

Announcements:

- ① Advance copy of notes in Week 2 folder in canvas.
- ② New practice problem for today's material
+ solutions for last week posted (Week 1 folder)
- ③ Weeks 1 reflections were great
- keep up the good work!

Common Question: "Which parts / how much will I need to know?"

General philosophy:

Understand concepts well enough to:

- i understand later lectures
- ii work through scientific papers (final project)

⇒ will work through detailed steps for some problems.
(others will be omitted for sake of time)

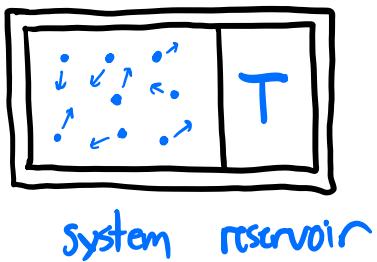
\Rightarrow emphasis on key assumptions & main results (^{& how to} apply them)

(algebra left for exercise... \Rightarrow will mark w/ *)

\Rightarrow IF in doubt: try practice problems!

Last time: A crash course in Equilibrium Statmech

① Exchange energy:



Boltzmann Distribution

$$p(\vec{s}) = \frac{e^{-\frac{E(\vec{s})}{kT}}}{Z} \quad \begin{array}{l} \text{energy of microstate } \vec{s} \\ \text{temperature of reservoir} \\ \uparrow \\ Z \leftarrow \text{normalization const} \end{array}$$

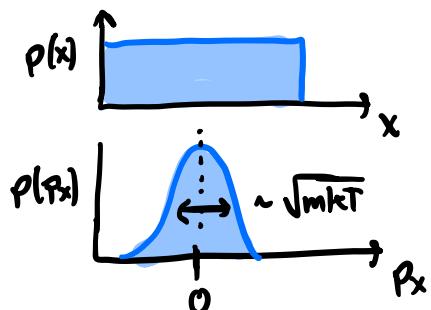
probability of microstate \vec{s}

Ideal Gas $[E(\vec{s}) = \sum_i \frac{\vec{p}_i^2}{2m}]$:

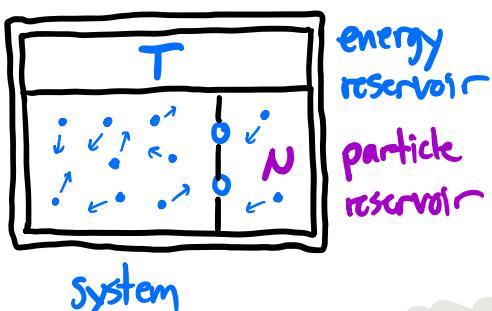
$$Z(N, V, T) \equiv \frac{1}{N!} \int \prod_{i=1}^N \frac{d\vec{x}_i d\vec{p}_i}{h_0^3} e^{-\frac{|\vec{p}_i|^2}{2mkT}}$$

$$\ln Z(N, V, T) \approx N \log \left[\frac{V}{N} e \cdot c_0(m, kT) \right]$$

Dist'n of single particle:



② Exchange particles + energy



$$p(\vec{s}) \propto e^{-\frac{E(\vec{s}) + N(\vec{s})\mu}{kT}} \quad \begin{array}{l} \text{chemical} \\ \text{potential} \\ \text{of reservoir} \end{array}$$

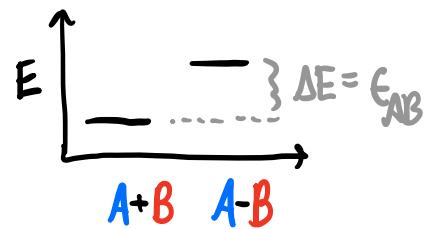
$$\frac{\text{Ideal gas}}{\text{gas}}: \quad \frac{\mu}{kT} \equiv -\frac{\partial \ln Z}{\partial N} = \log \left[\frac{c}{c_0(m, kT)} \right] \quad \begin{array}{l} \text{concentration} \\ c \equiv N/V \end{array}$$

Today: How does this apply to biology?

