MATHEMATICAL ANALYSIS OF BLOOD FLOW AND OXYGEN TRANSPORT IN MICROCIRCULATION

By

Jun Liu

A DISSERTATION

Submitted to Michigan State University in partial fulfillment of the requirements for the degree of

Applied Mathematics - Doctor of Philosophy

2020

ABSTRACT

MATHEMATICAL ANALYSIS OF BLOOD FLOW AND OXYGEN TRANSPORT IN MICROCIRCULATION

By

Jun Liu

This dissertation presents a mathematical analysis of oxygen convection, diffusion and consumption in a uniform and multi-capillary muscle tissue region. Capillaries are tiny vessels connecting arterioles with venules and forming networks through out the body. The diffusion of substrate, such as oxygen, from the microcirculation through capillaries and the its consumption by tissue cells are basic in human physiology. Blockage or shortage of blood in one or more capillaries due to thrombosis or systemic hypoperfusion could lead to pathological conditions such as stroke. However, transient process of capillary-tissue oxygen transport is poorly understood. The object of this thesis is to develop a mathematical and computationally efficient model that estimates transient oxygen concentration in three dimensional striated muscles (e.g. cardiac muscle), which is a four dimensional unsteady convection-diffusion-consumption moving boundary problem. In particular, we aim to simulate the consequential stages of pathological conditions such as hyperoxia or hypoxia, by determining oxygen concentration levels and its transport in order to better understand and predict adverse health effects. Our computational method is based on a compartmental modeling concept. It is simple, efficient and can be applied to boundaries of arbitrary shape. In Chapter 1 the problem is introduced. In Chapter 2 the discrete compartmental modeling is described. In Chapter 3 the discrete compartmental method is developed for 1D and 2D problems. In Chapter 4 the method is extended to 3D problems and is used to simulate the development and the recovery process of anoxia. In Chapter 5 theoretical analysis of the method is given. Chapter 6 contains discussions, conclusion and possible future work.

Copyright by JUN LIU 2020 I dedicate this dissertation to my parents, Shaojun Chen and Dr. Tieliang Liu, my husband Dr. Kaixu Yang, and many friends, who all have been supporting me during this hard time.

ACKNOWLEDGMENTS

Here, I would like to express my deepest gratitude to my advisor Dr. Chang Yi Wang for his guidance towards my studies and researches. Dr. Wang is extremely kind and knowledgeable. He always provide constructive insights and suggestions that help me make great progress. Without Dr. Wang's guidance, I wouldn't be able to have such a profound understanding in this gorgeous field.

I would also like to extend my sincere appreciation to my dissertation committee members, Dr. Milan Miklavcic, Dr. Moxun Tang and Dr. Guowei Wei. Their comments and suggestions are extremely beneficial for my research.

I am also grateful to the help I obtained from all the professors in the Department of Mathematics, both academically and in other aspects. During my Ph.D. life, I learn a lot from the courses offered by these excellent professors, and I'm able to apply the knowledge I learn to my research. The professors who I have worked with as a teaching assistant also impress me a lot by the way they deal with different kinds of difficulties.

During my Ph.D. life, I made a lot of friends and I never feel lonely because of them. Many thanks to my friends at Michigan State University. They either have graduated and become successful faculty members or scientists in big companies, or are still working hard pursuing their Ph.D. degree. I sincerely wish all of them a wonderful future.

Last but not least, I would like to express my sincere thanks to my parents for their support and concerns, as well as my husband for his accompany and encouragements.

TABLE OF CONTENTS

LIST O	OF TABLES	ix
LIST O	OF FIGURES	xi
KEY T	O SYMBOLS	xiv
KEY T	O ABBREVIATIONS	xvi
Chapte	er 1 Introduction	1
1.1	Biological Background	3
1.2	Literature Review	6
1.3	Objectives and Plan of the Current Research	14
Chapte	er 2 Discrete Compartment Method (DCM)	16
2.1	Idea of the Model	17
2.2	Multi-capillary Oxygen Transport in Striated Muscle	18
	2.2.1 The General Problem	18
	2.2.2 Assumptions	19
2.3	Discrete Compartmental Systems	20
2.0	2.3.1 Basic Terms and Definitions	$\frac{-}{21}$
	2.3.2 Graphic Representation	25
2.4	Application of the DCM	$\frac{20}{27}$
2.4 2.5	Discussion and Comparison with Previous Models	31^{21}
Chapte	er 3 Unsteady Diffusion-Consumption-Convection	36
3.1	One Dimensional Unsteady Diffusion-Consumption	36
0.1	3.1.1 Formulation	38
	3.1.2 The Crank-Gupta Problem	47
	31.3 Three Capillaries of Uneven Strength	54
3.2	Two Dimensional Unsteady Diffusion-Consumption	59
0.2	3.2.1 Formulation	61
	3.2.2 Two capillaries of uneven strength in a circular domain	70
	3.2.3 Nine capillaries of uneven strength in a rectangular domain	74
2 2	Two Dimensional Unsteady Diffusion-Consumption-Convection	77
0.0	3.3.1 Formulation: The Space and Time Step Matching Technique	80
	3.3.2 A Simplified Model. Unsteady	00
	Convection Permettion Consumption	ວາ
	3.3.3 Unsteady Convection-Diffusion-Consumption	82 88
Chart	m 4 The Three Dimensional Madeling	0.0
Unapte	er 4 Ine Inree Dimensional Modeling	96
4.1	Three-Dimensional Unsteady Diffusion-Consumption-Convection	96

4.1.1	Formulation
4.1.2	Three capillaries of uneven strength in a cuboid domain 105
4.1.3	The Krogh Tissue Cylinder
Simula	ating 3D Multi-Capillary Oxygen Transport using DCM 113
4.2.1	Anoxia Following Capillary Occlusion
	4.2.1.1 Recovery Through Eliminating Capillary Blockage 121
	4.2.1.2 Recovery Through Decreasing Consumption Rate 123
	4.2.1.3 Recovery Through Increasing Capillary Blood Velocity 125
	4.2.1.4 Recovery Through Increasing Oxygen Concentration in Blood 127
4.2.2	Anoxia Following Increased Tissue Oxygen Consumption
	4.2.2.1 Recovery Through Decreasing the Consumption Rate 131
	4.2.2.2 Recovery Through Increasing Capillary Blood Velocity 133
	4.2.2.3 Recovery Through Increasing Oxygen Concentration in Blood 136
. n 5	
er o	The Analytic Theory of the Discrete Compartmental Method 138
Numer	The Analytic Theory of the Discrete Compartmental Method 138 rical Error
Numer Conve	rical Error
Numer Conve	The Analytic Theory of the Discrete Compartmental Method 138 rical Error 139 rgence 141
Numer Conve	The Analytic Theory of the Discrete Compartmental Method 138 rical Error 139 rgence 141 Conclusions 151
Numer Conve er 6 Discus	The Analytic Theory of the Discrete Compartmental Method 138 rical Error 139 rgence 141 Conclusions 151 sion 151
Numer Conve er 6 Discus	The Analytic Theory of the Discrete Compartmental Method 138 rical Error 139 rgence 141 Conclusions 151 sion 151 Works 153
Numer Conve er 6 Discus Future	The Analytic Theory of the Discrete Compartmental Method 138 rical Error 139 rgence 141 Conclusions 151 ssion 151 e Works 153
Numer Conve er 6 Discus Future	The Analytic Theory of the Discrete Compartmental Method 138 rical Error 139 rgence 141 Conclusions 151 ssion 151 e Works 153 153
Numer Conve er 6 Discus Future NDIX	The Analytic Theory of the Discrete Compartmental Method 138 rical Error 139 rgence 141 Conclusions 151 ssion 151 e Works 153
	 4.1.2 4.1.3 Simula 4.2.1 4.2.2

LIST OF TABLES

Table 3.1:	1D schematic diagram of different type of boundaries and their labels. Label "BC21" = the left boundary compartment and label "BC12" = the right boundary compartment. "CC1" = capillary compartment of the $(m = 1)$ capillary. "IC" = inactivated compartment	46
Table 3.2:	Index table of different types of compartments. The corresponding relation- ships of the compartment label and the coefficients is given. Label " CCm " represents the <i>m</i> th capillary compartments, label "TC" represents the inte- rior tissue compartments, label "BC21" represents the left boundary com- partment and label "BC12" represents the right boundary compartment. K indicates the value of the consumption term.	47
Table 3.3:	Compartmental map for the Crank-Gupta problem.	50
Table 3.4:	Comparison for $C \times 10^6$ at different times. On each time level, the first row shows values taken from Hansen & Hougaard [29], the second row shows values from Crank and Gupta [12] with $\Delta x = 0.05$, the third row gives values obtained from DCM with $\Delta x = 0.05$ and the forth row the DCM with $\Delta x = 0.0125$.	51
Table 3.5:	Comparison for $C \times 10^6$ at different times. On each time level, the first row shows values taken from Hansen & Hougaard [29], the second row shows values from Crank and Gupta [12] with $\Delta x = 0.05$, the third row gives values obtained from DCM with $\Delta x = 0.05$ and the forth row the DCM with $\Delta x = 0.0125$.	52
Table 3.6:	Comparison of results at the sealed surface	53
Table 3.7:	Comparison of the oxygen depletion time with previous works. \ldots .	53
Table 3.8:	Comparison of oxygen depletion time (t^*) in different mesh size using DCM.	54
Table 3.9:	Schematic diagram of label changing following capillary blockage in the 1D example. Label "CCM" = capillary compartment corresponding to the oxygen concentration of the m^{th} capillary. "CC0" = capillary compartment corresponding to a blocked capillary.	57
Table 3.10:	Discrete compartmental map of 2D unsteady diffusion-consumption prob- lem over rectangular shaped domain. Label "TC" = tissue compartment; label "BC##"=boundary compartment of type ##; label "IC" = inacti- vated compartment	67

Table 3.11:	: Discrete compartmental map of 2D unsteady diffusion-consumption prob- lem over irregular shaped domain. Label "TC" = tissue compartment; label "BC##"=boundary compartment of type ##; label "IC" = inactivated	
	compartment	69
Table 3.12:	Locations and flux strength of nine capillaries used in the example	75
Table 3.13:	Discrete compartmental map of unsteady convection-permeation-consumption problem. Label "CC"=capillary compartment; label "CCA"=capillary compartment on the arterial end; label "CCV"=capillary compartment on the venous end; label "STC" = single layer tissue compartment; label "IC" = inactivated compartment	85
Table 3.14:	Discrete compartmental map of 2D unsteady convection-diffusion-consumption problem. Label "CC"=capillary compartment; label "CCA"=capillary compartment on the arterial end; label "CCV"=capillary compartment on the venous end; label "TC" = tissue compartment; label "CTC" = capillary neighboring tissue compartment; label "BC##"=boundary compartment of type ##; label "IC" = inactivated compartment	89
Table 4.1:	Locations and plasma oxygen concentration on the arterial end of three randomly distributed capillaries used in the example	105
Table 4.2:	Time to fully perfused (t_f) and to steady state (t_s) corresponding to different valid choices of spacial step size $(\Delta x) \ldots \ldots \ldots \ldots \ldots$	107
Table 4.3:	Convergence for concentration value $(\times 10^6)$ on a random point $(0.243, 0.525, 0.525, 0.525)$ corresponding to an interior tissue compartment for different choices of valid spacial step size (Δx)	.725) 108
Table 4.4:	Biophysical parameters used for the simulation of oxygen transport in multi-capillary tissue bed. R'_c , capillary radius; L' , capillary length; FCD, functional capillary density; v'_b , normal RBC velocity; C_a , arterial oxygen concentration; D' , tissue oxygen diffusivity; κ'_b , basal tissue oxygen consumption; κ'_{max} , maximal tissue oxygen consumption	113
Table 4.5:	Locations and plasma oxygen concentration on the arterial end of eight capillaries.	114

LIST OF FIGURES

Figure 1.1:	Top 10 global causes of deaths, 2016	5
Figure 1.2:	(a) A single Krogh Tissue Cylinder. Estimation of PO_2 within a circular cylinder of tissue surrounding a capillary of radius R_c ; r is the distance from the capillary center; R_t denotes the cylinder radius where oxygen flux becomes zero. (b) PO_2 at capillary declines monotonically both around and within the fibre. (c) Krogh's view of circular tissue cylinder stacking, where tissue supply voids are inevitable. This arrangement is also known as concurrent flow model	7
Figure 1.3:	(a) Oxygen concentration curves of seven unevenly distributed capillaries of unequal strength over a circular tissue region. Total flux given equals to total area of the circular region times the tissue oxygen consumption rate. At the point on upper right boundary, the concentration is zero. (b) The corresponding capillary supply regions.	11
Figure 3.1:	Compartmentalization, map and labels of a 1D discrete compartmental model	39
Figure 3.2:	1D compartmental model	40
Figure 3.3:	Calculation of capillary oxygen concentration after blocking the source. The three darker cells denote contiguous capillary compartments	43
Figure 3.4:	Oxygen diffusion from three capillaries of different strengths into a con- suming region at $t=0.001$, $t=0.01$ and $t=0.1$, compared with the analytic steady state solution	55
Figure 3.5:	Concentration profile at t=0.001, t=0.02 and t=0.2 times after a blockage occurred on middle capillary, compared with the analytic steady state solution. \ldots	56
Figure 3.6:	Concentration profile at t=0.002, t=0.02 and t=0.03 times after a blockage occurred on the right capillary. $\dots \dots \dots$	57
Figure 3.7:	schematic diagram of 2D planar capillary-tissue region and blockage on one capillary. Shaded area in part (b) represents the possible anoxic areas due to blockage on the right capillary.	59
Figure 3.8:	Example of 2D capillary shapes	62

Figure 3.9:	The 2D compartmental model	63
Figure 3.10:	Transient process of oxygen diffusion from two capillaries of different strengths into a circular consuming region. Dark regions show the zero oxygen area. The vertical and horizontal axes shows the compartment numbers used in each direction	72
Figure 3.11:	Transient process of oxygen diffusion from two capillaries of different strengths into a circular consuming region. Dark regions show the zero oxygen area. The vertical and horizontal axes shows the compartment numbers used in each direction	73
Figure 3.12:	Concentration profile of two unequal strength capillaries in a circular do- main, comparing to the analytic solution[68]	74
Figure 3.13:	Flux and supply boundary of two capillaries of unequal strength in a circular domain, comparing to the analytic solution [68]	74
Figure 3.14:	Oxygen concentration level curves of nine capillaries with different strengths at steady state. The vertical and horizontal axes shows the compartment numbers used in each direction.	76
Figure 3.15:	Schematic diagram for 2D capillary-tissue exchange with convection, dif- fusion and consumption with nondimensionalized parameters. v_b is the blood velocity; $D = 1$ is the normalized diffusion coefficient; κ is the tis- sue consumption coefficient; L is the length of the tissue region along the z-axis; W is the thickness of the tissue region along the x -axis; oxygen concentration on the arterial end of the capillary is normalized by itself and therefore equals to 1	78
Figure 3.16:	Lagrangian sliding fluid element method. With each Δt , oxygen in the capillary compartment slide instantaneously one segment downstream, after which the diffusion and consumption are computed.	81
Figure 3.17:	Compartment model for capillary-tissue exchange in well-perfused organ.	82
Figure 3.18:	Oxygen convection into a consuming region using a two region model. Red dots represent oxygen concentration flowing in capillary, blue dots represent oxygen concentration in adjacent tissue region with constant consumption and solid lines are analytic solutions at steady state	87
Figure 3.19:	Compartment model for capillary-tissue exchange with diffusion	88

Figure 3.20:	Concentration curves of a single capillary with blood velocity at $t=0.1$, $t=0.25$, $t=1$, $t=2.5$, $t=5$, $t=7.5$ and $t=10$. The vertical and horizontal axes shows the compartment numbers used in each direction	93
Figure 3.21:	Concentration profile on the capillary boundary and the tissue boundary, compared with the analytic solution. Circles are numerical solution of oxygen concentration on the tissue boundary. Triangles are numerical solution of oxygen concentration on the capillary wall. Solid lines represents the oxygen concentration profile obtained from the analytic solution. Horizontal axis shows the normalized capillary length and vertical axis show the normalized concentration value.	94
Figure 4.1:	A 3D compartment for deriving the difference equations for DCM	100
Figure 4.2:	Concentration profile of three capillaries of uneven strength in a cube domain at $t = 0.1$, $t = 0.2$, $t = 0.5$ and $t = 2.2$ (steady state).	106
Figure 4.3:	Convergence of the 3D algorithm on interior tissue compartments for dif- ferent choices of valid spacial step size (Δx) , at time $t = 0.1$. The vertical axis represents the concentration value $(\times 10^6)$ of the compartment and the horizontal axis is the inverse of spacial step size (Δx) . Vertical black lines divides the plane into sub-regions due to the sliding period corresponding to the compartment size. Short horizontal lines are the average of values in each rectangular region and the long horizontal line is calculated using the uniformly minimum variance unbiased estimator from the end of the smallest Δx obtained.	110
Figure 4.4:	The Krogh tissue cylinder	111
Figure 4.5:	Concentration curves of the Krogh tissue cylinder at $(C = 0.6, 0.7, 0.8, 0.9)$ at steady state from the numerical solution. The vertical and horizontal axes shows the compartment numbers used in each direction	112
Figure 4.6:	Concentration profile of the Krogh tissue cylinder on the capillary bound- ary and the tissue boundary. Circles are numerical solution of oxygen concentration on the capillary wall. Triangles are numerical solution of oxygen concentration on the tissue boundary. Solid lines represents the oxygen concentration profile obtained from the analytic solution. Hori- zontal axis shows the normalized capillary length and vertical axis show the normalized concentration value.	112

Figure 4.7:	Oxygen concentration profile of eight capillaries of uneven strength and distribution in a cuboid domain at steady state. Biophysical parameters collected in Table 4.4 is used to simulate the actual biological process. Under capillary blood velocity $1150\mu m/s$ and basal tissue oxygen consumption rate $1.67 \times 10^{-4} \text{ (ml } O_2)(\text{ml tissue})^{-1} s^{-1}$, oxygen concentration in this capillary-tissue system reaches the steady state at a normalized time of $t = 0.6$.	116
Figure 4.8:	The development of oxygen deficit by blocking one capillary closer to the middle of the tissue domain, at time $t = 0.01, 0.05, 0.1$ and 0.2. Anoxic areas are shown in white for contrast.	118
Figure 4.9:	The development of oxygen deficit by blocking one capillary near the tissue domain boundary, at time $t = 0.01, 0.05, 0.1$ and 0.2. Anoxic areas are shown in white for contrast.	120
Figure 4.10:	Recovery process of tissue oxygen distribution through unclog the blocked capillary, at time $t = 0.001, 0.05, 0.1$ and 0.2. Anoxic areas are shown in white for contrast.	122
Figure 4.11:	Recovery process of tissue oxygen distribution following a reduction of the tissue consumption, at time $t = 0.001, 0.05, 0.1$ and 0.2. Anoxic areas are shown in white for contrast.	124
Figure 4.12:	Recovery process following an increment in the capillary blood velocity, at time $t = 0.001, 0.05, 0.1$ and 0.2. Anoxic areas are shown in white for contrast.	126
Figure 4.13:	Recovery process of tissue oxygen distribution following increasing oxygen concentration in the arterial blood, at time $t = 0.001, 0.05, 0.1$ and 0.2. Anoxic areas are shown in white for contrast.	128
Figure 4.14:	The development of oxygen deficit by increasing the tissue oxygen con- sumption rate, at time $t = 0.01, 0.05, 0.1$ and 0.2. Anoxic areas are shown in white for contrast.	130
Figure 4.15:	Recovery process of tissue oxygen distribution following reducing the tis- sue consumption rate to original state, at time $t = 0.001, 0.05, 0.1$ and 0.2. Anoxic areas are shown in white for contrast.	132
Figure 4.16:	Recovery process of tissue oxygen distribution following increasing the capillary blood velocity to $1500 \mu m/s$, at time $t = 0.001, 0.01, 0.05$ and 0.1. Anoxic areas are shown in white for contrast.	134

Figure 4.17:	Recovery process of tissue oxygen distribution following doubling the cap-	
	illary blood velocity, at time $t = 0.001, 0.01, 0.05$ and 0.1. Anoxic areas are shown in white for contrast.	135
Figure 4.18:	Recovery process of tissue oxygen distribution following increasing oxygen concentration in the arterial blood, at time $t = 0.001, 0.01, 0.05$ and 0.1. Anoxic areas are shown in white for contrast.	137

KEY TO SYMBOLS

R_c	Normalized capillary radius
R_t	Normalized tissue radius of the Krogh-Cylinder Model
L	Normalized capillary length
W	Normalized width of the capillary-tissue region
Н	Normalized height of the capillary-tissue region
Ω	Normalized capillary-tissue domain
Ω_m	Normalized domain of the m^{th} capillary
Ω_c	Normalized total capillary domain
Ω_t	Normalized total tissue domain
O_i	The i^{th} normalized anoxia tissue region
0	Normalized total anoxia tissue region
М	Number of capillaries in the capillary-tissue region
v_b	Normalized capillary blood velocity
C_a	Normalized arterial oxygen concentration
D	Normalized tissue oxygen diffusion coefficient
κ	Normalized tissue oxygen consumption coefficient
C	Normalized oxygen concentration
C_c	Normalized oxygen concentration in the capillary region

C_t	Normalized oxygen concentration in the tissue region
Σ_{nb}	Operator representing the summation of compartment neighborhoods
p	The sliding period of capillary compartments
b	The sliding frequency of capillary compartments
A	The cross section area of a compartment
V	The volume of a compartment
N	Mass of oxygen molecules
J	Oxygen flux between adjacent compartments
Δx	The spacial step size
Δt	The time step size
Δt_{\pm}	The beginning of the time interval
Δt_{-}	The end of the time interval
t^*	The oxygen depletion time of the tissue region
t_f	The tissue fully perfused time of the tissue region
t_s	The time spent to reach steady state from transient state
n_{CC}	Number of compartments representing the cross sectional area of a capillary
q	Capillary oxygen flux strength
Р	Oxygen permeability through the capillary membrane wall
PO_2	Oxygen partial pressure

i, j, k, m, n	Numerical	indices
---------------	-----------	---------

Ω'	Capillary-tissue domain (1D: μm , 2D: μm^2 , 3D: μm^3)
Ω_m'	Domain of the m^{th} capillary (1D: μm , 2D: μm^2 , 3D: μm^3)
Ω_c'	Total capillary domain (1D: μm , 2D: μm^2 , 3D: μm^3)
Ω_t'	Total tissue domain (1D: μm , 2D: μm^2 , 3D: μm^3)
O_i'	The i^{th} anoxia tissue region (1D: μm , 2D: μm^2 , 3D: μm^3)
0	Total anoxia tissue region (1D: μm , 2D: μm^2 , 3D: μm^3)
R_c'	Capillary radius (μm)
L'	Capillary length (μm)
W'	The width of the capillary-tissue region (μm)
H'	The height of the capillary-tissue region (μm)
v_b'	Capillary blood velocity $(\mu m/s)$
C_a'	Arterial oxygen concentration ((ml O_2)/(ml blood))
D'	Tissue oxygen diffusion coefficient $(\mu m^2/s)$
κ'	Tissue oxygen consumption coefficient ((ml O_2)(ml tissue) ⁻¹ s ⁻¹)
C'	Oxygen concentration ((ml O_2)/(ml blood))
κ_b'	Basal tissue oxygen consumption coefficient ((ml O_2)(ml tissue) ⁻¹ s ⁻¹)
κ'_{max}	Maximal tissue oxygen consumption coefficient ((ml O_2)(ml tissue) ⁻¹ s ⁻¹)

KEY TO ABBREVIATIONS

DCM	Discrete Compartmental Method
SEM	Sliding Element Method
CC	Capillary Compartment
TC	Tissue Compartment
BC	Boundary Compartment
IC	Inactive Compartment
MI	Myocardial Infarction
AMI	Acute Myocardial Infarction
FCD	Functional Capillary Density
FVM	Finite Volume Method
PDE	Partial Differential Equations
RBC	Red Blood Cell

Chapter 1

Introduction

Our body constantly needs oxygen to stay alive. Oxygen were delivered and consumed by tissue through blood flow inside the arteries. However, the arteries have thick vessel walls almost impermeable to oxygen. The diffusion of oxygen (and nutrients) to tissue actually occurs in the more permeable connecting capillaries. We are interested in the possible unsteady change in oxygen concentration inside the capillary-tissue region.

Such a study is important because low oxygen delivery from the blood flow will result in insufficient oxygen concentration for the muscle tissue. The cause of low oxygen could be due to disease, low oxygen environment or excertion. In the muscle, low oxygen (hypoxia) may cause soreness or pain. In the heart muscle, it may cause a heart attack and in the brain, a stroke. Up to now, it is still difficult to measure the distribution of oxygen in a living body. The theory or its variations remains constrained by a simple mathematical model developed a century ago, with many deficiencies. The present research is to develop a more advanced theoretical model.

Traditional mathematical modeling of biological processes is as follows. The problem is described by partial differential equations which are then solved by numerical methods such as the finite difference methods or finite element methods. For our problem, the modeling is difficult because

1. The geometry is random and three dimensional due to natural dividing organism

- 2. The process is unsteady. This means time is an extra variable
- 3. The process involve diffusion oxygen diffuses into the tissue area
- 4. The process also involve convection oxygen is transported by blood flow in the capillary
- 5. Consumption the tissue will constantly consume the oxygen
- 6. Moving boundary problem if certain regions is devoid of oxygen supply, the concentration will have a moving boundary

Thus, it is a three-dimensional transient convection-diffusion-consumption moving boundary problem. It would be a severe challenge to solve this problem with PDE or even numerical method constructed from PDE.

This thesis presents a new method, names discrete compartmental method (DCM). The region is divided into many small cubes, called compartments, each represents part of a tissue or capillary based on their location. Based on their type, they are assigned of specific difference equations, constructed directly from the physical laws, to update their value in the next time step. By attaching the cubes together, we are able to simulate the oxygen concentration change of the entire domain.

In addition, using a sliding element method (SEM) together with the time matching method, the time derivative is naturally "eliminated" and the dimension of the problem was reduced from 4D to 3D. Since the method is constructed based on the real biological process, it provides accurate results.

1.1 Biological Background

The understanding of oxygen transport to tissue is basic and crucial in human physiology. A sufficient supply of oxygen to the cells is critical to any form of energy production [52]. In mammals, oxygen is extracted from the atmospheric air in the lungs, and transported by erythrocytes and dissolved in plasma through the circulation to the tissue. However, actual oxygen supply from blood to tissue only occurs in the microcirculation, where oxygen diffuses from capillaries into the tissue and is consumed there within the mitochondria.

1. Microcirculation

The microcirculation is the circulation of the blood in the smallest blood vessels, including terminal arterioles, metarterioles, capillaries, and venules. Within organ tissues, arterioles carry oxygenated blood to the capillaries, and blood flows out of the capillaries through venules into veins [66]. In the microcirculation, substances such as oxygen and nutrients are transported by flow convection [48]. During which process, the substrate leaves the plasma, crosses the vessel wall, and diffuses into tissue. Within the tissue, the substrate diffuses in a three dimensional region across many different histological structures and fluid spaces. Eventually, the substrate reaches the metabolic site in the cell and is consumed there [53].

2. Oxygen Transport in Striated Muscles

Capillaries are the smallest blood vessels connecting arterioles with venues and forming networks through the human body. The size of capillaries are approximately 5-8 μm in diameter [60]. There are approximately seven percent of the body's blood is in the capillaries which continuously exchange substances with the surrounding tissues, named capillary exchange [66]. In striated muscles, capillaries are long and parallel [38]. Glucose, amino acids, oxygen and other molecules exit capillaries by diffusion to reach the tissues and is consumed there [66]. This process depends on the difference of concentrate between the interstitial fluid and blood, with molecules moving in the direction of declining concentration of that substrate in solution [35].

3. Significant Problem: Hypoxia

Any form of energy production depends on a continuous supply of oxygen to the living cells. Blockage of blood flow in capillaries due to thrombosis, embolism or trauma will cause ischemia, leading to oxygen deficiency in tissue (hypoxia), which, if untreated, leads to absence of oxygen (anoxia), and eventually tissue death (necrosis). According to the recent result from the World Health Organization (WHO) [49], ischemic heart disease such as Myocardial infraction (MI) or acute myocardial infarction (AMI), commonly known as a heart attack, due to insufficient blood flow at part of the heart causing damage to the heart muscle have remained the top leading cause of death in the world during the past decade.



Top 10 global causes of deaths, 2016

Figure 1.1: Top 10 global causes of deaths, 2016.

Ischemic heart disease occurs when blood flow is insufficient in a part of the heart causing tissue death to the heart muscle. The most common symptom is chest pain, termed angina pectoris, due to the sudden ischemia of the heart muscle. The discomfort may quickly radiate into the shoulder, arm, back, neck, or jaw. Loss of consciousness or sudden death also occurs in MIs. Under such circumstance, time is of crucial importance. Acetylsalicylic acid is an appropriate immediate treatment for a suspected MI; however, it do not improve overall recovery. Thus, future research, especially theory for the occurrence and properties of MI is sorely needed. This thesis attempts to answer the following basic questions, which may help in the understanding, diagnosis and subsequent treatment of MI.

1. What is the transient oxygen concentration distribution in tissue supplied by a bunch of capillaries under both oxygen sufficient and insufficient conditions?

