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THE EFFECT OF CARBON MONOXIDE ON HAEM-FACILITATED OXYGEN DIFFUSION

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The aim of this paper is to quantify the effect of small quantities of carbon monoxide on the facilitated diffusion of oxygen by haemoglobin in the steady state. It is the first phase in the study of a mathematical model for carbon monoxide poisoning. Here we extend the Wyman model for facilitated diffusion to the case in which there are two ligands. The equations are solved using an asymptotic technique developed by Murray. We obtain accurate analytic approximations for the biologically important quantities of the problem for various percentages of carbon monoxide. These are the concentrations of free oxygen, haemoglobin, oxyhaemoglobin and carboxyhaemoglobin, and hence the saturation of the protein and the facilitated oxygen flux. The major effect of very small quantities of carbon monoxide on the oxygen flux is shown.

1. Introduction

It has been known for a long time that the result of exposure to carbon monoxide in the air is a gradual build-up of the complex carboxyhaemoglobin in the blood (e.g. ref. [1]). Because the back reaction $HbCO \rightarrow Hb + CO$ is very slow it is clear that a small concentration of carbon monoxide in the air eventually leads to a large concentration of HbCO in the blood. Thus the haemoglobin is not free to combine with oxygen, and cannot fulfil its task of transporting it round the body.

Here we shall be concerned with the effect of this build-up on the haem-facilitated diffusion of oxygen across membranes containing haemoglobin. The facilitation is effected by the diffusion of the oxygen-haemoglobin complex across the membrane. The purpose of the analysis here is to obtain quantitative results. We shall discuss in this note the steady-state problem and quantify the effects of various concentrations of carbon monoxide at the high-pressure side of the membrane. The more complicated unsteady problem for a particular concentration of carbon monoxide to find the length of time needed to achieve the steady state will be reported elsewhere.

The ultimate aim of this research is to obtain quantitative results, as regards time scales, for the effective treatment of patients with carbon monoxide poisoning by subjecting them to oxygen at high partial pressures (of the order of 400–600 torr). It is hoped that such quantitative information might help to prevent oxygen poisoning which is a serious problem with such treatment. It is hoped too that it might help in the decision between oxygen-tent treatment and blood transfusion.

Wittenberg [2] and Scholander [3] independently investigated the facilitated diffusion of oxygen through solutions containing haemoglobin. Later Wittenberg [4] conducted a series of experiments to elucidate the actual mechanism of the phenomenon. In these experiments a thin millipore membrane was placed between two regions, in one of which there was a high concentration of gas (oxygen or carbon monoxide), while in the other the pressure of gas was kept as low as possible. The flux of gas across the membrane was measured when haemoglobin was present and when it was not. It was found that the effect of the haemoglobin was approximately to double the oxygen flux. On the other hand there was no carbon monoxide facilitation.

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Wittenberg [4] proposed that the increased diffusion of oxygen was due to the formation of oxyhaemoglobin molecules and the translational diffusion of these. Wyman [5] produced a mathematical model based on this proposal and obtained approximate solutions which agreed well with experiment. This fundamental paper has been the basis of all subsequent haem-facilitated diffusional theories. The non-facilitation of carbon monoxide was explained by Murray and Wyman [6] using the Wyman model. Murray [7] used the model with slight modifications to obtain analytical solutions which also agreed well quantitatively with Wittenberg's [4] results while Kreuzer and Hoofd [8] and Kutchai et al [9] obtained numerical solutions. However the last two papers used fundamentally different boundary conditions to Murray's [7]; their results are also in general agreement with experiment. The whole question of boundary conditions was discussed by Mitchell and Murray [10] who proved that to a high degree of approximation the two different sets of boundary conditions give the same results and hence justify the simpler procedure put forward by Murray [7].

Here we use the Wyman model extended to the case of a mixture of oxygen and carbon monoxide and study the effect of various percentages of CO in the mixture in the steady state. As is intuitively clear the facilitated oxygen flux drops off to a negligible amount at quite small concetrations of carbon monoxide due to haemoglobin saturation and the high affinity of Hb for CO as compared to O_2.

The system of equations is solved using an asymptotic procedure, and the solutions show the major effect of minute quantities of carbon monoxide in haem-facilitated oxygen diffusion.

