Finding your center: the role of Min-protein oscillations in bacterial cell division

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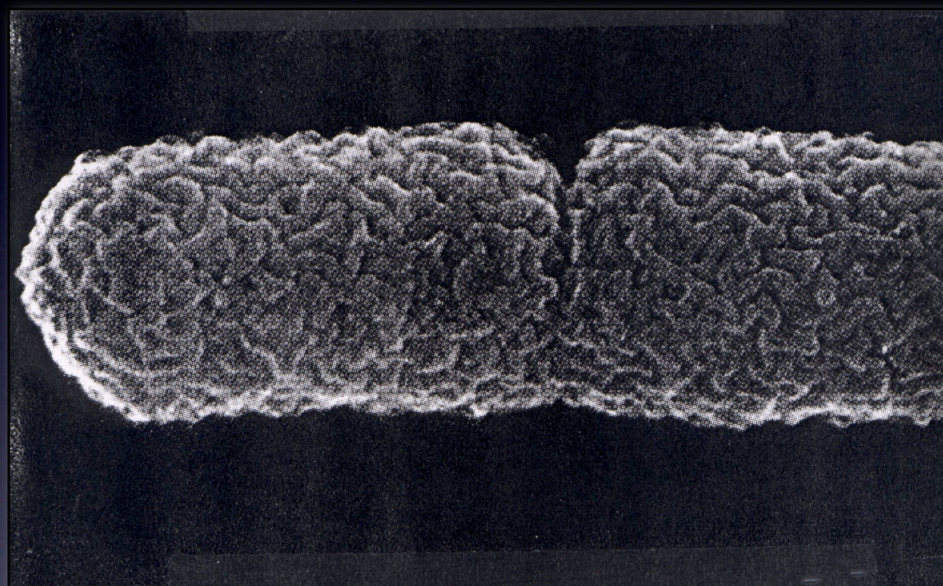
Dynamics Days 2008

Outline

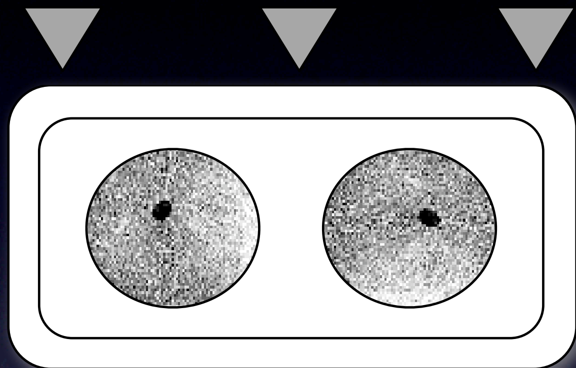
- Introduction to cell division in *E. coli*
- Two systems regulate division site placement
    - Nucleoid occlusion
    - Min proteins
- Min proteins oscillate from pole to pole!
- Modeling Min-protein oscillations in different geometries
- Oscillations as a cell geometry detection mechanism

E. coli cell division

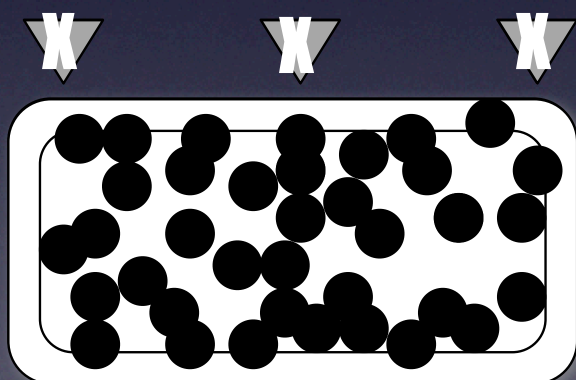


- Division accuracy: 0.50 +/- 0.02
- Placement of FtsZ ring: 0.50 +/- 0.01

The Min proteins



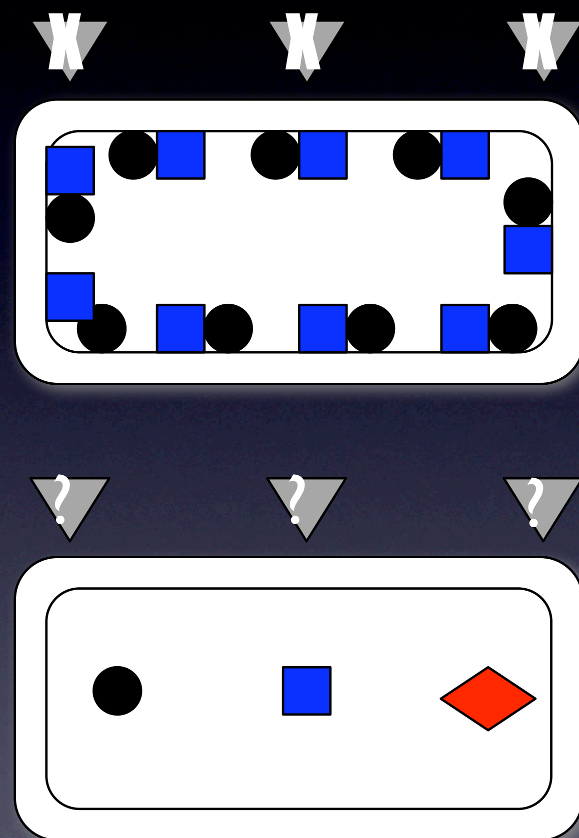
- Without Min proteins, minicelling phenotype (Min$^-$)



