

# Quantitative Understanding in Biology

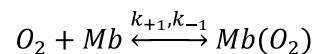
## Module II: Model Parameter Estimation

### Computer Laboratory

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#### 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:



We then have...

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

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

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

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

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

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:

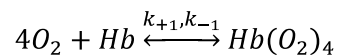
$P_{O_2}$ (mm Hg)	Percent saturation
3.08	2.21
4.61	3.59
6.77	6.08
10.15	10.50
12.31	14.09
15.38	19.34
18.77	28.45
22.77	40.33
25.85	50.00
30.15	60.50
36.00	69.89
45.23	80.11
51.69	83.98
61.85	88.95
75.38	93.37
87.08	95.86
110.5	98.07

### Hemoglobin Model 1

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

### Hemoglobin Model 2

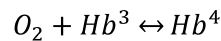
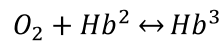
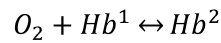
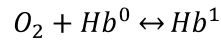
We know that hemoglobin has four binding sites. A simple model that takes this into account can be based on the simple equilibrium:



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.

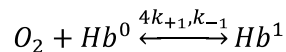
### Hemoglobin Model 3

An alternative approach would be to model the system as a multi-stage equilibrium. To keep our notation compact, we'll write  $\text{Hb}(\text{O}_2)_n$  as  $\text{Hb}^n$ , so free hemoglobin would be written as  $\text{Hb}^0$ , and fully saturated hemoglobin would be written as  $\text{Hb}^4$ .



**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.**

*Hint: If  $k_{+1}$  and  $k_{-1}$  are the rate constants for the association and dissociation at a single site, then the first equilibrium would be:*



*The factor of four in the forward reaction rate appears because there are four available sites in  $\text{Hb}^0$ .*

### 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

$$Y = \frac{[\text{O}_2]^n}{K_1 + [\text{O}_2]^n}$$

**Fit a Hill model to this 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.

## Further Reading

Read about the Monod-Wyman-Changeux (MWC) model.