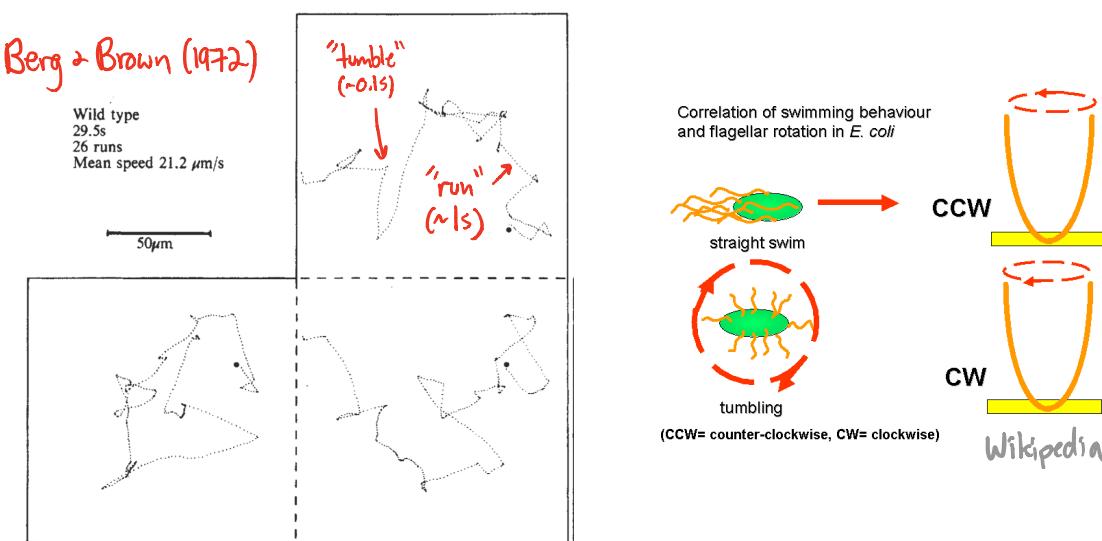
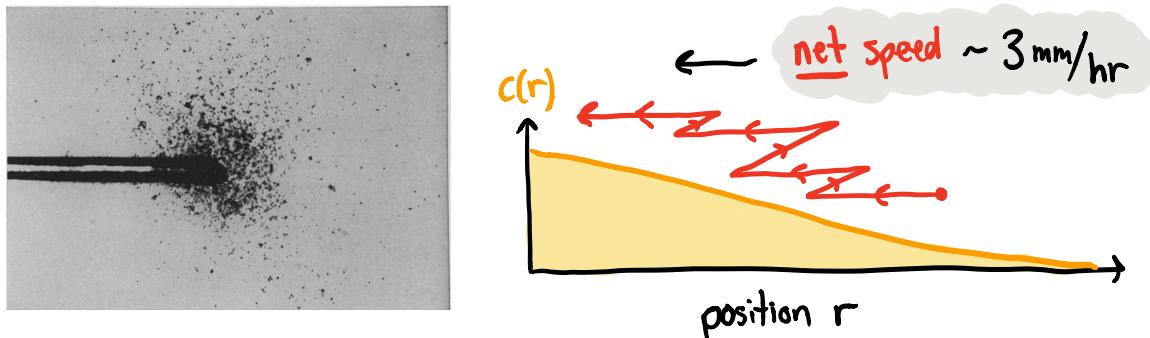


## Last time: Introduction to chemotaxis

① "Swimming" E. coli cells perform an active random walk



② Cells swim up concentration gradients by modulating  $P_r[\text{cw}]$

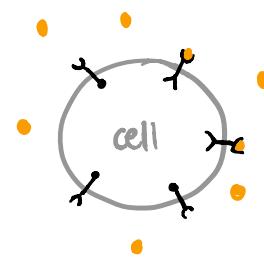


⇒ Today: how do cells sense + respond to environmental concentration gradients?

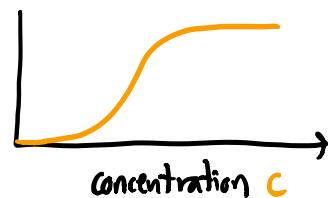
Simpler question: How do cells measure concentration levels?

