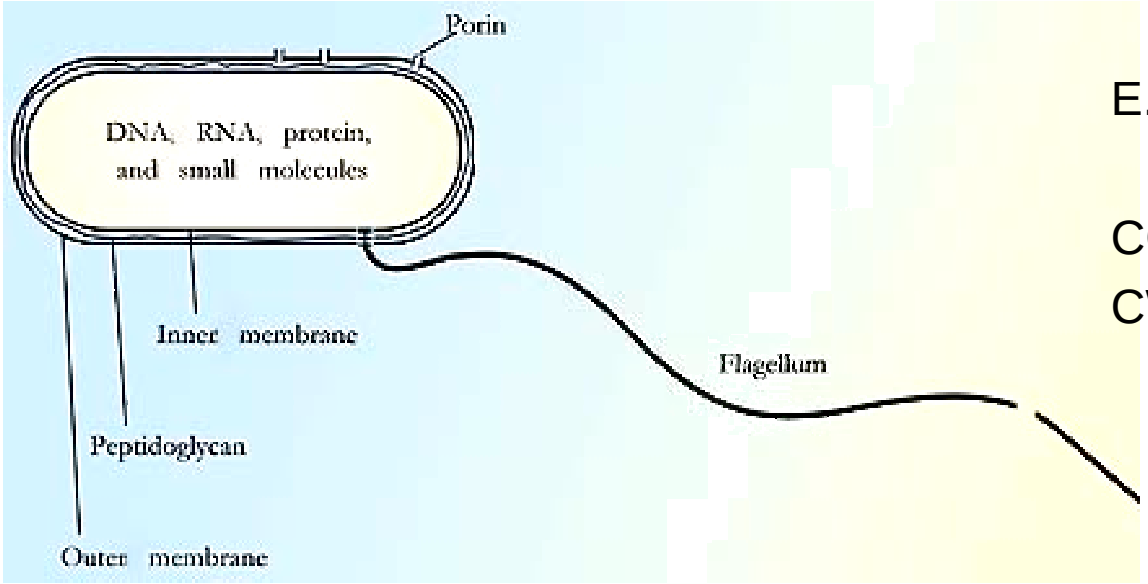
Bacterial chemotaxis and the question of high gain in signal transduction

