E. coli's division decision: modeling Min-protein oscillations

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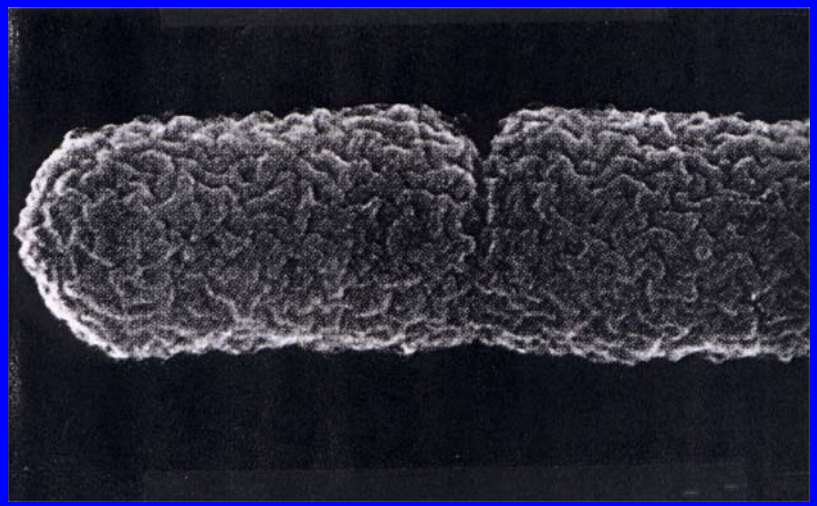
Support: NIH

Outline

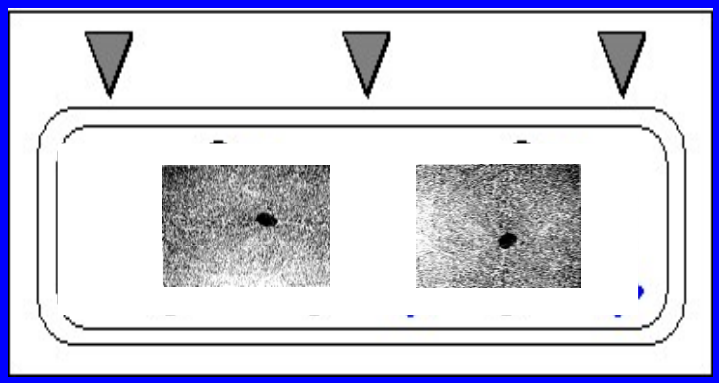
- Introduction to *E. coli* cell division
- Two systems regulate division site placement
  - Nucleoid occlusion
  - Min proteins
- Min proteins oscillate from pole to pole!
- Modeling Min-protein oscillations
- Why does *E. coli* need an oscillator?

E. Coli cell division

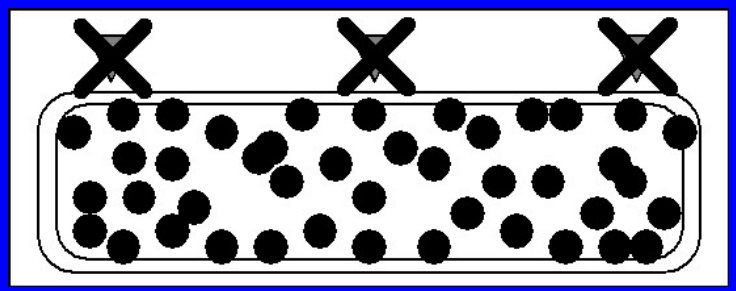


- Division accuracy: .50 +/- .02
- Placement of FtsZ ring: .50 +/- .01

Min proteins



- Without Min proteins, get minicelling phenotype (Min^-)



- If MinC is over-expressed, get filamentous growth (Sep^-)

Min proteins

- MinC

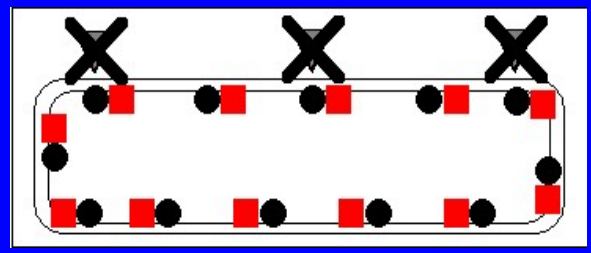
  Inhibits FtsZ ring formation

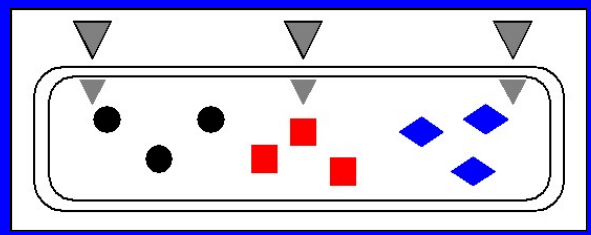
- MinD

  MinD:ATP recruits MinC to membrane

- MinE

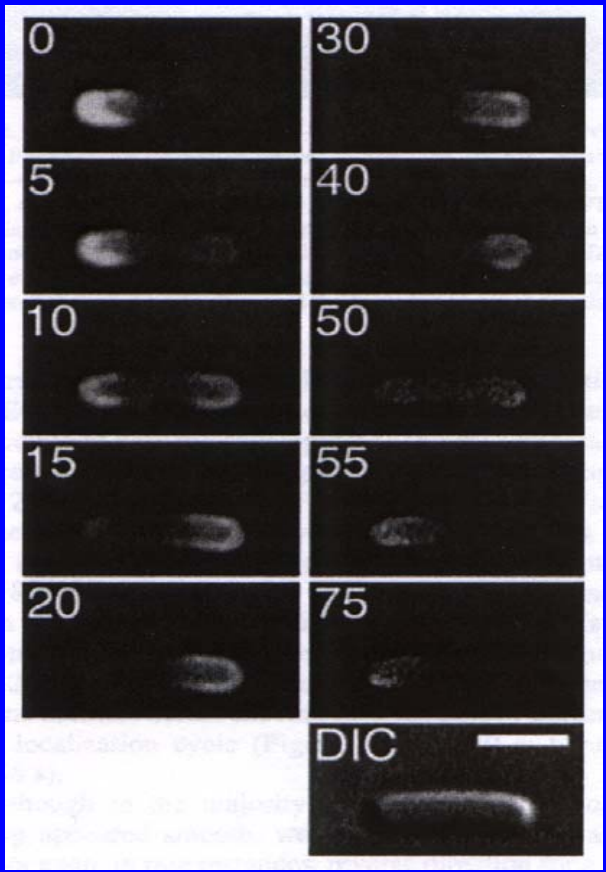
  Binds to MinD:ATP in membrane and induces ATP hydrolysis





What happens when all three Min proteins are present?