2. Where, when and how would hypoxia occur if one or more capillary were blocked?

3. Could the neighboring capillaries supply sufficient oxygen to the anoxic region? How soon and how much?

1.2 Literature Review

Representing the microcirculation process using mathematical modeling, especially on describing the concentration and consumption of oxygen in muscles, has received a lot of attention early in the beginning of 1910s and the precursor of this field is August Krogh[38] [39]. From observing the cross-section of striated muscle, he theorized that the rate of oxygen transport was related to the number and arrangement of capillaries in tissue and to the oxygen permeability of the capillary walls. Krogh's work in the early stage was only based on experimental and statistical results. However, his collaboration with mathematician Agner Erlang in 1919 opened the gate of mathematically modeling the microcirculation [38]. They developed the first theoretical analysis of oxygen supply within muscle tissue, which predicts the oxygen tension (partial pressure) distribution around a single capillary. Krogh's model assumed each capillary could be regarded as parallel to the muscle tissues and supplying an independent concentric tissue region surrounding that capillary. He also determined the average radius of such hypothetical tissue cylinder by counting the number of capillaries in a certain cross-section area. With the assistance of the mathematician Erlang, the mathematical description of such an ideal physical geometric arrangement, shown in Fig. 1.2, predicting the oxygen tension along the tissue cylinder, was known as the Krogh-Erlang equation

$$p(r) = p(Rc) - \frac{M_0}{4k} \left[R_t^2 \log \frac{r^2}{R_c^2} - \left(r^2 - R_c^2 \right) \right], \qquad (1.1)$$



Figure 1.2: (a) A single Krogh Tissue Cylinder. Estimation of PO_2 within a circular cylinder of tissue surrounding a capillary of radius R_c ; r is the distance from the capillary center; R_t denotes the cylinder radius where oxygen flux becomes zero. (b) PO_2 at capillary declines monotonically both around and within the fibre. (c) Krogh's view of circular tissue cylinder stacking, where tissue supply voids are inevitable. This arrangement is also known as concurrent flow model.

where R_t and R_c are the tissue and capillary radii with $R_c < r < R_t$, k is Krogh's oxygen (O₂) diffusion coefficient in tissue, and M_0 is a constant tissue demand for O₂. Other assumptions of the Krogh Tissue Cylinder model includes:

1. Tissue O_2 consumption is constant and uniform.

2. Tissue partial pressure or O_2 concentration (PO_2) at the capillary wall equals average capillary PO_2 .

3. Tissue O_2 solubility and diffusivity are uniform.

4. Axial (or longitudinal) diffusion of O_2 is not significant in comparison to radial diffusion.

5. Micro-vascular O_2 transport phenomena is steady.

6. All capillaries are parallel, unbranched, and equally spaced.

7. All capillaries receive equal convective O_2 supply.

Based on Krogh's initial steady state model, A. V. Hill [30] derived unsteady state equa-

tions in 1928. G. Thews in 1950 [64] and F. W. J. Roughton in 1952 [56], developed steady

and unsteady state equations for Krogh tissue cylinder. In 1957, Seymour S. Kety [36] developed the first model including intra-capillary conditions. He proposed for the first time that concentration of oxygen in capillaries should drop gradually from the arterial to the venous side. Jackob Blum [6], in 1960, gives another innovative contribution by adding the permeability of capillary wall and the metabolic rate in the tissue space to the Krogh tissue cylinder. However, Blum did not considered bound substrate such as O_2 in his work. His result is not adaptive to oxygen but can be applied to diffusible substrate such as glucose.

The increasing availability of computers by the 1960s encouraged many investigators started working not only on generalizing and completing the description of Krogh cylinder but also on developing new geometric models as well as exploring adaptive numerical techniques. Gonzalez-Fernandez[26], Filtcher [16] [17] and Reneau[55] in the period 1965 to 1975 studied the unsteady Krogh model. Reneau's work in 1966[55] introduced the finite difference equations to treat the nonlinear unsteady system for the first time. Salthe and Wang [59] studied the change of oxygen concentration following a capillary occlusion using the method of matched asymptotic expansions. More detailed presentations and discussions of the Krogh cylinder can be found in Middleman [44] and Lightfoot [42] and the reviews of Fletcher in 1977 [18] and Popel in 1989 [52].

Over more than half a century, the original framework build by Krogh, the Krogh tissue cylinder, has always been the foundation of studying and modeling oxygen transport. However, the concept of a "lethal corner" (i.e. tissue area close to the cylinder boundry on the venuous end) has been troublesome to many physiologists, since they are not able to isolate and identify a particular capillary and its associated cylinder of tissue, and then make the measurements in such tissue space. Although Silver [61], Whalen[70] and several others have measured low values of oxygen tension in the tissues of small animals, yet no experimental measurements could disprove or confirm the single tissue cylinder model.

For the purpose of determine if a single capillary model is valid for the predictions of the oxygen distribution, several attempts to model large capillary networks were made in the early 1970s. Hutten, Thews, and Vaupel [31] modeled considerably large capillary networks with an electronic analog model and concluded that single capillary may supply larger or smaller cross-sectional tissue area then that predicted from a single capillary model. Levit [41], using the method of Johnson [34], considered diffusional and time dependent interaction of adjacent capillaries. He argues that capillaries interactions are potentially important in determining the true venous outflow.

Most of the early modeling were based on Krogh's finding and assumed that the microcirculation was a passive network where blood is supplied by tube to a nonintereacting volume of tissue. However, experimental works in the late 1970s challenged this traditional view. It was observed that the microcirculatory environment is a much more complex locally regulated intereacting system. Goresky and Goldsmith [27] suggests that diffusional bypass may happen in cardiac muscle due to the diffusional interaction between adjacent groups of capillaries. Moreover, Goresky's study and those of Fable [15], Weiss [69] and others observed that in cardiac muscle, the blood flow and metabolic function are synchronized with the contractile cycle. Hence, both spatial and temporal relationships must be considered for any model attempting to describe substrate supply in cardiac muscle. For skeletal muscle, Groom, Plyley and their associates [51] found that a capillary unites with branches from an adjoining parallel network rather than rejoin its generating branch. This group's observation once again reveals the importance of capillary interaction to the determination of venous outflow. As a result, most assumptions for the Krogh model fails to be true and new adaptive models and numerical methods once again became necessary. With the development of modern technology, several physiology observations have became definite facts and widely accepted. They are mainly about the heterogeneity of microvasculature, such as 1) capillaries, even those in the skeletal muscle, are not uniformly distributed, 2) the size of capillaries are not quite the same, 3) the O_2 capacity of each capillary is different, and 4) stronger O_2 capillary capacity not only support adjacent area but compensates neighboring regions. With these new understandings on microvessel's heterogeneity, many of the previous assumptions made on developing mathematical model of blood-tissue exchange may not be applicable.

Considering the uneven capillary distribution and diffusional strength, Wang [68], in 1999, devised a method to compute the oxygen density supplied by capillaries in a simply connected circular region and a analytic solution is given. Wang defined the tissue region serviced by a certain capillary to be the capillary supply region. The analytical result shows that, the shapes of the supply region depend on both the location and the relative diffusion strength of the capillaries (Fig. 1.3). Wang argues that a partial blockage of a certain capillary may not cause anoxia near the blockage, but the neighboring capillaries may compensate by shifting capillary supply regions.



Figure 1.3: (a) Oxygen concentration curves of seven unevenly distributed capillaries of unequal strength over a circular tissue region. Total flux given equals to total area of the circular region times the tissue oxygen consumption rate. At the point on upper right boundary, the concentration is zero. (b) The corresponding capillary supply regions.

Following Wang's work, Go [1] [20] obtained the unsteady solution of oxygen distribution in circular region. However, he considered negative solutions as the hypoxia region which is far from accurate for the real case. Sun [62] extended Wang's method to rectangular shaped capillary-tissue regions. Again, his results would apply only to steady state situations.

On the order hand, in 1972, Crank and Gupta [12] [11] first discussed one dimensional moving boundary problem describing the oxygen diffusion and consumption phenomenon in the body tissue. In Crank and Gupta's first paper [12], an explicit finite difference method is used with Lagrange formula interpolation near the moving boundary. In their second paper [11], Forward Difference Spline (F.D.S.) Method and Forward Difference Polynomial (F.D.P.) Method are used to shift the mesh at each step to reduce the irregularities when crossing a mesh point. Two years later, Hansen and Hougaard [29] derived an integral equation for the position of the moving boundary and an integral formula for the concentration. The concentration is estimated asymptotically for small times and calculated numerically for later times. Berger, Ciment and Rogers [5] considered an equivalent problem as a non-linear equation on the fixed interval [0, 1] and solved it numerically using finite difference method where the negative part of the solution is set equal to zero before each step. However, their result has very low accuracy even with small mesh spacing due to modifying the original problem. Miller, Morton and Baines [45] used finite difference in time and finite element with adaptive mesh in space. In the begining of 1980s, Gupta and Kumar [28] considered numerical integration. Dahmardah & Mayers [13] obtained more accurate results by expanded the solution in a Fourier series.

Mitchell [46] applied integral method together with a novel transformation to remove the non-uniform initial profile. Mitchell & Vynnycky [47] connected the Keller box scheme with the boundary immobilization method and focused on finding the oxygen depletion time in 2015. More detailed discussions about the moving boundary problem can be found in Crank [10] [9] and Zerroukat [73].

Until recently, it has been admitted that capillaries are not evenly distributed but spatially heterogeneous and the O_2 capacities of each capillary are not identical but vary among different adjacent cells [14]. Moreover, it is also recently being discovered that local capillary capacity in muscle is primarily determined by muscle fiber type and fiber size [8]. For transient problems, such as abnormal perfusion with more than one capillary, the problem has not been studied at all. The difficulty is mainly due to the fact that the boundary of the ischemic area is no longer stationary. For example, assume there is a blockage of one capillary among many, the ischemic area may be decreasing over time by an increase in flux from the neighboring cells. In addition, unevenly and randomly distributed capillaries lead to restrictions on model construction which result in large amount of computation time. In addition, Whiteley et al. [71] recently examined the significance of axial diffusion in both the capillary and the tissue on a single capillary model. Using dimensional analysis and numerical methods, they found that axial diffusion in the capillary is negligible except within a small boundary layer at the inflow region of the order of the capillary radius. However, the effect of axial diffusion within the tissue was found to be small but significant.

Taking advantage of the increasing computing capability, more and more numerical methods are investigated to the study of oxygen transport in the micro-circulation. Goldman and Popel [21] calculated the steady-state blood flow and time-dependent oxygen transport in a three-dimensional capillary network using a finite difference based method. Using a slightly modified method, Goldman [22] simulated the capillary network oxygen transport during ischemia by comparing the result at different steady-states. Using the modified model, Goldman et al. [25] studied the role of heterogeneous capillary spacing and blood flow. Fraser et al. [19] compared the generated parallel capillary arrays with three-dimensional reconstructed capillary networks in modeling oxygen transport. Sun et al. [63] calculated the 2D steady-state solution of multi-capillaries with uneven location and strength in rectangular capillary-tissue beds.

Compartmantal method is a classic and commonly used mathematical analysis method on studying biological processes. Compartments in physiology are composed of sets of interconnected mixing chambers. Each component of the system being considered as homogeneous instantly mixed, with uniform concentration. A comprehensive introduction of the compartmental method can be found in Jacquez [32]. More recent applications and computational extensions of it can be found in Bassingthwaighte et al. [2]. The sliding (fluid) element method is a not so wellknown method which address the convection. It was first proposed in Bassingthwaighte et al. [3] for the computation of a 2-barrier, 3-region convection-permeation-diffusion models for blood-tissue exchange problem. The central idea of the sliding element algorithm is to set the time step equal to the length step divided by the fluid velocity. This computationally efficient method for convection has never been extended to a three dimensional model.

1.3 Objectives and Plan of the Current Research

After a century of study, many important questions regarding the transient process of oxygen concentration distribution in tissue remain open today. The mathematical modelling of the capillary supply to tissue generates a complex system of coupled mathematical expressions. A finely detailed geometry of capillary networks requires considerations of both physiologically interactive spatial effects and computationally attainable algorithm, since it is clear that interacting microcirculatory regions do not maintain a completely static condition. For striated muscle system, a mathematical model describing oxygen distribution from a resting state to a state of maximum activity and maintain functional state under hypoxic conditions for long periods of time is needed. A computational model which can reflect the adaptive process of capillary recruitment, increasing and decreasing blood flow, and metabolic activity would be a significant advance in the state of the art in modeling microcirculation.

The general object of this thesis is to develop a three dimensional mathematical model with possible extensions and computational efficiency, in order to provide a mathematical explanation for the transient state of tissue oxygen distribution. In particular, to provide a new research tool for the study of oxygen transport in striated muscles, the process and degree of tissue hypoxia and, in particular, the forming process and location of an anoxia in cardiac and skeletal muscles. This new method greatly improves the current frameworks on both mathematical and physiological applications. Major innovations include:

- 1. diffusion-consumption problem with moving boundaries,
- 2. diffusion-consumption problem with multiple unevenly distributed sources and different strength,
- 3. three dimensional space diffusion-consumption-convection problem modeling.
- 4. transient state solutions

In general, the new model is able to solve a three space dimensional, transient, moving boundary, convection-diffusion-consumption problem with multiple unevenly distributed sources of different strength. With this new model, certain significant physiological phenomena can be further studied, such as the approximation of local anoxia area caused by sudden blockage of one or more capillaries and the time for full recovery.

Chapter 2

Discrete Compartment Method (DCM)

In this section we develop the discrete compartment model for the transient diffusionconsumption-convection problem. First, we define the general problem of unsteady oxygen exchange problem in multiple capillary domain and discuss the assumptions. Second, we define the discrete compartment method (DCM), give definitions to the basic terms, introduce the graphic representation and discuss the basic compartmental difference equations. Lastly, we will discuss the differences of the present model with other models and give a visual explanation for demonstrating the essence of the discrete compartmental model. Important material on numerical accuracy will be discussed in detail later in Chapter 5.

The governing difference equations of discrete compartment methods are similar but different to those of finite difference methods, and the graphic representation of a discrete compartmental method are similar but different to those of finite volume methods. However, the greatest difference is that the discrete compartmental methods are derived from the basis of physical laws such as Fick's diffusion law, a starting point that turns out to have many advantages. Moreover, the discrete compartmental method can easily handle timedependent boundary conditions. At the same time, it is computationally efficient even for four dimensional problems. More advantages and differences to other numerical methods and mathematical models will be discussed in the last section of this chapter.

2.1 Idea of the Model

Consider the whole tissue space partitioned into finite number of contiguous tissue bins. For sufficient oxygen supply, each bin would consume one normalized unit of oxygen per normalized unit of time, and some of the bins are designated as capillaries which can deliver an amount of oxygen per unit of time. If oxygen supply is less than the minimum required, the bin is labeled hypoxic and available oxygen is consumed. On the other hand, by Fick diffusion law through a material, oxygen would diffuse from bins with a higher concentration into adjacent bins with a lower concentration. Under steady state, the oxygen content in each bin is assumed to be well mixed. Therefore, the whole system is a network of physical compartments. The resulting equations are similar to the discretized diffusion-consumption equations but are formulated from completely different principles. In the axial direction of the capillary, the key strategy in the approach to convection is to use a sliding fluid element algorithm, with the time step set equal to the length step divided by the fluid velocity. By matching the time and space steps, the capillary oxygen content flow down the capillary vessel one segment at a time and movement of single or a bunch of capillaries may stop in the case of capillary blockage. This not so well-known method, which address the convection, works perfectly with the compartmental method but has never been applied to a discrete model. A concrete introduction to the construction and application of the sliding element method on the discrete compartmental method (DCM) can be found in section 3.3.
2.2 Multi-capillary Oxygen Transport in Striated Muscle

2.2.1 The General Problem

Consider a 3D rectangular parallelopiped of tissue that has width W', height H', and length L', where the length is parallel to the z-axis (direction of blood flow), the width is parallel to the x-axis and the height is parallel to the y-axis. The origin of the Cartesian coordinates is at the center of the rectangular cross-section on the arterial (infusion) end. Consider n parallel capillaries of same length L' and radius R'_c located randomly along the center line. Blood enters the capillaries at the arterial end with velocity v'_b . As oxygen is convected through the capillary, it diffuses into the surrounding tissue both radially and axially under a constant diffusivity D' and is consumed in the tissue at a constant rate κ' per volume of tissue. The oxygen concentration in either blood or tissue is C' which is non-negative due to the physical fact that substrate concentration cannot be negative.

Normalize all length by the square root of the cross section area $\sqrt{W' \cdot H'}$, concentration by that on the arterial end C'_a , time by W'H'/D' and drop all primes. In terms of normalized parameters, the problem can be stated as: there are *n* parallel capillaries of same length *L* and radius R_c located heterogeneously along the center line of a tissue box that has width *W*, height *H*, and length *L*. Where $R_c = R'_c/\sqrt{W'H'}$, $W = W'/\sqrt{W'H'}$, H = $H'/\sqrt{W'H'}$, and $L = L'/\sqrt{W'H'}$. Blood enters the capillaries at the arterial end with velocity $v_b = v'_b\sqrt{W'H'}/D'$. While oxygen is convecting through the capillary, it diffuses into the surrounding tissue both radially and axially with unit constant diffusivity and is consumed there at a constant rate $\kappa = \kappa'W'H'/C_aD'$. The oxygen concentration in either blood or tissue is $C = C'/C_a$ which is always non-negative. We assume that oxygen has unlimited permeability through the thin capillary membrane.

2.2.2 Assumptions

- 1. The system is linear. Blood flow is constant. Both transfer and consumption coefficients are not concentration-dependent. Capillaries are long and parallel, such as those in the skeletal muscle or heart muscle. Moreover, the diffusivity of oxygen is isotropic(axially uniform) in tissue and the permeability of the capillary endothelium to the oxygen molecules is unlimited.
- 2. Only convection occurs in the capillary, i.e. oxygen is radially well-mixed in the capillary. Radial diffusion is infinitely fast inside the capillary so the radial concentration gradients are zero in the capillary. The radial diffusion relocation times for small solutes in capillaries is very short compare to capillary transit times and so negligible due to order of magnitude.
- 3. The outer domain boundary is reflecting. We considered a local tissue region. We assume similar diffusion also occurs inside of a similar neighboring domain. We assume the adjacent tissue regions have exactly the same reflected distribution of capillaries and identical (reflected) tissue oxygen concentration. This results in zero oxygen exchange between neighboring regions and no net oxygen flux across the boundary. It allow us to patch many solutions together and simulate much larger tissue regions.

2.3 Discrete Compartmental Systems

A discrete compartmental system is a system which is represented by finite number of interconnected microscopic subsystems of specific size in order, called discrete compartments, each of which is homogeneous and well-mixed. Each compartment interact with adjacent neighbors by exchanging material(mass), and for all such transfers between compartments and, to and from the environment on the boundary, the mass conservation condition holds. The system equations are difference equations, and the system can be used to approximate continuous systems described by partial differential equations. There is no specific compartmental mental system which is optimal for a continuous system, as it is in the traditional compartmental methods, but the approximation converges as the number of compartments is increased as the system is refined.

The discrete compartmental method (DCM) sounds similar to the finite volume method (FVM) [40] [65] as they both construct algebraic equations based on the flux change over the small volume surrounding each node point on a mesh. However, they are essentially two distinct methods and has each of its own advantages. FVM is a method for representing and evaluating partial differential equations in the form of algebraic equations, but DCM is a method for analyzing and simulating biological processes in the form of algebraic equations derived directly from physical laws. In FVM, fluxes at the surfaces of each finite volume are converted from volume integrals in a partial differential equation that contain a divergence term, using the divergence theorem, but in DCM, the fluxes are derived from the Fick's diffusion law. This intrinsic difference makes DCM a more flexible method and can be applied to simulate more complicated biological processes. Due to the difference on the construction method, another remarkable difference between the two methods are for FVM each nonoverlapping volume can be of arbitrary size and shape, but for DCM each compartment mush have the same size and shape.

2.3.1 Basic Terms and Definitions

A number of terms are used frequently in discrete compartmental analysis and in its application to the oxygen exchange problem in capillary beds. Variation of these terms in usage in different literature may cause confusion and overlap in the meaning of some of the terms. Here we define the commonly used terms more rigorously and will adhere to these definitions in the remainder of this thesis.

(a) Discrete Compartment and Compartmentalization

A discrete compartment is a small physiological space or physical volume which contains an amount of a material that acts kinetically like a distinct, homogeneous, wellmixed material. It is to be distinguished from a classical compartment which does not have a specific size and connectivity [33]. For example, the amount of oxygen in the whole plasma space of the body could be a compartment in the classical compartmental system, while the amount of oxygen in a specific small volume of the capillary or tissue space is a continuous compartment in the discrete compartment system.

Subdividing the spatial domain into homogeneous intervals in one spatial dimension, homogeneous areas in two spatial dimension, and homogeneous volumes in three spatial dimension, and represent each of them using discrete compartments is called compartmentalization. The shape of discrete compartments can only be triangular, rectangular or hexagon. Each compartment only interact with adjacent compartments by exchanging mass under a given transfer(diffusion) coefficient, and each compartment may or may not consume a certain amount of mass under a given consumption coefficient. In each time step we update the values in each compartment by balancing the mass.

(b) Cube Compartment

A cube compartment is a discrete compartment of cubic shape, which means it is threedimensional, bounded buy six square faces and has 12 edges and 8 vertices. Size of a cube compartment is determined by length of each sub-interval in one space dimension, area of each small square in two space dimension and it is exactly the volume of the cubic sub-space in three dimensional domain.

Cube compartments are utilized here for the following reasons: 1. it could seamlessly cover any problem domain(tissue region) without overlapping each other; 2. it is easy to construct and set up the difference equations of mass transfer between adjacent compartments under the Cartesian coordinate system; 3. it is computational efficient, especially in the three dimensional transient problems.

(c) Discrete Compartmental Space

A discrete compartmental space is a three dimensional space(preferably the smallest) formed by discrete compartments that covers the entire problem domain. For example, a 4 by 4 cube space formed by 16 small unit cube compartments is a continuous compartmental space for a sphere of radius 2. It is worth to notice that in any of the three space dimensions that make real sense, continuous compartments are in the form of three-dimensional compartments with volume. In general, a 1D continuous compartmental space looks like a cylinder, a 2D continuous compartmental space looks like a block.

(d) Active Compartment and Inactive Compartment

There are two general types of compartments in a continuous compartmental space: active compartment and inactive compartment. An active compartment is a compartment whose center is inside the problem domain. An inactive compartment is a compartment whose center is outside the problem domain. Notice that, the concept "center" is referring to the midpoint of a line segment in 1D space and the center of a square area in 2D space and the centroid is a 3D space. Inactive compartments are "ghost" compartments, they do not participate in any computation. The reason for accepting inactive compartments is for the convenience of programming, since in the reality computer data are stored in matrices but the problem domain may be irregular.

(e) Adjacent Neighbor and Contiguous Neighbor

Compartment B is called an adjacent neighbor of compartment A, if B has a common surface with A. Compartment C is called an contiguous neighbor of compartment A, if C has a common edge or common vertex with A. Each compartment has at most 2 adjacent neighbors, 0 contiguous neighbors in 1D space, at most 4 adjacent neighbors, 4 contiguous neighbors in 2D space, and at most 6 adjacent neighbors, 20 contiguous neighbors in 3D space. (Although a compartment only interacts with its adjacent neighbors, contiguous neighbors may appear in the equation to satisfy some mass conservation condition on the boundary.)

(f) Interior Compartment and Boundary Compartment

Active compartments can be further classified into two types: interior compartment and boundary compartment. An interior compartment is an active compartment whose adjacent neighbors are all active compartments. A boundary compartment is an active compartment whose has one or more adjacent neighbors that are inactive compartments.

(g) Discrete Compartmental Domain and Domain Boundary

The set of all active compartments is called the discrete compartmental domain; it is a subset of the discrete compartmental space. The set of all boundary compartments is called the discrete compartmental domain boundary; it is a subset of the continuous compartmental domain.

(h) Tissue Compartment and Capillary Compartment

Interior compartments can be eventually divide into two types: source(capillary) compartments and consuming(tissue) compartments, based on the position of their center in the problem domain. For simplicity, we avoid putting a source on the boundary or even too close to the boundary. Therefore, every boundary compartment is a consuming compartment.

(i) Type of Boundary Compartments

Boundary compartment can be eventually divide into different types based on the attendance of there active neighbors. Specific methods for classification and list of boundary types will be discussed for each individual problem.

(j) The Moving Boundary

During a transient process, oxygen deficient regions (transient zero oxygen concentration regions) may appear and their location is unknown apriori. In such a case a moving boundary exists. Let O_i denote the ith anoxia tissue region which appeared in the domain and "s" the total number of appeared oxygen-deficient regions, then

$$O = \bigcup_{i=1}^{s} O_i, \tag{2.1}$$

is the union of oxygen-deficient regions. Thus, ∂O is the collection of transient moving boundaries at the n^{th} time step.

(k) The Sliding Period

A sliding period is the duration of time for elements inside the source compartments to renew once or move one grid forward once. Its size is determined by the space step size and the velocity of element convection of the source capillary.

(l) Notation of Operators

For simplicity, we define the following operators in one, two and three dimensional space respectively:

$$\Sigma_{nb} : \Sigma_{nb} u_i^n = u_{i-1}^n + u_{i+1}^n$$

$$\Sigma_{nb} u_{i,j}^n = u_{i-1,j}^n + u_{i+1,j}^n + u_{i,j-1}^n + u_{i,j+1}^n$$

$$\Sigma_{nb} u_{i,j,k}^n = u_{i-1,j,k}^n + u_{i+1,j,k}^n + u_{i,j-1,k}^n + u_{i,j+1,k}^n + u_{i,j,k-1}^n + u_{i,j,k+1}^n$$
(2.2)

2.3.2 Graphic Representation

A map is a schematic plan of the continuous compartmental space which stores a label for each compartment indicating there type and any other additional information. Each label corresponds to a specific difference equation which should be applied to the corresponding compartment during the computation. The first part of a compartment label is two capital letters indicating the general type of the compartment. For example, for the problem of oxygen exchange in capillary beds, we have the following leading letters each corresponding to a basic compartment type:

- ' CC ' Capillary Compartment
- ' TC ' Tissue Compartment
- ' BC ' Boundary Compartment
- ' IC ' Inactive Compartment

Another part of the label are numbers distinguishing a fine sorted type or other information that indicating a compartment to be treated specifically during the computation. For example, an interior tissue compartment can be simply marked as "TC" and an inactive compartment can be simply marked as "IC" since there is no need to further distinguishing them. However, two capillary compartments with different strength may be marked as "CC001" and "CC002" to specify the coefficients being used during the calculation. Likewise, boundary compartments can be marked as "BC032" or "BC411" where the number indicates different boundary types.

The Map itself is stored in an individual matrix which has the same dimension as the continuous compartmental space it serves. In each time step we check the labels in Map one by one, and use the paired difference equation to update the value of the corresponding compartment. This process seem to be repetitive and redundant but actually has great advantage on the transient multi-capillary and tissue exchange problem. Consider the case where the blood flows inside one or more capillaries are suddenly decreased by different amounts due to a small artery occlusion, or the case where a block of tissue's consumption rate is suddenly increased due to exercise. In both of these cases we will need to make several adjustments to the coefficients for a specific part of the domain and keep the rest unchanged. A model which could easily process diverse time-dependent conditions is desired. The label of a compartment on the Map can be changed at any time step to satisfy time-dependent conditions. For example, if a capillary is closed (e.g. capillary blockage), we just need to rewrite its label on the Map to a proper label which corresponds to zero blood velocity. If the same capillary become open again later, the label is reestablished. If there is a change in the tissue consumption over part of the domain due to cell hypertrophy, a new tissue label is created, say "TC123", corresponding to an appropriate difference equation.

2.4 Application of the DCM

The computation of discrete compartmental method (DCM) is based on difference equations derived directly from physical laws. Detailed formulation will be discussed at the beginning of each individual problems in the following chapters. Here we use a 1D transient problem to introduce the computational method of discrete compartmental modeling.

Example: 1D problem modeling

Consider a one dimensional tissue region of length L = 1 where a capillary of radius $R_c(R_c < L)$ is located at the center of the x-y plane in the tissue region. The normalized diffusion coefficient D is 1, the consumption coefficient is κ , the oxygen concentration in the capillary is C_a and the blood velocity is v_b .

To apply the DCM, first determine the space step based on the size of the capillary. The position of capillary boundary is of crucial importance to the accuracy of the method. Thus the spacial step size is determined according to the cross-section area of the capillary. In a one dimensional problem, choice of Δx should be either equals to the diameter of the capillary, or there should exist a positive integer whose product with the space step equals the capillary diameter. Let \mathscr{X} be the set of valid choices of Δx , then

$$\mathscr{X} = \{ \Delta x \mid \exists a \in \mathbb{Z}^+ \quad s.t. \quad a\Delta x = 2R_c \}$$
(2.3)

i.e.

$$\Delta x = 2R_c, \quad R_c, \quad \frac{2R_c}{3}, \quad \cdots .$$
(2.4)

Determination of Δx for two and three dimensional problems will be discussed later at the beginning of each individual problems.

For the time step size, if convection inside the capillary is not considered, then Δt could be any small number provided the method converges and stable; if the convection is taken into account, then a sliding element method is used to deal with the transient convectiondiffusion-consumption process and Δt is determined by the sliding period. The fundamental requirement of the sliding element method is to match the space and time step so that the diffusion-consumption process takes exactly the same amount of time as the materials in the capillary compartments slide one complete grid forward. Let p be the sliding period for materials in the capillary compartment slid exactly one grid downstream into the next compartment, which means blood flow should travel a distance of Δx in the velocity of v_b during each p. Hence, the sliding period is determined by

$$p = \frac{\Delta x}{v_b},\tag{2.5}$$

which further determines the time step size Δt . If the stability condition is not satisfied, one

should choose to use the quotient of p with a positive integer, say b. Let \mathscr{T} be the set of valid choices of Δt , then

$$\mathscr{T} = \{ \Delta t \mid \exists b \in \mathbb{Z}^+ \quad s.t. \quad b\Delta t = p \}$$

$$(2.6)$$

i.e.

$$\Delta t = p, \quad \frac{p}{2}, \quad \frac{p}{3}, \quad \cdots .$$
(2.7)

By doing so, the diffusion-consumption is perfumed b times every time before one slid in the capillary. We call b the sliding frequency.

