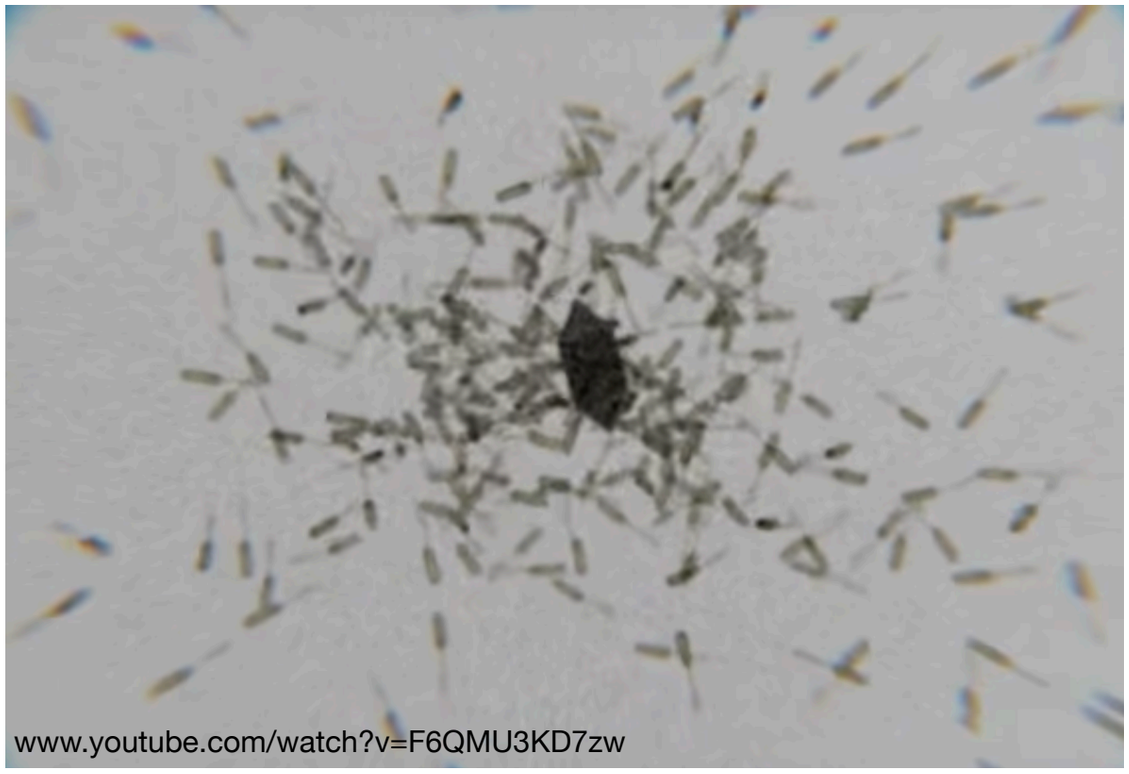
# ILAS Seminal-E2:

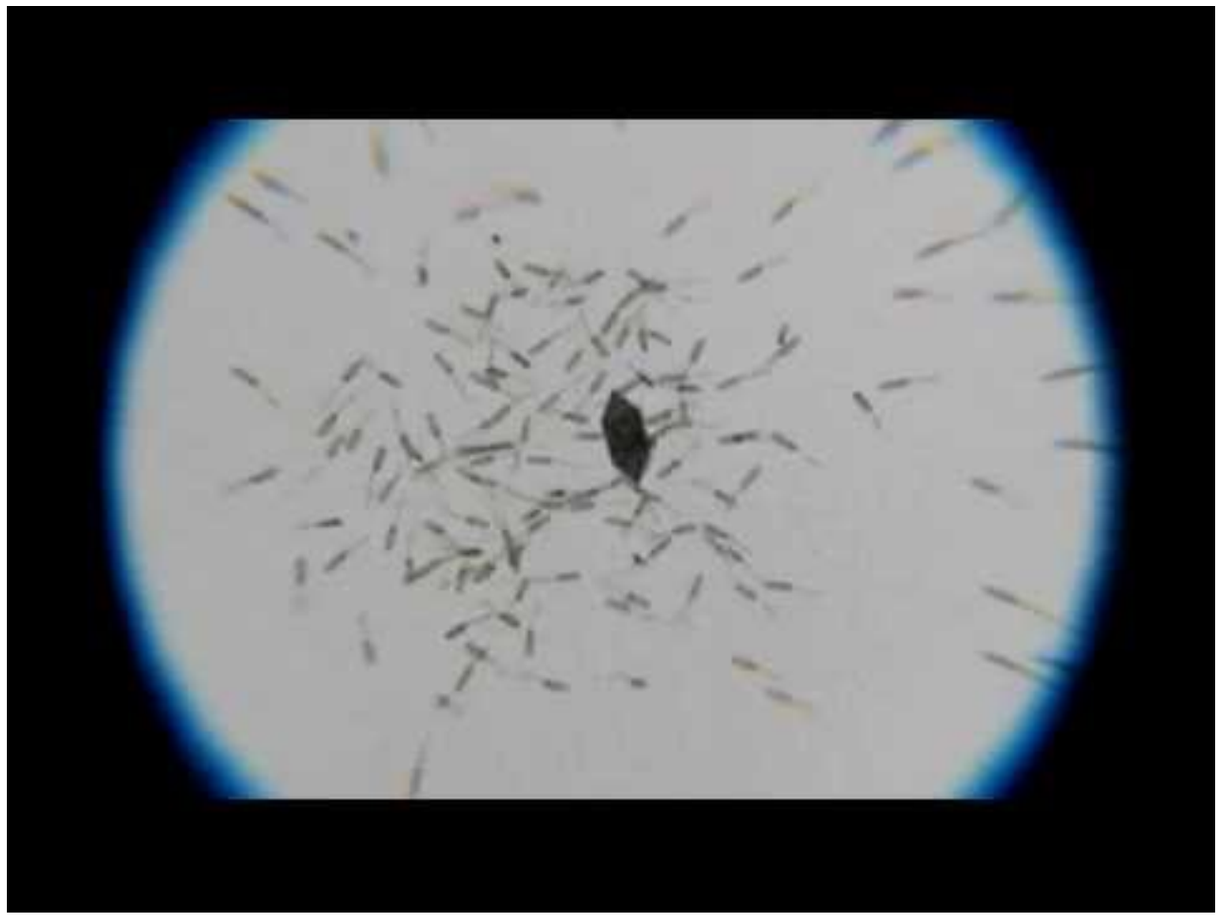
# Computer Simulations in Biology

## Chemotaxis - how bacteria search food



Bacteria can sense their environment and swim toward an attractant (e.g., sugar) or away from a repellant (e.g., a poison)

