Copyright Statement

The digital copy of this thesis is protected by the Copyright Act 1994 (New Zealand). This thesis may be consulted by you, provided you comply with the provisions of the Act and the following conditions of use:

- Any use you make of these documents or images must be for research or private study purposes only, and you may not make them available to any other person.

- Authors control the copyright of their thesis. You will recognise the author’s right to be identified as the author of this thesis, and due acknowledgement will be made to the author where appropriate.

- You will obtain the author’s permission before publishing any material from their thesis.

To request permissions please use the Feedback form on our webpage.
http://researchspace.auckland.ac.nz/feedback

General copyright and disclaimer

In addition to the above conditions, authors give their consent for the digital copy of their work to be used subject to the conditions specified on the Library Thesis Consent Form.
A Computational Model
of the Ocular Lens

Duane T K Malcolm
d.malcolm@auckland.ac.nz

Supervised by
Professor Peter Hunter
Associate Professor Paul Donaldson
Professor Joerg Kistler

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Bioengineering,
The University of Auckland, 2007.

Bioengineering Institute
The University of Auckland
New Zealand

December 2006
Abstract

The aim of this project is to develop a computational model of the structure and function of the ocular lens, specifically the solute and fluid transport in the lens.

The modelling framework was based on finite volume methods. The intracellular and extracellular solute fluxes were modelled using the Nernst-Plank equation with an extra term to capture solute fluxes due to advection. The modelling framework included equations describing the flux through the Na⁺/K⁺ pumps and K⁺ channels in the surface membrane, and Na⁺ and Cl⁻ channels in the fibre cell membrane. The intracellular fluid flow between adjacent fibre cells was modelled by a homogenised transmembrane fluid flow equation and the intracellular fluid flow along the fibre cell was modelled as Poiseuille flow. The extracellular fluid flow was modelled as Couette flow with an extra term to capture electro-osmotic flow. The fluid flow through the fibre cell membrane and surface membrane was modelled as transmembrane fluid flow. The governing equations account for the structural properties of the lens, such as the tortuosity of the extracellular cleft, the intracellular and extracellular volume fractions, and the membrane density.

A one-dimensional model of the Na⁺, K⁺, Cl⁻ and fluid transport in the frog lens was developed. This model was based on the analytic model developed by Mathias (1985b). The results were consistent with the results from the analytic model and experimental data.

Two versions of the two-dimensional model were developed. In the first model, the parameters were spatially constant except for the distribution of the Na⁺/K⁺ pump currents at the lens surface and the fibre cell angles. The second model was the same, except the extracellular cleft width and fibre cell height was spatially varied to represent the sutures and the diffusion barrier. These models were solved and compared with each other and with experimental data.

Compared to the first, the second model predicted a significantly larger circulation of solutes and fluid between the pole and equator. It predicted a 12-20% increase in the penetration of Na⁺, K⁺ and fluid into the lens. The second model also predicted a 300-400% increase in Cl⁻ penetration and, unlike the first model, a Cl⁻ circulation between the poles and equator. This is significant since Cl⁻ is not an actively transported solute. These results highlight the strong structure-function relationship in the lens and the importance of an accurate spatial representation of model parameters.

The direction of the current, solute fluxes and fluid flow that were predicted by the model were consistent with experimental data but the magnitude of the surface current was a tenth to a third of
the values measure by the vibrating probe.

To demonstrate the application of the lens model, the two-dimensional model was used to simulate age-related changes in lens physiology. This was done by increasing the radius of the lens to simulate growth with age. The model predicted an increase in the intracellular Na\(^+\) concentration, Cl\(^-\) concentration and potential, and a decrease in the intracellular K\(^+\) concentration with age. These trends were consistent with those observed by Duncan et al. (1989), except for the intracellular K\(^+\) concentration, where they reported no change with age.

The two-dimensional model forms a foundation for future developments and applications.
Acknowledgements

This five year project would not have happened without the generosity of many people and organisations. They have been generous with their time, knowledge and finance.

First I would like to express my gratitude to my supervisors, Peter Hunter, Paul Donaldson and Joerg Kistler, for their patience and support. A special thanks to Peter, who always has time for PhD students, for his support and guidance, and also for allowing me to freely explore ideas. He has shown much patience, especially during my Spark∗ endeavours.

I am also grateful for the support and guidance Marc Jacobs and Rick Mathias have given. Without Rick’s work on the microcirculation model, this modelling project would not exist.

I appreciate the financial support given by the Foundation for Research, Science and Technology and Auckland Uniservices. Without financial support I could not have done this project.

I would also like to thank the Maurice and Phyllis Paykel Trust, Sir John Logan Campbell Medical Trust, Royal Society of New Zealand and the University of Auckland Graduate Research Fund for funding my valuable conference trips within New Zealand and to Australia, USA, and Europe.

Many thanks, literally, to the opensource community. In the period of my PhD I used many opensource packages, namely, Octave, Maxima, Gmsh, NEdit, Inkscape, Gimp, Latex, GNUPlot, and the Sourcemage and Ubuntu Linux distributions.

This PhD certainly would not as stimulating as it has been without my friend and colleagues at the Bioengineering Institute, the Vision Lab and the university as a whole. I have met many great people in the five years who have supported in one way or another. I am very grateful for all for the fun times, support and knowledge.

I am grateful to the friends and family on the other side of my life for their support and encouragement. And also for making my ”spare time” relaxing and enjoyable.

Finally, I would like to acknowledge three important people, my parents Kura and Roger, and my partner Sally.

My father has a PhD in Physics and as a dyslexic kid I remember saying ”I want a DhP when I grow up”, only to be hassled about wanting to be a ”Damn Hopeless Person”. Fortunately, I learnt to spell and chose the better path. The point of that story is that my parents have been an inspiration to me, they have supported me in whatever I’ve wanted to do and gave me a world where I could
play with an inquisitive mind. I am like I am because of their loving support and guidance, for which I will alway be grateful.

Sally has spent seven of the last ten years putting up with, and supporting, a student boyfriend. This is testament of the love, support and guidance she has given. I will alway be grateful for that.
Naku Mataora

No tai mai au te karo iakoe
Te roa i to tere
Na te Kuere, Kuere, Ku-ooo-o-i
Oki mai oki mai

Ea’a te tau i Taunganui e
E tau ora te tau i Taunganui
E tini e mano te ano maira i te moana
E Aitu kake ki te akau e
Oro mai, Oro mai e Punua e

— Chant from Ngaputoru
# Contents

Abstract iii

Acknowledgements v

List of Figures xv

List of Tables xxii

Glossary of Symbols & Abbreviations xxiii

1 Introduction 1

1.1 Lens Structure and Function ................................. 2
    1.1.1 Lens Structure ..................................... 3
    1.1.2 Lens Function ..................................... 5

1.2 Thesis Objectives .................................. 10

1.3 Thesis Overview .................................. 13

2 A Mathematical Description of the Lens Structure 15

2.1 Reference Coordinate System ................................. 16

2.2 Fibre Coordinate System ................................ 16

2.3 Cleft Coordinate System ................................ 18

2.4 Cleft-Fibre Transformation ................................ 19
    2.4.1 Tortuosity ........................................ 20
    2.4.2 Derivative Transformation ........................... 20
    2.4.3 Conservation of Volume ............................ 21
    2.4.4 Conservative Governing Equations .................. 22

3 Solute Transport .................................. 27

3.1 Solute Fluxes ........................................ 27
    3.1.1 Solution Fluxes .................................... 27
3.1.2 Transmembrane Fluxes ........................................... 28
3.2 Solute Sources ......................................................... 31
  3.2.1 Reactions ......................................................... 31
  3.2.2 Transmembrane Fluxes ........................................ 32
3.3 Electroneutrality ..................................................... 33
3.4 Rate of Change of Concentration .................................. 34
3.5 Solute Transport in the Lens ........................................ 34
  3.5.1 Intracellular Fluxes ............................................ 36
  3.5.2 Surface Fluxes .................................................. 37
  3.5.3 Transmembrane Fluxes ........................................ 39
  3.5.4 Extracellular Solute Fluxes ................................... 39
  3.5.5 Electroneutrality ................................................ 41
  3.5.6 Rate of Change of Concentration .............................. 41

4 Fluid Dynamics .......................................................... 43
  4.1 Navier-Stokes Equations .......................................... 44
  4.2 Stokes Flow .......................................................... 45
  4.3 Couette Flow ........................................................ 45
  4.4 Poiseuille Flow ..................................................... 46
  4.5 Darcy Flow .......................................................... 47
  4.6 Electro-osmotic Flow ................................................ 48
    4.6.1 Electric Double Layer (Debye Shielding) .................. 49
    4.6.2 Electro-osmosis Between Parallel Plates .................. 52
  4.7 Transmembrane Fluid Flow ....................................... 55
  4.8 Fluid Transport in the Lens ...................................... 59
    4.8.1 Intracellular Velocity ...................................... 60
    4.8.2 Surface Velocity ............................................. 64
    4.8.3 Transmembrane Velocity .................................... 65
    4.8.4 Extracellular Velocity .............................. 65
    4.8.5 Conservation of Mass ...................................... 68

5 Numerical Methods .................................................... 71
  5.1 Meshing .............................................................. 71
    5.1.1 Mesh Generation .............................................. 72
    5.1.2 Mesh Extrusion ............................................... 72
    5.1.3 Face Center, Normal and Area ............................... 73
## 5.1.4 Element Center and Volume ............................. 74
5.2 Finite Volume Methods ..................................... 76
5.2.1 Linear Interpolation .................................. 77
5.3 Solving Static Problems ................................... 80
5.4 Adaptive Euler Method ................................... 84
5.5 Solution Algorithm for a Coupled Model ............... 87

### 6 Model Properties 91
6.1 Lens Structure ............................................ 92
6.1.1 Lens Geometry ......................................... 92
6.1.2 Fibre Cell Angles ..................................... 93
6.1.3 Cell Dimensions ....................................... 95
6.1.4 Tortuosity .............................................. 96
6.1.5 Extracellular Cleft Width .............................. 97
6.1.6 Membrane Density .................................... 98
6.1.7 Volume Fractions ...................................... 99
6.2 Solute Transport .......................................... 100
6.2.1 Solute Diffusion ....................................... 100
6.2.2 Ion Channels .......................................... 101
6.2.3 Na/K Pumps ........................................... 102
6.3 Fluid Transport ............................................ 105
6.3.1 Membrane Hydraulic Permeability ................... 106
6.4 Lens Physiological Properties ............................. 108
6.4.1 Electrical Potential .................................... 108
6.4.2 Solute Concentrations ................................. 111
6.4.3 Solute Fluxes .......................................... 112
6.4.4 Fluid Flow ............................................ 113

### 7 The One-Dimensional Model 119
7.1 Mesh ....................................................... 120
7.2 Governing Equations ..................................... 121
7.2.1 Solute Fluxes .......................................... 122
7.2.2 Fluid Velocities ....................................... 123
7.2.3 Conservation Equations ............................... 125
7.2.4 Initial Conditions ..................................... 125
7.3 Results and Discussion ................................... 126
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.3.1</td>
<td>Electrical Potential</td>
<td>126</td>
</tr>
<tr>
<td>7.3.2</td>
<td>Solute Concentrations</td>
<td>127</td>
</tr>
<tr>
<td>7.3.3</td>
<td>Solute Fluxes</td>
<td>129</td>
</tr>
<tr>
<td>7.3.4</td>
<td>Fluid Flow</td>
<td>131</td>
</tr>
<tr>
<td>7.3.5</td>
<td>Hydrostatic Pressure</td>
<td>132</td>
</tr>
<tr>
<td>7.4</td>
<td>Summary</td>
<td>133</td>
</tr>
<tr>
<td>8</td>
<td>The Two-Dimensional Model</td>
<td>135</td>
</tr>
<tr>
<td>8.1</td>
<td>Introduction</td>
<td>135</td>
</tr>
<tr>
<td>8.2</td>
<td>Mesh</td>
<td>136</td>
</tr>
<tr>
<td>8.3</td>
<td>Governing Equations</td>
<td>139</td>
</tr>
<tr>
<td>8.3.1</td>
<td>Solute Fluxes</td>
<td>140</td>
</tr>
<tr>
<td>8.3.2</td>
<td>Fluid Velocities</td>
<td>143</td>
</tr>
<tr>
<td>8.3.3</td>
<td>Conservation Equations</td>
<td>145</td>
</tr>
<tr>
<td>8.3.4</td>
<td>Initial Conditions</td>
<td>145</td>
</tr>
<tr>
<td>8.4</td>
<td>Results and Discussion</td>
<td>146</td>
</tr>
<tr>
<td>8.4.1</td>
<td>Electrical Potential</td>
<td>146</td>
</tr>
<tr>
<td>8.4.2</td>
<td>Solute Concentrations</td>
<td>149</td>
</tr>
<tr>
<td>8.4.3</td>
<td>Solute Fluxes</td>
<td>151</td>
</tr>
<tr>
<td>8.4.4</td>
<td>Current Density</td>
<td>160</td>
</tr>
<tr>
<td>8.4.5</td>
<td>Hydrostatic Pressure</td>
<td>163</td>
</tr>
<tr>
<td>8.4.6</td>
<td>Fluid Flow</td>
<td>164</td>
</tr>
<tr>
<td>8.5</td>
<td>Discussion</td>
<td>166</td>
</tr>
<tr>
<td>8.6</td>
<td>Age-Related Changes in Lens Properties</td>
<td>168</td>
</tr>
<tr>
<td>9</td>
<td>Conclusions &amp; Future Developments</td>
<td>171</td>
</tr>
<tr>
<td>9.1</td>
<td>Conclusions</td>
<td>171</td>
</tr>
<tr>
<td>9.2</td>
<td>Future Developments</td>
<td>173</td>
</tr>
<tr>
<td>9.2.1</td>
<td>Modelling Framework</td>
<td>173</td>
</tr>
<tr>
<td>9.2.2</td>
<td>Modelling the Lens</td>
<td>175</td>
</tr>
<tr>
<td>9.2.3</td>
<td>Modelling Other Biological Systems</td>
<td>177</td>
</tr>
<tr>
<td>A</td>
<td>Model Equations and Parameters</td>
<td>179</td>
</tr>
<tr>
<td>A.1</td>
<td>Model Equations</td>
<td>179</td>
</tr>
<tr>
<td>A.1.1</td>
<td>Tissue Properties</td>
<td>179</td>
</tr>
<tr>
<td>A.1.2</td>
<td>Solute Fluxes</td>
<td>179</td>
</tr>
<tr>
<td>A.1.3</td>
<td>Rate of Change of Concentration</td>
<td>181</td>
</tr>
</tbody>
</table>
List of Figures

1 Introduction
1.1 Structure of the eye ........................................... 2
1.2 Structure of the lens ............................................ 3
1.3 Cell types in the lens ........................................... 4
1.4 Fibre cell morphology ........................................ 5
1.5 Equivalent circuit model ....................................... 7
1.6 Key components of lens transport ............................... 9
1.7 Original work .................................................. 12

2 A Mathematical Description of the Lens Structure ........ 15
2.1 Lens and rectangular-Cartesian coordinate system ............................... 16
2.2 Fibre structure and fibre coordinate system ................................. 17
2.3 Fibre angles .................................................... 17
2.4 Lens tissue, extracellular cleft, and cleft coordinate system ................. 18
2.5 Transformation from a tortuous to linearised cleft ........................... 19
2.6 Gradients along a tortuous and linear cleft ................................ 21
2.7 Extracellular cross-sectional surface area in the tortuous and linearised blocks ... 23
2.8 Particle transit times in a tortuous and linear cleft ....................... 25

3 Solute Transport .................................................. 27
3.1 Solute transport through membranes .................................. 28
3.2 Transmembrane solute fluxes between the intracellular and extracellular space ... 32
3.3 Ion fluxes and transport proteins in the lens model. Note: this figure is a copy of Figure 1.6, reproduced for convenience. ........................................... 35
3.4 Ion fluxes, fluid velocity and the dependent variables, potential and pressure, in the lens model .......................... 36
3.5 Intracellular fluxes in the fibre and cross-fibre directions ............. 36
# List of Figures

## 4 Fluid Dynamics

4.1 Chapter layout ................................................. 43
4.2 Fluid velocity profile between parallel plates .................. 45
4.3 Fluid velocity profile in a tube .................................. 47
4.4 The electric double layer ........................................ 49
4.5 The potential and charge density between parallel plates .......... 54
4.6 The pressure and electro-osmotic driven fluid velocity between parallel plates .... 55
4.7 Adjacent fibre cells separated by a semipermeable membrane ....... 56
4.8 Transmembrane fluid flow between fibre cells .................. 57
4.9 Pore density in a membrane .................................... 58
4.10 Fluid flow and transport proteins in the lens model. .............. 59
4.11 Ion fluxes, fluid velocity and the dependent variables, potential and pressure, in the lens model ......................................................... 60
4.12 The intracellular fluid flow in the fibre and cross-fibre directions. .... 61
4.13 Poiseuille flow along fibre cells ................................ 61
4.14 Transmembrane flow between adjacent fibre cells ................. 63
4.15 Lens tissue and the extracellular cleft. .......................... 66

## 5 Numerical Methods

5.1 Extruding a face in the mesh ..................................... 72
5.2 Element extrusion about the $x$-axis ............................. 74
5.3 Approximation of field values and gradients ...................... 77
5.4 Alternative approximation of field values and gradients .......... 78
5.5 Approximation of the field gradient at the boundary ............... 80
5.6 Model of the fluid flow through a tube .......................... 80
5.7 Tube pressure .................................................... 85
5.8 Tube fluid velocity .............................................. 85
5.9 Solution algorithm ............................................... 88

## 6 Model Properties

6.1 Elliptic cross-section of the lens ................................ 92
6.2 Cell types in the lens ........................................... 93
6.3 Three dimensional fibre cell structure of the lens ................ 94
6.4 Fibre angle ......................................................... 95
6.5 Fibre cell morphology ................................. 95
6.6 Fibre cell invaginations at the suture lines .......... 96
6.7 Spatial variation cleft width ............................ 98
6.8 Structure of the sutures ................................. 99
6.9 Na\(^+\)/K\(^+\) pump model at the equator .......... 103
6.10 Na\(^+\)/K\(^+\) pump model at the anterior pole ...... 104
6.11 Maximum Na\(^+\)/K\(^+\) pump rate at the lens surface ..... 104
6.12 Immunostaining of AQP0 and AQP1 in the mouse lens .... 106
6.13 Gap junction structure ............................... 108
6.14 Intracellular and extracellular potentials in the frog lens ...... 108
6.15 Graph of the age-related intracellular potential for human lenses ... 110
6.16 Extracellular potassium concentration predicted by the analytic model .... 112
6.17 Measured currents at the surface of the lens .......... 113
6.18 Extracellular hydrostatic pressure and fluid flow predicted by the analytic model ... 114
6.19 Ussing-chamber used to measure the fluid movement in the rabbit lens ...... 115
6.20 Ussing-type chamber used to measure the fluid movement in the bovine lens ... 116

7 The One-Dimensional Model .......................... 119
7.1 The region of the lens represented by the model .... 119
7.2 Mesh representing the one-dimensional model .......... 120
7.3 The dependent variables, solute fluxes and fluid velocities in the one-dimensional lens model .................. 122
7.4 Mesh convergence ........................................... 126
7.5 Intracellular Na\(^+\) concentration convergence ........ 127
7.6 Graph of the modelled and measured potentials ........ 128
7.7 Graph of the modelled concentrations ................ 129
7.8 Graph of the modelled Na\(^+\) and Cl\(^-\) fluxes .......... 130
7.9 A graph of the predicted fluid flow velocity .......... 131
7.10 A graph of the hydraulic pressure .................. 132

8 The Two-Dimensional Model ......................... 135
8.1 Slice of the lens represented by the two-dimensional model ...... 136
8.2 Mesh representing the two-dimensional model .......... 137
8.3 Fibre angle .............................................. 137
8.4 Spatial variation of the cell height and cleft width
8.5 Spatial variation of the membrane density
8.6 Spatial variation of the volume fractions
8.7 Ion fluxes, fluid velocity and the dependent variables, potential and pressure, in the two-dimensional lens model
8.8 Maximum Na\(^+\)/K\(^+\) pump rate at the lens surface
8.9 Spatial variation of the intracellular hydraulic conductivity
8.10 Spatial variation of the extracellular hydraulic conductivity and electro-osmotic coefficient
8.11 Modelled potential
8.12 Modelled and measured radial potential profiles
8.13 Modelled Na\(^+\), K\(^+\) and Cl\(^-\) concentrations
8.14 Radial profiles of the intracellular Na\(^+\) concentration
8.15 Modelled Na\(^+\), K\(^+\) and Cl\(^-\) fluxes
8.16 Modelled net Na\(^+\), K\(^+\) and Cl\(^-\) fluxes
8.17 Surface Na\(^+\), K\(^+\) and Cl\(^-\) flux
8.18 Na\(^+\), K\(^+\) and Cl\(^-\) penetration into the lens.
8.19 Current density
8.20 Net current density and flow
8.21 Surface current
8.22 Modelled hydraulic pressure
8.23 Modelled fluid velocity
8.24 Net fluid velocity and flow
8.25 Fluid velocity at the lens surface predicted by Model A and Model B.
8.26 Fluid penetration
8.27 The age-related change in potential and Na\(^+\) and K\(^+\) concentrations in the human lens
8.28 Modelled change in potential with lens growth.
8.29 Modelled change in Na\(^+\), K\(^+\) and Cl\(^-\) concentrations with lens growth.