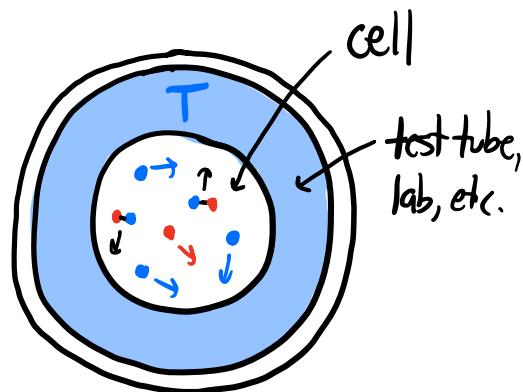
⇒ will illustrate w/ a few case studies...

Case Study #1: How do cells build costly molecules ?

⇒ suppose cell has precursors $A + B$
+ wants to build $A-B$ complex:



Question: Can we get thermal noise to build this far vs?



⇒ How many $A-B$ molecules (N_{AB}) @ thermal equilibrium,
starting from $N_A = N_B = N_0$ @ $T = 0$?

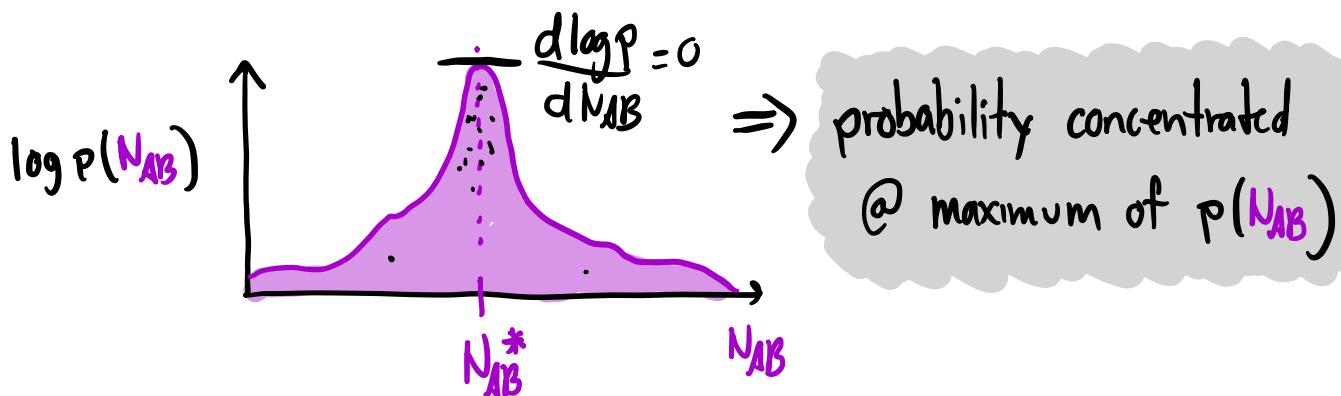
⇒ must have: $N_A = N_0 - N_{AB}$, $N_B = N_0 - N_{AB}$

Probability of N_{AB} macrostate is

$$p(N_{AB}) = \sum_{\vec{s} \in N_{AB}} \frac{1}{Z} e^{-\frac{E(\vec{s})}{kT}}$$

$$p(N_{AB}) \propto \frac{\left(\frac{\int d\vec{x} d\vec{p} \dots}{(N_0 - N_{AB})!} \right)^{N_0 - N_{AB}}}{Z_A(N_0 - N_{AB})} \cdot \frac{\left(\frac{\int d\vec{x} d\vec{p} \dots}{(N_0 - N_{AB})!} \right)^{N_0 - N_{AB}}}{Z_B(N_0 - N_{AB})} \cdot \frac{\left(\frac{\int d\vec{x} d\vec{p} \dots}{N_{AB}!} \right)^{N_{AB}}}{Z_{AB}(N_{AB})} e^{-\frac{\epsilon_{AB} N_{AB}}{kT}}$$

$$\propto \exp \left[\ln Z_A(N_0 - N_{AB}) + \ln Z_B(N_0 - N_{AB}) + \ln Z_{AB}(N_{AB}) - \frac{\epsilon_{AB} N_{AB}}{kT} \right]$$