Min proteins oscillate from pole to pole

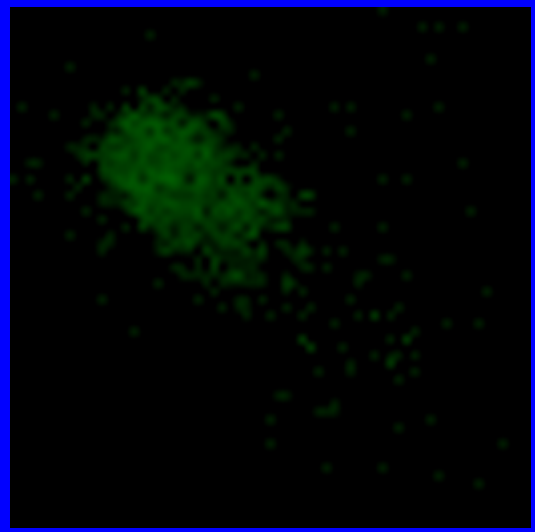


Hale *et al.* (2001)

MinD-GFP

- *In vivo* oscillations require MinD and MinE but not MinC.

MinD: the movie



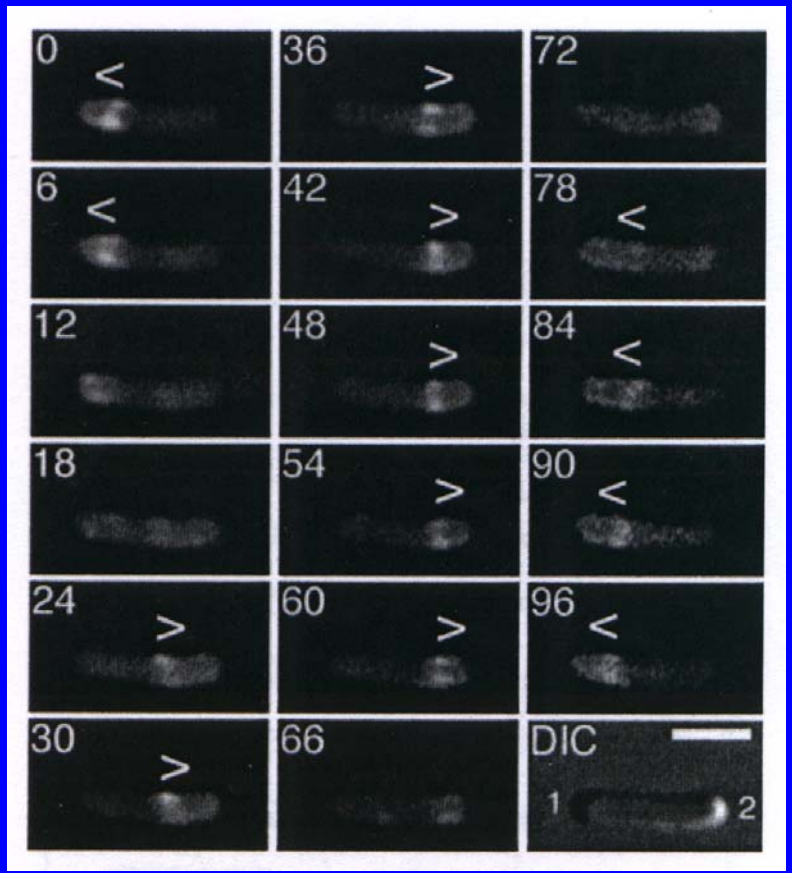
P. deBoer

MinD-GFP

Phenomenology of Min oscillations

- MinD polar regions grow as end caps.
- MinE ring caps MinD polar region.

MinE ring caps MinD polar region



Hale *et al.* (2001)

MinE-GFP

- MinE ring is membrane bound.
- Ring appears near cell center and moves toward pole.
- Some MinE is also found in polar region.

Phenomenology of Min oscillations

- MinD polar regions grow as end caps.
- MinE ring caps MinD polar region.
- Oscillation frequency:
  - [MinE] ↑ ⇨ frequency ↑,
  - [MinD] ↑ ⇨ frequency ↓.

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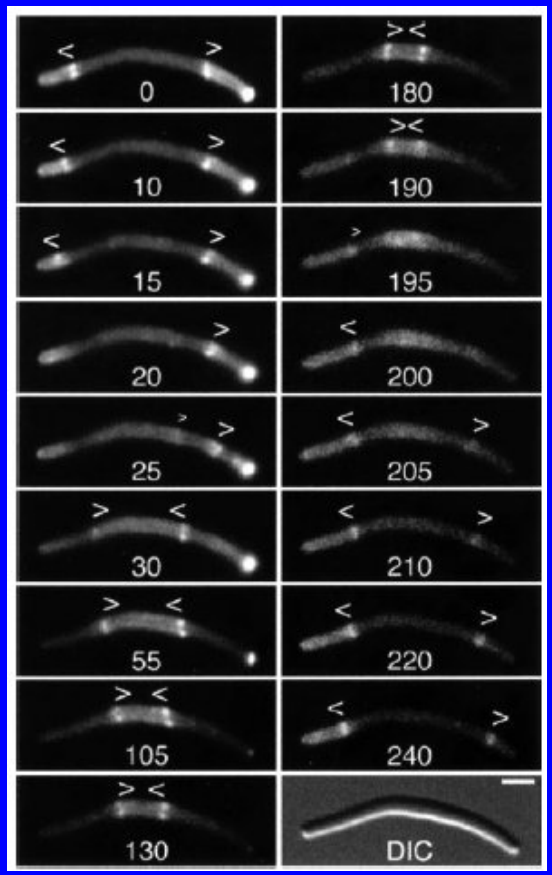
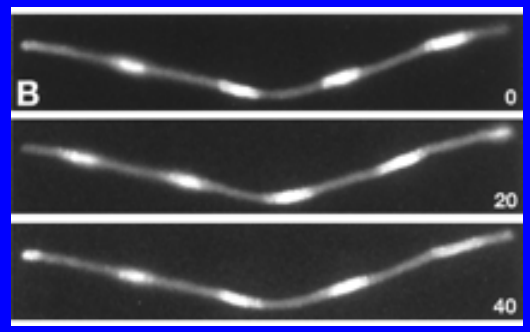


Hale *et al.* (2001)

