THE FACILITATED DIFFUSION OF OXYGEN
BY HEMOGLOBIN AND MYOGLOBIN

S. I. RUBINOW AND M. DEMBO, *Biomathematics Division, Graduate School of
Medical Sciences, Cornell University, and Memorial Sloan-Kettering
Cancer Center, New York 10021*

ABSTRACT   We have clarified the use of Wyman's differential equation for the
facilitated oxygen flux through a slab of solution of myoglobin or hemoglobin by
showing that there is a unique choice of boundary condition on the carrier concentra-
tion to be employed in conjunction with it.   The singular perturbation solution of
Wyman's equation, due to Murray, and Mitchell and Murray, has been extended.   By
means of it, the paradox of Wittenberg, that the facilitated oxygen flux per mole of
heme is apparently independent of the protein carrier, has been resolved.

INTRODUCTION

The phenomenon of facilitated diffusion exhibited by solutions of hemoglobin and
myoglobin was discovered by Wittenberg (1) and independently by Scholander (2).
An excellent and comprehensive review of the facilitated diffusion of oxygen by myo-
globin can be found elsewhere (3).   Wittenberg (4) presented extensive quantitative
data showing the dependence of the facilitated flux on the initial concentration of the
carrier molecule placed in solution, whether hemoglobin or myoglobin.   A principal
result of his work was to display the dependence of the facilitated flux on the total
concentration of heme groups of the carrier molecules.   It was observed that the experi-
mental points appeared to lie on a single curve, regardless of whether the heme was in
the hemoglobin or myoglobin.   The fact that the facilitated flux per mole of heme
increases initially to a maximum and then decreases was explained qualitatively as a
decrease of the diffusion coefficient of the carrier molecule with increasing carrier con-
centration.   However, the deeper puzzle contained in Wittenberg's results, hitherto
unexplained on theoretical grounds, is why hemoglobin and myoglobin, having
markedly different reaction rates for combining with oxygen and different transla-
tional diffusion constants, should behave so similarly (per oxygen combining site) in
facilitating the flux of oxygen through a solution. This paradox of the data was clearly
expounded by Wittenberg himself (3).

We have solved the differential equation of Wyman (5) governing the concentration
of oxygen in a slab of solution containing protein carrier molecules, by the method of
singular perturbation theory.   In doing so we follow Murray (6) and extend the work
of Mitchell and Murray (7).   With the aid of the solution, we show that the paradox
of Wittenberg is only apparent and is due to a combination of circumstances.   First,
the theoretically predicted oxygen flux through a slab of myoglobin solution is very

close to that through a slab of hemoglobin solution. That is so because the advantage myoglobin possesses in being able to diffuse faster than the heavier hemoglobin is to a large extent offset by the fact that oxygen leaves the myoglobin less readily than it leaves hemoglobin, on the low pressure side of the slab. Second, the measured facilitated oxygen currents at large myoglobin concentrations were systematically underestimated, because of the autoxidation of myoglobin occurring during the experiments.

FORMULATION

Our starting point is the steady-state reaction-diffusion equation for oxygen concentration $c(x)$ in a slab $0 < x < 1$ containing a carrier molecule (see Rubinow, 8).

$$D(\mathrm{d}^2c/\mathrm{d}x^2) = k_+ h_0 c + (1/D_p)(k_+ c + k_-)(Dc - A + jx). \quad (1)$$

Here D is the translational diffusion constant of oxygen, k_+ and k_- are the forward and back reaction rates of the reaction oxygen + carrier $\rightleftharpoons$ oxy-carrier, h_0 is the total initial concentration of carrier, D_p is the translational diffusion constant of the carrier protein, and A and j are constants of integration to be determined. The boundary conditions satisfied by $c(x)$ are that

$$c(0) = c_0, \quad c(l) = c_l, \quad -D(\mathrm{d}c/\mathrm{d}x)_{x=0} = -D(\mathrm{d}c/\mathrm{d}x)_{x=l} = j. \quad (2)$$

Note that j represents the steady-state current density of the oxygen flux. The carrier concentration in the slab $h(x)$, which is the heme group concentration, and the concentration $y(x)$ of the oxygen-carrier complex are related to c by means of the equations

$$Dc + D_p y = A - jx, \quad (3)$$

$$h + y = h_0. \quad (4)$$

Hence, it can be seen from Eq. 3 that the boundary conditions on $\mathrm{d}c/\mathrm{d}x$ in Eq. 2 are a consequence of the condition that the carrier molecules are constrained to the slab, i.e., that $\mathrm{d}y/\mathrm{d}x$ and $\mathrm{d}h/\mathrm{d}x$ must vanish at the boundaries.

Eq. 1 is the same as the equation of Wyman (5), and can be recognized as such explicitly if we replace A and j by the expressions

$$A = Dc_0 + D_p y_0, \quad (5a)$$

and

$$j = \frac{1}{l}[D(c_0 - c_l) + D_p(y_0 - y_l)], \quad (5b)$$

where $y_0 = y(0)$ and $y_l = y(l)$. These relations follow directly from Eq. 3, evaluated at the boundaries.

