Review

Turing-Gierer-Meinhardt models

Local excitation, global inhibition

$$\frac{\partial a}{\partial t} = r_a + k_a \frac{a^2}{i} - \gamma_a a + D_a \frac{\partial^2 a}{\partial x^2}$$

$$\frac{\partial i}{\partial t} = k_i a^2 - \gamma_i i + D_i \frac{\partial^2 i}{\partial x^2}$$

variables

a: concentration activator
i: concentration inhibitor
t: time
x: position

constants (parameters)

r_a: basal activator synthesis rate
k_a, k_i: rate constant for synthesis
γ_a,γ_i : decay rates
D_a, D_i: diffusion constants

$$\frac{\partial a}{\partial t} = r_a + k_a \frac{a^2}{i} - \gamma_a a + D_a \frac{\partial^2 a}{\partial x^2}$$

$$\frac{\partial i}{\partial t} = k_i a^2 - \gamma_i i + D_i \frac{\partial^2 i}{\partial x^2}$$

choose dimensionless variable

normalize 4 variables

$$\frac{\partial A}{\partial \tau} = 1 + R\frac{A^2}{I} - A + \frac{\partial^2 A}{\partial s^2}$$

$$\frac{\partial I}{\partial \tau} = Q\left(A^2 - I\right) + P\frac{\partial^2 I}{\partial s^2}$$

homogeneous solution

$\partial / \partial s = \partial / \partial t = 0$

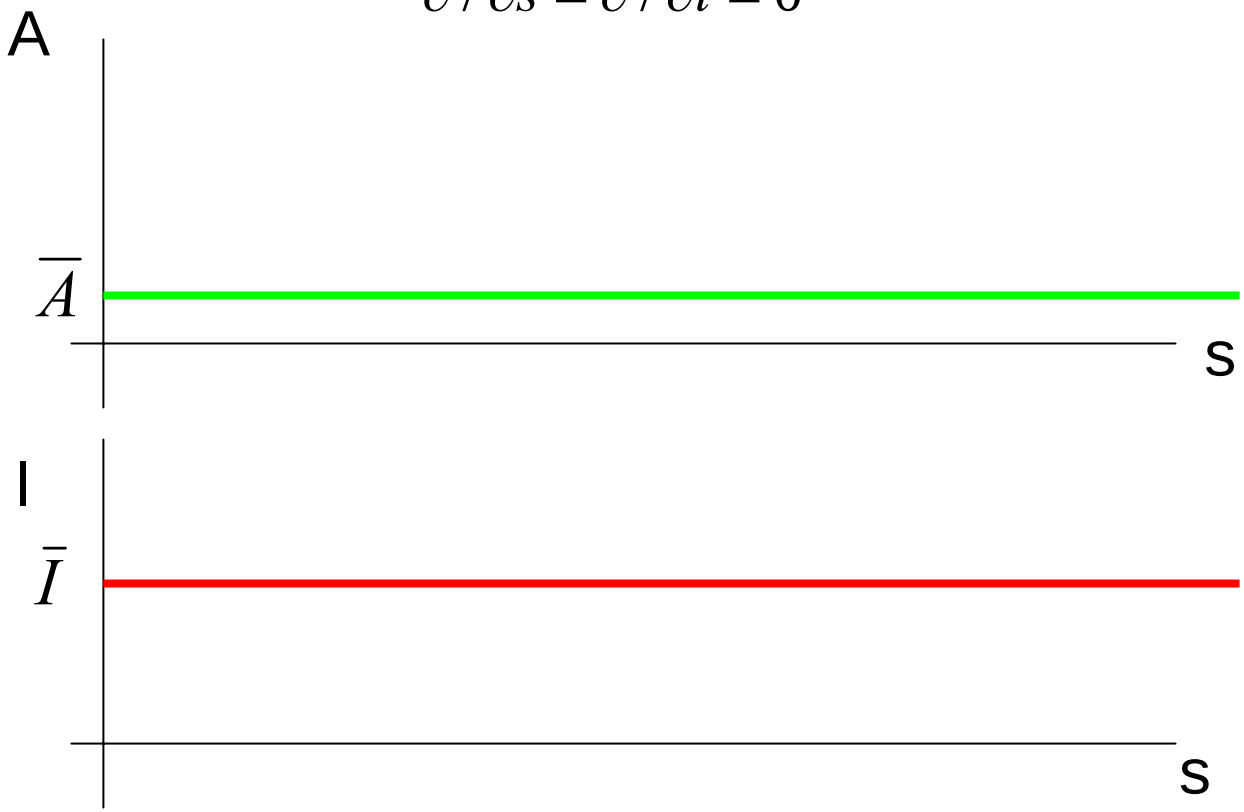
$$\bar{A} = R + 1$$

$$\bar{I} = (R+1)^2$$

only one fixed point, since both A and I >0

homogeneous solution

$$\partial / \partial s = \partial / \partial t = 0$$



stability of homogeneous solution

$$\begin{bmatrix} \frac{2R\bar{A}}{\bar{I}} - 1 & -\frac{R\bar{A}^2}{\bar{I}^2} \\ 2\bar{A}Q & -Q \end{bmatrix} = \begin{bmatrix} \frac{R-1}{R+1} & -\frac{R}{(R+1)^2} \\ 2(R+1)Q & -Q \end{bmatrix}$$

trace < 0
det > 0

$$\downarrow$$

$$\frac{R-1}{R+1} < Q$$

$$Q > 0$$

or in general
real part of eigenvalues > 0

inhomogeneous solution:

