

## Modeling signal transduction

Receptor - ligand binding - assumed to be elementary reaction  
 Methylation, phosphorylation reactions – catalyzed by enzymes,  
 Michaelis-Menten kinetics assumed  
 Dephosphorylation, protein degradation – spontaneous or catalyzed  
 Protein synthesis –catalyzed by mRNA

Continuous and deterministic models.

Steps: Designate one component as signal and one as response;

Write rates of change for the concentration of components;

Find steady state concentrations;

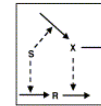
Determine the dependence of the steady state response on the signal strength

J. Tyson, K. Chen, B. Novak, *Curr. Opin. Cell Biology* 15, 221 (2003)

## Feed-forward loop

The signal acts on R both directly, and through an intermediary. S is assumed to work at saturation (plentiful substrate). The catalyzed decay is assumed to be elementary.

Incoherent feed-forward



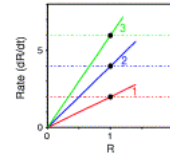
$$\frac{dR}{dt} = k_1 S - k_2 X R$$

$$\frac{dX}{dt} = k_3 S - k_4 X$$

Steady state:

$$X_{SS} = \frac{k_3 S}{k_4}$$

$$R_{SS} = \frac{k_1 k_4}{k_2 k_3}$$



## Perfect adaptation

Assume that S has several step changes,

assume  $k_1 = k_2 = k_3 = k_4 = k$

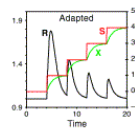
$$X_{SS}^1 = S^1 \quad \frac{dX}{dt} = k(S - X) \quad X_{SS}^2 = S^2$$

X increases until it reaches another steady state

$$R_{SS}^1 = I \quad \frac{dR}{dt} = kS - k X R$$

R increases, then starts to decrease, and finally settles into a new steady state

$$R_{SS}^2 = I = R_{SS}^1$$



adaptation

## Ex: Coherent feed-forward loop

The synthesis of protein R is activated by two catalysts: S and X. The degradation of R is not catalyzed. S activates the synthesis of X, while X decays freely.

1. Draw two network diagrams for this process.
2. Write down the equations for the rate of change of the concentrations of R and X.
3. Assume that X is in a steady state. How does the rate of synthesis and decay of R depend on the concentration of R and S?
4. Find the steady state concentration of R. How does this differ from the case when only S catalyzes R synthesis?
5. What is your expectation for the dynamical behavior of R if S goes through consecutive step changes?

## Positive feedback

R is catalyzing the phosphorylation of E, and  $E_p$  feeds back to R  
Assume Michaelis-Menten kinetics for the phosphotransfer.



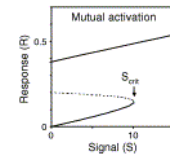
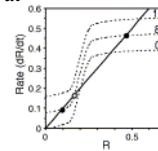
$$\frac{dR}{dt} = k_0 E_p(R) + k_1 S - k_2 R$$

$$\frac{dE_p}{dt} = k_3 R \frac{E_T - E_p}{K_{M3} + E_T - E_p} - k_4 \frac{E_p}{K_{M4} + E_p}$$

Steady state for  $E_p$   $E_{p,ss} = E_T G\left(k_3 R, k_4, \frac{K_{M3}}{E_T}, \frac{K_{M4}}{E_T}\right)$

## Positive feedback (cont.)

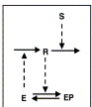
$$\frac{dR}{dt} = k_0 E_T G(k_3 R, \dots) + k_1 S - k_2 R$$



For  $S < S_{crit}$  there are three possible steady-state R values.  
Two of these solutions are stable - **bistability**  
At  $S = S_{crit}$  the response increases abruptly and irreversibly -  
**one-way switch**

## Negative feedback

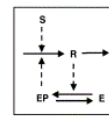
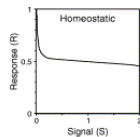
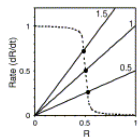
R inhibits the enzyme catalyzing its synthesis.