We stress here that the abovementioned derivation of Eq. 1 shows that Wyman's equation is consistent only with the boundary conditions given in Eq. 2. Indeed, if it were assumed instead that h and y were prescribed at the boundaries, then the right-hand side of Eq. 4 would contain a term linear in x, and the same linear term would also appear added to

	k_+	k_-	α^*
	$M^{-1}s^{-1}$	s^{-1}	
Hemoglobin	2.85×10^6	40	0.081
Myoglobin	14×10^6	11	0.0044

$A = 11.5 \, cm^2$; Millipore thickness = 1.50×10^{-2} cm; σ at 20°C = 1.8×10^{-3} mM/torr (from Sendroy et al. [15]); $\rho = 0.79$.
*Corresponding to $p_0 = 100$ torr.

h_0 in Eq. 1. These comments should serve to settle the apparent controversy that has arisen in the literature (9–12) regarding the proper choice of boundary conditions. Hence, the quantity $y_0 - y_l$ appearing in Wyman's form of Eq. 1 is a quantity to be determined from j in accordance with Eq. 5b, and one that can not be initially prescribed.

To solve Eq. 1, we introduce the nondimensional variables and parameters,

$$x/l = x', \quad c/c_0 = c', \quad c_l/c_0 = c_1, \quad k_-/k_+c_0 = \alpha, \quad D_p h_0/Dc_0 = \beta,$$

$$D_p/k_+ c_0 l^2 = \epsilon, \quad A/Dc_0 = A', \quad jl/Dc_0 = j', \tag{6}$$

and drop the primes. Then Eq. 1 becomes

$$\epsilon(d^2c/dx^2) = \beta c + (c + \alpha)(c - A + jx), \quad 0 < x < 1, \tag{7}$$

subject to the boundary conditions

$$c(0) = 1, \qquad c(1) = c_1,$$

$$(dc/dx)_{x=0} = (dc/dx)_{x=1} = -j. \tag{8}$$

Eq. 7 shows that there are only three intrinsic nondimensional parameters to the problem, α, β, and ϵ, a useful simplification both for understanding and for computation.

The values of some of the dimensional parameters for hemoglobin and myoglobin, as suggested by Wittenberg (3), are shown in Table I, together with the inferred value of α. The values of β and ϵ depend on D and D_p and are therefore dependent on the concentration of protein. Hence, these parameters change as h_0 changes, as shown by Wittenberg and Riveros-Moreno (3, 13). From the curves given there, it can be seen that typical values are $D \sim 10^{-5}$ $cm^2 \, s^{-1}$ and $D_p \sim 5 \times 10^{-7} \, cm^2 \, s^{-1}$, so that $\beta \sim 2$ and $\epsilon \sim 10^{-6}$ for both hemoglobin and myoglobin. Because ϵ, a very small quantity, is the coefficient of the highest derivative term in Eq. 7, solving the latter equation may be treated as a singular perturbation problem (6).

DISCUSSION OF SOLUTION

The derivation of the singular perturbation solution to Eqs. 7 and 8 is given in the Appendix. It depends on the assumptions that $\epsilon \ll 1$, and that α and β are $O(1)$ with respect to ϵ. The uniformly valid approximation to the exact solution is given to order ϵ as

$$c(x) = c^{(0)}(x) + \epsilon^{1/2}\Big\{c^{(1)}(x) + \tilde{c}^{(1)}(\xi) + \bar{c}^{(1)}(\eta)$$

$$+ [(1 + \alpha)j^{(0)}/\gamma^3]\left[\frac{\alpha\beta}{(1 + \alpha)^2} + \gamma\xi\right] - [(c_1 + \alpha)j^{(0)}/\delta^3]\left[\frac{\alpha\beta}{(c + \alpha)^2} + \delta\eta\right]\Big\}$$

$$+ \epsilon\Big\{c^{(2)}(x) + \tilde{c}^{(2)}(\xi) + \bar{c}^{(2)}(\eta) - [(1 + \alpha)/\delta^2]\Big[A^{(2)} - j^{(1)}\xi$$

$$+ \frac{(j^{(0)})^2\alpha\beta}{(1 + \alpha)^2\gamma^6}\Big(2(1 + \alpha) + a^2\beta^2/(1 + \alpha)^3 + 2\alpha\beta\gamma\xi/(1 + \alpha)$$

$$+ (1 + \alpha)(\gamma\xi)^2\Big)\Big] -[(c_1 + \alpha)/\delta^2]\Big[A^{(2)} - j^{(2)} + j^{(1)}\eta$$

$$+ \frac{(j^{(0)})^2\alpha\beta}{(c_1 + \alpha)^2\delta^6}\Big(2(c_1 + \alpha) + \alpha^2\beta^2/(c_1 + \alpha)^3 + \frac{2\alpha\beta}{c_1 + \alpha}\delta\eta$$

$$+ (c_1 + \alpha)(\delta\eta)^2\Big)\Big]\Big\}\Big\} + O(\epsilon^{3/2}), \tag{9}$$

where the quantities on the right are all defined by Eqs. A3, A4, A7–A11, and A14–A19 of the Appendix. The first term on the right, $c^{(0)}(x)$, was obtained by Murray (6). The first two terms of the related expansion of $y(x)$, obtainable from Eq. 9 by means of Eq. 3, were given by Mitchell and Murray (7).

The importance of the boundary layer contributions in the neighborhood of the boundaries is illustrated in Fig. 1, which shows $c(x)$ to orders unity, $\epsilon^{1/2}$, and ϵ, as a function of the "stretched" distance coordinate $\eta = (1 - x/l)\epsilon^{-1/2}$ in the boundary layer associated with the low pressure side of the slab. For Fig. 1, numerical values of the parameters were chosen appropriate to myoglobin, and it was assumed that $c_1 = 0$. With $l \sim 2.4 \times 10^{-2}$ cm, the width of the boundary layer is seen from the figure to be about $2.5\ \epsilon^{1/2}\ l \sim 6 \times 10^{-5}$ cm, and is quite small. Nevertheless, even for hemoglobin, this width represents about 100 times the molecular diameter, 60 Å (Perutz et al., 14).

