The Monod-Wyman-Changeux model for equilibrium and kinetic O_2 binding.

To fit the kinetic parameters the Monod-Wyman-Changeux (MWC) equation was extended to incorporate rate parameters.

The MWC model, originally developed by Niesel, assumes two conformational states of the hemoglobin, T (tense) and R (relaxed). Hemoglobin may exist in ten forms, $T_{0\text{-}4}$ and $R_{0\text{-}4}$, the subscript (0-4) denoting the number of oxygen molecules bound. In each state, the four oxygen binding sites have the same oxygen affinity with oxygen binding parameters defined as K_T and K_R respectively, and rate parameters denoted k_T, k'_T, k_R and k'_R respectively, where the k is dissociation and the k' association; $K=k'/k$. The association can be expressed in $sec^{-1}mol^{-1}$ or in $sec^{-1}kPa^{-1}$. Since saturation is against oxygen pressure P, we will use the second form.

Since the Hb has four binding locations, from the forms T_n, R_n n molecules can dissociate so the k has to be multiplied by n, whereas $4-n$ molecules can associate and the k' has to be multiplied by $(4-n)$:

$$n\,k_X X_n = (4-[n-1])\,k'_X P\,X_{n-1} \qquad X = R \text{ or } T,\; n = 1\text{-}4$$

from which can be solved:

$$X_n = \binom{4}{n}(K_XP)^n X_0 = \binom{4}{n}(K_XP)^{n-4} X_4 \qquad X = R \text{ or } T,\; n = 0\text{-}4^{(1\dagger)}$$

Then, the total amount of species X, X_t, is - note, that $X_4 = (K_XP)^4X_0$:

$$X_t = \sum_{n=0}^{4}\binom{4}{n}(K_XP)^n X_0 = (1 + K_XP)^4 X_0 = \{1 + 1/(K_XP)\}^4 X_4 \qquad X = R \text{ or } T$$

and the total amount of oxygen bound to form X, denoted here as XO_2:

$$XO_2 = \sum_{n=0}^{4} n\binom{4}{n}(K_XP)^n X_0 = 4\,K_XP\,(1 + K_XP)^3 X_0 = 4\{1 + 1/(K_XP)\}^3 X_4 \qquad X = R \text{ or } T$$

Also, a parameter is needed for the equilibrium between T and R state. Either

$$T_0 = L_0 R_0 \quad \text{or} \quad T_4 = L_4 R_4 \;\text{ - note, that } L_4 = (K_T/K_R)^4L_0.$$

Then the total amount of hemoglobin is:

$$c_{Hb,t} = \{L_0(1 + K_TP)^4 + (1 + K_RP)^4\}R_0 = [L_4\{1 + 1/(K_TP)\}^4+\{1 + 1/(K_RP)\}^4]\,R_4$$

and the total amount of bound oxygen – note, that this can be up to 4 times the total amount of Hb:

$$c_{O2Hb} = 4\{L_0K_TP(1 + K_TP)^3 + K_RP(1 + K_RP)^3\}R_0 = 4\,[L_4\{1 + 1/(K_TP)\}^3+\{1 + 1/(K_RP)\}^3]\,R_4$$

so that saturation S is:

$$S = \frac{L_0K_TP(1 + K_TP)^3 + K_RP(1 + K_RP)^3}{L_0(1 + K_TP)^4 + (1 + K_RP)^4} = \frac{L_4\{1 + 1/(K_TP)\}^3+\{1 + 1/(K_RP)\}^3}{L_4\{1 + 1/(K_TP)\}^4+\{1 + 1/(K_RP)\}^4}$$

and the desaturation 1–S:

$$1-S = \frac{L_0(1 + K_TP)^3 + (1 + K_RP)^3}{L_0(1 + K_TP)^4 + (1 + K_RP)^4} = \frac{L_4/(K_TP)\{1 + 1/(K_TP)\}^3+1/(K_RP)\{1 + 1/(K_RP)\}^3}{L_4\{1 + 1/(K_TP)\}^4+\{1 + 1/(K_RP)\}^4}$$