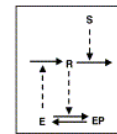
$$\frac{dR}{dt} = k_0 E(R) - k_1 S R$$

$$\frac{dE}{dt} = -k_3 R \frac{E}{K_{M3} + E} + k_4 \frac{E_T - E}{K_{M4} + E_T - E}$$

$$E_{ss} = E_T \left( 1 - G\left(k_3 R, k_4, \frac{K_{M3}}{E_T}, \frac{K_{M4}}{E_T}\right) \right)$$



Positive feedback



Negative feedback

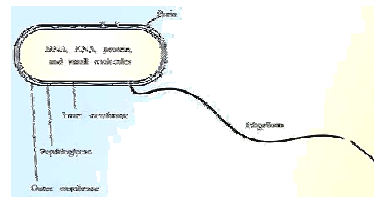
1. What other difference is between these two processes besides the nature of the feedback? Is it important for the end result?
2. The negative regulation in all these examples was taken into account as a catalysis of the degradation process. How would you represent negative regulation of the synthesis?

### Example: Modeling signal transduction in bacterial chemotaxis

System is biologically defined; known motile behavior  
**Input:** concentration of proteins in the signal transduction network  
**Hypotheses:** receptor state determines the transmitter's efficiency  
**Validation:** reproduces known output.  
**Explored:** changes in reaction rates.  
**Insight:** overall behavior is robust to changes in individual rates .

N. Barkai and S. Leibler, *Nature* 387, 913 (1997)  
 P. A. Spiro, J. S. Parkinson, H. G. Othmer, *PNAS* 94, 7263 (1997)

### E. coli live in the gut and feed on amino-acids

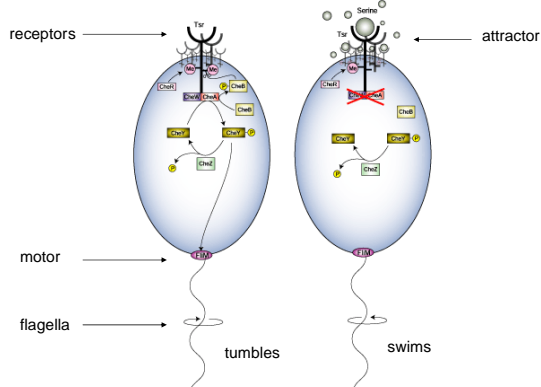


E. coli moves by rotating its flagella  
 CCW- flagella rotate together  
 CW- flagella independent

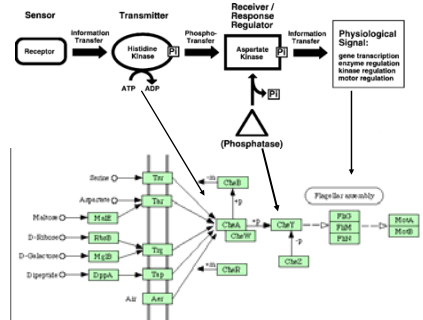
In homogenous environments the motion is a random combination of runs and tumbles



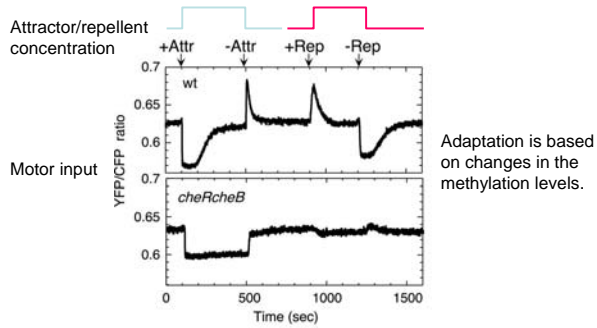
### Bacteria change the direction of their motion in response to chemical signals



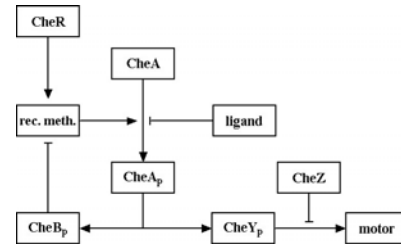
### The signal transduction network is an example of a two-component pathway



### Bacteria respond to concentration changes but adapt to a constant stimulus



### Negative feedback as the source of adaptation



The steady state concentrations are determined by the equilibrium between activation and inhibition.

