STOCHASTIC MODELS OF OXYGEN TRANSPORT
IN RESPIRING TISSUES

by

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ABSTRACT

CURRAN, THOMAS COOKE. Stochastic Models of Oxygen Transport in
Respiring Tissues. (Under the direction of DR. HARVEY GOLD.)

Longmuir and co-workers have reported that respiration of certain
tissue slices is approximated more closely by Michaelis-Menten kinetics
than by predictions based upon the classically accepted diffusion
model. From this and other experimental findings, Longmuir proposed
that a carrier is involved in tissue oxygen transport. This investi-
gation develops and examines two stochastic models based upon the
biological hypothesis of a fixed site carrier network for tissue
oxygen transport. Both models are examined under steady-state
assumptions.

In the development of the first of these models, it is assumed
that oxygen transport by ordinary diffusion is negligible. Equations
describing the kinetics of oxygen consumption are obtained for both
a fixed, known arrangement of binding sites and an unknown arrange-
ment of binding sites that is specified only by a probability con-
straint. It is shown that in both cases the predicted kinetics are
Michaelis-Menten in form. The case of the unknown arrangement of
binding sites is also examined in more detail for a variety of
special cases including surface site inactivation and irreversible
inhibition.

The second model incorporates a second type of site into the
same general framework as a discrete approximation of the role of
ordinary diffusion. It is then shown that this second mode of
oxygen transport results in kinetic expressions that are not of the
Michaelis-Menten form. A qualitative analysis of this departure is presented.

In the presentation of both models the biological implications of the various mathematical assumptions are discussed. In addition, the relevance of the mathematical predictions to experimental applications is examined.
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LIST OF SYMBOLS

Sections in parentheses denote analogous terms for diffusion-binding site model.

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<td>any event having o(h) probability</td>
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<td>S_{i,j}</td>
<td>2.1.1</td>
<td>site in j^{th} position of layer i</td>
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1. INTRODUCTION

The purpose of this investigation is to examine the kinetics of respiring tissue slices in the light of certain hypotheses concerning the mechanism of tissue oxygen transport. The approach used in this study is to develop mathematical models that approximately describe these biological hypotheses and to employ these models to obtain kinetic expressions which may then be compared with observed kinetics of these tissue slices. While other mathematical models have been used for this purpose, recent experimental evidence has led to additional biological hypotheses concerning tissue oxygen transport. The models proposed here attempt to incorporate these hypotheses into oxygen transport models describing the observable kinetics of oxygen consumption.

1.1 Background

The biological system under investigation is a respiring tissue slice of known dimensions suspended in a solution containing oxygen. The slice is assumed to have uniform thickness and the surface area is large relative to the thickness. The concentration of oxygen in solution is assumed to be known and uniform throughout the solution and it is assumed that the rate of oxygen consumption by the tissue can be experimentally determined from this information. The conditions under which the measurements are made on this system are assumed to closely approximate steady-state conditions. That is, for a fixed concentration of oxygen in the solution, the instantaneous rate of oxygen consumption is independent of the time at which this rate is
determined. Thus, for a given tissue, each value of oxygen concentration in solution is associated with a unique rate of oxygen consumption. This description of the biological system is based upon current biological research in this area (Longmuir and Sun, 1970).

In this investigation, mathematical models based upon certain hypotheses concerning the mechanism of tissue oxygen transport are developed. The models are employed to examine the compatibility of these hypotheses with the empirical rate determinations. From these models, it is possible to obtain equations that describe oxygen consumption by the tissue as a function of oxygen concentration in solution and of certain parameters specific for the dimensions and type of tissue. In this way, the consistency of the hypothetical transport mechanism with the behavior of the empirically determined variables may be examined.

1.2 Literature

The process by which oxygen enters tissue was originally thought to be passive diffusion. Measured values for the diffusion coefficient of oxygen through non-respiring tissue were slightly less than those through water (Krogh, 1919). In general, the diffusion coefficient of oxygen through non-respiring tissue was found to be approximately equal to the diffusion coefficient of oxygen through water multiplied by the fraction of the tissue that was water (Longmuir and Bourke, 1960). However, in further experimental work with respiring kidney, heart, and liver tissue slices, higher diffusion coefficients for oxygen were found (Longmuir and McCabe, 1964). Moreover, the experimental data did not agree with the predictions of
the Warburg model for the respiration rate of tissue slices (Longmuir and Bourke, 1960). In the Warburg model, the lowest concentration of oxygen in solution at which the tissue respires maximally is defined to be the critical oxygen concentration. Assuming the validity of the Warburg model, the respiration rates of tissue slices in solution were examined in these experiments and the critical oxygen concentrations were determined. The Warburg model predicts that the critical oxygen concentration for a slice increases as the square of the slice thickness, while in these experiments it was found that a five fold increase in slice thickness produced at most a two fold increase in the critical oxygen concentration. It was also found that the respiration rate for slices of kidney, heart, and liver tissue approximated Michaelis-Menten kinetics (Longmuir and McCabe, 1964). Further investigation has supported the hypothesis that the kinetics of these respiring tissue slices are better approximated by Michaelis-Menten kinetics than by predictions from the Warburg model (Longmuir et al., 1971).

Since Michaelis-Menten kinetics are often associated with enzyme reactions, these findings might suggest a dominant role for one of the enzyme systems involved in oxygen consumption. If the rate of tissue oxygen transport were orders of magnitude greater than the rates of the enzyme reactions involved in tissue oxygen consumption, then the enzyme system could be regarded as the limiting factor in determining the kinetics of tissue oxygen consumption. While the kinetics of each of the enzymes involved in tissue oxygen consumption may be assumed to conform to Michaelis-Menten kinetics it is unlikely that the sum of
their activities would result in Michaelis-Menten kinetics (Longmuir, 1966a). If one of these enzymes played a rate-limiting role in oxygen consumption then the rate of tissue oxygen consumption might be approximated by the kinetics of this dominant enzyme and therefore closely resemble Michaelis-Menten kinetics. The inability to account for the kinetics of oxygen uptake by tissue slices in terms of accepted mechanisms led Longmuir and Sun (1970) to re-examine the process of oxygen transport in tissues.

Two mathematical models, based upon different hypotheses, have been developed recently to examine tissue oxygen consumption. One of these models examines respiration under the hypothesis that oxygen transport occurs primarily by extracellular diffusion (Hills, 1970) while the other is based upon the hypothesis that a carrier network is involved in oxygen transport (Gold, 1969). Incorporation of experimental data into the equations of the first model leads to a contradiction of its underlying hypothesis and supports the hypothesis of a carrier (Gold and Longmuir, 1971). The carrier model was developed by Gold (1969) and is based upon a hypothesis due to Longmuir (Longmuir and McCabe, 1964; Longmuir, 1966a).

The discrepancies between the predictions of the Warburg model and the experimental results for tissue oxygen consumption led Longmuir to propose that oxygen transport through tissue might involve a carrier (1966a; 1966b). The existence and nature of this proposed carrier are still being investigated by Longmuir and co-workers but certain general observations on the nature of such a carrier have been discussed (Gold, 1969).
Such a carrier could either be fixed or mobile. A mobile carrier could be freely diffusible and combine with oxygen at the surface of a tissue and then diffuse through the tissue until the oxygen is consumed. Another possibility for a mobile carrier would be one that combines with oxygen at the surface of a cell and then diffuses across the cell. The oxygen molecule could then dissociate and move to another cell by passive diffusion. However, no possible carrier molecule has yet been found in sufficient quantity to support these hypotheses (Longmuir et al., 1971). Another possibility for a carrier system would be a network of fixed binding sites throughout the tissue. In this system oxygen would migrate from site to site under the influence of an attractive potential (Gold, 1969). Experimental evidence has indicated that such a network is not unreasonable (Longmuir et al., 1971). It has been suggested that these binding sites could be distributed throughout the endoplasmic reticulum (Longmuir et al., 1971). Experimental results have indicated that brain tissue slices do not approximate Michaelis-Menten kinetics as closely as tissue slices of kidney, heart, and liver. If a fixed site carrier were assumed to be associated with the endoplasmic reticulum, the results for brain tissue could be explained by the lack of an extensive endoplasmic reticulum network (Longmuir, 1970).

1.3 General Comments on Mathematical Models

Before developing the specific models for this study, the general nature and purpose of these models is discussed.
1.3.1 Description

The mathematical models in this investigation consist of several basic parts:

(1) The biological hypothesis.
(2) The abstraction of the features involved in the hypothesis.
(3) The formulation of equations to describe the abstraction.
(4) The specification of the parameters in the equations.
(5) The development of the equations to obtain solutions for the variables of interest.
(6) The interpretation of these solutions in terms of the biological system in question.

As the model is developed there is a constant iterative interplay between the biology and the mathematics of the problem. This interplay involves comparisons between the predictions of the model and the known behavior of the biological system as well as the possible design of new experiments to serve as further tests of the hypotheses used in the model.

For any biological system it is possible to write equations which describe the system to some degree. In order to solve these equations, however, it is frequently necessary to make simplifying assumptions that widen the gap between the model and the biological system. In general, the precision of the model's solutions increases as the degree of complexity of the equations is decreased by simplifying assumptions. However, the accuracy of these solutions may
decrease if the equations are so simplified that they no longer approximate the biological system.

Thus the dynamic phase of modeling consists in part in establishing a compromise between biological reality and mathematical tractability. The standards that govern this compromise are biological since the problem in question is biological.

1.3.2 Purpose

One purpose of a model is to gain some understanding of the biological system under investigation. A model provides a link between a hypothesis concerning the system and the observable behavior of the system. In this way the mathematical model does not replace biological intuition, but rather augments this intuition by serving as an additional means of examining different hypotheses. In view of this, the model must provide sufficient information about the system so that it can be tested.

It should be noted that there is no certainty that models for different hypotheses will predict discernibly different behavior for the system under investigation. Different models might predict the same behavior for the system within the limitations of the experimental framework. This could occur, for example, when two models differ only in parameters that are not experimentally observable. As a consequence, it is easier to show that a model is not a true representation of the system than to definitely establish that a model is an accurate description of the system.
1.3.3 Stochastic and Deterministic Models

Stochastic models incorporate a probabilistic structure as an essential part of the model while a deterministic model may have a probabilistic term appended for the purpose of accounting for experimental variability. This difference in the nature of the stochastic element of the model has been described as inherent irreproducibility versus experimental irreproducibility (Bartholomay, 1962b). The models in this investigation incorporate the probabilistic structure as an inherent part of the model.

While the stochastic model assumes a basic indeterminacy, this need not involve a philosophical commitment to the underlying indeterminacy of the system but rather an acknowledgement that it is unlikely that the system is sufficiently described so as to be completely deterministic.

There is no a priori guarantee that a deterministic model and a stochastic model of the same biological system will agree in any particular sense. It is possible for the expected values of a stochastic model to agree with the predictions of a deterministic model and it is possible to have no agreement (Bartholomay, 1962a).\(^1\) In the case where the expected value of a stochastic model agrees with a deterministic model, the variance term for the stochastic model may give additional insight into the nature of the system. On the other hand, it may happen that for a given experimental situation the variance of the stochastic model is inconsequential.

\(^1\)van der Vaart, H. R. 1967. Lecture notes. Department of Statistics, North Carolina State University at Raleigh.
indicating that the deterministic model is sufficient in these instances (Heyde and Heyde, 1971). However, it should be noted that in such a case it is necessary to first examine the stochastic model before this conclusion may be reached. In any case, since the stated purpose of a model is to increase understanding of the system, it does not seem necessary to restrict the types of models investigated for a given system.
2. TWO MODELS FOR TISSUE OXYGEN TRANSPORT

The two models developed in this study are stochastic models for tissue oxygen transport patterned after Longmuir's hypothesis of a carrier. Stochastic models are employed in order to complement the deterministic approach used by Gold (1969). Not only is the comparison of the deterministic and stochastic treatments of interest but also the investigation of particular aspects of tissue oxygen transport that might be more amenable to a stochastic treatment. The approach employed in formulating these models is similar to the approaches that have been employed by various investigators in treating enzyme kinetics (Bartholomay, 1962a; Jachimowski et al., 1964; Heyde and Heyde, 1969). The present development differs from these other approaches in that generating functions are not employed but rather a steady-state assumption is introduced to permit solutions to be obtained primarily by the techniques of linear algebra. The nature of this assumption is discussed in section 2.1.3.6.

The first model in this study is called the binding site model and is similar to the deterministic model developed by Gold (1969). The second model is termed the diffusion-binding site model and is more general.

In the binding site model, it is assumed that there is a network of binding sites throughout the tissue and that oxygen transport through the tissue occurs by oxygen migrating from one binding site to another under an attractive potential. In the development of this model, the contribution of ordinary diffusion to oxygen transport is assumed to be negligible. Expressions for tissue oxygen consumption
are obtained and the behavior of these kinetic expressions are examined under various conditions.

The diffusion-binding site model involves binding sites but also incorporates ordinary diffusion into the transport process. Therefore it is more general than the binding site model but the equations are more complex and the analysis is less complete than for the simpler model.

2.1 Binding Site Model

2.1.1 Abstraction of Binding Sites

The tissue is considered to be a rectangular solid partitioned into cubes of equal volume by a three dimensional lattice. The vertices of the lattice are termed sites. The surface area of the rectangular solid is much greater than its thickness. This corresponds to the experimental situation described by Longmuir (1966a). By this construction, two opposite faces of the solid are much greater in surface area than the remaining four faces. For this reason it is assumed that the oxygen entering these four faces is negligible compared to the total amount of oxygen entering the tissue. Therefore, not more than two opposite faces of the tissue are considered to be exposed to the solution and the distinction is made between the one-sided case and the two-sided case. In the two-sided case, opposite faces of the tissues are exposed to the solution. In both cases, an exposed face is termed a surface layer.

Each site is contained in a rectangle parallel to a surface layer. These rectangles are called layers and are numbered from 1 to
where \( l \) is a surface layer and \( n \) is the total number of layers.

The sites in each layer are numbered from 1 to \( m \). The exact pattern of this indexing need not be specified, although for convenience the same pattern is used in each layer. Thus each site may be denoted as \( S_{i,j} \) where \( i \) is the layer that contains the site and \( j \) is the position of the site in the layer.

The sites are divided into the two distinct categories of binding sites and non-binding sites. The distribution of binding sites in the tissue is discussed in more detail in later sections, as the model is developed.

2.1.2 Assumptions

The following assumptions serve as the basic description of the binding site model:

1. All oxygen enters the tissue by binding to a site in a surface layer.

2. All oxygen returning to the solution from the tissue is returned from a binding site in a surface layer.

3. Oxygen is transported through the tissue solely by migration from one binding site to another.

4. A binding site is in one of two states at any given time. These two states are defined as occupied or unoccupied depending upon whether or not the binding site contains an oxygen molecule at that time. A binding site contains at most one oxygen molecule at any particular time.

5. Non-binding sites and unoccupied binding sites are referred to as being empty.
6. Oxygen is consumed only at binding sites.

7. If a site is occupied, the probability of the oxygen being consumed is independent of the behavior of any other site.

8. The probability of an oxygen molecule transferring from one binding site to another depends upon the distance between the sites, the probability that the donor site is occupied, and the probability that the acceptor is unoccupied.

2.1.3 Formulation

This section consists of the mathematical development of the binding site model. Although this development proceeds sequentially, certain mathematical details have been placed in the appendix in an attempt to minimize departures from the exposition of the essential parts of the model.

2.1.3.1 Notation

The notation employed in the development of the binding site model is patterned after the conventions employed by Feller (1950). The following list indicates the notation used for the events of interest:

<table>
<thead>
<tr>
<th>Notation of Events</th>
<th>Description of Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N_{i,j}(t)$</td>
<td>$S_{i,j}$ has no oxygen at time $t$, that is $S_{i,j}$ is empty at time $t$.</td>
</tr>
<tr>
<td>$B_{i,j}$</td>
<td>$S_{i,j}$ is a binding site.</td>
</tr>
<tr>
<td>$C_{i,j}(t,t+h)$</td>
<td>$S_{i,j}$ receives an oxygen from solution in time interval $[t, t+h)$.</td>
</tr>
</tbody>
</table>
$R_{i,j}(t, t+h)$ $S_{i,j}$ releases an oxygen into solution in time interval $[t, t+h]$.

$U_{i,j}(t, t+h)$ $S_{i,j}$ consumes an oxygen in time interval $[t, t+h]$.

$i', j', T_{i,j}(t, t+h)$ An oxygen transfer from $S_{i',j'}$ to $S_{i,j}$ in time interval $[t, t+h]$, where $(i', j') \neq (i, j)$.

$E(h)$ Any event having $o(h)$ probability; that is, $\lim_{h \to 0} \frac{1}{h} \mathbb{P}(E(h)) = 0$.

The following notation is also used:

$P_{i,j}(t) = \mathbb{P}(I_{i,j}(t))$ 

$P_{i,j}^B(t) = \mathbb{P}(I_{i,j}(t) | B_{i,j})$ where $\mathbb{P}(I_{i,j}(t) | B_{i,j})$ denotes the probability of event $I_{i,j}(t)$ given that $S_{i,j}$ is a binding site.

$f_{i,j} = \mathbb{P}(B_{i,j})$.

Figure 1 summarizes the notation and terminology for events and the notation for probabilities used in the development of the model.

2.1.3.2 Assignment of Probabilities

While the general physical assumptions of the model were presented in section 2.1.2, this section presents the basic probability statements describing the behavior at a site and these constitute the specific mathematical assumptions of the model. These statements are developed in the form of conditional probability equations given
Figure 1. Summary of notation and terminology for the binding site model.
that a particular site is, or is not, a binding site. Therefore, the basic equations characterizing the model are obtained as conditional probability statements given a particular arrangement of binding sites in the tissue.

Two different treatments for specifying the arrangement of binding sites will be examined. The first treatment considers the arrangement of binding sites to be fixed and known in advance and therefore the probability that a particular site is a binding site is either zero or one. In the second treatment the arrangement of binding sites is unknown and is specified only by the probability that a particular site is a binding site. The general development of this section and the following section, section 2.1.3.3, applies to both treatments. Further discussion of the differences between these two specifications of the arrangement of binding sites is presented in sections 2.1.3.4 and 2.1.5.

In assigning probabilities to the events in the model it is assumed that the probability that a site changes state more than once during a time interval \([t, t+h]\) is \(o(h)\).

The probability statements describing the event that an oxygen in solution becomes bound to a site in the tissue during a time interval \([t, t+h]\) are:
\[ P(C_{i,j}(t, t+h) | \bar{B}_{i,j}) = 0 \]

and \[ P(C_{i,j}(t, t+h) | B_{i,j}) = b_i c h P(N_{i,j}(t) | B_{i,j}) + o(h) \]

\[ = b_i c h P^B_{i,j}(t) + o(h) \]

where \( b_i = 0 \) if layer \( i \) is not a surface layer and \( c \) is the concentration of oxygen in solution.

The first equation corresponds to the assumption that non-binding sites are not involved in oxygen transport. The second equation states that the probability of an oxygen in solution being bound by a site during this time interval, given that the site is a binding site, is, within \( o(h) \), equal to the product of a parameter \( b_i \), the concentration of oxygen in solution, the length of the interval, and the probability that the site was unoccupied at the beginning of the interval given that the site is a binding site. As indicated, the parameter \( b_i \) is non-zero only for surface layer sites and this corresponds to assumption 1 in section 2.1.2. The use of the zero-valued parameter \( b_i \) for interior layers is for convenience in developing the general equations of the model.

Recalling that \( f_{i,j} = P(B_{i,j}) \), the above equations may be combined and written as:

\[ P(C_{i,j}(t, t+h)) = b_i c h P^B_{i,j}(t) f_{i,j} + o(h). \]

The equations describing the release of oxygen from a site into the solution during the time interval \([t, t+h)\) are:
\[ P(R_{i,j}(t, t+h) | B_{i,j}) = 0 \]

and

\[ P(R_{i,j}(t, t+h) | B_{i,j}) = r_{i} h \ P(\overline{N}_{i,j}(t) | B_{i,j}) + o(h) \]

\[ = r_{i} h [1 - \ p_{i,j}^{B}(t)] + o(h) \]

where \( r_{i} \) is zero if layer \( i \) is not a surface layer.

As before, the first equation indicates that non-binding sites are not involved in oxygen transport. The second equation states that the probability of release from a site, given that the site is a binding site, is, within \( o(h) \), equal to the product of a parameter \( r_{i} \), the length of the time interval, and the probability that the site was occupied at time \( t \) given that the site is a binding site.

The non-zero value for the parameter \( r_{i} \) if layer \( i \) is a surface layer corresponds to assumption 2 in section 2.1.2. As with the parameter \( b_{i} \), the subscripted notation for \( r_{i} \) is introduced for convenience in further development of the equations. These two equations may be combined and rewritten as:

\[ P(R_{i,j}(t, t+h)) = r_{i} h [1 - \ p_{i,j}^{B}(t)] + o(h). \quad \text{(2.1.3.2-2)} \]

The equations describing the probability of oxygen consumption at a site during a time interval \([t, t+h]\) are:

\[ P(U_{i,j}(t, t+h) | \overline{B}_{i,j}) = 0 \]

\[ P(U_{i,j}(t, t+h) | B_{i,j}) = u_{h} \ P(\overline{N}_{i,j}(t) | B_{i,j}) + o(h) \]

\[ = u_{h} [1 - \ p_{i,j}^{B}(t)] + o(h). \]
The first equation indicates that non-binding sites do not consume oxygen and corresponds to assumption 6 in section 2.1.2. The second equation states that the conditional probability of a site consuming oxygen during this interval given that the site is a binding site is, within o(h), equal to the product of a parameter \( u \), the length of the interval, and the probability that the site was occupied at time \( t \) given that the site is a binding site. These two equations may be combined to give:

\[
P[U_{i,j}(t, t+h)] = uh[1 - P^B_{i,j}(t)] f_{i,j} + o(h) .
\]

The equations describing the probability of an oxygen transfer from site \( S_{i',j'} \) to site \( S_{i,j} \) during the time interval \([t, t+h)\) are:

\[
P_{i',j',t_i,j}(t, t+h) | \overline{B}_{i',j'} \cap \overline{B}_{i,j} = 0
\]

\[
P_{i',j',t_i,j}(t, t+h) | B_{i',j'} \cap \overline{B}_{i,j} = d(i',j',i,j) hP[N_{i',j'}(t) | B_{i',j}] P[N_{i,j}(t) | B_{i,j}] + o(h)
\]

\[
= d(i',j',i,j) h[1 - P^B_{i',j'}(t)] f_{i,j} + o(h) .
\]

The first equation corresponds to assumption 3 of section 2.1.2, which states that oxygen migrates only between binding sites. In the last equation, it is assumed that, within an o(h) term, the probability of an oxygen transfer from \( S_{i',j'} \) to \( S_{i,j} \) in time interval \([t, t+h)\) given that both are binding sites is equal to the product of a parameter \( d(i',j',i,j) \), the length of the interval, the probability that \( S_{i',j'} \) is occupied at time \( t \) given that it is a binding site,
and the probability that $S_{i,j}$ is unoccupied at time $t$ given that $S_{i,j}$ is a binding site. The parameter $d(i',j',i,j)$ is a value of the function $d(\ ,\ ,\ ,\ )$. This function is defined to be a non-negative monotone non-increasing function of the distance between $S_{i',j'}$ and $S_{i,j}$ for $(i',j') \neq (i,j)$. The value of zero is assigned to $d(i,j,i,j)$. The event that an oxygen leaves and returns to the same site during the time interval $[t, t+h)$ requires that this site change state twice during the interval and this has been defined to be an $o(h)$ event. The event that an oxygen remains at a site during the time interval $[t, t+h)$ is not considered as a transfer and is treated separately. Therefore the value of zero is arbitrarily assigned to the parameter $d(i,j,i,j)$ for convenience in developing the equations of the model.

Since the value of the function is determined by the distance separating two sites it follows that $d(i',j',i,j) = d(i,j,i',j')$. The parameter $d(i',j',i,j)$ incorporates the effect of distance between two sites into the probability of a transfer.

The above equations for oxygen transfer may be combined to give:

$$P_{i',j',i,j}^{T}(t, t+h) = d(i',j',i,j)h[1 - P_{i',j',i,j}^{B}(t)] P_{i,j}^{B}(t)$$

$$\cdot f_{i',j',i,j}^{f} + o(h) \ .$$ 2.1.3.2-4

The above probabilities define the basic events at a site. The following two events are introduced to summarize these basic events.

