NONLINEAR DIFFUSION-REACTION PROBLEMS

IN

BIOLOGICAL SYSTEMS

THESIS

BY

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To

MY FATHER AND MOTHER

who have given so much ---

and asked for so little in return.

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SYNOPSIS

The mathematical description of various processes such as diffusion-reaction mechanism occurring in biological systems leads to a system of non-linear differential equations. The thesis deals with two types of applications: (i) the oxygenation of blood in lung capillaries, and (ii) the interaction of diffusion reaction in artificial, enzymatically active membranes. Accordingly, the work has been divided into two parts.

PART I

CHAPTER 1: This chapter deals with the general introduction of the physiological background of the problem together with a brief literature review.

The process of respiration essentially involves an uptake of oxygen from the atmosphere and disposal of carbon-dioxide. Oxygen is carried by the blood perfusing the pulmonary circulation which simultaneously gives up the additional carbon dioxide that it has brought from the tissues. Of the total amount of oxygen carried by the blood, a small amount (0.3%) is dissolved physically in the plasma whereas quite a significant part of it (20.1%) combines chemically with haemoglobin which augments the transfer of oxygen from a region of higher concentration to that of lower concentration. Gas exchange process in the lungs between air in the alveolar region and blood flowing through the capillaries depends mainly on three transport mechanisms, namely, molecular diffusion, facilitated diffusion, and convection.

Murray (1971) has proposed a mathematical model for studying the facilitated diffusion of oxygen across a membrane containing haemoglobin solution. Singh et.al (1978) have discussed the facilitated diffusion transport of O_2 and CO_2 across a membrane containing haemoglobin in acqueous solution when O_2 and CO_2 diffused in the opposite directions. Colton and Drake (1971) have shown that the boundary conditions affect greatly the oxygen transport to blood flowing in a tube. As a result by modifying the boundary conditions Singh et al. (1977) have applied their model to study behaviour of O_2 and CO_2 in the presence of haemoglobin in pulmonary capillaries.

However the above studies do not account for the transfer of O_2 and CO_2 due to convection. The present study presents a mathematical analysis of gas exchange in pulmonary capillaries by taking into account the convective effect of the blood. Since the process of gas exchange leading to the oxygenation of the blood in the lungs is very fast, it will be difficult to set up an experimental study to determine the effects of various parameters on equilibration rate. Further it is proposed here to study analytically the effects of various physiological parameters on equilibration rate in pathological conditions. This study is relevant for understanding the altered respiratory physiology in conditions of hypoxia at high altitude, anaemias, emphysema, fibrosis, etc...

CHAPTER 2: It describes a theoretical model for studying the rate of oxygenation of blood in pulmonary capillaries. The model deals with the convective effect of the blood on the transport of oxygen and carbon dioxide due to their pure diffusional flux as well as the facilitated diffusion. The venous (deoxygenated) blood enters the capillary at $z = 0$ and it traverses a length L to return as fully oxygenated (arterial) blood. As the blood enters the capillary, it loses the carbon dioxide and gains oxygen. The gases, oxygen and carbon dioxide, in the blood combine reversibly with the haemoglobin as

$$Hb + O_2 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} HbO_2$$

$$Hb + CO_2 \underset{m_2}{\overset{m_1}{\rightleftharpoons}} HbCO_2 ,$$

In the first stage of the analysis, the equilibrium solution of the system is obtained which helps us in verifying the results obtained from this model with the available physiological data for the arterial blood.

The model confirms the well-known Bohr's and Haldane's effects and the analysis shows that once equilibrium is reached no further diffusion of gases across the membrane takes place and the species acquire the material balance through the process of chemical combination. It has been shown that in arterial blood, about 92% of the haemoglobin combines with O_2 and the arterial PO_2 and PCO_2 are the same as the alveolar PO_2 and PCO_2 respectively. The concentration of $HbCO_2$ is shown to vary linearly as PCO_2 changes from 40 mm Hg to 46 mm Hg. It is shown that the concentration of free haemoglobin not combining with O_2 or CO_2 increases with decrease in PO_2 and that the percentage of free haemoglobin at a given PO_2 is independent of the concentration of the total haemoglobin present in the blood.

In the second stage of the analysis, the distance traversed by the blood in pulmonary capillaries before equilibration is reached, is determined by setting up an appropriate eigenvalue problem. The governing equations of the model are linearized about the equilibrium solution. A scale analysis appropriate to physiological situations is used to obtain the solution. Furthermore, the model is used to predict the equilibrium length under various pathological conditions.