2. Wyman model for two ligands

We consider a layer of solution l cm thick, the membrane, in which we have haemoglobin, which combines reversibly with oxygen and carbon monoxide. Let the concentration of free oxygen be c_1, of free carbon monoxide be c_2, of haemoglobin be c_3, of oxyhaemoglobin be c_4, and of carboxyhaemoglobin be c_5. Let their fluxes be similarly J_1, J_2, J_3, J_4, and J_5, their rates of loss through reaction be $\rho_1, \rho_2, \rho_3, \rho_4$, and ρ_5 and their diffusion coefficients be D_1, D_2, D_3, D_4, and D_5. In view of the size of the molecules of the haem-complexes it is reasonable to assume that they and haemoglobin all diffuse with the same diffusion coefficient D, that is $D_3=D_4=D_5=D$. The experimental value for D is taken from Riveros-Moreno and Wittenberg [11], for D_1 from Wittenberg [12], and for D_2 from Longmuir and Roughton [13].

The reactions of the haemoglobin with the ligands are taken to be described by the rate constants k_1, k_{-1}, k_2, k_{-2}, where

$$\mathrm{Hb} + \mathrm{O_2} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{HbO_2}, \qquad \mathrm{Hb} + \mathrm{CO} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathrm{HbCO}. \tag{1,2}$$

Since haemoglobin has four binding sites per molecule this is not a completely accurate description of the kinetics; k_1 and k_2 depend on the saturation of the haemoglobin molecule, although k_{-1} and k_{-2} can certainly be taken constants. We take values of k_{-1} and k_{-2} from Wittenberg [12] and Gibson [14]. Wyman [5] suggested taking an average value for the "on" constants k_1 and k_2, which we also do here. This is undoubtedly a major assumption. However previous work on facilitated diffusion has been done on this basis, experimentally by Wittenberg [12] in the case of oxygen and Brunori et al [15] in the case of carbon monoxide, whence we take our values of k_1 and k_2, and theoretically by Murray [7] and Murray and Wyman [6]. These theoretical studies give results in accordance with known biological facts.

The equation for a chemical species under reaction and diffusion in one dimension is given by

$$\frac{\partial c_i}{\partial t} = -\rho_i + D_i \frac{\partial^2 c_i}{\partial x^2}, \qquad i = 1, 2, \ldots, 5, \tag{3}$$

where D_i is the diffusion coefficient (assumed constant), ρ_i is the rate of loss of c_i through reaction, and x is the distance measured from the high-pressure side of the membrane.

The law of mass action applied to (1) and (2) gives

$$\rho_1 = k_1 c_1 c_3 - k_{-1} c_4, \qquad \rho_2 = k_2 c_2 c_3 - k_{-2} c_5, \qquad \rho_3 = \rho_1 + \rho_2, \qquad \rho_4 = -\rho_1, \qquad \rho_5 = -\rho_2, \quad (4)$$

and the equations (3) and (4) become, in the steady state,

$$D_1 c_1'' = k_1 c_1 c_3 - k_{-1} c_4 = \rho_1, \qquad D_2 c_2'' = k_2 c_2 c_3 - k_{-2} c_5 = \rho_2 \quad (5, 6)$$

$$Dc_3'' = \rho_1 + \rho_2, \qquad Dc_4'' = -\rho_1, \qquad Dc_5'' = -\rho_2, \quad (7\text{–}9)$$

where primes denote differentiation with respect to x.

We specify c_1 and c_2 at $x=0$ and $x=l$, although the values at $x=l$ cannot be determined with any great accuracy. The boundary conditions on c_3, c_4, and c_5 are that there is no flux of protein through the walls of the membrane, and so we have

$$\frac{dc_3}{dx} = \frac{dc_4}{dx} = \frac{dc_5}{dx} = 0, \quad \text{at } x=0 \text{ and } x=l. \quad (10)$$

As a result of Murray's [7] and Mitchell and Murray's [10] analysis we can use, in most practical circumstances, the mathematically simpler boundary conditions

$$c_i = c_i(0) \quad \text{at } x=0, \qquad c_i = c_i(l) \quad \text{at } x=l, \qquad (i=3,4,5), \quad (11)$$

where the values of $c_i(0)$, $c_i(l)$ for $i = 3, 4, 5$ are to be determined later. The conditions under which we can do this are when the ratio of the diffusion time to the reaction time is very small (see next section).

