

Announcements:

- ① Advance copy of notes in Week 2 folder in canvas.
- ② New practice problem for today's material
- 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:

- ① understand later lectures
- ② work through scientific papers (final project)

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

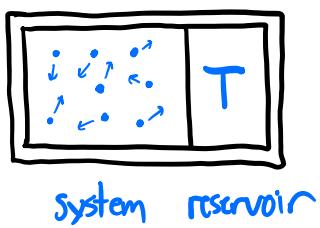
\Rightarrow emphasis on key assumptions & main results (^{+ how to}
_{apply them})

(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

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

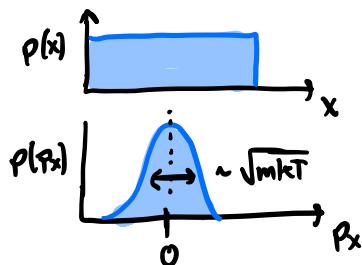
probability of microstate \vec{s}

Ideal Gas:

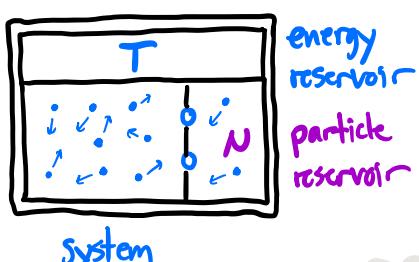
$$Z(N, V, T) \equiv \frac{1}{N!} \int \prod_{i=1}^N \frac{d\vec{x}_i d\vec{p}_i}{h_0^3} e^{-\frac{|\vec{p}_i|^2}{2m kT}}$$

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

Dist'n of single particle:



② Exchange particles + energy



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

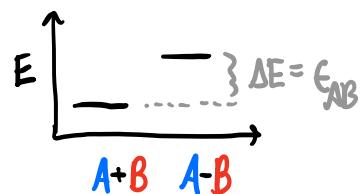
$$\frac{\text{Ideal gas}}{\text{gas}}: \quad \frac{\mu}{kT} \equiv -\frac{\partial \ln Z}{\partial N} = \log \left[\frac{c e}{c_0(m, kT)} \right] \quad \begin{array}{l} \text{concentration} \\ c = N/V \end{array}$$

Today: How does this apply to biology?

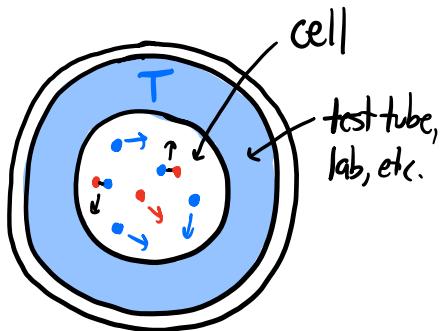
⇒ will illustrate w/ a few case studies...

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 for us?



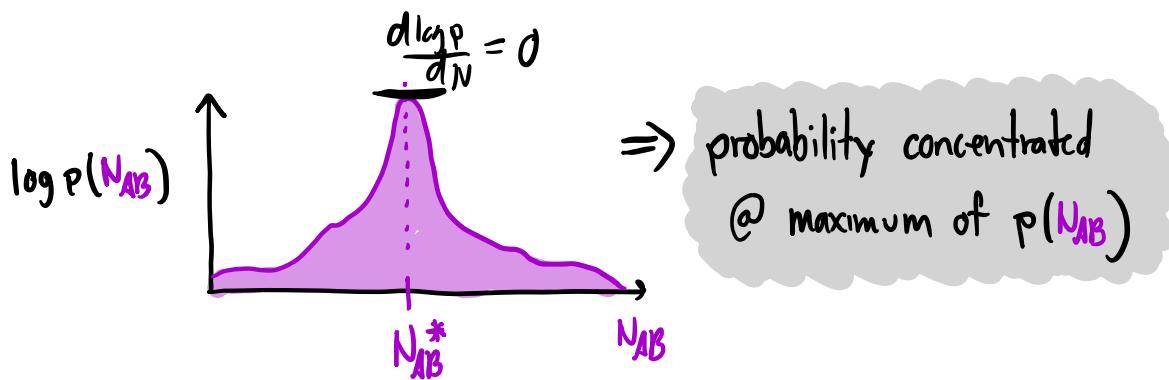
⇒ How many $A-B$ molecules (N_{AB}) @ thermal equilibrium,
starting from $N_A = N_B = N_0$ @ $T = 0$?