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

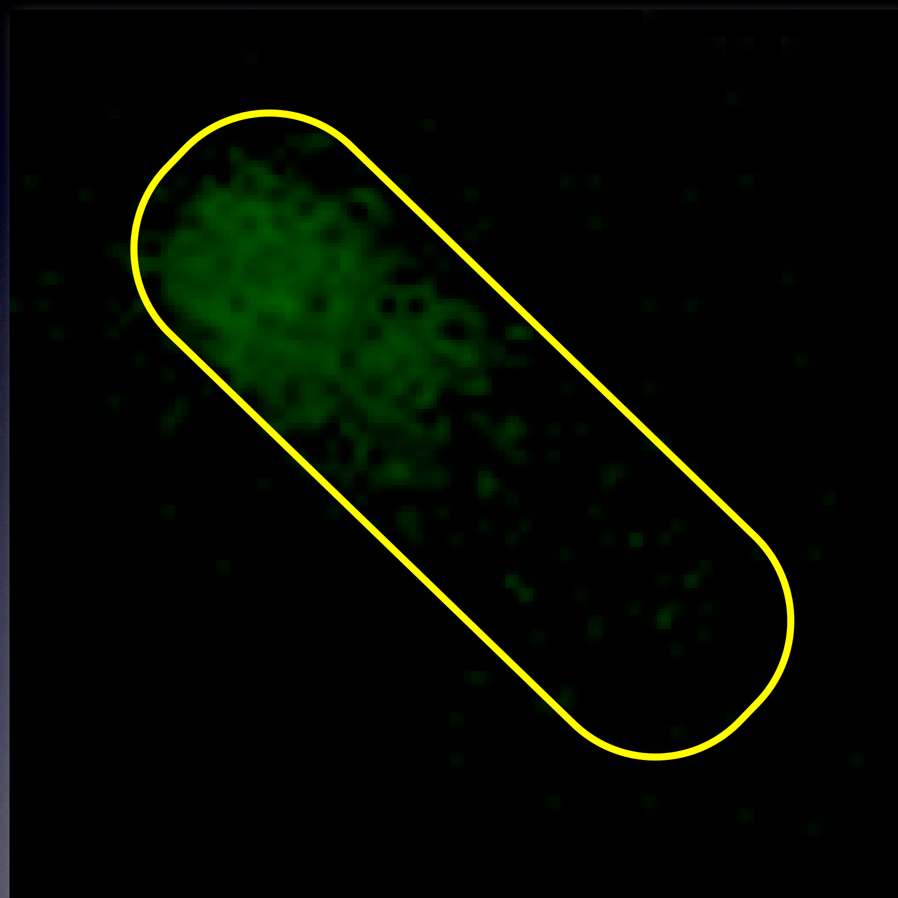
The Min proteins (cont.)

- MinC
  - Inhibits FtsZ ring formation
- MinD
  - Goes to the membrane when bound to ATP
  - 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 oscillations

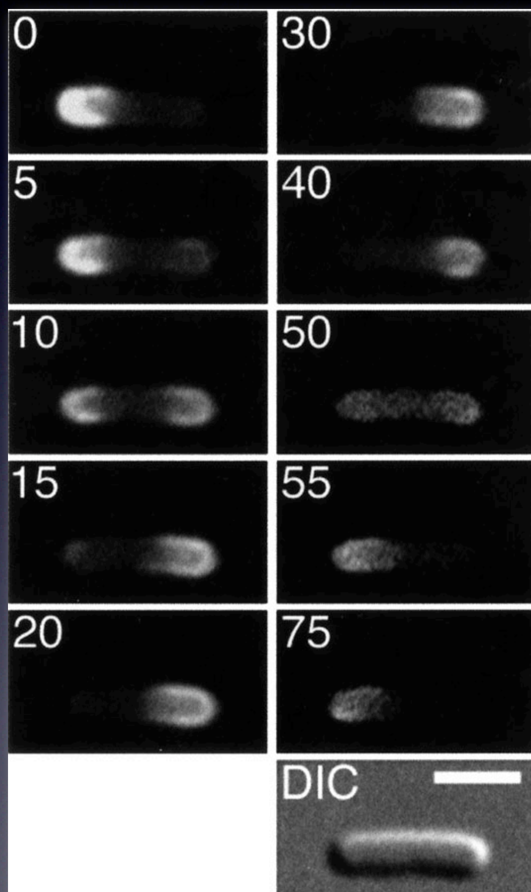


MinD-GFP

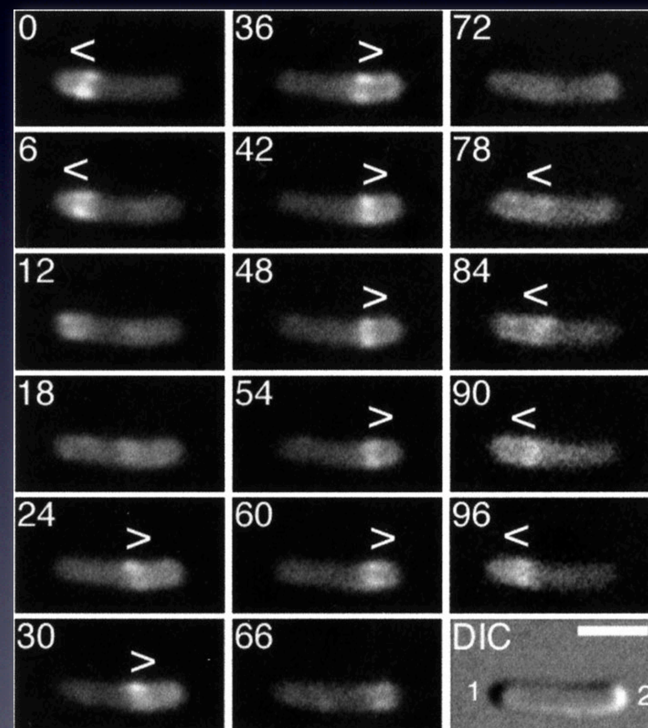
(P. de Boer)