This analysis shows that in a normal subject, the blood is completely oxygenated within approximately one thirtieth part of the capillary. It is found that the dissolved O_2 takes the longest in reaching equilibration whereas CO_2 attains equilibration at the fastest rate - a result which may explain certain borderline respiratory disorders. It is found that the alveolar PCO_2 and the forward and backward reaction rates for CO_2 with Hb do not materially affect the equilibrium length. It is further shown that the length of the pulmonary capillaries over which complete equilibrium occurs, increases as:

a) the speed of blood increases in hyperkinetic conditions

b) the alveolar PO_2 falls

c) the concentration of the total haemoglobin increases

d) the caliber of the pulmonary capillary increases

e) the diffusion coefficient of the species decreases

f) the dissociation rate of oxyhaemoglobin increases or the association rate decreases.

These results have been applied in various pathological conditions, like high altitude, anaemia, muscular exercise, meditation, fever, smoking, polycythaemia, hyper and hypo-ventilation etc.

However, it should be noted that the above mathematical analysis is done only for physiological data. Further, the system of equations, obtained after linearization has also been solved for the arbitrary values of the parameters without neglecting any term. A complete mathematical analysis, which is called here exact analysis, is also given. The results obtained by two methods are qualitatively the same.

The latter method eventually leads to a transcendental equation in k which has been solved numerically to obtain the smallest root to determine the rate at which equilibration is achieved.

It is noteworthy that the intermediate terms occurring in computation are of higher orders. From the convergence point of view, the solution of the transcendental equation requires much more significant places than are normally available on the computer. Hence, a highly skilled multi-precision technique will be described in Appendix-I. This technique allows us to make the computation upto any number of significant digits. By this technique it was possible to obtain an acceptable solution of the physical problem.

CHAPTER 3: The governing equations developed in Chapter-2 are solved numerically by using the well-known semi-implicit scheme for various sets of initial data. The radial as well as axial concentration profiles of various species are calculated. The average partial pressure of oxygen in the blood is also computed at every cross section of the capillary. The results have been discussed under normal as well as pathological conditions. It has been found that if the venous blood returning to the lungs is less saturated compared to that under normal conditions, the blood will traverse a larger distance in the capillary, before getting fully oxygenated.

CHAPTER 4: The model developed in Chapter 2 for the oxygenation of blood describing the simultaneous diffusion of oxygen and carbon dioxide is based on one step kinetics. However, one step kinetics leads to a hyperbolic, rather than sigmodial oxy-haemoglobin saturation curve. In view of the structural configuration of haemoglobin the four step scheme due to Adair seems to be more accurate and has accordingly been adopted in this chapter.

Besides, the saturation function obtained by earlier investigators does not include the simultaneous effect of CO_2. However, the present analysis is of importance as it incorporates this short-coming as well.

This analysis exhibits an explicit dependence of CO_2 on the fractional saturation of haemoglobin with O_2. A set of equilibrium constants arising in the oxygen dissociation curve has been obtained by the least square method of optimization suggested by Marquardt (1963). It has been shown that the values of these constants lead to a saturation function which fits in very well with the one based on experimental data.

Furthermore, the analysis shows that under normal physiological situations main bulk of oxygenated oxyhaemoglobin exists in fully saturated form. Thesd results are applied under various pathological conditions as high altitude, anaemic conditions etc.

<u>APPENDIX-I:</u> The intermediate terms involved in computation of a root of transcendental equation, discussed in Chapter-2, are of higher orders. A programming technique is developed in this Appendix, which improves the calculations.

As is well known, floating point computation is by nature, inexact, that is to say, in floating-point arithmetic, the following more prevalent limitations are frequently observed:

i) The results are usually inaccurate because of errors arising from too many round-offs, etc.

ii) The calculations are restricted to a specified number of significant decimal places beyond which the computer can neither read nor execute/write.

From the point of convergence, it may sometimes be required to include much more significant places than are normally available with the existing computers. The transcendental equation of Chapter-2 requires at least 50 decimal place calculations in order to obtain any acceptable solution.

By splitting the mantissa of a multiple precision number into BLOCKS of constant width, it has been shown that the precision of a computer can be increased as high as we please by merely developing a FORTRAN program that can force the computer to perform all arithmetical calculations upto any desired number of significant decimal places. Some of the salient features of such a programming are summarized as follows:

1. It reduces inherent errors arising due to approximate nature of representing in some finite number of digits a number that cannot ordinarily be represented exactly in the number of digits available with the particular installation being used.