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

Probability of N_{AB} macrostate is $p(N_{AB}) = \sum_{S \in N_{AB}} \frac{1}{Z} e^{-\frac{E(S)}{kT}}$ *

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

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



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

$$= \boxed{\frac{N_A}{kT} + \frac{N_B}{kT} - \frac{N_{AB}}{kT} - \frac{\epsilon_{AB}}{kT}}$$

$\Downarrow \log(C_A/C_A^0)$

* $\Rightarrow \log\left(\frac{c_{AB}}{c_{AB}^{\circ}} \frac{c_A^{\circ}}{c_A} \frac{c_B^{\circ}}{c_B}\right) = -\frac{\epsilon_{AB}}{kT}$ @ equilibrium

\Rightarrow often conventional to define quantity ΔG :

$$\frac{\Delta G}{kT} = \frac{\Delta E + \mu_{AB} - \mu_A - \mu_B}{kT} = \frac{\Delta E}{kT} + \log\left(\frac{c_{AB}}{c_{AB}^{\circ}} \frac{c_A^{\circ}}{c_A} \frac{c_B^{\circ}}{c_B}\right)$$

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}° , ..., separately)

\Rightarrow e.g. when $c_{AB}=c_A=c_B = \frac{1 \text{ mole}}{1 \text{ liter}} = 1 \text{ "Molar"}$ = 1 M R

$\sim 10^9$ molecules
per cell.

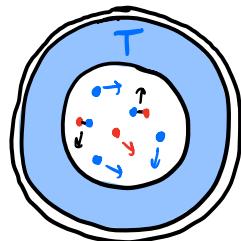
$\Rightarrow \Delta G \equiv \Delta G_0$ change in free energy
in "standard conditions"

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

can rewrite our result as:

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

(@ thermal equilibrium)

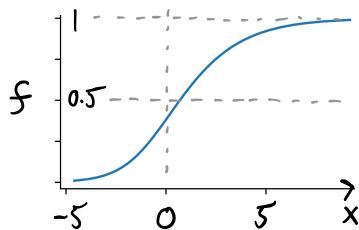


$$N_A = (1-f) N_0$$

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

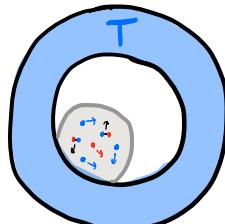
\Rightarrow can also write as function of $f \equiv \frac{N_{AB}}{N_0}$ (fraction molecules converted)

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



\Rightarrow depends on absolute concentration!

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



Prefer
to run
in smaller
volume?

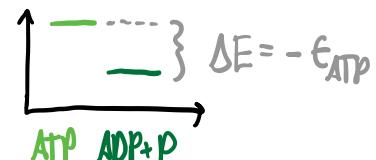
\Rightarrow upshot: when $\Delta G^\circ > 0$, % molecules converted is low!

How do cells get around this limitation?

