

Transfer of oxygen into haemoglobin solution

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Transfer of Oxygen into Haemoglobin Solution

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Summary. It is shown that, when oxygen and haemoglobin are diffusing through haemoglobin solutions, the concentration of total haemoglobin will be constant, independent of the reaction scheme of haemoglobin with oxygen.

Solutions of transport equations for the cases of oxygen uptake in a stationary and in a moving flat film of haemoglobin solution are given. The influence of the diffusion of haemoglobin is shown.

Advancing front equations, corrected for physically dissolved oxygen, are derived by formal integration of the transport equations. It is shown that these derived formulas are good approximations of the solutions of the transport equations when the diffusion of haemoglobin is neglected.

Key words: Oxygen Transfer — Haemoglobin — Facilitated Diffusion — Oxygenators.

A number of studies on the diffusion of oxygen in haemoglobin solutions and whole blood have been published. Their primary goal has been to describe the oxygen uptake in the lungs and the oxygen release in the tissues. During the last 10 years new interest has arisen in connection with the problems in artificial gas exchangers.

In oxygen transfer in haemoglobin systems there are three interacting phenomena: convection, diffusion, and chemical reaction. For several geometric configurations and boundary conditions numerical results of equations, describing oxygen transfer in various haemoglobin or blood systems, are available but almost always approximations were made, such as chemical equilibrium between oxygen and haemoglobin, neglecting the diffusion of haemoglobin, or assuming a simple one-step reaction for the oxygen-haemoglobin system. In this paper the influence of diffusion of haemoglobin is studied using an equilibrium relation between oxygen pressure and haemoglobin saturation in the case of:

1. non-stationary oxygen uptake in a non-moving flat film,
2. stationary oxygen uptake in a moving flat film with parabolic velocity profile.

Comparison of computed numerical results, including diffusion of haemoglobin, with experimental results provides some indication concerning the influence of reaction velocity on the transfer process.

Since the influence of haemoglobin diffusion on oxygen transport depends on the transfer of all (oxy-) haemoglobin species the differential equations used, describing oxygen concentration and haemoglobin saturation, are based on the transfer equations of all species involved.

1. Transfer Equations

Diffusion processes are normally described by one or a set of differential equation(s) holding in every point of the medium in which transfer occurs. Many solutions of this (these) equation(s) are possible but boundary values for the particular problem determine the specific solution.

When oxygen passes through haemoglobin solutions it will react with haemoglobin to form oxyhaemoglobin. The transfer of all the species involved in the reaction can be described by:

$$\frac{\partial [X]}{\partial t} = -\vec{v} \cdot \text{grad} [X] + \text{div} (D_X \text{grad} [X]) + R_X \quad (1)$$

where

- $[X]$ = the concentration of a certain species X ,
- R_X = rate of production of species X by chemical reaction,
- D_X = diffusion coefficient of X ,
- \vec{v} = velocity of fluid.

[We will refer to an equation of type (1) for species X as Eq. (X).]

In this paper we limit ourselves to the assumption that in all situations the oxyhaemoglobin molecules remain in the four-heme form.

Eq. (1) holds for oxygen of concentration C and for all haemoglobin species with concentration $H_{i,j}$ where $i = 0, 1, 2, 3$ or 4 indicates the number of O_2 molecules bound to haemoglobin and j distinguishes the various forms of oxyhaemoglobin with the same number of oxygen molecules.

Taking into account all forms of haemoglobin there is a relation between R_C and the various $R_{H_{i,j}}$, when R_C and $R_{H_{i,j}}$ are the rates of production by chemical reaction of C and $H_{i,j}$ respectively:

$$R_C + \sum_{i=1}^4 i \sum_j R_{H_{i,j}} = 0. \quad (2)$$

For all possible forms of haemoglobin:

$$\sum_{i=0}^4 \sum_j R_{H_{i,j}} = 0. \quad (3)$$

We also assume that the diffusion coefficient is the same for all haemoglobin molecules. When defining $b = \sum_i \sum_j H_{i,j}$ as the total haemo-

globin concentration (tetrameric) we now can derive a differential equation for b as a function of time and place. Adding all equations describing $H_{i,j}$ and using (1) we get:

$$\frac{\partial b}{\partial t} = -\vec{v} \cdot \text{grad } b + \text{div } (D_H \text{ grad } b). \quad (4)$$

Because of Eq. (3) there is no reaction term left. Eq. (4) shows that in a system where O_2 and haemoglobin species are moving and the mentioned assumptions apply, the local total haemoglobin concentration is only affected by gradients of b .

We consider here only situations where b is a uniform concentration at the start. In this case, if there is no change in boundary values of b , no gradients of b will occur and b has a constant value throughout the whole process. The conclusion that b is constant is required for the derivation of Eq. (7) below but also circumvents the need of proving it again for a certain specific problem as was the case hitherto (e.g. Kutchai, 1971a; Kreuzer, 1970; Zilversmit, 1965).