We note that there is a significant change in slope at the boundary, and indeed in the oxygen concentration in the boundary layer, when the contribution of order ϵ is included. In view of the smallness of ϵ, this surprising result occurs both because c_1 is zero on the low pressure side and because α is significantly smaller for myoglobin than for hemoglobin (see Table I). Mathematically, we find that there are terms of order $(c_1 + \alpha)^{-1}$ appearing in $\bar{c}^{(1)}(\eta)$ and terms of order $(c_1 + \alpha)^{-2}$ appearing in $\bar{c}^{(2)}(\eta)$ (see Eqs. A14 and A17). Consequently, when $c_1 = 0$, the relevant measure of importance of these terms is $\epsilon^{1/2}/\alpha$ and ϵ/α^2. For hemoglobin, we see from the Table that, with $\epsilon = 10^{-6}$, $\epsilon^{1/2}/\alpha \sim 0.01$, which is negligible. That is why the zero-order solution is adequate to represent the experimental results for it. For myoglobin, by contrast, $\epsilon^{1/2}/\alpha \sim 0.2$, so that it is necessary to utilize the full expression given by Eq. 9.
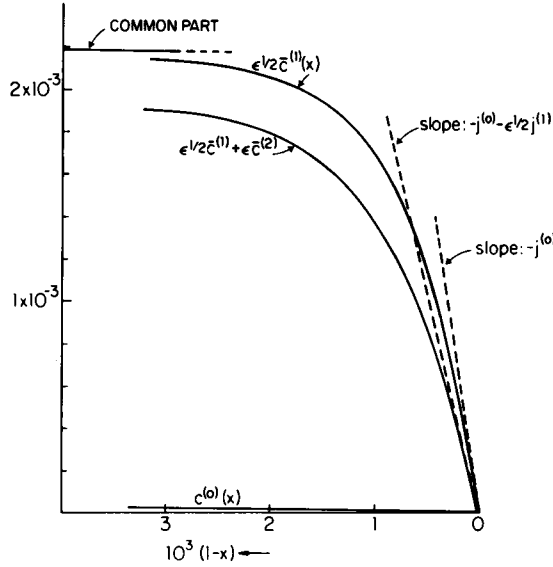
FIGURE 1 The oxygen concentration in the boundary layer associated with the low pressure side of a slab of myoglobin solution to orders unity, $\epsilon^{1/2}$, and ϵ, based on Eq. 9, with $\bar{c}_i = 0$, $\alpha = 0.5 \times 10^{-2}$, and $\beta = 2.3$. The abscissa represents the stretched coordinate distance $\eta = (1 - x/l)\epsilon^{-1/2}$. The order $\epsilon^{1/2}$ concentration function is asymptotic to the line labeled "common part."

The facilitated current density found simultaneously with the solution (Eq. 9) is given by Eq. A20. The nonfacilitated flux is readily recognized to be, in nondimensional variables, the quantity $1 - c_1$. Hence, the facilitated current density is $j_F = j - (1 - c_1)$, or, from Eq. A20,

$$
\begin{aligned}
j_F = {} & (1 - c_1)\alpha\beta/(1 + \alpha)(c_1 + \alpha) + (1 - c_1)[1 + \alpha\beta/(1 + \alpha)(c_1 + \alpha)] \\
& \times \{-\epsilon^{1/2}\alpha\beta[1/\gamma(1 + \alpha)^2 + 1/\delta(c_1 + \alpha)^2] \\
& + \epsilon(\alpha^2\beta^2[1/\gamma(1 + \alpha)^2 + 1/\delta(c_1 + \alpha)^2] \\
& + (1 - c_1)[1 + \alpha\beta/(1 + \alpha)(c_1 + \alpha)][1/12\gamma^4 + 5(1 + \alpha)/6\gamma^2 \\
& - 5/12\gamma^2(1 + \alpha) - 1/2(1 + \alpha)^2 - 1/12\delta^4 - 5(c_1 + \alpha)/6\delta^6 \\
& + 5/12\delta^2(c_1 + \alpha) + 1/2(c_1 + \alpha)^2])\} + O(\epsilon^{3/2}).
\end{aligned}
\tag{10}
$$

When c_1 is $O(1)$, or when c_1 is zero and $\epsilon^{1/2}/\alpha$ is small, the terms above in $\epsilon^{1/2}$ and ϵ are negligible, and the facilitated flux reduces to the first term on the right, or, expressed dimensionally,

$$
j_F = \frac{(c_0 - c_l)}{l} D_p h_0 K/(c_0 + K)(c_l + K),
\tag{11}
$$

where $K \equiv k_-/k_+$ is the dissociation constant of the reaction. This expression was given by Murray (6), and is in satisfactory agreement with observations of hemoglobin.

The first two terms of Eq. 10 (through the order $\epsilon^{1/2}$ term) were given by Mitchell and Murray (7).

