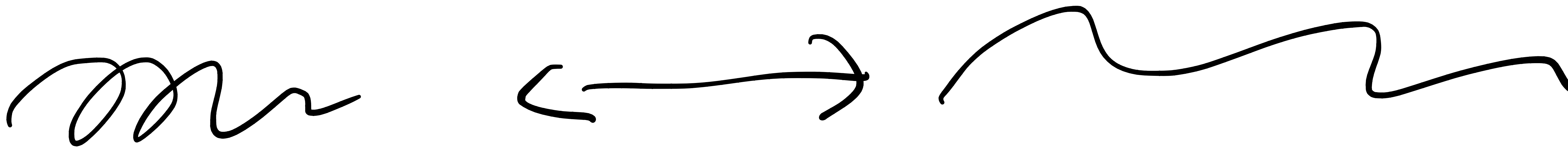
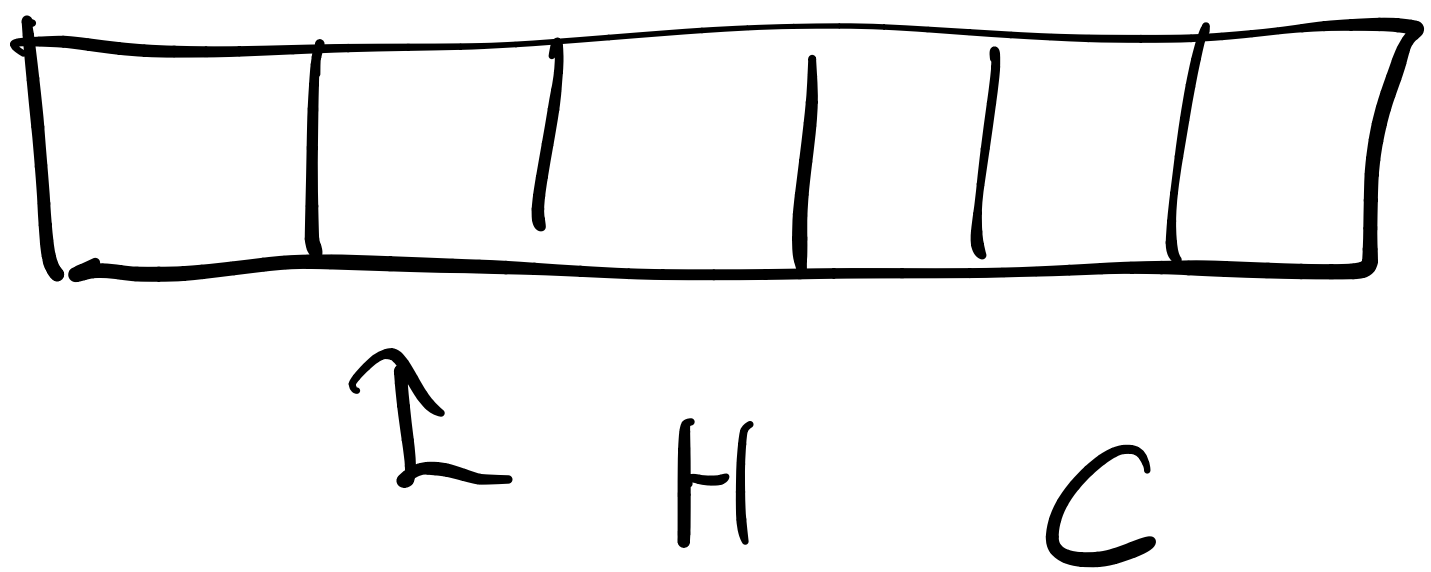
Lecture 24