2. The working of the computer proceeds just as if it were a decimal computer. Naturally, we should expect better results even for the same number of digits as the computer normally takes.

3. It takes due care of very low/high numbers occurring in intermediate calculations as one word space is being provided to store the exponent itself.

4. Being problem oriented in nature, the FORTRAN language is most commonly understood by a large section of programmers. It is mainly for this reason that although it requires comparatively more time and space, one can save one's own valuable time in learning complicated assembly languages which differ from computer to computer.

5. It can be easily extended to complex numbers.

APPENDIX-II: A complete listing of the subroutine subprogrammes in FORTRAN is given for the algorithms developed in Appendix-I.

PART II

CHAPTER 1: The coupling of diffusion and reaction in artificial, enzymatically active membranes gives rise to various phenomena of biological significance such as hysteresis, oscillations, and pattern formation. The mathematical description of the interaction of diffusion and enzyme reaction in artificial membranes eventually leads to a non-linear system of algebraic equations. These equations involve the state of the system which may be a vector of concentrations in the discrete case or a vector of concentration profiles in the continuous case. In addition there may be a number of parameters describing the chemistry, environment, and the geometry of the system. In practice, it is, generally, not desirable to vary all the parameters at the same time independently, and hence, we vary one parameter at a time in this study.

Thus the motivation of this study is to find a family of solutions depending on the parameter. Hence, the present investigation deals with the development of some efficient algorithms for exploring a whole connected set of solutions.

CHAPTER 2: By using continuity properties, Kubicek (1976) has developed a numerical algorithm for extending a smooth arc of solutions from a starting point ($u_o \lambda_o$). However, the bifurcation points and the bifurcating branches of solutions are ignored by such an algorithm. In this chapter an attempt is made to modify this method by providing the following possibilities for exploring all the branches of solutions which are connected to the starting point.

i) location of bifurcation points,

ii) distinction of bifurcation points from turning points,

and

iii) computation of points on bifurcation branches in the vicinity of a bifurcation point in order to treat them as starting points in a subsequent application of the continuation method.

This technique is easy to implement numerically and allows the computation to proceed past turning points as well as along unstable solutions.

This method is applied to a model, proposed by Kernevez et al. (1979) for studying the phenomenon of spontaneous pattern formation by a mathematical representation of immobilized enzyme ribbon. This model is an open system where an external reservoir supplies a flow of substrates which are consumed in an enzyme reaction inhibited by excess of one of the substrates and activated by the other.

It has been found that the behaviour of the solutions for the same system for finite N by using the different approximations for the boundary conditions is not similar.

Also for the distributed system it has been shown that:

i) the bifurcations are unilateral,

ii) each primary bifurcation branch attached to the ith eigen-function of the Laplacian operator with Neumann boundary conditions forms a closed loop passing through the two bifurcation points, on the trivial branch, corresponding to the ith eigen-value.

iii) the secondary bifurcation branch attached to the secondary bifurcation points lying on the primary bifurcation branches corresponding to successive eigenfunctions ($w_i, i > 1$) forms a "lemniscate shaped curve" and

iv) the behaviour of the system is much simpler compared to that in zero dimensional system.

Furthermore, it has been shown that this simple model exhibits a hysteresis phenomenon.

CHAPTER 3: The method described in Chapter-2 uses the natural basis of some finite dimensional space and becomes very time consuming as the number of degrees of freedom increases. Hence, the present chapter is devoted to a numerical method, called the "Faedo-Galerkin method", in order to reduce the degrees of freedom by choosing some other appropriate basis. The set of first M eigen-functions of the Laplacian operator with Neumann boundary conditions have been used as the basis of some finite dimensional space. This method is found to save the computer time significantly and the first few eigen-functions are enough to obtain a good approximation of the exact solutions. The results have been computed in zero and one, dimensions, and are compared with the one obtained by the technique described in Chapter 2. The following phenomena, observed in the approximate problem, have been justified mathematically.

i) If (u_0, λ_0) is a simple bifurcation point of the original problem, the pair of bifurcation branches intersect at the bifurcation point if it is symmetry breaking otherwise the pair of branches forms a degenerate hyperbola around that point.

ii) The simple bifurcation points on the trivial branch are found only corresponding to the eigenfunctions used in the approximation, and

iii) The symmetry breaking bifurcations are unilateral.

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