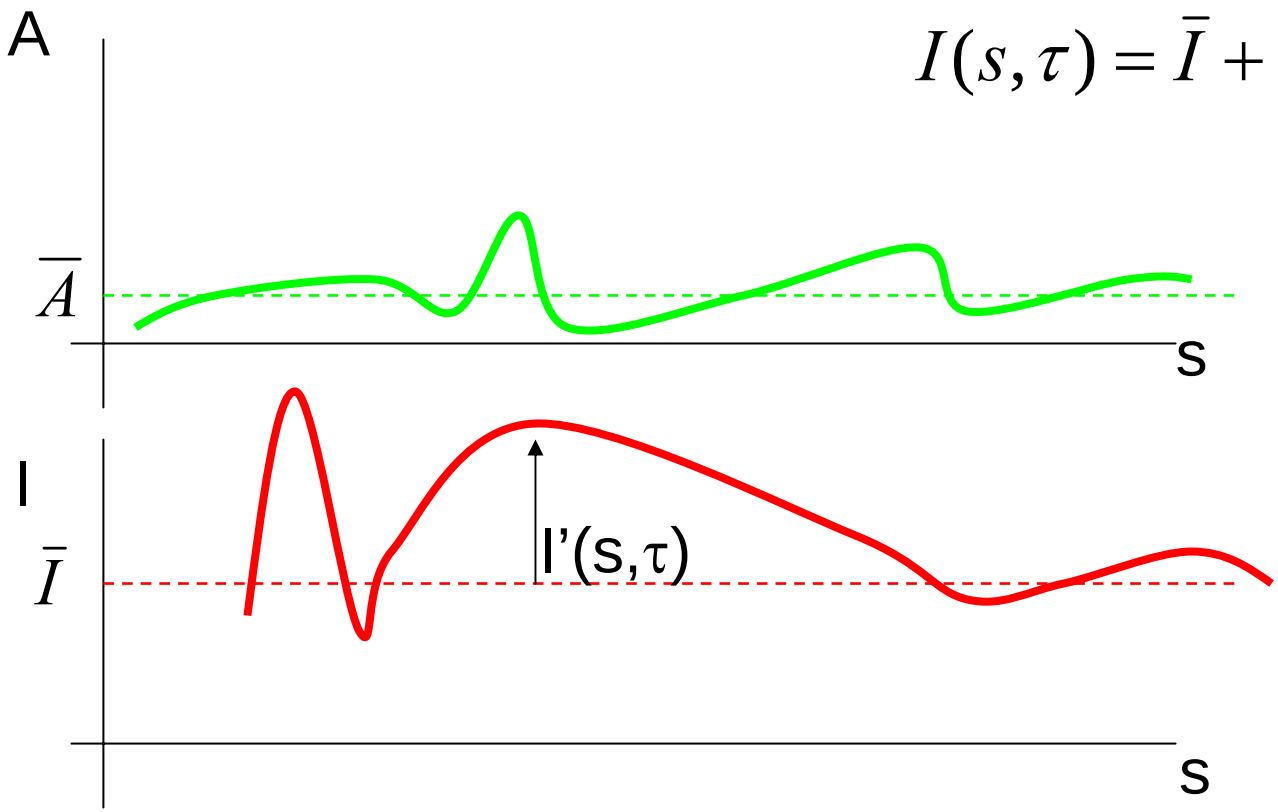
$$A(s,\tau) = \bar{A} + A'(s,\tau)$$

$$I(s,\tau) = \bar{I} + I'(s,\tau)$$

inhomogeneous solution

$$A(s,\tau) = \overline{A} + A'(s,\tau)$$

$$I(s,\tau) = \bar{I} + I'(s,\tau)$$



$$A(s,\tau) = \overline{A} + A'(s,\tau)$$
$$I(s,\tau) = \overline{I} + I'(s,\tau)$$

$\longrightarrow$

$$\frac{\partial A'}{\partial \tau} = \frac{R-1}{R+1} A' - \frac{R}{(1+R)^2} I' + \frac{\partial^2 A'}{\partial s^2}$$
$$\frac{\partial I'}{\partial \tau} = 2Q(1+R)A' - QI' + P\frac{\partial^2 I'}{\partial s^2}$$

trial solution:

$$A'(s,\tau) = \hat{A}(\tau)\cos(\frac{s}{\ell})$$
$$I'(s,\tau) = \hat{I}(\tau)\cos(\frac{s}{\ell})$$

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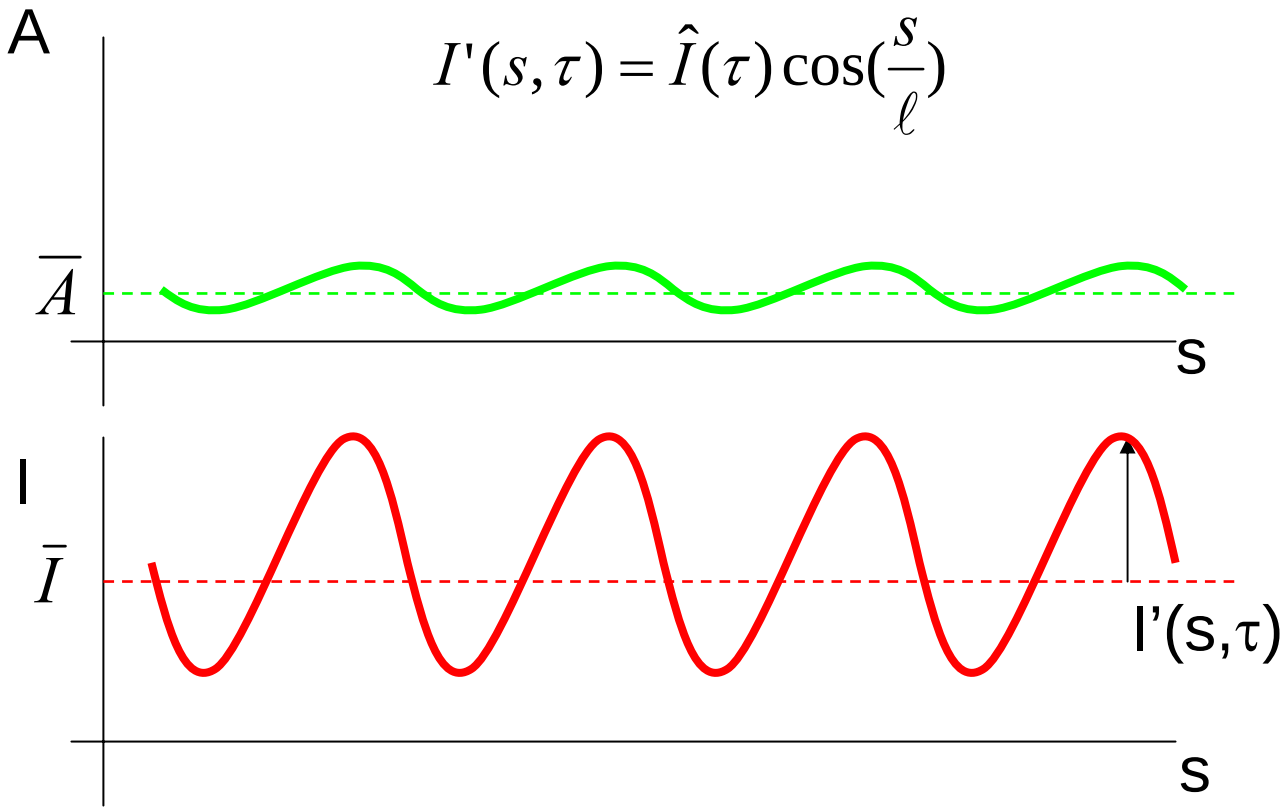
$$I'(s,\tau) = \hat{I}(\tau)\cos(\frac{s}{\ell})$$



