L14: 13 Lectures past and 13 to go

Part I: ‘The cell as a well-stirred bioreactor’

*topics*
- Lambda phage lysis-lysogeny switch
- Synthetic genetic switch
- Switches as memory storage
- Chemotaxis: perfect adaptation or not?
- Synthetic genetic oscillators

*main assumption*
- well-stirred reactor
- absence of chemical gradients
  (justification: small cells, diffusion mixes)

Switch from Systems Microbiology to Systems Cell Biology

The importance of diffusion and gradients for cellular regulation

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Part II: Systems Cell Biology

‘Importance of gradients and diffusion in cellular regulation’

After two lectures on diffusion and reaction-diffusion equations, we will focus during the coming lectures on the following biological systems:

1. Eukaryotic chemotaxis
   Gradient sensing in *Dictyostelium* (aka ‘amoeba’)

2. Computing the middle of a cell
   Pole-to-pole oscillations in *Escherichia coli*

3. Self organization of the cytoskeleton

Prokaryotic versus eukaryotic cells

e.g E. coli, cyanobacteria
~ 10^6 bp, ~ 5000 genes
**Prokaryotic versus eukaryotic cells**

- **Eukaryotic Cell**
  - Nucleus
  - Chloroplasts
  - Mitochondria
  - Ribosomes

**e.g. yeast, amoeba, plants, flies, man & mice ...**

~ $10^9$ bp, ~ 40000 genes !!

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**Topic I: 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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**gfp-minC**
GFP-minD

gfp-minE is localized in a ring
Recent results demonstrate that the min proteins assemble in helices.

**Topic II: Gradient sensing**

similar to chemotaxis of E. coli, but now we cannot ignore the spatial dimensions

my favorite movie ...

neutrophil chasing a bacterium

*Dictyostelium* (amoeba)
sensing a gradient of cAMP

uniform step in cAMP

cAMP gradient
Response of Dictyostelium to cAMP

- **Uniform step in cAMP**
- **Cyclic AMP gradient**

**Initial distribution** $t \sim 3 \text{ s}$

**Steady-state distribution** $t \to \infty$

**Uniform and transient**

**Polarized and persistent**

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**GFP-PH** binds special lipids in membrane: PIP2 and PIP3

**Geometry of cell:**
- Circular
- Inside cytoplasm: well-stirred
- Inside membrane: diffusion-limited

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The molecules in the model:

- Plasma Membrane
- Cytosol
- Endoplasmic Reticulum

- Receptor Regulated Step
- PI
- PI(4,5)P2
- PIPK
- DGK
- DG
- Inositol
- IP3
- CDP,DG
- CDP,DGS
- PA
- PIP
- PIS

**Aggregation of a population of amoeba**

**Biological function:**
- Development of a multicellular structure
Topic III: Self-organization of the cytoskeleton
Center finding in an eukaryotic cell: fission yeast
The importance of the cytoskeleton

powerful reporter

**PH-GFP**
Positive feedback as a mechanisms for spontaneous cell polarization?

Cue-dependent polarization

Random polarization

- Neutrophils/Dictyostelium
- Yeast
- Light
- Fucus zygote
- Sperm
- Xenopus egg

No gradient

Lacking BUD1

No stimulus

Uniform activation

What is the dynamics of this symmetry breaking?

Experimental probe: Gic2p\(_{(1-208)}\)\(^{-}\)GFP (CRIB-GFP)

In the absence of the actin cytoskeleton symmetry breaking still occurs, but Cdc42p activity patch is immobilized.