Heamoglobin and Myoglobin

Outline
1. Binding reaction, Scatchard plot
2. Binding to n independent sites
3. Hill equation, Hill coefficient
4. MWC model

1. Simple binding reaction

\[ P + L \rightleftharpoons P \cdot L \]

\( E_b \) - binding energy

Free \( F_{\text{free}} \)

Bound \( F_{\text{bound}} \)

\( F_{\text{bound}} = -E_b \) (\( E_b > 0 \))

Estimate entropy in the free state:

\[ S = \log \omega \]

\( \omega \) - # of states per molecule

\[ [L] = \frac{N_L}{V} \] concentration

\[ Y = \frac{e^{-E_b/T}}{1 + e^{-E_b/T}} \]

\[ Y = \frac{e^{-E_b/T}}{1 + e^{-E_b/T}} + \frac{e^{-E_b/T}}{e^{-E_b/T} + e^S} = \frac{e^{-E_b/T}}{e^{-E_b/T} + e^S} \]

\[ e^S = \frac{[L]}{k_d + [L]} \]

\( k_d = e^{E_b/T} \)

* Scatchard Plot

\[ Y(k_d + [L]) = [L] \]

\[ Y = \frac{1}{k_d} - \frac{Y}{k_d} \]

\[ Y = \frac{1}{k_d} - \frac{Y}{k_d} \]
2. Independent sites

occupancy of a site

\[ Y = \frac{[L]}{K_d + [L]} \]

occupancy of the protein

\[ Y_p = \frac{n[L]}{K_d + n[L]} \]

Scatchard plot

\[ \frac{Y}{n[L]} = \frac{1}{K_d} - \frac{Y}{n[K_d]} \]

\[ Y_p = \frac{n}{K_d + n[K_d]} \]

3. Cooperative binding to n sites

Hill model of hemoglobin (1910)

n sites, either all occupied or all vacant

\[ M + n[L] \rightleftharpoons ML_n \]

\[ k_d^{(n)} = \frac{[M][L]^n}{[ML_n]} \]

Hill equation

\[ Y = \frac{[L]^n}{K_d^{(n)} + [L]^n} \]

Scatchard is non-linear

\[ \frac{Y}{[L]} = \frac{K_d^{(n)}}{K_d^{(n)}} \]

\[ \log \frac{Y}{1-Y} = n \log [L] - \log K_d^{(n)} \]
Hemoglobin (1910)

\[ [L] = pO_2 \]

\[ \Rightarrow \text{ need a better model} \]

Monod - Wyman - Changeux model (1965)

1. Hemoglobin consists of \( n = 4 \) domains
2. All domains can be either in R or in T states
3. \( O_2 \) binds to the R state with higher affinity
4. In the unbound form, T state has a lower energy

Parameters of the model:

\[ L = \frac{[T]}{[R]} = e^{-AE_{RT}} \]

\[ L = \frac{[R] + [O_2]}{[R]} = \frac{[L]}{E_{RT}} \]

\[ C = \frac{K_T}{K_R} = \frac{E_{RT}}{E_{RT}} \]

\[ L = \sum_{i=0}^{n} \left[ w(R_i) + w(T_i) \right] \text{, where } w(R) = \alpha_i C_i \]

\[ w(T) = L \cdot (1 + \alpha C)^n \]

\[ = (1 + \alpha C)^n + L(1 + \alpha C)^n \]
\[
Y = \frac{\sum_{i=0}^{N} \left[ w(E_i) + w(0) \right]}{\sum_{i=0}^{N} w(E_i)}
\]

\[
\sum_{i=0}^{N} w(E_i) = \sum_{i=0}^{N} C_i x_i^d = \alpha \sum_{i=0}^{N} C_i x_i^{d-1} = \frac{\alpha}{2} \text{C} \alpha = \frac{\alpha}{2}(1+\alpha)^{d-1}
\]

\[
Y = \frac{\alpha (1+\alpha)^{d-1} + Lc(1+\alpha C)^{d-1}}{(1+\alpha)^{d} + L(1+\alpha C)^{d}}
\]

- effect of parameters \( d \) and \( I \)
- Bohr effect
- Heterotropic regulation
SCATCHARD PLOT

HILL PLOT

SENSITIVITY OF MWC TO PARAMETERS