Helix Coil Model

eg

$$\boxed{H \mid C \mid C \mid C \mid \overbrace{H \mid H}^{\sim -J} \mid C \mid C}$$

$C \sim 0$ $\quad$ $H \sim 1$

Energy 0 $\quad$ energy $-\epsilon$

$N=7$

$HHHCCCC$ vs $\underbrace{HCCHCCH}_{K^3}$

weight

$\tau^2 K^3$

Can "solve" $\Leftarrow$ exact formula for $Z(N, K, \tau)$

"Zipper" approximation, all H's are next to each other

$\tau \gg 1$

$N=7$, $H=4$

$-3J-4\epsilon$ all $\tau^3 \kappa^4$

HHHHCCC or CHHHHCC

or CCHHHHC or CCCHHHH

only 4 cfgs vs $\binom{7}{4}$

$$Z = 1 + \sum_{n_H=1}^{N} (N-n_H+1)\, \kappa^{n_H} \tau^{(n_H-1)}$$

$$Z = 1 + \sum_{n_H=1}^{N} (N - n_H + 1)\, K^{n_H} \tau^{(n_H - 1)}$$

$$= 1 + \frac{1}{\tau} \sum_{n_H=1}^{N} (N - n_H + 1) \left[K \tau \right]^{n_H}$$

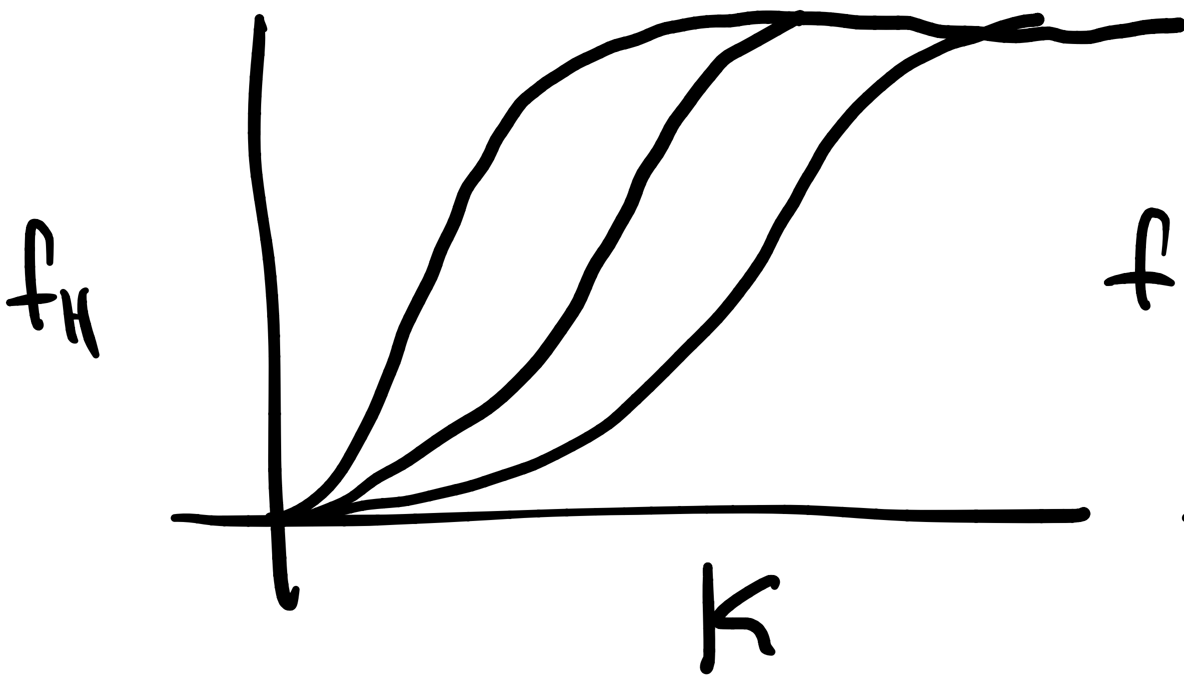
$$= 1 + \frac{1}{\tau} \left[\sum_{n_H=1}^{N} \overbrace{(N+1)}^{\text{const}} \left[K\tau \right]^{n_H} + \sum_{n_H=1}^{N} n_H \left[K\tau \right]^{n_H} \right]$$

