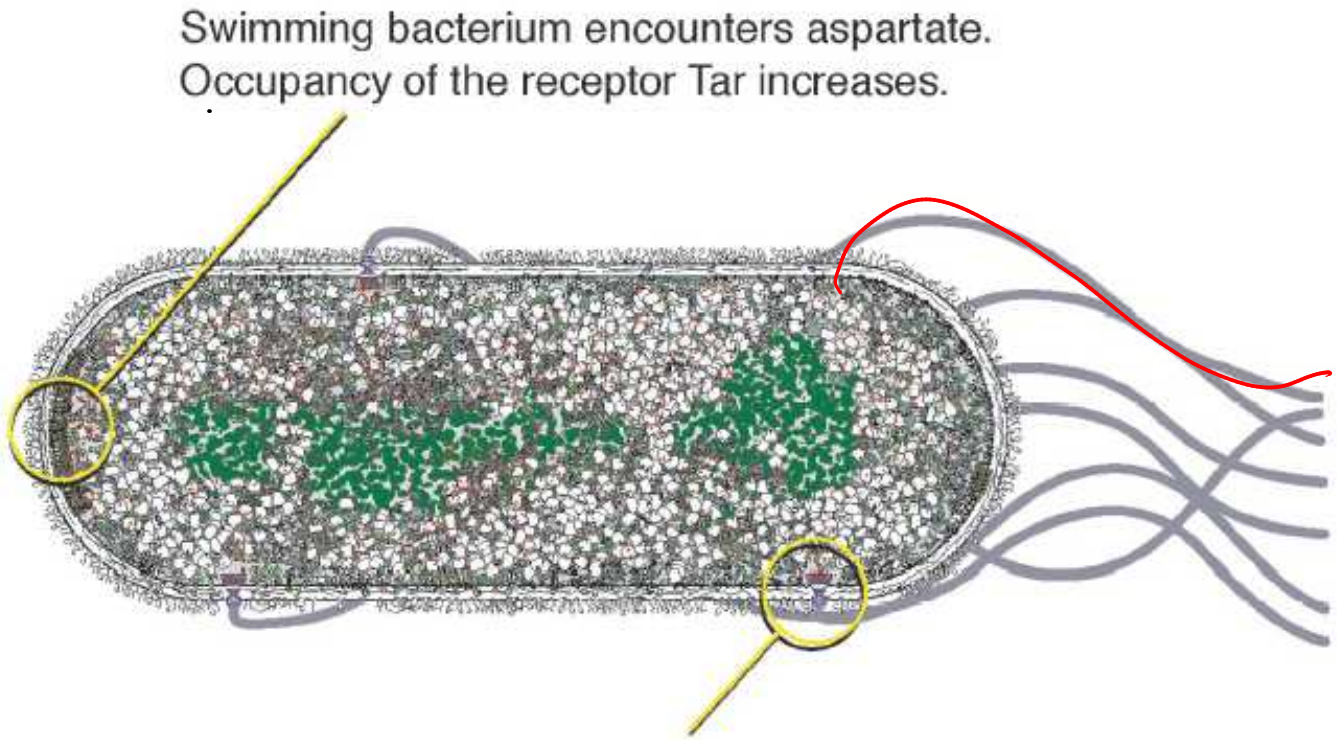
Bacterial Chemotaxis



We will discuss the strategies of how bacteria swim towards food:

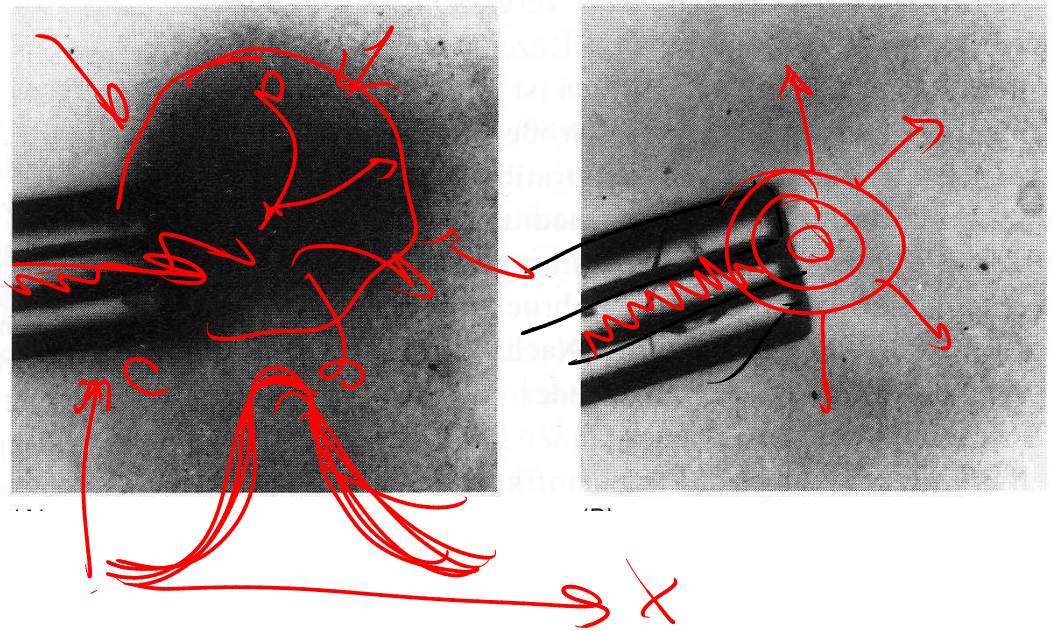
- How do they detect the food source
- How do they move at low Reynolds numbers
- How do they control this movement

Chemotaxis

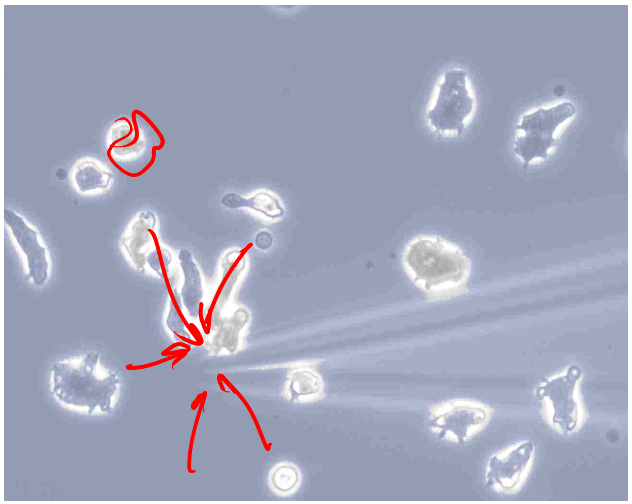
Definition :

„The directed motion of organisms towards or away from chemical attractants or repellents.“

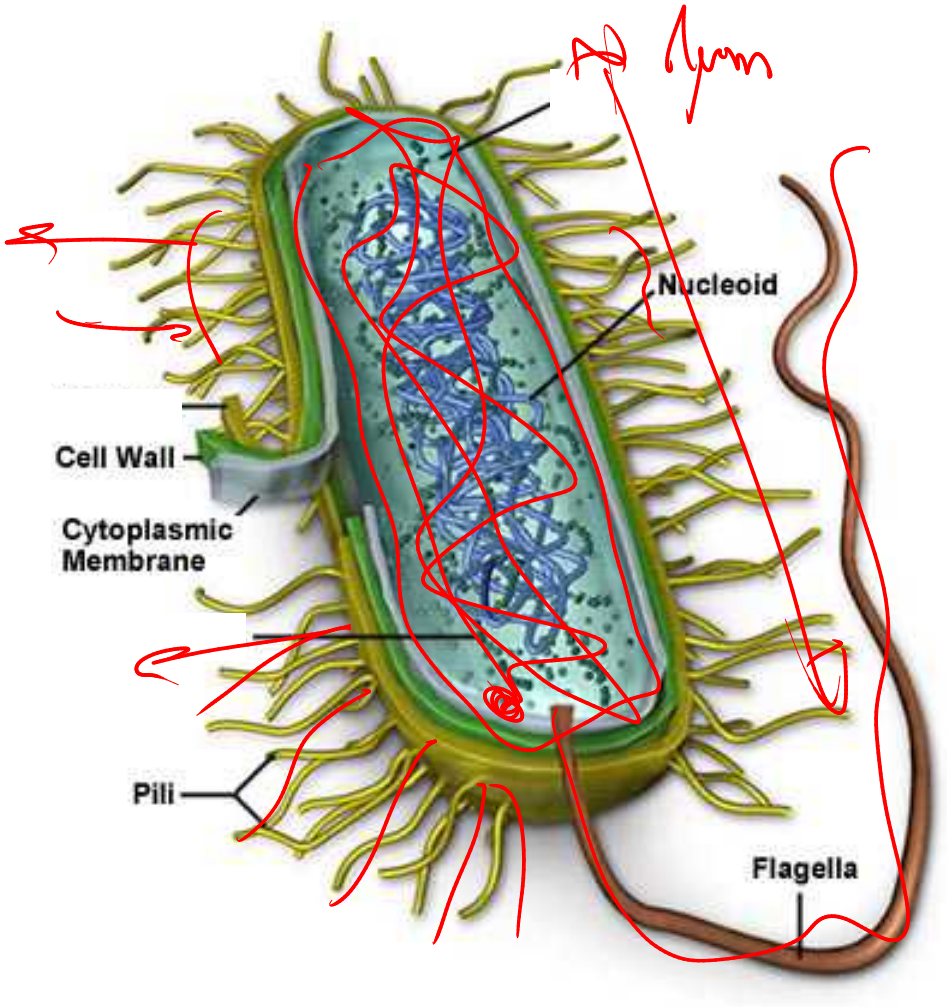
Chemotaxis of bacteria:
Salmonella typhimurium are attracted by Serin (left) and repelled by Phenol (right)



The amoeba *Dictyostelium Discoideum* runs towards increasing concentrations of cAMP.



External Polymers in Bacteria



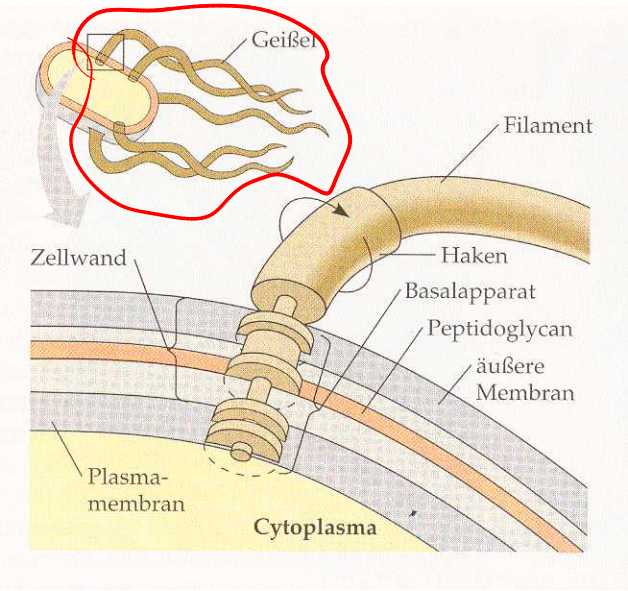
Typically, two different External Polymers are found in Bacteria:

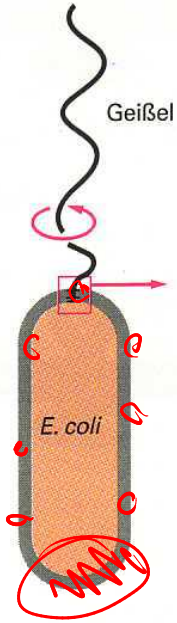
o Bacteria can move with Pili by extending and retracting them inside the cell body (Type IV pilia). They are used to glue bacteria to each other to form biofilms, connect different bacteria for exchanging plasmids or let them attach to surfaces.

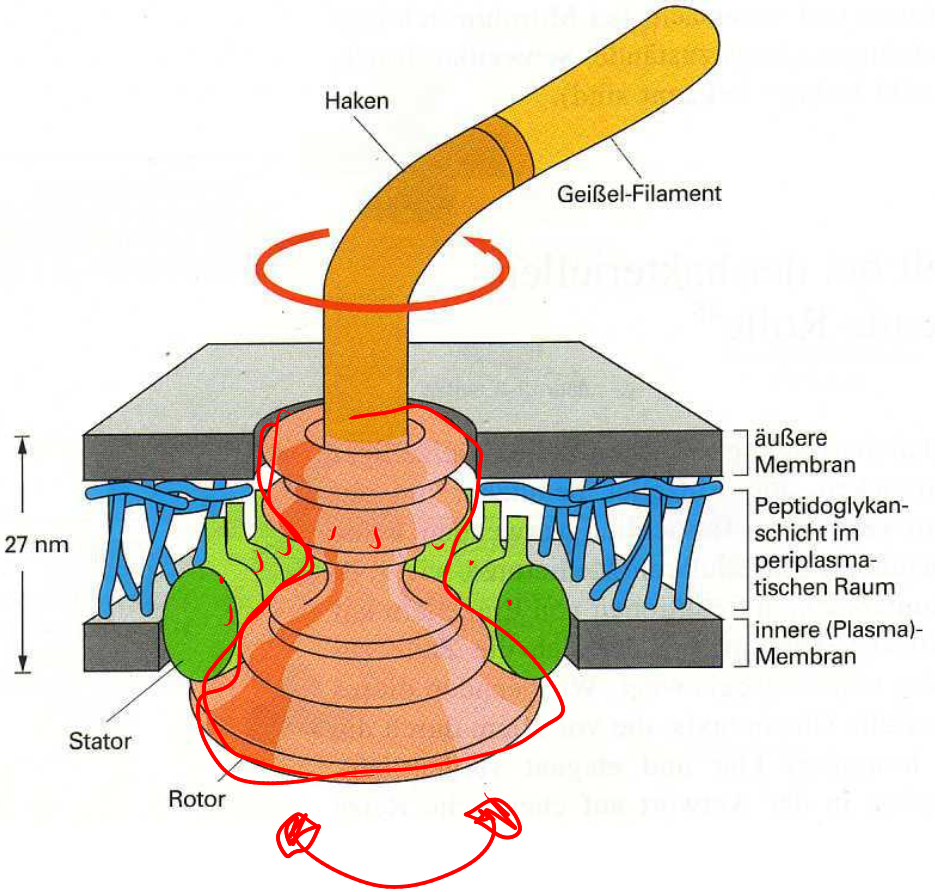
o Flagella are used to swim. Often, Bacteria have several Flagella.

Flagella Motor

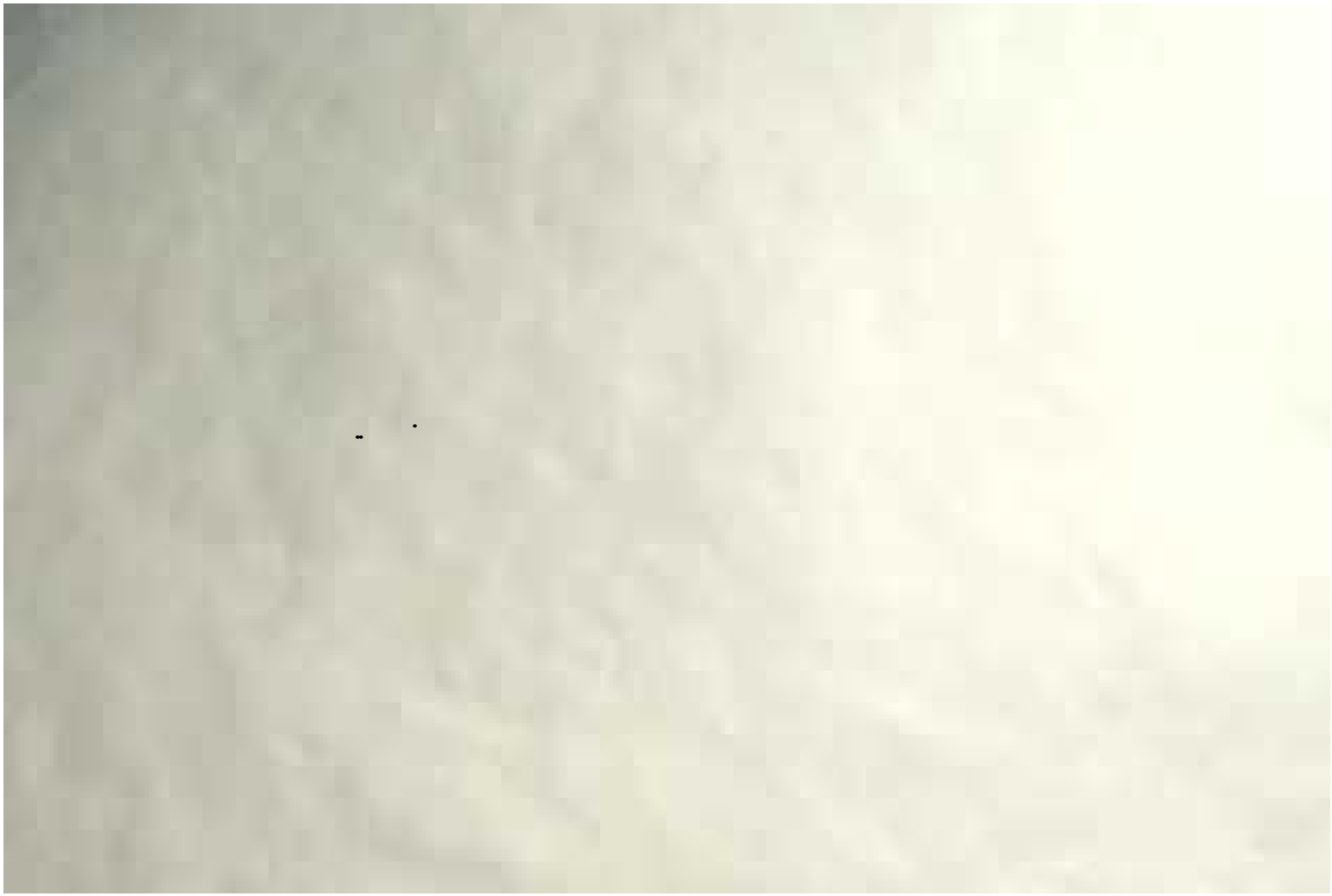
Bacteria swim with the help of Flagella (Geißel) which are rotated by transmembrane motors. A Flagella can rotate with up to 150 turns per second.





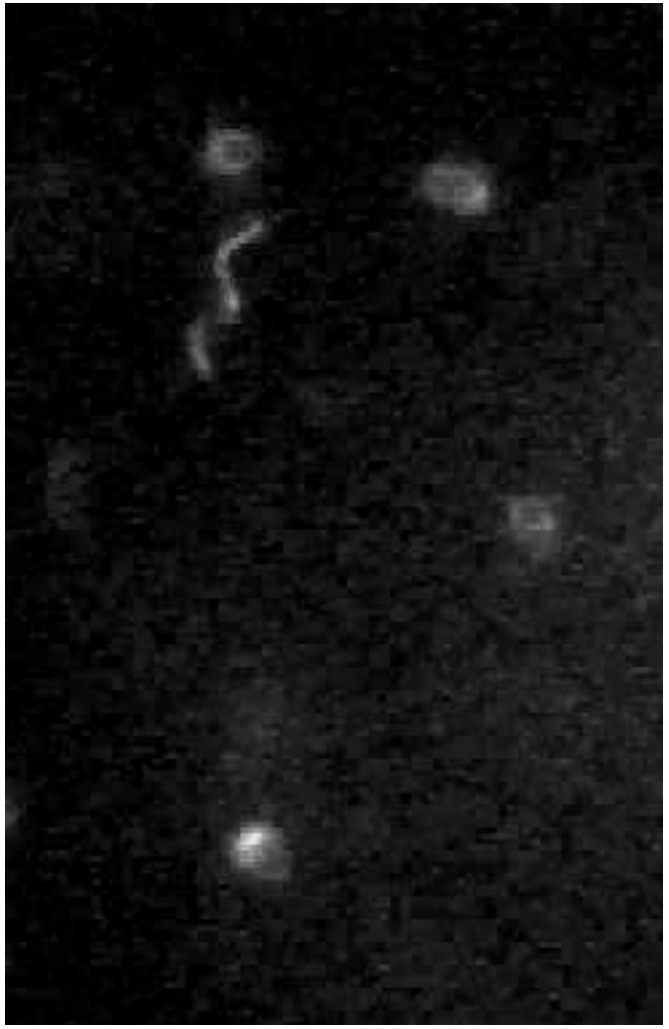


Flagella Motor

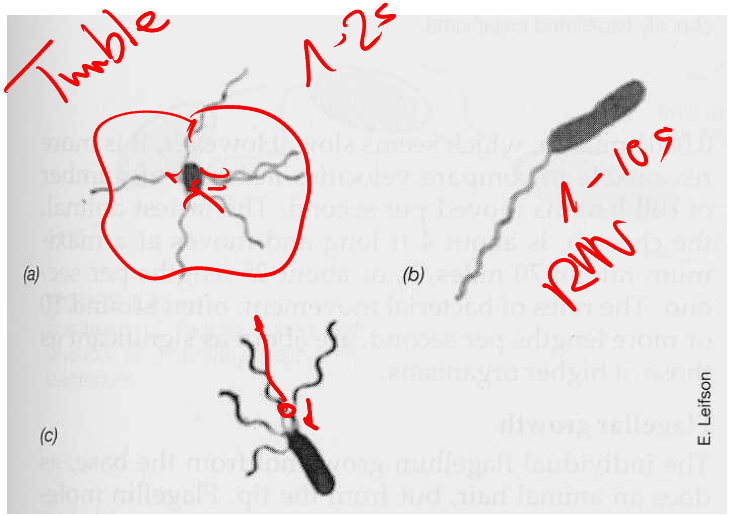


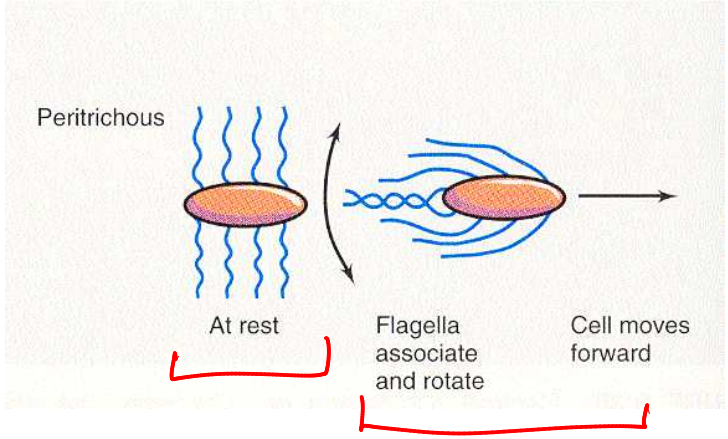
Bacteria move by rotating the Flagella

At small scales, viscosity of water dominates and effects by inertia are absent. Thus swimming strategies are very much different from what we know at large scales. A good strategy is to swim by "drilling holes with a screw".



