7.81J/8.591J/9.531J

Systems Biology

Introducing ...

Lectures:	Recitations:
TR 1:00 -2:30 PM	W 4:00 - 5:00 PM
Alexander van Oudenaarden	Juan Pedraza

Text books: none

Handouts will be available on-line

Good reference (biology textbook):

Molecular biology of the cell

Alberts et al.

Matlab will be used intensively during the course, make sure you known (or learn) how to use it (necessary for problem sets)

Intrinsic challenge of this class:

mixed audience with wildly different backgrounds

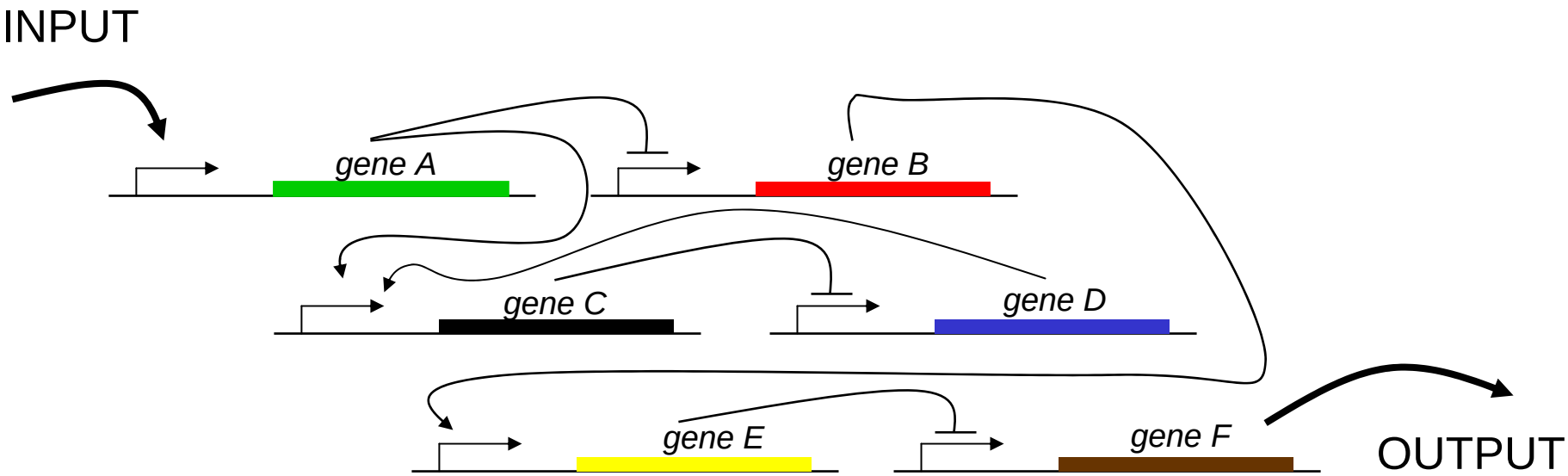
$\Rightarrow$ read up on your biology or math if needed

$\Rightarrow$ recitations (W 4PM,) are intended to
close the gaps and prepare for homework

Systems Biology ?

Systems Biology ≈ Network Biology

GOAL: develop a quantitative understanding of the biological function of genetic and biochemical networks



- function of gene product A-F can be known in detail but this is not sufficient to reveal the biological function of the INPUT-OUTPUT relation
- a system approach (looking beyond one gene/protein) is necessary to reveal the biological function of this whole network
- what is the function of the individual interactions (feedbacks and feedforwards) in the context of the entire network ?

Three levels of complexity

I Systems Microbiology (14 Lectures)

'The cell as a well-stirred biochemical reactor'

II Systems Cell Biology (8 Lectures)

'The cell as a compartmentalized system with concentration gradients'

III Systems Developmental Biology (3 Lectures)

'The cell in a social context communicating with neighboring cells'

I Systems Microbiology (14 Lectures)

'The cell as a well-stirred biochemical reactor'

L1	Introduction
L2	Chemical kinetics, Equilibrium binding, cooperativity
L3	Lambda phage
L4	Stability analysis
L5-6	Genetic switches
L7	*E. coli* chemotaxis
L8	Fine-tuned versus robust models
L9	Receptor clustering
L10-11	Stochastic chemical kinetics
L12-13	Genetic oscillators
L14	Circadian rhythms

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Introduction phage biology

Phage genome:
48512 base pairs ~ 12 kB
‘phage.jpg’ ~ 10 kB

Image removed due to copyright considerations.
See Ptashne, Mark. *A genetic switch: phage lambda.* 3rd ed. Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory Press, 2004.