When $c_1 = 0$ and $\epsilon^{1/2}/\alpha$ is not too small, then Eq. 10 can be written as

$$j_F \doteq \beta/(1 + \alpha) + [1 + \beta/(1 + \alpha)]\{- \epsilon^{1/2}\beta/\delta\alpha + \epsilon/2\alpha^2[1 + \beta/(1 + \alpha)]\}. \quad (12)$$

We can anticipate that the correction term to the above expression is $O(\epsilon^{3/2}/\alpha^3)$. In terms of dimensional quantities, Eq. 12 assumes the form

$$j_F \doteq D_p h_0 c_0 / l(c_0 + K) + D_p D c_0 / l^2 K [1 + D_p h_0 / D(c_0 + K)]$$
$$\times \{- h_0 / D[DD_p/k_+(DK + D_p h_0)]^{1/2} + c_0/2lk_+ K[1 + D_p h_0 / D(c_0 + K)]\}. \quad (13)$$

From either of the above two expressions for j_F we can recognize the biophysical significance of the additional terms of order $\epsilon^{1/2}$ and ϵ appearing in it. These terms represent a net negative contribution to the facilitated flux that is significant when K/c_0 is small. In other words, the relative inability of O_2 molecules to leave the oxy-carrier complex rather than join it, as represented by a smaller value of K, leads to a reduction in facilitation. For hemoglobin, this reduction is insignificant. For myoglobin, for which K is about 20 times smaller than it is for hemoglobin, the reduction is important. Speaking generally, we can say that facilitated diffusion requires that $\alpha \gg \epsilon$, and it is obvious that there can be no facilitation when $\alpha = 0$, as then the ligand does not get off the carrier.

We are now in a position to comment on some of the previous mathematical efforts to resolve the Wittenberg paradox. Murray (6) was primarily concerned with the exploitation of Eq. 5b. Mitchell and Murray (7) reconsidered the singular perturbation solution using the proper coundary conditions, and could have resolved in large part the paradox of Wittenberg, but they did not exploit the further consequences of their results.

Kreuzer and Hoofd (9) employed a semi-analytical approach and solved Wyman's equation numerically, utilizing the physically correct conditions (Eq. 2). When these authors considered the case of myoglobin, they too found that the calculated facilitated flux was almost double the experimental value (10). Kreuzer and Hoofd's assumed form of the solution in the boundary layers is equivalent to the solution (Eq. 9) to order $\epsilon^{1/2}$. However, j was determined from the gradient of the solution evaluated at a boundary point. Hence, as we see from Eq. A5 with $n = 1$, they only determined j to zero order, i.e., $j^{(0)}$.

COMPARISON WITH WITTENBERG'S WORK

The total facilitated current of O_2 through the Millipore membrane, J_F, in microliters per minute is given in terms of the facilitated current density as

$$J_F = \rho A j_F, \quad (14)$$

where A is the cross-sectional area and ρ the porosity, or fractional volume occupied by

pores, of the Millipore membrane. Hence, ρA is the area of the membrane available for diffusion. Because J_F was measured as a function of pressure, comparison of the theoretical expression (Eq. 14) with experiment requires the conversion of the concentration appearing in j_F to pressure by means of Henry's law, $c_{0,l} = \sigma p_{0,l}$, where σ is the solubility constant. Similarly, the nonfacilitated oxygen current J_N is

$$J_N = \frac{\rho A \sigma (p_0 - p_l)}{l} D. \tag{15}$$

Here l is to be interpreted as the length of a pore, which is greater than the thickness of the Millipore membrane, due to pore tortuosity. The values of ρ and A were reported by Wittenberg (4) (see Table I), D is given in ref. 3 (see also 9), and σ is known from the work of Sendroy et al. (15). Consequently, Eq. 15 may be used to determine l from measurements of J_N versus $(p_0 - p_l)$. We have adopted the value $l = 2.45 \times 10^{-2}$ cm, based on the slope of Fig. 1 of Wittenberg (4), in which J_N for a solution of ferric hemoglobin is reported. Thus, all the parameters of the problem are completely determined. This same value of l was also utilized for the case of myoglobin.

In Fig. 2 we show the predicted nonfacilitated flux J_N and the total flux, $J_N + J_F$, as a function of oxygen partial pressure p_0, when hemoglobin is the carrier. In obtaining J_F from Eq. 10, we have set $c_1 = 0$. Note that for $p_0 \geq 100$ torr, the curve for J_F is a straight line with the same slope as that for J_N, just as in the experimental curves of Fig. 1. This is a consequence of the fact that the terms in $\epsilon^{1/2}$ and ϵ in Eq. 10 are
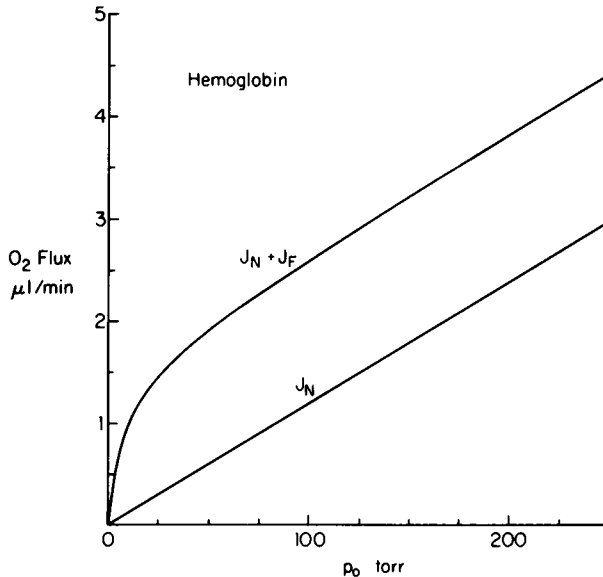