⇒ Lecture 3:

Ligand/receptor  
binding



$$\Pr[X] = \frac{C^n}{K_m^n + C^n}$$



⇒ simplest approach: fraction of active receptors,  $f_R^*(c)$   
gives readout of concentration level  
(e.g. by phosphorylating other proteins)

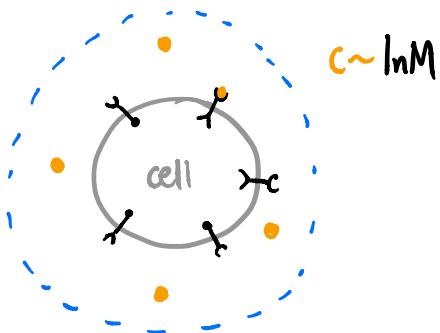
Problem: chemotaxis works @ extremely low concentrations!

⇒ e.g.  $c \sim 3 \text{ nM}$  in microfluidic chambers  
(Mao et al PNAS 2003)

How low is this?

$$3 \text{ nM} = \frac{3 \times 10^{-9} \text{ moles}}{\text{L}} \cdot \frac{6 \times 10^{23}}{1 \text{ mole}} \cdot \frac{1 \text{ L}}{1000 \text{ cm}^3} \cdot \left( \frac{1 \text{ cm}}{10^4 \text{ nm}} \right)^3 \approx 2 \text{ nm}^{-3}$$

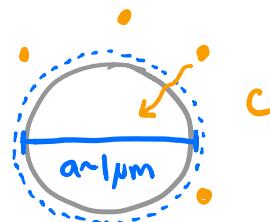
$\Rightarrow$  only a handful of molecules  
in neighborhood of cell...



$\Rightarrow$  Additional constraint: "shot noise" in molecular arrivals

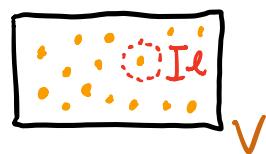
Berg & Purcell ('77): what's the best that E.coli could do?

Idea: maximum # of detected • molecules  
eventually limited by diffusion:



① Lecture 5: if wait for time  $\tau$ , molecules can reach  
cell from distance  $l \sim \sqrt{D\tau}$  away

② At equilibrium, each of  $N = cV$  molecules  
has probability  $\sim l^3/V$  of falling in this region



③ Lecture 5: each of these has probability  $\sim \frac{a}{\ell}$   
of ever reaching cell (vs diffusing away to  $\infty$ ...)

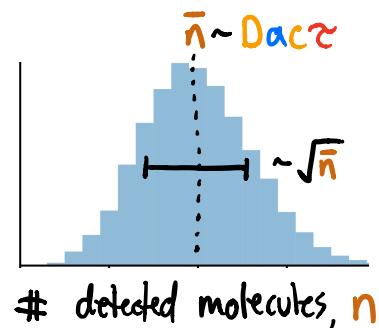
$\Rightarrow$  each of  $N = c \cdot V$  molecules has probability

$$P_d \sim \frac{\ell^3}{V} \cdot \frac{a}{\ell} \sim \frac{D_a \tau}{V} \text{ of being detected}$$

④ Lecture 1: actual # of detected molecules ( $n$ )  
= binomial distribution w/

Mean:  $\langle n \rangle \equiv \bar{n} = N \cdot P_d \sim D_a c \tau$

Variance:  $\langle (n - \bar{n})^2 \rangle = N \cdot P_d (1 - P_d) \approx \bar{n}$



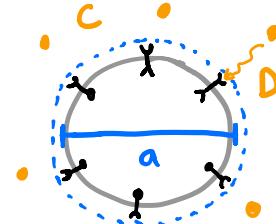
$\hookrightarrow$  i.e.  $n \approx \bar{n} \pm \sqrt{\bar{n}}$  ("shot noise")

$\Rightarrow$  could estimate concentration as  $\hat{c} = \frac{n}{D_a \tau}$

$$\Rightarrow \hat{c} = \frac{\bar{n} \pm \sqrt{\bar{n}}}{D_a \tau} = c \pm \sqrt{\frac{c}{D_a \tau}}$$

$$\Rightarrow \text{Relative error: } \frac{\delta c}{c} = \left| \frac{\hat{c} - c}{c} \right| = \frac{1}{c} \sqrt{\frac{c}{D_{ac}\tau}} = \sqrt{\frac{1}{\bar{n} D_{ac}\tau}}$$