Let $A_{i,j}(t, t+h)$ denote the event that an oxygen molecule arrives at $S_{i,j}$ in time interval $[t, t+h)$ and let $L_{i,j}(t, t+h)$ denote the
event that an oxygen molecule leaves \( S_{i,j} \) in time interval \([t, t+h)\),
that is:

\[
A_{i,j}(t, t+h) = \overline{N}_{i,j}(t+h) \cap N_{i,j}(t) \cap B_{i,j} = \overline{N}_{i,j}(t+h) \cap N_{i,j}(t)
\]
\[2.1.3.2-5\]

\[
L_{i,j}(t, t+h) = N_{i,j}(t+h) \cap \overline{N}_{i,j}(t) \cap B_{i,j} = N_{i,j}(t+h) \cap \overline{N}_{i,j}(t)
\]
\[2.1.3.2-6\]

Since it has been assumed that the probability that a site
changes state more than once in the interval \([t, t+h)\) is \(o(h)\), the
following relations hold:

\[
A_{i,j}(t, t+h) = C_{i,j}(t, t+h) \cup \left( \bigcup_{i'} \bigcup_{j'} \bigcup_{t_i,j_i,t_i,j_i} T_{i',j',t_i,j_i}(t, t+h) \right) \cup E(h)
\]
\[2.1.3.2-7\]

\[
L_{i,j}(t, t+h) = R_{i,j}(t, t+h) \cup U_{i,j}(t, t+h) \cup \left( \bigcup_{i'} \bigcup_{j'} \bigcup_{t_i,j_i} T_{i',j',t_i,j_i}(t, t+h) \right) \cup E(h)
\]
\[2.1.3.2-8\]

2.1.3.2 Development of Basic Equations

In developing the model, the basic equations are developed in
terms of \( f_{i,j} P^B_{i,j}(t) \), the probability that \( S_{i,j} \) is an unoccupied
binding site. The following relations are employed in obtaining
probabilities:

\[
\{N_{i,j}(t+h) \cap B_{i,j}\} = \{N_{i,j}(t+h) \cap N_{i,j}(t) \cap B_{i,j}\} \{N_{i,j}(t+h) \cap \overline{N}_{i,j}(t) \cap B_{i,j}\}
\]
\[2.1.3.3-1\]
\[ [N_{i,j}(t) \cap B_{i,j}] = [N_{i,j}(t) \cap N_{i,j}(t) \cap B_{i,j}] \cap \{ \overline{N_{i,j}(t) \cap N_{i,j}(t)} \} \]

Therefore, using equation 2.1.3.2-5,

\[ [N_{i,j}(t+h) \cap N_{i,j}(t) \cap B_{i,j}] \cup \{ A_{i,j}(t, t+h) \} = [N_{i,j}(t) \cap B_{i,j}] \]

and

\[ P[N_{i,j}(t+h) \cap N_{i,j}(t) \cap B_{i,j}] + P[A_{i,j}(t, t+h)] = P[N_{i,j}(t) \cap B_{i,j}] \]

From equation 2.1.3.3-1,

\[ P[N_{i,j}(t+h) \cap B_{i,j}] = P[N_{i,j}(t+h) \cap N_{i,j}(t) \cap B_{i,j}] + P[N_{i,j}(t+h) \cap \overline{N_{i,j}(t)}] \]

Using equation 2.1.3.3-3 and equation 2.1.3.2-6 gives:

\[ P[N_{i,j}(t+h) \cap B_{i,j}] = P[N_{i,j}(t) \cap B_{i,j}] - P[A_{i,j}(t, t+h)] + P[L_{i,j}(t, t+h)] \]

Using expressions 2.1.3.2-7 and 2.1.3.2-8 it follows that:

\[ P[N_{i,j}(t+h) \cap B_{i,j}] = P[N_{i,j}(t) \cap B_{i,j}] - P[C_{i,j}(t, t+h)] \]

\[ - P\{ \bigcup_{i,j} U_{i,j}[T_{i,j}(t, t+h)] \} \]

\[ + P[R_{i,j}(t, t+h)] + P[U_{i,j}(t, t+h)] \]

\[ + P\{ \bigcup_{i,j} U_{i,j}[T_{i,j}(t, t+h)] \} + o(h) \]
Using expressions 2.1.3.2-1 through 2.1.3.2-4, the above expression may be rewritten as:

\[
P[N_{i,j}(t+h) \cap B_{i,j}] = P[N_{i,j}(t) \cap B_{i,j}] - b_{i,j} \chi_{f, i,j} P_{i,j}^B(t)
\]

\[+ \Sigma \Sigma d(i',j',i,j) hf_{i',j,'} [1 - P_{i,j}^B(t)] f_{i',j,'} P_{i,j}^B(t)
\]

\[+ r_{i,j} hf_{i,j} [1 - P_{i,j}^B(t)] + uhf_{i,j} [1 - P_{i,j}^B(t)]
\]

\[+ \Sigma \Sigma d(i,j,i',j') hf_{i,j} [1 - P_{i,j}^B(t)] f_{i',j'} P_{i',j'}^B(t) + o(h)
\]

\[= P[N_{i,j}(t) \cap B_{i,j}] - b_{i,j} \chi_{f, i,j} P_{i,j}^B(t)
\]

\[+ \Sigma \Sigma d(i',j',i,j) hf_{i',j,'} f_{i,j} P_{i,j}^B(t)
\]

\[+ \Sigma \Sigma d(i',j',i,j) hf_{i',j,'} P_{i,j}^B(t) f_{i,j} P_{i',j'}^B(t)
\]

\[+ r_{i,j} hf_{i,j} - r_{i,j} hf_{i,j} P_{i,j}^B(t) + uhf_{i,j} P_{i,j}^B(t)
\]

\[+ \Sigma \Sigma d(i,j,i',j') hf_{i,j} f_{i',j'} P_{i',j'}^B(t)
\]

\[+ \Sigma \Sigma d(i,j,i',j') hf_{i,j} f_{i',j'} P_{i',j'}^B(t) + o(h) .
\]

Since \(d(i,j,i',j') = d(i',j',i,j)\) by the symmetry of transfer probabilities the terms containing \(P_{i,j}^B(t) P_{i',j'}^B(t)\) cancel out giving:

\[
P[N_{i,j}(t+h) \cap B_{i,j}] = P[N_{i,j}(t) \cap B_{i,j}] - b_{i,j} \chi_{f, i,j} P_{i,j}^B(t)
\]

\[+ \Sigma \Sigma d(i',j',i,j) hf_{i',j,'} f_{i,j} P_{i,j}^B(t) + r_{i,j} hf_{i,j} - r_{i,j} hf_{i,j} P_{i,j}^B(t)
\]

\[+ uhf_{i,j} - uhf_{i,j} P_{i,j}^B(t) + \Sigma \Sigma d(i,j,i',j') hf_{i,j} f_{i',j'} P_{i',j'}^B(t)
\]

\[+ \Sigma \Sigma d(i,j,i',j') hf_{i,j} f_{i',j'} P_{i',j'}^B(t) + o(h) .
\]
Since \( P(N_i,j(t) \cap B_{i,j}) = P(N_i,j(t) \mid B_{i,j}) P(B_{i,j}) = P_{i,j}^B(t) f_{i,j} \), the
above may be rewritten as:

\[
\begin{align*}
\frac{f_{i,j}^B P_{i,j}^B(t+h)}{h} & = f_{i,j}^B P_{i,j}^B(t) - b_{i,j} P_{i,j}^B(t) \\
& - \sum \sum d(i',j',i,j) h f_{i',j',i,j} f_{i,j} P_{i,j}^B(t) \\
& + r_{i,j} f_{i,j} - r_{i,j} P_{i,j}^B(t) + u_{i,j} f_{i,j} - u_{i,j} P_{i,j}^B(t) \\
& + \sum \sum d(i,j,i',j') h f_{i',j',i,j'} f_{i',j'} P_{i',j'}^B(t) + o(h).
\end{align*}
\]

The above expression may be divided by \( h \) and rearranged to give:

\[
\frac{1}{h} [f_{i,j}^B P_{i,j}^B(t+h) - f_{i,j}^B P_{i,j}^B(t)] = -[b_{i,j} f_{i,j} + r_{i,j} f_{i,j} + u_{i,j} f_{i,j}] P_{i,j}^B(t) + \\
\sum \sum d(i',j',i,j) f_{i',j',i,j} f_{i,j} P_{i,j}^B(t) \\
+ \sum \sum d(i,j,i',j') f_{i,j} f_{i',j'} P_{i',j'}(t) \\
+ r_{i,j} f_{i,j} + u_{i,j} f_{i,j}.
\]

Taking the limit of the above expression as \( h \) approaches zero
gives:

\[
\frac{d}{dt} [f_{i,j}^B P_{i,j}^B(t)] = -[b_{i,j} f_{i,j} + r_{i,j} f_{i,j} + u_{i,j} f_{i,j}] + \\
\sum \sum d(i',j',i,j) f_{i',j',i,j} f_{i,j} P_{i,j}^B(t) + \\
+ \sum \sum d(i,j,i',j') f_{i,j} f_{i',j'} P_{i',j'}(t) \\
+ r_{i,j} f_{i,j} + u_{i,j} f_{i,j}.
\]

2.1.3.3-5
This differential equation holds for all indices \((i,j)\) and serves as the basic equation of the model. Before solving these equations certain assumptions are introduced and discussed.

### 2.1.3.4 Layer Equilibrium Assumption

In solving the equations of the model it is assumed that all of the binding sites within a given layer are at equilibrium with respect to each other. This is termed the "layer equilibrium assumption" and may be stated mathematically as:

\[
P_{i,j}^B(t) = P_{i,j}'^B(t)
\]

where \(S_{i,j}\) and \(S_{i,j}'\) are binding sites.

Since the incorporation of an additional assumption into a mathematical model presents a potential problem of overspecification, this section discusses both the consistency of the layer equilibrium assumption with the previous assumptions and the restrictions on the physical system under which the assumption may be expected to be experimentally applicable. In order to facilitate this discussion it is convenient to first examine the distribution of binding sites in the tissue.

In the development of the equations of the model the quantities \(f_{i,j} = P(B_{i,j})\) have denoted the probability that \(S_{i,j}\) is a binding site. In the initial treatment of this model, the arrangement of binding sites is assumed to be fixed. That is, it is assumed that the arrangement of binding sites is known. It is therefore more appropriate to introduce an indicator function \(g_{i,j}\) such that
\[
g_{i,j} = \begin{cases} 
0 & \text{if } S_{i,j} \text{ is not a binding site} \\
1 & \text{if } S_{i,j} \text{ is a binding site} 
\end{cases}
\]

Since the arrangement of binding sites is assumed to be known and fixed in advance the quantities \(g_{i,j}\) may be substituted for the \(f_{i,j}\) in the preceding development. That is, once the distribution of binding sites is specified the probability that a particular site \(S_{i,j}\) is a binding site is either 0 or 1 which is equivalent to the value of the indicator function \(g_{i,j}\). Although the arrangement of binding sites is assumed to be known and fixed the particular assignment of sites is arbitrary subject to certain constraints developed later in this section. A different approach to the assignment of binding sites is discussed in section 2.1.5 together with the relative merits of each approach.

The following argument establishes that a departure from the layer equilibrium condition results in a driving force favoring the return to a condition of layer equilibrium.

Let \(S_{i,j}\) and \(S_{i,k}\) be given as distinct binding sites in layer \(i\). That is,

\[
g_{i,j} = g_{i,k} = 1.
\]

Assume that \(d(i,j,i,k) = d(i,k,i,j)\) is non-zero.

Suppose that \(P_{i,j}^B(t)\) is greater than \(P_{i,k}^B(t)\) for some arbitrary, but fixed, value of \(t\). That is, suppose that at time \(t\) the
probability of \( S_{i,j} \) being unoccupied is greater than the probability of \( S_{i,k} \) being unoccupied.

Using the indicator function notation and equation 2.1.3.2-4 gives:

\[
P_{i,j}^{T_{i,k}}(t, t+h) = d(i, j, i, k) h g_{i,j} [1 - p_{i,j}^B(t)] g_{i,k}^{B} p_{i,k}^B(t) + o(h)
\]

and

\[
P_{i,k}^{T_{i,j}}(t, t+h) = d(i, k, i, j) h g_{i,k} [1 - p_{i,k}^B(t)] g_{i,j}^{B} p_{i,j}^B(t) + o(h).
\]

Since \( S_{i,j} \) and \( S_{i,k} \) are binding sites both \( g_{i,j} \) and \( g_{i,k} \) are unity giving:

\[
P_{i,j}^{T_{i,k}}(t, t+h) = d(i, j, i, k) h [1 - p_{i,j}^B(t)] p_{i,k}^B(t) + o(h)
\]

2.1.3.4-4

and

\[
P_{i,k}^{T_{i,j}}(t, t+h) = d(i, k, i, j) h [1 - p_{i,k}^B(t)] p_{i,j}^B(t) + o(h).
\]

2.1.3.4-5

Since \( d(i, j, i, k) = d(i, k, i, j) \), subtraction gives:

\[
P_{i,j}^{T_{i,k}}(t, t+h) - P_{i,k}^{T_{i,j}}(t, t+h) = d(i, j, i, k) h [p_{i,k}^B(t) - p_{i,j}^B(t)] + o(h).
\]

2.1.3.4-6

It should be noted that it is not necessary to assume that the \( o(h) \) terms in equations 2.1.3.4-4 and 2.1.3.4-5 are identical in the
case where \( p_{i,j}^B(t) \) is not equal to \( p_{i,k}^B(t) \) in order to establish the
sign of the left hand side of equation 2.1.3.4-6. Since \( \lim_{h \to 0} \frac{o(h)}{h} \)
is zero, \( h \) may be chosen sufficiently small so that the left hand side
of equation 2.1.3.4-6 has the same sign as the term \( p_{i,k}^B(t) - p_{i,j}^B(t) \).
Therefore, by equation 2.1.3.4-3 it follows that:

\[
P(i_j,t_i,k(t,t+h)) < P(i_j,t_i,k(t,t+h)) \]

This means that if the probability of being unoccupied at time
t is greater for \( S_{i,j} \) than \( S_{i,k} \) then in the next time interval oxygen
is more likely to transfer from \( S_{i,k} \) to \( S_{i,j} \) than from \( S_{i,k} \) to \( S_{i,j} \).
That is, the probability structure of the model dictates that if two
binding sites in a layer are sufficiently close so that the transfer
parameter is non-zero then, at a particular time, oxygen transfers
are more likely to occur from the binding site with a higher prob-
ability of being occupied to the binding site with a lower probability
of being occupied, than the reverse.

In obtaining this result the contribution of other sites to
oxygen transport has been neglected. Therefore this result is not
sufficient to guarantee the reasonableness of the layer equilibrium
assumption. As stated in section 1.1, the concentration of oxygen
in solution is assumed to be uniform so that departures from layer
equilibrium in the surface layer are not a result of gradations in
the oxygen concentration of the solution. A major determinant in
discussing the reasonableness of the layer equilibrium assumption is
the specific arrangement of binding sites in the tissue. If the
arrangement of binding sites were uniform, for example \( f_{i,j} \) equal 1
for all \((i,j)\), then the layer equilibrium assumption is reasonable. However, for irregular arrangements it would not follow that the layer equilibrium assumption applies. Therefore the introduction of the layer equilibrium assumption restricts the region of applicability of the model to those cases for which the assumption approximately describes the biological system.

Therefore the reasonableness of the layer equilibrium assumption depends upon the arrangement of the binding sites in the tissue. In view of this, two constraints are imposed upon this arrangement. The binding sites within each layer are assumed to be sufficiently dense so that for any two binding sites there is an interconnecting set of binding sites in the same layer. Secondly, it is assumed that if a column normal to the surface is passed through the tissue there is no appreciable gradient from layer to layer in the density of binding sites. With these assumptions regarding the regularity of the arrangement of binding sites, the above discussion shows that any departure from a state of equilibrium results in a driving force to restore the condition of layer equilibrium. In particular, this driving force serves not only to return the tissue to layer equilibrium but also to establish layer equilibrium from any given initial condition for the tissue.

The characteristics of the layer equilibrium assumption that have been discussed in this section serve as the justification for introducing this assumption. The properties of this assumption in the model indicate the possibility of attaining the layer equilibrium condition experimentally. If the tissue slice can be maintained at
a constant solution oxygen concentration for a sufficient time interval then the model predicts that layer equilibrium will be attained.

While the length of this time interval depends upon the parameters of the system, the primary interest is oxygen consumption under steady-state conditions and it is assumed that the layer equilibrium assumption approximately describes the biological system at the steady-state. The steady-state condition is introduced in section 2.1.3.6.

Introducing the layer equilibrium assumption into the model permits the suppression of the second index on the variable $P_{i,j}^B(t)$, that is

$$P_{i,j}^B(t) = P_{i}^B(t) \quad \text{for all binding sites in layer } i.$$

Making this substitution in equation 2.1.3.3-5 and using the indicator functions gives

$$\frac{d}{dt} \left[ g_{i,j} P_{i}^B(t) \right] = -[b_{i} c g_{i,j} + r_{i} g_{i,j} + u g_{i,j}$$

$$+ \sum \sum d(i',j',i,j) g_{i',j',i,j} g_{i,j} P_{i}^B(t)$$

$$+ \sum \sum d(i,j,i',j') g_{i,j,i',j'} g_{i,j} P_{i}^B(t)$$

$$+ r_{i} g_{i,j} + u g_{i,j}.$$

The next step in the development of the equations for the model is to sum the above differential equation over the index $j$. In its present form the equation describes the behavior at a particular site.
After introducing the layer equilibrium assumption it becomes convenient to sum the equations for each site in a layer to give equations that summarize the behavior of all sites in a layer. Recalling that each layer was assumed to contain \( m \) sites let \( m_i \) denote the number of binding sites in layer \( i \). Therefore

\[
m_i = \sum_j g_{i,j} \quad \text{for all } i.
\]

Summing the above equation over the index \( j \) gives:

\[
\frac{d}{dt} [m_i P_i^B(t)] = -[b_i c m_i + r_i m_i + u m_i
\]

\[
+ \sum_{i',j} \sum_{j'} d(i',j',i,j) g_{i',j',i,j} P_i^B(t)
\]

\[
+ \sum_{i',j} \sum_{j'} d(i,j,i',j') g_{i,i',j,j} P_i^B(t)
\]

\[
+ r_i m_i + u m_i .
\]

Recalling the symmetry of the function \( d( , , , ) \), it is convenient to introduce the following notation:

\[
d(i',i) = d(i,i') = \sum_j \sum_{j'} d(i,j,i',j') g_{i,j,i',j'}
\]

\[
= \sum_j \sum_{j'} d(i',j',i,j) g_{i',j',i,j} .
\]

The notational similarity between this newly defined quantity and the previously defined parameter for site to site transfers is intended to reflect that the parameter \( d(i,i') \) includes all site to
site transfer parameters involved in a direct oxygen transfer from layer \( i \) to layer \( i' \).

Making this substitution in equation 2.1.3.4-7 gives:

\[
\frac{d}{dt} \left[ m_i P_i^B(t) \right] = \left[ b_i c m_i + r_i m_i + u m_i + \sum_{i'} d(i',i) \right] P_i^B(t)
+ \sum_{i'} d(i',i) P_{i'}^B(t) + r_i m_i + u m_i \quad \text{for} \ i = 1, \ldots, n.
\]

2.1.3.4-8

2.1.3.5 Matrix Form of the Equations

Since the model involves a system of equations, it is convenient to express these equations in matrix form. In defining the following matrices and vectors, \( n \) is the number of layers in the model.

Let \( e_i \) be the \( n \)-dimensional column vector whose only non-zero entry is a 1 in the \( i^{th} \) row.

Let \( M \) be the \( n \times n \) diagonal matrix whose \( i^{th} \) diagonal element is \( m_i \).

Let \( E_{i,j} \) be the \( n \)-dimensional square matrix whose only non-zero entry is a 1 in row \( i \) and column \( j \).

Let \( A_1(c) \) be the \( n \)-dimensional square matrix of the form:

\[
\begin{bmatrix}
    b_i c m_i + r_i m_i + u m_i + \sum_{i'} d(i',1) & -d(2,1) & -d(3,1) & \ldots & -d(n,1) \\
    -d(1,2) & u m_2 + \sum_{i'} d(i',2) & -d(3,2) & \ldots & -d(n-1,2) \\
    \vdots & \ddots & \ddots & \ddots & \ddots \\
    \vdots & \ddots & \ddots & \ddots & \ddots \\
    -d(1,n) & \cdots & \cdots & u m_n + \sum_{i'} d(i',n) & \\
\end{bmatrix}
\]
The form $A_1(c)$ is that:

1. The diagonal elements are positive.
2. The off-diagonal elements are non-positive.
3. An off-diagonal element in position $(i,j)$ is equal to $-d(j,i) = -d(i,j)$.
4. The $i^{th}$ diagonal element is $u_m i$ plus the sum of the absolute values of the off-diagonal elements in that row and, for the first diagonal element, the term $b_1 c_m + r_1 m_1$.

Let

$$X_1 = \begin{bmatrix} u + r_1 \\
    u \\
    \vdots \\
    u \\
\end{bmatrix}.$$

Let $A_2(c) = A_1(c) + (b_n c_m + r_m n) E_{nn}$.

Let

$$X_2 = \begin{bmatrix} u + r_1 \\
    u \\
    \vdots \\
    u \\
    u + r_n \end{bmatrix}.$$
It should be noted that \( A_2(c) \) has the same four properties listed for \( A_1(c) \) with the exception that for property 4 the \( n^{th} \) diagonal element also contains the quantity \( b_n c_m \). Recall that in section 2.1.3.2 \( b_i \) and \( r_i \) were defined to be zero unless layer \( i \) was a surface layer.

From this, and the above matrix notation, the system of equations determined by equation 2.1.3.4-8 may be summarized as:

\[
MY'(t) = -A_1(c)Y(t) + MX_1 \quad \text{for the one-sided case} \quad 2.1.3.5-1
\]

and

\[
MY'(t) = -A_2(c)Y(t) + MX_2 \quad \text{for the two-sided case} \quad 2.1.3.5-2
\]

where \( Y(t) = \sum_{i=1}^{n} P_i(t) e_i \).

This matrix form of the equations for the model is the form that is employed in solving the model.

2.1.3.6 Steady-State Condition

As stated in section 1.1, it is assumed that all measurements on the biological system are under approximate steady-state conditions. For this model, the steady-state condition means that the probability distributions for site occupation are independent of time. For the biological system, it is assumed that the response of the tissue to a change in oxygen concentration is sufficiently fast relative to the rate of change in solution concentration so that the tissue may be considered to be under approximate steady-state conditions. In introducing this assumption it is assumed that the
steady-state is a reasonable approximation of the experimental procedures employed by Longmuir and coworkers (Longmuir and Sun, 1970). For the equations of this model, the steady-state condition corresponds to setting $Y'(t) = 0$ in equations 21.13.5-1 and 21.13.5-2. At the steady-state, the dependence of $Y(t)$ upon $t$ may be suppressed and the equations for the binding site model become:

$$A_1(c) Y = MX_1 \quad \text{for the one-sided case} \quad 2.1.3.6-1$$

and

$$A_2(c) Y = MX_2 \quad \text{for the two-sided case} \quad 2.1.3.6-2$$

It was observed in section 2.1.3.5 that the diagonal elements of $A_1(c)$ and $A_2(c)$ are greater than the sum of the absolute values of the off-diagonal elements in their respective rows. Thus, $A_1(c)$ and $A_2(c)$ are diagonally dominant matrices and this is sufficient to guarantee the existence of $A_1^{-1}(c)$ and $A_2^{-1}(c)$ (Hearon, 1963). Therefore, in both cases, the existence and uniqueness of a solution for $Y$ is established.

Before employing these equations, it should be verified that the steady-state condition, $Y'(t) = 0$, is consistent with the previous development of the model. Therefore, it is shown below that, as time increases, the vector, $Y'(t)$, in equations 21.3.5-1 and 21.3.5-2 approaches the zero vector, for fixed $c$. This discussion is valid for both cases, $k = 1$ and $k = 2$.

Let $h(t) = Y(t) - Y$, thus $h(t)$ is the difference between the time dependent solution and the steady-state solution.
\[ h'(t) = Y'(t) = -A_k(c)Y(t) + MX_k \] from equations 2.1.3.5-1 and 2.1.3.5-2

\[ = -A_k(c)[h(t) + Y] + MX_k \] since \( h(t) + Y = Y(t) \)

\[ = -A_k(c)h(t) - A_k(c)A_k^{-1}(c)MX_k + MX_k \] since \( Y = A_k^{-1}MX_k \)

\[ = -A_k(c)h(t) - MX_k + MX_k \]

\[ h'(t) = -A_k(c)h(t) \]

To determine the behavior of \( h(t) \) as \( t \) increases, it is necessary to consider the eigenvalues of \( A_k(c) \). A sufficiently accurate estimate of the eigenvalues of \( A_k(c) \) is provided by Gershgorin's theorem (Marcus and Minc, 1964, Chapter III):

If \( A = (a_{i,j}) \) is an \( n \times n \) matrix, then the eigenvalues of \( A \) lie in the closed region of the complex plane determined by the discs

\[ |a_{i,i} - z_i| \leq \sum_{j \neq i} a_{i,j} \text{ for } i = 1, \ldots, n. \]

For the matrices \( A_1(c) \) and \( A_2(c) \) these discs are of the form

\[ |b_1cm_1 + r_1m_1 + um_1 + \sum_{j \neq i} a_{i,j} - z_i| \leq \sum_{j \neq i} a_{i,j} \text{, by property 4 in section 2.1.3.5, and therefore the eigenvalues of } A_1(c) \text{ and } A_2(c) \text{ have positive real parts. Thus the eigenvalues of } -A_1(c) \text{ have negative real parts and this is sufficient to guarantee that } h(t) \text{ approaches the zero vector as } t \text{ increases (Struble, 1962, Chapter 4).} \]

Since \( h(t) \) approaches 0, for fixed \( c \), it follows that all solutions to the time dependent equations approach the steady-state solutions as \( t \) increases.
At the steady-state, with the dependence on time suppressed, equation 2.1.3.4-8 may be written as:

\[ 0 = -[b_i c_i m_i + r_i m_i + u_i m_i + \sum_{i'} d(i',i)]p_{i'}^B + \sum_{i'} d(i',i)p_i^B, + r_i m_i + u_i m_i \]

for \( i = 1, \ldots, n \)  

2.1.3.6-3

2.1.3.7 A Measure of Oxygen Consumption

In the previous sections, expressions were obtained for the probability that a particular site in the tissue is unoccupied at a given time. For this investigation, the quantity of interest is the rate of tissue oxygen consumption under steady-state conditions. This section introduces random variables related to this quantity and incorporates the results of previous sections in order to obtain expressions for the expected values and variances of these new random variables.

In section 2.1.3.2, the probabilities of the basic events in the model were defined for time intervals \([t, t+h]\). These probabilities were functions of both the length of the time interval and the particular time at which the interval began. However, at the steady-state \( p_{i,j}^B(t) \) is constant, and may therefore be denoted \( p_{i,j}^B \), so that the functional dependence of these probabilities with respect to a time interval does not involve the time at which the interval began but only the length of the interval.

For each site, \( s_{i,j} \), in the model, a non-negative, integer valued random variable, denoted as \( 0_{i,j}(c,s) \), is introduced. This random variable assumes the integer value \( k \) if site \( s_{i,j} \) consumes \( k \) molecules of oxygen during a time interval of length \( s \) at the
steady-state where \( c \) is the concentration of oxygen in solution.

The following equation defines a random variable, denoted as 

\[ O_T(c,s) \]

that takes on the value \( k \) if the entire tissue consumes \( k \) molecules of oxygen during a time interval of length \( s \) at the steady-state where \( c \) is the concentration of oxygen in solution:

\[ O_T(c,s) = \sum_i \sum_j O_{i,j}(c,s). \]

Therefore, the following relations for the expected value and the variance of this random variable hold:

\[
E_{O_T}(c,s) = \sum_i \sum_j E_{O_{i,j}}(c,s) \tag{2.1.3.7-1}
\]

\[
\text{VAR } O_T(c,s) = \sum_i \sum_j \text{VAR } O_{i,j}(c,s) + \sum_i \sum_j \sum_{j'} \text{COV}[O_{i,j}(c,s), O_{i,j'}(c,s)] \tag{2.1.3.7-2}
\]

\[(i,j) \neq (i',j') .\]

Differential equations may be employed to obtain expressions for the above quantities involving the parameters of the model, as is shown below.

Since, at the steady-state, the amount of oxygen consumed during a certain time interval depends only upon the length of the time interval and not upon the time at which the interval begins the following relations hold:

\[
E_{O_T}(c, s+h) - E_{O_T}(c,s) = E_{O_T}(c,h) \]

\[
E_{O_{i,j}}(c, s+h) - E_{O_{i,j}}(c,s) = E_{O_{i,j}}(c,h) . \tag{2.1.3.7-3}
\]
From the definition of $O_{i,j}(c,h)$ and equation 2.1.3.2-3, it follows that at the steady-state the following relations are valid, as $h$ approaches zero:

\[
P(O_{i,j}(c,h) = 0) = 1 - uh_{i,j}(1-P_{i,j}^B) + o(h)
\]

\[
P(O_{i,j}(c,h) = 1) = uh_{i,j}(1-P_{i,j}^B) + o(h)
\]

\[
P(O_{i,j}(c,h) > 1) = o(h)
\]

\[
EO_{i,j}(c,h) = uh_{i,j}(1-P_{i,j}^B) + o(h)
\]

\[
VAR O_{i,j}(c,h) = uh_{i,j}(1-P_{i,j}^B) + o(h).
\]

Therefore, from equation 2.1.3.7-3 it follows that:

\[
EO_{i,j}(c, s+h) = EO_{i,j}(c,s) = uh_{i,j}(1-P_{i,j}^B) + o(h).
\]

Dividing both sides of the above equation by $h$ and taking the limit as $h$ approaches zero gives:

\[
\frac{d}{ds} EO_{i,j}(c,s) = uf_{i,j}(1-P_{i,j}^B).
\]

Integrating the above equation with respect to $s$ and employing the initial condition that $EO_{i,j}(c,0) = 0$ gives:

\[
EO_{i,j}(c,s) = usf_{i,j}(1-P_{i,j}^B).
\]

The above equation and equation 2.1.3.7-1 give:

\[
EO_T(c,s) = \sum_{i} \sum_{j} usf_{i,j}(1-P_{i,j}^B).
\]
As defined in equation 2.1.3.2-3, all of the information needed to calculate the probability of an oxygen consumption during time interval \([t, t+h]\) by site \(S_{i,j}\) is contained in \(p_{i,j}(t)\) and parameters that are constant for the system. This is characteristic of Poisson processes and gives the following equations at the steady-state:

\[
\text{VAR } O_T(c,s+h) - \text{VAR } O_T(c,s) = \text{VAR } O_T(c,h) .
\]

2.1.3.7-7

From the definition of \(O_T(c,h)\) it follows that:

\[
\text{VAR } O_T(c,h) = \sum \sum \text{VAR } O_{i,j}(c,h) + \sum \sum \sum \text{COV}(O_{i,j}(c,h), O_{i',j'}(c,h))
\]

\((i,j) \neq (i',j') .

From assumption 7 in section 2.1.2 regarding independence it follows that:

\[
\text{COV}(O_{i,j}(c,h), O_{i',j'}(c,h)) = 0 \text{ for } (i,j) \neq (i',j') .
\]

Using the above two equations and equation 2.1.3.7-4 gives:

\[
\text{VAR } O_T(c,h) = \sum \sum u_i h f_{i,j}(1-p_{i,j}^B) + o(h) .
\]

Combining the above with equation 2.1.3.7-7, dividing by \(h\), and taking the limit as \(h\) approaches zero gives:

\[
\frac{d}{ds} \text{VAR } O_T(c,s) = \sum \sum u_i f_{i,j}(1-p_{i,j}^B) .
\]

Integrating with respect to \(s\) and using the initial condition that
VAR \( O_T(c,0) = 0 \) gives:

\[
VAR O_T(c,s) = \sum_i \sum_j u_{i,j} f_{i,j} (1 - P_{i,j}^B).
\]

Since the arrangement of binding sites is assumed to be known, the indicator functions may be introduced into equations 2.1.3.7-6 and 2.1.3.7-8 giving:

\[
EO_T(c,s) = \sum_i \sum_j u_{i,j} g_{i,j} (1 - P_{i,j}^B).
\]

and

\[
VAR O_T(c,s) = \sum_i \sum_j u_{i,j} s_{i,j} (1 - P_{i,j}^B).
\]

Now introducing the layer equilibrium assumption of section 2.1.3.4 into the above equation gives:

\[
EO_T(c,s) = \sum_i \sum_j u_{i,j} g_{i,j} (1 - P_{i}^B)
= \sum_i u_{i} (1 - P_{i}^B)
\]

and

\[
VAR O_T(c,s) = \sum_i \sum_j u_{i,j} s_{i,j} (1 - P_{i}^B)
= \sum_i u_{i} (1 - P_{i}^B)
\]

where \( m_i \) is the number of binding sites in layer \( i \).