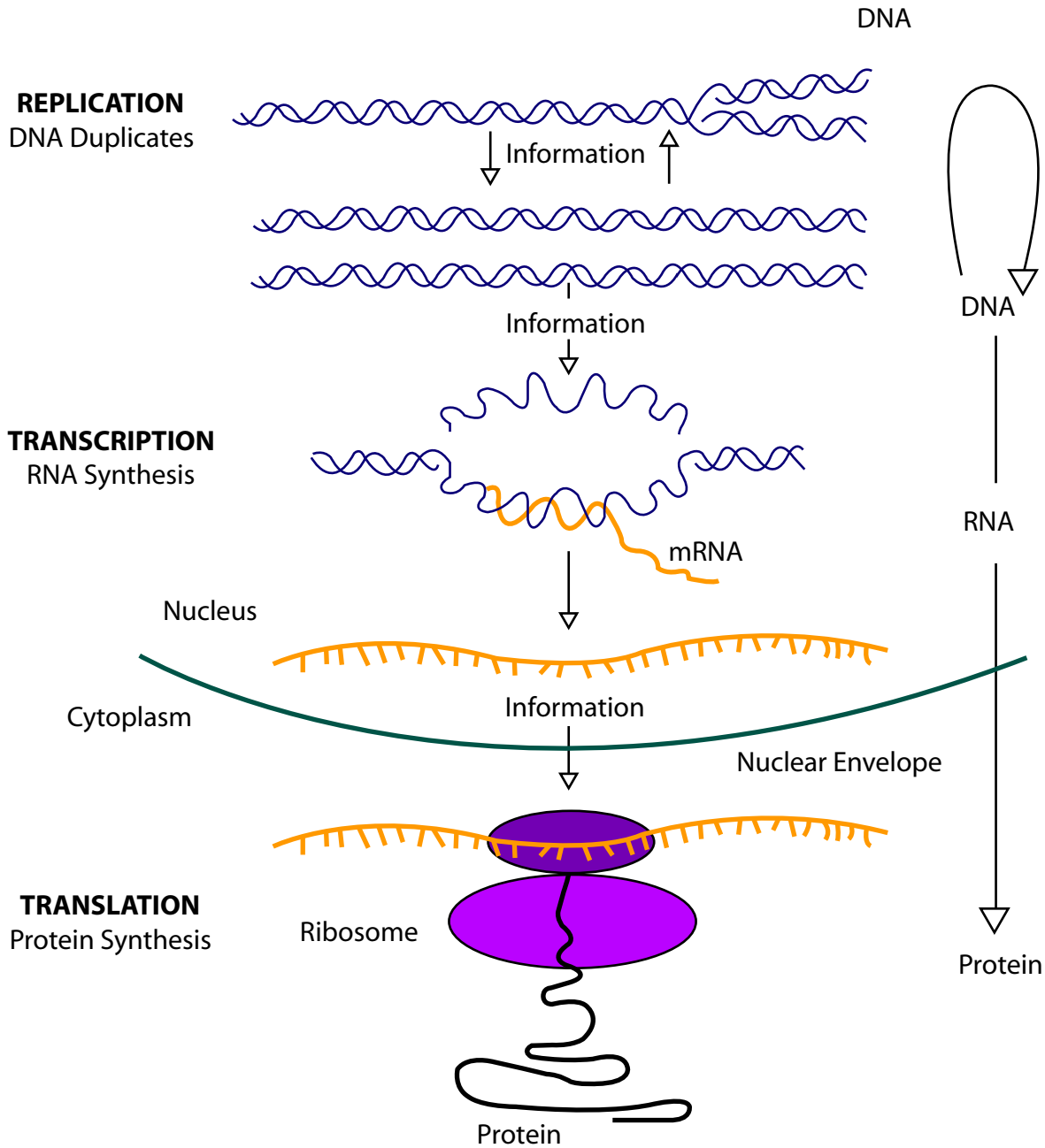

Image by MIT OCW.

The central dogma defines three major groups of biomolecules (biopolymers):

1. **DNA (passive library, 6×10^9 bp, 2 m/cell, 75×10^{12} cells/human, total length 150×10^{12} m/human ~ 1000 $r_{sun\text{-}earth}$)**

2. **RNA ('passive' intermediate)**
3. **Proteins (active work horses)**

The fourth (and final) group consists of so-called 'small molecules'.

4. **Small molecules (sugars, hormones, vitamines, 'substrates' etc.)**

The lysis-lysogeny decision:

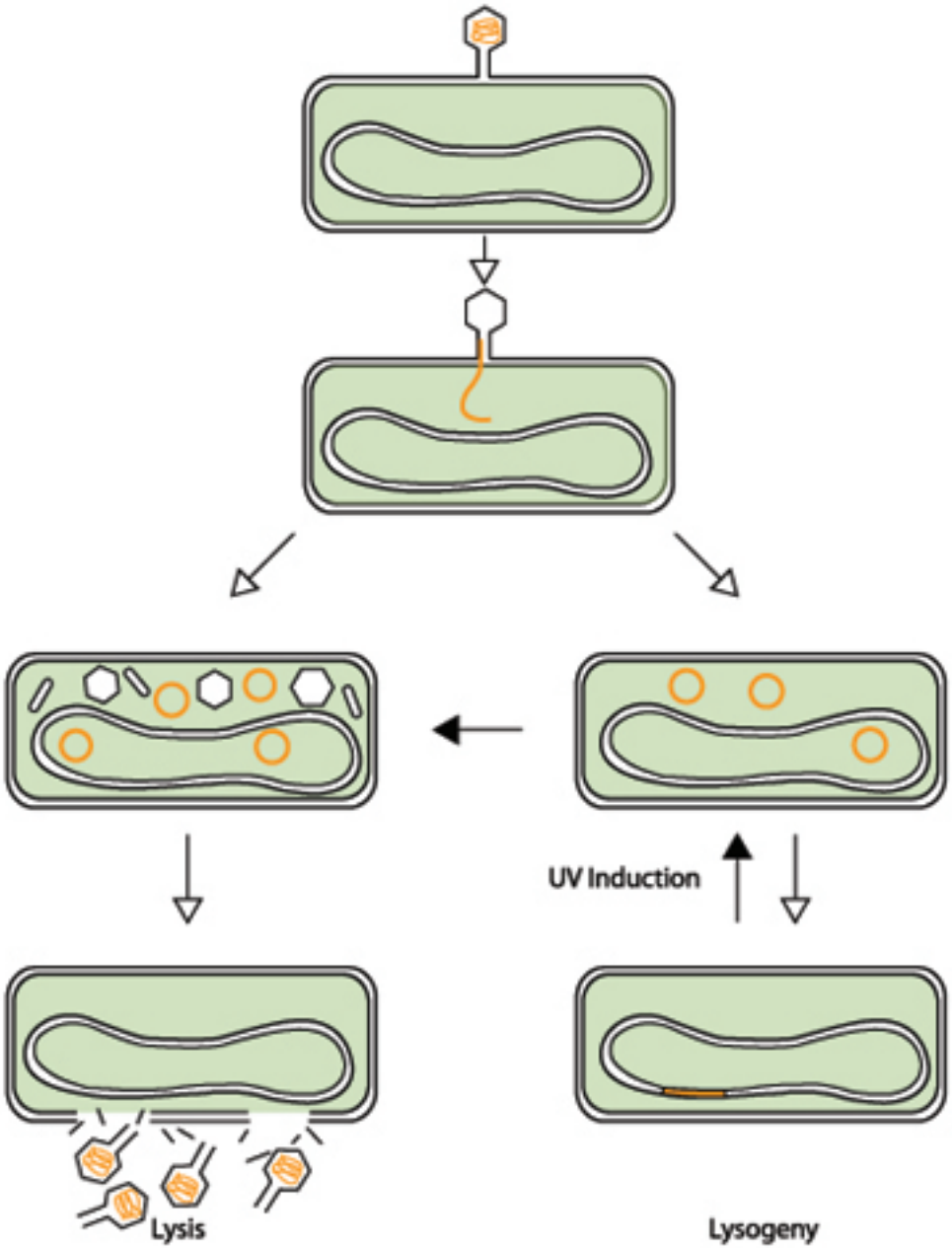

Image by MIT OCW.

As the phage genome is injected phage genes are transcribed and translated by using the host's machinery.