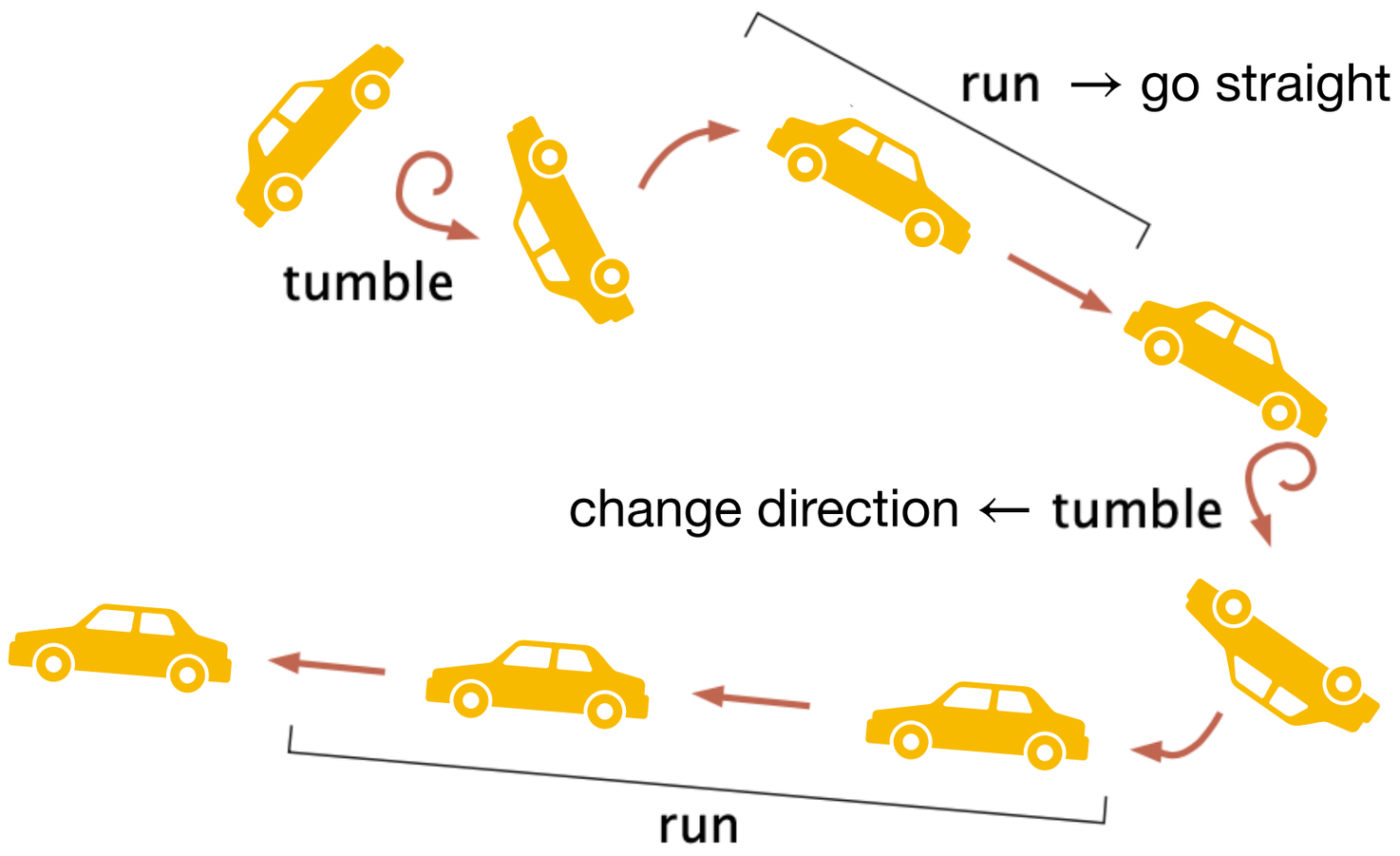
Such mechanism is called **chemotaxis**



www.youtube.com/watch?v=F6QMU3KD7zw

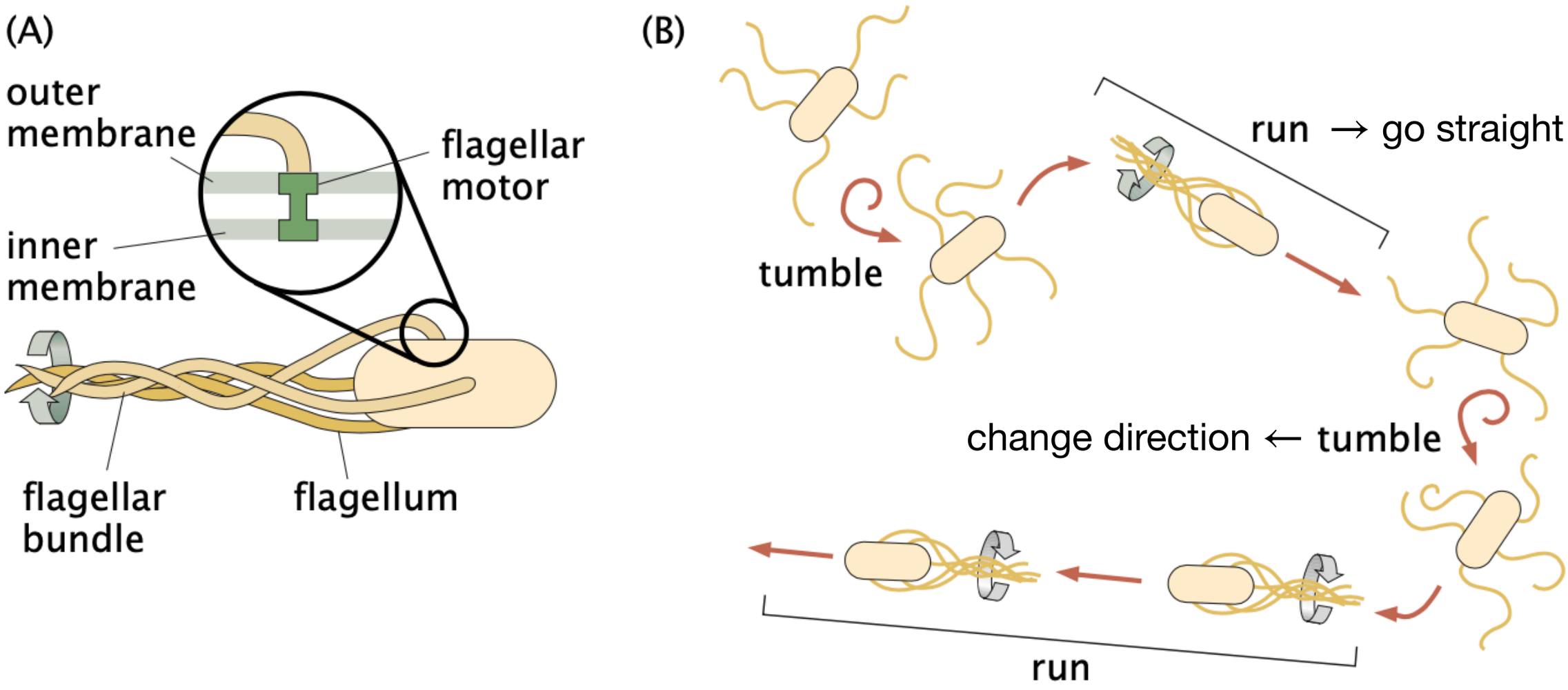
Bacteria do not have a nose connected to a brain, so how do they do this?