3. Asymptotic solutions

Adding (7), (8) and (9) and integrating twice, making use of (10), we have

$$c_3 + c_4 + c_5 = c_t = \text{constant}, \quad (12)$$

the conservation equation for the protein.

We now non-dimensionalize the equations, so that the only parameters of the problem are non-dimensional ones independent of the system of units chosen. We define the new dimensionless variables by

$$\tilde{x} = \frac{x}{l}, \quad \tilde{c}_1 = \frac{c_1}{c_1(0)}, \quad \tilde{c}_2 = \frac{c_2}{c_2(0)}, \quad \tilde{c}_3 = \frac{c_3}{c_t}, \quad \tilde{c}_4 = \frac{c_4}{c_t}, \quad \tilde{c}_5 = \frac{c_5}{c_t}. \quad (13)$$

Here $\tilde{c}_4$ and $\tilde{c}_5$ are the partial saturations of the haemoglobin with oxygen and carbon monoxide respectively.

Let us define $\gamma_1 = c_1(0)$, $\gamma_2 = c_2(0)$, and let $\gamma_2 = \lambda\gamma_1$, so that λ is the ratio of the concentration of carbon monoxide to that of oxygen on the high-pressure side of the membrane.

The full system of equations becomes, in dimensionless form,

$$\frac{D_1\gamma_1}{l^2}\frac{d^2\tilde{c}_1}{d\tilde{x}^2} = k_1\gamma_1 c_t \tilde{c}_1\tilde{c}_3 - k_{-1}c_t\tilde{c}_4 = \rho_1, \qquad \frac{D_2\gamma_2}{l^2}\frac{d^2\tilde{c}_2}{d\tilde{x}^2} = k_2\gamma_2 c_t\tilde{c}_2\tilde{c}_3 - k_{-2}c_t\tilde{c}_5 = \rho_2, \quad (14, 15)$$

$$\frac{Dc_t}{l^2}\frac{d^2\tilde{c}_4}{d\tilde{x}^2} = -\rho_1, \qquad \frac{Dc_t}{l^2}\frac{d^2\tilde{c}_5}{d\tilde{x}^2} = -\rho_2, \qquad \tilde{c}_3 + \tilde{c}_4 + \tilde{c}_5 = 1. \quad (16\text{–}18)$$

Adding (14) and (16) and integrating twice,

$$D_1\gamma_1\tilde{c}_1 + Dc_t\tilde{c}_4 = A_1\tilde{x} + B_1. \quad (19)$$

Similarly, from (15) and (17),

$$D_2\gamma_2\tilde{c}_2 + Dc_t\tilde{c}_5 = A_2\tilde{x} + B_2. \tag{20}$$

Using the boundary conditions (11), these become

$$D_1\gamma_1\tilde{c}_1 + Dc_t\tilde{c}_4 = D_1\gamma_1 + Dc_t\tilde{c}_4(0) + \tilde{x}\{D_1\gamma_1(\tilde{c}_1(1) - 1) + Dc_t(\tilde{c}_4(1) - \tilde{c}_4(0))\}, \tag{21}$$

$$D_2\gamma_2\tilde{c}_2 + Dc_t\tilde{c}_5 = D_2\gamma_2 + Dc_t\tilde{c}_5(0) + \tilde{x}\{D_2\gamma_2(\tilde{c}_2(1) - 1) + Dc_t(\tilde{c}_5(1) - \tilde{c}_5(0))\}. \tag{22}$$

For convenience in what follows we drop the tildes, but it should be kept in mind that all quantities are now non-dimensional. A prime now represents differentiation with respect to the new (nondimensional) x.

