J. theor. Biol. (1971) **32**, 185–190

Transport through Hemoglobin Solutions: A Sensitivity Analysis

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(*Received* 28 *August* 1970, *and in revised form* 30 *November* 1970)

A sensitivity analysis has been used in an attempt to elucidate the mechanism of the interaction of the effect of carbon dioxide diffusion upon the facilitated transport of oxygen in dilute hemoglobin solutions. The primary mechanism of oxygen augmentation is shown to be the parallel diffusion of the oxyhemoglobin association, as had been previously suggested. At film thicknesses in the range of 10^{-4} to 10^{-3} cm, the carbaminyl hemoglobin reaction begins to alter the oxyhemoglobin gradient (steepening it in the case of counter-current oxygen–carbon dioxide fluxes) thereby affecting the augmentation. The bicarbonate reaction exerts a similar, somewhat stronger, effect at phase lengths of 0·01 to 0·1 cm.

1. Introduction

The complicated, heterogeneous nature of blood has impeded the development of an understanding of such factors as the uptake and discharge of gases like oxygen and carbon dioxide, and a number of questions have been answered only partially or inadequately. Of special interest here are questions such as under what circumstances is the oxygenation of blood diffusion or reaction rate controlling in both *in vivo* and *in vitro* situations, and what is the effect of carbon dioxide transfer on oxygenation in both *in vivo* and *in vitro* cases.

A simple model, in the sense of Kac (1969), has been developed for exploring questions such as those above, with the anticipation that the results might both provide some insight concerning the nature of the chemical

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reaction effect on transport and also guide the development of more complete models for further study. Furthermore, the analysis presented here and previously (Ulanowicz & Frazier, 1970) may provide a framework for the interpretation of experimental data and for the development of a diagnostic tool for the study of abnormal and impaired hemoglobins. However, it must be kept in mind that the results from simplistic models such as this may not be directly and quantitatively applicable to the *in vivo* situation.

The diffusion of oxygen and carbon dioxide through hemoglobin is representative of the broad category of multi-component diffusion accompanied by multiple reactions. A full and complete analysis of such a system requires the solution of a set of coupled, non-linear transport equations. In lieu of this, considerable information concerning the qualitative behavior of the coupling can be obtained from a linearized near-equilibrium model of a dilute Hb solution. This model is described elsewhere (Ulanowicz & Frazier, 1970), and includes the following reversible set of chemical reactions (Roughton, 1964):

$$H^+ + Hb \underset{k_1^r}{\overset{k_1^f}{\rightleftarrows}} HHb^+, \tag{1}$$

$$H^+ + HbO_2 \underset{k_2^r}{\overset{k_2^f}{\rightleftarrows}} HHbO_2^+, \tag{2}$$

$$O_2 + Hb \underset{k_3^r}{\overset{k_3^f}{\rightleftarrows}} HbO_2, \tag{3}$$

$$H^+ + HCO_3^- \underset{k_4^r}{\overset{k_4^f}{\rightleftarrows}} CO_2, \tag{4}$$

$$CO_2 + Hb \underset{k_5^r}{\overset{k_5^f}{\rightleftarrows}} HbCOO^- + H^+. \tag{5}$$

The model considered here can be expanded to include additional reactions that take place in this system, such as $O_2 + HbO_2 = HbO_4$, as quantitative information concerning their rates becomes available.

The mathematical solution to this model consists of complicated combinations of matrices and partitioned matrices, which make them amenable to numerical computation, but difficult to trace for the mechanisms of prognosticated qualitative behavior. Thus, for example, one may calculate that the reaction-augmented diffusion of oxygen through hemoglobin, under certain conditions, may be significantly affected by the concomitant flux of carbon dioxide. However, to state with any degree of quantitative certainty which elements of reaction and diffusion contribute to this interaction over various ranges of parameters requires separate analysis. To this end, we have employed a primitive form of parameter sensitivity analysis to deduce which reaction and diffusion fluxes are most important in the coupling.