Réka Albert

Department of Physics

E. coli lives in the gut and takes up nutrients through its pores



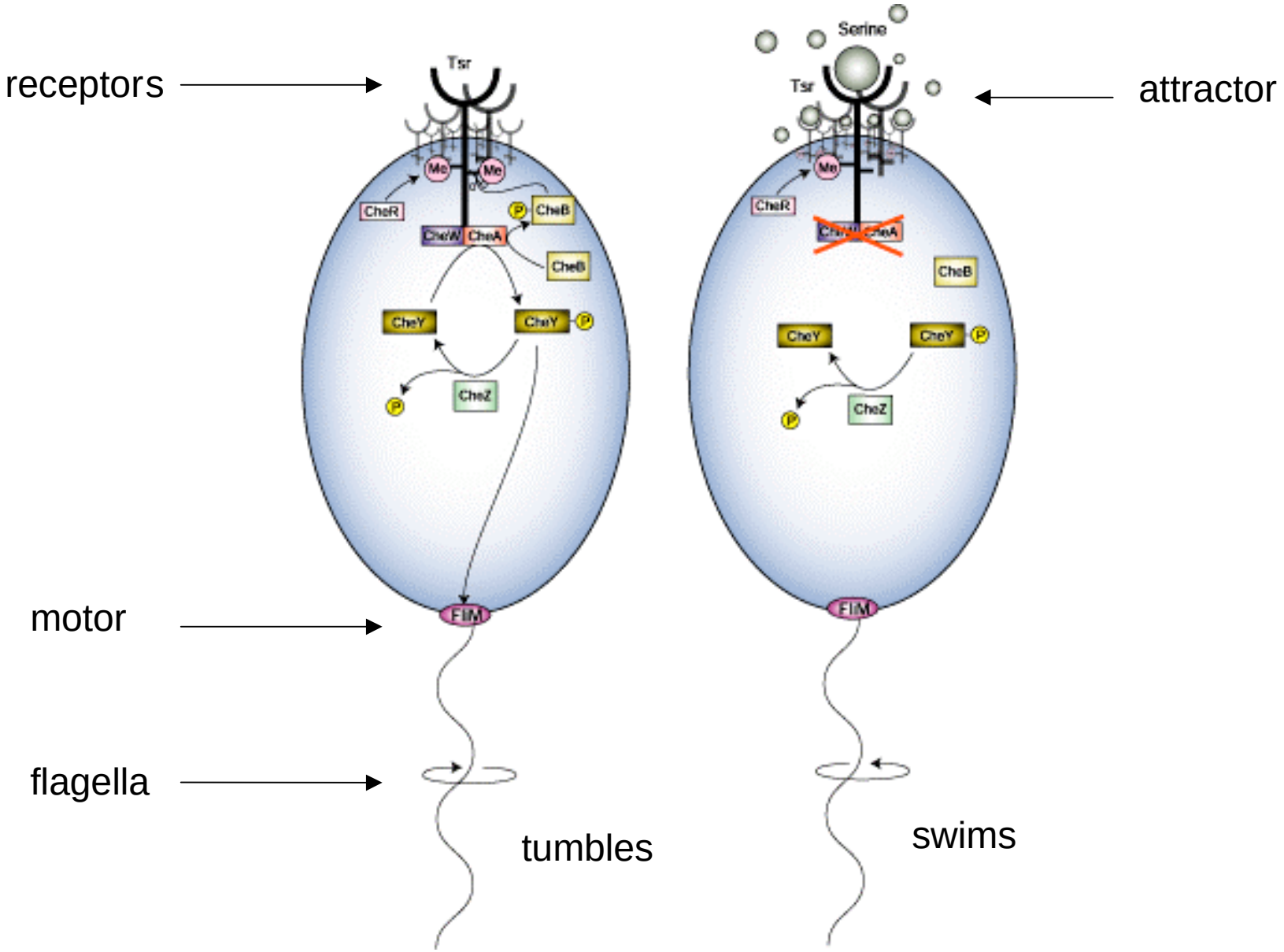
E. coli moves by rotating its flagella

CCW- flagella rotate together

