A Simple Chemical Kinetic Model for Facilitated Diffusion

APPLIED MATHEMATICS
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Introduction

Facilitated diffusion is now one of the established mechanisms by which oxygen and carbon monoxide are transported in muscle respiration, with the role of the facilitating protein filled by hemoglobin and/or myoglobin. Mathematical models based on reaction diffusion equations were proposed and approximate solutions were studied analytically and numerically by several authors in the 1960's and 1970's [3, 7, 4, 2]. Solutions to the reaction-diffusion models provide a good qualitative match with the experimental results, but the mathematical models are missing a simple but profound insight into the mechanism of the facilitation.

> "How could a fly hope to increase his rate of progress by alighting on the back of a tortoise?"
>
> **- J. Wyman, 1966** [7]

Mathematical Model

We will model a one dimensional system in which oxygen and a carrier molecule are present in solution using the set of reversible reactions seen below. (A schematic diagram of the system can be seen under the title of this poster.)

$$S \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} P, \quad E + S \overset{K_2}{\rightleftharpoons} ES, \quad \widetilde{E} + P \overset{K_3}{\rightleftharpoons} \widetilde{E}P, \quad ES \underset{k_{-4}}{\overset{k_{+4}}{\rightleftharpoons}} \widetilde{E}P, \quad E \underset{k_{-5}}{\overset{k_{+5}}{\rightleftharpoons}} \widetilde{E}.$$

Note that S and P represent the free oxygen at $x = 0$ and $x = L$ respectively. Similarly, E and $\widetilde{E}$ represent the carrier molecules while ES and $\widetilde{E}P$ represent the oxygen-carrier complex at $x = 0$ or $x = L$.

$$\begin{aligned}
\frac{dc_E}{dt} &= k_{-2}c_{ES} + k_{-5}c_{\widetilde{E}} - (k_{+2}c_S + k_{+5})\,c_E, & c_E(0) &= e_0 \\
\frac{dc_S}{dt} &= k_{-1}c_P + k_{-2}c_{ES} - (k_{+2}c_E + k_{+1})\,c_S, & c_S(0) &= s_0 \\
\frac{dc_{ES}}{dt} &= k_{+2}c_E c_S + k_{-4}c_{\widetilde{E}P} - (k_{-2} + k_{+4})\,c_{ES}, & c_{ES}(0) &= 0 \\
\frac{dc_{\widetilde{E}P}}{dt} &= k_{+4}c_{ES} + k_{+3}c_P c_{\widetilde{E}} - (k_{-4} + k_{-3})\,c_{\widetilde{E}P}, & c_{\widetilde{E}P}(0) &= 0 \\
\frac{dc_P}{dt} &= k_{-3}c_{\widetilde{E}P} + k_{+1}c_S - \left(k_{+3}c_{\widetilde{E}} + k_{-1}\right)c_P, & c_P(0) &= p_0 \\
\frac{dc_{\widetilde{E}}}{dt} &= k_{+5}c_E + k_{-3}c_{\widetilde{E}P} - (k_{+3}c_P + k_{-5})\,c_{\widetilde{E}}, & c_{\widetilde{E}}(0) &= \widetilde{e}_0
\end{aligned}$$

By the law of mass action, the system is governed by the previous set of six ordinary differential equations with initial conditions, where c_X respresents the concentration of reactant X. We will assume, as in classical Michaelis-Menten analysis, that the association-dissociation reactions are rapid, so that

$$c_{ES} = K_2 c_E c_S, \quad c_{\widetilde{E}P} = K_3 c_{\widetilde{E}} c_P.$$

Define the total oxygen flux to be

$$\frac{dc_P^t}{dt} = \frac{dc_P}{dt} + \frac{dc_{\widetilde{E}P}}{dt}.$$

Results

We discover that the kinetics of the system can be significantly different depending on whether the system is closed or open. In Gibbs' statistical mechanics, these are known as canonical and grand canonical ensembles, respectively.

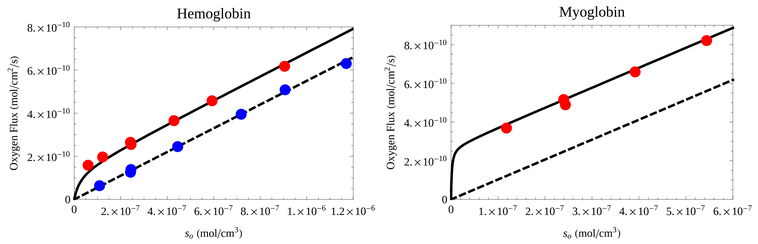

Figure 1: Total Oxygen flux *vs* s_0 (Grand Canonical Scenario). The solid curves show the total flux in the presence of the carrier molecule, while the dashed curves show the flux if the carrier was not present. Results are compared with Wittenberg's data [5].

Canonical Scenario: $\mathbf{c_S^t = s_0,\ c_P^t = p_0}$

We immediately see that the total oxygen flux in the canonical scenario is zero since

$$c_P^t = c_{\widetilde{E}P} + c_P = p_0.$$

Grand Canonical Scenario: $\mathbf{c_S = s_0,\ c_P = p_0}$

In the special case where $k_{\pm 4} = k_{\pm 5}$ and $K_2 = K_3$, which is the system of interest for facilitated diffusion, we obtain the following expression for the total oxygen flux.

$$\frac{dc_P^t}{dt} = \left(1 + \frac{k_{-4}k_{+4}K_2 e_0^t}{k_{-1}\left(k_{-4}(1 + K_2 s_0) + k_{+4}(1 + K_2 p_0)\right)}\right)\left(k_{+1}s_0 - k_{-1}p_0\right)$$

The presence of the enzyme increases the total oxygen flux *for any values of the rate constants*. In other words, for the grand canonical scenario, enhancement is guaranteed as long as the enzyme is present in the system initially.

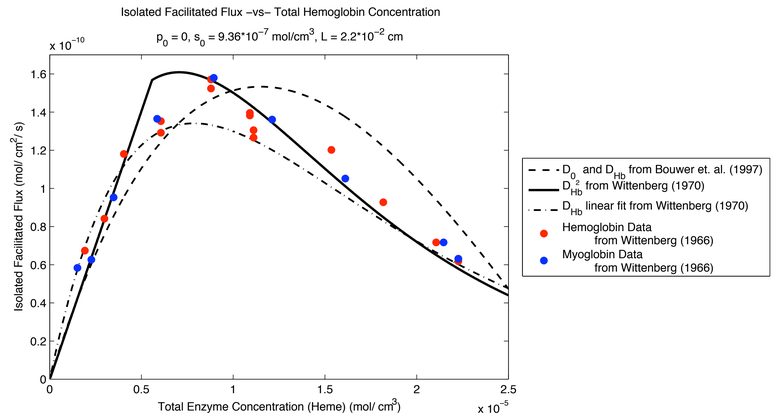

Figure 2: Facilitated Flux -vs- e_0^t (Grand Canonical Scenario). Values from different sources were used for the diffusion constant of hemoglobin, D_{Hb}, which is itself a function of e_0^t [1, 6]. Numerical results are compared with Wittenberg's experimental data [5].

Conclusions

Our simple model shows excellent qualitative and quantitative agreement with established experimental results.

We see that the true cause of the enhanced diffusion is that the system is open with respect to free oxygen.

References

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