Which set of phage proteins are expressed determines the fate of the phage: lysis or lysogeny

The lysis-lysogeny decision is a genetic switch

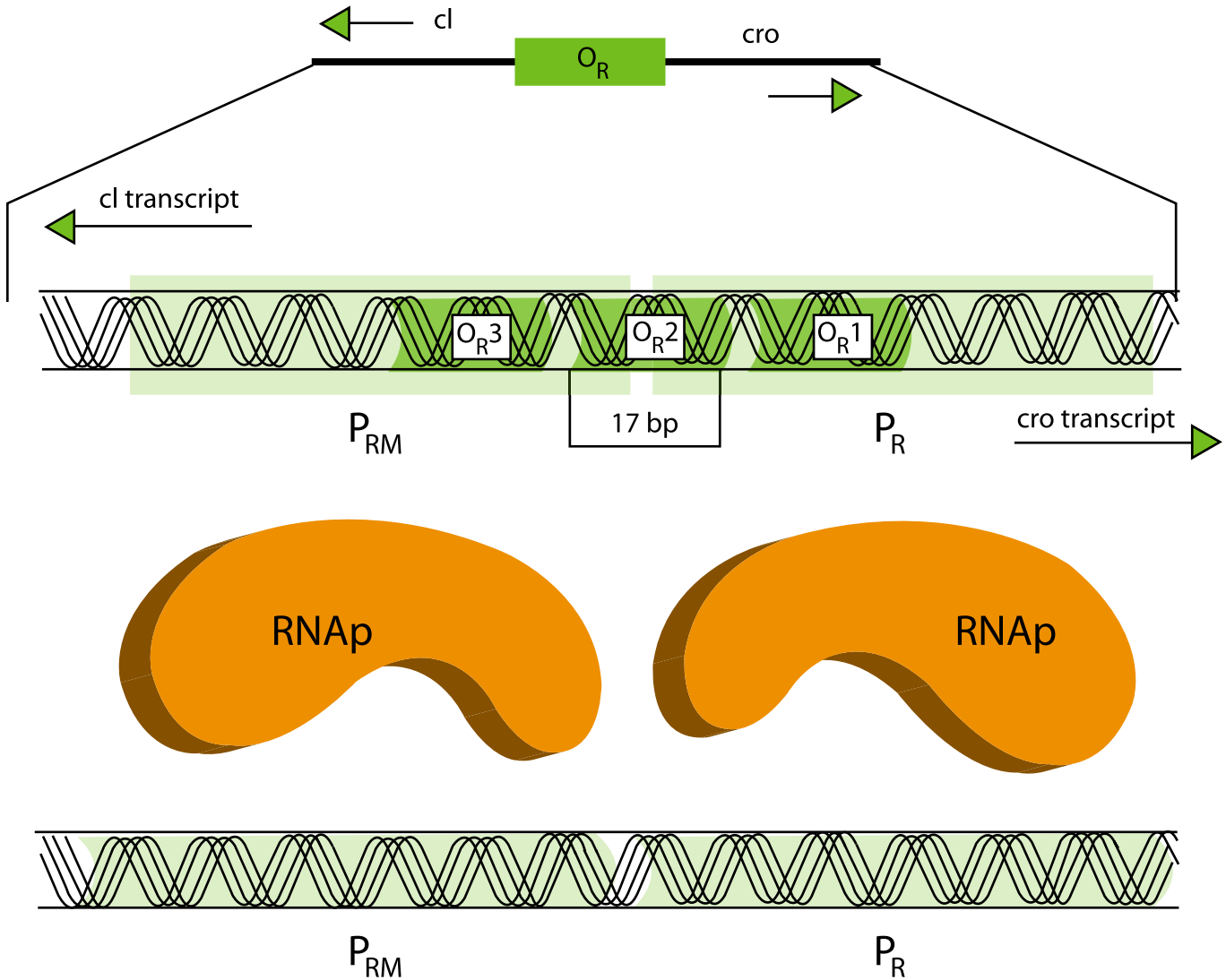

Image by MIT OCW. After Ptashne, Mark. *A genetic switch : phage lambda.* 3rd ed. Cold Spring Harbor, N.Y. : Cold Spring Harbor Laboratory Press, 2004.

Single repressor dimer bound - three cases:

I Negative control, dimer binding to OR2 inhibits RNAp binding to right P_R promoter.

Positive control, dimer binding to OR2 enhances RNAp binding to left P_{RM} promoter.

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See Ptashne, Mark. *A genetic switch: phage lambda.*
3rd ed. Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory Press, 2004.

II Negative control, dimer binding to OR1 inhibits RNAp binding to right P_R promoter.

Negative control, dimer binding to OR1 inhibits RNAp binding to left P_{RM} promoter (too distant).

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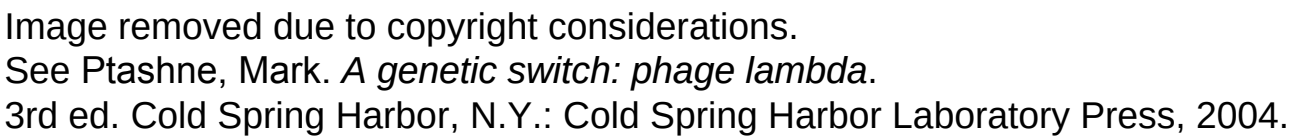
See Ptashne, Mark. *A genetic switch: phage lambda*.
3rd ed. Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory Press, 2004.

III Negative control, dimer binding to OR3 inhibits RNAp binding to left P_{RM} promoter.

Positive control, dimer binding to OR3 allows RNAp binding to right P_R promoter.



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See Ptashne, Mark. *A genetic switch: phage lambda*.
3rd ed. Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory Press, 2004.

Repressor-DNA binding is highly cooperative

intrinsic association constants:

$K_{OR1} \sim 10\ K_{OR2} \sim 10\ K_{OR3}$

However $K_{OR2}^{*} >> K_{OR2}$ (positive cooperativity)