Equation (14) gives

$$(D_1/k_1c_tl^2)\,c_1'' = c_1c_3 - (k_{-1}/k_1\gamma_1)\,c_4$$

which on substituting for c_3 and c_4 from (18), (19) and (20) becomes

$$\frac{D_1}{k_1c_tl^2}\,c_1'' = c_1\left\{1 - \frac{1}{Dc_t}(A_1x + B_1 - D_1\gamma_1c_1) - \frac{1}{Dc_t}(A_2x + B_2 - D_2\gamma_2c_2)\right\} - \frac{k_{-1}}{k_1\gamma_1}\frac{1}{Dc_t}(A_1x + B_1 - D_1\gamma_1c_1)$$

which we write as

$$c_1'' = \alpha_1 + \beta_1x + (\delta_1 + \zeta_1x)c_1 + \eta_1c_1^2 + \theta_1c_1c_2\ , \tag{23}$$

where

$$\alpha_1 = -\frac{B_1k_{-1}l^2}{D_1D\gamma_1}, \quad \beta_1 = -\frac{A_1k_{-1}l^2}{D_1D\gamma_1}, \quad \delta_1 = \frac{k_1c_tl^2}{D_1}\left\{1 - \frac{B_1}{Dc_t} - \frac{B_2}{Dc_t} + \frac{k_{-1}D_1}{k_1Dc_t}\right\}$$

$$\zeta_1 = \frac{k_1c_tl^2}{D_1}\left\{-\frac{A_1}{Dc_t} - \frac{A_2}{Dc_t}\right\}, \qquad \eta_1 = \frac{k_1\gamma_1l^2}{D}, \qquad \theta_1 = \frac{k_1l^2D_2\gamma_2}{D_1D}. \tag{24}$$

Similarly (15) gives

$$(D_2/k_2c_tl^2)\,c_2'' = c_2c_3 - (k_{-2}/k_2\gamma_2)\,c_5$$

which on substituting from (18), (19) and (20) becomes

$$\frac{D_2}{k_2c_tl^2}\,c_2'' = c_2\left\{1 - \frac{1}{Dc_t}(A_1x + B_1 - D_1c_1\gamma_1) - \frac{1}{Dc_t}(A_2x + B_2 - D_2\gamma_2c_2)\right\} - \frac{k_{-2}}{k_2\gamma_2}\frac{1}{Dc_t}(A_2x + B_2 - D_2\gamma_2c_2)$$

which we write in the form

$$c_2'' = \alpha_2 + \beta_2x + (\delta_2 + \zeta_2x)c_2 + \eta_2c_2^2 + \theta_2c_1c_2, \tag{25}$$

where

$$\alpha_2 = -\frac{B_2k_{-2}l^2}{D_2D\gamma_2}, \quad \beta_2 = -\frac{A_2k_{-2}l^2}{D_2D\gamma_2}, \quad \delta_2 = \frac{k_2c_tl^2}{D_2}\left\{1 - \frac{B_1}{Dc_t} - \frac{B_2}{Dc_t} + \frac{k_{-2}D_2}{k_2Dc_t}\right\}$$

$$\zeta_2 = \frac{k_2c_tl^2}{D_2}\left\{-\frac{A_1}{Dc_t} - \frac{A_2}{Dc_t}\right\}, \quad \eta_2 = \frac{k_2\gamma_2l^2}{D}, \quad \theta_2 = \frac{k_2l^2D_1\gamma_1}{D_2D}. \tag{26}$$

Typical values for the parameters in these equations are given in table 1.

Table 1

k_1 ($cm^3\,mol^{-1}\,s^{-1}$)	k_{-1} (s^{-1})	k_2 ($cm^3\,mol^{-1}\,s^{-1}$)	k_{-2} (s^{-1})	D_1 ($cm^2\,s^{-1}$)	D_2 ($cm^2\,s^{-1}$)	D ($cm^2\,s^{-1}$)	l (cm)	c_t ($mol\,cm^{-3}$)	γ_1 ($mol\,cm^{-3}$)
2.85×10^{9}	40	2×10^{8}	8×10^{-3}	1.2×10^{-5}	1.3×10^{-5}	2.45×10^{-7}	2.2×10^{-2}	1.2×10^{-5}	2×10^{-7}

