PS#4 due today (in class or before 3pm, Rm. 68-371)

**Topic I: Systems Cell Biology**

**Spatial oscillation in E. coli**

similar to genetic oscillators, but now we cannot ignore the spatial dimensions

**biological function:**

determine the center of the cell, to prepare for proper cell division

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**How does this work?**

**modeling efforts:**

- Meinhardt and de Boer, *PNAS* **98**, 14202 (2001);
- Kruse, *Biophys. J.* **82**, 618 (2002);

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**Summary of main functions of proteins:**

- **FtsZ** polymerizes in a contractile Z-ring that initiates septum formation
- **MinC** inhibits formation of Z-ring
- **MinD** membrane associated protein that recruits minC and minE to membrane
- **MinE** 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

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

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

Howard et al. model (PRL)

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

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Howard et al. model (PRL)

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

biological interpretation:
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.

stability analysis

1. find fixed point
\[ \frac{\partial}{\partial t} = 0 \]
\[ \frac{\partial}{\partial x} = 0 \]
(e.g. numerically: how_homog.m)
different random initial conditions relax to same fixed point
result: one fixed point:
\[ d = 1383 \quad e = 82 \]
\[ D = 117 \quad E = 3 \]

2. find stability matrix (Jacobian)
\[
A = \begin{bmatrix}
-\frac{\sigma_1}{1+\sigma_1 e} & \sigma_2 e & 0 & \frac{\sigma_1 D \rho_d}{1+\sigma_1 e^2} + \sigma_2 e \\
\frac{\sigma_1}{1+\sigma_1 e} & -\sigma_2 e & 0 & -\frac{\sigma_1 D \rho_d}{(1+\sigma_1 e)^2} - \sigma_2 d \\
-\frac{\sigma_4 e \sigma_4}{(1+\sigma_1 D)^2} - \sigma_3 E & 0 & -\sigma_3 D & \frac{\sigma_4}{1+\sigma_1 D} \\
+\frac{\sigma_4 e \sigma_4}{(1+\sigma_1 D)^2} + \sigma_3 E & 0 & \sigma_3 D & -\frac{\sigma_4}{1+\sigma_1 D}
\end{bmatrix}
\]
3. Test stability of fluctuations around homogeneous solution

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

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

Howard et al.: Results

**Main differences:**
- ATP cycle
- 1D versus 3D (projected on 2D)

**Symbols and Equations:**

- $\rho_d$: membrane bound minD:ATP complexes
- $\rho_{de}$: membrane bound minD:minE:ATP complexes
- $\rho_{D:ADP}$: concentration cytoplasmic minD bound to ADP
- $\rho_{D:ATP}$: concentration cytoplasmic minD bound to ATP
- $\rho_E$: concentration cytoplasmic minE

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

**Reaction 1:**

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

\[
\frac{d\rho_{D:ADP}}{dt} = \frac{d^2\rho_{D:ADP}}{dx^2} - \sigma_{D:ADP}^\text{ADP->ADP} \rho_{D:ADP} + \sigma_{D:ATP} \rho_{D:ATP} \\
\frac{d\rho_{D:ATP}}{dt} = \frac{d^2\rho_{D:ATP}}{dx^2} + \sigma_{D:ATP}^\text{ATP->ADP} \rho_{D:ADP} - [\sigma_D + \sigma_{D:ATP} (\rho_D + \rho_{ATP})] \rho_{D:ATP} \\
\frac{d\rho_E}{dt} = \frac{d^2\rho_E}{dx^2} + \sigma_{E} \rho_E - \sigma_{E} \rho_D \rho_E \\
\frac{d\rho_d}{dt} = -\sigma_d \rho_d + \sigma_d \rho_D \rho_{S} + \sigma_d \rho_{ADP} \rho_{ADP} \\
\frac{d\rho_{de}}{dt} = -\sigma_{de} \rho_{de} + \sigma_{de} \rho_D \rho_{S} \rho_E
\]
Reaction 2:
minE binds minD-ATP in membrane 
\[ \sim [\text{minE}]^*[\text{minD}] \]