2. Sensitivity Analysis

The behavior of this system with one-dimensional transfer and values of the parameters taken from the literature (see Ulanowicz & Frazier, 1970, for a summary) is shown as Fig. 1. Along the ordinate is plotted the so-called augmentation coefficient $J_{O_2}/J_{O_2\,\text{inert}}$ which is the quotient of the oxygen flux as calculated divided by the oxygen flux computed as if oxygen were inert chemically. Thus, a value of $J_{O_2}/J_{O_2\,\text{inert}}$ of unity indicates no augmentation of the mass transfer while a value greater than unity indicates facilitated diffusion.

If the only reaction occurring in this system were the oxyhemoglobin association, the facilitation curve would be a simple sigmoid, levelling out at about $J_{O_2}/J_{O_2\,\text{inert}} = 1{\cdot}13$ for a dilute solution, as shown by the broken curve in Fig. 1. Deviation from this behavior indicates the interference of

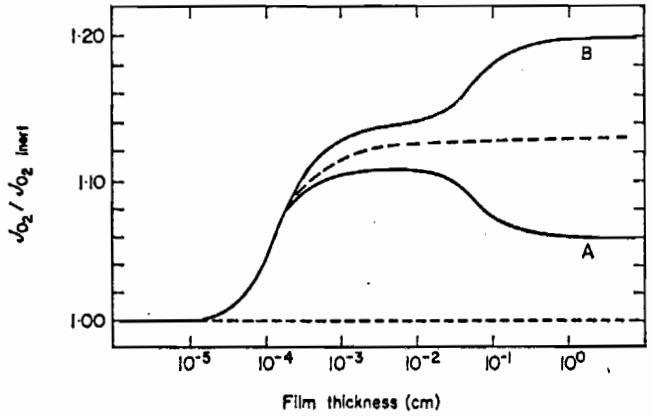

FIG. 1. Effect of CO_2 on the oxygen augmentation coefficient for a 5 g/100 ml. Hb solution. Curve A, co-current transfer; curve B, counter-current transfer; ----, O_2 transfer only.

carbon dioxide transport with its associated reactions, as shown by curves A and B. The mechanism of this interference can be identified by use of a sensitivity analysis.

A quantitative estimate of how important any one process is in the overall augmentation scheme can be had by calculating how "sensitive" the augmentation is to a change in the characteristic parameter of a given process. For example, the partial derivative of the augmentation coefficient with respect to D_{HbO_2},

$$\frac{\partial}{\partial D_{HbO_2}}(J_{O_2}/J_{O_2\,\text{Inert}}),$$

should provide one with a measure of the contribution of the diffusion of oxyhemoglobin to the facilitation. Now, the value of the various parameters in this system differ significantly in magnitude, and the above derivatives indicate the sensitivity of the augmentation to a unit change in the parameter under investigation, so an index of the *relative* importance of, say, the diffusion of oxyhemoglobin, would be the dimensionless quantity

$$D_{HbO_2}\frac{\partial}{\partial D_{HbO_2}}(J_{O_2}/J_{O_2\,\text{inert}}).$$

Such a quantity is referred to as a "sensitivity index".

The systematic consideration and calculation of the parameter sensitivity coefficients (the partial derivatives alone) is provided by Tomovic (1963). Because of the complicated manner in which the parameters are combined in this system, however, we have here resorted to a good approximation of the sensitivity index which is very easy to obtain once one has the apparatus available for calculating augmentation coefficients, $J_{O_2}/J_{O_2\,\text{inert}}$. First, the augmentation coefficient at the exact value of the parameter is calculated (Ulanowicz & Frazier, 1970). Next, the parameter is increased by some small amount, say 1%, and the augmentation coefficient is recalculated. The difference between the two values of the augmentation coefficient, divided by the parameter perturbation, is a difference quotient closely approximating the sensitivity coefficient. Multiplication by the original value of the parameter yields the sensitivity index.