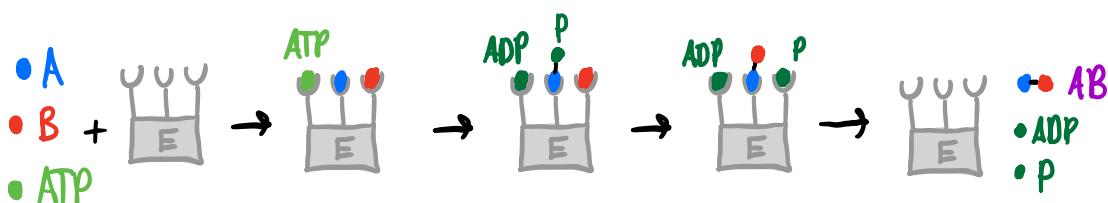
⇒ one method: couple to energy releasing reaction

often w/ ATP = "energy currency of cell"

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

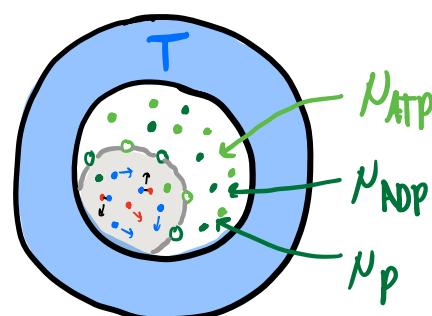


⇒ coupling often implemented using enzyme (E):



⇒ Let's imagine that cell has
big reservoir of $\text{ATP} (\rightarrow \text{ADP}, \text{P})$

$$\Rightarrow \frac{\mu_{\text{ATP}}}{kT} = \log \left(\frac{c_{\text{ATP}}}{c_{\text{ATP}}^0} \right), \text{ etc}$$

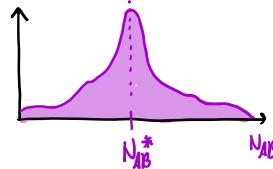


\Rightarrow Probability of N_{AB} macrostate is now:

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

new terms from ATP

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



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

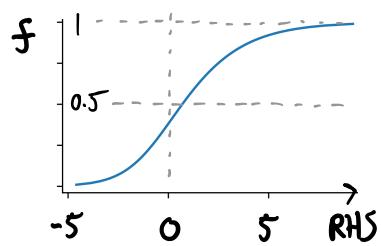
$\rightarrow \log \left(\frac{c_A}{c_A^0} \right)$

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

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

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

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



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

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

@ cellular conditions:

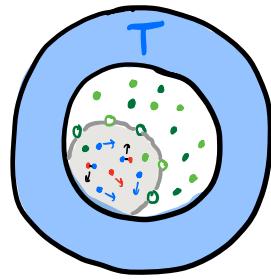
$$[ATP] \approx 5 \times 10^{-3}, [ADP] \approx 5 \times 10^{-4}, [P] \approx 10^{-2}$$

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

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?

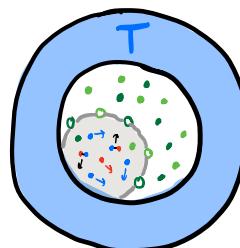
\Rightarrow if whole cell was in equilibrium:

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

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

back to
where we
started!

True equilibrium = death!



Some components
must be held
out-of-equilibrium

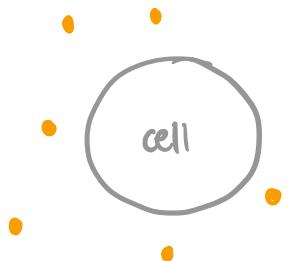
Question:

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)

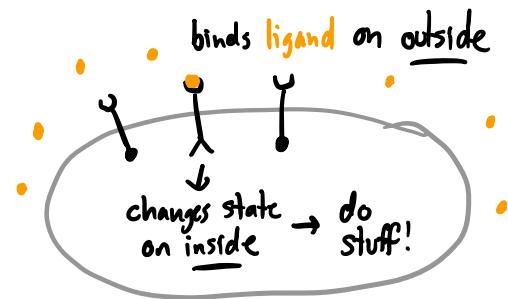
Case Study #2:

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

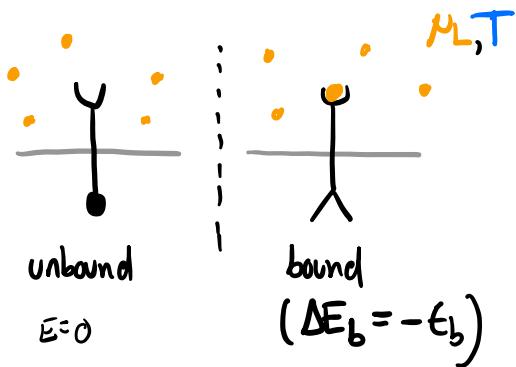


E.g. *atoS* gene (E.coli): binds acetoacetate

⇒ turns on acetoacetate metabolism ⇒ growth!