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See Ptashne, Mark. *A genetic switch: phage lambda*.
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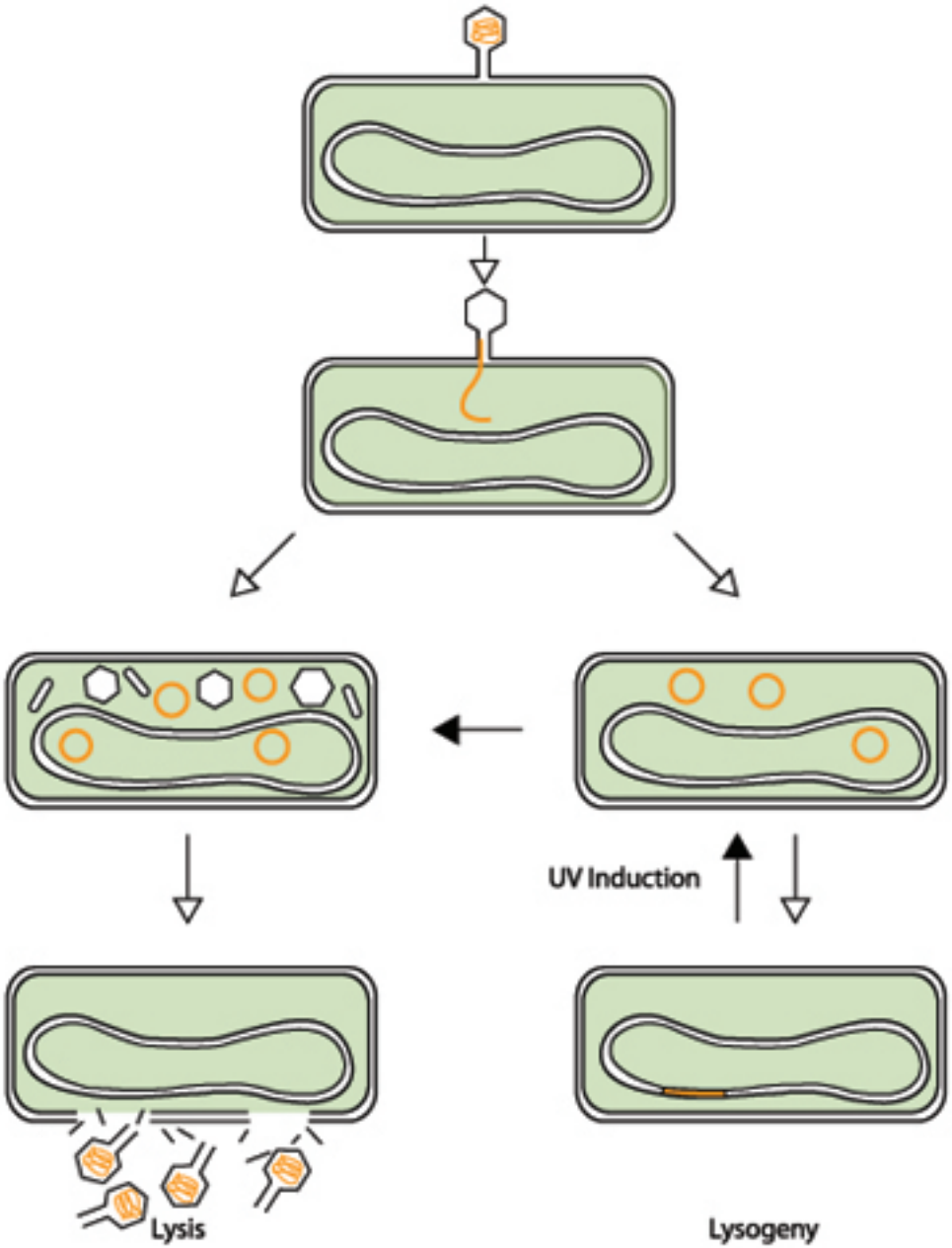
Flipping the switch by UV:



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In lysogenic state, [repressor] is maintained at constant level by negative feedback

UV radiation induces SOS response (DNA damage)
protein RecA becomes specific protease for λ repressor

after cleavage monomers cannot dimerize anymore,
[repressor dimers] decreases,
when all repressors vacate DNA, Cro gene switches on.

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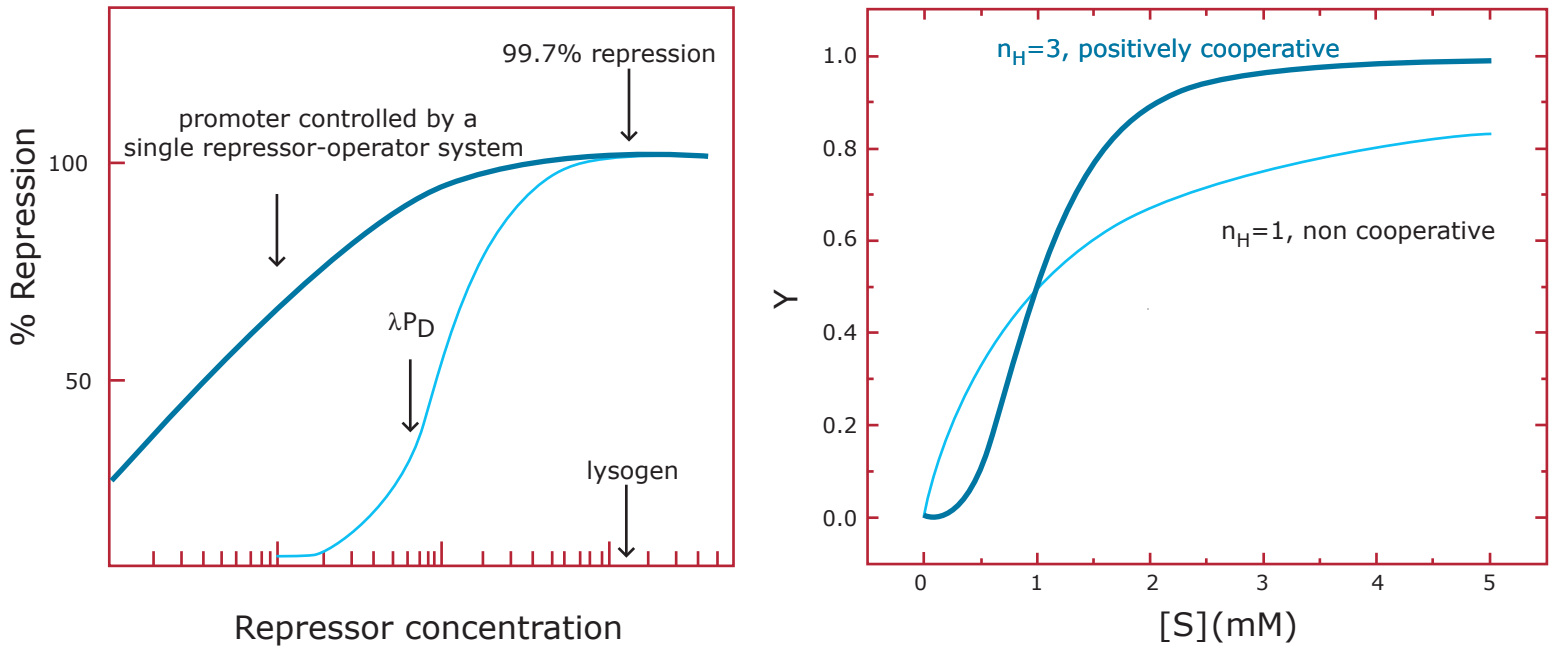
Cooperative effects make sharp switch ('well defined' decision)



Images by MIT OCW.