MinE-GFP



MinD-GFP

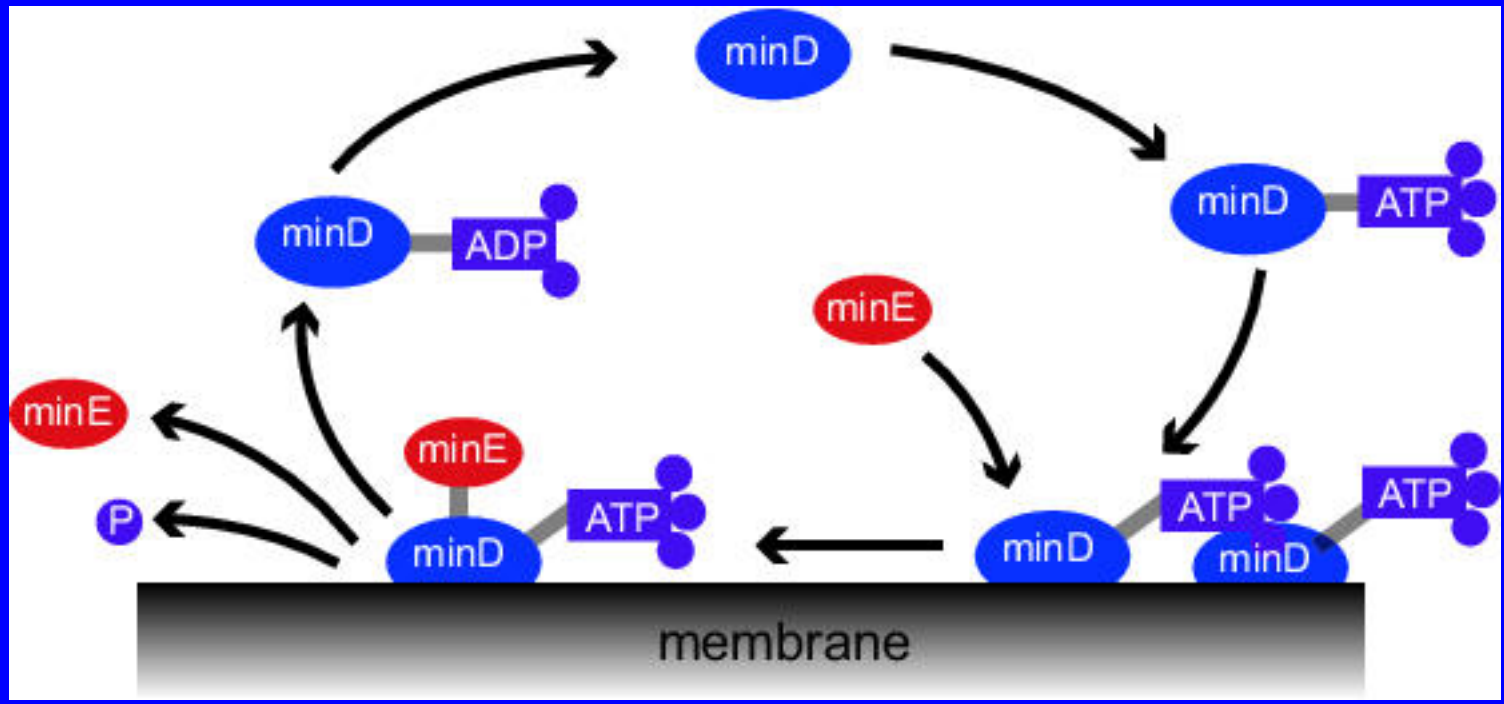
Raskin and de Boer (1999)

- Wavelength of oscillations is ~10 microns.

Previous models fail to reproduce observed behavior

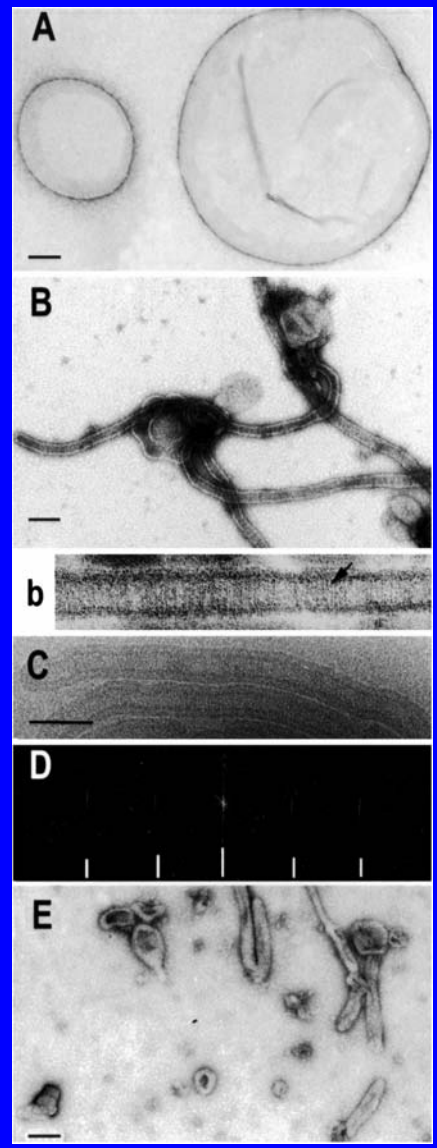
- Howard *et al.* (2001)
  - MinD polar region fails to reform at poles.
- Meinhardt and de Boer (2001)
  - Requires new protein synthesis.
- Kruse (2002)
  - No MinE ring, requires fast membrane diffusion.

A model with only known interactions reproduces observed behavior



Evidence from *in vitro* studies

A. Phospholipid vesicles
B. MinD:ATP binds to vesicles and deforms them into tubes
C. MinD:ATP polymerizes on vesicles
D. Diffraction pattern indicates well-ordered lattice of MinD:ATP
E. MinE induces hydrolysis of MinD:ATP and disassembly of tubes



Hu *et al.* (2002)

Equations for model

$$\frac{d\rho_{D:ADP}}{dt} = \mathcal{D}_D \nabla^2 \rho_{D:ADP} + \sigma_{de}\rho_{de} - \frac{\rho_{D:ADP}}{\tau_{ADP\to ATP}}$$

$$\frac{d\rho_{D:ATP}}{dt} = \mathcal{D}_D \nabla^2 \rho_{D:ATP} + \frac{\rho_{D:ADP}}{\tau_{ADP\to ATP}} - [\sigma_D + \sigma_{dD}(\rho_d + \rho_{de})]\rho_{D:ATP}$$

$$\frac{d\rho_E}{dt} = \mathcal{D}_E \nabla^2 \rho_E + \sigma_{de}\rho_{de} - \sigma_E \rho_d \rho_E$$