$$A(s,\tau) = \overline{A} + A'(s,\tau)$$

$$I(s,\tau) = \bar{I} + I'(s,\tau)$$

$$A'(s,\tau) = \hat{A}(\tau)\cos(\frac{s}{\ell})$$

$$I'(s,\tau) = \hat{I}(\tau)\cos(\frac{s}{\ell})$$

$$\longrightarrow$$

$$\frac{d\hat{A}}{d\tau} = \left(\frac{R-1}{R+1} - \frac{1}{\ell^2}\right)\hat{A} - \frac{R}{(1+R)^2}\hat{I}$$

$$\frac{d\hat{I}}{d\tau} = 2Q(1+R)\hat{A} - \left(Q + \frac{P}{\ell^2}\right)\hat{I}$$

stability inhomogeneous solution

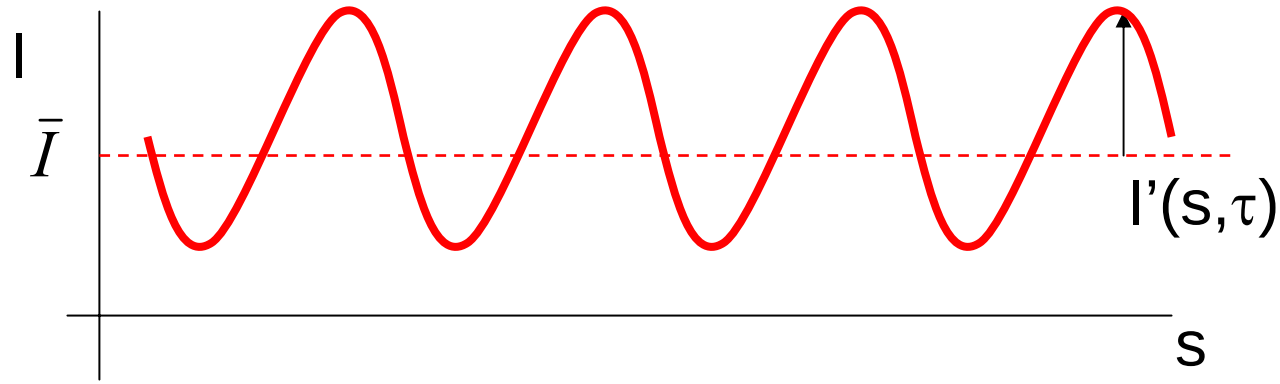
$$-\left(\frac{R-1}{R+1} - \frac{1}{\ell^2}\right)\left(Q + \frac{P}{\ell^2}\right) + \frac{2QR}{1+R} > 0$$

$$Q + \frac{P}{\ell^2} - \left(\frac{R-1}{R+1} - \frac{1}{\ell^2}\right) < 0$$

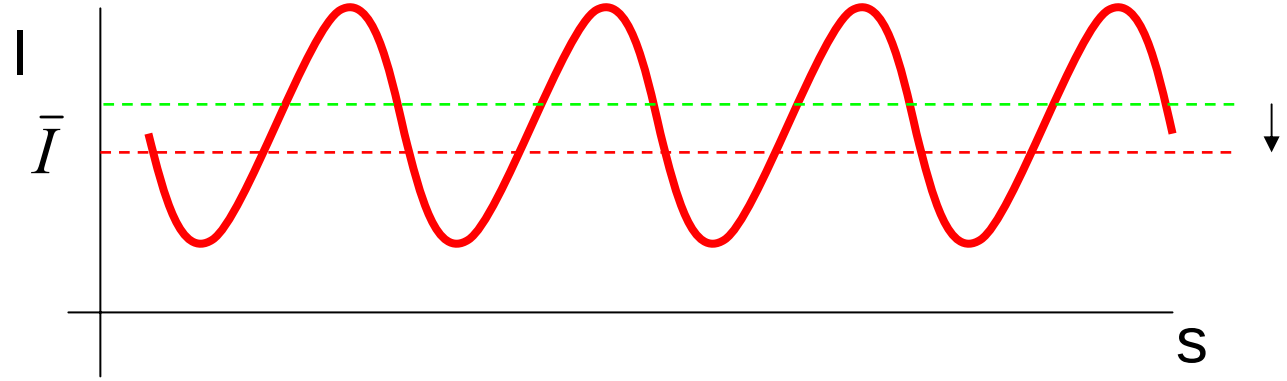
$$\longrightarrow \quad \frac{Q}{P} > \frac{R-1}{R+1}$$

homogeneous stability: $$Q > \frac{R-1}{R+1}$$

stability against spatial distrubance: $$\frac{Q}{P} > \frac{R-1}{R+1}$$

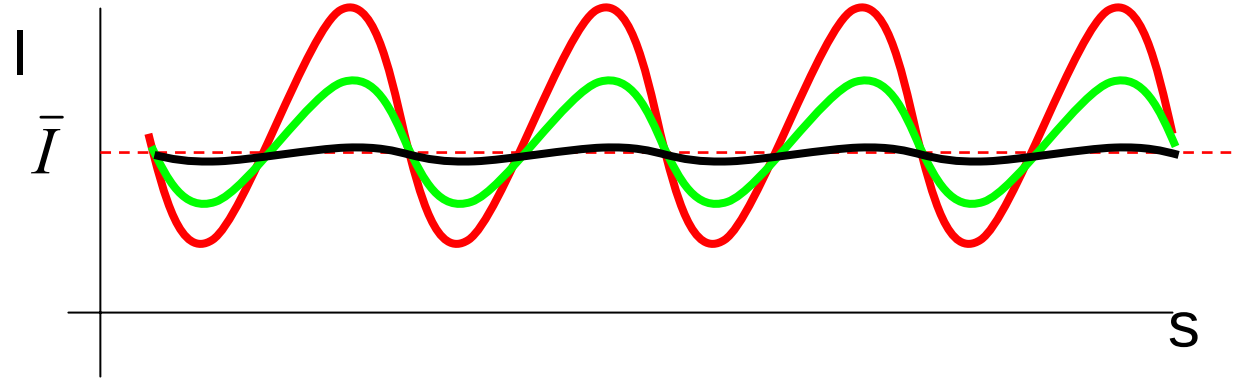


if P < 1 (D_i<D_a), systems is always stable, against any perturbation both spatial and temporal



homogeneously stable:

$\bar{I}$ relaxes back to previous value after small uniform disturbance



stable against spatial disturbance:

I' relaxes back to $\bar{I}$ after small spatial disturbance

Introducing the molecules:

- **FtsZ** function: Assembly of a polymeric ring of the tubulin-like GTPase FtsZ (Z ring).

The Z-ring is localized to the center by the actions of the **MinC**, **MinD**, and **MinE** proteins.

- **MinC** inhibits the initiation of the Z ring.
  MinC colocalizes with **MinD**.
  In wild-type (WT) cells, MinC/D forms a polar pattern that oscillates between the poles, keeping the center free for initiation of cell division.

Thus, virtually all of **MinC/D** dynamically assembles on the membrane in the shape of a test tube covering the membrane from one pole up to approximately midcell.