Min-protein oscillations

Hale et al. (2001)

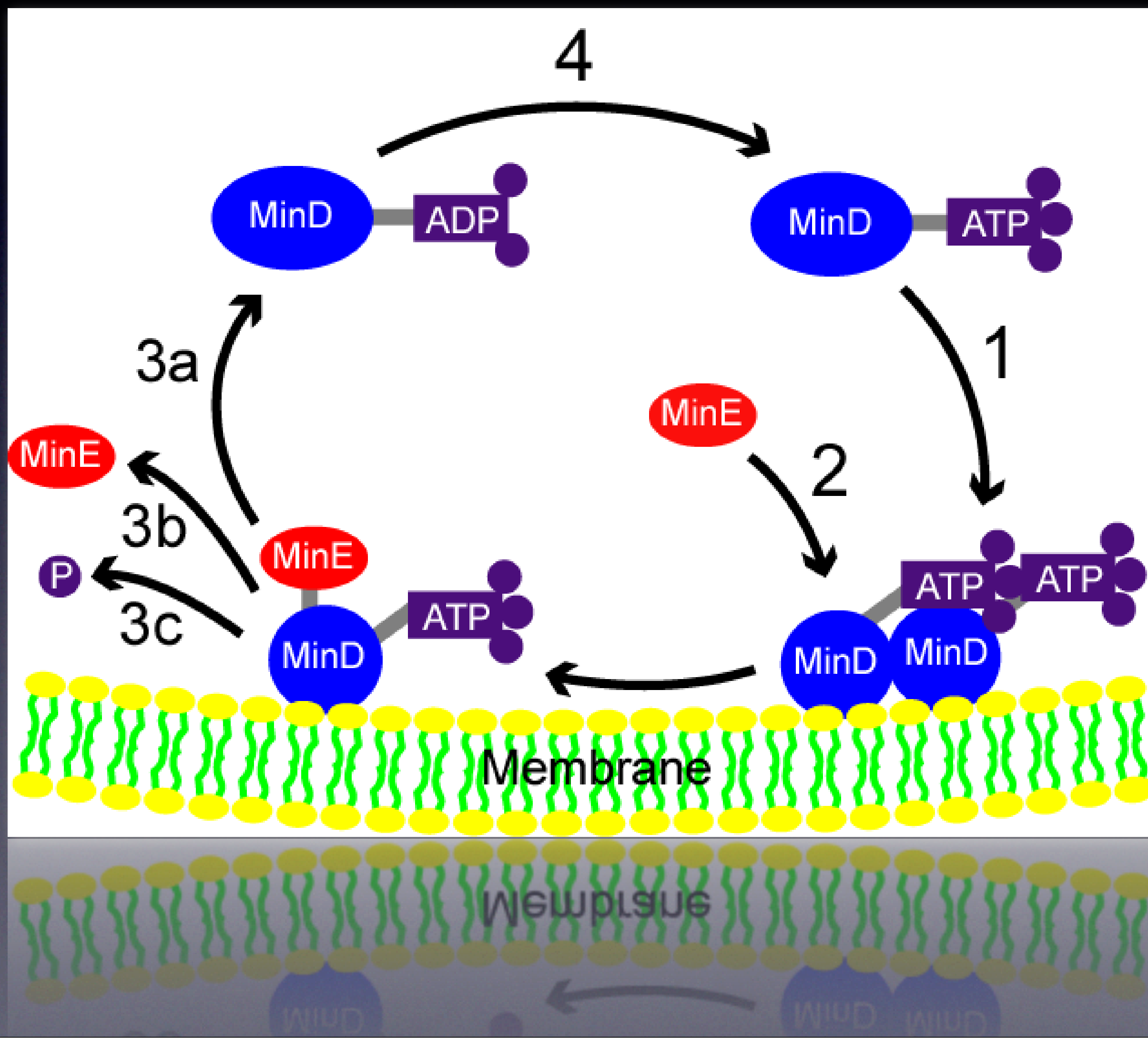


MinD-GFP



MinE-GFP

The model



4
MinD
ADP
MinD
ATP
1
3a
MinE
2
MinE
3b
MinE
P
3c
ATP
MinD
ATP
ATP
MinD
MinD
Membrane

Reaction-diffusion equations

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

MinE

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

ies MinD

$$\frac{d\rho_{D:ATP}}{dt} = \mathcal{D}_D \nabla^2 \rho_{D:ATP} + \frac{\rho_{D:ADP}}{\tau_{D:ADP \rightarrow D:ATP}} - [\sigma_D + \ldots$$

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

MinD:MinE:AT

Membrane densities

$$\frac{d\rho_d}{dt} = -\sigma_{de} \rho_{de} + [\sigma_D + \sigma_{dD}(\rho_d + \rho_{de})]\rho \ldots$$