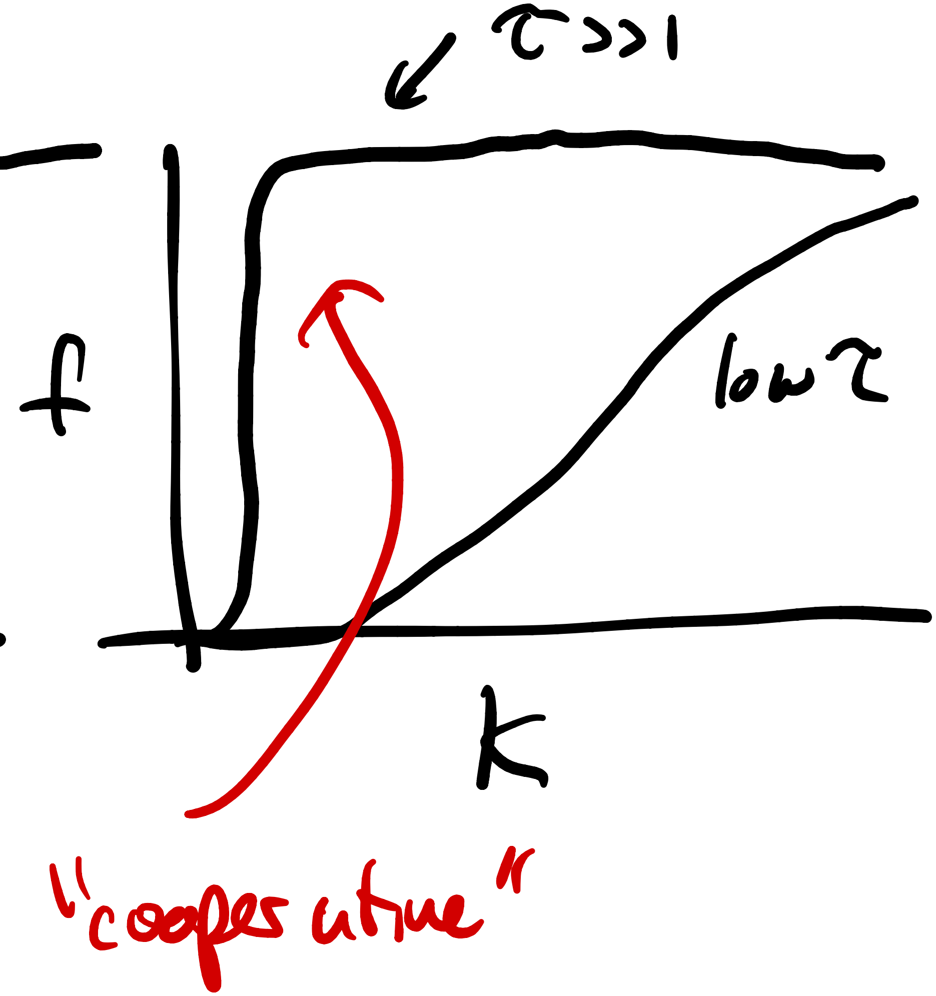
$$\sum_{n=1}^{N} x^n = \frac{(x^N - 1)x}{x - 1}$$

derivative

$$Z = 1 + K\left[\frac{(K\tau)^{N+1} - N(K\tau) - (K\tau) + N}{(K\tau - 1)^2}\right]$$

$$f_H = \frac{K}{N}\frac{\partial \ln Z}{\partial K}$$





How get Z exactly:

"transfer matrices"

weight of state in column for residue i following row i-1

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

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

CC CH HC HH

$Z = \Sigma$ bottom row of W^N

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

pick bottom row

add colums

→ what if $N \to \infty$

eigenvalues

$$W = U D U^T \qquad D = \begin{pmatrix} a & 0 \\ 0 & b \end{pmatrix}$$

$$D^N = \begin{pmatrix} a^N & 0 \\ 0 & b^N \end{pmatrix}$$

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

Ising model

$$Z = \mathrm{Tr}[\,\omega^N\,]$$
$$= \lambda_1^N + \lambda_2^N$$
$$= \lambda_1^N\left(1+\left(\frac{\lambda_2}{\lambda_1}\right)^N\right)$$
$$\simeq \lambda_1^N$$