Moving and Tumbling Bacteria





Depending on the Rotation direction, several Flagella either form a bundle and allow forward simming or they "repell" each other and block swimming. The latter is due to inward propagation of interaction defects, given by the geometry of the flagella.

Moving and Tumbling Bacteria

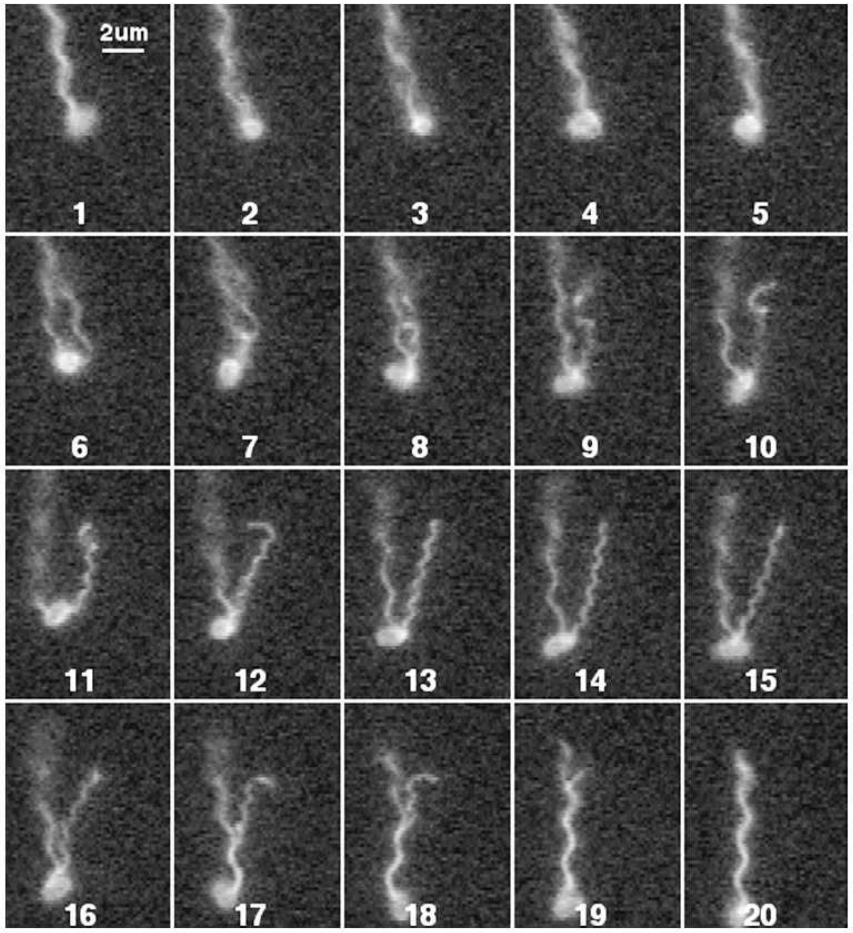


FIG. 7. *E. coli* with two flagellar filaments, one undergoing a polymorphic transformation. Successive fields are shown.

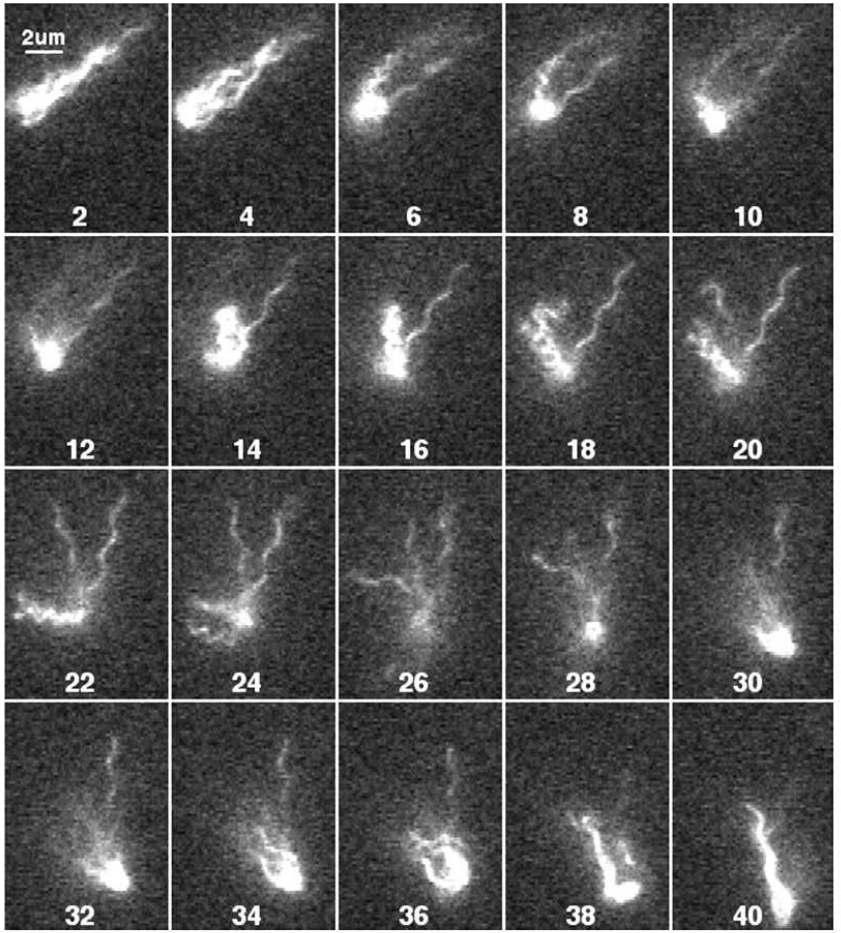
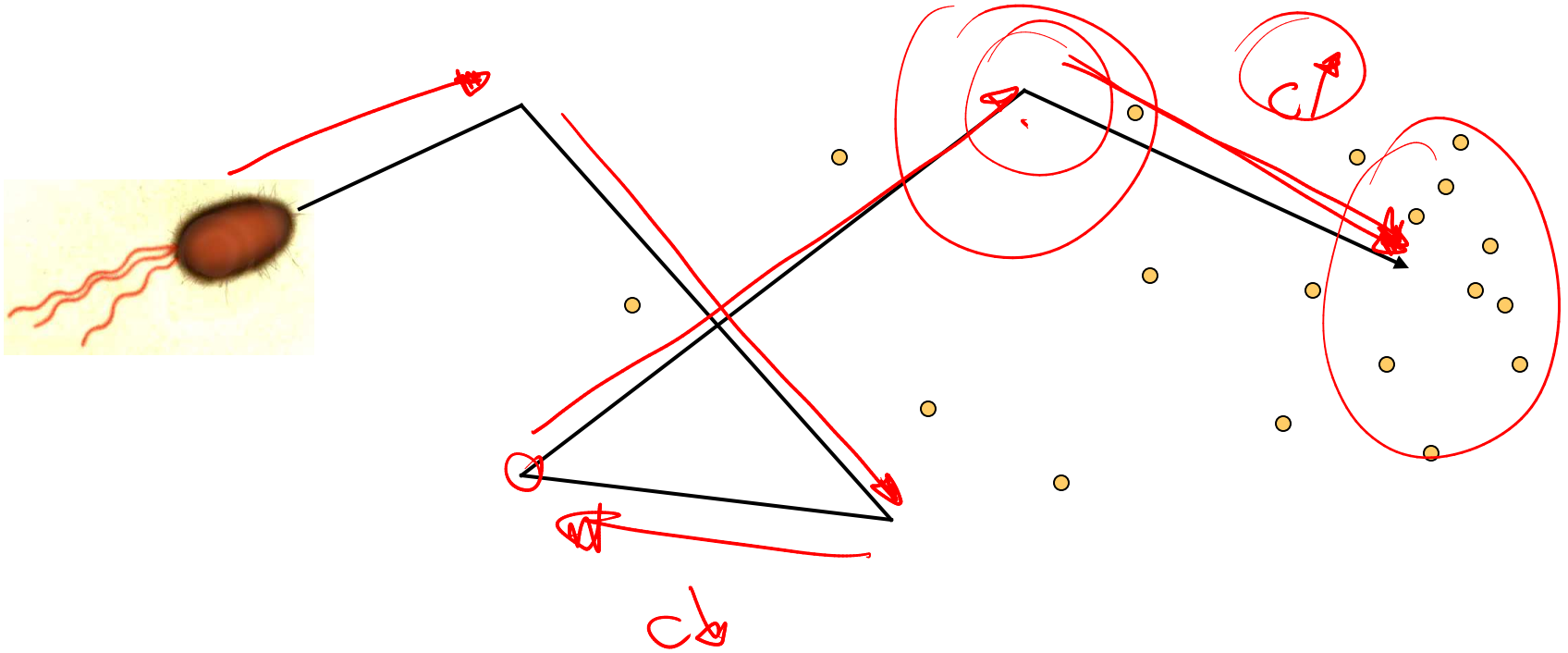


FIG. 9. *E. coli* cell with several flagellar filaments, all but one undergoing polymorphic transformations. Every other field is shown.

From: Real-Time Imaging of Fluorescent Flagellar Filaments, LINDA TURNER, WILLIAM S. RYU, AND HOWARD C. BERG, JOURNAL OF BACTERIOLOGY, May 2000, p. 2793–2801

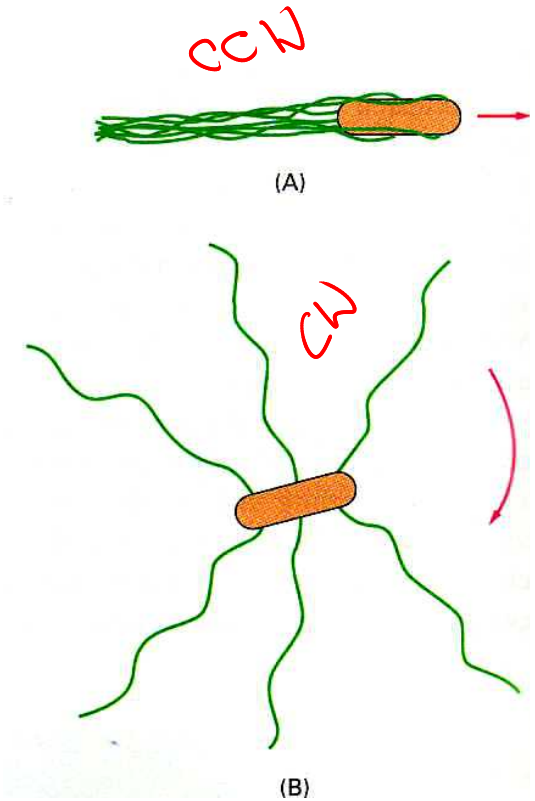
Strategy of Chemotaxis

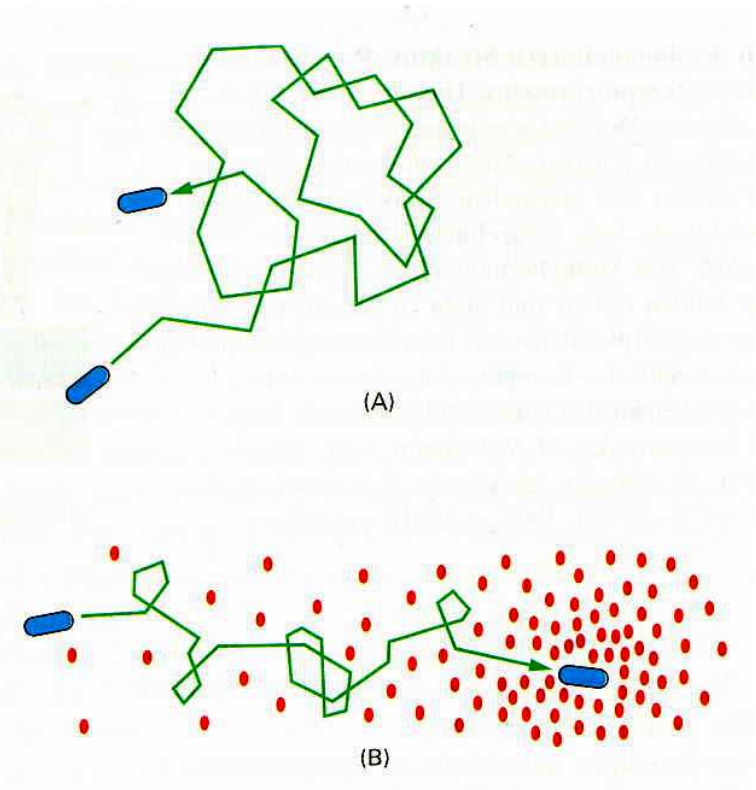
- *E. coli* Bacteria have efficient molecular motors for locomotion
- They move by switching between direction runs and random tumble motions.



Bacteral Chemotaxis

The bacterial flagella are arranged into bundles which diverge into separate bundles when they drive clock wise (CW) and converge to a single bundle when they are rotating counter clockwise (CCW). The Bacteria thus has two states of motion
(A) swimming in a straight line (v=14-30μm/sec, in average for 0.8s) and
(B) tumble, in average for 0.2s.
If for the bacteria the concentratrion of an attractant increases over time, tumbling is suppressed. As result, the bacteria performs a biased diffusion process towards increasing concentration of the attractant.

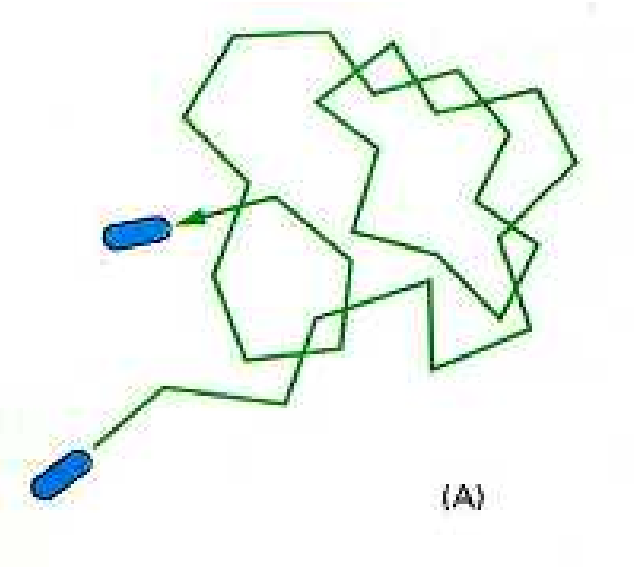




Run and Tumble Movement

The movement of E.coli is a sequence of straight movements, followed by short phases of reorientations.

This Run and Tumble movement can be described as diffusion process with an exponential distributed step length $v\tau$. It yields the effective diffusion coefficient:



$$D_{ST} = \frac{\mathbf{v}^2 \tau}{3(1-\alpha)}$$

Run velocity v,
Average run time τ
Orientation factor α.

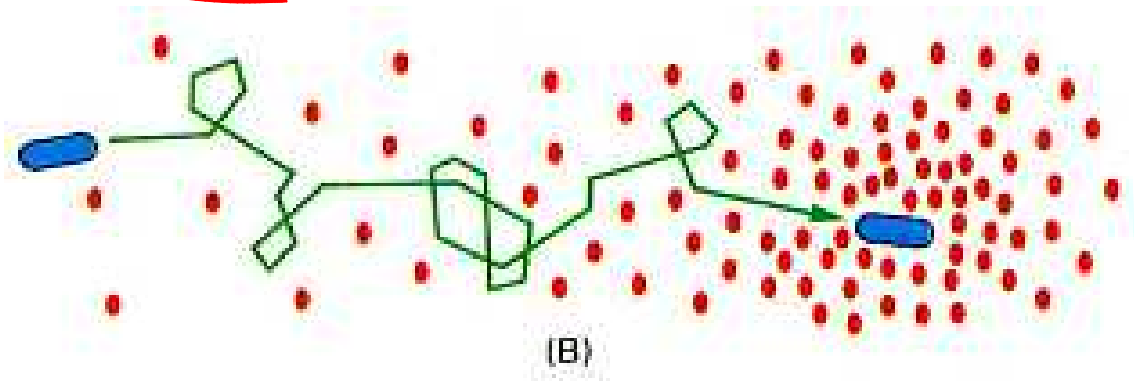
The orientation factor α describes the average reorientation after each tumble phase $\alpha = \langle \cos\vartheta \rangle$. Equal distributions into all directions (random walk) equals $\alpha=0$, no reorientation $\alpha=1$.

With $v=30\mu m/sec$ and $\tau = 0{,}8sec$, $\alpha=0$ one obtains $D_{ST}=240\ \mu m^2/sec$.

For comparison: small biomolecules (sugars, peptides etc.) : $D=400\ \mu m^2/sec$!!!

Mechanism of average chemotactic drift

The temporal increase of the attractant concentration leads to an temporary extension of the run phase. As result, the random walk is unbalanced and we obtain an average drift velocity into the direction of higher concentration of the attractant. => Biased Random Walk



Constraints:

- only ~ 1,000 receptors
- only 1 s to evaluate concentration

Performance:

- can detect < 1% change of occupancy
- can operate over 5 orders of magnitude in ambient concentration

Optical Methods: 3D Tracker

Proc. Nat. Acad. Sci. USA
Vol. 71, No. 4, pp. 1388–1392, April 1974

Temporal Stimulation of Chemotaxis in *Escherichia coli*

(bacterial taxis/temporal gradients/alanine aminotransferase/three-dimensional tracking)

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Communicated by Keith R. Porter, November 29, 1973

ABSTRACT **We used the tracking microscope to study the chemotactic responses of *E. coli* to temporal gradients of L-glutamate generated in isotropic solutions by the action of the enzyme alanine aminotransferase. Positive gradients suppress directional changes which occur spontaneously in the absence of a stimulus. Negative gradients have little effect. The data can be fit with a model in which the suppression is proportional to the time rate of change of the fractional amount of chemoreceptor bound. The model accounts for the behavior of individual cells and populations of cells in spatial gradients. A computer simulation of the motion in spatial gradients indicates that if the bacteria have a "memory," its decay time cannot be much longer than a few seconds. The relationship between the responses observed in these experiments and in experiments in which solutions of an attractant at different concentrations are mixed is discussed.**

Tactic responses in bacteria occur when the intensity of a spatially uniform stimulus changes with time. This was shown for phototaxis and for chemotaxis by Engelmann in 1883 (1) and for thermotaxis by Metzner in 1920 (2). Engelmann found that when a uniformly illuminated preparation of his *Bacterium photometricum* was suddenly darkened, every bacterium backed up, stopped, and then resumed its normal motion. An identical response was observed when the preparation was suddenly exposed to CO_2. Metzner examined the motion of *Spirilla* in a thin chamber which could be uniformly heated or cooled. Some species responded by shuttling back and forth only when the temperature was lowered; others did so only when it was raised.

of serine and aspartate. When the bacteria moved up these gradients they changed direction less frequently; when they moved down, their motion was largely unperturbed. However, we were not able to determine the functional dependence of the response on the stimulus; the analysis was complicated by the fact that the stimulus depended on the motion of the cells.