# Imagine a car that can only do two things: go straight (run) or change to a random direction (tumble)




This is basically what bacteria do!

# Many bacteria move around by **run** and **tumbling**

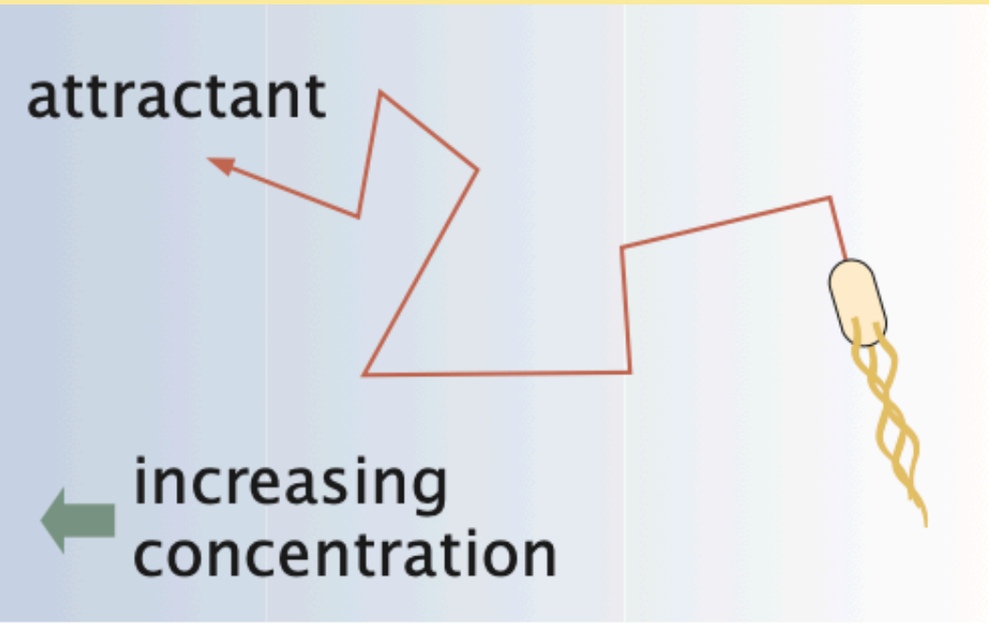



Run = counter-clockwise rotation of flagella, going straight

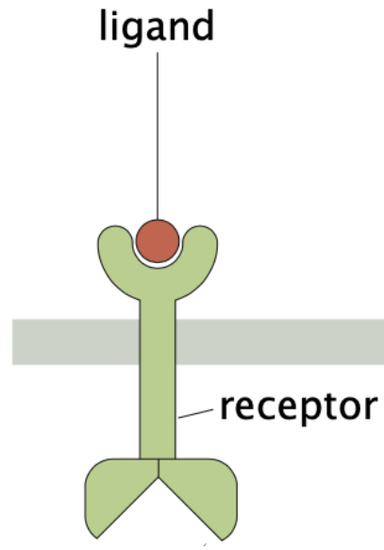
Tumbling = clockwise rotation of flagella, change to a random direction

Phillips, “Phisical Biology of the Cell”, chapter 19

# Bacteria perform chemotaxis by adapting their rate of tumbling




Bacteria can **sense** the local concentration of the attractant (or repellant) using a receptor on the cell surface (their “nose”)

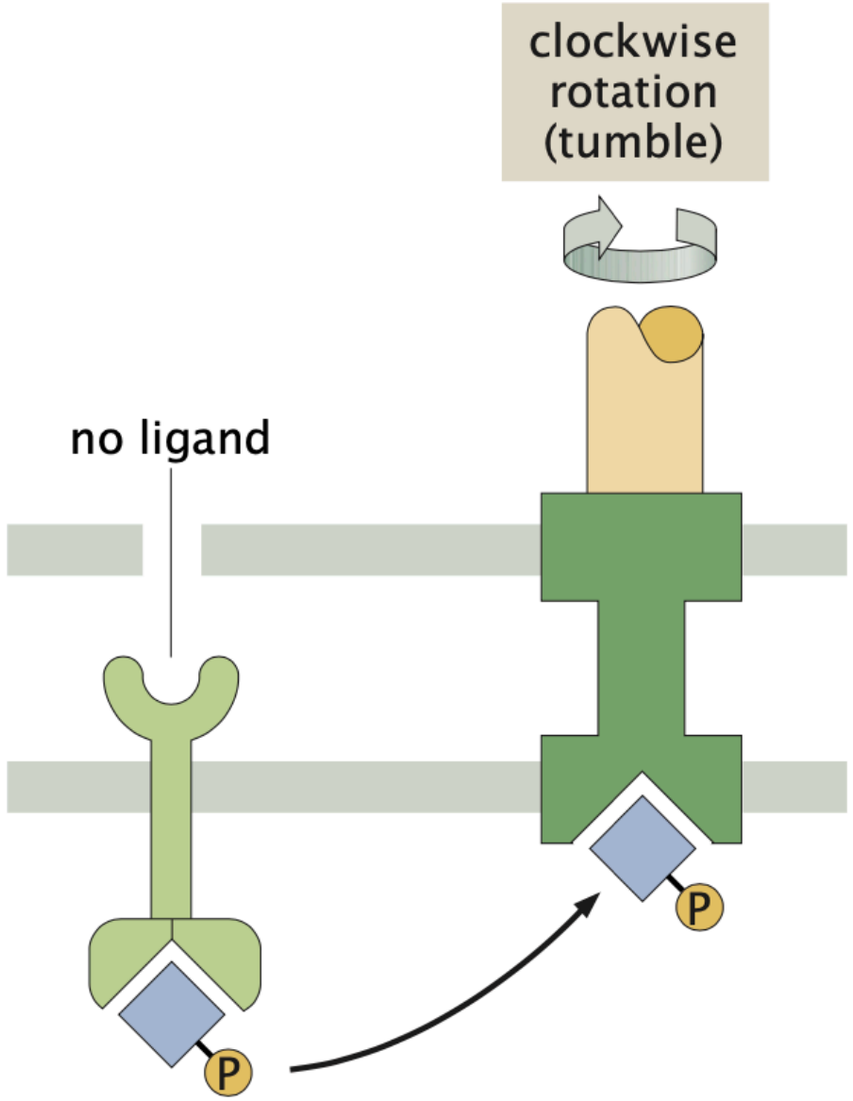



Tumbling rate is modified depending on the concentration:

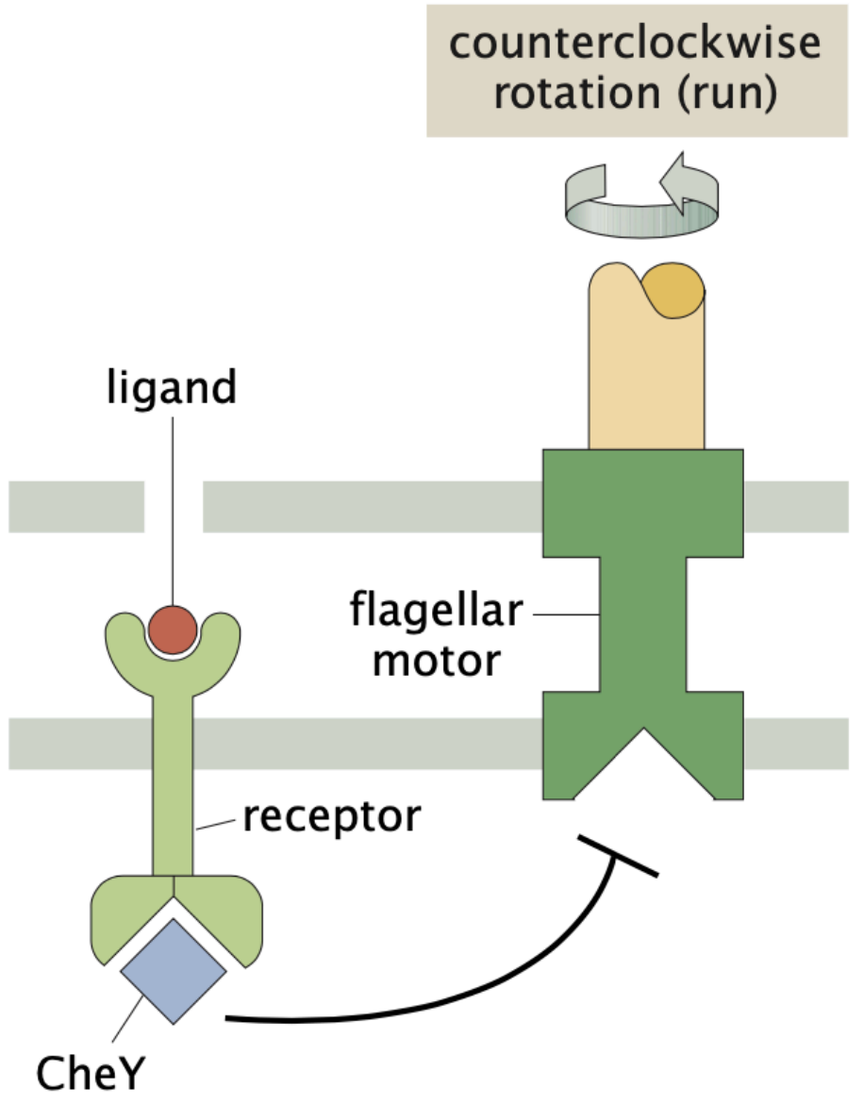
- no change in concentration? → constant tumbling rate
- concentration increasing? → good direction: stop tumbling, run!
- concentration decreasing? → search elsewhere: stop running, tumble!

