$$\frac{dm}{dt} = D_m \frac{\partial^2 m}{\partial x^2} - k_{-1} m + P(x)$$

$$P(x) = k_o + k_E R^*(x) E_m(x)$$

A. Before receptor stimulation only a small number of effectors (inactive) bound to membrane
B. After receptor stimulation, membrane bound effectors will be stimulated to produce more phospholipid second mesengers
C. Local phospholipid increase leads to increased translocation of effector molecules
D. receptor can signal to more effectors leading to even more phospholipid production and further depletion of cytosolic effector molecules.

E_m: effector concentration in membrane
E_c: effector concentration in cytosol.

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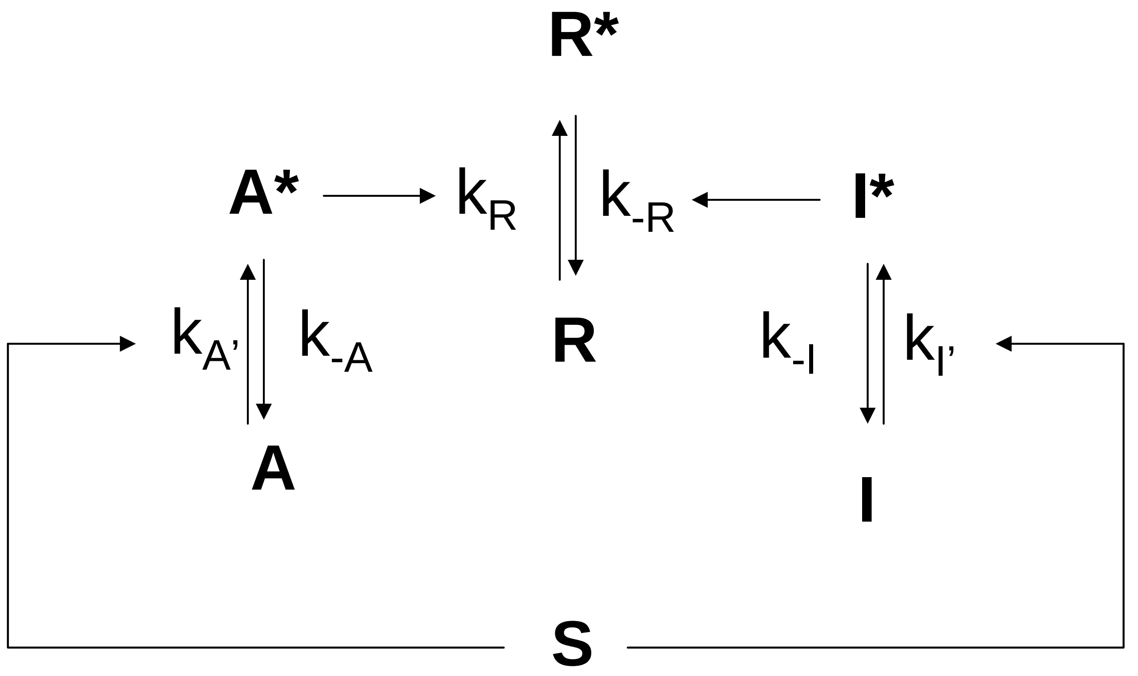
Molecules ??

Image removed due to copyright considerations. See Levchenko, A., and P. A. Iglesias. "Models of eukaryotic gradient sensing: application to chemotaxis of amoebae and neutrophils." *Biophys J*. 82 (1 Pt 1)(Jan 2002): 50-63.

receptor binding $\rightarrow$
G-protein activation $\rightarrow$
activation of PI3K (activator) $\rightarrow$
activation of PTEN (inhibitor) $\rightarrow$
P3 ~ R* (binding PH domains)

Perfect adaptation module:



$$\frac{dR^*}{dt} = -k_{-R} I^* R^* + k_R A^* R$$

$$\frac{dA^*}{dt} = -k_{-A} A^* + k_A^{'} S A = -k_{-A} A^* + k_A^{'} S (A_{tot} - A^*)$$

$$\frac{dI^*}{dt} = -k_{-I} I^* + k_I^{'} S I = -k_{-I} I^* + k_I^{'} S (I_{tot} - I^*)$$

