Derivation of the Crick–Wyman Equation for Allosteric Proteins Defining the Difference between the Number of Binding Sites and the Hill Coefficient

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http://dx.doi.org/10.1016/j.jmb.2013.03.014
Edited by P. Wright

Abstract

In response to a 100-word footnote in the 1965 article by Monod, Wyman, and Changeux, a detailed manuscript signed by Francis Crick and Jeffries Wyman with 6000 words and 30 equations entitled “A Footnote on Allostery” circulated in 1965 among a limited group of scientists interested in allosteric interactions. This interesting and provocative document is published in this special issue for the first time. An intriguing equation in their text relates the difference between n (the number of ligand binding sites) and n′ (the Hill coefficient) to the ratio of the saturation functions Y for oligomers with n − 1 and n binding sites. A compact derivation of this equation was not provided by Crick and Wyman, but one is presented here based on a definition of Y involving the binding polynomial and its first derivative.

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In the Crick–Wyman text published in this issue, a novel equation for allosteric proteins is presented [their Eq. (16)],1 which relates the difference between n, the number of binding sites, and n′, the Hill coefficient,2 to the ratio of the ligand binding function, Y, for oligomers with n − 1 and n ligand binding sites. For the equation in question, the Crick–Wyman text states “By rather tedious algebra it can be shown that, for an oligomer made of n protomers, n′ is given by the formula”1:

\[ n-n' = (n-1) \left( \frac{Y_{n-1}}{Y_n} \right) \]  (1)

The text then adds: “One naturally suspects that there is a simple derivation of it, but we have been unable to discover it.” For this equation, Yn is defined as:

\[ Y_n = \frac{\alpha (1+\alpha)^n-1 + Lc(1+c\alpha)^n-1}{(1+\alpha)^n + L(1+c\alpha)^n} \]  (2)

and n′ is defined as:

\[ n' = \frac{d \ln \left( \frac{Y_n}{1-Y_n} \right)}{d \ln \alpha} \]  (3)

In these equations, L (the allosteric constant) is the ratio of the concentrations of the T and R states in the absence of ligand, c is the ratio of the ligand dissociation constants for the R and T states, and α is the concentration of ligand normalized to the dissociation constant of the R state.3

Crick and Wyman converted Eq. (3) directly to Eq. (4) below, but since the justification may not be immediately evident, we note that Eq. (3) can be simplified based on the relation d ln α = \frac{dα}{α} plus the relation d ln \left( \frac{Y_n}{1-Y_n} \right) = d \ln Y_n - d \ln (1-Y_n) = \frac{dY_n}{Y_n} - d\left( \frac{1-Y_n}{1-Y_n} \right) = d\frac{1}{Y_n} + \frac{1}{1-Y_n} = \frac{dY_n}{Y_n(1-Y_n)} to give:
Derivation of the Crick–Wyman Equation

\[ n' = \frac{\alpha}{\bar{Y}_n (1-\bar{Y}_n)} \left( \frac{d\bar{Y}_n}{d\alpha} \right) \quad (4) \]

A relatively compact derivation of Eq. (1) can be achieved by redefining \( \bar{Y}_n \) in terms of the binding polynomial \( P_n = (1 + \alpha)^n + L(1 + \alpha)^n \) and its first derivative \( P'_n = n(1 + \alpha)^{n-1} + Lc(1 + \alpha)^{n-1} \), following general principles described by Wyman and previously applied to allosteric interactions by Edelstein and Bardsley:

\[ \bar{Y}_n = \frac{\alpha P'_n}{nP_n} \quad (5) \]

Throughout the derivation presented here, the prime indicates differentiation with respect to \( \alpha \), with the exception of \( n' \) for the Hill coefficient, which respects the original nomenclature of Crick and Wyman but does not imply differentiation. For Eq. (5), \( P_n \) is identical with the denominator of Eq. (2) and the ratio \( P'_n/P_n \) multiplied by \( \alpha/n \) is identical with \( \bar{Y}_n \) as defined in Eq. (2). In the derivation presented below, we have elected to provide full details of the steps in order to insure that all phases can be readily followed.