Note: several layers of cooperativity:
dimerization, cooperative repressor binding

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The Flagellum

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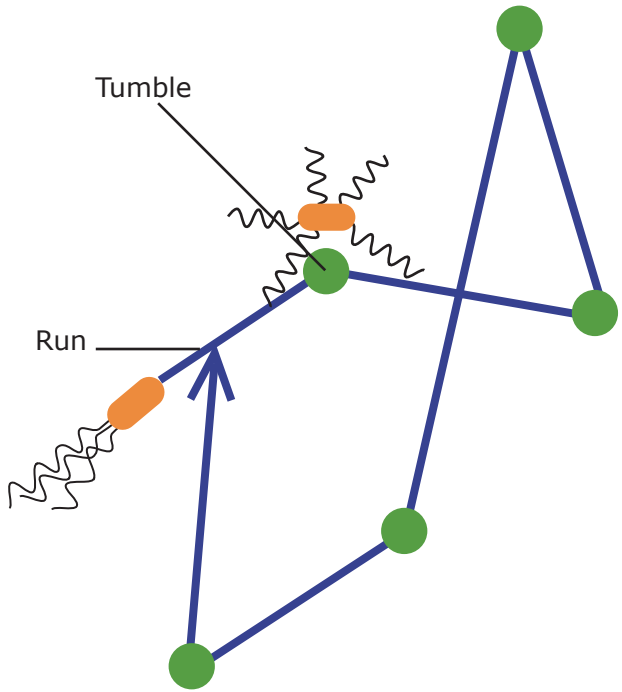
Absence of chemical attractant



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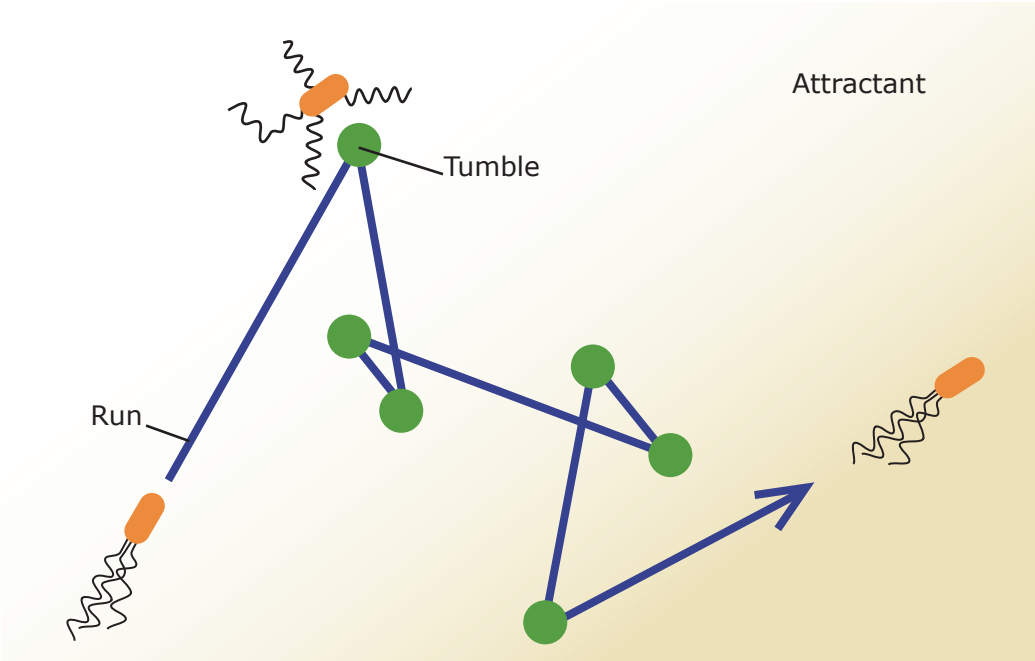
Presence of chemical attractant



Chemical Gradient Sensed in a Temporal Manner

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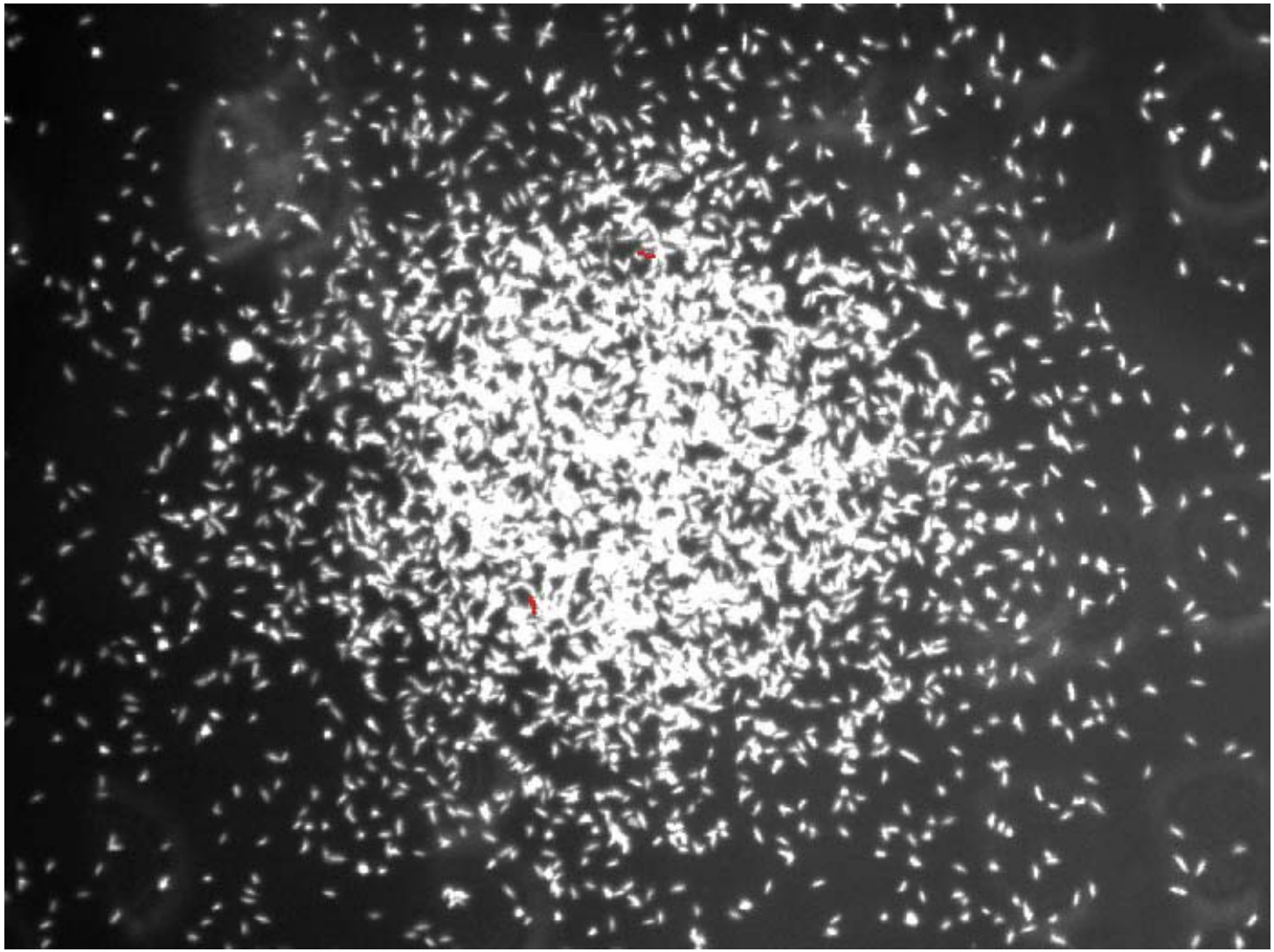


Figure 1A in Mittal, N., E. O. Budrene, M. P. Brenner, and A. Van Oudenaarden. "Motility of Escherichia coli cells in clusters formed by chemotactic aggregation." *Proc Natl Acad Sci U S A*. 100, no. 23 (Nov 11, 2003): 13259-63. Epub 2003 Nov 03.