The following development facilitates the evaluation of the above equations by eliminating the dependence upon all but the surface layer probabilities.
At the steady-state, equation 2.1.3.6-3,

\[ 0 = - \left[ b_i c m_i + r_i m_i + u m_i + \sum_{i'} d(i',i) p_{i'}^B \right] p_i^B + \sum_{i'} d(i',i) p_{i'}^B + r_i m_i + u m_i \]

may be summed over the index \( i \) to give,

\[ 0 = - \sum_i b_i c m_i p_i^B + \sum_i r_i m_i (1 - p_i^B) + \sum_i u m_i (1 - p_i^B) \]

which may be rearranged to give:

\[ \sum_i b_i c m_i p_i^B = \sum_i r_i m_i (1 - p_i^B) + \sum_i u m_i (1 - p_i^B) \]  \hspace{1cm} 2.1.3.7-11

This last equation may be viewed as a balance relation for the steady-state indicating that the expected number of oxygen molecules entering the tissue is equal to the probability of molecules leaving the tissue plus the probability of molecules being consumed. Recalling that the parameters \( b_i \) and \( r_i \) are zero unless layer \( i \) is a surface layer, the above equation may be combined with equations 2.1.3.7-9 and 2.1.3.7-10 to give:

\[ \text{EO}_T(c,s) = \text{VAR}_T(c,s) = \text{sm}_1 b_1 c p_1^B - \text{sm}_1 r_1 (1 - p_1^B) \] \hspace{1cm} \text{(one-sided case)}

\[ \text{EO}_T(c,s) = \text{VAR}_T(c,s) = \text{sc}(m_1 b_1 p_1^B + m_n b_n p_n^B) \]

\[ - \text{sr}_1 m_1 (1 - p_1^B) - \text{sr}_n m_n (1 - p_n^B) \] \hspace{1cm} \text{(two-sided case)}.

In this investigation, oxygen consumption is the quantity of interest and this is expressed as a rate. Since the process is composed of discrete events the derivative with respect to time is not defined. Therefore the rate of oxygen consumption is defined as a
time average rather than as an instantaneous value. The random variable employed is defined as:

\[ R(c, s) = \frac{1}{s} O_T(c, s) \]

where \( s \) is the length of the time interval.

In the experimental situation, the rate of oxygen consumption may be measured as a continuous process since the discontinuities are small relative to the sensitivity of the measuring device. It is assumed that under steady-state conditions, this experimental determination is equal to the rate determined by a time average.

From equations 2.1.3.7-9, 2.1.3.7-10 and 2.1.3.7-11 it follows that:

\[
ER(c, s) = m_{b_1} c_{P_1}^{B} - m_{r_1} (1-P_1^{B})
\]

(one-sided case) 2.1.3.7-12

\[
\text{VAR} \ R(c, s) = \frac{1}{s} [m_{b_1} c_{P_1}^{B} - m_{r_1} (1-P_1^{B})]
\]

(one-sided case) 2.1.3.7-13

\[
ER(c, s) = m_{b_1} c_{P_1}^{B} + m_{b_n} c_{P_n}^{B} - m_{r_1} (1-P_1^{B}) - m_{r_n} (1-P_n^{B})
\]

(two-sided case) 2.1.3.7-14

\[
\text{VAR} \ R(c, s) = \frac{1}{s} [m_{b_1} c_{P_1}^{B} + m_{b_n} c_{P_n}^{B} - m_{r_1} (1-P_1^{B}) - m_{r_n} (1-P_n^{B})]
\]

(two-sided case). 2.1.3.7-15

2.1.4 Solution of Equations for the One-Sided Case

The final equations of the previous section indicate that at the steady-state the expected value and the variance of the rate of oxygen consumption may be expressed in terms of surface layer probabilities.
In this section, expressions for the surface layer probabilities are obtained and employed to describe the kinetics of the one-sided case.

2.1.4.1 Surface Layer Probabilities

The basic equation for the one-sided case is equation 2.1.3.6-1:

$$A_1(c) Y = MX_1.$$

The solution of this equation for the probability vector $Y$ may be written formally as:

$$Y = A_1^{-1}(c) MX_1.$$

However, since only the first element of the probability vector is needed it suffices to lower triangularize the basic equation.

By construction, in section 2.1.3.5, the matrix $A_1(c)$ is a type 1 matrix as defined in Appendix 5.1. Let $L$ be the matrix that lower triangularizes $A_1(c)$ without multiplying the first row of $A_1(c)$ as described in proposition 2 of Appendix 5.1. Since only the first row of $A_1(c)$ involves $c$, it follows that $L$ does not depend upon $c$.

In this triangularization it is convenient to write $A_1(c)$ in the form:

$$A_1(c) = (bc+r)m_1 E_{11} + uM + Z$$

with the obvious identification of the elements of the matrix $Z$.

Since $b_1$ is the only non-zero $b_i$ the subscript may be suppressed. It should be observed that all of the row sums of $Z$ are zero. Therefore

$$LA_1(c) = L[(bc+r)m_1 E_{11} + uM + Z]Y = LMX_1 = L(uM + rm_1 E_{11})Y$$

or

$$[(bc+r)m_1 E_{11} + uLM + LZ]Y = (uLM + rm_1 E_{11})Y.$$
Let $w_1, w_2, \ldots, w_n$ be the elements of the first row of $ULM$ and let $z_1, z_2, \ldots, z_n$ be the elements of the first row of $LZ$. From the above equation it follows that:

$$(bc+r)m_1p_1^B + \sum_{i=1}^{n} w_i p_1^B + \sum_{i=1}^{n} z_i p_1^B = \sum_{i=1}^{n} w_i + r m_1.$$  \hspace{1cm} 2.1.4.1-2

Since $L A_1(c)$ is a lower triangular matrix, $w_i$ is equal to $-z_i$ for $i$ greater than $1$. From the construction of $L$ and the fact that the row sums of $LZ$ are zero and therefore:

$$\sum_{i=1}^{n} z_i = 0$$

or

$$z_1 = - \sum_{i=2}^{n} z_i = \sum_{i=2}^{n} w_i.$$  \hspace{1cm} 2.1.4.1-2

Therefore equation 2.1.4.1-2 may be written as

$$(bc+r)m_1p_1^B + w_1 p_1^B + \sum_{i=2}^{n} (w_i + z_i) p_1^B + z_1 p_1^B = \sum_{i=1}^{n} w_i + r m_1$$

or

$$(bc+r)m_1p_1^B + w_1 p_1^B + \sum_{i=2}^{n} w_i p_1^B = \sum_{i=1}^{n} w_i + r m_1.$$  \hspace{1cm} 2.1.4.1-2

Letting $w$ denote $\sum_{i=1}^{n} w_i$, this last expression may be written as:

$$(bc m_1 + r m_1 + w) p_1^B = w + r m_1.$$
or

\[
P_1^B = \left[ \frac{w + rm_1}{bcm_1 + rm_1 + w} \right].
\]

2.1.4.1-3

Since all of the elements of \( L \) are non-negative, as shown in proposition 2 of Appendix 5.1, it follows that \( w \) is non-negative. Furthermore, since \( L \) and \( X_1 \) do not depend upon \( c \), the constant \( w \) is not a function of the oxygen concentration in solution.

2.1.4.2 Steady-State Kinetics

In this section, previous results are employed to obtain expressions for the expected value and the variance of tissue oxygen consumption for the one-sided case and the dependence of these quantities upon the oxygen concentration in solution is explicitly shown.

Equations 2.1.3.7-12 and 2.1.4.1-3 may be combined to give:

\[
ER(c,s) = m_1bcP_1^B - m_1r(1-P_1^B)
\]

\[
= (m_1bc + m_1r)P_1^B - m_1r
\]

\[
= (m_1bc + m_1r) \left[ \frac{w + rm_1}{m_1bc + rm_1 + w} \right] - m_1r
\]

\[
= \frac{w m_1 bc}{m_1bc + rm_1 + w}
\]

\[
= \frac{w c}{r + w/m_1} + \left( \frac{1}{b} \right).
\]
Therefore,

\[ ER(c, s) = \frac{Vc}{c + k} \] \hspace{1cm} 2.1.4.2-1

where \( V = w \) and \( K = \frac{r + w/m_1}{b} \).

Similarly, equations 2.1.3.7-13 and 2.1.4.1-3 may be used to obtain:

\[ \text{VAR } R(c, s) = \frac{1}{s} \frac{Vc}{c + k} \] \hspace{1cm} 2.1.4.2-2

Since the parameters \( V \) and \( K \) do not depend upon the concentration of oxygen in solution, the expected rate of tissue oxygen consumption agrees with Michaelis-Menten kinetics. The variance is a monotonically decreasing function of the length of the time interval. While the lower limit of this function is zero, practical limitations of the experimental situation would require a finite time interval and therefore a non-zero value for the variance.

While this section has established that the expected kinetics for the one-sided case of the binding site model conform to Michaelis-Menten kinetics, the next section introduces a modification to the basic model that simplifies the equations to facilitate further analysis.

2.1.5 Modified Binding Site Model

In the development of the model to this point, it has been assumed that the arrangement of binding sites in the tissue is completely specified and known as discussed in section 2.1.3.4. It was
shown in the previous section that the kinetics of tissue oxygen consumption for the one-sided case conformed to Michaelis-Menten kinetics. In order to further explore the properties of the binding site model this section introduces a modification of the basic model regarding the arrangement of binding sites. Although this modification results in a weaker specification of the binding site distribution the resulting equations permit a more complete analysis of the behavior of the model.

The modification is that the arrangement of binding sites is specified in probability rather than being fixed. It is assumed that the probability of a site in layer $i$ being a binding site is $f_1$, where $f_1$ is a common value for all sites in layer $i$. Therefore in the modified binding site model the constraint on the distribution of binding sites is in terms of the expected number of binding sites per layer. The rationale for this modification is that oxygen transport through the tissue may be adequately described by specifying only the expected number of binding sites per layer rather than the actual position of each binding site in the layer.

Since the value of $f_{i,j}$ was left as arbitrary in obtaining equation 2.1.3.3-5 it suffices to use this equation as the starting point for the development of the modified binding site model. Recalling that equation 2.1.3.3-5 was
\[
\frac{d}{dt} [P_{i,j}^{B}(t)] = -[b_{1}c + r_{1} + u] + \sum_{i',j'} d(i',j',i,j) f_{i',j'}^{1} P_{i,j}^{B}(t) + \sum_{i',j'} d(i,j',i,j) f_{i,j'} P_{i,j}^{B}(t)
\]

which may now be written as

\[
\frac{d}{dt} [f_{i} P_{i,j}^{B}(t)] = -[b_{1}c + r_{1} + u] f_{i} + \sum_{i',j'} d(i',j',i,j) f_{i',j'} f_{i} P_{i,j}^{B}(t) + \sum_{i',j'} d(i,j',i,j) f_{i,j'} f_{i} P_{i,j}^{B}(t)
\]

Assuming that \(f_{i}\) is non-zero for all layers, this equation may be divided by \(f_{i}\) to give:

\[
\frac{d}{dt} P_{i,j}^{B}(t) = -[b_{1}c + r_{1} + u + \sum_{i',j'} d(i',j',i,j) f_{i',j'}] P_{i,j}^{B}(t) + \sum_{i',j'} f(i,j,i',j') f_{i,j'} P_{i,j}^{B}(t) + r_{1} + u .
\]

This serves as the basic equation for the modified binding site model.
2.1.5.1 Formulation of Equations

In this section the equations of the modified binding site model are formulated using assumptions paralleling those for the basic model.

2.1.5.1.1 Layer Equilibrium Assumption

As in section 2.1.3.4 the layer equilibrium assumption regarding equilibrium among the sites within a layer is introduced. For the modified binding site model this assumption may be stated as:

\[ P_{i,j}(t) = P_{i,j'}(t) \quad \text{for all } j, j' \]

or

\[ P_{i,j}(t) = P_{i,j'}(t) \quad \text{for all } j, j' \]

While the justification for this assumption may be developed along the same line as in section 2.1.3.4 it is of interest to examine one of the consequences of this assumption for the modified model.

Suppose that in the previous development of the model each layer was a plane consisting of a countably infinite number of sites.

Let \( S_{i',j} \) be an arbitrary, but fixed, site in the model. This site determines a line passing through \( S_{i',j} \) and perpendicular to a surface layer. Each site in the tissue may be denoted as \( S(i,d,a) \) where \( i \) is the layer containing the site, \( d \) is the minimum distance from the site to the perpendicular determined by \( S_{i',j'} \), and \( a \) is an angle determined from an arbitrary, but fixed, reference line segment for each layer. The angle \( a \) may be restricted to be a non-negative
angle less than 180 degrees. The following equation serves as a definition of a quantity denoted as E.T.P. \((S_{i,j,i}, i)\) and called the expected transfer position from \(S_{i,j,i}\) to layer \(i:\)

\[
\text{E.T.P. } (S_{i,j,i}, i) = \sum_k (d_k, a_k) P_{i,j,i}(t, t+h) \]

where \((d_k, a_k)\) are the coordinates of \(S_{i,j,k}\) as indicated in the representation \(S(i, d_k, a_k)\). This quantity may be viewed as indicating the position in layer \(i\) that oxygen from \(S_{i,j,i}\) would transfer to on the average in time interval \([t, t+h]\). It does not necessarily indicate what would happen on any particular transfer but rather what the net effect of numerous such transfers could be.

In order to ensure that such a quantity exists, in the sense that the series in equation 2.1.3.4-2 is absolutely convergent, it is sufficient to assume that there is a finite distance such that the probability of a transfer from \(S_{i,j,i}\) to a site beyond that distance in time interval \([t, t+h]\) is zero. It is shown below that, under the conditions of layer equilibrium, whenever the vector quantity \(\text{E.T.P. } (S_{i,j,i}, i)\) exists it lies on the perpendicular determined by \(S_{i,j,i}\).

For each site \(S_{i,j,k}\) with coordinates \((d_k, a_k)\), there exists a site \(S_{i,j,k'}\) with coordinates \((-d_k, a_k)\). By construction, it follows that \(S_{i,j,k}\) and \(S_{i,j,k'}\) are equidistant from \(S_{i,j,i}\). Under the conditions of layer equilibrium, the following holds:

\[
P_{i,k}(t) = P_{i,k'}(t)
\]
and therefore the following is also true:

\[ P_{i,k}^B(t) = P_{i,k}(t). \]

From these relations and assumption (8) in section 2.1.2, that the probability of a transfer from one site to another depends only upon the probability that the first site is occupied, the probability that the second site is unoccupied, and the distance between them the following relation is valid:

\[ P_{i',j'}^T_{i,k}(t, t+h) = P_{i',j'}^T_{i,k}(t, t+h). \]

This implies that:

\[ (d_{i,k}a_k)P_{i',j'}^T_{i,k}(t, t+h) + (-d_{i,k}a_k)P_{i',j'}^T_{i,k}(t, t+h) = (0, a) \]

2.1.5.1.1-2

where \( a \) is an angle that need not be specified.

Since this relation holds for all pairs of sites in layer \( i \) it follows that, under the conditions of layer equilibrium, the vector quantity E.T.P. \( (S_{i',j'}, i) \) lies on the perpendicular determined by \( S_{i',j'} \). Moreover, since \( S_{i',j'} \) was chosen as an arbitrary site in the tissue, this result applies to all sites in the model.

For the particular case under investigation in this study the layers are not infinite planes but rectangles of finite dimensions. However, it was stated in section 1.1 that the surface area of the tissue is much larger than the thickness. Thus, by assuming that transfer probabilities decrease rapidly as the distance between sites increases, most sites in the tissue would transfer oxygen as if each
layer were a plane. That is, for most sites in the tissue the expected transfer position could be assumed to lie on the perpendicular determined by the site and a surface layer. Since this study is concerned with the oxygen consumption of the entire tissue slice it is assumed that the contribution of sites near the boundary of each rectangular layer is negligible compared to the role of the sites that behave as if they were in a layer of infinite dimensions.

This particular development illustrates the principle difference between the binding site model and the modified binding site model. Since the binding sites are specified only in probability the expected transfer position lies on a perpendicular to the point of entry on the surface layer. In the case of the binding site model in which the location of each binding site in a layer is specified it might occur that such a path has probability zero for lack of binding sites on that perpendicular.

For the modified binding site model, as with the basic model, it may be shown that any departure from layer equilibrium results in a restoring force favoring the return to layer equilibrium. Since the proof is almost identical to that given in section 2.1.3.4, it is not repeated here.

The introduction of this assumption permits the suppression of the second subscript on $P^B_i,j(t)$ and equation 2.1.5-2 may be written as:

$$
\frac{d}{dt} P^B_i(t) = -[b_i c + r_i + u + \sum_j \sum_{i'} d(i',j',i,j)f_{i',j'}]P^B_i(t)
$$

$$
+ \sum_j \sum_{i'} d(i,j,i',j')f_{i',j'}P^B_i(t) + r_i + u.
$$

2.1.5.1.1-3
The following equation serves as a definition of a quantity called the net \( k \) layer transfer probability and is denoted as \( \ell_k \) where \( k \) is a non-negative integer:

\[
\ell_k = \sum_{j'} d(i, j, i', j') = \sum_{j'} d(i', j', i, j)
\]

2.1.5.1.1-4

where \( k = |i' - i| \).

The definition of this quantity serves as another illustration of the basic nature of the layer equilibrium assumption in the modified model. Implicit in this definition is the assumption that \( \ell_k \) does not depend upon the index \( j \) appearing in the defining equation. This lack of dependence upon \( j \) is due to both the layer equilibrium assumption and the approximation of the behavior of a model in which each layer is an infinite plane.

The quantity \( \ell_k \) may be interpreted as an indicator of the likelihood of an oxygen transfer from \( S_{i,j} \) to a position in the \( k \)th layer from layer \( i \).

It should be noted that since \( d(i', j', i, j) \) was defined to be a non-negative, monotone non-increasing function of the distance between \( S_{i', j'} \) and \( S_{i, j} \), it follows that:

\[
\ell_1 \geq \ell_2 \geq \cdots \geq \ell_{n-1}.
\]

Introducing this quantity into equation 2.1.5.1.1-3 and rearranging terms gives:
\[
\frac{d}{dt} P_i^B(t) = -(b_i c + \sum_{i'} \ell_{i-i'} f_{i'} + r_i + u) P_i^B(t)
+ \sum_{i'} \ell_{i-i'} f_{i'} P_i^B(t) + r_i + u
\]

or

\[
\frac{d}{dt} P_i^B(t) = -b_i c P_i^B(t) - \sum_{i'} \ell_{i-i'} f_{i'} P_i^B(t)
+ \sum_{i'} \ell_{i-i'} f_{i'} P_i^B(t) + r_i [1-P_i^B(t)] + u[1-P_i^B(t)].
\]

2.1.5.1.2 Matrix Form of the Equations

As for the basic model, the equations for the modified model may be summarized in matrix form. Recall that \( e_i \) denotes the n-dimensional column vector whose only non-zero is a 1 in the \( i \)th row and \( E_{i,j} \) is the n-dimensional square matrix whose only non-zero entry is a 1 in row \( i \) and column \( j \).

Let \( A_i(c) \) be the n-dimensional square matrix of the form

\[
\begin{pmatrix}
 b_1 c + r_1 + u + \sum_{i \neq 1} f_{1-i} \ell_{1-i} & -f_2 \ell_1 & -f_3 \ell_1 & \cdots & -f_n \ell_{n-1} \\
-f_1 \ell_1 & u + \sum_{i \neq 2} \ell_{2-i} f_{2-i} & -f_3 \ell_1 & \cdots & -f_n \ell_{n-2} \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
-f_1 \ell_{n-1} & \cdots & \cdots & \cdots & u + \sum_{i \neq n} f_{n-i} \ell_{i-n}
\end{pmatrix}
\]
The form of $\bar{A}_1(c)$ is that

1. the diagonal elements are positive,
2. the off-diagonal elements are non-positive,
3. an off-diagonal element in position $(i,j)$ is equal to $-\ell_j \ell_i |j-i|$, and
4. the diagonal element in the $i^{th}$ row is $u$ plus the sum of the absolute values of the off-diagonal terms in that row and, for the first diagonal element, the term $b_1 c + r_1$.

Let

$$X_1 = \begin{bmatrix} u+r_1 \\ u \\ . \\ . \\ . \\ u \end{bmatrix}$$

and

$$X_2 = \begin{bmatrix} u+r_1 \\ u \\ . \\ . \\ . \\ u \\ u+r_n \end{bmatrix}$$

as in section 2.1.3.5.

Let $\bar{A}_2(c) = \bar{A}_1(c) + (b \cdot c + r_n) E_{nn}$.
With this notation the basic equations for the modified binding site model as given in equation 2.1.5.1.1-5 may be summarized as:

\[ \bar{Y}'(t) = \bar{A}_1(c)\bar{Y}(t) + X_1 \] for the one-sided case \hspace{1cm} 2.1.5.1.2-1

and

\[ \bar{Y}'(t) = \bar{A}_2(c)\bar{Y}(t) + X_2 \] for the two-sided case \hspace{1cm} 2.1.5.1.2-2

where \( \bar{Y}(t) = \sum_{i=1}^{n} P^B_i(t)e_i \).

2.1.5.1.3 Steady-State Assumption

As in section 2.1.3.6, the model is investigated at steady-state. This corresponds to setting \( \bar{Y}'(t) \) equal to 0 in equations 2.1.5.1.2-1 and 2.1.5.1.2-2 and gives:

\[ \bar{A}_1(c)\bar{Y} = X_1 \] for the one-sided case \hspace{1cm} 2.1.5.1.3-1

and

\[ \bar{A}_2(c)\bar{Y} = X_2 \] for the two-sided case \hspace{1cm} 2.1.5.1.3-2

These equations serve as the basic steady-state equations for the modified binding site model. It may be shown that these steady-state equations are consistent with the original equations. The proof is similar to that of section 2.1.3.6 and is not repeated.

Under the steady-state assumption equation 2.1.5.1.1-5 may be written as:

\[ 0 = -(b_i c + \sum_{i'} \ell_{i'i'} f_{i'1} + r_i + u)P^B_{i1} + \sum_{i'} \ell_{i'i'} f_{i'1} P^B_{i1} + r_i + u. \] 2.1.5.1.3-3
2.1.5.1.4 Measure of Oxygen Consumption

From equations 2.1.3.7-6 and 2.1.3.7-8 it follows that

\[ EO_T(c,s) = \sum_i \sum_j usf_i(1-P_i^B) \]

and

\[ VAR O_T(c,s) = \sum_i \sum_j usf_i(1-P_i^B) \cdot \]

Recalling that there are \( m \) sites per layer the above equations become

\[ EO_T(c,s) = \sum_i usmf_i(1-P_i^B) \] \hspace{1cm} 2.1.5.1.4-1

and

\[ VAR O_T(c,s) = \sum_i usmf_i(1-P_i^B) \cdot \] \hspace{1cm} 2.1.5.1.4-2

In comparing the binding site model with the modified binding site model it should be observed that \( mf_i \) is the expected number of binding sites in layer \( i \) of the modified model. Recalling that \( m_i \) was the exact number of binding sites in layer \( i \) of the basic model, the similarity between the above two equations and equations 2.1.3.7-9 and 2.1.3.7-10 is apparent.

Multiplying equation 2.1.5.1.3-3 by \( f_i \) and summing over \( i \) gives

\[ O = - \sum_i f_i b_i c_{P_i^B} + \sum_i r_i f_i(1-P_i^B) + \sum_i u f_i(1-P_i^B) \cdot \]

Multiplying by \( m \) and rearranging terms gives

\[ \sum_i f_i b_i c_{P_i^B} = \sum_i r_i f_i m(1-P_i^B) + \sum_i u f_i m(1-P_i^B) \cdot \] \hspace{1cm} 2.1.5.1.4-3
This serves as the balance equation for the modified binding site model and may be used with equations 2.1.5.1.4-1 and 2.1.5.1.4-2 to give

$$\text{EO}_T(c,s) = \text{VAR } O_T(c,s) = \text{sm} f_1 b_1 c p_1^B - \text{sm} r f_1 (1-p_1^B)$$

(one-sided case)

and

$$\text{EO}_T(c,s) = \text{VAR } O_T(c,s) = \text{smcf} f_1 b_1 p_1^B + \text{smcf} b_n p_n^B$$

$$- \text{smr} f_1 (1-p_1^B) - \text{smr} f_n (1-p_n^B)$$

(two-sided case).

As in section 2.1.3.7 the random variable $R(c,s) = \frac{1}{s} O_T(c,s)$ is introduced to describe the rate of oxygen consumption and gives:

$$\text{ER}(c,s) = \text{mf}_1 b_1 c p_1^B - \text{mr} f_1 (1-p_1^B)$$

(one-sided case) 2.1.5.1.4-4

$$\text{ER}(c,s) = \text{mcf} f_1 b_1 p_1^B + \text{mcf} b_n p_n^B - \text{mr} f_1 (1-p_1^B) - \text{mr} f_n (1-p_n^B)$$

(two-sided case) 2.1.5.1.4-5

and

$$\text{VAR } R(c,s) = \frac{1}{s} \text{ER}(c,s)$$

(both cases). 2.1.5.1.4-6

2.1.5.2 Solution of Equations for Surface Layers

As the final equations of the previous section indicate, at the steady-state the expected value and the variance of the rate of oxygen consumption may be expressed in terms of surface layer probabilities. This is the same as for the basic model. In this section the surface layer probabilities are obtained for both the one- and two-sided cases.
2.1.5.2.1 Surface Layer Probabilities for the One-Sided Case

The basic equation for the one-sided case is equation

2.1.5.1.3-1:

$$\bar{A}_1(c)\bar{Y} = \bar{X}_1.$$ 

As in section 2.1.4.1, the solution of this equation for the probability vector, \(\bar{Y}\), may be written formally as:

$$\bar{Y} = \bar{A}_1^{-1}(c) \bar{X}_1.$$ 

However, since only the first element of the probability vector is needed it suffices to lower triangularize the basic equation.

By construction, the matrix \(\bar{A}_1(c)\) is a type 1 matrix as defined in Appendix 5.1. Let \(L\) be the matrix that lower triangularizes \(\bar{A}_1(c)\) without multiplying the first row of \(\bar{A}_1(c)\) as described in proposition 2 of Appendix 5.1. Since only the first row of \(\bar{A}_1(c)\) involves \(c\), it follows that \(L\) does not depend upon \(c\). In this triangularization it is convenient to write \(\bar{A}_1(c)\) in the form:

$$\bar{A}_1(c) = (bc+r) E_{11} + uI + \bar{Z}.$$ 

with the obvious identification of the elements of the matrix \(\bar{Z}\).