With respect to Eq. (4), it is useful to note that \( 1-\bar{Y}_n \) can also be expressed in terms of \( P_n \) and \( P_{n-1} \) since:

\[ 1-\bar{Y}_n = 1- \frac{\alpha(1 + \alpha)^{n-1} + Lc(1 + \alpha)^{n-1}}{(1 + \alpha)^n + L(1 + \alpha)^n} \]

\[ = \frac{(1 + \alpha)^n + L(1 + \alpha)^n - \alpha(1 + \alpha)^{n-1} - Lc(1 + \alpha)^{n-1}}{P_n} \quad (6) \]

Rearranging the numerator of Eq. (6) and simplifying yields:

\[ 1-\bar{Y}_n = \frac{P_{n-1}}{P_n} \quad (7) \]

In addition, for Eq. (4), \( d\bar{Y}_n/da \), which we represent as \( \bar{Y}'_n \), can be expressed as:

\[ \bar{Y}'_n = \frac{1}{\bar{Y}_n} \left( 1- \frac{P_{n-1}}{P_n} \right)' = -\frac{P_{n-1}'}{P_n} \]

\[ = -\frac{P_{n-1}P'_n - P'_n P_{n-1}}{P_n^2} = -\frac{P_{n-1}'}{P_n} + \frac{P'_n P_{n-1}}{P_n^2} \quad (8) \]

The Eq. (4) for \( n' \) can therefore be recast on the basis of Eqs. (7) and (8) as:

\[ n' = \frac{\alpha}{\bar{Y}_n} \frac{1}{P_n} \left( -\frac{P_{n-1}'}{P_n} + \frac{P'_n P_{n-1}}{P_n^2} \right) \]

\[ = \frac{\alpha}{\bar{Y}_n} \left( -\frac{P_{n-1}'}{P_n} + \frac{P'_n}{P_n} \right) \quad (9) \]

Since according to Eq. (5), \( \frac{\alpha}{\bar{Y}_n} \), Eq. (9) can be transformed to yield:

\[ n' = \frac{\alpha}{\bar{Y}_n} \left( -\frac{n-1}{\alpha} \bar{Y}_{n-1} + \frac{n}{\alpha} \bar{Y}_n \right) = -(n-1) \bar{Y}_n^{-1} + n \quad (10) \]

Equation (10) is readily rearranged to give Eq. (1), thereby completing the derivation.

A related but somewhat simpler version of the derivation can also be achieved by beginning with a form of Eq. (4) for differentiation with respect to \( \log \alpha \):

\[ n' = \frac{1}{\bar{Y}_n} \frac{1}{(1-\bar{Y}_n)} \left( \frac{d\bar{Y}_n}{d \log \alpha} \right) \quad (11) \]

From the previously established relationship of Eq. (7):

\[ n' = -\frac{1}{\bar{Y}_n} \left( \frac{d \log P_{n-1}}{d \log \alpha} \right) = -\frac{1}{\bar{Y}_n} \left( \frac{d \log P_n}{d \log \alpha} \right) \quad (12) \]

Further rearrangement and application of the logarithmic form of Eq. (5), \( n \bar{Y}_n = \frac{d \log P_n}{d \log \alpha} \), yields:

\[ n' = -\frac{1}{\bar{Y}_n} \left( \frac{d \log P_{n-1}}{d \log \alpha} - \frac{d \log P_n}{d \log \alpha} \right) \]

\[ = \frac{1}{\bar{Y}_n} \left( n \bar{Y}_n \bar{Y}_{n-1} \right) \quad (13) \]

which simplifies to Eq. (10) and thereby completes the alternative derivation.

From the basic relationship of Eq. (1), it is clear that \( \bar{Y}_n = \bar{Y}_n' \) when \( n' = 1 \), or in other terms, the ligand binding function is independent of the number of binding sites, thereby reducing the binding curve to a simple rectangular hyperbola, characteristic of non-cooperative behavior. In contrast, for \( n' > 1 \), \( \bar{Y}_n \rightarrow \bar{Y}_n' \), the binding functions are sigmoidal, and the degree of cooperativity increases with the number of binding sites.

Acknowledgement

The critical suggestions by Attila Szabo for simplifying an earlier version of the derivation are gratefully acknowledged, as well as helpful comments by Marc Delarue and Marie Prevost.

Available online 19 March 2013

Keywords:
- Allostery;
- Hill coefficient;
- Cooperativity
References