Ligand Binding

$$M + L \rightleftharpoons ML \qquad K_b$$

low K_d
high affinity

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

2 other considerations

↳ K_{off}

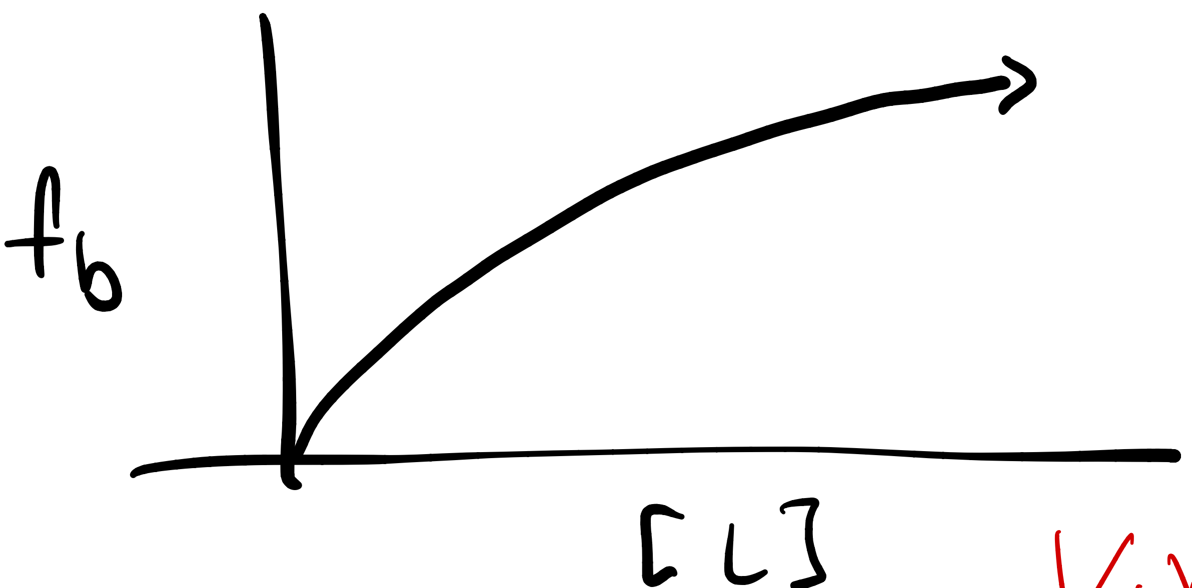
↳ bio availability

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

$$K_b = \frac{k_{on}}{k_{off}} = \frac{[ML]}{[M][L]}$$