$$0 = \left. \frac{\partial \log p(N_{AB})}{\partial N_{AB}} \right|_{N_{AB}^*} = \underbrace{\frac{\partial \log Z_A}{\partial N_A} (-1)}_{\frac{N_A}{kT}} + \underbrace{\frac{\partial \log Z_B}{\partial N_B} (-1)}_{\frac{N_B}{kT}} + \underbrace{\frac{\partial \log Z_{AB}}{\partial N_{AB}}}_{-\frac{\epsilon_{AB}}{kT}} - \frac{\epsilon_{AB}}{kT}$$

$$\downarrow \log \left(\frac{c_A}{c_R} \right)$$

$$\Rightarrow \log \left(\frac{C_{AB}}{C_{AB}^{\circ}} \frac{C_A^{\circ}}{C_A} \frac{C_B^{\circ}}{C_B} \right) = - \frac{E_{AB}}{kT} \quad @ \text{ equilibrium}$$

\Rightarrow often conventional to define quantity ΔG :

$$\frac{\Delta G}{kT} \equiv \frac{\Delta E + \mu_{AB} - \mu_A - \mu_B}{kT} = \frac{\Delta E}{kT} + \log \left(\frac{C_{AB}}{C_{AB}^{\circ}} \frac{C_A^{\circ}}{C_A} \frac{C_B^{\circ}}{C_B} \right)$$

change in "free energy" of $A + B \rightarrow AB$ reaction

↓ entropy!
(practice problem)

\Rightarrow previous result implies that $\Delta G = 0$ @ equilibrium

Payoff: can measure ΔG @ other concentrations,

(harder to measure ΔE , C_{AB}°, \dots , separately)

\Rightarrow e.g. when $C_{AB} = C_A = C_B = \frac{1 \text{ mole}}{1 \text{ liter}} = 1 \text{ "Molar"} = 1 \text{ M}$

$\sim 10^9$ particles
per
E.coli

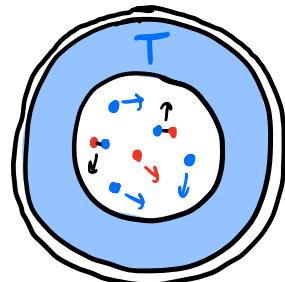
$\Rightarrow \Delta G \equiv \Delta G_0$ change in free energy
in "standard conditions"

\Rightarrow if define molar concentrations $[A] \equiv \frac{c_A}{1M}$, etc.

can rewrite our result as :

$$\Rightarrow \log\left(\frac{[AB]}{[A][B]}\right) = -\frac{\Delta G_0}{kT}$$

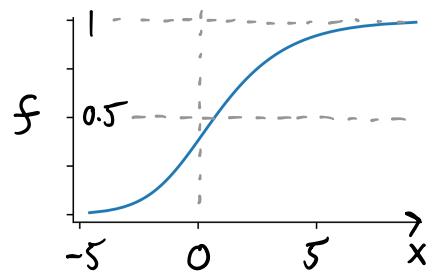
(@ thermal equilibrium)



$$N_A = N_0(1-f)$$

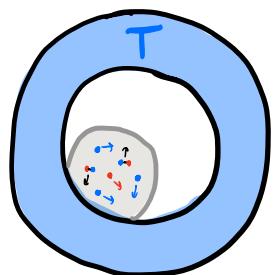
\Rightarrow can also write as function of $f \equiv \frac{N_{AB}}{N_0}$ (fraction molecules converted)

$$\log\left[\frac{f}{(1-f)^2}\right] = -\frac{\Delta G_0}{kT} + \underbrace{\log\left(\frac{N_0/V}{1M}\right)}_x$$



\Rightarrow depends on absolute concentration!

(not just relative #s of $A+B$ vs $A-B$)



Prefer to run in smaller volume?

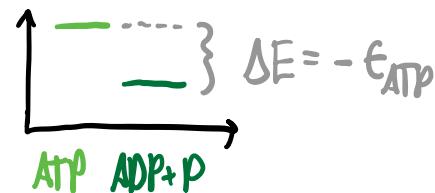
\Rightarrow upshot: when $\Delta G_0 > 0$, % molecules converted is low!

How do cells get around this limitation?