# Tumbling is controlled by changing the direction of flagella depending on ligand binding to receptor

Free receptor promotes tumbling



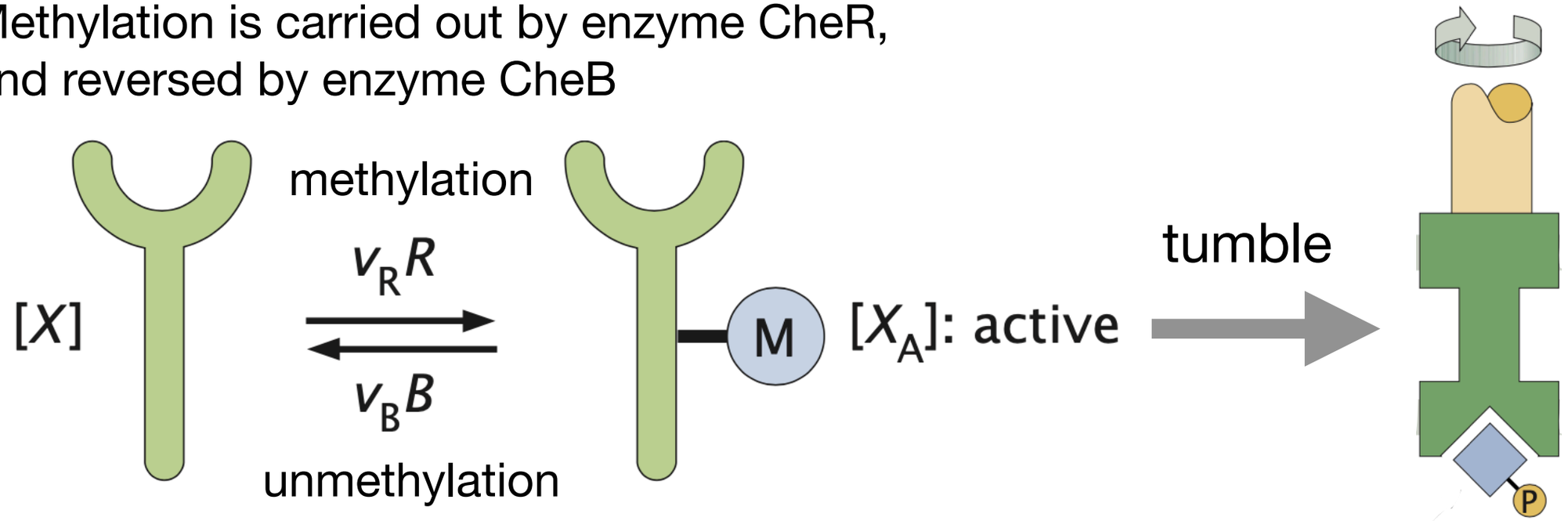

Ligand-bound receptor inhibits tumbling



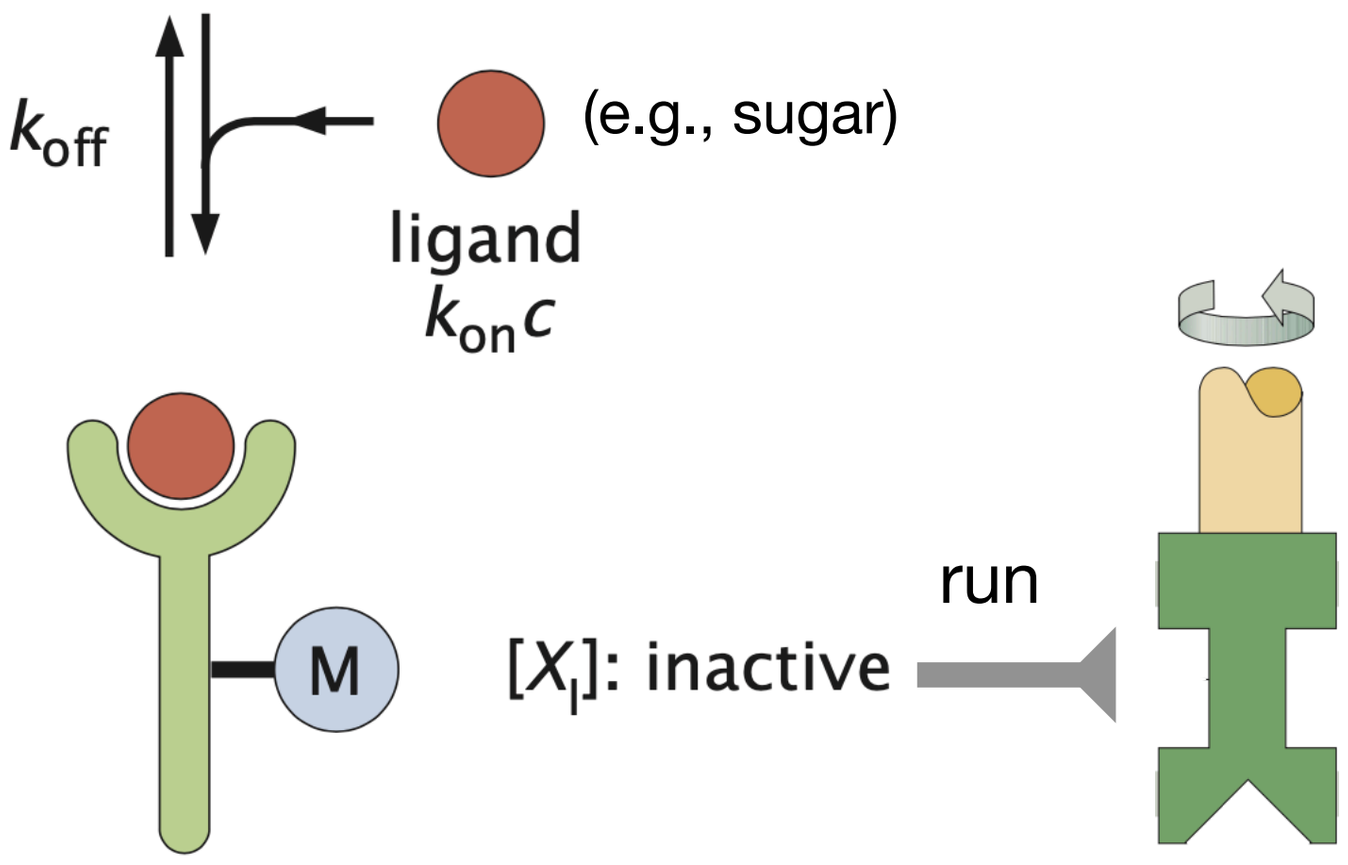

Phillips, “Phisical Biology of the Cell”, chapter 19

# Regulation of receptor methylation ensures tumbling rate returns to equilibrium value after stimulus disappears

Methylation is carried out by enzyme CheR, and reversed by enzyme CheB




If the ligand concentration is uniform, regardless of its value, after some time the amount of methylated free receptor $[X_A]$ comes back to its equilibrium value, producing the same tumbling rate. Such mechanism is called **adaptation**, and it ensures that chemotaxis works over a wide range of concentrations, while not affecting the bacterium behavior in a uniform environment.



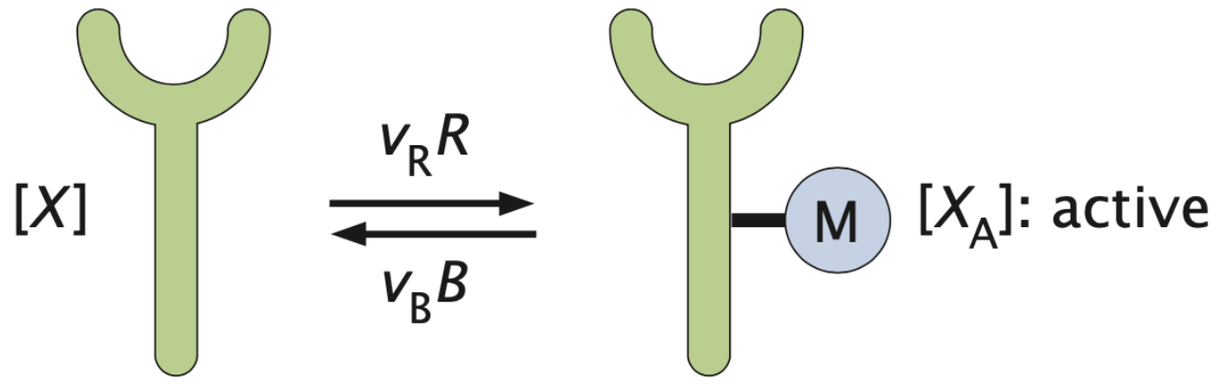

Phillips, “Phisical Biology of the Cell”, chapter 19

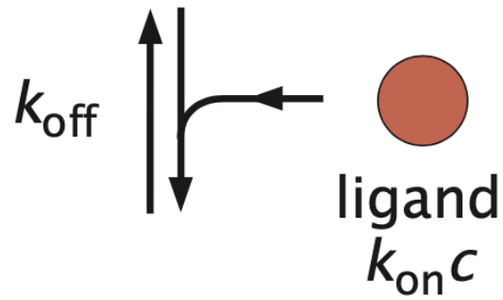
# A model of **sensing** and **adaptation** during chemotaxis

$$\frac{dX}{dt} = k_B B \frac{X_A}{A + X_A} - k_R R$$

$$\frac{dX_A}{dt} = -k_B B \frac{X_A}{A + X_A} + k_R R - k_{on} c X_A + k_{off} X_I$$

$$\frac{dX_I}{dt} = k_{on} c X_A - k_{off} X_I$$




$X$: Tar receptor (for aspartate, glutamate and maltose), non methylated

$X_A$: active receptor (methylated, unbound ligand), for tumbling

$X_I$: inactive receptor (methylated, bound ligand)