The fractional oxygen saturation of haemoglobin is defined as

$$S = (\sum_{i=0}^4 i \sum_j H_{i,j}) / 4b. \quad (5)$$

We can easily see that the summation

$$\frac{1}{4b} \sum_{i=1}^4 i \sum_j \text{Eq. } (H_{i,j}) \quad (6)$$

leads to

$$\frac{\partial S}{\partial t} = -\vec{v} \cdot \text{grad } S + \text{div } (D_H \text{ grad } S) + R_S \quad (7)$$

where

$$R_S = \sum_{i=1}^4 i \sum_j R_{H_{i,j}} = -R_C / 4b. \quad (8)$$

Thus the saturation may be expressed by a transfer equation as if S were a transported species itself.

Eq. (C) and Eq. (4 b S) can be added to give

$$\frac{\partial}{\partial t} (C + 4bS) = -\vec{v} \cdot \text{grad } (C + 4bS) + \text{div } [\text{grad } (D_c C + 4bDS)]. \quad (9)$$

In addition to Eq. (C) and Eq. (S) we need equations for R_C and R_S depending on C and S . The formulation of these equations depends on the assumed reaction scheme for haemoglobin and oxygen.

The assumption of near equilibrium means that the saturation curve may be used as a second relation required in addition to (9). We may

qualitatively understand the meaning of this assumption from following considerations.

Generally we may state according to basic theory of reaction kinetics (Laidler, 1965) that

$$-R_C = f_1 C - f_2 \quad (10)$$

where f_1 is a function of all terms $H_{i,j}$ of haemoglobin combining with one or more molecules of oxygen (forward reaction) and f_2 is a function of all terms $H_{i,j}$ slowing down the overall rate (back reaction). f_1 and f_2 are always positive.

Defining C^e as the concentration of oxygen for $R_C = 0$ (equilibrium) we get

$$R_C = (C^e - C) f_1. \quad (11)$$

Relation (10) holds when only one O_2 molecule is involved in each reaction step. If there are more molecules involved per step then (10) will be a polynome and Eq. (11) still holds as a first order approximation.

The assumption of near-equilibrium means that $C^e - C$ is small compared to C^e . In this case a significant value of R_C is obtained only when f_1 is very large. Indeed f_1 may be large since it may contain reaction velocity constants of large numerical value.

2. Non-Steady State Oxygen Diffusion in a Non-Moving Film of Haemoglobin Solution; One-Dimensional Problem

We will mathematically describe the problem of a flat thin layer of haemoglobin solution of thickness d . At $t < 0$ this film is in equilibrium with a gaseous atmosphere containing oxygen at a partial pressure P_0 . The oxygen concentration in the layer will be C_0 according to Henry's law

$$C_0 = \alpha P_0 \quad (12)$$

where α = the solubility in mol/l/mm Hg.

At time $t = 0$ the gaseous atmosphere changes abruptly to a P_{O_2} of P_1 . Oxygen will diffuse into the haemoglobin layer and react with haemoglobin to produce oxyhaemoglobin. In this case Eq. (9) reduces to:

$$\partial(4 b S + C)/\partial t = D_C \partial^2 C/\partial x^2 + 4 b D_H \partial^2 S/\partial x^2. \quad (13)$$

The boundary conditions are:

$t < 0$ $P_{O_2} = P_0$ and $C = C_0$ in the entire layer,

$t \geq 0$ $P_{O_2} = P_1$ and $C = C_1$ at $x = 0$ (the liquid-gas interphase).

$\partial C/\partial x = 0$ at $x = d$ because no transfer of oxygen is occurring at this surface. Together with the saturation curve as the relation between S and C , Eq. (13) with the boundary conditions can be solved. The standard oxygen dissociation curve at pH 7.4 and 25°C was used.

In order to get a better insight into the influence of the various parameters on the solutions of the equation, we will make all variables and parameters dimensionless.

$$\begin{aligned} C^* &= C/C_1 \\ b^* &= 4b/C_1 \\ y &= x/d \\ t^* &= tD_C/d^2 \\ D^* &= b^*D_H/D_C. \end{aligned} \tag{14}$$

Eq. (13) becomes with (14)

$$\partial(C^* + b^*S)/\partial t = \partial^2 C^*/\partial y^2 + D^* \partial^2 S/\partial y^2. \tag{15}$$

The diffusion coefficient of haemoglobin, D_H , has often been neglected hitherto because it is small compared with the diffusion coefficient of oxygen, D_C . But on the other hand the molar haemoglobin concentration is usually much larger than the oxygen concentration so that the respective fluxes of oxygen and haemoglobin may be of comparable size.

Eq. (15) is solved numerically following an adapted Crank-Nicholson difference scheme. Convergence of the method is proved both by changing the number of grid points into which the film is divided and by the number of time steps. Typical numerical results of profiles are shown in Figs. 1, 2 and 3. The boundary values are $P_0 = 0$ and $P_1 = 0.9$ atm according to the experiments of Klug *et al.* (1956) or $P_0 = 0$ and $P_1 = 0.2$ atm (air). For $P_1 = 0.9$ there exists a sharp boundary between oxygenated and nonoxygenated haemoglobin. With $P_1 = 0.2$ the diffusion of haemoglobin is relatively more important (see Fig. 3) and the oxygenation boundary is less sharp.