The oxygen concentration in the next time step of each compartment is determined by difference equations derived from Ficks' diffusion law and balance of mass. For example, oxygen concentration in the next time step of a tissue compartment in the 1D problem is given by

$$C_i^{n+1} = \max\left\{ C_i^n + \frac{\Delta t}{(\Delta x)^2} \left[\Sigma_{nb} C_i^n - 2C_i^n \right] - \Delta t \cdot \kappa, 0 \right\}.$$
(2.8)

Notice how the maximum function guarantees that the oxygen concentration will never became negative, which means over each time step, a tissue compartment will either consume $\Delta t \cdot \kappa$ amount of oxygen or whatever is available. (Details about the formulation will be given at the beginning of each individual problem.)

Instead of considering a Dirichlet boundary condition on the capillary wall, capillary blood flow is part of the problem and oxygen concentration inside each capillary is computed simultaneously with tissue oxygen concentration. This could be a great challenge using other numerical methods but naturally possible in DCM. The advantages of doing so includes: 1. it provides an out flow at the end of each time step, 2. it could apply to possible cessation of oxygen supply.

Consider when one of the source capillary is blocked. In such case, oxygen will continue diffuse out from that capillary due to the difference of the partial pressures. The oxygen concentration inside the capillary well gradually decrease. As the oxygen pressure gradient gets smaller and the out flow of the oxygen will slow down. When the pressure difference becomes zero this capillary no longer supply oxygen to the surrounding tissue. Assume there is a well oxygenated capillary nearby, then the oxygen will gradually flow to regions with low partial pressure. With the help of nearby normal capillaries, tissue cells next to the blocked capillary may still be alive. Such complicated and physiological process can be simulated easily using the discrete compartmental model.

Oxygen concentration of a capillary compartment at the end of the present time step (denoted by a subscript "+") is given by

$$C_i^{n_+} = C_i^n + \frac{\Delta t}{(\Delta x)^2} \left[\Sigma_{nb} C_i^n - 2C_i^n \right].$$
(2.9)

Notice the difference of the above equation with Eq. (2.8) is the absence of a consumption term, and a maximum function is not needed since its magnitude will be positive. If the capillary occupies more than one compartment, i.e. $\Delta x < R_c$, then an average of the capillary's encompassing compartments will be needed to compute the oxygen concentration. Capillary oxygen concentration will then be updated after each exchange. At the beginning of the next step (denoted by a subscript "-")

$$C_i^{n+1_-} = C_a. (2.10)$$

Necessary Components for Stability

In the next few chapters we will gradually construct the governing continuous compartmental differential equation for capillary-tissue oxygen exchange problem from one dimensional transient problems to three dimensional transient problems. One essential requirement is that the resulting method should be convergent and stable. The essential condition that must be satisfied while applying the continuous compartment method is:

for an *d*-dimensional transient problem, we require

$$\frac{\Delta t}{(\Delta x)^2} \leqslant \frac{1}{2d} \tag{2.11}$$

in the compartmental difference equations. Theoretical proof is given in Chapter 5.

2.5 Discussion and Comparison with Previous Models

Two most commonly used methods on studying oxygen transportation problem in human muscle tissue are the methods based on the Krogh cylinder model and the finite difference method. They both have several drawbacks on solving the oxygen delivery problem which can be handled easily by the discrete compartmental method.

A major shortcoming of the Krogh cylinder model and its extensions is the ignorance of the concurrent flows from neighboring capillaries, which results in unrealistic phenomena when applying to tissue beds with multiple capillaries. For a stack of Krogh cyliners, blockage of one capillary will only affect oxygen concentration in that single cylinder, but in reality, as the concentration of a local area starts decreasing, oxygen will flow in from neighboring tissue cylinders driven by the partial pressure difference, which results in the cylinder boundary shifting towards the blocked capillary and the cylinder shape will no longer be maintained. In addition, Krogh cylinder model assumes that capillaries are evenly distributed, which is not true in reality.

Due to the development of computer technology and advance in computational speed, numerical methods such as finite difference method has been more and more commonly used as a tool to solve problems that can be described by partial differential equations. However, for complicated biological processes, both the pde system and the numerical equations are difficult to construct. For example, our oxygen transport problem is a three-dimensional transient convection-diffusion-consumption moving boundary problem. Movement of the oxygen is governed by different partial differential equations in different parts of the domain. In addition, location of the moving boundary is unknown. Hence, it is difficult to set up the boundary condition for pde equations.

The present discrete compartmental modeling is designed for solving transient convectiondiffusion-consumption problems arising from the capillary-tissue oxygen exchange problem. It has many intrinsic advantages comparing with existing methods. First of all, the resulting difference equations are derived directly from Fick's law of diffusion, which makes it easy to construct and extend to three dimensional problems with practical significance. For example, it could deal with unevenly distributed capillaries, the occurrence of ischemic regions and their moving boundaries easily. Second, it is easy to manipulate the time dependent boundary conditions, which are essential for the physiological problem since the consequences of increasing and decreasing blood flow and tissue consumption rate are of great importance. Third, it is easy to deal with sources(capillaries) of uneven strengths and locations. Moreover, the difference equation system is similar to that of the finite difference method and thus easy to compute using modern computer technology.

Algorithm Analogy

Imagine a row of sensible kids, each stands one foot away from another. A teacher with a bag of candy is standing on one end of the row. In the beginning, each kid has 0 candy in his hand, and the teacher hold 10 candies in her hand. Afterwards, for each minute, each kid compare the number of candies he has with each one of his two neighbors and exchanges x candies, where x is the integer difference of number of candies in their hand times 0.4. The teacher and the kid standing on other end will have only one neighbor. After exchanging candies, each kid eats 1 candy if he has some or 0 candy if he has nothing. If a kid has a fraction of one candy he will eat all he has. The teacher does not eat any candy. This completes one round. At the beginning of each round, the teacher always holds 10 candies in his hand.

Therefore in the first round, the first kid gets 4 candies $((10 - 0) \times 0.4)$ from the teacher and 0 candy $((0 - 0) \times 0.4)$ from the kid on the right, and eats 1 candy; every other kid gets 0 candy and eat 0 candy. At the end of the first round, the teacher has 6 candies (10 - 4) in his hand, the first kid on the left has 3 candies in his hand, and the rest kids have 0 candies in their hands. At the beginning of the second round, the teacher holds 10 candies in his hand again, the first kid on the left has 3 candies (0 + 4 - 1) in his hand, and the rest kids have 0 candies in their hand. During the second round, the first kid on the left gets 2.8 candies $((10 - 3) \times 0.4)$ from the teacher and gives the second kid 1.6 candies $((0 - 4) \times 0.4)$; the second kid on the left gets 1.6 candies from his left neighbor and exchange 0 candy $((0 - 0) \times 0.4)$ with his right neighbor; the rest kids get 0 candy from their neighbor. In the second round, each of the first two kids on the left eats a candy and each of the rest kids eats 0 candy. At the end of the second round, the teacher has 7.2 candies (10 - 2.8) in his hand, the first kid from the left has 3.2 candies (3+2.8-1.6-1) in his hand, and the second kid from the left has 0.6 candy (1.6 - 1) in his hand, and the rest kids has 0 candies in their hands. The first round starts at time zero and finishes at the end of the first minute. The second round starts at the beginning of the second minute and finishes at the end of it.

Notice how balance of mass is hold in the first two rounds. At the end of the second round, there are totally 3.8 candies (3.2+0.6) left in kids hand. During the first two rounds, 3 candies (1+2) were eaten by the kids. The sum of them is equivalent to the number of candies that the teacher gives out in the first two rounds, which is 6.8 candies (4+2.8). In other words, the mass of candies that is being send out by the teacher is conserved with the mass of candies eaten by the kids plus the mass of candies that left in the kids hands.

There can be more than one teacher, teachers can stand anywhere in the middle of the line(but they may not stand together), and different teacher can hold different number of candies in there hand at the beginning of each round. For example, consider a teacher stands in the middle of the line. The kid on his left has 5 candies, the kid on his right has 9 candies at the end of the previous step and this teacher hold 12 candies in his hand every time. Then, in the next step, this teacher will give the kid on his left 2.8 candies($(12 - 5) \times 0.4$) and the kid on his right 1.2 candies($(12 - 9) \times 0.4$). This teacher has 8 candies(12-2.8-1.2) left in his hand at the end of this round, but he will take some from the candy bag and has 12 candies again in his hand at the beginning of the next round.

In the candy game, the teacher and kids plays the role of compartments, where the teacher is a capillary compartment or source compartment that delivers the candy(material) and each kid is a tissue compartment that consumes the candy(material). The uniform distance between each two of them, 1 feet, is the space step, and the consistent time duration of each round, 1 minute, is the time step. The ratio 0.4 multiplied to the candy(mass) difference is the transfer(diffusion) coefficient, and the number of candies that a kid eats in each round is the consumption coefficient. The number of candies left in each kid's hand at the end of each round is the updated (concentration) value of that compartment after each time step.

Notice that, if a kid is standing next to the teacher, then he will always have some candy to eat and he will have more candies than others have who are further to the teacher; if a kid is standing very far away from the teacher, then he will gets less candy or perhaps even no candy at all. Due to the consumption, there is a boundary of the diffusion. For example, if there is only one teacher standing on the left end and holding only 10 candies at the beginning of each round, then some kid on the right and every kid on his right may never get a candy. If a kid do not have any candy to eat over a very long time, he may starve to death just like tissue cells in human body dying from lack of oxygen.

Chapter 3

Unsteady

Diffusion-Consumption-Convection

In this chapter we apply the discrete compartmental method to one and two dimensional unsteady diffusion-consumption problems. The Crank-Gupta problem[12] is used as a test case to check the accuracy. The example of multiple capillaries in one dimensional regions gives an idea of how the model deals with time-dependent boundary conditions. Then we extend the method to two dimensional space and explore the unsteady state of the capillary supply region, which attracted much attention in the past but only the steady state solutions have been obtained[68]. Lastly we consider the problem in a circular domain and discuss the treatment of boundary condition on irregular boundaries.

3.1 One Dimensional Unsteady Diffusion-Consumption

In general, the problem of one dimensional unsteady diffusion and consumption describing the oxygen transfer from capillary to tissue after normalization can be stated as follows. Consider M capillaries with the same radius R'_c but with different blood oxygen concentration C'_m , where m = 1, 2, ..., M, located irregularly in a bounded region $\Omega' = [0, W']$. The domain of each capillary is

$$\Omega'_m = \left\{ x' : x' \in \Omega' \text{ and } |x' - x'm| \leqslant R'_C \right\},\$$

where x_m' is the center of each capillary. Therefore, the total capillary domain is

$$\Omega_c' = \bigcup_{m=1}^M \Omega_m'$$

and the absorbing tissue domain is

$$\Omega_t' = \Omega' \setminus \Omega_c'.$$

Driven by the passive diffusion due to the partial pressure difference, oxygen molecules permeate out from each capillary, and diffuse into the surrounding tissue at rate D' and were consumed there at a rate of κ' . The oxygen concentration in the tissue area can be described as a non-negative function of space and time C'(x', t'), i.e. $C'(x', t') \ge 0$ for all x'and t'. Thus, the governing equation to this one dimensional diffusion-consumption problem is

$$\frac{\partial C'}{\partial t'} = D' \frac{\partial^2 C'}{\partial x'^2} - \kappa', \qquad x' \in \Omega'_t, \ t' \in [0, \infty).$$
(3.1)

with associated zero flux boundary conditions

$$C'_{x'}(0,t') = C'_{x'}(W',t') = 0.$$
(3.2)

Inside each capillary and on the capillary wall the concentration is C'_m , differing in capillary strength

$$C'(x',t') = C'_m, \qquad x' \in \Omega'_m, \ t' \in [0,\infty), \ m = 1, ..., M.$$
(3.3)

Normalize all lengths by W', time by W'^2/D' and concentration by the average of that

on the arterial end C'_a and drop primes. In terms of normalized parameters the equations are

$$\frac{\partial C}{\partial t} = \frac{\partial^2 C}{\partial x^2} - \kappa, \qquad x \in \Omega_t, \ t \in [0, \infty)$$
(3.4)

$$C(x,t) = C_m, \qquad x \in \Omega_m, \ t \in [0,\infty), m = 1, \cdots, M$$
(3.5)

$$C_x(0,t) = C_x(1,t) = 0. (3.6)$$

where $\kappa = \kappa' W'^2 / C'_a D'$.

If oxygen deficient occurs, the flux and the concentration value equals zero on the moving boundaries ∂O^n

$$\left. \frac{\partial C}{\partial x} \right|_{x \in \partial O^n} = C|_{x \in \partial O^n} = 0. \tag{3.7}$$

Oxygen deficit region and its moving boundaries are defined in section 2.3.1.

3.1.1 Formulation

Instead of approaching from partial differential equations, the discrete compartmental system is constructed directly from the physical problem. Consider a one dimensional array of ordered identical cube compartments with equal longitudinal length Δx and cross-section area A. Assume there are m unevenly distributed capillaries. The Δx is required to be chosen carefully so that the uniform capillary diameter $2R_c$ can be divided evenly by Δx . For example, if $R_c = 0.05$ after normalization, then 0.1, 0.05 and 0.025 are good choices for the Δx , but 0.09, 0.07 or 0.03 are not.



Figure 3.1: Compartmentalization, map and labels of a 1D discrete compartmental model.

Align the center of the capillary-tissue region with the center of a single compartment with width Δx and generate the compartment array. Then, each compartment corresponds to a sub-interval of the capillary-tissue domain of the same length, except the two end compartments. This discretization error can be reduced by choosing a small and proper Δx .

The key strategy of constructing the discrete compartmental model is to classify and label the type of each compartment, depending on the location of their centers. Theses labels will be stored in a separate array called the map and will be used as a guidance to assign different algorithms to each compartment during the iteration. We distinguish between tissue, capillary of different strengths and different type of boundaries. For example, if the center of a compartment is located inside a capillary region, then this compartment is marked as a capillary compartment. The first compartment will be marked as a left boundary compartment ("BC21") and the last a right boundary compartment ("BC12"). Notice that because Δx is appropriately chosen at the beginning, the total volume of each capillary is kept constant during the discretization. Figure 3.1 shows an example of the construction of maps of a 1D capillary-tissue region with two capillaries under two different sizes of Δx . Different numbers are used as labels for each compartment. In the present example, "TC" means tissue compartment, "CCm" means the m^{th} capillary compartment, "BC21" means a boundary compartment whose right neighbor is a tissue compartment and "BC12" means a boundary compartment whose left neighbor is a tissue compartment. As shown in this figure, the second capillary is shifted a little to the left under a relatively large Δx , but this displacement error was reduced greatly under a smaller Δx .



Figure 3.2: 1D compartmental model

Now we derive the governing difference equations for updating oxygen concentration in different types of compartments in the 1D discrete compartmental system. Consider the i^{th} compartment. As shown in Fig 3.2, it is in between the $(i-1)\Delta x$ and $i\Delta x$. Following Fick's law of diffusion, each compartment exchanges oxygen with adjacent compartments. Let C_i be the oxygen concentration of the i^{th} compartment, then the mass of oxygen molecules in this compartment can then be expressed as $C_i \cdot A \cdot \Delta x$. Let J_1 be the amount of oxygen flows into the i^{th} compartment from the $(i-1)^{th}$ compartment through the cross section area A at $(i-1)\Delta x$ and J_2 the amount of oxygen leaving the i^{th} compartment towards the $(i+1)^{th}$ compartment at $i\Delta x$. For simplicity, let N_i denote the mass of oxygen molecules in the i^{th} compartment for now. Consider small time step Δt such that

$$t = \Delta t \cdot n. \tag{3.8}$$

The net movement of particles across the cross section area A during a time interval Δt from the $(i-1)^{th}$ compartment to the i^{th} compartment is

$$J_1^n = -\frac{N_i^n - N_{i-1}^n}{A \cdot \Delta t}.$$
 (3.9)

Multiplying the top and bottom of the right hand side by Δx and rewriting, we have

$$J_1^n = -\frac{\Delta x}{\Delta t} \cdot \left[\frac{N_i^n}{A \cdot \Delta x} - \frac{N_{i-1}^n}{A \cdot \Delta x} \right].$$
(3.10)

The mass concentration is defined as mass per unit volume, and hence

$$C_i^n = \frac{N_i^n}{A \cdot \Delta x} \tag{3.11}$$

is the oxygen concentration in the i^{th} compartment. Thus our expression of the net oxygen flux from the left simplifies to

$$J_1^n = -\frac{\Delta x}{\Delta t} \cdot \left[C_i^n - C_{i-1}^n\right]. \tag{3.12}$$

Similarly, the net oxygen flux from the i^{th} compartment to the $(i + 1)^{th}$ compartment can be expressed as

$$J_2^n = -\frac{\Delta x}{\Delta t} \cdot \left[C_{i+1}^n - C_i^n\right]. \tag{3.13}$$

1. Difference Equation of Capillary Compartments:

We start from the case $\Delta x = 2R_c$, which means each capillary is represented by a single compartment. Assume the i^{th} compartment is a capillary compartment. Since the permeability for gas through the capillary membrane is unlimited, the oxygen molecules diffuse from the erythrocyte inside the capillary following Fick's diffusion law under the normalized diffusive constant $D = (\Delta x)^2 / \Delta t$ (substitute back the parameters used for normalization and their units, we have $W'^2/(W'^2/D') = D'$). Since the capillary itself does not consume any oxygen, the net oxygen flux difference in the i^{th} compartment can be found by taking difference of the inflow 3.12 and outflow 3.13

$$J_1^n - J_2^n = \frac{\Delta x}{\Delta t} \left[C_{i-1}^n - 2C_i^n + C_{i+1}^n \right].$$
(3.14)

Balancing the mass flow though the cross section area A with the change of oxygen concentration in the i^{th} capillary compartment over a short time period Δt yields

$$D \cdot \left[C_i^{n-} - C_i^n\right] \cdot A \cdot \Delta x = \left[J_1^n - J_2^n\right] \cdot A \cdot \Delta t, \qquad (3.15)$$

where n_{-} represents the time at the end of the *n*th time interval. Substitute 3.15 into 3.14 and simplify, the oxygen concentration in a capillary compartment at the end of the n^{th} time interval is

$$C_i^{n-} = C_i^n + \frac{\Delta t}{(\Delta x)^2} \left[C_{i-1}^n - 2C_i^n + C_{i+1}^n \right].$$
(3.16)

The oxygen concentration of the mth capillary compartment in the beginning of the

next time interval is

$$C_i^{n+1} = C_m, \quad m = 1, ..., M.$$
 (3.17)

Now we extend the above idea to the general case, where $\Delta x \leq 2R_c$. One major problem arises from this situation is the asymmetry of neighboring tissue oxygen concentrations on the two sides. The strategy is to construct an algorithm from the real physiological process. Let the capillaries and tissues complete exchanging and consuming oxygen using equation 3.16 during the time interval Δt , then average the oxygen inside the capillary at the end of each time interval $t_{-} = \Delta t \cdot n_{-}$.

Notice that, there is no need to distinguish compartments of the same capillary between the interior and the boundary ones and assign with different difference equations. The discrete compartmental method can self-adjust during the physiological processes.



Figure 3.3: Calculation of capillary oxygen concentration after blocking the source. The three darker cells denote contiguous capillary compartments.

Figure 3.3 demonstrates the change in oxygen concentration after blocking the source in the case of $\Delta x = \frac{2}{3}R_c$. In this example, the three capillary compartments were labeled as "CC88" and the surrounding compartments are labeled as "TC" in the map. The initial oxygen concentration in each capillary compartment is 1 and the oxygen concentration is 0.5 in the two left neighboring tissue cells but 0 in the two right neighboring tissue cells. Due to the uneven partial pressure on the two sides, the oxygen concentrations inside each of the three capillary compartment are different after one step of diffusion and the concentration in the interior capillary compartment is unaffected. In this situation, the average of the three capillary compartments is calculated and reassigned to all of three for the beginning of the next diffusion and consumption step. Notice in reality the mixing process happens concurrently with the diffusion, therefore the process does not take any extra time during the computations.

2. Difference Equation of Tissue Compartments:

Oxygen is consumed in the tissue by chemical reaction (to CO_2) at a constant rate κ . Thus, combining Fick's first law with the mass conservation, the change of oxygen concentration in the i^{th} compartment over a short time period Δt is

$$D \cdot \left[C_i^{n+1} - C_i^n \right] \cdot A \cdot \Delta x = \left[J_1^n A - J_2^n A - \kappa \cdot A \cdot \Delta x \right] \cdot \Delta t.$$
 (3.18)

Substitute in J_1^n , J_2^n from 3.12 and 3.13, oxygen concentration in an tissue compartment at the next time step can be estimated by

$$C_i^{n+1} = C_i^n + \frac{\Delta t}{(\Delta x)^2} \left[C_{i-1}^n - 2C_i^n + C_{i+1}^n \right] - \Delta t \cdot \kappa.$$
(3.19)

However, in the case of hypoxia there may not be sufficient oxygen for tissue consumption. In other words, the local available oxygen is less than the necessary consumption rate

$$C_{i}^{n} + \frac{\Delta t}{(\Delta x)^{2}} \left[C_{i-1}^{n} - 2C_{i}^{n} + C_{i+1}^{n} \right] < \Delta t \cdot \kappa,$$
(3.20)

which will result the oxygen concentration value to be negative in the next time step. In this case, we require that each tissue compartment can only consume the amount of oxygen that are available, which means such tissue compartment will consume all oxygen it has and its the concentration in the next time step is set to zero

$$C_i^{n+1} = 0. (3.21)$$

Combining the two cases, the governing equation of an interior tissue compartment can be written as

$$C_i^{n+1} = \max\left\{C_i^n + \frac{\Delta t}{(\Delta x)^2} \left[C_{i-1}^n - 2C_i^n + C_{i+1}^n\right] - \Delta t \cdot \kappa, 0\right\}.$$
 (3.22)

Notice that, in the above equation $\Delta t/(\Delta x)^2$ must be less than 0.5 for stability and convergence in one dimensional problems. (A proof is given in Chapter 5.)

3. Difference Equation of Boundary Compartments:

There are two type boundary compartments in the one dimensional discrete compartmental model, the left boundary compartment and the right compartment. Table 3.1 shows a schematic diagram of the two boundary compartments and their labels. Here, label "BC21" represents the left boundary compartment and label "BC12" represents the right boundary compartment.

IC	BC21	TC	TC	•••	TC	CC1	TC	•••	TC	BC12	IC
----	------	----	----	-----	----	-----	----	-----	----	------	----

Table 3.1: 1D schematic diagram of different type of boundaries and their labels. Label "BC21" = the left boundary compartment and label "BC12" = the right boundary compartment. "CC1" = capillary compartment of the (m = 1) capillary. "IC" = inactivated compartment.

Consider the left boundary compartment, labeled as "BC21", which has oxygen concentration C_1^n . Based on equation 3.22, its oxygen concentration in the next time step is

$$C_1^{n+1} = \max\left\{C_1^n + \frac{\Delta t}{(\Delta x)^2} \left[C_0^n - 2C_1^n + C_2^n\right] - \Delta t \cdot \kappa, 0\right\},\tag{3.23}$$

where C_0^n is an inactive compartment on the left of the left boundary compartment and is located outside the domain boundary. Recall that the outer domain boundary is assumed to be reflecting, which implies that the oxygen concentration of the 0^{th} compartment is always identical to the concentration of the 2^{nd} compartment and so there is no net flux cross the boundary, i.e. $C_0^n \equiv C_2^n$ for all n. Therefore, the difference equation gives the oxygen concentration of the left boundary compartment in the next time step can be generally written as

$$C_{i}^{n+1} = \max\left\{C_{i}^{n} + \frac{2\Delta t}{(\Delta x)^{2}}\left[C_{i+1}^{n} - C_{i}^{n}\right] - \Delta t \cdot \kappa, \ 0\right\}.$$
 (3.24)

Similarly, for the right boundary compartment, labeled as "BC12", oxygen concentration in the next time step is

$$C_{i}^{n+1} = \max\left\{C_{i}^{n} + \frac{2\Delta t}{(\Delta x)^{2}}\left[C_{i-1}^{n} - C_{i}^{n}\right] - \Delta t \cdot \kappa, 0\right\}.$$
 (3.25)

Summary

There are in total four types of compartments in the one dimensional problem. The difference equation governing each of them can be summarized to one single equation:

$$C_i^{n+1} = \max\left\{C_i^n + \frac{\Delta t}{(\Delta x)^2} \left[a \cdot C_{i-1}^n - 2C_i^n + b \cdot C_{i+1}^n\right] - \Delta t \cdot K, \ 0\right\}.$$
 (3.26)

Different parameters should be employed while applying to different type of compartments. Table 3.2 gives a summary of the corresponding relationships of the compartment label and the coefficients.

Compartment Type	a	b	Κ
CCm	1	1	0
TC	1	1	κ
BC21	0	2	κ
BC12	2	0	κ

Table 3.2: Index table of different types of compartments. The corresponding relationships of the compartment label and the coefficients is given. Label "CCm" represents the *m*th capillary compartments, label "TC" represents the interior tissue compartments, label "BC21" represents the left boundary compartment and label "BC12" represents the right boundary compartment. K indicates the value of the consumption term.

3.1.2 The Crank-Gupta Problem

Introduction

The one dimensional moving boundary problem describing the oxygen diffusion and consumption phenomenon in the body tissue is first discussed by Crank and Gupta [12] [11] due to interest in medical research concerning the uptake of oxygen by tissue. As one of the simplest examples of a moving boundary problem, it has been used as a test case in the development of new methods thereafter and is known as the Crank-Gupta problem. Hansen and Hougaard [29], obtained an integral formula for the concentration. Their results are probability the most accurate available and we shall compare our results with both Crank and Gupta [12] and Hansen and Hougaard [29].

Statement of the problem

In the Crank-Gupta problem, oxygen is allowed to diffuse into a medium which simultaneously consumes the oxygen at a constant rate. The problem has two parts: first, the oxygen concentration at the surface of the medium(could be considered as a capillary) is kept constant until oxygen does not diffuse any further into the medium and a steady-state is reached. The supply of oxygen is then removed abruptly and the surface is sealed. No further oxygen passed in or out and the medium continues to absorb the available oxygen. Consequently, the point marking the furthest depth of diffusion in the steady-state begins to move towards the sealed surface at x = 0.

In non-dimensional form, the second part of the problem can be expressed in discrete compartmental system as an array of I + 1 cube compartments of side length $\Delta x = 1/I$, each of which is centered at position $\Delta x \cdot i$ and has oxygen concentration C_i^n at time $\Delta t \cdot n$. Initially, each compartment has oxygen concentration

$$C_i^0 = \frac{1}{2}(1 - \Delta x \cdot i)^2, \quad i = 0, 1, \cdots, I.$$
 (3.27)

At the beginning, each compartment exchange oxygen with its neighbors over each small

time period Δt with constant diffusion coefficient of D = 1 and consume the oxygen simultaneously at a constant rate of $\kappa = 1$.

Using partial differential equations, the problem is originally expressed as

$$\frac{\partial C}{\partial t} = \frac{\partial^2 C}{\partial x^2} - 1, \quad 0 \leqslant x \leqslant s(t), \quad t \ge 0$$
(3.28)

with associated boundary conditions

$$\frac{\partial C}{\partial x} = 0$$
, at the sealed surface $x = 0$, (3.29)

$$C = \frac{\partial C}{\partial x} = 0$$
, at the moving boundary $x = s(t)$, (3.30)

and the initial condition

$$C = \frac{1}{2}(1-x)^2, \quad 0 \le x \le 1, \quad t = 0,$$
(3.31)

with s(0) = 1. Here C(x, t) denotes the oxygen concentration at a point, x, and time, t, and s(t) the position of the moving boundary.

Notice that, the major challenge of the problem is to trace the location of the moving boundary, in the meanwhile determining the oxygen concentration through the medium as a function of time. Since not only the oxygen concentration is zero but its gradient is also zero on the boundary, there is no explicit relationship which contains the velocity of the moving boundary. However, if the discrete compartmental model is used to analyze the problem, there is no need to specify the location of the boundary.

Implementation of the DCM

To apply the discrete compartmental method, one need to construct an appropriate compartmental map and to determine the label of each compartment. Table 3.3 shows the compartmental map for the Crank-Gupta problem with the following properties: 1. only one boundary compartment is needed on the left side, 2. the number of tissue compartments depends on the choice of Δx , 3. there is no need to specify the right boundary compartment, 4. the nearest compartment with zero concentration would be the moving boundary.

IC	BC21	TC	•••								
----	------	----	----	----	----	----	----	----	----	----	-----

Table 3.3: Compartmental map for the Crank-Gupta problem.

The difference equation updating the value of each compartment corresponding to each label is given by equation (3.26) and coefficients of which is given by table 3.2.

Results and discussion

Following the discrete compartment model, computations were carried out for different compartment sizes ($\Delta x = 0.05$ and $\Delta x = 0.0125$). Interpolation is applied to improve the accuracy of the results. Table 3.4 and table 3.5 shows the comparison of results to that from Crank and Gupta [12] with $\Delta x = 0.05$ and Hansen & Hougaard [29] at different times. Before a moving boundary appears, i.e. Eq. (3.30), our result is very close to that of Crank and Gupta [12] using a finite difference method. At all times, the values obtained using $\Delta x = 0.0125$ are in a very good agreement with those from Hansen & Hougaard [29]. It should be noted that both numerical solutions using relatively larger grid ($\Delta x = 0.5$) involve large errors on the moving boundary and are unstable due to discontinuity in the gradient there. As the moving boundary gets very close at larger t (e.g. t = 1.95), that error is enlarged since too few grids are left and are not enough to represent the remaining subtle changes.