Most of **MinE** accumulates at the rim of this tube, in the shape of a ring (the E ring). The rim of the **MinC/D** tube and associated E ring move from a central position to the cell pole until both the tube and ring vanish. Meanwhile, a new **MinC/D** tube and associated E ring form in the opposite cell half, and the process repeats, resulting in a pole-to-pole oscillation cycle of the division inhibitor.
A full cycle takes about 50 s.

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How does this work ?

modeling efforts:

- Meinhardt and de Boer, *PNAS* **98**, 14202 (2001);
- Howard *et al*., *Phys. Rev. Let.* **87**, 278102 (2001);
- Kruse, *Biophys. J.* **82**, 618 (2002);
- Huang, Meir, and Wingreen, *PNAS* **100**, 12724 (2003).

Summary of main functions of proteins:

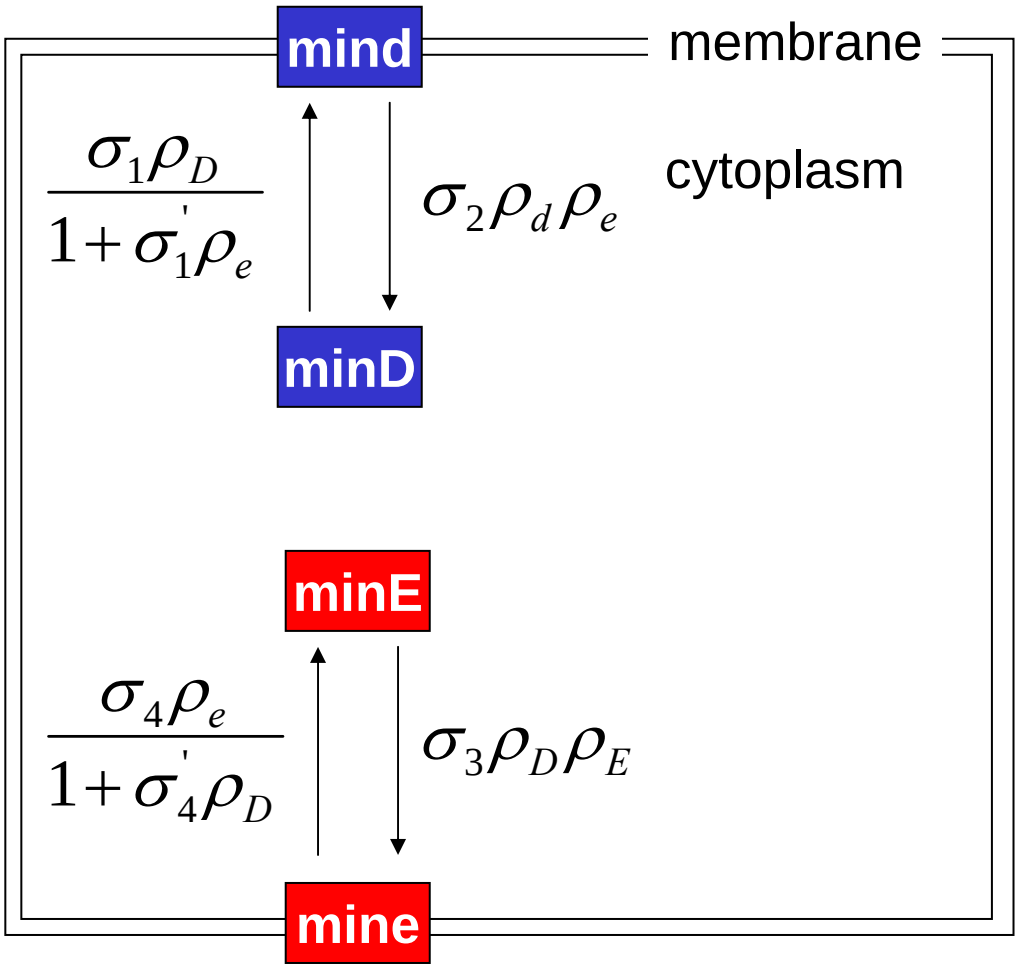
polymerizes in a contractile Z-ring that initiates septum formation

inhibits formation of Z-ring

membrane associated protein that recruits minC and minE to membrane

ejects minC/minD from membrane into cytoplasm

Howard et al. model (PRL)

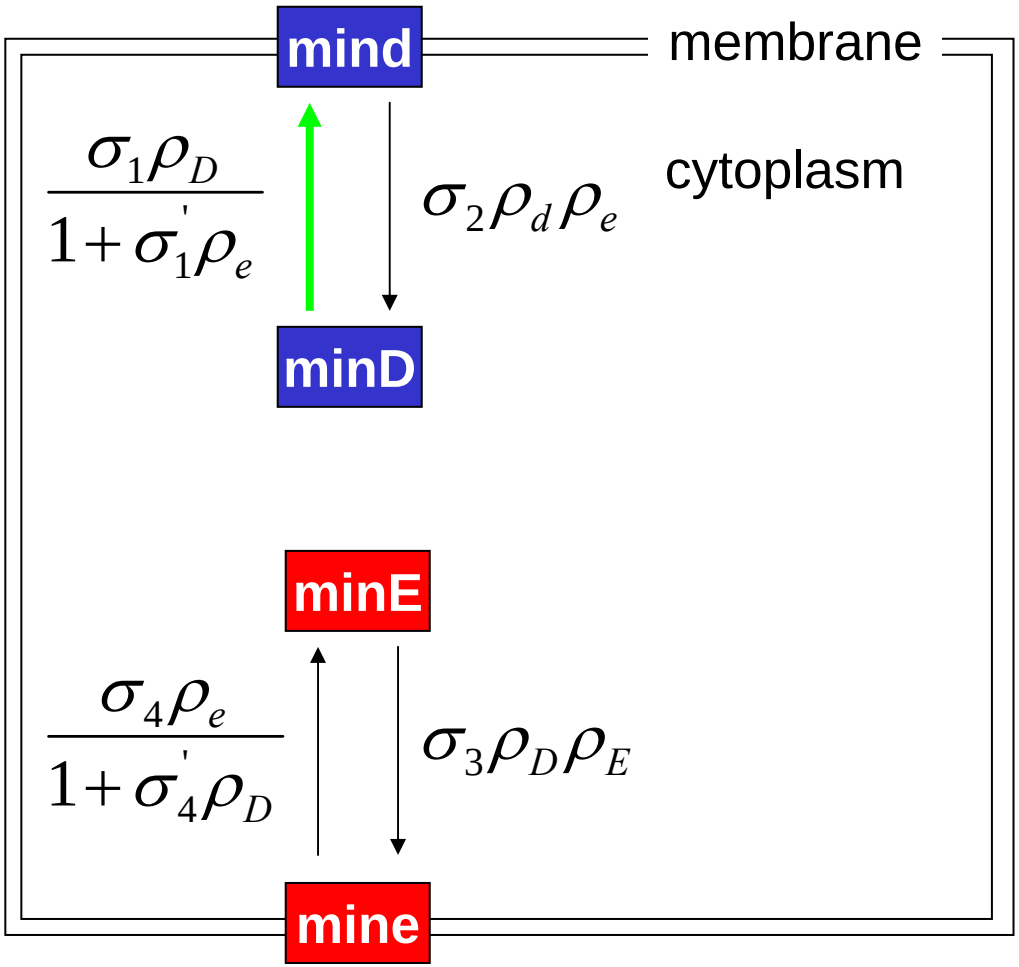


in words:

- first order reactions for own species
- **e** inhibits membrane association of **D** (MM)
- **e** enhances membrane dissociation of **d** (linear)
- **D** enhances membrane association of **E** (recruitment, linear)
- **D** inhibits membrane dissociation of **E** (MM)

- **d** and **e** do not diffuse
- **D** and **E** diffuse

Howard et al. model (PRL)

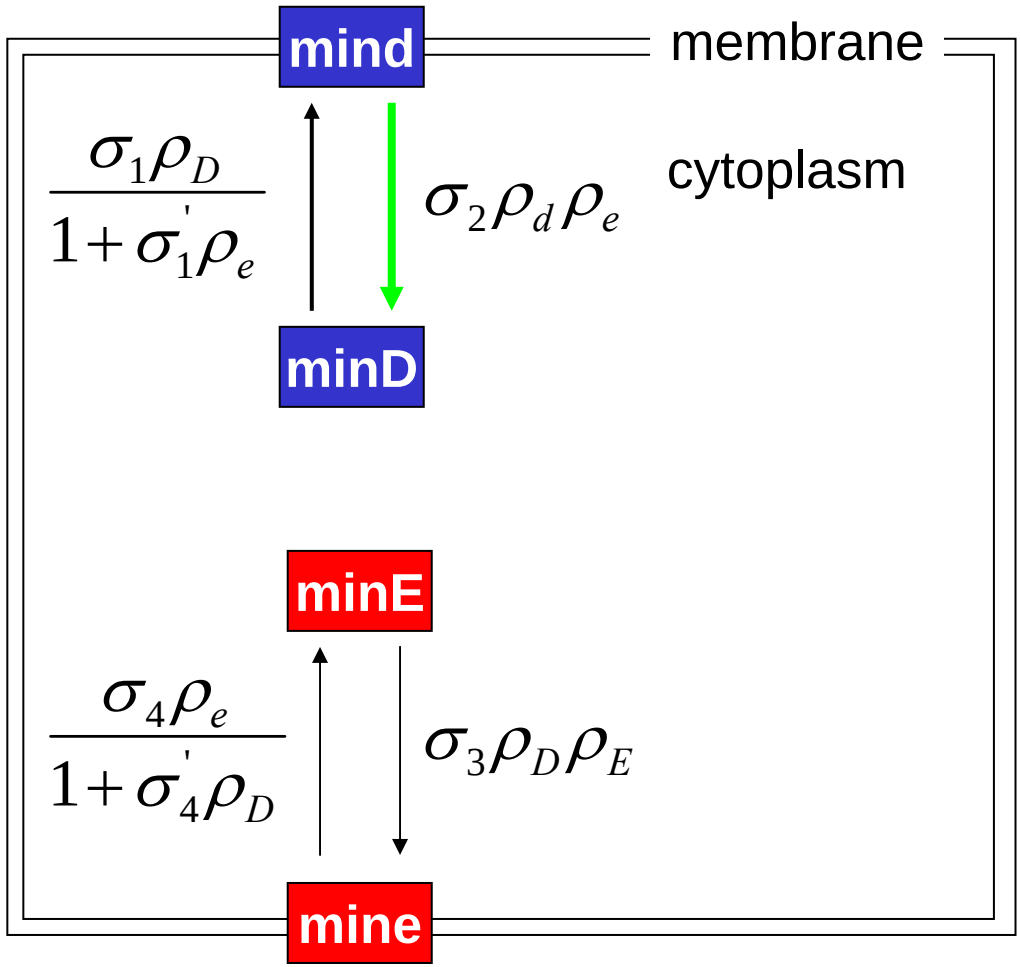


association of cytoplasmic minD with membrane is inhibited by mine in membrane MM takes care of singularity as minE goes to zero.

<u>biological interpretation:</u>

mine in membrane spatially blocks membrane for minD similar to minC blocking FtZ association with membrane

Howard et al. model (PRL)