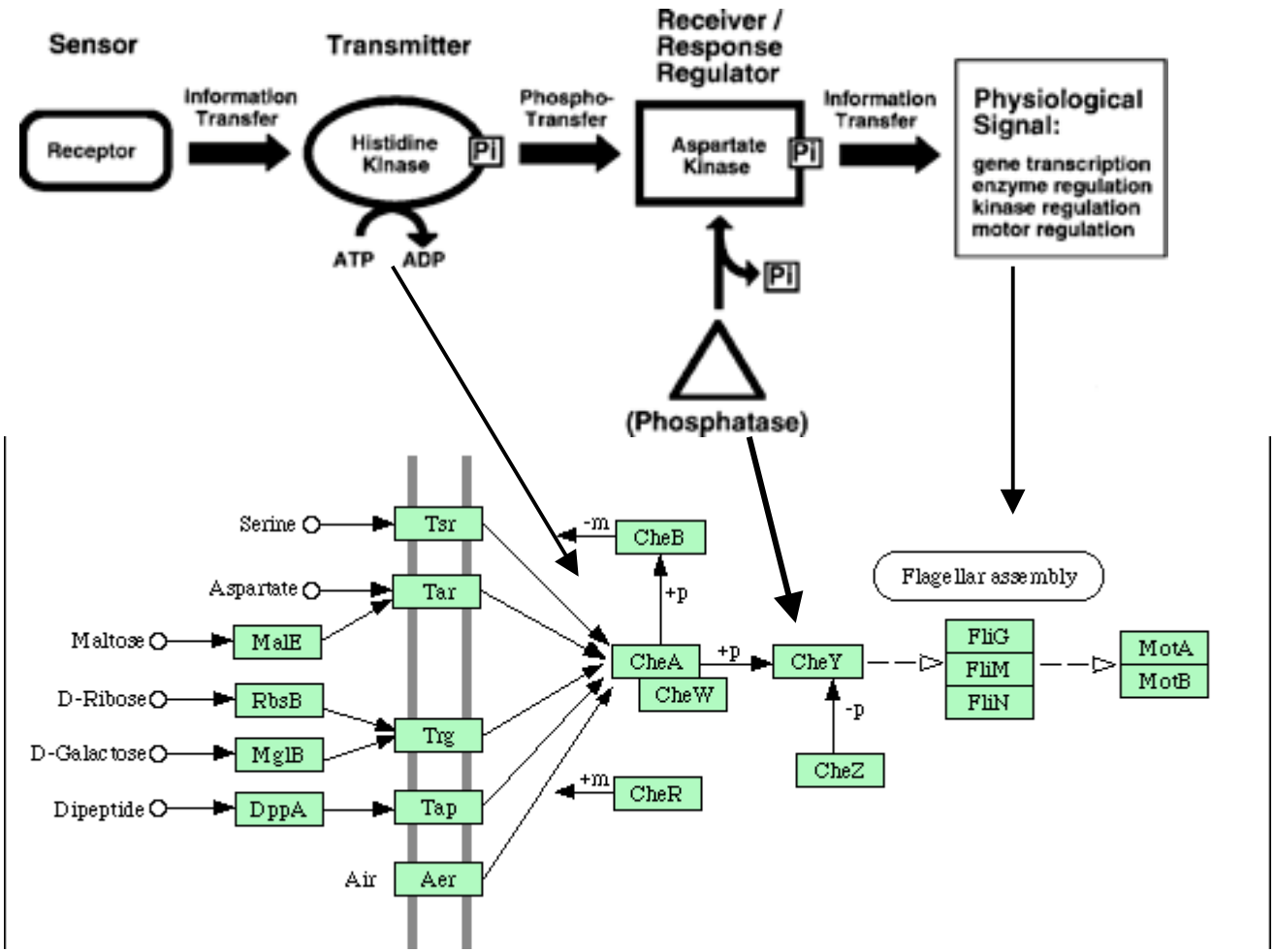
CW- flagella independent

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



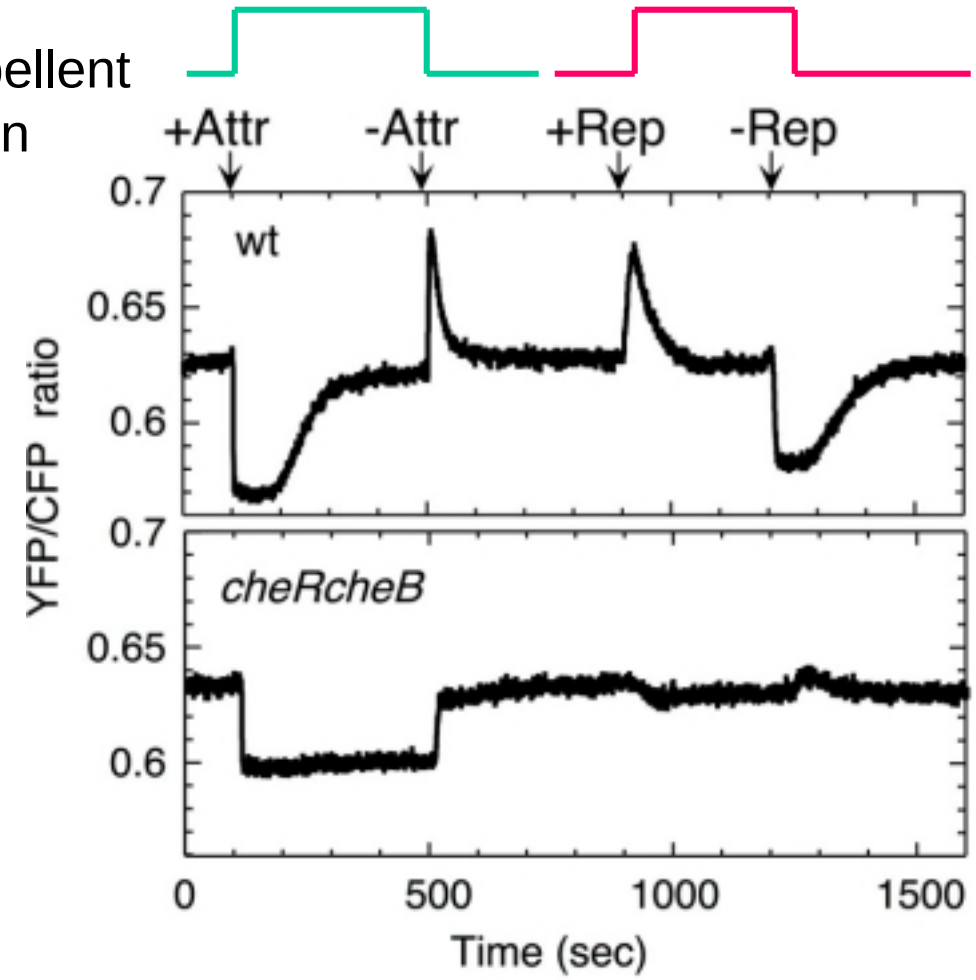
The signal transduction network is an example of a two-component pathway