We may now estimate the size of the numbers $A_i, B_i, \alpha_i, \beta_i, \delta_i, \zeta_i, \eta_i$, and θ_i, $i = 1, 2$, using the facts that $c_1(1) \ll 1, c_2(1) \ll 1, c_4(0) - c_4(1) < 1, c_5(0) - c_5(1) < 1$. They are

$$A_1 = -O(10^{-12}), B_1 = O(10^{-12}), \alpha_1 = -O(10^5), \beta_1 = O(10^5), \delta_1 \lesssim O(10^6), \zeta_1 = O(10^6), \eta_1 = O(10^6),$$

$$\theta_1 = O(10^6\lambda); A_2 = -O(10^{-12}), B_2 = O(10^{-12}), \alpha_2 = -O(10^3\lambda^{-1}), \beta_2 = O(10^3\lambda^{-1}), \delta_2 \lesssim O(10^5),$$

$$\zeta_2 = O(10^5), \eta_2 = O(10^4\lambda), \text{ and } \theta_2 = O(10^4).$$

Defining

$$\epsilon_2 = 10^{-5}, \quad a_2 = \epsilon_2\alpha_2, \quad b_2 = \epsilon_2\beta_2, \quad d_2 = \epsilon_2\delta_2, \quad f_2 = \epsilon_2\zeta_2, \quad g_2 = \epsilon_2\eta_2, \quad h_2 = \epsilon_2\theta_2, \tag{27}$$

we have

$$\epsilon_2 c_2'' = a_2 + b_2 x + (d_2 + f_2 x)\, c_2 + g_2 c_2^2 + h_2 c_1 c_2 \tag{28}$$

where

$$d_2,\ f_2 = O(1), \quad a_2,\ b_2 = O(10^{-2}\lambda^{-1}), \quad g_2 = O(10^{-1}\lambda), \quad h_2 = O(10^{-1}).$$

Similarly, defining

$$\epsilon_1 = 10^{-6}, \quad a_1 = \epsilon_1\alpha_1, \quad b_1 = \epsilon_1\beta_1, \quad d_1 = \epsilon_1\delta_1, \quad f_1 = \epsilon_1\zeta_1, \quad g_1 = \epsilon_1\eta_1, \quad h_1 = \epsilon_1\theta_1 \tag{29}$$

we have

$$\epsilon_1 c_1'' = a_1 + b_1 x + (d_1 + f_1 x)\, c_1 + g_1 c_1^2 + h_1 c_1 c_2 \tag{30}$$

where

$$a_1,\ b_1,\ f_1,\ g_1 = O(1), \quad d_1 \leqslant O(1), \quad h_1 = O(\lambda).$$

Thus as in previous work a small parameter multiplies the highest derivative in our equation and we have in general a singular perturbation problem, since on setting $\epsilon = 0$ the order of the equation is reduced and we cannot then satisfy all the boundary conditions at $x = 0$ and $x = 1$. We would thus expect the solution to consist of three parts, (a) an outer solution valid away from the boundaries, obtained by setting $\epsilon = 0$, (b) an inner solution valid near $x = 0$, which satisfies the boundary condition there and matches onto the outer solution outside a small singular region, and (c) a similar inner solution near $x = 1$. In the singular regions where the inner solutions are valid we require $\epsilon_1 c_1''$ to be $O(1)$, so we define inner variables $\xi = x/\epsilon_1^{1/2}$ and $\eta = (1-x)/\epsilon_1^{1/2}$ for the inner solutions valid near $x = 0$ and $x = 1$ respectively. Then $\epsilon_1\, d^2c_1/dx^2$ becomes $d^2c_1/d\xi^2$ near $x = 0$ and $d^2c_1/d\eta^2$ near $x = 1$. Hence the thickness of the singular regions near the boundaries is $O(\epsilon_1^{1/2})$, or in dimensional terms $O(10^{-5})$ cm. This is so small that it is most unlikely biologically that the concentrations could change drastically in these regions, and so we conclude that the outer solution must satisfy the boundary conditions. This procedure has been justified mathematically by Mitchell and Murray [10] for the case in which there is only *one* substrate, that is the equation

$$\epsilon_1 c_1'' = a_1 + b_1 x + (d_1 + f_1 x)\, c_1 + g_1 c_1^2. \tag{31}$$

Let the solutions to equations (28) and (30) above be $c_1 = c_1(x;\epsilon_1)$ and $c_2 = c_2(x;\epsilon_1)$; let c_1^* satisfy (31). Then