In the experiments described here, the concentration of an attractant is changed enzymatically. The medium is homogeneous and isotropic; therefore, the stimulus is independent of the motion of the cells. We use alanine aminotransferase to generate or to destroy L-glutamate via the reaction:

$$\text{L-alanine} + \text{2-oxoglutarate} \rightleftharpoons \text{pyruvate} + \text{L-glutamate.} \quad [1]$$

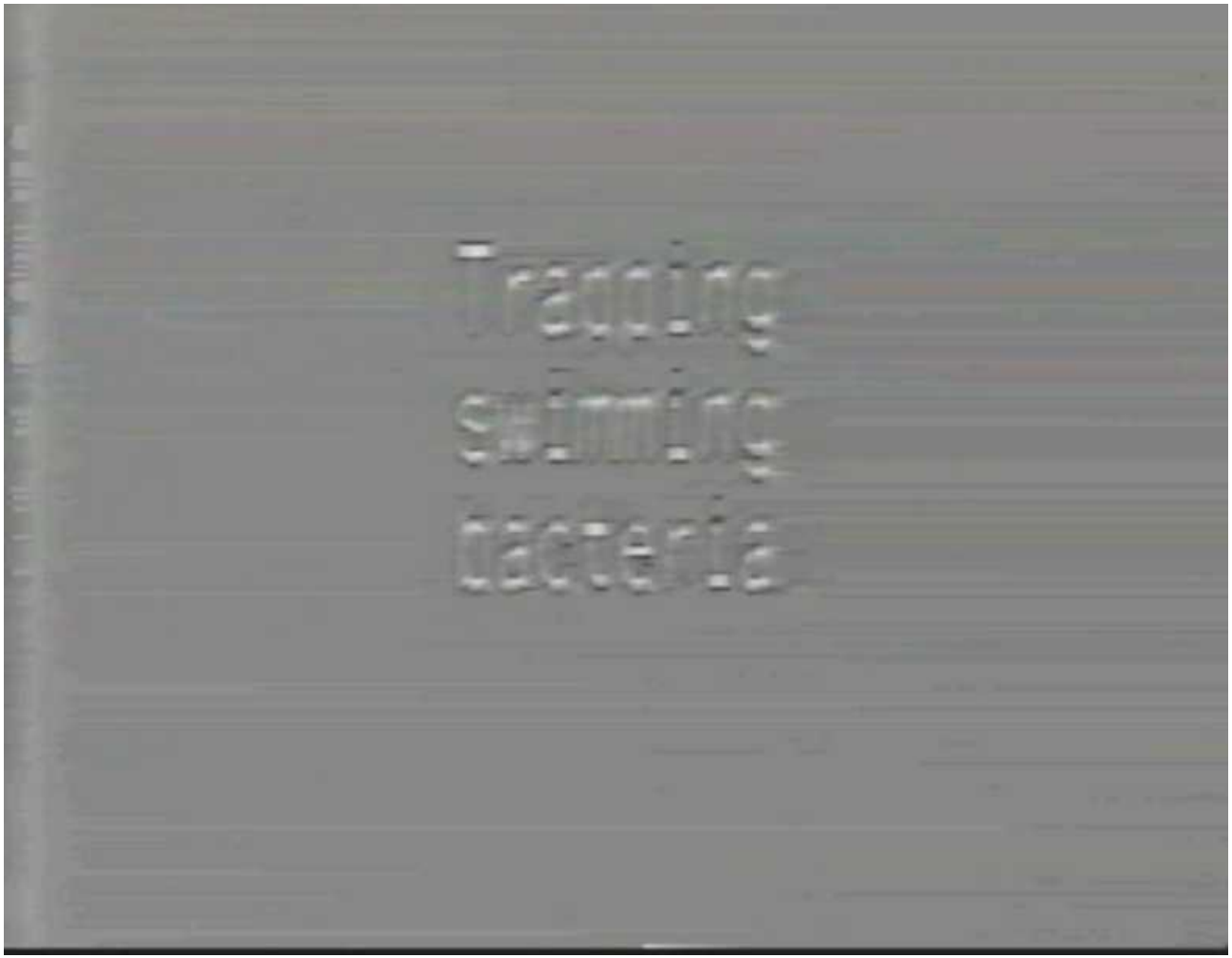
Glutamate is sensed by the aspartate receptor and alanine by the serine receptor, so the experiments are done with the serine taxis mutant AW518 (7). Neither 2-oxoglutarate nor pyruvate is chemotactically active (7).

We observe a response when glutamate is generated but not when it is destroyed. The data in positive gradients are best explained with a model, suggested by the work of Mesibov, Ordal, and Adler (8), in which the suppression of directional changes is proportional to the time rate of change of the fractional amount of chemoreceptor bound.

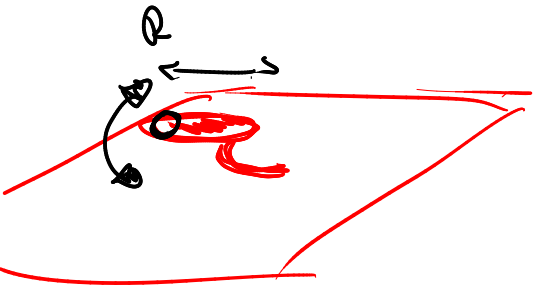
MATERIALS AND METHODS

Reagents. All solutions were prepared from reagent-grade

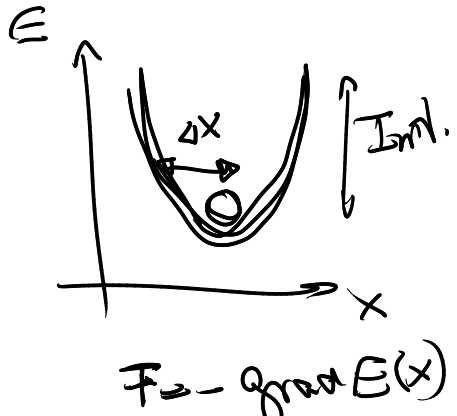
Optical Methods: Optical Tweezer



Tethering on Substrates



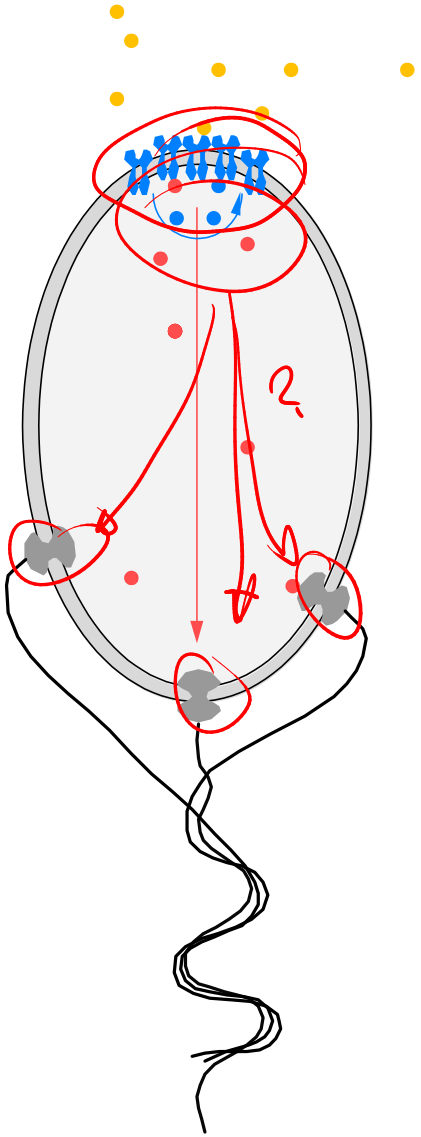
System Characteristics of the biological Network



- Measurement of relative concentrations over time, not absolute concentration
- Exact adaptation
- Sensitivity by Amplification
- Combination of signals from attractants and repellants.

The range of concentrations which triggers chemotaxis ranges over 5 orders of magnitude (nM->mM) !

Input :
Attraktorconcentration



stimulus

processing

signal

response

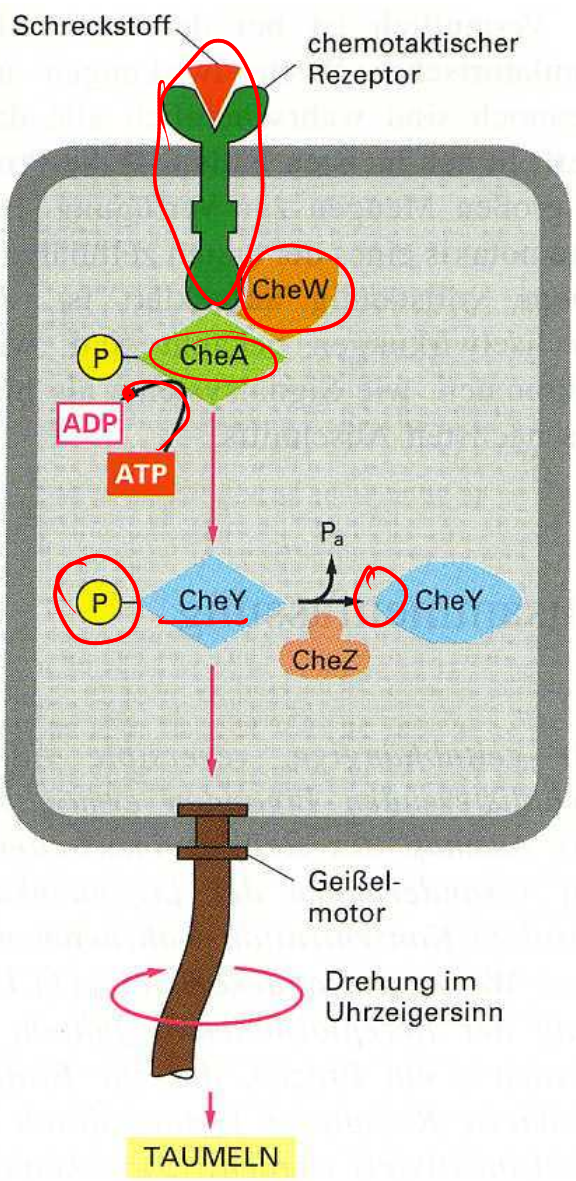
Output :
Tumble movement

Genetic analysis of protein network

Table 1 Components of the chemotaxis signal transduction system[a]

Gene	Mutant phenotype	Function	Molecular weight native/monomer (kd)	Cellular location	Monomers per cell
tar	run/tumble[?]	aspartate receptor	120/60	transmembrane	10,000
cheA	run	histidine kinase	250/73	cytoplasm	2500
cheA$_s$	ND[c]	ND	220/67	cytoplasm	2500
cheW	run	kinase regulator	36/18	cytoplasm	5000
cheY	run	response regulator	14/14	cytoplasm	12,000
cheZ	tumble	phosphatase activator	>500/24	cytoplasm	24,000
cheR	run	methyltransferase	32/32	cytoplasm	200
cheB	tumble	methylesterase/amidase	37/37	cytoplasm	2000
fliG	Fla/Mot/Che	motor switch	ND/37	motor	ND
fliM	Fla/Mot/Che	motor switch	ND/38	motor	ND
fliN	Fla/Mot/Che	motor switch	ND/15	motor	ND

The intracellular signal network

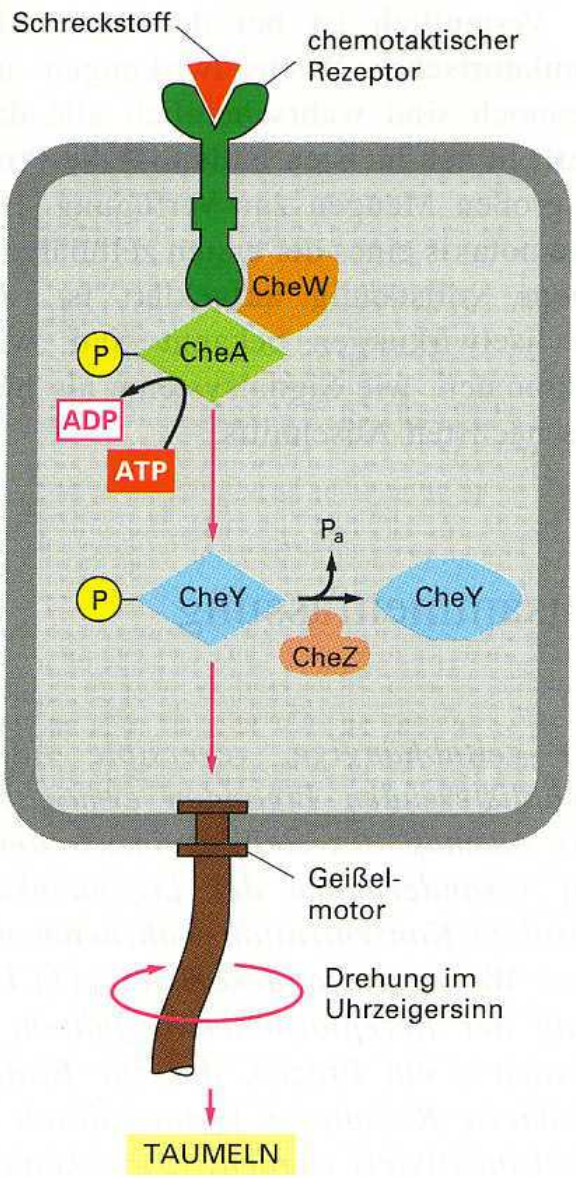


From genetic analysis, four cytoplasmatic proteins *CheA, CheW, CheY and CheZ* are known to connect the chemotactic receptors with the flagella motor.

CheW: Regulator
CheA : Proteinkinase
CheY : Response Regulator
CheZ : Phosphatase-activating Protein

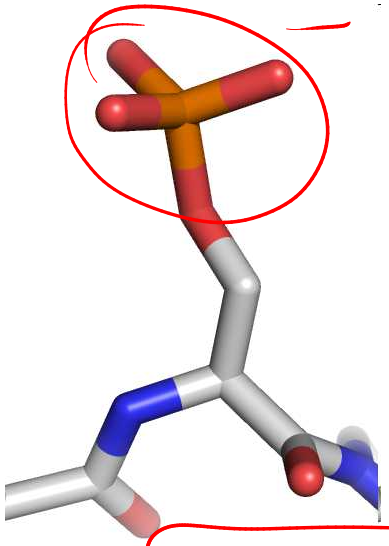
Regulated by the receptor, *CheA* transfers a phosphorylation onto the small *CheY* protein. *CheY-p* diffuses to the motor protein and induces a transition towards the tumble movement.

The intracellular signal network



Phosphorylation

is the addition of a phosphate (PO_4) group to a protein molecule or a small molecule. Reversible phosphorylation of proteins is an important ***regulatory mechanism***. Enzymes called ***kinases*** (phosphorylation) and ***phosphatases*** (dephosphorylation) are involved in this process. Many enzymes are switched ***"on"*** or ***"off"*** by phosphorylation and dephosphorylation. Reversible phosphorylation results in a ***conformational change*** in the structure in many enzymes.

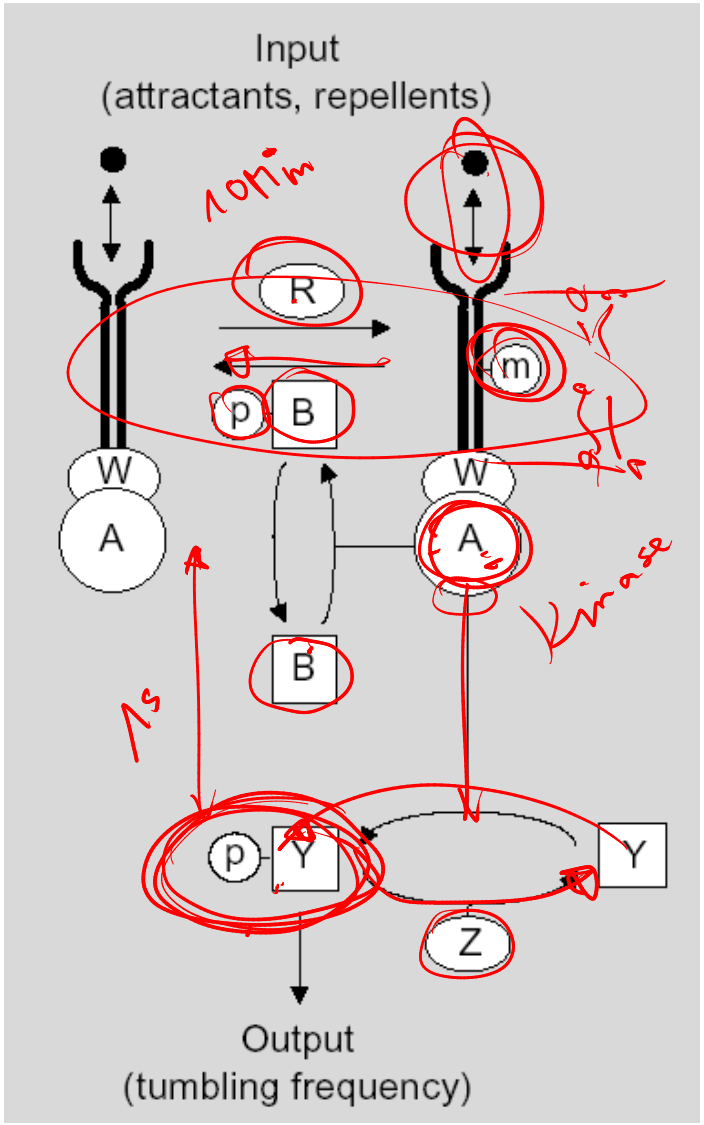


A phosphorylated serine residue
(from: http://en.wikipedia.org/wiki/Phosphorylation

For example, phosphorylation replaces ***neutral hydroxyl groups*** on serines, threonines or tyrosines with ***negatively charged phosphates*** with pKs near 1.2 and 6.5. Thus, near pH 6.5 they add 1.5 negative charges and above pH 7.5 they add 2 negative charges.

It is estimated that 1/10th to 1/2 of proteins are phosphorylated (in some cellular state).

The intracellular signal network



CheR : Methyltransferase
CheB : Methylesterase

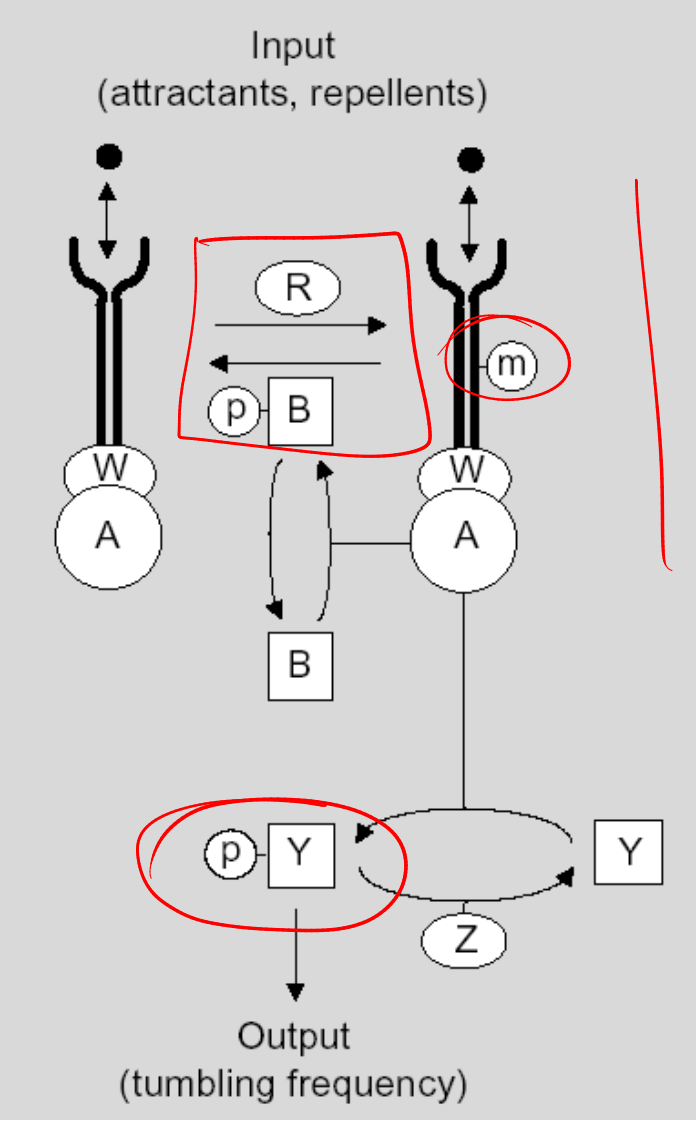
The receptors become more sensitive with its methylation. The methylation is performed by the protein CheR, the desensitising demethylation the phosphorylated p-CheB. The phosphorylation of CheB is triggered by CheA. This results in a negative feedback loop. Activated receptors become less sensitive via CheA und p-CheB.

Methylation

denotes the attachment or substitution of a methyl group on various substrates. Besides DNA methylation, typically at CpG sequence sites, Protein methylation typically takes place on arginine or lysine amino acid residues. Arginine can be methylated once or twice, Lysine can be methylated once, twice or three times. Protein methylation is one type of post-translational modification.