A Model Equations and Parameters
A.1 Fibre angle
A.2 Cleft width and cell height
A.3 Membrane density
A.4 Intracellular and extracellular volume fractions
A.5 Maximum Na\(^+\)/K\(^+\) pump rate at the lens surface
LIST OF FIGURES

A.6 Intracellular hydraulic conductivity ................................. 187
A.7 Extracellular hydraulic conductivity and electro-osmotic coefficient .................. 187

B Dimensional Analysis of Extracellular Fluid Flow .............................. 189
B.1 Fluid velocities along the extracellular cleft ............................... 189
B.2 Extracellular cleft approximated by parallel discs ........................... 190

C Analytic Models ........................................................................ 197
C.1 Donnan equilibrium of a passive cell ......................................... 198
C.2 Analytic and modelled solutions for heat conduction ....................... 199
C.3 Fluid flow in a tube ................................................................. 200
C.4 Analytic and modelled velocity profiles for fluid flow in a tube .......... 201
C.5 Analytic and modelled pressure profiles for fluid flow in a tube .......... 201
**List of Tables**

6  **Model Properties**

6.1 Lens geometry and fibre cell dimensions ......................................... 93
6.2 Properties of the Na\(^+\)/K\(^+\) pumps ........................................... 103
6.3 Membrane water permeability and hydraulic conductivity for fibre and epithelial cells .................................................. 107
6.4 Measured lens potentials ................................................................. 109
6.5 Computed intracellular ion concentrations ...................................... 111
6.6 Summary of fluid flow studies ......................................................... 117

7  **The One-Dimensional Model**

7.1 Mesh parameters ................................................................. 121
7.2 Tissue properties ................................................................. 121
7.3 Solute transport properties ....................................................... 124
7.4 Fluid flow parameters ............................................................. 125
7.5 Initial conditions. ................................................................. 126
7.6 The mean modelled and measured concentrations ...................... 128

8  **The Two-Dimensional Model**

8.1 Mesh parameters ................................................................. 136
8.2 Tissue properties ................................................................. 138
8.3 Solute transport parameters ....................................................... 142
8.4 Fluid flow parameters ............................................................. 144
8.5 Initial conditions. ................................................................. 145
8.6 The mean modelled potentials .................................................... 146
8.7 The mean modelled and measure concentrations ...................... 149
8.8 Mean modelled hydraulic pressure ............................................ 163
## Glossary of Symbols & Abbreviations

### Scalar Symbols

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$a$</td>
<td>fibre cell height</td>
</tr>
<tr>
<td>$A$</td>
<td>area</td>
</tr>
<tr>
<td>$b$</td>
<td>fibre cell width</td>
</tr>
<tr>
<td>$c$</td>
<td>cross-fibre direction</td>
</tr>
<tr>
<td>$C$</td>
<td>concentration</td>
</tr>
<tr>
<td>$D$</td>
<td>diffusion coefficient</td>
</tr>
<tr>
<td>$e$</td>
<td>electron charge</td>
</tr>
<tr>
<td>$E_a$</td>
<td>Nernst potential</td>
</tr>
<tr>
<td>$f$</td>
<td>fibre direction</td>
</tr>
<tr>
<td>$F$</td>
<td>Faraday constant</td>
</tr>
<tr>
<td>$F$</td>
<td>body force</td>
</tr>
<tr>
<td>$g$</td>
<td>membrane ion conductance</td>
</tr>
<tr>
<td>$h$</td>
<td>linearised extracellular cleft width</td>
</tr>
<tr>
<td>$I_{max}$</td>
<td>maximum Na$^+$/K$^+$ pump current density</td>
</tr>
<tr>
<td>$I_p$</td>
<td>Na$^+$/K$^+$ pump current density</td>
</tr>
<tr>
<td>$j_{\alpha,m}$</td>
<td>cell membrane flux</td>
</tr>
<tr>
<td>$j_{\alpha,s}$</td>
<td>lens surface flux</td>
</tr>
<tr>
<td>$J_w$</td>
<td>fluid mass flow</td>
</tr>
<tr>
<td>$k$</td>
<td>electro-osmotic coefficient</td>
</tr>
<tr>
<td>$k_B$</td>
<td>Boltzmann constant</td>
</tr>
<tr>
<td>$K$</td>
<td>hydraulic conductivity</td>
</tr>
<tr>
<td>$K_{1/2\alpha}$</td>
<td>half-maximal concentrations</td>
</tr>
<tr>
<td>$L_m$</td>
<td>transmembrane hydraulic permeability</td>
</tr>
<tr>
<td>$L_p$</td>
<td>intercellular hydraulic permeability</td>
</tr>
<tr>
<td>$L_s$</td>
<td>surface membrane hydraulic permeability</td>
</tr>
<tr>
<td>$O_s$</td>
<td>osmolarity</td>
</tr>
<tr>
<td>$N_0$</td>
<td>Avagadro number</td>
</tr>
<tr>
<td>$p$</td>
<td>pressure</td>
</tr>
<tr>
<td>$P_m$</td>
<td>membrane solute permeability</td>
</tr>
<tr>
<td>$R$</td>
<td>radius</td>
</tr>
<tr>
<td>Symbol</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>$s$</td>
<td>source</td>
</tr>
<tr>
<td>$T$</td>
<td>temperature</td>
</tr>
<tr>
<td>$V$</td>
<td>volume</td>
</tr>
<tr>
<td>$V_m$</td>
<td>transmembrane potential</td>
</tr>
<tr>
<td>$z$</td>
<td>valency</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>solute species</td>
</tr>
<tr>
<td>$\varepsilon_0$</td>
<td>permittivity of vacuum</td>
</tr>
<tr>
<td>$\varepsilon_r$</td>
<td>dielectric constant</td>
</tr>
<tr>
<td>$\zeta$</td>
<td>zeta potential (cell membrane potential)</td>
</tr>
<tr>
<td>$\eta$</td>
<td>fibre coordinate system</td>
</tr>
<tr>
<td>$\tilde{\eta}$</td>
<td>cleft coordinate system</td>
</tr>
<tr>
<td>$\lambda_D$</td>
<td>Debye length</td>
</tr>
<tr>
<td>$\Lambda_e$</td>
<td>extracellular volume fraction</td>
</tr>
<tr>
<td>$\Lambda_i$</td>
<td>intracellular volume fraction</td>
</tr>
<tr>
<td>$\mu$</td>
<td>dynamic viscosity</td>
</tr>
<tr>
<td>$\nu$</td>
<td>kinematic viscosity</td>
</tr>
<tr>
<td>$\xi$</td>
<td>wiggle factor</td>
</tr>
<tr>
<td>$\rho$</td>
<td>mass density</td>
</tr>
<tr>
<td>$\rho_c$</td>
<td>charge density</td>
</tr>
<tr>
<td>$\rho_m$</td>
<td>membrane density</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>membrane reflectance</td>
</tr>
<tr>
<td>$\tau$</td>
<td>tortuosity</td>
</tr>
<tr>
<td>$\phi$</td>
<td>potential</td>
</tr>
</tbody>
</table>
Vector & Matrix Symbols

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$i$</td>
<td>current density vector</td>
</tr>
<tr>
<td>$j$</td>
<td>solute flux vector</td>
</tr>
<tr>
<td>$n$</td>
<td>unit normal vector</td>
</tr>
<tr>
<td>$u$</td>
<td>fluid velocity vector</td>
</tr>
</tbody>
</table>

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP</td>
<td>Anterior Pole</td>
</tr>
<tr>
<td>AQP</td>
<td>Aquaporin</td>
</tr>
<tr>
<td>EDL</td>
<td>Electric Double Layer</td>
</tr>
<tr>
<td>EQ</td>
<td>Equator</td>
</tr>
<tr>
<td>FVM</td>
<td>Finite Volume Methods</td>
</tr>
<tr>
<td>PP</td>
<td>Posterior Pole</td>
</tr>
</tbody>
</table>
1 Introduction

Lens cataract is a common disease involving severe visual impairment in more than 20 million people worldwide. Although it is a multifactorial disease, the biggest contributing factor is old age. Given our globally aging population, the social and economic costs of lens cataract are quite staggering. While the median age for cataract development is 70 years, the mean age at cataract surgery is 75 years, highlighting the rapid progression of this disease. Presently, the demand for cataract surgery far exceeds limited public health resources. In the USA, cataract surgery is the most commonly performed surgical procedure and costs around $3.5 billion per year. In Australia, where it has been estimated that the population will increase by 22% between 1996 and 2021, the incidence of age-related cataract will disproportionately increase by 76% during the same period. Thus it is expected that the burden of cataract-impaired vision will increasingly outstrip the resources available for its eradication. The alternative approach is to delay the onset of cataract. It has been predicted that a delay of 5 years will halve the incidence of age-related nuclear cataract, greatly reducing the need for, and expense associated with, surgical intervention.

Development of effective anti-cataract therapies first requires a knowledge of normal structure and function of the transparent lens, to understand the processes impaired during cataract formation. In accumulating this knowledge, most lens researchers have tended to adopt a reductionist approach and have focused on a single aspect of lens function. This leads to a fragmented approach to our understanding of the maintenance of lens transparency with gaps in the relationship between isolated research efforts. To address this, a platform is required that allows research into the structure and function of the lens to be integrated. In this thesis I present the development of a computational framework that is based on finite volume methods, which I have used to develop an integrative model of the structure and transport processes of the lens.

Although the lens is a complex system, this initial model only captures key aspects of lens structure
and function. This introduction provides a general overview of the lens before focusing on the key transporter properties included in the model. Although this current model only captures a subset of transport processes, it already provides unique insights into transport processes which are difficult to observe experimentally. As the model evolves it will provide a valuable tool in understanding the function of the lens and, with increased complexity and accuracy, assist in the search for effective targeted anti-cataract therapies.

1.1 Lens Structure and Function

The ocular lens along with the cornea, aqueous humor and vitreous humor form a compound lens whose function is to focus light onto the retina of the eye (see Figure 1.1). Even though the lens has the highest refractive index, it only contributes to about one-third of the total refractive power of the compound lens. The lens is important because of its ability to change shape to focus an image on the retina, thus allowing the eye to focus on objects at different distances.

![Figure 1.1: Structure of the eye.](image)

There are four parts of the eye that are associated with the lens: the ciliary body, ciliary muscles, aqueous humor and vitreous humor.

The ciliary body releases nutrients into the posterior chamber of the aqueous humor. The nutrients are mixed through the aqueous humor and supply nutrients to the cornea and lens, which are avascular. Additionally, the aqueous humor washes away waste released by the lens. The waste is
1.1 Lens Structure and Function

removed from the aqueous humor at the apex between the iris and cornea where there is a filtration system. It is the blockage of this filter that leads to glaucoma.

The ciliary muscles are responsible for changing the focal length of the lens. The lens is suspended between the aqueous humor and vitreous humor by the zonular ligaments (zonules). The zonules attach the equator of the lens to the ciliary muscles. When the ciliary muscles contract the zonules pull on the lens equator and deform the anterior surface of the lens, thus focussing light on the retina.

1.1.1 Lens Structure

The lens is described as an asymmetrical oblate spheroid (Kuszak, Zoltoski & Sivertson 2004). Figure 1.2 shows a more spherical lens that may be representative of a lens from a small animal, such as a mouse or frog. The lens has three landmarks: the anterior pole (AP); the posterior pole (PP); and the equator (EQ); and the cell body is divided into two zones: the nucleus; and the cortex. The poles are aligned with the axis of revolution and the geometry of the lens is symmetric about this axis.

Figure 1.2: Structure of the lens. The bulk of the lens is composed of fibre cells and the anterior surface of the lens is covered with a monolayer of epithelial cells. This body of cells is surrounded by a tough collagenous capsule (not shown here). EQ - equator, AP - anterior pole, PP - posterior pole.

The main body of the lens is surrounded by a tough collagenous capsule. Beneath the capsule and only on the anterior surface of the lens is a single layer of epithelial cells (Type 0-2 cells) (see Figure 1.3). Near the equator the epithelial cells differentiate and begin to elongate to form fibre cells (Type 3 cells). The basal end of the fibre cells migrate towards the posterior pole while the
apical end wraps around the modiolus and migrates towards the anterior pole. The differentiated fibre cells are added as layers to the existing body of fibre cells (Type 4-5 cells). As the differentiated fibre cells migrate towards the center they lose their major intracellular organelles and become transparent mature fibre cells.

Figure 1.3: Cell types in the lens. The cortical cells, Type 0-5 cells, terminate near the anterior and posterior surfaces and the nuclear fibre cells terminate at the suture lines. Reproduced from Zampighi et al. (2000).

The discrimination between the cortex and nucleus depends on the termination of the fibre cells (see Figure 1.3). The fibre cells in the cortex terminate at the apical interface near the anterior surface and at the capsule at the posterior surface. The apical interface is the region of separation between the epithelial cell layer and the underlying fibre cells. The fibre cells in the nucleus terminate at the anterior and posterior suture lines.

The sutures form at the polar regions of the lens where the fibre cells converge. The sutures are important because they are thought to form a paracellular pathway from the surface to the nucleus of the lens (Zampighi et al. 2000).
1.1 Lens Structure and Function

1.1.1 Lens Structure

Figure 1.4: Change in fibre cell morphology, where cells become less regular with depth into the lens. The fibre cells near the surface are hexagonal with broad and narrow sides and the fibre cells near the center are elliptic. Scalebar: 4 µm (A) $r/a = 0.95$; (B) $r/a = 0.8$; (C) $r/a = 0.7$; where $r$ is the radial location of the sample and $a$ is the radius of the lens. Reproduced from Jacobs et al. (2004).

A cross-section through the equator shown in Figure 1.4 reveals the hexagonal profile of the fibre cells. Near the surface the fibre cells have a regular honeycomb-like structure which becomes less regular deeper into the lens. In Figure 1.4 the green labelling indicates the cell membrane and the red labelling, the gap junctions. The gap junction plaques, which are mostly localised to the broadsides, couple the cytoplasm of adjacent fibre cells in the radial direction creating a preferred direction of transport. There are less gap junctions on the narrow side, hence no coupling in the angular direction. The intracellular coupling in the radial direction forms, effectively, sheets of fibre cells.

1.1.2 Lens Function

Two important properties of the lens that allow it to perform the function of focusing light onto the retina are accommodation and transparency. Any issue with either of these properties can lead to eyesight problems. For example, two common problems are cataracts, due to a loss of transparency, and presbyopia, due to the inability of the lens to deform.

To be transparent, the lens lacks blood vessels, the mature fibre cells lack major internal organelle, and the fibre cells form a highly organised structure where the extracellular cleft between cells are less than the wavelength of visible light. All of these properties allow light to pass through the lens with minimal scattering.

To maintain transparency, nutrients must be delivered into and waste removed from the lens. Nutri-
ents are required to repair oxidative damage and to regulate cell volume. Oxidative damage results in the precipitation of macromolecules which lead to the opacification of the lens. Without cell volume regulation the lens looses its highly organised cell structure, which leads to light scattering.

**Early Studies of Lens Transport**

Initially the lens was thought to be lifeless, but in the last fifty years a more accurate perception of the physiological function of the lens has evolved.

The first view of the lens as a living system was as one large cell where nutrient and waste were transported through the lens by passive diffusion. However, using the Einstein diffusion relationship, the predicted time required for sugar to passively diffuse to the center of large mammalian lenses is too long (Mathias, Rae & Baldo 1997). Furthermore, a study by Fischbarg et al. (1999) showed that through passive diffusion alone, glucose would penetrate the outer 10% of the lens before it was completely consumed. Therefore, transport through passive diffusion alone was insufficient and more specialised delivery mechanisms must exist.

The specialised mechanism for transport was thought to be driven by the epithelial layer, where the $\text{Na}^+/\text{K}^+$ pumps localised to the epithelial layer would generate anterior-posterior transport through the lens. Early studies used Ussing chambers to isolate the anterior and posterior surfaces in order to measure the physiological properties and transport across the epithelial surface (Kinsey & Reddy 1965, Candia, Bentley, Mills & Toyofuku 1970, Candia, Bentley & Mills 1971, Kinsey & McGrady 1971, Candia 1973, Duncan, Juett & Croghan 1977, Delamere & Duncan 1979). From this series of experiments it was proposed there was an anterior-posterior movement of current, but this view was challenged by the vibrating probe experiments.

Vibrating probe experiments showed that current entered the lens at the poles and exited at the equator (Robinson & Patterson 1983, Parmelee 1986) and that these currents were carried by $\text{Na}^+$ and $\text{K}^+$ (Reszelbach & Patterson 1985). These results were supported by the microcirculation model.
1.1 LENS STRUCTURE AND FUNCTION

Microcirculation Model

The microcirculation model was developed by Mathias (1985b) from a series of studies investigating the electrical properties and fluid transport in biological tissues, specifically the lens.

Impedance studies that measured the electrical properties of the frog and rat lenses led to the equivalent circuit model shown Figure 1.5 (Eisenberg, Barcilon & Mathias 1979, Mathias, Rae & Eisenberg 1979, Mathias, Rae & Eisenberg 1981). The solute transport was modelled as a current through the equivalent circuit, where the current was the sum of the charge carried by Na\(^+\), K\(^+\) and Cl\(^-\). The intracellular and extracellular spaces and transport proteins were modelled by electrical components.

![Equivalent circuit used by Mathias (1985a) to model the current flow in the lens. The intracellular and extracellular resistance (R_i and R_e) along the radial direction accounts for gap junction and cell fusion in the intracellular space, and the tortuosity and volume fraction in the extracellular space. The leak of conductance of Na\(^+\) and Cl\(^-\) through the fibre cell membrane and K\(^+\) through the surface membrane is represented by resistors in series with their associated Nernst potential. The Na\(^+\)/K\(^+\) pumps, which are localised to the surface membrane, are represented by a charge pump with a fixed outward current. The Na\(^+\)/K\(^+\) pumps drive the current circulation through the lens. Reproduced Mathias et al. (1997).](image)

A series of subsequent studies led to a better understanding of the fluid transport in the lens. Mathias (1983) characterised the tortuosity of the extracellular cleft in biological tissues. McLaughlin & Mathias (1985) investigated the electro-osmotic fluid flow in the renal proximal tubules. They concluded that Helmholtz-type electro-osmosis could be important in other tissues, such as in the extracellular cleft of the lens. Mathias (1985a) investigated the hydrostatically and osmotically driven fluid transport in the intercellular space of the epithelial layer. The governing equations were simplified by performing a non-dimensional analysis and exploiting the length:width ratio of
the extracellular cleft and the hydraulic:solute ratios of the membrane permeability.

In 1985, Mathias coupled the equivalent circuit model and the fluid transport models to develop a one-dimensional analytic model of the transport in the lens. The solute flux was modelled as a current in the equivalent circuit model. The fluid flow was modelled using Poiseuille flow and electro-osmotic flow along the extracellular cleft. The transport across the fibre cell membrane and surface membrane was approximated as isotonic fluid transport.

The model predicted a Na\(^+\) circulation, which accounted for a majority of the current, and a small Cl\(^-\) circulation within the lens. Na\(^+\) would enter the lens via the extracellular space, cross the fibre cell membrane, and exit via the intracellular space. The fluid, through isotonic water transport, would follow the Na\(^+\) flux. Later, Mathias et al. (1997) used this model to infer the angular circulation of solutes and fluid in the lens.

Although this model was relatively simple, it was able to simulate key components of lens transport and give valuable insights into the transport process. These insights led to the microcirculation hypothesis where current and fluid enters the lens at the poles via the extracellular space, cross the fibre cell membrane and exits at the equator via the intracellular space. Although, this model was not universally accepted, later independent studies supported the model.

**Evidence for the Microcirculation Model**

Using a three-chambered Ussing apparatus, the current and Na\(^+\) flux were shown to enter the rabbit lens at the polar surfaces and exit at the equatorial surface, and the K\(^+\) flux was transported in the opposite direction (Candia & Zamudio 2002, Candia 2004). Using the same Ussing apparatus, the fluid flow in the bovine lens was shown to enter at the anterior pole and exit at the equator and, to a lesser extent, at the posterior pole (Candia & Gerometta 2003, Candia 2004).

Furthermore, evidence from molecular studies measured a spatial difference in the expression and activity of key transport proteins.

Functional Na\(^+\)/K\(^+\) pumps, which drive the transport in the lens, are localised to the anterior and equatorial surfaces with the highest pump currents found at the equator (Delamere & Dean 1993, Gao, Sun, Yatsula, Wymore & Mathias 2000, Candia & Zamudio 2002, Tamiya, Dean, Paterson & Delamere 2003, Delamere & Tamiya 2004).
A spatial distribution of the density and regulation of gap junctions (Cx43, Cx46 and Cx50), which couple the cytoplasm of adjacent fibre cells, is also found in the lens (Zampighi et al. 2000). Near the surface, the gap junctions are localised to the broad side of the fibre cells suggesting transport is directed in the radial direction, whereas deeper inside the lens they are more evenly distributed around the surface of the fibre cells, suggesting a more isotropic transport (Donaldson, Kistler & Mathias 2001, Jacobs, Donaldson, Cannell & Soeller 2003, Cannell, Jacobs, Donaldson & Soeller 2004, Jacobs et al. 2004).

Aquaporin water channels (AQP0, AQP1) are distributed such that the hydraulic permeability of the surface membrane is higher than that of the fibre cell membrane (Patil, Saito, Yang & Wax 1997, Varadaraj, Kushmerick, Baldo, Bassnett, Shiels & Mathias 1999). The higher hydraulic permeability of the surface membrane would be needed to cope with the water transport across the fibre cell membrane, which forms the bulk of the lens.

**Current View of Lens Transport**

The results of these studies form our current understanding of the transport in the lens. The key component involved in the Na\(^+\), K\(^+\) and Cl\(^-\) transport are the Na\(^+\)/K\(^+\) pumps, Na\(^+\), K\(^+\) and Cl\(^-\) channels, and the gap junctions (see Figure 1.6). The key components involved in the fluid transport are aquaporin water channels embedded in the fibre cell membrane and the surface membrane.

There is a high density of functional Na\(^+\)/K\(^+\) pumps and K\(^+\) channels localised to the epithelial cells and differentiating fibre cells. These pumps maintain a negative electromotive potential that is required to control the cell volume and is the only known force that drives the circulation in the lens. Throughout the lens are Na\(^+\) and Cl\(^-\) channels, which allow Na\(^+\) and Cl\(^-\) leak conductances, and also gap junctions (Cx50 and Cx46), which couple the intracellular spaces in the radial direction.
At the surface of the lens, the Na\(^+\)/K\(^+\) pumps transport Na\(^+\) out of, and K\(^+\) into, the lens. This generates an electrochemical gradient through the lens that results in a net circulating current. The current enters at poles via the extracellular space, crosses into the intracellular space through Na\(^+\) and Cl\(^-\) channels embedded in the fibre cell membrane, and flows via gap junction to the equatorial surface where it is ejected by the Na\(^+\)/K\(^+\) pumps. The current is mostly carried by Na\(^+\) but there is also a small Cl\(^-\) component. The K\(^+\) that is pumped into the lens flows back out the surface through the K\(^+\) channels.

The solute flux through the lens creates a small standing osmotic gradient across the fibre cell membrane that opposes the standing hydraulic pressure. The hydraulic and osmotic pressures in the lens generate a circulating fluid flow that follows the Na\(^+\) circulation.

**Summary**

The perception of transport in the lens has evolved from what was thought to be a lifeless system to a complex system with a microcirculation. A series of experimental studies led to the development of an analytic model of the current and fluid transport in the lens. The prediction from the model formed the basis for the microcirculation hypothesis, where current and fluid enters the lens via the extracellular space at the poles and exits via the intracellular space at the equator. Evidence from subsequent independent studies support this hypothesis.

The remainder of this section covers the limitations of the analytic model and the need for an alternative approach, which leads on to the objectives of this thesis.

### 1.2 Thesis Objectives

In order to solve the equations in the analytic model developed by Mathias (1985b), a number of assumptions were made: the intracellular potential, concentration, and pressure were assumed to be spatially uniform; the Nernst potentials were spatially uniform; the membrane conductances were spatially uniform; and the intracellular pressure was assumed to be zero. The limitations of the analytic equations made it difficult to include spatially varying parameters, include more complex transport protein models and to model two and three dimensional transport in the lens. An alternative approach to overcome these limitation and extend this work is a computational model based on numerical methods.
The primary aim of this thesis is to develop a computational model of the structure and function of the ocular lens. Although the framework developed is used to model the solute and fluid transport in the lens, it is intended to be generic such that additional physical processes, such as volume regulation, can be added. A numerical approach using finite volume methods is used to overcome the limitations of an analytic approach.

The models developed in this thesis are based on the analytic model developed by Mathias (1985b). Since the analytic model was developed over 20 years ago, the literature is reviewed for more recent studies of structural, solute transport and fluid transport properties that are required for the model (Chapter 6).

The framework is used to develop a one-dimensional model and, results are compared to the results from the analytic model and experimental data, to ensure that the framework is capable of modelling the transport of solutes and fluid in the lens.

Two two-dimensional models are developed and solved. The first model, which is based on the one-dimensional model, has spatially uniform parameters, except for the fibre cell angles and the distribution of Na\(^+\)/K\(^+\) pump currents at the surface of the lens. In the second model the extracellular cleft width and the fibre cell height are spatially varied to represent the sutures and diffusion barrier. The results from these two-dimensional models are compared with each other to assess the influence of the sutures and diffusion barrier, and with experimental data to assess how well the models represents the real lens.

Finally, the second two-dimensional model is used to simulate age-related changes in lens physiology. The purpose of this application is to demonstrate the use of the lens model in understanding experimental results and lens function. The model simulates the growth of the lens with age by increasing its radius. The results from the model are compared to observations by Duncan et al. (1989) on the age-related changes in human lens properties.
In summary, the thesis objectives are:

- To develop a modelling framework based on finite volume methods.
- To review the literature for more recent model parameters.
- To develop a one-dimensional numerical model based on the analytic model and to compare the results with results from the analytic model and experimental data.
- To develop a two-dimensional numerical model that is an extension of the one-dimensional model.
- To develop a two-dimensional numerical model that includes a representation of the sutures and diffusion barrier.
- To compare the two-dimensional models with each other, and with experimental data.
- To model the age-related changes in lens properties using the two-dimensional numerical model.

Figure 1.7 shows the extension from the one-dimensional analytic model by Mathias (1985b) to the one- and two-dimensional numerical models and highlights (in green) the original work associated with this thesis.

![Figure 1.7: The extension of the analytic model by Mathias (1985b) to the one- and two-dimensional numerical models. The highlighted boxes indicate the original work associated with this thesis.](image-url)
1.3 Thesis Overview

Chapter 1: Introduction & Historical Overview. An introduction to the motivation for developing a model, the eye and lens structure and function, and an overview of the lens model and thesis objectives.

Chapter 2: A Mathematical Description of the Lens Structure. Three coordinate systems are introduced: the reference; fibre; and cleft coordinate systems. These are used in Chapter 3 and Chapter 4 to define the solute and fluid transport equations. The process to transform equations and parameters from the cleft coordinate system to the fibre coordinate system is also covered.

Chapter 3: Solute Transport. This chapter is divided into two parts. The first part covers the theory of solute transport through fluids, membranes and transport proteins, the treatment of transmembrane fluxes as source terms in bidomain models, the electroneutrality condition, and the rate of change of concentration equations. The second part applies the theory to the lens to obtain the solute flux, solute source and conservation equations for the lens model.

Chapter 4: Fluid Dynamics. This chapter is also divided into two parts. The first part covers the theory of fluid dynamics, where the Navier-Stokes equations are used to derive the Stokes flow, Couette flow and Poiseuille flow equations. The theory of electro-osmotic flow near a charged surface and between parallel plates, and transmembrane fluid flow is covered. The second part applies the fluid dynamics theory to the lens to obtain the fluid velocity, fluid source and conservation of mass equations for the lens model.

Chapter 5: Numerical Methods. The mesh generation process, bidomain models, finite volume approximations and solution methods are described in this chapter. In the final section, the solution algorithm of a fully coupled model is detailed.

Chapter 6: Lens Properties of the Model. Lists and describes the parameters needed for the lens model and experimental data needed for comparison with the model results.