Chemotaxis of *Escherichia coli*

Images removed due to copyright considerations.

absence aspartate gradient → random walk (diffusion)

presence aspartate gradient → biased random walk towards aspartate source

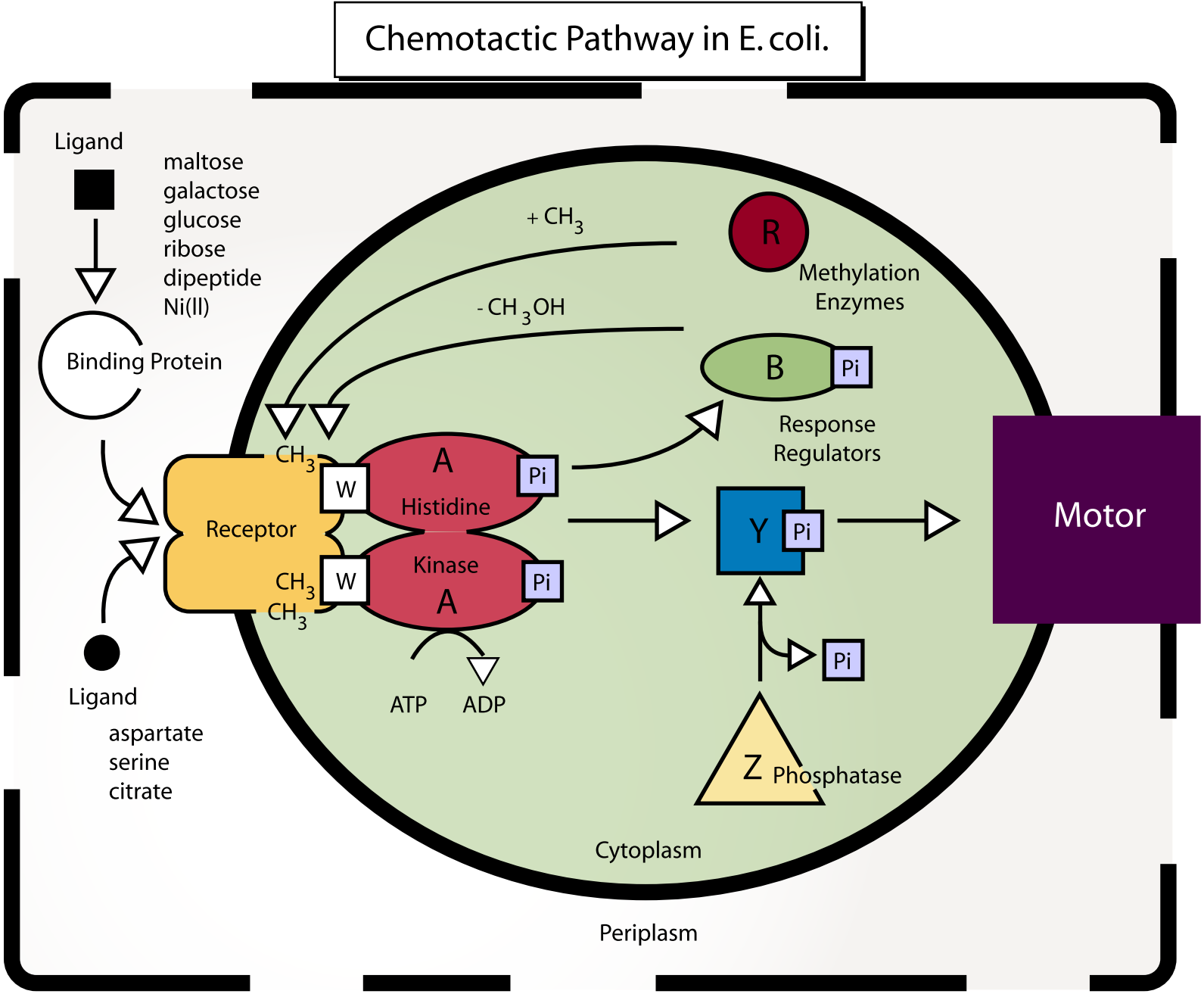
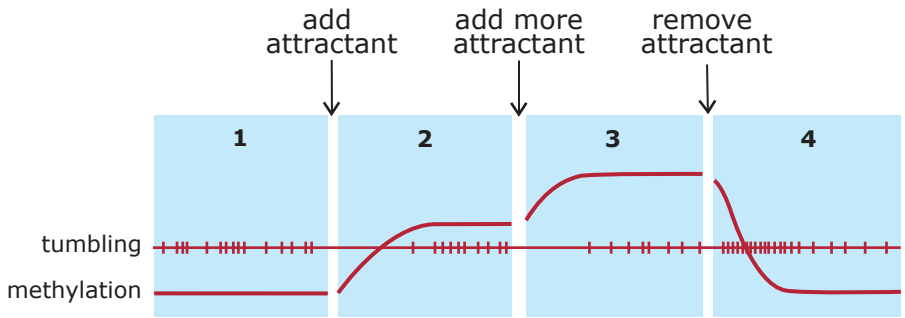