competition between entropy & enthalpy



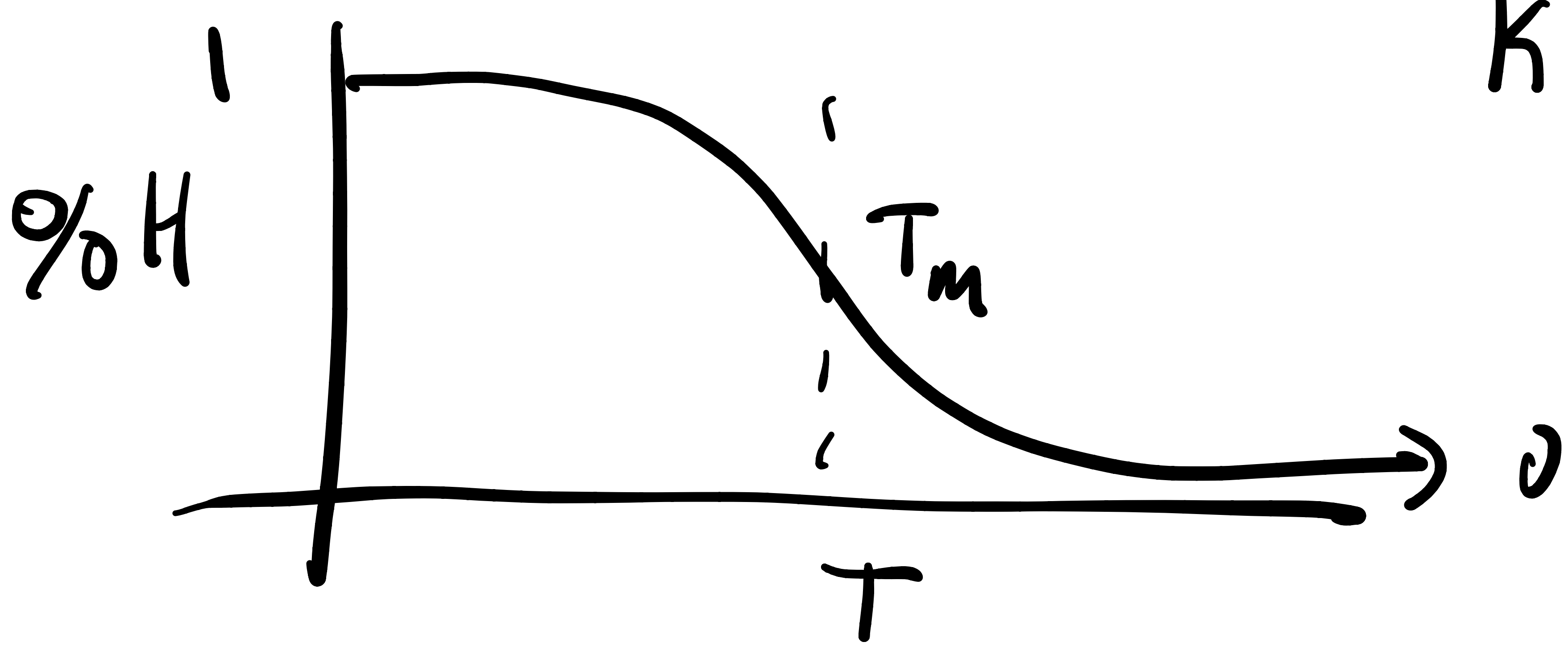
$Z \Leftarrow$ partition function, total weight of all states