From: http://en.wikipedia.org/wiki/Methylation

The intracellular signal network



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Adaption

Robustness in bacterial chemotaxis

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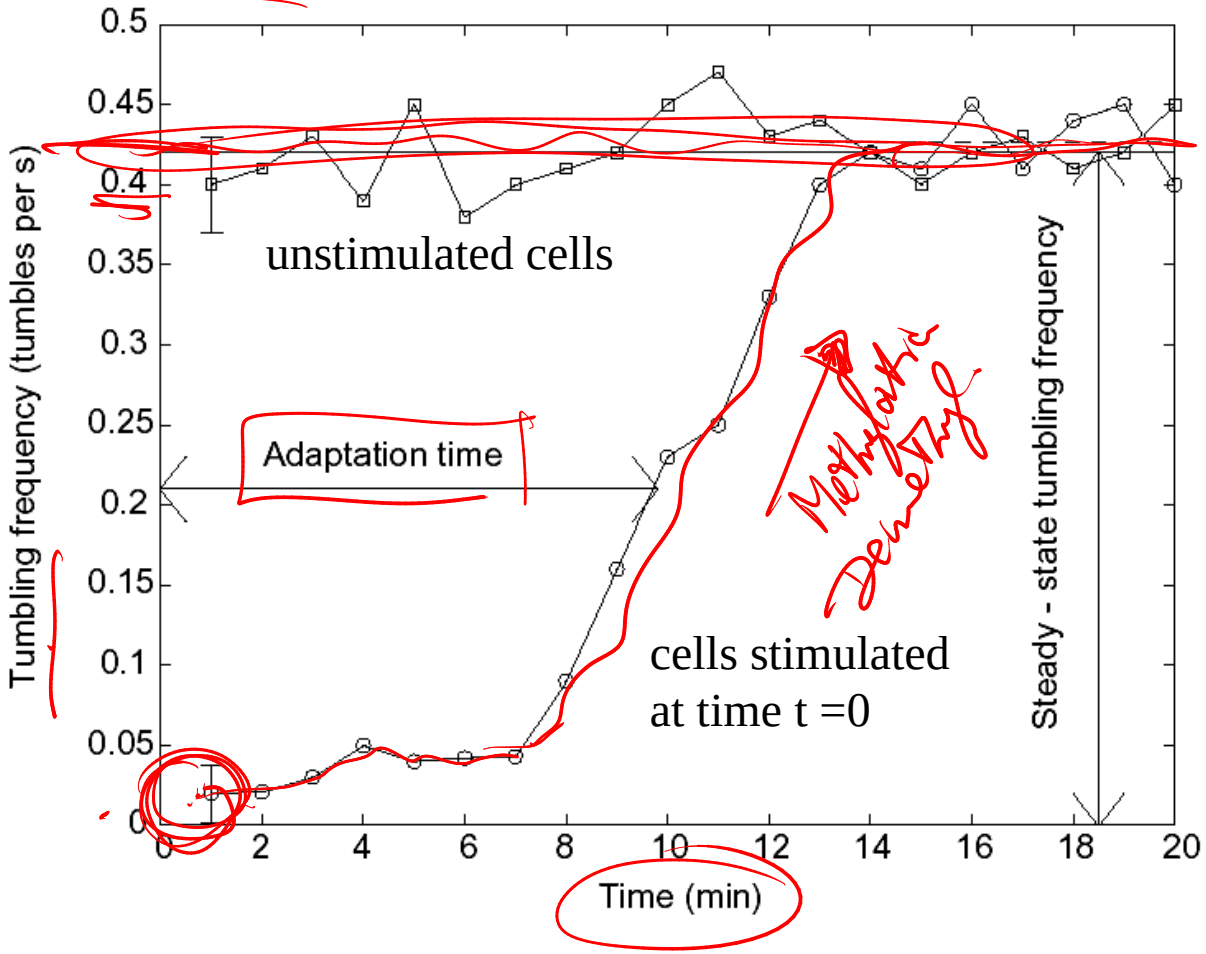
Networks of interacting proteins orchestrate the responses of living cells to a variety of external stimuli[1], but how sensitive is the functioning of these protein networks to variations in their biochemical parameters? One possibility is that to achieve appropriate function, the reaction rate constants and enzyme concentrations need to be adjusted in a precise manner, and any deviation from these 'fine-tuned' values ruins the network's performance. An alternative possibility is that key properties of

Bakteria adapt their signal response

After addition of an attractant at t=0: The frequency of tumbling reduces very fast.
After an adaptation time τ the frequency increases and levels out at the previous value.



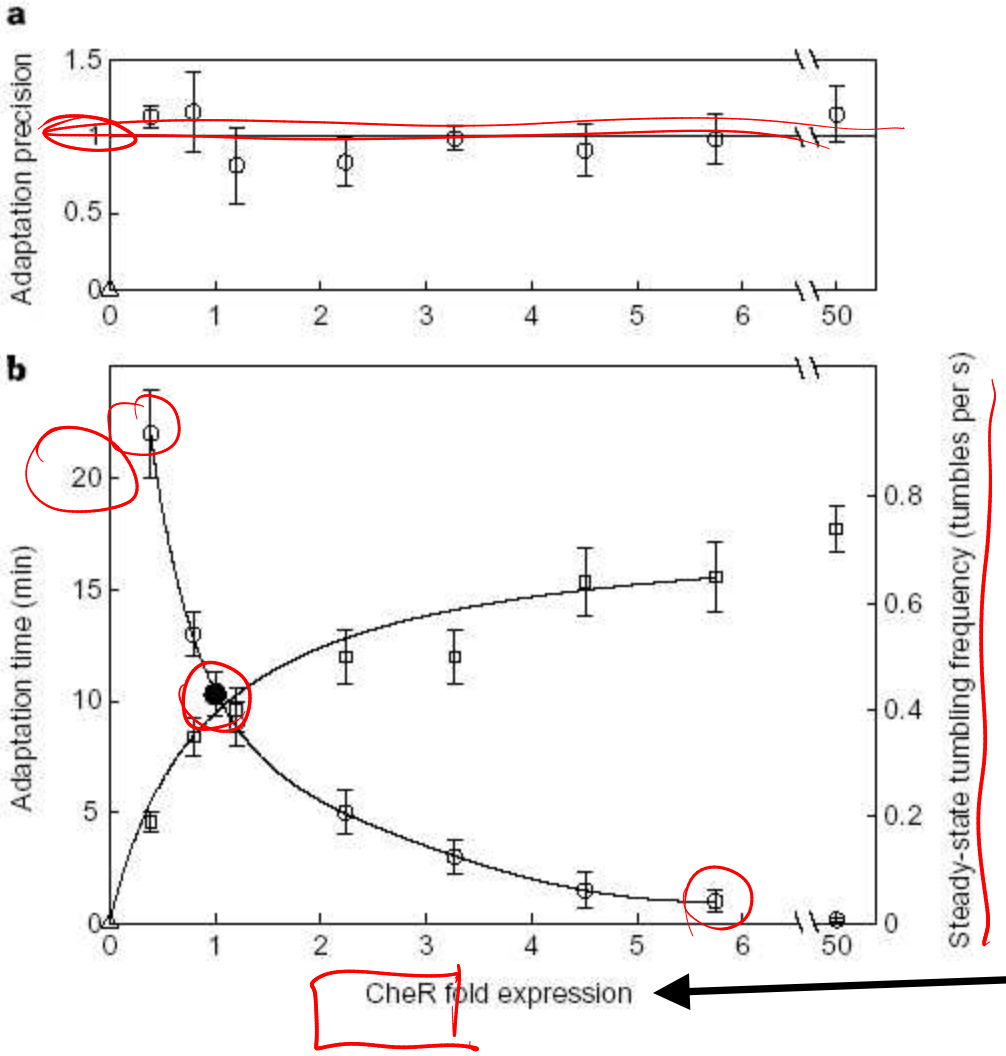
Advantage:

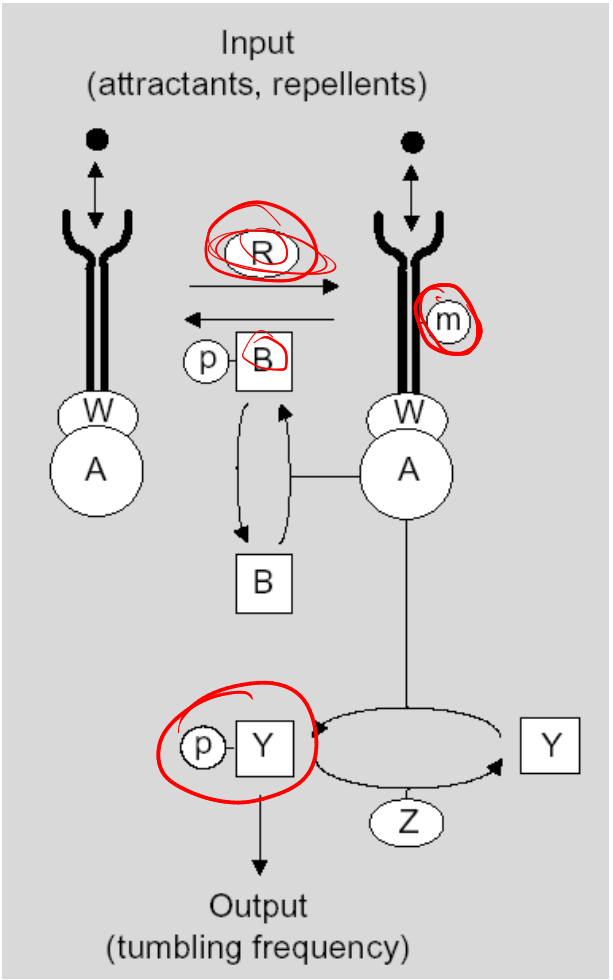
A bacteria can detect the change of an attractant over a very large range of concentrations: from 10^{-10} M to 10^{-3} M.

System response is fast <200ms, Adaptation slow (10 minutes)

Adaption under changed concentration of CheR

The precision of adaptation does not depend on the concentration of CheR





CheR is increased by expression from a plasmid under the external control of a Lac Operon.

Adaption under changed concentration of CheR

Die Adaptionspräzision ist unabhängig von CheR

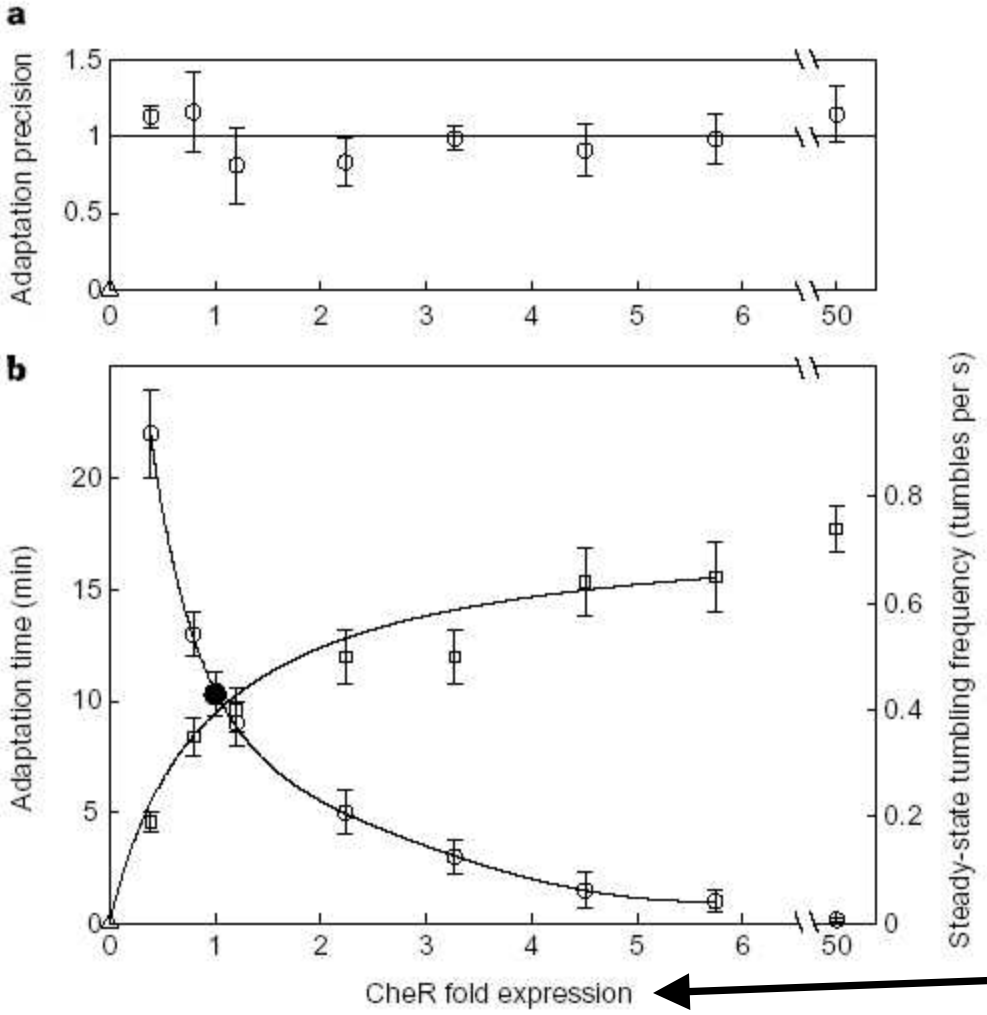


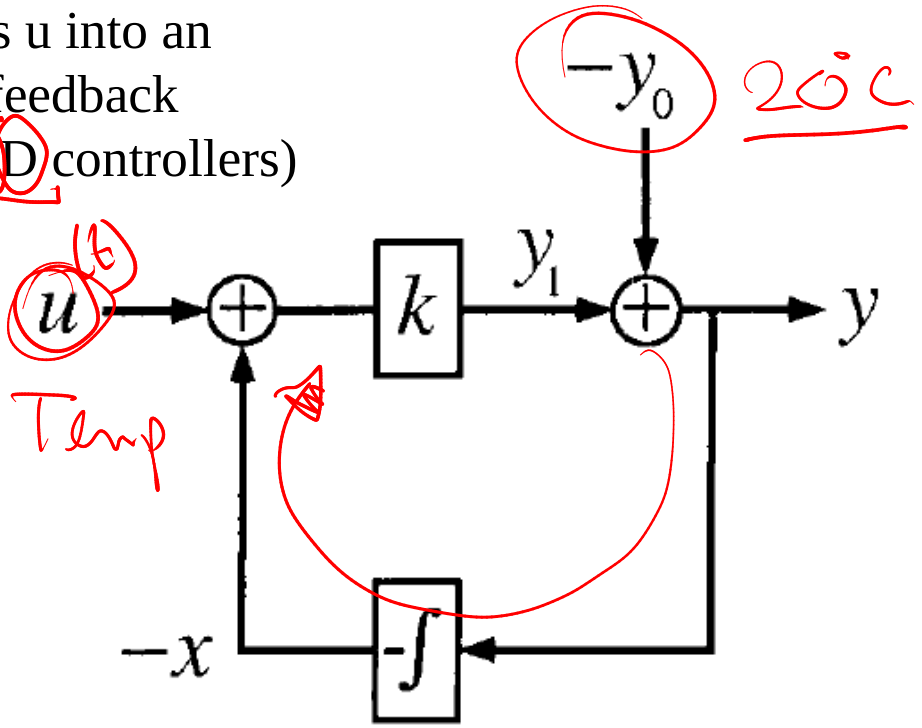
Figure 2 Chemotaxis behaviour of cells with varying intracellular concentration of the protein CheR. CheR was expressed from the plasmid pUA4 with varying levels of IPTG induction in a strain deleted for *cheR* (RP4968). **a**, Precision of adaptation, defined as the ratio between the steady-state tumbling frequency of unstimulated cells and cells stimulated with 1 mM L-aspartate. A precision of 1.0 corresponds to exact adaptation. Cells lacking CheR (RP4968 with the control vector pHSG575, triangle) did not respond to attractants, but showed a persistent response of about 0.6 tumbles per s to repellent (50 mM L-leucine). **b**, Average steady-state tumbling frequency of unstimulated cells (open squares, right scale), and average adaptation time to a step-like stimulation with 1 mM L-aspartate (open circles, left scale). Solid circle, wild-type strain (RP437 + pHSG575). Triangle, tumbling frequency of RP4968 + pHSG575. Lines are guides to the eye. Relative CheR expression was measured by immunoblots. 'Wild-type' CheR concentration was defined as the induction level where the adaptation time was equal to that of RP437 + pHSG575. Immunoblots also showed that the level of other chemotaxis proteins (CheB and CheY) did not vary measurably with CheR expression. Errors in relative CheR level are estimated to be under 30%. Mean and standard deviation of triplicate experiments are shown.

CheR is increased by expression from a plasmid under the external control of a Lac Operon.

Comparision with Integral feedback control

Doyl (1999)

The shown feedback control amplifies u into an output y. This is reduced via intragal feedback slowly to zero. (see integral part of PID controllers)



u: Input signal
(conc. of attractant)

x: *Integral feedback*
(Amount of Methylation)

y_0: Desired size

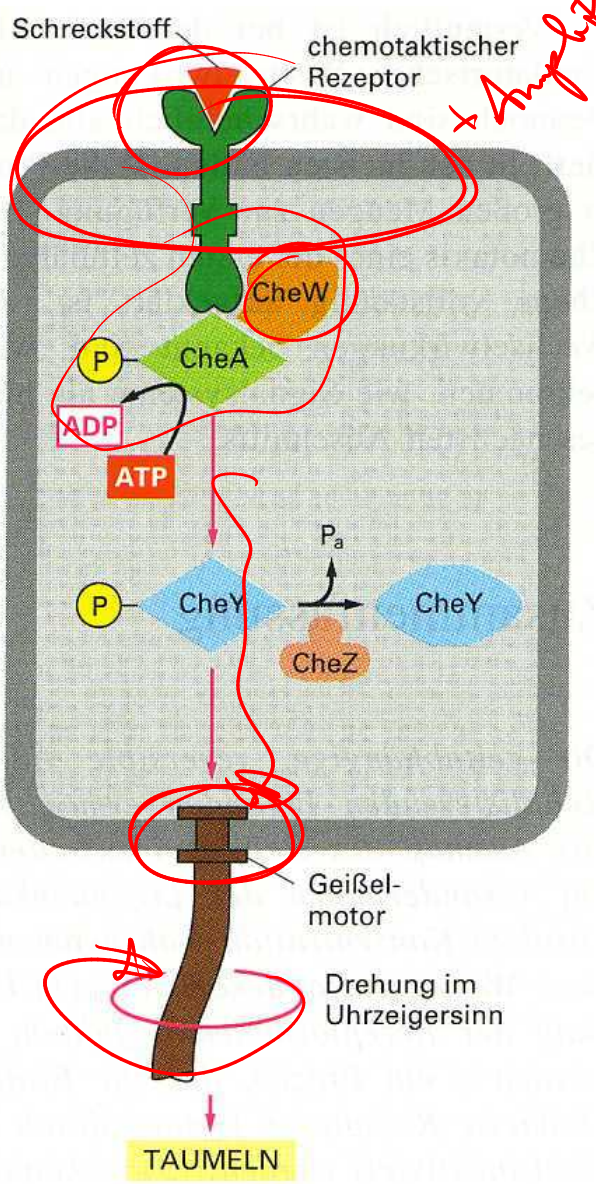
y_1-y_0: deviation

y: Output signal
(Receptor activity)

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

Sensitivity of Motor Activation

The intracellular signal network

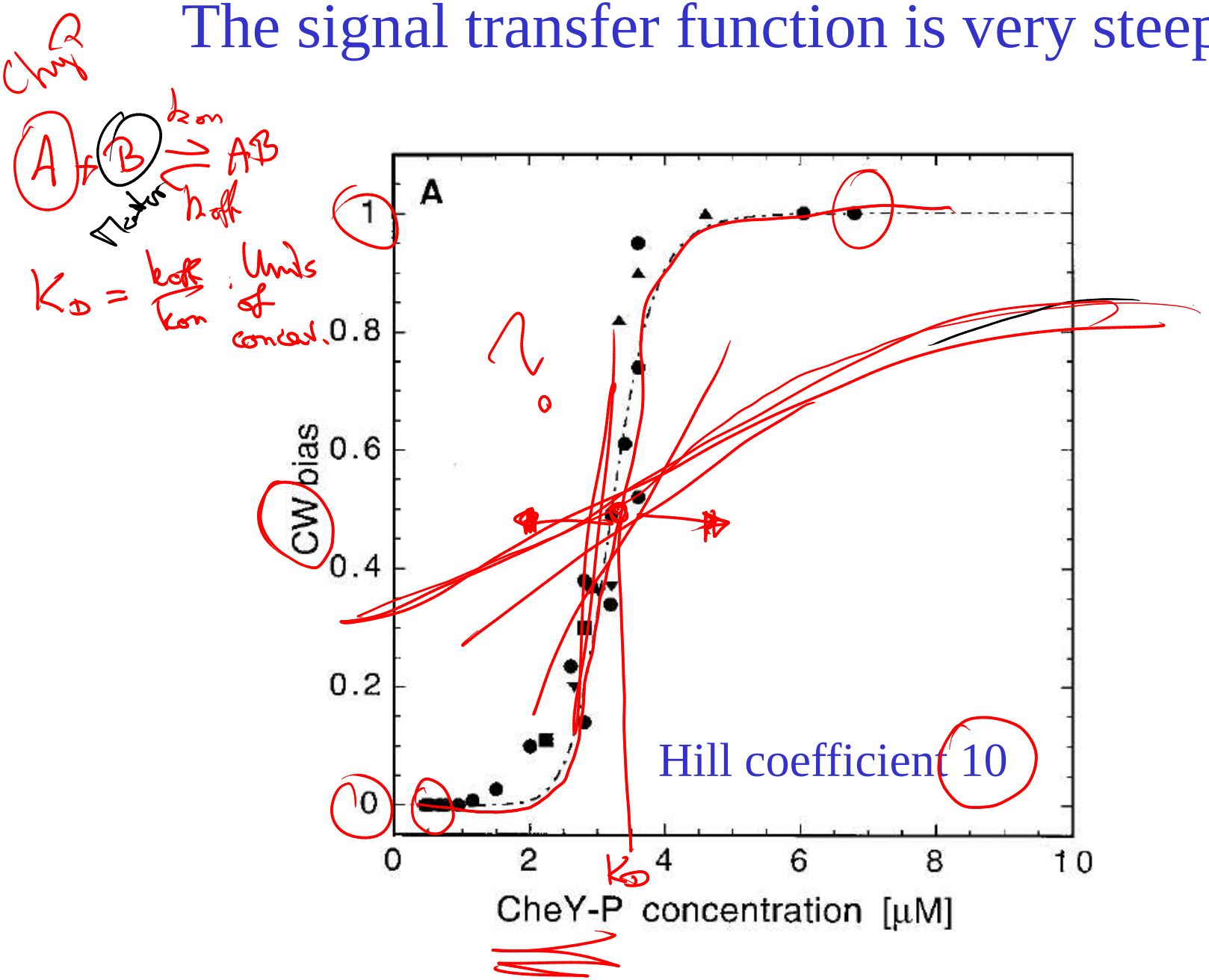


From genetic analysis, four cytoplasmatic proteins *CheA, CheW, CheY and CheZ* are known to connect the chemotactic receptors with the flagella motor.