$$f_{bound} = \frac{[ML]}{[M] + [ML]} = \frac{1}{1 + K_d/[L]}$$

$$f([L]=K_d)=\frac{1}{2}$$



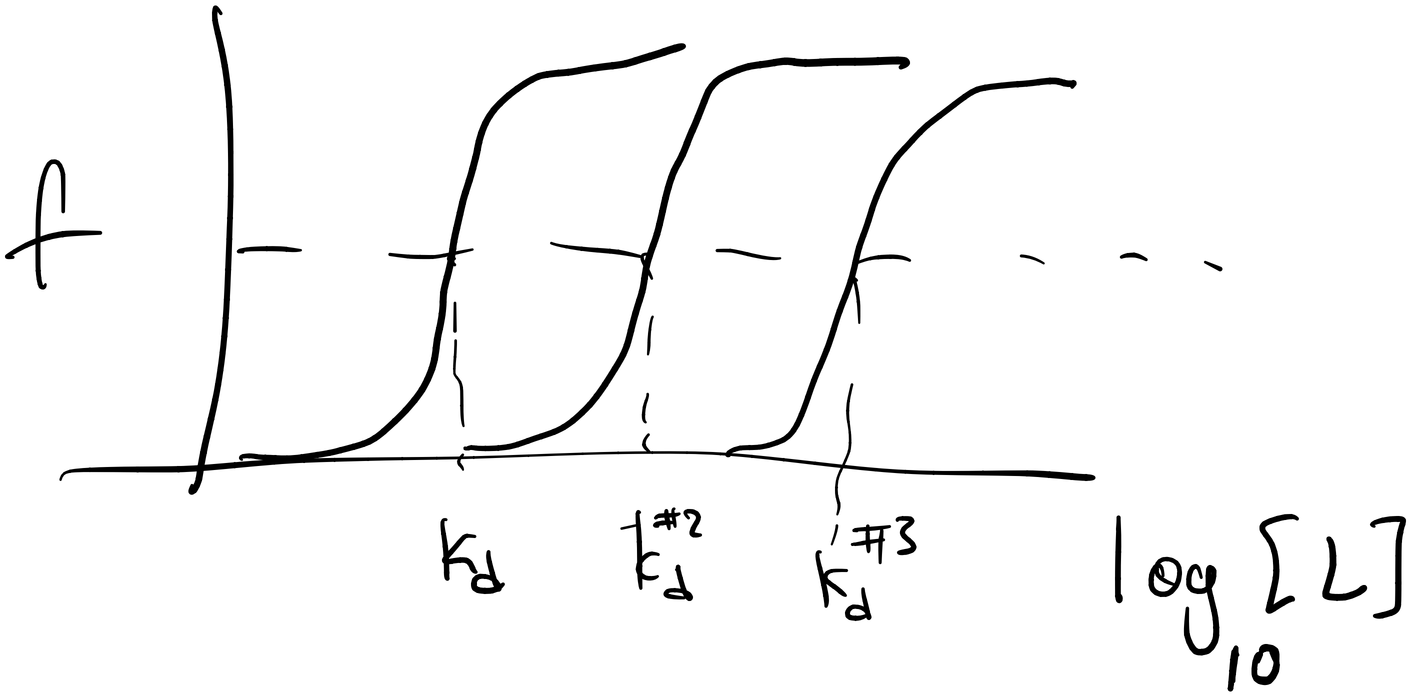
$$\frac{1}{1+K_d/[L]}$$

$\Delta G = -kT\ln K_d$

$1/(1+K_d) \sim \frac{1}{1+e^{-\beta\varepsilon}}$

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

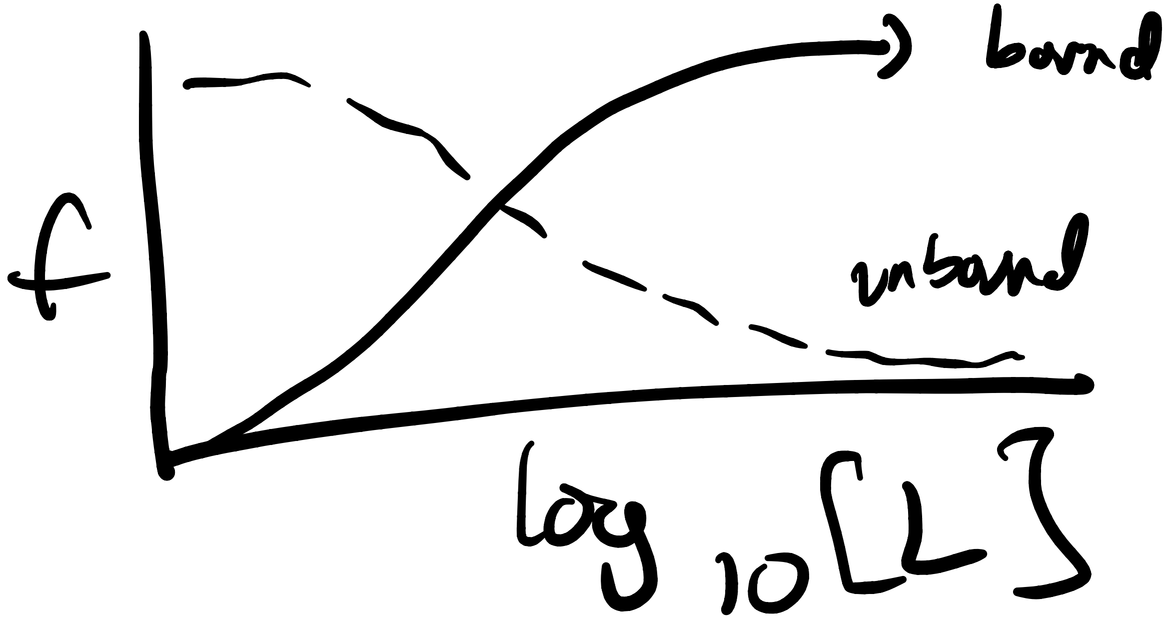
$$K=K_b[L] \longrightarrow \;=\; K/(1+K)$$