Main assumption: k_{-A} & k_{-I} >> k'_A & k'_I (A_{tot}>>A*, I_{tot}>>I*)

$$\frac{dR^*}{dt} = -k_{-R} I^* R^* + k_R A^* R$$

$$\frac{dA^*}{dt} = -k_{-A} A + k_A S$$

$$\frac{dI^*}{dt} = -k_{-I} I + k_I S$$

$$k_A^{'} = k_A A_{tot}$$

$$k_I^{'} = k_I I_{tot}$$

Steady state:

$$A_{ss}^{*} = \frac{k_A}{k_{-A}} S$$

$$I_{ss}^{*} = \frac{k_I}{k_{-I}} S$$

$$R_{ss}^{*} = \frac{k_R A_{ss}^{*} / I_{ss}^{*}}{k_R A_{ss}^{*} / I_{ss}^{*} + k_{-R}}$$

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for the rest of the calculations

ignore ‘*’ for I and A !

Now introduce diffusion:

- only I diffuses, other components are local

$$\frac{\partial I(x,t)}{\partial t} = -k_{-I} I(x,t) + k_I S(x,t) + D \frac{\partial^2 I(x,t)}{\partial x^2}$$

- assume signal S varies linearly with S

$$S(x) = s_o + s_1 x$$

- no flux boundary conditions for I

$$\frac{\partial I(0,t)}{\partial x} = \frac{\partial I(1,t)}{\partial x} = 0$$

in steady state,this system can be solved analytically !

$$\frac{\partial I(x,t)}{\partial t} = -k_{-I} I(x,t) + k_I S(x,t) + D \frac{\partial^2 I(x,t)}{\partial x^2}$$

steady-state:

$$\frac{\partial^2 I(x)}{\partial x^2} = \frac{k_{-I}}{D} I(x) - \frac{k_I}{D}\left[s_o + s_1 x\right]$$

$$\frac{\partial^2 I(x)}{\partial x^2} = aI(x) - b - cx$$

MATLAB can solve this for you:

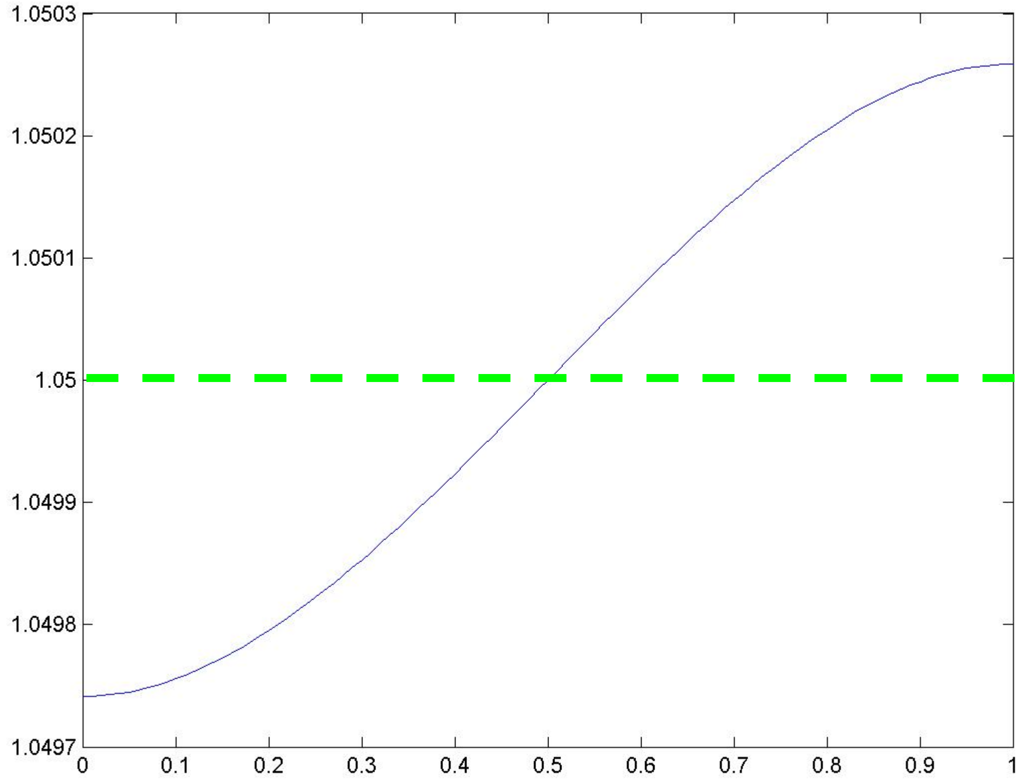
```
>> dsolve('D2x=a*x-b-c*t','Dx(0)=0,Dx(1)=0')

ans =

(b+c*t)/a+c*(-1+cosh(a^(1/2)))/a^(3/2)/sinh(a^(1/2))*cosh(a^(1/2)*t)
-c/a^(3/2)*sinh(a^(1/2)*t)
```