$t \setminus x$	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
	223605	217168	198777	170979	137379	101928	68291	39451	17581	4129
0.060	223746	217330	198992	171251	137684	102227	68548	39645	17705	4186
0.000	223615	217175	198783	170980	137376	101920	68283	39443	17574	4118
	223605	217268	198777	170979	137379	101928	68291	39451	17579	4122
	143177	139294	128082	110787	89295	65892	43018	23059	8232	603
0 100	143287	139414	128338	110996	89502	66112	43228	23232	8342	619
0.100	143181	139298	128084	110787	89289	65878	42995	23041	8271	774
	143177	139294	128082	110787	89295	65892	43018	23058	8231	608
	109129	106019	97025	83117	65795	46941	28667	13204	2873	0
0 1 2 0	109228	106125	97149	83265	65963	47115	28827	13324	2924	0
0.120	109131	106020	97024	83114	65790	46936	28661	13193	2838	0
	109129	106019	97025	83117	65795	46941	28667	13203	2875	0
0.140	77850	75351	68130	56988	43197	28416	14638	4204		
	77937	75442	68233	57105	43322	28536	14730	4249	0	0
	77850	75350	68128	56984	43190	28407	14640	4186	0	0
	77850	75351	68130	56988	43197	28415	14637	4203		

Table 3.4: Comparison for $C \times 10^6$ at different times. On each time level, the first row shows values taken from Hansen & Hougaard [29], the second row shows values from Crank and Gupta [12] with $\Delta x = 0.05$, the third row gives values obtained from DCM with $\Delta x = 0.05$ and the forth row the DCM with $\Delta x = 0.0125$.

$t \setminus x$	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
	63078	60845	54403	44503	32353	19583	8251	1005		
0 150	63157	60928	54496	44602	32453	19668	8298	1007	0	0
0.100	63069	60837	54394	44494	32344	19570	8217	996	0	0
	63077	60845	54403	44503	32353	19582	8250	1000		
	48823	46840	41136	32434	21927	11304	2890			
0 160	48893	46912	41212	32511	21996	11346	2890	0	Ο	0
0.100	48822	46837	41132	32428	21918	11303	2874	0	0	0
	48823	46840	41136	32433	21927	11303	2888			
	21781	20287	16066	9942	3523					
0 180	21824	20328	16096	9950	3506	0	0	0	0	0
0.100	21776	20282	16058	9932	3506	0	0			0
	21781	20287	16065	9941	3519					
	9021	7817	4578	799						
0 100	9039	7827	4575	750	0	0	0	0	0	0
0.190	9007	7801	4554	788	0	0	0	0	0	0
	9021	7817	4576	787						
	2884	1914	32							
0 105	2880	1909	0	0	0	0	0	0	Ο	0
0.190	2867	1885	0	U	U	U	U	U	U	U
	2883	1912	33							

Table 3.5: Comparison for $C \times 10^6$ at different times. On each time level, the first row shows values taken from Hansen & Hougaard [29], the second row shows values from Crank and Gupta [12] with $\Delta x = 0.05$, the third row gives values obtained from DCM with $\Delta x = 0.05$ and the forth row the DCM with $\Delta x = 0.0125$.

Method\Time	0.05	0.1	0.16	0.18	0.19	0.195	0.197	0.1974
Crank & Gupta [12]	247841	143287	48893	21834	9030	2880	-	-
Hansen & Hougaard [29]	247687	143177	48893	21824	9039	2884	-	-
Dahmardah & Mayers [13]	247687	143177	48823	21781	9021	2883	491	40
$DCM(\Delta x=0.0125)$	247687	143177	48823	21781	9021	2883	503	39

Table 3.6: Comparison of results at the sealed surface.

Table 3.6 provides a comparison for the result at the sealed surface as obtained from (i) Crank & Gupta [12] with $\Delta x = 0.5$, (ii) Hansen & Hougaard [29] using integral method, (iii) Dahmardah & Mayers [13] using Fourier expansion and (iv) DCM with $\Delta x = 0.0125$. Our results are in good agreement with those of Hansen & Hougaard [29] and Dahmardah & Mayers [13] even in large times.

Method	Oxygen depletion time
Crank & Gupta [12]	0.196349
Hansen & Hougaard [29]	0.1972-0.1977
Miller, Morton & Baines [45]	0.196-0.198
Gupta & Kumar [28]	0.19732
(unequal intervals)	0.19734
Dahmardah & Mayers [13]	0.197434
Mitchell [46]	0.197432
Mitchell & Vynnycky [47]	0.197435
DCM ($\Delta x=0.0125$)	0.197437

Table 3.7: Comparison of the oxygen depletion time with previous works.
Table 3.7 shows the comparison of oxygen depletion time with many previous works and Table 3.8 shows the comparison of oxygen depletion time in different mesh size using DCM . It is seen from the tables that our result converges quickly as the size of Δx decreases and agree with those accurate methods with $\Delta x = 0.0125$ and smaller.

Δx	0.1	0.05	0.025	0.0125	0.00625	0.003125
t^*	0.196	0.197	0.1975	0.197437	0.197437	0.197437

Table 3.8: Comparison of oxygen depletion time (t^*) in different mesh size using DCM.

3.1.3 Three Capillaries of Uneven Strength

As a multi-capillary example, consider three capillary of diameter 0.02 and uneven strength in a one-dimensional tissue region of unit length and unit consumption rate. As an illustrative example, let the first capillary centered at x = 0.21, the second at x = 0.61 and the third at x = 0.91. Let the consumption rate be $\kappa = 1$. Computations in this example were carried out with compartment size of $\Delta x = 0.02$ and time step size $\Delta t = 0.0001$. The analytical solution used for comparison is found by solving differential equation (3.4) over each interval.

(a) The oxygen concentration is originally zero everywhere and the capillary concentration is suddenly raised and kept at 0.08, 0.03 and 0.05 respectively. There is no flux on the tissue boundary. All values here are normalized. Figure 3.4 shows the transient concentration profiles at t = 0.001, t = 0.01 and t = 0.2. An analytic steady state solution is obtained from solving the partial differential equations. As $t \to \infty$, the transient numerical solution approaches the analytic steady state solution

$$C(x) = \begin{cases} 0.5 (x^2 + 0.12) & 0 \le x \le 0.2 \\ 0.5 (x^2 - 1.083x + 0.3499) & 0.22 \le x \le 0.6 \\ 0.5 (x^2 - 1.77x + 0.5294) & 0.62 \le x \le 0.9 \\ 0.5 (x^2 - 2x + 1.094) & 0.92 \le x \le 1. \end{cases}$$
(3.32)



Figure 3.4: Oxygen diffusion from three capillaries of different strengths into a consuming region at t=0.001, t=0.01 and t=0.1, compared with the analytic steady state solution.

(b) The initial oxygen concentration is at the steady state of part (a). The second capillary is blocked at t = 0. Note that a blockage does not mean the capillary concentration suddenly drops to zero. A blocked capillary no longer provides new oxygen but the remaining oxygen inside would gradually diffuse out. Figure 3.5 shows the transient concentration profiles at t = 0.001, t = 0.02 and t = 0.2. As $t \to \infty$, the transient solution approaches

$$C(x) = \begin{cases} 0.5 (x^2 + 0.12) & 0 \le x \le 0.2 \\ 0.5 (x^2 - 1.208x + 0.3774) & 0.22 \le x \le 0.9 \\ 0.5 (x^2 - 2x + 1.094) & 0.92 \le x \le 1. \end{cases}$$
(3.33)

which is the analytic steady state solution under the new initial conditions.



Figure 3.5: Concentration profile at t=0.001, t=0.02 and t=0.2 times after a blockage occurred on middle capillary, compared with the analytic steady state solution.

(c) The initial oxygen concentration is at the steady state of part (b). The third capillary is blocked at t = 0. Figure 3.5 shows the transient concentration profiles at t = 0.002, t = 0.02 and t = 0.3. As t > 0.0272, the tissue compartments in the middle of the right two capillaries begin to suffer anoxia and two moving boundaries occur. At t = 0.03, an anoxic zone of zero oxygen concentration exists in the interval $0.6 \le x \le 1$. Note that the gradient of the oxygen concentration at the supply boundary is zero as predicted (Eq. (3.30)).



Figure 3.6: Concentration profile at t=0.002, t=0.02 and t=0.03 times after a blockage occurred on the right capillary.

Table 3.9 shows how the boundary condition is easily changed in DCM by relabeling the capillary compartments. Each raw of labels corresponds to part (a), (b) and (c) in the above example. At the beginning, there are three capillaries labeled as "CC1", '1CC2" and "CC3" respectively, each of which determines the amount of oxygen concentration for that capillary compartment at the beginning of each time step. While the second capillary is blocked, label "CC2" is replaced by "CC0", which corresponds to a particular algorithm for blocked capillaries (diffusion only and no further update of incoming oxygen concentration). While the third capillary is blocked, label "CC3" is replaced by "CC3" is replaced by "CC0" as well. Besides relabeling, no further action is requires for changing the boundary condition.

	TC	CC1	TC	•••	TC	CC2	TC	•••	TC	CC3	TC	•••
	TC	CC1	TC		тс	CC0	TC		TC	CC3	TC	•••
•••	TC	CC1	TC		TC	CC0	TC		TC	CC0	TC	•••

Table 3.9: Schematic diagram of label changing following capillary blockage in the 1D example. Label "CCM" = capillary compartment corresponding to the oxygen concentration of the m^{th} capillary. "CC0" = capillary compartment corresponding to a blocked capillary.

Discussion

The solution of part (a) shows that with capillaries of different strengths, tissue oxygen concentration is changing at different speeds and the supply boundaries are closer to the weaker sources. Part (b)'s result shows that blockage of a capillary may not cause serious oxygen deficit overtime if neighbor sources are strong enough to compensate. Part (c) shows the method can easily treat moving boundary problems. Such problems has no analytic solutions to compare with.

Transient solutions of this one dimensional problem illustrate many innovative advances of DCM. However, it also shows the limits of using low dimensional models. The zero concentration profile over the domain $0 \le x \le 0.2$ never recovered. This is because there is only one pathway in the 1D domain and tissue regions are isolated. If there are other pathways, would the oxygen could diffuse around any blockage and replenish anoxic tissues? We shall explore this possibility by building 2D and 3D compartmental models.

3.2 Two Dimensional Unsteady Diffusion-Consumption

The discrete compartment model has showed some advantages on solving the one dimensional unsteady diffusion-consumption problem. In 2D, it is more difficult to predict when and where the anoxia regions will appear. The advantages of DCM will be extended to handle such difficulty.

Figure 3.7 shows a schematic diagram of 2D capillary-tissue region with two capillaries of uneven strength. An important question we wish to answer is, where and when would anoxia occur if one or more capillaries was blocked. For example, if the capillary on the right was blocked, will the ischemia area only happen around the capillary or elsewhere or both?



Figure 3.7: schematic diagram of 2D planar capillary-tissue region and blockage on one capillary. Shaded area in part (b) represents the possible anoxic areas due to blockage on the right capillary.

The problem of two dimensional unsteady diffusion and consumption problem describing

the oxygen transfer from capillary to tissue after normalization can be generally stated as follows. Consider M capillaries of same radius R'_c and different oxygen concentration C'_M located irregularly in a bounded region $\Omega' \in \mathbf{R}^2$. Define individual capillary domain

$$\Omega'_m = \left\{ (x', y') : (x', y') \in \Omega' \text{ and } (x' - x'_m)^2 + (y' - y'_m)^2 \leqslant (R'_c)^2 \right\},\$$

where (x'_m, y'_m) are the coordinates of the center of each capillary. Thus, the total capillary domain is

$$\Omega_c' = \bigcup_{m=1}^M \Omega_m'$$

and the absorbing tissue domain is

$$\Omega_t' = \Omega' \setminus \Omega_c'$$

Driven by the passive diffusion due to the partial pressure differences, oxygen diffuse out from each capillary into the surrendering tissue and is consumed. The governing partial differential equation to this unsteady diffusion-consumption problem is

$$\frac{\partial C'}{\partial t'} = D' \left(\frac{\partial^2 C'}{\partial x'^2} + \frac{\partial^2 C'}{\partial y'^2} \right) - \kappa', \qquad (x', y') \in \Omega'_t, \ t' \in [0, \infty)$$
(3.34)

where D' is the diffusion constant, C'(x', y', t') is the non-negative oxygen concentration (or partial pressure) and k' is the constant consumption per volume of tissue. Inside each capillary and on the capillary wall the concentration is C'_M , differing in the capillary strength

$$C'(x', y', t') = C'_m, \qquad (x', y') \in \Omega'_m, \ t' \in [0, \infty), \ m = 1, \cdots, M.$$
 (3.35)

On the tissue boundary $\partial \Omega'$ there is no flux or the normal derivative of concentration is zero

$$\left. \frac{\partial C'}{\partial n} \right|_{(x',y') \in \partial \Omega'} = 0. \tag{3.36}$$

Normalize all length by $\tilde{L} = \sqrt{A(\Omega')}$, the square root of Ω' 's area, the concentration by the average on the arterial end C'_a , time by \tilde{L}^2/D' and drop primes. In terms of normalized parameters the equations are

$$\frac{\partial C}{\partial t} = \left(\frac{\partial^2 C}{\partial x^2} + \frac{\partial^2 C}{\partial y^2}\right) - \kappa, \qquad (x, y) \in \Omega_t, \ t \in [0, \infty),$$
(3.37)

$$C(x, y, t) = C_m,, \qquad (x, y) \in \Omega_m, \ t \in [0, \infty), \ m = 1, \cdots, M,$$
 (3.38)

$$\left. \frac{\partial C}{\partial n} \right|_{(x,y) \in \partial \Omega} = 0, \tag{3.39}$$

where $\kappa = \kappa' \tilde{L}^2 / C'_a D'$.

If oxygen deficient occurs, the flux and the concentration value equals zero on the moving boundaries ∂O

$$\frac{\partial C}{\partial n}\Big|_{(x,y)\in\partial O} = C|_{(x,y)\in\partial O} = 0 \tag{3.41}$$

Oxygen deficit region and its moving boundaries are defined in section 2.3.1.

3.2.1 Formulation

Now we construct the 2D discrete compartmental system directly from the physical problem.

The general problem after normalization can be stated as follows.

Consider a two dimensional discrete compartmental space of packed ordered identical

compartments with equal side length Δx and cross-section area A. The key of solving capillary-tissue exchange problem using the discrete compartmental model is to maintain the cross section area of each capillary. Moreover, the shape of capillary compartments need be approximately radially symmetric. Thus, in two dimensional modeling, the choice of Δx must satisfy

$$\Delta x = \sqrt{\frac{\pi R_c^2}{n_{CC}}} \tag{3.42}$$

where $n_{CC} = 1, 4, 5, 9, 13, \dots$ So that the total area of the capillary compartments is consistent with the original circular area and the direction of oxygen flux is kept radially uniform. Figure 3.8 shows some examples of good and bad capillary compartment arrangements.



Figure 3.8: Example of 2D capillary shapes.

Now we derive the governing difference equations for updating oxygen concentration in different types of compartments in 2D discrete compartmental system. Figure 3.9 shows the local arrangement of nine cube compartments. The $(i, j)^{th}$ cell has four adjacent neighbors

$$(i-1,j), (i,j-1), (i+1,j), (i,j+1),$$

$$(3.43)$$

as well as four diagonal neighbors

$$(i-1, j-1), (i-1, j+1), (i+1, j-1), (i+1, j+1).$$
 (3.44)

Let $C_{i,j}^n$ denote the oxygen concentration of the $(i,j)^{th}$ compartment at time $\Delta t \cdot n$. The mass change inside this closed volume $V = (\Delta x)^3$ over a short time period Δt is

$$\left[C_{i,j}^{n+1} - C_{i,j}^n\right] \cdot V. \tag{3.45}$$



Figure 3.9: The 2D compartmental model.

Following the work in section 3.1.1, the oxygen fluxes across the cross sections of an area A from/to the top, left, bottom or right neighbor compartments during a time interval Δt

are

$$J_1^n = -\frac{\Delta x}{\Delta t} \cdot \left[C_{i,j}^n - C_{i-1,j}^n \right], \qquad J_2^n = -\frac{\Delta x}{\Delta t} \cdot \left[C_{i,j}^n - C_{i,j-1}^n \right],$$

$$J_3^n = -\frac{\Delta x}{\Delta t} \cdot \left[C_{i+1,j}^n - C_{i,j}^n \right], \qquad J_4^n = -\frac{\Delta x}{\Delta t} \cdot \left[C_{i,j+1}^n - C_{i,j}^n \right].$$
(3.46)

1. Difference Equation of Capillary Compartments:

Consider the case $\Delta x = \sqrt{\pi R_c^2}$, which means each capillary is represented by a single compartment. Assume the $(i, j)^{th}$ compartment is a unobstructed capillary compartment, where oxygen diffused out over each time step following the normalized diffusion constant $D = (\Delta x)^2 / \Delta t$ and the compartment itself does not consume any oxygen. Thus, the concentration change in the $(i, j)^{th}$ capillary compartment over the time period Δt can be described as

$$[(J_1^n + J_2^n - J_3^n - J_4^n) \cdot A] \cdot \Delta t.$$
(3.47)

Balance of mass flow through the cross section area A with the oxygen concentration change in the i, j^{th} capillary compartment over the time period Δt yields

$$D \cdot \left[C_{i,j}^{n_{-}} - C_{i,j}^{n} \right] \cdot V = \left[\left(\sum_{m=1}^{4} J_{m}^{n} \right) \cdot A \right] \cdot \Delta t, \qquad (3.48)$$

where n_{-} represents time at the end of the n^{th} time interval. Substituting in J_1^n , J_2^n , J_3^n , J_4^n , from (3.46) and simplifying give the oxygen concentration in the $(i, j)^{th}$ capillary compartment at the end of the *n*th time interval

$$C_{i,j}^{n-} = C_{i,j}^{n} + \frac{\Delta t}{(\Delta x)^2} \left[\Sigma_{nb} C_{i,j}^{n} - 4C_{i,j}^{n} \right], \qquad (3.49)$$

where

$$\Sigma_{nb}C_{i,j}^n = C_{i-1,j}^n + C_{i,j-1}^n + C_{i+1,j}^n + C_{i,j+1}^n.$$
(3.50)

The oxygen concentration of the m^{th} unobstructed capillary compartment in the begining of the next time interval is

$$C_{i,j}^{n+1} = C_m. (3.51)$$

Now extend the above idea to the general case, where $\Delta x \leq \sqrt{\pi R_c^2}$. As shown in figure 3.8(a), while one capillary is represented by more then one compartment, each of the compartment may have different values after one exchange process and a compartment in the middle is isolated to the tissue region whose value will not be changed during the exchange process. Since oxygen is assumed to be well mixed inside the capillary, an average of the oxygen concentration over each capillary's compartments shall be taken and reassigned back to them at the end of each time interval $t_{-} = \Delta t \cdot n_{-}$.

For capillaries with reducing strength, a new value of C_m should be used in the next time step $t_{n+1} = \Delta t \cdot (n+1)$. For blocked capillaries,

$$C_{i,j}^{n+1} = C_{i,j}^{n-}. (3.52)$$

2. Difference Equation of Tissue Compartments:

Consider the interior tissue compartments which consume oxygen at a constant rate of κ . The concentration change caused by the difference between inflows, outflows and

consumption in the i, j^{th} compartment over the time period Δt can be described as

$$[(J_1^n + J_2^n - J_3^n - J_4^n) \cdot A - \kappa \cdot V] \cdot \Delta t.$$
(3.53)

Now, balance Equation (3.53) with Equation (3.45) gives

$$D \cdot \left[C_{i,j}^{n+1} - C_{i,j}^n \right] \cdot V = \left[\left(\sum_{m=1}^4 J_m^n \right) \cdot A - \kappa \cdot V \right] \cdot \Delta t.$$
(3.54)

Substituting in J_1^n , J_2^n , J_3^n , J_4^n , from (3.46) and simplifying yield

$$C_{i,j}^{n+1} = C_{i,j}^{n} + \frac{\Delta t}{(\Delta x)^2} \left[\Sigma_{nb} C_{i,j}^{n} - 4C_{i,j}^{n} \right] - \Delta t \cdot \kappa,$$
(3.55)

where

$$\Sigma_{nb}C_{i,j}^n = C_{i-1,j}^n + C_{i,j-1}^n + C_{i+1,j}^n + C_{i,j+1}^n.$$
(3.56)

Consider local oxygen deficiency, where

$$C_{i,j}^{n} + \frac{\Delta t}{(\Delta x)^{2}} \left[\Sigma_{nb} C_{i,j}^{n} - 4C_{i,j}^{n} \right] < \Delta t \cdot \kappa.$$
(3.57)

In this case, the tissue compartment consumes all the remaining oxygen during that time step, which results

$$C_{i,j}^{n+1} = 0. (3.58)$$

Combining the oxygen sufficient case with the oxygen deficient case, the governing

difference equation of an interior tissue compartment is

$$C_{i,j}^{n+1} = \max\left\{C_{i,j}^{n} + \frac{\Delta t}{(\Delta x)^{2}} \left[\Sigma_{nb}C_{i,j}^{n} - 4C_{i,j}^{n}\right] - \Delta t \cdot \kappa, \ 0\right\},$$
(3.59)

where $\Delta t/(\Delta x)^2$ shall be less than 0.25 in the two dimensional problem for stability and convergence. See section 5 for a theoretical proof.

3. Difference Equation of Boundary Compartments:

For a rectangular shaped domain in two dimensional space, there are eight type of boundary compartments. As shown in table 3.10, these boundary compartments can be classified into two groups: tissue compartment with one inactive neighbor(located on the side) and tissue compartment with two inactive neighbors(located on the corner).

IC	IC	IC	IC	IC
IC	BC40	BC31	BC50	IC
IC	BC21	TC	BC22	IC
IC	BC60	BC32	BC70	IC
IC	IC	IC	IC	IC

Table 3.10: Discrete compartmental map of 2D unsteady diffusion-consumption problem over rectangular shaped domain. Label "TC" = tissue compartment; label "BC##"=boundary compartment of type ##; label "IC" = inactivated compartment.

Consider the boundary compartment on the middle of the left margin, labeled as "BC21", which has oxygen concentration $C_{2,1}^n$ at time $t_n = \Delta t \cdot n$. Based on equation 3.59, its oxygen concentration in the next time step is

$$C_{2,1}^{n+1} = \max\left\{C_{2,1}^n + \frac{\Delta t}{(\Delta x)^2} \left[\Sigma_{nb}C_{2,1}^n - 4C_{2,1}^n\right] - \Delta t \cdot \kappa, 0\right\},\tag{3.60}$$

where

$$\Sigma_{nb}C_{2,1}^n = C_{1,1}^n + C_{2,0}^n + C_{3,1}^n + C_{2,2}^n.$$
(3.61)

Because the $(2,0)^{th}$ compartment is an inactivated compartment, its value equals to the $(2,2)^{th}$ compartment for all times so that no flux crosses the boundary, i.e. $C_{2,0}^n \equiv C_{2,2}^n$ for all n. Hence, the difference equation gives the oxygen concentration for boundary compartments labeled as "BC21" is in general

$$C_{i,j}^{n+1} = \max\left\{C_{i,j}^n + \frac{\Delta t}{(\Delta x)^2} \left[C_{i-1,j}^n + C_{i+1,j}^n + 2C_{i,j+1}^n - 4C_{i,j}^n\right] - \Delta t \cdot \kappa, 0\right\}.$$
(3.62)

Governing difference equations for boundary compartments labeled as "BC22", "BC31" and "BC32" in table 3.10 can be derived in the same way.

Now, consider the boundary compartment on the left up corner, labeled as "BC41", whose oxygen concentration at time $t_n = \Delta t \cdot n$ is $C_{1,1}^n$. Based on equation 3.59, its oxygen concentration in the next time step is

$$C_{1,1}^{n+1} = \max\left\{C_{1,1}^n + \frac{\Delta t}{(\Delta x)^2} \left[\Sigma_{nb}C_{1,1}^n - 4C_{1,1}^n\right] - \Delta t \cdot \kappa, 0\right\},\tag{3.63}$$

where

$$\Sigma_{nb}C_{1,1}^n = C_{0,1}^n + C_{1,0}^n + C_{2,1}^n + C_{1,2}^n.$$
(3.64)

However, both the $(0,1)^{th}$ and the $(1,0)^{th}$ compartments are inactivated compartments, which means they are outside the boundary. Due to the reflecting boundary condition, $C_{0,1}^n$ is assumed to be identical to $C_{2,1}^n$ and $C_{1,0}^n$ is assumed to be identical to $C_{1,2}^n$ for all n. Therefore, the difference equation updates the oxygen concentration for a compartments labeled as 'BC40" is generally

$$C_{i,j}^{n+1} = \max\left\{C_{i,j}^{n} + \frac{\Delta t}{(\Delta x)^2} \left[2\left(C_{i+1,j}^{n} + C_{i,j+1}^{n}\right) - 4C_{i,j}^{n}\right] - \Delta t \cdot \kappa, 0\right\}.$$
 (3.65)

Governing difference equations for boundary compartments labeled as "BC50", "BC60" and "BC70" in table 3.10 can be derived in the same way.

IC	IC	IC	IC	IC
BC31	BC51	IC	IC	IC
TC	TC	BC52	IC	IC
TC	TC	TC	BC53	IC
TC	TC	TC	BC22	IC

Table 3.11: Discrete compartmental map of 2D unsteady diffusion-consumption problem over irregular shaped domain. Label "TC" = tissue compartment; label "BC##"=boundary compartment of type ##; label "IC" = inactivated compartment.

For circular tissue domain or any other irregular shaped domains, a discretization method is used. Table 3.11 shows a local compartment map over a piece of curved boundary. Connecting the centers of boundary compartments "BC51", "BC52" and "BC53" yields a discretized boundary. Consider the boundary labeled as "BC52" with oxygen concentration $C_{i,j}^n$ at time t_n . A reflecting boundary condition implies that, towards this compartment, oxygen concentration of the $(i-1,j)^{th}$ (top) inactive neighbor is identical to that of the $(i, j-1)^{th}$ (left) tissue neighbor and oxygen concentration of the $(i, j+1)^{th}$ (right) inactive neighbor is equals to that of the $(i+1, j)^{th}$ (bottom) tissue neighbor. Therefore, the difference equation updates the oxygen concentration of this boundary compartment is

$$C_{i,j}^{n+1} = \max\left\{C_{i,j}^n + \frac{\Delta t}{(\Delta x)^2} \left[2C_{i,j-1}^n + 2C_{i+1,j}^n - 4C_{i,j}^n\right] - \Delta t \cdot \kappa, 0\right\}.$$
 (3.66)

Similarly, the difference equation for compartment "BC51" is

$$C_{i,j}^{n+1} = \max\left\{C_{i,j}^n + \frac{\Delta t}{(\Delta x)^2} \left[C_{i,j-1}^n + 3C_{i+1,j}^n - 4C_{i,j}^n\right] - \Delta t \cdot \kappa, 0\right\}.$$
 (3.67)

and for compartment "BC53" is

$$C_{i,j}^{n+1} = \max\left\{C_{i,j}^n + \frac{\Delta t}{(\Delta x)^2} \left[3C_{i,j-1}^n + C_{i+1,j}^n - 4C_{i,j}^n\right] - \Delta t \cdot \kappa, 0\right\}.$$
 (3.68)

3.2.2 Two capillaries of uneven strength in a circular domain

Consider, after normalization, a circular region of unit radius contains two capillaries at arbitrary locations and different diffusion strengths. Let q_m be the rate of amount of oxygen (per length of capillary) out of the *m*th capillary, with radius R_c centered at $r = r_m$ and $\theta = \theta_m$. Let $q_1 = 2/3$, $r_1 = 0.5$, $\theta = 0$, $q_2 = 1/3$, $r_2 = 0.5$, $\theta = \pi$. The boundary and initial conditions are that there is no flux on the circular boundary and the oxygen concentration is zero everywhere over the tissue region when t = 0. The consumption is $\kappa = 1$ per volume or whatever is available. As $t \to \infty$, the transient solution should approach the steady state solution

$$C = \frac{r^2}{4} - \sum_{j=1}^{N} \frac{q_j}{2} \ln p_j + \sum_{n=0}^{\infty} r^n \left(A_n \cos n\theta + B_n \sin n\theta \right), \qquad (3.69)$$

where

$$A_{n} = \frac{1}{2m} \sum_{j=1}^{N} q_{j} a_{j}^{m} \cos(m\alpha_{j}), \qquad (3.70)$$

and

$$B_n = \frac{1}{2m} \sum_{j=1}^N q_j a_j^m \sin(m\alpha_j), \quad m \ge 1,$$
(3.71)

as found analytically by Wang [68] Fig. 3.12.

Here we used $\Delta x = 0.01$ and $\Delta t = 0.00002$. The supply boundary is found by drawing the flux lines and searching for curves that starting from any point close to the saddle point and end close to a node point. Figure 3.10 shows the transient concentration profiles at t = 0.0002, t = 0.003, t = 0.006, t = 0.009, t = 0.012, t = 0.018, t = 0.024 and t = 0.048. As the figure shows, the majority of the tissue region is nourished in a very short time, but for region away from both capillaries, it takes much more time for oxygen to be delivered. Those regions are in great danger if the capillary supply was decreased or the tissue consumption was increased. Actually, it takes t = 6.64 for the entire region to be fully nourished and for the concentration profile to reach the steady state. Figure 3.12 shows the comparison of the concentration profile at steady state with the analytical solution found by Wang [68]. Our DCM is extremely accurate as the concentration level curve agrees perfectly with the analytic solution even near the circular boundary.