$c$: ligand concentration

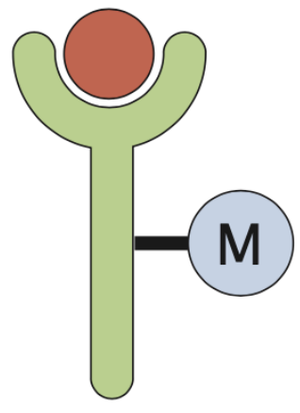
$B$: CheB enzyme unmethylating the receptor

$R$: CheR enzyme methylating the receptor

$A$: Michaelis constant for the receptor methylation by CheB

$k_B$ and $k_R$: rates of reactions by CheB and CheR

$k_{on}$ and $k_{off}$: rate of ligand binding/unbinding to/from the receptor




Phillips, “Phisical Biology of the Cell”, chapter 19

# Setting the model parameters

$$\frac{dX}{dt} = k_B B \frac{X_A}{A + X_A} - k_R R$$

$$\frac{dX_A}{dt} = -k_B B \frac{X_A}{A + X_A} + k_R R - k_{on} c X_A + k_{off} X_I$$

$$\frac{dX_I}{dt} = k_{on} c X_A - k_{off} X_I$$

$X$: Tar receptor (for aspartate, glutamate and maltose), non methylated

$X_A$: active receptor (methylated, unbound ligand), for tumbling

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$k_{on}$ and $k_{off}$: rate of ligand binding/unbinding to/from the receptor

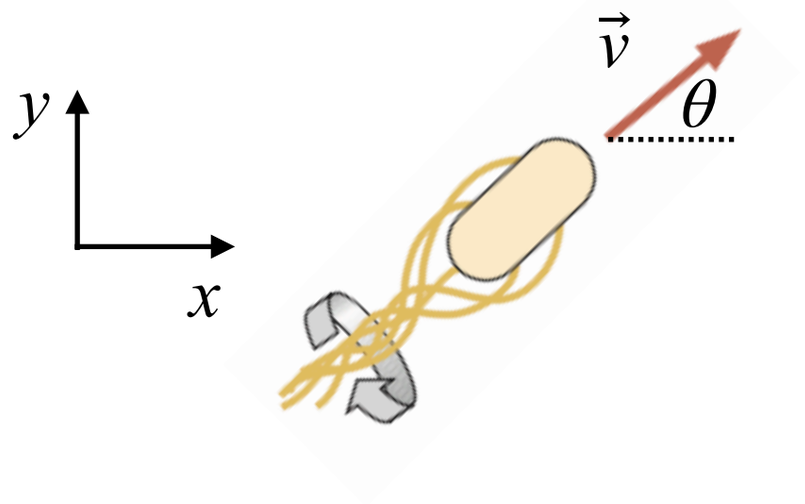
$$c = 0 - 10\mu M$$
$$k_{on} = 1\mu M^{-1} s^{-1}$$
$$k_{off} = 1 s^{-1}$$
$$B = 2\mu M$$
$$R = 1\mu M$$
$$k_B = 0.1 s^{-1}$$
$$k_R = 0.1 s^{-1}$$
$$A = 1\mu M$$
$$dt = 0.01 s$$
$$X(t=0) = 1\mu M$$
$$X_A(t=0) = 1\mu M$$
$$X_I(t=0) = 1\mu M$$

Based on:
Bray et al. "Computer simulation of the phosphorylation cascade controlling bacterial chemotaxis." Molecular Biology of the Cell 4.5 (1993): 469-482.

# A model of bacterial motion in 2 dimensions

$$\frac{dr_x}{dt} = v_x = v\cos(\theta)$$

$$\frac{dr_y}{dt} = v_y = v\sin(\theta)$$




$v = \sqrt{v_x^2 + v_y^2} = 20\mu m/s$ is the modulus of the bacterium velocity, to be kept constant.

The direction of motion $\theta$ (between 0 and $2\pi$ radiants) changes randomly (tumbling) at a rate $k_{tum}$ .

**How to tumble:**

To implement tumbling in a simulation, we need to compute the probability that the bacterium tumbles at each time step $dt$, which is given by:

$P_{tum} \approx k_{tum} dt$

and then change the direction of motion $\theta$ randomly with this probability: generate a random number between 0 and 1 with np.random.rand(), if this number is lower than $P_{tum}$ then tumble, otherwise continue to run.

The new random direction of motion can be selected by first generating a random number uniformly distributed between 0 and 1 with np.random.rand(), and then multiplying by $2\pi$.