FIGURE 2   Nonfacilitated flux J_N and total flux $J_N + J_F$ through a slab of hemoglobin solution are shown as a function of oxygen partial pressure p_0, based on Eqs. 10, 14, and 15; $c_1 = 0$, $h_0 = 10$ mM, and other parameters as in the Table.
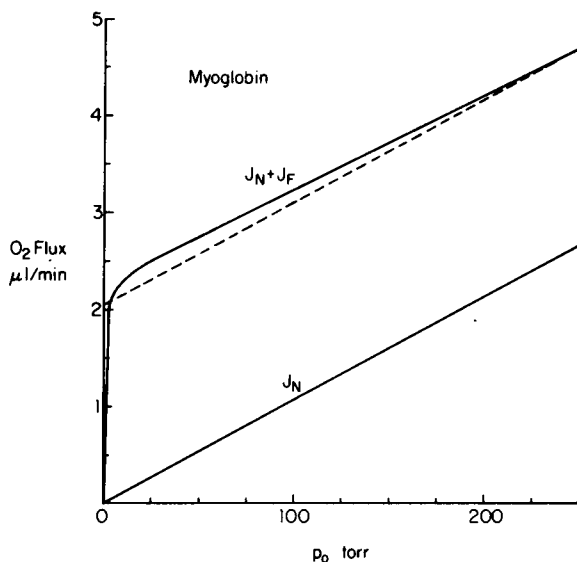
FIGURE 3 J_N and $J_N + J_F$ through a slab of myoglobin as a function of p_0, based on Eqs. 10, 14, and 15; $c_1 = 0$, $h_0 = 10$ mM, and other parameters as in the Table. The dashed line has been drawn parallel to J_N.

negligible, so that the facilitated flux is essentially determined by the expression given in Eq. 11, which is independent of p_0 when p_0 is large.

By contrast, the theoretical curves for J_N and $J_N + J_F$ are not parallel for the case of myoglobin as carrier, as shown in Fig. 3. Because of the importance of the higher order terms, there is here no unambiguous definition of facilitated flux, independent of the value of p_0. We remark that the two curves must ultimately converge for p_0 (and hence c_0) $\rightarrow \infty$, because ϵ, α, and β all vanish in this limit. We have seen previously that facilitation disappears if α vanishes. An important cautionary note is that Eq. 10 can not be used to determine the flux if p_0 becomes very large: it is known that the error involved in utilizing an asymptotic sequence is of the order of the last term in the sequence, and it can be seen from Eq. 12 that as c_0 approaches infinity, the term of order ϵ increases without limit. This property can be anticipated if we recall that, in the derivation of the solution (see Appendix), α is assumed to be $O(1)$ with respect to $\epsilon^{1/2}$, and since $\epsilon^{1/2}/\alpha$ is $O(c_0^{1/2})$, this condition is clearly violated for c_0 sufficiently large.

In determining experimentally the facilitated flux for myoglobin, Wittenberg defined J_F as the intercept with the ordinate scale of the slope of the curve for $J_N + J_F$ at high values of p_0. While this is a convenient approximation for hemoglobin, it is not so for myoglobin, and it is desirable that future observations of the facilitated flux of myoglobin should indicate the value of p_0 at which the observations are made.

Using Eq. 10, we have calculated the facilitated flux defined at $p_0 = 300$ torr, as a function of heme concentration h_0, inserting for D and D_p the values obtained from
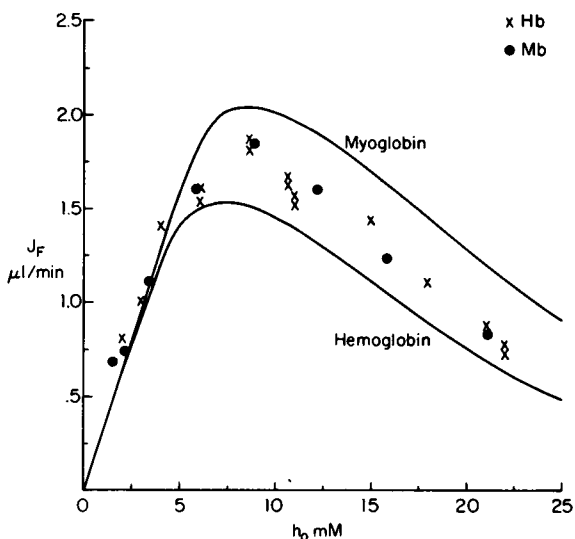
FIGURE 4 The solid curves represent the facilitated flux J_F through a slab of hemoglobin solution or myoglobin solution, and are shown as functions of the heme concentration h_0, based on Eqs. 10 and 14; $c_1 = 0$, $p_0 = 300$ torr, and other parameters are as in the Table. The experimental observations of Wittenberg (4) are superposed.

the smoothed representation of the data given in refs. 3 and 13. The results both for hemoglobin and myoglobin are shown in Fig. 4, with the experimental observations of Wittenberg superposed. Note that there are two distinct theoretical curves that, although virtually identical at small values of h_0, are distinct and different at large values of h_0, when the higher order terms in j_F, linear in h_0, are more significant (see Eq. 13). It is important to realize that we have made no adjustments in parameters to fit the theoretical curves to the experimental data, which we could easily do. For example, by increasing the value of $\rho A \sigma / l$ assigned to hemoglobin, the theoretical curve for it is raised, so that an excellent fit to the data is obtained. By deliberately choosing $\rho A \sigma / l$ to accord to the one observation available for determining it, we are emphasizing that there are still uncertainties in observation of the parameters entering the theory, so that a perfect fit with the data cannot yet be expected. By the same token, if a different value of l were assigned to the Millipore membrane utilized in the myoglobin experiments, the theoretical curve for myoglobin of Fig. 4 could be lowered. Furthermore, Wittenberg reported that at the end of each experiment, from 10 to 25% of the myoglobin was rendered incapable of reacting with oxygen because of conversion to the ferric state. This strongly suggests that, under ideal conditions, the experimentally observed oxygen currents for myoglobin in Fig. 4 would be larger, and in better agreement with the theory.