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

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

ρ_D = MinD in cytoplasm

ρ_E = MinE in cytoplasm

ρ_d = MinD:ATP in membrane

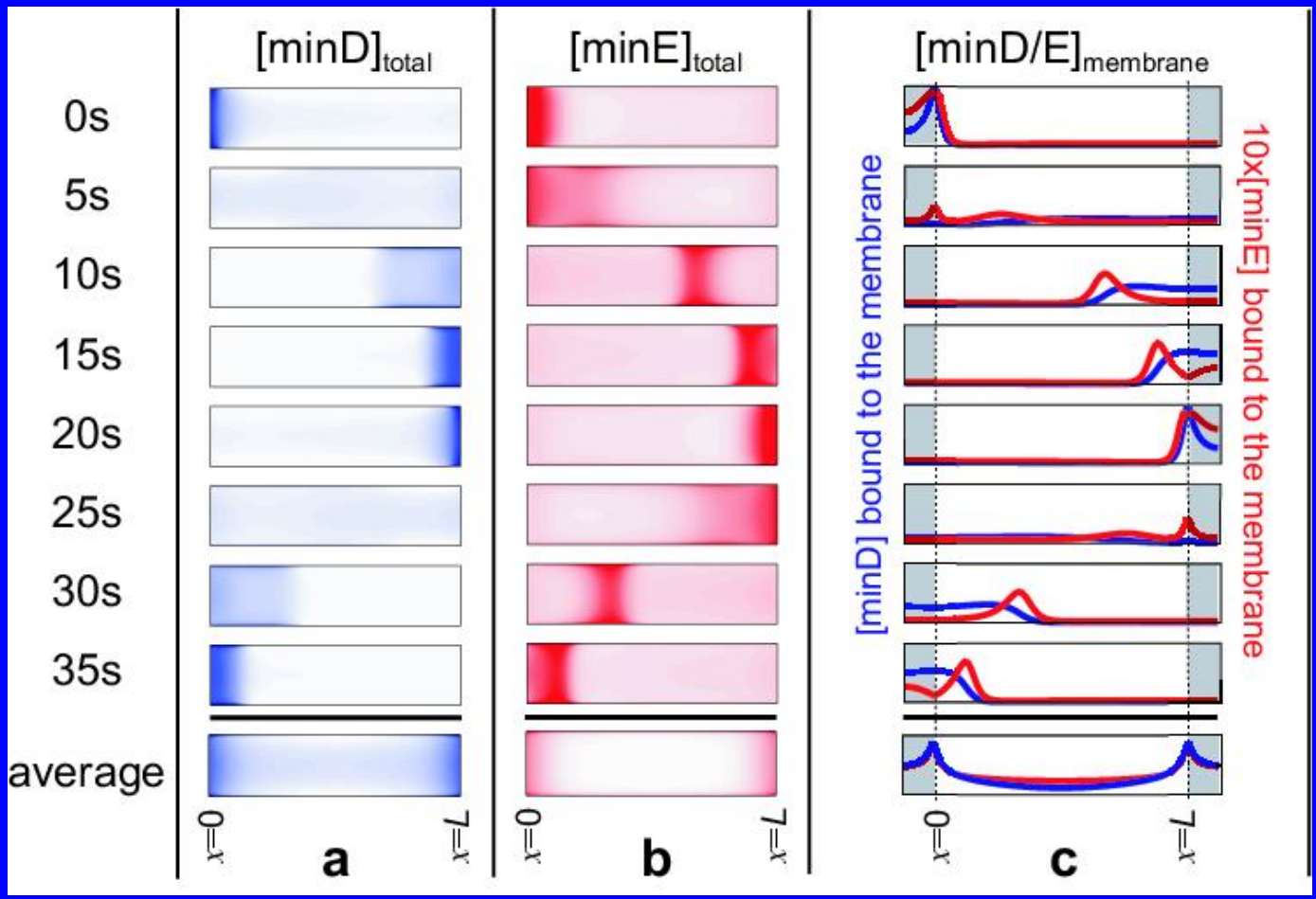
ρ_{de} = MinE:MinD:ATP in membrane

$$\sigma_D = 0.025\left(\frac{\mu\text{m}}{s}\right);\ \sigma_{dD} = 0.001\left(\frac{\mu\text{m}^3}{s}\right)$$

$$\sigma_E = 0.16\left(\frac{\mu\text{m}^3}{s}\right);\ \sigma_{de} = 0.8\left(\frac{1}{s}\right)$$

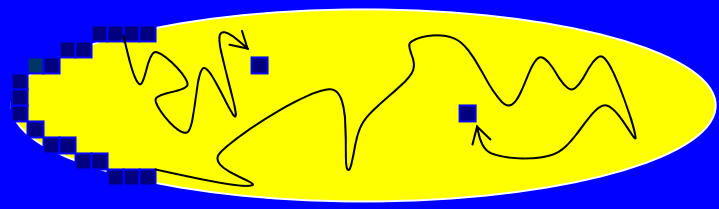
$$\mathcal{D}_D = \mathcal{D}_E = 2.5\left(\frac{\mu\text{m}^2}{s}\right)$$

MinD end caps and MinE ring



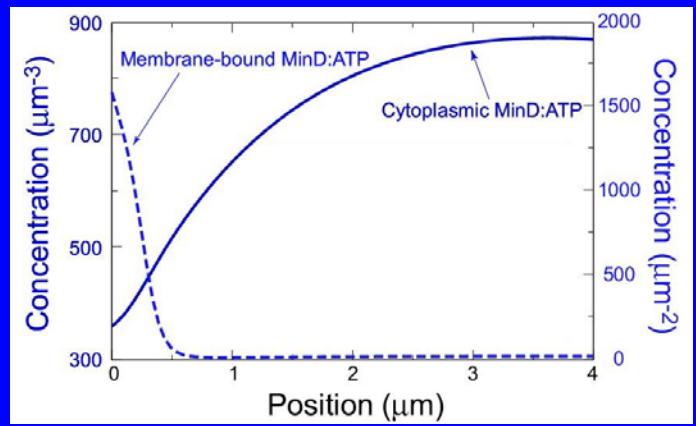
Mechanism for growth of MinD polar regions

- MinD ejected from old end cap diffuses in cytoplasm.



- Slow nucleotide exchange implies uniform reappearance of MinD:ATP.

- Capture of MinD:ATP by old end cap leads to maximum of cytoplasmic MinD:ATP at opposite pole.