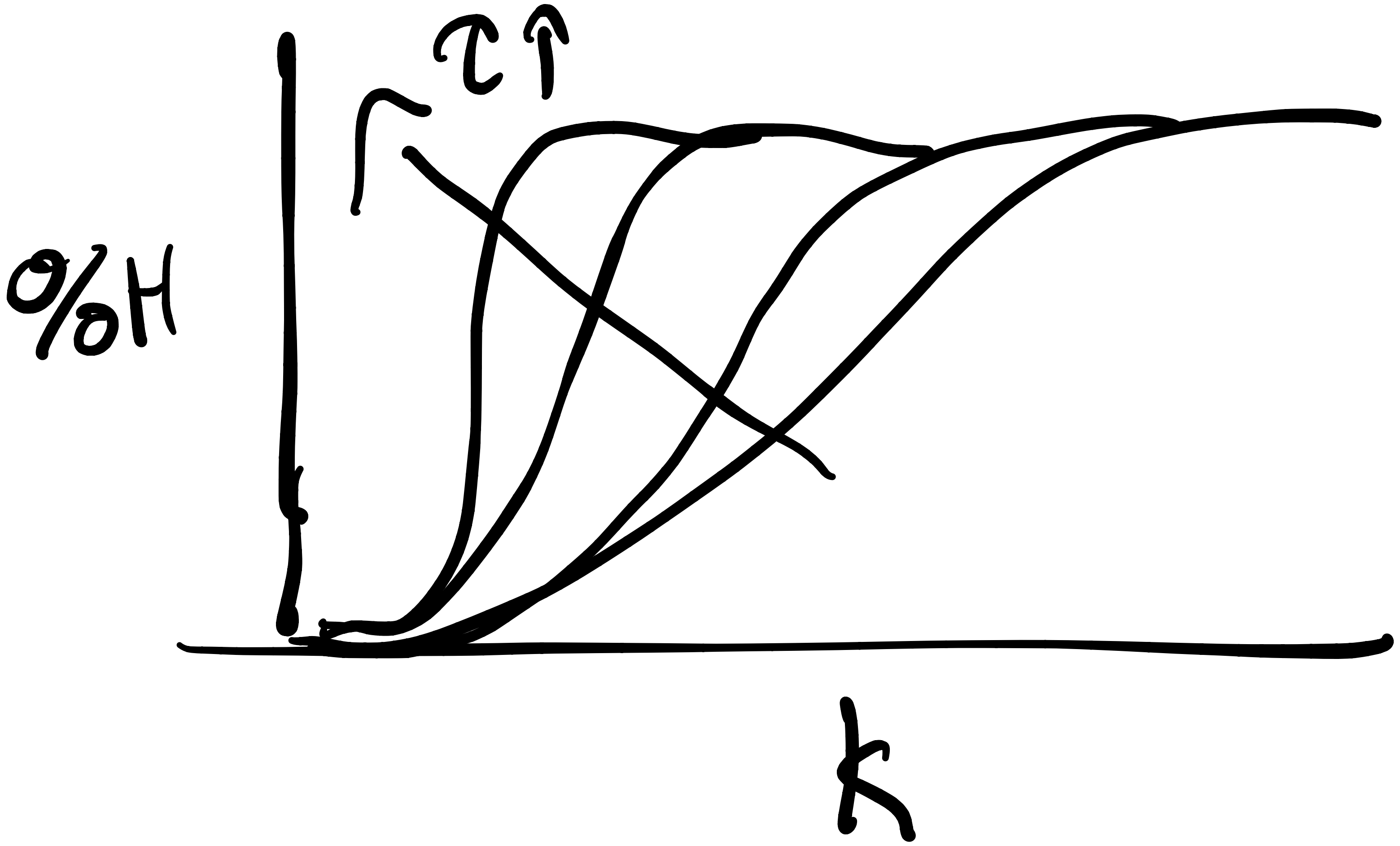
$$A = -k_B T \ln Z = \langle \varepsilon \rangle - T \langle S \rangle$$

$$-\frac{\partial \ln Z}{\partial \beta}$$

$$\langle S \rangle = \frac{A - \langle \varepsilon \rangle}{T} = \sum_i p_i \ln p_i \qquad p_i = \frac{e^{-\beta \varepsilon_i}}{Z}$$