### Modeling the signal transduction network

Input: ligand (signal) concentration

Variables: concentrations of

- the different (ligand bound, methylated,...) states of the receptor complex
- CheR, CheB, CheB<sub>p</sub>, CheY, CheZ

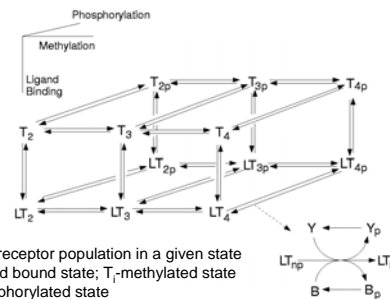
Output: the concentration of CheY<sub>p</sub>

Method: differential equations describing the reaction kinetics.

Three types of reaction: ligand binding, phosphorylation, methylation.

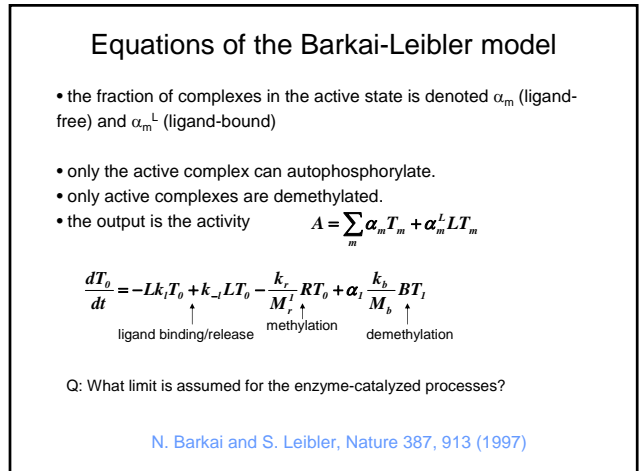
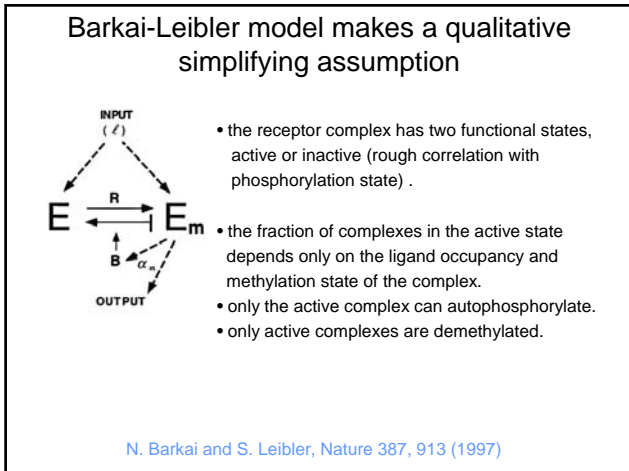
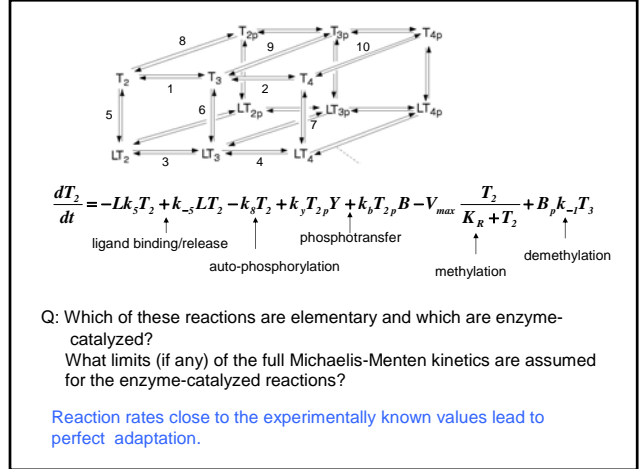
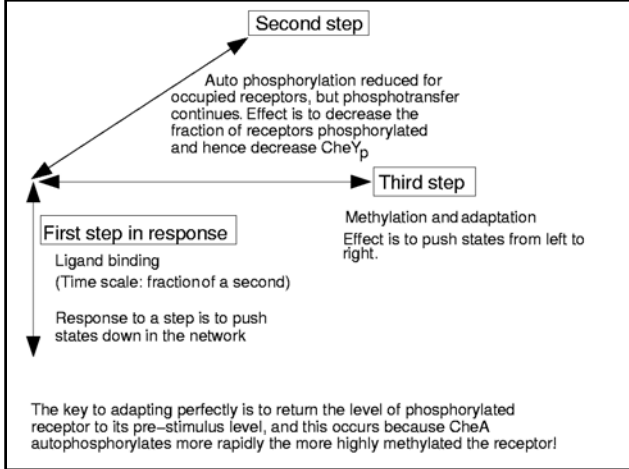
N. Barkai and S. Leibler, *Nature* 387, 913 (1997)  
 P. A. Spiro, J. S. Parkinson, H. G. Othmer, *PNAS* 94, 7263 (1997)