Figure 3.10: Transient process of oxygen diffusion from two capillaries of different strengths into a circular consuming region. Dark regions show the zero oxygen area. The vertical and horizontal axes shows the compartment numbers used in each direction.



Figure 3.11: Transient process of oxygen diffusion from two capillaries of different strengths into a circular consuming region. Dark regions show the zero oxygen area. The vertical and horizontal axes shows the compartment numbers used in each direction.



Figure 3.12: Concentration profile of two unequal strength capillaries in a circular domain, comparing to the analytic solution[68].

In addition, Figure 3.13 shows the plot of streamlines and the supply boundary curve found by searching the flux line that starts from a saddle point and end at a node point. Our result again agrees perfectly with those found analytically by Wang [68].



Figure 3.13: Flux and supply boundary of two capillaries of unequal strength in a circular domain, comparing to the analytic solution [68].

3.2.3 Nine capillaries of uneven strength in a rectangular domain

Consider nine capillaries of uneven strength in a squared region of unit side length. Table 3.12 shows the randomly generated location and flux strength corresponding to each capillary [62]. The boundary and initial conditions are that there is no flux on the circular boundary and the oxygen concentration is zero everywhere over the tissue region when t = 0. The

consumption is $\kappa = 1$ per volume or whatever is available. The sum of flux equals to 1 here, so that the tissue region is guaranteed be fully perfused at the steady state. As $t \to \infty$, the transient solution should approach the steady state solution. Note that, DCM can easily deal with tissue oxygen deficiency cases. The purpose of this example and the above one is to validate DCM with existing results.

m	x_m	y_m	flux strength of the m^{th} capillary, Q_m
1	0.501	0.498	0.044
2	0.721	0.235	0.089
3	0.242	0.754	0.133
4	0.091	0.046	0.133
5	0.633	0.932	0.089
6	0.867	0.354	0.023
7	0.425	0.301	0.133
8	0.664	0.316	0.178
9	0.723	0.833	0.178

Table 3.12: Locations and flux strength of nine capillaries used in the example.

Following the discrete compartmental method, computations were carried out with $\Delta x = 0.01$ and $\Delta t = 0.0000166$. Figure 3.14 shows the oxygen concentration level curves at steady state, where the tissue domain is fully nourished as expected. Our result agrees well with the analytic result found by Sun [62]. Actually, DCM is more accurate near the tissue boundary comparing to the analytic solution using a matching technique with first 40 terms in each set of coefficients, as the level curves are more perpendicular to the domain boundary.



Figure 3.14: Oxygen concentration level curves of nine capillaries with different strengths at steady state. The vertical and horizontal axes shows the compartment numbers used in each direction.

Remark: If capillary flux strength is given instead of concentration, in the difference equation for capillary compartments (3.49), we simply replace the concentration difference in the corresponding direction by the flux strength. For example, for a tissue compartment neighboring the m^{ht} capillary, say its (i + 1, j) neighbor is a capillary compartment, then the governing difference equation for that tissue cell is

$$C_{i,j}^{n+} = C_{i,j}^{n} + \frac{\Delta t}{(\Delta x)^2} \left[C_{i-1,j}^{n} + C_{i,j-1}^{n} + C_{i,j+1}^{n} - 3C_{i,j}^{n} + Q_m \right].$$
(3.72)

Discussion

In this section, we constructed the discrete compartment model in two-dimensional tissue region with multiple capillaries of uneven location and different strength. Two examples are demonstrated and the result at steady state agrees perfectly with the analytical solutions. It is shown by the steady state solution that oxygen coming out from stronger capillary will diffuse further and help nourishing low oxygen tension area. In addition to that, the transient solutions show that the time taken for oxygen to be delivered to region away from the capillaries could be considerable. However, a 2D model can not be used to explain the real biological phenomena, since the real capillary-tissue region is 3D. That means there are more pathways for oxygen to move and the oxygen concentration profile changes from the arterial end to the veinous end. In order to extend the DCM to 3D, we will first introduce the sliding element method and construct the 2D discrete compartmental model with the convection of oxygen inside the capillary taking into account.

3.3 Two Dimensional Unsteady Diffusion-Consumption-Convection

For oxygen transport to tissue, the convection due to blood flow cannot be ignored. We consider the convection of oxygen in capillary together with diffusion and consumption in tissue. Starting from a two-dimensional problem, introduce the sliding fluid element method on the discrete compartment model inside capillary compartments and combine it with the diffusion-consumption process in the tissue compartments. The three-dimensional transient problem is introduced in the following chapter..



Figure 3.15: Schematic diagram for 2D capillary-tissue exchange with convection, diffusion and consumption with nondimensionalized parameters. v_b is the blood velocity; D = 1 is the normalized diffusion coefficient; κ is the tissue consumption coefficient; L is the length of the tissue region along the z-axis; W is the thickness of the tissue region along the x-axis; oxygen concentration on the arterial end of the capillary is normalized by itself and therefore equals to 1.

Consider blood with velocity v'_b inside a long and straight capillary with radius R'_c centered along the z'-axes, where substrates and oxygen permeate through the capillary membrane wall with permeability P, diffuse into the nearby tissue region of length L' and thickness W' with diffusivety D', and was consumed there at constant rate κ' . Assume solutes are radially well mixed inside the capillary and the axial diffusion rate inside the capillary is neglected in comparison to transverse diffusion. Let $C'_c(z', t')$ and $C'_t(x', z', t')$ be the oxygen concentration inside the capillary and tissue respectively, with C'_c being nonnegative for any x', z', and t'. The governing partial differential equations to this unsteady convection-diffusion-consumption problem are

$$\frac{\partial C'_t}{\partial t'} = D' \left(\frac{\partial^2 C'_t}{\partial x'^2} + \frac{\partial^2 C'_t}{\partial z'^2} \right) - \kappa', \tag{3.73}$$

in the tissue region, and

$$\frac{\partial C_c'}{\partial t'} = -v_b' \cdot \frac{\partial C_c'}{\partial z'} \tag{3.74}$$

inside the capillary, where $0 \leq x' \leq W'$, $0 \leq z' \leq L'$ and $t' \geq 0$. Assume there is no flux on the boundary of tissue region. The permeability H is infinite for gas solute like oxygen. Thus the capillary and tissue oxygen concentration are equivalent on the capillary wall at $x' = R'_c$.

Normalize all lengths by the thickness of the region W', concentration by that of the arterial end C_a , time by W'^2/D' and drop primes. In terms of normalized parameters, the governing equations and boundary conditions are

$$\frac{\partial C_t}{\partial t} = \max\left\{ \left(\frac{\partial^2 C_t}{\partial x^2} + \frac{\partial^2 C_t}{\partial z^2} \right) - \kappa, 0 \right\}, \quad x \in (R_c, 1], \ z \in [0, L], \ t \in [0, \infty)$$
(3.75)

$$\frac{\partial C_c}{\partial t} = -v_b \cdot \frac{\partial C_c}{\partial z}, \quad x \in [0, R_c], \ z \in [0, L], \ t \in [0, \infty)$$
(3.76)

$$C_c(0,t) = 1, (3.77)$$

$$C_c(z,t) = C_t(R_c, z, t),$$
 (3.78)

$$\frac{\partial C_t}{\partial x}\Big|_{x=1} = \left.\frac{\partial C_t}{\partial z}\right|_{z=\{0,L\}} = 0,\tag{3.79}$$

where $\kappa = \kappa' W'^2 / D'C_a$, $v_b = W'v'_b / D'$, $R_c = R'_c / W'$ and L = L' / W'. This two region and one barrier model is illustrated in Figure 3.15.

If oxygen deficient occurs, the flux and the concentration value equals zero on the moving boundaries ∂O^n

$$\left. \frac{\partial C}{\partial n} \right|_{(x,z)\in\partial O^n} = C|_{(x,z)\in\partial O^n} = 0 \tag{3.80}$$

Oxygen deficit region and its moving boundaries are defined in section 2.3.1.

3.3.1 Formulation: The Space and Time Step Matching Technique

Consider a two dimensional discrete compartmental domain of ordered identical cube compartments with equal side length Δx and cross-section area A. Since oxygen is assumed to be radially well mixed inside the capillary, the choice of Δx is arbitrary in the 2D problems. The strategies for diffusion and consumption in the tissue region are the same as those in section 3.2. In this section, we shall focus on developing the discrete compartmental model for convection.

The fundamental strategy in this approach is to match the extravascular diffusion to the intravascular convection, so that the oxygen flux changes in both regions are adequately accounted for independent of the choice of compartment size. Figure 3.16 demonstrates the main idea and basic steps of this blood-tissue exchange algorithm. With the chosen Δx , the capillary is divided into N cube compartments of equal dimensions, indexed k = 1, Nbeginning at the inflow and the capillary plasma transit time $t = \Delta t \cdot n$. Now, we further "split" the time step interval Let

$$\Delta t_{+} = \text{begining of the time interval}$$

$$\Delta t_{-} = \text{end of the time interval}$$
(3.81)

and hence $\Delta t = \Delta t_{-} - \Delta t_{+}$. Before the time begins, the strength of the capillary is given by specifying the concentration on the arterial end. At beginning of each time interval Δt_{+} , the contents in each capillary compartment slides one segment downstream such that the concentration in the k^{th} compartment is replaced by that in the $(k-1)^{th}$, at which moment change in the tissue region is frozen. Thereafter, during the time interval Δt , diffusion and consumption occur in the tissue region. At the end of the current time interval Δt_{-} , the exchange pauses again and oxygen inside the capillary compartments slide one grid down for the next time step. The outflow at time t_+ would be the concentration of the N^{th} capillary compartment at time t_- .

Notice that, over each time interval, the sliding process in the capillary takes infinitesimally small amount of time. The reason is that the oxygen concentration in the capillary compartments is equivalent to the boundary condition for the concentration changes in the tissue region. On the other hand, the diffusion-consumption process takes the entire interval of time over each time step, Δt , which is determined by matching the time and space steps so that contents inside the capillary compartments slide exactly one segment at a time.



Figure 3.16: Lagrangian sliding fluid element method. With each Δt , oxygen in the capillary compartment slide instantaneously one segment downstream, after which the diffusion and consumption are computed.

3.3.2 A Simplified Model: Unsteady

Convection-Permeation-Consumption

Consider a problem with single layer of tissue region and no diffusion in the longitudinal direction in order to focus on developing the discrete compartmental algorithm for convectionpermeation-consumption problem based on the sliding element method. This simplified model serves as a basis for more complex models.

Consider a 1-barrier, 2-region model accounting for oxygen convection along a capillary with velocity v_b . Oxygen permeates into adjacent cell regions and was consumed there at a constant rate κ . Let $C_c(z,t)$ and $C_t(z,t)$ be the oxygen concentration in capillary and tissue region respectively. In non-dimensional form, this unsteady convection-permeationconsumption problem can be expressed using partial differential equations as

$$\frac{\partial C_c}{\partial t} = -v_b \cdot \frac{\partial C_c}{\partial z} + (C_t - C_z), \qquad (3.82)$$

$$\frac{\partial C_t}{\partial t} = (C_c - C_t) - \kappa. \tag{3.83}$$



Figure 3.17: Compartment model for capillary-tissue exchange in well-perfused organ.

Now we solve this problem from a compartmental point of view. Figure 3.17 shows the discrete compartmentalized capillary-tissue region. Oxygen is well-perfused in the tissue

region without longitudinal diffusion. With a selected space step Δx , the corresponding sliding period is determined by

$$p = \frac{\Delta x}{v_b}.\tag{3.84}$$

Table 3.13 shows a sample map of discrete compartmental modeling used for this problem, where interior capillary compartments, the capillary compartment on the arterial end, the capillary compartment on the venous end, tissue compartments and inactivated compartments are distinguished. Arterial capillary compartment shall be assigned an initial value at the beginning and can be changed at anytime during the process. Depending on the size of p, we classify the computational process into a basic case and a general case. The basic case: $p \leq (\Delta x)^2/2d$, where d is the space dimension of the problem. This usually happens when Δx or v_b is relatively large. In such case, we set

$$\Delta t = p. \tag{3.85}$$

and the sliding and diffusing process will happen alternatively, switching back and forth.

As time begins, contents in the capillary slides down stream one grid a time. In the beginning time step Δt_+

$$C_{0,k}^{n+} = C_{0,k-1}^{n-}. (3.86)$$

Then, oxygen permeates into the tissue region due to the partial pressure difference and consumption κ (or whatever remains) over the time step Δt is

$$C_{1,k}^{(n+1)-} = \max\left\{C_{1,k}^{n+} + \Delta t \cdot \left(C_{0,k}^{n+} - C_{1,k}^{n+} - \kappa\right), 0\right\}.$$
(3.87)

Combining the above two equations and drop " \pm " subscripts, the governing difference equation of concentration change of tissue compartments over one complete time interval Δt

$$C_{1,k}^{n+1} = \max\left\{C_{1,k}^n + \Delta t \cdot \left(C_{0,k-1}^n - C_{1,k}^n - \kappa\right), \ 0\right\}.$$
(3.88)

During the same time interval, capillary compartments lost an equivalent amount of oxygen which permeated into tissue cells. Balancing the inflow and outflow, concentration inside a capillary compartment at the end of the previous time step is

$$C_{0,k}^{(n+1)_{-}} = C_{0,k}^{n_{+}} + \Delta t \cdot \left(C_{1,k}^{n_{+}} - C_{0,k}^{n_{+}} \right).$$
(3.89)

Associate the above with Equation 3.86 and drop " \pm " subscripts gives the governing difference equation for capillary compartments

$$C_{0,k}^{n+1} = C_{0,k-1}^n + \Delta t \cdot \left(C_{1,k}^n - C_{0,k-1}^n \right).$$
(3.90)

At the beginning of the next time step Δt_+ , the diffusion-consumption pause for a moment and oxygen inside the capillary compartments moves another whole block forward.

CCA	$\mathbf{C}\mathbf{C}$	$\mathbf{C}\mathbf{C}$	$\mathbf{C}\mathbf{C}$	$\mathbf{C}\mathbf{C}$	CCV
IC	STC	STC	STC	STC	IC

Table 3.13: Discrete compartmental map of unsteady convection-permeation-consumption problem. Label "CC"=capillary compartment; label "CCA"=capillary compartment on the arterial end; label "CCV"=capillary compartment on the venous end; label "STC" = single layer tissue compartment; label "IC" = inactivated compartment.

The general case: $p > (\Delta x)^2/2d$ happens when one or both of Δx and v_b are relatively small. In such case, we let

$$\Delta t = \frac{p}{b},\tag{3.91}$$

where b is the least positive whole number such that $p/b \leq (\Delta x)^2/2d$. Then, Eq. 3.86 is called for every b steps during the computation and when b = 1 it covers the basic case.

Note that, using extra sliding step will not cause convergence problems but will result in higher concentration values, which means the computational errors may be larger. **Example 3.3.1.** As an illustrative example, consider a capillary of length L = 1 and blood velocity $v_b = 1$ adjacent to tissue cells that consumes oxygen a constant rate $\kappa = 0.2$. Initially the concentrations are zero everywhere until a constant unit amount of oxygen is suddenlyinfused at the arterial end of the capillary, or $C_c(0, t) = 1$. Assume the outer tissue boundary is reflecting, which means that there is no flux from or to the neighboring regions. Using the discrete compartment model with the sliding element technique, the calculation is carried with $\Delta x = 0.01$ and $\Delta t = 0.01$. Figure 3.18 shows the numerical results of transient concentration profiles in both regions at t = 0.5, t = 1, t = 5, and t = 10. As $t \to \infty$, the unsteady solution approaches

$$C_c(z) = 1 - \frac{\kappa}{v} \cdot z, \qquad (3.92)$$

$$C_t(z) = 1 - \kappa - \frac{\kappa}{v} \cdot z, \qquad (3.93)$$

which is the steady state solution.



Figure 3.18: Oxygen convection into a consuming region using a two region model. Red dots represent oxygen concentration flowing in capillary, blue dots represent oxygen concentration in adjacent tissue region with constant consumption and solid lines are analytic solutions at steady state.

As the figure shows, under the given velocity $v_b = 1$, blood slides to the middle of the capillary at t = 0.5 and slides to the veinous end of the capillary at t = 1. Oxygen concentration in the tissue region gradually increases with the movement of blood in the capillary. Oxygen in the capillary and tissues on the arterial end first reaches the steady state solution with a difference of 0.2, which is the given consumption rate κ . At t = 5, oxygen concentration in both regions gradually approaches the stead state solution and the their difference gradually approaches $\kappa = 0.2$. At t = 10, oxygen concentration in both regions reaches the steady state solution. The numerical solution using DCM with the sliding element method agrees perfectly with the analytic solution.

3.3.3 Unsteady Convection-Diffusion-Consumption

Now add oxygen diffusion within the tissue and develop the discrete compartmental model. The partial differential equations for the unsteady convection-diffusion-consumption problem are derived at the beginning of this section 3.3.

Consider a two space dimensional discrete compartmental space of ordered identical cube compartments with equal side length Δx and cross-section area A(Fig. 3.19). Differing from the diffusion-consumption problem in section 3.2, the choice of Δx is arbitrary in 2D convection-diffusion-consumption model with a single capillary. Since we assumed oxygen to be well mixed inside capillary, one single row of compartments is adequate to represent the capillary region. Therefore, compartments with side length of any reasonably small Δx can be used but there lower surfaces have to be matched perfectly with the capillary compartments. On the other hand, it is advantageous to choose a Δx that divide the tissue region exactly to reduce the discretization error. With a fixed Δx , the corresponding time step Δt is determined by equation 2.5.



Figure 3.19: Compartment model for capillary-tissue exchange with diffusion.

Table 3.14 shows a sample Map for this problem, in addition to the problem with two layers, tissue compartments are further divided. Capillary adjacent tissue compartments are marked out differently as wells as the different types of boundary compartments. At the venous end, one extra compartment is added in order to quantify the oxygen concentration through the outflow. The governing difference equations for a tissue compartment and the boundary tissue compartments not adjacent to the capillary are identical to the compartments with the same label in section 3.2. Here, we focus on deriving the difference equation for the capillary compartment and neighboring capillary compartments.

CCA	CC	CC	CC	CC	CCV
IC	BC11	CTC	CTC	BC12	IC
IC	BC21	\mathbf{TC}	\mathbf{TC}	BC22	IC
IC	BC60	BC32	BC32	BC70	IC

Table 3.14: Discrete compartmental map of 2D unsteady convection-diffusion-consumption problem. Label "CC"=capillary compartment; label "CCA"=capillary compartment on the arterial end; label "CCV"=capillary compartment on the venous end; label "TC" = tissue compartment; label "CTC" = capillary neighboring tissue compartment; label "BC##"=boundary compartment of type ##; label "IC" = inactivated compartment.

Similar to the two layer model, a given concentration value from blood on the arterial end of the capillary is initially stored in the source compartment

Label "**CCA**":
$$C_{i,k}^0 = C_A$$
. (3.94)

1. Difference Equation of Capillary Compartments:

As time begins, oxygen inside the capillary compartments slides instantaneous down stream at the beginning of time step Δt_+

$$C_{i,k}^{n_{+}} = C_{i,k-1}^{n_{-}}.$$
(3.95)
From their to the end of time step Δt_{-} , oxygen diffuses into the neighboring tissue regions driven by the partial pressure difference. Balancing the mass or concentration in a capillary cell at the end of each time step gives

$$C_{i,k}^{(n+1)_{-}} = C_{i,k}^{n_{+}} + \frac{\Delta t}{(\Delta x)^{2}} \left(C_{i+1,k}^{n_{+}} - C_{i,k}^{n_{+}} \right).$$
(3.96)

Substitute into Eq. (3.95), drop subscripts and simplify give the differential equation for capillary compartments

Label "**CC**":
$$C_{i,k}^{n+1} = C_{i,k-1}^n + \frac{\Delta t}{(\Delta x)^2} \left[C_{i+1,k}^n - C_{i,k-1}^n \right].$$
 (3.97)

The outflow at the end of each time step is found by

Label "**CCV**":
$$C_{i,k}^{n+1} = C_{i,k-1}^{n}$$
 (3.98)

2. Difference Equation of Capillary Neighboring Tissue Compartments:

Oxygen diffused from the capillary continuously exchange among the tissue compartments due to the partial pressure difference and κ or consumed within the tissue. Similarly to section 3.2, concentration in a tissue compartment at the end of each time step can be find as

$$C_{i,k}^{(n+1)_{-}} = \max\left\{C_{i,k}^{n_{+}} + \frac{\Delta t}{(\Delta x)^{2}} \left[\Sigma_{nb}C_{i,k}^{n_{+}} - 4C_{i,k}^{n_{+}}\right] - \Delta t \cdot \kappa, \ 0\right\},\tag{3.99}$$

where

$$\Sigma_{nb}C_{i,k}^{n+} = C_{i-1,k}^{n+} + C_{i,k-1}^{n+} + C_{i+1,k}^{n+} + C_{i,k+1}^{n+}.$$
(3.100)

In the capillary, oxygen slide from the $(i-1, k-1)^{th}$ capillary neighbor to the $(i-1, k)^{th}$ capillary neighbor and diffuse into the tissue during each time interval. Thus, for a tissue compartment adjacent to a capillary, the infusion of oxygen for time interval Δt_{+} can be expressed as

$$C_{i-1,k}^{n_{+}} = C_{i-1,k-1}^{n_{-}}.$$
(3.101)

Substitute the above relation into Eq. (3.99) and drop subscripts on t. The difference equation for concentration tissue compartment adjacent to a capillary is

Label "**CTC**":
$$C_{i,k}^{n+1} = \max\left\{C_{i,k}^{n} + \frac{\Delta t}{(\Delta x)^{2}}\left[C_{i-1,k-1}^{n} + C_{i+1,k}^{n} + C_{i,k-1}^{n} + C_{i,k+1}^{n} - 4C_{i,k}^{n}\right] - \Delta t \cdot \kappa, 0\right\},$$

(3.102)

3. Difference Equation of Boundary Compartments Adjacent to a Capillary

Combining the technique above for tissue compartments adjacent to a capillary and the compartmental treatment on the reflecting boundary in section 3.2, difference equations for tissue compartments adjacent to a capillary are

Label "**BC11**":
$$C_{i,k}^{n+1} = \max\left\{C_{i,k}^{n} + \frac{\Delta t}{(\Delta x)^2} \left[C_{i-1,k-1}^{n} + C_{i+1,k}^{n} + 2C_{i,k+1}^{n} - 4C_{i,k}^{n}\right] - \Delta t \cdot \kappa, 0\right\},$$

(3.103)

and

Label "BC12":
$$C_{i,k}^{n+1} = \max\left\{C_{i,k}^{n} + \frac{\Delta t}{(\Delta x)^2} \left[C_{i-1,k-1}^{n} + C_{i+1,k}^{n} + 2C_{i,k-1}^{n} - 4C_{i,k}^{n}\right] - \Delta t \cdot \kappa, 0\right\}$$
 (3.104)

Example 3.3.2. Consider a capillary-tissue domain as diagrammed in Figure 3.15. As an illustrative example, a single capillary of length L = 40, radius $R_c = 0.1$ and blood velocity $v_b = 20$ is adjacent to a rectangular tissue region of width W = 1. Oxygen concentration on the arterial end is $C_a = 1$, the diffusion constant is D = 2 and the consumption coefficient is $\kappa = 0.1$. Assume the outer tissue boundary is reflecting, which means that there is no flux from or to the neighboring regions.

We aim to compute the steady state solution from the transient state. Assume there are initially zero oxygen everywhere and at starting time blood with oxygen suddenly flows in. Our numerical solution is computed under of $\Delta x = 0.05$ and $\Delta t = 0.0005$. The space step size is determined by the capillary radius, such that the R_c is an integral multiple of Δx and the time step size is determined following the convergence theorem (see section 5 for the theorem and proof).

A transient solution is calculated until reaching steady state. Figure 3.20 shows the transient oxygen concentration profiles in the tissue region at t=0.1, t=0.25, t=1, t=2.5, t=5, t=7.5 and t=10. As the figure shows, under the given velocity $v_b = 20$, blood slides around 40 capillary compartments down stream at t = 0.1. Different from the previous simple model, where only one layer of tissue compartment is considered, movement of the plasma inside the capillary slows down while flowing further to the veinous end. This is because the tissue region is thicker and consumes more oxygen. Hence more oxygen diffuses out to the tissue and less oxygen lefts inside the capillary. At t = 10, the entire tissue is perfused with oxygen. Horizontally, the concentration is higher on the arterial end and gradually decreases towards the veinous end. Vertically, the concentration is higher over tissue regions near the capillary and slightly lower over tissue regions away from the capillary.



Figure 3.20: Concentration curves of a single capillary with blood velocity at t=0.1, t=0.25, t=1, t=2.5, t=5, t=7.5 and t=10. The vertical and horizontal axes shows the compartment numbers used in each direction.



Figure 3.21: Concentration profile on the capillary boundary and the tissue boundary, compared with the analytic solution. Circles are numerical solution of oxygen concentration on the tissue boundary. Triangles are numerical solution of oxygen concentration on the capillary wall. Solid lines represents the oxygen concentration profile obtained from the analytic solution. Horizontal axis shows the normalized capillary length and vertical axis show the normalized concentration value.

At t = 15, the unsteady solution approaches the steady state solution, which is obtained from solving the differential equations over the capillary region and the tissue region. Figure 3.21 shows the comparison of the numerical solution and the analytic solution of oxygen concentration on the tissue boundary and on the capillary wall. The numerical solution using DCM with the sliding element method agrees perfectly with the analytic solution.

Discussion

In this section, we constructed 2D discrete compartment model with the convection of oxygen inside the capillary taking into account. Two examples are demonstrated and the result at steady state agrees perfectly with the analytical solutions. It is shown by the steady state solution that the oxygen concentration inside the capillary decreases from the arterial end to the veinous end. In addition to that, the transient solutions show that the velocity of oxygen (not plasma) inside the capillary may not be constant or even linear, but depends on the oxygen concentration of the surrounded tissues. Again, a 2D model can not be used to explain the real biological phenomena. We will construct the 3D discrete compartmental model in the following chapter.

Chapter 4

The Three Dimensional Modeling

The problem of capillary-tissue supply is unlikely to be limited to 2D tissue cross section area, 3D tissue cylinder with a single capillary or a 3D steady state. None of these could represent the real, especially transient physiological phenomena. In this chapter, we extend the techniques of the previous chapters and develop the 3D discrete compartmental model for simulating the transient process of multi-capillary oxygen supply to striated muscle tissue.

4.1 Three-Dimensional Unsteady Diffusion-Consumption-Convection

The problem of three-dimensional unsteady convection, diffusion and consumption problem describing the oxygen transfer from capillary to tissue can be generally stated as follows. Consider M straight capillaries of same radius R'_c , same blood flow velocity v'_b in the direction of z', but different oxygen concentration C'_m , where m = 1, 2, ..., M, located irregularly in a bounded and non-simply connected tissue region $\Omega' \in \mathbf{R}^3$. Define individual capillary domain

$$\Omega'_m = \left\{ (x', y', z') : (x', y', z') \in \Omega' \text{ and } (x' - x'_m)^2 + (y' - y'_m)^2 \leqslant (R'_c)^2 \right\},$$
(4.1)

where (x'_m, y'_m, z') are the coordinates of points along the center line of each capillary. Thus, the total capillary domain is

$$\Omega_c' = \bigcup_{m=1}^M \Omega_m' \tag{4.2}$$

and the absorbing tissue domain is

$$\Omega_t' = \Omega' \setminus \Omega_c'. \tag{4.3}$$

Assume oxygen permeate through the thin capillary membrane wall without resistance and diffuse into the nearby tissue region at a diffusion rate D' and is consumed in the tissue at a rate of κ' . Let $C'_t(x', y', z', t')$ be the function of non-negative oxygen concentration of the tissue region and $C'_c(z', t')$ the non-negative oxygen function in the capillaries, the governing partial differential equations to this unsteady convection-diffusion-consumption problem are

$$\frac{\partial C'_t}{\partial t'} = D' \left(\frac{\partial^2 C_t}{\partial x'^2} + \frac{\partial^2 C'_t}{\partial y'^2} + \frac{\partial^2 C'_t}{\partial z'^2} \right) - \kappa', \quad (x', y', z') \in \Omega'_t, \ t' \in [0, \infty), \tag{4.4}$$

and

$$\frac{\partial C'_c}{\partial t'} = -v'_b \cdot \frac{\partial C'_c}{\partial z'}, \quad (x', y', z') \in \Omega'_c, \ t' \in [0, \infty).$$

$$(4.5)$$

On the outer tissue boundary $\partial \Omega'$ there is no flux or the normal derivative of concentration is zero

$$\left. \frac{\partial C'}{\partial n} \right|_{(x',y',z') \in \partial \Omega'} = 0. \tag{4.6}$$

On the arterial end of each capillary (z' = 0), the concentration is C'_m , differing in capillary strength

$$C'(x', y', 0, t') = C'_m, \qquad (x', y', 0) \in \Omega'_m, \ t' \in [0, \infty), \ m = 1, \cdots, M.$$
(4.7)

Since the permeability through the capillary wall can be regarded as infinite for gas solutes like oxygen, the boundary conditions are

$$C'_t(x', y', z', t') = C'_c(z', t'), \quad (x', y', z') \in \partial\Omega'_c$$
(4.8)

Normalize all lengths by $\tilde{L} = \sqrt{A(\Omega' \cap \{z = 0\})}$, the square root of the cross sectional area of Ω' on the *xy*-plane, concentration by the average on the arterial end C'_a , time by \tilde{L}^2/D' and drop primes. In terms of normalized parameters, the governing equations and boundary conditions are

$$\frac{\partial C_t}{\partial t} = \left(\frac{\partial^2 C_t}{\partial x^2} + \frac{\partial^2 C_t}{\partial y^2} + \frac{\partial^2 C_t}{\partial z^2}\right) - \kappa, \quad (x, y, z) \in \Omega_t, \ t \in [0, \infty)$$
(4.9)

$$\frac{\partial C}{\partial t} = -v_b \cdot \frac{\partial C}{\partial z}, \quad (x, y, z) \in \Omega_c, \ t \in [0, \infty)$$
(4.10)

$$C_t(x, y, z, t) = C_c(z, t), \quad (x, y, z) \in \partial\Omega_c,$$
(4.11)

$$C(x, y, 0, t) = C_m, \qquad (x, y, 0) \in \Omega_m, \ t \in [0, \infty), \ m = 1, \cdots, M,$$
(4.12)

$$\left. \frac{\partial C_t}{\partial n} \right|_{(x,y,z) \in \partial \Omega} = 0, \tag{4.13}$$

where $\kappa = \kappa' \tilde{L}^2 / D' C'_a$, $v_b = \tilde{L} v'_b / D'$ and $R_c = R'_c / \tilde{L}$.