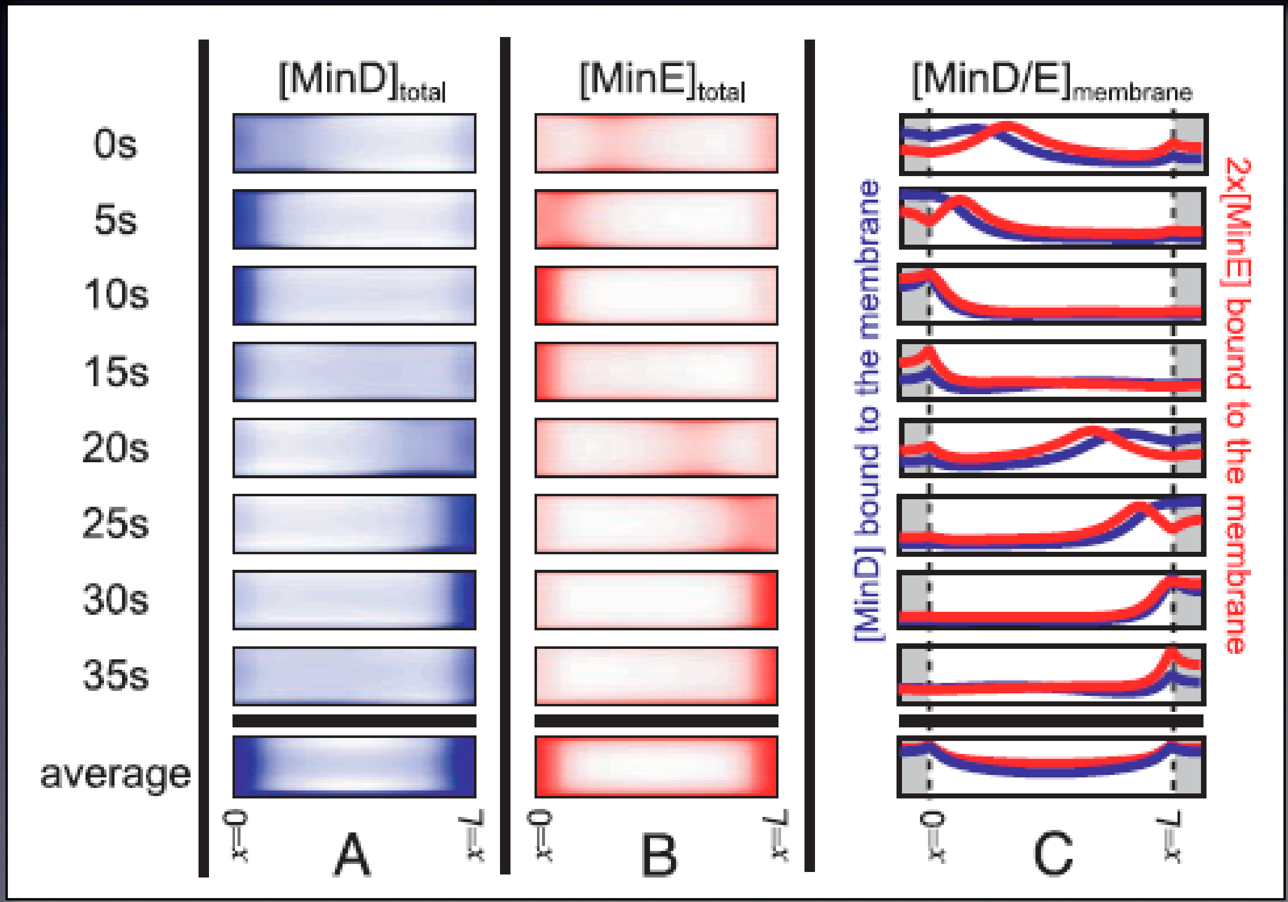
$$\sigma_D = 0.025 \left(\frac{\mu\text{m}}{\text{s}}\right); \quad \sigma_{dD} = 0.001 \left(\frac{\mu\text{m}^3}{s}\right);$$

$$\sigma_E = 0.3 \left(\frac{\mu\text{m}^3}{s}\right); \quad \sigma_{de} = 0.5 \left(\frac{1}{s}\right)$$

$$\tau_{ADP \rightarrow ATP} = 1 s; \quad \mathcal{D}_D = \mathcal{D}_E = 2.5 \left(\frac{\mu\text{m}^2}{s}\right)$$

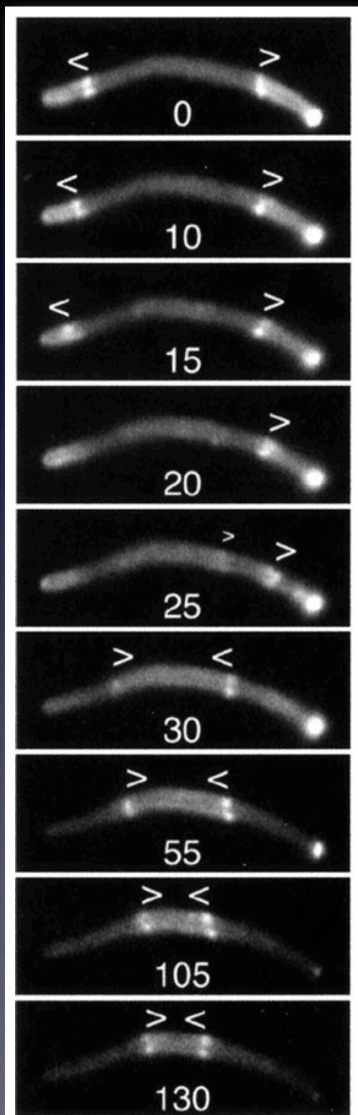
MinD binding → MinE binding → Dissociation → Nucleotide exchange

Oscillations in rod-shaped cells



(Huang *et al. PNAS* 2003)