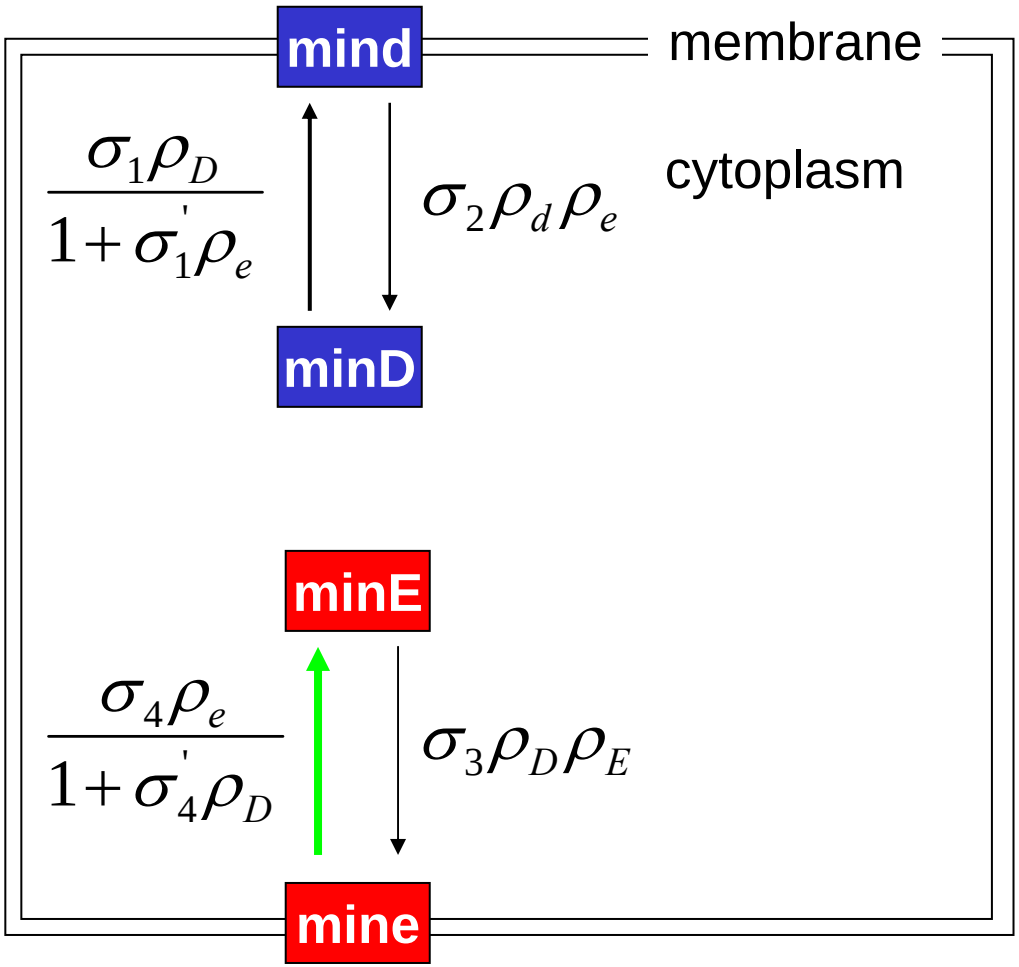


dissociation of membrane mind is stimulated by mine in membrane, after mind is ejected mine stays in membrane

<u>biological interpretation:</u>

binding of mine to mind lowers affinity of mind with membrane but membrane affinity of mine remains unchanged

Howard et al. model (PRL)

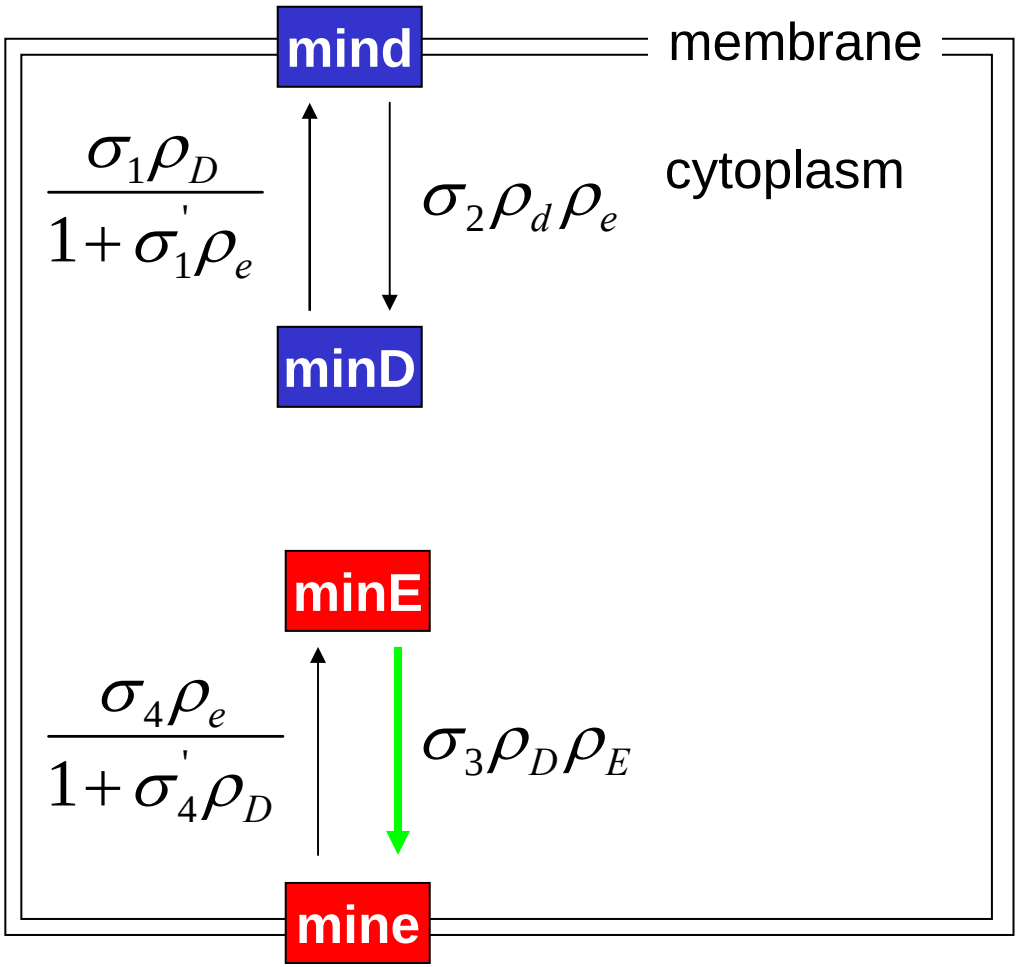


dissociation of membrane
mine is inhibited by minD
in cytoplasm
MM takes care of singularity

<u>biological interpretation:</u>

?

Howard et al. model (PRL)



association of cytoplasmic minE with membrane is stimulated by minD in cytoplasm after delivery of minE to the membrane, minD dives back in the cytoplasm

<u>biological interpretation:</u>

minD-minE complex has high affinity to membrane since the diffusion of this complex doesn't appear in the model it should be very fast.

system of equations:

$$\frac{\partial \rho_D}{\partial t} = D_D \frac{\partial^2 \rho_D}{\partial x^2} - \frac{\sigma_1 \rho_D}{1 + \sigma_1' \rho_e} + \sigma_2 \rho_e \rho_d$$

$$\frac{\partial \rho_d}{\partial t} = \frac{\sigma_1 \rho_D}{1 + \sigma_1' \rho_e} - \sigma_2 \rho_e \rho_d$$

$$\frac{\partial \rho_E}{\partial t} = D_E \frac{\partial^2 \rho_E}{\partial x^2} - \sigma_3 \rho_D \rho_E + \frac{\sigma_4 \rho_e}{1 + \sigma_4' \rho_D}$$

$$\frac{\partial \rho_e}{\partial t} = \sigma_3 \rho_D \rho_E - \frac{\sigma_4 \rho_e}{1 + \sigma_4' \rho_D}$$

stability analysis

1. find fixed point $\frac{\partial}{\partial t} = 0$

(e.g. numerically: how_homog.m) $\frac{\partial}{\partial x} = 0$

different random initial conditions relax to same fixed point

result: one fixed point:

d = 1383 e = 82

D = 117 E = 3

2. find stability matrix (Jacobian)

$$A = \begin{bmatrix} \dfrac{-\sigma_1}{1+\sigma_1' e} & \sigma_2 e & 0 & \dfrac{\sigma_1 D \sigma_1'}{(1+\sigma_1' e)^2} + \sigma_2 d \\ \dfrac{\sigma_1}{1+\sigma_1' e} & -\sigma_2 e & 0 & -\dfrac{\sigma_1 D \sigma_1'}{(1+\sigma_1' e)^2} - \sigma_2 d \\ -\dfrac{\sigma_4 e \sigma_4'}{(1+\sigma_4' D)^2} - \sigma_3 E & 0 & -\sigma_3 D & \dfrac{\sigma_4}{1+\sigma_4' D} \\ +\dfrac{\sigma_4 e \sigma_4'}{(1+\sigma_4' D)^2} + \sigma_3 E & 0 & \sigma_3 D & -\dfrac{\sigma_4}{1+\sigma_4' D} \end{bmatrix}$$