If oxygen deficiency occurs, the flux and the concentration value equals zero on the

moving boundaries ∂O^n

$$\frac{\partial C_t}{\partial n}\Big|_{(x,y,z)\in\partial O^n} = C_t|_{(x,y,z)\in\partial O^n} = 0.$$
(4.14)

Oxygen deficit region and its moving boundaries are defined in section 2.3.1. Note the governing equations are 3D and unsteady.

4.1.1 Formulation

Consider a three-dimensional discrete compartmental space of identical cube compartments with side length Δx . It is of much importance to define the cross-section area of each capillary. Hence, in three dimensional modeling, the choice of Δx must satisfy

$$\Delta x = \sqrt{\frac{\pi R_c^2}{n_{CC}}} \tag{4.15}$$

where $n_{CC} = 1, 4, 5, 9, 13, 21...$, which is the same as in 2D modeling. Again, shapes of capillary compartment arrangements need to be approximately radially symmetric.

The formulation of governing difference equations for 3D modeling follows the same procedure of the 1D and 2D modeling. The (i, j, k)th cell has six adjacent neighbors

$$(i-1,j,k), (i+1,j,k), (i,j-1,k), (i,j+1,k), (i,j,k-1), (i,j,k+1).$$
 (4.16)

Let $C_{i,j,k}^n$ denote the oxygen concentration of the $(i, j, k)^{th}$ compartment at time $\Delta t \cdot n$. The change in mass inside this closed volume $V = (\Delta x)^3$ over a short time period Δt is

$$\left[C_{i,j,k}^{n+1} - C_{i,j,k}^{n}\right] \cdot V. \tag{4.17}$$



Figure 4.1: A 3D compartment for deriving the difference equations for DCM.

In the direction of the positive z-axis, the oxygen flux across each side from/to the top, bottom, left, right, back and front neighboring compartments during a time interval Δt are

$$J_{1}^{n} = -\frac{\Delta x}{\Delta t} \left[C_{i,j,k}^{n} - C_{i-1,j,k}^{n} \right], \qquad J_{2}^{n} = -\frac{\Delta x}{\Delta t} \left[C_{i+1,j,k}^{n} - C_{i,j,k}^{n} \right], J_{3}^{n} = -\frac{\Delta x}{\Delta t} \left[C_{i,j,k}^{n} - C_{i,j-1,k}^{n} \right], \qquad J_{4}^{n} = -\frac{\Delta x}{\Delta t} \left[C_{i,j+1,k}^{n} - C_{i,j,k}^{n} \right],$$
(4.18)
$$J_{5}^{n} = -\frac{\Delta x}{\Delta t} \left[C_{i,j,k}^{n} - C_{i,j,k-1}^{n} \right], \qquad J_{6}^{n} = -\frac{\Delta x}{\Delta t} \left[C_{i,j,k+1}^{n} - C_{i,j,k}^{n} \right].$$

A schematic diagram is given in Fig. 4.1.

1. Difference Equation of Tissue Compartments:

Consider the interior tissue compartments which constantly consume oxygen at the rate κ . The concentration change caused by the difference between inflows, outflows and

consumption in the $(i, j, k)^{th}$ compartment over the time period Δt can be described as

$$[(J_1^n + J_3^n + J_5^n - J_2^n - J_4^n - J_6^n) \cdot A - \kappa \cdot V] \cdot \Delta t, \qquad (4.19)$$

where $A = (\Delta x)^2$ is the single face area of a cube compartment and $V = (\Delta x)^3$ the volume of a cube compartment. Balancing Equation (4.19) with Equation (4.17) gives

$$D \cdot \left[C_{i,j,k}^{n+1} - C_{i,j,k}^n \right] \cdot V = \left[\left(\sum_{m=1}^6 J_m^n \right) \cdot A - \kappa \cdot V \right] \cdot \Delta t.$$
(4.20)

Substituting fluxes by concentration differences from (4.18) and simplifying yields

$$C_{i,j,k}^{n+1} = C_{i,j,k}^n + \frac{\Delta t}{(\Delta x)^2} \left[\Sigma_{nb} C_{i,j,k}^n - 6C_{i,j,k}^n \right] - \Delta t \cdot \kappa, \qquad (4.21)$$

where

$$\Sigma_{nb}C_{i,j,k}^n = C_{i-1,j}^n + C_{i+1,j}^n + C_{i,j-1}^n + C_{i,j+1}^n + C_{i,j,k-1}^n + C_{i,j,k+1}^n.$$
(4.22)

Now, consider the situation of a local oxygen deficiency, where

$$C_{i,j,k}^{n} + \frac{\Delta t}{(\Delta x)^2} \left[\Sigma_{nb} C_{i,j,k}^{n} - 6C_{i,j,k}^{n} \right] < \Delta t \cdot \kappa,$$
(4.23)

in which case the tissue compartment will consume all the available oxygen over that time step, and thus

$$C_{i,j,k}^{n+1} = 0. (4.24)$$

Combining the oxygen sufficient case with the oxygen deficient case, the governing

difference equation of an interior tissue compartment is

$$C_{i,j,k}^{n+1} = \max\left\{C_{i,j,k}^{n} + \frac{\Delta t}{(\Delta x)^2} \left[\Sigma_{nb}C_{i,j,k}^{n} - 6C_{i,j,k}^{n}\right] - \Delta t \cdot \kappa, \ 0\right\},\tag{4.25}$$

where $\Delta t/(\Delta x)^2$ shall be less than 1/6 in the three dimensional problem for stability and convergence. See Chapter 5 for the theoretical proof of convergence.

2. Difference Equation of Capillary Compartments:

In the three dimensional problem, oxygen inside the capillary compartments not only diffuse into the tissue region but also flow downstream at the same time. Dealing with this complex situation, we shall extend the discrete compartmental technique introduced in sections 3.2 and 3.3. The fundamental idea is to execute the 3D diffusion and sliding process by a time-space matching technique.

Consider the case $\Delta x = \sqrt{\pi R_c^2}$, where each capillary is represented by a single row of compartments. Each capillary compartment has four tissue neighbors and two capillary neighbors. The concentration change in the $(i, j)^{th}$ capillary compartment over the time period Δt can be described as

$$[(J_1^n + J_3^n - J_2^n - J_4^n) \cdot A] \cdot \Delta t.$$
(4.26)

Balancing of mass flow with concentration change in the $(i, j, k)^{th}$ capillary compartment over the time period Δt yields

$$D \cdot \left[C_{i,j,k}^{n_{+}} - C_{i,j,k}^{n} \right] \cdot V = \left[\left(\sum_{m=1}^{4} J_{m}^{n} \right) \cdot A \right] \cdot \Delta t, \qquad (4.27)$$

where n_+ represents time at the end of the *n*th time interval. Substitute in J_1^n , J_2^n , J_3^n , J_4^n , from (4.18) and simplify. The oxygen concentration in the $(i, j, k)^{th}$ capillary compartment at the end of the *n*th time interval is

$$C_{i,j,k}^{n_{+}} = C_{i,j,k}^{n} + \frac{\Delta t}{(\Delta x)^{2}} \left[\sum_{(i,j)_{nb}} C_{i,j,k}^{n} - 4C_{i,j,k}^{n} \right],$$
(4.28)

where

$$\sum_{(i,j)_{nb}} C^n_{i,j,k} = C^n_{i-1,j,k} + C^n_{i,j-1,k} + C^n_{i+1,j,k} + C^n_{i,j+1,k}.$$
(4.29)

and

$$\Delta t = \frac{p}{b},\tag{4.30}$$

in which p is the sliding period determined by $\Delta x/v_b$ and b is any positive integer. Here Δt is chosen to that give the desired accuracy and also satisfies the condition of convergence. During each sliding period, the diffusion-consumption is executed for every Δt and oxygen in each capillary compartment slide one segment downstream for every $b \cdot \Delta t$. Thus, the oxygen concentration of a capillary compartment in the beginning of the next time interval is

$$C_{i,j,k}^{n+1} = C_{i,j,k-1}^{n+}.$$
(4.31)

For the general case $\Delta x \leq \sqrt{\pi R_c^2}$, where each capillary is represented by more then one row of compartments, an average of the oxygen concentration over each capillary's cross-section area shall be taken and reassigned after the diffusion process by Eq. (4.28).

3. Difference Equation of Boundary Compartments:

Consider a cuboid discrete compartmental space, where the boundary compartments can be divided into three categories: 1. tissue compartment with one inactive neighbor(a side boundary), tissue compartment with two inactive neighbors(an edge boundary), 3. tissue compartment with three inactive neighbors(a corner boundary). The derivation of the governing difference equation for boundary tissue compartments satisfying the reflecting boundary condition follows a similar process as in section 3.2.1. For example, if a boundary compartment on the corner, whose $(i - 1, j, k)^{th}$, $(i, j - 1, k)^{th}$ and $(i, j, k - 1)^{th}$ neighbors are inactive compartments, then the difference equation updating oxygen concentration of this compartment is

$$C_{i,j,k}^{n+1} = \max\left\{C_{i,j,k}^{n} + \frac{\Delta t}{(\Delta x)^2} \left[2C_{i+1,j,k}^{n} + 2C_{i,j+1,k}^{n} + 2C_{i,j,k+1}^{n} - 6C_{i,j,k}^{n}\right] - \Delta t \cdot \kappa, 0\right\}.$$
(4.32)

4.1.2 Three capillaries of uneven strength in a cuboid domain

Consider three capillary of uneven strength and random distribution in a cube region, $\Omega = W \times H \times L = 1 \times 1 \times 1$. Locations and plasma oxygen concentration on the arterial end of the capillaries are randomly generated and shown in table 4.1. The uniform capillary radius R_c is set to be 0.056419 for demonstration, the blood velocity $v_b = 180$, and the tissue consumption coefficient $\kappa = 1$.

x_m	y_m	C_a of the m^{th} capillary
0.679	0.390	0.311
0.258	0.299	0.186
0.511	0.605	0.473

Table 4.1: Locations and plasma oxygen concentration on the arterial end of three randomly distributed capillaries used in the example.

Assume this cubic multi-capillary tissue domain initially has zero oxygen everywhere. Blood with oxygen suddenly flows into the capillaries and the oxygen starts to diffuse into the surrounding tissue. Figure 4.2 shows the computed oxygen concentration profiles at time t = 0.1, t = 0.2, t = 0.5 and t = 2.2. The domain is gradually filled with oxygen and finally reaching a steady state, which is determined by comparing the concentration values of each compartment over a constant time period and see if the difference of every corresponding compartment is less then a given threshold.



t = 0.1





Figure 4.2: Concentration profile of three capillaries of uneven strength in a cube domain at t = 0.1, t = 0.2, t = 0.5 and t = 2.2 (steady state).

Of interest is time when the domain becomes fully perfused, t_f , which is found by searching for zero-concentration compartments over each time step. If every compartment has a nonzero value, we say the domain is fully perfused; if the tissue domain has both zero and nonzero compartments, we say the domain is partially perfused. The first time when the domain changed from partially perfused to fully perfused is the domain fully perfused time.

Another subject of interest is the time for the transient solution of the whole domain to reach a steady state, t_s . Since between two adjacent time steps the difference between the concentration profiles is very small, t_s is determined by comparing the concentration values of each compartment over a longer time period say t = 0.1. If the difference of every corresponding compartment is less then 1×10^{-6} , we say the transient solution has reached a steady state.

Δx	0.1	0.05	0.02	0.0111111	0.00995803
t_f	0.1511	0.1367	0.1965	0.2059	0.2047
t_s	2.200	2.200	2.200	2.200	2.200

Table 4.2: Time to fully perfused (t_f) and to steady state (t_s) corresponding to different valid choices of spacial step size (Δx)

Table 4.2 shows the time to full perfusion (t_f) and to steady state (t_s) corresponding to different choices of spacial step size (Δx) . As we can see that the full perfusion time is highly influenced by the compartment size but converges to a certain value. The steady state time is much more stable and not being influenced by the compartment's size. This makes sense because when there are too few compartments, the boundary compartments are thicker and closer to the center, thus become nonzero earlier while not influencing the stability.

We are also interested about the numerical convergence of this algorithm under transient

state. Figure 4.3 shows effect of space step size at time t = 0.1 for two locations, the oxygen concentration of the compartment at the center and at a random location. The vertical axis represents the concentration value($\times 10^6$) of the compartment and the horizontal axis is the inverse of spacial step sizes (Δx) corresponding to different valid capillary shapes. For each location, 24 different spacial step sizes are tested. It can be seen from both Fig. 4.3(a) and Table 4.3, that the concentration quickly converges to within a certain range and oscillate inside that range as the size of Δx decreases. This oscillation phenomenon may due to the different cross sections of approximating the capillary compartment by squares. For example, using 1, 4 or 9 compartments to approximate the capillary cross section the shape is a square, but using 5 or 13 compartments, the capillary is cross-shaped. To further analyze the convergence, we divide the result into sub-groups and calculate there averages.

Δx	0.1	0.05	0.02	0.0111111
t = 0.1	28437	40875	42190	41207
t = 0.2	59394	72609	70437	68811
t = 0.5	97947	108828	104477	102693
t = 1	107338	117156	113228	111468
t = 2	108028	117751	113936	112178
t = 4	108031	117754	113940	112182
t = 8	108031	117754	113940	112182

Table 4.3: Convergence for concentration value $(\times 10^6)$ on a random point (0.243, 0.525, 0.725) corresponding to an interior tissue compartment for different choices of valid spacial step size (Δx)

Due to the convergence constraint and the given blood velocity, smaller Δx requires larger sliding frequencies corresponding to a smaller sliding period and thus requires extra sliding steps during each time step. Vertical black lines in the figure divides the plane into sub-regions corresponding to different sliding frequencies b = 1, 2, 3 and 4 from left to right. Average of values in each sub-region is represented by the short black lines. Starting from the smallest Δx on the right end, convergence of the points is estimated using the uniformly minimum variance unbiased estimator and represented by the long horizontal black line. We found that, although individual points vibrate around the line without a clear pattern, the average values of each sub-region gradually converge to the estimated value as expected.



(b) Concentration value (×10⁶) on the central point (0.5, 0.5, 0.5)

Figure 4.3: Convergence of the 3D algorithm on interior tissue compartments for different choices of valid spacial step size (Δx), at time t = 0.1. The vertical axis represents the concentration value($\times 10^6$) of the compartment and the horizontal axis is the inverse of spacial step size (Δx). Vertical black lines divides the plane into sub-regions due to the sliding period corresponding to the compartment size. Short horizontal lines are the average of values in each rectangular region and the long horizontal line is calculated using the uniformly minimum variance unbiased estimator from the end of the smallest Δx obtained.

4.1.3 The Krogh Tissue Cylinder

In this section, we reexamine the clasical work of the oxygen transport from a single capillary to its surrounding tissues by Krogh [38], taking account of the blood flow through the capillary as well as the oxygen diffusion in the tissue in the axial direction. We shall compute the steady state solution from unsteady state, and compare the results with the analytic solution.



Figure 4.4: The Krogh tissue cylinder

Figure 4.4 shows the schematic diagram of a Krogh capillary-tissue cylinder model. In the example we use a Krogh cylinder of 110 μ m diameter tissue surrounding a 10 μ m diameter capillary of 1000 μ m long. The tissue diffusivities are 900 μ m²/s, which is assumed to be the same in the axial and radial direction. The blood flow inside the capillary is 400 μ m/sec. To determine the normalized concentrations, it is sufficient to only specify the ratio of the tissue oxygen consumption to the oxygen concentration on the arterial side of the capillary. Here we used $\kappa'/C_a = 0.002 \text{ sec}^{-1}$.



Figure 4.5: Concentration curves of the Krogh tissue cylinder at (C = 0.6, 0.7, 0.8, 0.9) at steady state from the numerical solution. The vertical and horizontal axes shows the compartment numbers used in each direction.

We aim to compute the steady state solution from the transient state. Assume there are initially zero oxygen everywhere and at starting time blood with oxygen suddenly flows in. Our numerical solution is computed under space step of $\Delta x = 0.0590818$, which is determined by the normalized capillary radius and using four compartments to represent one capillary $(\pi \cdot R_c^2 = 4 \cdot (\Delta x)^2)$. A transient solution is calculated until reaching steady state. Figure 4.5 shows the oxygen concentration curves for typical values obtained from the numerical solution. Figure 4.6 shows almost perfect agreement of the numerical and the analytic solution on the tissue boundary and on the capillary wall. Derivation of the analytic solution can be find in the Appendix 6.2.



Figure 4.6: Concentration profile of the Krogh tissue cylinder on the capillary boundary and the tissue boundary. Circles are numerical solution of oxygen concentration on the capillary wall. Triangles are numerical solution of oxygen concentration on the tissue boundary. Solid lines represents the oxygen concentration profile obtained from the analytic solution. Horizontal axis shows the normalized capillary length and vertical axis show the normalized concentration value.

4.2 Simulating 3D Multi-Capillary Oxygen Transport

Parameter	Value	Reference
R_c'	$2-5\mu m$	[37] $[54]$
L'	150 - 1000 μm	[58] $[23]$
FCD	1000 - 1500 capillaries / mm^2	[67]
v_b'	130 - 1500 $\mu m/s$	[24]
C_a	$3 \times 10^{-3} \;(\text{ml}\; O_2)/(\text{ml}\; \text{blood})$	[50]
D'	$1.21 - 2.41 \times 10^{-5} \ cm^2/s$	[24] $[72]$
κ_b'	$1.67 \times 10^{-4} \text{ (ml } O_2)(\text{ml tissue})^{-1} s^{-1}$	[24]
κ'_{max}	$3 \times 10^{-3} \text{ (ml } O_2)(\text{ml tissue})^{-1} s^{-1}$	[4]

using DCM

Table 4.4: Biophysical parameters used for the simulation of oxygen transport in multicapillary tissue bed. R'_c , capillary radius; L', capillary length; FCD, functional capillary density; v'_b , normal RBC velocity; C_a , arterial oxygen concentration; D', tissue oxygen diffusivity; κ'_b , basal tissue oxygen consumption; κ'_{max} , maximal tissue oxygen consumption.

Consider a cube shaped multi-capillary bad with biological parameters are shown in table 4.4. As an illustrative example, let capillary radius $R'_c = 2.8 \mu m$, capillary length $L' = 240 \mu m$ and functional capillary density FCD = 1250 capillaries/ mm^2 . Consider 8 capillaries and a square cross sectional tissue domain. The dimensions of the tissue region is then calculated from the functional capillary density, $\Omega' = W' \times H' \times L' = 80 \mu m \times 80 \mu m \times 240 \mu m$ and $\Omega = W \times L \times H = 1 \times 1 \times 3$ after normalization. Table 4.5 shows the capillary locations (from reference [67]) and the plasma oxygen concentration on the arterial end for each capillary. All the initial oxygen concentrations on the arterial end were set to be lower than that in the artery and were randomly generated from the range of [0.8, 1]. Note that, the normalized arterial oxygen concentration equals 1. Based on the convergence analysis result in section 4.1.2, we use 13 compartments to represent each capillary, which determines the space step $\Delta x = 0.0172057$.

The steady state solution was first established from transient solution of zero oxygen everywhere and then blood suddenly flows into the capillaries. The tissue diffusivity $24.1 \mu m/s$ is assumed to be the same in the axial and radial direction. Under the basal tissue oxygen consumption rate and a blood velocity of $1150 \mu m/s$, oxygen concentration in the modeled capillary-tissue system reaches steady state at normalized time t = 0.6.

m	x_m	y_m	C_a of the m^{th} capillary
1	0.385	0.879	0.960
2	0.183	0.673	0.935
3	0.837	0.855	0.978
4	0.602	0.690	0.928
5	0.138	0.365	0.931
6	0.691	0.428	0.995
7	0.310	0.161	0.976
8	0.760	0.203	0.962

Table 4.5: Locations and plasma oxygen concentration on the arterial end of eight capillaries.

Figure 4.7 shows the concentration profile of the capillary-tissue region at steady state. Capillary-tissue region with oxygen concentration lower than 0.0001 is considered as anoxia. Note that there is a tiny oxygen deficient region on the top corner of the top layer. Oxygen diffused to that part was depleted during the same time step and so it is at the borderline to anoxia.

We shall use this steady state result as the initial condition to simulate the development of anoxia and its recovery in the following examples. We shall use the DCM to develop tissue anoxia from two different ways: 1. by blocking capillaries and 2. by increasing the tissue oxygen consumption rate. In the first case, the recovery process will be simulated by unclogging the blocked capillary. In both cases, the recovery process will be simulated by decreasing the consumption rate, by increasing capillary blood velocity and by increasing oxygen concentration in the incoming plasma.



Figure 4.7: Oxygen concentration profile of eight capillaries of uneven strength and distribution in a cuboid domain at steady state. Biophysical parameters collected in Table 4.4 is used to simulate the actual biological process. Under capillary blood velocity $1150\mu m/s$ and basal tissue oxygen consumption rate 1.67×10^{-4} (ml O_2)(ml tissue)⁻¹ s⁻¹, oxygen concentration in this capillary-tissue system reaches the steady state at a normalized time of t = 0.6.

4.2.1 Anoxia Following Capillary Occlusion

In the previous subsection, the steady state oxygen concentration in a capillary-tissue region with 8 capillaries of uneven strength and experimental parameters are established. Now, consider one capillary is suddenly blocked, which means blood in that capillary suddenly stopped flowing. That means, new oxygen will stop entering the blocked capillary and only the remaining oxygen in the blocked capillary is available for the surrounding tissue.

Figure 4.8 shows the change of oxygen concentration after blocking a capillary (m = 4) which is closer to the middle of the tissue domain at time t = 0.01, 0.05, 0.1 and 0.2. At t = 0.1, oxygen level around the blocked capillary decreased dramatically. However, the first oxygen deficient region appears on the top margin (at t = 0.05), which is far away from the blocked capillary and close to two healthy capillaries. This happens because oxygen always diffuse from high concentration region to low concentration region, which enables capillaries to support each other and balancing the oxygen distribution in the tissue region. This surprising result is different from the traditional view, that tissue surrounding the blocked capillary will be anoxic first. At t = 0.2 several oxygen deficient areas occur in separate locations. The distribution of oxygen concentration reaches steady state again at t = 0.6. Since the response time should be short in the reality, we shall use this result at t = 0.2 as the initial condition on the next simulation.

The present result shows that, while occlusion happens, oxygen is redistributed to reach a new balance with minimum anoxic area and this area may not occur near the blocked capillary. Afterwards, anoxia may occur in several places.



t = 0.01



t = 0.2

t = 0.1

Figure 4.8: The development of oxygen deficit by blocking one capillary closer to the middle of the tissue domain, at time t = 0.01, 0.05, 0.1 and 0.2. Anoxic areas are shown in white for contrast.

Figure 4.9 shows the results of oxygen distribution from blocking a capillary near the outer tissue boundary (m = 1), after time t = 0.01, 0.05, 0.1 and 0.2. At t = 0.01, oxygen concentration around the blocked capillary decreased greatly but unevenly due to the distribution of other healthy capillaries. At t = 0.05, a significant anoxic area appears on the veinous end. At t = 0.1, the zero oxygen region expands and extends to the arterial end. Besides that, additional small anoxia regions starts to occur elsewhere near the veinous end. The oxygen deficient regions keep expending from t = 0.1 to t = 0.2. Since the boundary is defined to be reflected, this example demonstrates the result of blocking a bunch of four neighboring capillaries.

This section is important for the study of heart attack and its recovery. A heart attack or Myocardial infarction (MI) is the death of a segment of heart muscle usually caused by a loss of blood supply. The blood is usually cut off when an artery supplying the heart muscle is blocked by a blood clot. During a heart attack, the heart muscle loses oxygen supply and is damaged. If impaired blood flow to the heart lasts long enough, the heart cells die, chiefly through necrosis, and do not grow back. Treatment of an MI is timecritical. Common treatments include nitroprusside, theophyline, coronary artery bypass surgery, and thrombolysis, where the blood flow is restored; supplemental oxygen, where oxygen concentration in the artery blood is increased and so on. In the following subsections, DCM is applied to simulate different types of the recovery process.

For convenience, note that t = 0.01 is corresponding to 2.6556 seconds, t = 0.05 is corresponding to 13.278 seconds and t = 0.2 is corresponding to 53.112 seconds.



t = 0.01





Figure 4.9: The development of oxygen deficit by blocking one capillary near the tissue domain boundary, at time t = 0.01, 0.05, 0.1 and 0.2. Anoxic areas are shown in white for contrast.

4.2.1.1 Recovery Through Eliminating Capillary Blockage

In the previous simulation, one of the eight capillaries of uneven strength and distribution was blocked, causing oxygen deficient in several separate regions (Figure 4.8). Now, consider the blocked capillary was unblocked and resumes flow. We are interested in the transient recovery process of tissue oxygen redistribution. Using the results from blocking the capillary (m = 4) for a duration of t = 0.2 as the initial condition here, we restore the blood flow of that capillary. Thus, original rate of oxygen flows into the recovered capillary again and diffuse into the surrounding tissue region.

Figure 4.10 shows the oxygen concentration profiles after the blocked capillary is unclogged after time t = 0.001, 0.05, 0.1 and 0.2. At t = 0.001, the recovered capillary was infused again with oxygenated blood and re-nourish the surrounding tissue. At t = 0.05, oxygen deficient region in the middle has fully recovered but other anoxic regions remain. From t = 0.05 to t = 0.1, the rest zero oxygen region shrunk greatly but still remain existed. The concentration profile reaches a fully nourished steady state again at t = 0.5.

The result shows that, after eliminating the capillary blockage of a single capillary, oxygen deficient regions near the blocked capillary will be recovered first. Anoxia tissue regions away from the blocked capillary will need to wait a longer time for oxygen to diffuse there, and thus have a greater chance to encounter tissue death.



Figure 4.10: Recovery process of tissue oxygen distribution through unclog the blocked capillary, at time t = 0.001, 0.05, 0.1 and 0.2. Anoxic areas are shown in white for contrast.

4.2.1.2 Recovery Through Decreasing Consumption Rate

In section 4.2.1, anoxia in capillary-tissue region with 8 capillaries of uneven strength and experimental parameters was simulated by suddenly stopping the blood flow velocity inside a capillary from steady state. Now, assume that capillary was still blocked and the living system responds to anoxia by decreasing oxygen consumption. That means, the amount of oxygen entering the system per time period remains the same as after the capillary occlusion, but the less oxygen was consumed during each time period. So that extra oxygen will flow towards anoxic regions. In reality, the basal tissue consumption rate can be further reduced by decreasing the temperature, such as putting tissues into ice.

Consider the oxygen consumption rate is reduced from $1.67 \times 10^{-4} \text{ (ml } O_2)\text{(ml tissue)}^{-1}$ s^{-1} to $1.55 \times 10^{-4} \text{ (ml } O_2)\text{(ml tissue)}^{-1} s^{-1}$ at time t = 0.2 after the capillary blockage happens. Figure 4.11 shows the recovery process of the tissue oxygen distribution after reducing the oxygen consumption rate at time t = 0.001, 0.05, 0.1 and 0.2. At t = 0.001, there is no significant change on the concentration profile. At t = 0.05, every anoxic region is slightly reduced but none fully recovered. The zero oxygen regions continue to shrink from t = 0.05 to t = 0.2.

The oxygen distribution reaches steady state t = 0.6 after the reduction of the consumption rate. Under the selected new consumption rate, a significant oxygen deficient region still exists at the middle of the top margin on the top layer. Tissues in this region are certainly going to die if nothing else happens, and tissues surround the blocked capillary on the veinous end are in great danger. In addition, the top corner on the top level, which used to have the lowest concentration in the steady state in the beginning (4.2), was no longer the most anoxic.



Figure 4.11: Recovery process of tissue oxygen distribution following a reduction of the tissue consumption, at time t = 0.001, 0.05, 0.1 and 0.2. Anoxic areas are shown in white for contrast.

t = 0.2

t = 0.1

4.2.1.3 Recovery Through Increasing Capillary Blood Velocity

In section 4.2.1, we developed anoxia in a capillary-tissue region with 8 capillaries of uneven strength from steady state by blocking a single capillary and reduced the total oxygen supply. Now, assume the living system is attempting to avoid tissue death by increasing the blood velocity in the other healthy capillaries. That means, more oxygen will enter the region in the same amount of time, resulting an increase on the amount to oxygen supply to tissue. Physically, increasing of the heartbeat due to many reasons will lead to an increase of the blood flow.

Assume the blood velocity of the seven healthy capillaries is suddenly increased from $1150\mu m/s$ to $1500\mu m/s$, at time t = 0.2 after the capillary blockage happens. The resulting oxygen concentration redistribution process at time t = 0.001, 0.05, 0.1 and 0.2 is shown in Figure 4.12. At t = 0.001, there is no significant change on the concentration profiles. However, at t = 0.05 most of the anoxic region has already recovered, leaving only tissues near the blocked capillary and in the middle of two blocked capillaries (the boundary is reflecting). Although the majority of the anoxia region recovered quickly, a zero oxygen region exists at t = 0.2. Actually, the oxygen distribution reaches steady state at t = 0.5 with that region remain anoxic.