Striped oscillations in long cells



MinD

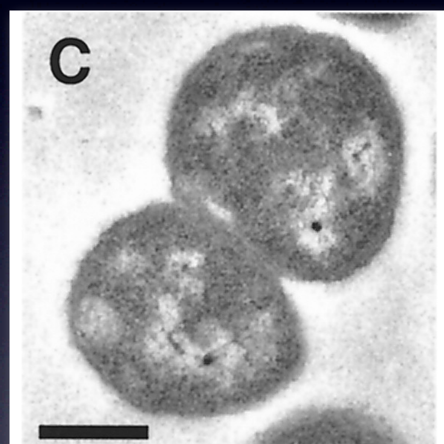
MinE

- Stripes form with wavelength of ~10 microns

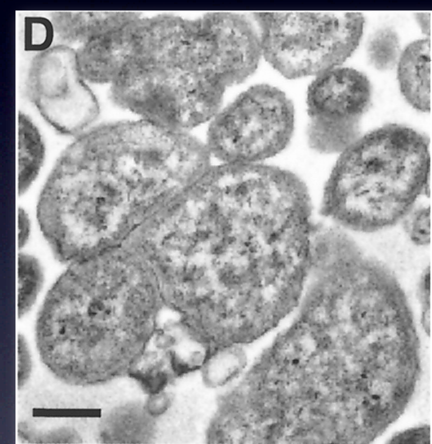
Min oscillations in round cells

- Do spatial oscillations occur in other cells?

(Szeto 2001)



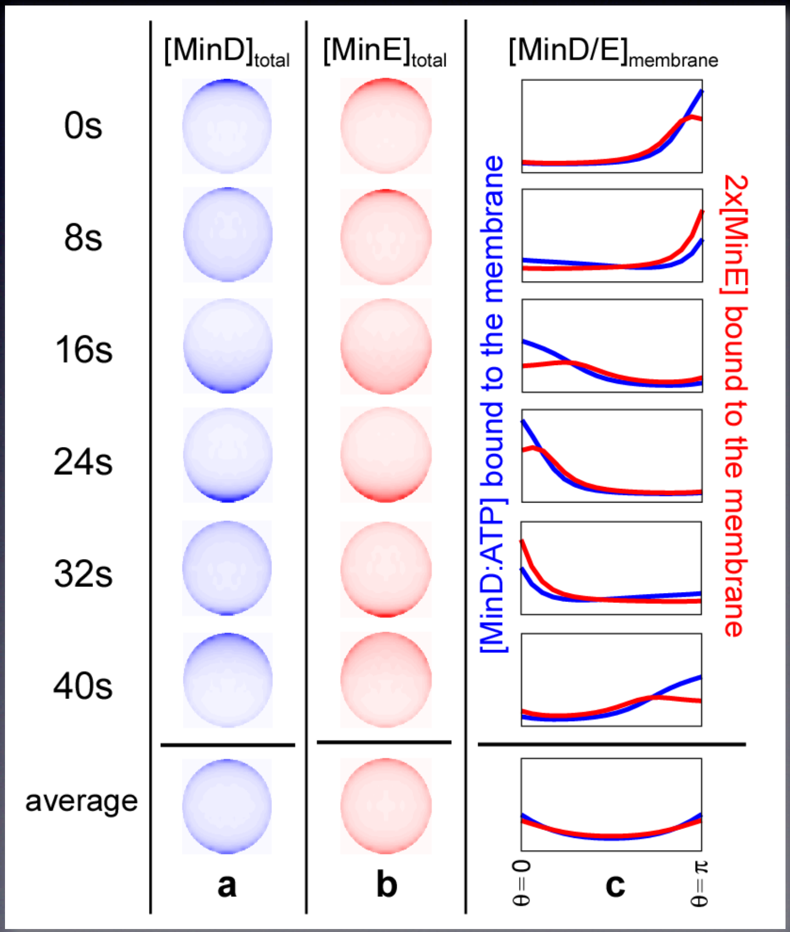
(Wild type)



($MinD_{Ng}^{-}$)

- Loss of $MinD_{Ng}$ results in abnormal cell division
- $MinD_{Ng}$ and MinD oscillate in round *rodA* E. coli mutants

Modeling round cell oscillations



$R = 0.5\mu m$

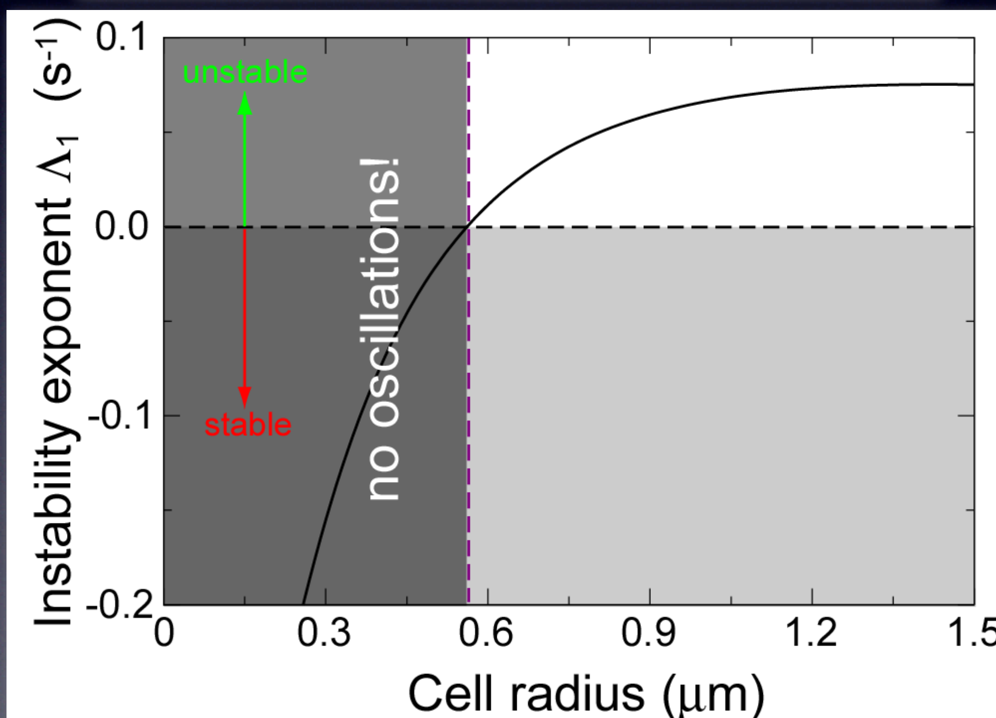
- Oscillations without a MinE ring in spherical cells
- Minimum radius below which oscillations do not occur