Bacteria respond to concentration changes but adapt to a constant stimulus

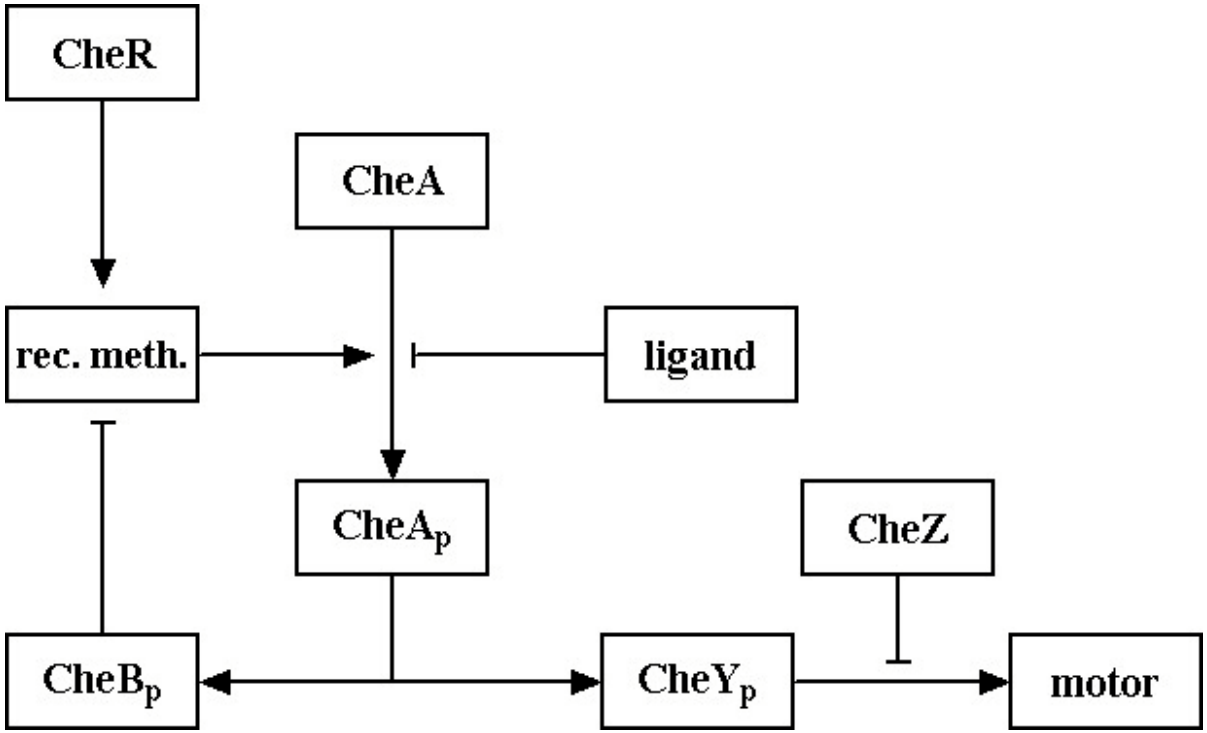
Attractor/repellent concentration

Motor input



Adaptation is based on changes in the methylation levels.