Comparison with Experimental Values. Klug *et al.* (1956) published experiments on the same system as considered here. These authors determined the time for a thin haemoglobin layer to be saturated to $1/3$ and $1/2$ as a function of haemoglobin concentration.

Their experimental values and our numerical results are compared in Fig. 4. We see that the calculated results agree fairly well with the experiments when b is smaller than 30 g%. At higher haemoglobin concentration the deviation between theory and experiment cannot be explained by existing uncertainty in diffusion coefficients. Finite reaction velocity in any case slows down the oxygen uptake as compared to equilibrium situation. The discrepancy between numerical results and experi-

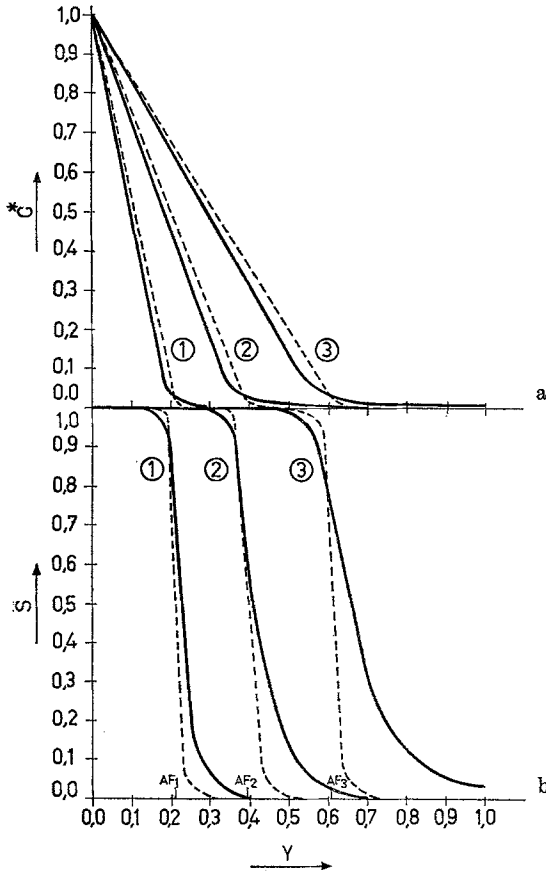


Fig. 1. a) C^* as a function of y with t^* as a parameter. b) S as a function of y with t^* as a parameter. ---- $D_H = 0$; — $D_H = 0.45 \cdot 10^{-6}$ cm²/sec. $[Hb_4] = 10$ g⁰/₀ = $1.55 \cdot 10^{-3}$ mol/l; $P_1 = 0.9$ atm; $C_1 = 0.943 \cdot 10^{-3}$ mol/l. $t^* = \frac{t \cdot D}{d^2}$. (1) $t^* = 0.160$; (2) $t^* = 0.544$; (3) $t^* = 1.36$.

These graphs are typical and do not differ in shape by changing b between 5 and 40 g⁰/₀. The oxygenation front is less sharp when $D_H \neq 0$. The lines indicated by AF_1 , AF_2 and AF_3 are the places of the oxygenation front calculated by the advancing front hypothesis

ments might be caused by finite reaction velocity, by inaccuracy in the measurements, or perhaps by an alternative reaction scheme for the reaction of O_2 with haemoglobin.

In Fig. 4 the triangles are the results calculated by Kutchai *et al.* (1971a). Kutchai takes into account the reaction velocity by approaching the 4-step reaction by a 1-step reaction scheme. His results deviate from

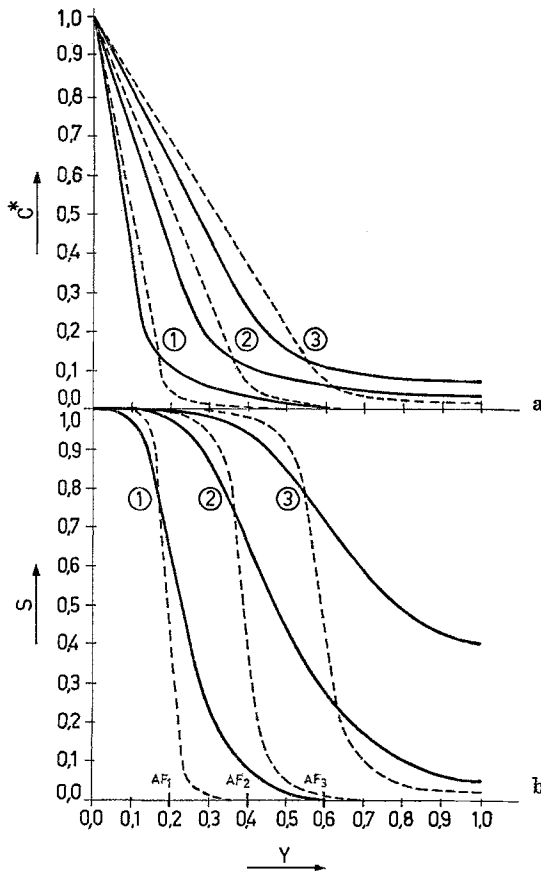


Fig. 2. a) C^* as a function of y with t^* as a parameter. b) S as a function of y with t^* as a parameter. ---- $D_H = 0$; — $D_H = 0.45 \cdot 10^{-6}$ cm²/sec. $[Hb_4] = 10$ g⁰/₀ = $1.55 \cdot 10^{-3}$ mol/l; $P_1 = 0.2$ atm; $C_1 = 0.21 \cdot 10^{-3}$ mol/l. (1) $t^* = 0.538$; (2) $t^* = 2.42$; (3) $t^* = 5.64$.