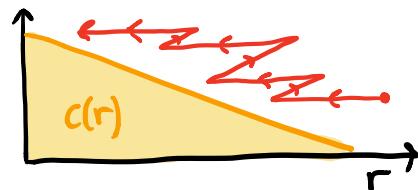
"Berg-Purcell limit"  $\frac{\delta c}{c} \gtrsim \frac{1}{\sqrt{D_{ac}\tau}}$   
on precision of conc. measurements



$\Rightarrow$  e.g. E. coli sensing  $\sim 3\text{nM}$  glucose for  $\tau \sim 1\text{s}$ :

$$\frac{\delta c}{c} \gtrsim \left[ 500 \text{ nm}^2/\text{s} \cdot 1\mu\text{m} \cdot 3\text{nM} \cdot 1\text{s} \right]^{-\frac{1}{2}} \approx 3\% \text{ error}$$

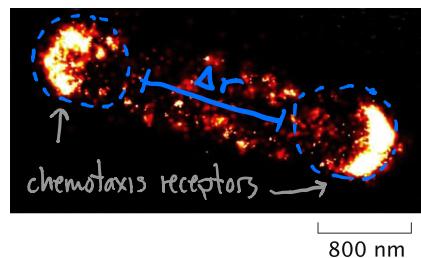
Question: How does this limit chemotaxis?



$\Rightarrow$  Measured gradient:  $\hat{c}(r+\Delta r) - \hat{c}(r) \approx \frac{dc}{dr} \Delta r \pm \delta c$

$\Rightarrow$  Min. measurable gradient:  $\frac{1}{c} \frac{dc}{dr} \gtrsim \frac{1}{\Delta r} \cdot \frac{\delta c}{c}$

e.g. E. coli measuring gradient across cell ( $\Delta r \sim 1\text{ }\mu\text{m}$ )



$$\Rightarrow \frac{1}{c} \frac{dc}{dr} \gtrsim \frac{3\%}{1\mu\text{m}} \approx 30 \text{ mm}^{-1}$$

but experiments much lower...



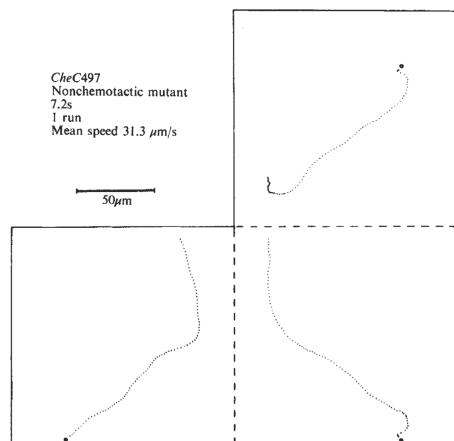
cells would need to count for  $\tau \sim \text{hrs}!$

Question: why don't E. coli just measure really carefully @ beginning & swim straight @ target?

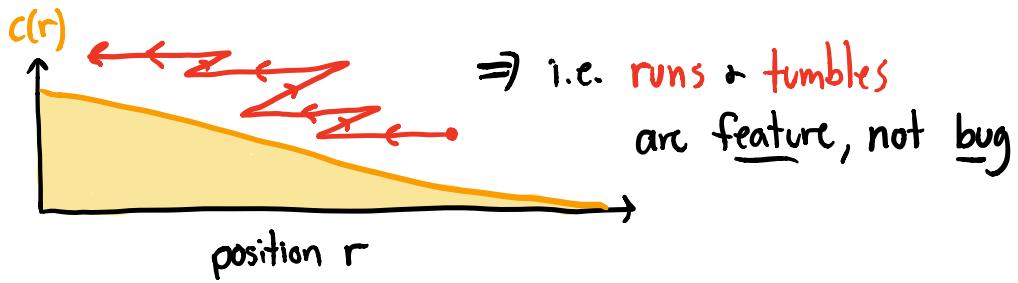
$\Rightarrow$  Rotational Diffusion

$$\text{Diagram of a wavy path with arrows indicating rotation.} \quad \langle \Theta(t)^2 \rangle = 2 D_\Theta t$$

disorient them after  $\tau_B \sim 10\text{s}$



$\Rightarrow$  E. coli must use runs to measure conc. gradients



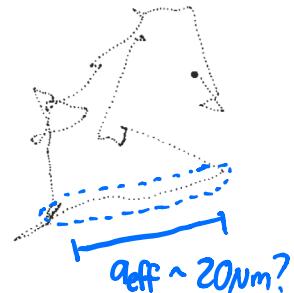
$\Rightarrow$  How does this evade gradient detection limit?