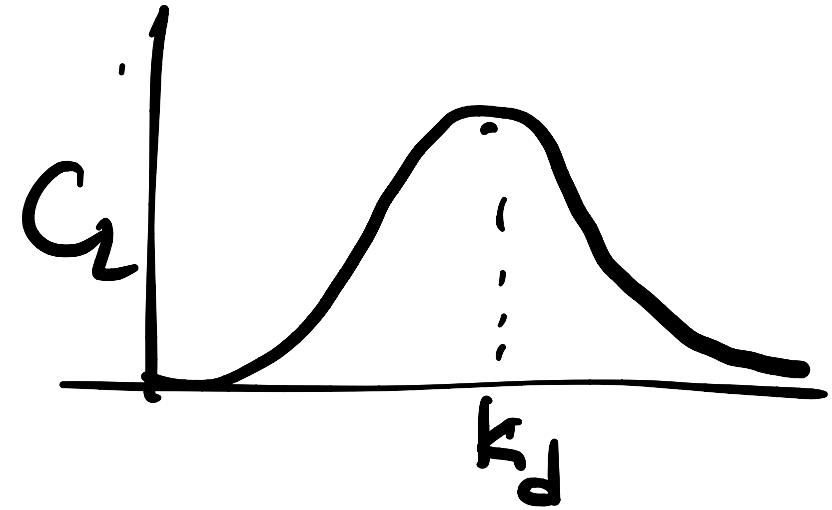


real K_ds range from pM – mM

Binding capacity

$$C_L = \frac{df}{d\log_{10}[L]} = 2.3\frac{df}{d\ln L}$$





$$C_L = 2.3 \frac{df}{d\ln(L)} \rightarrow 2.3 \frac{K[L]}{(1+K[L])^2}$$

$$= 2.3\, f_{bound}\, f_{unbound}$$

$$= 2.3\, f_{bound}\,(1 - f_{bound})$$

$[L]$ is the free ligand conc.