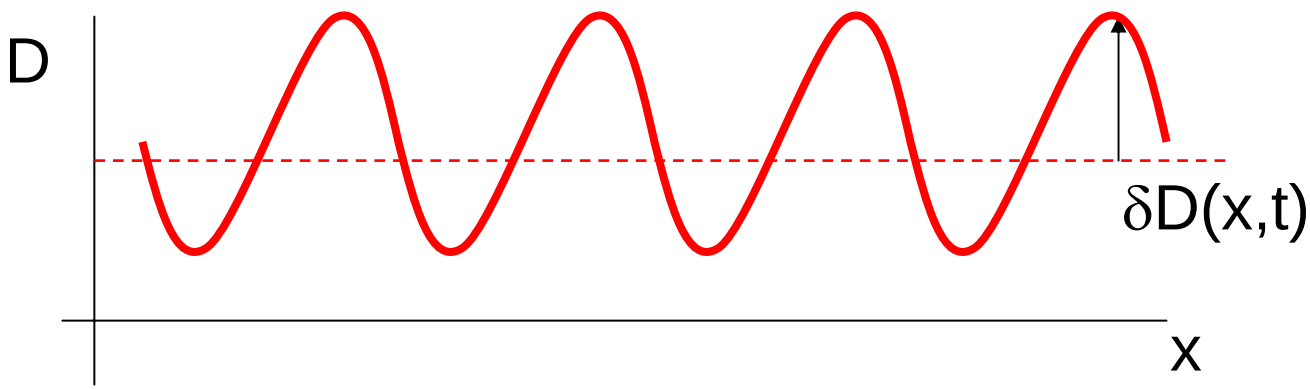
3. test stability of fluctuations around homogeneous solution

$$\delta E(x,t) = \hat{E}(t)\cos(qx)$$

$$\delta e(x,t) = \hat{e}(t)\cos(qx)$$

$$\delta D(x,t) = \hat{D}(t)\cos(qx)$$

$$\delta d(x,t) = \hat{d}(t)\cos(qx)$$

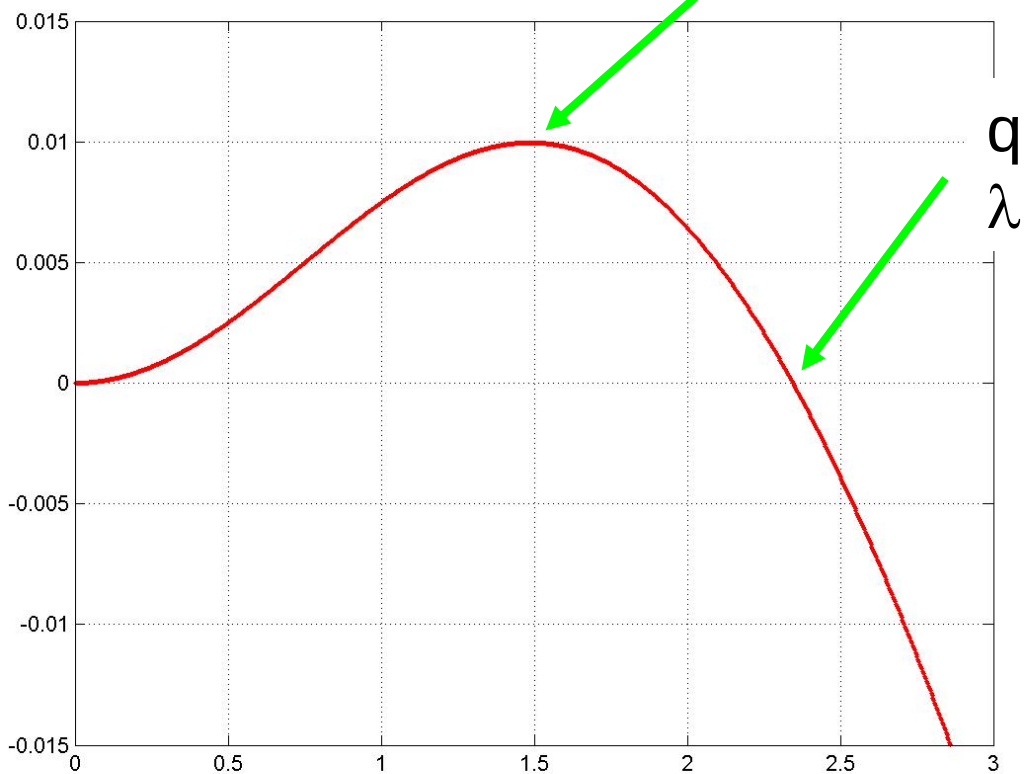


3. test stability of fluctuations around homogeneous solution

$$\hat{A} = \begin{bmatrix} \frac{-\sigma_1}{1+\sigma_1' e} - D_D q^2 & \sigma_2 e & 0 & \frac{\sigma_1 D \sigma_1'}{(1+\sigma_1' e)^2} + \sigma_2 d \\ \frac{\sigma_1}{1+\sigma_1' e} & -\sigma_2 e & 0 & -\frac{\sigma_1 D \sigma_1'}{(1+\sigma_1' e)^2} - \sigma_2 d \\ -\frac{\sigma_4 e \sigma_4'}{(1+\sigma_4' D)^2} - \sigma_3 E & 0 & -\sigma_3 D - D_E q^2 & \frac{\sigma_4}{1+\sigma_4' D} \\ +\frac{\sigma_4 e \sigma_4'}{(1+\sigma_4' D)^2} + \sigma_3 E & 0 & \sigma_3 D & -\frac{\sigma_4}{1+\sigma_4' D} \end{bmatrix}$$

4. - determine eigenvalues of stability matrix,
- find real part of eigenvalues,
- plot the largest as a function of q.
(e.g. how_eig.m)

$q = 1.5\ (\mu m)^{-1}$
$\lambda = 2\pi/q = 4.2\ \mu m$



$q = 2.3\ (\mu m)^{-1}$
$\lambda = 2\pi/q = 2.7\ \mu m$

Howard *et al.*: Results

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Huang, Meir, and Wingreen, *PNAS* **100**, 12724 (2003).

main differences:

- ATP cycle
- 1D versus 3D (projected on 2D)