In ellipsoidal cells, the oscillations spontaneously orient along the long axis of the cell.

Huang & Wingreen *Phys. Bio.* **1** (2004)

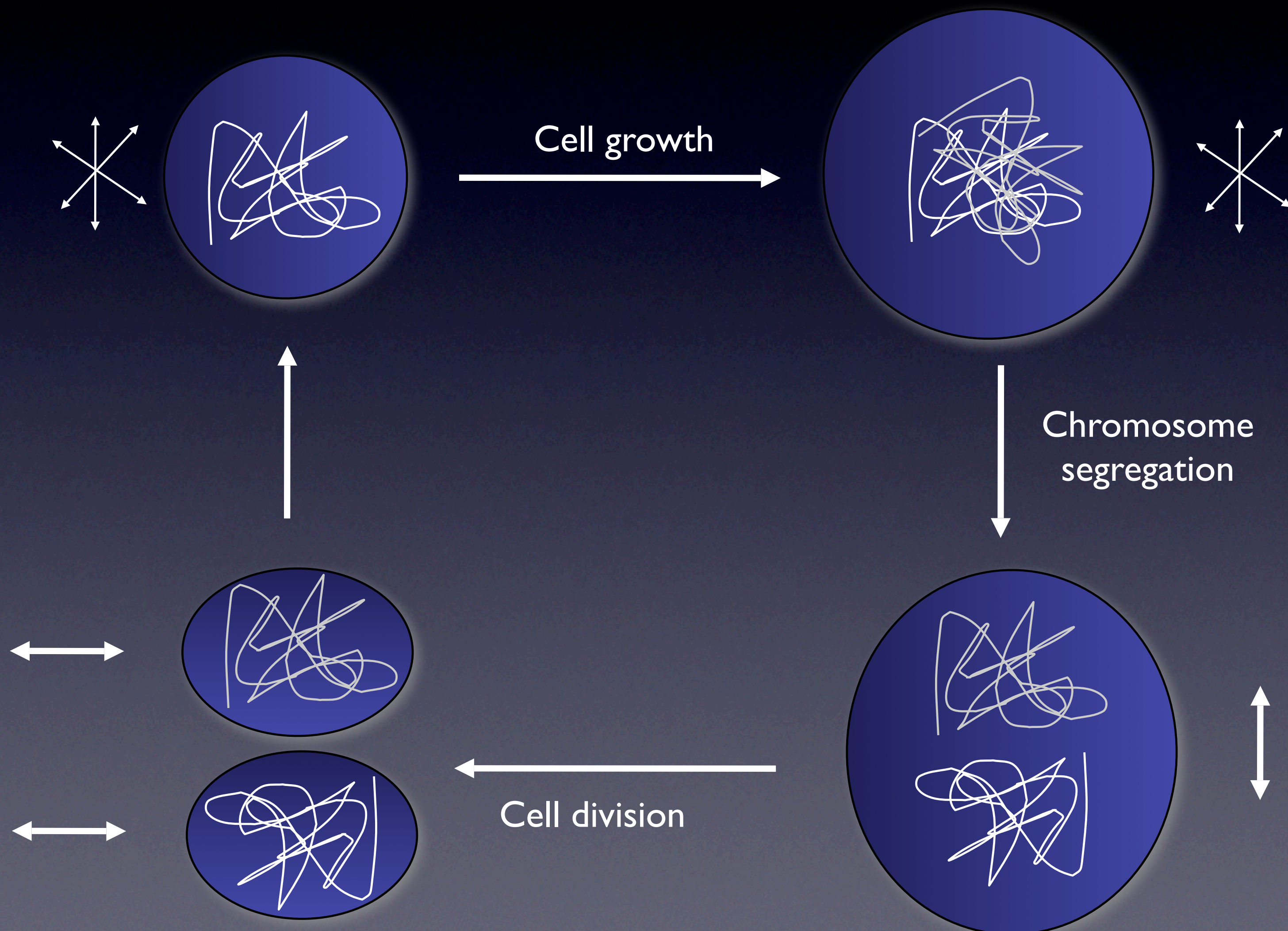
Linear stability analysis

$$\rho(t) = \rho_0 e^{\Lambda t}\left(1 + \varepsilon \cos(\theta)\right)$$

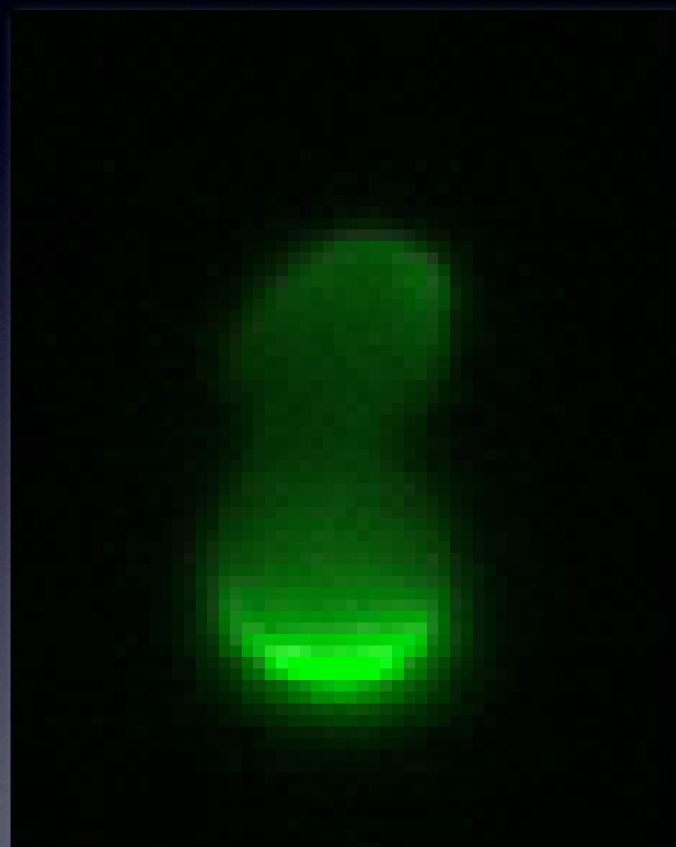


- Linear stability predicts a minimum oscillation radius of 0.56μm which agrees with the full non-linear simulations