These graphs are typical and do not differ in shape by changing b between 5 and 40 g⁰/₀. The oxygenation front is less sharp when $D_H \neq 0$. The lines indicated by AF_1 , AF_2 and AF_3 are the places of the oxygenation front calculated by the advancing front hypothesis

ours in the wrong direction because reaction velocity slows down the oxygen uptake and thus his values for $t^{1/2}$ and $t^{1/3}$ should lie above our curve rather than below. In our opinion the grid size in his computer program was too large. Kutchai calculated the saturation and oxygen concentration only at 10 points of the film. As we can see from Fig. 1 the saturation changes over 80% within $1/20$ part of the film.

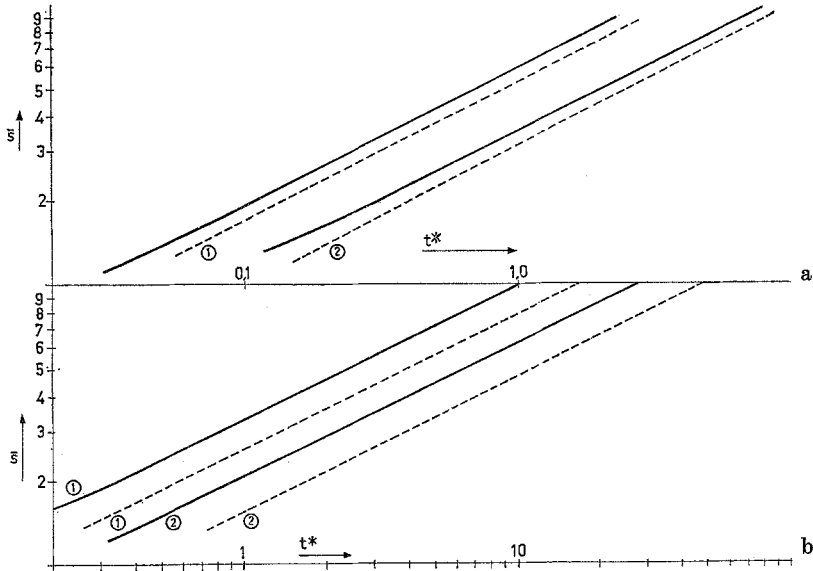


Fig.3. Average saturation as a function of time. For $\bar{S} > 0.2$ the solid lines are straight. ----- $D_H = 0$; ——— $D_H \neq 0$; a) $C_1 = 0.943 \cdot 10^{-3}$ mol/l; b) $C_1 = 0.21 \cdot 10^{-3}$ mol/l. (1) $b = 10$ g $^{\circ}$ /o, $D_H = 4.5 \cdot 10^{-7}$ cm 2 /sec; (2) $b = 30$ g $^{\circ}$ /o, $D_H = 0.94 \cdot 10^{-7}$ cm 2 /sec.

The influence of the diffusion of haemoglobin is larger if the O_2 gradients are smaller (C_1 smaller). The dotted lines are very well predicted by the advancing front hypothesis

In our program we proved also convergence when the number of grid points increases. We needed up to at least 80 steps to get accurate results.

The same criticism holds for Moll (1968) although he used a lower pO_2 at the boundary and finite reaction velocity, so his saturation profile in the film will be much smoother. We didn't use the same boundary conditions as Moll so that we are not able to compare his results with ours. Furthermore we doubt whether the reaction $Hb_4 \rightleftharpoons 4 O_2$ can be approximated by a one step reaction scheme over the whole range of 0–100% saturation.

It is interesting to see that at higher haemoglobin concentrations the difference between the calculated results with $D_H = 0$ and $D_H \neq 0$ still remains. This is to be expected since the values of D^* in (15) are quite independent of the haemoglobin concentration in the range studied here (Table 1) even though the numerical value of the diffusivity of haemoglobin varies ten-fold.

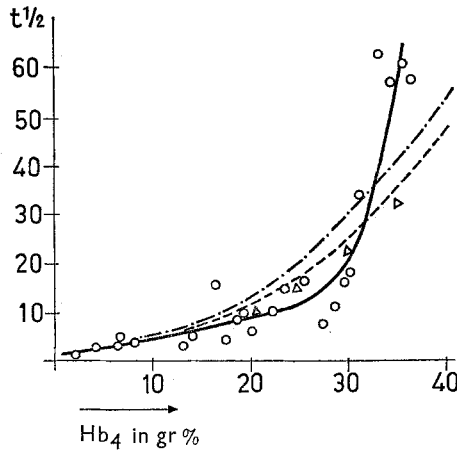


Fig. 4. Computed results compared with experiments of Klug *et al.* (1956) and calculations of Kutchai (1971a). $t^{1/2}$ in seconds. o — data and regression line respectively from experiments by Klug *et al.* (1956); — — — theoretical curve when $D_H = 0$; — — — theoretical curve where D_H is taken from Table 1; Δ — numerical results of Kutchai (1971a)

Advancing Front Hypothesis. The advancing front hypothesis assumes a sharp boundary between saturated and unsaturated haemoglobin, a linear $[O_2]$ gradient in the saturated layer, $[O_2] = C_0$ and $S = S_1$ in the unsaturated layer.