Therefore the following equations hold:

$$L\bar{A}_1(c)\bar{Y} = L[(bc+r) E_{11} + uI + \bar{Z}]\bar{Y} = L\bar{X}_1 = L(uI + rE_{11})\bar{Y}$$

$$= [(bc+r) E_{11} + uLI + L\bar{Z}]\bar{Y} = [uLI + rE_{11}]\bar{Y}.$$ 

It should be observed that all of the row sums of \(\bar{Z}\) are zero.
Let \( w_1, w_2, \ldots, w_n \) be the elements of the first row of \( uL \) and let \( z_1, z_2, \ldots, z_n \) be the elements of the first row of \( LZ \). From the above equation it follows that:

\[
(bc+r)y_1 + \sum_{i=1}^{n} w_i y_i + \sum_{i=1}^{n} z_i y_i = \sum_{i=1}^{n} w_i + r.
\]

Since \( LA_1(c) \) is a lower triangular matrix, \( w_i \) is equal to \(-z_i\) for \( i \) greater than 1. From the construction of \( L \) and the fact that the row sums of \( Z \) are zero, it follows that the row sums of \( LZ \) are zero and therefore:

\[
\sum_{i=1}^{n} z_i = 0
\]

or

\[
z_1 = -\sum_{i=2}^{n} z_i = \sum_{i=2}^{n} w_i.
\]

Recalling that the \( i^{th} \) element of \( y \) is \( p_i^B \), equation 2.1.5.2.1-2 may be written as:

\[
(bc+r)p_1^B + w_1p_1^B + \sum_{i=2}^{n} (w_i + z_i)p_i^B + z_1p_1^B = \sum_{i=1}^{n} w_i + r
\]

or

\[
(bc+r)p_1^B + w_1p_1^B + \sum_{i=2}^{n} w_ip_i^B = \sum_{i=1}^{n} w_i + r.
\]

Letting \( w \) denote \( \sum_{i=1}^{n} w_i \), this last expression may be written as:

\[
(bc+r + w)p_1^B = w + r.
\]
This is the first scalar equation of the lower triangularized system of equations.

Since all of the elements of \( L \) are non-negative, as shown in proposition 2 of Appendix 5.1, it follows that \( w \) is non-negative. Furthermore, since \( L \) and \( X_1 \) do not depend upon \( c \), the constant \( w \), is not a function of the oxygen concentration in solution.

2.1.5.2.2 Surface Layer Probabilities for the Two-Sided Case

Prior to solving the two-sided case, it is convenient to employ certain symmetry properties in order to simplify the equations. In the model it is assumed that the parameters \( b_i \), \( r_i \), and \( f_i \) are functions only of the distance between layer \( i \) and the surface. This may be expressed mathematically in the following relationships, where \( n \) is the number of layers in the tissue:

\[
\begin{align*}
  b_i &= b_{n-i+1} \quad \text{2.1.5.2.2-1} \\
  r_i &= r_{n-i+1} \quad \text{2.1.5.2.2-2} \\
  f_i &= f_{n-i+1} \quad \text{2.1.5.2.2-3}
\end{align*}
\]

Since the parameters \( b_i \) and \( r_i \) are zero except for surface layers, it is assumed in the first two relations that the parameters describing the interaction of surface layer sites with the solution are the same for both surfaces. The third relation is concerned with the parameters describing the distribution of binding sites in the tissue. It is assumed that the initial condition of the tissue is that the binding sites are uniformly distributed in the tissue and
therefore all layers have a common value for the parameter $f_i$. The symmetry condition of equation 2.1.5.2.2-3 is introduced to describe certain types of inhibition. For such cases, it is assumed that the inhibitor is introduced into the solution and enters the tissue through both surface layers. The symmetry of the biological system is then offered as a justification for the assumption in equation 2.1.5.2.2-3 concerning the symmetric distribution of binding sites in the tissue.

These relationships are sufficient to establish that:

$$y_i = y_{n-i+1} \quad \text{for all } i,$$

as shown below.

Let $H = (h_{i,j}) = [e_{e_{n-1}} \cdots e_1]$; that is,

$$h_{i,j} = \begin{cases} 1 & \text{if } i+j = n+1 \\ 0 & \text{otherwise} \end{cases}.$$

It should be noted that:

$$H^{-1} = H.$$

Observing that $HX_2 = X_2$ and $HA_2(c)H = A_2(c)$ under the above symmetry conditions and employing equation 2.1.5.1.3-2 tives:

$$Y = A_2^{-1}(c)X_2 = H^{-1}A_2^{-1}(c)H^{-1}HX_2 = H^{-1}A_2^{-1}(c)X_2 = HY,$$

completing the proof that

$$y_i = y_{n-i+1} \quad \text{for all } i.$$
Using probability notation this means that: $p_i^B = p_{n-i+1}^B$ and since $f_i = f_{n-i+1}$, $p_i = p_{n-i+1}$.

Therefore, the probability that a site in the model is unoccupied remains invariant under a reflection through the mid-plane of the tissue. This symmetry in the model may now be employed to reduce the number of equations needed for the two-sided case.

Equation 2.1.5.1.3-3 may be written as:

$$ (b_i c + r_i + u + \sum_{i'} \ell_{i'i} | f_{i'i} | p_{i'i}^B ) p_i^B = \sum_{i'} \ell_{i'i} | f_{i'i} | p_{i'i}^B = r_i + u $$

for $i = 1, \ldots, n$. 2.1.5.2.2-4

The n-i+1 equation is:

$$ (b_{n-i+1} c + r_{n-i+1} + u + \sum_{i'} \ell_{i'i} | f_{i'i} | p_{n-i+1,i'}^B ) p_{n-i+1,i'}^B = \sum_{i'} \ell_{i'i} | f_{i'i} | p_{i'i}^B = r_{n-i+1} + u. $$

Using the symmetry relations introduced in this section permits writing the above equation as:

$$ (b_i c + r_i + u + \sum_{i'} \ell_{i'i} | f_{i'i} | p_{i'i}^B ) p_i^B = \sum_{i'} \ell_{i'i} | f_{i'i} | p_{i'i}^B = r_i + u. $$

Employing the symmetry conditions

$$ f_{i'i} = f_{n-i'+1} $$ and $$ p_{i'i}^B = p_{n-i'+1}^B $$

it follows that:
\[
\sum_{i'=1}^{n} \ell |i'-(n-i+1)| f_{i'} p_{i}^{B} = \sum_{i'=1}^{n} \ell |i-(n-i'+1)| f_{n-i'+1} p_{i}^{B}
\]

\[
= \sum_{k=n}^{1} \ell |i-k| f_{k} p_{k}^{B}
\]

\[
= \sum_{i'=1}^{n} \ell |i'-i| f_{i'} p_{i}^{B}
\]

and

\[
\sum_{i'=1}^{n} \ell |i'-(n-i+1)| f_{i'} p_{i}^{B} = \sum_{i'=1}^{n} \ell |i-(n-i'+1)| f_{n-i'+1} p_{n-i'+1}
\]

\[
= \sum_{k=n}^{1} \ell |i-k| f_{k} p_{k}^{B}
\]

\[
= \sum_{i'=1}^{n} \ell |i'-i| f_{i'} p_{i}^{B}
\]

Therefore the \(n-i+1\) equation may be written as:

\[
(b_{i} c + r_{i} u + \sum_{i'=1}^{n} \ell |i'-i| f_{i'}) p_{i}^{B} - \sum_{i'=1}^{n} \ell |i'-i| f_{i'} p_{i}^{B} = r_{i} + u,
\]

which is the same as the \(i^{th}\) equation. That is, for the two-sided case, equation \(i\) and equation \(n-i+1\) are identical. Therefore, if \(n\) is even there are \(n/2\) different equations and if \(n\) is odd there are \((n+1)/2\) different equations. In either case, since \(p_{i}^{B} = p_{n-i+1}^{B}\), the number of different equations is equal to the number of unknowns.
Let $n$ be even, then:

$$\sum_{i'=1}^{n} \ell_{i'-i} f_{i'} P_i^B = \frac{n/2}{\sum_{i'=1}^{n} \ell_{i'-i} f_{i'} P_i^B} + \frac{n}{\sum_{i'= \frac{n+1}{2}}^{n} \ell_{i'-i} f_{i'} P_i^B}$$

$$= \frac{n/2}{\sum_{i'=1}^{n} \ell_{i'-i} f_{i'} P_i^B} + \frac{1}{\sum_{i'= \frac{n}{2}}^{n} \ell_{(n-i'+1)-i} f_{i'} P_i^B}$$

$$= \sum_{i'=1}^{n/2} \left( \ell_{i'-i} + \ell_{(n-i'+1)-i} \right) f_{i'} P_i^B$$

and similarly:

$$\sum_{i'=1}^{n} \ell_{i'-i} f_{i'} P_i^B = \frac{n/2}{\sum_{i'=1}^{n} \ell_{i'-i} f_{i'} P_i^B} + \frac{n}{\sum_{i'= \frac{n+1}{2}}^{n} \ell_{i'-i} f_{i'} P_i^B}$$

Let $n$ be odd, then

$$\sum_{i'=1}^{n} \ell_{i'-i} f_{i'} P_i^B = \frac{n-1}{2} \sum_{i'=1}^{n} \ell_{i'-i} f_{i'} P_i^B + \frac{n}{\sum_{i'= \frac{n+1}{2}}^{n} \ell_{i'-i} f_{i'} P_i^B}$$

$$= \sum_{i'=1}^{n-1} \ell_{i'-i} f_{i'} P_i^B + \frac{1}{\sum_{i'= \frac{n}{2}}^{n} \ell_{(n-i'+1)-i} f_{n-i'+1} P_i^B}$$

$$= \sum_{i'=1}^{n-1} \ell_{i'-i} f_{i'} P_i^B + \frac{1}{\sum_{i'= \frac{n}{2}}^{n} \ell_{(n-i'+1)-i} f_{i'} P_i^B}$$

$$= \sum_{i'=1}^{n-1} \left( \ell_{i'-i} + \ell_{(n-i'+1)-i} \right) f_{i'} P_i^B$$

and, similarly:
\[
\sum_{i' = 1}^{n} \ell_{i' - i} f_{i' P_{B}} = \sum_{i' = 1}^{n-1} \left[ \ell_{i' - i} + \ell_{(n-i'+1) - i} \right] f_{i' P_{B}} \\
+ \ell_{\left\lfloor \frac{n+1}{2} - i \right\rfloor} \frac{f_{n+1}}{2} \frac{P_{B}}{n+1} 
\]

Employing the above relations, equation 2.1.5.2.2-4 may be written as:

\[
\left( b_{i} c + r_{i} + u_{i} \right) + \sum_{i' = 1}^{n/2} \left( \ell_{i' - i} + \ell_{(n-i'+1) - i} \right) f_{i' P_{B}} - \sum_{i' = 1}^{n/2} \left( \ell_{i' - i} + \ell_{(n-i'+1) - i} \right) f_{i' P_{B}} = r_{i} + u
\]

when \( n \) is even and \( 1 \leq i \leq n/2 \)

and

\[
\left( b_{i} c + r_{i} + u_{i} \right) + \sum_{i' = 1}^{n+1/2} \left( \ell_{i' - i} + \ell_{(n-i'+1) - i} \right) f_{i' P_{B}} + \ell_{\left\lfloor \frac{n+1}{2} - i \right\rfloor} \frac{f_{n+1}}{2} \frac{P_{B}}{n+1} = r_{i} + u
\]

when \( n \) is odd. In either case, the equations may be written in matrix form as \( \bar{A}_{R}(c)\bar{Y} = \bar{X}_{R} \), where the subscript \( R \) indicates that the number of equations has been reduced.
The dimensions of $\overline{A}_R(C)$, $\overline{Y}$, and $\overline{X}$ depend upon $n$. If $n$ is even then $\overline{A}_R(C)$ is an $n/2$ square matrix and $\overline{Y}$ and $\overline{X}$ are $(n/2)$ by 1 vectors. If $n$ is odd, then $\overline{A}_R(C)$ is an $(n+1)/2$ square matrix and $\overline{Y}$ and $\overline{X}$ are $(n+1)/2$ by 1 vectors. The following relations hold for the vectors:

$$\overline{Y} = \sum_{i=1}^{n/2} p_i^B e_i \quad \text{if } n \text{ is even}$$

$$\overline{Y} = \sum_{i=1}^{(n+1)/2} p_i^B e_i \quad \text{if } n \text{ is odd}$$

$$\overline{X} = r e_1 + u 1$$

It follows by inspection of equations 2.1.5.2.2-5 and 2.1.5.2.2-6 that: (1) the off diagonal elements of $\overline{A}_R(C)$ are non-positive and (2) since $u > 0$, the diagonal element is greater than the negative sum of the off-diagonal elements in that row. Therefore $\overline{A}_R(C)$ is a type 1 matrix, as defined in Appendix 5.1.

It also follows by inspection that only the first element of the first row of $\overline{A}_R(C)$ involves the terms $bc+r$ and that all of the diagonal elements contain the term $u$ so that $\overline{A}_R(C)$ may be written as:

$$\overline{A}_R(C) = (bc+r) E_{11} + u 1 + Z,$$

where $Z$ is a matrix with zero row sums. Therefore the equation $\overline{A}_R(C)\overline{Y} = \overline{X}$ may be solved for $y_1 = p_1^B$ using the same techniques employed in section 2.1.5.2.1. The form of the solution is

$$(bc+r+w')p_1^B = w'+r$$

2.1.5.2.2-7
where \( w' \) is a non-negative number resulting from the triangularization process and is independent of \( c \).

In employing the symmetry relations for the two-sided case to reduce the number of equations it is possible to examine a certain equivalency between the two cases. In this section a reflective barrier is introduced to illustrate this relationship.

Consider the one-sided case with \( n \) layers and a reflecting barrier parallel to the surface whose distance from layer \( n \) is equal to half the inter-layer distance in the tissue.

Now consider the two-sided case with \( 2n \) layers and layers of the same dimensions as in the one-sided case. This two-sided model may be superimposed upon the one-sided model so that the two-sided case is bisected by the reflective barrier and so that site \( S_{i,j} \) in the one-sided model coincides with site \( S_{i,j} \) in the two-sided model for \( i = 1, \ldots, n \).

By construction, each site \( S_{i,j} \) in the one-sided model has an image site \( S_{2n-i+1,j} \) in the two-sided model relative to the reflective barrier. In assigning probabilities to oxygen transfers between sites a distance function was introduced in equation 2.1.3.2-4.

Analogously, for the one-sided case with the reflective barrier, it is assumed that the probability of an oxygen transfer from \( S_{i,j} \) to \( S_{i',j'} \) in time interval \( [t, t+h) \) by way of the reflective barrier is:

\[
d(i,j,2n-i'+1,j') p_{i',j'}^{B}(t) f_i(1-p_{i,j'}^{B}(t)) + o(h)
\]

where the distance function is taken to be the value appropriate for a transfer from \( S_{i,j} \) to \( S_{2n-i'+1,j'} \), the image site of \( S_{i',j'} \). That
is, transfers by way of the reflective barrier occur as if the
distance between the sites was the distance between the originating
site and the image of the terminating site.

It should be noted that, since the probability of a site
changing state more than once during a time interval \([t, t+h]\) is \(o(h)\),
the probability of a transfer from \(S_{i,j}\) to \(S_{i,j}\) by way of the
reflective barrier in time interval \([t, t+h]\) is \(o(h)\).

After dividing by \(h\), eliminating the dependence upon \(t\) at the
steady-state, and employing the layer equilibrium the above expression
may be written as:

\[
d(i,j,2n-i'+1,j')f_{i'}P_{i'}^{B}f_{i}[1-P_{i'}^{B}] .
\]

Now observing that for the two-sided case with 2n layers, the
symmetry conditions of this section are:

\[
f_{2n-i'+1} = f_{i'}
\]

and

\[
P_{2n-i'+1}^{B} = P_{i'}^{B}
\]

the above expression is identical to:

\[
d(i,j,2n-i'+1,j')f_{2n-i'+1}P_{2n-i'+1}^{B}f_{i}[1-P_{i}^{B}] .
\]

The last expression results from the probability of a transition from
\(S_{i,j}\) to \(S_{2n-i'+1,j}\) in the two-sided model.

The only discrepancy between the two cases is that the equations
for the two-sided case include expressions for the transfer of an
oxygen from \( S_{i,j} \) to its image site \( S_{2n-i+1,j} \). However, at the steady-state the probability of a transfer to \( S_{i,j} \) from \( S_{2n-i+1,j} \) is equal to the probability of a transfer from \( S_{i,j} \) to \( S_{2n-i+1,j} \) so that these terms cancel and there is no net transfer of oxygen between these sites.

Therefore, at the steady-state, there is no difference in the equations for two \( n \) layer one-sided models separated by a reflective barrier and one \( 2n \) layer two-sided model. It should be noted that in this discussion, the symmetry of the oxygen distribution about the mid-plane of the tissue was sufficient to establish the equivalence between these two cases. Therefore, if the symmetry condition is established then the equivalence of the kinetics applies even if the tissue is not at steady-state.

From an experimental viewpoint this result indicates that a tissue slice of a given thickness, say \( h \), would respire at twice the rate of a tissue slice with half the thickness and half the volume and placed against a reflective barrier. While experimental verification of this prediction would support this model, deviations from this result would also be of interest. In particular, this prediction is a consequence of both the modified model together with the additional assumption that oxygen transfers between two sites via the reflective barrier have the same probability as oxygen transfers between two sites of equivalent straight line distance. Therefore, experimental falsification of this prediction may be attributable either to flaws in the model or failure to experimentally realize this additional assumption.
2.1.5.3 Steady-State Kinetics

In this section, previous results are employed to obtain expressions for the expected value and the variance of tissue oxygen consumption in which the dependence upon the oxygen concentration in solution is explicitly shown.

For the one-sided case, equations 2.1.5.1.4-4 and 2.1.5.2.1-3 may be combined to give:

\[ \text{ER}(c,s) = mf_1 b P_1^B - mrf_1 (1 - P_1^B) \]

\[ = (mf_1 bc + mrf_1) P_1^B - mrf_1 \]

\[ = (mf_1 bc + mrf_1) \left( \frac{w + r}{bc + r + w} \right) - mrf_1 \]

\[ = \frac{w mf_1 bc}{bc + r + w} \]

\[ = \frac{(wmf_1) c}{c + \frac{(r + w)}{b}}. \]

Therefore,

\[ \text{ER}(c,s) = \frac{Vc}{c + K} \]  \hspace{1cm} 2.1.5.3-1

where \( V = wmf_1 \) and \( K = \frac{r + w}{b} \).

Similarly, equations 2.1.5.1.4-6 and 2.1.5.2.1-3 may be used to obtain:

\[ \text{VAR R}(c,s) = \frac{1}{s} \frac{Vc}{c + K}. \]  \hspace{1cm} 2.1.5.3-2
Analogously, for the two-sided case, equations 2.1.5.1.4-5, 2.1.5.1.4-6 and 2.1.5.2.2-7 may be used with the symmetry relations of section 2.1.5.2.2 to give:

\[ ER(c,s) = \frac{V'c}{c+K'} \]  
\[ \text{VAR} \ R(c,s) = \frac{1}{s} \frac{V'c}{c+K'} \]  

where \( V' = 2mf_Iw' \) and \( K' = \frac{r+\omega'}{b} \).

For both cases, since \( K, K', V \) and \( V' \) do not depend upon the concentration of oxygen in solution, the expected rate of tissue oxygen consumption agrees with Michaelis-Menten kinetics. The variance expressions are monotonically decreasing functions of the length of the time interval. While the lower limit of these functions is zero, practical limitations of the experimental situation would require a finite time interval and therefore a non-zero value for the variance.

2.1.5.4 Special Cases of the Modified Model

In the equations for the kinetics in the general case for the modified model, the parameters \( w \), or \( w' \), result from the matrix triangularization scheme. To facilitate a more explicit evaluation of these parameters, it is assumed that

\[ \ell_i = 0 \quad \text{for} \ i > 1. \]

This corresponds to the biological assumption that oxygen transfers over distances greater than or equal to twice the minimum distance
between adjacent layers may be neglected. This is used as an approximation to the general case. All of the cases treated in this section are based upon this assumption.

In section 2.1.5.2.2, the relationship between the equations for the one-sided case and those of the two-sided case were discussed. The addition of the above assumption results in a further equivalence between the two cases. In particular, as shown below, the expected rate of oxygen consumption for a \(2n\) layer two-sided model is twice that of an \(n\) layer one-sided model.

From equation 2.1.5.2.2-5, it follows that the \(n\) distinct equations for the \(2n\) layer two-sided model are of the form:

\[
(b_i c + r_i u + \sum_{i'=1}^{n} \left[ \ell_{i' - i} + \ell_{(2n-i'+1)-i} \right] f_{i' i}) P_i^B
\]

\[
- \sum_{i'=1}^{n} \left[ \ell_{i' - i} + \ell_{(2n-i'+1)-i} \right] f_{i' i} P_i^B
\]

\[
= r_i + u \quad \text{for} \quad i = 1, \ldots, n.
\]

Since \(\ell_i = 0\) for \(i > 1\), this reduces to:

\[
(b_i c + r_i u + \ell_i f_{i-1} + \ell_{i+1} f_i) P_i^B - \ell_i f_{i-1} P_{i-1}^B - \ell_{i+1} f_i P_{i+1}^B = r_i + u
\]

where \(f_0 = 0\).

But, since \(P_n^B = P_{n+1}^B\) by the symmetry relations of section 2.1.5.2.2, the above equations are identical to the \(n\) equations for the \(n\) layer one-sided model. Therefore, in the matrix triangularization, the parameters \(w\) and \(w'\) are equal and by equations 2.1.5.3-1...
and 2.1.5.3-3 the expected rate of oxygen consumption for the 2n
layer two-sided model is twice the expected rate for the n layer
one-sided model.

2.1.5.4.1 Uniform Distribution of Sites

In addition to the restriction on oxygen transfers across more
than one layer, this section introduces the requirement that

\[ f_i = f \] for all values of i.

With this common value for the parameter \( f_i \), each site in the tissue
has the same probability of being a binding site. Thus, the binding
sites are considered to be uniformly distributed throughout the
tissue.

2.1.5.4.1.1 One-Sided Case. With this distribution of binding
sites, the matrix equation for the one-sided case, equation 2.1.5.1.3-1,
becomes:

\[
\begin{bmatrix}
bc+r+u+fl_1 & -fl_1 & \cdots & 0 & 0 & 0 \\
-fl_1 & u+2fl_1 & -fl_1 & \cdots & 0 & 0 \\
0 & -fl_1 & u+2fl_1 & \cdots & 0 & 0 \\
0 & 0 & 0 & \cdots & 0 & 0 \\
0 & 0 & 0 & \cdots & 0 & 0 \\
0 & 0 & 0 & \cdots & 0 & 0 \\
\end{bmatrix}
\begin{bmatrix}
P^B_1 \\
P^B_2 \\
P^B_3 \\
P^B_{n-2} \\
P^B_{n-1} \\
P^B_n \\
\end{bmatrix}
= 
\begin{bmatrix}
u+r \\
u \\
u \\
u \\
u \\
u \\
\end{bmatrix}. 
\]
Dividing the above matrix equation by the scalar $f L_1$ gives:

\[
\begin{bmatrix}
\frac{b}{c} + r + \frac{1}{f L_1} + 1 & -1 & \ldots & 0 & 0 & 0 \\
-1 & \frac{u}{f L_1} + 2 & -1 & \ldots & 0 & 0 \\
0 & -1 & \frac{u}{f L_1} + 2 & \ldots & 0 & 0 \\
\vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\
0 & 0 & 0 & \frac{u}{f L_1} + 2 & -1 & 0 \\
0 & 0 & 0 & \frac{u}{f L_1} + 2 & -1 & \frac{u}{f L_1} \\
0 & 0 & 0 & \frac{u}{f L_1} + 1 & \frac{u}{f L_1} + r + \frac{1}{f L_1}
\end{bmatrix}
\begin{bmatrix}
P_1^B \\
P_2^B \\
P_3^B \\
\vdots \\
P_{n-1}^B \\
P_{n-2}^B \\
P_n^B
\end{bmatrix}
= 
\begin{bmatrix}
p_1 + r \\
p_2 \\
p_3 \\
\vdots \\
p_{n-2} \\
p_{n-1} \\
p_n
\end{bmatrix}
\begin{bmatrix}
P_1^B \\
P_2^B \\
P_3^B \\
\vdots \\
P_{n-1}^B \\
P_{n-2}^B \\
P_n^B
\end{bmatrix}
\begin{bmatrix}
\frac{u}{f L_1} \\
\frac{u}{f L_1} \\
\frac{u}{f L_1}
\end{bmatrix}
\]

In order to solve the above matrix for $P_1^B$, it is sufficient to lower triangularize the matrix. As described in the appendix, the above matrix is a special case of a type 3 matrix and may be triangularized according to the scheme presented in the appendix. By employing this scheme, the lower triangular form of the above matrix becomes:
\[
\begin{bmatrix}
  d_n & 0 & 0 & \ldots & 0 & 0 & 0 \\
  -1 & d_{n-1} & 0 & \ldots & 0 & 0 & 0 \\
  0 & -1 & d_{n-2} & \ldots & 0 & 0 & 0 \\
  \vdots & \vdots & \vdots & \ldots & \vdots & \vdots & \vdots \\
  \vdots & \vdots & \vdots & \ldots & \vdots & \vdots & \vdots \\
  0 & 0 & 0 & \ldots & d_3 & 0 & 0 \\
  0 & 0 & 0 & \ldots & -1 & d_2 & 0 \\
  0 & 0 & 0 & \ldots & 0 & -1 & d_1 \\
\end{bmatrix}
\]

where
\[d_1 = \frac{u}{\ell_1} + 1\]

\[d_{n-i} = \frac{u}{\ell_1} + 2 - \frac{1}{d_{n-i-1}}\text{ for } n-1 > i \geq 1,\]

and
\[d_n = \frac{bc + r}{\ell_1} + 1 - \frac{1}{d_{n-1}}.\]

In the above square matrix, \(n\) is the dimension and, as shown in corollary 2 for proposition 5 of the appendix, \(d_n\) may be considered as a sequence and the limit of this sequence is given by:

\[\lim_{n \to \infty} d_n = \frac{bc + r}{\ell_1} + \frac{u + \sqrt{u^2 + 4uf_\ell_1}}{2f_\ell_1}.
\]

Therefore if the original matrix had been reduced without dividing by
the scalar $f_{1n}$, the first element of the first row of the lower triangular form would be $f_{1n}d_n$. From the above equation it may be seen that the limit of $f_{1n}d_n$ is

$$bc + r + u - \sqrt{u^2 + 4uf_{1n}}.$$ 

Recalling equation 2.1.5.2.1-3, this limit may be used as an approximate value of the quantity $bc + r + w$ if the tissue is sufficiently thick so that the number of layers is large. Thus $w$ would be approximated by

$$\frac{1}{2} \left( u + \sqrt{u^2 + 4uf_{1n}} \right).$$

2.1.5.4.1.2 Two-Sided Case. In treating the two-sided case, the distinction must be made between a tissue with an even number of layers and one with an odd number of layers. It has already been established that $ER(c, s)$ and $VAR R(c, s)$ for a $2n$ layer two-sided model are twice the values for an $n$ layer one-sided model. Thus it suffices to treat the case where the number of layers is $2n - 1$.

For a tissue with $2n - 1$ layers, equation 2.1.5.2.2-6 may be written as:

$$\sum_{i=1}^{n-1} \left[ \ell_{1'i'-1} + \ell_{(2n-1)'-1} \right] f_{1'i'} + \ell_{n-1} f_n p_B

- \sum_{i=1}^{n-1} \left[ \ell_{1'i'-1} + \ell_{(2n-1)'-1} \right] f_{1'i'} p_B^n + \ell_{n-1} f_n p_B^n

= r_1 + u \quad \text{for} \quad 1 \leq i \leq n.$$
Since in this section \( l_i \) is zero for \( i \) greater than 1, \( b_1 \) equals \( b \), \( r_1 \) equals \( r \), and \( f_1 \) equals \( f \) for all layers, the above equation may be expressed in the following n-dimensional matrix equation:

\[
\begin{bmatrix}
bc+u+ufl_1 & -f1 & 0 & \ldots & 0 & 0 & 0 \\
-f1 & u+2f1 & -f1 & \ldots & 0 & 0 & 0 \\
0 & -f1 & u+2f1 & \ldots & 0 & 0 & 0 \\
\cdot & \cdot & \cdot & \ldots & \cdot & \cdot & \cdot \\
\cdot & \cdot & \cdot & \ldots & \cdot & \cdot & \cdot \\
\cdot & \cdot & \cdot & \ldots & \cdot & \cdot & \cdot \\
0 & 0 & 0 & \ldots & u+2f1 & -f1 & 0 \\
0 & 0 & 0 & \ldots & -f1 & u+2f1 & -f1 \\
0 & 0 & 0 & \ldots & 0 & -2f1 & u+2f1
\end{bmatrix}
\begin{bmatrix}
p^B_1 \\
p^B_2 \\
p^B_3 \\
p^B_{n-2} \\
p^B_{n-1} \\
p^B_n
\end{bmatrix}
= \begin{bmatrix}
u+r \\
u \\
u \\
\cdot \\
\cdot \\
\cdot \\
\cdot \\
u \\
\cdot \\
u
\end{bmatrix}
\]

Dividing the above matrix equation by the scalar \( f1 \) gives a special case of a type 3 matrix as defined in the appendix. Lower triangularizing this matrix according to the scheme indicated in the appendix gives:
\[
\begin{bmatrix}
  d_n & 0 & 0 & \ldots & 0 & 0 & 0 \\
-1 & d_{n-1} & 0 & \ldots & 0 & 0 & 0 \\
0 & -1 & d_{n-2} & \ldots & 0 & 0 & 0 \\
\vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\
0 & 0 & 0 & \ldots & d_3 & 0 & 0 \\
0 & 0 & 0 & \ldots & -1 & d_2 & 0 \\
0 & 0 & 0 & \ldots & 0 & -2 & 0 \\
\end{bmatrix}
\]

where:

\[
d_1 = \frac{u}{\varepsilon \ell_1} + 2
\]

\[
d_2 = \frac{u}{\varepsilon \ell_1} + 2 - \frac{2}{d_1}
\]

\[
d_3 = \frac{u}{\varepsilon \ell_1} + 2 - \frac{1}{d_2}
\]

\[
\vdots
\]

\[
d_i = \frac{u}{\varepsilon \ell_1} + 2 - \frac{1}{d_{i-1}}
\]

\[
\vdots
\]
\[ d_{n-1} = \frac{u}{f_1'} + 2 - \frac{1}{d_{n-2}} \]
\[ d_n = \frac{bc+r+u}{f_1'} + 2 - \frac{1}{d_{n-1}} \]

Using corollary 2 to proposition 5 in the appendix, the limit of \( d_n \), as \( n \) increases, is equal to \( \frac{bc+r+u+\sqrt{u^2+4uf_1'}}{f_1'} \). Thus for sufficiently large thickness, \( w' \) may be approximated by
\[ \frac{1}{2} \left( u + \sqrt{u^2+4uf_1'} \right) \]
It should be noted that this limit is the same value that would be obtained for an even number of layers. This is reasonable since it would be expected that the difference between an even and an odd number of layers would become negligible as the tissue thickness increases.