$$\frac{1}{c} \frac{dc}{dr} \gtrsim \frac{1}{\Delta r} \cdot \frac{\delta c}{c}$$

$\uparrow$        $\uparrow$

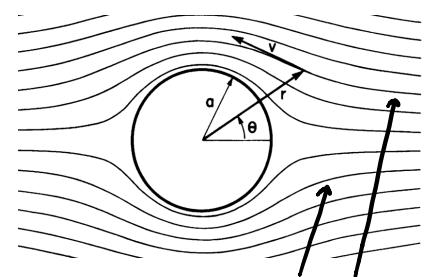
Question: does swimming increase intake of attractant?

(+ decrease  $\delta c/c$ ?)



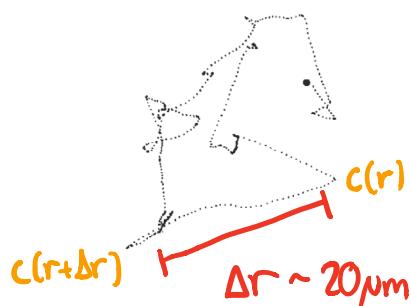
$\Rightarrow$  Berg & Purcell '77: no!

(@ low Reynolds #, E.coli drags local neighborhood along w/ it)



new fluid pushed out of way...

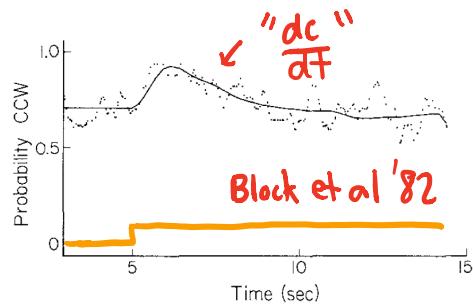
$\Rightarrow$  Instead: Swimming increases  $\Delta r_{\text{eff}} \approx v \cdot \tau$ !



$$\frac{1}{c} \frac{dc}{dr} \gtrsim \frac{3\%}{20 \mu\text{m}} \approx 1-2 \text{ mm}^{-1}$$

(consistent w/ experimental values ✓)

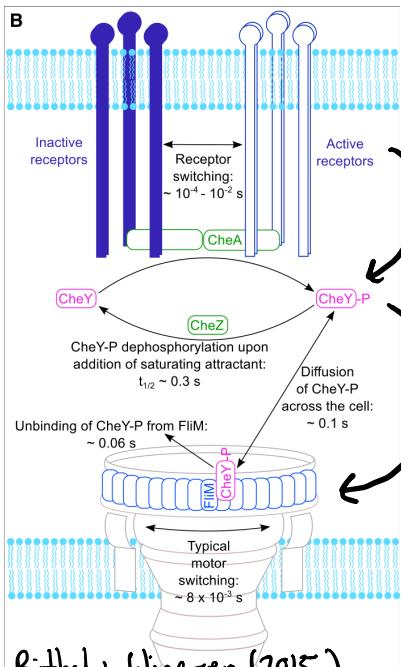
$\Rightarrow$  cells must be able to measure gradients over time!



$\Rightarrow$  requires memory ( $t \sim 1\text{s}$ ) & adaptation ( $t \gg 1\text{s}$ )

Next: how do real cells actually do this?

## E. coli's Chemotaxis Pathway :

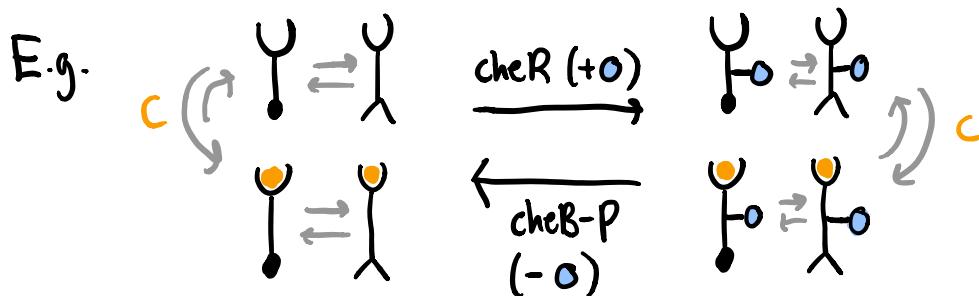


Bitbol & Wingreen (2015)