$$c_1(x;\epsilon_1) = c_1^*(x;\epsilon_1) + O(\lambda). \tag{32}$$

since the perturbation based on λ is regular. But we know from Mitchell and Murray's [10] result that

$$c_1^*(x;\epsilon_1) = c_1^*(x;0) + O(\epsilon_1^{1/2}) \tag{33}$$

and as in (32),

$$c_1(x;0) = c_1^*(x;0) + O(\lambda). \tag{34}$$

Hence

$$c_1(x;\epsilon_1) = c_1(x;0) + O(\epsilon_1^{1/2}) + O(\lambda). \tag{35}$$

Let $c_i^{(0)} = c_i(x;0)$, $i = 1, 2, 3, 4, 5$; then we have

$$a_1 + b_1 x + (d_1 + f_1 x)c_1^{(0)} + g_1 c_1^{(0)2} + h_1 c_1^{(0)} c_2^{(0)} = 0, \tag{36}$$

with conditions

$$c_1^{(0)}(0) = 1, \quad c_1^{(0)}(1) = c_1(1), \quad c_2^{(0)}(0) = 1, \quad c_2^{(0)}(1) = c_2(1). \tag{37}$$

Henceforth we drop the superscripts. Substituting back for c_3 and c_4 in (36) from (18), (19) and (20),

$$c_1 c_3 - (k_{-1}/k_1\gamma_1)c_4 = 0. \tag{38}$$

We have shown that there is no boundary layer for oxygen or for oxyhaemoglobin; hence equation (38) shows that there is none for pure haemoglobin, and from (12), the conservation of protein, there is none for carboxy-haemoglobin. Hence from (17)

$$c_2 c_3 - (k_{-2}/k_2\gamma_2)c_5 = 0, \tag{39}$$

or substituting for c_3 and c_5 from (18), (19) and (20),

$$a_2 + b_2 x + (d_2 + f_2 x)c_2 + g_2 c_2^2 + h_2 c_1 c_2 = 0. \tag{40}$$

The problem is now reduced from a system of five second order non-linear differential equations to five algebraic equations for our five unknowns, which can be solved once we know the values of $c_1(1)$ and $c_2(1)$. These constants depend on how quickly the gases reach the low-pressure side of the membrane and the rate at which they are removed. We shall find solutions for typical values of these parameters. We know from Wittenberg's [12] experiments that a typical value for $c_1(1)$ is 10^{-2}. We now wish to estimate $c_2(1)$ for this value of $c_1(1)$. It seems reasonable to postulate conditions such that the concentration of carbon monoxide at the low-pressure side of the membrane depends largely on the flux of carbon monoxide across the membrane compared to the flux of oxygen. This is physically equivalent to assuming that the method used in removing the gas is not extremely selective in the sense of pumping away one gas much faster than the other.

The total oxygen flux (free and bound) is given, in dimensional terms, by

$$F_{O_2} = -l^{-1}\{D_1\gamma_1\, dc_1/dx + Dc_t\, dc_4/dx\}$$

which from (19) is

$$F_{O_2} = l^{-1}\{D_1\gamma_1(1 - c_1(1)) + Dc_t(c_4(0) - c_4(1))\}. \tag{41}$$

Similarly the total carbon monoxide flux is

$$F_{CO} = l^{-1}\{D_2\gamma_2(1 - c_2(1)) + Dc_t(c_5(0) - c_5(1))\}. \tag{42}$$

If the concentration at the low-pressure side were proportional to the flux we would have

$$F_{CO}/F_{O_2} = \gamma_2 c_2(1)/\gamma_1 c_1(1) = \lambda\, c_2(1)/c_1(1)$$

that is

$$\lambda c_2(1)\{D_1\gamma_1(1 - c_1(1)) + Dc_t(c_4(0) - c_4(1))\} = c_1(1)\{D_2\gamma_2(1 - c_2(1) + Dc_t(c_5(0) - c_5(1))\}. \tag{43}$$