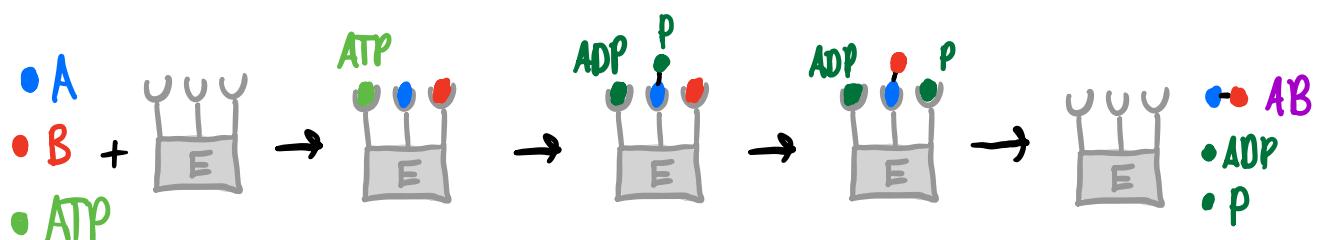
⇒ one method: couple to energy releasing reaction

often w/ $\text{ATP} = \text{"energy currency of cell"}$

ATP hydrolysis: $\text{ATP} \rightleftharpoons \text{ADP} + \text{P}$

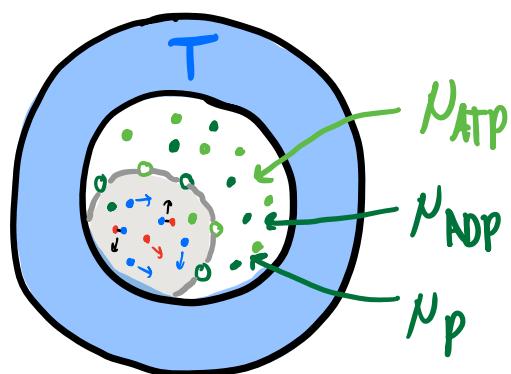


⇒ coupling often implemented using enzyme (E):



⇒ Let's imagine that cell has big reservoir of ATP (ADP, P)

$$\Rightarrow \frac{\mu_{\text{ATP}}}{kT} = \log \left(\frac{c_{\text{ATP}}}{c_{\text{ADP}}^{\circ}} \right), \text{ etc}$$



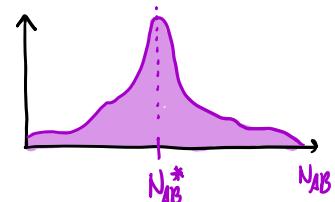
\Rightarrow Probability of N_{AB} macrostate is now:

$$\rho(N_{AB}) \propto \exp \left[\ln Z_A(N_0 - N_{AB}) + \ln Z_B(N_0 - N_{AB}) + \ln Z_{AB}(N_{AB}) - \frac{\epsilon_{AB} N_{AB}}{kT} \right]$$

+ $\frac{\epsilon_{ATP} N_{AB}}{kT}$ + $\frac{N_{ATP} N_{AB}}{kT}$ - $\frac{N_{ADP} N_{AB}}{kT}$ - $\frac{N_p N_{AB}}{kT}$

new terms from ATP

\Rightarrow maximum of $\log \rho(N_{AB})$ now occurs when



$$0 = \frac{\partial \log \rho(N_{AB})}{\partial N_{AB}} = \frac{\mu_A}{kT} + \frac{\mu_B}{kT} - \frac{\mu_{AB}}{kT} - \frac{\epsilon_{AB}}{kT} + \frac{\epsilon_{ATP}}{kT} + \frac{N_{ATP}}{kT} - \frac{N_{ADP}}{kT} - \frac{N_p}{kT}$$

$$\log \left(\frac{c_A}{c_A^0} \right)$$

algobm.