2.1.5.4.2 Surface Site Inactivation

In the previous section it was assumed that all sites had the same probability of being binding sites. This section and the next alter this assumption in order to examine the effects of binding site inhibition. This section discusses the case of surface site inactivation in which the surface layer sites are preferentially inhibited.

For this case, the \( f_i \) are assumed to have a common value, say \( f \), for \( i \) greater than 1. With these assumptions, matrix equation 2.1.5.4.1.1-1 for the one-sided case becomes:
If the above coefficient matrix is divided by the scalar $f \ell_1$, the resultant matrix is a type 3 matrix. Employing the scheme indicated in the appendix to triangularize a type 3 matrix, the following matrix is obtained before eliminating the second element in the first row:
\[
\begin{pmatrix}
\frac{bc + ru}{\ell_1} + 1 & -1 & 0 & \ldots & 0 & 0 & 0 \\
-\frac{f}{\bar{f}} & \frac{u}{\ell_1} + \frac{f}{\bar{f}} + 1 - \frac{1}{d_{n-2}} & 0 & \ldots & 0 & 0 & 0 \\
0 & -1 & d_{n-2} & \ldots & 0 & 0 & 0 \\
0 & 0 & 0 & \ldots & d_3 & 0 & 0 \\
0 & 0 & 0 & \ldots & -1 & d_2 & 0 \\
0 & 0 & 0 & \ldots & 0 & -1 & d_1
\end{pmatrix}
\]

where
\[
d_1 = \frac{u}{\ell_1} + 1
\]
\[
d_2 = \frac{u}{\ell_1} + 2 - \frac{1}{d_1}
\]
\[
\vdots
\]
\[
\vdots
\]
\[
d_1 = \frac{u}{\ell_1} + 2 - \frac{1}{d_{i-1}}
\]
\[ d_{n-2} = \frac{u}{f \ell_1} + 2 - \frac{1}{d_{n-3}}. \]

Using techniques similar to those in the previous section and in the appendix for type 3 matrices, it follows that, as \( n \) increases,

\[ f \ell_1 d_{n-2} \] approaches \( f \ell_1 + \frac{1}{2} \left( u + \sqrt{u^2 + 4uf \ell_1} \right) \). Continuing the triangularization of the matrix with this limit used to approximate \( f \ell_1 d_{n-2} \) gives:

\[
\begin{align*}
    u + \frac{f_1}{f} - 2u + \frac{f_1}{f} \sqrt{u^2 + 4uf \ell_1} \\
    2 \left( \frac{f_1^2}{f^2} + \frac{u}{f \ell_1} \frac{f_1}{f} - \frac{u}{f \ell_1} \right)
\end{align*}
\]

as an approximate value for \( w \) for large \( n \).

It is not necessary to consider the two-sided case in detail since the relationship between the 2n layer two-sided model and the n layer one-sided model has been established. Moreover, in the previous section it was shown that as the number of layers increases the difference in kinetics between a tissue with an even number of layers and one with an odd number of layers becomes negligible.

2.1.5.4.3 Irreversible Inhibition

The previous section considered the change in oxygen consumption as a result of surface site inactivation. The present section
examines the case of irreversible inhibition and serves as a generalization of the case of surface site inactivation. In the treatment of irreversible inhibition it is assumed initially that each site in the tissue has the same probability of being a binding site. Then an irreversible inhibitor is added to the system. It is assumed that this inhibitor diffuses into the tissue and that once it is bound to a binding site the site is permanently inactivated. The one-sided case is considered first.

It is assumed that a certain fraction, say $\theta$, of this inhibitor progresses beyond the first layer. Of this amount, the fraction $\theta$ progresses beyond the second layer. In this manner, the fraction $\theta$ of the inhibitor that reaches a certain layer proceeds into the next layer of the tissue.

Let $f$ denote the original fraction of binding sites in the tissue. It is assumed that these sites are uniformly distributed throughout the tissue. Let $f_\theta$ denote the fraction of binding sites in the surface layer that are blocked by the inhibitor. Since $\theta$ of the inhibitor progresses beyond the first layer, it is assumed that $\theta f_\theta$ of the binding sites in the second layer are inactivated by the inhibitor. In general, it is assumed that $\theta^{k-1} f_\theta$ of the binding sites in layer $k$ are inactivated by the inhibitor. Thus the probability that a site in layer $k$ is an unblocked binding site is $(1-\theta^{k-1} f_\theta)f$. This is the quantity that is denoted as $f_k$ in the general model. Thus, recalling that $L_i$ is assumed to be zero for $i > 1$, the matrix equation 2.1.3.6-1 may be written as:
where \( f_k = (1 - \theta^{k-1}f_{\theta})f_{\ell_1} \).

The above matrix equation may be written as:

\[
(bc+r)E_{11}Y + MY = X_{-1}.
\]

It may be verified that \( \frac{1}{f_{\ell_1}}M \) is a type 2 matrix, as defined in the appendix, and may be lower triangularized according to the scheme specified in the appendix for this type of matrix. From this triangularization, \( w \) may be evaluated by \( f_{d_n}^{(n)} \), where \( d_n^{(n)} \) is the first element in the first row of the lower triangular matrix. It is shown in the appendix that \( d_n^{(n)} \) converges as \( n \) increases. While no closed form is given for this limit, two different techniques are given in the appendix for evaluating this limit for a given choice of parameters. The first technique is to evaluate the limit
of the sequence \( d_1^{(1)}, d_2^{(2)}, d_3^{(3)}, \ldots \), which is essentially the same technique employed in the previous sections for type 3 matrices. The second technique is to approximate a particular \( d_n^{(n)} \) within the bounds given in the appendix. Then using this value in the iterative formulas, it is shown in the appendix that the percentage error decreases by at least a factor of \( \left( \frac{1}{a+1} \right)^2 \) with each iteration, where \( a = \frac{u}{f_\ell} \).

As in the previous sections it is not necessary to treat the two-sided model separately for odd and even number of layers. Using the formulas in the appendix for error propagation for a type 2 matrix, it can be shown that as the number of layers increases the difference between an even and an odd number of layers becomes negligible since both cases have the same limit for \( d_n^{(n)} \), and hence for \( w' \).

2.1.6 Interpretation

In developing a mathematical model for a biological system, part of the interplay between the biology and the mathematics is in the interpretation of the equations of the model. Since these equations are intended to describe the biology it is reasonable to expect that they reflect some general properties of the biological system. These interpretations are presented in this section. To facilitate this discussion, comparisons between the basic and the modified model are discussed first.
2.1.6.1 Comparison of the Basic and the Modified Models

In comparing the basic and the modified models it is useful to examine the interrelationships between the parameters in the equations of these models.

Consider the matrix form of the equations for the basic model as presented in section 2.1.3.5. Recalling the definition of \( d(i,i') \) given in section 2.1.3.4 as

\[
d(i,i') = \sum_j \sum_{j'} d(i,j,i',j') g_{i,j} g_{i',j'}
\]

and that the indicator function \( g_{i,j} \) may be treated as a random variable, it is possible to consider the expected value of the matrix \( A_1(c) \). To do this it is necessary to assume some distributional form for the indicator functions. For this discussion it is assumed that the \( g_{i,j} \)'s are independent binomial variables and that the probability that \( g_{i,j} \) equals 1 is equal to \( f_i \). This is equivalent to saying that the probability that a site in layer \( i \) is a binding site is \( f_i \) and that the probability of a particular site being a binding site is independent of the assignment of other binding sites in the tissue. With this assumption it follows that

\[
E g_{i,j} = f_i
\]

\[
E m_l = E \sum_{j=1}^m g_{i,j} = f_i^m
\]

and

\[
E g_{i,j} g_{i',j'} = f_i f_{i'}
\]
Therefore the following relations hold:

\[ Ebicm = bcfm \]

\[ Erim = rifm \]

\[ Eum = ufm \]

and

\[ Ed(i,j,i',j')g_{ij,j'i',j'} = d(i,j,i',j')f_{i'i'} \]

Using equation 2.1.5.1.1-4 with this last expression gives:

\[ E \sum_{j,j'} d(i,j,i',j')g_{ij,j'i',j'} = mFk_{i'i'} \]

where \( k = |i-i'| \).

With these equations it may be seen that the expected value of the matrix \( A(c) \) in section 2.1.3.5, denoted as \( EA(c) \), may be written as

\[ EA(c) = mF\overline{A}(c) \]

where \( F \) is the diagonal matrix with \( f_i \) as the \( i \)th element

and \( \overline{A}(c) \) is the matrix defined in

section 2.1.5.1.2 for the modified model.

The matrix equation for the one-sided case of the basic model was given in equation 2.1.3.6-1 as

\[ A(c)Y = MX \]

The expected value of the right hand side of this equation is
Having calculated these expected values it is possible to replace all of the parameters in equation 2.1.3.6-1 for the basic model with their expected values. This gives

\[ E A_1(c) Y = E(MX_1) \]

or

\[ mF A_1(c) Y = mF X_1 . \]

Premultiplying this last equation by \((mF)^{-1}\) gives:

\[ \overline{A}_1(c) Y = \overline{X}_1 , \]

which is the matrix equation (2.1.5.1.3-1) for the one-sided case of the modified model. A similar argument shows that the same relationship holds for the two-sided cases. Therefore the introduction of an average site distribution in the modified model has the effect of replacing the parameters in the matrix equation of the modified model with average parameter values.

In developing the modified model it was observed that the primary difference from the basic model was in the conceptualization of the binding sites. The basic model assumes that the arrangement of binding sites is known and fixed while the modified model assumes that the binding sites are, in a sense, smeared throughout each layer. It was seen that if the binding site arrangement were generated by a set of independent binomial variables having the same probability within each layer then the expected values of the parameters in the basic model were identical to those of the modified
model. With this in mind, the applicable experimental situation for each model may be considered to further illustrate the conceptual difference between the two models. The basic model with the known and fixed arrangement of binding sites corresponds to the situation in which repeated experimental measurements are made upon the same tissue slice. The modified model does not so much correspond to an experimental situation as it does to a simplification of the basic model. Since the specific arrangement of binding sites is essentially an unknown it is assumed that it is sufficient to specify the arrangement only in terms of the expected number of binding sites per layer. Having introduced this simplification it is then feasible to examine the kinetics of tissue oxygen consumption in more detail. The relative merits of these additional results depend, of course, upon the degree to which the simplified model approximates the biological system. Thus the trade-off was made between a specific description of an unobservable quantity which gives limited information concerning experimentally observable quantities and a general description of the unobservable which yields more results concerning the observable quantities. The similarity of the equations for the two approaches does serve to lend some credence to the reasonableness of the general description.

In discussing the differences in these two approaches, it has not been mentioned what would apply if the same experiment were performed on numerous similar tissues. If the underlying probability distribution that generated the arrangement of binding sites were known then the results for the basic model could be used as conditional
expectations to determine the expected rate of oxygen consumption for this more general situation. The practical problems associated with this would be two-fold. First, the nature of the binding site probability distribution is unknown and, second, the rate parameters in the kinetics expressions of the basic model would have to be determined more explicitly in order to make these calculations. It should be noted that this is not equivalent to taking the expected values of the parameters in the equations for the basic model and then solving the resulting equation as was discussed in this section. What is required for this case is the expected value of the vector of site occupation probabilities. Thus the matrix equation for the basic model must first be solved for $\mathbf{Y}$ and then the expected value of the matrix $A^{-1}_1(c)\mathbf{M}$ must be determined. This is not equivalent to inverting the expected value of $A_1(c)$ and multiplying by the expected value of $\mathbf{M}$. While discussing this point it should be noted that although this aspect of the problem would present mathematical difficulties this may not be important biologically. For example, if the binding sites in each layer were generated by a set of identically distributed independent binomial random variables then some estimate of the varying parameters may be computed. The critical parameter would be the number of binding sites in the layer. The range of this quantity would serve as an indication of the range in the rate constants. The DeMoivre-Laplace limit theorem may be used to obtain approximate estimates of this range (Feller, 1950, Chapter VII). Recall that $m$ is the number of sites in a layer and let $f$ denote the probability that a site is a binding site. An
intuitive way of phrasing the question would be to ask how large
does \( m \) have to be so that 95 percent of the tissues would have the
number of binding sites agreeing, within 1 percent, with the expected
number? From an experimental viewpoint this could be viewed as
asking how large \( m \) has to be for 95 percent of these tissues to have
experimentally indistinguishable kinetics. Using the above limit
theorem gives a bound of the form:

\[
m \geq (4 \times 10^4) \frac{1}{f} \quad \text{or} \quad mf \geq (4 \times 10^4).
\]

As would be expected, as \( f \) approaches zero this bound increases to
maintain this constraint on percent error.

To illustrate the relevance of this constraint with respect to
the biological system it is convenient to use a simplified numerical
example. Assuming that a layer is square and observing that \( mf \) is
the expected number of binding sites in a layer the above constraint
would be satisfied if there were 200 binding sites on the edge. It
has been conjectured that for the binding sites to serve as an
effective means of oxygen transport the spacing between adjacent
binding sites would be on the order of 30 angstroms (Longmuir et al.,
1971). This spacing would mean that an edge of .6 microns would be
required and this is considerably less than the diameter of a cell.

2.1.6.2 Interpretation of Equations

Having shown the relationship between the parameters of the
basic and the modified models in the above section and having
previously discussed the relationships between the one- and the two-
sided cases of the modified model, only the one-sided case of the
modified model is treated in detail.
Equation 2.1.5.1.3-1 serves as the basic matrix equation of the modified model at the steady-state, where the matrix is presented in section 2.1.5.1.2. With the exception of the $\lambda_k$'s, all of the parameters in this equation were discussed in section 2.1.3.2. In section 2.1.5.1.1, it was indicated that the parameter $\lambda_k$ may be viewed as indicating the likelihood of an oxygen transfer from a site in layer $i$ to a site in the $k$th layer from layer $i$. It was also seen that $\lambda_k \geq \lambda_{k+1}$ for $k = 1, \ldots, n-1$ which agrees with the intuitive interpretation that the probability of a transfer between two layers is a function of the distance between the two layers. Also, the term $\lambda_0$ does not appear in the matrix which corresponds to the layer equilibrium assumption.

Recalling that the vector $\mathbf{Y}$ was defined as $\mathbf{Y} = \sum_{i=1}^{n} P_{i}^{B} \mathbf{e}_{i}$, this vector may be viewed as indicating the expected fraction of unoccupied binding sites in each layer. Therefore these quantities are inversely related to the expected concentration of oxygen in each layer.

With this interpretation of the $\lambda_k$'s and the vector $\mathbf{Y}$, each row of the matrix equation may be thought of as a description of the corresponding layer of the tissue. In examining the $i$th row in detail, it is convenient to use the diagonal element as a reference point. The terms involving the $\lambda_k$'s may be viewed as describing oxygen arriving at the $i$th layer, while the negative terms may be viewed as indicating oxygen leaving the $i$th layer. The off-diagonal term in the $j$th column of the $i$th row may be interpreted as
indicating the transfer of oxygen from layer i to layer j. In light of this, it is reasonable that this term consists of two factors, \( \ell_{i-j} \) and \( f_j \), where \( \ell_{i-j} \) indicates the likelihood of a transfer over this distance and \( f_j \) is the probability that a site in layer j is a binding site. The fact that the oxygen transfer terms in the \( i^{th} \) row sum to zero indicates that the net direction of oxygen movement depends upon only the gradient of the probabilities that sites in given layers are unoccupied. This is seen when the \( i^{th} \) row is multiplied by the vector \( X \).

The remaining parameters in the diagonal elements involve consumption and interaction with the solution. These terms are all positive and it may appear inconsistent with the previous interpretation that the consumption term is positive while it indicates oxygen being removed from the \( i^{th} \) layer. However, in considering the consumption term the vector \( X_1 \) must also be included. It is the appearance of \( u \) in the \( i^{th} \) row of the vector \( X_1 \) that indicates that oxygen is being removed from the \( i^{th} \) layer. If the vector \( X_1 \) is subtracted from both sides of the equation, the consumption term for the \( i^{th} \) row becomes \(-u(1-P_1^B)\) which is compatible with the previous interpretation that a negative sign indicates a net oxygen loss from the \( i^{th} \) layer at the steady-state.

The fact that only the first row of the matrix equation has terms involving the oxygen in solution corresponds to the assumption that only the surface layer interacts directly with the solution. The term \( bc \) indicates oxygen entering the tissue, while \( r \) is treated in the same manner as \( u \) and the term \(-r(1-P_1^B)\) indicates a loss of
oxygen to the solution by the surface layer. Thus each row of the matrix equation describes the state of the corresponding layer in the tissue.

The only remaining parameter in the model for the one-sided case that has not been discussed is $w$. This parameter arises in the triangularization of the matrix as indicated in section 2.1.5.2.1. The mathematical process of triangularization may be viewed as an attempt to construct a one layer tissue which behaved in the same manner as the original $n$ layer tissue slice. While the interior layers of the original slice interact only indirectly with the solution, the process of triangularization attempts to adjust the parameters of the surface layer to account for the behavior of all of the interior layers. Thus $w$ may be interpreted as an adjustment of the consumption term $u$ to give an effective overall consumption term for the entire tissue.

In the final equation for the expected rate of oxygen consumption, equation 2.1.5.3-1, it was found that this equation had the form of Michaelis-Menten kinetics where

$$V = wmf_1$$

and

$$K = \frac{r + w}{b}.$$

From the previous interpretation of $w$, it is seen that $V$ is the product of the expected number of binding sites in the surface layer, $mf_1$, and the adjusted consumption term. It should be noted
that the dependence of $V$ upon the number of layers is through the term $w$ determined by the matrix triangularization. The Michaelis constant $K$ is the ratio of oxygen leaving the tissue, $r+w$, to $b$ which controls the rate at which oxygen enters the tissue for a given concentration.

2.1.7 Summary

The basic assumptions underlying the binding site model are somewhat similar to those in the deterministic model developed by Gold (1969). The deterministic model examined the one-sided case with an equal number of binding sites in each interior layer and where transfers over a distance of more than one layer are neglected. Under these conditions, the deterministic model predicted Michaelis-Menten kinetics. The stochastic binding site model developed here also predicts Michaelis-Menten kinetics for this case and shows that the same results apply under more general conditions.

The binding site model was examined for two different types of constraints on the distribution of binding sites. In the basic model it was assumed that the distribution of binding sites is known and that this distribution is sufficiently dense so that the layer equilibrium assumption was valid. Under these conditions it was shown in section 2.1.4.2 that tissue oxygen consumption conformed to Michaelis-Menten kinetics for the one-sided case. In the modified model, the distribution of binding sites was specified only in terms of the expected number of binding sites per layer. It was shown in section 2.1.5.3 that the steady-state kinetics for tissue oxygen consumption conformed to Michaelis-Menten kinetics for both the
one- and the two-sided cases. In addition to the general form of the kinetics equation, the specific forms of the parameters in the Michaelis-Menten kinetics equations were examined for various special cases of the modified model. The reason for the differing degrees of development between the basic and modified model may be seen by comparing the matrix equations of sections 2.1.3.5 and 2.1.5.1.2. Although both $A_{1}(c)$ and $\overline{A}_{1}(c)$ are symmetric type 1 matrices, the transfer parameters for the modified model may be expressed in terms of the distance between the layers and the probability of a site in the layer being a binding site. This difference makes it possible to develop iterative formulas for the Michaelis-Menten parameters. Also the symmetry argument for the two-sided case of the modified model may be developed if the binding site probability distribution is symmetric with respect to the mid-plane of the tissue whereas for the basic model it would be necessary to require that the particular realization of the binding site distribution have this symmetry.

In discussing the symmetry of the two-sided case of the modified model it was shown in section 2.1.5.2.2 that at the steady-state there is no difference in kinetics between two n-layer one-sided models separated by a reflecting barrier and one 2n-layer two-sided model.

As discussed in section 1.2, one of the experimental results that led Longmuir to suggest the hypothesis of a carrier was the finding that the critical oxygen tension did not vary with tissue thickness in the way the classical diffusion model predicted (Longmuir and Bourke, 1960). For the classical model, the critical oxygen
tension is determined experimentally as the lowest concentration, or partial pressure, of oxygen in solution at which the tissue respires maximally. For the binding site model the dependence of kinetics upon thickness is determined by the parameter \( w \) or \( w' \). The experimental results have indicated that as the tissue thickness increases the amount of change in the critical oxygen tension decreases and becomes negligible. In the special cases of the binding site model, it has been noted that if \( w \) is considered as \( w(n) \), where \( n \) is the number of layers in the tissue, \( w(n) \) forms a monotone increasing sequence bounded above, and is therefore convergent. Thus, as \( n \) increases, \( w(n) \) increases but the rate of increase must necessarily become negligible since the limit of the sequence is finite. As before, by symmetry, the same results are true for \( w' \) in the two-sided case. In the particular case of section 2.1.4.1-1, where the sites are uniformly distributed and transfers across distances of more than one layer are neglected, \( w(l) \) is equal to \( u + f l_1 \) while the sequence \( w(n) \) is bounded above by \( u + 2f l_1 \). Therefore \( w(l) \) is at least 50 percent of the value of the limit of the sequence. This not only corresponds with this aspect of the experimental results but may also explain the marked difference between cell and tissue respiration rates. It has been noted that the half rate of partial pressure of oxygen differs by more than an order of magnitude depending upon the organizational level of the cells (Longmuir, 1966a). The order of magnitude increase in going from liver cells to liver tissue was another result that led Longmuir to
hypothesize a carrier whose efficiency was associated with the structural properties of the tissue.

In discussing the binding site model it has been assumed that the role of ordinary diffusion in oxygen transport is negligible. This is similar to the assumptions in the model developed by Gold (1969). The next type of model discussed is an extension of the basic binding site model in order to examine the effect of such an assumption.

2.2 The Diffusion - Binding Site Model

The diffusion-binding site model is an extension of the binding site model in an attempt to incorporate ordinary diffusion processes into a carrier network model. In the binding site model, oxygen was transported through the tissue solely by migration from one binding site to another. The contribution of passive diffusion to this process was assumed to be negligible. While this may be viewed as an approximation, this section investigates the possibility of incorporating a discrete approximation of ordinary diffusion into the framework of a binding site model.

In extending the binding site model, the complexity of the equations is increased and thus, while the diffusion-binding site model is an attempt at a more general framework, there are certain restrictions imposed by the mathematical complexity. Therefore, while the binding site model is conceptually a special case of the diffusion-binding site model, there is not a strict one to one correspondence in the mathematical development. As with the basic binding site model, only the one-sided case is considered.
2.2.1 Abstraction of Sites

The abstraction of the diffusion-binding site model is similar to that of the binding site model. The tissue is again viewed as being composed of n layers, each consisting of a regular network of sites. In the binding site model some of these sites were binding sites and these were the only sites involved in oxygen transport. In the diffusion-binding site model, there are two different types of sites. A site is either a binding site or a diffusion site. Both types of sites are involved in oxygen transport but only the binding sites consume oxygen. The diffusion sites are incorporated as a discrete approximation to ordinary diffusion. This is similar to other treatments using random-walk models to approximately describe diffusion (Feller, 1950; Glasstone et al., 1941).

The equations for the diffusion-binding site model are developed in a manner similar to that of the binding site model. The principal difference in the basic equations is that the probability of an oxygen transfer between two sites is now a function of the types of sites involved. This increases the complexity of the equations since the diffusion-binding site model has four different types of transfers while the binding site model had only one. A consequence of this is that the results of the diffusion-binding site model are obtained for less general conditions.

2.2.2 Assumptions

The following assumptions serve as the basic description of the diffusion-binding site model:
1. All oxygen enters the tissue by occupying a site in a surface layer.

2. All oxygen returning to the solution from the tissue is returned from a site in a surface layer.

3. Oxygen is transported through the tissue by migration from site to site.

4. A site is in one of two states at any given time, either occupied or unoccupied depending upon whether or not the site contains an oxygen molecule at that time. A site contains at most one oxygen molecule at any particular time.

5. If a site is occupied, the probability of the oxygen being consumed is independent of the behavior of any other site.

6. Oxygen is consumed only at binding sites.

7. The probability of an oxygen molecule transferring from one site to another depends upon the types of sites involved as well as the distance between the two sites and the probability that the donor site is occupied and that the acceptor site is unoccupied.

2.2.3 Formulation and Development of the Model

As for the binding site model, this section consists of the mathematical development of the model. This development of the diffusion-binding site model closely parallels the development of the binding site model. For this reason, the algebraic details of this development are condensed in certain steps.
2.2.3.1 Notation

The notation for the diffusion-binding site model differs slightly from that of the previous model to allow for the fact that non-binding sites are now diffusion sites and may be occupied by oxygen. The sites of the model are again denoted as $S_{i,j}$ where $i$ indicates the layer and $j$ indicates the position of the site in layer $i$. It should be noted that in the diffusion-binding site model it is not necessary to distinguish between an unoccupied site and an empty site. The following list indicates the notation for certain events:

<table>
<thead>
<tr>
<th>Notation of Event</th>
<th>Description of Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N_{i,j}(t)$</td>
<td>$S_{i,j}$ has no oxygen at time $t$</td>
</tr>
<tr>
<td>$B_{i,j}$</td>
<td>$S_{i,j}$ is binding site</td>
</tr>
<tr>
<td>$\overline{B}_{i,j}$</td>
<td>$S_{i,j}$ is a diffusion site</td>
</tr>
<tr>
<td>$C_{i,j}(t,t+h)$</td>
<td>$S_{i,j}$ receives an oxygen from solution in time interval $[t, t+h)$</td>
</tr>
<tr>
<td>$R_{i,j}(t,t+h)$</td>
<td>$S_{i,j}$ releases an oxygen into solution in time interval $[t,t+h)$</td>
</tr>
<tr>
<td>$U_{i,j}(t,t+h)$</td>
<td>$S_{i,j}$ consumes an oxygen in time interval, $[t,t+h)$</td>
</tr>
</tbody>
</table>
An oxygen transfers from $S_{i',j}$, to $S_{i,j}$ in time interval $[t,t+h)$

$E(h)$ Any event having $o(h)$ probability.

