Quantitative Understanding in Biology
Problem Set 3: Model Parameter Estimation

Jason Banfelder

Due: December 19th, 2017

Introduction

In class we used the Michaelis-Menten model to describe oxygen binding to myoglobin. Here we will see how this model could be derived from assuming that oxygen and myoglobin reach an equilibrium according to the simple mechanism:

$$O_2 + Mb \xleftrightarrow{k_{+1},k_{-1}} Mb(O_2)$$

We then have...

$$[Mb(O_2)] = \frac{k_{+1}}{k_{-1}}[O_2][Mb] \tag{1}$$

...or, writing the equilibrium constant in terms of the dissociation reaction...

$$[Mb(O_2)] = \frac{1}{K_1}[O_2][Mb] \tag{2}$$

Now, the fraction of myoglobin sites that are occupied is...

$$Y = \frac{[Mb(O_2)]}{[Mb] + [Mb(O_2)]} = \frac{\frac{1}{K_1}[O_2][Mb]}{[Mb] + \frac{1}{K_1}[O_2][Mb]} = \frac{[O_2]}{K_1 + [O_2]} \tag{3}$$

This looks like the Michaelis-Menten equation without the V_{max}. **Why is this appropriate here?**

Hemoglobin Data

Keener and Sneyd (*Mathematical Physiology*, 2004) give the following data for hemoglobin saturation:

P_{O_2} (mm Hg)	Percent saturation
3.08	2.21
4.61	3.59
6.77	6.08
10.15	10.50
12.31	14.09
15.38	19.34
18.77	28.45
22.77	40.33
25.85	50.00
30.15	60.50
36.00	69.89
45.23	80.11
51.69	83.98
61.85	88.95
75.38	93.37
87.08	95.86
110.5	98.07

Hemoglobin Model 1

Fit the Michaelis-Menten model to this data; evaluate and comment.

Hemoglobin Model 2

We know that hemoglobin has four binding sites. A simple model that takes this into account can be based on the equilibrium:

$$4O_2 + \mathrm{Hb} \xleftrightarrow{k_{+1},k_{-1}} \mathrm{Hb}(O_2)_4$$

Derive a model for this proposed mechanism, and fit it to the data. Comment on both the quality of the fit and the biochemical feasibility of this mechanism.

Hemoglobin Model 3

An alternative approach would be to model the system as a multi-stage equilibrium. To keep our notation compact, well write $Hb(O_2)_n$ as Hb^n, so free hemoglobin would be written as Hb^0, and fully saturated hemoglobin would be written as Hb^4.

$$\begin{aligned} O_2 + Hb^0 &\longleftrightarrow Hb^1 \\ O_2 + Hb^1 &\longleftrightarrow Hb^2 \\ O_2 + Hb^2 &\longleftrightarrow Hb^3 \\ O_2 + Hb^3 &\longleftrightarrow Hb^4 \end{aligned}$$

As a first approximation, assume that all of the binding sites are identical and independent. Derive a model for this system in terms of the dissociation equilibrium constant for a single site; fit and comment as appropriate.

Getting started: If k_+ and k_- are the rate constants for the association and dissociation at a single site, then the first equilibrium would be:

$$O_2 + Hb^0 \xleftrightarrow{4k_+,k_-} Hb^1 \tag{4}$$

The factor of four in the forward reaction rate appears because there are four available sites in Hb^0.

$$\begin{aligned} O_2 + Hb^0 &\xleftrightarrow{4k_+,k_-} Hb^1 \\ 4k_+[O_2][Hb^0] &= k_-[Hb^1] \\ \boxed{[Hb^1] &= \frac{4}{K_{eq}}[O_2][Hb^0]} \end{aligned}$$

Hemoglobin Model 4

Assume four-stage equilibrium as above, but allow the equilibrium constants to differ at each stage. Derive a model. What relationship would you expect among these constants if the model is to exhibit positive cooperativity? Fit your model to the data and (you guessed it) comment.

Hemoglobin Model 5a and 5b

In class we also used the more empirical Hill model. For our system, this would be:

$$Y = \frac{[\mathrm{O_2}]^n}{K^n + [\mathrm{O_2}]^n} \tag{5}$$

Fit a Hill model to the data. Do this twice, once using linear regression of an appropriately transformed system, and once using non-linear regression. As usual, comment.

Model Comparison

Compare the models developed above. Is it appropriate to use an F-test to compare these models?

Which one do you think is best, and why?

Challenge (optional)

Determine the 95% confidence envelope for the Hill model's parameters using the F-test method.

Logistics

For your derivations, feel free to write (neatly!) by hand, and scan as a PDF.

Submit your response as an Rmd file (and supplemental scanned PDF with derivations) by 11:59pm Tuesday, 19 December 2017. You must work in groups of four or five, with a single submission per group.

Further Reading

For a more contemporary approach to modeling these systems, you can read about the Monod-Wyman-Changeux (MWC) model.