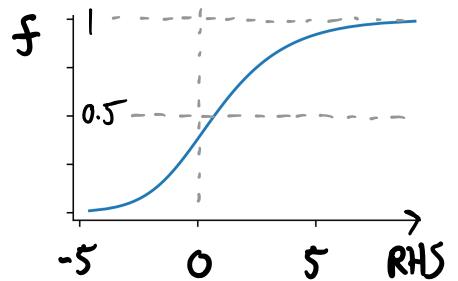
$$\Rightarrow \log \left(\frac{[AB]}{[A][B]} \right) = - \frac{\Delta G^\circ_{AB}}{kT} + \frac{\Delta G^\circ_{ATP}}{kT} + \log \left(\frac{[ATP]}{[ADP][P]} \right)$$

\Rightarrow can rearrange in terms of $f \equiv \frac{N_{AB}}{N_0}$ (fraction molecules converted)

$$\log \left[\frac{f}{(1-f)^2} \right] = - \frac{\Delta G_o^{AB}}{kT} + \log \left[\frac{N_0}{V} \frac{1}{1M} \right]$$

$$+ \frac{\Delta G_o^{ATP}}{kT} + \log \left(\frac{[ATP]}{[ADP][P]} \right)$$

$\underbrace{\Delta G_o^{ATP}/kT}$



$\Delta G_o^{ATP} \approx 12kT \Rightarrow$ extra free energy can allow A-B to form!

\Rightarrow but depends on concentrations of ATP, ADP, P!

@ cellular conditions:

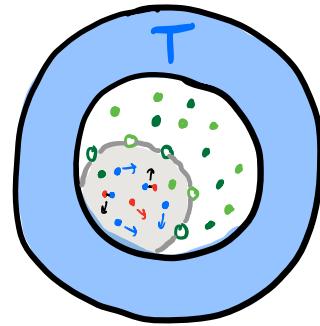
$$[ATP] \approx 5 \times 10^{-3}, [ADP] \approx 5 \times 10^{-4}, [P] \approx 10^{-2}$$

$$\Rightarrow \Delta G^{ATP} \equiv \Delta G_o^{ATP} + kT \log \left(\frac{[ATP]}{[ADP][P]} \right) \approx 20kT$$

But: if keep same # of ATP molecules + add more ADP/P

\Rightarrow can drive $\Delta G^{ATP} < \Delta G^{AB} \Rightarrow N_{AB} \ll N_0$

\Rightarrow i.e. can't prevent thermal noise
from running $A+B \rightarrow A-B$ in reverse!



Crucial question: what sets $[ATP]$, $[ADP]$, $[P]$ in cell?

\Rightarrow Another application of Equilibrium Statmech?

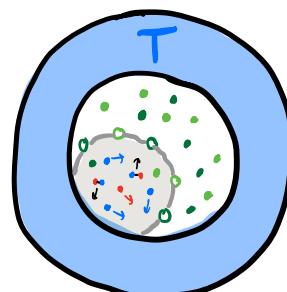
\Rightarrow if whole cell was in equilibrium:

$$\log\left(\frac{[ATP]}{[ADP][P]}\right) = -\frac{\Delta G_{\circ}^{ATP}}{kT} \Rightarrow \Delta G^{ATP} = 0$$

$$\Rightarrow \log\left(\frac{[AB]}{[A][B]}\right) = -\frac{\Delta G_{\circ}^{AB}}{kT}$$

back to
where we
started!

True equilibrium = death!



Some components
must be held
out-of-equilibrium

Question:

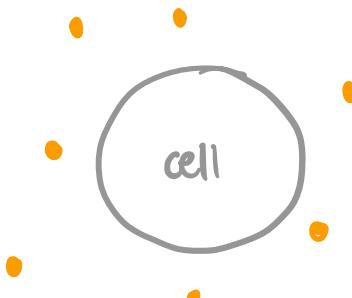
How to set things up to reach equilibrium
for some components ($A + B + ATP \rightleftharpoons A \cdot B + ADP + P$)

but not for all ($ATP \rightleftharpoons ADP + P$)?

\Rightarrow will see how later in course (dynamics)

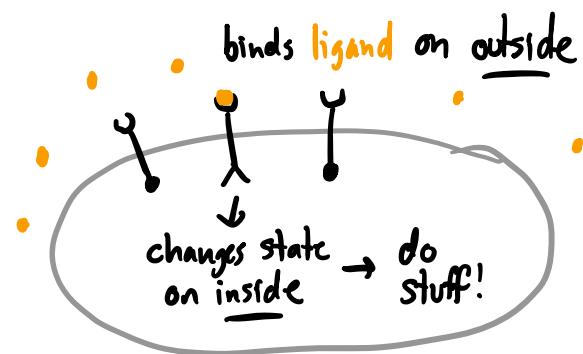
Case Study #2:

How do cells measure the state of the environment?