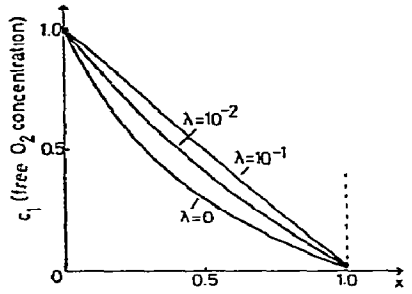

Fig. 1. The concentration of free oxygen, c_1, as a function of the distance across the membrane, x, for selected values of λ, the ratio of the carbon monoxide to the oxygen concentration at the high-pressure side of the membrane: c_1 is the concentration relative to its value at the high-pressure side of the membrane, 2×10^{-7} mole cm^{-3}, and x is the distance relative to the membrane thickness. Parameter values are as in table 1.

If we assume that $c_2(1) \lesssim O(10^{-2})$ we have

$$\lambda c_2(1) D_1 \gamma_1 (1 - c_1(1)) \lesssim O(10^{-14}\lambda), \qquad \lambda c_2(1) Dc_t (c_4(0) - c_4(1)) \lesssim O(10^{-14}\lambda),$$

$$c_1(1) D_2 \gamma_2 (1 - c_2(1)) = O(10^{-14}\lambda), \qquad c_1(1) Dc_t = (10^{-14}). \tag{44}$$

Hence for the right hand side of equation (43) to be of the same order as the left hand side we require $c_5(0) - c_5(1) = O(\lambda)$. Hence $c_5(0) - c_5(1) = O(\lambda)$ if $c_2(1) \lesssim O(10^{-2})$. But

$$c_5(1) = \frac{(k_2\gamma_2/k_{-2})\, c_2(1)}{1 + (k_1\gamma_1/k_{-1})\, c_1(1) + (k_2\gamma_2/k_{-2})\, c_2(1)}, \tag{45}$$

which is an increasing function of $c_2(1)$ as $c_2(1)$ increases, so we have $c_5(0) - c_5(1) = O(\lambda)$ if $c_2(1) > O(10^{-2})$ also. Hence

$$c_5(0) - c_5(1) = O(\lambda). \tag{46}$$

Hence we have an estimate for $c_5(1)$ and can find the unknowns $c_2(1)$, $c_3(1)$, and $c_4(1)$ from our algebraic equations. This enables us to find the magnitude of the facilitated oxygen diffusion, the saturations of the protein with oxygen and carbon monoxide, namely c_4 and c_5, and the concentration of free oxygen and carbon monoxide, given on solving the simultaneous quadratic algebraic equations (28) and (30). The detailed expressions are given in the next section.

4. Numerical results

Since λ is small we get a good approximate expression for the free oxygen concentration from equation (36) using (35), ignoring the terms of $O(\epsilon_1^{1/2})$ and $O(\lambda)$, namely

$$a_1 + b_1 x + (d_1 + f_1 x)\, c_1 + g_1 c_1^2 = 0, \tag{47}$$

which gives

$$c_1 = \frac{-(d_1 + f_1 x) + \{(d_1 + f_1 x)^2 - 4g_1(a_1 + b_1 x)\}^{1/2}}{2g_1}, \tag{48}$$

where the positive root of the quadratic is taken since c_1 is a concentration. This is a hyperbola, shown for selected values of λ in fig. 1.

From (22) using (46), ignoring terms of $O(\lambda)$, $c_5 = c_5(0)$, so that from (18), (38) and (39),

$$c_5 = \frac{k_2\gamma_2/k_{-2}}{1 + k_1\gamma_1/k_{-1} + k_2\gamma_2/k_{-2}}. \tag{49}$$

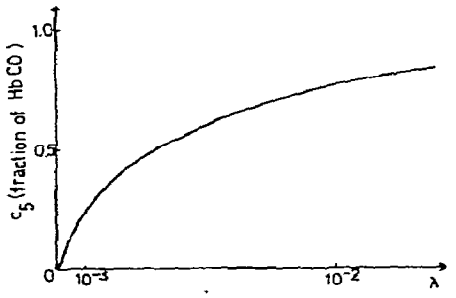

Fig. 2. The fraction of carboxyhaemoglobin, c_5, as a function of λ, the CO to O_2 ratio at the high pressure side.