Chapter 7: The One-Dimensional Model. First, the mesh, governing equations and model parameters for the one-dimensional model are covered, then the model results are discussed and a brief summary given. The results are discussed in comparison to the analytical model by Mathias (1985b) and experimental data.
Chapter 8: The Two-Dimensional Model. The mesh, governing equations and parameters for the two-dimensional models are covered. The results from these models are compared and discussed with each other and with experimental data. The application of the model to simulated age-related changes in lens physiology is described and the results are discussed in comparison to observations by Duncan et al. (1989).

Chapter 9: Conclusions & Future Developments. The key findings of this project are presented. The future developments section discusses potential improvements to the modelling framework, improvements to and application of the lens model, and the application of the modelling framework to other biological systems.
A Mathematical Description of the Lens Structure

A mathematical framework is required to capture the structure of the lens and to derive, express and solve the solute and fluid transport equations for the lens. The mathematical framework introduced in this chapter is required for the following two chapters, which cover the derivation of the solute and fluid transport equations in the lens (Chapters 3 and 4, respectively).

Often the transport of fluid or solutes is aligned with the underlying structure of the medium. Defining equations to describe the transport through this structure in terms of the reference coordinate system can be difficult, especially if the properties of the structure are anisotropic and the axis of anisotropy changes. However, by defining a new material coordinate system that is aligned with the underlying structure, it is easier to derive the transport equations. Furthermore, by knowing the relationship between coordinate systems, the equations and properties can be transformed from one coordinate system to another.

The lens tissue has a fibre structure and, at the subcellular level, the extracellular cleft is tortuous (see Section 6.1). To derive the fluid and solute transport equations for the intracellular and extracellular space of the lens, three coordinate systems are introduced: the reference; the fibre; and the cleft coordinate systems. The reference coordinate system provides a frame of reference for the whole lens and is used to define the geometry of the lens (see Section 2.1). The fibre coordinate system is aligned with the fibre cell structure and is used to derive the intracellular transport equations (see Section 2.2). The cleft coordinate system is aligned with the tortuous path of the extracellular cleft and is used to derive the extracellular transport equations (see Section 2.3). It is more convenient to express and solve the extracellular transport equations in the same coordinate system as the intracellular transport equations. The transformation of these equations from the cleft to the fibre coordinate system is covered in Section 2.4.
2.1 Reference Coordinate System

The reference coordinate system is used to define the geometry and provide a frame of reference for the lens. A rectangular-Cartesian coordinate system is sufficient for the model in this study since it is a one- and two-dimensional model. For a three-dimensional model, a spherical or an oblate spheroidal coordinate system may be more suitable.

The reference coordinate system has three axes: $x$, $y$ and $z$ (see Figure 2.1). The $x$-axis is aligned with the anterior pole (AP) and posterior pole (PP) of the lens and the $y$- and $z$-axes are perpendicular to the $x$-axis. Since we assume the lens is symmetric about the poles, the directions of the $y$- and $z$-axes are not important. The models in this study use only the $x$ and $y$ axes.

Figure 2.1: A rectangular-Cartesian coordinate system is used to define the geometry of the lens. EQ - equator, AP - anterior pole, PP - posterior pole.

2.2 Fibre Coordinate System

The lens has a highly organised architecture that forms three principal axes of structure and coupling. The bulk of the lens is made up of fibre cells which are laid down to form arcs between the anterior pole (AP) and posterior pole (PP) (Figure 2.2). These fibre cells are coupled via gap junctions in the radial direction to form sheets that extend from the nucleus to the surface. Fibre cells in adjacent sheets can be coupled via gap junctions but the coupling is low at the periphery and increases towards the center of the lens. The transport within the lens is aligned with these

---

1In reality, the fibre cell orientation for lenses with a line, "Y" or star suture is not symmetric about the poles. The frog lens has a line suture, but the asymmetry of the fibre cell orientation is ignored in the two-dimensional model for the sake of simplicity.
2.2 Fibre Coordinate System

Figure 2.2: A cut-away view of the lens and a magnified view of the lens fibre structure with the fibre coordinate system.

The fibre coordinate system is a curvilinear coordinate system with three axes: the fibre axis $\eta_f$; cross-fibre axis $\eta_c$; and the sheet axis $\eta_s$. The fibre axis ($\eta_f$) is aligned with the axis of the fibre cells. The cross-fibre axis ($\eta_c$) is orthogonal to the fibre axis and aligned with the sheet. The sheet axis ($\eta_s$) is orthogonal to the fibre and cross-fibre axes which is normal to the sheet (see Figure 2.2b).

Figure 2.3: The fibre angle ($\gamma_f$), cross-fibre angle ($\gamma_c$), and the sheet angle ($\gamma_s$) which describe the relationship between the reference and fibre coordinate system.

The fibre coordinate systems is defined in terms of the reference coordinate system by three angles: fibre angle ($\gamma_f$), the cross-fibre angle ($\gamma_c$), and the sheet angle ($\gamma_s$) (see Figure 2.3). The fibre angle ($\gamma_f$) is the angle between the $x$-axis and the fibre axis ($\eta_f$) in the $x$-$y$ plane. The cross-fibre angle ($\gamma_c$) is the angle between the cross-fibre axis ($\eta_c$) and the $x$-$y$ plane. The sheet angle ($\gamma_s$) is the angle between the fibre axis ($\eta_f$) and the $x$-$y$ plane. In the two-dimensional model, the sheet axis ($\eta_s$) is...
ignored and we assume the cross-fibre angle ($\gamma_c$) is zero, therefore the fibre coordinate system is described by only the fibre angle ($\gamma_f$).

### 2.3 Cleft Coordinate System

At the subcellular level, the extracellular cleft is tortuous (see Figure 2.4). To derive the transport equations and properties along the cleft, we introduce a new cleft coordinate system, which follows the tortuous path of the cleft. It is more convenient to express the transport equations and properties in terms of the fibre coordinate system. The transformation between the coordinate systems is described in Section 2.4.

![Figure 2.4: A magnified view of the lens tissue structure, extracellular cleft and the cleft coordinate system.](image)

The cleft coordinate system is a curvilinear coordinate system with three axes: the cleft fibre axis $\tilde{\eta}_f$; the cleft cross-fibre axis $\tilde{\eta}_c$; and the cleft sheet axis $\tilde{\eta}_s$ (see Figure 2.4b). The $\tilde{\eta}_s$-axis is perpendicular to the cleft membrane. The $\tilde{\eta}_f$-axis is aligned with the cleft path and inline with the $\eta_f$-$\eta_s$-plane. Similarly, the $\tilde{\eta}_c$-axis is aligned with the cleft path and inline with the $\eta_c$-$\eta_s$-plane. By this convention, the $\tilde{\eta}_f$- and $\tilde{\eta}_c$-axes will be orthogonal to the $\tilde{\eta}_s$-axis but the $\tilde{\eta}_f$- and $\tilde{\eta}_c$-axes may not be orthogonal. Since it is assumed that there is no tortuosity in the fibre ($\eta_f$) direction of the lens, the fibre axis ($\eta_f$) and cleft fibre axis ($\tilde{\eta}_f$) are aligned. In this case, the $\tilde{\eta}_f$- and $\tilde{\eta}_c$-axes are orthogonal. This assumption may fail at the center of the lens where it is tortuous in directions other than the cross-fibre direction.

As a convention, the variables and parameters that are defined with respect to the cleft coordinate system are denoted with a tilde ($\sim$). For example, $\hat{h}$ is the width of the cleft along the $\tilde{\eta}_s$ axis and
\( \partial \phi_e / \partial \tilde{\eta}_c \) is the potential gradient along the path of the cleft in the \( \tilde{\eta}_c \) direction, whereas \( \partial \phi_e / \partial \eta_c \) is the pressure gradient in the cross-fibre (\( \eta_c \)) direction.

### 2.4 Cleft-Fibre Transformation

The extracellular transport equations are derived with respect to the cleft coordinate system which follows the path of the cleft. But it is more convenient to solve these equations in the same coordinate system as the intracellular transport equations. This section covers the transformation of equations and properties from the cleft coordinate system to the fibre coordinate system.

To transform the equations, we assume the tortuous cleft is linearised. This assumption is valid only if the region of interest is much larger than the cleft width (\( h \)), the characteristic length of the extracellular space. Figure 2.5 shows a block of lens tissue with a tortuous extracellular space (a) and the equivalent block of lens tissue where the extracellular space has been 'linearised' (b). These two blocks are called the tortuous tissue and the linearised tissue.

![Figure 2.5: The transformation of the tortuous extracellular space to obtain the equivalent linearised extracellular space.](image)

To ensure the model predicts the same results after the transformation, certain properties need to be maintained in the transformation. These properties include the field gradients, the extracellular volume, and any conservation equation, for example, the conservation of mass equation or the rate of change of concentration equation.
2.4.1 Tortuosity

Mathias (1983) described the relationship between the hydraulic conductivity of a tissue to the cellular structure of the tissue. He described a tortuosity factor which is derived from the measurable morphological and geometric parameters of the tissue. This section summarises Mathias’ derivation of tortuosity in terms of the extracellular cleft of the lens.

To describe the tortuosity of the extracellular cleft, consider the path lengths of the cleft in the tortuous block compared to the linearised block (see Figure 2.5). In the fibre and cross-fibre directions, respectively, the path lengths are $\Delta \tilde{\eta}_f$ and $\Delta \tilde{\eta}_c$ for the tortuous block, and $\Delta \eta_f$ and $\Delta \eta_c$ in the linearised block. The tortuosities of the lens tissue in the fibre and cross-fibre directions, $\tau_f$ and $\tau_c$ respectively, are then defined by

$$\tau_f = \frac{1}{\xi_f^2} \quad \text{and} \quad \tau_c = \frac{1}{\xi_c^2}$$

(2.1)

where the wiggle factors ($\xi_f$ and $\xi_c$) are the ratios of the tortuous path lengths to the linearised path lengths,

$$\xi_f = \frac{\Delta \tilde{\eta}_f}{\Delta \eta_f} = \frac{\partial \tilde{\eta}_f}{\partial \eta_f}$$

(2.2)

and

$$\xi_c = \frac{\Delta \tilde{\eta}_c}{\Delta \eta_c} = \frac{\partial \tilde{\eta}_c}{\partial \eta_c}$$

(2.3)

2.4.2 Derivative Transformation

The transport equations contain terms for the concentration, potential and velocity gradients. Since the transport equations are derived with respect to the cleft coordinate system, the field gradients are calculated in terms of the path length of the cleft. As an example, consider the one-dimensional tortuous and linearised clefts shown in Figure 2.6. Respectively, the potential gradients in the
Figure 2.6: The potential gradient in the tortuous and the linearised clefts.

tortuous and linearised clefts are:

\[
\frac{\partial \phi}{\partial \tilde{\eta}} = \frac{\phi_2 - \phi_1}{\Delta \tilde{\eta}} \quad \text{as} \quad \Delta \tilde{\eta} \to 0 \\
\frac{\partial \phi}{\partial \eta} = \frac{\phi_2 - \phi_1}{\Delta \eta} \quad \text{as} \quad \Delta \eta \to 0
\]

To ensure the potential gradient calculated in the linearised cleft is equal to the potential gradient in the tortuous cleft, it needs to be scaled by the ratio of the path lengths, the wiggle factor \((\xi)\),

\[
\frac{\partial \phi}{\partial \eta} = \xi \frac{\partial \phi}{\partial \tilde{\eta}} = \frac{\Delta \tilde{\eta}}{\Delta \eta} \frac{\phi_2 - \phi_1}{\Delta \tilde{\eta}} = \frac{\phi_2 - \phi_1}{\Delta \eta} \tag{2.4}
\]

Therefore, the relationship between field gradients with respect to the cleft and fibre coordinate systems is

\[
\frac{d\phi}{d\tilde{\eta}} = \frac{d\phi}{d\eta} \frac{d\eta}{d\tilde{\eta}} = \frac{1}{\xi} \frac{d\phi}{d\eta} \tag{2.5}
\]

where \(\xi\) is the wiggle factor (see Section 2.4.1).

### 2.4.3 Conservation of Volume

The extracellular volume in the linearised block after transformation must be the same as the extracellular volume in the tortuous block. Respectively, the extracellular volume in the tortuous and linearised blocks are

\[
\tilde{V}_e = \Delta \tilde{\eta} f \Delta \tilde{h} \quad \text{and} \quad V_e = \Delta \eta f \Delta h
\]
where \( \tilde{h} \) and \( h \) are the cleft widths. Since the path lengths (\( \Delta \eta_f \) and \( \Delta \eta_c \)) in the linearised block are shorter than the path length in the tortuous block (\( \Delta \tilde{\eta}_f \) and \( \Delta \tilde{\eta}_c \)), the volumes are equalised by a compensatory increase in the effective cleft width (\( h \)) in the linearised block. By ensuring the volumes are equal \( (V_e = \tilde{V}_e) \), the relationship between the effective cleft width (\( h \)) and the actual cleft width (\( \tilde{h} \)) can be calculated as,

\[
h = \xi_f \xi_c \tilde{h}
\]  

(2.6)

### 2.4.4 Conservative Governing Equations

Transport equations are derived from conservation principals. If these conservation equations are derived with respect to the cleft coordinate system, their conservative nature must be maintained when they are transformed to the fibre coordinate system. To ensure the conservative nature of these equations is maintained, consider a typical conservation equation, the conservation of mass equation,

\[
-\nabla \cdot \mathbf{u} + s = 0
\]  

(2.7)

where \( \mathbf{u} \) is a velocity vector \([m/s]\) and \( s \) is volume source term \([s^{-1}]\). The integral of Equation (2.7) over the extracellular volume of the tortuous and linearised blocks, \( \tilde{V}_e \) and \( V_e \), respectively, must be equal, i.e.,

\[
-\int_{\tilde{V}_e} \nabla \cdot \mathbf{\tilde{u}} \, d\tilde{V} + \int_{\tilde{V}_e} \tilde{s} \, d\tilde{V} = -\int_{V_e} \nabla \cdot \mathbf{u} \, dV + \int_{V_e} s \, dV
\]

where \( \mathbf{\tilde{u}}, \tilde{s} \), and \( \tilde{V}_e \) are the velocity vector, source term, and volume for the tortuous block, and \( \mathbf{u}, s, \) and \( V_e \) are the velocity vector, source term, and volume for the linearised block. It is unreasonable to expect transfer of mass between the divergence term and the source term, therefore these terms can be separated and maintained individually,

\[
\int_{\tilde{V}_e} \nabla \cdot \mathbf{\tilde{u}} \, d\tilde{V} = \int_{\tilde{V}_e} \nabla \cdot \mathbf{u} \, dV
\]

(2.8)

\[
\int_{\tilde{V}_e} \tilde{s} \, d\tilde{V} = \int_{V_e} s \, dV
\]

The source term describes the mass created per unit volume per unit time. Since the extracellular
volume is the same in both blocks \((V_e = \tilde{V}_e)\), then the source term must be the same in both blocks \((s_e = \tilde{s}_e)\) to ensure the integral of the sources in both blocks are equal.

The volume integrals in Equation (2.8) can be converted to surface integrals using the Gauss divergence theorem,

\[
\oint_{A_e} u \cdot n \, dA_e = \oint_{\tilde{A}_e} \tilde{u} \cdot n \, d\tilde{A}_e \tag{2.9}
\]

where \(n\) is the surface normal. The discrete form of this equation is,

\[
\sum_{i=1}^{N} u_i A_i = \sum_{i=1}^{N} \tilde{u}_i \tilde{A}_i \tag{2.10}
\]

where \(u_i\) and \(A_i\) are the velocity normal to the face and area of face \(i\) of the linearised block, and \(\tilde{u}_i\) and \(\tilde{A}_i\) are the velocity normal to the face and area of face \(i\) in the tortuous block. The product of the velocity normal to a face and the area of the face is the mass flow \((J_w)\) through the face, \(i.e., J_w = uA\). If the mass flow through the same face of both blocks is equal and this is satisfied for all faces, then Equation (2.10) will be satisfied.

\[\text{Figure 2.7: The surface area of the extracellular cleft of the tortuous and linearised blocks. The solute flow and fluid flow through these surface areas must be equal to ensure the equations governing continuity are maintained in the transformation between the tortuous and linearised block.}\]

Consider the front face of the tortuous and linearised block whose normal is in the positive fibre direction (see Figure 2.7). The area of the extracellular space on this face for the tortuous block is,

\[
\tilde{A}_f = 2 \tilde{h} \Delta \tilde{\eta}_c \tag{2.11}
\]
and for the linearised block is

\[ A_f = 2 \, h \, \Delta \eta_c \]  \hspace{1cm} (2.12)

where the '2' accounts for two clefts in the block. The subscript \( f \) on the variable \( A \) denotes the direction of the face normal. According to Equation (2.10), the mass flows \( (J_w = u \, A) \) through these areas must be equal, therefore

\[ \tilde{u}_f \, \tilde{A}_f = u_f \, A_f \]

\[ \tilde{u}_f \, 2 \tilde{h} \, \Delta \tilde{\eta}_c = u_f \, 2 \, h \, \Delta \eta_c \]

This equation can be rearranged to give

\[ u_f = \tilde{u}_f \, \frac{\tilde{h}}{h} \, \frac{\Delta \tilde{\eta}_c}{\Delta \eta_c} \]

By substituting Equations (2.3) and (2.6), we can obtain the relationship between the velocity that is defined with respect to the cleft coordinate system and the velocity that is defined with respect to the fibre coordinate system,

\[ u_f = \frac{1}{\xi_f} \, \tilde{u}_f \]  \hspace{1cm} (2.13)

Similarly, the relationship for the velocities in cross-fibre direction can be derived,

\[ u_c = \frac{1}{\xi_c} \, \tilde{u}_c \]  \hspace{1cm} (2.14)

The validity of this transformation can be checked by comparing the time it takes for a particle to flow through the tortuous cleft and the linearised cleft. If the transformation is valid, the transit times will be the same. Consider the tortuous and linearised clefts shown in Figure 2.8. The transit time \( (\Delta \tilde{t}) \) for a particle in the tortuous cleft is given by

\[ \Delta \tilde{t} = \frac{\Delta \tilde{\eta}}{\tilde{u}} \]

and the transit time \( (\Delta t) \) for a particle in the linearised cleft is given by

\[ \Delta t = \frac{\Delta \eta}{u} \]  \hspace{1cm} (2.15)
Substituting Equation (2.13) into Equation (2.15) gives

$$\Delta t = \xi \frac{\Delta \eta}{\bar{u}}$$

and substituting Equation (2.2) gives

$$\Delta t = \frac{\Delta \tilde{\eta} \Delta \eta}{\Delta \eta \bar{u}} = \frac{\Delta \tilde{\eta}}{\bar{u}} = \Delta \tilde{t}$$

Therefore, the transit times are the same, supporting the validity of the transformation.

The coordinate systems and transformation methods presented in this chapter are used in the next two chapters on solute transport and fluid dynamics to derive and express the solute and fluid transport equations in the lens.
3 Solute Transport

3.1 Solute Fluxes

The solute fluxes can occur through a fluid or through a membrane. The governing equations describing these solute fluxes, which are different in each case, are described in the following two subsections.

3.1.1 Solution Fluxes

The solute flux in a fluid is governed by diffusion, electro-diffusion (if the solute is charged) and advection. Diffusion is the random walk of particles due to Brownian motion. Electro-diffusion is the flux of a charged particle due to the force applied by an electric field. Advection is the transport of a solute by a fluid that is moving. Benedek & Villas (2000c) and Benedek & Villas (2000a) discusses the physical origin of these transport processes in more detail.

The flux \( j \) of a solute in a solution is described by the Nernst-Plank equation with an added term to include advection - this is called the advective-Nernst-Plank equation,

\[
\mathbf{j}_\alpha = -D_\alpha \nabla C_\alpha - z_\alpha e \frac{D_\alpha}{k_B T} \nabla \phi C_\alpha + \mathbf{u} C_\alpha \tag{3.1}
\]

where the subscript \( \alpha \) indicates the solute species, \( j \) is the flux vector \([\text{mol}/(\text{m}^2 \cdot \text{s})]\), \( z \) is the valency, \( C \) is the concentration \([\text{mol}/\text{m}^3]\), \( D \) is the diffusion coefficient \([\text{m}^2/\text{s}]\), \( \phi \) is the electrical potential \([\text{V}]\), \( \mathbf{u} \) is the fluid velocity vector \([\text{m/s}]\), and \( k_B, T \) and \( e \) are the Boltzmann constant \((\text{J/K})\), the absolute temperature \((\text{K})\), and the charge on an electron \((\text{C})\), respectively.
3.1.2 Transmembrane Fluxes

Solute transport through membranes is facilitated by membrane proteins. These are diverse in types and functions. In this study, three main categories of membrane proteins are considered: gap junctions, ion channels, and ion pumps. The mechanism of solute transport through these protein classes is detailed in the following subsections.

Convention: Solute flux from the intracellular space to the extracellular space (out of the cell) is considered positive.

Gap Junctions

Figure 3.1 shows a) a block of lens tissue, b) a magnified section of the intercellular membrane with gap junction channels, and c) an idealised view of the channel. The lens has two types of gap junction, Cx46 and Cx50. These channels are embedded in the membranes between adjacent cells and allow solutes and water to flow between the cells. Gap junctions are thought to transport water, small ions, and small molecules, but for the purpose of deriving the flux equation, we will assume the channels are non-selective. An equation for the flux through a membrane is more useful than an equation for the flux through a single pore. Therefore, we will derive the flux equation for a pore and then integrate this over all pores in the membrane.

![Figure 3.1: Solute transport through membranes via pores. These pores may be non-selective channels, such as connexins, or selective channels, such as sodium ion channels.](image)

The length of the pore is $\Delta x$ and the cross-sectional area of the pore is $a_p = \pi r^2$, where $r$ is the mean radius of the pore. The advective-Nernst-Plank equation (Equation (3.1)) can be used to...
describe the solute flux through one pore,

\[
\dot{j}_{\alpha,p} = -D_{\alpha} \frac{dC_{\alpha}}{dx} - z_{\alpha} e \frac{D_{\alpha}}{k_B T} \frac{d\phi}{dx} C_{\alpha} + u_p C_{\alpha}
\]

(3.2)

where \(u_p\) is the fluid velocity in the pore. The solute is assumed to be much smaller than the pore and is assumed to move freely through the pore without binding to the walls. In this case, the diffusion coefficient \((D)\) in the pore is the same as the diffusion coefficient in the cell interior. The solute concentration \((C)\) and potential \((\phi)\) are assumed to vary linearly between the openings of the pore, therefore they can be approximated by

\[
\frac{dC_{\alpha}}{dx} = \frac{C_{\alpha,2} - C_{\alpha,1}}{\Delta x} \quad \text{and} \quad \frac{d\phi}{dx} = \frac{\phi_2 - \phi_1}{\Delta x} = \frac{\Delta \phi}{\Delta x}
\]

where the subscripts 1 and 2 refer to the inlet and outlet of the pore. The solute concentration in the pore is approximated by the mean concentration,

\[
\bar{C}_{\alpha} = \frac{C_{\alpha,1} + C_{\alpha,2}}{2}
\]

Substituting these approximations into Equation (3.2) gives,

\[
\dot{j}_{\alpha,p} = -\frac{D_{\alpha}}{\Delta x} \Delta C_{\alpha} - z_{\alpha} e \frac{D_{\alpha}}{k_B T} \Delta \phi \bar{C}_{\alpha} + u_p \bar{C}_{\alpha}
\]

(3.3)

The pore density \((\rho_p)\) is defined as the number of pores per unit area of membrane [pores/m²]. The pore density is used to integrate the flux through one pore over all pores in the membrane to give the membrane flux equation. The solute flow rate through one pore is given by \(J_p = \dot{j}_p a_p\). This can be multiplied by the pore density \((\rho_p)\) to get the flux \((\dot{j}_m)\) through the membrane,

\[
\dot{j}_m = \rho_p \dot{j}_p a_p = -\frac{D \rho_p a_p}{\Delta x} \Delta C - \frac{z e D \rho_p a_p}{k_B T} \Delta \phi \bar{C} + u_p \rho_p a_p \bar{C}
\]

(3.4)

or

\[
\dot{j}_m = -P_m \Delta C - P_m \frac{z e}{k_B T} \Delta \phi \bar{C} + u_m \bar{C}
\]

(3.5)

where \(P_m\), the solute permeability [m/s], is given by

\[
P_m = \frac{D \rho_p a_p}{\Delta x}
\]

(3.6)
and \( u_m \), the transmembrane membrane velocity \([\text{m/s}]\), is given by

\[
u_m = u_p a_p \rho_p \tag{3.7}
\]

**Ion Channels**

The lens model in this study includes three types of ion channels, the Na\(^+\), K\(^+\), and Cl\(^-\) channel. The Na\(^+\) and Cl\(^-\) channels are found in the fibre cell membrane and couple the intracellular and extracellular spaces. The K\(^+\) channels are found at the surface of the lens and couple the intracellular space to the outside of the lens.

