Statisical Themodyanmics Approach to ligand binding

CCB 342: Physical Chemistry of biochemical systems, Spring 2012

1 Partition function approach to allostery

The partition function is the sum of the relative probabilities of all states. We can arbitrarily set the concentration of protein to be unity:

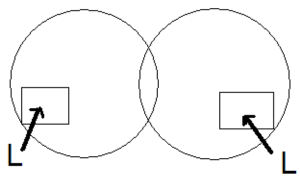

Figure 1: *Simple model for a dimeric protein binding a ligand "L"*

$$[P] = 1$$

$$\frac{[P_\alpha]}{[P][L]} = k$$

$$[P_\alpha] = k[L]; \quad [P_\beta] = k[L]$$

$$\frac{[P_{\alpha\beta}]}{[P_\alpha][L]} = k \Rightarrow [P_{\alpha\beta}] = k^2[L]^2$$

Note the the partition function is just the sum of the relative populations (concentrations) of all species:

$$Q = 1 + 2k[L] + k^2[L]^2 = q_0 + q_1\lambda + q_2\lambda^2 = \sum_{i=0}^{N} q_i\lambda^i$$

In general, Q will be a polynomial in the concentration of ligand; this is sometimes called the *binding polynomial*. Now, compute the fraction of binding sites that contain ligands:

$$\bar{y} = \frac{\left(\frac{0}{2}\right)1 + \left(\frac{1}{2}\right)2k\lambda + \left(\frac{2}{2}\right)k^2\lambda^2}{1 + 2k\lambda + k^2\lambda^2} = \frac{1}{2}\frac{\sum iq_i\lambda^i}{\sum q_i\lambda^i}$$

$$= \frac{\lambda}{2}\frac{\sum iq_i\lambda^{i-1}}{\sum q_i\lambda^i} = \frac{\lambda}{2}\frac{\partial \ln Q}{\partial \lambda}$$

$$\boxed{\bar{y} = \frac{\lambda}{N}\frac{\partial \ln Q}{\partial \lambda} = \frac{1}{N}\frac{\partial \ln Q}{\partial \ln \lambda}} \quad (1)$$

Since this is *uncoupled* binding:

$$Q = 1 + 2k\lambda + k^2\lambda^2 = (1 + k\lambda)^2$$

[Very advanced: See Onufriev, Case, Ullmannn, *Biochemistry* **40**, 3413 (2001) for a generalization.]
Suppose we just have a simple acid-base equilibrium:

$$AH \Leftrightarrow A^- + H^+$$
$$Q = 1 + k\lambda$$

$$\bar{y} = \lambda \frac{\partial \ln Q}{\partial \lambda} = \frac{\lambda k}{1 + \lambda k}$$

Now, $k = 10^{pK_a}$ and $\lambda = 10^{-pH}$; hence:

$$\bar{y} = \frac{10^{pK_a - pH}}{1 + 10^{pK_a - pH}} \tag{2}$$

This yields the usual sigmoidal binding curve discussed in class. Compare the discussion in section 4.8 of your text.

2 Hemoglobin-like model

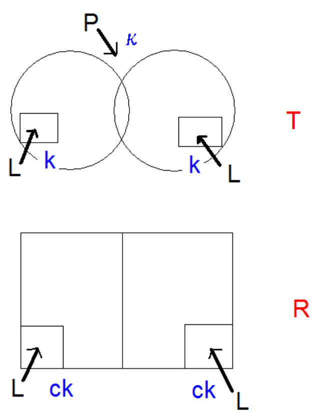

Figure 2: *A more complex model, binding two ligands, with a protein conformational change coupled to ligand binding.*

Now we consider the more complex model shown at the left. We can define some new constants, then make a table of relative probabilities:

$$\frac{[T^P]}{[T][P]} = \kappa; \quad \mu \equiv [P]$$

$$\frac{[R]}{[T]} = L$$

λ	T	T^P	R
0	1	$\mu\kappa$	L
1	$k\lambda$	$\mu\kappa k\lambda$	$Lck\lambda$
1	$k\lambda$	$\mu\kappa k\lambda$	$Lck\lambda$
2	$k^2\lambda^2$	$\mu\kappa k^2\lambda^2$	$Lc^2k^2\lambda^2$

Adding up all 12 elements of the Table gives the partition function:

$$Q = (1 + k\lambda)^2(1 + \mu\kappa) + L(1 + ck\lambda)^2 \tag{3}$$

Now suppose we have no phosphate present, so that $\mu = 0$:

$$\begin{aligned}
\bar{y} &= \frac{1}{2}\frac{\partial \ln Q}{\partial \ln \lambda} = \frac{\lambda}{2Q}\left(\frac{\partial Q}{\partial \lambda}\right) \\
&= \frac{\lambda}{2Q}\frac{\partial}{\partial \lambda}\left[(1 + k\lambda)^2 + L(1 + ck\lambda)^2\right] \\
&= \frac{\lambda}{2Q}\left[2(1 + k\lambda)k + 2L(1 + ck\lambda)ck\right] \\
&= \frac{(1 + k\lambda)k\lambda + L(1 + ck\lambda)ck\lambda}{(1 + k\lambda)^2 + L(1 + ck\lambda)^2}
\end{aligned} \tag{4}$$

If $L = 0$, get simple non-cooperative binding; for $L < 1$ and $c > 1$ (that is, T state is favored in the absence of ligand, but the R state has a higher affinity), get "hemoglobin-like" cooperative binding.

When $\mu > 0$, get a *linkage* between $\overline{y_L}$ and $\overline{y_P}$.