In Fig. 5 the facilitated oxygen current J_F is displayed as a function of the product $D_p h_0$. The motivation for such a presentation of the data arises from Eq. 5b and the replacement of $y_0 - y_l$ there by $h_0(Y_0 - Y_l)$, where Y represents the saturation function, or fraction of carrier sites bound to ligand molecules. The simplistic as-
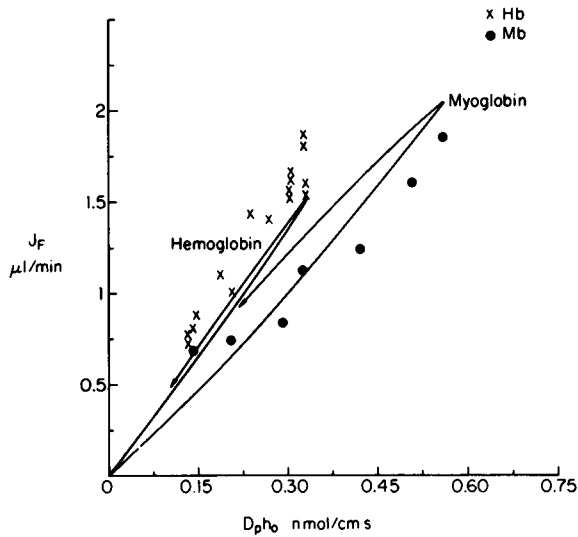
FIGURE 5   The same functions and data as in Fig. 4, with the abscissa changed to $h_0 D_p$. The arrowheads on the theoretical curves represent the direction of increasing h_0.

sumption that local reaction equilibrium is established between ligand and carrier, or nearly so, leads to the conclusion that $Y_0 \sim 1$, $Y_l \sim 0$, and $Y_0 - Y_l$ is constant, so that the resulting plot of J_F versus $D_p h_0$ should be linear. The figure shows that the relationship between these quantities is indeed approximately linear, but the "slope" is not the same for hemoglobin and myoglobin, as the zero-order theory for j_F, Eq. 11, incorrectly predicts. As seen from the figure, the theoretical curves based on Eq. 14 are distinct and not straight lines, even for the case of hemoglobin, because of the higher order terms resulting from Eq. 10. The arrowheads on the theoretical curves indicate the direction of increasing h_0. If the result is viewed in terms of the saturation function, we see from Eq. 3 that $y_0 = (A - Dc_0)/D_p$ and $y_l = (A - j)/D_p$. Hence, the major difference in $Y_0 - Y_l$ between myoglobin and hemoglobin occurs because Y_l is larger for myoglobin than for hemoglobin, as suggested previously by B. Wittenberg.[1]

We conclude that the theory of facilitated diffusion, based on the singular perturbation solution of Wyman's equations, satisfactorily describes the experimental observations of facilitated oxygen transport through slabs of hemoglobin and myoglobin solutions.

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[1]Wittenberg, B. 1968. Personal communication to J. D. Murray.

APPENDIX: SINGULAR PERTURBATION SOLUTION

We present here an asymptotic solution of Eq. 7 by singular perturbation methods (see Cole, 16). Thus, we assume for the outer solution, valid in the interior region of the solution and away from the boundaries, the expansions

$$c(x) = \sum_{n=0}^{\infty} c^{(n)}(x)\epsilon^{n/2}, \quad A = \sum_{n=0}^{\infty} A^{(n)}\epsilon^{n/2}, \quad j = \sum_{n=0}^{\infty} j^{(n)}\epsilon^{n/2}. \quad (A1)$$

By substituting these expressions into Eq. 7 and equating the coefficients of $\epsilon^{n/2}$ to zero, we obtain the following equations for the first three powers of $\epsilon^{1/2}$, as much of the expansion as we need to obtain.

$$\epsilon^0: 0 = \beta c^{(0)} + (c^{(0)} + \alpha)(c^{(0)} - A^{(0)} + j^{(0)}x),$$

$$\epsilon^{1/2}: 0 = \beta c^{(1)} + (c^{(0)} + \alpha)(c^{(1)} - A^{(1)} + j^{(1)}x)$$
$$+ c^{(1)}(c^{(0)} - A^{(0)} + j^{(0)}x),$$

$$\epsilon^1: [d^2 c^{(0)}/dx^2] = \beta c^{(2)} + (c^{(0)} + \alpha)(c^{(2)} - A^{(2)} + j^{(2)}x)$$
$$+ c^{(1)}(c^{(1)} - A^{(1)} + j^{(1)}x) + c^{(2)}(c^{(0)} - A^{(0)} + j^{(0)}x). \quad (A2)$$

Thus, the functions $c^{(n)}(x)$, comprising the outer expansion of $c(x)$, are expressible recursively as solutions of algebraic equations, e.g.,

$$c^{(0)} = \tfrac{1}{2}(A^{(0)} - j^{(0)}x - \alpha - \beta) + [\tfrac{1}{4}(A^{(0)} - j^{(0)}x - \alpha - \beta)^2 + \alpha(A^{(0)} - j^{(0)}x)]^{1/2},$$

$$c^{(1)} = [c^{(0)} + \alpha][A^{(1)} - j^{(1)}x]/[\alpha + \beta + 2c^{(0)} - A^{(0)} + j^{(0)}x],$$

$$c^{(2)} = [d^2c^{(0)}/dx^2 + (c^{(0)} + \alpha)(A^{(2)} - j^{(2)}x) - c^{(1)}(c^{(1)} - A^{(1)} + j^{(1)}x)]/$$
$$[\alpha + \beta + 2c^{(0)} - A^{(0)} + j^{(0)}x]. \quad (A3)$$