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

Idea: The cell contains a large set of receptors and other proteins
Input: ligand concentration
Variables: concentrations of

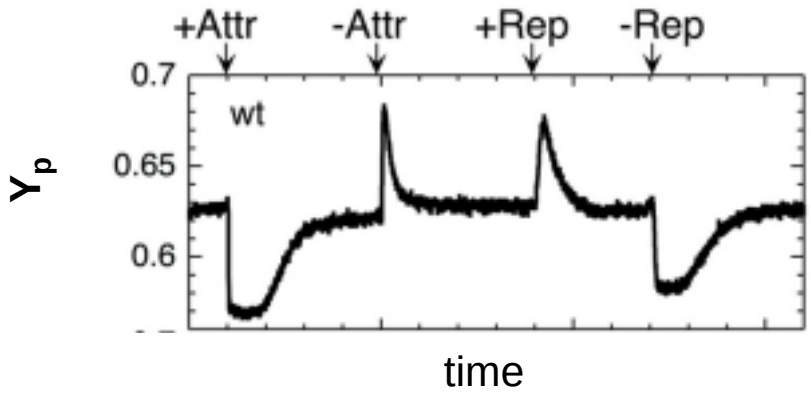
- the different (ligand bound, methylated) states of the receptor complex
- CheR, CheB, $CheB_p$, CheY, CheZ

Output: the concentration of $CheY_p$

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 immediate response of the system to ligand addition

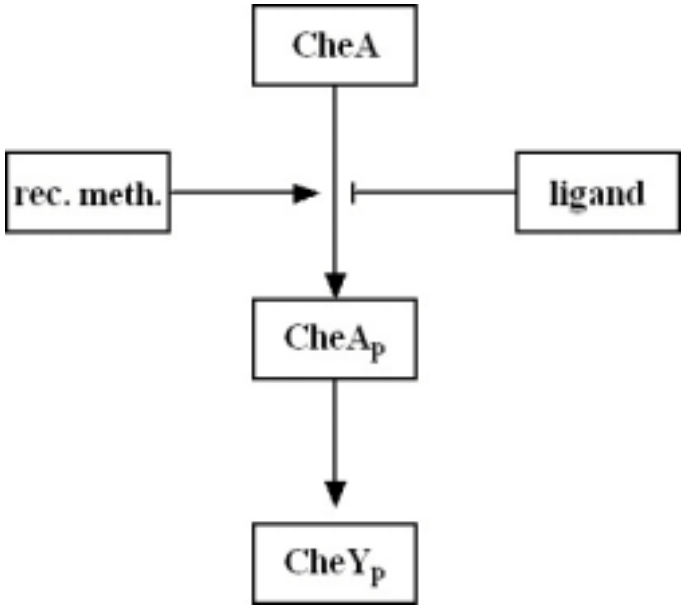


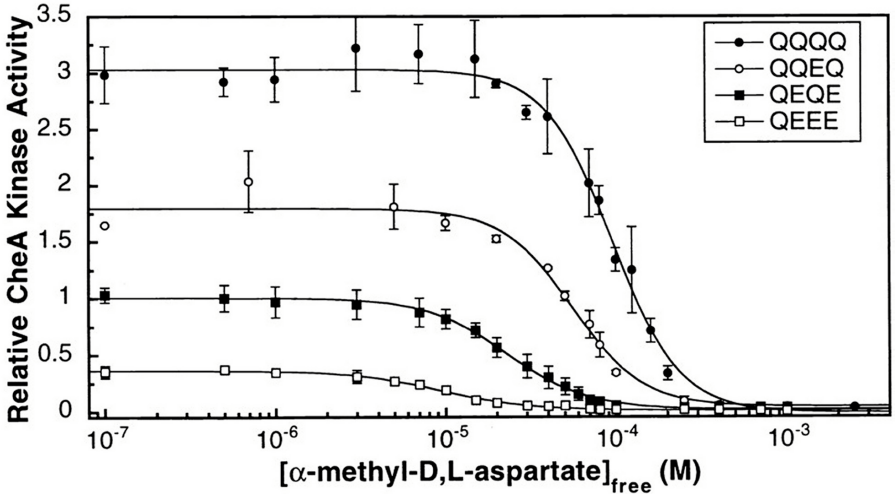
- The amplitude of the initial peaks depends on the added ligand, and also on the methylation state of the receptors.