$$[L]_{tot} = [L] + [ML]$$

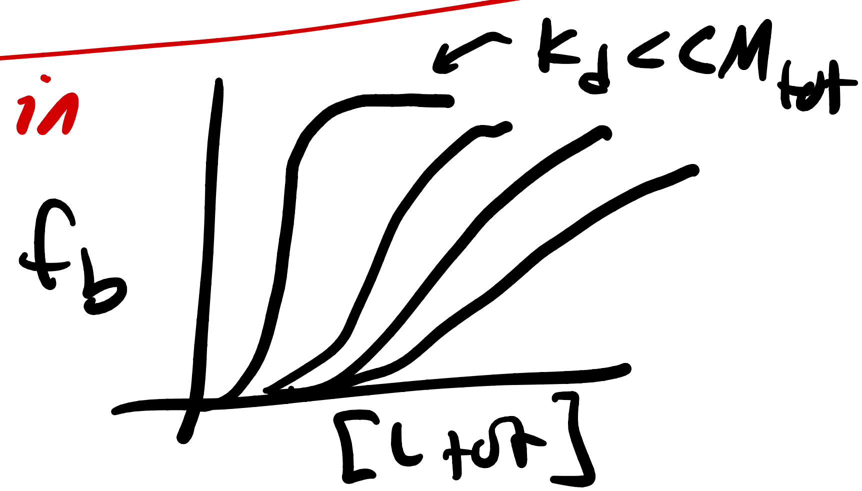
$$[M]_{tot} = [M] + [ML]$$

$$K_b = \frac{[ML]}{([M_{tot}] - [ML])([L_{tot}] - [ML])}$$

solve for M_L

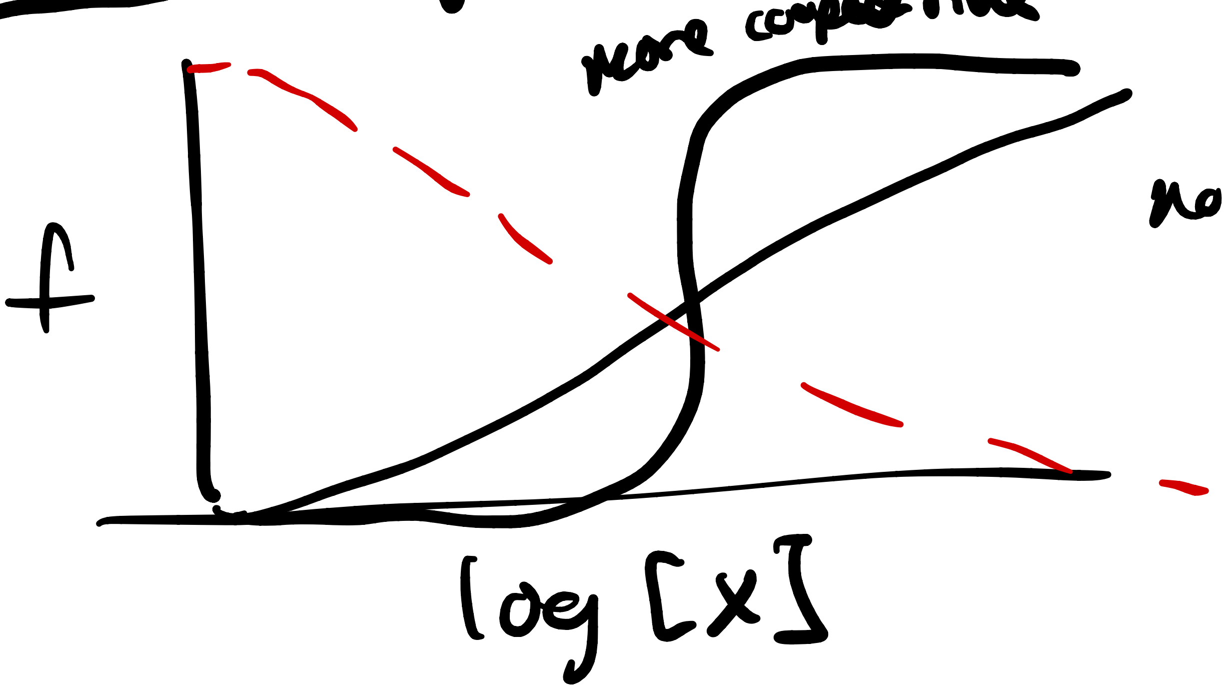
$$f = \frac{[ML]}{[M_{tot}]}$$

plug in



Hill plot

cooperativity

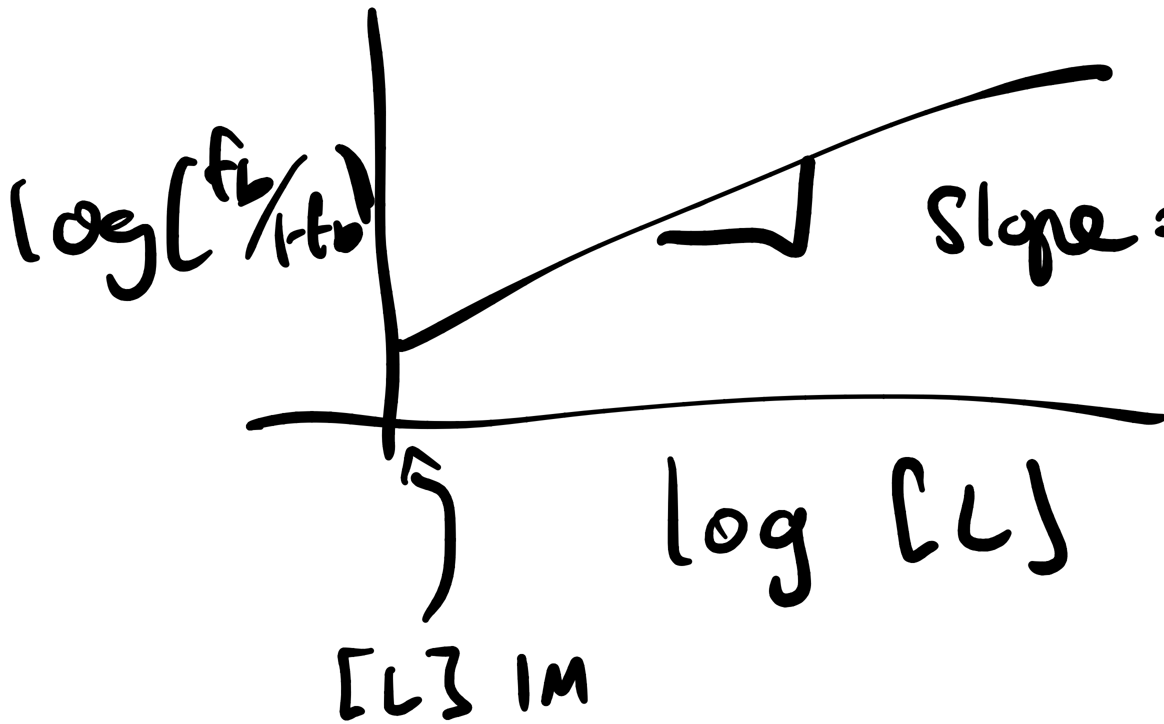


$$f_b = \frac{[L]K_b}{1+[L]K_b}$$

$$f_u = 1 - f_b = \frac{1}{1+K_b[L]}$$

$$\log\left(f_b/f_u\right) = \log\left([L]K_b\right) = \log[L] + \log K_b$$

$$\log\left(f_b/f_u\right) = \log\left([L]K_b\right) = \log[L] + \log K_b$$



Slope = 1, not coop

$$\frac{d\,\log\left[f_b/(1-f_b)\right]}{d\,\log[L]} = n \quad \text{hill coeff}$$

non coop
$n=1$

coop
$n>1$

$$\frac{1}{1+\left(K_d/[L]\right)^n} = f_{bound}$$