If xf is the distance of the saturation front to the liquid-gas interface, a relationship can be found for xf as a function of time. For the average oxygen saturation of the haemoglobin layer one can derive:

$$S(t) = \sqrt{\frac{2tD_C(C_1 - C_0)}{d^2} \frac{1}{4b(1 - S_1)}} (1 - S_1) + S_1. \quad (16)$$

Marx *et al.* (1960) gave a solution of Eq. (15) for $D_H = 0$ by means of an analog computer and concluded in a qualitative way that the advancing front assumptions are valid [Eq. (16)]. Quantitative conclusions, however, cannot be deduced from their report.

If we assume that $D_H = 0$ and integrate Eq. (15) over the thickness of the film, we arrive at:

$$\frac{d}{dt} \int_0^1 C^* dy + b^* \frac{d}{dt} \int_0^1 S dy = \left. \frac{\partial C}{\partial y} \right|_{y=0}^{y=1} \quad (17)$$

Dividing Eq. (17) into a zone of fully oxygenated and a zone of partially

Table 1. D^* as a function of b

b g $^{\circ}$ / l	$D_H \cdot 10^7$ cm 2 /sec	$D_C \cdot 10^5$ cm 2 /sec	D^*
10	4.5	1.6	0.185
20	2.05	1.2	0.224
25	1.3	1	0.222
30	0.94	0.83	0.224
35	0.65	0.67	0.222
40	0.44	0.58	0.199

10 g $^{\circ}$ / l = 1.55 10^{-3} mol/ l ; C_1 = 0.943 10^{-3} mol/ l .

$$D^* = b^* \frac{D_H}{D_C}; \quad b^* = \frac{4b}{C_1}; \quad D^* = \frac{4b}{C_1} \frac{D_H}{D_C}.$$

The values of D_C are taken from Kreuzer (1970) and those of D_H from data of Keller and Friedlander (1966) and compiled by Kreuzer (1970).

oxygenated haemoglobin (S_i) and using relations of $S(y)$ and $C(y)$ following the advancing front hypothesis provides:

$$S(t) = \sqrt{\frac{2t D_C (C_1 - C_0)}{d^2 [4b(1 - S_i) + \frac{1}{2}(C_1 - C_0)]}} (1 - S_i) + S_i. \quad (18)$$

The difference between Eqs. (16) and (18) is that in Eq. (18) $\frac{1}{2}(C_1 - C_0)$ accounts for the uptake of unbound oxygen. Indeed Eq. (18) describes (within the accuracy of the numerical scheme used, which has an error of less than 0.5% average saturation) the results given in Fig. 3 adequately for the case of $D_H = 0$. The solution of Eq. (15) for \bar{S} with $D_H = 0$ is predicted very well by Eq. (18) over a wide range of C_1 , b and S_i . The accuracy of the approximation depends on the value of C_1 and of the product $4b(1 - S_i)$. Our calculations show that the accuracy is good when $4b(1 - S_i) > 10^{-3}$ mol/ l and $C_1 > 0.410^{-3}$ mol/ l ($P_1 > 0.4$ atm). The difference between (18) and (16) depends on the values of the factors mentioned above and may be between 1 and 10% average saturation.

Hill (1929) described the oxygenation process for $S_i = 0$ by solving the diffusion equation without chemical reaction for x smaller than xf . At $x = xf$ the oxygen transport is coupled with chemical reaction. Hill (1929) and also Roughton (1959) did the same for $D_H \neq 0$ by solving the same diffusion equation for the diffusion of haemoglobin at x larger than xf . In fact both authors included in their calculations the effect of the physically dissolved oxygen but arrived at equations different from (18). Hill and Roughton concluded that their numerical results could be approximated relatively well by Eq. (16). They defined a factor

h_i in such a manner that Eq.(19a) provides the same results as their numerical solutions.

$$\bar{S} = h_i \sqrt{\frac{2t D_C C_1}{d^2 4b}} \tag{19a}$$

where $i = 1$ when $D_H = 0$ and $i = 2$ when $D_H \neq 0$. h_1 is a function of C_1/b and h_2 is a function of C_1/b and D_H/D_C . Roughton (1959) presented explicit formulas of h_1 and h_2 .