Increasing the blood velocity by $50\mu m$ every time, we found the anoxic region can be fully recovered at $v_b = 1750\mu m$. It takes t = 0.1922 for the entire tissue region to be perfused and t = 0.5 to reach the steady state. The result shows us, by increasing the blood velocity, the majority of the oxygen deficient region can be recovered in a short time. However, if the velocity is not fast enough, some anoxic regions may exist permanently, leading to tissue death.


t = 0.1

t = 0.2

Figure 4.12: Recovery process following an increment in the capillary blood velocity, at time t = 0.001, 0.05, 0.1 and 0.2. Anoxic areas are shown in white for contrast.

4.2.1.4 Recovery Through Increasing Oxygen Concentration in Blood

In this simulation, we started with the oxygen shortage developed in section 4.2.1 by blocking a single capillary. Assume the oxygen concentration in the incoming blood in the remaining capillaries is suddenly increased by a certain amount, which means the total amount of oxygen entering the capillary-tissue region will increase during each time period. Here, we increase the arterial oxygen concentration C_a by 10%, at time t = 0.2 after the single capillary occlusion occurs. Oxygen therapy, also known as supplemental oxygen, is a commonly used medical treatment which increases the oxygen concentration in the artery blood.

Figure 4.13 shows the oxygen concentration profiles following increasing oxygen concentration in blood, at time t = 0.001, 0.05, 0.1 and 0.2. The recovery process is very similar to the result from increasing the blood velocity in the previous part 4.2.1.3. There is no immediate change on the concentration profile at t = 0.001 but the anoxia region shrunk greatly at t = 0.05. With the applied 10% increment on the blood oxygen concentration, the oxygen distribution reaches steady state at t = 0.6 with a small zero oxygen area at the top margin on the veinous end.

Note that, the anoxic regions could fully recovers with a greater increment on the oxygen concentration in the artery blood. Here, we are aiming to explore and predict the location for possible tissue death under severe cases. As the result shows, tissue death caused by capillary occlusion may not happen on tissues neighboring the blocked capillary nor on tissues initially having the lowest oxygen concentration but elsewhere.



0



Figure 4.13: Recovery process of tissue oxygen distribution following increasing oxygen concentration in the arterial blood, at time t = 0.001, 0.05, 0.1 and 0.2. Anoxic areas are shown in white for contrast.

4.2.2 Anoxia Following Increased Tissue Oxygen Consumption

In section 4.2, the steady state of oxygen concentration in capillary-tissue region with 8 capillaries of uneven strength and experimental parameters are calculated. Now, consider the tissue oxygen consumption is suddenly increased. Increments on oxygen consumption caused by muscle movement are usually accompanied by the increase of the blood velocity or blood oxygen concentration. Here, we consider the case of acute exertion without proper warm-up and focus on the occurrence of the resulting oxygen shortage and its recovery processes.

Consider the tissue oxygen consumption rate is suddenly increased by 50%, from the basal rate $1.67 \times 10^{-4} \text{ (ml } O_2)(\text{ml tissue})^{-1} s^{-1}$ to $2.505 \times 10^{-4} \text{ (ml } O_2)(\text{ml tissue})^{-1} s^{-1}$ after the steady state in section 4.2. Figure 4.14 shows the change of oxygen concentration at time t = 0.01, 0.05, 0.1 and 0.2. Comparing to the result from blocking capillaries in section 4.2.1, the oxygen shortage occurs more separately in the tissue domain at t = 0.01 and affects not only the veinous end at all levels. The oxygen deficient area expands to the arterial end over time. The distribution of oxygen concentration reaches steady state again at t = 0.4. Since the response time should be short in the reality, we shall use this result at t = 0.2 as the initial condition of the following subsections.



t=0.01





Figure 4.14: The development of oxygen deficit by increasing the tissue oxygen consumption rate, at time t = 0.01, 0.05, 0.1 and 0.2. Anoxic areas are shown in white for contrast.

4.2.2.1 Recovery Through Decreasing the Consumption Rate

In the previous subsection 4.2.2, anoxia in capillary-tissue region with 8 capillaries of uneven strength and experimental parameters was developed by suddenly increasing the tissue oxygen consumption rate. Now, assume the tissue oxygen consumption rate has decreased back to the original $1.67 \times 10^{-4} \text{ (ml } O_2)(\text{ml tissue})^{-1} s^{-1}$ from $2.505 \times 10^{-4} \text{ (ml } O_2)(\text{ml tissue})^{-1} s^{-1}$, at time t = 0.2. That means, although the amount of oxygen entering the system remains the same, the oxygen concentration will be redistributed since every tissue cell consumes less oxygen per time step allowing extra oxygen to flow back to anoxia regions.

Figure 4.15 shows the recovery process of the tissue oxygen distribution after reducing the oxygen consumption rate at time t = 0.001, 0.01, 0.05 and 0.2. During the recovery process, each of the oxygen deficient region gradually shrink and eventually disappear. The oxygen distribution reaches steady state again t = 0.6, which is longer than the time taken during the anoxia development process in the previous section 4.2.2.

Comparing the recovered area between different time periods, we observed that, even a full recovery at the end is guaranteed, it took less time for the oxygen perfused region to expand to tissues close to the capillaries than to tissues far from the capillaries.



Figure 4.15: Recovery process of tissue oxygen distribution following reducing the tissue consumption rate to original state, at time t = 0.001, 0.05, 0.1 and 0.2. Anoxic areas are shown in white for contrast.

0.0001

t = 0.1

0.0001

t = 0.2

4.2.2.2 Recovery Through Increasing Capillary Blood Velocity

In section 4.2.2, anoxia is developed by suddenly increasing the tissue oxygen consumption rate at steady state. Muscle exercise always followed by an increase in the blood velocity. From rest to exercise, blood flow velocity in the muscle capillaries can increase more then tenfold [43]. Here, we consider two cases. Case 1: the capillary blood flow velocity is suddenly increased to $1500 \mu m/s \ t = 0.2$ after the rise of tissue oxygen consumption rate, and case 2: the capillary blood flow velocity is suddenly doubled. We are interested in how soon all the anoxia regions are fully recovered.

Figure 4.16 shows the oxygen redistribution process at time t = 0.001, 0.01, 0.05 and 0.1 after suddenly increasing the capillary blood velocity to $1500\mu m/s$. The oxygen deficient regions were fully perfused with oxygen at t = 0.0569. Figure 4.17 shows the oxygen concentration profiles t = 0.001, 0.01, 0.05 and 0.1 after the capillary blood velocity is suddenly doubled. At t = 0.0298, the anoxia regions have fully recovered. Comparing the two results, we can see that there are significant zero oxygen regions remains at t = 0.01 in both cases, However, a faster blood velocity lead to a much smaller fully-perfusion time, which means faster further expansion of perfused region towards tissues located away from the capillaries.



t = 0.001





Figure 4.16: Recovery process of tissue oxygen distribution following increasing the capillary blood velocity to $1500 \mu m/s$, at time t = 0.001, 0.01, 0.05 and 0.1. Anoxic areas are shown in white for contrast.



t = 0.05

Figure 4.17: Recovery process of tissue oxygen distribution following doubling the capillary blood velocity, at time t = 0.001, 0.01, 0.05 and 0.1. Anoxic areas are shown in white for contrast.

t = 0.1

4.2.2.3 Recovery Through Increasing Oxygen Concentration in Blood

In this simulation, we started with the oxygen shortage developed in section 4.2.2 by increasing the tissue oxygen consumption rate. Assume the oxygen concentration in the incoming blood has suddenly increased at time t = 0.2 after the consumption rate has increased. Here, we increase the arterial oxygen concentration C_a by 10%, which means the total amount of oxygen entering the capillary-tissue region is increased by 10% during each following time period.

Figure 4.18 shows the oxygen concentration profiles following increasing oxygen concentration in blood, at time t = 0.001, 0.01, 0.05 and 0.1. The recovery process is very similar to the result from increasing the blood velocity in the previous part 4.2.2.2. There is no immediate change on the concentration profile at t = 0.001 but the anoxia region shrunk greatly at t = 0.01. With the applied 10% increment on the blood oxygen concentration, the anoxic tissue region is fully recovered at t = 0.0668.

Note that both increasing the blood velocity and increasing the oxygen concentration in the incoming blood increases the amount of oxygen entering the capillary-tissue region. Hence, the resulting recovery process are similar, but increasing the arterial oxygen concentration will lead to a higher oxygen concentration in tissues closer to the artery end.





Figure 4.18: Recovery process of tissue oxygen distribution following increasing oxygen concentration in the arterial blood, at time t = 0.001, 0.01, 0.05 and 0.1. Anoxic areas are shown in white for contrast.

Chapter 5

The Analytic Theory of the Discrete Compartmental Method

The proposed Discrete Compartment Method (DCM) is a numerical method that approximates the solution of a transient diffusion-consumption-convection system by solving corresponding difference equations on a discrete domain with finite number of compartments. In the examples from previous sections, we have validated the accuracy of steady state solutions obtained using DCM by comparing them with analytic solutions of the differential equation. However, for transient problems we generally do not have the exact solution to compare against, nor do we have any highly accurate solution computed by other means or experimental results (for example, transient problems in 2D and 3D; transient problems in 1D with anoxic region.) In such cases, we mush rely on some combination of the following techniques to gain confidence in our numerical results:

- Validation on test problems. The model with particular implementation should be tested on simple problems for which the true solution is known, or on problems for which a highly accurate comparison solution can be computed by other methods. Experimental results may also be available for comparison in some cases.
- Theoretical analysis of convergence and accuracy. Ideally one would like to prove that the numerical result converges to the correct solution as the compartment

is refined and obtain reasonable error estimates for the numerical error that will be observed on any particular discrete domain.

In this chapter we concentrate on the theoretical analysis. Here we consider only the diffusion consumption problem on a bounded cubic domain. We will also assume the problem is well-posed, which means there exist a unique solution and it depends continuously upon its initial value. In addition, we assume there is no moving boundary in the tissue region for all t.

5.1 Numerical Error

In order to talk about accuracy or convergence, we first need to quantify the error and obtain reasonable error estimates. Numerical solution using DCM is influenced by two sources of error:

- **Discretization error**, the difference between the exact analytical solution of the partial differential equation and the exact solution of the compartmental difference equation.
- Round-off error, the difference between the exact solution of the compartmental difference equation and the numerical result using finite-precision. It is also called rounding error, which is incurred after a repetitive number of calculations due to inexactness in the representation of real numbers on a computer.

In one dimensional problem we have an approximation C_i^n for each compartment using the discrete compartment method. For comparison, we let u(x,t) represent the analytical solution of the partial differential equation and u_i^n represent the exact value we are hoping to approximate well. For a finite difference method we may choose to compare with the pointwise value

$$u_i^n = u(i\Delta x, n\Delta t), \tag{5.1}$$

but for a discrete compartment method we may want to instead use

$$u_{i}^{n} = \frac{1}{\Delta x} \int_{x_{i-1/2}}^{x_{i+1/2}} u(x, n\Delta t) dx.$$
 (5.2)

However, the pointwise value (5.1) for the compartment centered at x_i agrees with the compartment average (5.2) to $\mathcal{O}(\Delta x)$ if the function u(x,t) is sufficiently smooth. Since the present discrete compartment method is second-order accurate (will prove in the next section), comparison with the pointwise value can be used for simplicity. The global error at time $T = N\Delta t$ can then be represented as

$$E^N = C^N - u^N. ag{5.3}$$

Note that for time dependent problems, errors generally grow with time, and the number of time steps to reach time level n+1 will grow to infinity (in the limit that must be considered in proving convergence) as we refine the grid. So we should not expect that any finite grid could yield good solutions at arbitrarily large times.

We say that the method is convergent at time T in the norm $|| \cdot ||$ if

$$||E^{N}|| \to 0, \quad \Delta x, \Delta t \to 0,$$
 (5.4)

and the method is pointwise convergent as the compartment is refined if the method is

convergent in the ∞ -norm

$$||E||_{\infty} = \max_{i \in Z^*} |E_i|.$$
(5.5)

We say that the method is accurate of order (\tilde{p}, \tilde{q}) if

$$||E^{N}|| = \mathcal{O}(\Delta x^{\tilde{p}}) + \mathcal{O}(\Delta t^{\tilde{q}})$$
(5.6)

which means there exist a constant B, such that

$$||E^{N}|| \leq B\left(\Delta x^{\tilde{p}} + \Delta t^{\tilde{q}}\right).$$
(5.7)

5.2 Convergence

Consider the Crank-Gupta problem

$$\begin{cases} \frac{\partial C}{\partial t} = \frac{\partial^2 C}{\partial x^2} - 1, & 0 \leq x \leq s(t), & t \geq 0\\ \frac{\partial C}{\partial x} = 0, & \text{at} \quad x = 0, \\ C = \frac{\partial C}{\partial x} = 0, & \text{at} \quad x = s(t), \\ C(x,0) = \frac{1}{2}(1-x)^2, & 0 \leq x \leq 1, \end{cases}$$
(5.8)

where s(0) = 1, and the discrete compartment method

$$\begin{cases} C_{i}^{n+1} = \max\left\{C_{i}^{n} + \alpha \cdot \left[C_{i-1}^{n} - 2C_{i}^{n} + C_{i+1}^{n}\right] - \Delta t \cdot \kappa, 0\right\}, & n \ge 0\\ C_{0}^{n+1} = \max\left\{C_{0}^{n} + 2\alpha \cdot \left[C_{1}^{n} - C_{0}^{n}\right] - \Delta t \cdot \kappa, 0\right\}, & n \ge 0,\\ C_{I}^{n+1} = \max\left\{C_{I}^{n} + 2\alpha \cdot \left[C_{I-1}^{n} - C_{i}^{n}\right] - \Delta t \cdot \kappa, 0\right\}, & n \ge 0,\\ C_{i}^{0} = \frac{1}{2}(1 - \Delta x \cdot i)^{2}, & i = 0, 1, \cdots, I, \end{cases}$$

$$(5.9)$$

where $\alpha = \Delta t / (\Delta x)^2$.

Theorem 5.2.1. If $0 < \alpha \leq 1/2$, we have the solution of (5.9) pointwise converges to the solution of (5.8), i.e.

$$||E^n||_{\infty} \to 0, \quad \text{as} \quad \Delta x, \Delta t \to 0, \quad \forall n \in \mathbb{N}.$$
 (5.10)

Proof. First, we show that C_i^n is decreasing w.r.t i in the region where its values are positive. We have

$$C_{i+1}^{0} - C_{i}^{0} = \frac{1}{2} \left[1 - (i+1)\Delta x \right]^{2} - \frac{1}{2} \left(1 - i\Delta x \right)^{2}$$

$$= (i+\frac{1}{2})\Delta x^{2} - \Delta x$$
(5.11)

Since $\Delta x = 1/I$, for i = 1, ..., I - 1 we have

$$(i+\frac{1}{2})\Delta x^2 - \Delta x = \frac{i+\frac{1}{2}}{I}\Delta x - \Delta x = -\frac{I-i-\frac{1}{2}}{I^2} < 0.$$
 (5.12)

Combining with (5.11) we have

$$C_{i+1}^0 - C_i^0 < 0, \quad \text{for } i = 1, ..., I - 1.$$
 (5.13)

Now consider the region where C_{i+1}^{n+1} and $C_i^{n+1} > 0$,

$$C_{i+1}^{n+1} - C_i^{n+1} = (1 - 2\alpha)C_{i+1}^n + \alpha(C_i^n + C_{i+2}^n) - \Delta t \cdot \kappa$$
$$- (1 - 2\alpha)C_i^n - \alpha(C_{i-1}^n + C_{i+1}^n) - \Delta t \cdot \kappa$$
$$= (1 - 2\alpha)(C_{i+1}^n - C_i^n) + \alpha(C_{i+2}^n - C_{i+1}^n + C_i^n - C_{i-1}^n)$$
(5.14)

Assume $C_{i+1}^n - C_i^n < 0$, we have by (5.14) that

$$C_{i+1}^{n+1} - C_i^{n+1} < 0, (5.15)$$

because $\alpha \ge 0$ and $1 - 2\alpha \ge 0$. Recall by (5.13), this is also true for n = 0. Thus by induction, we have

$$C_{i+1}^n - C_i^n < 0 (5.16)$$

for all i = 1, ..., I - 1 such that $C_i^n > 0, \forall n \in \mathbb{N}$.

On the left boundary, since $C_0^{n+1} < C_0^n$, by (5.9) we have

$$C_0^{n+1} = (1 - 2\alpha)C_0^n + 2\alpha \cdot C_1^n - \Delta t \cdot \kappa < C_0^n.$$
(5.17)

Simplify and rewrite gives

$$C_0^n > C_1^n - \frac{\Delta t \cdot \kappa}{2\alpha} = C_1^n - \frac{\Delta x^2 \cdot \kappa}{2} \to C_1^n \quad \text{as} \quad \Delta x \to 0,$$
(5.18)

 $\forall n \in \mathbb{N} \text{ such that } C_i^n > 0.$

Thus, the solution C_i^n is decreasing strictly before it reaches 0. Moreover, we have by (5.14) and (5.11) that

$$|C_{i+1}^{n+1} - C_i^{n+1}| \leqslant |C_{i+1}^n - C_i^n| \to 0 \quad \text{as} \quad \Delta x \to 0.$$
(5.19)

Let \tilde{i}_n be such that $C_{\tilde{i}_n}^n$ and $C_{\tilde{i}_n+1}^n = 0$, by (5.19) we have $\forall \epsilon > 0, \exists \delta > 0$ s.t.

$$|C^n_{\widetilde{i}_n}| < \epsilon \quad \text{when} \quad \Delta x < \delta, \tag{5.20}$$

i.e. the numerical solution is asymptotically continuous as $\Delta x \to 0$.

Next, we show that the numerical solution converges to the original solution in its positive values. Let

$$E_i^n = C_i^n - u(i\Delta x, n\Delta t), \qquad (5.21)$$

then for i = 1, ..., I - 1 such that $C_i^n > 0$

$$E_{i}^{n+1} = C_{i}^{n+1} - u(i\Delta x, (n+1)\Delta t)$$

$$= (1 - 2\alpha)C_{i}^{n} + \alpha(C_{i-1}^{n} + C_{i+1}^{n}) - \Delta t \cdot \kappa - u(i\Delta x, (n+1)\Delta t) \qquad (5.22)$$

$$= (1 - 2\alpha)[E_{i}^{n} + u(i\Delta x, n\Delta t)] + \alpha[E_{i-1}^{n} + u((i-1)\Delta x, n\Delta t) + E_{i+1}^{n}$$

$$u((i+1)\Delta x, n\Delta t)] - \Delta t \cdot \kappa - u(i\Delta x, (n+1)\Delta t), \qquad (5.23)$$

 $\forall n \in \mathbb{N}$. Consider the Taylor expansion of the analytical solution terms in equation (5.23) at $(i\Delta x, n\Delta t)$

$$u((i-1)\Delta x, n\Delta t) = u(i\Delta x, n\Delta t) - \Delta x \cdot \frac{\partial u}{\partial x}\Big|_{(i\Delta x, n\Delta t)} + \mathcal{O}(\Delta x^2),$$
(5.24)

$$u((i+1)\Delta x, n\Delta t) = u(i\Delta x, n\Delta t) + \Delta x \cdot \frac{\partial u}{\partial x}\Big|_{(i\Delta x, n\Delta t)} + \mathcal{O}(\Delta x^2), \quad (5.25)$$

$$u(i\Delta x, (n+1)\Delta t) = u(i\Delta x, n\Delta t)) + \Delta t \cdot \frac{\partial u}{\partial t}\Big|_{(i\Delta x, n\Delta t)} + \mathcal{O}(\Delta t^2).$$
(5.26)

Put these back into (5.23), we have

$$E_{i}^{n+1} = (1 - 2\alpha)E_{i}^{n} + \alpha \left[E_{i-1}^{n} + E_{i+1}^{n}\right] + (1 - 2\alpha) \cdot u(i\Delta x, n\Delta t) + \alpha \left[u(i\Delta x, n\Delta t) - \Delta x \cdot \frac{\partial u}{\partial x}\Big|_{(i\Delta x, n\Delta t)} + \mathcal{O}(\Delta x^{2}) + u(i\Delta x, n\Delta t) + \Delta x \cdot \frac{\partial u}{\partial x}\Big|_{(i\Delta x, n\Delta t)} + \mathcal{O}(\Delta x^{2})\right] - \Delta t \cdot \kappa - \left[u(i\Delta x, n\Delta t)) + \Delta t \cdot \frac{\partial u}{\partial t}\Big|_{(i\Delta x, n\Delta t)} + \mathcal{O}(\Delta t^{2})\right] = (1 - 2\alpha)E_{i}^{n} + \alpha \left[E_{i-1}^{n} + E_{i+1}^{n}\right] + \mathcal{O}(\Delta x^{2}) + \mathcal{O}(\Delta t).$$
(5.27)

Since $\alpha \ge 0$ and $1 - 2\alpha \ge 0$, by the triangle inequality,

$$|E_i^{n+1}| \leqslant (1-2\alpha)|E_i^n| + \alpha|E_{i-1}^n| + \alpha|E_{i+1}^n| + B \cdot (\Delta x^2 + \Delta t)$$
(5.28)

for some constant B > 0. Take supremum over positive region, we have

$$\sup_{1 \leq i \leq \widetilde{i}_{n+1}} |E_i^{n+1}| \leq \sup_{1 \leq i \leq \widetilde{i}_{n+1}} |E_i^n| + B \cdot (\Delta x^2 + \Delta t)$$
(5.29)

$$\leq \sup_{1 \leq i \leq \tilde{i}_0} |E_i^n| + nB \cdot (\Delta x^2 + \Delta t)$$
(5.30)

Observe that

$$E_i^0 = \frac{1}{2}(1 - i\Delta x)^2) - \frac{1}{2}(1 - i\Delta x)^2) = 0.$$
 (5.31)

We have

$$\sup_{1 \le i \le \widetilde{i}_{n+1}} |E_i^{n+1}| \le nA \cdot (\Delta x^2 + \Delta t) \to 0 \quad \text{as} \quad \Delta x, \Delta t \to 0.$$
(5.32)

Therefore, for each (i, n), where i = 1, ..., I - 1 and $n \in \mathbb{N}$, such that $C_i^n > 0$, we have

$$|E_i^n| = |C_i^n - u(i\Delta x, n\Delta t)| \to 0 \quad \text{as} \quad \Delta x, \Delta t \to 0.$$
(5.33)

On the right boundary, obviously we have

$$|E_I^n| = 0 \quad \forall n \in \mathbb{N}.$$
(5.34)

On the left boundary, we have

$$E_0^{n+1} = C_0^n - u(0, (n+1)\Delta t)$$
(5.35)

$$= (1 - 2\alpha)C_0^n + 2\alpha C_1^n - \Delta t \cdot \kappa - C(0, (n+1)\Delta t)$$
(5.36)

$$= (1 - 2\alpha) \left[E_0^n + u(0, n\Delta t) \right] + 2\alpha \left[E_1^n + u(\Delta x, n\Delta t) \right]$$
(5.37)

$$-\Delta t \cdot \kappa - u(0, (n+1)\Delta t) \tag{5.38}$$

 $\forall n \in \mathbb{N}$. Consider the Taylor expansion of the analytical solution terms in equation (5.35) at $(i0, n\Delta t)$

$$u(\Delta x, n\Delta t) = u(0, n\Delta t) + \Delta x \cdot \frac{\partial u}{\partial x}\Big|_{(0, n\Delta t)} + \mathcal{O}(\Delta x^2),$$
(5.39)

$$u(0, (n+1)\Delta t) = u(0, n\Delta t)) + \Delta t \cdot \frac{\partial u}{\partial t}\Big|_{(0, n\Delta t)} + \mathcal{O}(\Delta t^2).$$
(5.40)

Put these back into (5.35), we have

$$E_0^{n+1} = (1 - 2\alpha)E_0^n + (1 - 2\alpha)u(0, n\Delta t) + 2\alpha E_1^n + 2\alpha \left[u(0, n\Delta t) + \Delta x \cdot \frac{\partial u}{\partial x} \Big|_{(0, n\Delta t)} + \mathcal{O}(\Delta x^2) \right] - \Delta t \cdot \kappa - \left[u(0, n\Delta t)) + \Delta t \cdot \frac{\partial u}{\partial t} \Big|_{(0, n\Delta t)} + \mathcal{O}(\Delta t^2) \right] = (1 - 2\alpha)E_0^n + 2\alpha E_1^n + \mathcal{O}(\Delta x^2) + \mathcal{O}(\Delta t)$$
(5.41)

where (5.41) is because $\partial u/\partial x = 0$ at x = 0. Since $0 < \alpha \leq 1/2$

$$\begin{split} |E_0^{n+1}| &\leq |E_0^n| + |E_1^n| + B_1 \cdot (\Delta x^2 + \Delta t) \\ &\leq |E_0^{n-1}| + |E_1^{n-1}| + |E_1^n| + 2B_1 \cdot (\Delta x^2 + \Delta t) \\ &\leq \dots \leq \\ &\leq |E_0^0| + \sum_{k=0}^n |E_1^k| + nB_1 \cdot (\Delta x^2 + \Delta t) \\ &= 0 + \sum_{k=0}^n |E_1^k| + nB_1 \cdot (\Delta x^2 + \Delta t), \end{split}$$
(5.42)

for some constant $B_1 > 0$. Together with (5.33), we have

$$|E_0^n| = |C_0^n - u(0, n\Delta t)| \to 0 \quad \text{as} \quad \Delta x, \Delta t \to 0.$$
(5.43)

To handle the zero value part, recall by (5.20) that the numerical solution C_i^n is asymptotically continuous. Thus $\forall \epsilon > 0, \exists \delta \text{ s.t.}$ (by (5.33))

$$|C_{\tilde{i}n}^n - u(\tilde{i}_n \Delta x, n\Delta t)| < \epsilon \quad \text{if} \quad \max(\Delta x, \Delta t) < \delta.$$
(5.44)

By (5.20), $\exists \delta_1 > 0$ s.t.

$$|C_{\tilde{i}_n}^n| < \epsilon \quad \text{for} \quad \Delta x < \delta_1.$$
(5.45)

Combining (5.44) and (5.45), we have

$$|u(\widetilde{i}_{n}\Delta x, n\Delta t)| = |u(\widetilde{i}_{n}\Delta x, n\Delta t) - C_{\widetilde{i}_{n}}^{n} + C_{\widetilde{i}_{n}}^{n}|$$

$$\leq |u(\widetilde{i}_{n}\Delta x, n\Delta t) - C_{\widetilde{i}_{n}}^{n}| + |C_{\widetilde{i}_{n}}^{n}|$$

$$< 2\epsilon.$$
(5.46)

Since u(x, t) is non-increasing and positive in x, we have

$$0 < u((\widetilde{i}_n + 1)\Delta x, n\Delta t) < u(\widetilde{i}_n \Delta x, n\Delta t).$$
(5.47)

Recall by definition of \tilde{i}_n we have $C_{\tilde{i}_n+1}^n = 0$, i.e.

$$|C_{\widetilde{i}_n+1}^n - u((\widetilde{i}_n+1)\Delta x, n\Delta t)| \le 2\epsilon.$$
(5.48)

Therefore, C_i^n is also convergent to u(x,t) in the zero value region. Combining (5.33) and (5.48), we have

$$C_i^n \to u(i\Delta x, n\Delta t) \quad \text{as} \quad \Delta x, \Delta t \to 0,$$
(5.49)

 $\forall i = 1, ..., I \text{ and } \forall n \in \mathbb{N}, \text{ i.e.}$

$$||E^{n}||_{\infty} = ||C^{n} - u^{n}||_{\infty} \to 0, \quad \text{as} \quad \Delta x, \Delta t \to 0, \quad \forall n \in \mathbb{N}.$$
(5.50)

Remark 5.2.1. The result can be easily extended to two-dimensional cases with $0 < \alpha \leq 1/4$ and three-dimensional cases with $0 < \alpha \leq 1/6$.

When the sliding element method (SEM) is introduced to deal with the convection, the time step size is dependent on the blood velocity. Since our the original goal is to simulate and analyze real biological process, biological parameters are used through out the computation. For some combination of the parameters, we will need to adjust the sliding frequency b accordingly to maintain the method's stability. Based on the stability condition of the discrete compartment method and the definition of the sliding period p, we have the following corollary.

Corollary 5.2.1. When the sliding element method (SEM) is used along with the discrete compartment method (DCM), for the convergence of an *m*-dimensional problem, we require

$$b \geqslant \frac{2m}{\Delta x \cdot v_b}.\tag{5.51}$$

where v_b is the normalized blood velocity and $b \in \mathbb{Z}^+$ is the sliding frequency.

Proof. For method convergence, we require

$$\frac{\Delta t}{(\Delta x)^2} \leqslant \frac{1}{2m}.\tag{5.52}$$

By the definition of Δt (4.30), we have

$$\frac{p}{b} \leqslant \frac{(\Delta x)^2}{2m}.\tag{5.53}$$

Finally, apply the definition of p gives

$$\frac{\Delta x}{b \cdot v_b} \leqslant \frac{(\Delta x)^2}{2m}.\tag{5.54}$$

Rewriting and simplifying the above equation yields the desired inequality (5.51).

The above corollary is crucial to the development of the discrete compartment model. It helps determining the smallest b under selected blood velocity and space step size, which satisfies the stability condition with the best accuracy.