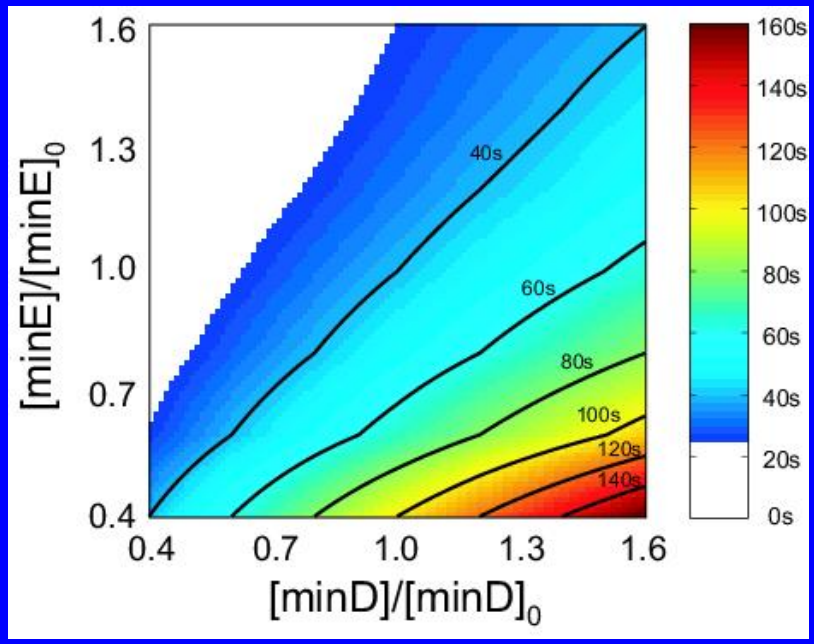


MinDE movie

MinE

MinD

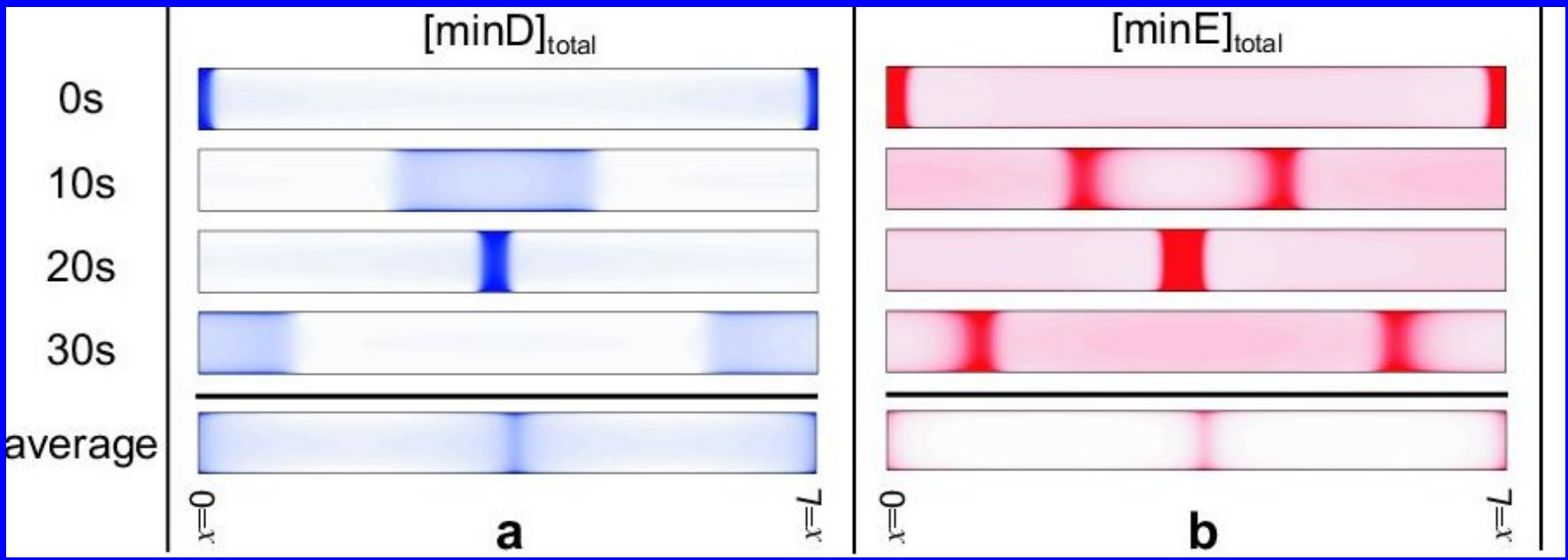
Frequency of oscillations ~ [MinE]/[MinD]



4 micron cell

- No oscillations for [MinE] too high, or for [MinD] too low.
- Minimum oscillation period 25s.

“Zebra stripe” oscillations in long cells



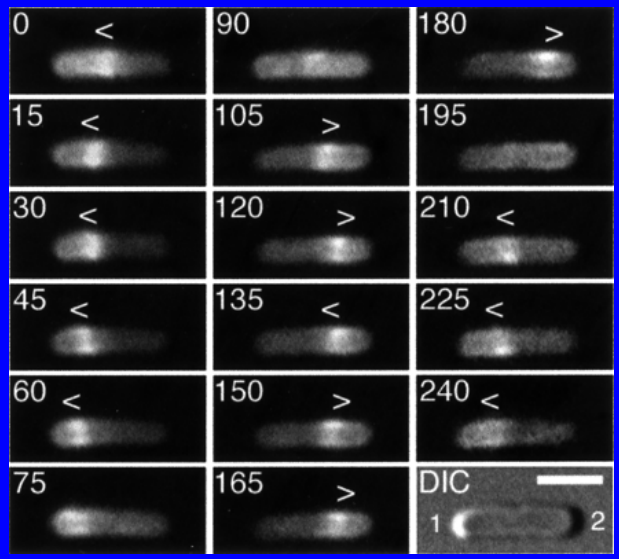
- Stripes form with wavelength of ~10 microns

Predictions of model

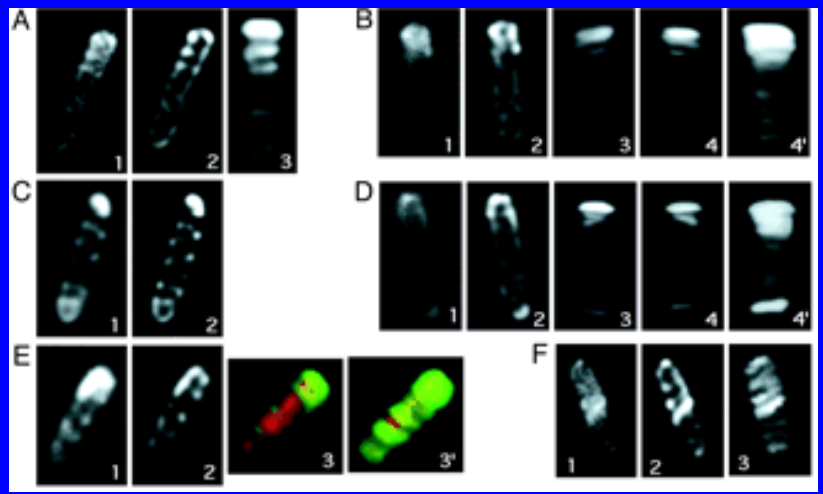
- Delay in MinD:ATP recovery is essential. (Verified by Joe Lutkenhaus – nucleotide exchange rate is slow, ~2 / s.)
- Rate of hydrolysis of MinD:ATP by MinE sets oscillation frequency.
- Diffusion length of MinD before rebinding to membrane sets oscillation wavelength.