CheW: Regulator
CheA : Proteinkinase
CheY : Response Regulator
CheZ : Phosphatase-activating Protein

Regulated by the receptor, *CheA* transfers a phosphorylation onto the small *CheY* protein. *CheY-p* diffuses to the motor protein and induces a transition towards the tumble movement.

The signal transfer function is very steep



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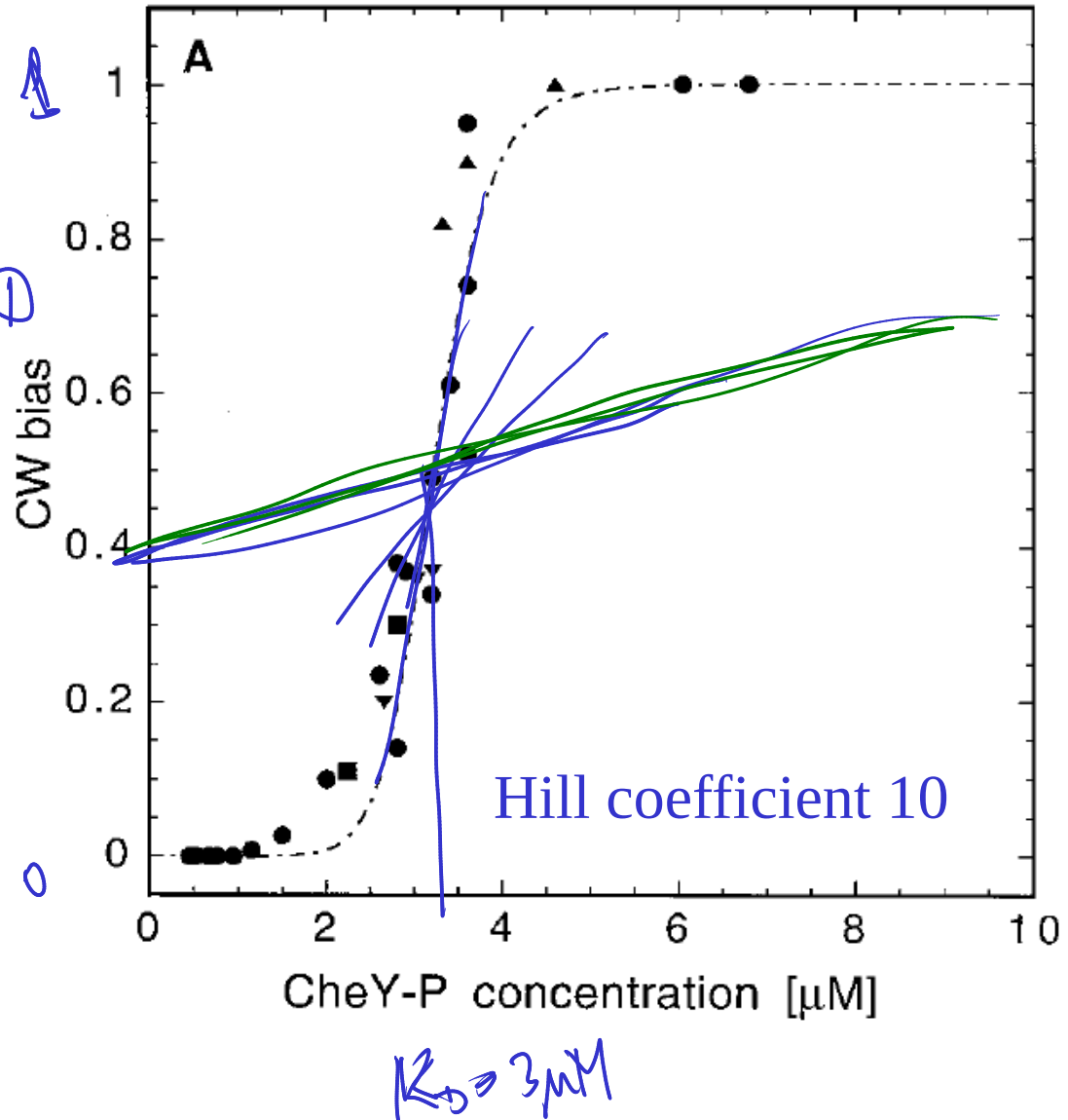


Hill Equation

Binding a ligand to a receptor is often enhanced if there are already other ligands present (cooperative binding). The Hill coefficient, provides a way to quantify this effect, initially used for O_2-binding to Hemoglobin.

$$\theta = \frac{[L]^n}{K_d + [L]^n}$$

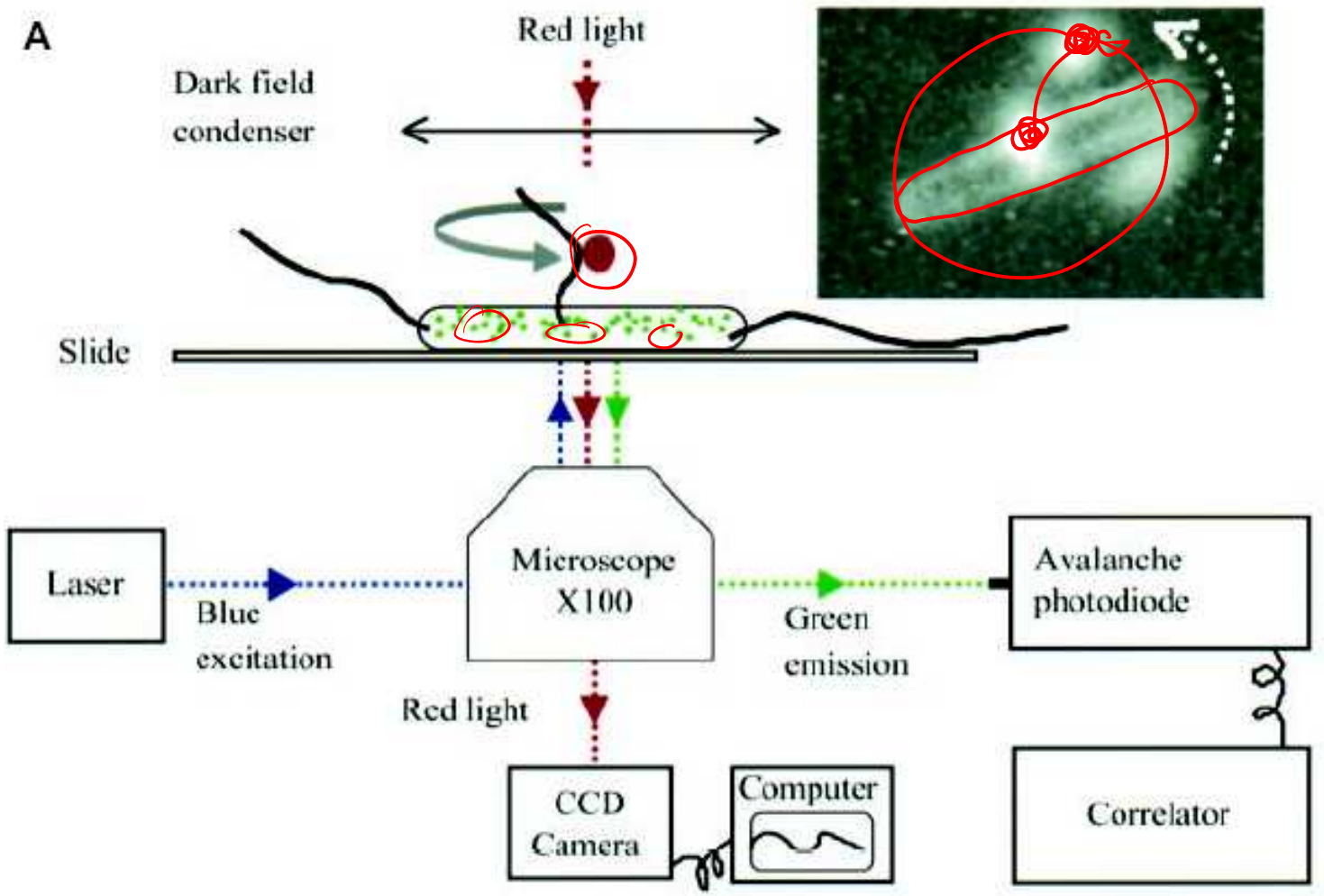
θ - fraction of ligand binding sites filled
[L] - ligand concentration
K_d - dissociation constant

Hill coefficient n.

Describes the cooperativity of ligand binding:
n > 1 - Positively cooperative reaction: Once one ligand molecule is bound to the enzyme, its affinity for other ligand molecules increases.
n < 1 - Negatively cooperative reaction: Once one ligand molecule is bound to the enzyme, its affinity for other ligand molecules decreases.
n = 1 - Noncooperative reaction: Independent binding to the receptor. Same as Langmuir equation.

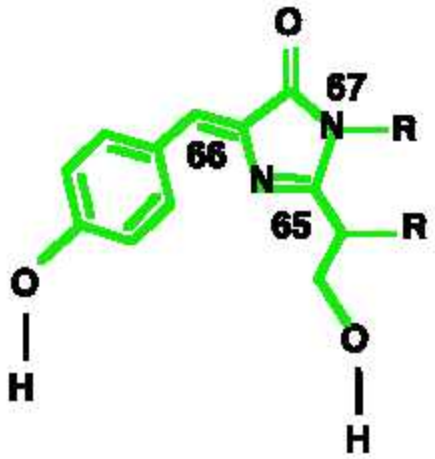
Measurement of Motor signal transduction

Cluzel et al.

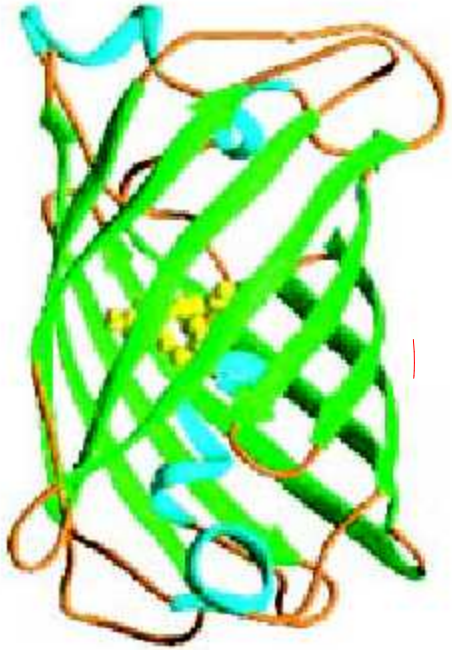


Green-fluorescent Protein

The three amino acids
Ser^{65}, Tyr^{66}, and Gly^{67}
form the GFP chromophore



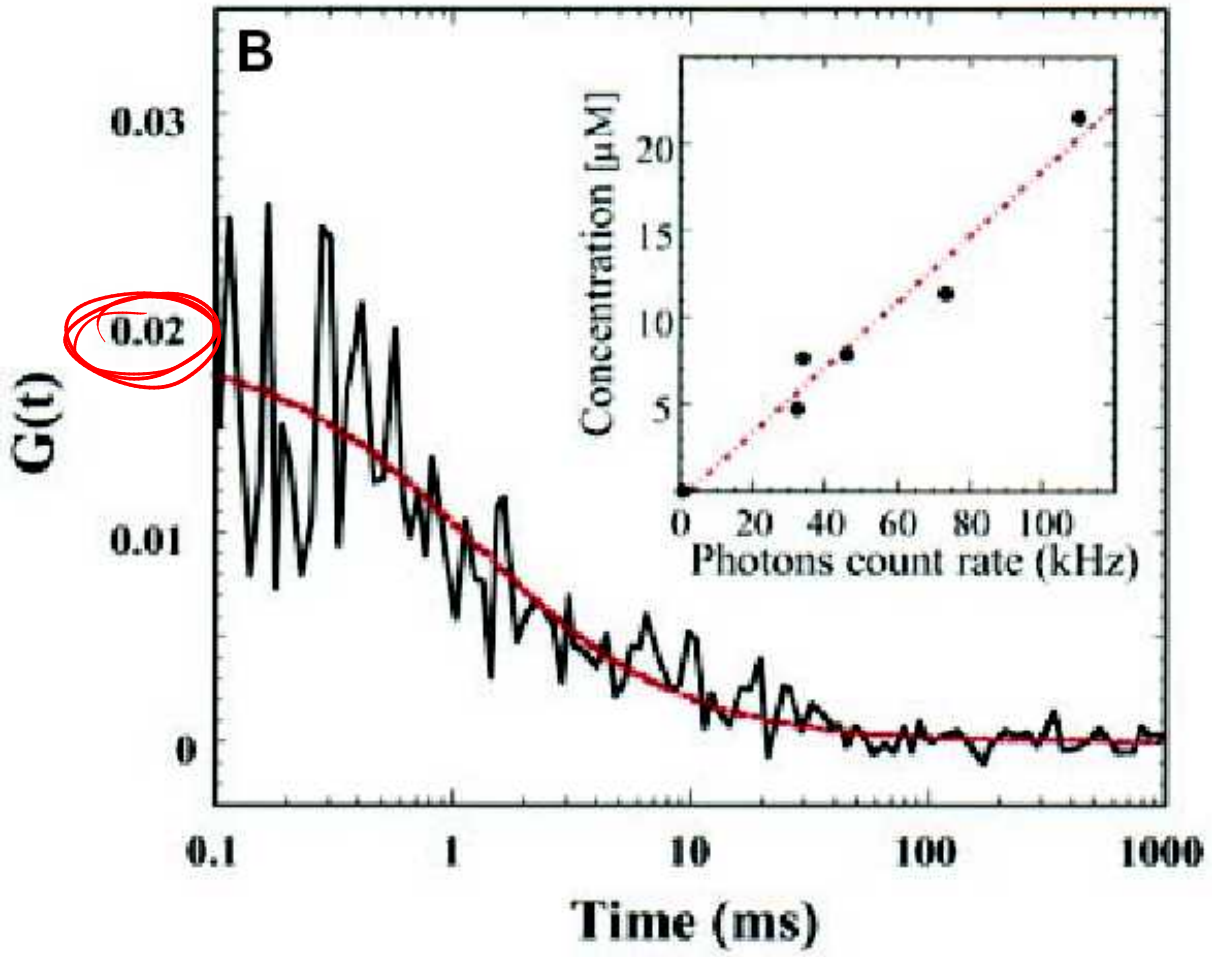
Green fluorescent protein (GFP)
From jellyfish *Aequorea victoria*



GFP can be genetically linked to other proteins ("fused"). Cluzel et al. have constructed CheY-P–GFP under the control of a Lac promotor.

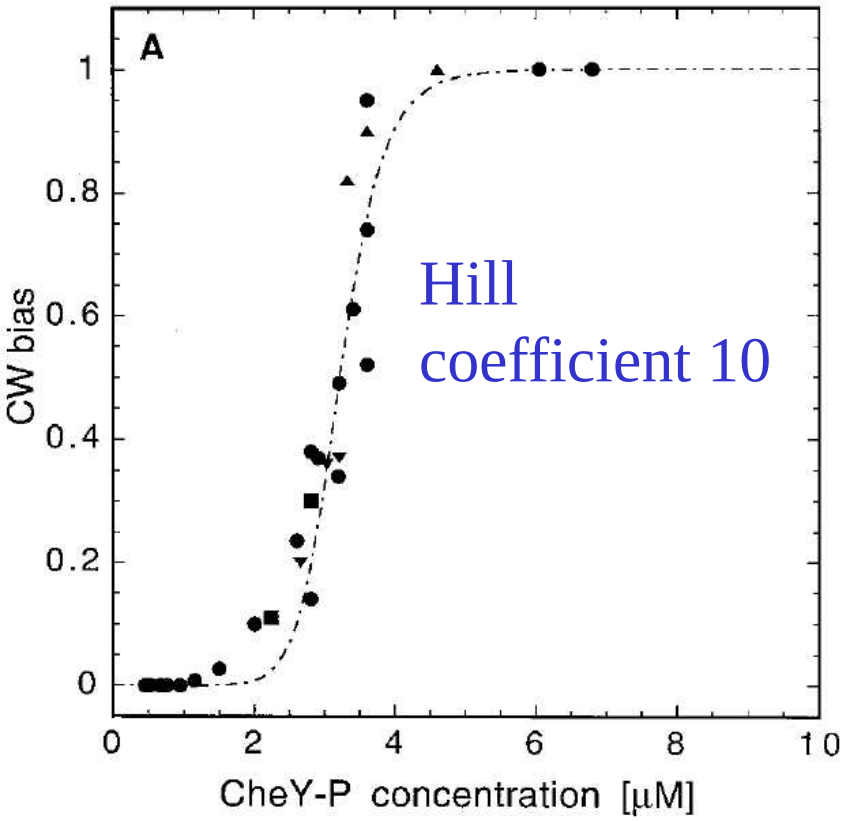
Fluorescence Correlation allows the calibration of the protein concentration inside a cell

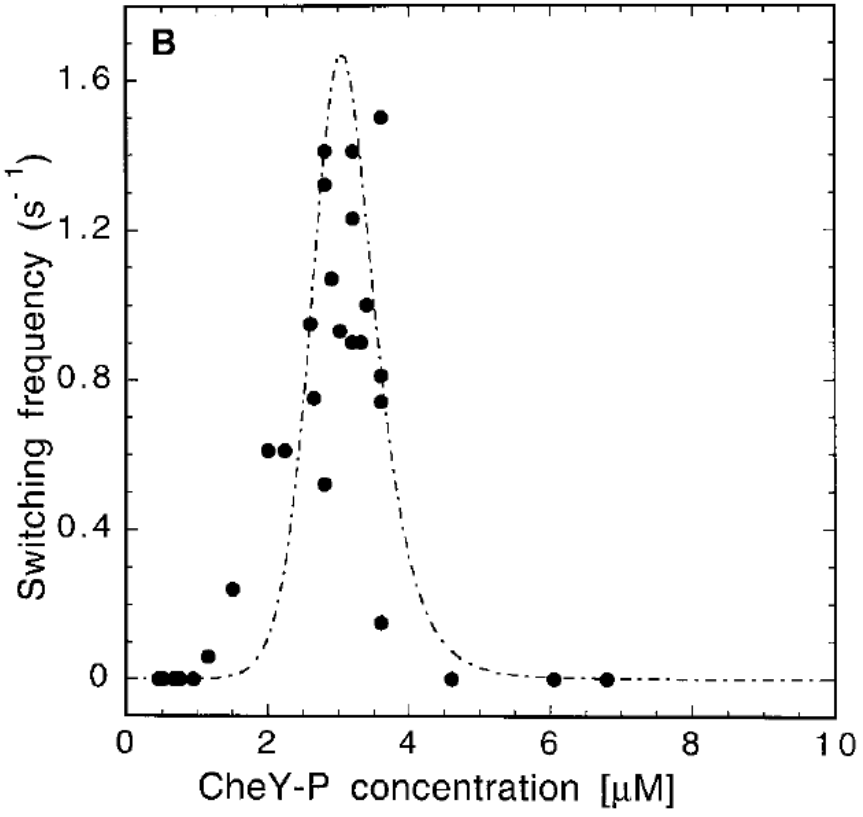
FCS



The signal transfer function is very steep

On-Off characteristic, Amplification factor 10
Total amplification 60 (bei Front-end Verstärkung 3-5)





Collective Effects in Receptor-Field

-> Slides from Talk of Tom Duke,
Cavendish Laboratory, UK

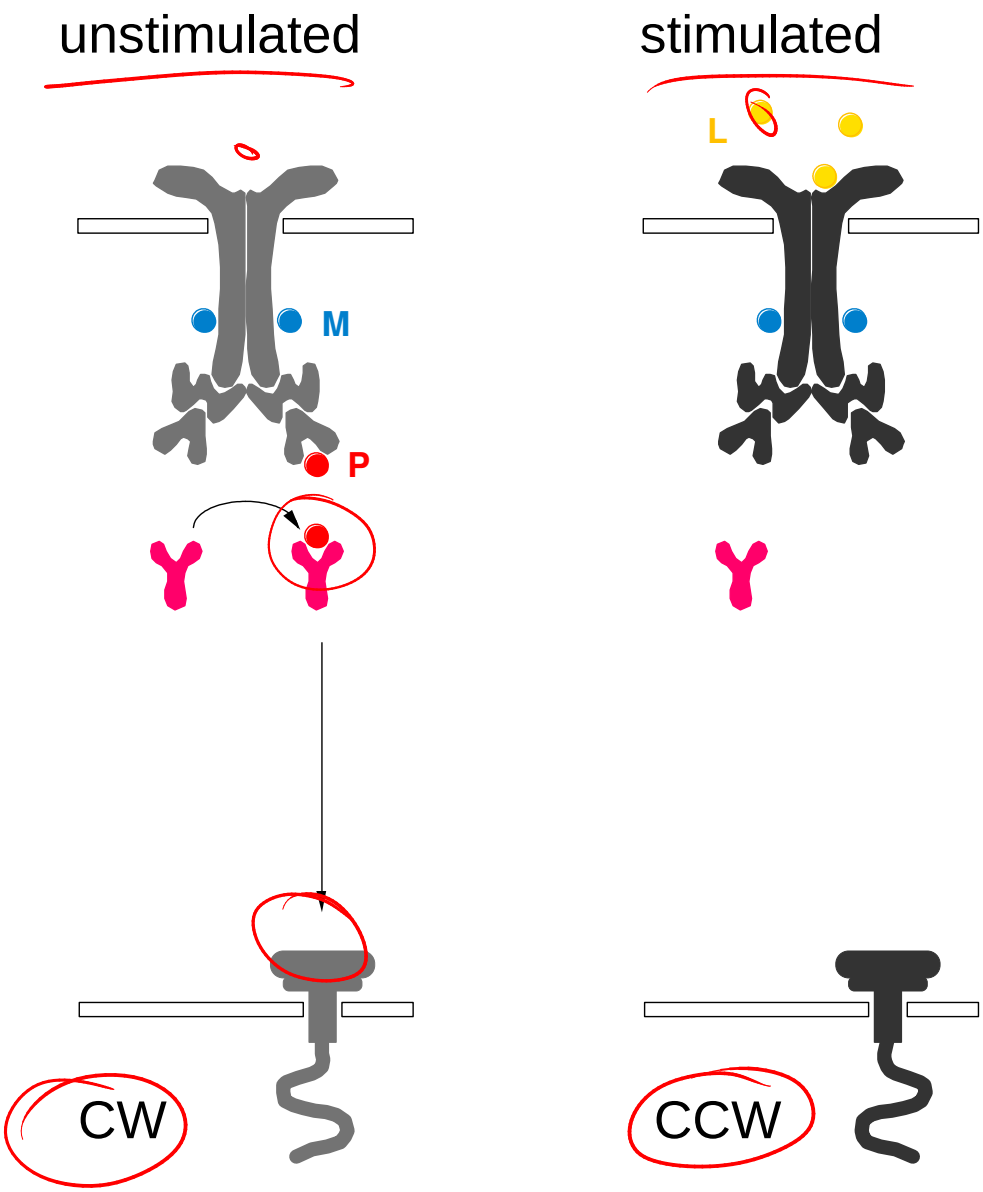
Signal processing by clusters of membrane receptors

