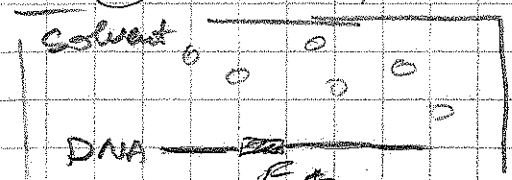
Protein-DNA interactions

(1) One specific site



$M = \frac{V}{v}$ ← total volume; ← elementary volume

E ← energy of specific binding

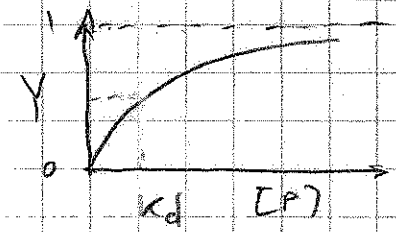
$$\binom{M}{P} = \frac{M!}{P!(M-P)!} \qquad \binom{M}{P-1} = \frac{M!}{(P-1)!(M-P+1)!}$$

$$\frac{\binom{M}{P}}{\binom{M}{P-1}} = \frac{M-P+1}{P} \simeq \frac{M}{P}$$

$$Y = \frac{e^{-E}\binom{M}{P-1}}{e^{-E}\binom{M}{P-1} + \binom{M}{P}} = \frac{e^{-E}}{e^{-E} + \binom{M}{P}\Big/\binom{M}{P-1}} \simeq \frac{e^{-E}}{e^{-E} + \frac{M}{P}}$$

$$= \frac{P/M}{P/M + e^{E}} = \frac{P/V}{P/V + e^{E}/V} = \frac{[P]}{[P] + \underbrace{e^{E}/V}_{K_d}}$$

$$K_d \equiv \frac{e^{E}}{V}$$



(2) One specific sites, many non-specific sites

E - specific energy

ε - non-specific energy

D - # of non-specific sites on DNA $= \frac{\text{DNA volume}}{v}$

$$Y = \frac{e^{-E}\cdot Z(P-1)}{e^{-E}Z(P-1) + Z(P)}$$

where $Z(P)$ - partition function for P proteins to be in the solvent or on non-specific DNA.

$$Z(P) = \sum_{k=0}^{P} e^{-k\varepsilon}\binom{M-D}{P-k}\binom{D}{k}$$

← proteins on DNA; ← proteins in solvent; ↳ # of proteins on DNA

Note:

$$\binom{A}{b} = \frac{A!}{(A-b)!\,b!} \simeq \frac{A^b}{b!}$$

$b \ll A$

then $\binom{M-D}{P-k}\binom{D}{k} \simeq (M-D)^{P-k}\, D^k \cdot \frac{1}{k!(P-k)!} =$

$$= M^P\left(1-\frac{D}{M}\right)^{P-k}\left(\frac{D}{M}\right)^k \cdot \frac{P!}{k!(P-k)!}\,\frac{1}{P!}$$

$$= \left(1-\frac{D}{M}\right)^{P-k}\left(\frac{D}{M}\right)^k\binom{P}{k}\cdot\frac{M^P}{P!}$$

$$Z(P) \approx \left[\sum_{k=0}^{P} \underbrace{\binom{P}{k} (1-\pi)^{P-k} \pi^k \cdot e^{-\varepsilon k}}_{\text{Binomial prob of putting } k \text{ particles on DNA if } \pi\text{- prob to be on DNA; } \pi \equiv \frac{D}{M}} \right] \frac{M^P}{P!}$$

$$= \left(1 - \pi + \pi e^{-\varepsilon}\right)^P \cdot \frac{M^P}{P!}$$

$$\frac{Z(P)}{Z(P-1)} = \left(1 + \pi\left(e^{-\varepsilon} - 1\right)\right) \frac{M}{P} \quad ; \text{ if } \varepsilon = 0 \text{ (no affinity for non-spec DNA), then } \frac{Z(P)}{Z(P-1)} = \frac{M}{P} \text{ as above.}$$