Open questions

Hale *et al.* (2001)



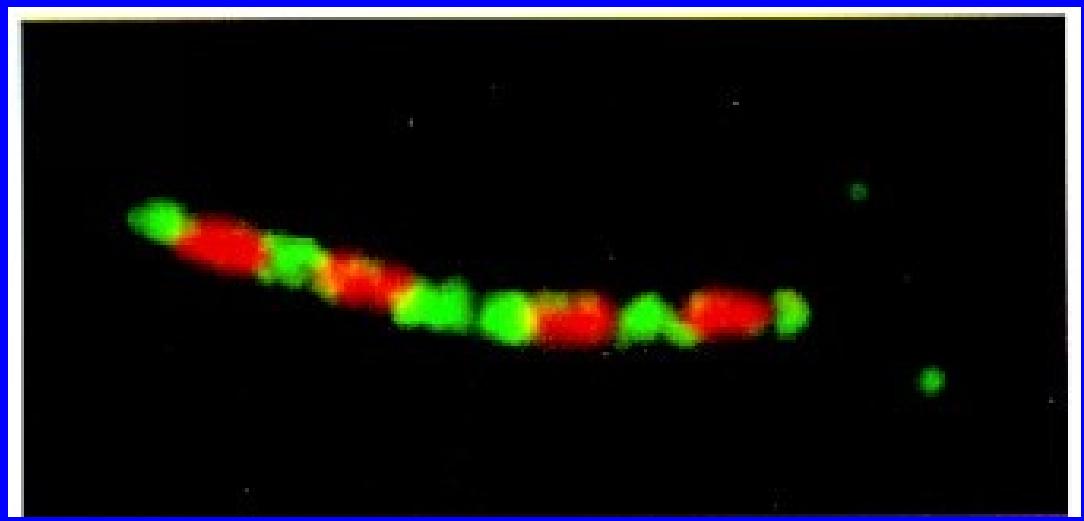
Shih *et al.* (2001)



- MinE ring moving in reverse.
- Role of MinE and MinD dimerization.
- Helical morphology of MinD polymers.

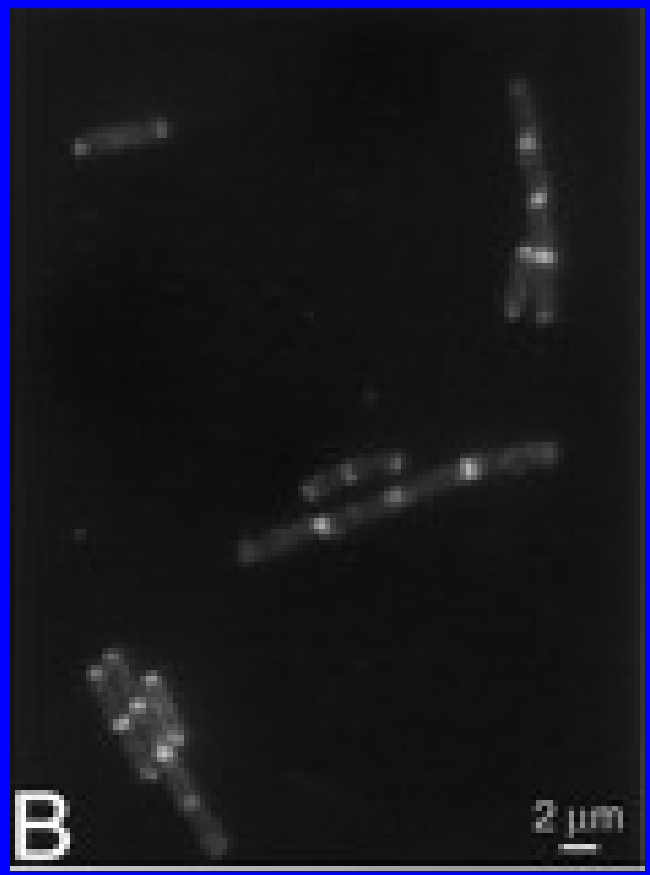
Why does *E. coli* need an oscillator?

In *B. subtilis*, minicelling is prevented by MinCD homologs, but polar regions are static.