(†) $\binom{4}{n} = \frac{4!}{n!(4-n)!} = 1, 4, 6, 4, 1$ for $n = 0 - 4$

The definition with L_4 is useful as it was shown that the model can be fitted at a wide range of conditions by using essentially only one variable, K_T , while K_R is constant and L_4 is almost constant. Note, that the amount of 'reduced Hb' available for O_2 $c_{RedHb} = 4c_{Hb} - c_{O2Hb}$ is:

$$c_{RedHb} = \{4L_0(1 + K_TP)^3 + (1 + K_RP)^3\}R_0 = 4[L_4/(K_TP)\{1 + 1/(K_TP)\}^3 + (1/K_RP)\{1 + 1/(K_RP)\}^3]\, R_4$$

The rate parameters in the MWC model are derived similarly. Dissociation k will be from the occupied sites:

$$k\, c_{O2Hb} = k_TTO_2 + k_RRO_2 = k_T\, 4K_TP\,(1 + K_TP)^3\, T_0 + k_R\, 4K_RP\,(1 + K_RP)^3\, R_0$$

$$= 4\{L_0\, k_T\, K_TP\,(1 + K_TP)^3 + k_R\, K_RP\,(1 + K_RP)^3\}R_0$$

or $$= 4[L_4\, k_T\, \{1 + 1/(K_TP)\}^3 + k_R\, \{1 + 1/(K_RP)\}^3]R_4$$

so that – note, that $k_XK_X = k'_X$:

$$k = \frac{L_0\, k'_T\,(1 + K_TP)^3 + k'_R\,(1 + K_RP)^3}{L_0K_T(1 + K_TP)^3 + K_R(1 + K_RP)^3} = \frac{L_4\, k_T\, \{1 + 1/(K_TP)\}^3 + k_R\, \{1 + 1(K_RP)\}^3}{L_4\, \{1 + 1/(K_TP)\}^3 + \{1 + 1/(K_RP)\}^3}$$

And association will be to the unoccupied sites:

$$k'\, c_{RedHb} = k'_T(4T_t - TO_2) + k'_R(4R_t - RO_2) = k'_T\, 4\,(1 + K_TP)^3\, T_0 + k'_R\, 4\,(1 + K_RP)^3\, R_0$$

$$= 4\{L_0\, k'_T\,(1 + K_TP)^3 + k'_R\,(1 + K_RP)^3\}R_0$$

or $$= 4[L_4\, k'_T/(K_TP)\{1 + 1/(K_TP)\}^3 + k'_R/(K_RP)\{1 + 1/(K_RP)\}^3]R_4$$

so that – again using $k_X = k'_X/K_X$:

$$k' = \frac{L_0\, k'_T\,(1 + K_TP)^3 + k'_R\,(1 + K_RP)^3}{L_0(1 + K_TP)^3 + (1 + K_RP)^3} = \frac{L_4\, k_T\, \{1 + 1/(K_TP)\}^3 + k_R\, \{1 + 1(K_RP)\}^3}{(L_4/K_T)\, \{1 + 1/(K_TP)\}^3 + (1/K_R)\{1 + 1/(K_RP)\}^3}$$

leading to an 'apparent equilibrium parameter' – which of course is not constant:

$$K = k'/k = \frac{L_0\, K_T\,(1 + K_TP)^3 + K_R\,(1 + K_RP)^3}{L_0(1 + K_TP)^3 + (1 + K_RP)^3} = \frac{L_4\, \{1 + 1/(K_TP)\}^3 + \{1 + 1(K_RP)\}^3}{(L_4/K_T)\, \{1 + 1/(K_TP)\}^3 + (1/K_R)\{1 + 1/(K_RP)\}^3}$$

so that $KP(1–S) = S$ is indeed valid. Note, that the 'apparent P_{50}'= 1/K.

References:

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