- The growth exponent Λ_1 increases with radius, favoring oscillations along the long axis between 0.56μm and 1.5μm

Importance of oscillations in round cells



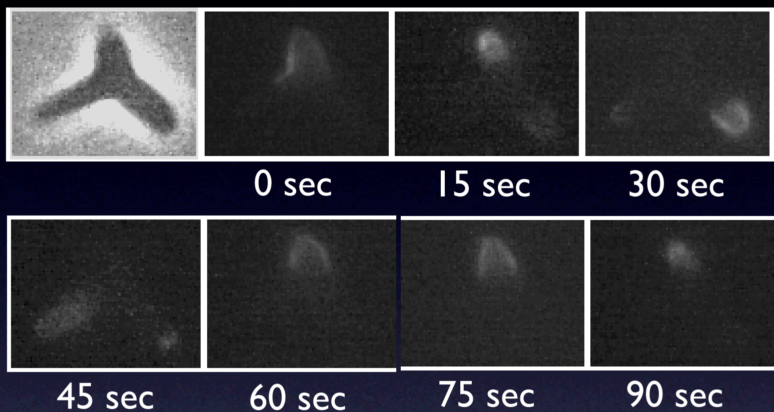
What happens in real cells?

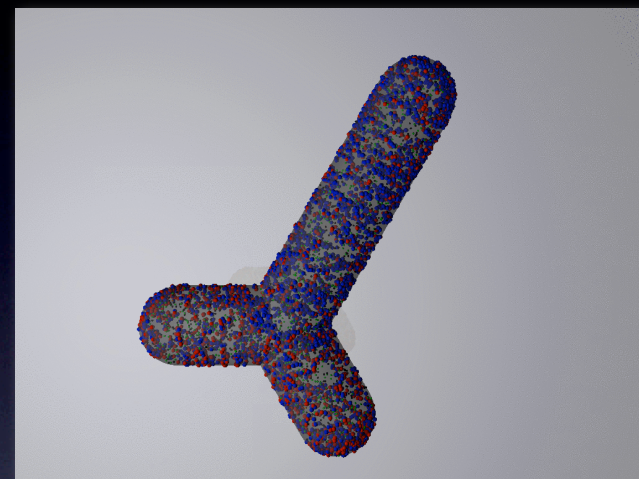


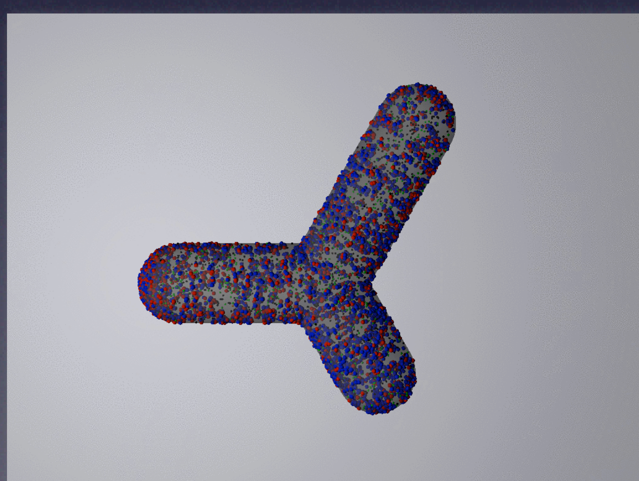
(Y. Shih, L. Rothfield)