The most basic and common model for the solute flux through a membrane via ion channels is (Hille 2001),

\[
j_{\alpha,ic} = \frac{g_{\alpha}}{F} (V_m - E_{\alpha}) \tag{3.8}
\]

where the subscript \( \alpha \) indicates the species of the solute, \( j \) is the solute flux \([\text{mol}/(\text{m}^2 \text{s})]\), \( g \) is the conductivity per membrane area \([\text{S/m}^2]\), \( F \) is the Faraday constant \([\text{C/mol}]\), \( V_m \) is the transmembrane potential \([\text{V}]\), and \( E \) is the Nernst potential.

The transmembrane potential is given by \( V_m = \phi_e - \phi_i \). The Nernst potential is given by,

\[
E_{\alpha} = \frac{k_B T}{z_{\alpha} e} \ln \left( \frac{C_{\alpha,e}}{C_{\alpha,i}} \right) \tag{3.9}
\]

where \( C \) is the concentration \([\text{mol/m}^3]\) on opposing sides of the membrane.

The conductivity \((g)\) of ion channels can be time-dependent and sensitive to voltage, temperature, concentration, and pH. For the models in this study it is sufficient to assume the conductivity of ion channels are temporally constant since the model is a steady-state model of a normal lens and the conductivity values for a normal lens are used.

**Na\(^+\)/K\(^+\)-ATPase Pumps**

Na\(^+\)/K\(^+\) pumps consume ATP to pump three Na\(^+\) ions out of the cell for every two K\(^+\) ions pumped into the cell. Mathias (1985b) modelled these pumps using a temporally constant pump rate \((I_p = \...)
2.3 μA/cm²). Gao et al. (2000) presented more complex models for the current through the α₁ and α₂ isoforms of the Na⁺/K⁺ pumps (see Section 6.2.3). In these models, the pump currents depended on the intracellular Na⁺ concentration, and the K⁺ concentration and pH outside the lens.

The pump rate or current through the Na⁺/K⁺ pumps is usually given as \( I_p \, [\text{A}/\text{m}^2] \), in which case, the Na⁺ and K⁺ flux through the Na⁺/K⁺ pumps is given by,

\[
\begin{align*}
\dot{j}_{\text{Na},p} &= \frac{3}{F} I_p \\
\dot{j}_{\text{K},p} &= -\frac{2}{F} I_p
\end{align*}
\]  

(3.10)

### 3.2 Solute Sources

A positive source is the creation of a solute and a negative source is the consumption of a solute. Generally, solutes are created or consumed through reactions but a pseudo-source arises in bidomain models where transmembrane fluxes are treated as sources due to the inability of the model to discretely represent the cell membrane. Both forms of solute sources are covered below.

#### 3.2.1 Reactions

The rate a reaction occurs depends on many factors: temperature; pressure; the concentration of the reactants; the presence of a catalyst; and the complexity of the reaction, for instance, the number of bonds broken and formed during a reaction. Hence, reactions can range from simple to complex. To describe the relationship between reactions and solute sources in modelling, we will consider the following first-order reaction:

\[
[A] \xrightarrow{k} [B]
\]

(3.11)

where solute A reacts to form solute B with a forward rate constant \( k \, [\text{s}^{-1}] \). The solute sources \( s_A \) and \( s_B \), which are the rate of change of solutes A and B, depends on the concentration of solute A,

\[
\begin{align*}
\dot{s}_A &= \frac{dC_A}{dt} = -k \, C_A \\
\dot{s}_B &= \frac{dC_B}{dt} = k \, C_B
\end{align*}
\]

where \( C_A \) and \( C_B \) are the concentrations \([\text{mol}/\text{m}^3]\) of solutes A and B.
3.2.2 Transmembrane Fluxes

When modelling a block of tissue, elements in the mesh are usually much larger than the cells. In this case, an element cannot discretely represent the intracellular and extracellular spaces and the cell membrane. Instead, the intracellular and extracellular spaces are assumed to coexist in the same space and the cell membranes are assumed to be homogeneously smeared throughout the element - this type of model is called a bidomain model. As a consequence, transmembrane fluxes are treated as solute sources.

To derive the relationship between solute sources and transmembrane fluxes, consider the element shown in Figure 3.2. The element bounds both the intracellular and extracellular space which is separated by a membrane. The volumes of the element, intracellular space and extracellular space are $V_t$, $V_i$ and $V_e$, respectively, the membrane area in the element is $A_m$, and the transmembrane flux is $j_m$, where a flux out of the cell is a positive flux.

A solute source is the change in the number of particles in a unit volume per unit time. The solute flow ($J_m$), which is the number of particles crossing the membrane per unit time, is given by $J_m = j_m A_m$. Therefore, the number of particles leaving the intracellular volume per unit time is $-J_m$ and entering the extracellular space per unit time is $J_m$. The source term is then given by dividing these values by the volumes of the intracellular and extracellular spaces, i.e.,

$$s_i = \frac{-J_m}{V_i} = \frac{-j_m A_m}{V_i}$$
$$s_e = \frac{J_m}{V_e} = \frac{j_m A_m}{V_e}$$

The membrane density, which is the membrane area per volume of tissue, is $\rho_m = A_m / V_t$. This is a commonly measured tissue property, hence it is convenient to express the solute sources in terms
3.3 Electroneutrality

of the membrane density,

\[ s_i = \frac{-j_m \rho_m}{\Lambda_i} \]  
\[ s_e = \frac{j_m \rho_m}{\Lambda_e} \]

where \( \Lambda_i \) and \( \Lambda_e \), respectively, are the intracellular and extracellular volume fractions, which are given by \( \Lambda_i = V_i/V_t \) and \( \Lambda_e = V_e/V_t \).

3.3 Electroneutrality

The flux of charged solutes in a solution or through a membrane generally depends on the electrical potential. The electroneutrality condition is used to calculate this electrical potential. In this section, we introduce the electroneutrality condition and derive the weak form of the electroneutrality condition.

The electroneutrality condition states that the net sum on charge in a volume is zero. In reality, there does exist an imbalance of charge, but it is very small, so small it has a negligible effect on the solute concentrations. For example, to generate a 25 mV potential across a cell membrane, one in every hundred thousand ions needs to be pulled from the solution and attached to the membrane (Benedek & Villas 2000a). Furthermore, any system where the charge density is significantly perturbed away from equilibrium will generate such extremely large electric forces on the ions that it will return the system to equilibrium very quickly. Benedek & Villas (2000a) gives a good example of these forces - "An imbalance of charge as small as one unbalanced negative charge out of \( 10^{18} \) positive charges produces sufficient electrostatic repulsion to tear apart a solid 10 cm in size [diameter]."

The mathematical form of electroneutrality condition is,

\[ \sum_\alpha z_\alpha C_\alpha = 0 \]  

where the subscript \( \alpha \) indicates the solute species, \( z \) is the valency and \( C \) is concentration. To ensure this condition is satisfied, one needs to account for all charged solute species including proteins bound to membranes. This can be difficult to do in a model, especially basic models at an early stage of development. The weak form of the electroneutrality condition can be used to
overcome this issue,

$$\sum_{\alpha} z_{\alpha} \frac{dC_{\alpha}}{dt} = 0$$  \hspace{1cm} (3.15)

If we assume the initial condition of the system is electrically neutral, the weak form of the electroneutrality condition ensures electroneutrality is maintained. This equation can be applied to a subset of all solute species if we assume the solute species that are not included have no significant influence on the electrical potential.

### 3.4 Rate of Change of Concentration

The solute fluxes and fluid flow are governed, in part, by concentration gradients, therefore it is important to model the rate of change of solute concentrations. The solute concentration ($C$) is a measure of the number of solute particles per unit volume. The solute concentration within a volume can change due to solute fluxes through the surface of the volume or due to a solute source within the elements. The rate of change of a solute concentration is governed by the divergence of the flux vector and by the solute source,

$$\frac{dC_{\alpha}}{dt} = -\nabla \cdot j_{\alpha} + s_{\alpha}$$  \hspace{1cm} (3.16)

where $\alpha$ indicates the solute species, $j$ is the solute flux vector and $s$ is the solute source.

### 3.5 Solute Transport in the Lens

Figure 3.3 shows the solute fluxes and transport proteins in the lens model. $K^+$ channels and $Na^+/K^+$ pumps are localised to the surface membrane of the lens and transport $Na^+$ and $K^+$ between the intracellular space and outside of the lens. $Na^+$ channels and $Cl^-$ channels are localised to the fibre cell membrane and transport $Na^+$ and $Cl^-$ between the intracellular space and the extracellular space. Adjacent cells are coupled via gap junctions, which are essentially non-selective solute and water channels. At the surface, $Na^+$, $K^+$ and $Cl^-$ are free to diffuse between the extracellular space and the outside of the lens. The transport $Na^+$, $K^+$ and $Cl^-$ are modelled but impermeant anions are not since they are assumed to be immobile.

The main driver of the solute fluxes in the lens are the $Na^+/K^+$ pumps. They transport $Na^+$ out of
the lens and K$^+$ into the lens. This generates an electrochemical gradient. The electrochemical gradient causes Na$^+$ to enter the lens via the extracellular space, crosses the fibre cell membrane and exits via the intracellular space. K$^+$ is pumped into the intracellular space by Na$^+$/K$^+$ pumps and transported back out, down the electrochemical gradient, via the K$^+$ channels at the surface of the lens. Although, there is no K$^+$ transport across the fibre cell membrane, there can be transport that is localised to the intracellular and to the extracellular spaces. For example, K$^+$ can enter the intracellular space at the anterior surface, flow through the intracellular space and exit the intracellular space at the posterior surface. Cl$^-$ can enter the lens through the extracellular space but not through the surface membrane into the intracellular space. It enters the intracellular space via Cl$^-$ channels in the fibre cell membrane. There is a small Cl$^-$ circulation between the intracellular and extracellular space that generally follows the Na$^+$ flux.

The solute fluxes along with the fluid velocities and dependent variables are summarised by the schematic shown in Figure 3.4. The solute fluxes can be categorised into the intracellular fluxes, the surface fluxes, the transmembrane fluxes and the extracellular fluxes.

The model has ten dependent variables: the intracellular and extracellular ion concentrations ($C_{Na_i}, C_{K_i}, C_{Cl_i}, C_{Na_e}, C_{K_e}, C_{Cl_e}$); the intracellular and extracellular electrical potentials ($\phi_i, \phi_e$); and the intracellular and extracellular hydraulic pressures ($p_i, p_e$). The ion concentrations ($C_{Na_o}, C_{K_o}, C_{Cl_o}$), electrical potential ($\phi_o$) and hydraulic pressure ($p_o$) outside the lens act as boundary conditions to the surface and extracellular flux equations.

In addition to the equations governing the solute fluxes there are the conservation equations governing solute concentration and charge conservation (the electroneutrality condition). These equations are covered following the flux equations.
Figure 3.4: Ion fluxes ($j$), fluid velocity ($u$) and the dependent variables: concentration ($C$), potential ($\phi$) and pressure ($p$); in the lens model. The subscripts $Na$, $K$, $Cl$ and $A$ indicate the solute species, where $A$ refers to the impermeant anions, subscripts $i$ and $e$ indicate the intracellular and extracellular spaces, subscripts $f$ and $c$ indicate the fibre and cross-fibre directions, subscripts $m$ and $s$ indicate the membrane and surface, and subscript $o$ indicates the outside of the lens.

### 3.5.1 Intracellular Fluxes

The fluxes in the intracellular space are modelled along the fibre and cross-fibre directions (see Figure 3.5). The fluxes in the fibre direction pass through the cytoplasm and the fluxes in the cross-fibre direction pass through the cytoplasm, intercellular membrane and surface membrane. The fluxes through the intercellular membrane occur via non-selective gap junctions whereas the fluxes through the surface membrane occurs via the $Na^+/K^+$ pumps and $K^+$ channels.

Figure 3.5: Intracellular fluxes in the fibre and cross-fibre directions. The fluxes in the fibre direction mainly pass through the cytoplasm whereas the fluxes in the cross-fibre direction pass through the cytoplasm and intercellular membranes.
3.5 Solute Transport in the Lens

Fibre Direction

The fluxes along the axis of the fibre cells occur in a fluid, hence they are modelled using the advective-Nernst-Plank equation,

$$ j_{\alpha,f} = -D_{\alpha,f} \frac{dC_{\alpha}}{d\eta_f} - z_{\alpha} e \frac{D_{\alpha,f}}{k_B T} \frac{d\phi}{d\eta_f} C_{\alpha} + u_f C_{\alpha} $$  \hspace{1cm} (3.17)

where the subscript $\alpha$ indicates the solute species, $j$ is the solute flux [mol/(m$^2$s)], $C$ is the concentration [mol/m$^3$], $\phi$ is the potential [V], $u$ is the fluid velocity [m/s], and $D_f$ is the diffusion coefficient [m$^2$/s].

Cross-Fibre Direction

An element in the lens model usually spans many cells. In this case, it is difficult to discretely model the flux through each cell cytoplasm and through each membrane contained in the element. Instead, we homogenise the flux equations to obtain one equation that describes the flux through the element. The homogenised transmembrane fluxes can be modelled using the advective-Nernst-Plank equation where the diffusion coefficient represents the effective diffusion coefficient through the cells and intercellular membranes. Studies have measured this effective diffusion coefficient to be a hundred time less than the diffusion coefficient within cytoplasm (Cannell et al. 2004). Hence, the cross-fibre flux equation for the intracellular space is

$$ j_{\alpha,c} = -D_{\alpha,c} \frac{dC_{\alpha}}{d\eta_c} - z_{\alpha} e \frac{D_{\alpha,c}}{k_B T} \frac{d\phi}{d\eta_c} C_{\alpha} + u_c C_{\alpha} $$  \hspace{1cm} (3.18)

where the subscript $\alpha$ indicates the solute species, $\tilde{j}$ is the solute flux along the cleft [mol/(m$^2$s)], $C$ is the concentration [mol/m$^3$], $\phi$ is the potential [V], $\tilde{u}$ is the fluid velocity along the cleft [m/s], and $D$ is the diffusion coefficient in a free solution [m$^2$/s].

3.5.2 Surface Fluxes

At the surface of the lens, the intracellular space is coupled to the outside of the lens via $K^+$ channels and $Na^+/K^+$-pumps in the membrane. The fluxes through the surface of the lens are normal to the surface membrane and aligned with the cross-fibre axis, hence the surface fluxes act as a boundary condition for the intracellular fluxes in the cross-fibre direction.
The flux through the K$^+$ channel is described by Equation (3.8),

$$j_{K,ic} = \frac{g_K}{F} (V_m - E_K)$$  \hspace{1cm} (3.19)

where $j_K$ is the K$^+$ flux [mol/(m$^2$ s)], $g_K$ is the conductivity per membrane area (S/m$^2$), $V_m$ is the transmembrane potential (V), and $E_K$ is the Nernst potential. The transmembrane potential is given by $V_m = \phi_o - \phi_i$. The Nernst potential is given by,

$$E_K = \frac{k_B T}{z_K e} \ln \left( \frac{C_{K,o}}{C_{K,i}} \right)$$  \hspace{1cm} (3.20)

where $z_K$ is the valency, $C_{K,o}$ is the K$^+$ concentration outside the lens, and $C_{K,i}$ is the K$^+$ concentration in the intracellular space at the surface.

A modified form of the Na$^+$/K$^+$ pump models proposed by Gao et al. (2000) is used in the lens model (see Equations (6.5) and (6.6) in Section 6.2.3). Since the models in this thesis do not include the concentration of H$^+$, the contribution from the Hill function (Hille 2001) term in Equation (6.5) that depends on the H$^+$ concentration is evaluated and included in the maximum current parameter ($I_{max}$). Therefore, the models for the $\alpha_1$ and $\alpha_2$ isoforms of the Na$^+$/K$^+$ pumps are,

$$I_{p1} = I_{max1} \left( \frac{C_{Na}}{C_{Na} + K_{Na1}} \right)^3 \left( \frac{C_{Ko}}{C_{Ko} + K_{K1}} \right)^2$$  \hspace{1cm} (3.21)

$$I_{p2} = I_{max2} \left( \frac{C_{Na}}{C_{Na} + K_{Na2}} \right)^3 \left( \frac{C_{Ko}}{C_{Ko} + K_{K2}} \right)^2$$  \hspace{1cm} (3.22)

where the subscript 1 and 2 associate the parameter with the $\alpha_1$ and $\alpha_2$ isoforms of the Na$^+$/K$^+$ pumps and $I_{max}$ is the maximum current rates through the pumps. The $K$ values are given by,

$$K_{Na1} = (\sqrt{2} - 1)K_{1/2,Na1} \quad K_{Na2} = (\sqrt{2} - 1)K_{1/2,Na2}$$

$$K_{K1} = (\sqrt{2} - 1)K_{1/2,K1} \quad K_{K2} = (\sqrt{2} - 1)K_{1/2,K2}$$

$K_{1/2,Na}$ and $K_{1/2,K}$ are the Na$^+$ and K$^+$ concentrations at which the pump current is half the maximum current ($I_{max}$).

Given the pumps rate ($I_{p1}$ and $I_{p2}$) at a certain position on the surface of the lens, the Na$^+$ and K$^+$
fluxes are given by

\[ j_{Na,p} = 3 \frac{I_{p1} + I_{p2}}{F} \]  (3.23)
\[ j_{K,p} = -2 \frac{I_{p1} + I_{p2}}{F} \]  (3.24)

### 3.5.3 Transmembrane Fluxes

Inside the lens, the intracellular and extracellular space are coupled via sodium and chloride channels in the fibre cell membrane. There are no K\(^+\) channels. Therefore, the transmembrane fluxes are

\[ j_{Na,m} = j_{Na,ic} \]
\[ j_{K,m} = 0 \]
\[ j_{Cl,m} = j_{Cl,ic} \]

where \( j_{Na,ic} \) and \( j_{K,ic} \), the fluxes through the Na\(^+\) and K\(^+\) ion channels [mol/(m\(^2\)s)], are given by Equation (3.8).

Since the lens model is a bidomain model, the transmembrane fluxes are treated as source terms (see Section 3.2.2). The intracellular and extracellular source terms due to transmembrane Na\(^+\) and Cl\(^-\) fluxes are given by,

\[ s_{ai} = \frac{j_{\alpha,m} \rho_m}{\Lambda_i} \]  (3.25)
\[ s_{ae} = \frac{j_{\alpha,m} \rho_m}{\Lambda_e} \]  (3.26)

where \( j_{\alpha,m} \) is the net ion transmembrane flux for solute \( \alpha \), \( \rho_m \) is the membrane density [m\(^{-1}\)], and \( \Lambda_i \) and \( \Lambda_e \) are the intracellular and extracellular volume fractions.

### 3.5.4 Extracellular Solute Fluxes

Figure 3.6 shows a magnified view of the lens tissue and the solute fluxes \( (j_f \) and \( j_c \)) in the extracellular cleft. See Chapter 2 for a description of the fibre and cleft coordinate systems which are
used to orient the tissue and cleft shown in Figure 3.6. The fluxes along the cleft can be described by the advective-Nernst-Plank equation (Equation (3.1)). Because the cleft is narrow compared to its length, we assume there is no flux in the sheet direction ($\eta_s$). Therefore, the solute flux in the cleft fibre ($\eta_f$) and cleft cross-fibre ($\eta_c$) directions are given by

$$\tilde{j}_{\alpha,f} = -D_{\alpha,f} \frac{dC_\alpha}{d\eta_f} - z_\alpha e \frac{D_{\alpha,f}}{k_B T} \frac{d\phi}{d\eta_f} C_\alpha + \tilde{u}_f C_\alpha$$  \hspace{1cm} (3.27)$$
$$\tilde{j}_{\alpha,c} = -D_{\alpha,c} \frac{dC_\alpha}{d\eta_c} - z_\alpha e \frac{D_{\alpha,c}}{k_B T} \frac{d\phi}{d\eta_c} C_\alpha + \tilde{u}_c C_\alpha$$  \hspace{1cm} (3.28)$$

where the subscript $\alpha$ indicates the solute species, $\tilde{j}$ is the solute flux along the cleft [mol/(m$^2$s)], $C$ is the concentration [mol/m$^3$], $\phi$ is the potential [V], $\tilde{u}$ is the fluid velocity along the cleft [m/s], and $D$ is the diffusion coefficient in a free solution [m$^2$/s].

It is more convenient to express and solve the extracellular flux equations in the same coordinate system as the intracellular flux equations, which are defined in terms of the fibre coordinate system. The transformation of equations and parameters between the cleft and fibre coordinate system is described in Section 2.4. The transformations for the flux vectors can be derived by following the derivation in Section 2.4.4, i.e.,

$$j_{\alpha,f} = \frac{1}{\xi_f} \tilde{j}_{\alpha,f} \text{ and } j_{\alpha,c} = \frac{1}{\xi_c} \tilde{j}_{\alpha,c}$$

where $\xi_f$ and $\xi_c$ are the wiggle factors in the fibre and cross-fibre directions (see Section 2.4.1). The transformations for the concentration and potential gradients can be derived by following the
derivation in Section 2.4.2, i.e.,

\[
\frac{dC_\alpha}{d\tilde{\eta}_f} = \frac{1}{\xi_f d\tilde{\eta}_f} \frac{dC_\alpha}{d\tilde{\eta}_c} = \frac{1}{\xi_c d\tilde{\eta}_c} \frac{dC_\alpha}{d\tilde{\eta}_c}
\]

Substituting these transformations into Equations (3.27) and (3.28) gives

\[
j_{\alpha,f} = -D_{\alpha,f} \tau_f \frac{dC_\alpha}{d\tilde{\eta}_f} - z_\alpha e D_{\alpha,f} \frac{k_B T \tau_f}{\xi_f d\tilde{\eta}_f} C_\alpha + u_f C_\alpha
\]

(3.29)

\[
j_{\alpha,c} = -D_{\alpha,f} \tau_c \frac{dC_\alpha}{d\tilde{\eta}_c} - z_\alpha e D_{\alpha,f} \frac{k_B T \tau_c}{\xi_c d\tilde{\eta}_c} C_\alpha + u_c C_\alpha
\]

(3.30)

where \(\tau_f\) and \(\tau_c\) are the tortuosities in fibre and cross-fibre directions (see Section 2.4.1).

### 3.5.5 Electroneutrality

The electroneutrality is maintained by ensuring the volume integral of the weak form of the electroneutrality condition (Equation (3.15) with Equation (3.16) substituted) is satisfied over the intracellular volume \(V_i\) and over the extracellular volume \(V_e\),

\[
-\int_{V_i} \sum_\alpha z_\alpha \nabla \cdot j_{\alpha i} \, dV_i + \int_{V_i} \sum_\alpha z_\alpha s_{\alpha i} \, dV_i = 0
\]

(3.31)

\[
-\int_{V_e} \sum_\alpha z_\alpha \nabla \cdot j_{\alpha e} \, dV_e + \int_{V_e} \sum_\alpha z_\alpha s_{\alpha e} \, dV_e = 0
\]

(3.32)

where the subscripts \(\alpha\), \(i\) and \(e\) indicates the solute species, intracellular space and the extracellular space, respectively, \(j\) is the flux vector [mol/(m² s)], which is composed of the fibre and cross-fibre fluxes, \(s\) is the solute source [mol/(m³ s)], and \(z\) is the solute valency.

### 3.5.6 Rate of Change of Concentration

The rate of change of the solute concentration is given by Equation (3.16),

\[
\frac{dC}{dt} = -\nabla \cdot j + s
\]

(3.33)
where \( \mathbf{j} \) is the solute flux vector \([\text{mol}/(\text{m}^2 \text{s})]\) and \( s \) is the solute source \([\text{mol}/(\text{m}^3 \text{s})]\). This equation is applied to each species in both the intracellular space and the extracellular space,

\[
\frac{dC_{\alpha i}}{dt} = -\nabla \cdot \mathbf{j}_{\alpha i} + s_{\alpha,i} \tag{3.34}
\]

\[
\frac{dC_{\alpha e}}{dt} = -\nabla \cdot \mathbf{j}_{\alpha e} + s_{\alpha,e} \tag{3.35}
\]

where the subscripts \( \alpha, i \) and \( e \) indicate the species, the intracellular space and the extracellular space and \( s_\alpha \) is the solute source \([\text{mol}/(\text{m}^3 \text{s})]\). Given a volume element, Equations (3.34) and (3.35), respectively, are integrated over the intracellular and extracellular components (\( V_i \) and \( V_e \)) of the total volume,

\[
\int_{V_i} \frac{dC_{\alpha i}}{dt} \, dV_i = -\int_{V_i} \nabla \cdot \mathbf{j}_{\alpha i} \, dV_i + \int_{V_i} s_{\alpha,i} \, dV_i \tag{3.36}
\]

\[
\int_{V_e} \frac{dC_{\alpha e}}{dt} \, dV_e = -\int_{V_e} \nabla \cdot \mathbf{j}_{\alpha e} \, dV_e + \int_{V_e} s_{\alpha,e} \, dV_e \tag{3.37}
\]

The next chapter discusses the theory of fluid dynamics followed by the derivation of the fluid transport equations for the lens.
Fluid Dynamics

The fluid dynamics in the lens is complex. However, it is possible to extrapolate the equations describing the intracellular and extracellular fluid flow at the cellular level to obtain equations describing the fluid flow in the whole lens. Furthermore, by making valid assumptions about flow conditions and structure in the lens the complex Navier-Stokes equations can be significantly simplified. Figure 4.1 shows the outline of the sections in this chapter and the series of simplifications leading to governing equations for the fluid flow in the lens. The theory covered in Sections 4.1 to 4.4 is summarised from Currie (1974).

