Tomorrow Recitation Topic
'Reaction-Diffusion Equations'

PS #4 due Next Tuesday
11/15/05

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**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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**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.
gfp-minC

GFP-minD

gfp-minE is localized in a ring

gfp-minE is localized in a ring
FtsZ is necessary for forming the septum

In FtsZ- cells, gfp-MinD also oscillates

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);
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)

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in words:
- first order reactions for own species
- \( e \) interacts with 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:
- binding of mine to minD lowers affinity of minC with membrane but membrane affinity of mine remains unchanged
Howard et al. model (PRL)

**Biological interpretation:**
- Dissociation of membrane mine is inhibited by minD in cytoplasm.
- MM takes care of singularity.

**System of equations:**

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

**Stability analysis:**

1. Find fixed point: \( \frac{\partial}{\partial t} = 0 \)

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

Different random initial conditions relax to same fixed point.

Result: one fixed point:

\[
\begin{align*}
d &= 1383 \\
e &= 82 \\
D &= 117 \\
E &= 3
\end{align*}
\]
2. find stability matrix (Jacobian)

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

3. test stability of fluctuations around homogeneous solution

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

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

\[ q = 1.5 \text{ (\mu m)}^{-1} \]
\[ \lambda = 2\pi/q = 4.2 \text{ \mu m} \]
\[ q = 2.3 \text{ (\mu m)}^{-1} \]
\[ \lambda = 2\pi/q = 2.7 \text{ \mu m} \]
Howard et al.: Results

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

**main differences:**

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

\[
\rho_d: \text{membrane bound minD:ATP complexes} \\
\rho_{de}: \text{membrane bound minD:minE:ATP complexes} \\
\rho_{D,\text{ADP}}: \text{concentration cytoplasmic minD bound to ADP} \\
\rho_{D,\text{ATP}}: \text{concentration cytoplasmic minD bound to ATP} \\
\rho_e: \text{concentration cytoplasmic minE} \\
\rho_{E}: \text{concentration cytoplasmic minE} \\
\text{only minD-ATP can associate with membrane} \\
\text{minE only binds minD-ATP oligomers in membrane} \\
\text{only minD-minE-ATP complex can dissociate from membrane}
\]

**Reaction 1:**

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

\[
\rho_{D,\text{ATP}} = \frac{d\rho_{D,\text{ATP}}}{dt} = D_d \frac{d^2\rho_{D,\text{ATP}}}{dx^2} + \sigma_d \rho_d + \sigma_{de} \rho_{de} \\
\rho_{D,\text{ADP}} = \frac{d\rho_{D,\text{ADP}}}{dt} = D_d \frac{d^2\rho_{D,\text{ADP}}}{dx^2} + \sigma_d \rho_d + \sigma_{de} \rho_{de} \\
\rho_e = \frac{d\rho_e}{dt} = -\sigma_e \rho_e + \frac{[\sigma_d + \sigma_{de}(\rho_d + \rho_{de})] \rho_{D,\text{ATP}}}{\rho_{D,\text{ADP}}} \\
\rho_{de} = \frac{d\rho_{de}}{dt} = -\sigma_{de} \rho_{de} + \sigma_e \rho_d \rho_e
\]
Reaction 2:
minE binds minD-ATP in membrane
\(~ [\text{minE}]^* [\text{minD}]\)

\[
\begin{align*}
\frac{dp_{D,\text{ADP}}}{dt} &= D_D \frac{d^2 p_{D,\text{ADP}}}{dx^2} - \sigma_D^{\text{ADP}\rightarrow\text{ATP}} p_{D,\text{ADP}} + \sigma_d p_d \\
\frac{dp_{D,\text{ATP}}}{dt} &= D_D \frac{d^2 p_{D,\text{ATP}}}{dx^2} + \sigma_D^{\text{ATP}\rightarrow\text{ADP}} (\rho_d + p_d) \rho_{D,\text{ATP}} \\
\frac{dp_{E}}{dt} &= D_E \frac{d^2 p_E}{dx^2} + \sigma_E p_E - \sigma_{d,E} p_d p_E \\
\frac{dp_{F}}{dt} &= -\sigma_E p_d + [\sigma_d + \sigma_{d,E} (p_d + \rho_{d,E})] \rho_{D,\text{ATP}} \\
\frac{dp_{F}}{dt} &= -\sigma_{d,E} p_d + \sigma_E p_d p_E
\end{align*}
\]

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

\[
\begin{align*}
\frac{dp_{D,\text{ADP}}}{dt} &= D_D \frac{d^2 p_{D,\text{ADP}}}{dx^2} + \sigma_D^{\text{ADP}\rightarrow\text{ATP}} (\rho_d + p_d) p_{D,\text{ATP}} \\
\frac{dp_{D,\text{ATP}}}{dt} &= D_D \frac{d^2 p_{D,\text{ATP}}}{dx^2} + \sigma_D^{\text{ATP}\rightarrow\text{ADP}} p_{D,\text{ADP}} - [\sigma_d + \sigma_{d,E} (p_d + \rho_{d,E})] p_{D,\text{ATP}} \\
\frac{dp_{E}}{dt} &= D_E \frac{d^2 p_E}{dx^2} + \sigma_E p_{\text{ATP}} - \sigma_{d,E} p_d p_E \\
\frac{dp_{F}}{dt} &= -\sigma_E p_d + [\sigma_d + \sigma_{d,E} (p_d + \rho_{d,E})] p_{D,\text{ATP}} \\
\frac{dp_{F}}{dt} &= -\sigma_{d,E} p_d + \sigma_E p_d p_E
\end{align*}
\]

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

\[
\begin{align*}
\frac{dp_{D}}{dt} &= D_D \frac{d^2 p_{D}}{dx^2} - \sigma_D p_D^2 + [\sigma_d p_d + \sigma_{d,E} p_d] p_{D,\text{ATP}} \\
\frac{dp_{L}}{dt} &= \left(\sigma_d + \sigma_{d,E} p_d\right) p_{D,\text{ATP}} - \sigma, p_D \\
\frac{dp_{D,\text{ATP}}}{dt} &= D_D \frac{d^2 p_{D,\text{ATP}}}{dx^2} - [\sigma_d + \sigma_{d,E} (p_d + \rho_{d,E})] p_{D,\text{ATP}} + \sigma_{d,E} p_d \\
\frac{dp_{E}}{dt} &= \sigma_d (p_d - \rho_{d,E}) p_D - \sigma, p_E \\
\frac{dp_{E}}{dt} &= D_E \frac{d^2 p_E}{dx^2} + [\sigma_d (p_d - \rho_{d,E})] p_D + \sigma, p_E \\
\frac{dp_{D,\text{ATP}}}{dt} &= D_D \frac{d^2 p_{D,\text{ATP}}}{dx^2} - \sigma_E p_{D,\text{ATP}} + \sigma, p_D
\end{align*}
\]