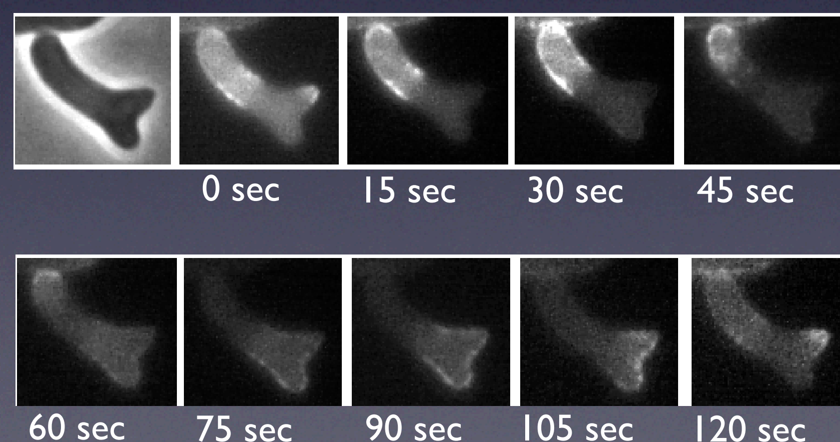
MinD-GFP

Branched cell shapes



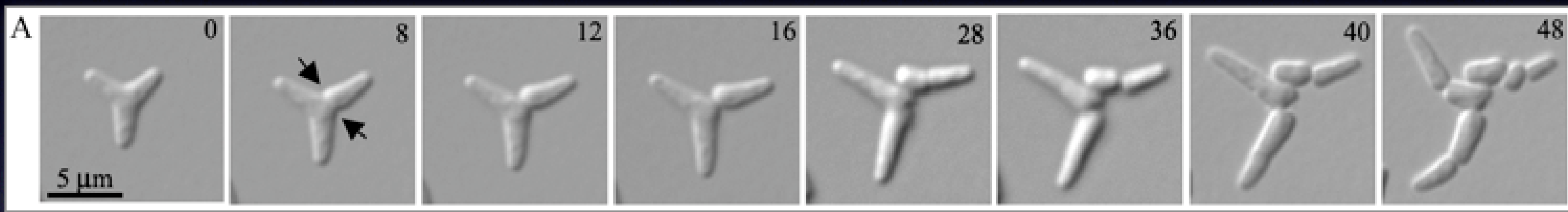




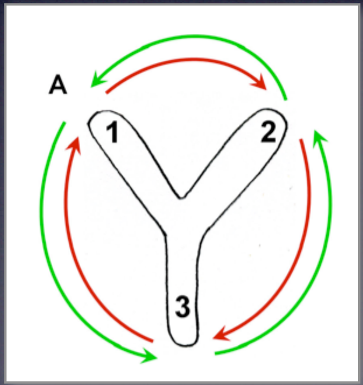


Varma, Huang, Young *J. Bacteriol.* (2008)

Min-protein regulation of cell shape



- Min oscillations select division planes near the point where the branches meet, thereby creating rod-shaped daughter cells
- Growth rate is nearly identical to wild-type

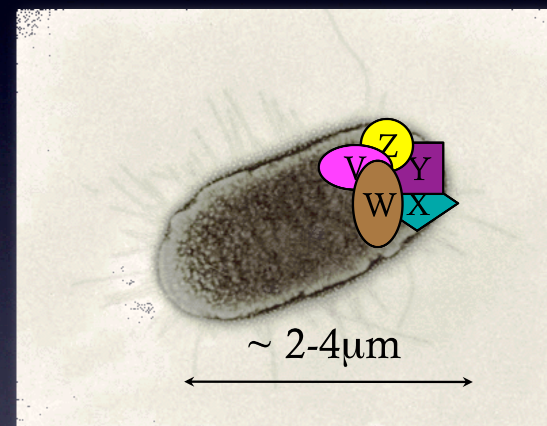


Conclusions

- 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,
  - Filamentous cell has "zebra stripe" pattern.
- Min oscillations observed in round cells are well-reproduced by our model.
- Protein oscillators may form a general mechanism by which the cell detects and exploits its own geometry,

Protein localization at bacterial poles

- Protein-protein interactions



- Turing oscillations
- Curvature
- Membrane organization and mechanics

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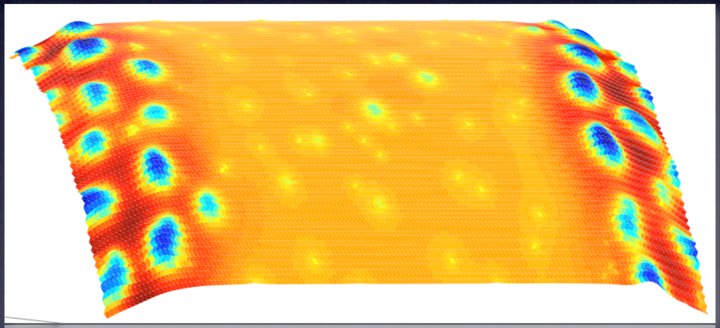
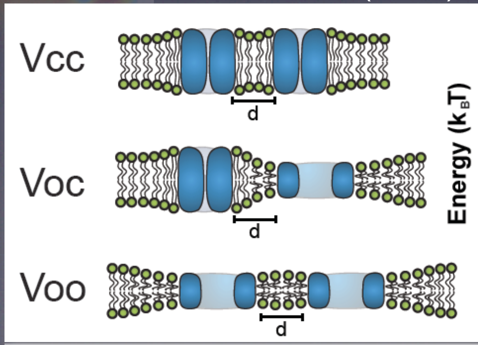
Huang et al, *PLoS Comp Biol* 2 (2006)



Ursell *et al*, *PLoS CB* 3 (2007)



Looking for postdocs

How is bacterial cell shape determined?
How does cell shape affect the organization of the cell?

Help shape the world!

STANFORD
BIOENGINEERING

Acknowledgments

Princeton
Wingreen Lab
Bonnie Bassler
Tom Silhavy
Zemer Gitai

Ranjan Mukhopadhyay (Clark)
Yigal Meir (Ben Gurion)
Tristan Ursell (Caltech)
Rob Phillips (Caltech)

Experimentalists
Piet de Boer (Case Western)
Joe Lutkenhaus (Kansas State)
Yu-Ling Shih, Larry Rothfield (UCHC)

Funding
NIH K25 Award
Helen Hay Whitney Foundation