# Simulating a bacterium in a box using boundary conditions

$$\frac{dr_x}{dt} = v_x = v\cos(\theta)$$

$$\frac{dr_y}{dt} = v_y = v\sin(\theta)$$

if $r_x < -L/2 \rightarrow$ set $r_x = -L/2$ and $v_x = -v_x$

if $r_x > +L/2 \rightarrow$ set $r_x = +L/2$ and $v_x = -v_x$

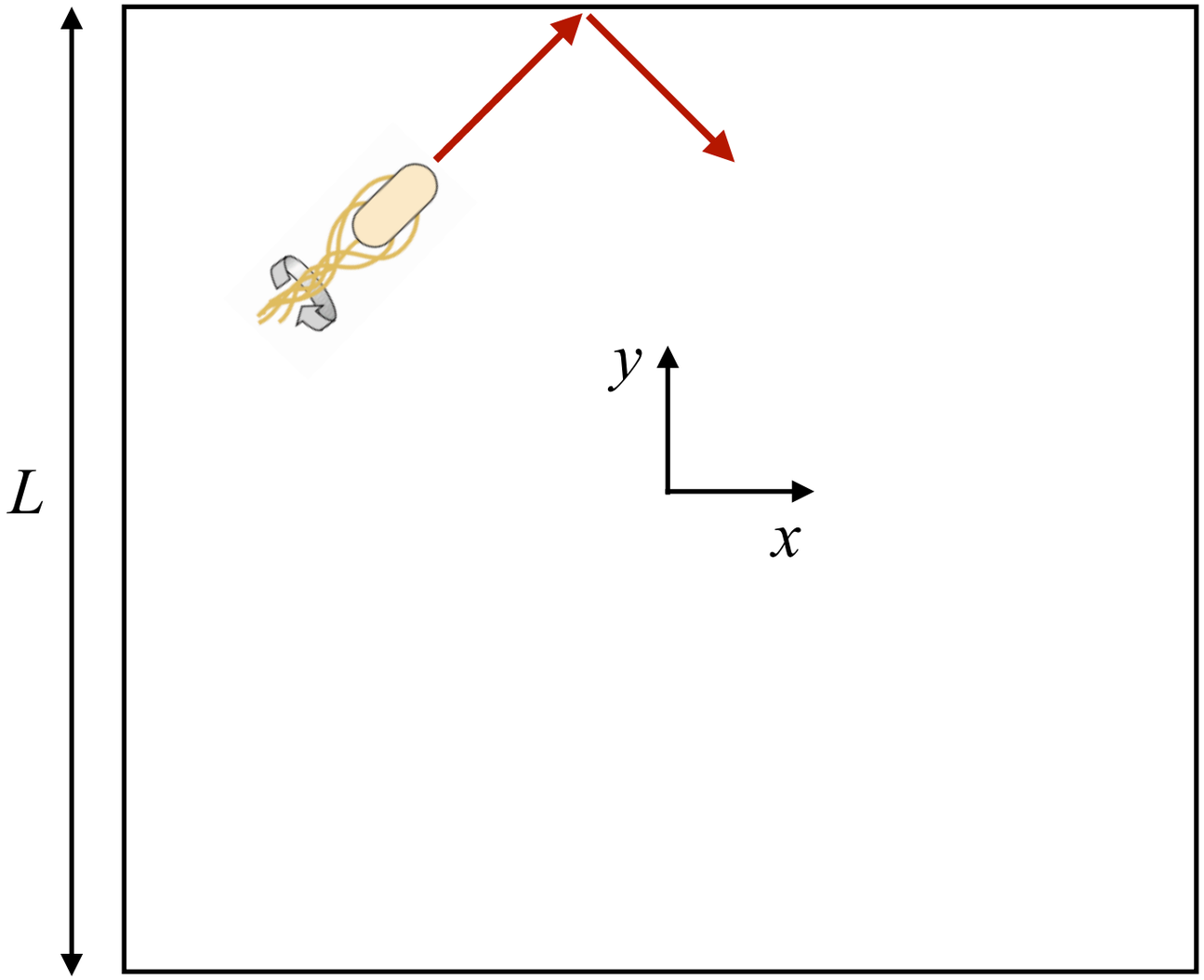
if $r_y < -L/2 \rightarrow$ set $r_y = -L/2$ and $v_y = -v_y$

if $r_y < +L/2 \rightarrow$ set $r_y = +L/2$ and $v_y = -v_y$

Box boundary acts as a mirror. If boundary is crossed, position and velocity are changed.

L = 2000 $\mu$m (2 mm) is a reasonable value to use in the simulations

Within the box, there will be a space-dependent attractant concentration affecting the bacterium motion



# Full model links sensing and adaptation to running and tumbling

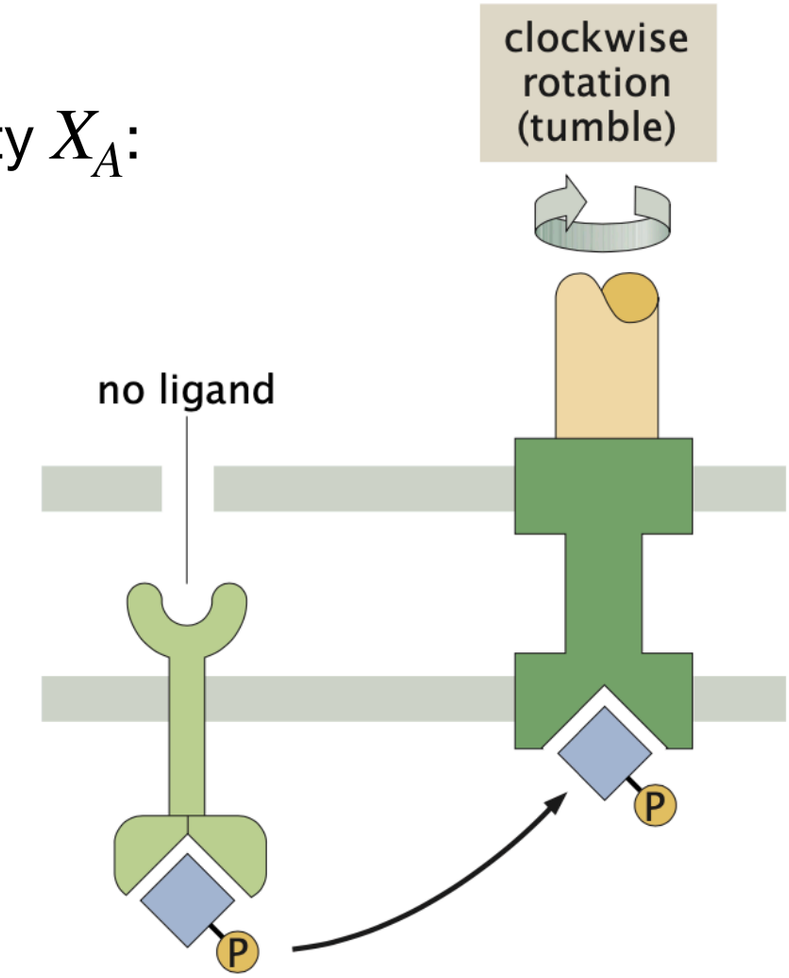
The tumbling frequency $k_{tum}$ increases with receptor activity $X_A$:

$$k_{tum} = \alpha \frac{X_A^n}{\bar{X}_A^n + X_A^n}$$

where $\bar{X}_A = \frac{Ak_R R}{k_B B - k_R R}$ is the concentration of active receptors at equilibrium, and

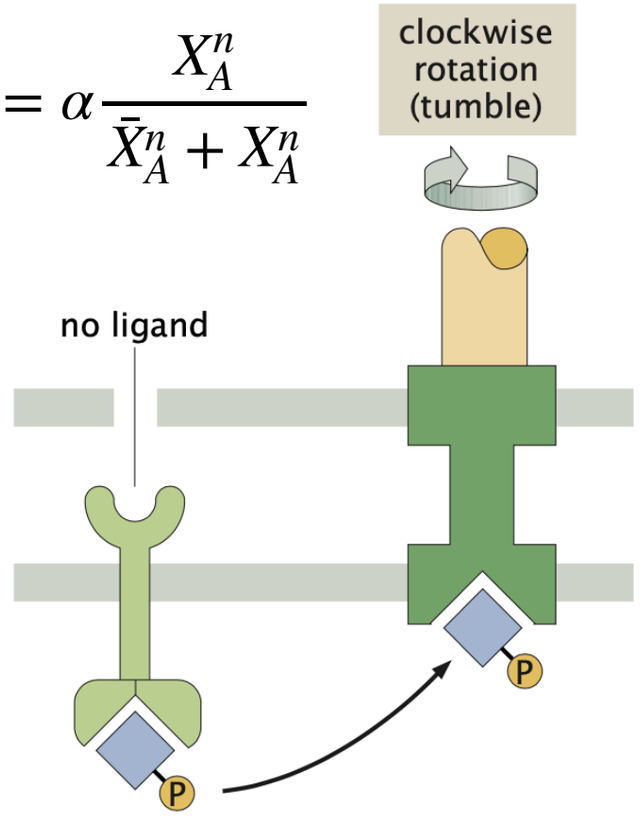
$n$ represents the number of active receptors that bind cooperatively to induce a change in tumbling frequency. You may choose $n$ between $n$ =1 (no cooperativity) and $n$ =20 (highly cooperative).