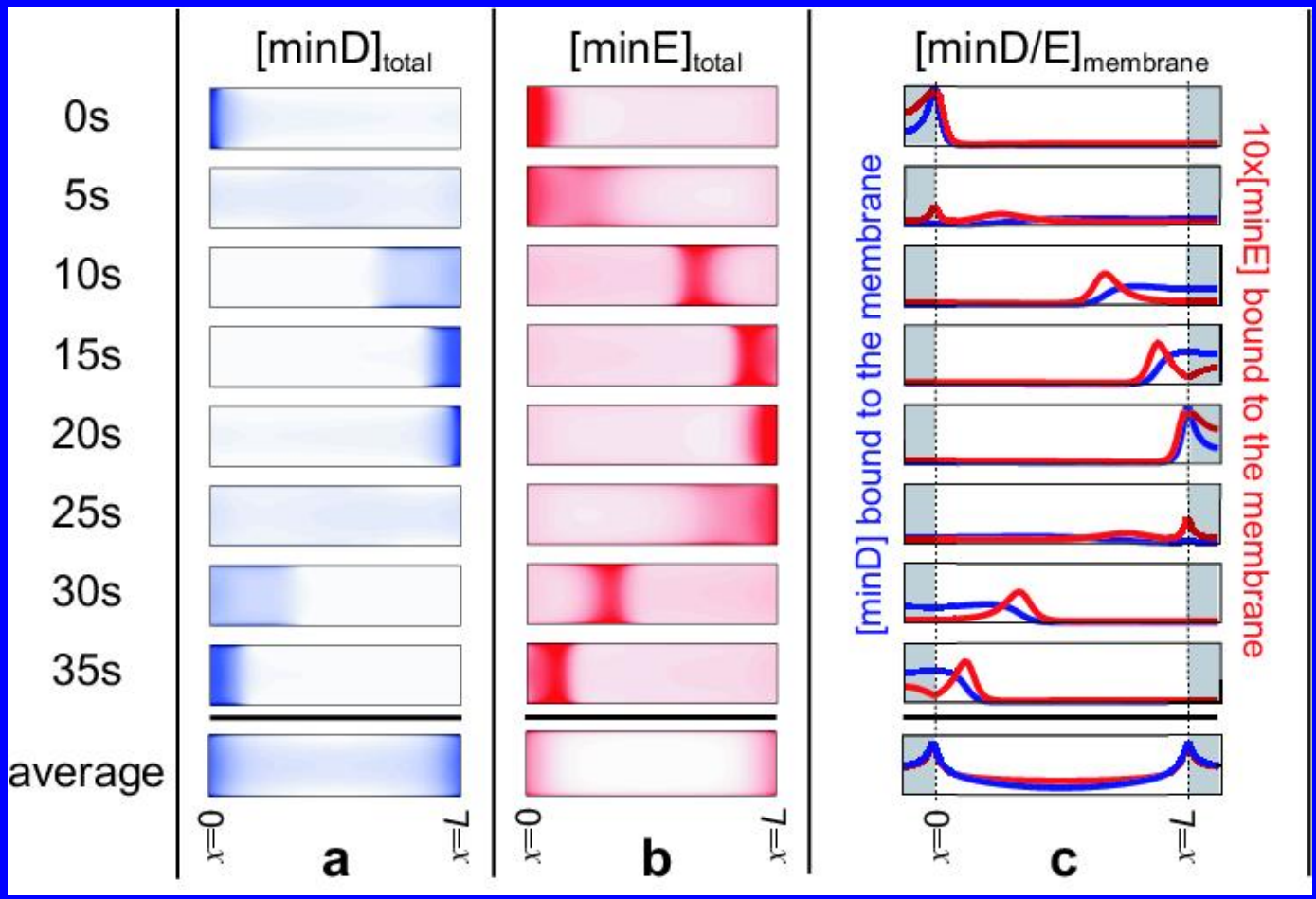
Marston *et al*. (1998)

In *B. subtilis,* targeting of MinD to cell poles requires DivIVA, etc.



DivIVA antibody staining

In *E. coli*, Min oscillations “target” MinD to poles

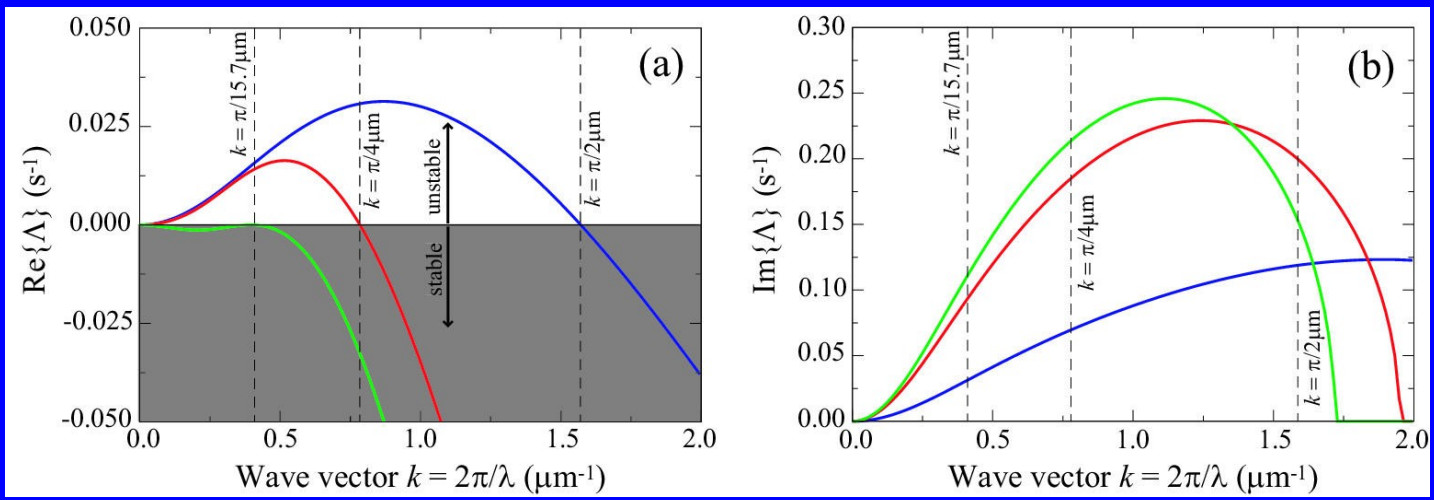


Polar targeting mechanism: oscillations prefer long axis of cell

Linear stability analysis

- Find static solution in an infinite cell
- Look for growth or decay of small perturbations

$$\rho_i(\vec{x},t) = \rho_i^0 + \delta\rho_i\, e^{ikz+\Lambda t}$$

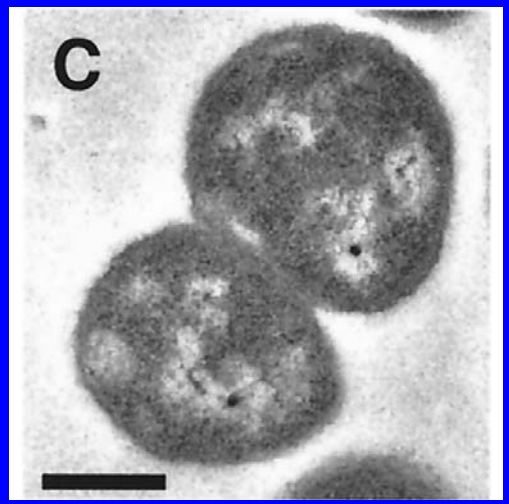


Conclusions

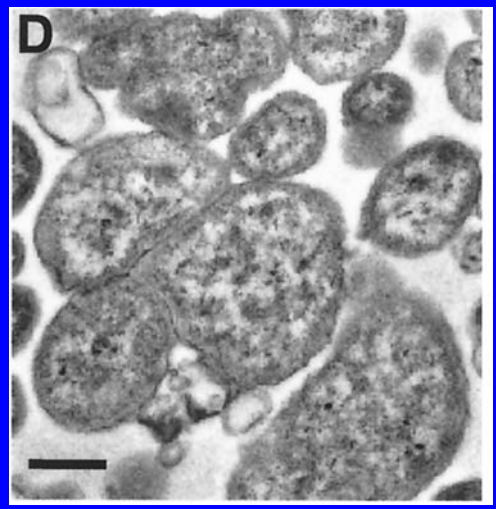
- Division-site placement in *E. coli* is regulated by Min proteins, which oscillate from pole to pole.
- A simple model reproduces the observed behavior:
  - MinD polar regions grow as end caps,
  - MinE ring sits at edge of MinD polar region,
  - Oscillation frequency ~ [MinE] / [MinD],
  - Filamentous cell has “zebra stripe” pattern.
- Min oscillations achieve polar targeting of MinD.
- Open question – what role do Min proteins play in division accuracy?

