Reminder PS due dates:
PS#4, coming Tuesday 11/15/05
PS#5, Tuesday 11/29/05
Final PS, Tuesday 12/13/05

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

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:

- **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)

- 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

biological interpretation:

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

biological interpretation:

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

biological interpretation:
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.

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.

System of equations:

\[
\begin{align*}
\frac{\partial \rho_d}{\partial t} &= D_d \frac{\partial^2 \rho_e}{\partial x^2} - \frac{\sigma_1 \rho_e}{1 + \sigma_1 \rho_e} + \frac{\sigma_2 \rho_e \rho_d}{1 + \sigma_1 \rho_e} \\
\frac{\partial \rho_e}{\partial t} &= -\frac{\sigma_1 \rho_e}{1 + \sigma_1 \rho_e} - \frac{\sigma_2 \rho_e \rho_d}{1 + \sigma_1 \rho_e} \\
\frac{\partial \rho_D}{\partial t} &= D_E \frac{\partial^2 \rho_E}{\partial x^2} - \frac{\sigma_3 \rho_D \rho_E}{1 + \sigma_4 \rho_D} - \frac{\sigma_4 \rho_E}{1 + \sigma_4 \rho_D} \\
\frac{\partial \rho_E}{\partial t} &= \frac{\sigma_3 \rho_D \rho_E}{1 + \sigma_4 \rho_D} - \frac{\sigma_4 \rho_E}{1 + \sigma_4 \rho_D}
\end{align*}
\]

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:
   - \( d = 1383 \)
   - \( e = 82 \)
   - \( D = 117 \)
   - \( E = 3 \)

2. Find stability matrix (Jacobian):

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

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

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

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

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

\[ \delta D(x,t) \]

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

\[ q = 1.5 \text{ (\mu m)}^{-1} \]
\[ \lambda = \frac{2\pi}{q} = 4.2 \text{ \mu m} \]

\[ q = 2.3 \text{ (\mu m)}^{-1} \]
\[ \lambda = \frac{2\pi}{q} = 2.7 \text{ \mu m} \]

Howard et al.: Results

\[ \hat{A} = \begin{bmatrix} 0 & \frac{-\sigma_1}{1+\sigma_1 e} & \sigma_2 e & 0 & \frac{-\sigma_i D \sigma_i^*}{(1+\sigma_1 e)^2} + \sigma_d \frac{-\sigma_i D \sigma_i^*}{(1+\sigma_1 e)^2} - \sigma_d \frac{\sigma_i D}{1+\sigma_1 D} \\
\frac{-\sigma_1}{1+\sigma_1 e} & 1+\sigma_1 e & -\sigma_2 e & 0 & \frac{-\sigma_i D \sigma_i^*}{(1+\sigma_1 e)^2} + \sigma_d \frac{-\sigma_i D \sigma_i^*}{(1+\sigma_1 e)^2} - \sigma_d \frac{\sigma_i D}{1+\sigma_1 D} \\
\frac{-\sigma_1 e \sigma_4}{(1+\sigma_1 D)^2} & -\sigma_1 e \sigma_4 & 0 & \frac{\sigma_i D}{1+\sigma_1 D} & \frac{\sigma_i D}{1+\sigma_1 D} \\
\frac{-\sigma_1 e \sigma_4}{(1+\sigma_1 D)^2} & +\sigma_1 e \sigma_4 & 0 & \frac{\sigma_i D}{1+\sigma_1 D} & \frac{\sigma_i D}{1+\sigma_1 D} \end{bmatrix} \]
main differences:
- ATP cycle
- 1D versus 3D (projected on 2D)