$$\frac{\partial \log f}{\partial \log x} = \left(\frac{\partial x}{\partial \log x}\right)\left(\frac{\partial \log f}{\partial x}\right) = x\,\frac{\partial \log(f)}{\partial x}$$

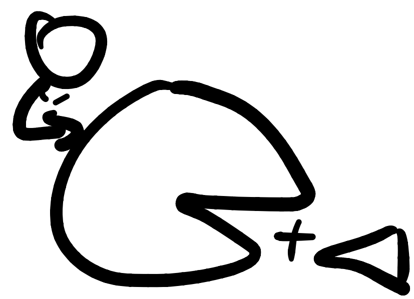
Binding of multiple ligands

$$M + L \underset{K_b^1}{\rightleftharpoons} ML + L \underset{K_b^2}{\rightleftharpoons} ML_2 + L \underset{K_b^3}{\rightleftharpoons} ML_3 \cdots$$

positive coop, K's increase

neg coop, K's decrease

allostery:



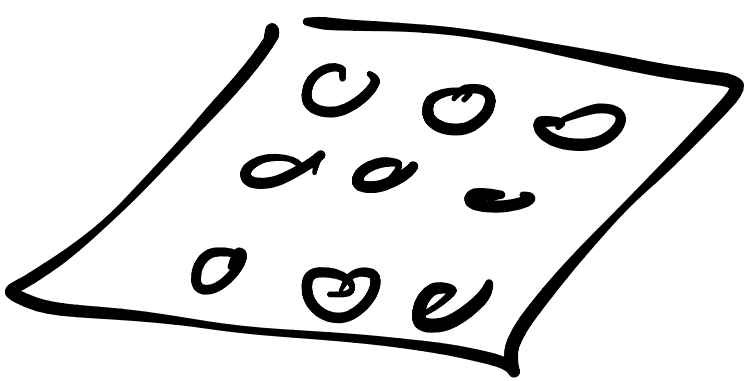
$$\beta_N = K_1 K_2 \cdots K_N$$

$$= \frac{[ML_N]}{[M][L]^N}$$

S binding sites

$$f_b = \frac{1}{S} \frac{\sum i \beta_i [L]^i}{\sum \beta_i [L]^i}$$

← grand canonical



$$P = \sum \beta_i [L]^i$$