Min proteins in spherical cells: Neisseria gonorrhoeae

Szeto *et al.* (2001)

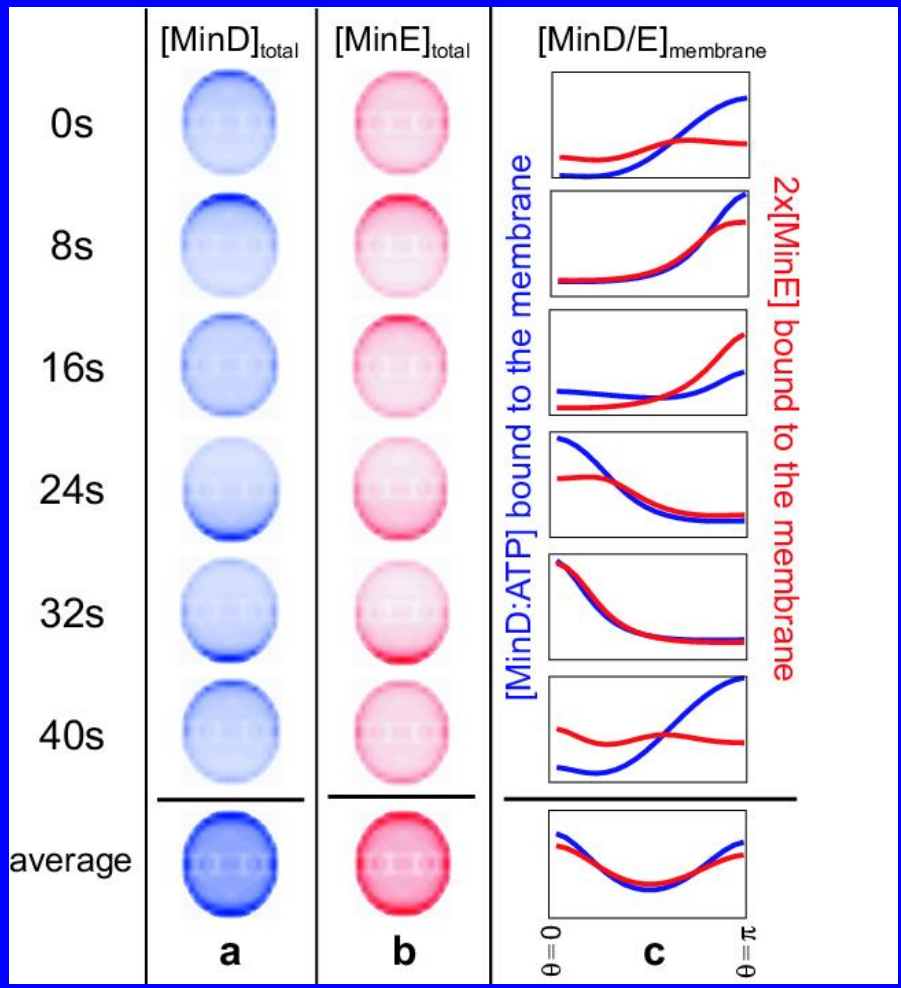


Wild type



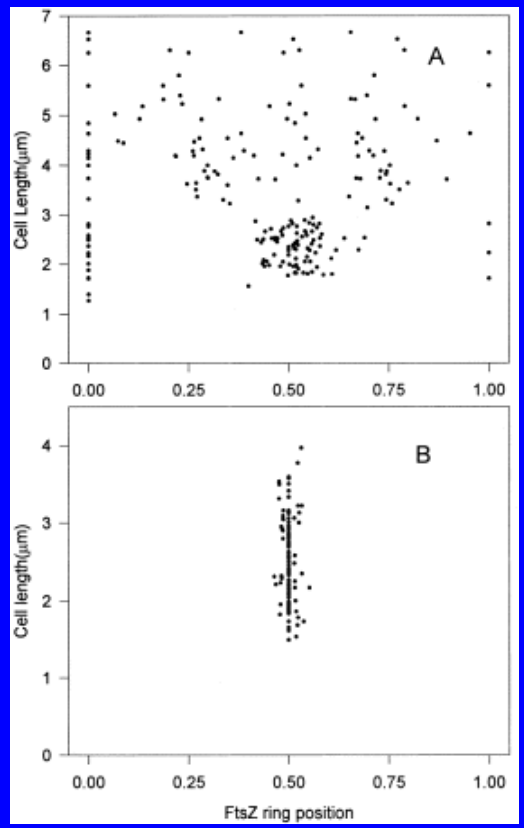
$MinD_{Ng}^{-}$

Min-protein oscillations in nearly round cells



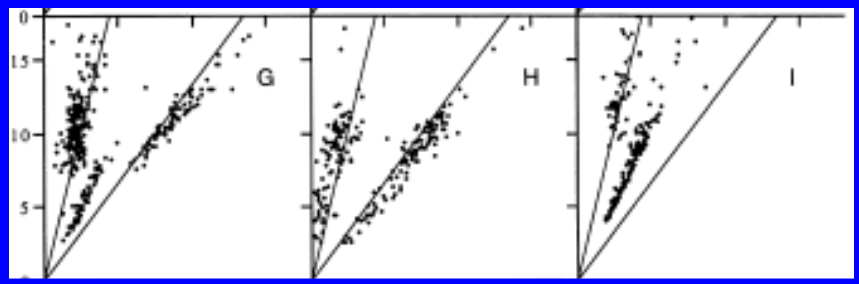
In *E. coli*, accuracy of FtsZ ring placement does require Min

Yu and Margolin (1999)



FtsZ ring position

Placement of FtsZ ring by Min system



FtsZ ring

- In mutant with defect in nucleoid occlusion, FtsZ ring placement follows predicted nodes of MinD oscillations.

In *B. subtilis*, accuracy of FtsZ ring placement does not require Min