$$K = \frac{p_H}{p_C} \sim e^{-\beta \Delta G_{fold}}$$

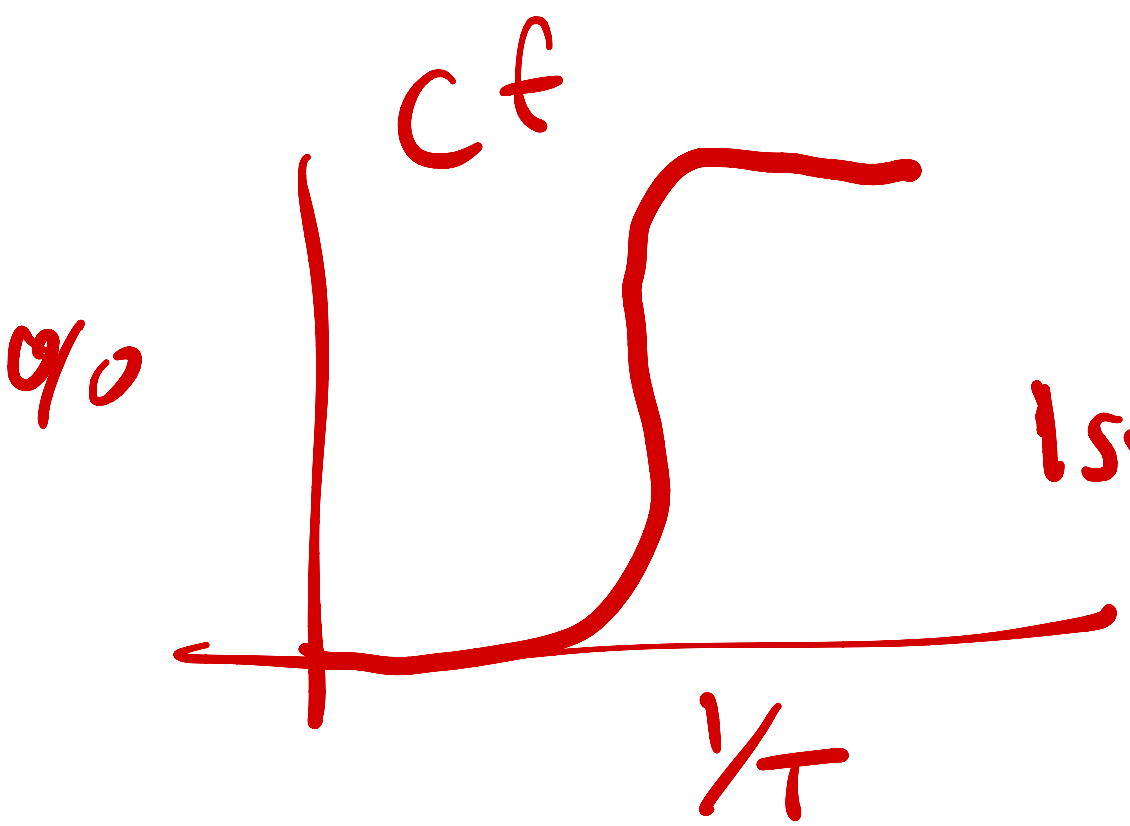




τ is interaction between neighbors

τk^2

HH



1st order phase transition

Zipper model, τ big so that all H's are together

C H C C C H H C vs C H H H C C C C

lots of weights for 3 H's

doesn't happen

weight $k^3 \tau^2$

general case $\binom{N}{m}$ sequences with m H's

Zipper model, $N-m+1 = \omega(m)$

$$Z = \sum_m \omega(m) P(m)$$

$$\langle m \rangle = k \frac{\partial \ln Z}{\partial k} = \sum_{m=0}^{N} m \underbrace{\left[\frac{w(m)\, z^{m-1} k^{m}}{Z} \right]}_{P(m)}$$

$$= \frac{\partial \ln Z}{\partial \ln k} \leftarrow \text{like } e^{-\beta h}$$

1d ising model

Exact solution:

method called "transfer matrices"

$$W = \begin{array}{c|cc} & H & C \\ \hline H & k\tau & 1 \\ C & k & 1 \end{array}$$

