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

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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*gfp-minC*
**GFP-minD**

**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)

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.

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

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

biological interpretation:
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:

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

stability analysis

1. find fixed point

\[
\frac{\partial}{\partial t} = 0
\]

(e.g. numerically: how_homog.m)

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)

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

3. test stability of fluctuations around homogeneous solution

\[
\begin{align*}
\delta E(x, t) &= \hat{E}(t) \cos(q x) \\
\delta e(x, t) &= \hat{e}(t) \cos(q x) \\
\delta D(x, t) &= \hat{D}(t) \cos(q x) \\
\delta d(x, t) &= \hat{d}(t) \cos(q x)
\end{align*}
\]
3. Test stability of fluctuations around homogeneous solution

\[
\hat{A} = \begin{bmatrix}
-\sigma_1 - D_0 q^2 & \sigma_2 e & 0 & 0 \\
\frac{\sigma_1}{1+\sigma_1 e} & -\sigma_2 e & 0 & 0 \\
-\frac{\sigma_4}{(1+\sigma_4 q)^2} & -\sigma_4 E & 0 & \frac{\sigma_4}{1+\sigma_4 q} \\
-\frac{\sigma_4 e e}{(1+\sigma_4 q)^2} & +\sigma_4 E & 0 & -\frac{\sigma_4}{1+\sigma_4 q}
\end{bmatrix}
\]

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


**Main differences:**
- ATP cycle
- 1D versus 3D (projected on 2D)
ρ_d: membrane bound minD:ATP complexes  
ρ_de: membrane bound minD:minE:ATP complexes  
ρ_{D:ADP}: concentration cytoplasmic minD bound to ADP  
ρ_{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-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  

\[
\begin{align*}
\frac{dp_{D:ADP}}{dt} &= D_D \frac{d^2 p_{D:ATP}}{dx^2} - \sigma_{D:ADP\rightarrow D:ATP} p_{D:ADP} + \sigma_{D} p_d p_E \\
\frac{dp_{D:ATP}}{dt} &= D_D \frac{d^2 p_{D:ATP}}{dx^2} + \sigma_{D:ATP\rightarrow D:ATP} p_{D:ATP} - \left[\sigma_D + \sigma_{Dd}(p_d + p_{de})\right] p_{D:ATP} \\
\frac{dp_E}{dt} &= D_E \frac{d^2 p_E}{dx^2} + \sigma_E p_E - \sigma_{E} p_d p_E \\
\frac{dp_d}{dt} &= -\sigma_{D} p_d p_E + \left[\sigma_D + \sigma_{Dd}(p_d + p_{de})\right] p_{D:ATP} \\
\frac{dp_{de}}{dt} &= -\sigma_{Dd} p_d p_E + \sigma_E p_d p_E
\end{align*}
\]

Reaction 2:  
minE binds minD-ATP in membrane  
\sim [\text{minE}\]^*[\text{minD}]

\[
\begin{align*}
\frac{dp_{D:ADP}}{dt} &= D_D \frac{d^2 p_{D:ATP}}{dx^2} - \sigma_{D:ADP\rightarrow D:ATP} p_{D:ADP} + \sigma_{D} p_d p_E \\
\frac{dp_{D:ATP}}{dt} &= D_D \frac{d^2 p_{D:ATP}}{dx^2} + \sigma_{D:ATP\rightarrow D:ATP} p_{D:ATP} - \left[\sigma_D + \sigma_{Dd}(p_d + p_{de})\right] p_{D:ATP} \\
\frac{dp_E}{dt} &= D_E \frac{d^2 p_E}{dx^2} + \sigma_E p_E - \sigma_{E} p_d p_E \\
\frac{dp_d}{dt} &= -\sigma_{E} p_d p_E + \left[\sigma_D + \sigma_{Dd}(p_d + p_{de})\right] p_{D:ATP} \\
\frac{dp_{de}}{dt} &= -\sigma_{Dd} p_d p_E + \sigma_E p_d p_E
\end{align*}
\]
Reaction 3:
minD-minE-ATP complex disassociates from membrane hydrolyzing ATP
\[ \sim [\text{mine}] \]

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

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

\[
\frac{dp_{D,ADP}}{dt} = D_D \frac{d^2 p_{D,ADP}}{dx^2} - \rho_{D,ADP}^D p_{D,ADP} + \sigma_a p_a
\]
\[
\frac{dp_{D,ATP}}{dt} = D_D \frac{d^2 p_{D,ATP}}{dx^2} + \rho_{D,ATP}^D p_{D,ADP} - \left[ \sigma_D + \sigma_{ADP} (p_d + p_{de}) \right] p_{D,ATP}
\]
\[
\frac{dp_E}{dt} = D_E \frac{d^2 p_E}{dx^2} + \sigma_a p_a - \rho_d p_d p_E
\]
\[
\frac{dp_d}{dt} = -\sigma_D p_d + \left[ \sigma_E + \sigma_{ADP} (p_d + p_{de}) \right] p_{D,ATP}
\]
\[
\frac{dp_{de}}{dt} = -\sigma_d p_{de} + \sigma_E p_d p_E
\]

Stochastic reaction-diffusion equations:

http://mesord.sourceforge.net/