Comparing Eq.(19a) with Eq.(18) shows that when Eq.(18) provides a good approximation of the numerical results:

$$h_1 = \sqrt{\frac{1}{1 + 1/2 C_1/4b}} \tag{19b}$$

We also computed h_1 and h_2 values and compared them with data published by Roughton (1959) in Tables 2 and 3. As far as h_1 is concerned the difference becomes larger for higher values of C_1/b . The approximations of Hill are less satisfactory in this range. Our data for h_2 in Table 3 are calculated from Fig.3. To be able to compare our values with the results of Roughton the table from Roughton (1959) was interpolated. Here we see that the deviation is getting larger when C_1/b becomes smaller which is just the opposite of h_1 . In this paper we will not further discuss the deviation between the data of Roughton and ours.

Table 2. Values of factor h_1 for various values of C_1/b when $D_H = 0$. The first row of figures are from Roughton (1959), the second row of figures are calculated by the author

C_1/b	0.005	0.0202	0.0824	0.191	0.356	0.592	0.92
h_1	1	0.995	0.985	0.97	0.948	0.92	0.885
	0.998	0.995	0.980	0.955	0.921	0.878	0.827

Table 3. Values of factor h_2 for various values of b/C_1 and D_H/D_C . The first row of figures are a result of interpolation of a table from Roughton (1959), the second row of figures are calculated by the author from Fig.3

		b/C_1				
		6.5	19	29	89	
		0.0114	—	1.08	—	1.38
				1.07		1.27
	$\frac{D_H}{D_C}$	0.0281	1.05	—	1.28	—
			1.05		1.22	

Kutchai (1971b) concluded that the advancing front hypothesis predicts very well the results of Klug *et al.* (1956). This conclusion is misleading. Recalculating the diffusion coefficients of oxygen from his results provides values of D_{O_2} which are not in agreement with the values Kreuzer published in his review of 1970 and Kutchai himself used in a previous paper (1971a).

3. Steady-State Oxygen Diffusion in a Moving Flat Film of Haemoglobin Solution; Two-Dimensional Problem

We now consider a haemoglobin solution streaming in a film along a flat plate or between two flat membranes. In both cases there exists a laminar parabolic flow in the z direction for low Reynolds numbers. In the case of the flat plate, where film thickness = d , oxygen diffuses at $x = 0$ from the gas into the region where the velocity gradient is zero. With the flat membrane, where film thickness = $2d$, oxygen diffuses from both sides into the region where the oxygen gradient is maximum. In the case of two membranes we will consider only half of the film. Eq. (9) now reduces to:

$$v_z(x) \frac{\partial}{\partial z} (4bS + C) = D_C \frac{\partial^2 C}{\partial x^2} + 4b D_H \frac{\partial^2 S}{\partial x^2} \quad (20)$$

with the boundary conditions:

<i>flat plate</i>	<i>flat membrane</i>	
$x = d; \quad \frac{\partial C}{\partial x} = 0$	$x = d; \quad \frac{\partial C}{\partial x} = 0$	(21)
$x = 0$ and $z \geq 0$	$x = 0$ and $z \geq 0$	
$C = C_1$	$C = C_1$	
$z < 0$ all x $S = S_i, C = C_0$	$z < 0$ all x $S = S_i, C = C_0$	

Again we make the problem dimensionless by

$$\begin{aligned}
 C^* &= C/C_1 & z^* &= \frac{zD_C}{d^2 v_g} \\
 b^* &= 4b/C_1 & & \\
 y &= x/d & & \\
 D^* &= b^* D_H/D_C & & \text{where } v_g = \text{average velocity} \\
 v^* &= \frac{v}{v_g} & & \text{of the film}
 \end{aligned} \quad (22)$$

$$v^* \frac{\partial}{\partial z^*} (C^* + b^* S) = \frac{\partial^2 C^*}{\partial y^2} + D^* \frac{\partial^2 S}{\partial y^2}. \tag{23}$$

Eq.(23) with boundary conditions is numerically solved.

Define $\bar{S}(z^*) \equiv \int_0^1 v^*(z^*, y) S(z^*, y) dy$. (24)

Solutions of \bar{S} are shown in Fig. 5.

Here again the influence of the diffusion of Hb_4 is small due to the high oxygen gradients.

In the case of a flat film approximate solutions can be obtained directly from the advancing front hypothesis (see also Lightfoot, 1968; Buckles, 1966), or by integrating the transport equations similar to Eq.(17).

We get for the flat plate:

$$\bar{S} = S_i + (1 - S_i) \left(-\frac{1}{2} p^3 + \frac{3}{2} p \right) \tag{25}$$

$$z^* = 3/2 \left[-p^4 \frac{1}{8} \left(\frac{1}{2} + Q \right) + \frac{1}{4} p^2 (1 + Q) \right]$$