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

$\rho_d$: 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
minE 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

\[
\begin{align*}
\frac{d\rho_D}{dt} &= D_D \frac{d^2 \rho_D}{dx^2} - \sigma_D \rho_{D:ADP} + \sigma_d \rho_d \\
\frac{d\rho_{D:ATP}}{dt} &= D_D \frac{d^2 \rho_{D:ATP}}{dx^2} + \sigma_D \rho_{D:ADP} - [\sigma_D + \sigma_{de} (\rho_d + \rho_E)] \rho_{D:ATP} \\
\frac{d\rho_E}{dt} &= D_E \frac{d^2 \rho_E}{dx^2} + \sigma_d \rho_d - \sigma_E \rho_d \rho_E \\
\frac{d\rho_{de}}{dt} &= -\sigma_d \rho_{de} + \sigma_{de} \rho_d \rho_E \\
\end{align*}
\]
Reaction 2:
minE binds minD-ATP in membrane
\[ \sim [\text{minE}] \cdot [\text{minD}] \]

\[
\frac{dp_{D,ADP}}{dt} = D_D \frac{d^2 p_{D,ADP}}{dx^2} - \sigma_D^{\text{ADP} \to \text{ATP}} p_{D,ADP} + \sigma_{de} \rho_d
\]

\[
\frac{dp_{D,ATP}}{dt} = D_D \frac{d^2 p_{D,ATP}}{dx^2} + \sigma_D^{\text{ADP} \to \text{ATP}} p_{D,ADP} - [\sigma_d + \sigma_{ad} (\rho_d + \rho_E)] p_{D,ATP}
\]

\[
\frac{dp_E}{dt} = D_e \frac{d^2 p_E}{dx^2} + \sigma_{de} \rho_d - \sigma_{eE} \rho_d \rho_E
\]

\[
\frac{dp_d}{dt} = -\sigma_{eD} \rho_d + \sigma_{dE} \rho_d \rho_E
\]

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

\[
\frac{dp_{D,ADP}}{dt} = D_D \frac{d^2 p_{D,ADP}}{dx^2} - \sigma_D^{\text{ADP} \to \text{ATP}} p_{D,ADP} + \sigma_{de} \rho_d
\]

\[
\frac{dp_{D,ATP}}{dt} = D_D \frac{d^2 p_{D,ATP}}{dx^2} + \sigma_D^{\text{ADP} \to \text{ATP}} p_{D,ADP} - [\sigma_d + \sigma_{ad} (\rho_d + \rho_E)] p_{D,ATP}
\]

\[
\frac{dp_E}{dt} = D_e \frac{d^2 p_E}{dx^2} + \sigma_{de} \rho_d - \sigma_{eE} \rho_d \rho_E
\]

\[
\frac{dp_d}{dt} = -\sigma_{eD} \rho_d + \sigma_{dE} \rho_d \rho_E
\]

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

\[
\frac{dp_{D,ADP}}{dt} = D_D \frac{d^2 p_{D,ADP}}{dx^2} - \sigma_D^{\text{ADP} \to \text{ATP}} p_{D,ADP} + \sigma_{de} \rho_d
\]

\[
\frac{dp_{D,ATP}}{dt} = D_D \frac{d^2 p_{D,ATP}}{dx^2} + \sigma_D^{\text{ADP} \to \text{ATP}} p_{D,ADP} - [\sigma_d + \sigma_{ad} (\rho_d + \rho_E)] p_{D,ATP}
\]

\[
\frac{dp_E}{dt} = D_e \frac{d^2 p_E}{dx^2} + \sigma_{de} \rho_d - \sigma_{eE} \rho_d \rho_E
\]

\[
\frac{dp_d}{dt} = -\sigma_{eD} \rho_d + \sigma_{dE} \rho_d \rho_E
\]

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

creation of membrane associated minD

Huang

Howard

removal of membrane associated minD

Huang

Howard

creation of membrane associated minE

Huang

Howard

removal of membrane associated minE

Huang

Howard
What about spherical cells: *Neisseria gonorrhoeae*

Huang and Wingreen

minD-ATP oscillates, both no minE ring

Stability analysis
Cells always find the long-axis