Tom Duke — *Cavendish Laboratory*
Ian Graham

Dennis Bray — *Anatomy Department*

University of Cambridge

Protein network



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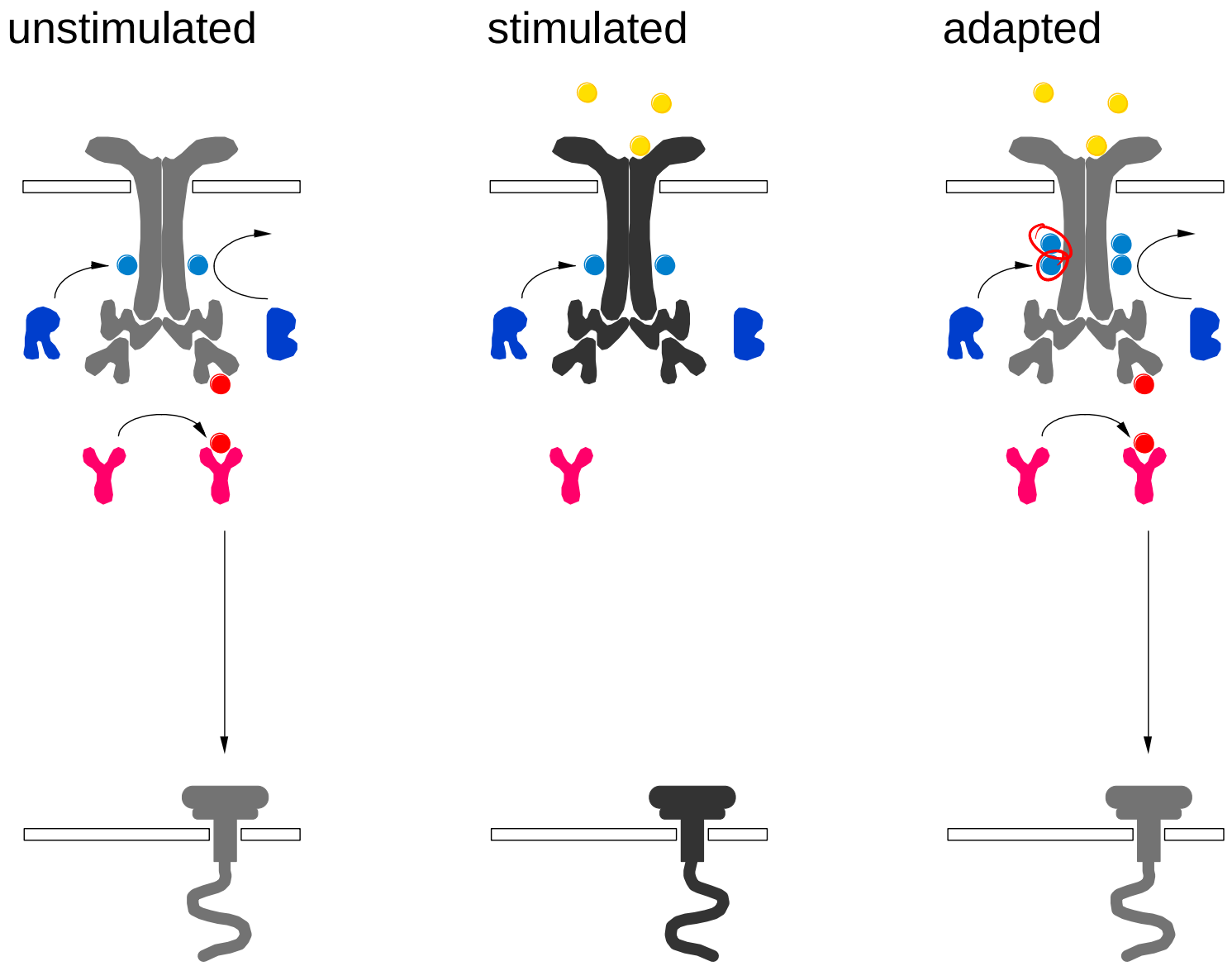
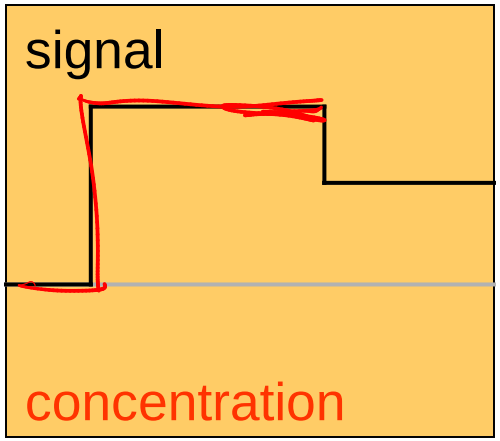


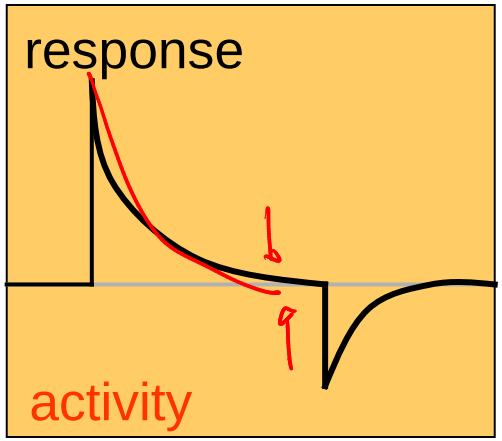
Exact adaptation

Barkai & Leibler '97

If modification enzyme Che B binds only to active receptors, steady-state activity is independent of ambient concentration

→ Robust, exact adaptation





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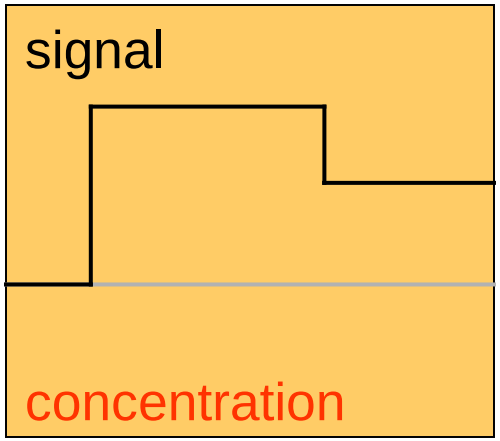
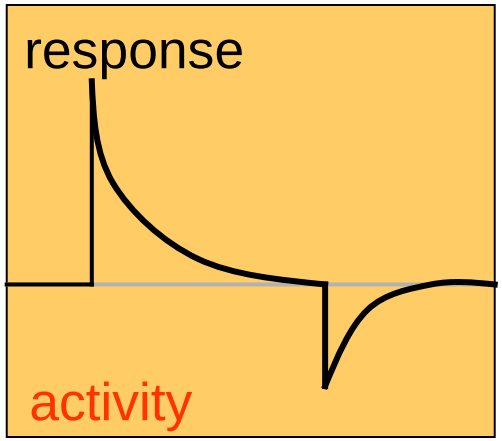




Separation of time scales:

- conformational transition
- ligand release
- phosphorylation
- methylation

10^{-5} s ?

10^{-3} s

10^{-1} s

10 min

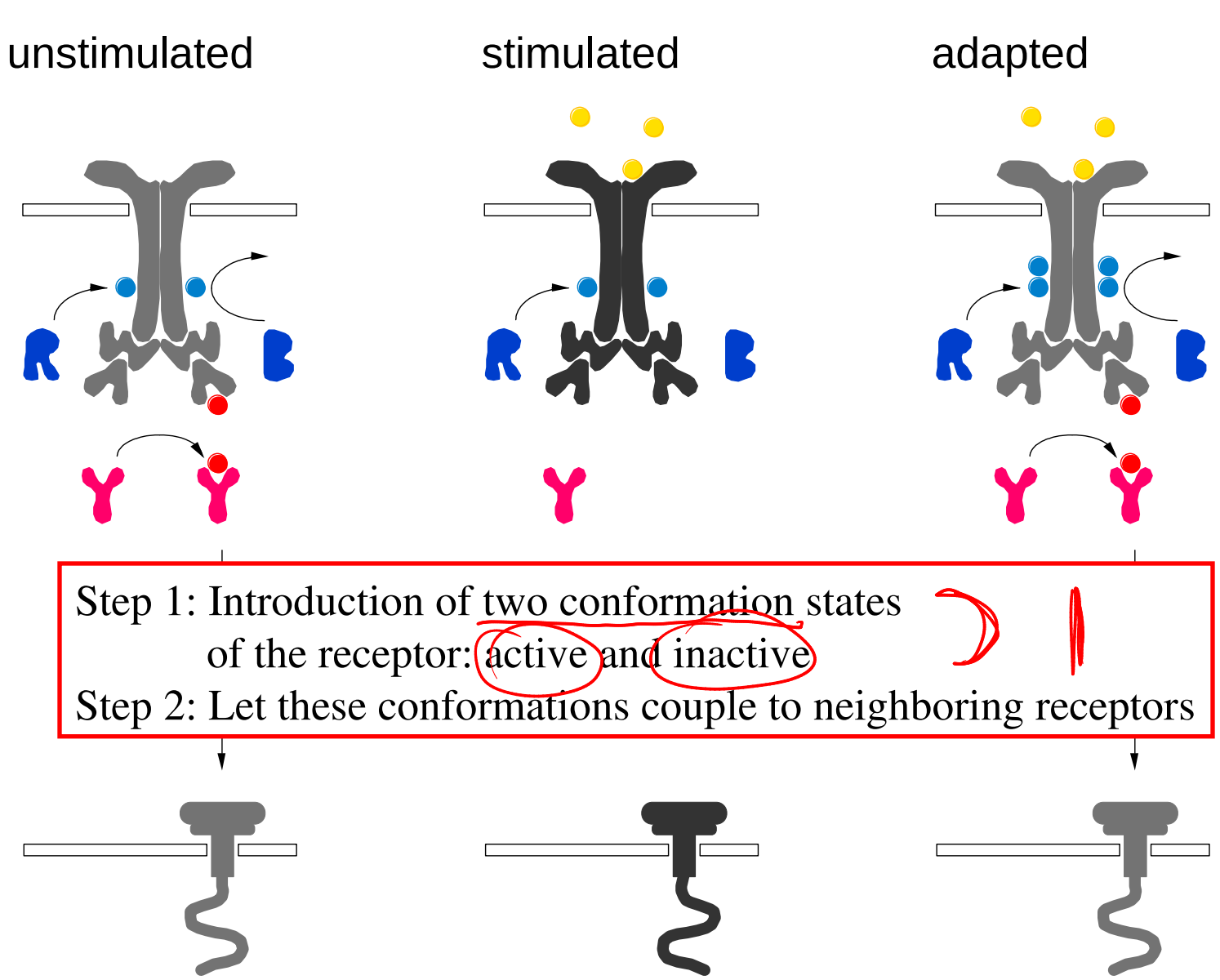
fast dynamics

response time

<< 0.1 s

adaptation time

Protein network

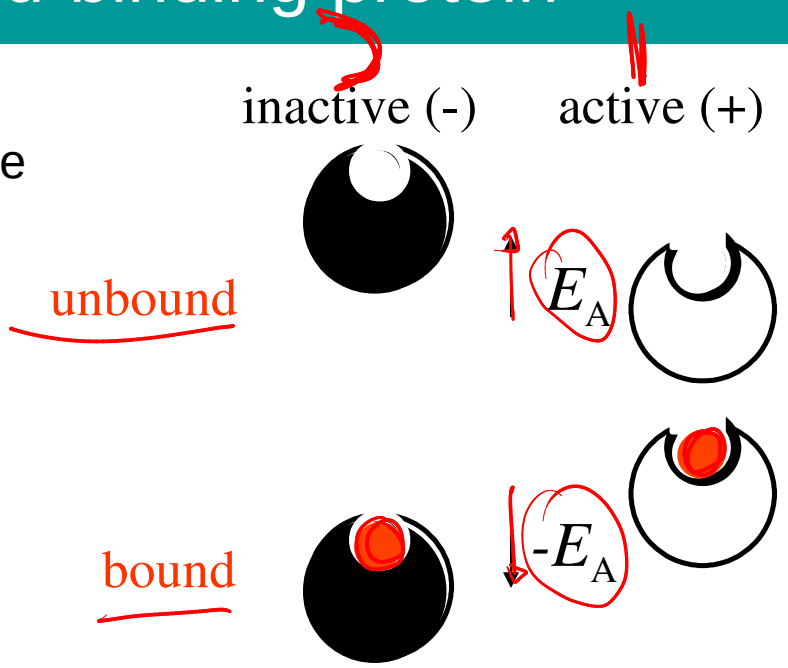


Two-state ligand-binding protein

ligand binds more strongly to inactive state

$$\frac{K_d^+}{K_d^-} = e^{2E_A}$$

$$K_d = \sqrt{K_d^+ K_d^-}$$



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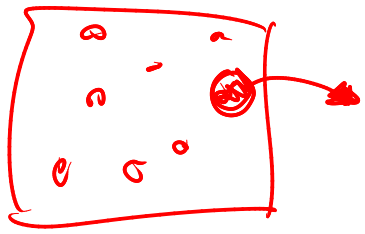
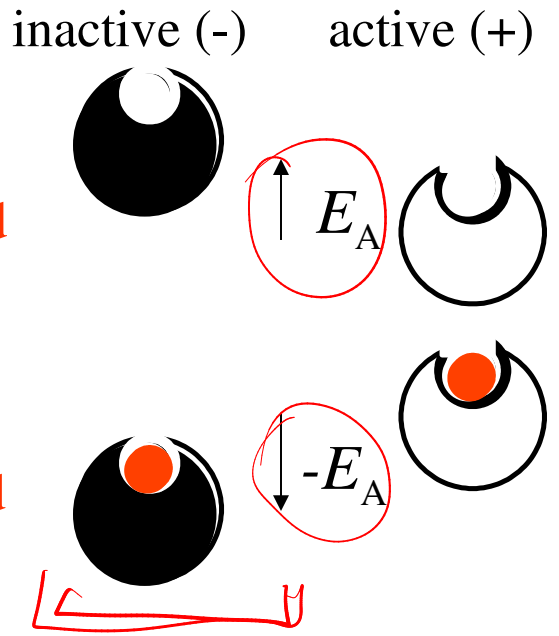




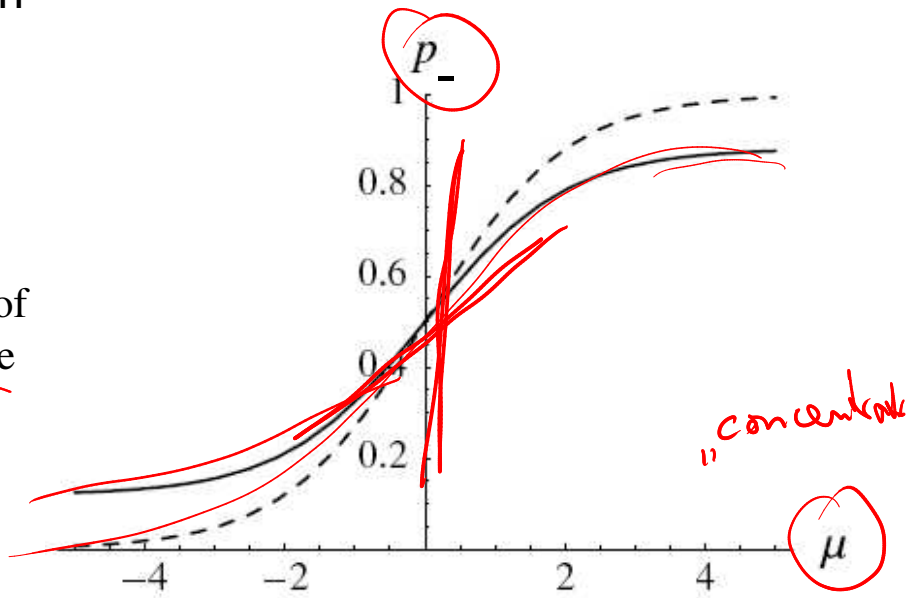
mean activity depends on ligand concentration

$$\mu = \log\left(\frac{c}{K_d}\right)$$

Chemical potential of bound ligand

$$p_- = \frac{1 + e^{\mu + E_A}}{(1 + e^{E_A})(1 + e^{\mu})}$$

Probability of inactive state



Parallel to binding, receptors become inactive (-):
Fast way to some sort of 'adaption' behaviour

Simple model: thermodynamics

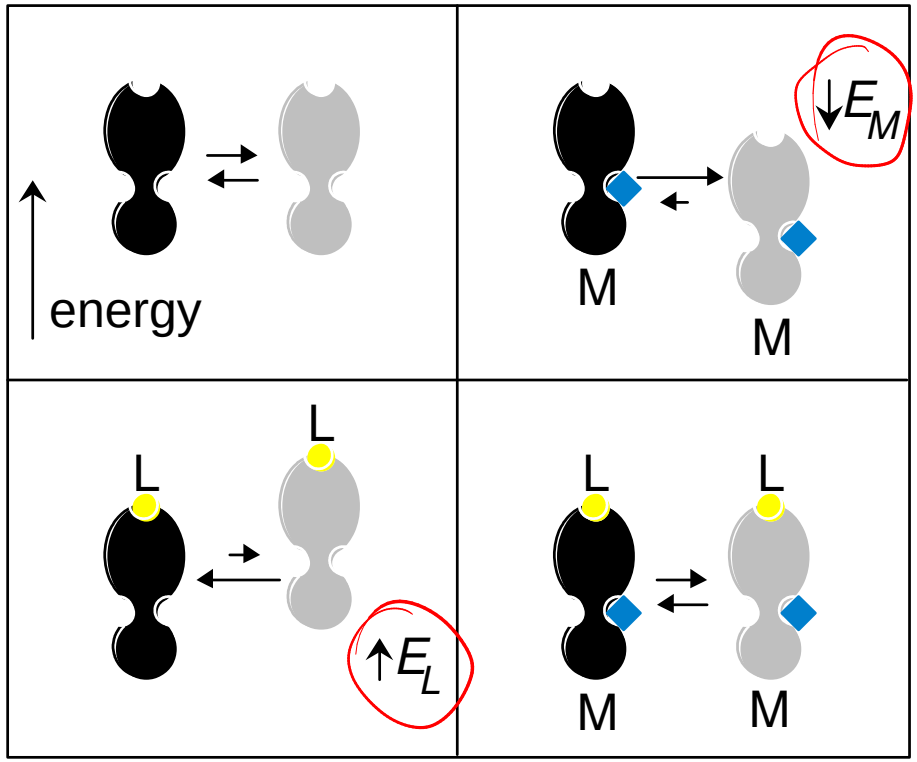
Consider different receptors i with three states:

$$s_i = \begin{cases} -1 & \text{inactive} \\ +1 & \text{active} \end{cases}$$

$$\lambda_i = \begin{cases} 0 & \text{unliganded} \\ 1 & \text{liganded} \end{cases}$$

$$\mu_i = \begin{cases} 0 & \text{unmodified} \\ 1 & \text{modified} \end{cases}$$