weights

HH	$\Leftarrow$	$k^2\tau$
HC	$\Leftarrow$	k
CH	$\Leftarrow$	k
CC	$\Leftarrow$	1

$$W \cdot W = \begin{pmatrix} k\tau & 1 \\ k & 1 \end{pmatrix}\begin{pmatrix} k\tau & 1 \\ k & 1 \end{pmatrix}$$

$$= \begin{pmatrix} k^2\tau^2 + k & k\tau + 1 \\ k^2\tau + k & k + 1 \end{pmatrix}$$

$$Z = \begin{pmatrix} 0 \\ 1 \end{pmatrix}^T W^N \begin{pmatrix} 1 \\ 1 \end{pmatrix}$$

$$Z_2 = k^2\tau + 2k + 1$$

need to add this bottom row

$$M = U D U^{-1} \qquad D = \begin{pmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{pmatrix}$$

diagonalizable

$$M \cdot M = U D U^{-1} \cdot U D U^{-1} = U D \cdot D U^{-1}$$

$$M^N = U D^N U^{-1} \qquad D^N = \begin{pmatrix} \lambda_1^N & 0 \\ 0 & \lambda_2^N \end{pmatrix}$$

$$Z = \begin{pmatrix} 0 \\ 1 \end{pmatrix}^T U D^N U^{-1} \begin{pmatrix} 1 \\ 1 \end{pmatrix}$$

Ising model: $N \to \infty$

$\mathrm{Tr}[ABC]$
$= \mathrm{Tr}[BCA]$
$= \mathrm{Tr}[CAB]$

$$Z = \mathrm{Tr}(\omega^N) = \mathrm{Tr}[U D^N U^{-1}]$$
$$= \mathrm{Tr}[U^{-1} U D^N]$$
$$= \mathrm{Tr}[D^N]$$
$$= \lambda_1^N + \lambda_2^N$$

$Z \approx \lambda_1^N$ if $N \uparrow$

$A \propto -k_B T \ln Z = -N k_B T \ln \lambda_1$

magnetization for any β, J, h

(Cooperative) Ligand binding

$$M + L \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} ML$$

$$K_b^{(eq)} = \frac{[ML]}{[M][L]} \qquad K_d = \frac{[M][L]}{[ML]}$$

units of M

$$f_b = \frac{[ML]}{[M] + [ML]} = \frac{K\cancel{[M]}[L]}{\cancel{[M]} + K\cancel{[M]}[L]}$$