\[
\frac{dp_{D,ATP}}{dt} = D_D \frac{d^2 p_{D,ATP}}{dx^2} - \sigma_D^{ADP\rightarrow ATP} p_{D,ATP} + \sigma_d p_d
\]
\[
\frac{dp_{D,ADP}}{dt} = D_D \frac{d^2 p_{D,ADP}}{dx^2} + \sigma_D^{ADP\rightarrow ATP} p_{D,ADP} - [\sigma_D + \sigma_{ad}(p_d + p_e)] p_{D,ATP}
\]
\[
\frac{dp_E}{dt} = D_E \frac{d^2 p_E}{dx^2} + \sigma_E p_e - \sigma_E p_d p_E
\]
\[
\frac{dp_d}{dt} = -\sigma_E p_d p_E + [\sigma_D + \sigma_{ad}(p_d + p_e)] p_{D,ATP}
\]
\[
\frac{dp_e}{dt} = -\sigma_d p_d + \sigma_E p_d p_E
\]

Reaction 3:
minD-minE-ATP complex disassociates from membrane hydrolyzing ATP 
\[ \sim [\text{minE}] \]

\[
\frac{dp_{D,ATP}}{dt} = D_D \frac{d^2 p_{D,ATP}}{dx^2} - \sigma_D^{ADP\rightarrow ATP} p_{D,ATP} + \sigma_{de} p_d
\]
\[
\frac{dp_{D,ADP}}{dt} = D_D \frac{d^2 p_{D,ADP}}{dx^2} + \sigma_D^{ADP\rightarrow ATP} p_{D,ADP} - [\sigma_D + \sigma_{ad}(p_d + p_e)] p_{D,ATP}
\]
\[
\frac{dp_E}{dt} = D_E \frac{d^2 p_E}{dx^2} + \sigma_E p_e - \sigma_E p_d p_E
\]
\[
\frac{dp_d}{dt} = -\sigma_E p_d p_E + [\sigma_D + \sigma_{ad}(p_d + p_e)] p_{D,ATP}
\]
\[
\frac{dp_e}{dt} = -\sigma_d p_d + \sigma_E p_d p_E
\]

Reaction 4:
charging of minD in cytoplasm from ADP to ATP bound

\[
\frac{dp_{D,ATP}}{dt} = D_D \frac{d^2 p_{D,ATP}}{dx^2} - \sigma_D^{ADP\rightarrow ATP} p_{D,ATP} + \sigma_d p_d
\]
\[
\frac{dp_{D,ADP}}{dt} = D_D \frac{d^2 p_{D,ADP}}{dx^2} + \sigma_D^{ADP\rightarrow ATP} p_{D,ADP} + [\sigma_D + \sigma_{ad}(p_d + p_e)] p_{D,ATP}
\]
\[
\frac{dp_E}{dt} = D_E \frac{d^2 p_E}{dx^2} + \sigma_E p_e - \sigma_E p_d p_E
\]
\[
\frac{dp_d}{dt} = -\sigma_E p_d p_E + [\sigma_D + \sigma_{ad}(p_d + p_e)] p_{D,ATP}
\]
\[
\frac{dp_e}{dt} = -\sigma_d p_d + \sigma_E p_d p_E
\]

Stochastic reaction-diffusion equations:
http://mesord.sourceforge.net/
Comparision of reactions of two models

creation of membrane associated minD

first order +
autocatalytic
(linear, oligomerization)

Huang

removal of membrane associated minD

linear with mine
(e also leaves membrane)

Huang

creation of membrane associated minE

linear with E,
and \( \sim \) to minD
in membrane

membrane recruitment by \( d' \)

Huang

removal of membrane associated minE

linear with mine
minD is not bound
to mine
(inhibited by cytoplasmic minD)

Huang

Howard
What about spherical cells: *Neisseria gonorrhoeae*

minD-ATP oscillates, both no minE ring

Huang and Wingreen

Cells always find the long-axis

Reconstructing minCDE wave in vitro

Reconstructing minCDE wave in vitro