We choose $\alpha = 2s^{-1}$, so that the tumbling frequency when $X_A = \bar{X}_A$ is $k_{tum} = 1s^{-1}$, a reasonable experimental value

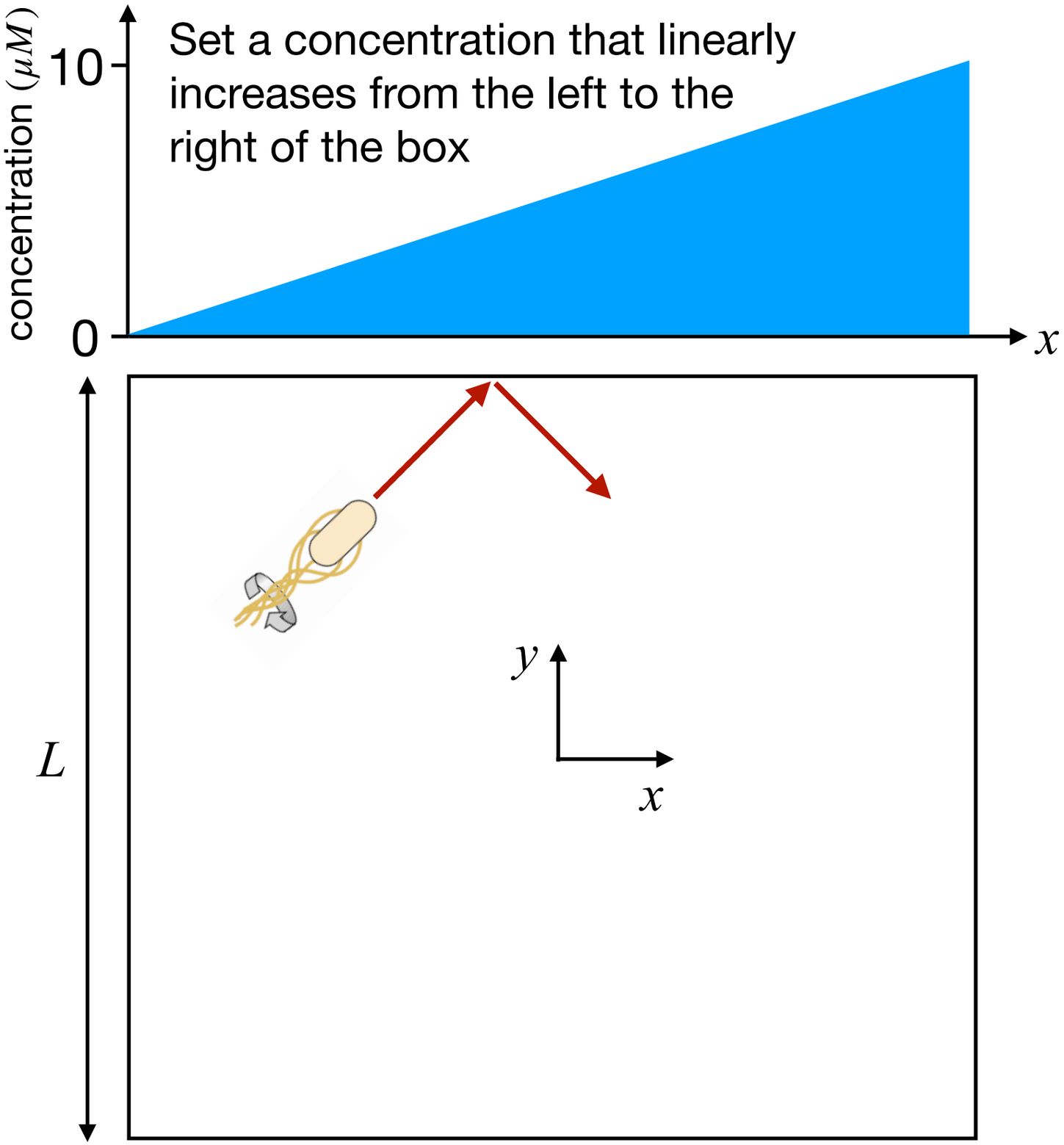


# How to test that our bacterium model works:

$$k_{tum} = \alpha \frac{X_A^n}{\bar{X}_A^n + X_A^n}$$




As the bacterium senses the concentration and adapts the tumbling rate to it, is should spend more time in the region with higher concentration of attractant



# How to build a complete bacterium simulation:

Write a function that performs the bacterial chemotaxis simulation, this function should take as input the model parameters, initial conditions (receptor concentrations, bacterium position and velocity direction), settings for space-dependent attractant concentration (e.g., values of $c$ at $x = 0$ and $x = L$), time-step and simulation time, and return the trajectory of receptor concentrations and bacterium positions:

1. Set initial conditions according to input parameters.
2. Set total number of simulation steps and start main loop over steps.
3. Compute the attractant concentration as a function of the current position.
4. Compute probability to tumble from the concentration of active receptors.
5. Tumble (change velocity angle) according to the computed probability.
6. Compute the derivatives of the receptor concentrations as a function of current receptor and attractant concentrations, and model parameters.
7. Compute velocity along x and y from velocity angle and modulus.
8. Update receptor concentrations and bacterium position according to the Euler algorithm, applying boundary conditions if necessary.
9. Repeat loop steps 3-8 until end of the simulation.

# Task:

A. Implement regulatory network of sensing and adaptation, showing how the amount of active receptor changes upon a sudden change in ligand concentration (**sensing**), and also showing that the amount of active receptor should eventually go back to its equilibrium value before the signal (**adaptation**).
B. Implement the full model of bacterial chemotaxis, showing that bacteria spend more time in regions with higher attractant concentration.

References:


- Phillips, “Phisical Biology of the Cell”, chapter 19
- Goldbeter, A., and Daniel E. Koshland Jr. "Simple molecular model for sensing and adaptation based on receptor modification with application to bacterial chemotaxis." Journal of molecular biology 161.3 (1982): 395-416.
- Bray, Dennis, et al. "Computer simulation of the phosphorylation cascade controlling bacterial chemotaxis." Molecular Biology of the Cell 4.5 (1993): 469-482.