**Figure 4.1:** The chapter layout which describes how the Navier-Stokes equations are simplified to obtain the governing equations for the fluid flow in the whole lens.
4.1 Navier-Stokes Equations

The Navier-Stokes equations, which describe the motion of a fluid, are derived from three conservation principals, the conservation of mass, momentum, and energy, respectively. Under isothermal conditions the two relevant Navier-Stokes equations (Currie (1974) and Ferziger & Peric (1997)) are:

\[
\frac{\partial \rho}{\partial t} + \frac{\partial}{\partial x_k} (\rho u_k) = 0 \quad \text{Continuity equation (4.1)}
\]

\[
\rho \frac{\partial u_j}{\partial t} + \rho u_k \frac{\partial u_j}{\partial x_k} = -\frac{\partial p}{\partial x_j} + \frac{\partial}{\partial x_i} \left( \sigma_{ij} \right) + \rho f_j \quad \text{Momentum equation (4.2)}
\]

The fluid dynamics in the lens is complex. However, it is possible to extrapolate the equations describing the intracellular and extracellular fluid flow at the cellular level to obtain equations describing the fluid flow in the whole lens. Furthermore, by making valid assumptions about flow conditions and structure in the lens the complex Navier-Stokes equations can be significantly simplified. Figure 4.1 shows the outline of the sections in this chapter and the series of simplifications leading to governing equations for the fluid flow in the lens.

where \( \rho \) is the density \([\text{kg/m}^3]\), \( u \) is the velocity \([\text{m/s}]\), \( \sigma \) is the stress \([\text{N/m}^2]\) and \( f \) is the body force per unit mass \([\text{N/kg}]\) (or the acceleration \([\text{m/s}^2]\)) acting on the fluid.

The fluid in the lens is assumed to be an incompressible Newtonian fluid with a spatially constant viscosity\(^1\). These assumptions simplify the continuity and momentum equations to give

\[
\frac{\partial u_k}{\partial x_k} = 0 \quad \text{(4.3)}
\]

\[
\rho \frac{\partial u_j}{\partial t} + \rho u_k \frac{\partial u_j}{\partial x_k} = -\frac{\partial p}{\partial x_j} + \mu \frac{\partial^2 u_j}{\partial x_i \partial x_i} + \rho f_j \quad \text{(4.4)}
\]

where \( p \) is the hydrostatic pressure \([\text{N/m}^2]\) in the fluid and \( \mu \) is the dynamic viscosity \([\text{Ns/m}^2]\) of the fluid. The relationship between the kinematic viscosity \( \nu \ [\text{m}^2/\text{s}] \), and the dynamic viscosity \( \mu \), is given by \( \nu = \mu / \rho \).

\(^1\)Note that the refractive index of the lens changes between the periphery and center due to a change in the concentration of a macromolecule called crystallines. The inhomogeneous distribution of crystallins and other macromolecules may result in an inhomogeneous fluid viscosity but this is not included in the present analysis.
4.2 Stokes Flow

The fluid flow in the lens can be described as slow, 'creeping', or low-Reynolds number flow. In this case, the nonlinear convective term in the momentum equation can be neglected. It is also reasonable to assume that the fluid flow in a normal lens is near or at steady-state at all times, this allows us to neglect the transient term. These simplifications reduce the Navier-Stokes equations to

\[
\frac{\partial u_k}{\partial x_k} = 0 \tag{4.5}
\]

\[\frac{\partial p}{\partial x_j} + \mu \frac{\partial^2 u_j}{\partial x_i \partial x_i} + \rho f_j = 0 \tag{4.6}\]

These are called the Stokes flow equations. Notice these equations are linear, which makes them much easier to solve.

4.3 Couette Flow

Couette flow is a special case of Stokes flow between parallel plates. In this case, the exact solution for the velocity profile can be derived (see Figure 4.2). The size of the plates in the \(x\)- and \(y\)-directions is assumed to be large compared to the distance \(h\) between the plates, therefore we can assume there are no edge effects and that the velocity profile is steady. If the flow is unidirectional in the \(x\)-direction \((v = 0\) and \(w = 0\)) then the Stokes flow equations (Equations (4.5) and (4.6)), with no body force terms, reduce to

\[
\frac{\partial^2 u}{\partial z^2} = \frac{1}{\mu} \frac{\partial p}{\partial x}
\]
Integrating twice with respect to \( z \) gives

\[
 u(z) = \frac{1}{\mu} \frac{\partial p}{\partial x} \left( \frac{z^2}{2} + bz + c \right) \quad (4.7)
\]

The no-slip boundary conditions \( u(h/2) = u(-h/2) = 0 \text{ m/s} \) at the surface of the plates can be applied to Equation (4.7) to determine the coefficients \( b = 0, c = -h^2/8 \). Therefore, the velocity profile between the plates is given by

\[
 u(z) = \frac{1}{\mu} \frac{\partial p}{\partial x} \left( \frac{z^2}{2} - \frac{h^2}{8} \right) \quad (4.8)
\]

The mean velocity \( \bar{u} \), which is calculated by integrating the velocity profile between the plates and dividing by the distance between the plates, is

\[
 \bar{u} = \frac{1}{h} \int_{-h/2}^{h/2} u(z) \, dz = -\frac{h^2 \, dp}{12\mu \, dx} \quad (4.9)
\]

The maximum velocity \( \hat{u} \), which occurs at the midway between the plates \( (z = 0) \), is

\[
 \hat{u} = \frac{h^2 \, dp}{8\mu \, dx} \quad (4.10)
\]

### 4.4 Poiseuille Flow

Poiseuille flow is a special case of Stokes flow in a tube with a constant elliptical cross-section. In this case, the exact solution for the velocity profile can be derived. Figure 4.3 shows the flow velocity profile and the shape of the tube cross-section, which is described by the radii of the principal axes \( r_a \) and \( r_b \). Since there is no flow in the radial direction \( (v = 0 \text{ and } w = 0) \) the Stokes flow equations (Equations (4.5) and (4.6)) reduce to

\[
 \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} = \frac{1}{\mu} \frac{dp}{dx} \quad (4.11)
\]

Equation (4.11) can be solved to obtain the velocity profile (Currie 1974),

\[
 u(y, z) = \frac{1}{2\mu \, dx \, r_a^2 + r_b^2} \frac{dp}{dx} \left( \frac{y^2}{r_a^2} + \frac{z^2}{r_b^2} - 1 \right) \quad (4.12)
\]
Figure 4.3: The fluid velocity profile in a tube with an elliptic cross-section. a) The \( x \)-velocity profile where the darker intensity is a higher velocity. b) The velocity profile in the \( xy \)-plane. c) The velocity profile in the \( xz \)-plane.

The mean velocity (\( \bar{u} \)), which is calculated by integrating Equation (4.12) over the cross-section and dividing by the cross-sectional area, is

\[
\bar{u} = -\frac{1}{4\mu} \frac{dP}{dx} \frac{r_a^2 r_b^2}{r_a^2 + r_b^2}
\]

(4.13)

The maximum velocity (\( \hat{u} \)), which is at the center of the tube (\( y = 0 \) and \( z = 0 \)), is

\[
\hat{u} = -\frac{1}{2\mu} \frac{dP}{dx} \frac{r_a^2 r_b^2}{r_a^2 + r_b^2}
\]

(4.14)

4.5 Darcy Flow

The fluid flow in the lens could be modelled as Darcy’s flow. Darcy’s law is a phenomenologically derived constitutive equation that describes the flow (\( u \)) of a fluid through a porous medium in terms of the permeability of the medium (\( \kappa \)), viscosity of the fluid (\( \mu \)), and pressure gradient (\( P \)) (Perry & Green 1997),

\[
u = \frac{-\kappa}{\mu} \nabla P
\]

Darcy’s law is valid for slow viscous flows and is commonly used to study groundwater flows.

The permeability (\( \kappa \)) is empirically based and represents the bulk permeability of the medium. Although Darcy’s law is suitable for modelling the fluid flow in the lens, it would be difficult to
measure the intracellular, extracellular and membrane permeabilities of the lens, let alone the spatial variation of these. For this reason, the intracellular, extracellular and membrane permeabilities of the lens are theoretically derived from our knowledge of the cellular structure of the lens.

4.6 Electro-osmotic Flow

If a fluid containing excess charge is subjected to an electric field, the excess charge will experience a force and begin to flow. Due to solute drag the excess charge will cause the surrounding fluid to flow. This phenomenon is known as electro-osmosis.

McLaughlin & Mathias (1985) covers the theoretical derivation and experimental investigation of Helmholtz-type electro-osmosis in the renal proximal tubule. They concluded that electro-osmosis could be important in other tissues including the extracellular space of the lens. Later, Mathias (1985b) included electro-osmosis in his one-dimensional model of the lens and showed that electro-osmosis contributed to around a third of the extracellular velocity. It is therefore important to include electro-osmosis in the models developed in this project.

Helmholtz-type electro-osmosis is not considered to occur in the intracellular space because of the large width of the intracellular space and the small electric field generated in this space. However, Mathias (1985b) suggest that Schmid-type electro-osmosis might occur through gap junctions embedded in the membrane separating the intracellular compartments. The analysis and inclusion of Schmid-type electro-osmosis is beyond the scope of this project.

This section will introduce the electric double layer (EDL), a layer near a charged surface which contains excess charge, and derive an expression for the charge density and potential near the surface. This theory is then extended to obtain an expression for the charge density and potential between parallel plates which, with an electric field, gives an expression for the body forces acting on the fluid. This body force expression is included in the Stokes flow equations to derive the electro-osmotic flow between parallel plates (Couette flow). This theory is required for the fluid flow in the extracellular space of the lens.

\footnote{Fischbarg et al. (1999) measured the bulk permeability of the lens but did not distinguish between the intracellular and extracellular permeabilities.}
4.6 Electro-osmotic Flow

4.6.1 Electric Double Layer (Debye Shielding)

Consider a surface with fixed charges attached to it; for example, a cell membrane with embedded charged proteins (see Figure 4.4a). The surface charge density ($\sigma$) creates an electric field that emanates from the surface. In an electrolyte solution the surface charge will be neutralised by ions drawn from the solution. However, due to Brownian motion these ions do not quite reach the surface, instead they create an envelope or feathered layer near the surface called the electrical double layer (EDL). This layer is also referred to as Debye shielding. This section will derive the electrical potential ($\phi(z)$) and charge density ($\rho_c(z)$) perpendicular to the charged surface. For more detail on the following derivation see Benedek & Villas (2000a).

![Diagram of an electric double layer (EDL) with positive ions attracted to the negatively charged membrane.](a)

**Figure 4.4:** (a) An electric double layer (EDL) where positive ions are attracted to the negatively charged membrane. (b) The charge density ($\rho_c$) and potential ($\phi$) decays to zero further away from the membrane.

The charge density ($\rho_c(z)$) of the EDL perpendicular to the surface can be derived from the Nernst-Plank equation (See Section 3.1). The Nernst-Plank equation describes the diffusive and electro-diffusive flux of ions in a fluid. The one-dimensional Nernst-Plank equation is

$$ j_\alpha = -D_\alpha \frac{dC_\alpha(z)}{dz} - z_\alpha e \frac{D_\alpha}{k_B T} \frac{d\phi(z)}{dz} C_\alpha(z) $$

where $j_\alpha$, $z_\alpha$, $C_\alpha$ and $D_\alpha$ are the flux (mol/(m².s)), valency, concentration (mM) and diffusion coefficient (m²/s) of solute $\alpha$, respectively; $\phi$ is the electrical potential (V), and $k_B$, $T$ and $e$ are the Boltzmann constant (J/K), the absolute temperature (K), and the charge on an electron (C), respectively. The subscript $\alpha$ indicates the species of the solute.
At equilibrium the flux of the ions in the fluid is zero, therefore the Nernst-Plank equation becomes

\[ \frac{dC_\alpha(z)}{dz} + \frac{z_\alpha e}{k_B T} \frac{d\phi(z)}{dz} C_\alpha(z) = 0 \]

Dividing by \( C_\alpha \), substituting \( \frac{1}{C_\alpha} \frac{dC_\alpha}{dz} \) with \( \frac{d}{dz} \ln C_\alpha \), and integrating gives

\[ \ln C_\alpha(z) + \frac{z_\alpha e}{k_B T} \phi(z) + a = 0, \]

which, when rearranged, gives the Boltzmann relation,

\[ C_\alpha(z) = A e^{-z_\alpha e \phi(z)/k_B T} \quad (4.16) \]

Far from the surface \( (x \to \infty) \), the concentration tends to \( C_\alpha(\infty) \) and the potential \( (\phi) \) tends to a constant which is chosen to be zero. Substituting these boundary conditions into Equation (4.16) gives

\[ C_\alpha(z) = C_\alpha(\infty) e^{-z_\alpha e \phi(z)/k_B T} \]

The charge density \( (\rho_c(z)) \) [C/m\(^3\)] is defined by

\[ \rho_c(z) = \sum_\alpha z_\alpha e C_\alpha(z) N_0 = \sum_\alpha z_\alpha e C_\alpha(\infty) N_0 e^{(-z_\alpha e \phi(z)/k_B T)} \quad (4.17) \]

where the Avagadro number \( N_0 \), is the number of particles per mole \( (N_0 = 6.022 \times 10^{23}) \).

The one-dimensional Poisson equation, which relates the second derivative of the potential \( (\phi) \) to the charge density \( (\rho_c) \), is

\[ \frac{d^2\phi}{dz^2} = -\frac{dE_z}{dz} = -\frac{1}{\varepsilon_r \varepsilon_0} \rho_c(z) \quad (4.18) \]

where \( \varepsilon_r \) is the dielectric constant of the fluid and \( \varepsilon_0 \) is the permittivity of vacuum [C/(V.m)].

Substituting Equation (4.17) into Equation (4.18) gives the Poisson-Boltzmann equation,

\[ \frac{d^2\phi}{dz^2} = -\frac{1}{\varepsilon_r \varepsilon_0} \sum_\alpha z_\alpha e C_\alpha(\infty) N_0 e^{(-z_\alpha e \phi(z)/k_B T)} \quad (4.19) \]
This is a difficult equation to solve but it can be linearised for small values of the exponential using
\[ e^{\pm z} \approx 1 \pm z \quad \text{for} \quad |z| << 1 \quad (4.20) \]

Thus, if the electrolytic solution contains monovalent ions and the absolute potential is much less than \( k_B T / e \) (25.9 mV at \( T = 300 \text{ K} \)) then Equation (4.19) can be linearised,
\[
\frac{d^2 \phi}{dz^2} = -\frac{1}{\varepsilon_r \varepsilon_0} \sum_{\alpha} z_\alpha e C_\alpha(\infty) N_0 \left( 1 - \frac{z_\alpha e}{k_B T} \phi(z) \right) \quad (4.21)
\]
The \( \sum_{\alpha} z_\alpha e C_\alpha(\infty) \) term in the expanded form of this equation can be eliminated since the electroneutrality condition states that \( \sum_{\alpha} z_\alpha e C_\alpha(\infty) = 0 \). Equation (4.21) then reduces to the linearised Poisson-Boltzmann equation,
\[
\frac{d^2 \phi}{dz^2} = \frac{1}{\lambda_D^2} \phi(z) \quad (4.22)
\]
where \( \lambda_D \) is the Debye length,
\[
\lambda_D = \sqrt{\frac{\varepsilon_r \varepsilon_0 k_B T}{e^2 \sum_{\alpha} z_\alpha^2 C_\alpha(\infty) N_0}} \quad (4.23)
\]

**Solving the Linearised Poisson-Boltzmann Equation**

The general solution to the linearised Poisson-Boltzmann equation (Equation (4.22)) is
\[
\phi(z) = Ae^{-z/\lambda_D} + Be^{-z/\lambda_D} \quad (4.24)
\]
The boundary conditions for a surface with a fixed charge (\( \sigma \)) are
\[
\phi(z) \xrightarrow{z \to \infty} 0 \quad \text{and} \quad \frac{d\phi}{dz}(0) = -E_x(0) = -\frac{\sigma}{\varepsilon_r \varepsilon_0} \quad (4.25)
\]
Applying these boundary conditions to Equation (4.24) gives,
\[
\phi(z) = \phi(0)e^{-z/\lambda_D} = \lambda_D \frac{\sigma}{\varepsilon_r \varepsilon_0} e^{-z/\lambda_D} \quad (4.26)
\]
Using the Poisson equation (Equation (4.18)), we can derive the equation describing the charge density,

\[ \rho_c(z) = -\frac{\sigma}{\lambda_D} e^{-z/\lambda_D} \] (4.27)

These equations show that the potential (\(\phi\)) and the charge density (\(\rho_c\)) decay to zero away from the charged surface with a space constant of \(\lambda_D\) (see Figure 4.4b).

**Example**

As an example, consider the charge density and potential near a cell membrane. The electrolytic solution contains 107 mM of Na\(^+\), 110 mM of Cl\(^-\), and 3 mM of K\(^+\) at a temperature of 310 K. Solving Equation (4.23) (with \(E_r = 80\), \(E_0 = 8.85 \times 10^{-12}\) C/(V m), \(k_B = 1.38 \times 10^{-23}\) J/K, \(e = 1.6 \times 10^{-19}\) C, and \(N_0 = 6.022 \times 10^{23}\)) gives a Debye length (\(\lambda_D\)) of about 1 nm. The zeta potential, which is the potential at the membrane surface, is assumed to be \(-15\) mV (Mathias 1985b). By substituting the zeta potential into Equation (4.26) with \(x = 0\), we can calculate the surface charge density (\(\sigma\)) to be \(-11 \times 10^{-3}\) C/m\(^2\). Now the Debye length (\(\lambda_D\)) and surface charge density (\(\sigma\)) can be substituted into Equations (4.26) and 4.27 to calculate the potential and charge density, respectively, in the solution (see Figure 4.4b).

### 4.6.2 Electro-osmosis Between Parallel Plates

The extracellular cleft of the lens is similar to a pair of parallel plates and the fluid flow can be described as creeping flow. In this case, the flow can be modelled as Couette flow, but unlike the derivation in Section 4.3, the body force term is included to account for forces due to electro-osmosis. Therefore, we start with the following simplified Stokes flow equation,

\[ \frac{d^2 u}{dz^2} = \frac{1}{\mu} \frac{dp}{dx} - \frac{1}{\mu} F_x \] (4.28)

where \(z\) is perpendicular and \(x\) is parallel to the plates, and \(F_x\) is the body force per unit volume [N/m\(^3\)]. An electric field \(E\) (with component \(E_x = \frac{dE}{dx}\) in the \(x\)-direction), acts on an element of fluid that contains an excess charge as a body force, where the force per unit volume is given by

\[ F_x = \rho_c E_x = -\rho_c \frac{d\phi}{dx} \] (4.29)
The potential ($\phi$) between parallel surfaces is given by (McLaughlin & Mathias 1985)

$$\phi(z) = \frac{\zeta \cosh(z/\lambda_D)}{\sinh(h/2\lambda_D)}$$  \hspace{1cm} (4.30)

where the potential at the surface, the zeta potential ($\zeta$), is assumed to be much less than $k_B T/e$ ($\approx 25.9$ mV for $T = 300$K) to ensure that the linearization of the Poisson-Boltzmann equation remains valid. The zeta potential is defined as,

$$\zeta = \lambda_D \frac{\sigma}{\varepsilon_r \varepsilon_0}$$

By substituting the second derivative of Equation (4.30) into the Poisson equation (Equation (4.18)), an expression for the charge density between parallel plates can be derived,

$$\rho_c(z) = -\varepsilon_r \varepsilon_0 \frac{d^2 \phi}{dz^2} = -\frac{\varepsilon_r \varepsilon_0 \zeta}{\lambda_D^2} \frac{\cosh(z/\lambda_D)}{\sinh(h/2\lambda_D)}$$  \hspace{1cm} (4.31)

Substituting Equations (4.29)-4.31 into Equation (4.28) gives the $x$-momentum equation for the extracellular fluid,

$$\frac{d^2 u}{dz^2} = \frac{1}{\mu} \frac{dp}{dx} - \frac{\varepsilon_r \varepsilon_0 \zeta}{\mu \lambda_D^2} \frac{d\phi}{dx} \left( \frac{\cosh(z/\lambda_D)}{\sinh(h/2\lambda_D)} \right)$$

Integrating this twice with respect to $z$ gives

$$u(z) = \frac{1}{2 \mu} \frac{dp}{dx} z^2 - \frac{\varepsilon_r \varepsilon_0 \zeta}{\mu} \frac{d\phi}{dx} \left( \frac{\cosh(z/\lambda_D)}{\sinh(h/2\lambda_D)} \right) + bz + c$$

The values of the coefficients ($b$ and $c$) are calculated using the no-slip boundary conditions ($u(\pm h/2) = 0$), which gives

$$u(z) = \frac{1}{\mu} \frac{dp}{dx} \left( \frac{z^2}{2} - \frac{h^2}{8} \right) - \frac{\varepsilon_r \varepsilon_0 \zeta}{\mu} \frac{d\phi}{dx} \left( \frac{\cosh(z/\lambda_D)}{\sinh(h/2\lambda_D)} - \frac{\cosh(h/2\lambda_D)}{h} \right)$$  \hspace{1cm} (4.32)

The mean velocity ($\bar{u}$), which is calculated by integrating the velocity profile between the plates and dividing by the distance between the plates, is

$$\bar{u} = -\frac{h^2}{12 \mu} \frac{dp}{dx} + \frac{\varepsilon_r \varepsilon_0 \zeta}{\mu} \frac{d\phi}{dx} \left( \coth(h/2\lambda_D) - \frac{2\lambda_D}{h} \right)$$  \hspace{1cm} (4.33)
The maximum velocity ($\dot{u}$), which occurs midway between the plates ($z = 0$), is

$$\dot{u} = -\frac{h^2}{8\mu} \frac{dp}{dx} + \frac{\varepsilon_0 \varepsilon \zeta d\phi}{\mu} \frac{dx}{d\phi} \coth(h/2\lambda_D)$$

**Example**

Following on from the example in Section 4.6.1, consider the potential, charge density and fluid velocity between parallel plates. The potential and charge density between the parallel plates can be calculated using Equations (4.30) and 4.31, respectively, with the parameters from the example in Section 4.6.1 (see Figure 4.5). The fluid viscosity is assumed to be that of water, $0.7 \times 10^{-3}$ Pa.s. The analytic model by Mathias (1985b) predicted an extracellular hydrostatic pressure of 8 kPa and an extracellular potential of about 22 mV at the center of a 1.6 mm radius lens. If we assume the pressure and potential gradients are linear, then the pressure gradient is approximately 5 MPa/m and the potential gradient is approximately 14 V/m. Solving Equation (4.32) with these parameters gives the fluid velocity between the plates. Furthermore, the components of the net velocity due to the hydrostatic pressure and the electro-osmotic forces can be determined by solving the terms in Equation (4.32) independently. The hydrostatic pressure component, electro-osmotic force component and the net velocity are shown in Figure 4.6.

![Figure 4.5: The potential and charge density between parallel plates. The zeta potential $\zeta$, is $-15$ mV and the Debye length $\lambda_D$ is 1 nm.](image)

4.7 Transmembrane Fluid Flow

So far we have discussed fluid flow in open domains. This can describe the fluid flow in the extracellular space and along the fibre cells. However, the fluid flow between the intracellular and extracellular spaces, between adjacent fibre cells, and through the surface of the lens, passes through a membrane. This type of fluid flow is called transmembrane flow and is treated differently to flow in an open domain. This section discusses the governing equations for transmembrane flow.

**Convention:** Fluid flow from the intracellular space to the extracellular space (out of the cell) is considered positive.

Figure 4.7 shows two cells separated by a porous membrane. Fluid is driven through this membrane by hydrostatic pressure gradients and, if the membrane is semi-permeable, by osmotic pressure gradients. A semi-permeable membrane allows only a fraction of the molecules to freely pass through its pores.