$$= \frac{1}{1 + 1/K_b[L]} = \frac{1}{1 + K_d/[L]}$$

Compare to $$A \rightleftharpoons B$$

$$K_{eq} = \frac{[B]}{[A]} = \frac{k_f}{k_b}$$

$$M + L \rightleftharpoons ML$$

$$K_{eq} = \frac{[ML]}{[M][L]} = \frac{k_f}{k_b}$$

$$\frac{[ML]}{[M]} = \frac{k_f [L]}{k_b}$$

K_d is concentration when half bound

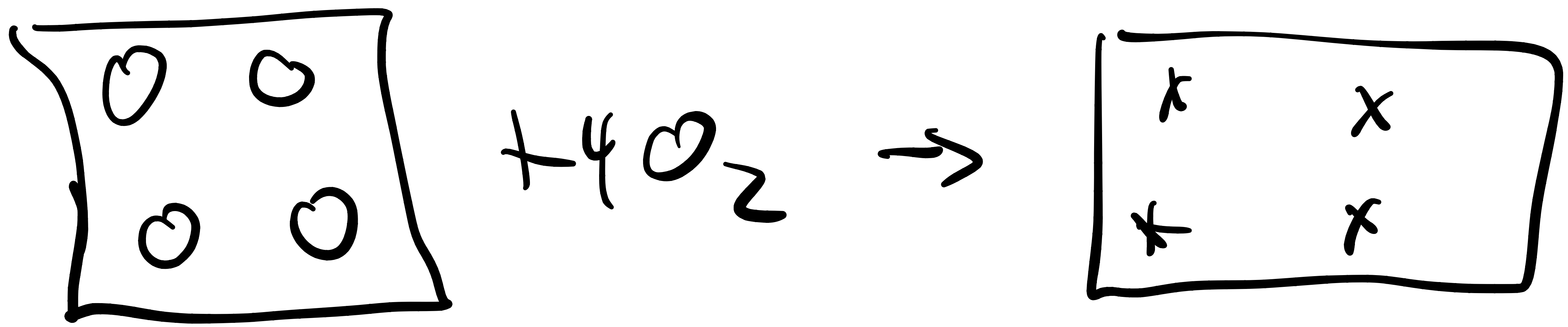
lower K_d is higher affinity

for a drug nM or pM affinity

other considerations:

- specificity, K_d to everything else
- availability / membrane permeability
- K_{off} molecule, low K_{off}

Cooperativity



Hemoglobin

same units

$$M + L \rightleftharpoons ML \qquad K_1 = \frac{[ML]}{[M][L]}$$

$$ML + L \rightleftharpoons ML_2$$

$$ML_2 + L \rightleftharpoons ML_3$$

$$ML_3 + L \rightleftharpoons ML_4 \qquad K_4 = \frac{[ML_4]}{[ML_3][L]}$$

$$M + L \rightleftarrows ML \qquad K_1 = \frac{[ML]}{[M][L]}$$

$$ML + L \rightleftarrows ML_2$$

$$ML_2 + L \rightleftarrows ML_3$$

$$ML_3 + L \rightleftarrows ML_4 \qquad K_4 = \frac{[ML_4]}{[ML_3][L]}$$

$$M + nL \rightleftarrows ML_n \qquad \beta_n = \frac{[ML_n]}{[M][L]^n}$$

$$\beta_n = K_1 K_2 \cdot K_3 \cdots K_n$$

$$f_b = \frac{1}{n} \cdot \frac{([ML] + 2[ML_2] + 3[ML_3] \cdots)}{([M] + [ML] + \cdots [ML_n])}$$

fraction of L that are bound to an M

$$= \frac{1}{n} \frac{d \ln[P]}{d \ln[L]}$$

$$= \frac{1}{n} \frac{(\beta_1 [L] + 2\beta_2 [L]^2 + 3\beta_3 [L]^3 + \cdots)}{(1 + \beta_1 [L] + \beta_2 [L]^2 + \cdots)}$$

define

$$P = 1 + \beta_1 [L] + \beta_2 [L]^2 + \cdots \beta_n [L]^3$$

β_i are like $e^{-\Delta G/RT}$

$M + nL \rightleftarrows ML_n$

$$[L]^i = \left[e^{-(\mu-\mu^0)/RT}\right]^i$$

$$P = \sum_{i=1}^{n_{sites}} e^{-\frac{1}{RT}[\Delta G_i + i\Delta\mu]}$$

← like partition funct for grand canonical ensemble how do we measure / quantify cooperativity