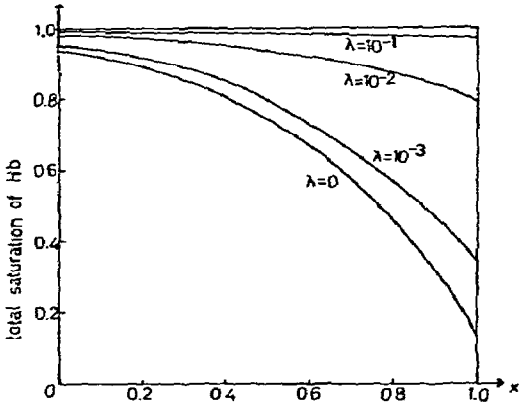

Fig. 3. The saturation of haemoglobin with both oxygen and carbon monoxide, $c_4 + c_5$, as a function of the distance across the membrane, x.

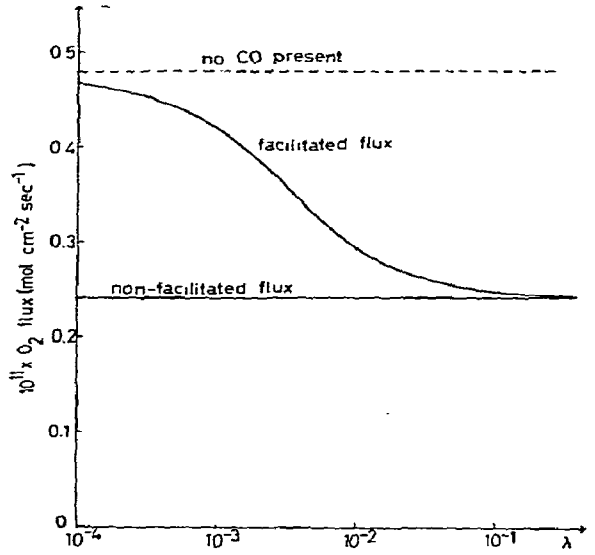

Fig. 4. The facilitated flux of oxygen, given its concentration γ_1 at the high-pressure side of the membrane, as a function of λ.

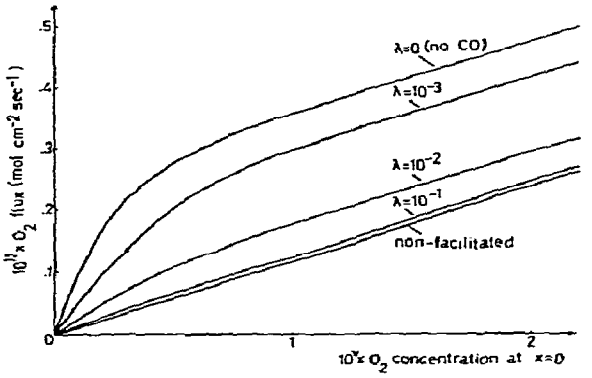

Fig. 5. The facilitated flux of oxygen as a function of its concentration at the high-pressure side of the membrane for selected values of λ. The values of all the parameters except γ_1 are as in table 1.

This concentration is plotted in fig. 2.

Solving (49), (18) and (38) for c_3 and c_4 in terms of c_1 we have

$$c_4 = \frac{k_1\gamma_1 c_1(1-c_5(0))}{k_1\gamma_1 c_1 + k_{-1}}, \qquad c_3 = \frac{k_{-1}(1-c_5(0))}{k_1\gamma_1 c_1 + k_{-1}}. \tag{50, 51}$$

We can now find the saturation of the protein with each substrate throughout the membrane. This is shown in fig. 3.

From (50), since $c_1(0)$ and $c_1(1)$ are given, then $c_4(0) - c_4(1)$ depends only on $c_5(0)$. Hence we can plot the facilitated flux against λ for our given concentration of oxygen γ_1, shown in fig. 4. We also show the flux dependence on this concentration for selected values of λ (fig. 5).

The results show the major effect of even very small quantities of carbon monoxide in the mixture. From fig. 5

a concentration of only one part of carbon monoxide per thousand reduces the oxygen facilitation by about 25% and from fig. 2 it builds up a proportion of about 25% carboxyhaemoglobin in the protein.

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