The following notation is also used:

$$P_{i,j}(t) = P\{N_{i,j}(t)\}$$

$$P^B_{i,j}(t) = P\{N_{i,j}(t)|B_{i,j}\}$$

$$P^D_{i,j}(t) = P\{N_{i,j}(t)|\bar{B}_{i,j}\}$$

$$f_{i,j} = P\{B_{i,j}\}.$$  

### 2.2.3.2 Assignment of Probabilities

The assignment of probabilities for the diffusion-binding site model is quite similar to that employed in section 2.1.3.2 for the binding site model. The differences are due to the role of the diffusion sites in oxygen transport. For this reason, the probability assignments are presented in abbreviated form. Again, it is assumed that the probability that a site changes state more than once during a time interval $[t,t+h)$ is $o(h)$.

$$P[C_{i,j}(t,t+h)|B_{i,j}] = b^B_{i}c_{i}P[N_{i,j}(t)|B_{i,j}] + o(h)$$

$$= b^B_{i}c_{i} P^B_{i,j}(t) + o(h)$$

2.2.3.2-1
\[
P(C_{i,j}(t,h) | B_{i,j}) = b_i \cdot P(N_{i,j}(t) | B_{i,j}) + o(h)
\]
\[
= b_i \cdot P(D_{i,j}(t) + o(h)
\]

\[
P(R_{i,j}(t,h) | B_{i,j}) = r_i \cdot P(N_{i,j}(t) | B_{i,j}) + o(h)
\]
\[
= r_i \cdot [1-P_{i,j}(t)] + o(h)
\]

\[
P(R_{i,j}(t,h) | B_{i,j}) = r_i \cdot P(N_{i,j}(t) | B_{i,j}) + o(h)
\]
\[
= r_i \cdot [1-P_{i,j}(t)] + o(h)
\]

\[
P(U_{i,j}(t,h) | B_{i,j}) = u_i \cdot P(N_{i,j}(t) | B_{i,j}) + o(h)
\]
\[
= u_i \cdot [1-P_{i,j}(t)] + o(h)
\]

\[
P(U_{i,j}(t,h) | B_{i,j}) = 0
\]

\[
P(T_{i,j}(t,h) | B_{i,j}) = d_{BB}(i',j',i,j) \cdot P(N_{i,j}(t) | B_{i,j}) + o(h)
\]
\[
= d_{BB}(i',j',i,j) \cdot [1-P_{i,j}(t)] + o(h)
\]

2.2.3.2-7
\[ P(i', j', T_{i, j}(t, t+h) | B_{i, j} \cap \overline{B}_{i, j}) \]

\[ = d_{BD}(i', j', i, j) h P(\overline{N}_{i', j', j}(t) | B_{i', j', j}) P(N_{i, j}(t) | \overline{B}_{i, j}) + o(h) \]

\[ = d_{BD}(i', j', i, j) h [1 - P_{i, j}(t)] P_{i, j}(t) + o(h) \quad 2.2.3.2-8 \]

\[ P(i', j', T_{i, j}(t, t+h) | \overline{B}_{i, j} \cap B_{i, j}) \]

\[ = d_{BD}(i', j', i, j) h P(\overline{N}_{i', j', j}(t) | \overline{B}_{i', j', j}) P(N_{i, j}(t) | B_{i, j}) + o(h) \]

\[ = d_{BD}(i', j', i, j) h [1 - P_{i, j}(t)] P_{i, j}(t) + o(h) \quad 2.2.3.2-9 \]

\[ P(i', j', T_{i, j}(t, t+h) | \overline{B}_{i, j} \cap \overline{B}_{i, j}) \]

\[ = d_{DD}(i', j', i, j) h P(\overline{N}_{i', j', j}(t) | \overline{B}_{i', j', j}) P(N_{i, j}(t) | \overline{B}_{i, j}) \]

\[ = d_{DD}(i', j', i, j) h [1 - P_{i, j}(t)] P_{i, j}(t) \quad 2.2.3.2-10 \]

The above probability statements are based upon the same reasoning employed in section 2.1.3.2 for the binding site model. In the case of transfer probabilities there are four different types of transfers and the parameter \( d_{s_1, s_2}^{i', j', i, j} \) is employed to indicate that the transfer probability is a function of the distance between the sites, as in the previous model, as well as the type of site \( s_1 \) that the oxygen is leaving and the type \( s_2 \) to which the oxygen is going. For common indices \((i, j) = (i', j')\) the parameter is zero. The reason for this assignment is similar to that for the binding
site model in that oxygen remaining at a site is not considered to be transferred and is treated separately.

Again, since it is assumed that only surface sites interact with the solution, the parameters \( b_i^b, b_i^d, r_i^b, \) and \( r_i^d \) are zero if layer \( i \) is not a surface layer. For each type of transfer, the distance function is assumed to have the same properties indicated in section 2.1.3.2 for the previous model.

As before in section 2.1.3.2, these basic events for a site may be summarized by the two events \( A_{i,j}(t,t+h) \) and \( L_{i,j}(t,t+h) \) which indicate oxygen arriving at \( S_{i,j} \) in time interval \([t,t+h)\) and oxygen leaving \( S_{i,j} \) in time interval \([t,t+h)\) respectively. It should be recalled that \( L_{i,j}(t,t+h) \) consists of consumption as well as transfers and release to solution. These two events are defined as:

\[
A_{i,j}(t,t+h) = \overline{N}_{i,j}(t+h) \cap N_{i,j}(t) \tag{2.2.3.2-11}
\]

\[
L_{i,j}(t,t+h) = N_{i,j}(t+h) \cap \overline{N}_{i,j}(t) \tag{2.2.3.2-12}
\]

Since it has also been assumed that the probability of a site changing state more than once in a time interval \([t,t+h)\) is \( o(h) \), the following relations hold:

\[
A_{i,j}(t,t+h) = C_{i,j}(t,t+h) \cup \bigcup_{i'} \bigcup_{j'} T_{i,j}(t,t+h) \cup E(h) \tag{2.2.3.2-13}
\]

\[
L_{i,j}(t,t+h) = R_{i,j}(t,t+h) \cup U_{i,j}(t,t+h) \cup \bigcup_{i'} \bigcup_{j'} T_{i',j}(t,t+h) \cup E(h) \tag{2.2.3.2-14}
\]
From equation 2.2.3.2-13 and the previous equations of this section the following expression is obtained:

\[ P_{A_{i,j}}(t, t+h) = b_{i,j}^{B}Q_{i,j}^{B}(t)f_{i,j}^{B} + b_{i,j}^{D}Q_{i,j}^{D}(t)(1-f_{i,j}) \]

\[ + \sum_{i',j'} \left( d_{BB}(i',j',i,j)hf_{i',j'}^{B}[1-P_{i',j'}^{B}(t)f_{i',j'}^{B} + d_{BD}(i',j',i,j)hf_{i',j'}^{B}(1-f_{i',j'})P_{i,j}^{D}(t) \right. \]

\[ + d_{DB}(i',j',i,j)h(1-f_{i',j'})[1-P_{i',j'}^{D}(t)f_{i',j'}^{D} + d_{DD}(i',j',i,j)h(1-f_{i',j'})[1-P_{i',j'}^{D}(t)(1-f_{i',j'})P_{i,j}^{D}(t) \]  

\[ + o(h) . \]  

Employing equation 2.2.3.2-14 and the previous equations of this section gives the following expression:

\[ P_{L_i,j}(t, t+h) = r_{i,j}^{B}[1-P_{i,j}^{B}(t)]f_{i,j}^{B} + r_{i,j}^{D}[1-P_{i,j}^{D}(t)](1-f_{i,j}) \]

\[ + uh[1-P_{i,j}^{B}(t)]f_{i,j} \]

\[ + \sum_{i',j'} \left( d_{BB}(i,j',i',j')hf_{i,j'}^{B}[1-P_{i,j'}^{B}(t)f_{i,j'}^{B} + d_{BD}(i,j',i',j')hf_{i,j'}^{B}(1-f_{i,j'})P_{i,j}^{D}(t) \right. \]

\[ + d_{DB}(i,j',i',j')h(1-f_{i,j'})[1-P_{i,j'}^{D}(t)f_{i,j'}^{D} + d_{DD}(i,j',i',j')h(1-f_{i,j'})[1-P_{i,j'}^{D}(t)(1-f_{i,j'})P_{i,j}^{D}(t) \]  

\[ + o(h) . \]  

\[ 2.2.3.2-15 \]

\[ 2.2.3.2-16 \]
These last two equations will be employed in the next section to obtain expressions for the probability that a site is unoccupied at a given time.

2.2.3.3 Development of Basic Equations

The basic equations for the diffusion-binding site model are developed in terms of \( P_{i,j}(t) \) which was defined to be \( P[N_{i,j}(t)] \), the probability that \( S_{i,j} \) was unoccupied at time \( t \). The first step is to obtain differential equations involving \( P_{i,j}(t) \).

Observe that

\[
N_{i,j}(t+h) = [N_{i,j}(t+h) \cap N_{i,j}(t)] \cup [N_{i,j}(t+h) \cap \overline{N}_{i,j}(t)]
\]

and

\[
[N_{i,j}(t+h) \cap N_{i,j}(t)] \cup [N_{i,j}(t+h) \cap \overline{N}_{i,j}(t)] = N_{i,j}(t)
\]

may be written as

\[
N_{i,j}(t+h) = [N_{i,j}(t+h) \cap N_{i,j}(t)] \cup L_{i,j}(t,t+h) \cup E(h)
\]

and

\[
[N_{i,j}(t+h) \cap N_{i,j}(t)] \cup A_{i,j}(t,t+h) \cup E(h) = N_{i,j}(t)
\]

by employing equations 2.2.3.2-11 and 2.2.3.2-12. The probabilities of these events may be written as:

\[
P[N_{i,j}(t+h)] = P[N_{i,j}(t+h) \cap N_{i,j}(t)] + P[L_{i,j}(t,t+h)] + o(h)
\]

and
\[ P[N_{i,j}(t+h) \cap N_{i,j}(t)] + P[A_{i,j}(t,t+h)] + o(h) = P[N_{i,j}(t)] . \]

Combining these two expressions gives:

\[ P[N_{i,j}(t+h)] = P[N_{i,j}(t)] - P[A_{i,j}(t,t+h)] + P[L_{i,j}(t,t+h)] + o(h) \]

or

\[ P_{i,j}(t+h) = P_{i,j}(t) - P[A_{i,j}(t,t+h)] + P[L_{i,j}(t,t+h)] + o(h) . \]

Dividing this last equation by \( h \) and rearranging terms gives:

\[ \frac{1}{h} \left[ P_{i,j}(t+h) - P_{i,j}(t) \right] = -\frac{1}{h} P[A_{i,j}(t,t+h)] + \frac{1}{h} P[L_{i,j}(t,t+h)] + \frac{o(h)}{h} . \]

By inspection of equations 2.2.3.2-15 and 2.2.3.2-16 it may be verified that the limit of the above expression as \( h \) approaches zero exists and yields the following equation:
This differential equation is valid for all indices \((i,j)\). The next section discusses certain simplifying assumptions that are introduced prior to obtaining expressions for the kinetics of this model.

2.2.3.4 Introduction of Simplifying Assumptions

This section discusses two assumptions that are introduced to facilitate the solution of the model for expressions describing the kinetics of tissue oxygen consumption. The first assumption is similar to the layer equilibrium assumption for the binding site...
model as discussed in section 2.1.3.4 while the second assumption corresponds to the steady-state assumption of section 2.1.3.6.

Since there are two types of sites involved in oxygen transport for the diffusion-binding site model, the layer equilibrium assumption may be stated as:

$$P^B_{i,j}(t) = P^B_{i,j'}(t) \text{ for all binding sites } S_{i,j} \text{ and } S_{i,j'} \text{ in layer } i$$

and

$$P^D_{i,k}(t) = P^D_{i,k'}(t) \text{ for all diffusion sites } S_{i,k} \text{ and } S_{i,k'} \text{ in layer } i.$$ 

The justification of this assumption with respect to each type of site is essentially the same as in section 2.1.3.4 for the binding site model and is not repeated here. Since there are two types of sites involved, the assumptions regarding the density of sites within a layer and the gradient of this density from layer to layer apply to both types of sites. Again, departures from this condition result in a net restoring force favoring the return to a condition of layer equilibrium. However, since some of the sites in a layer consume oxygen while others do not, and the two types of sites are assumed to have different affinities for oxygen, the layer equilibrium assumption is stated separately for the two different types of sites.

The second assumption is that the tissue is at the steady-state in the sense that:

$$\frac{d}{dt} P^B_{i,j}(t) = \frac{d}{dt} P^D_{i,j'}(t) = 0 \text{ for all site indices.}$$

This implies that the time-dependence of these probabilities may be
suppressed and written as:

\[ p^B_{i,j}(t) = p^B_{i,j} \]

and

\[ p^D_{i',j'}(t) = p^D_{i',j'} . \]

Rather than assuming the existence of the steady-state, an alternate approach would be to develop the model as a finite state Markov chain. In such a formulation each state could correspond to an \( m \times n \) matrix whose elements are either zero or one denoting whether the site is unoccupied or occupied. The equations for such a treatment could be developed from the basic equations employed here to describe the various possible events. This Markov chain formulation would permit the use of theorems establishing the existence and uniqueness of a steady-state distribution for irreducible aperiodic finite-state Markov chains (Feller, 1950, Chapter XV). However, the present development is more convenient for examining oxygen consumption at the steady-state which is the quantity of interest in this investigation.

Combining the steady-state assumption with the layer equilibrium assumption gives:

\[ p^B_{i,j}(t) = p^B_{i} \]

and

\[ p^D_{i,j}(t) = p^D_{i} . \]
As in the treatment of the binding site model it is convenient to introduce the indicator function \( g_{i,j} \) such that

\[
g_{i,j} = \begin{cases} 
0 & \text{if } S_{i,j} \text{ is a diffusion site (i.e. not a binding site)} \\
1 & \text{if } S_{i,j} \text{ is a binding site} .
\end{cases}
\]

This is equivalent to the indicator function introduced in section 2.1.3.4 for the binding site model. The principle reason for using this notation is that it is assumed that the arrangement of binding sites is fixed and known. Once this is assumed then the probability that a particular site is a binding site is either zero or one. Therefore it is appropriate to use the indicator function for the probability that a site is a binding site.

With these assumptions and employing the indicator functions, equation 2.2.3.3-1 may be written as:

\[
0 = -b_i^B c_i^B g_{i,j} - b_i^D c_i^D (1-g_{i,j}) \\
- \sum_{i'} (1-p_{i'}^B) p_{i'}^B \sum_{j'} d_{BB}(i',j',i,j) g_{i',j'} g_{i,j} \\
- \sum_{i'} (1-p_{i'}^D) p_{i'}^D \sum_{j'} d_{BD}(i',j',i,j) g_{i',j'} (1-g_{i,j}) \\
- \sum_{i'} (1-p_{i'}^D) p_{i'}^D \sum_{j'} d_{DB}(i',j',i,j) (1-g_{i',j'}) g_{i,j} \\
- \sum_{i'} (1-p_{i'}^D) p_{i'}^D \sum_{j'} d_{DB}(i',j',i,j) (1-g_{i',j'}) (1-g_{i,j}) \\
+ r_i^B (1-p_{i}^B) g_{i,j} + r_i^D (1-p_{i}^D) (1-g_{i,j}) \\
+ u(1-p_{i}^B) g_{i,j}
\]
+ \sum_{i'} (1-P_i^B) P_{i'}^B \sum_{j} d_{BB}(i,j,i',j') g_{i,j} g_{i',j'}

+ \sum_{i'} (1-P_i^B) P_{i'}^D \sum_{j} d_{BD}(i,j,i',j') g_{i,j} (1-g_{i',j'})

+ \sum_{i'} (1-P_i^D) P_{i'}^B \sum_{j} d_{BB}(i,j,i',j') (1-g_{i,j}) g_{i',j'}

+ \sum_{i'} (1-P_i^D) P_{i'}^D \sum_{j} d_{DD}(i,j,i',j') (1-g_{i',j'}) (1-g_{i,j})

2.2.3.4-1

As in section 2.1.3.4, it is convenient to sum the above equation over j in order to obtain an equation summarizing the behavior of all sites in layer i. Prior to this summation it is convenient to introduce the following notation.

Let \( \tau_{BB}(i',i) = \sum_{j} \sum_{j'} d_{BB}(i',j',i,j) g_{i',j} g_{i,j} \)

\( \tau_{BD}(i',i) = \sum_{j} \sum_{j'} d_{BD}(i',j',i,j) g_{i',j'} (1-g_{i,j}) \)

\( \tau_{DB}(i',i) = \sum_{j} \sum_{j'} d_{DB}(i',j',i,j) (1-g_{i',j'}) g_{i,j} \)

and \( \tau_{DD}(i',i) = \sum_{j} \sum_{j'} d_{DD}(i',j',i,j) (1-g_{i',j'}) (1-g_{i,j}) \).

It should be noted that while \( \tau_{BB}(i',i) = \tau_{BB}(i,i') \) and \( \tau_{DD}(i',i) = \tau_{DD}(i,i') \) such symmetry relations are not valid in general for \( \tau_{BD}(i,i') \) and \( \tau_{DB}(i,i') \). The reason for this is that the above quantities summarize the transfer parameters involved in each type of transfer from one layer to another. Therefore \( \tau_{BB}(i',i) \) involves terms for all the binding sites in layer i' and all the binding sites in layer i. The symmetry results since \( \tau_{BB}(i,i') \)
involves exactly the same sites. However \( \tau_{BD}(i',i) \) involves the
binding sites of layer \( i' \) and the diffusion sites of layer \( i \) which
are not the same as the binding sites of \( i \) and diffusion sites of \( i' \)
which are involved in \( \tau_{BD}(i,i') \). Thus the symmetry does not hold in
general for \( \tau_{BD}(, ,) \) and \( \tau_{DB}( , ,) \).

Recalling, as in section 2.1.3.4, there are \( m \) sites per layer
and \( m_i \) binding sites in layer \( i \), that is

\[
m_i = \sum_j g_{i,j}
\]

equation 2.2.3.4-1 may be summed over \( j \) to give:

\[
0 = -b_i c_{PB}^{B_i m_i} - b_i c_{PD}^{D_i (m-m_i)} + r_i^{B}(1-P_i^{B})m_i + r_i^{D}(1-P_i^{D})(m-m_i) + u(1-P_i^{B})m_i - \sum_{i'} (1-P_i^{B}) P_i^{B} \tau_{BB}(i',i)
+ \sum_{i'} (1-P_i^{B}) P_i^{B} \tau_{BB}(i,i') - \sum_{i'} (1-P_i^{D}) P_i^{D} \tau_{BD}(i',i)
+ \sum_{i'} (1-P_i^{D}) P_i^{D} \tau_{BD}(i,i') - \sum_{i'} (1-P_i^{D}) P_i^{B} \tau_{DB}(i',i)
+ \sum_{i'} (1-P_i^{B}) P_i^{D} \tau_{BD}(i,i')
\]
\[- \sum_{i'} (1-P^D_{i'}) P^D_{i'} t^D_{DD}(i',i) \]

\[+ \sum_{i'} (1-P^D_{i'}) P^D_{i'} t^D_{DD}(i,i') \]

2.2.3.4-2

2.2.3.5 Steady-State Constraints

The steady-state assumption was introduced in the previous section. This section develops certain constraints associated with the steady-state condition. In discussing these constraints, it is convenient to present the mathematical quantities in equation 2.2.3.4-2 with a verbal description of the associated oxygen movement. This is done in the following illustration:

<table>
<thead>
<tr>
<th>From binding sites in layer i:</th>
<th>Mathematical Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>To consumption</td>
<td>[u(1-P^B_i)m_i]</td>
</tr>
<tr>
<td>To solution</td>
<td>[r^B_i(1-P^B_i)m_i]</td>
</tr>
<tr>
<td>To binding sites</td>
<td>[\Sigma (1-P^B_{i'}) P^B_{i'} t^B_{BB}(i,i')]</td>
</tr>
<tr>
<td>To diffusion sites</td>
<td>[\Sigma (1-P^B_{i'}) P^B_{i'} t^B_{BD}(i,i')]</td>
</tr>
</tbody>
</table>

| To binding sites in layer i:  |                         |
| From solution                | \[b^B_{i'} c^B_{i'} m_{i'}\] |
| From binding sites           | \[\Sigma (1-P^B_{i'}) P^B_{i'} t^B_{BB}(i',i)\] |
| From diffusion sites         | \[\Sigma (1-P^D_{i'}) P^B_{i'} t^D_{DB}(i',i)\] |
From diffusion sites in layer $i$:

- To solution \( r_i^D (1 - p_i^D) (m - m_i) \)
- To binding sites \( \Sigma (1 - p_i^B) p_i^B t_{DB}^{i,i'} \)
- To diffusion sites \( \Sigma (1 - p_i^D) p_i^D t_{DD}^{i,i'} \)

To diffusion sites in layer $i$:

- From solution \( b_i^D c p_i^D (m - m_i) \)
- From binding sites \( \Sigma (1 - p_i^B) p_i^D t_{BD}^{i,i'} \)
- From diffusion sites \( \Sigma (1 - p_i^D) p_i^D t_{DD}^{i,i'} \)

The above illustration summarizes all oxygen movement involving sites in layer $i$. Since the tissue is assumed to be at the steady-state with no net change in the probability of site occupation it is possible to equate the oxygen arriving at binding sites in layer $i$ to the oxygen leaving these binding sites. A similar balance equation may be written for the diffusion sites in layer $i$. From the above chart these balance equations may be written as:

\[
u(1-p_i^B) m_i + r_i^B (1-p_i^B) m_i + \Sigma (1-p_i^B) p_i^B t_{BB}^{i,i'} + \Sigma (1-p_i^D) p_i^D t_{BD}^{i,i'} + \Sigma (1-p_i^B) p_i^D t_{DB}^{i,i'}
\]

\[= b_i^B c p_i^B m_i + \Sigma (1-p_i^B) p_i^B t_{BB}^{i,i'} + \Sigma (1-p_i^D) p_i^B t_{DB}^{i,i'} \]

for binding sites in layer $i$  \[2.2.3.5-1\]

and
\[
\begin{align*}
\ell_i^D (1 - p_i^D (m - m_i)) + \sum_{i'} (1 - p_i^D) P_{i'i}^D \ell_{DB}(i, i') + \sum_{i'} (1 - p_i^D) P_{i'i}^D \ell_{DD}(i, i') \\
= b_i^D c_i^D(m - m_i) + \sum_{i'} (1 - p_i^B) P_{i'i}^D \ell_{BB}(i', i) + \sum_{i'} (1 - p_i^D) P_{i'i}^D \ell_{DB}(i', i)
\end{align*}
\]

for diffusion sites in layer \(i\).  \(2.2.3.5-2\)

Observe that the sum of the above balance equations is equal to equation 2.2.3.4-2. These relations are employed in the next section to obtain matrix equations for the model.

2.2.3.6 Matrix Form of the Equations

In this section the equations for the diffusion-binding site model are written in matrix form. With the system of equations summarized in matrix form it is possible to obtain the form of the solution for the kinetics of tissue oxygen consumption.

It was pointed out in the previous section that if the steady-state constraint for diffusion sites, equation 2.2.3.5-2, is subtracted from the basic model equation, equation 2.2.3.4-2, the result is the steady-state constraint equation for binding sites, equation 2.2.3.5-1. This equation may be rearranged and written as:

\[
\begin{align*}
b_i^B c_i^B m_i + \sum_{i'} \ell_{BB}(i', i)p_i^B - \sum_{i'} \ell_{BB}(i', i)p_i^B p_i^B - \sum_{i'} \ell_{BB}(i', i)p_i^B = \\
+ \sum_{i'} \ell_{BB}(i', i)p_i^B p_i^B + \sum_{i'} (1 - p_i^D) p_i^B \ell_{DB}(i', i) \\
- \sum_{i'} (1 - p_i^B) p_i^D \ell_{DB}(i', i') + u_{i'i}^B m_i + r_{i'i}^B m_i \\
= um_i + r_{i'i}^B m_i.
\end{align*}
\]  \(2.2.3.6-1\)
Recalling from section 2.2.3.4 that \( \lambda_{BB}(i,i') = \lambda_{BB}(i',i) \) it follows that the cross-product terms involving \( P_i^B \) in the above equation cancel out.

For notational convenience let

\[
q_i = \sum_{i'} (1 - P_i^D) P_i^B \lambda_{DB}(i',i) - \sum_{i'} (1 - P_i^B) P_i^D \lambda_{BD}(i,i').
\]

From the chart in section 2.2.3.5, it can be seen that \( q_i \) is the difference between the probability of oxygen transferring to binding sites in layer \( i \) from diffusion sites and the probability of oxygen transferring from binding sites in layer \( i \) to diffusion sites. This quantity will be discussed in more detail in later sections discussing qualitative kinetics.

Equation 2.2.3.6-1 may now be written as:

\[
(b_i^c m_i + r_i^m_i + u_i + \sum_{i'} \lambda_{BB}(i',i)) P_i^B = \sum_{i'} \lambda_{BB}(i,i') P_i^B + q_i
\]

\[
= u_i + r_i^m_i.
\]

The following development closely parallels that of section 2.1.3.5 for the binding site model. The notation employed is chosen to reflect these similarities where possible.
Let \( Z \) denote the following \( n \times n \) matrix:

\[
Z = \begin{bmatrix}
\Sigma \ell_{BB}(i',1) & -\ell_{BB}(1,2) & -\ell_{BB}(1,3) & \cdots & -\ell_{BB}(1,n) \\
-\ell_{BB}(2,1) & \Sigma \ell_{BB}(i',2) & -\ell_{BB}(2,3) & \cdots & -\ell_{BB}(2,n) \\
\vdots & \vdots & \ddots & \ddots & \vdots \\
\vdots & \vdots & \ddots & \ddots & \vdots \\
-\ell_{BB}(n,1) & -\ell_{BB}(n,2) & -\ell_{BB}(n,3) & \cdots & \Sigma \ell_{BB}(i',n)
\end{bmatrix}
\]

that is \( Z = (z_{i,j}) \) where 
\[
z_{i,i} = \Sigma \ell_{BB}(i',i)
\]

\[
z_{i,j} = -\ell_{BB}(i,j) \quad \text{for } i \neq j.
\]

Observe that since \( \ell_{BB}(i,i') = \ell_{BB}(i',i) \), the matrix \( Z \) has zero row sums and is symmetric.

Let

\[
M = \begin{bmatrix}
m_1 & 0 & 0 & \ldots & 0 \\
0 & m_2 & 0 & \ldots & 0 \\
0 & 0 & m_3 & \ldots & 0 \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
0 & 0 & 0 & \ldots & m_n
\end{bmatrix}
\]

that is \( M \) is a diagonal matrix with the \( i^{\text{th}} \) diagonal element equal \( m_i \).
Let \( \mathbf{q} \) be the vector

\[
\begin{pmatrix}
q_1 \\
q_2 \\
q_3 \\
\vdots \\
q_n
\end{pmatrix}
\]

and

\[
P = \begin{pmatrix}
P_1^B \\
P_2^B \\
P_3^B \\
\vdots \\
P_n^B
\end{pmatrix}
\]

With this notation and recalling that \( b_i^B \) and \( r_i^B \) are zero except for the surface layer it follows that the system of equations described by equation 2.2.3.6-3 may be written as:

\[
(b^B c_m + r^B m_e)P_{1e_1}^B + (Z + uM)P + q = r^B m_e e_1 + uM_1.
\]
The subscripts on $b_1^B$ and $r_1^B$ are suppressed since these are the only non-zero values of $b_1^B$ and $r_1^B$. This equation serves as the basic matrix equation for the diffusion-binding site model.

Let the matrix $A$ be defined as:

$$A(c) = (b_{cm_1}^B + r_{m_1}^B)E_{11} + Z + uM.$$  

With this notation the basic matrix equation may be written as:

$$A(c)P + q = r_{m_1}^B E_{11} + uM.$$  \hspace{1cm} (2.2.3.6-5)

Observe that the matrix $A(c)$ is a type 1 matrix as defined in the appendix. Moreover, since $Z$ is symmetric, $A(c)$ is a symmetric matrix, and a symmetric diagonally dominant type 1 matrix is a type 4 matrix as defined in the appendix. The importance of this property will be seen in section 2.2.4.2 in developing qualitative kinetics expressions.