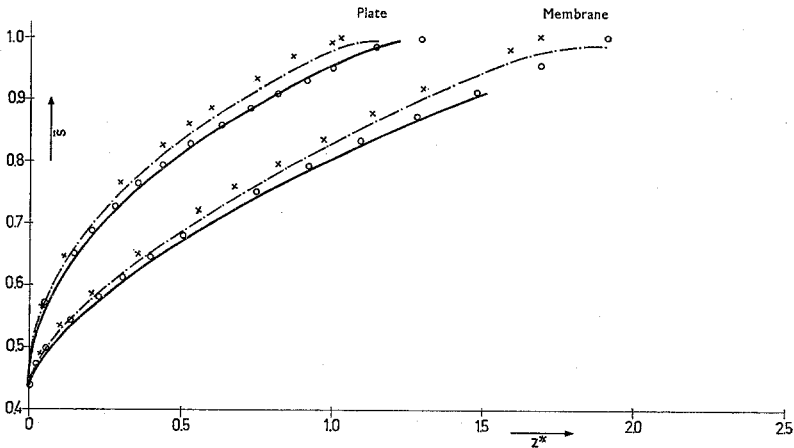


Fig. 5. Saturation as a function of z^* in the case of flat plate flow and flat membrane flow. — $D_H = 0$; - - - $D_H = 0.49 \cdot 10^{-6} \text{ cm}^2/\text{sec}$; \circ corrected advancing front equation; \times uncorrected advancing front equation; $Hb_4 = 0.1125 \cdot 10^{-2} \text{ mol/l}$; $C_1 = 0.943 \cdot 10^{-3} \text{ mol/l}$; $C_0 = 0.16 \cdot 10^{-4} \text{ mol/l}$; $S_i = 0.44$.

There is fairly good agreement between the solid lines for $D_H = 0$ and the circles for the corrected advancing front equation

and for the flat membrane (see also appendix 1):

$$\bar{S} = S_t + (1 - S_t) \left(-\frac{1}{2} p^3 + \frac{3}{2} p^2 \right) \quad (26)$$

$$z^* = 3 \left[-p^4 (1/32 + Q/16) + p^3 (1/9 + Q/6) \right]$$

where

$$p = xf/d$$

$$Q = \frac{(1 - S_t) 4b}{1/2 (C_1 - C_0)}. \quad (27)$$

The results are also shown in Fig. 5. For the case of the flat plate the advancing front gives slightly better results than for the flat membrane. In this case again the advancing front equations corrected for the physically dissolved O_2 provide better results in predicting \bar{S} when $D_H = 0$.

Lightfoot (1968) introduced, in his equations for the flat membrane, by intuition a factor $1/2 (C_1 - C_0)$ to correct for the physically dissolved oxygen and arrived at the following equation for z^* :

$$z^* = 3 \left[-p^4 (1/16 + Q/16) + p^3 (1/6 + Q/6) \right]. \quad (28)$$

Conclusions

We can conclude that for the transfer of oxygen into haemoglobin solution, the oxygen saturation of haemoglobin obeys the same type of differential equation as does oxygen. The conditions are that haemoglobin remains tetrameric and that the diffusion coefficient of haemoglobin does not change with the number of oxygen molecules combined with haemoglobin. Under these conditions and for the condition that $\text{grad}(b) = 0$ at the boundaries, we proved that the total haemoglobin concentration is constant.

We have shown that the influence of the diffusion of haemoglobin has a considerable effect on the oxygenation process. This influence is larger when the oxygen partial pressure at the boundary, i.e. the $[O_2]$ gradients in the layer, become smaller.

Comparison of the theory with experimental results does not lead to a clear-cut conclusion as to whether chemical reaction velocity plays a role or not. For haemoglobin concentrations lower than 30 g 0 / $_0$ there is fair agreement between theory and experiment. Reaction velocity, however, slows down the process and therefore the theory would deviate more from the experimental results. At higher haemoglobin concentrations the deviation is more pronounced. A change in D_{O_2} of more than 20 0 / $_0$ would be required to account for this deviation. Reaction velocity would approach theory and experiment but then its effect should be

larger at high haemoglobin concentrations than at lower haemoglobin concentrations. Experiments with lower $[O_2]$ gradients might give better insight into the role of reaction velocity.

Furthermore, the validity of the advancing front hypothesis is tested when D_H is assumed to be zero. Formal integration of the equation involved gives formulas in which a term accounts for the physically dissolved oxygen. The first question, however, is which equation one adopts to describe the system (e.g. $D_H = 0$ or $D_H \neq 0$) and the second is which approximation is applied to the solution.

We showed the validity of the advancing front hypothesis in the case of flat-film flow. Formulas (24) and (25) may be very useful in the case of membrane oxygenators and vertical plate oxygenators.

Symbols

α	solubility	C^e	equilibrium concentration
b	total concentration of haemoglobin	D_H	diffusion coefficient of haemoglobin
d	film thickness	D_C	diffusion coefficient of oxygen
h_1, h_2	correction factors	D_X	diffusion coefficient of X
k_i	reaction velocity constant of i^{th} reaction step (back reaction)	D^*	dimensionless diffusion coefficient
k_i'	as k_i (forward reaction)	K_i	k_i'/k_i
p	x/d	P_{O_2}, P_1	boundary conditions of O_2
t	time		partial pressure
\vec{v}	velocity vector	R_C	reaction velocity of oxygen
v	average velocity	$R_{H_{i,j}}$	reaction velocity of haemoglobin species
x	position in x -direction	R_X	reaction velocity of species X
x_f	position of oxygenation front when fluid-gas interface at $x = 0$	R_s	saturation velocity
y	x/d	S	oxygen saturation of haemoglobin
z	position in z -direction	\bar{S}	average oxygen saturation
b^*	dimensionless haemoglobin concentration	S_i	initial saturation
t^*	dimensionless time	X	species such as $O_2, Hb_4,$ $Hb_4O_2, Hb_4O_4, Hb_4O_6, Hb_4O_8$
v^*	dimensionless velocity	$[X]$	concentration of species X
z^*	dimensionless distance		
C_0, C_1	boundary conditions of $[O_2]$		

Appendix I

Derivation of corrected advancing front equation for the flat membrane case.