$$H = \sum_i \lambda_i s_i E_L + \mu_i s_i E_M$$



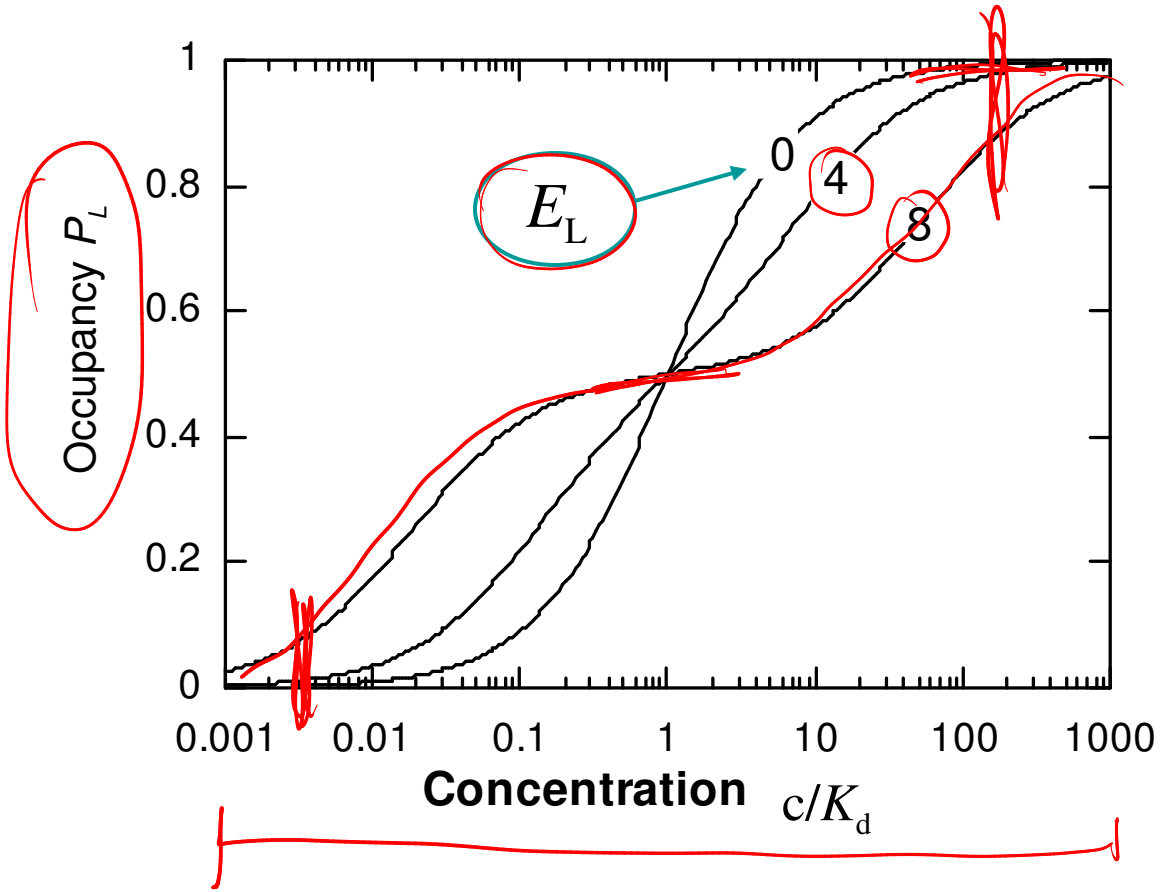
for the symmetric case $E_L = -E_M$

the adapted system with $P(s_i)=0.5$ has $\sum_i \lambda_i = \sum_i \mu_i$

Simple model:
sensitivity to fractional change in concentration

Sensitivity of adapted system ∝ change in ligand occupancy

→ depends on shape of ligand-binding curve



$$P_L = \frac{\alpha(\alpha+\beta)}{\alpha^2+2\alpha\beta+1}$$

$$\alpha = \frac{c}{K_d}$$

$$\beta = \cosh\left(\frac{E_L}{2}\right)$$

Model:
sensitivity to fractional change in concentration

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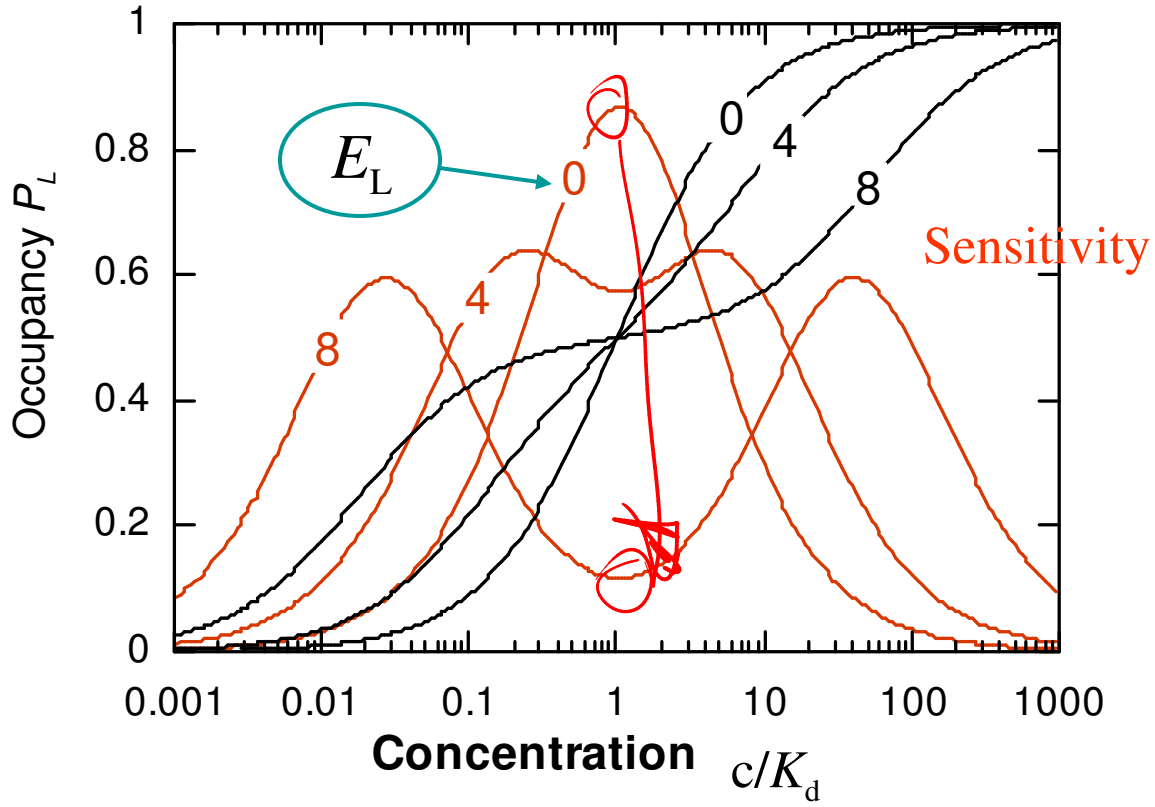


$$P_L = \frac{\alpha(\alpha+\beta)}{\alpha^2+2\alpha\beta+1}$$

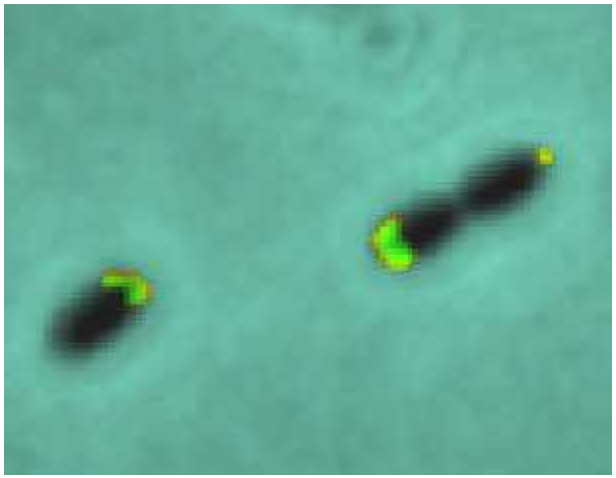
$$\alpha = \frac{c}{K_d}$$

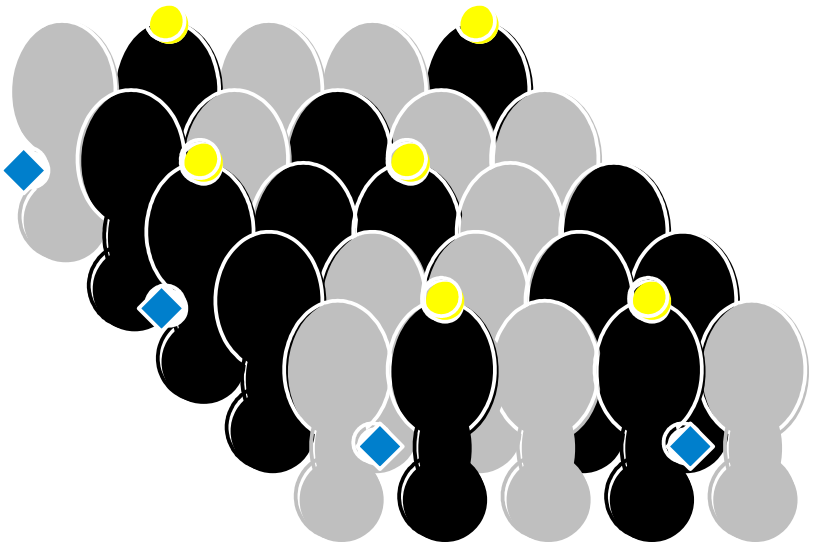
$$\beta = \cosh\left(\frac{E_L}{2}\right)$$

Conformation-dependent coupling

Shi & Duke '99

Receptors are clustered together





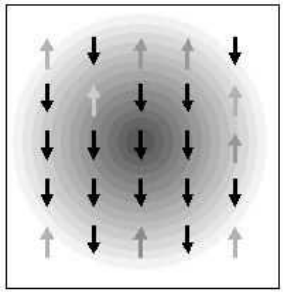
energy reduced by J if neighbour in same conformation

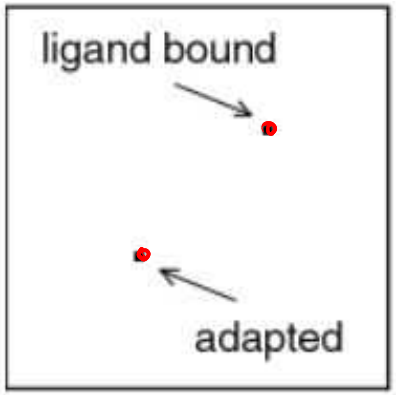
$$H = \sum_i \lambda_i s_i E_L + \mu_i s_i E_M + \sum_{i,j} J s_i s_j$$

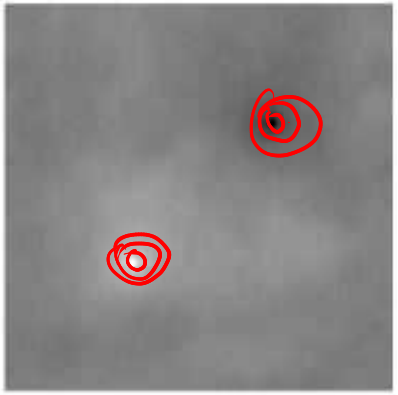
random field Ising model: possible phase transition at $J = J^*$

Conformational spread

Ligand affects the receptor to which it is bound and, *via* conformational coupling, also influences other receptors in the immediate vicinity







Realm of influence becomes very large close to the phase transition

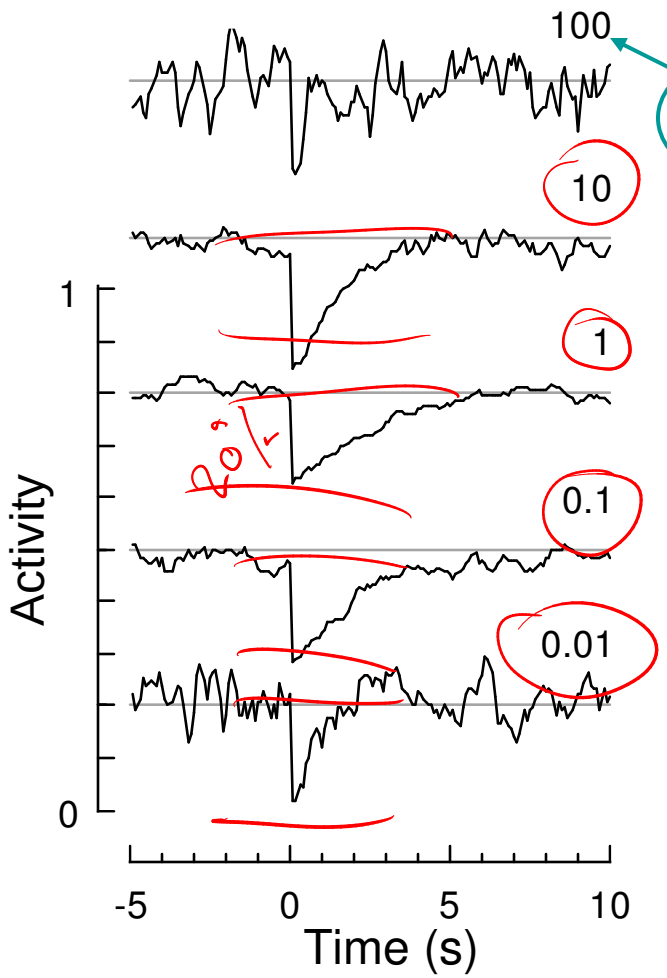
correlation length $\zeta \sim \left(1 - \frac{J}{J^*}\right)^{-1}$

enhancement $\sim \zeta^2 \sim \left(1 - \frac{J}{J^*}\right)^{-2}$

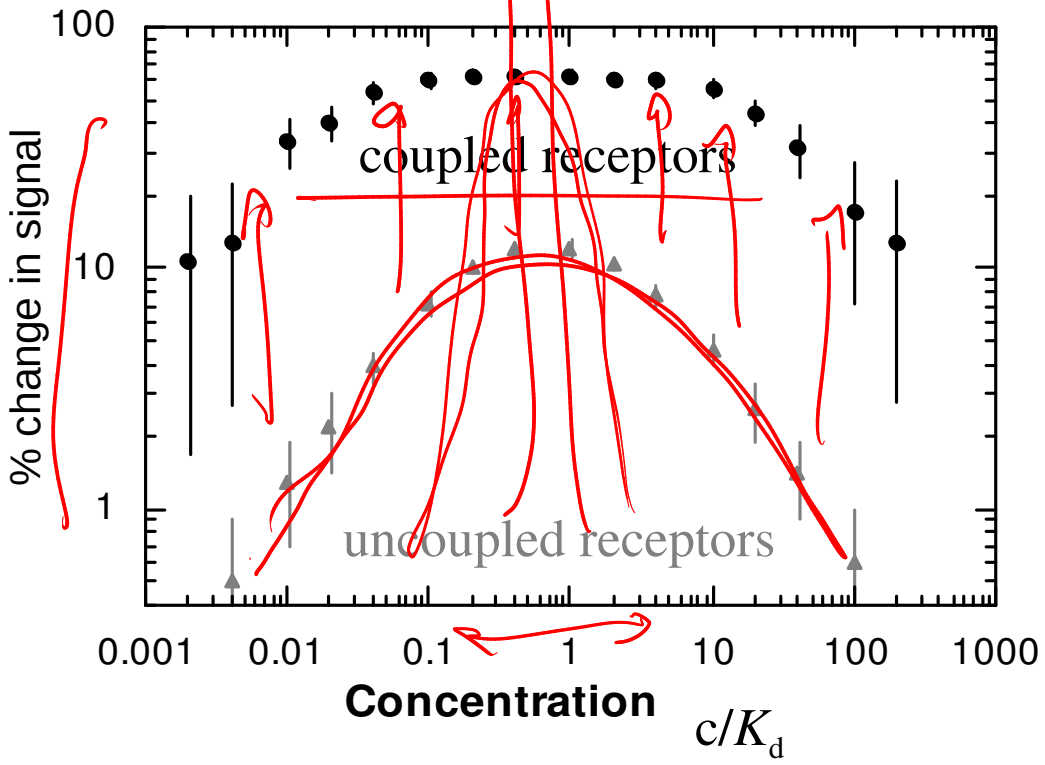
Response to doubling of concentration

Duke & Bray '99

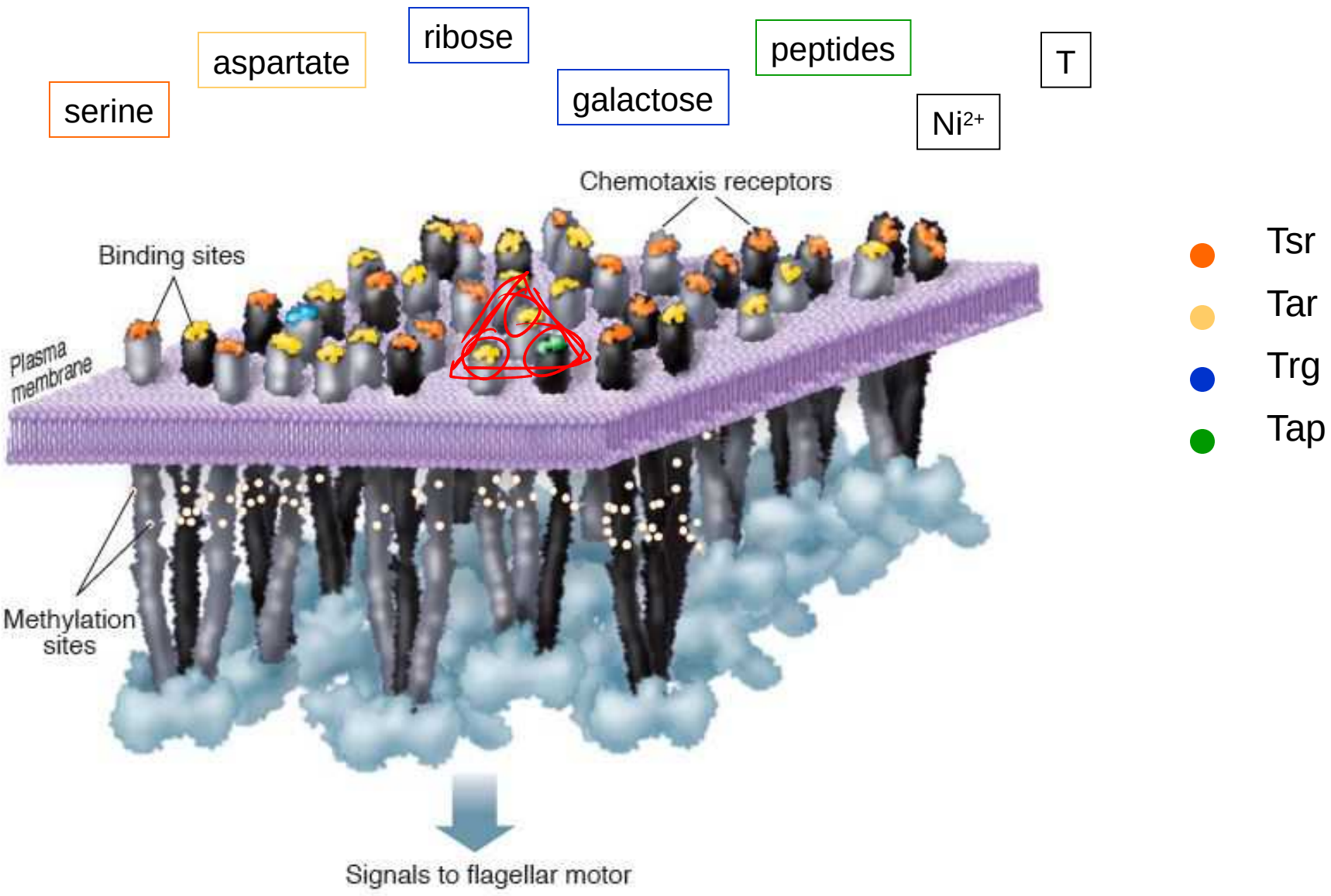
System responds sensitively over a wide range of ambient concentrations:



$$\left(1 - \frac{J}{J^*}\right) = 0.1$$



Mixed receptor clusters



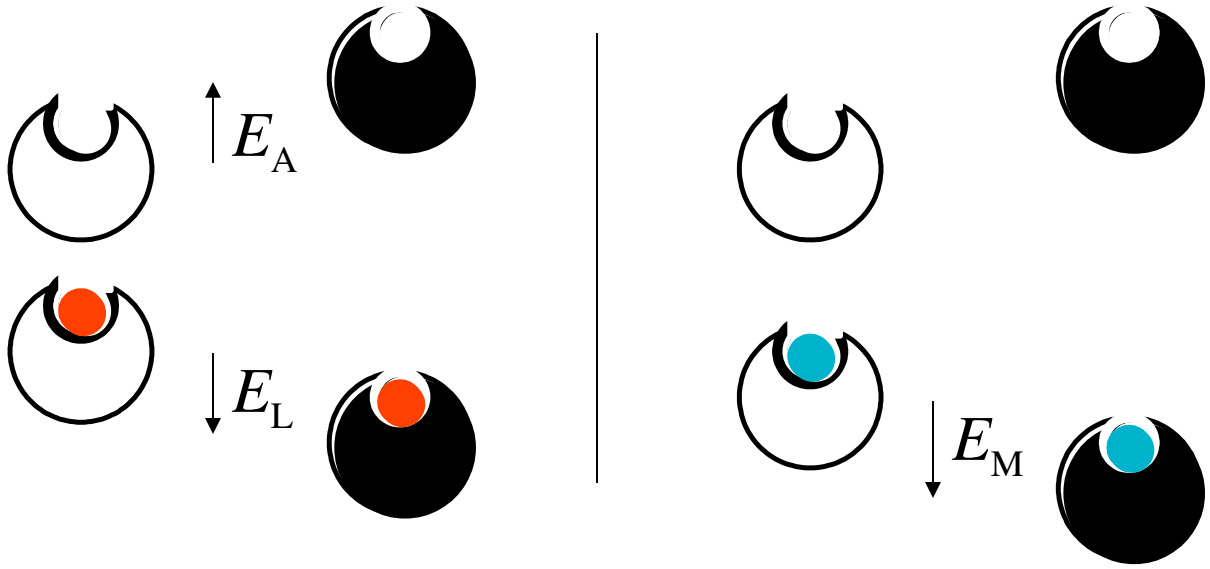
Two-state protein binding different ligands