- Idea: keep the receptors in a fixed methylation state, and study the variation of the initial response with added ligand.

J. A. Bornhorst and J. J. Falke, Journ. Gen. Physiol. 118, 693 (2001)

Scaling with ligand concentration





- The data can be fitted with Hill functions

$$\frac{Y_p(L)}{Y_p(0)} = 1 - \frac{L^H}{K_A^H + L^H}, \quad H \in [1,2)$$

- The initial amplitudes and K_A values depend on the methylation level.

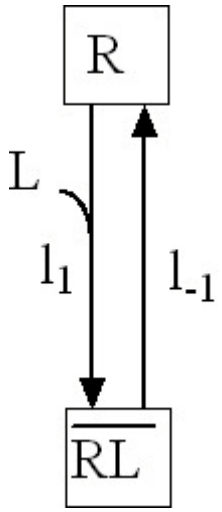
Simplest assumption

Assume that in ligand-bound receptor complexes CheA cannot autophosphorylate.

Then $Y_p(L)$ is proportional with R

Mass-action kinetics: $$\frac{dR}{dt} = -l_1 L\, R + l_{-1}\overline{RL}$$

$$R_t = R + \overline{RL}$$



Result: $$\frac{R}{R_t} = 1 - \frac{L}{K_D + L}, \quad K_D = \frac{l_{-1}}{l_1}$$

Experiments: $$\frac{Y_p(L)}{Y_p(0)} = 1 - \frac{L^H}{K_A^H + L^H}, \quad H \in [1,2)$$

methylation-dependent $H,\ K_A,$ $\quad K_A \neq \frac{l_{-1}}{l_1}$

Gain in signal transduction

Input: ligand concentration

Transduction: CheA autophosphorylation

Output: $CheY_p$

Intuitive assumption: output depends linearly on the input

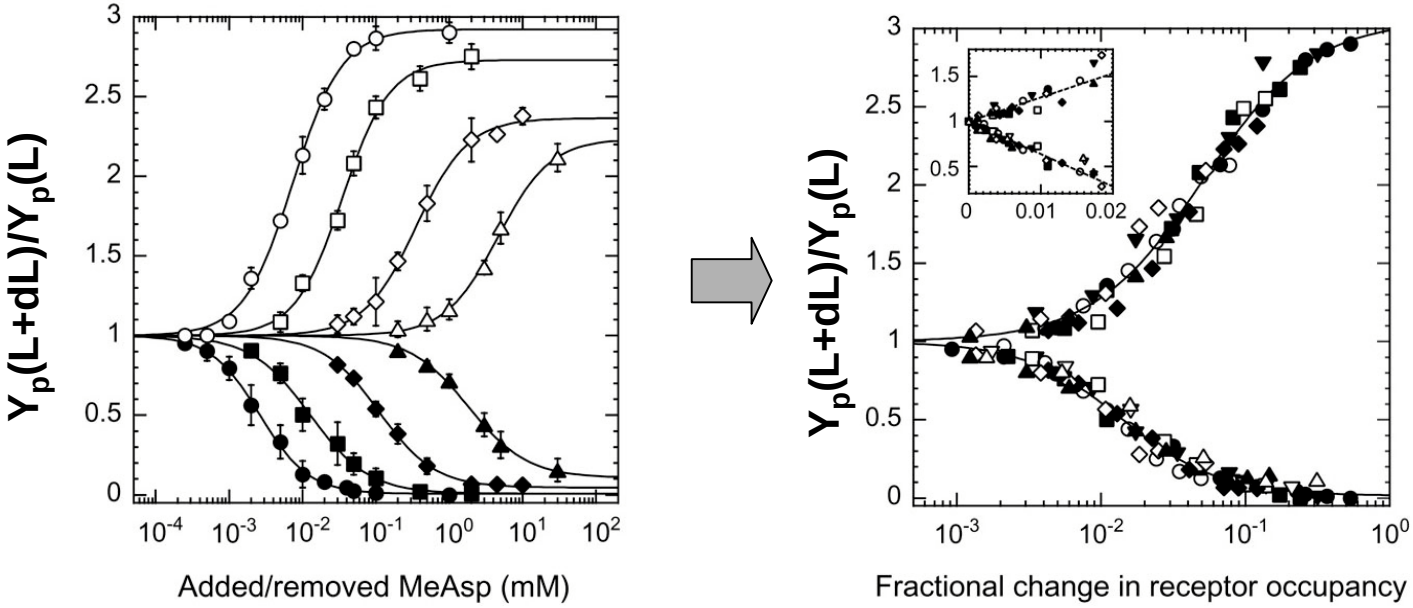
gain: $$g = \frac{\textbf{relative change in output}}{\textbf{relative change in input}} = \frac{\frac{dO}{O}}{\frac{dI}{I}}$$