Similar to Eq. (17) we get from (23):

$$\int_0^1 v^* \frac{\partial}{\partial z^*} (C^* + b^* S) dy = \int_0^1 \left(\frac{\partial^2 C^*}{\partial y^2} + D^* \frac{\partial^2 S}{\partial y^2} \right) dy. \quad (29)$$

Since v^* is only a function of y we get

$$\int_0^1 \frac{\partial}{\partial z^*} v^* (C^* + b^* S) dy = \int_0^1 \frac{\partial^2 C^*}{\partial y^2} dy + D^* \int_0^1 \frac{\partial^2 S}{\partial y^2} dy. \quad (30)$$

We now are allowed to interchange the differential and integral signs. The right part of Eq. (30) may be rewritten leading to:

$$\begin{aligned} \frac{d}{dz^*} \int_0^1 (C^* + b^* S) v^* dy &= \left(\frac{\partial C^*}{\partial y} \right)_{y=1} - \left(\frac{\partial C^*}{\partial y} \right)_{y=0} + D^* \left(\frac{\partial S}{\partial y} \right)_{y=1} \\ &\quad - D^* \left(\frac{\partial S}{\partial y} \right)_{y=0}. \end{aligned} \quad (31)$$

Because of the boundary conditions

$$\left(\frac{\partial C^*}{\partial y} \right)_{y=1} = D^* \left(\frac{\partial S}{\partial y} \right)_{y=1} = 0.$$

Also $D^* \left(\frac{\partial S}{\partial y} \right)_{y=0} = 0$ because no transfer of haemoglobin occurs through the membrane-haemoglobin interface. In fact this last condition is in contradiction to the chemical equilibrium assumption. Since we compared the advancing front equations with theory when $D^* = 0$ we will not go into details about this last condition. When we assume a sharp border between the oxygenated and non-oxygenated region at position $y = p$, we can rewrite Eq. (31) as:

$$\frac{d}{dz^*} \left[\int_0^p (C^* + b^* S) v^* dy + \int_p^1 (C^* + b^* S) v^* dy \right] = - \left(\frac{\partial C^*}{\partial y} \right)_{y=0}. \quad (32)$$

Because of the advancing front hypothesis:

$$y < p \quad S = 1 \quad \text{and} \quad C^* = 1 - \left(\frac{1 - C_0^*}{p} \right) y \quad (33)$$

$$y \geq p \quad S = S_i \quad \text{and} \quad C^* = C_0^*. \quad (34)$$

So

$$\left(\frac{\partial C^*}{\partial y} \right)_{y=0} = - \frac{1 - C_0^*}{p}. \quad (35)$$

Because of the parabolic velocity profile:

$$v^* = 3y - \frac{3}{2} y^2. \quad (36)$$

After substitution of Eqs. (33, 34) and (35) into (32) we arrive at forms we can integrate. Thus we get:

$$\begin{aligned} \frac{d}{dz^*} \left[\left(\frac{3}{2} p^2 - \frac{1}{2} p^3 \right) [(1 - C_0^*) + (1 - S_i) b^*] - (1 - C_0^*) \left(p^2 - \frac{3}{8} p^3 \right) \right. \\ \left. + (1 + b^* S_i) \right] = \left(\frac{1 - C_0^*}{p} \right). \end{aligned} \quad (37)$$

Since p is a function of z^* we get:

$$\left[\left(3p - \frac{3}{2} p^2 \right) [(1 - C_0^*) + (1 - S_i) b^*] - (1 - C_0^*) \left(2p - \frac{9}{8} p^2 \right) \right] \frac{dp}{dz^*} = \frac{1 - C_0^*}{p}. \quad (38)$$

We multiply Eq. (38) by $p \cdot dz^*/[1/2 (1 - C_0^*)]$,

integrate subsequently and get:

$$z^* = 3 [-p^4 (1/32 + Q/16) + p^3 (1/9 + Q/6)]. \quad (39)$$

Eq. (39) is the same as the second part of Eq. (26).

Substitution of (33), (34) and (36) into Eq. (24) leads to:

$$\begin{aligned} \bar{S} &= \int_0^p \left(3y - \frac{3}{2} y^2 \right) dy + S_i \int_p^1 \left(3y - \frac{3}{2} y^2 \right) dy = \frac{3}{2} p^2 - \frac{1}{2} p^3 \\ &+ S_i \left(1 - \frac{3}{2} p^2 + \frac{1}{2} p^3 \right) = S_i + (1 - S_i) \left(-\frac{1}{2} p^3 + \frac{3}{2} p^2 \right). \end{aligned} \quad (40)$$

Eq. (40) is the same as the first part of Eq. (26).

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