E.g. want to detect concentration of target chemical ("ligand")

⇒ one common sol'n:
"receptor" proteins
embedded in membrane



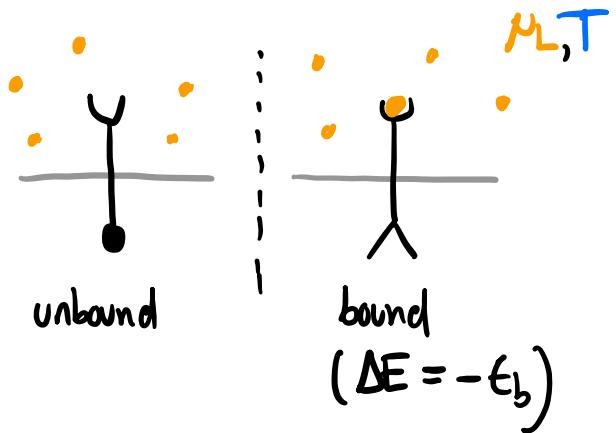
E.g. *atoS* gene (E.coli): binds acetoacetate

⇒ turns on acetoacetate metabolism ⇒ growth!

{ signal
transduction

⇒ can we model this process w/ stat mech?

Focus on single receptor:



Boltzmann distribution:

$$\rho(\text{unbound}) = \frac{1}{Z} \cdot e^{-\frac{(-\epsilon_b)}{kT} + \frac{(1) \cdot \nu_L}{kT}}$$

$$\rho(\text{bound}) = \frac{1}{Z} \cdot e^{-\frac{(0)}{kT} + \frac{\sigma \cdot \nu_L}{kT}}$$

$\log\left(\frac{C_L}{C_{L^0}}\right)$

$$\Rightarrow \rho(\text{unbound}) = \frac{e^{\frac{\epsilon_b}{kT} + \log\left(\frac{C_L}{C_{L^0}}\right)}}{1 + e^{\frac{\epsilon_b}{kT} + \log\left(\frac{C_L}{C_{L^0}}\right)}} = \frac{[L]}{K_m + [L]}$$

"Michaelis
(constnm)"

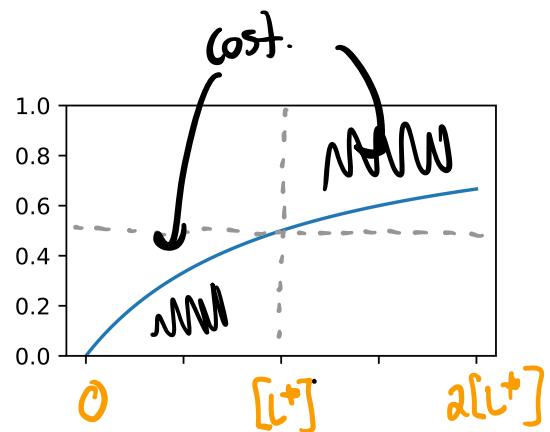
where $K_m \equiv \exp\left[-\frac{\epsilon_b}{kT} + \log\left(\frac{C_{L^0}}{1_m}\right)\right]$

← single "free parameter"

\Rightarrow If cell wants to detect when $[L]$ reaches $[L^*]$,

\Rightarrow can tune K_m s.t. $\rho(\text{unbound}) \approx \frac{1}{2}$ when $[L] = [L^*]$

$$\Rightarrow \rho(L) = \frac{[L]}{[L^+] + [L]}$$



Problem: fixing set point $[L^*]$ also fixes responsiveness!