2.2.3.7 A Measure of Oxygen Consumption

Although the diffusion-binding site model differs from the binding site model in that two types of sites are involved in oxygen transport rather than just one, in both models oxygen is consumed only at binding sites. As a consequence, if $O_T(c,s)$ is the random variable denoting the amount of oxygen consumed during a time interval of length $s$ at solution concentration $c$ then the expressions

$$EO_T(c,s) = \sum_{i,j} us_{ij} (1-P_{ij}^B)$$

and
\[
\text{VAR } O_T(c,s) = \sum \sum u_{g_{i,j}} (1-P^B_{i,j})
\]

may be obtained in exactly the same manner as in section 2.1.3.7 for the binding site model. Then, defining \( R(c,s) = \frac{1}{s} O_T(c,s) \) to express the rate of oxygen consumption it follows that

\[
\text{ER}(c,s) = \sum \sum u_{g_{i,j}} (1-P^B_{i,j})
\]

and

\[
\text{VAR } R(c,s) = \frac{1}{s} \text{ER}(c,s).
\]

Introducing the layer equilibrium assumption of section 2.2.3.4 that \( P^B_{i,j} = P^B_i \) and recalling that \( \sum g_{i,j} = m_i \) gives

\[
\text{ER}(c,s) = \sum u m_i (1-P^B_i)
\]

and

\[
\text{VAR } R(c,s) = \frac{1}{s} \text{ER}(c,s).
\]

Summing equation 2.2.3.4-2 over \( i \) and rearranging terms gives:

\[
\sum u (1-P^B_i) m_i + r^B (1-P^B_i) m_i + r^D (1-P^D_i) (m-m_i) = b^B c m_i + b^D c^D (m-m_i).
\]

This serves as the balance equation for the diffusion-binding site model indicating that the sum of the probabilities for oxygen leaving the tissue and being consumed is equal to the sum of the probabilities of oxygen entering the tissue. This is what would be expected at the steady-state and is similar to equation 2.1.3.7-11.
for the binding site model. Using this equation and equations 2.2.3.7-1 and 2.2.3.7-2 gives

\[ ER(c, s) = b^B cP_1^B m_1 - r^B (1 - P_1^B) m_1 + b^D cP_1^D (m - m_1) - r^D (1 - P_1^D) (m - m_1) , \]

2.2.3.7-4

and

\[ \text{VAR } R(c, s) = \frac{1}{s} \text{ER}(c, s) . \]

2.2.3.7-5

As with the binding site model, the above equations indicate that the expected rate of oxygen consumption may be expressed in terms of surface layer probabilities.

2.2.4 Solution of Equations

In this section the results of the previous sections are employed to obtain expressions for the kinetics of tissue oxygen consumption. The first part uses the matrices of section 2.2.3.6 to solve for \( P_1^B \) while the second part consolidates all of the results for the diffusion-binding site model to obtain kinetics expressions. As in the treatment of the basic binding site model, only the one-sided case is considered.

2.2.4.1 Surface Layer Binding Site Probabilities

In section 2.2.3.7 it was shown that the expected rate of oxygen consumption could be expressed in terms of the surface layer probabilities. This section employs the matrices of section 2.2.3.6 to solve for \( P_1^B \), the surface layer binding site probability.
Given equation 2.2.3.6-5

\[ A(c)P + q = r^{B}m_{1}e_{1} + uM \]

where \( A(c) = (b^{B}cm_{1} + r^{B}m_{1})E_{11} + Z + uM \)

let \( T \) denote the matrix that lower triangularizes the type 1 matrix \( A(c) \) as indicated in proposition 2 of the appendix. Therefore

\[ TA(c)P + Tq = T(r^{B}m_{1}e_{1} + uM) \]

and, since \( T \) does not multiply the first row of \( A(c) \),

\[ [(b^{B}cm_{1} + r^{B}m_{1})E_{11} + TZ + uTM]P + Tq = r^{B}m_{1}e_{1} + uM. \]

Let \( z_{1}, z_{2}, \ldots, z_{n} \) denote the first row of \( TZ \), \( w_{1}, w_{2}, \ldots, w_{n} \) denote the first row of \( uTM \), and \( \tau_{1}, \tau_{2}, \ldots, \tau_{n} \) the first row of \( T \).

Since \( Z \) is a zero row sum matrix, \( TZ \) is a zero row sum matrix

and therefore

\[ \sum_{i=1}^{n} z_{i} = 0 \quad \text{for} \quad z_{1} = -\sum_{i=2}^{n} z_{i}. \]

But \( TA(c) \) is lower triangular giving

\[ -z_{i} = w_{i} \quad \text{for} \quad i > 1 \]

or

\[ -\sum_{i=2}^{n} z_{i} = \sum_{i=2}^{n} w_{i}. \]

Therefore

\[ z_{1} = \sum_{i=2}^{n} w_{i} \]
or
\[ z_1 + w_1 = \sum_{i=1}^{n} w_i. \]

Let \( w = z_1 + w_1 = \sum_{i=1}^{n} w_i. \)

The first scalar equation summarized in matrix equation 2.2.4.1-1 may be written as:

\[ (b^B c_m_1 + r^B m_1 + w) P_1^B + \sum_{i=1}^{n} \tau_i q_i = r^B m_1 + w. \]

Therefore
\[ P_1^B = \frac{r^B m_1 + w - q}{b^B c_m_1 + r^B m_1 + w}. \]

\[ q = \sum_{i=1}^{n} \tau_i q_i. \]

Recalling that the matrix \( T \) does not depend upon solution oxygen concentration it follows that \( w \) does not depend upon \( c \). It should be noted that \( q \) is a function of \( c \) which is the principle difference between the above equation and the corresponding equation, equation 2.1.4.1-3, for the binding site model in which the dependence of \( P_1^B \) upon concentration was explicitly expressed.

2.2.4.2 Kinetics

This section employs the results of previous sections to obtain kinetic expressions and to give a qualitative analysis of these results.
In order to develop these expressions, first consider equation 2.2.3.5-2 which was the steady-state balance equation for diffusion sites:

\[ r^D_i (1 - p^D_i) (m - m_1) + \sum_{i'} (1 - p^D_i) p^B_{i'i} T_{DB}(i, i') + \sum_{i'} (1 - p^D_i) p^D_{i'i} T_{DD}(i, i') \]

\[ = b^D_i c p^D_i (m - m_1) + \sum_{i'} (1 - p^B_{i'i}) p^D_{i'i} T_{BD}(i', i) + \sum_{i'} (1 - p^D_{i'i}) p^D_{i'i} T_{DD}(i', i) . \]

Summing the above equation over \( i \) and rearranging terms gives:

\[ b^D_i c p^D_i (m - m_1) - r^D_i (1 - p^D_i) (m - m_1) \]

\[ = \sum_i \left[ \sum_{i'} (1 - p^D_i) p^B_{i'i} T_{DB}(i, i') - \sum_{i'} (1 - p^B_{i'i}) p^D_{i'i} T_{BD}(i', i) \right] \]

\[ = \sum_i \left[ \sum_{i'} (1 - p^D_i) p^B_{i'i} T_{DB}(i', i) - \sum_{i'} (1 - p^B_{i'i}) p^D_{i'i} T_{BD}(i, i') \right] . \]

by interchanging the order of summation, and then interchanging notation.

Recalling the definition of \( q_i \) in equation 2.2.3.6-2 and letting

\[ Q = \sum_i q_i \]

\[ 2.2.4.2-1 \]

gives

\[ b^D c p^D_i (m - m_1) - r^D_i (1 - p^D_i) (m - m_1) = Q . \]

\[ 2.2.4.2-2 \]

Using this result in equation 2.2.3.7-4 gives:

\[ ER(c, s) = b^B c p^B m_1 - r^B (1 - p^B) m_1 + Q . \]

\[ 2.2.4.2-3 \]
Substituting equation 2.2.4.1-2 for $p_1^B$ in the above expression gives:

$$ER(c, s) = \frac{wc + [Q-q]c + \frac{r_B^B}{b} [Q-q] + Qw/b^B m_1}{c + \frac{r_B^B m_1 + w}{b^B m_1}}.$$  \hspace{1cm} 2.2.4.2-4

This equation serves as the kinetic expression for tissue oxygen consumption in the diffusion-binding site model. In contrast to the binding site model for which equation 2.1.4.2-1 satisfies Michaelis-Menten kinetics, the above equation indicates that the incorporation of diffusion sites for oxygen transport results in a departure from Michaelis-Menten kinetics. Moreover, this departure is concentration dependent. Graphical presentations of the kinetics equation are discussed below in order to more specifically determine the form of this departure.

Equation 2.2.4.2-4 may be written in the form:

$$ER(c, s) = \frac{wc + \alpha(c)}{c + K}.$$  \hspace{1cm} 2.2.4.2-5

where $K = \frac{r_B^B m_1 + w}{b^B m_1}$

and $\alpha(c) = [Q-q]c + \frac{r_B^B}{b} [Q-q] + Qw/b^B m_1$.

A convenient graphical form for the presentation of data following Michaelis-Menten kinetics is the Lineweaver-Burk plot of the inverse rate versus the inverse concentration. For example, in equation
2.2.4.2-5, if \( \omega(c) \) were identically zero this would result in the straight line plot of

\[
\frac{1}{ER(c,s)} = \frac{1}{w} + \frac{K}{w} \frac{1}{c} .
\]

If such a plot were made for the data fitting equation 2.2.4.2-5, the following relations would hold:

\[
\frac{1}{ER(c,s)} = \frac{c+K}{wc+\omega(c)} < \frac{c+K}{wc} = \frac{1}{w} + \frac{K}{w} \frac{1}{c} \text{ if } \omega(c) > 0
\]

and

\[
\frac{1}{ER(c,s)} = \frac{c+K}{wc+\omega(c)} > \frac{c+K}{wc} = \frac{1}{w} + \frac{K}{w} \frac{1}{c} \text{ if } \omega(c) < 0 .
\]

Since \( w \) and \( K \) are unknown parameters it is necessary to further examine \( \omega(c) \) to increase the usefulness of the previous inequalities for empirical applications. To facilitate this analysis, certain results from various sections are listed below with the appropriate reference:

1. \( A(c) \) is a type 4 matrix (section 2.2.3.6).

2. \( \tau_1, \tau_2, \ldots, \tau_n \) are the elements of the first row of the matrix \( T \) which lower triangularizes \( A(c) \) (section 2.2.4.1).

3. All elements of \( T \) are non-negative, all off-diagonal elements are less than 1, and \( \tau_1 \) equals 1 (section 2.2.3.6 and proposition 7 of the appendix).

4. \( q_i = \sum (1-p^D_{i,i'})p^B_{i,i'}\ell_{DB}(i,i') - \sum (1-p^B_{i,i'})p^D_{i,i'}\ell_{BD}(i,i') \) (equation 2.2.3.6-2).
5. \( q = \sum_{i=1}^{n} \tau_i q_i \) (equation 2.2.4.1-3).

6. \( Q = \sum_{i=1}^{n} q_i \) (equation 2.2.4.2-1).

The term \( q_i \) is proportional to the difference between the expected number of oxygen transfers from diffusion sites to layer \( i \) binding sites and the expected number of oxygen transfers from layer \( i \) binding sites to diffusion sites. If the tissue were at equilibrium, that is if the consumption term were zero, then each \( q_i \) would be zero. For this investigation the consumption term is non-zero and the resulting departure from equilibrium is due to oxygen consumption at the binding sites. Therefore it is reasonable to assume that the non-zero consumption term results in positive values of the \( q_i \)'s. Since \( \tau_i \) equals 1 and the remaining \( \tau_i \) are non-negative fractions it follows that, for this case,

\[
Q \geq q \geq 0
\]

and

\[
\alpha(c) \geq 0 \quad \text{for } q_i \geq 0 .
\]

It is now possible to make some general observations about the behavior of \( \alpha(c) \) under these conditions. Since all sites are unoccupied for \( c \) equal zero, the \( q_i \)'s are zero and \( \alpha(c) \) is zero. For increasing values of \( c \), \( \alpha(c) \) would be positive. If the concentration, \( c \), were sufficiently high so that the tissue became saturated then the \( q_i \)'s might approach zero but the sign of \( \alpha(c) \)
would remain positive. If such concentrations were attainable experimentally then $\alpha(c)$ would be approximately zero for small concentrations, become more positive as $c$ increased, pass through a maximum and then possibly decrease.

If $\alpha(c)$ behaves in this manner it is then possible to examine the qualitative appearance of a Lineweaver-Burk plot of the kinetics. The plot of equation 2.2.4.2-5 for the diffusion-binding site model would approach the Michaelis-Menten straight line plot of equation 2.2.4.2-6 for high values of $1/c$. For decreasing values of $1/c$ the diffusion-binding site plot would lie below the straight line plot of equation 2.2.4.2-6 attaining some maximum deviation and then possibly approaching the straight line plot again if saturation concentrations are experimentally attainable.

2.2.5 Interpretation

In section 2.1.6.2 intuitive interpretations were offered for various quantities in the binding site model. This same type of analysis may be performed for the diffusion-binding site model. Since the diffusion-binding site model has both binding sites and diffusion sites involved in oxygen transport it would be expected that the quantities arising in the binding site model would be a subset of those appearing in the more complex diffusion-binding site model. This may be verified by comparing equations 2.1.3.6-3 and 2.2.3.6-3. Although there are notational differences, the primary difference is the appearance of the $q_i$ terms in the diffusion-binding site equations. Because of this basic correspondence the interpretation of the quantities in the matrix equation 2.2.3.6-4 for the
diffusion-binding site model is analogous to that of section 2.1.6 for the binding site model with the obvious exception of the vector \( q \). Therefore this section deals primarily with only the interpretations for these new quantities.

As in section 2.1.6.2, the terms in the \( i \)th row of the matrix may be viewed as indicating net gain or loss of oxygen by the binding sites in layer \( i \). Therefore in equation 2.2.3.6-4 the \( q_i \) term may be viewed as indicating a net gain if positive or a net loss if negative. One of the major differences between the equations of the two models is that the concentration dependent terms are not simply linear in the matrix equation for the diffusion-binding site model. The non-linear concentration dependence of the vector \( q \) arises since the steady-state balance between the binding and diffusion sites depends upon the site occupation probabilities which are a function of concentration.

Equation 2.2.3.7-2 indicates that the variance of the rate of oxygen consumption approaches zero as the length of the time interval over which this rate is determined increases. This agrees with the results for the binding site model and is reasonable for a steady-state process. Again, as with the binding site model, practical limitations of the experimental situation would dictate a non-zero lower bound for this quantity.

2.2.6 Summary

The diffusion-binding site model is a generalization of the binding site model incorporating a second type of site into the oxygen transport process. These sites are termed diffusion sites and
do not consume oxygen. As indicated in section 2.2.1, this is intended to serve as a discrete approximation of the contribution of ordinary diffusion to tissue oxygen transport.

The development of the model was similar to the treatment of the binding site model. It was indicated in section 2.2.3.4 that the layer equilibrium assumption becomes a property of the model for each type of site if the distribution of this type is sufficiently dense in each layer and the gradient of this distribution is relatively uniform from layer to layer. The steady-state assumption was introduced and in section 2.2.3.5 the consequences of this assumption were utilized to decompose the general equations of the model. In section 2.2.4.2 kinetic expressions were obtained indicating that the additional type of site in the model results in departures from Michaelis-Menten kinetics and that the magnitude of the departure is concentration dependent. This served to indicate the anticipated form of the departure from Michaelis-Menten kinetics in a Lineweaver-Burk plot of experimental data.

In comparing the treatment of the diffusion-binding site model with that for the binding site model, it should be noted that there is no treatment of a modified model in which an average site distribution is employed as in section 2.1.5. As discussed in section 2.1.7, the simplification of the site distribution in the modified binding site model made it possible to obtain iterative formulas for the Michaelis-Menten parameters. Although a similar assumption can be made for the diffusion-binding site model, the appearance of the concentration dependent $q_i$ terms restricts the development of
comparable iterative formulas. Therefore, the weakened assumption regarding site distribution does not afford the same dividends in terms of parameter evaluation. For this reason, the diffusion-binding site model is not examined for an average site distribution.
3. CONCLUSIONS

In discussing the results of this investigation it is convenient to first compare the two models developed here and then to compare these models with previous models. The major points of comparison between experimental results and the predictions of the models developed here are then briefly summarized.

3.1 Comparison of the Two Models

Throughout the development of the diffusion-binding site model similarities with the binding site model were discussed. It was observed in section 2.2.5 that the equations of the binding site model were a subset of the equations for the diffusion-binding site model. For example, if the $t_{BD}$ and $t_{DB}$ terms are zero then the $q_i$'s and $Q$ are zero and, as seen from equation 2.2.4.2-4, the resultant kinetics are Michaelis-Menten in form as would be expected. However, although the equations for one are a subset of the equations for the other, the same relationship does not apply to the models since the assumptions introduced into the diffusion-binding site model are slightly different than those for the binding site model. As an illustration of this point, the validity of the layer equilibrium assumption depends upon the communication among all oxygen transport sites of the same type within a layer. Thus, for the diffusion-binding site model communication is required between the diffusion sites in a layer while this is an unnecessary constraint for the non-binding sites in the binding site model. Furthermore, it was shown in section 2.1.3.6 that the binding site model approached
the steady-state while this was merely assumed for the diffusion-binding site model. The primary reason for this discrepancy is that the complexity of the equations for the diffusion-binding site model prevent a simple matrix formulation of the equations prior to the introduction of the steady-state assumption.

Although the steady-state kinetics expressions are obtained for the one-sided case of both models for a specified arrangement of sites, the binding site model yields a more precise prediction. In addition, as discussed in section 2.2.6, the use of an average site distribution facilitates a more detailed analysis of the binding site model while a similar assumption for the diffusion-binding site model would not permit as convenient a development of iterative formulas for the parameters in the kinetics expressions. Therefore, as would be anticipated, the diffusion-binding site model offers a more general conceptualization and less specific predictions.

3.2 Comparison with Previous Models

In developing new mathematical models it is useful to examine comparisons with previous models to see what, if any, advantages the new models offer. The point of reference chosen for this study is the fixed-site model developed by Gold (1969). As discussed in section 1.2 this model appears to suggest a reasonable explanation of experimental data by using the biological hypotheses of Longmuir.

As indicated previously, although the present models are conceptually similar to Gold's they are developed in a stochastic rather than deterministic framework. One consequence of this structural difference is that the stochastic models are formulated
in terms of the probability of site occupation which is a continuous variable as opposed to the fraction of sites occupied which is used in the deterministic model and is discrete valued. Since both developments employ the derivatives of their respective site occupation variables the stochastic treatment permits a more rigorous mathematical development.

In the formulation of transfers in the deterministic model Gold introduces two quantities: one reflecting the average number of sites in an adjacent layer which are near a particular site and the second indicating the average transfer rate to these sites. The product of these two parameters is then used in the same manner as the sum of all transfer parameters in the modified binding site model. While the modified binding site model facilitates the interpretation of this parameter by decomposing it into more elementary events it was also seen in the basic binding site model that such a parameter could have different values for different sites in a layer once the arrangement of sites is specified.

The treatment of the deterministic model corresponds to the special case of the one-sided modified model in which transfers over more than one layer are neglected. Under these conditions Gold investigated the case of uniform site distribution and surface site inactivation. There cases were considered in sections 2.1.5.4.1.1 and 2.1.5.4.2. Thus results for the modified binding site model for unequal expected number of binding sites per layer, two-sided cases, more than one layer transfers, and irreversible inhibition all represent new results within essentially the same conceptual framework
as the deterministic model. One result of particular interest is
the determination of how quickly \( V_{\text{max}} \) approaches its maximum value
as a function of tissue thickness. This was examined for the modi-
fied model with uniform site distribution and only one layer transfers.
The implications of this result were discussed in section 2.1.7.

The stochastic models also showed that the layer equilibrium
assumption, the equivalent of which was tacitly assumed in the
deterministic model, is an expected property of the model for certain
arrangements of sites under certain biologically reasonably constraints.
And, of course, the results regarding variances were not discussed
in the deterministic model.

Most of the above comments apply to comparisons with the binding
site model. The diffusion-binding site model is a generalization of
the previous models to incorporate a second mode of oxygen transport.
Therefore this incorporation of a discrete approximation to diffusion
is a more general model and the results regarding the form of these
kinetics are entirely new.

3.3 Comparison with Experimental Results

This section summarizes the various comparisons made between
experimental results and the predictions of the models developed
here. The principal agreement is in the qualitative form of the
kinetics. As discussed in section 1.2, Longmuir and co-workers have
found that the experimental results for tissue oxygen consumption agree
more closely with Michaelis-Menten kinetics than the predictions of
the classical Warburg model (Longmuir et al., 1971). It was shown in
sections 2.1.4.2 and 2.1.5.3 that the basic and the modified binding
site models predict Michaelis-Menten kinetics. It was shown in section 2.2.4.2 that the incorporation of ordinary diffusion into the oxygen transport mechanism in the diffusion-binding site model results in the prediction of kinetics that depart from the Michaelis-Menten kinetics form. The magnitude of this departure depends upon the relative amount of oxygen transport occurring by ordinary diffusion and may be consistent with the variation in experimental results found for different types of tissue (Longmuir et al., 1971).

In comparing experimental results with predictions of the Warburg model, Longmuir (1966a) found that the dependency of kinetics upon tissue thickness was much less than predicted by the Warburg model. It was shown in section 2.1.7 that the binding site model predictions are compatible with this relative insensitivity to tissue thickness. Moreover, this was seen to afford an explanation for the marked difference between cell and tissue respiration rates.

While these specific points indicate general agreement between experimental results and the predictions of the models developed here, the additional predictions developed for various special cases provide a basis for further examination of these models and their underlying hypotheses.
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5. APPENDIX. MATRIX TECHNIQUES

The matrix techniques included in this appendix are used in the development of both models. For the sake of continuity in the presentation of the models, these techniques are presented separately. The purpose of this section is to indicate the operations performed upon certain types of matrices that occur in examining these models.

The notation \( \sum_{j=1}^{n} a_{i,j} \) is used to represent \( \sum_{j=1}^{n} a_{i,j} - a_{i,i} \).

5.1 Definition 1 - Type 1 Matrix

An \( n \times n \) matrix, \( A = (a_{i,j}) \), is said to be a type 1 matrix if:

1. \( a_{i,j} \leq 0 \) for \( i \neq j \).

2. \( a_{i,i} \geq \sum_{j=1}^{n} a_{i,j} \).

3. \( a_{i,i} > \sum_{j=1}^{n} a_{i,j}, a_{n,n} > 0 \).

It is unnecessary to prove a type 1 matrix, \( A \), can be lower triangularized, but it is convenient that the exact scheme for this triangularization be specified. The following proposition is sufficient to guarantee the validity of this scheme.

PROPOSITION 1

Let \( A = (a_{i,j}) \) be a type 1 matrix. Let \( B = (b_{i,j}) \) be the \( n \times n \) matrix formed from \( A \) by leaving the \( n \)th row unchanged and eliminating all elements in column \( n \) other than \( a_{n,n} \) by elementary operations. Then \( B \) is a type 1 matrix.
PROOF: If \( i = n \), then the properties are true since \( b_{n,j} = a_{n,j} \). So only the case where \( i \neq n \) need be considered in this proof.

For \( i \neq n \), \( b_{i,j} = a_{i,j} - \frac{a_{i,n}}{a_{n,n}} a_{n,j} \).

(1) SHOW: \( b_{i,j} \leq 0 \) for \( i \neq j \). That is, show

\[
\frac{a_{i,j}}{a_{n,n}} a_{n,j} \leq 0 \text{ for } i \neq j.
\]

PROOF: If \( j = n \) then \( b_{i,n} = 0 \) and the result is immediate.

If \( j \neq n \), then \( a_{i,j} \leq 0 \), \( a_{i,n} \leq 0 \), and \( a_{n,j} \leq 0 \), since

\[
i \neq j.
\]

\[
=> \frac{a_{i,n}}{a_{n,n}} \leq 0, \text{ since } a_{i,n} \leq 0 \text{ and } a_{n,n} > 0.
\]

\[
=> \frac{a_{i,n}}{a_{n,n}} a_{n,j} \geq 0, \text{ since } a_{n,j} \leq 0.
\]

\[
=> -\frac{a_{i,n}}{a_{n,n}} a_{n,j} \leq 0
\]

\[
=> a_{i,j} - \frac{a_{i,n}}{a_{n,n}} a_{n,j} \leq 0, \text{ since } a_{i,j} \leq 0 \text{ for } i \neq j.
\]

This completes the proof of part 1.

(2) SHOW: \( b_{i,i} = -\sum_{j=1}^{n} b_{i,j} \); that is, show that

\[
b_{i,i} = a_{i,i} - \frac{a_{i,j}}{a_{n,n}} a_{n,j} \geq -\sum_{j=1}^{n} \left( \frac{a_{i,j}}{a_{n,n}} a_{n,j} \right) = -\sum_{j=1}^{n} b_{i,j}.
\]
PROOF: \( a_{i,i} \geq -\sum_{j=1}^{n} a_{i,j} \) since A is type 1.

\[ a_{n,n} \geq -\sum_{j=1}^{n} a_{n,j} \] since A is type 1.

But \( -\sum_{j=1}^{n-1} a_{n,j} = -\sum_{j=1}^{n-1} a_{n,j} \).

Therefore \( a_{n,n} \geq -\sum_{j=1}^{n-1} a_{n,j} \)

\[ \Rightarrow a_{i,n} \leq -\sum_{j=1}^{n-1} a_{i,j} \frac{a_{i,n}}{a_{n,n}} \text{, having multiplied by} \frac{a_{i,n}}{a_{n,n}} \]

which is less than or equal to zero since \( i \neq n \).

\[ \Rightarrow -a_{i,n} \geq \sum_{j=1}^{n-1} a_{i,j} \frac{a_{i,n}}{a_{n,n}} \]

But \( \sum_{j=1}^{n-1} a_{i,j} \frac{a_{i,n}}{a_{n,n}} = \sum_{j=1}^{n-1} a_{i,j} \frac{a_{i,n}}{a_{n,n}} + a_{n,i} \frac{a_{i,n}}{a_{n,n}} \).

Therefore, \( -a_{i,n} \geq \sum_{j=1}^{n-1} a_{i,j} \frac{a_{i,n}}{a_{n,n}} + a_{n,i} \frac{a_{i,n}}{a_{n,n}} \)

\[ \Rightarrow -a_{n,i} \frac{a_{i,n}}{a_{n,n}} \geq \sum_{j=1}^{n-1} a_{i,j} \frac{a_{i,n}}{a_{n,n}} + a_{i,n} \]

Therefore, \( a_{i,i} - a_{n,i} \frac{a_{i,n}}{a_{n,n}} \geq -\sum_{j=1}^{n-1} a_{i,j} + \sum_{j=1}^{n-1} a_{i,j} \frac{a_{i,n}}{a_{n,n}} + a_{i,n} \)

since \( a_{i,i} \geq -\sum_{j=1}^{n-1} a_{i,j} \).
Therefore, \( a_{i,i} - a_{n,i} \frac{a_{i,n}}{a_{n,n}} \geq \sum_{j=1}^{n} (a_{i,j} - a_{n,j} \frac{a_{i,n}}{a_{n,n}}) \)

since \( a_{i,n} = a_{n,n} \frac{a_{i,n}}{a_{n,n}} \).

(3) SHOW: \( b_{i,i} > - \sum_{j>i} b_{i,j} \). That is, show that

\[
\begin{align*}
b_{i,i} &= a_{i,i} - a_{n,n} \frac{a_{i,n}}{a_{n,n}} > \sum_{j>i} (a_{i,j} - a_{n,j} \frac{a_{i,n}}{a_{n,n}}) \\
&= \sum_{j>i} b_{i,j}.
\end{align*}
\]

Recall that the case where \( i = n \) is not included.