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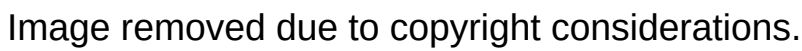
ρ_d: membrane bound minD:ATP complexes
ρ_{de}: membrane bound minD:minE:ATP complexes
$\rho_{D:ADP}$: concentration cytoplasmic minD bound to ADP
$\rho_{D:ATP}$:concentration cytoplasmic minD bound to ATP
ρ_E : concentration cytoplasmic minE

only minD-ATP can associate with membrane
minE only binds minD-ATP oligomers in membrane
only minD-minE-ATPcomplex can dissociate from membrane

Reaction 1:

minD-ATP binds both linearly and autocatalytically to minD-ATP in membrane



minD forms polymers in membrane

$$\frac{d\rho_{D:ADP}}{dt} = D_D \frac{d^2\rho_{D:ADP}}{dx^2} - \sigma_D^{ADP\to ATP}\rho_{D:ADP} + \sigma_{de}\rho_{de}$$

$$\frac{d\rho_{D:ATP}}{dt} = D_D \frac{d^2\rho_{D:ATP}}{dx^2} + \sigma_D^{ADP\to ATP}\rho_{D:ADP} - \left[\sigma_D + \sigma_{dD}\left(\rho_d + \rho_{de}\right)\right]\rho_{D:ATP}$$

$$\frac{d\rho_E}{dt} = D_E \frac{d^2\rho_E}{dx^2} + \sigma_{de}\rho_e - \sigma_E\rho_d\rho_E$$

$$\frac{d\rho_d}{dt} = -\sigma_E\rho_d\rho_E + \left[\sigma_D + \sigma_{dD}\left(\rho_d + \rho_{de}\right)\right]\rho_{D:ATP}$$

$$\frac{d\rho_{de}}{dt} = -\sigma_{de}\rho_{de} + \sigma_E\rho_d\rho_E$$

Reaction 2:

minE binds minD-ATP in membrane
~ [minE]*[mind]

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$$\frac{d\rho_{D:ADP}}{dt} = D_D \frac{d^2\rho_{D:ADP}}{dx^2} - \sigma_D^{ADP\rightarrow ATP}\rho_{D:ADP} + \sigma_{de}\rho_{de}$$

$$\frac{d\rho_{D:ATP}}{dt} = D_D \frac{d^2\rho_{D:ATP}}{dx^2} + \sigma_D^{ADP\rightarrow ATP}\rho_{D:ADP} - \left[\sigma_D + \sigma_{dD}\left(\rho_d + \rho_{de}\right)\right]\rho_{D:ATP}$$

$$\frac{d\rho_E}{dt} = D_E \frac{d^2\rho_E}{dx^2} + \sigma_{de}\rho_e - \sigma_E\rho_d\rho_E$$

$$\frac{d\rho_d}{dt} = -\sigma_E\rho_d\rho_E + \left[\sigma_D + \sigma_{dD}\left(\rho_d + \rho_{de}\right)\right]\rho_{D:ATP}$$

$$\frac{d\rho_{de}}{dt} = -\sigma_{de}\rho_{de} + \sigma_E\rho_d\rho_E$$

Reaction 3:

minD-minE-ATP complex disassociates from membrane hydrolyzing ATP
~ [mine]

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$$\frac{d\rho_{D:ADP}}{dt} = D_D \frac{d^2\rho_{D:ADP}}{dx^2} - \sigma_D^{ADP\rightarrow ATP}\rho_{D:ADP} + \sigma_{de}\rho_{de}$$

$$\frac{d\rho_{D:ATP}}{dt} = D_D \frac{d^2\rho_{D:ATP}}{dx^2} + \sigma_D^{ADP\rightarrow ATP}\rho_{D:ADP} - \left[\sigma_D + \sigma_{dD}\left(\rho_d + \rho_{de}\right)\right]\rho_{D:ATP}$$

$$\frac{d\rho_E}{dt} = D_E \frac{d^2\rho_E}{dx^2} + \sigma_{de}\rho_{de} - \sigma_E\rho_d\rho_E$$

$$\frac{d\rho_d}{dt} = -\sigma_E\rho_d\rho_E + \left[\sigma_D + \sigma_{dD}\left(\rho_d + \rho_{de}\right)\right]\rho_{D:ATP}$$

$$\frac{d\rho_{de}}{dt} = -\sigma_{de}\rho_{de} + \sigma_E\rho_d\rho_E$$

Reaction 4:

charging of minD in cytoplasm
from ADP to ATP bound

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$$\frac{d\rho_{D:ADP}}{dt} = D_D \frac{d^2\rho_{D:ADP}}{dx^2} - \sigma_D^{ADP\rightarrow ATP}\rho_{D:ADP} + \sigma_{de}\rho_{de}$$

$$\frac{d\rho_{D:ATP}}{dt} = D_D \frac{d^2\rho_{D:ATP}}{dx^2} + \sigma_D^{ADP\rightarrow ATP}\rho_{D:ADP} - \left[\sigma_D + \sigma_{dD}\left(\rho_d + \rho_{de}\right)\right]\rho_{D:ATP}$$

$$\frac{d\rho_E}{dt} = D_E \frac{d^2\rho_E}{dx^2} + \sigma_{de}\rho_{de} - \sigma_E\rho_d\rho_E$$

$$\frac{d\rho_d}{dt} = -\sigma_E\rho_d\rho_E + \left[\sigma_D + \sigma_{dD}\left(\rho_d + \rho_{de}\right)\right]\rho_{D:ATP}$$

$$\frac{d\rho_{de}}{dt} = -\sigma_{de}\rho_{de} + \sigma_E\rho_d\rho_E$$

$$\frac{d\rho_D}{dt} = \mathrm{D}_D \frac{d^2\rho_D}{dx^2} - \sigma_A \rho_D + \sigma_P \rho_{D:ADP}$$

$$\frac{d\rho_d}{dt} = \left(\sigma_D + s_d \rho_d\right)\rho_{D:ATP} - \sigma_e \rho_e$$

$$\frac{d\rho_{D:ATP}}{dt} = \mathrm{D}_D \frac{d^2\rho_{D:ATP}}{dx^2} - \left(\sigma_D + s_d \rho_d\right)\rho_{D:ATP} + \sigma_A \rho_D$$

$$\frac{d\rho_e}{dt} = \sigma_{dE}\left(\rho_d - \rho_e\right)\rho_E - \sigma_e \rho_e$$

$$\frac{d\rho_E}{dt} = \mathrm{D}_E \frac{d^2\rho_E}{dx^2} - \sigma_{dE}\left(\rho_d - \rho_e\right)\rho_E + \sigma_e \rho_e$$

$$\frac{d\rho_{D:ADP}}{dt} = \mathrm{D}_D \frac{d^2\rho_{D:ADP}}{dx^2} - \sigma_P \rho_{D:ADP} + \sigma_e \rho_e$$