The velocity \( u_m \) of the fluid flowing through the membrane is given by

\[
 u_m = -L_p \Delta p + \sigma L_p RT \Delta O s
\]  

where \( L_p \) is the hydraulic permeability \([m^3/(N.s)]\), \( \sigma \) is the reflectance of the membrane, \( R \) is the
gas constant \([J/(\text{mol.K})]\), and \(T\) is the temperature \([\text{K}]\). The pressure difference \((\Delta p)\) is given by \(\Delta p = p_2 - p_1\) and the osmolarity difference \((\Delta Os)\) \([\text{mol/m}^3]\) is given \(\Delta Os = Os_2 - Os_1\). The osmolarity is given by

\[
Os = \sum_{\alpha} C_\alpha
\]  

(4.35)

where \(\alpha\) indicates the solute species. The pressure and concentration within each cell is assumed to be spatially constant.

Benedek & Villas (2000b) gives a more detailed discussion on the physical origin of fluid flow due to hydrostatic and osmotic pressures.

**Hydraulic Permeability**

The hydraulic permeability is usually measured experimentally, but it is possible to determine the hydraulic permeability theoretically. One can derive the equation describing the fluid flow through a single pore and integrate this over all the pores embedded in the membrane. This process is described below.

Figure 4.8 shows a magnified view of the membrane separating adjacent fibre cells and the pores in the membrane. In the lens, these pores could be gap junctions and aquaporin channels. Gap junctions allow water and solutes to pass freely whereas aquaporin channels allow only water to pass freely. Consider a single pore, if we idealise a pore to be a tube with a constant circular cross-
section, assume the velocity of the fluid through the pore is slow and assume the pore diameter is much smaller than the pore length, then we can assume the fluid flow through a pore can be described by Poiseuille flow. Therefore, the mean pore velocity \( \bar{u}_p \) is given by Equation (4.13) with \( b = a \),

\[
\bar{u}_p = -\frac{a^2}{8\mu} \frac{dp}{dx}
\]

(4.36)

where \( a \) is the radius of the pore [m], \( \mu \) is the dynamic viscosity of the fluid [Pa s], and \( p \) is the pressure [Pa]. The hydraulic permeability of the membrane is independent of the type of pressure across the membrane. Therefore, the pressure term \( p \) can represent a hydrostatic pressure, osmotic pressure, or the sum both. If we assume the pressure gradient through the pore is linear, then \( dp/dx = \Delta p/\Delta x \), where \( \Delta p = p_2 - p_1 \) is the pressure difference across the pore and \( \Delta x \) is the length of the pore. Therefore, the mean pore velocity is

\[
\bar{u}_p = -\frac{a^2}{8\mu \Delta x} \Delta p
\]

(4.37)

How does the pore velocity relate to the membrane velocity? This is best answered by considering the section of membrane shown in Figure 4.9. The area of the membrane is \( A_m = \Delta x_m \Delta y_m \), the cross-sectional area of each pore is \( A_p = \pi a^2 \), and the number of pores is \( N_p \). Given these geometric properties, the volume flow \( A_m u_m \) [m\(^3\)/s], through the membrane must equal to the
Figure 4.9: A section of membrane containing pores. The area of the membrane is $A_m = \Delta x_m \Delta y_m$, and the cross-sectional area of the pores is $A_p$. The pore density is $\rho_p = N_p / A_m$, where $N_p$ is the number of pores in the section of membrane.

The volume flow through all the pores is

$$A_m u_m = N_p \bar{u}_p A_p$$

Therefore, the transmembrane velocity $u_m$ [m/s] is

$$u_m = \frac{N_p \bar{u}_p A_p}{A_m} = \rho_p A_p \bar{u}_p$$

where $\rho_p = N_p / A_m$ is the pore density [pores/m²]. By substituting the equations for the pore velocity (Equation (4.37)) and the cross-sectional area of the pore, we get

$$u_m = -\frac{\rho_p \pi a^4}{8 \mu \Delta x} \Delta p = -\frac{\Gamma_p a^2}{8 \mu \Delta x} \Delta p$$  (4.38)

where $\Gamma_p$ is the ratio of pore area to membrane area ($\Gamma_p = \rho_p \pi a^2$). Equation (4.38) can be expressed in terms of the membrane hydraulic permeability $L_p$ [m³/(N s)],

$$u_m = -L_p \Delta p \quad \text{where} \quad L_p = \frac{\Gamma_p a^2}{8 \mu \Delta x}$$  (4.39)

In the two-dimensional model, the gap junctions embedded in the membrane that separates the intercellular compartments are idealised in the same way in order to estimate the hydraulic permeability of the intracellular space including the cell to cell connections.
4.8 Fluid Transport in the Lens

Figure 4.10 shows the fluid flow and transport proteins in the lens model. Water is typically transported through membranes via water channels called aquaporins (AQP). Transmembrane water transport in the lens is primarily through AQP0 and AQP1 channel. AQP0 is localised to the fibre cell membrane and the intercellular membrane, and AQP1 is localised to the surface membrane.

Figure 4.10: Fluid flow and transport proteins in the lens model.

There are two forces that generate fluid flow in the lens: osmotic forces and electro-osmotic forces. The Na\(^+\)/K\(^+\) pumps at the surface of the lens generate the electrochemical gradient that results in the transport of solute through the lens. These solute fluxes generate osmotic gradients across the fibre cell membrane, the surface membrane and possibly the intercellular membranes in the intracellular space. Electro-osmosis is the flow of charged fluid in an electric field and this is thought to occur along the extracellular cleft (see Section 4.6). Both the osmotic forces and electro-osmotic forces generate fluid flow across the membranes which in turn generates a hydrostatic pressure that causes fluid to flow through the lens. The analytic model of this transport developed by Mathias (1985b) predicted isotonic transport across the fibre cell membrane where water would follow the solute flux. Considering Na\(^+\) constitutes the majority of the solute flux, water would follow the Na\(^+\) flux. Therefore, water would enter the lens via the extracellular space, cross the fibre cell membrane and exit via the intracellular space.

These fluid velocities along with the solute fluxes and dependent variables are summarised by the schematic shown in Figure 4.11. The fluid velocities can be categorised into the intracellular velocities, the surface velocity, the transmembrane velocity and the extracellular velocities.

As mentioned in Section 3.5, the model has ten dependent variables: the intracellular and extracellular ion concentrations \((C_{Na_i}, C_{K_i}, C_{Cl_i}, C_{Na_e}, C_{K_e}, C_{Cl_e})\); the intracellular and extracellular
Figure 4.11: Ion fluxes \( (j) \), fluid velocity \( (u) \) and the dependent variables: concentration \( (C) \), potential \( (\phi) \) and pressure \( (p) \); in the lens model. The subscripts \( \text{Na}, \text{K}, \text{Cl} \) and \( A \) indicate the solute species, where \( A \) refers to the impermeant anions, subscripts \( i \) and \( e \) indicate the intracellular and extracellular spaces, subscripts \( f \) and \( c \) indicate the fibre and cross-fibre directions, subscripts \( m \) and \( s \) indicate the membrane and surface, and subscript \( o \) indicates the outside of the lens. Note: this figure is a copy of Figure 3.4, reproduced for convenience.

This section develops the fluid velocity equations and the conservation of mass equations for the lens based on the theory covered in the first part of this chapter.

### 4.8.1 Intracellular Velocity

Figure 4.12 shows the intracellular fluid flow in the fibre and cross-fibre direction. In the fibre direction, the fluid flow follows the fibre cell axis. The fibre cells are approximated as tubes with elliptic cross-sections and the flow is assumed to be Poiseuille flow. The flow in the cross-fibre direction passes through the cell cytoplasms and intercellular membranes. The governing equations for these flows are developed below.
Fibre Direction

Since there is no experimental data for the hydraulic conductivity along a fibre cell, it is derived from what we know about the fluid inside the cell and the shape of the cell. A fibre cell can be idealised as a long tube with an elliptic cross-section. The diameter of major and minor axes are equal to the thickness \( (a) \) and width \( (b) \) of the fibre cell (see Figure 4.13). By assuming the fibre cell is a tube, the fluid flow can be modelled as Poiseuille flow if the fluid velocity is slow and if the cross-section of the tube is constant. It is reasonable to assume the intracellular fluid velocity is slow since we assume the extracellular velocity is slow. Although, the fibre cells do taper between the equator and the poles (Kuszak, Zoltoski & Sivertson 2004), we assume the tapering is gradual and does not add significant error to the Poiseuille flow equation.

Since the fluid flow is assumed to be Poiseuille flow, Equation (4.13) can be used to describe the
mean velocity \((u_{i,f})\) along the fibre cell,

\[ u_{i,f} = -K_{i,f} \frac{\partial p_i}{\partial \eta_f} \tag{4.40} \]

where \(p_i\) is the intracellular pressure \([N/m^2]\) and \(K_{i,f}\), the hydraulic conductivity \([m^4/(N \cdot s)]\) along the fibre cell, is given by

\[ K_{i,f} = \frac{1}{16 \mu} \frac{a^2b^2}{a^2 + b^2} \tag{4.41} \]

where \(\mu\) is the fluid viscosity \([(N \cdot s)/m^2]\), and \(a\) and \(b\), respectively, are the thickness and width of the fibre cell.

**Cross-Fibre Direction**

The fluid flow in the cross-fibre direction passes through cell cytoplasms and membranes (see Figure 4.14a). An element in a model usually contains many cells and it is difficult to discretely model the flow through each cell cytoplasm and membrane in the element. Instead, we homogenise the flow equations to obtain one equation that describes the net flow through the element.

To homogenise the flow equations, we assume the fluid flow is primarily restricted by the membranes. Studies have measured the diffusion between cells to be a hundred time less than in the cell cytoplasm (Cannell et al. 2004). Assuming the fluid experiences the same difference, then the hydraulic resistance between cells is much greater than within cell cytoplasms. In this case, the solute concentrations and pressure within cells would reach equilibrium faster than between adjacent cells, hence the concentration and pressure fields can be assume to be step-functions (see Figure 4.14b). Given the pressure gradient within a cell is small compared to the pressure difference between cells, the fluid flow can be modelled as transmembrane flow that is driven by the pressure and concentration drop across the membrane.

The transmembrane velocity through the intercellular membrane is given by (see Section 4.7),

\[ u_{i,c} = L_p (-\Delta p_i - \sigma_i RT \Delta O_{s_i}) \tag{4.42} \]

where \(\Delta p_i\) and \(\Delta O_{s_i}\) are the pressure \([Pa]\) and osmolarity \([mol/m^3]\) difference between adjacent cells, \(L_p\) is the hydraulic permeability \([m^3/(N \cdot s)]\), \(\sigma\) is the reflectance of the membrane, \(R\) is the
gas constant \([J/(mol.K)]\), and \(T\) is the temperature [K]. The osmolarity is given by

\[
Os_i = \sum_\alpha C_{\alpha i}
\]  

(4.43)

where the subscript \(\alpha\) indicates the solute species and \(i\) indicates the intracellular space.

In the model, the intracellular concentration and pressure fields are continuous fields with continuous gradients. To relate the concentration and pressure gradients to the step-function assumption shown in Figure 4.14b, consider the definition of the concentration and pressure gradients,

\[
\frac{dC_i}{d\eta_c} = \frac{\Delta C_i}{\Delta \eta_c} \quad \text{and} \quad \frac{dp_i}{d\eta_c} = \frac{\Delta p_i}{\Delta \eta_c}.
\]
If $\Delta \eta_c = b$, the distance between cell centers, then

$$\Delta C_i = b \frac{dC_i}{d\eta_c} \quad \text{and} \quad \Delta p_i = b \frac{dp_i}{d\eta_c}.$$  

Substituting these into Equation (4.42) gives the intracellular fluid velocity in terms of continuous concentration and pressure fields,

$$u_{i,c} = b L_p \left( -\frac{dp_i}{d\eta_c} + \bar{\sigma}_i RT \frac{dC_i}{d\eta_c} \right) \quad (4.44)$$

where $\bar{\sigma}$ is the homogenised membrane reflectance.

### 4.8.2 Surface Velocity

At the surface of the lens, fluid is transported between the intracellular space and the outside of the lens via aquaporin channels in the surface membrane. This fluid flow is modelled as transmembrane flow, therefore the transmembrane velocity is given by Equation (4.34),

$$u_{i,c} = -L_s(p_o - p_i) - \sigma_s RT L_s (O_{s_o} - O_{s_i}) \quad (4.45)$$

where $p_o$ and $C_o$ are the pressure and osmolarity outside the lens, $p_i$ and $O_{s_i}$ are the pressure and osmolarity in the intracellular space, and $L_s$ and $\sigma_s$ are the hydraulic permeability and reflectance of the surface membrane. The osmolarities are given by

$$O_{s_i} = \sum_{\alpha} C_{\alpha i} \quad \text{and} \quad O_{s_o} = \sum_{\alpha} C_{\alpha o} \quad (4.46)$$

where the subscript $\alpha$ indicates the solute species and $i$ and $o$ indicates the intracellular space and outside the lens.

This transmembrane velocity is normal to the outer surface and the surface normal is aligned with the cross-fibre direction, hence the transmembrane velocity acts a boundary condition for the intracellular fluid velocity in the cross-fibre direction.
4.8.3 Transmembrane Velocity

The fluid flow between the intracellular and extracellular space is modelled as transmembrane flow (see Section 4.7). The transmembrane fluid velocity \( u_m \) is given by

\[
 u_m = -L_p \Delta p + \sigma_m L_p RT \Delta Os
\]  

(4.47)

where \( L_p \) is the hydraulic permeability \([m^3/(N.s)]\), \( \sigma_m \) is the reflectance of the membrane, \( R \) is the gas constant \([J/(mol.K)]\), and \( T \) is the temperature \([K]\). The pressure difference \( \Delta p \) is given by \( \Delta p = p_e - p_i \) and the osmolarity difference \( \Delta Os \) is given \( \Delta Os = Os_e - Os_i \), where the subscripts \( i \) and \( e \) denote the intracellular and extracellular spaces. The osmolarity is given by

\[
 Os_i = \sum_\alpha C_{\alpha i} \quad \text{and} \quad Os_e = \sum_\alpha C_{\alpha e}
\]  

(4.48)

where the subscript \( \alpha \) indicates the solute species and \( i \) and \( e \) indicates the intracellular and extracellular space. The pressure and concentration is assumed to be spatially constant across the width and height of the cell but not necessarily along the length of the cell.

Since the lens model is a bidomain model, the transmembrane flow is treated as a source term. In this case, the intracellular and extracellular source terms are

\[
 s_i = -\frac{u_m \rho_m}{\Lambda_i}
\]  

(4.49)

\[
 s_e = \frac{u_m \rho_m}{\Lambda_e}
\]  

(4.50)

where \( \rho_m \) is the membrane density \([m^{-1}]\), and \( \Lambda_i \) and \( \Lambda_e \) are the intracellular and extracellular volume fraction. Fluid entering the extracellular space from the intracellular space is considered positive flow, hence the negative sign in Equation (4.49). The derivation of the fluid source terms in relation to the transmembrane velocity is similar to the derivation for the solute source terms described in Section 3.2.2.

4.8.4 Extracellular Velocity

Figure 4.15 shows a block of lens tissue and a magnified view of the extracellular cleft. The fluid flow in the extracellular cleft can be described by the Stokes flow equations, but these equations
can be simplified, making them easier to solve. Mathias (1985a) simplified the two-dimensional Navier-Stokes equations to get one-dimensional fluid flow equations by using dimensional analysis and exploiting the smallness of the ratio between the width and length of the extracellular space. Appendix B covers the application of the same analysis to the three-dimensional Stokes flow equations to get two-dimensional fluid flow equations along the extracellular cleft.

From the dimensional analysis, the simplified Stokes flow equations for the extracellular cleft are

\[
\begin{align*}
\frac{\partial \tilde{u}_{e,f}}{\partial \tilde{\eta}_f} + \frac{\partial \tilde{u}_{e,f}}{\partial \tilde{\eta}_c} &= s_e \quad (4.51) \\
\frac{\partial^2 \tilde{u}_{e,f}}{\partial \tilde{\eta}_f^2} &= \frac{1}{\mu} \frac{\partial p_e}{\partial \tilde{\eta}_f} + \frac{\rho_c(\tilde{\eta}_s)}{\mu} \frac{d\phi_e}{d \tilde{\eta}_f} \quad (4.52) \\
\frac{\partial^2 \tilde{u}_{e,c}}{\partial \tilde{\eta}_c^2} &= \frac{1}{\mu} \frac{\partial p_e}{\partial \tilde{\eta}_c} + \frac{\rho_c(\tilde{\eta}_s)}{\mu} \frac{d\phi_e}{d \tilde{\eta}_c} \quad (4.53)
\end{align*}
\]

where the subscripts \(e\) denotes the extracellular space, \(f\) the fibre directions, \(c\) the cross-fibre direction, and \(s\) the sheet direction, \(\tilde{u}\) is the cleft velocity \([\text{m/s}]\), \(s\) is the fluid source \([\text{m}^{-1}]\), \(p\) is the pressure \([\text{Pa}]\), \(\phi\) is the potential \([\text{V}]\), \(\mu\) is the fluid viscosity \([\text{Pa s}]\), and \(\rho_c\) is the charge density \([\text{C/m}^3]\) (see Section 4.6.1). The dimensional analysis showed that the fluid velocity in the \(\tilde{\eta}_s\) direction is insignificant compared to the \(\tilde{\eta}_f\) and \(\tilde{\eta}_c\) velocities, hence it is assumed to be zero.

Although the extracellular cleft is tortuous, the radius of curvature of the cleft is assumed to be large compared to the cleft width. In this case, the cleft can be assumed to be flat parallel plates allowing the same methods used to derive Couette flow (see Section 4.3) and electro-osmotic flow between parallel plates (see Section 4.6.2) to be used to derive the fluid velocity equations from the

**Figure 4.15:** A magnified view of the lens tissue structure and extracellular cleft. Note: this figure is a copy of Figure 2.4, reproduced for convenience.
momentum equations (Equation (4.52) and 4.53),

\[
\begin{align*}
\tilde{u}_{e,f} &= -\tilde{K}_e \frac{\partial \tilde{p}_e}{\partial \tilde{\eta}_f} + \tilde{k}_e \frac{\partial \tilde{\phi}_e}{\partial \tilde{\eta}_f} \\
\tilde{u}_{e,c} &= -\tilde{K}_e \frac{\partial \tilde{p}_e}{\partial \tilde{\eta}_c} + \tilde{k}_e \frac{\partial \tilde{\phi}_e}{\partial \tilde{\eta}_c}
\end{align*}
\]  
(4.54)

\(\tilde{K}_e\) is the hydraulic conductivity \([m^2/(Pa\,s)]\) and \(\tilde{k}_e\) is the electro-osmotic coefficient \([m^2/(V\,s)]\). The hydraulic conductivity and electro-osmotic coefficient are given by

\[
\tilde{K}_e = \frac{\tilde{h}^2}{12\mu}
\]  
(4.56)

and

\[
\tilde{k}_e = \frac{\varepsilon_r\varepsilon_0\zeta}{\mu}\left(\coth\left(\frac{\tilde{h}}{2\lambda_D}\right) - \frac{2\lambda_D}{\tilde{h}}\right)
\]  
(4.57)

where \(\tilde{h}\) is the cleft width \([m]\), \(\mu\) is the fluid viscosity \([Pa\,s]\), \(\varepsilon_r\) is the dielectric constant of the fluid, \(\varepsilon_0\) is the permittivity of vacuum \([C/(V\,m)]\), \(\zeta\) is the potential at the surface of the membrane, and \(\lambda_D\) is the Debye length. See Section 4.6.2 for more details on the derivation of the hydraulic conductivity and the electro-osmotic coefficient and their associated parameters.

It is more convenient to express and solve the extracellular velocity equations in the same coordinate system as the intracellular velocity equations, the fibre coordinate system. The transformation of equations and parameters between the cleft and fibre coordinate system is described in Section 2.4. The transformations for the velocity vectors, which can be derived by following the derivation in Section 2.4.4, are

\[
\begin{align*}
\tilde{u}_{e,f} &= \frac{1}{\xi_f} \tilde{u}_{e,f} \quad \text{and} \quad \tilde{u}_{e,c} = \frac{1}{\xi_c} \tilde{u}_{e,c}
\end{align*}
\]

where \(\xi\) is the wiggle factor (see Section 2.4.1). The transformations for the pressure and potential gradients, which can be derived by following the derivation in Section 2.4.2, are

\[
\begin{align*}
\frac{dp_e}{d\tilde{\eta}_f} &= \frac{1}{\xi_f} \frac{dp_e}{d\eta_f} \quad \frac{dp_e}{d\tilde{\eta}_c} = \frac{1}{\xi_c} \frac{dp_e}{d\eta_c} \\
\frac{d\phi_e}{d\tilde{\eta}_f} &= \frac{1}{\xi_f} \frac{d\phi_e}{d\eta_f} \quad \frac{d\phi_e}{d\tilde{\eta}_c} = \frac{1}{\xi_c} \frac{d\phi_e}{d\eta_c}
\end{align*}
\]
Substituting these transformations into Equations (4.54) and (4.55) gives

\[ u_{e,f} = -\tilde{K}_e \tau_f \frac{d\phi_e}{d\eta_f} + \tilde{k}_e \tau_f \frac{d\phi_e}{d\eta_f} \tag{4.58} \]

\[ u_{e,c} = -\tilde{K}_e \tau_c \frac{d\phi_e}{d\eta_c} + \tilde{k}_e \tau_c \frac{d\phi_e}{d\eta_c} \tag{4.59} \]

where \( \tau \) is the tortuosity (see Section 2.4.1). The hydraulic conductivity and electro-osmotic coefficient remain untransformed and are defined by Equations (4.56) and (4.57). These parameters can be transformed by replacing the cleft width \( \tilde{h} \) with the relationship for the effective cleft width \( h \) (Equation (2.6)). Since the cleft width \( \tilde{h} \) is an experimentally measured property, it is more convenient to keep the parameters in this form.

### 4.8.5 Conservation of Mass

Mass needs to be conserved in both the intracellular and the extracellular space. The general conservation of mass equation from the Stokes flow equations (see Section 4.2) is

\[ \nabla \cdot \mathbf{u} = s \tag{4.60} \]

where \( \mathbf{u} \) is the fluid velocity vector and \( s \) is the fluid source term.

From the dimensional analysis covered in Appendix B, the conservation of mass equation for the extracellular space is

\[ \frac{\partial \tilde{u}_{e,f}}{\partial \tilde{\eta}_f} + \frac{\partial \tilde{u}_{e,c}}{\partial \tilde{\eta}_c} = s_e \tag{4.61} \]

where the subscripts \( e \) denotes the extracellular space, \( f \) the fibre directions, and \( c \) the cross-fibre direction, \( \tilde{u} \) is the cleft velocity \([m/s]\), \( s \) is the extracellular fluid source \([m^{-1}]\).

This equation, which is defined in terms of the cleft coordinate system, can be transformed to the fibre coordinate system according to the derivations in Section 2.4. The transformations for the velocity gradients are,

\[ \frac{d\tilde{u}_{e,f}}{d\tilde{\eta}_f} = \frac{1}{\xi_f} \frac{d\tilde{u}_{e,f}}{d\eta_f} \]

\[ \frac{d\tilde{u}_{e,c}}{d\tilde{\eta}_c} = \frac{1}{\xi_c} \frac{d\tilde{u}_{e,c}}{d\eta_c} \]
where $\xi$ is the wiggle factor (see Section 2.4.1). Substituting these into Equation (4.61) gives

$$\frac{1}{\xi_f} \frac{\partial \tilde{u}_{e,f}}{\partial \eta_f} + \frac{1}{\xi_c} \frac{\partial \tilde{u}_{e,c}}{\partial \eta_c} = s_e$$  \hspace{1cm} (4.62)

The transformations for the velocity vectors are,

$$\tilde{u}_{e,f} = \xi_f u_{e,f} \quad \text{and} \quad \tilde{u}_{e,c} = \xi_c u_{e,c}$$

Substituting these into Equation (4.62) gives

$$\frac{\partial u_{e,f}}{\partial \eta_f} + \frac{\partial u_{e,c}}{\partial \eta_c} = s_e \quad \text{or} \quad \nabla \cdot u_e = s_e$$  \hspace{1cm} (4.63)

where $u_e$ is the extracellular fluid velocity vector and $s_e$ is the extracellular fluid source term. The source term is unchanged by the transformation.

The conservation of mass equation for the intracellular space is (from Equation (4.5))

$$\nabla \cdot u_i = s_i$$  \hspace{1cm} (4.64)

where $u_i$ is the extracellular fluid velocity vector and $s_i$ is the extracellular fluid source term.