To obtain the inner solution near $x = 0$, we introduce the stretched variable ξ and assume that c is given as

$$c(x) = \tilde{c}(\xi) = 1 + \sum_{n=1}^{\infty} \tilde{c}^{(n)}(\xi)\epsilon^{n/2}, \quad x = \epsilon^{1/2}\xi. \quad (A4)$$

The choice of expansion in powers of $\epsilon^{1/2}$ is motivated by the requirement that near the boundaries, the derivative term in Eq. 7 should be as important as the other terms in the Equation (6). $\tilde{c}(\xi)$ must satisfy the boundary conditions on $c(x)$ at $x = 0$ and must match, for large values of ξ, the outer solution at small values of x. In view of Eq. 8, it follows that

$$\tilde{c}(0) = 1, \quad \left(\frac{d\tilde{c}}{d\xi}\right)_{\xi=0} = -j,$$

$$\text{or} \quad \tilde{c}^{(n)}(0) = 0, \quad \left(\frac{d\tilde{c}^{(n)}}{d\xi}\right)_{\xi=0} = -j^{(n-1)}, \quad n = 1, 2, 3, \ldots. \quad (A5)$$

By substituting Eq. A4 into Eq. 7 and again equating coefficients of $\epsilon^{n/2}$ to zero, we obtain

$$\epsilon^0: 0 = \beta + (1 + \alpha)(1 - A^{(0)}),$$

$$\epsilon^{1/2}: [d^2\bar{c}^{(1)}/d\xi^2] = (2 + \alpha + \beta - A^{(0)})\bar{c}^{(1)} + (1 + \alpha)(-A^{(1)} + j^{(0)}\xi),$$

$$\epsilon^1: [d^2\bar{c}^{(2)}/d\xi^2] = (2 + \alpha + \beta - A^{(0)})\bar{c}^{(2)} + (1 + \alpha)(-A^{(2)} + j^{(1)}\xi)$$
$$+ \bar{c}^{(1)}(\bar{c}^{(1)} - A^{(1)} + j^{(0)}\xi). \quad (A6)$$

The first equation above determines $A^{(0)}$ uniquely as

$$A^{(0)} = 1 + \frac{\beta}{1 + \alpha}. \quad (A7)$$

The solution to the second equation in A6 that satisfies the condition that $\bar{c}^{(1)}$ vanish at $\xi = 0$ is

$$\bar{c}^{(1)} = -(1 + \alpha)j^{(0)}/\gamma^3 \{[\alpha\beta/(1 + \alpha)^2](1 - e^{-\gamma\xi}) + \gamma\xi\},$$

$$\gamma^2 \equiv 2 + \alpha + \beta - A^{(0)} = 1 + \alpha + \alpha\beta/(1 + \alpha). \quad (A8)$$

In obtaining A8, we have set to zero the coefficient of the term $e^{\gamma\xi}$ appearing in the general solution to the equation because of the requirement of matching with $c^{(1)}$ and have satisfied the boundary condition (A5) on the gradient of $\bar{c}^{(1)}$, from which we infer that

$$A^{(1)} = -j^{(0)}\alpha\beta/\gamma(1 + \alpha)^2. \quad (A9)$$

We proceed in a similar manner to obtain the inner expansion in the neighborhood of the boundary $x = 1$. Thus, we assume that c is expressible there as

$$c(x) = \bar{c}(\eta) = c_1 + \sum_{n=1}^{\infty} \bar{c}^{(n)}(\eta)\epsilon^{n/2}, \quad 1 - x = \epsilon^{1/2}\eta, \quad (A10)$$

$\bar{c}(\eta)$ must satisfy the boundary conditions on $c(x)$ at $x = 1$ and must match for large values of η, the outer solution at large values of x. In view of Eq. 8, it follows that

$$\bar{c}(0) = c_1, \quad (d\bar{c}/d\eta)_{\eta=0} = -j,$$

$$\text{or} \quad \bar{c}^{(n)}(0) = 0, \quad (d\bar{c}^{(n)}/d\eta)_{\eta=0} = -j^{(n-1)}, \quad n = 1, 2, 3, \ldots. \quad (A11)$$

By substituting Eq. A10 into Eq. 7 and equating coefficients of $\epsilon^{n/2}$ to zero, we obtain

$$\epsilon^0: 0 = \beta c_1 + (c_1 + \alpha)(c_1 - A^{(0)} + j^{(0)}),$$

$$\epsilon^{1/2}: [d^2\bar{c}^{(1)}/d\eta^2] = [2c_1 + \alpha + \beta + j^{(0)} - A^{(0)}]\bar{c}^{(1)} + (c_1 + \alpha)(j^{(1)} - A^{(1)} - j^{(0)}\eta),$$

$$\epsilon^1: [d^2\bar{c}^{(2)}/d\eta^2] = [2c_1 + \alpha + \beta + j^{(0)} - A^{(0)}]\bar{c}^{(2)} + (c_1 + \alpha)(j^{(2)} - A^{(2)} - j^{(1)}\eta)$$
$$+ \bar{c}^{(1)}(\bar{c}^{(1)} + j^{(1)} - A^{(1)} - j^{(0)}\eta). \quad (A12)$$