⇒ can we model this process w/ stat mech?

Focus on single receptor:



Boltzmann distribution:

$$\rho(\xi) = \frac{1}{Z} e^{-\frac{(-\epsilon_b)}{kT} + \frac{\mu_L}{kT}}$$

$$\rho(\xi) = \frac{1}{Z} e^{-\frac{\Omega}{kT} + \frac{\Omega}{kT}}$$

$$* \Rightarrow \rho(\xi) = \frac{e^{\frac{\epsilon_b}{kT} + \log\left(\frac{c_L}{c_0}\right)}}{1 + e^{\frac{\epsilon_b}{kT} + \log\left(\frac{c_L}{c_0}\right)}} = \frac{[L]}{K_m + [L]}$$

"Michaelis
constant"

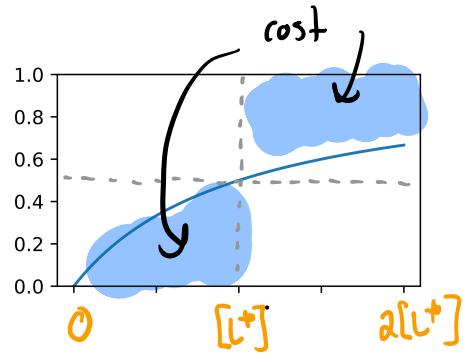
where $K_m \equiv \exp\left[-\frac{\epsilon_b}{kT} + \log\left(\frac{c_0}{[L]}\right)\right]$

← single free parameter

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

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

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



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

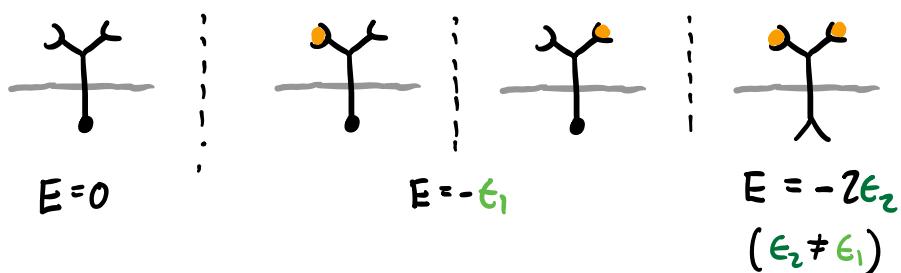
\Rightarrow would love to have something like a switch:



\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:

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

" $p(\text{态} 4)$

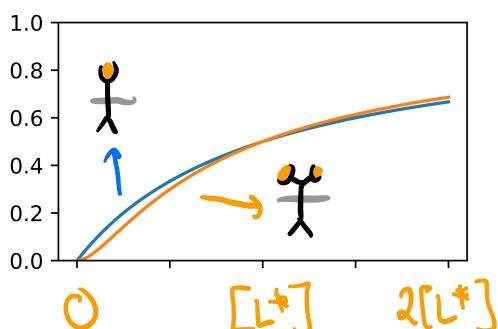
$$* \Rightarrow p(\text{态} 3) = \left(\frac{[L]}{K_m} \right)^2 / \left[1 + \left(\frac{[L]}{K_m} \right) e^{\frac{E_1 - E_2}{kT}} + \left(\frac{[L]}{K_m} \right)^2 \right]$$

where $K_m = \exp \left[-\frac{E_2}{kT} + \log \left(\frac{C}{I_m} \right) \right]$