Equations (4.64) and (4.63) are integrated over the intracellular space and the extracellular space, respectively, with the intracellular and extracellular source terms (Equations (4.49) and (4.50)) substituted to give

$$\int_{V_i} \nabla \cdot u_i \, dV_i = \int_{V_i} s_i \, dV_i$$  \hspace{1cm} (4.65)

$$\int_{V_e} \nabla \cdot u_e \, dV_e = \int_{V_e} s_e \, dV_e$$  \hspace{1cm} (4.66)

where the subscripts $i$ and $e$ denote the intracellular and extracellular spaces, $u$ is the fluid velocity vector, $V$ is the volume and $s$ is the fluid source.

The previous chapter on solute transport and this chapter on fluid dynamics, derives the solute and fluid transport equations for the lens. The next chapter describes how these transport equations are solved, using finite volume methods, on a meshed domain.
5 Numerical Methods

Chapters 3 and 4 cover the derivation of the governing equations for the solute and fluid transport in the lens. This chapter covers the numerical methods used to solve these equations over a domain representing the lens. The development of the numerical framework to solve the lens model started by using the simplest finite volume methods, which proved to be sufficient. Only the Euler method was modified to include adaptive time-stepping in order to reduce the solution time of the model. Although the framework is sufficient for solving the lens model, further developments are required to improve the efficiency and accuracy of the solution algorithm.

The chapter is divided into five sections. Section 5.1 covers the meshing procedure. Section 5.2 describes the discretisation of equations and the approximation of field values and gradients using finite volume methods. Sections 5.3 and 5.4 cover the solution methods for static and time-dependent problems, respectively. Finally, Section 5.5 describes the solution algorithm for solving the coupled solute and fluid transport equations.

5.1 Meshing

The meshes in this project are limited to two dimensions. The one-dimensional model of the lens is represented by a single row of two-dimensional elements. A mesh is generated in two steps: the first step involves generating a two-dimensional mesh of the domain; the second step effectively extrudes the mesh about the x-axis and calculates the axisymmetric properties of the mesh. These properties include the face center, normal and area, and the element center and volume.

The discretised units of a finite volume mesh are usually called "control volumes" or "cells" but the terms "volume" and "cell" are often used in biological systems, which may lead to some confusion, therefore the discretised units of a mesh are called "elements" in this project.
5.1.1 Mesh Generation

The template mesh is generated using a meshing program called Gmsh. Gmsh provides tools to define the geometry of a domain, which can then be meshed using one-, two- and three-dimensional elements. The standard elements for a two-dimensional mesh are triangles and for a three-dimensional mesh are tetrahedrals, but other element types are available. Gmsh also allows a solver to be linked through a socket and offers post-processing tools and plugins. For more detail on Gmsh and its capabilities, see the Gmsh website (www.geuz.org/gmsh) for documentation and tutorials.

Appendix D lists the .geo files that Gmsh reads to generate the geometry of the domain. The domain can then be meshed and saved to a file. Gmsh outputs a mesh as a list of nodes with their locations, and list of elements, where each element is defined by a list of nodes.

5.1.2 Mesh Extrusion

The one- and two-dimensional models of the lens are assumed to be symmetric about the $x$-axis. To capture this symmetry in the model, the mesh is extruded about the $x$-axis by an angle $\theta_e$. In the extrusion, the two-dimensional faces and elements in the mesh become three-dimensional. To ensure both the face centers and normals, and the element centers are localised to the $x$-$y$ plane, the mesh is extruded by half $\theta_e$ above and below the $x$-$y$ plane (see Figure 5.1).

![Figure 5.1: Extrusion of a face by sweeping the line representing the face about the $x$-axis by an angle $\Delta \theta_{pp}$. The area face is calculated by integrating infinitesimal area elements ($dA$) of the face.](image.png)

Finite volume methods and the modelling framework require knowledge of the face centers, normals and areas, and the element centers and volumes. The equations used to calculate these properties are covered below.
5.1.3 Face Center, Normal and Area

A three-dimensional face is created by extruding a two-dimensional face from the mesh about the $x$-axis (see Figure 5.1). Since the face is extruded by $\theta_{pp}/2$ above and below the $x$-$y$ plane, the face center and face normal lie in the $x$-$y$ plane, hence we can ignore the $z$ direction.

A two-dimensional face is defined by two nodes whose coordinates are $[x_1, y_1]$ and $[x_2, y_2]$, where the subscript indicates the local node number. The axis along the length of the face is defined as the $s$-axis. The length of the line ($\Delta s$) is given by

$$\Delta s = \sqrt{\Delta x^2 + \Delta y^2}$$

where $\Delta x = x_2 - x_1$ and $\Delta y = y_2 - y_1$.

The face area can be calculated by integrating infinitesimal area elements ($dA$) between 0 and $\Delta s$ (see Figure 5.1),

$$A_f = \int_0^{\Delta s} dA = \Delta c \Delta s \left( \frac{y_1 + y_2}{2} \right)$$

The center of mass principal is used to calculate the face center,

$$x_f = \frac{1}{A_f} \int_0^{\Delta s} x \, dA = x_1 + \frac{\Delta x}{3} \left( \frac{y_1 + 2y_2}{y_1 + y_2} \right)$$

$$y_f = \frac{1}{A_f} \int_0^{\Delta s} y \, dA = y_1 + \frac{\Delta y}{3} \left( \frac{y_1 + 2y_2}{y_1 + y_2} \right)$$

The face normal is the normalised vector perpendicular line, which is given by

$$n_x = \frac{-\Delta y}{\sqrt{\Delta x^2 + \Delta y^2}} \quad n_y = \frac{\Delta x}{\sqrt{\Delta x^2 + \Delta y^2}}$$
5.1.4 Element Center and Volume

Each element in the mesh is extruded about the $x$-axis, where the center and volume of the extruded element is calculated (see Figure 5.2a). The element created when extruding a two-dimensional face about the $x$-axis is called the face-element (see Figure 5.2b). The center and volume of the face-element is needed to calculate the center and volume of an element from the mesh.

![Figure 5.2: Extrusion of an element about the $x$-axis (a). The nodes are labelled $k = 1$ to $4$ in a clockwise sequence. Face 3-4 is extruded about the $x$-axis to obtain the face-element (b). The face-element is divided into infinitesimal volume elements ($dV_s$), which are integrated to determine the total volume of the face-element. The face-elements for the faces in the element are summed to determine the total volume of the element.](image)

The equation for the line representing the face is

$$y = \frac{\Delta y}{\Delta x} x + y_1 - \frac{\Delta y}{\Delta x} x_1$$  \hspace{1cm} (5.1)

where $\Delta x = x_2 - x_1$ and $\Delta y = y_2 - y_1$. The volume of an infinitesimal slice transverse to the $x$-axis is

$$V_s = \frac{\Delta \theta_e}{2} y^2 dx$$

and the center of mass is,

$$x_s = x \quad \text{and} \quad y_s = \frac{2}{3} y$$

The volume of the face-element is given by integrating volumes of the infinitesimal slices ($dV_s$) between $x_1$ and $x_2$,

$$V_{fe} = \frac{\Delta \theta_e}{2} \int_{x_1}^{x_2} y^2 dx$$  \hspace{1cm} (5.2)
Substituting Equation (5.1) into Equation (5.2) and integrating gives

\[ V_{fe} = \frac{\Delta \theta_e \Delta x}{6} (y_1^2 + y_1 y_2 + y_2^2) \]

The center of the face-element is calculated by using the center of mass principal,

\[
\begin{align*}
  x_{fe} &= \frac{\int_{x_1}^{x_2} x \frac{\Delta \theta_e}{2} y^2 \, dx}{\int_{x_1}^{x_2} \frac{\Delta \theta_e}{2} y^2 \, dx} = \frac{\int_{x_1}^{x_2} x y^2 \, dx}{\int_{x_1}^{x_2} y^2 \, dx} \\
  y_{fe} &= \frac{\int_{x_1}^{x_2} \frac{2}{3} y \frac{\Delta \theta_e}{2} y^2 \, dx}{\int_{x_1}^{x_2} \frac{\Delta \theta_e}{2} y^2 \, dx} = \frac{2 \int_{x_1}^{x_2} y^3 \, dx}{3 \int_{x_1}^{x_2} y^2 \, dx}
\end{align*}
\]

(5.3) \hspace{1cm} (5.4)

Substituting Equation (5.1) into Equations (5.3) and (5.4) and integrating gives

\[
\begin{align*}
  x_{fe} &= \frac{(3 x_2 + x_1) y_2^2 + (2 x_2 + 2 x_1) y_1 y_2 + (x_2 + 3 x_1) y_1^2}{4 (y_2^2 + y_1 y_2 + y_1^2)} \\
  y_{fe} &= \frac{(2 y_1 + \Delta y) (2 y_1^2 + 2 \Delta y y_1 + \Delta y^2)}{2 (3 y_1^2 + 3 \Delta y y_1 + \Delta y^2)}
\end{align*}
\]

(5.5) \hspace{1cm} (5.6)

The element volume is calculated by summing the volumes created by sweeping each face bounding the element. The sequence of nodes defining the element are sequential in the clockwise direction. The volume of the element is given by,

\[ V_e = \sum_{k=1}^{n-1} V_{fe}(k, k+1) + V_{fe}(n, 1) \]

where \( k \) is the node number and \( n \) is the number of nodes in the element. The numbers in the brackets define the node numbers of the face.

The element center is calculated using the center of mass principal,

\[
\begin{align*}
  x_e &= \frac{1}{V_e} \left( \sum_{k=1}^{n-1} (x_{fe}(k, k+1) V_{fe}(k, k+1)) + x_{fe}(k, k+1) V_{fe}(n, 1) \right) \\
  y_e &= \frac{1}{V_e} \left( \sum_{k=1}^{n-1} (y_{fe}(k, k+1) V_{fe}(k, k+1)) + y_{fe}(k, k+1) V_{fe}(n, 1) \right)
\end{align*}
\]
5.2 Finite Volume Methods

The aim of finite volume methods (FVM) is to ensure that the integral of a conservation equation is satisfied over a domain. It does so by discretising the conservation equation and the domain using numerical techniques, and then ensuring the integral of the discretised equation is satisfied for each element in the discretised domain (mesh). This section covers the basic theory of finite volume methods that is used to develop the model of the lens. Much of what is covered in the section is summarised from Ferziger & Peric (1997) and Versteeg & Malalasekera (1995).

Consider the integral of a generic equation for the conservation of a field \( \phi \) over a domain \( \Omega \),

\[
\int_{\Omega} \nabla \cdot (\phi \mathbf{v}) \, d\Omega = \int_{\Omega} \nabla \cdot (\Gamma \nabla \phi) \, d\Omega + \int_{\Omega} q_\phi \, \Omega \tag{5.7}
\]

where \( \mathbf{v} \) is the velocity vector, \( \Gamma \) is the diffusion coefficient and \( q_\phi \) is the source term. The first term describes the advection of \( \phi \), the second term the diffusion of \( \phi \) and the third term the source of \( \phi \).

The divergence terms, the first and second terms, can be reduced to surface integral using the Gauss divergence theorem to give,

\[
\oint_{S} \phi \mathbf{v} \cdot \mathbf{n} \, dS = \oint_{S} \Gamma \nabla \phi \cdot \mathbf{n} \, dS + \int_{\Omega} q_\phi \, \Omega \tag{5.8}
\]

where \( \mathbf{n} \) is the normal vector to the surface \( S \).

Each term in Equation (5.8) needs to be discretised so that the equation can be applied to the elements in the mesh. The discretised form of Equation (5.8) is

\[
\sum_{f} \phi_f \mathbf{v}_f A_f = \sum_{f} \Gamma \nabla \phi_f A_f + q_{\phi,e} V_e \tag{5.9}
\]

where \( f \) is the index of the face, \( \phi_f \) is the potential values at the face, \( \nabla \phi_f \) is the potential gradient normal to the face, \( q_{\phi,e} \) is the element potential source, \( \mathbf{v}_f \) is the velocity normal to the face, \( A_f \) is the area of face, and \( V_e \) is the volume of the element. The discretisation of this equation assumes the face properties are spatially constant over the area of the face, and the element source term is spatially constant through the element.

In finite volume methods, the field values (\( \phi_e \)) are stored at the element centers. This means the potential values (\( \phi_f \)) and gradients (\( \nabla \phi_f \)) at the face need to be approximated from the potential
values ($\phi_v$) at the center of the elements. In this project, linear interpolation methods are used to approximate these.

### 5.2.1 Linear Interpolation

A simple linear interpolation method is used to approximate the potential value ($\phi_f$) and gradient ($\nabla \phi_f$) at the face center. The scheme assumes the potential varies linearly between the centers of the elements (see Figure 5.3).

![Linear interpolation scheme on an orthogonal grid.](image)

The linear approximation of the field value ($\phi_f$) at the face center in the orthogonal grid shown in Figure 5.3, is,

$$
\phi_f \approx (1 - \xi) \phi_1 + \xi \phi_2
$$

(5.10)

where $\phi_f$ is the potential value at face center, $\phi_1$ and $\phi_2$ are the potential values at the center of elements 1 and 2. The interpolation factor $\xi$ is given by

$$
\xi = \frac{\Delta x_{1f}}{\Delta x_{1f} + \Delta x_{2f}}
$$

where $\Delta x_{1f}$ is the distance between the center of element 1 and face center, and $\Delta x_{2f}$ is the distance between the center of element 2 and the face center.

Using the same linear approximation, the potential gradient ($\nabla \phi_f$) at the face center can be calcu-
\[ \nabla \phi_f \approx \frac{\phi_2 - \phi_1}{\Delta x_{12}} \]  

(5.11)

where \( \Delta x_{12} \) is the distance between the centers of elements 1 and 2.

The mesh used in the two-dimensional lens models is non-orthogonal (Figure 5.4a). However, we assume the divergence from orthogonality is small such that Equations (5.10) and (5.11) can still be used to approximate the field values and gradients. In this case, the lines between the element centers and face center are not colinear, and the field gradient \( (\nabla \phi_f) \) is calculated at a location away from the face center. Also, the direction of the gradient value diverges away from the face normal \( (n) \).

![Figure 5.4: Linear interpolation (a) and an alternative linear interpolation (b) schemes on a non-orthogonal grid.](image)

An alternative linear interpolation scheme is used to determine more accurate approximation of the field values and gradients at the face centers (see Figure 5.4b). This interpolation scheme has a larger the template, or footprint, for calculating the field values and gradients. Using Equation (5.10), the field value at locations \( A \) and \( B \) are calculated by interpolating the values between the element centers 1 and 3, and 2 and 4, respectively. The locations of \( A \) and \( B \) are calculated such that the line segment between locations \( A \) and \( B \) intersects the face center and is normal to
the face. Using the potential values $\phi_A$ and $\phi_B$, the field value at the face center ($\phi_f$) is given by,

$$\phi_f \approx (1 - \xi) \phi_A + \xi \phi_B \quad (5.12)$$

The interpolation factor $\xi$ is given by

$$\xi = \frac{\Delta x_{Af}}{\Delta x_{Af} + \Delta x_{Bf}}$$

where $\Delta x_{Af}$ and $\Delta x_{Bf}$ are the distances between the face center and locations $A$ and $B$, respectively.

The potential gradient is given by

$$\nabla \phi_f \approx \frac{\phi_B - \phi_A}{\Delta x_{AB}} \quad (5.13)$$

where $\Delta x_{AB}$ is the distance between locations $A$ and $B$.

The lens model is solved to steady-state using the linear interpolation scheme given by Equations (5.10) and (5.11). At steady-state the alternative linear interpolation scheme is used to calculate the field values and gradients at the face centers. These are compared to the values calculated during the solution of the model, to determine the error introduced by the near-orthogonal assumption. This is discussed in Chapter 8 on the two-dimensional model, and the assumption does not influence the one-dimensional model since the element centers are colinear.

**Boundary Conditions**

The boundary conditions in the lens model are defined as fixed field values at the centers of the boundary faces (see Figure 5.5). Since the boundary value is defined at the face center, there is no need to interpolate the value at the element center to the face, but the field gradient would need to be approximated. The field gradient at a boundary face center is approximated by,

$$\nabla \phi_{bc} \approx \frac{\phi_1 - \phi_{bc}}{\Delta x} \quad (5.14)$$

where $\phi_{bc}$ is the field value at the boundary, $\phi_1$ is the field value at the element center, $\Delta x$ is the distance between the element center and face center at the boundary.
Like the approximation of field gradients at faces between two elements, the divergence of the mesh from being orthogonal is assumed to be small. This is the case at the boundaries of the two-dimensional mesh for the lens model. Further developments are required to implement approximation methods that work for more general cases.

### 5.3 Solving Static Problems

This section described the process of solving a static problem by solving a model of the fluid flow through a tube. A similar model is covered in Appendix C.3, where the results from the model are compared to an analytic solution. Figure 5.6 shows a tube with a circular cross section.

The tube has a length $L = 2 \text{ m}$ and radius $r = 50 \text{ mm}$. There is no flow through the left boundary, i.e., the fluid velocity is fixed at $0 \text{ m/s}$ and at the right boundary, the pressure is fixed at $0 \text{ Pa}$.

The fluid flow through the tube is assumed to be Poiseuille flow (see Section 4.4), where the mean
5.3 Solving Static Problems

fluid velocity is given by,

\[ \bar{u} = -K \frac{dp}{dx} \]  
(5.15)

where \( K \), the hydraulic conductivity, is

\[ K = \frac{r^2}{8\mu} \]  
(5.16)

where \( \mu \) is the viscosity of the fluid (\( \mu = 0.7 \times 10^{-3} \text{ Pa s} \)).

The wall of the tube is permeable, where fluid flows into the tube with a velocity \( u_m \), which is dependent on the location along the tube \( x \),

\[ u_m = L_p x \]  
(5.17)

where \( L_p = 1 \times 10^{-3} \text{ s}^{-1} \) is the hydraulic permeability of the wall.

Discretisation the Domain

The tube is discretised into three elements, where the center of the element is \( x_e \). For all elements, the length is \( \Delta x \), the surface area of the face is \( \Delta A_f \), the surface area of the wall is \( \Delta A_w \), and the volume is \( \Delta V_e \).

Conservation of Mass

The conservation of mass equation is required to ensure continuity over the domain and in each element,

\[ \int_V \nabla \cdot u \, dV + \int_V s_w \, dV = 0 \]  
(5.18)

where \( s_w \) is the volume source. The volume integral of the divergence term can be reduced to a surface integral using the Gauss divergence theorem,

\[ \oint_A u \cdot n \, dA + \int_V s_w \, dV = 0 \]  
(5.19)
where \( \mathbf{n} \) is the face normal. The discretised form of Equation (5.19) is

\[
\sum_{f} u_{f} \Delta A_{f} + s_{w} \Delta V_{e} = 0
\]

(5.20)

where \( u_{f} \) is the fluid velocity normal to the face, \( \Delta A_{f} \) is the area of the face, and \( \Delta V_{e} \) is the volume of the element.

The velocity through the wall is treated as a volume source \( (s_{w}) \),

\[
s_{w} = u_{m} \frac{\Delta A_{w}}{\Delta V_{e}} = \frac{2 u_{m}}{r}
\]

(5.21)

where \( \Delta A_{w} \) is the wall surface area for the element, and \( \Delta V_{e} \) is the volume of the element.

Equation (5.20) is applied to each element in the discretised tube to ensure mass is conserved in the whole tube. The application of the equation to each element forms a row in a system of linear equations, which can be solved to determine the element pressures.

**Conservation of Mass in Elements**

**Element 1** is bounded by two faces: 1 and 2. Applying the conservation of mass equation (Equation (5.20)) to element 1 gives,

\[
u_{1} \Delta A_{f} - u_{2} \Delta A_{f} + s_{w} \Delta V_{e} = 0
\]

(5.22)

where the fluid entering the element is positive volume flow. The fluid velocity through face 1 is a fixed boundary condition with a value \( u_{bc} \) and the velocity though face 2 is governed by Poiseuille flow (Equation (5.15)),

\[
u_{1} = u_{bc}
\]

(5.23)

\[
u_{2} = -K \frac{p_{2} - p_{1}}{\Delta x}
\]

(5.24)

where the pressure gradient in Equation (5.15) is approximated by a linear function (see Section 5.2.1). Substituting the terms for the face velocities into the conservation of mass equation for
5.3 Solving Static Problems

Element 1 (Equation (5.22)) gives

\[ u_{bc} \Delta A_f + K \frac{p_2 - p_1}{\Delta x} \Delta A_f + s_w \Delta V_e = 0 \]  

(5.25)

**Element 2** is bounded by two faces: 2 and 3. Applying the conservation of mass equation (Equation (5.20)) to element 2 gives

\[ u_2 \Delta A_f - u_3 \Delta A_f + s_w \Delta V_e = 0 \]  

(5.26)

The fluid velocity through face 2 and 3 are governed by Poiseuille flow (Equation (5.15)), therefore

\[ u_2 = -K \frac{p_2 - p_1}{\Delta x} \]  

(5.27)

\[ u_3 = -K \frac{p_3 - p_2}{\Delta x} \]  

(5.28)

Substituting these into Equation (5.26) gives

\[ -K \frac{p_2 - p_1}{\Delta x} \Delta A_f + K \frac{p_3 - p_2}{\Delta x} \Delta A_f + s_w \Delta V_e = 0 \]  

(5.29)

**Element 3** is bounded by two faces: 3 and 4. Applying the conservation of mass equation (Equation (5.20)) to element 3 gives

\[ u_3 \Delta A_f - u_4 \Delta A_f + s_w \Delta V_e = 0 \]  

(5.30)

The fluid velocity through face 3 and 4 are governed by Poiseuille flow (Equation (5.15)), therefore

\[ u_3 = -K \frac{p_3 - p_2}{\Delta x} \]  

(5.31)

\[ u_4 = -K \frac{p_{bc} - p_3}{0.5 \Delta x} \]  

(5.32)

Substituting these into Equation (5.26) gives

\[ -K \frac{p_3 - p_2}{\Delta x} \Delta A_f + K \frac{p_{bc} - p_3}{0.5 \Delta x} \Delta A_f + s_w \Delta V_e = 0 \]  

(5.33)
Assembly of $A p = b$

Equation (5.25), (5.29) and (5.33) each form a row in a system of linear equations, where the coefficients multiplying the pressure term are assembled into the $A$ matrix, and the terms that are independent of pressure form the RHS vector $b$. The assembled system is,

$$
A p = b
$$

$$
\begin{bmatrix}
-\frac{K}{\Delta x} A_f & \frac{K}{\Delta x} A_f & 0 \\
\frac{K}{\Delta x} A_f & -2 \frac{K}{\Delta x} A_f & \frac{K}{\Delta x} A_f \\
0 & \frac{K}{\Delta x} A_f & -3 \frac{K}{\Delta x} A_f
\end{bmatrix}
\begin{bmatrix}
-p \\
-2 \frac{K}{\Delta x} A_f - s_w A_f
\end{bmatrix}
$$

Solution of $A p = b$

The system of linear equations can be solved using a standard solver. An LU decomposition solver (DGESV routine from the LAPACK library) is used to solve the conservation of mass and conservation of charge (electroneutrality) equations for the lens model.

The solved pressure field from the system of linear equations is shown in Figure 5.7 with the analytic solution for the pressure. These pressures are substituted in the velocity equations (Equation (5.24), (5.28) and (5.32)) to determine the velocity field, which is shown in Figure 5.8 with the analytic solution for the velocity. The results show the convergence of the solution as the resolution of the mesh increases, especially in the pressure field.

The analytic solutions for the velocity and pressure in the tube are

$$
\begin{align*}
    u(x) &= \frac{L_p x^2}{r} \\
p(x) &= \frac{-L_p x^3}{3 r K} + \frac{L_p L^3}{3 r K}
\end{align*}
$$

5.4 Adaptive Euler Method

The time-dependent component of the lens model is the rate of change of the solute concentrations. A solution method is required to step the concentration field in the model through time until they converge.
The rate of change of the concentrations depend on the solute concentration fields, potential fields and fluid velocity, \( i.e., \frac{dC}{dt} = f(C, \phi, u) \). The potential field depends on the concentration fields and fluid velocity, \( i.e., \phi = f(C, u) \). The fluid velocity depends on the concentration fields and potential field, \( i.e., u = f(C, \phi) \). Hence we end up with a highly non-linear coupled system. This limits the number of solution methods that can be used to solve the lens model to explicit, predictor-corrector and iterative methods.

The difference between these methods is the stability, accuracy, efficiency and complexity of the method. Since we are only interested in the steady-state solution of the lens model (at this stage), the accuracy of the solution method is not crucial, but the stability and efficiency are. Furthermore, we wanted an easy method to implement.
The first solution method applied to the lens model was the Euler method (Press, Flannery, Teukolsky & Vetterling 1989). Given the rate of change of concentration \( \frac{dC^n}{dt} \) at a given iteration \( n \), the Euler method increments the current concentration \( C^n \) by the amount it would change in a given time interval \( \Delta t \), to obtain the concentration \( C^{n+1} \) at the next iteration \( n + 1 \),

\[
C^{n+1} = C^n + \frac{dC^n}{dt} \Delta t
\]

(5.35)

This method is sufficient for simple problems, but for the lens model the method required a small time-step at the start of the solution process to maintain stability, which resulted in long solution times. Near the converged solution, the lens model could cope with larger time-steps without any instabilities. This led to the modification of the Euler method to include an adaptive component, resulting in the adaptive Euler method.