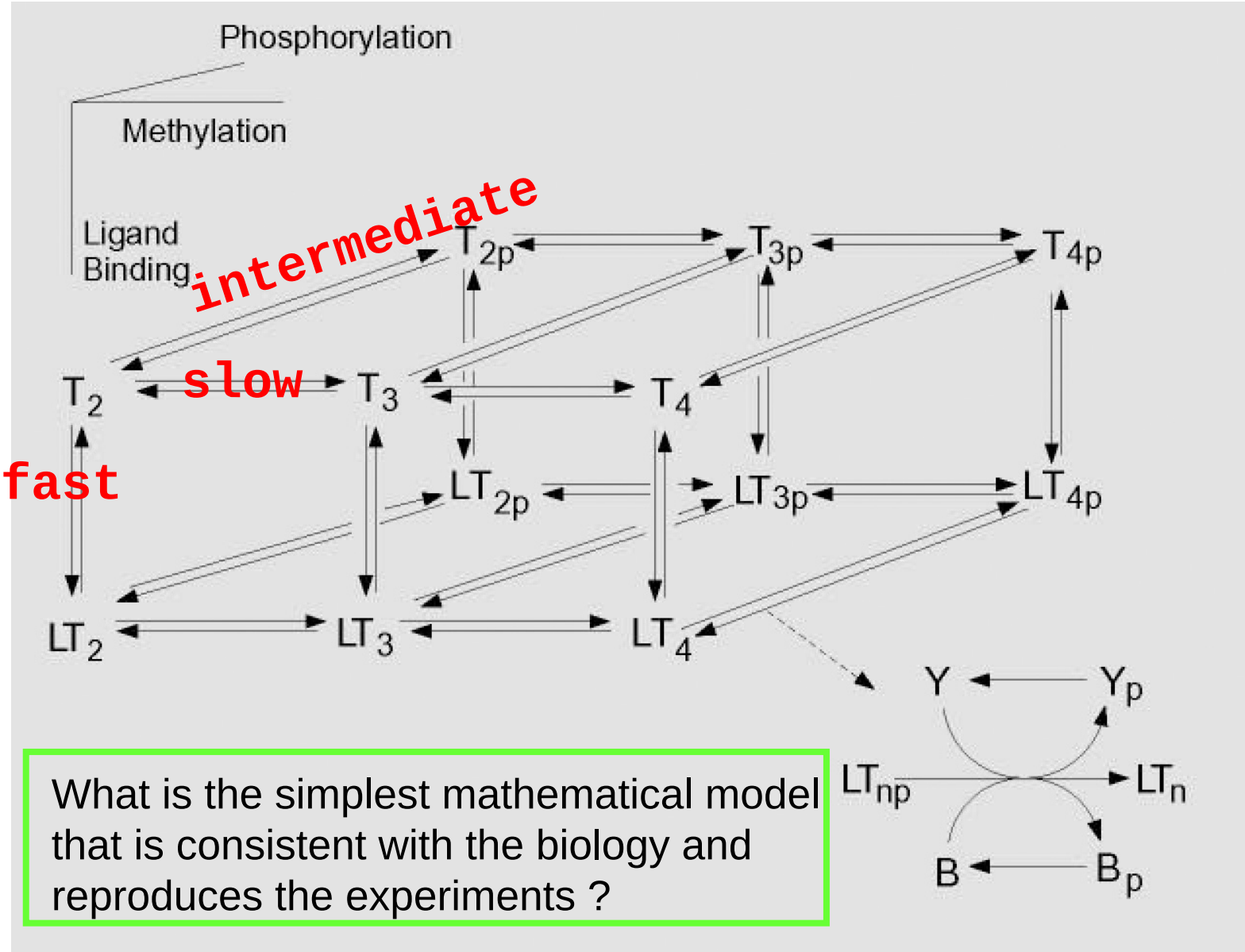
Image by MIT OCW. After figure 4 in Falke, J. J., R. B. Bass, S. L. Butler, S. A. Chervitz, and M. A. Danielson. "The two-component signaling pathway of bacterial chemotaxis: a molecular view of signal transduction by receptors, kinases, and adaptation enzymes." *Annu Rev Cell Dev Biol* 13 (1997):457-512.

Adaptation:



Correlation of Receptor Methylation with Behavioral Response

Image by MIT OCW.



What is the simplest mathematical model that is consistent with the biology and reproduces the experiments ?

Figures 2 in Spiro, P. A., J. S. Parkinson, and H. G. Othmer. "A model of excitation and adaptation in bacterial chemotaxis." *Proc Natl Acad Sci U S A.* 94, no. 14 (Jul 8, 1997): 7263-8.

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'The cell as a well-stirred biochemical reactor'

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II Systems Cell Biology (8 Lectures)

'The cell as a compartmentalized system with concentration gradients'

L15	Diffusion, Fick's equations, boundary and initial conditions
L16	Local excitation, global inhibition theory
L17-18	Models for eukaryotic gradient sensing
L19-20	Center finding algorithms
L21-22	Modeling cytoskeleton dynamics

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Eukaryotic Chemotaxis

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How is this different from E. coli chemotaxis ?

temporal versus spatial sensing

cyclic AMP (cAMP) is an attractant for Dictyostelium (social amoeba)

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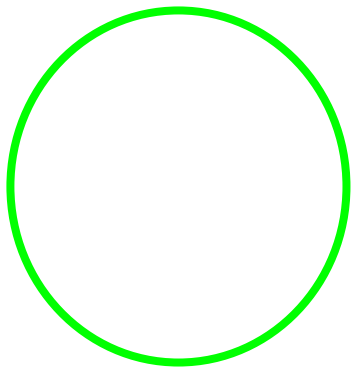
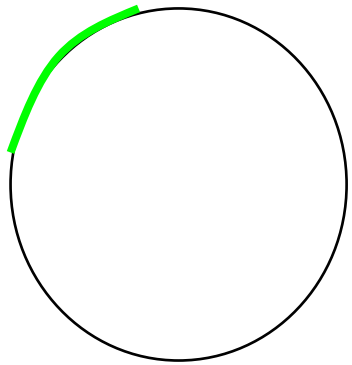
Response of Dictyostelium to cAMP

uniform step in cAMP

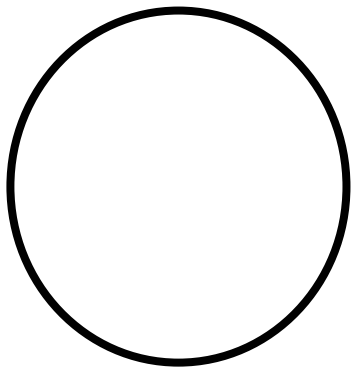
cAMP gradient

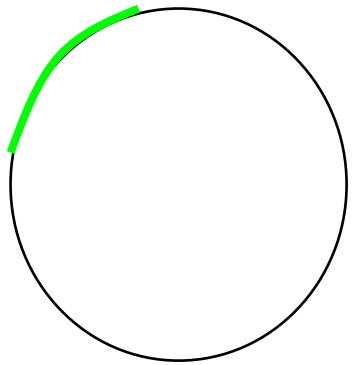
initial distribution t ~ 3 s





steady-state distribution t → ∞





uniform and transient

polarized and persistent

geometry of cell: circular
inside cytoplasm: well-stirred
inside membrane: diffusion-limited