The solution to the first equation above determines $j^{(0)}$ uniquely with the aid of Eq. A7 as

$$j^{(0)} = (1 - c_1)[1 + \alpha\beta/(1 + \alpha)(c_1 + \alpha)]. \quad (A13)$$

The solution to the second equation that satisfies the conditions that $\bar{c}^{(1)}$ vanish at $\eta = 0$ and matches, for large values of η, the appropriate terms in $c^{(0)}(x)$ and $c^{(1)}(x)$ at large values of x is

$$\bar{c}^{(1)} = [(c_1 + \alpha)/\delta^3] j^{(0)}\{[\alpha\beta/(c_1 + \alpha)^2](1 - e^{-\delta\eta}) + \delta\eta\},$$

$$\delta^2 = 2c_1 + \alpha + \beta + j^{(0)} - A^{(0)} = c_1 + \alpha + [\alpha\beta/(c_1 + \alpha)]. \quad (A14)$$

with $A^{(1)}$ given by Eq. A9 and Eq. A13. In obtaining Eq. A14, we imposed the boundary condition A11 on the gradient of $\bar{c}^{(1)}(\eta)$ for $\eta = 0$, which determines $j^{(1)}$ uniquely as

$$j^{(1)} = - j^{(0)}\alpha\beta[1/\gamma(1 + \alpha)^2 + 1/\delta(c_1 + \alpha)^2], \quad (A15)$$

In a similar manner we find that the solutions to the equations of order ϵ in the inner regions are as follows,

$$\bar{c}^{(2)}(\xi) = [(1 + \alpha)/\gamma^2]\bigg\{A^{(2)}(1 - e^{-\gamma\xi}) - j^{(1)}\xi$$
$$+ [(j^{(0)})^2\alpha\beta/(1 + \alpha)^2\gamma^6]\bigg[(2(1 + \alpha) + \alpha^2\beta^2/(1 + \alpha)^3)(1 - e^{-\gamma\xi})$$
$$+ \frac{2\alpha\beta}{(1 + \alpha)}\gamma\xi + (1 + \alpha)(\gamma\xi)^2 - \frac{\alpha\beta}{3(1 + \alpha)}(e^{-\gamma\xi} - e^{-2\gamma\xi})$$
$$- \frac{1}{2(1 + \alpha)^3}[\alpha\beta - (1 + \alpha)^2][\alpha\beta + \tfrac{1}{2}(1 + \alpha)^2]\gamma\xi e^{-\gamma\xi}$$
$$- \tfrac{1}{4}[\alpha\beta - (1 + \alpha)^2](\gamma\xi)^2 e^{-\gamma\xi}\bigg]\bigg\}, \quad (A16)$$

$$\bar{c}^{(2)}(\eta) = [(c_1 + \alpha)/\delta^2]\bigg\{(A^{(2)} - j^{(2)})(1 - e^{-\delta\eta}) + j^{(1)}\eta$$
$$+ \frac{(j^{(0)})^2\alpha\beta}{(c_1 + \alpha)^2\delta^6}\bigg[\bigg\{2(c_1 + \alpha) + \frac{\alpha^2\beta^2}{(c_1 + \alpha)^3}\bigg\}(1 - e^{-\delta\eta})$$
$$+ \frac{2\alpha\beta}{(c_1 + \alpha)}\delta\eta + (c_1 + \alpha)(\delta\eta)^2 - \frac{\alpha\beta}{3(c_1 + \alpha)}(e^{-\delta\eta} - e^{-2\delta\eta})$$
$$- \frac{1}{2(c_1 + \alpha)^3}[\alpha\beta - (c_1 + \alpha)^2][\alpha\beta + \tfrac{1}{2}(c_1 + \alpha)^2]\delta\eta e^{-\delta\eta}$$
$$- \tfrac{1}{4}[\alpha\beta - (c_1 + \alpha)^2](\delta\eta)^2 e^{-\delta\eta}\bigg]\bigg\}, \quad (A17)$$

whence, with the aid of Eqs. A5 and A11,

$$A^{(2)} = - j^{(1)}[\alpha\beta/\gamma(1 + \alpha)^2] + (j^{(0)})^2\{(1/12\gamma^4) + (5/6)[(1 + \alpha)/\gamma^6]$$
$$- [5/12\gamma^2(1 + \alpha)] - [1/2(1 + \alpha)^2]\}, \quad (A18)$$

$$j^{(2)} = A^{(2)} - j^{(1)}[\alpha\beta/\delta(c_1 + \alpha)^2] + (j^{(0)})^2\{-(1/12\delta^4)$$
$$- (5/6)[(c_1 + \alpha)/\delta^6] + [5/12\delta^2(c_1 + \alpha)] + [1/2(c_1 + \alpha)^2]\}. \quad (A19)$$

From Eqs. A1, A13, A15, and A19, we determine the current density to order ϵ as

$$j = (1 - c_1)[1 + \alpha\beta/(1 + \alpha)(c_1 + \alpha)]\left\{1 - \epsilon^{1/2}\alpha\beta\left[\frac{1}{\gamma(1 + \alpha)^2} + \frac{1}{\delta(c_1 + \alpha)^2}\right]\right.$$

$$+ \epsilon\left(\alpha^2\beta^2\left[\frac{1}{\gamma(1 + \alpha)^2} + \frac{1}{\delta(c_1 + \alpha)^2}\right]^2 + (1 - c_1)\left[1 + \frac{\alpha\beta}{(1 + \alpha)(c_1 + \alpha)}\right]\right.$$

$$\times\left[\frac{1}{12\gamma^4} + \frac{5}{6}\frac{(1 + \alpha)}{\gamma^6} - \frac{5}{12\gamma^2(1 + \alpha)} - \frac{1}{2(1 + \alpha)^2}\right.$$

$$\left.\left.\left. - \frac{1}{12\delta^4} - \frac{5}{6}\frac{(c_1 + \alpha)}{\delta^6} + \frac{5}{12\delta^2(c_1 + \alpha)} + \frac{1}{2(c_1 + \alpha)^2}\right]\right)\right\} + O(\epsilon^{3/2}). \quad (A20)$$

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