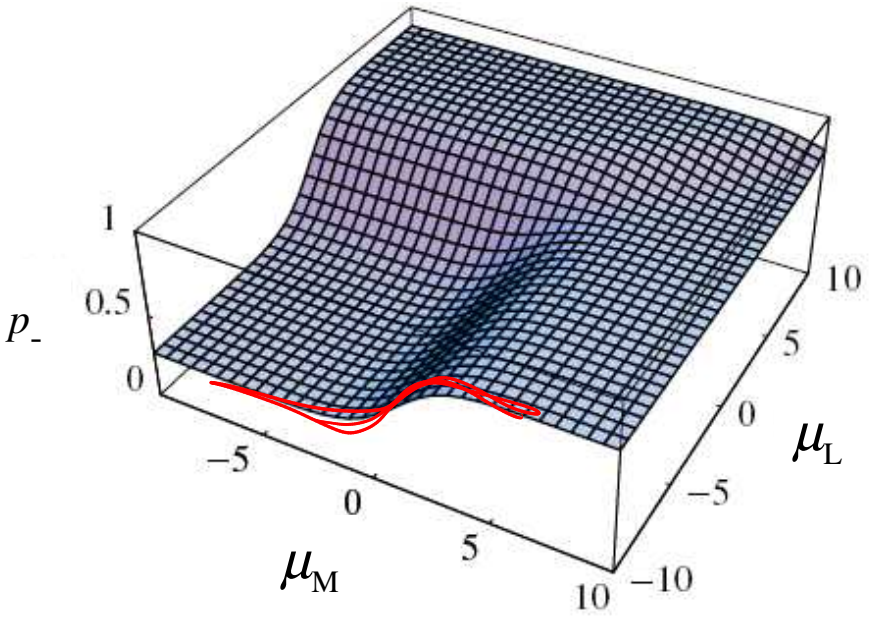
Exclusive binding
of two different ligands
L and M

$$\mu_L = \log\left(\frac{c}{K_d^L}\right)$$

$$\mu_M = \log\left(\frac{c}{K_d^M}\right)$$

response ~ L OR M





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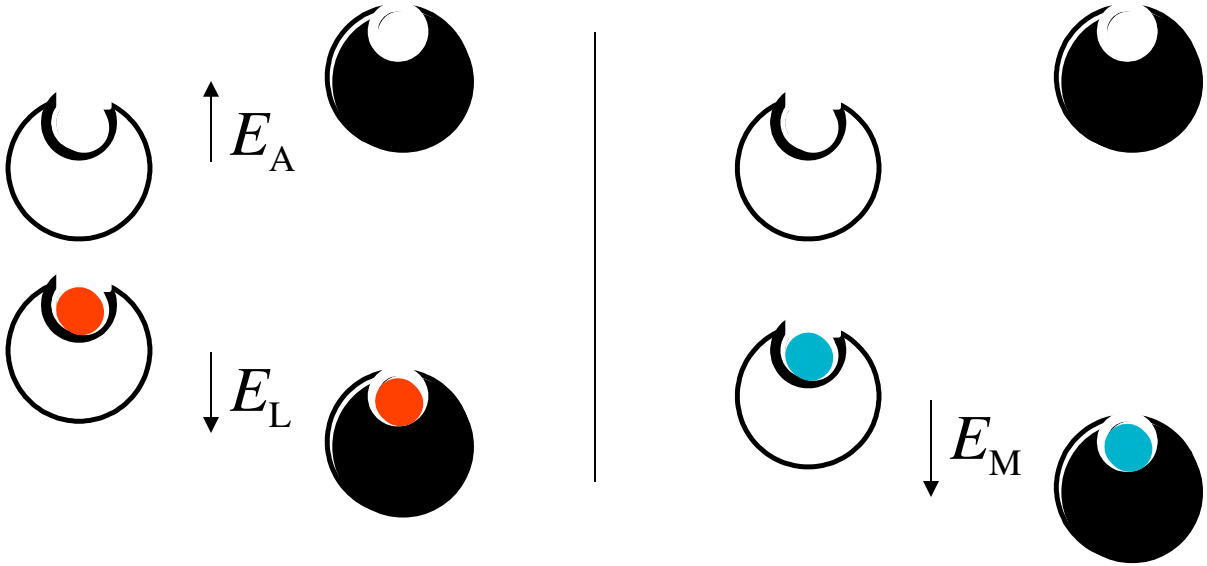

$$\mu_L = \log\left(\frac{c}{K_d^L}\right)$$

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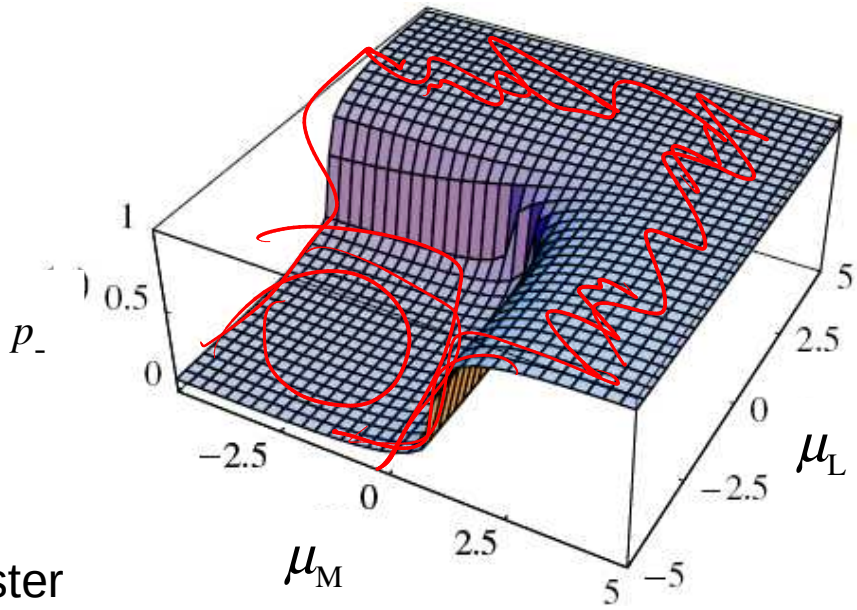
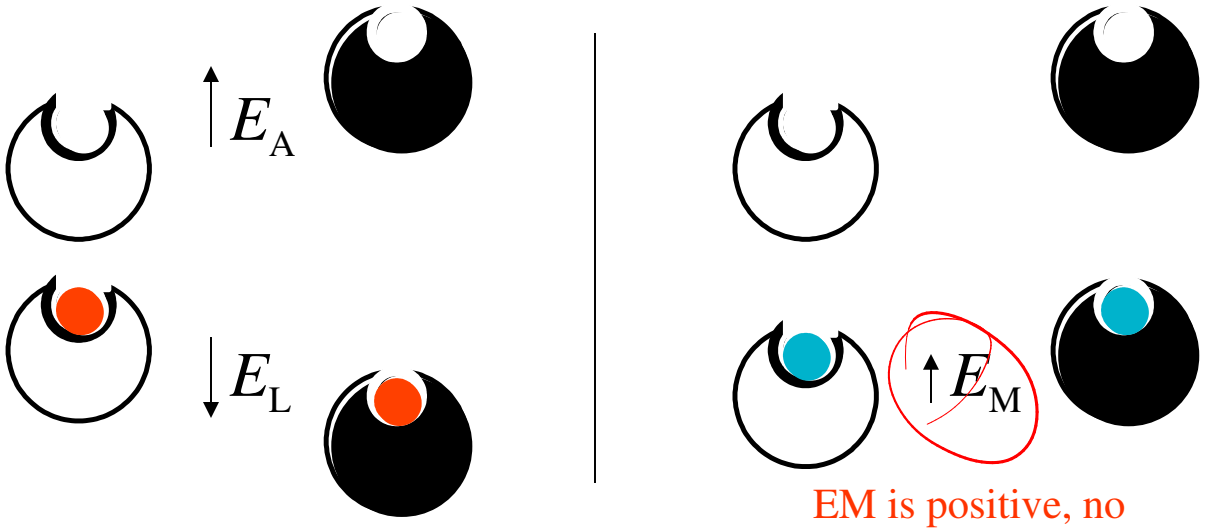
response ~ L OR M



switch sharpened by cooperativity in a cluster

Two-state ligand-binding protein

Exclusive binding
of two different ligands
L and M

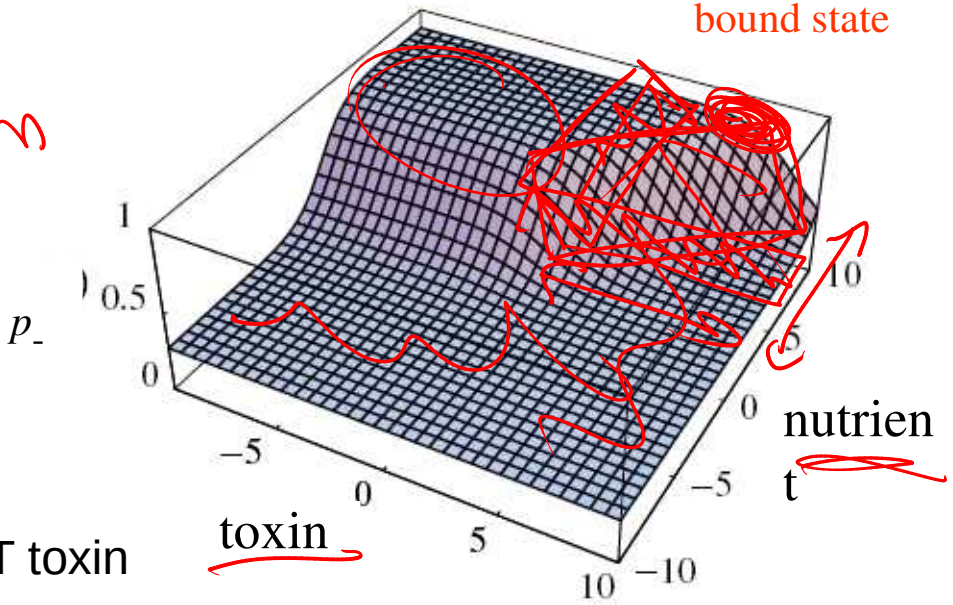


EM is positive, no stabilization of inactive bound state

$$\mu_L = \log\left(\frac{c}{K_d^L}\right)$$

$$\mu_M = \log\left(\frac{c}{K_d^M}\right)$$

response ~ L AND NOT M

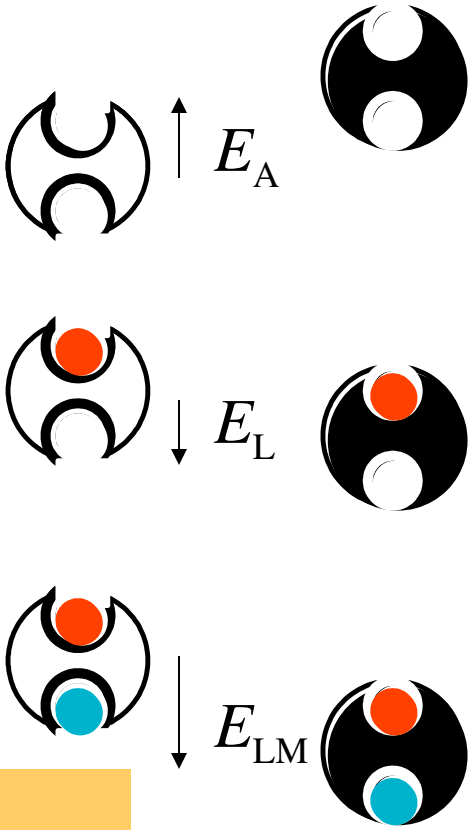


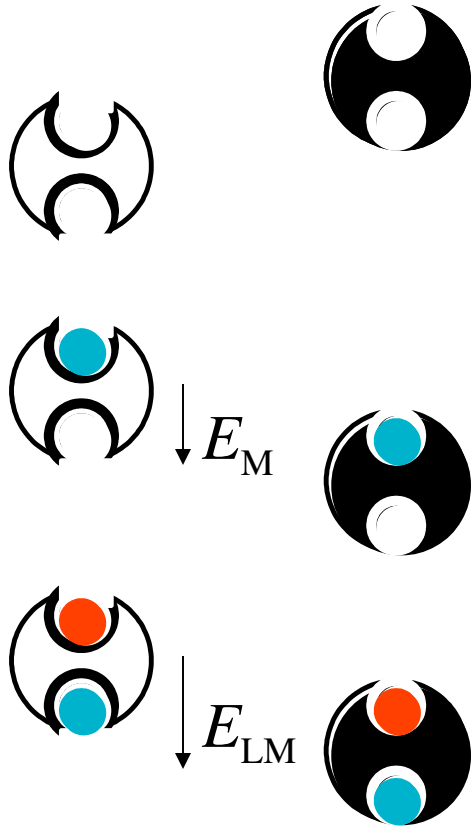
- eg. extend run IF
  increasing amount of nutrient AND NOT toxin

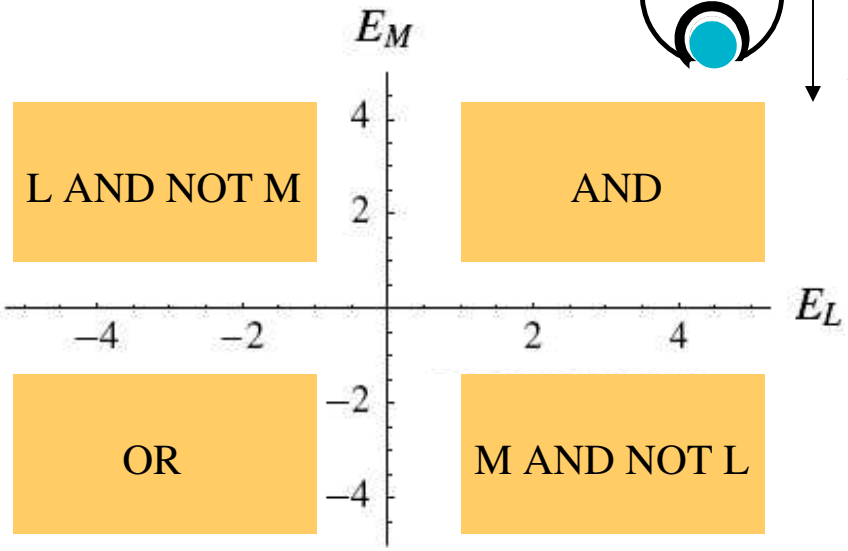
Two-state ligand-binding protein

Non-exclusive binding of two different ligands L and M

$$E_L + E_M = E_A + E_{LM}$$



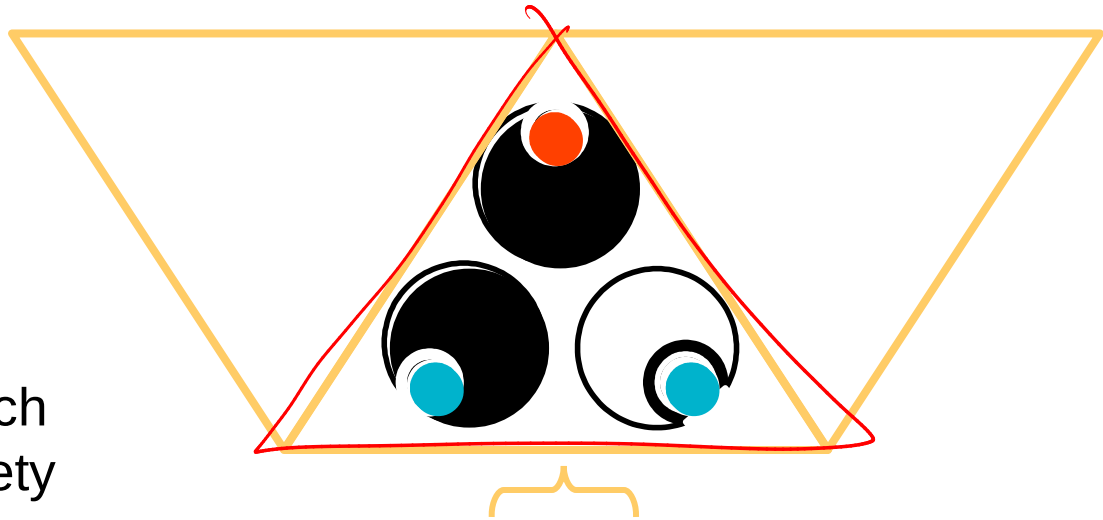




Introducing neighborhood of two receptors allows to introduce E_{LM} parameter depending on the combined state. As result, logical gates are possible.

Receptor trimers as logic elements

Cluster is an extended array of trimers of receptors



mixing different receptors in each trimer group provides a variety of basic logical elements

The logical repertoire of ligand-binding proteins

Ian Graham and Thomas Duke, 2005 *Phys. Biol.* **2** 159-165 doi:10.1088/1478-3975/2/3/003

Abstract. Proteins whose conformation can be altered by the equilibrium binding of a regulatory ligand are one of the main building blocks of signal-processing networks in cells. Typically, such proteins switch between an 'inactive' and an 'active' state, as the concentration of the regulator varies. We investigate the properties of proteins that can bind two different ligands and show that these proteins can individually act as logical elements: their 'output', quantified by their average level of activity, depends on the two 'inputs', the concentrations of both regulators. In the case where the two ligands can bind simultaneously, we show that all of the elementary logical functions can be implemented by appropriate tuning of the ligand-binding energies. If the ligands bind exclusively, the logical repertoire is more limited. When such proteins cluster together, cooperative interactions can greatly enhance the sharpness of the response. Protein clusters can therefore act as digital logical elements whose activity can be abruptly switched from fully inactive to fully active, as the concentrations of the regulators pass threshold values. We discuss a particular instance in which this type of protein logic appears to be used in signal transduction—the chemotaxis receptors of *E. coli*.

Summary

Receptor cluster is a sophisticated analog computer

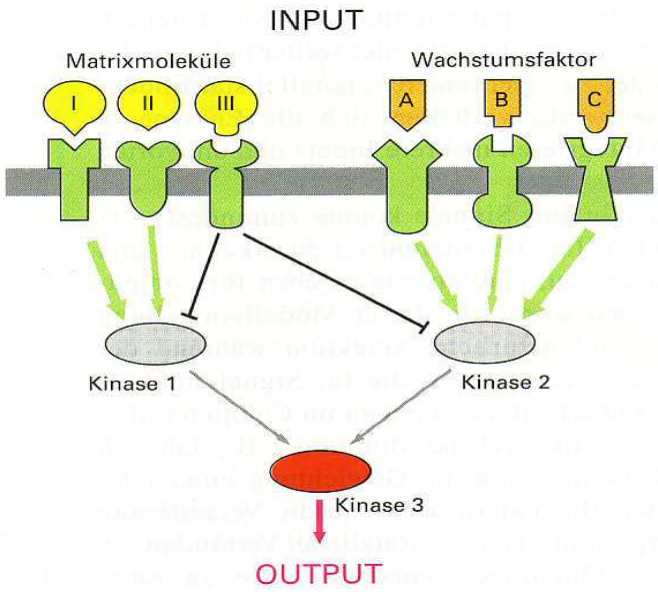
adaptation (exact) → differentiation of signal

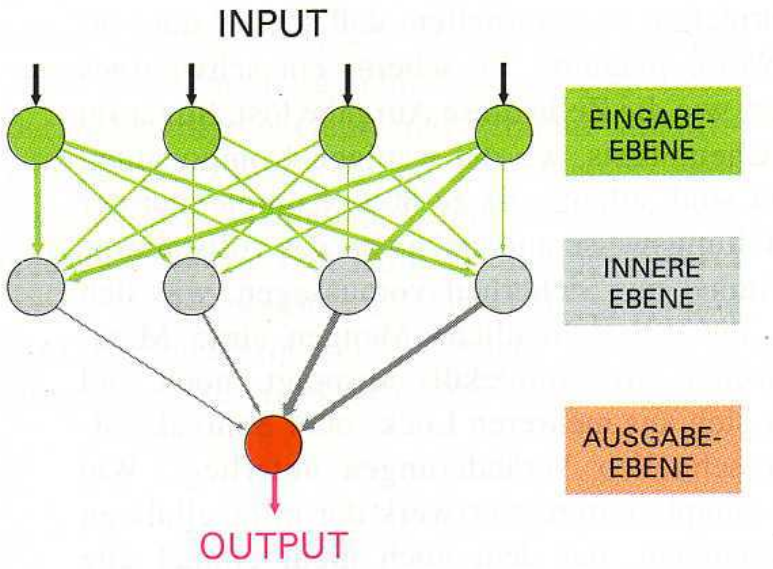
clustering (maybe tunable) → sensitivity over wide range

coupling of different receptors → logical responses to combined stimuli

Verhalten sich Signal-Netzwerke wie neuronale Netze, welche durch Evolution geschult wurden?

Bray 1991





Zusammenfassung

- Diffusion ist eine Zufallsbewegung, die auf mikroskopischen Längen eine schnelle Verteilung von Stoffen ermöglicht, auf makroskopischen Skalen aber als Transportmechanismus versagt.
- E.coli kann Gradienten über einen künstlichen Suchmechanismus und einen Vergleich der Konzentrationen über die Zeit detektieren.
- Systembiologie (computational systems biology) entwickelt quantitative Modelle komplexer biologischer Organismen zur Vorhersage von Systemantworten auf äußere Reize.