\Rightarrow Behavior depends on E_1 vs E_2 !

independent binds-

$$\textcircled{1} \quad \text{If } \underbrace{E_1 = E_2}_{\text{}} \Rightarrow p(\text{态} 3) = \left(\frac{[L]}{K_m + [L]} \right)^2 =$$

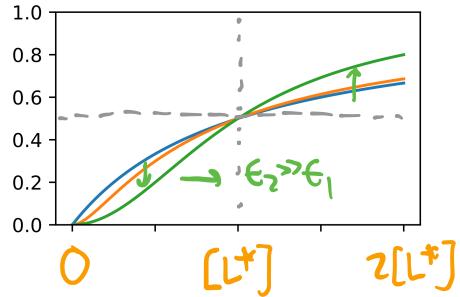


$$= \left[\frac{[L]}{(\sqrt{2}-1)[L^*] + [L]} \right]^2$$

② if $\underbrace{\epsilon_2}_{\text{"strong cooperative binding"} \rightarrow} \gg \epsilon_1 \Rightarrow p(\text{bound}) = \frac{([L]/[L^+])^2}{1 + ([L]/[L^+])^2}$

Hill function
(n=2)

\Rightarrow much more sensitive:

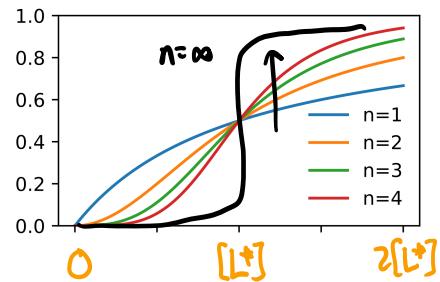


\Rightarrow can extend to more ligands *

$$p(\text{bound}) \approx \frac{([L]/[L^+])^n}{1 + ([L]/[L^+])^n}$$

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

"Hill function"



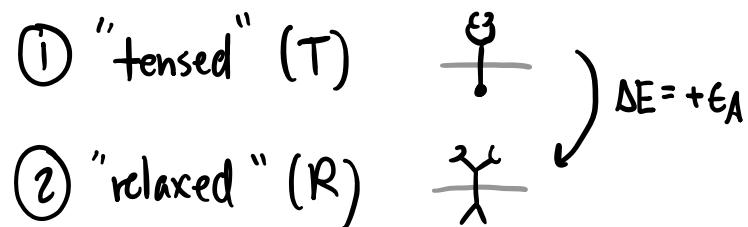
(e.g. hemoglobin binding oxygen, n=4)

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:



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

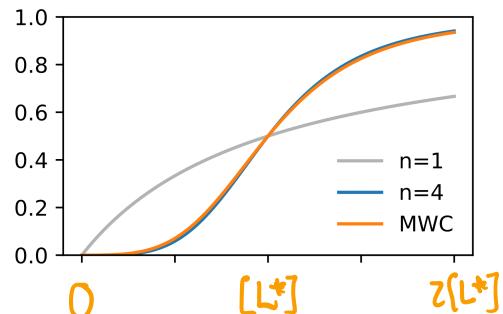
$$\begin{aligned} \Rightarrow \frac{p(T)}{p(R)} &= \frac{p(\text{---}) + p(\text{---}) + p(\text{---}) + p(\text{---})}{p(\text{---}) + p(\text{---}) + p(\text{---}) + p(\text{---})} \\ &= e^{-\frac{\epsilon_A}{kT}} \frac{\left[1 + e^{\frac{-\epsilon_R - \epsilon_L}{kT}}\right]^n}{\left[1 + e^{\frac{-\epsilon_T - \epsilon_L}{kT}}\right]^n} \quad (\text{since everything is independent!}) \end{aligned}$$

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

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

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

\Rightarrow looks like
Hill function:



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

\Rightarrow for more info (\approx more bio examples)

see Chapter 7 of Physical Biology of the Cell