$$I(x) = \frac{k_I}{k_{-I}}\left(s_o + s_1\left(x - \frac{\sinh \sigma x}{\sigma} + \frac{\cosh \sigma x}{\sigma}\frac{\cosh \sigma - 1}{\sinh \sigma}\right)\right)$$

I(x)



x

$k_I/k_{-I}=1$

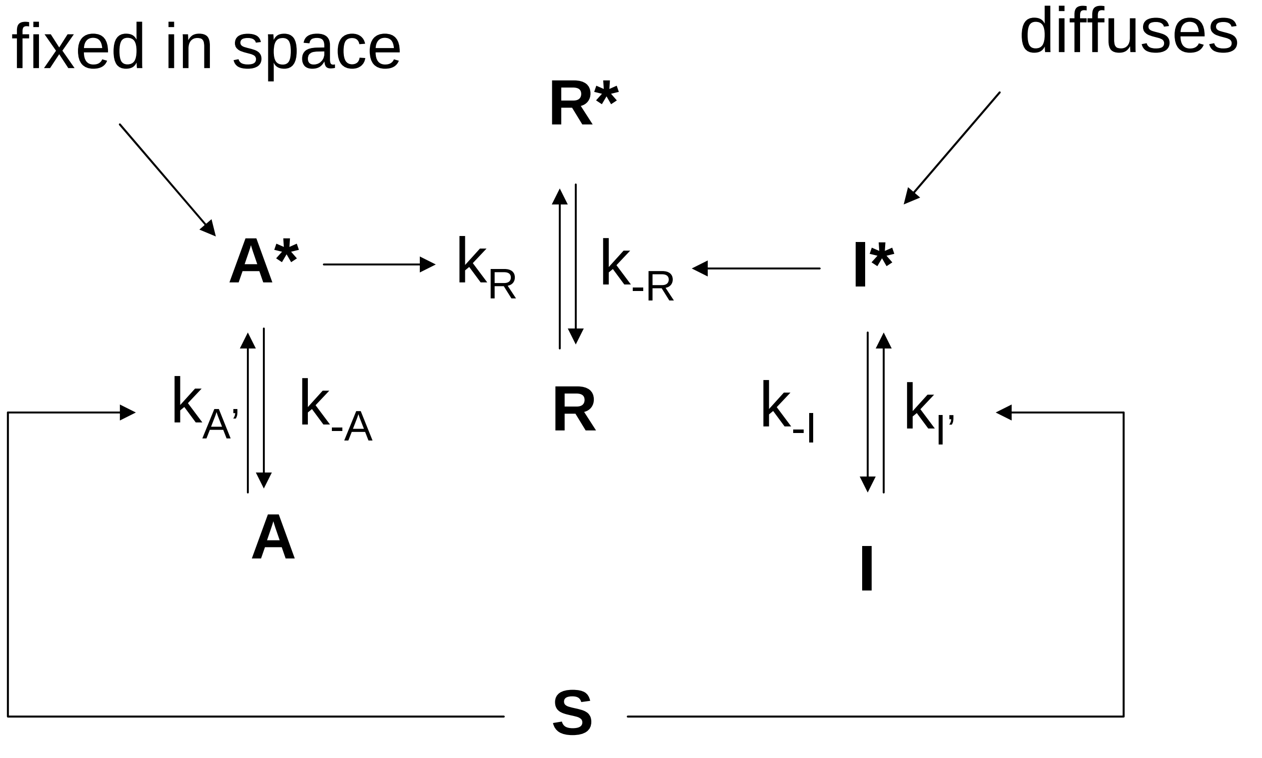
$s_0=1\ \mu M$

$s_1=0.1\ \mu M$

$\sigma=0.25\ (\mu m)^{-1}$

$$\sigma \equiv \sqrt{k_{-I}/D}$$

Remember: Perfect adaptation module:



Steady state:

$$A_{ss}^{*} = \frac{k_A}{k_{-A}} S$$

$$I_{ss}^{*} = \frac{k_I}{k_{-I}} S$$

$$R_{ss}^{*} = \frac{k_R A_{ss}^{*} / I_{ss}^{*}}{k_R A_{ss}^{*} / I_{ss}^{*} + k_{-R}}$$

independent of S,
perfect adaptation

A does not diffuse, so
A(x) directly reflects S(x)

For finding R* only the ratio A/I is important

$$A(x) = \frac{k_A}{k_{-A}}\left(s_o + s_1 x\right)$$

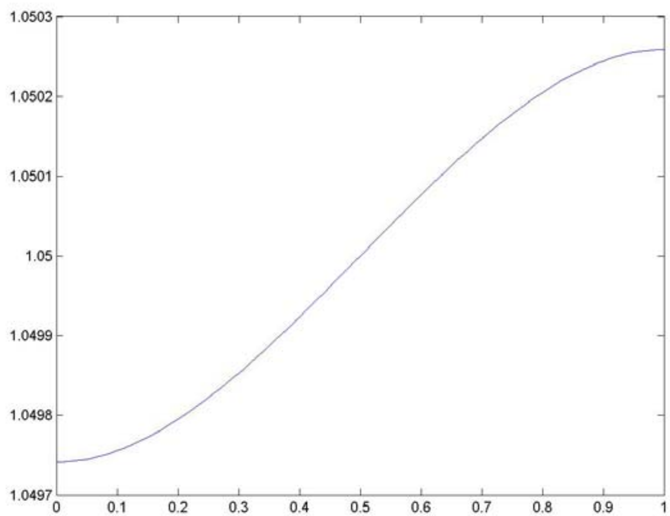
$$I(x) = \frac{k_I}{k_{-I}}\left(s_o + s_1\left(x - \frac{\sinh \sigma x}{\sigma} + \frac{\cosh \sigma x}{\sigma} \frac{\cosh \sigma - 1}{\sinh \sigma} \right)\right)$$

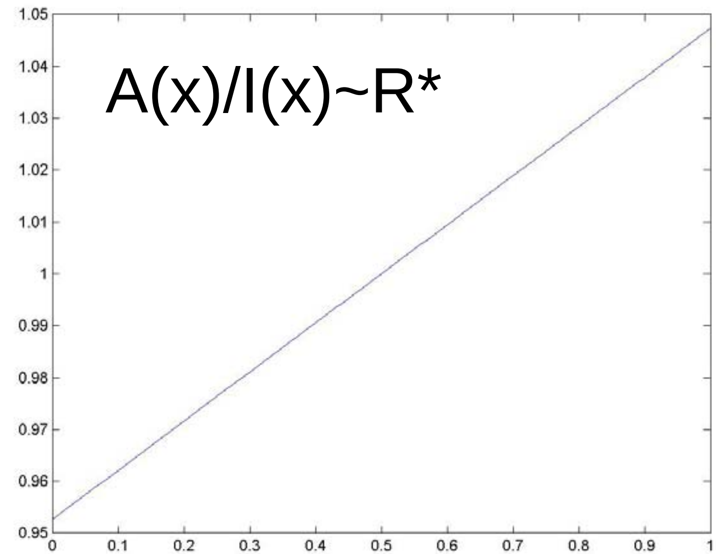
$$\frac{A(x)}{I(x)} = \frac{k_A k_{-I}}{k_{-A} k_I}\left(1 + \frac{s_1}{s_0 + s_1 x}\left(\frac{\cosh \sigma x}{\sigma} \frac{\cosh \sigma - 1}{\sinh \sigma} - \frac{\sinh \sigma x}{\sigma} \right)\right)^{-1}$$

small $\sigma \equiv \sqrt{k_{-I} / D} \sim 0.4$

well mixed, A/I directly reflects signal

I(x)





x

x

$$I(x) = I(\bar{S}) = const$$

$$A(x) = A(S)$$

$$R^*(x) = A(S) / I(\bar{S})$$