$$= \frac{M}{P}\left(1 - \frac{D}{M} + \frac{D}{M} e^{-\varepsilon}\right)$$

$$= \frac{M-D}{P} + \frac{D}{P} e^{-\varepsilon}$$

$$Y = \frac{e^{-E}}{e^{-E} + \frac{Z(P)}{Z(P-1)}} = \frac{e^{-E}}{e^{-E} + \underbrace{\frac{M-D}{P}}_{\substack{\#\text{ of states in solvent} \\ \text{per protein}}} + \underbrace{\frac{D}{P}}_{\substack{\#\text{ of states on DNA} \\ \text{per protein}}} e^{-\varepsilon}}$$

$$= \frac{P/(M-D)}{P/(M-D) + e^{E}\left(1 + \frac{D}{M-D} \cdot e^{-\varepsilon}\right)}$$

recall

$$M = \frac{V}{v} \; ; \; D = \frac{\text{DNA vol}}{v}$$

$$\Rightarrow M - D = \frac{\text{Solvent Volume}}{v}$$

$$= \frac{[P]v}{[P]v + e^{E}\left(1 + [DNA] \cdot v \cdot e^{-\varepsilon}\right)}$$

where $[P] \equiv \dfrac{P}{\text{solvent volume}}$; $[DNA] = \dfrac{D}{\text{solvent volume}}$

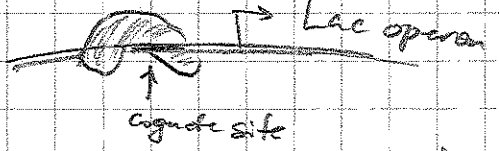
$$= \frac{[P]}{[P] + e^{E}/v\left(1 + \frac{[DNA]}{e^{\varepsilon}/v}\right)} = \frac{[P]}{[P] + \underbrace{K_d\left(1 + \frac{[DNA]}{K_d^{ns}}\right)}_{K_d^{eff}}}$$

K_d^{eff} - higher than K_d due to non-spec. Binding

$$K_d \equiv \frac{e^{E}}{v} \; , \; K_d^{ns} \equiv \frac{e^{\varepsilon}}{v}$$

Example: Lac repressor

Function:
repress Lac operon



Lactose	Lac repressor	Lac operon	K_d
+	unbound	expressed	10^{-9} M
−	bound	repressed	10^{-12} M

[P] = 10 molecules per E.coli cell $\simeq 10 \cdot 10^{-9}$ M

① Naive approach, i.e. disregarding non-specific binding

$$Y^{-lac} = \frac{[P]}{[P]+k_d} = \frac{10\cdot10^{-9}}{10\cdot10^{-9}+10^{-12}} = \frac{1}{1+10^{-3}} = 0.999\ldots \quad \underline{\text{bound!}}$$

$$2\,k_d^{-lac} = 10^{-12}\,M$$

$$Y^{+lac} = \frac{10\cdot10^{-9}}{10\cdot10^{-9}+10^{-3}} = \frac{10}{11} = 0.9 \quad \underline{\text{also bound, but shouldn't}}$$

② Take into account non-specific Binding to DNA

$K_d^{ns} \simeq 10^{-6}$ M irrespective of lactose

[DNA] = $5\cdot10^6$ bp / cell / ~10 bp footprint

$$\left(1+\frac{[DNA]}{K_d^{ns}}\right) = 1+\frac{5\cdot10^6\cdot10^{-9}}{10^{-6}\cdot10} = 1+500 \simeq 500$$

$$Y^{-lac} = \frac{10^{-8}}{10^{-8}+10^{-12}\cdot500} = 0.95 \quad \underline{\text{bound}}$$

$$Y^{+lac} = \frac{10^{-8}}{10^{-8}+10^{-9}\cdot563} \simeq 10^{-2} \quad \underline{\text{non-bound}}$$