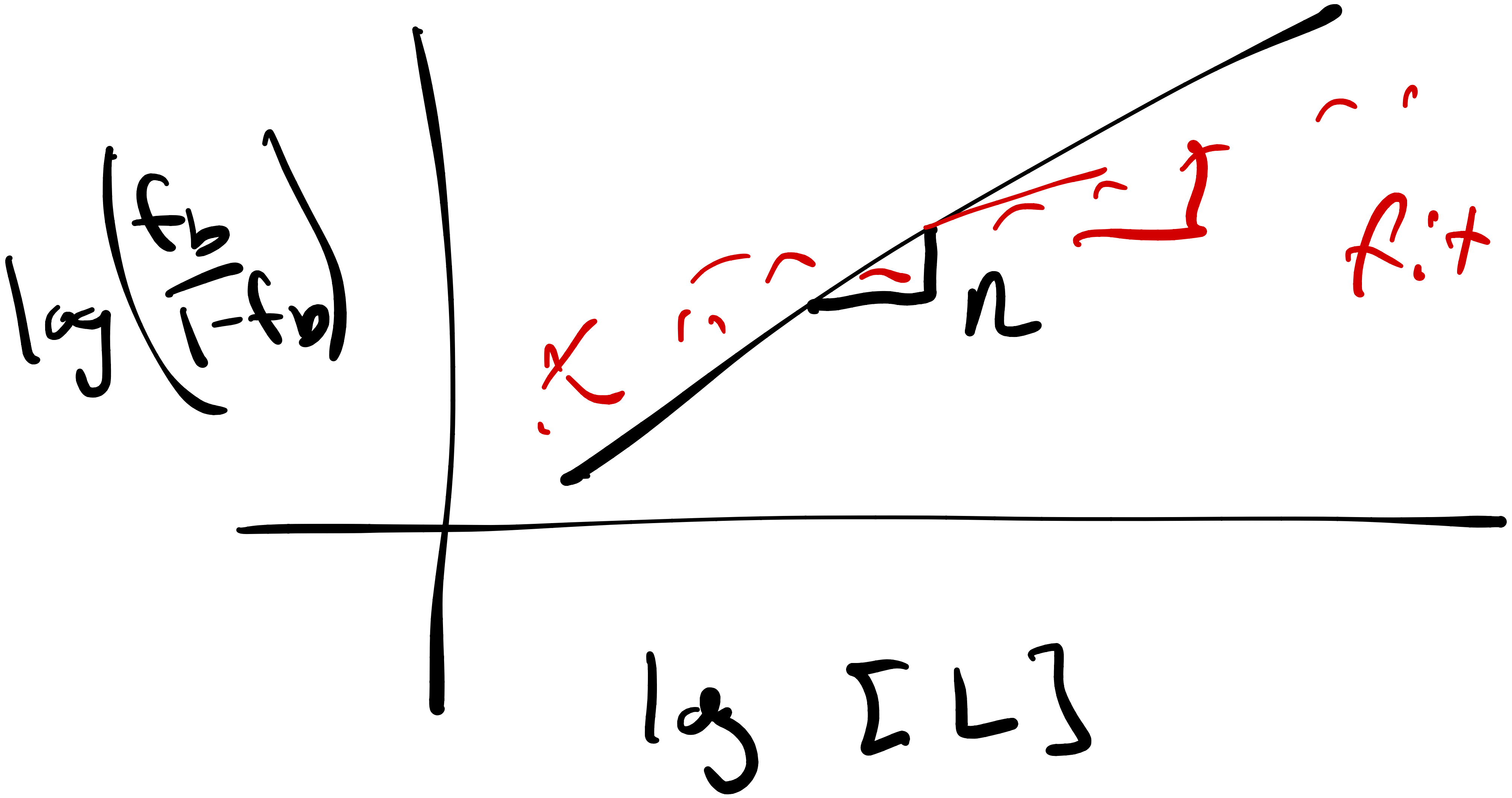
$$M + nL \rightleftarrows ML_n$$ all or nothing

$$f_b = \frac{[ML_n]}{[M] + [ML_n]} \qquad K = \frac{[ML_n]}{[M\ ][L]^n}$$

$$= \frac{\cancel{[M]}[L]^n K}{\cancel{[M]} + \cancel{[M]}[L]^n K} = \frac{1}{1 + \frac{1}{KL^n}} \sim \frac{1}{1 + \left(\frac{K_d}{L}\right)^n}$$

$$f_u = 1 - f_b$$

$\ln\left(\frac{f_b}{1-f_b}\right)$ vs $\log[L]$



fit to line

$n_H \Leftarrow$ hill coeff

$n_H = 1$, no coop

$n_H < 1$ anti cooperativity