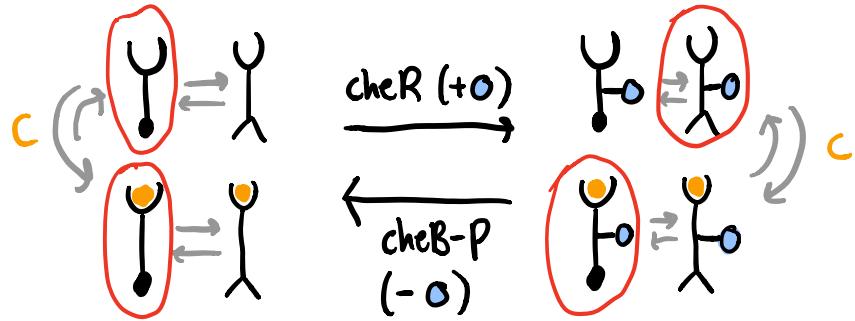
- ① active receptor complexes  
phosphorylate cheY protein
- ② cheY-P catalyzes switch  
to CW motion (tumble)

Upshot: tumbling rate increases  
w/ # active receptors

- ③ Receptor activity controlled by ligand binding  
& post-transcriptional modification (methylation)

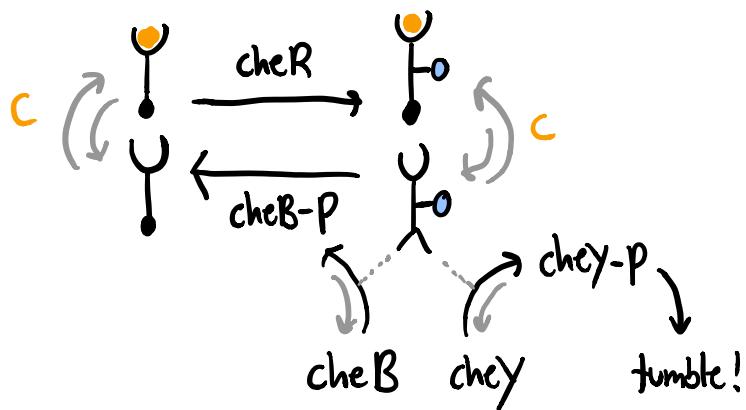


$\Rightarrow$  Free energy landscape favors:

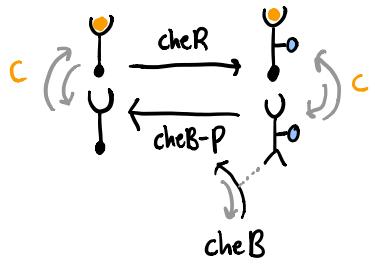


$$\Rightarrow \Pr[\text{active} | \text{X}] \approx 0, \quad \Pr[\text{active} | \text{O}] \equiv f_m^*(c) \quad \begin{array}{c} \text{graph} \\ \text{e.g. } K_m^n / (K_m^n + c^n) \end{array}$$

#### ④ Demethylation enzymes (cheB) regulated by receptors!



Minimal  
toy model:



$$\frac{d[B^*]}{dt} = k_{on}^B [M^*][B] - k_{off}^B [B^*]$$

$$\frac{d[M]}{dt} = k_{on}^M [R]_0 - k_{off}^M [B^*] \quad (\text{saturated enzymes...})$$