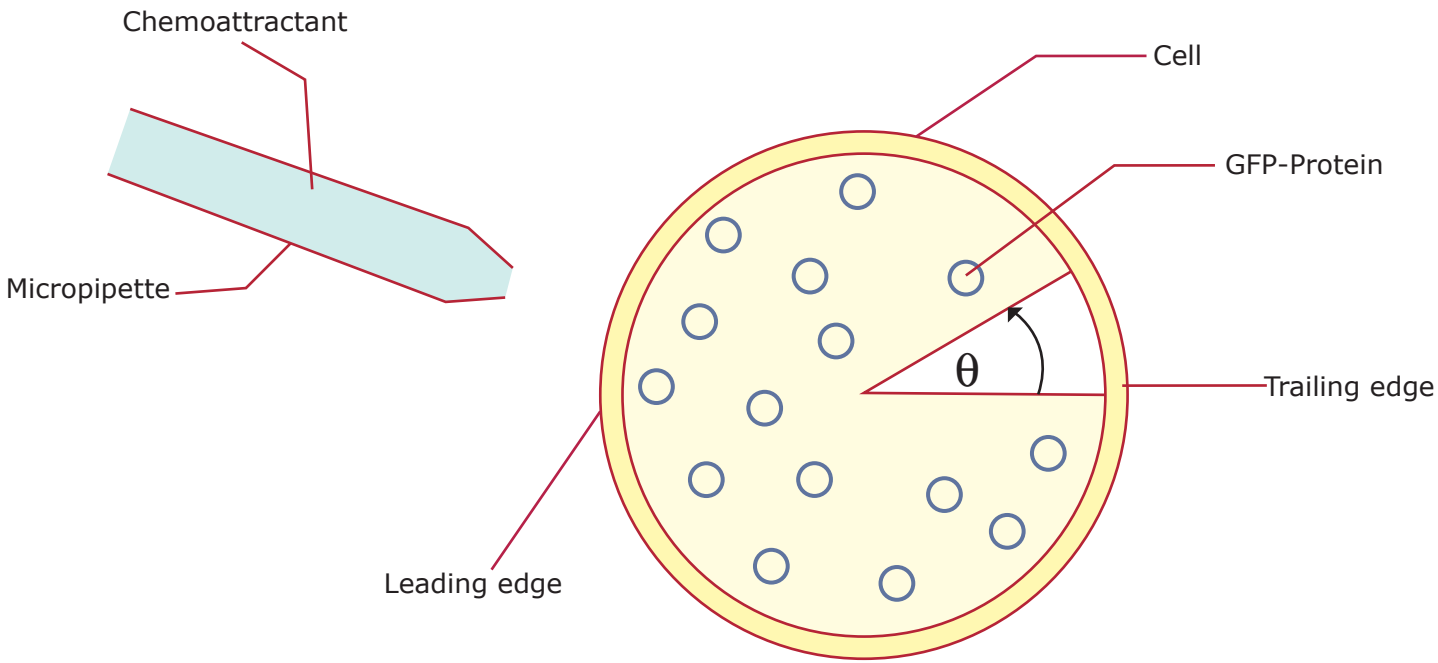
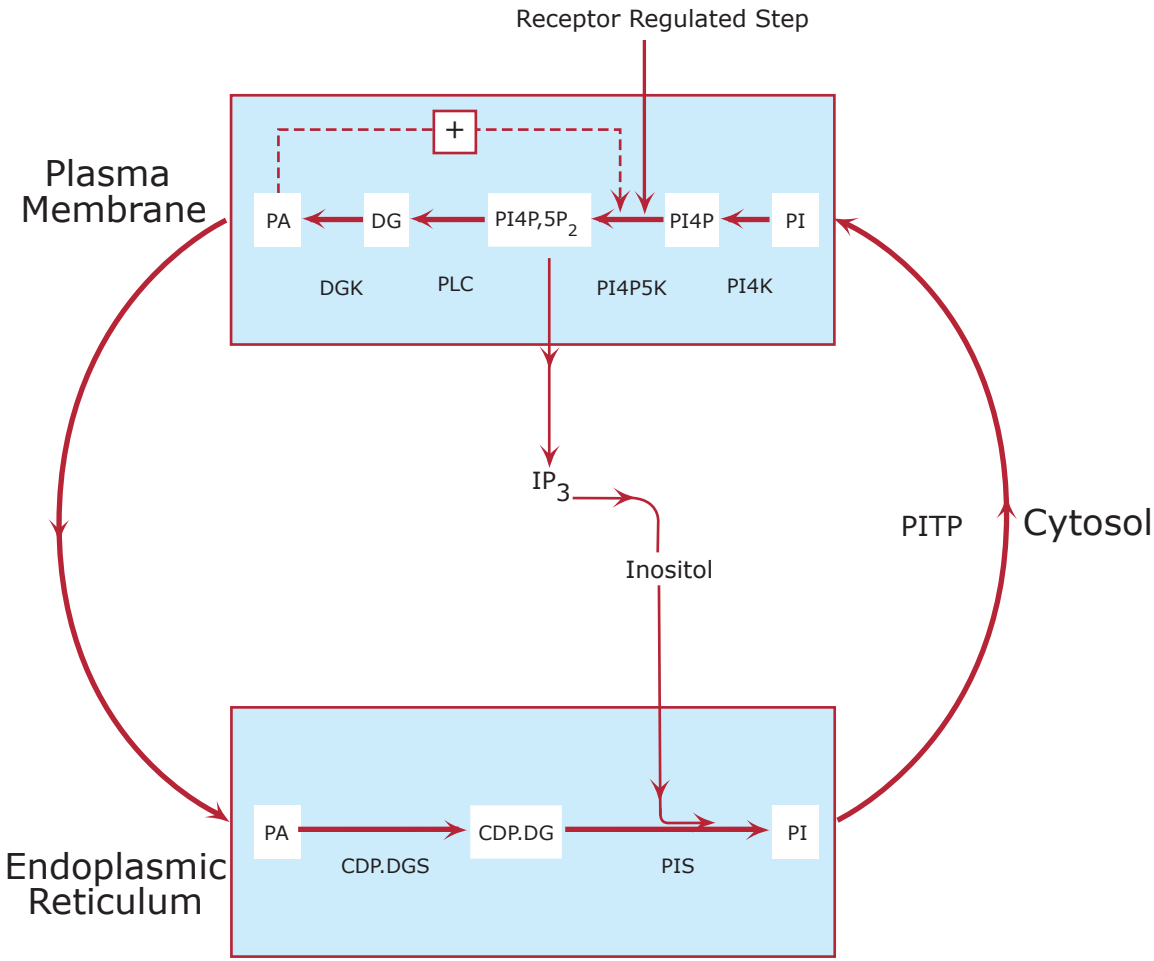


Image by MIT OCW.

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

The molecules in the model:



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how to find the middle of a cell ?

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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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Recent results demonstrate that the min proteins assemble in helices

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Center finding in an eukaryotic cell: fission yeast
The importance of the cytoskeleton

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III Systems Developmental Biology (3 Lectures)

'The cell in a social context communicating with neighboring cells'

L23 Quorum sensing
L24-25 Drosophila development

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'The cell in a social context communicating with neighboring cells'

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L24-25	Drosophila development

major advantage of Drosphila:

each stripe in the embryo corresponds to certain body parts in adult fly

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interpreting the bicoid gradient (created by maternal effects) by zygotic effect (gene expression by embryo itself)

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hunchback reads the bicoid gradient

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Center finding in the Drosophila embryo

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