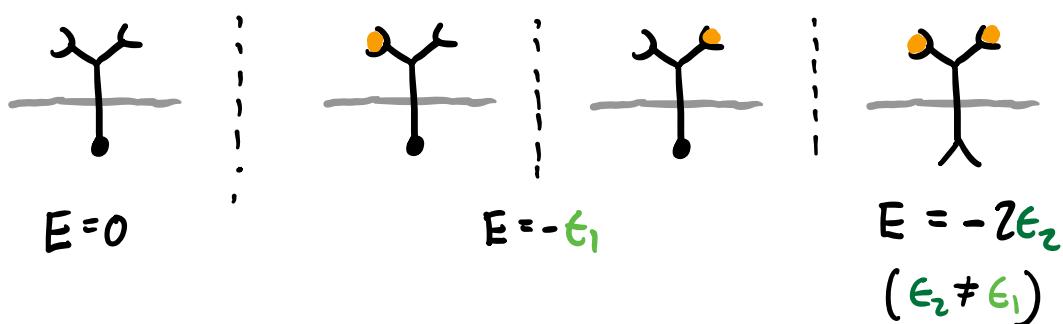
\Rightarrow would love to have something like a switch:



\Rightarrow how can cells implement this behavior using our simple statmech toolbox?

One Mechanism: **cooperativity**

\Rightarrow suppose receptor can bind multiple particles @ once:



Boltzmann factors become:

$$p(\text{态 1}) = \frac{e^{0+0}}{Z} ; \quad p(\text{态 2}) = \frac{e^{\frac{E_1}{kT} + \frac{\mu_L \cdot 1}{kT}}}{Z} ; \quad p(\text{态 3}) = \frac{e^{\frac{2E_2}{kT} + \frac{\mu_L \cdot 2}{kT}}}{Z}$$

" $p(\text{态 4})$

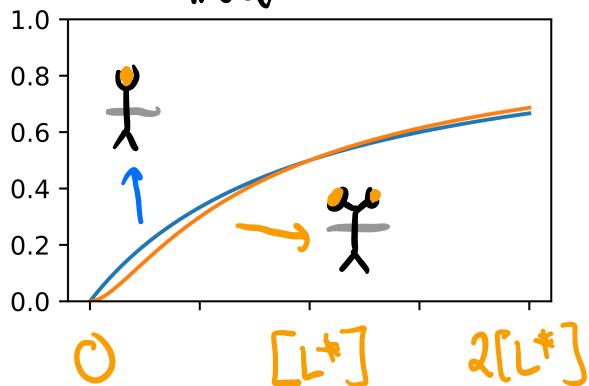
$$\Rightarrow p(\text{态 1}) = \left(\frac{[L]}{K_m} \right)^2 / \left[1 + \left(\frac{[L]}{K_m} \right) e^{\frac{E_1 - E_2}{kT}} + \left(\frac{[L]}{K_m} \right)^2 \right]$$

algebra.

$$\text{where } K_m \equiv \exp \left[-\frac{E_2}{kT} + \log \left(\frac{q}{1M} \right) \right]$$

\Rightarrow Behavior depends on E_1 vs E_2 !

$$\textcircled{1} \quad \text{If } \underbrace{E_1 = E_2}_{\text{independent.}} \Rightarrow p(\text{态 1}) = \left(\frac{[L]}{K_m + [L]} \right)^2 = f(L)^2$$



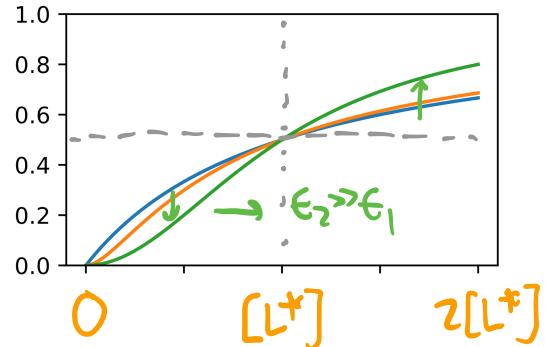
$$= \left[\frac{[L]}{(\sqrt{2}-1)[L^*] + [L]} \right]^2$$

② if $\epsilon_2 \gg \epsilon_1 \Rightarrow$

cooperative.

$$P(\text{L}) = \frac{(\epsilon_L / \epsilon_{L^*})^2}{1 + (\epsilon_L / \epsilon_{L^*})^2}$$

\Rightarrow much more sensitive:

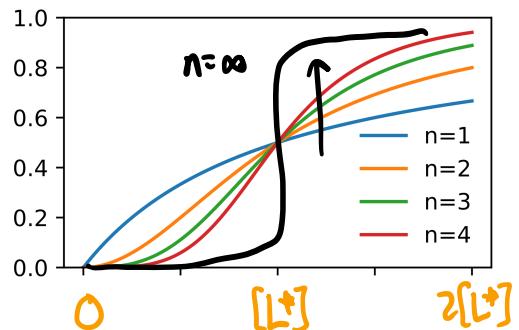


\Rightarrow can extend to more ligands ...

$$P(\text{L}) \approx \frac{(\epsilon_L / \epsilon_{L^*})^n}{1 + (\epsilon_L / \epsilon_{L^*})^n}$$

when $\epsilon_n \gg \binom{n}{k} \epsilon_k$

"Hill function"



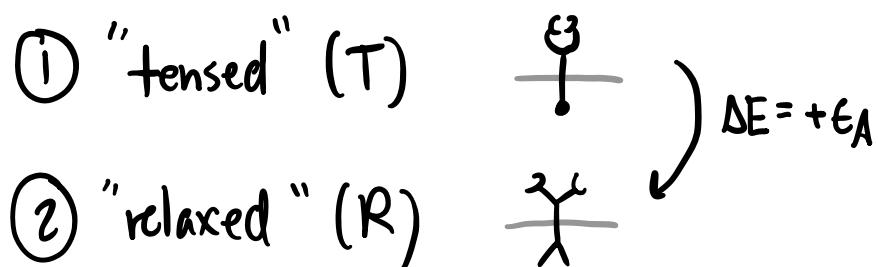
(e.g. hemoglobin binding oxygen, $n=4$)

Problem: how can a receptor distinguish
 $n-1$ vs n bound ligands when $n \gg 1$?

i.e., does our "solution" rely on a super-intelligent receptor?

One solution: allostery ("MWC model")

Idea: suppose receptor has 2 conformational states:



\Rightarrow ligands bind independently in both states,
but w/ different binding energies ($\Delta E = -\epsilon_R, -\epsilon_T$)

$$\Rightarrow \frac{p(T)}{p(R)} = \frac{p(\text{R}) + p(\text{R}^*) + p(\text{T}) + p(\text{T}^*)}{p(\text{R}) + p(\text{R}^*) + p(\text{T}) + p(\text{T}^*)}$$

exercise.

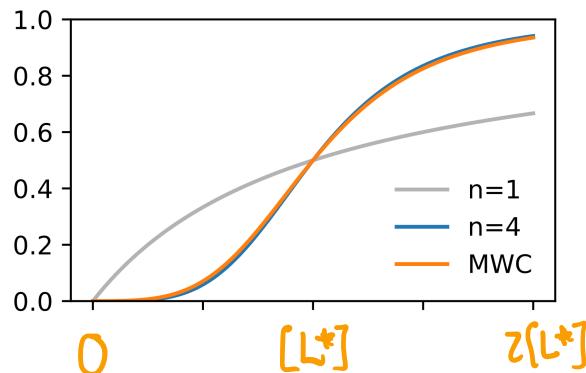
$$= e^{-\frac{\epsilon_A}{kT}} \frac{\left[1 + e^{+\frac{\epsilon_R + \epsilon_L}{kT}}\right]^n}{\left[1 + e^{+\frac{\epsilon_T + \epsilon_L}{kT}}\right]^n} \quad (\text{since everything is independent!})$$

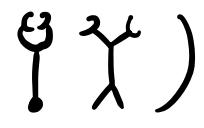
$$\Rightarrow \frac{P(+)}{P(-)} = e^{-\frac{\epsilon_A}{kT}} \left[\frac{1 + [L]/K_m}{1 + ([L]/K_m) e^{\frac{\epsilon_T - \epsilon_R}{kT}}} \right]^n$$

$$\text{where } K_m = \exp \left[-\frac{\epsilon_R}{kT} + \log \left(\frac{C_L}{1M} \right) \right]$$

$$\Rightarrow \text{when } \frac{\epsilon_A}{n} \gg kT \text{ & } \epsilon_R - \epsilon_T - \frac{\epsilon_A}{n} \gg kT$$

\Rightarrow looks like
Hill function:



\Rightarrow achieved w/ very simple implementation (just 2 states )

\Rightarrow for more info (& more bio examples)

see Chapter 7 of Physical Biology of the Cell