Figure 2 is a plot of the sensitivity indices of the three major reaction rate coefficients as a function of phase length under the conditions of curve B in Fig. 1. Coincident with the initial rise of the oxygen faciliation coefficient, as shown in Fig. 1, is the sensitivity index of the oxyhemoglobin reaction, characterized by k_3^f. This index peaks at about 10^{-4} cm which is on the order of magnitude of the red blood cell. The carbaminyl reaction sensitivity occurs over the range 10^{-4} to 10^{-3} cm, the same range over which the oxygen augmentation as calculated by the multi-reaction scheme first differs from that predicted by the uni-reaction oxyhemoglobin scheme. The sensitivity index of the bicarbonate reaction appears in the range 0·01 to 0·1 cm, exactly where the oxygen flux undergoes accelerated augmentation in the multi-reaction scheme.

When the sensitivity indices of the diffusion parameters were calculated, only two of the diffusion coefficients were of significance, D_{O_2} and D_{HbO_2}. These were almost equal in magnitude and opposite in sign throughout the whole range of film thicknesses as shown in Fig. 3. The sensitivities of the other diffusion parameters were less than 5% of those presented here. This confirms that the primary mechanism of oxygen augmentation is the parallel

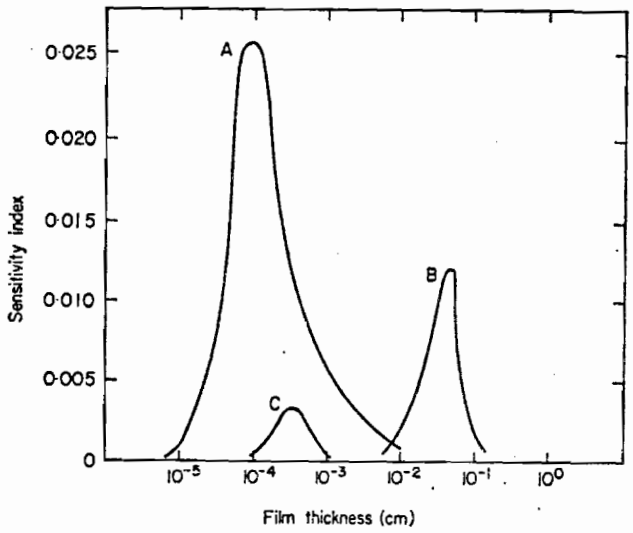

FIG. 2. Sensitivity of the oxygen flux to the reaction rate coefficients. Curve A, rate coefficient k_3'; curve B, rate coefficient k_4'; curve C, rate coefficient k_5'.

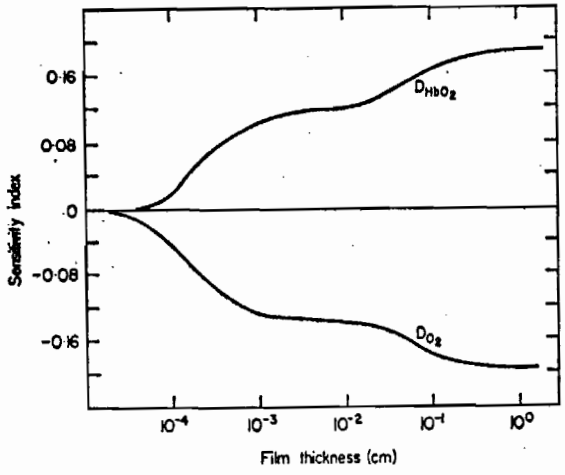

FIG. 3. Sensitivity of the oxygen flux to the diffusion coefficients.

diffusion of the oxyhemoglobin species, as suggested by Fatt & LaForce (1961) and also Keller & Friedlander (1966), and that coupling of the oxygen flux to the other fluxes in the mixture is of secondary importance in the dilute solutions considered here.

Beginning around 10^{-4} the oxyhemoglobin species, diffusing into a counter gradient of carbon dioxide, finds its own gradient steepened *via* the kinetics of the carbaminyl reaction. The parallel flux of oxygen and thereby the oxygen augmentation is increased above what it would be in the single oxyhemoglobin reaction scheme. In like manner at larger phase lengths, a further increase in facilitation is achieved *via* the bicarbonate reaction.

The authors acknowledge the University of Tennessee Computational Center for providing computer time for these calculations.

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