PROOF: \( a_{n,n} \geq - \sum_{j=1}^{n-1} a_{n,n} \), since \( A \) is type 1.

\[
\Rightarrow \quad 1 \geq \left( \frac{1}{a_{n,n}} \right) \sum_{j=1}^{n-1} a_{n,n}, \text{ since } a_{n,n} > 0.
\]

\[
\Rightarrow \quad a_{i,n} \leq \left( \frac{1}{a_{n,n}} \right) \sum_{j=1}^{n-1} a_{n,n}, \text{ inequality reversed since } a_{i,n} \leq 0 \text{ for } i \neq n.
\]

\[
\Rightarrow \quad -a_{i,n} \geq \left( \frac{1}{a_{n,n}} \right) \sum_{j=1}^{n-1} a_{n,n}.
\]

But,

\[
\begin{align*}
a_{i,n} \sum_{j=1}^{n-1} \frac{a_{i,n}}{a_{n,n}} &= \frac{a_{i,n}}{a_{n,n}} \sum_{j=1}^{n-1} a_{n,n} + \frac{a_{i,n}}{a_{n,n}} \sum_{j=1}^{n-1} a_{n,n} \\
&= \frac{a_{i,n}}{a_{n,n}} \sum_{j=1}^{n-1} a_{n,n} + \frac{a_{i,n}}{a_{n,n}} \sum_{j=1}^{n-1} a_{n,n}.
\end{align*}
\]
\[
\begin{align*}
&\frac{a_{i,n}^{n-1}}{a_{n,n}^{i}} \geq \sum_{j=i}^{n-1} a_{n,j} \geq 0 .
\end{align*}
\]

Therefore, 
\[-a_{i,n} \geq \frac{a_{i,n}^{n-1}}{a_{n,n}^{i}} \sum_{j=i}^{n-1} a_{n,j} \geq 0 .\]  \(5.1\)

Also, \(a_{i,i} > \sum_{j>i} a_{i,j}\), since \(A\) is type 1.

\[
\Rightarrow a_{i,i} + a_{i,n} > \sum_{j>i}^{n-1} a_{i,j}, \text{ since } i \neq n .
\]  \(5.2\)

From inequalities, 5.1 and 5.2, it follows that:

\[
\begin{align*}
a_{i,i} + a_{i,n} - a_{i,n} &> \sum_{j>i}^{n-1} a_{i,j} + \frac{a_{i,n}^{n-1}}{a_{n,n}^{i}} \sum_{j>i}^{n-1} a_{n,j} .
\end{align*}
\]

\[
\Rightarrow a_{i,i} > \sum_{j>i}^{n-1} \left( a_{i,j} - \frac{a_{i,n}a_{n,j}}{a_{n,n}} \right) + \frac{a_{i,n}}{a_{n,n}} a_{n,i}
\]

\[
\Rightarrow a_{i,i} - \frac{a_{i,n}}{a_{n,n}} a_{n,i} > \sum_{j>i}^{n-1} \left( a_{i,j} - \frac{a_{i,n}}{a_{n,n}} a_{n,j} \right)
\]

\[\Rightarrow \frac{a_{i,n}}{a_{n,n}} a_{n,i} = -\sum_{j>i}^{n-1} \left( a_{i,j} - \frac{a_{i,n}}{a_{n,n}} a_{n,j} \right), \text{ since } a_{i,n} - \frac{a_{i,n}}{a_{n,n}} a_{n,n} = 0 .\]

This completes the proof of part (3) and therefore completes the proof of proposition 1.

In the proof, the fact that \(a_{n,n}\) is positive while the \(a_{n,j}\)'s are non-positive for \(j \neq n\) is sufficient to guarantee that the elementary operations are performed by non-negative matrices.
Since a type 1 matrix is defined in terms of row properties, it follows that the upper left-hand \((n-1)\) by \((n-1)\) matrix,

\[ A_{n-1} = (a_{i,j}^{(n-1)}) \text{ where } a_{i,j}^{(n-1)} = b_{i,j}, \]

is also a type 1 matrix. This is immediate since \(b_{i,n} = 0\) for \(i \neq n\) and \(a_{n-1,n-1} = b_{n-1,n-1} > b_{n-1,n} = 0\), by property 3 of the definition. This result is used in the following proposition.

**PROPOSITION 2**

If \(A\) is a type 1, \(n \times n\) matrix, there exists a matrix \(L\), consisting of non-negative elements, such that \(LA\) is a lower triangular type 1 matrix.

**PROOF:** Since \(A\) is a type 1 matrix, it can be reduced as in proposition 1. The upper left-hand \(n-1\) square sub-matrix is type 1 and can then be reduced by the technique in proposition 1. This process can be continued on the successive sub-matrices until \(A\) has been reduced to lower triangular form. Since in each reduction, the pivot element is positive while the elements above the pivot element are non-positive, all elementary matrices involved in the reductions are non-negative matrices.

Q.E.D.

In this triangularization it is not necessary to multiply the first row of the matrix \(A\). An additional result of this scheme is that the diagonal elements of the lower triangular form are all positive, indicating that a type 1 matrix is non-singular. This serves as an alternate method of establishing the existence of the inverses used in developing both models.
5.2 Definition 2 - Type 2 Matrix

An n by n type 2 matrix is a type 1 matrix having the following form:
\[
\begin{bmatrix}
    a + (1-\theta f) & -(1-\theta f) & 0 & \ldots & 0 & 0 & 0 & 0 \\
    -(1-f) & a + (1-f) + (1-\theta^2 f) & -(1-\theta^3 f) & \ldots & 0 & 0 & 0 & 0 \\
    0 & -(1-\theta f) & a + (1-\theta f) + (1-\theta^3 f) & \ldots & 0 & 0 & 0 & 0 \\
    \ddots & \ddots & \ddots & \ddots & \ddots & \ddots & \ddots & \ddots \\
    0 & 0 & 0 & \ldots & a + (1-\theta^{n-4} f) & -(1-\theta^{n-2} f) & 0 \\
    & & & & & & & \\
    & & & & & & & \\
    & & & & & & & \\
    0 & 0 & 0 & \ldots & -(1-\theta^{n-3} f) & [a + (1-\theta^{n-3} f) + (1-\theta^{n-1} f)] & -(1-\theta^{n-1} f) & \\
    0 & 0 & 0 & \ldots & 0 & -(1-\theta^{n-2} f) & a + (1-\theta^{n-2} f) & \\
\end{bmatrix}
\]
where \(|\theta| \leq 1, |f| \leq 1\),

that is, \(m_{1,1} = a + (1-\theta f)\); \(a > 0\)

\[ m_{2,1} = -(1-f) \]

\[ m_{i,i-1} = -(1-\theta^{i-2}f) \quad ; \quad 2 < i < n \]

\[ m_{i,i+1} = -(1-\theta^i f) \quad ; \quad 1 < i < n \]

\[ m_{i,i} = a + (1-\theta^{i-2}f) + (1-\theta^i f) \quad ; \quad a > 0; 1 < i < n \]

\[ m_{n,n} = a + (1-\theta^{n-2}f) \quad ; \quad a > 0. \]

This matrix may be lower triangularized according to the scheme for type 1 matrices. It may be verified that this lower triangular matrix is of the form:

\[
\begin{bmatrix}
  d_n & 0 & 0 & \ldots & 0 & 0 & 0 \\
-(1-f) & d_{n-1} & 0 & \ldots & 0 & 0 & 0 \\
0 & -(1-\theta f) & d_{n-2} & \ldots & 0 & 0 & 0 \\
\vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\
0 & 0 & 0 & \ldots & d_3 & 0 & 0 \\
0 & 0 & 0 & \ldots & -(1-\theta^{n-3}f) & d_2 & 0 \\
0 & 0 & 0 & \ldots & 0 & -(1-\theta^{n-2}f) & d_1 \\
\end{bmatrix}
\]
where \[ d_1 = a + (1 - \theta^{n-2} f) \]

\[ d_2 = a + (1 - \theta^{n-3} f) + (1 - \theta^{n-1} f) - \frac{(1 - \theta^{n-2} f)(1 - \theta^{n-1} f)}{d_1} \]

\[ \vdots \]

\[ d_i = a + (1 - \theta^{n-i-1} f) + (1 - \theta^{n-i+1} f) - \frac{(1 - \theta^{n-i} f)(1 - \theta^{n-i+1} f)}{d_{i-1}} \]

\[ \vdots \]

\[ d_n = a + (1 - \theta f) - \frac{(1 - \theta f)(1 - f)}{d_{n-1}}. \]

Since a type 2 matrix is a type 1 matrix, the lower triangular matrix is still a type 1 matrix. Therefore, it follows that

\[ 0 \leq 1 - \theta^{n-i} f < d_{i-1} \text{ and } 0 \leq \frac{(1 - \theta^{n-i} f)}{d_{i-1}} < 1 \quad \text{for } 1 < i \leq n. \]

These inequalities and the previous equations give the following bounds for the diagonal elements of the lower triangular matrix:

\[ a + (1 - \theta^{n-i-1} f) \leq d_i < a + (1 - \theta^{n-i-1} f) + (1 - \theta^{n-i+1} f) \quad \text{for } 1 < i < n \]

and

\[ a < d_n < a + (1 - \theta f). \]

It is useful to consider how these iterative formulas propagate errors in the calculation of \( d_1 \). Suppose that \( \hat{d}_{i-1} = d_{i-1} + h \).
Let \( d_1 = a^+(1 - \theta^{n-1} f) + (1 - \theta^{n-1} f) \cdot \frac{(1 - \theta^{n-1} f)(1 - \theta^{n-1} f)}{d_{i-1}} \).

Thus \( \hat{d}_1 - d_1 = (1 - \theta^{n-1} f)(1 - \theta^{n-1} f)[\frac{1}{d_{i-1}} - \frac{1}{\hat{d}_{i-1}}] \]

\[ = \frac{(1 - \theta^{n-1} f)(1 - \theta^{n-1} f)}{d_{i-1} \hat{d}_{i-1}} \cdot h. \]

This permits the calculation of the fraction error,

\[ \frac{\hat{d}_1 - d_1}{d_1} = \frac{(1 - \theta^{n-1} f)}{\hat{d}_{i-1}} \cdot \frac{(1 - \theta^{n-1} f)}{d_{i-1}} \cdot \frac{h}{d_{i-1}}. \]

Since it has already been established that \( a^+(1 - \theta^{n-1} f) < d_{i-1} \)
\( < a^+(1 - \theta^{n-1} f) + (1 - \theta^{n-1} f) \), it is reasonable to require that
\( a^+(1 - \theta^{n-1} f) \leq \hat{d}_{i-1} \leq a^+(1 - \theta^{n-1} f) + (1 - \theta^{n-1} f) \). With this requirement, and the bounds upon \( d_1 \), it follows that:

\[ \frac{\hat{d}_1 - d_1}{d_1} < \frac{1}{a + 1} \cdot \frac{1}{a + 1} \cdot \frac{h}{d_{i-1}} < \frac{h}{d_{i-1}}. \]

Under these conditions it also follows that
\( a^+(1 - \theta^{n-1} f) < \hat{d}_1 < a^+(1 - \theta^{n-1} f) + (1 - \theta^{n-1} f) \) since

\[ \frac{(1 - \theta^{n-1} f)(1 - \theta^{n-1} f)}{\hat{d}_{i-1}} \leq \frac{(1 - \theta^{n-1} f)(1 - \theta^{n-1} f)}{a^+(1 - \theta^{n-1} f)} < (1 - \theta^{n-1} f). \]

These two results show that, if \( d_1 \) is approximated by \( \hat{d}_1 \) which
is sufficiently close, the percentage error in the calculations for
succeeding diagonal elements through the iterative formulas decreases.
In order to consider how these diagonal elements depend upon
the dimension of the matrix it is convenient to use a superscript to
indicate the dimension of the matrix. This notation, and the previous
iterative equations, give:

\[
\begin{align*}
d_{n-1}^{(n)} &= a + (1-\theta^{i-1})f + (1-\theta^{i+1})f - \frac{(1-\theta^{i}f)(1-\theta^{i+1}f)}{d_{n-i-1}^{(n)}} \quad \text{for } 1 < n-i < n \\
d_{n+1}^{(n+1)} &= a + (1-\theta^{i-1})f + (1-\theta^{i+1})f - \frac{(1-\theta^{i}f)(1-\theta^{i+1}f)}{d_{n+1-i-1}^{(n+1)}} \quad \text{for } 1 < n+1-i < n+1 \\
d_1^{(n)} &= a + (1-\theta^{n-2})f \\
d_1^{(n+1)} &= a + (1-\theta^{n-1})f \\
d_n^{(n)} &= a + (1-\theta f) - \frac{(1-\theta f)(1-f)}{d_{n-1}^{(n)}} \\
d_{n+1}^{(n+1)} &= a + (1-\theta f) - \frac{(1-\theta f)(1-f)}{d_{n}^{(n+1)}}.
\end{align*}
\]

PROPOSITION 3

With the above notations, \(d_{n+1}^{(n+1)} > d_n^{(n)}\) and \(d_{n+1-i}^{(n+1)} > d_{n-i}^{(n)}\).

PROOF:

\[
d_{n+1}^{(n+1)} - d_n^{(n)} = \frac{(1-\theta f)(1-f)}{d_{n-1}^{(n)}d_n^{(n+1)}} \left[ d_n^{(n+1)} - d_{n-1}^{(n)} \right].
\]
Thus to establish that \( d_{n+1}^{(n+1)} > d_{n}^{(n)} \), it suffices to show that
\[
d_{n+1-i}^{(n+1)} - d_{n-i}^{(n)} > 0.
\]

\[
d_{n+1-i}^{(n+1)} - d_{n-i}^{(n)} = \frac{(1-\theta^n_f)(1-\theta^{i+1}_f)}{d_{n-i-1}^{(n)} d_{n-i}^{(n+1)}} \left[ d_{n-i}^{(n+1)} - d_{n-i-1}^{(n)} \right].
\]

Thus to establish that \( d_{n+1-i}^{(n+1)} > d_{n-i}^{(n)} \) by induction, it suffices to show that \( d_{2}^{(n+1)} > d_{1}^{(n)} \).

\[
d_{2}^{(n+1)} - d_{1}^{(n)} = \left[ a+(1-\theta^{n-2}_f) + (1-\theta^n_f) - \frac{(1-\theta^{n-1}_f)(1-\theta^n_f)}{a+(1-\theta^{n-1}_f)} \right]
- [a+(1-\theta^{n-2}_f)]
\]

\[
= \frac{a(1-\theta^n_f)}{a+(1-\theta^{n-1}_f)} > 0.
\]

Q.E.D.

Since it has already been established that \( d_{n}^{(n)} \) and \( d_{n-i}^{(n)} \) are bounded above, this proposition is sufficient to guarantee that
\[
\lim_{n \to \infty} d_{n}^{(n)} \quad \text{and} \quad \lim_{n \to \infty} d_{n-i}^{(n)}
\]
exist.
5.3 **Definition 3 - Type 3 Matrix**

A type 3 matrix is of the form:

\[
\begin{bmatrix}
  a_{1,1} & -a_{1,1} & 0 & 0 & 0 & \ldots & 0 & 0 & 0 \\
  -a_{2,1} & a_{2,2} & -1 & 0 & 0 & \ldots & 0 & 0 & 0 \\
  0 & -1 & a+2 & -1 & 0 & \ldots & 0 & 0 & 0 \\
  0 & 0 & -1 & a+2 & -1 & \ldots & 0 & 0 & 0 \\
  \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\
  0 & 0 & 0 & 0 & 0 & \ldots & a+2 & -1 & 0 \\
  0 & 0 & 0 & 0 & 0 & \ldots & -1 & a+2 & -1 \\
  0 & 0 & 0 & 0 & 0 & \ldots & 0 & -p & a+p \\
\end{bmatrix}
\]

where all parameters are positive and \( p = 1 \) or 2.

That is,

\[
m_{i,i} = a+2, \ a > 0
\]

\[
m_{i,i-1} = m_{i,i+1} = -1, \text{ except for } i=1, 2 \text{ or } n.
\]

\[
m_{2,3} = -1
\]

\[
m_{n,n-1} = -1 \text{ or } -2
\]

\[
m_{n,n} = a - m_{n,n-1}
\]

\[
m_{1,1}; m_{2,2} > 0; \ m_{1,2} \text{ and } m_{2,1} < 0.
\]
As with a type 2 matrix, a type 3 matrix may be reduced to the form:

\[
\begin{pmatrix}
  a_{1,1} & -a_{1,2} & 0 & 0 & \ldots & 0 & 0 & 0 \\
  -a_{2,1} & a_{2,2} & -1 & 0 & \ldots & 0 & 0 & 0 \\
  0 & -1 & d_{n-2}^{(n)} & 0 & \ldots & 0 & 0 & 0 \\
  0 & 0 & -1 & d_{n-3}^{(n)} & \ldots & 0 & 0 & 0 \\
  \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\
  0 & 0 & 0 & 0 & \ldots & d_3^{(n)} & 0 & 0 \\
  0 & 0 & 0 & 0 & \ldots & -1 & d_2^{(n)} & 0 \\
  0 & 0 & 0 & 0 & \ldots & 0 & -p & d_1^{(n)} \\
\end{pmatrix}
\]

It may be verified that:

\[
d_1^{(n)} = a + p
\]

\[
d_2^{(n)} = a + 2 - \frac{p}{d_1^{(n)}}
\]

\[
\vdots
\]

\[
d_i^{(n)} = a + 2 - \frac{1}{d_{i-1}^{(n)}}
\]

\[
\vdots
\]

\[
d_{n-2}^{(n)} = a + 2 - \frac{1}{d_{n-3}^{(n)}}
\]
PROPOSITION 4

For a type 3 matrix, \( d^{(n)}_i > d^{(n)}_{i-1} \) for \( i \geq 3 \).

PROOF: \[
d^{(n)}_1 - d^{(n)}_{i-1} = [a + 2 - \frac{1}{d^{(n)}_{i-1}}] - [a + 2 - \frac{1}{d^{(n)}_{i-2}}] = \frac{d^{(n)}_{i-1} - d^{(n)}_{i-2}}{d^{(n)}_{i-1} d^{(n)}_{i-2}}
\]

if \( p = 1 \) then \[
d^{(n)}_2 - d^{(n)}_1 = [a + 2 - \frac{1}{a+1}] - [a+1] = 1 - \frac{1}{a+1} = \frac{a+1-1}{a+1} = \frac{a}{a+1} > 0
\]

if \( p = 2 \) then \[
d^{(n)}_3 - d^{(n)}_2 = [a + 2 - \frac{(a+2)}{(a+2)^2 - 2}] - [a+2 - \frac{2}{a+2}] = (a+2)^2 - 4
\]

This completes the proof by induction. Q.E.D.

PROPOSITION 5

For a type 3 matrix, the sequence \( d^{(n)}_{n-2} \) is convergent and the limit is \( \frac{a+2 + \sqrt{a^2 + 4a}}{2} \).

PROOF: By inspection it follows that each \( d^{(n)}_i \) is bounded above by \( a+2 \). Moreover by construction it may be seen that

\[
d^{(n+1)}_1 = d^{(n)}_1
\]

\[
d^{(n+1)}_2 = d^{(n)}_2
\]
\[ d_{i}^{(n+1)} = d_{i}^{(n)} \]

\[ d_{n+1-3}^{(n+1)} = d_{n-2}^{(n)} \]

From proposition 4 it follows that

\[ d_{n+1-2}^{(n+1)} > d_{n+1-3}^{(n+1)} \]

Therefore

\[ d_{n+1-2}^{(n+1)} > d_{n-2}^{(n)} \]

and since all terms in the sequence are bounded above it follows that the sequence \( \{ d_{n-2}^{(n)} \} \) converges.

In order to determine this limit it suffices to observe that

\[ d_{n+1-2}^{(n+1)} = a + 2 - \frac{1}{d_{n+1-3}^{(n+1)}} \]

\[ = a + 2 - \frac{1}{d_{n-2}^{(n)}} \]

Using this iterative formula to evaluate the limit, denoted as \( d_{-2} \), gives:

\[ d_{-2} = a + 2 - \frac{1}{d_{-2}} \]
Employing the quadratic formula gives:

\[ d_{-2} = \frac{a + 2 \pm \sqrt{a^2 + 4a}}{2} \]

Since \[ d_{-2} > d_{1}^{(n)} = a + p > \frac{a + 2 - \sqrt{a^2 + 4a}}{2} \]

it follows that

\[ d_{-2} = \frac{a + 2 + \sqrt{a^2 + 4a}}{2} \]

Q.E.D.

The following corollaries to proposition 5 involve extensions of the triangularization for special cases of a type 3 matrix.

**COROLLARY 1:** If \( a_{2,2} = a + 2 \) then the sequence \( \{d_{n-1}^{(n)}\} = \{a + 2 - \frac{1}{d_{n-2}}\} \)

converges to the limit \( d_{-1} = \frac{a + 2 + \sqrt{a^2 + 4a}}{2} \).

**PROOF:** It was shown in proposition 5 that the sequence \( \{d_{n-2}^{(n)}\} \)

converges, therefore \( \{d_{n-1}^{(n)}\} \) converges. Using the limit of the \( d_{n-2}^{(n)} \) sequence to evaluate \( d_{-1} = a + 2 - \frac{1}{d_{-2}} \) completes the proof.

Q.E.D.

**COROLLARY 2:** If \( a_{1,2} = a_{2,1} = 1 \)

\[ a_{2,2} = a + 2 \]

and \( a_{1,1} = a' + a + 1 \)
then the sequence \( \{d_n^{(n)}\} = \{a' + a + 1 - \frac{1}{d_{n-1}^{(n)}}\} \) converges to
\[
d = a' + \frac{a + \sqrt{a^2 + 4a}}{2}.
\]

PROOF: Corollary 1 established that \( \{d_{n-1}^{(n)}\} \) converged, therefore \( \{d_n^{(n)}\} \) is convergent. Observing that
\[
d = \lim_{n \to \infty} \left[ (a' - 1) + a + 2 - \frac{1}{d_{n-1}^{(n)}} \right]
\]
\[
= \left[ (a' - 1) + a + 2 + \frac{\sqrt{a^2 + 4a}}{2} \right]
\]
\[
= a' + \frac{a + \sqrt{a^2 + 4a}}{2}
\]
completes the proof.

Q.E.D.

The properties defining a type 1 matrix are essentially row properties of the matrix. The following type of matrix is a type 1 matrix but has an additional property that applies to the columns of the matrix.

5.4 Definition 4 - Type 4 Matrix

An \( n \times n \) matrix \( A = (a_{i,j}) \) is said to be a type 4 matrix if \( A \) is a type 1 matrix satisfying the additional constraint that
\[
a_{i,i} > -\sum_{j=1}^{n} a_{j,i}.
\]

The following proposition is a modification of proposition 1 for type 1 matrices.
PROPOSITION 6

Let \( A = (a_{i,j}) \) be a type 4 matrix. Let \( B = (b_{i,j}) \) be the \( n \times n \) matrix formed from \( A \) by leaving the \( n^{th} \) row unchanged and eliminating all elements in column \( n \), other than \( a_{n,n} \), by elementary operations. Let \( C = (c_{i,j}) \) be the upper left hand \((n-1)\) square matrix contained in \( B \). Then \( C \) is a type 4 matrix.

PROOF: It has already been established in proposition 1 that \( B \) is a type 1 matrix. Since the type 1 properties are row properties and the first \( n-1 \) entries in column \( n \) of matrix \( B \) are zero it follows that \( C \) is a type 1 matrix. Therefore it suffices to show that

\[
\sum_{j=1}^{n-1} c_{i,j} > \sum_{j=1}^{n-1} c_{j,i}.
\]

As in the proof of proposition 1 it follows that

\[
c_{i,j} = b_{i,j} = a_{i,j} - \frac{a_{i,n}}{a_{n,n}} a_{n,j}.
\]

Therefore it must be shown that

\[
a_{i,i} - \frac{a_{i,n}}{a_{n,n}} a_{n,i} - \sum_{j=1}^{n-1} \left( a_{j,i} - \frac{a_{j,n}}{a_{n,n}} a_{n,i} \right) > \sum_{j=1}^{n-1} a_{j,i} + \sum_{j=1}^{n-1} \frac{a_{j,n}}{a_{n,n}} a_{n,i}.
\]

or

\[
a_{i,i} > \sum_{j=1}^{n-1} a_{j,i} + \sum_{j=1}^{n-1} \frac{a_{j,n}}{a_{n,n}} a_{n,i}.
\]

Since \( A \) is a type 4 matrix:

\[
\sum_{j=1}^{n-1} a_{n,n} > \sum_{j=1}^{n-1} a_{j,n}.
\]

\[
=> 1 > \sum_{j=1}^{n-1} \frac{a_{j,n}}{a_{n,n}}.
\]
\[ \Rightarrow -a_{n,i} > \sum_{j=1}^{n-1} \frac{a_{j,n} a_{n,i}}{a_{n,n}} , \text{ since } a_{n,i} \leq 0. \]

Also since $A$ is type 4:

\[ a_{i,i} > -\sum_{j=1}^{n-1} a_{i,j} = -\sum_{j=1}^{n-1} a_{j,i} - a_{n,i}. \]

Therefore

\[ a_{i,i} > -\sum_{j=1}^{n-1} a_{i,j} - a_{n,i} > -\sum_{j=1}^{n-1} a_{j,i} + \sum_{j=1}^{n-1} \frac{a_{j,n} a_{n,i}}{a_{n,n}}. \]

completing the proof.

The following proposition regarding the triangularization of type 4 matrices is a modification of proposition 2 for type 1 matrices.

**PROPOSITION 7**

If $A$ is a type 4, $n \times n$ matrix, there exists a matrix $L$ consisting of non-negative elements such that $LA$ is a lower triangular type 1 matrix.

Moreover, the first row of $L$ has a 1 in the first position and all other elements in the first row are non-negative numbers less than 1.

**PROOF:** That $L$ consists of non-negative elements and $LA$ is a lower triangular type 1 matrix are immediate results of proposition 2 for type 1 matrices. Therefore it is sufficient to show that the off-diagonal elements of $L$ are less than 1.
The matrix $L$ may be written as the product of $(n-1)$ matrices 

$$L = L^{(2)} L^{(3)} \ldots L^{(n)}$$

where the matrix $L^{(k)}$ eliminates all elements above the diagonal in column $k$ of the matrix $L^{(k+1)} L^{(k+2)} \ldots L^{(n)}$. Let $A^{(k)} = (a_{i,j}^{(k)}) = L^{(k+1)} \ldots L^{(n)} A$. From the previous proposition it follows that the upper left hand $k \times k$ submatrix of $A^{(k)}$ is a type 4 matrix and therefore

$$\sum_{j=1}^{k-1} a_{j,k}^{(k)} < a_{k,k}^{(k)}.$$

By construction, $L^{(k)}$ is an upper triangular matrix with:

$$\xi_{i,i}^{(k)} = 1$$

$$\xi_{i,k}^{(k)} = - \frac{a_{i,k}^{(k)}}{a_{k,k}^{(k)}} \quad \text{for } i = 1, \ldots, k-1.$$

Therefore, since type 4 matrices are diagonally dominant,

$$\sum_{i=1}^{k-1} \xi_{i,k}^{(k)} < 1.$$

This establishes that the off-diagonal elements of $L^{(k)}$ are less than 1 and that $L^{(k)}$ is diagonally dominant.

To examine the first row of $L$ it is convenient to pre-multiply $L$ by the vector $e_1'$ whose only non-zero element is a 1 in the first position. This premultiplication is equivalent to

$$e_1' L^{(2)} L^{(3)} \ldots L^{(n)}.$$. 
Let

\[(1) h' = \xi_1 L^{(2)} \ldots L^{(i)} .\]

It follows that

\[(2) h' = [1 \quad L^{(2)}_{1,2} \quad 0 \ldots 0] .\]

Observing the properties of this vector, the proof may be completed by induction. Assume that \((1)^{h'}_i\) has the following properties:

1. The first element is equal to 1.
2. At most, only the first \(i\) elements are non-zero.
3. All elements, other than the first, are less than 1.

Now consider

\[(i+1)^{h'} = (1)^{h'}_i L^{(i+1)} .\]

Recalling that \(L^{(i+1)}\) is an upper triangular matrix whose only non-zero element in the first column is a 1 in the first position, it follows that \((i+1)^{h'}_i\) has a 1 in the first position.

Since the elements below the diagonal of \(L^{(i+1)}\) are zero and only the first \(i\) elements of \((1)^{h'}_i\) are non-zero it follows that, at most, only the first \((i+1)\) elements of \((i+1)^{h'}_i\) may be non-zero.

From the structure of these matrices and vectors it suffices to show that element \((i+1)\) of \((i+1)^{h'}_i\) is less than 1. This element may be written as:

\[L^{(i+1)}_{1,i+1} (1)^{h'}_1 + L^{(i+1)}_{2,i+1} (1)^{h'}_2 + \ldots + L^{(i+1)}_{1,i+1} (1)^{h'}_{i+1} .\]
Since the elements of \((i)\mathbf{h}\) are less than or equal to 1 and it has been shown that \(\sum_{j=1}^{i} t_{i,j}^{(i+1)} < 1\) it follows that the \(i+1\) element of \((i+1)\mathbf{h}\) is less than 1. This completes the proof that \((i)\mathbf{h}'\) has these properties for \(i = 2, \ldots, n\) and since this holds for \((n)\mathbf{h}'\) this completes the proof of the proposition. Q.E.D.