Remark 5.2.2. In original coefficients with units and the way of normalization used in this thesis, an m-dimensional DCM+SEM scheme is convergent, if

$$b \geqslant \frac{2m \cdot D'}{\Delta x \cdot \tilde{L} \cdot v'_{b}} \tag{5.55}$$

where $\tilde{L} = \sqrt{A(\Omega' \cap \{z = 0\})}$ is the square root of the cross sectional area of the capillarytissue region Ω' on the *xy*-plane in the unit of length, D' is the diffusion coefficient in the unit of area per time, v'_b is blood velocity in the unit of length per time and $b \in \mathbb{Z}^+$.

Chapter 6

Conclusions

6.1 Discussion

The delivery of oxygen through capillaries and blood flow in the microcirculation is critical in human physiology. Due to the advance of technology, it has been shown that many of the macro-cycle system of major diseases, such as all kinds of stroke, ischemic heart disease, high blood pressure, vascular occlusive diseases, diabetes, malignant tumor metastasis, etc, has its occurrence and development not in the macro-circulation but in the micro-circulation.

A three-dimensional discrete compartmental model is developed to estimate the oxygen concentration provided by multiple straight capillaries with different strengths among striated muscles. A reflecting boundary condition is assumed and blood flow velocity inside the capillary is considered. Supply of oxygen from capillaries and tissue and the tissue oxygen concentration level is critical in the function of all living creatures. Using the present method, multiple capillaries with arbitrary characteristics in a three dimensional absorbing tissue domain were first modeled in this paper. The proposed discrete compartmental method is advantageous when compared to other methods due to the following four major reasons:

1. The solution is transient. Previous works has obtained steady-state solutions in many different setups, but the transient solution is more important has not been studied.

Actually, a true steady state may never exist in reality since the oxygen partial pressure inside the capillary changes with breathing and cardiac pulse. Also, the tissue consumption rate changes from rest to normal movement, to physical exercise.

- 2. The model is three-dimensional. Previous works only studied two-dimensional transient problems with multiple capillaries, but these results cannot reveal the physiology of the three-dimension case. In two-dimensional models, the axial diffusion in tissue was neglected. However, recent experiments on the tissue surrounding a capillary clearly indicated that axial diffusion have significant effect on the oxygen concentration profiles.
- 3. The model deals with anoxia among multiple capillaries. Some authors studied anoxia using the Krogh tissue cylinder with a single capillary, but such case may never exist in reality due to the concurrent flow. It is evident that capillaries have different potential strengths and the distribution is uneven. Also the previous models do not predict the location of anoxia which actually occurs somewhere away from a blocked capillary.
- 4. The model is constructed directly from Fick's Law of diffusion. Therefore, the model is easier to apply to three-dimensional case than previous models. At the same time, the resulting difference equation is easy to compute using modern computer technology. The model itself and its construction method can be applied to future studies of more complicated biological systems.

The three major results are 1. The three dimensional transient oxygen concentration can be solved in tissue supplied by a bunch of capillaries 2. If one capillary is blocked, tissue anoxia dose not occur in the vicinity of the blocked capillary but occurs in some affected region which is susceptible to low oxygen concentration 3. If neighboring capillaries are well oxygenated, tissue anoxia may not occur at any time.

The present model is a significant contribution to the research field of both numerical methods and micro-circulation. It reveals and simulates many important biological processes which are not measurable or observable by experiments. Also, it demonstrates a successful and novel way of developing efficient computational model for complicated biological phenomena. Lastly and most importantly, it provides a new research tool with many possible extensions on similar transport problems, especially for the study of heart attack and stroke and their recovery.

6.2 Future Works

The three dimensional discrete compartmental modeling along with the time and space matching technique is first developed in this paper. The discrete compartmental model is designed especially for the oxygen transport problem in muscle tissue where the governing difference equations are derived directly from the Ficks' law of diffusion. Therefore, it is much simpler than any other traditional numerical methods such as finite difference method or finite element method and it can be used as a powerful tool to study the oxygen transport among cellular units and oxygen concentration among muscle tissue.

Possible extensions of the discrete compartmental model are:

1. consider diverse type of cells with different consumption rates,

2. apply the model to other substrates such as carbon dioxide or substrates with finite permeability,

3. instead of sudden blockage, consider different reduced blood velocities,

4. treatment of different boundary shapes,

5. use other compartment shapes such as hexagonal cube or tetrahedron,

6. instead of straight capillary, consider slightly curved capillaries,

7. instead of the zero oxygen area, study also the low oxygen areas,

8. simulation of large scaled tissue bed,

9. explore ways study low blood velocity without violate the convergence constraint,

10. study the change of individual and total outflow versus any abnormal oxygen distribution such as anoxia,

11. consider capillaries of different radius,

12. consider oxygen axial diffusion inside the capillary,

13. deal with capillary branching,

14. calculate the anoxia time of individual zero oxygen regions and predict tissue death time and location.

Theoretical proofs of consistency, convergence and stability of the discrete compartmental method with moving boundary property remain to be improved. The model can be also be applied to pharmacological problems such as the analysis of the drug delivery to tissues. APPENDIX

APPENDIX

Analytic Solution of Krogh Tissue Cylinder

A derivation of the steady state analytic solution of oxygen distribution in a Krogh cylinder is given below. The model consists of a single capillary from which oxygen diffuses into a surrounding cylinder of tissue. The equations governing this model were derived by Blum [6] in 1960, who also attempted to obtain their solution but end up with incorrect results. A correct mathematical analysis of a model for substrate concentration in tissue surrounding single capillries is given by Salathe and Wang [57] in 1980. We shall apply their method to the substrate of oxygen.

Frist, we will review and define the geometry and nature of the idealized cylindrical capillary bad.

- 1. A single capillary of radius R'_c and length L' is surrounded by a concentric cylinder of tissue of radius R'_t . Both ends of the tissue cylinder is bounded by planes normal to the capillary, and it is assumed that no oxygen crosses the boundary of the tissue cylinder including the ends and the cylindrical sides. The origin of a cylindrical coordinate system (x', z') is place on the symmetry axis at the arterial end.
- 2. Blood containing oxygen molecules at a concentration C'_a enters the capillary at the arterial end and flows down to the venous end at a uniform velocity v'_b . Inside the

capillary, we assume the hemoglobin was uniformly dissolved in the plasma and use the average oxygen concentration at any cross section of the capillary. We also assume that diffusion of oxygen inside the capillary are negligible compared to convection due to blood flow through capillary.

- 3. As the oxygen is convected through the capillary at any longitudinal distance z' from the entrance, it diffuses through the membrane into the surrounding tissue. The permeability, P, of the capillary endothelium to the oxygen molecules is unlimited.
- 4. In the surrounding tissue the diffusivities of the oxygen in the radial and axial direction, D', is assumed to be the same, i.e. isotropic diffusion.
- 5. The surrounding tissue cells are assumed to be similar and has uniformly distributed enzyme system that consumes the oxygen at a constant rate κ' .
- 6. Under the assumptions above, the concentration of oxygen in the capillary, C'_c is a founction only of the axial distance z', while the concentration in the surrounding tissue, C'_t , depends on both z and the radial diatance r'.

Normalize all length by the tissue radius R'_t and oxygen concentration by that on the arterial end C'_a . In terms of the nondimensional variables $C_c = C'_c/C'_a$, $C_t = C'_t/C_a$, $r = r'/R'_t$, $z = z'/R'_t$, $l = L'/R'_t$ and $R = R'_c/R'_t$, the governing equation in the tissue arround the capillary is

$$\frac{\partial^2 C_t}{\partial z^2} + \frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial C_t}{\partial r} \right) = \kappa, \quad 0 \leqslant z \leqslant l, \quad R \leqslant r \leqslant 1, \tag{1}$$

where $\kappa = \kappa' (R'_t)^2 / D' C'_a$.

Inside the capillary, the amount of oxygen passing through a cross section at a distance z' along the capillary can be denoted as $\pi R_c'^2 v_b' C_c'$, and the amount leaving the capillary at

the distance z' + dz' is $\pi R_c'^2 v \left[C_c' + dC_c'\right]$. The excess, which is the amount of oxygen diffused away to the surrounding tissues in a distance of dz' is $-\pi R_c'^2 v_b' (dC_c'/dz') dz'$. Meanwhile, the amount of oxygen permeates across through the surface of the capillary membrane enclosed by planes z' and z' + dz' is given by the product of that area, $2\pi R_c' dz'$, times the flow per unit area, $C_c' - C_t'|_{r'=R_c'}$. These two flows have to be equal in the steady state which gives the expressions of the changes of the oxygen concentration inside and on the boundary of the capillary cylinder.

$$\frac{dC'_c}{dz'} = -\frac{2P}{R'_c v'_b} \left[C'_c - C'_t |_{r'=R'_c} \right], \quad 0 \leqslant z' \leqslant L'$$
(.2)

After the normalization we have

$$\beta \frac{dC_c}{dz} = -\left[C_c - C_t|_{r=R}\right], \quad 0 \leqslant z \leqslant l \tag{.3}$$

where $\beta = R'_c v'_b / 4R'_t P$. The oxygen flux in the radial direction is

$$D\frac{\partial C'_t}{\partial r'}|_{r=R} = -P\left[C'_c - C'_t|_{r'=R'_c}\right], \quad 0 \leqslant z' \leqslant L', \tag{4}$$

and after normalization is

$$\frac{\partial C_t}{\partial r}|_{r=R} = -\eta \left[C_c - C_t|_{r=R}\right], \quad 0 \le z \le l, \tag{.5}$$

where $\eta = 2R'_t P/D'$. The inner and outer oxygen flows on the capillary membrane can then be related by

$$\gamma \frac{dC_c}{dz} = \frac{\partial C_t}{\partial r}|_{r=R}, \quad 0 \leqslant z \leqslant l \tag{.6}$$

where $\gamma = R'_c v'_b / 2D'$. Since we assumed that permeability is unlimited, the boundary condition on the capillary wall is given by taking the limit on equation (.3) with P going to infinity

$$C_c(z) - C_t(R, z) = 0, \quad 0 \le z \le l \tag{(.7)}$$

The other boundary conditions in terms of normalized veriables for this pair of differential equations are

$$C_c = 1, \quad z = 0$$
 (.8)

$$\frac{\partial C_t}{\partial r} = 0, \quad r = 1, \quad 0 \leqslant z \leqslant l \tag{.9}$$

$$\frac{\partial C_t}{\partial z} = 0, \quad z = 0, l, \quad R \leqslant r \leqslant 1.$$
(.10)

We shall solve (.1) for $C_t(r, z)$ in terms of $C_c(z)$ by separation of variables, then substitute it into (.6) to obtain the equation of $C_c(z)$. Assume the corresponding homogeneous PDE

$$\frac{\partial^2 C_t}{\partial z^2} + \frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial C_t}{\partial r} \right) = 0, \quad 0 \leqslant z \leqslant l, \quad R \leqslant r \leqslant 1, \tag{11}$$

has a solution of the form

$$C_t(r,z) = F(r)G(z).$$
(.12)

Substituting into (.11) yields

$$F(r)G''(z) + F''(r)G(z) + \frac{1}{r}F'(r)G(z) = 0.$$
(.13)

Separation of variables yields two ODE's

$$F''(r) + \frac{1}{r}F'(r) - \lambda^2 F(r) = 0 \text{ and } G''(z) + \lambda^2 G(z) = 0$$
(.14)

with boundary conditions

$$F'(1) = 0$$
, and $G'(0) = G'(l) = 0.$ (.15)

Combine the solutions to (.14) that satisfies these boundary consistions express the solution to (.11) by the eigenfunction expansion

$$C_t(r,z) = \sum_{n=1}^{\infty} a_n \left[K_1(\lambda_n) I_0(\lambda_n r) + I_1(\lambda_n) K_0(\lambda_n r) \right] \cos(\lambda_n z) + \frac{\kappa}{4} r^2 - \frac{\kappa}{2} \ln r + A_0 \quad (.16)$$

where $\lambda_n = n\pi/l$, for $n = 1, 2, 3, \cdots$. Substituting into the remaining boundary condition (.7) yields

$$C_c(z) = \sum_{n=1}^{\infty} a_n g_n \cos\left(\frac{n\pi z}{l}\right) + \frac{\kappa}{2} \left(\frac{R^2}{2} - \ln R\right) + A_0, \qquad (.17)$$

where

$$g_n = K_1(\lambda_n)I_0(\lambda_n R) + I_1(\lambda_n)K_0(\lambda_n R).$$
(.18)

From the orthogonality of the eigenfunctions $\cos(\frac{n\pi z}{l})$ on the interval $0 \leq z \leq l$ it follows that

$$a_n = \frac{2}{l g_n} \int_0^l C_c(z) \cos\left(\frac{n\pi z}{l}\right) dz,$$
(.19)

and

$$A_0 = \frac{1}{l} \int_0^l C_c(z) dz - \frac{\kappa}{2} \left(\frac{R^2}{2} - \ln R\right).$$
 (.20)

Substituting the solution of $C_t(r, z)$ with constants given explicitly in $C_c(z)$ into equation (.6) and together with the boundary condition (.8) yields

$$C_c(z) = \sum_{n=1}^{\infty} \frac{2f_n}{\gamma n \pi g_n} \sin\left(\frac{n\pi z}{l}\right) \int_0^l C_c(\omega) \cos\left(\frac{n\pi \omega}{l}\right) d\omega + \frac{\kappa}{2\gamma} \left(R - \frac{1}{R}\right) z + 1.$$
(.21)

where

$$f_n = \lambda_n \left[K_1(\lambda_n) I_1(\lambda_n R) - I_1(\lambda_n) K_1(\lambda_n R) \right].$$
(.22)

Multiply equation (.21) by $\cos\left(\frac{m\pi z}{l}\right)$ and integrate over dz from z = 0 to z = l yields a Fredholm integral equation of the second kind with separable kernel

$$c_m = b_m + \sum_{n=1}^{\infty} a_{mn} c_n, \quad m = 1, 2, 3, \cdots,$$
 (.23)

where

$$a_{mn} = \frac{2f_n}{\gamma n \pi g_n} \int_0^l \sin\left(\frac{n\pi z}{l}\right) \cos\left(\frac{m\pi z}{l}\right) dz$$
$$= \begin{cases} 0, & m = n \text{ or } m + n \text{ even} \\ \frac{4(l-1)f_n}{\gamma \pi^2 g_n \left(n^2 - m^2\right)}, & m + n \text{ odd}, \end{cases}$$
(.24)

$$b_m = \int_0^l \left[\frac{\kappa}{2\gamma} \left(R - \frac{1}{R} \right) z + 1 \right] \cos\left(\frac{m\pi z}{l}\right) dz$$
$$= \begin{cases} 0, & m \text{ even} \\ -\frac{\kappa l^2}{m^2 \pi^2 \gamma} \left(R - \frac{1}{R} \right), & m \text{ odd}, \end{cases}$$
(.25)
and

$$c_m = \int_0^l C_c(z) \cos\left(\frac{m\pi z}{l}\right) dz.$$
 (.26)

Equation (.23) represents an infinite set of linear algebric equations for the infinite set of unknown constants c_m , which can be truncated into the form

$$\overline{c_m} = b_m + \sum_{n=1}^N a_{mn} \overline{c_n}, \quad m = 1, 2, 3, \cdots,$$
(.27)

Writting in matrix form

$$\mathbf{C}_{m \times 1} = \mathbf{B}_{m \times 1} + \mathbf{A}_{m \times n} \mathbf{C}_{n \times 1}.$$
 (.28)

So that

$$(\mathbf{I} - \mathbf{A}) \mathbf{C} = \mathbf{B}. \tag{.29}$$

This "reduced" system can be solved as

$$\mathbf{C} = (\mathbf{I} - \mathbf{A})^{-1} \mathbf{B},\tag{.30}$$

where is can be shown that $\overline{c_m}$ converges to c_m as $N \to \infty$. By choosing a sufficiently large N, one can obtain a solution of c_m of any desired accuracy. Therefore, the solution to $C_c(z)$ and $C_t(r, z)$ are found as

$$C_t(r,z) = \sum_{n=1}^{\infty} \frac{2c_n}{l g_n} \left[K_1(\lambda_n) I_0(\lambda_n r) + I_1(\lambda_n) K_0(\lambda_n r) \right] \cos(\frac{n\pi z}{l}) + \frac{\kappa}{2} \left[\frac{r^2}{2} - \ln r - \frac{R^2}{2} + \ln R \right] + \frac{1}{l} \int_0^l C_c(z) dz,$$
(.31)

and

$$C_c(z) = \sum_{n=1}^{\infty} \frac{2c_n f_n}{\gamma n \pi g_n} \sin\left(\frac{n\pi z}{l}\right) + \frac{\kappa}{2\gamma} \left(R - \frac{1}{R}\right) z + 1, \qquad (.32)$$

where

$$\frac{1}{l} \int_0^l C_c(z) dz = \sum_{n=1}^\infty \frac{2c_n f_n}{\gamma(n\pi)^2 g_n} \left[1 - \cos(n\pi) \right] + \frac{\kappa l}{4\gamma} \left(R - \frac{1}{R} \right) + 1.$$
(.33)

This result is used for the comparison with the numerical solution obtained using DCM in example 4.1.3.

Note that, since the solution is obtained as an infinite series, it must be truncated after a finite number of terms for numerical computations. An error analysis of the applied method is given in [57]. In the example shown in this thesis, 100 terms were used in the expansion, and the error was exceedingly small.

BIBLIOGRAPHY

BIBLIOGRAPHY

- Keumseong Bang and JaeGwi Go. The simulation of oxygen diffusion following occlusion. Applied mathematics and computation, 183(2):1301–1309, 2006.
- [2] James B Bassingthwaighte, Erik Butterworth, Bartholomew Jardine, and Gary M Raymond. Compartmental modeling in the analysis of biological systems. In *Computational toxicology*, pages 391–438. Springer, 2012.
- [3] James B Bassingthwaighte, IS Joseph Chan, and CY Wang. Computationally efficient algorithms for convection-permeation-diffusion models for blood-tissue exchange. Annals of biomedical engineering, 20(6):687–725, 1992.
- [4] Daniel A Beard and James B Bassingthwaighte. Modeling advection and diffusion of oxygen in complex vascular networks. Annals of biomedical engineering, 29(4):298–310, 2001.
- [5] Alan E. Berger, Melvyn Ciment, and Joel C. W. Rogers. Numerical solution of a diffusion consumption problem with a free boundary. *SIAM Journal on Numerical Analysis*, 12(4):646–672, 1975.
- [6] Jacob J Blum. Concentration profiles in and around capillaries. American Journal of Physiology-Legacy Content, 198(5):991–998, 1960.
- [7] Walter F Boron and Emile L Boulpaep. Medical physiology E-book. Elsevier Health Sciences, 2016.
- [8] Alessandra Bosutti, Stuart Egginton, Yoann Barnouin, Bergita Ganse, Jörn Rittweger, and Hans Degens. Local capillary supply in muscle is not determined by local oxidative capacity. *Journal of experimental biology*, 218(21):3377–3380, 2015.
- [9] John Crank. Free and moving boundary problems. Clarendon press Oxford, 1984.
- [10] John Crank et al. The mathematics of diffusion. Oxford university press, 1979.
- [11] John Crank and Radhey S Gupta. A method for solving moving boundary problems in heat flow using cubic splines or polynomials. *IMA Journal of Applied Mathematics*, 10(3):296–304, 1972.
- [12] John Crank and Radhey S Gupta. A moving boundary problem arising from the diffusion of oxygen in absorbing tissue. IMA Journal of Applied Mathematics, 10(1):19–33, 1972.

- [13] HO Dahmardah and DF Mayers. A fourier-series solution of the crank—gupta equation. IMA Journal of Numerical Analysis, 3(1):81–86, 1983.
- [14] Stuart Egginton and Eamonn Gaffney. Experimental physiology-review article: Tissue capillary supply-it's quality not quantity that counts! *Experimental physiology*, 95(10):971–979, 2010.
- [15] H Fabel. Normal and critical o2 supply of the heart. In Oxygen transport in blood and tissue, pages 159–171. George Thieme Stuttgart, 1968.
- [16] John E Fletcher. A mathematical model of the unsteady transport of oxygen to tissues in the microcirculation. In Oxygen Transport to Tissue, pages 819–825. Springer, 1973.
- [17] John E Fletcher. A model describing the unsteady transport of substrate to tissue from the microcirculation. SIAM Journal on Applied Mathematics, 29(3):449–480, 1975.
- [18] John E Fletcher. Mathematical modeling of the microcirculation. Mathematical biosciences, 38(3-4):159-202, 1978.
- [19] Graham M Fraser, Daniel Goldman, and Christopher G Ellis. Comparison of generated parallel capillary arrays to three-dimensional reconstructed capillary networks in modeling oxygen transport in discrete microvascular volumes. *Microcirculation*, 20(8):748–763, 2013.
- [20] JaeGwi Go. Oxygen delivery through capillaries. Mathematical biosciences, 208(1):166– 176, 2007.
- [21] D Goldman and Aleksander S Popel. Computational modeling of oxygen transport from complex capillary networks. In Oxygen Transport to Tissue XXI, pages 555–563. Springer, 1999.
- [22] Daniel Goldman. Simulations of capillary network oxygen transport during transient ischemia in the presence and absence of tissue myoglobin. In Oxygen Transport To Tissue XXIII, pages 355–359. Springer, 2003.
- [23] Daniel Goldman. Theoretical models of microvascular oxygen transport to tissue. Microcirculation, 15(8):795–811, 2008.
- [24] Daniel Goldman, Ryon M Bateman, and Christopher G Ellis. Effect of sepsis on skeletal muscle oxygen consumption and tissue oxygenation: interpreting capillary oxygen transport data using a mathematical model. American Journal of Physiology-Heart and Circulatory Physiology, 287(6):H2535–H2544, 2004.
- [25] Daniel Goldman, Ryon M Bateman, and Christopher G Ellis. Effect of decreased o2 supply on skeletal muscle oxygenation and o2 consumption during sepsis: role of hetero-

geneous capillary spacing and blood flow. *American Journal of Physiology-Heart and Circulatory Physiology*, 290(6):H2277–H2285, 2006.

- [26] José M Gonzalez-Fernandez and Susie E Atta. Transport and consumption of oxygen in capillary-tissue structures. *Mathematical Biosciences*, 2(3-4):225–262, 1968.
- [27] Carl A Goresky and Harry L Goldsmith. Capillary-tissue exchange kinetics: diffusional interactions between adjacent capillaries. In Oxygen Transport to Tissue, pages 773–781. Springer, 1973.
- [28] Radhey S Gupta and Dhirendra Kumar. Complete numerical solution of the oxygen diffusion problem involving a moving boundary. *Computer Methods in Applied Mechanics* and Engineering, 29(2):233–239, 1981.
- [29] E Hansen and P Hougaard. On a moving boundary problem from biomechanics. J. Inst. Math. Appl., 13, 06 1974.
- [30] Archibald Vivian Hill. The diffusion of oxygen and lactic acid through tissues. Proceedings of the Royal Society of London. Series B, Containing Papers of a Biological Character, 104(728):39–96, 1928.
- [31] G Hutten, G Thews, and P Vaupel. Some special problems concerning the oxygen supply to tissue, as studied by an analogue computer. Oxygen Supply, Urban & Schwarzenberg, Munchen, page 25, 1973.
- [32] John A Jacquez. Compartmental analysis in biology and medicine, biomedware. Ann Arbor, MI, 512, 1996.
- [33] John Alfred Jacquez et al. Compartmental analysis in biology and medicine. 1972.
- [34] John A Johnson and Theodore A Wilson. A model for capillary exchange. American Journal of Physiology-Legacy Content, 210(6):1299–1303, 1966.
- [35] Leonard R Johnson. Essential medical physiology. Elsevier, 2003.
- [36] Seymour S Kety. Determinants of tissue oxygen tension. In Federation proceedings, volume 16, page 666, 1957.
- [37] Ronald J Korthuis. Skeletal muscle circulation. In Colloquium Series on Integrated Systems Physiology: From Molecule to Function, volume 3, pages 1–144. Morgan & Claypool Life Sciences, 2011.
- [38] August Krogh. The number and distribution of capillaries in muscles with calculations of the oxygen pressure head necessary for supplying the tissue. The Journal of physiology, 52(6):409–415, 1919.

- [39] August Krogh. The anatomy and physiology of capillaries, volume 18. Yale University Press, 1922.
- [40] Randall J LeVeque et al. *Finite volume methods for hyperbolic problems*, volume 31. Cambridge university press, 2002.
- [41] David G Levitt. Theoretical model of capillary exchange incorporating interactions between capillaries. American Journal of Physiology-Legacy Content, 220(1):250–255, 1971.
- [42] Edwin N Lightfoot et al. Transport phenomena and living systems. 1974.
- [43] Ted Lin and Chris Mowatt. Physiology of the circulation, page 315–343. Cambridge University Press, 4 edition, 2016.
- [44] Stanley Middleman. Transport phenomena in the cardiovascular system. John Wiley & Sons, 1972.
- [45] JV Miller, KW Morton, and MJ Baines. A finite element moving boundary computation with an adaptive mesh. IMA Journal of Applied Mathematics, 22(4):467–477, 1978.
- [46] S.L. Mitchell. An accurate application of the integral method applied to the diffusion of oxygen in absorbing tissue. *Applied Mathematical Modelling*, 38(17):4396 4408, 2014.
- [47] SL Mitchell and Michael Vynnycky. The oxygen diffusion problem: Analysis and numerical solution. Applied Mathematical Modelling, 39(9):2763–2776, 2015.
- [48] David L Nelson, Albert L Lehninger, and Michael M Cox. Lehninger principles of biochemistry. Macmillan, 2008.
- [49] WHO. "The top 10 causes of death." World Health Organization, 2018. http://www. who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death
- [50] Roland N Pittman. Regulation of tissue oxygenation. In Colloquium series on integrated systems physiology: from molecule to function, volume 3, pages 1–100. Morgan & Claypool Life Sciences, 2011.
- [51] MJ Plyley, Gloria J Sutherland, and AC Groom. Geometry of the capillary network in skeletal muscle. *Microvascular research*, 11(2):161–173, 1976.
- [52] Aleksander S Popel. Theory of oxygen transport to tissue. *Critical reviews in biomedical engineering*, 17(3):257, 1989.
- [53] Aleksander S Popel and Paul C Johnson. Microcirculation and hemorheology. Annu. Rev. Fluid Mech., 37:43–69, 2005.

- [54] RF Potter and AC Groom. Capillary diameter and geometry in cardiac and skeletal muscle studied by means of corrosion casts. *Microvascular research*, 25(1):68–84, 1983.
- [55] Daniel D Reneau, Duane F Bruley, and Melvin H Knisely. A mathematical simulation of oxygen release, diffusion, and consumption in the capillaries and tissue of the human brain. In *Chemical Engineering in Medicine and Biology*, pages 135–241. Springer, 1967.
- [56] Francis John Worsley Roughton. Diffusion and chemical reaction velocity in cylindrical and spherical systems of physiological interest. Proceedings of the Royal Society of London. Series B-Biological Sciences, 140(899):203-229, 1952.
- [57] Eric P Salathé and Tseng-Chan Wang. Substrate concentrations in tissue surrounding single capillaries. *Mathematical Biosciences*, 49(3-4):235–247, 1980.
- [58] Eric P Salathé, Tseng-Chan Wang, and Joseph F Gross. Mathematical analysis of oxygen transport to tissue. *Mathematical Biosciences*, 51(1-2):89–115, 1980.
- [59] Eric P Salathé and Tseng-Chang Wang. The development of anoxia following occlusion. Bulletin of mathematical biology, 44(6):851–877, 1982.
- [60] Lauralee Sherwood. Human physiology: from cells to systems. Cengage learning, 2015.
- [61] IA Silver. Some observations on the cerebral cortex with an ultramicro, membranecovered, oxygen electrode. *Medical electronics and biological engineering*, 3(4):377–387, 1965.
- [62] Liang Sun. Substrate diffusion and consumption in rectangular capillary-tissue bed. Letters in Biomathematics, 1(1):67–76, 2014.
- [63] Liang Sun, Junkoo Park, and Alessandra L. Barrera. A compartmental model for capillary supply. *Letters in Biomathematics*, 4(1):133–147, 2017.
- [64] Gerhard Thews. Uber die mathematische behandlung physiologischer diffusionsprozesse in zylinderförmigen objekten. Acta Biotheoretica, 10(3-4):105–138, 1953.
- [65] Eleuterio F Toro. Riemann solvers and numerical methods for fluid dynamics: a practical introduction. Springer Science & Business Media, 2013.
- [66] Gerard J Tortora and Bryan Derrickson. Principles of anatomy & physiology. John Wiley & Sons, Incorporated, 2017.
- [67] Karel Tyml, Odile Mathieu-Costello, Linong Cheng, and Earl G Noble. Differential microvascular response to disuse in rat hindlimb skeletal muscles. *Journal of Applied Physiology*, 87(4):1496–1505, 1999.

- [68] CY Wang and JB Bassingthwaighte. Capillary supply regions. *Mathematical biosciences*, 173(2):103–114, 2001.
- [69] Harvey R Weiss. Control of myocardial oxygenation—effect of atrial pacing. Microvascular research, 8(3):362–376, 1974.
- [70] WJ Whalen, D Buerk, and CA Thuning. Blood flow-limited oxygen consumption in resting cat skeletal muscle. American Journal of Physiology-Legacy Content, 224(4):763– 768, 1973.
- [71] Jonathan P Whiteley, David J Gavaghan, and Clive EW Hahn. Mathematical modelling of oxygen transport to tissue. *Journal of mathematical biology*, 44(6):503–522, 2002.
- [72] Jonathan P Whiteley, DJ Gavaghan, and Clive EW Hahn. Oxygen transport to muscle tissue where regions of low oxygen tension exist. *Mathematical and computer modelling*, 42(9-10), 2005.
- [73] Mohamed Zerroukat and Chris R Chatwin. *Computational moving boundary problems*, volume 8. Research Studies Press, 1994.