$$[M^*] = [M] \cdot \frac{K_m}{K_m + C} \quad (\text{fast!})$$

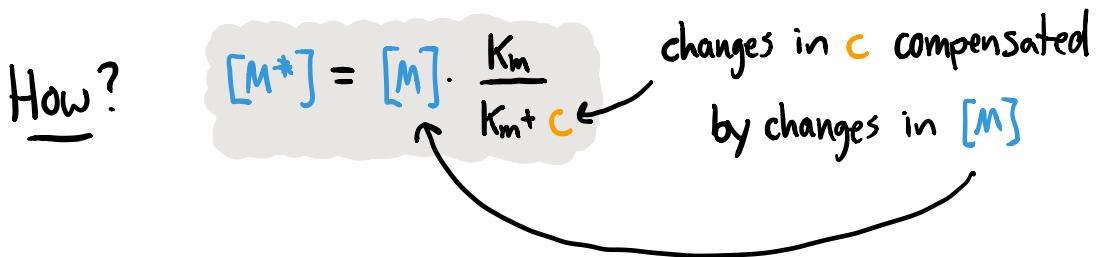
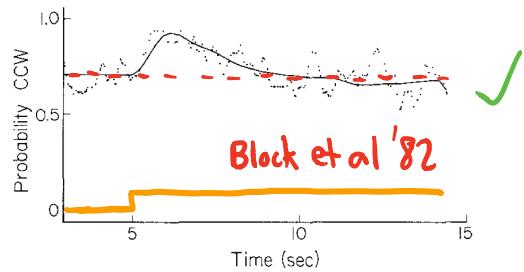
$\Rightarrow$  @ equilibrium :

$$\frac{d[M]}{dt} = k_{on}^M [R]_0 - k_{off}^M [B^*] = 0 \Rightarrow [B^*]_{eq} = \frac{k_{on}^M}{k_{off}^M} [R]_0$$

$$\frac{d[B^*]}{dt} = k_{on}^B [M^*][B] - k_{off}^B [B^*] = 0 \Rightarrow [M^*]_{eq} = \frac{k_{off}^B}{k_{on}^B} \frac{[B^*]_{eq}}{[B]_{eq}}$$

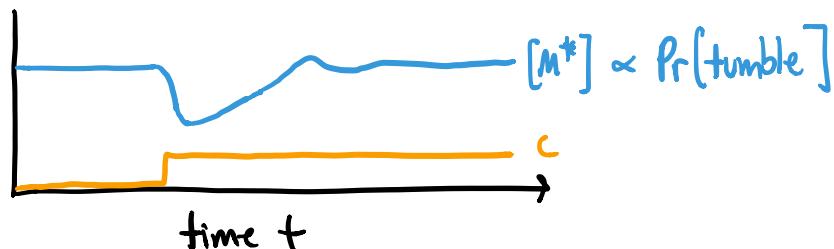
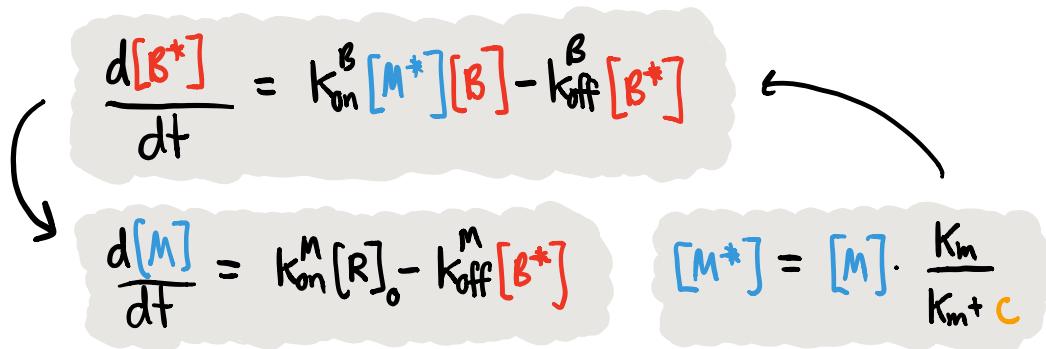
$$\Rightarrow [M^*]_{eq} = \frac{k_{on}^B k_{on}^M [R]_0}{k_{off}^B (k_{off}^M [B]_0 - k_{on}^M [R]_0)} \quad \text{independent of concentration } C!$$

$\Rightarrow$  steady state tumbling  
independent of  $C$ !



$\Rightarrow$  But takes finite time for  $[M]$  to catch up!

E.g. sudden  $C \rightarrow C + \delta_C \Rightarrow [M^*] < [M^*]_{eq}$



$\Rightarrow$  simple mechanism for measuring temporal gradients!

$\Rightarrow$  more realistic version: Tu et al (2008)

## Summary:

① Chemotaxis in E. coli strongly constrained by laws of physics!



② "Adaptation" + "memory" can be implemented w/  
simple molecular components