If the output is proportional with the input, g = constant.

A high gain indicates an amplification in signal transduction.

Implicit assumption: there is a constant gain between ligand occupancy, $o = \frac{L}{K_D + L}$ and $CheY_p$

Response to additional ligand scales with fractional change in receptor occupancy



The initial slope of the curve is ~35, indicating a surprisingly high amplification for the signal transduction network.

V. Sourjik and H. Berg, PNAS 99, 123 (2002)

General explanation of the high amplification

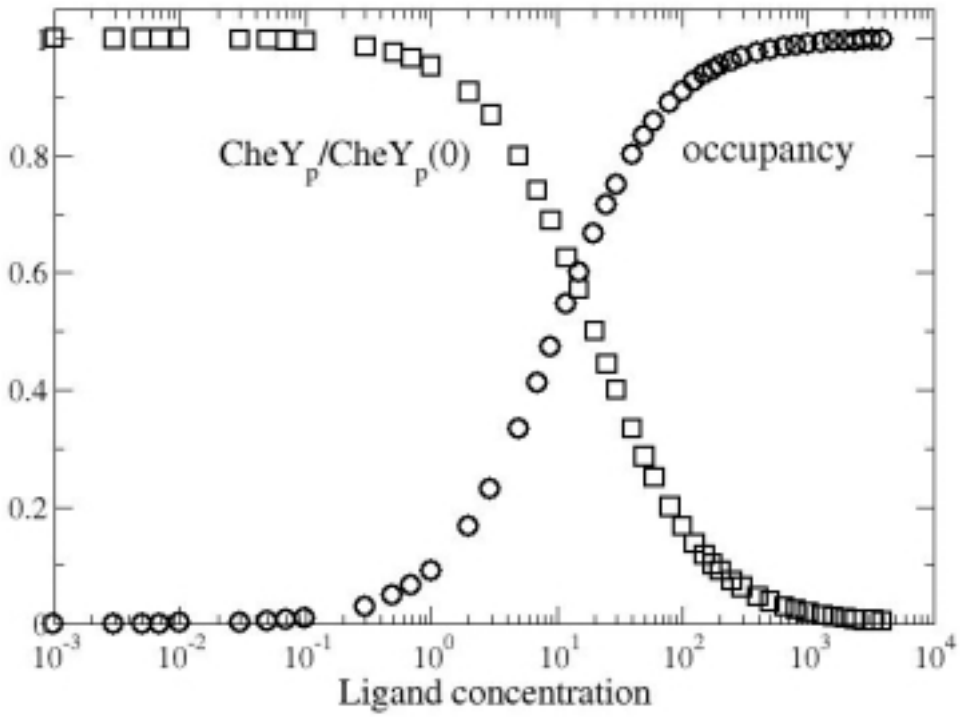
Assume that the functional form of the dependence of $CheY_p$ on the ligand concentration is $$\frac{Y_p(L)}{Y_p(0)} = 1 - \frac{L^H}{K_A^H + L^H}$$

The receptor occupancy is defined as $$o(L) = \frac{L}{K_D + L}$$

Then the signal amplification is $$\frac{d \ln Y_p}{d \ln o} = -\frac{H}{K_D} \frac{L^H (K_D + L)}{K_A^H + L^H}$$

The amplification is a continuously increasing function of the ligand concentration, so large amplifications are possible at high ligand levels.

$CheY_p$ decreases with increasing occupancy



In the high occupancy region the relative change is in occupancy is small, but since $CheY_p$ is small, its relative change is significant.