### The Spiro-Parkinson-Othmer model takes into account all reactions

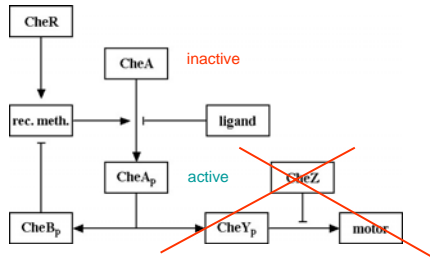


Edges mean mass transfer

P. A. Spiro, J. S. Parkinson, H. G. Othmer, *PNAS* 94, 7263 (1997)

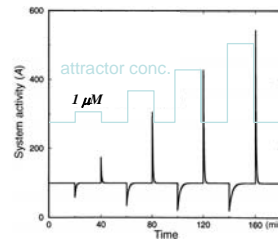


### Negative feedback as the source of adaptation



The steady state concentrations are determined by the occupancy of the active and inactive states.

### The Barkai-Leibler model exhibits perfect adaptation



Reference system

$$\alpha_0 = \alpha_0^L = \alpha_1^I = 0$$

$$\alpha_1 = \alpha_2^L = 0.1, \quad \alpha_2 = \alpha_3^I = 0.5$$

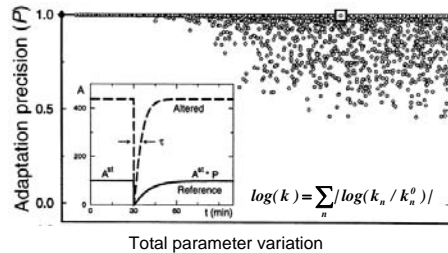
$$\alpha_3 = 0.75, \quad \alpha_4 = \alpha_4^I = 1$$

plausible values for rate constants

The system activity is independent of the constant ligand concentration.

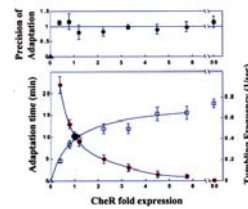
### Adaptation is robust to factor of two changes in the biochemical parameters

Step-like addition of a saturating amount (mM) of attractant



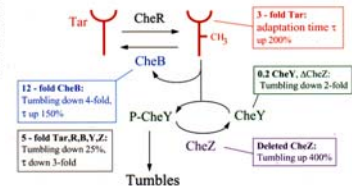
The adaptation time does depend on the biochemical parameters.

### Effect of varying CheR concentration



### Experimental confirmation of robustness

#### Varying different proteins in the network

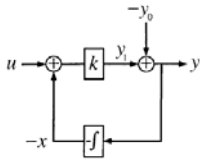


Adaptation precise to within 10% in all cases

U. Alon et al. Nature 397, 168 (1999)

$\tau$  - adaptation time

### Perfect adaptation due to integral feedback



$$\begin{matrix} \dot{x} = y & y(t) \rightarrow 0 \text{ as } t \rightarrow \infty \\ y = y_1 - y_0 & \text{iff} \\ = k(u - x) - y_0 & k > 0 \end{matrix}$$

M – total methylation level

$$\frac{dM}{dt} = r - bA$$

- r - global methylation rate
- b - global demethylation rate
- A – fraction of receptors in the active state

In effect, the biological system is using an engineering principle well known for effective adaptation.

T. M. Yi et al. PNAS 97, 4649 (2000)