The adaptive Euler method uses the Euler method to take one full time-step and two half time-steps to obtain two concentration fields \( C^{n+1,a} \) and \( C^{n+1,b} \) at the next time-step,

\[
C^{n+1,a} = C^n + \frac{dC^n}{dt} \Delta t
\]

\[
C^{n+1/2} = C^n + \frac{dC^n}{dt} \frac{\Delta t}{2}
\]

\[
C^{n+1,b} = C^{n+1/2} + \frac{dC^{n+1/2}}{dt} \frac{\Delta t}{2}
\]

The RMS difference between the two concentration fields is calculated by,

\[
\Delta C_{rms} = \sqrt{(C^{n+1,a} - C^{n+1,b})^2}
\]

(5.36)

If the Root-Mean-Squared (RMS) difference is less than a specified tolerance \( \Delta C_{rms} < Tol \), the concentration field is accepted \( C^{n+1} = C^{n+1,b} \) for the next iteration. If the RMS difference is less than half the tolerance, time-step size is doubled for the next iteration. If the RMS difference is greater than the specified tolerance \( \Delta C_{rms} > Tol \), the time-step size is halved and the adaptive Euler iteration is repeated without updating the current solution \( C^n \).

The time-step can be adjusted between iterations using more predictive methods, but the description of the adaptive Euler method above covers the basic concepts.
The next section describes how the methods described in this chapter are drawn together to form the modelling framework to solve a coupled model of the solute and fluid transport in the lens.

### 5.5 Solution Algorithm for a Coupled Model

The modelling code draws together the finite volume methods and solution methods to develop a modelling framework designed to solve the coupled solute and fluid transport equations on a meshed domain. Although the equations described in this thesis are specific to the lens, other transport equations can be integrated into the framework. It is designed to be flexible enough to allow new models to be added and existing models can be extended.

The solution algorithm uses the adaptive Euler method to solve the model until a converged steady-state solution is reached. Each iteration of the adaptive Euler method involves seven steps to solve the coupled transport equations, followed by a solution update step (see Figure 5.9).

The model begins with a mesh of the domain, the initial conditions \((C_0^\alpha, \phi^0)\) and boundary conditions \((C_{\alpha o}, \phi_o, p_o)\). Ideally, one would start with initial concentration fields that are close to the expected final concentration fields. In the case where this is unknown, the alternative is to start with concentration fields that sum to an electrically neutral system, and that minimise the transmembrane osmotic gradient. It is sufficient to assume the initial potential field is zero, which influences the first calculation of the pressure field and fluid velocity field. The correct potential field, which is calculated in step 4, is crucial for the subsequent calculation of the solute fluxes and solute sources. Solution fields that exist at the start of an iteration are called "current" and are denoted by the superscript "n"; while solution fields that are computed during the iteration are called "new" and are denoted by the superscript "n+1".

**Step 1:** Solves the conservation of mass equation (Equations (4.65) and (4.66)) to determine the pressure \((p^{n+1})\). The current concentration fields \((C^{n}_\alpha)\) and the current potential fields \((\phi^n)\) are substituted into the fluid velocity equations (Equations (4.40), (4.44), (4.45), (4.58) and (4.59)), and fluid source equations (Equations (4.49) and (4.50)), which are then substituted into the conservation of mass equation. This forms a system of linear equations where the pressure field is the unknown \((A \ p = b)\). This is solved as a static problem to determine the new pressure field \((p^{n+1})\). Section 5.3 covers the solution process of a similar problem.
Step 2: The current concentration fields ($C^n_\alpha$), current potential field ($\phi^n$) and new pressure field ($p^{n+1}$) are used to calculate the new fluid velocity field ($u^{n+1}$) (Equations (4.40), (4.44), (4.45), (4.58) and (4.59)).

Step 3: The current concentration fields ($C^n_\alpha$), current potential field ($\phi^n$) and new pressure field ($p^{n+1}$) are used to calculate the new fluid sources ($s^{n+1}$) (Equations (4.49) and (4.50)).

Step 4: The current concentration fields ($C^n_\alpha$) and new fluid velocity field ($u^{n+1}$) are substituted into the solute flux equations (Equations (3.17), (3.18), (3.19), (3.23), (3.24), (3.29) and (3.30)) and solute source equations (Equations (3.25) and (3.26)), which are then substituted into the

---

Figure 5.9: Solution algorithm for the solute and fluid transport equations of the lens model.
weak form of the electroneutrality equation (Equations (3.31) and (3.32)). This forms a system of linear equations where the potential field is the unknown ($A \phi = b$). This is solved as a static problem to determine the new potential field ($\phi^{n+1}$). Section 5.3 covers the solution process of an analogous problem where the pressure, velocity and fluid source variables can be considered to be the potential, solute flux and solute source terms, respectively.

**Step 5:** The current concentration fields ($C_n^\alpha$), new potential field ($\phi^{n+1}$) and new velocity field ($u^{n+1}$) are used to calculate the new solute fluxes ($j^{n+1}_\alpha$) (Equations (3.17), (3.18), (3.19), (3.23), (3.24), (3.29) and (3.30)).

**Step 6:** The current concentration fields ($C_n^\alpha$), new potential field ($\phi^{n+1}$) and new velocity field ($u^{n+1}$) are used to calculate the new solute sources ($s^{n+1}_\alpha$) (Equations (3.25) and (3.26)).

**Step 7:** The new solute flux ($j^{n+1}_\alpha$) and solute source values ($s^{n+1}_\alpha$) are substituted into the rate of change of concentration equations (Equations (3.36) and (3.37)) to calculate $dC^{n+1}_\alpha/dt$. These values are used in the adaptive Euler time-stepping method to determine the new concentration fields ($C^{n+1}_\alpha$).

Steps 1 to 7 are encapsulated in the adaptive Euler time-stepping method, which solves the coupled system of equations until the convergence criteria is met. In the lens models, the convergence criteria required that the rate of change of concentration ($dC_\alpha/dt$) in all elements be less than a set limit.

This concludes a series of chapters, which have defined the coordinate systems, derived solute and fluid transport equations, and described the numerical methods and solution algorithm required to solve the lens models. Now, we can start developing the lens models, beginning with next chapter, which reviews the literature for properties required for the lens models.
6 Model Properties

The lens model is a mathematical approximation of the real lens. The quality of the predictions from the model depends on the accuracy of our mathematical approximation of the lens physiology, which includes the geometry, cell structure and the transport of solutes and fluid.

This chapter covers the physiological properties that are required for the lens model. The lens model includes 22 solute flux and fluid velocity equations, 6 conservation equations (conservation of mass, charge and concentration in the intracellular and extracellular spaces) and 28 key model parameters for the lens. Many model parameters are derived from other parameters; for example, the membrane density depends on cell dimensions and tortuosity, and the hydraulic conductivity along a fibre cell depends on the cell dimensions and fluid viscosity.

Section 6.1 covers the structure of the lens, detailing the geometry of the lens and structure of the cells. Sections 6.2 and 6.3 cover the properties relating to the transport of solutes and fluid in the lens, respectively. And Section 6.4 reviews the literature for experimentally measured and theoretically predicted properties of the lens that can be compared with those predicted by the lens models (electrical potential, solute concentrations, solute fluxes and fluid flow).
6.1 Lens Structure

The lens structure has a strong influence on the solute and fluid transport in the lens. Key structural properties required for the lens models include:

- lens geometry ($r_{eq}$, $r_{ap}$, $r_{pp}$)
- fibre cell angles ($\gamma_f$)
- fibre cell dimensions ($a$, $b$)
- tortuosity ($\tau$)
- extracellular cleft width ($h$)
- membrane density ($\rho_m$) - calculated
- intracellular and extracellular volume fractions ($\Lambda_i$, $\Lambda_e$) - calculated

6.1.1 Lens Geometry

The lens is described as an asymmetrical oblate spheroid (Kuszak, Zoltoski & Sivertson 2004). The lens is considered asymmetric because the radius of the anterior surface tends to be smaller than the radius of the posterior surface. In general, larger animals have more asymmetric and oblate lenses whereas smaller animals have more spherical lenses. The anterior and posterior surfaces of the lens can be assumed to be oblate ellipsoids (see Figure 6.1), where the radius of the major axis is the equator radius ($r_{eq}$), and the radius of the minor axis for the anterior and posterior ellipsoids are the anterior pole and posterior pole radii ($r_{ap}$ and $r_{pp}$). Properties for the bovine, rabbit, chicken, frog and mouse lenses are listed in Table 6.1. For more detail of the geometric and fibre structure of the lens see the work by Kuszak, Zoltoski & Sivertson (2004) and Kuszak, Mazurkiewicz & Zoltoski (2006).

![Figure 6.1: An axial section of the lens showing the elliptic geometry of the lens.](image-url)

<table>
<thead>
<tr>
<th>Species</th>
<th>Equatorial radius ((r_{eq}))</th>
<th>Anterior radius ((r_{ap}))</th>
<th>Posterior radius ((r_{pp}))</th>
<th>Equatorial diameter</th>
<th>AP-PP thickness</th>
<th>Height ((a))</th>
<th>Width ((b))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bovine</td>
<td>8.50 mm</td>
<td>4.25 mm</td>
<td>6.90 mm</td>
<td>17.00 mm</td>
<td>11.15 mm</td>
<td>6.81 (\mu)m</td>
<td>2.33 (\mu)m</td>
</tr>
<tr>
<td>Rabbit</td>
<td>5.75 mm</td>
<td>3.66 mm</td>
<td>4.71 mm</td>
<td>11.49 mm</td>
<td>8.37 mm</td>
<td>7.14 (\mu)m</td>
<td>2.50 (\mu)m</td>
</tr>
<tr>
<td>Chicken</td>
<td>3.30 mm</td>
<td>0.67 mm</td>
<td>1.90 mm</td>
<td>6.60 mm</td>
<td>2.57 mm</td>
<td>6.58 (\mu)m</td>
<td>2.82 (\mu)m</td>
</tr>
<tr>
<td>Frog</td>
<td>1.9 mm</td>
<td>0.9 mm</td>
<td>1.37 mm</td>
<td>3.8 mm</td>
<td>2.27 mm</td>
<td>10 (\mu)m [^{[3]}]</td>
<td>3 (\mu)m [^{[3]}]</td>
</tr>
<tr>
<td>Mouse</td>
<td>1.25 mm</td>
<td>0.87 mm</td>
<td>1.08 mm</td>
<td>2.50 mm</td>
<td>1.95 mm</td>
<td>5.45 (\mu)m</td>
<td>1.64 (\mu)m</td>
</tr>
</tbody>
</table>

6.1.2 Fibre Cell Angles

It is convenient to define the solute and fluid transport equations and parameters with respect to the fibre and cross-fibre directions. The fibre coordinate system is described in Section 2.2, where the orientation of the fibre cells is described by a fibre angle \((\gamma_f)\). The cross-fibre \((\gamma_c)\) and sheet \((\gamma_s)\) angles are not required for the two-dimensional models, but need to be included for future the three-dimensional models.

Figure 6.2: The cell types in the lens. Reproduced from Zampighi et al. (2000). Note: this figure is a copy of Figure 1.3.
The bulk of the lens is made up of fibre cells that span in arcs between the anterior and posterior regions (see Figure 6.2). Zampighi et al. (2000) described the fibre cells in the inner cortex and nucleus as "omega-shaped". The differentiating fibre cells at the equatorial region form a complex structure called the modiolus. This structure forms a small component of the total lens, but there exists a high membrane density in this region. The modiolus may have a significant influence on the transport in the lens, and thus, the lens model.

Kuszak and colleagues (see Kuszak, Zoltoski & Tiedemann (2004) and associate references for a review of their work) have developed an idealised description of the fibre cell structure in the lens (see Figure 6.3). The fibre cell angles (γ_f) are idealised to follow the angular direction, but this description fails to capture the structure of the differentiating fibre cells and the "omega-shape" of the bulk of the fibre cells. However, their description does capture the twist of the fibre cells out of the axial plane as they span between the poles and the shape of the sutures; this is important for three-dimensional models.

![Figure 6.3: Three dimensional fibre cell structure of the lens. The fibre cells converge at the poles to form a) umbilical, b) line and c) 'Y' sutures. In lenses with line and 'Y' sutures the fibre cells twist as they span between the anterior and posterior poles. Reproduced from Kuszak, Zoltoski & Tiedemann (2004).](image-url)

The fibre angles used in the two-dimensional models are based on Kuszak's description. The fibre-
axis is assumed to be aligned with the angular-direction, the fibre-angle ($\gamma_f$) is given by,

$$\gamma_f = \sin^{-1} \left( \frac{x}{\sqrt{x^2 + y^2}} \right) \quad (6.1)$$

where $x$ and $y$ are the coordinates in the lens. If the $\gamma_f$ is negative, $\pi$ is added to make it positive giving a fibre angle between $0^\circ$ and $90^\circ$. This description of the fibre angle is shown in Figure 6.4.

![Figure 6.4: Spatial variation of the fibre angle.](image)

### 6.1.3 Cell Dimensions

Kuszak, Zoltoski & Sivertson (2004) review the geometry, fibre cell organisation and cell dimensions in the bovine, rabbit, chicken and mouse lenses. The cross-sectional profile of fibre cells can be assumed to be an elongated hexagon (see Figure 6.5). This hexagonal cross-section deteriorates closer to the center of the lens.

![Figure 6.5: Change in fibre cell morphology, where cells become less regular with depth into the lens. The fibre cells near the surface are hexagonal with broad and narrow sides and the fibre cells near the center are elliptic. Scalebar: 4 μm (A) $r/a = 0.95$; (B) $r/a = 0.8$; (C) $r/a = 0.7$; where $r$ is the radial location of the sample and $a$ is the radius of the lens. Reproduced from Jacobs et al. (2004). Note: this figure is a copy of Figure 1.4.](image)
The distance between the narrow side is the height \((a)\), and between the broad sides the width \((b)\), of the cell. Table 6.1 list the fibre cell dimensions at equator for the bovine, rabbit, chicken, frog and mouse lenses.

As the fibre cells converge on the sutures, the height of the cells taper (see Figure 6.3). In lenses with umbilical sutures, the cells taper to a point, and in lenses with line and 'Y' sutures, respectively the cells taper to \(\frac{1}{3} - \frac{1}{2}\) and \(\frac{1}{2} - \frac{2}{3}\) the cell height at the equator (Kuszak, Zoltoski & Sivertson 2004). This tapering increases the membrane density at the poles (see Equation (6.2)). At the sutures, the ends of the fibre cells become invaginated further increasing the membrane density (see Figure 6.6), but this increase is not captured by Equation (6.2).

![Figure 6.6: Fibre cell invaginations at the suture lines increase the membrane density at the poles, which may increase the transmembrane transport properties in this region. A cross-section through the basal ends of fibre cells at the posterior immediately beneath the capsule (A) and deeper into the lens (B). An electron micrograph of the fibre cells at the posterior suture (C). Scalebar: A,B) 1.2 \(\mu\)m; C) 1 \(\mu\)m. Reproduced from Zampighi et al. (2000) (A,B) and Gorthy & Anderson (1980) (C).](image)

### 6.1.4 Tortuosity

The tortuosity of the extracellular space in biological tissue effectively creates a longer path for solutes and fluid to travel. In this case, the actual solute flux and fluid velocity along the extracellular cleft is not the velocity seen at the macroscopic level, which is a homogenised velocity. The tortuosity parameter \((\tau)\) is a homogenised description the path of the extracellular cleft and scales
the solute and fluid transport equations to obtain the effective solute fluxes and fluid velocities.

The theoretical value of the tortuosity in the cross-fibre direction (radial direction) in lens was calculated to be 0.16, which is close to the experimentally measured value of 0.14 (Paterson & Delamere 2004). The value used in the lens model was 0.16, the same as the value used in the analytic model developed by Mathias (1985b). The tortuosity in the fibre direction was assumed to be 1.

Although, the tortuosity in the lens spatially varies, it is assumed to be spatially uniform in the lens model. This assumption neglects the change in the cross-sectional shape of fibre cells between the surface and nucleus of the lens (see Figure 6.5) and the high tortuosity at the sutures (see Figure 6.6).

### 6.1.5 Extracellular Cleft Width

The width of the extracellular cleft is one of the more important parameters in the lens model. The sutures and diffusion barrier were represented in the two-dimensional model (see Chapter 8) by spatially varying the cleft width. This had a significant influence on the magnitude and circulation of the solute fluxes and fluid flow in the lens.

In the one-dimensional and initial two-dimensional models, the extracellular cleft was set to the same value as the analytic model by Mathias (1985b), 40 nm, and was spatially constant. The two-dimensional model could then be modified to represent the sutures and diffusion barrier in lens by varying the cleft width.

The cleft width is interpolated between the equator (40 nm), poles (60 nm) and the center (10 nm) of the lens using Hill functions (Figure 6.7). The values at the landmarks and the interpolation profiles between the landmarks were chosen to reflect some observations of the lens documented in the literature. The cleft width dilates within 30° of the poles and linearly constricts between the polar surface and the center in order to represent the sutures. The extracellular diffusion barrier has been observed in many studies of the lens: Moffat, Landman, Truscott, Sweeney & Pope (1999) and Moffat & Pope (2002), who used MRI to image the age-related transport of water in human lenses; and Grey, Jacobs, Gonen, Kistler & Donaldson (2003) and Donaldson, Grey, Merriman-Smith, Sisley, Soeller, Cannell & Jacobs (2004), who imaged the diffusion of fluorescent macromolecules
in rat lenses. The diffusion barrier was represented in the model by a rapid constriction of the extracellular cleft about 400 \( \mu m \) into the lens between the equator and center. The cleft width at the equator (40 nm) is based on the value used by Mathias (1985\textit{b}) in the analytic model. The cleft width at the poles (60 nm) is based on the values measured by Zampighi et al. (2000) for the Type 0 cells, and the cleft width at the center (10 nm) is an estimate based on observations of the diffusion barrier.

![Figure 6.7: Spatial variation of the extracellular cleft width.](image)

Images of the sutures (Figure 6.8), however, show large dilation of the extracellular space. Therefore, it is unlikely the lens model captures the true structure of the suture. Further work is required to improve the representation of the sutures in the lens model, especially since the results from the two-dimensional models demonstrate the strong influence of the sutures.

### 6.1.6 Membrane Density

The membrane density \((\rho_m)\) is the membrane area in a unit volume of lens, which is important for the description of transmembrane solute and fluid transport, and calculating the intracellular and extracellular volume fractions.

Although the membrane density is an experimentally measured property of the lens, it is calculated from the cell dimensions and the tortuosity of the tissue. This is for convenience when calculating the membrane density at the sutures due to the tapering of the fibre cells. This method gives results that are similar to measured values but could be improved since it fails to capture the high membrane density at the modiolus (see Figure 6.2) and the fibre cell membrane invaginations at the sutures (see Figure 6.6).
The membrane density, as a function of cell dimensions and tortuosity, is given by,

\[ \rho_m = \frac{2b \xi_c}{ab} \]  \hspace{1cm} (6.2)

where \( a \) and \( b \) are the height and width of the fibre cells and \( \xi_c \) is the wiggle factor (associated to the tortuosity by \( \tau_c = 1/\sqrt{\tau_c} \)) in the cross-fibre direction (radial direction).

### 6.1.7 Volume Fractions

The intracellular and extracellular volume fractions are important for calculating the solute and fluid source terms, and are used in the conservation equations to account of the bidomain treatment of the lens model. The intracellular and extracellular volume fractions are given by,

\[ \Lambda_i = 1 - \frac{h \rho_m}{2} \]  \hspace{1cm} (6.3)

\[ \Lambda_e = \frac{h \rho_m}{2} \]  \hspace{1cm} (6.4)
where \( \rho_m \) is the membrane density and \( h \) is the width of the extracellular cleft. These equations assume the volume occupied by the membrane is insignificant.

### 6.2 Solute Transport

The solute transport equations for the lens are derived in Chapter 3. Key solute transport properties required for the lens models are the:

- solute diffusion coefficients \( (D_{\alpha i,f}, D_{\alpha i,c}, D_{\alpha e,f}, D_{\alpha e,c}) \)
- membrane conductivity through ion channels \( (g_{Na}, g_{K}, g_{Cl}) \)
- \( Na^+/K^+ \) pump properties \( (I_{max1}, I_{max2}, K_{\frac{1}{2}Na1}, K_{\frac{1}{2}Na2}, K_{\frac{1}{2}K1}, K_{\frac{1}{2}K2}) \)

#### 6.2.1 Solute Diffusion

A method of measuring the diffusion and permeabilities in the lens is to release fluorescence, measure the time-course of the fluorescence intensity and fit a diffusion model to the data. Three such studies were carried out by Rae, Bartling, Rae & Mathias (1996), Eckert, Adams, Kistler & Donaldson (1999), and Cannell et al. (2004).

Rae et al. (1996) injected Lucifer Yellow CH (MW 512.6) into epithelial and deep fiber cells in a rat lens using a patch electrode, and measured the spread of the dye between the epithelial and fiber cells, along fiber cells and between fiber cells. A diffusion model was fitted to the measured fluorescence intensity to estimate the diffusion and permeability values. They estimate the fiber-fiber cell permeability to be \( 2.8 \times 10^{-6} \, \text{cm/s} \). Rae et al. (1996) used this measurement of the fiber-fibre cell permeability to estimate the permeability of \( K^+ \) and \( Cl^- \) (MW 39 and 35, respectively). By assuming the permeability of \( K^+ \) and \( Cl^- \) would be proportional to the diffusion coefficient, they estimated the permeability to be ten-fold greater than the permeability of Lucifer Yellow CH, hence, \( 28 \times 10^{-6} \, \text{cm/s} \).

Eckert et al. (1999) performed a similar experiment measuring the diffusion and permeability of rhodamine-dextran (MW 10,0000) and Lucifer yellow (MW 457) fluorescence in the rat lens. For Lucifer yellow, they estimate the diffusion coefficient in the cytoplasm to be \( 0.7 \times 10^{-6} \, \text{cm}^2/\text{s} \) and permeability between fiber cells to be \( 31 \times 10^{-5} \, \text{cm/s} \).
Cannell et al. (2004) used 2-photon flash photolysis to release TPEFP, DMNB-caged fluorescein dextran, in the rat lens. The advantage of this technique is that the volume of the release is extremely small, $4 \times 10^{-15}$ l, therefore, the release can be confined to a single cell. The measured diffusion coefficient of fluorescein in free solution was $4 \times 10^{-6}$ cm$^2$/s and along a fiber cell, $4 \times 10^{-7}$ cm$^2$/s. The apparent diffusion coefficient between cells was $4 \times 10^{-8}$ cm$^2$/s, or 1% of the free diffusion coefficient.

Compared to the diffusion in free solution, the diffusion of the fluorescence molecules in the cytoplasm appears to be attenuated. This is assumed to be due to interactions with other large molecules in the cytoplasm and this is not experienced by small ions. Hence, the diffusion coefficients for Na\(^+\), K\(^+\) and Cl\(^-\) are assumed to be the same as the coefficients in free solution; these were sourced from Benedek & Villas (2000\(c\)). In the cross-fibre direction, it is assumed that the attenuation in the diffusion of the fluorescent molecules was due to the reduced transport through the membrane via gap junctions. This attenuation is assumed to also be experienced by small molecules. Based on the values measured by Cannell et al. (2004), the diffusion coefficients for Na\(^+\), K\(^+\) and Cl\(^-\) in the radial direction were assumed to be 1% the values in free solution. The diffusion of Na\(^+\), K\(^+\) and Cl\(^-\) in the extracellular cleft is assumed to be the same as the diffusion in free solution.

### 6.2.2 Ion Channels

A series of impedance experiments were carried out to measure the electrical properties of the lens (Eisenberg et al. 1979, Mathias et al. 1979, Mathias et al. 1981, Baldo & Mathias 1992). In these studies, current was applied to the lens over a range of frequencies, where the path of the current through the lens would depend on the frequency. By fitting the results from these experiments to an equivalent circuit model of the electrical coupling in the lens, the resistance of the intracellular and extracellular space, and that of the fibre cell and epithelial cell membranes, could be determined. In the study by Baldo & Mathias (1992), the spatial variation of the surface membrane conductance in the rat lens was measured. They reported a step change at the equator from 1.26 mS/cm$^2$ to 0.46 mS/cm$^2$ between the anterior and posterior poles, respectively. Mathias et al. (1997) provide a good review of these impedance studies.

For the one- and two-dimensional lens models, the Na\(^+\) and Cl\(^-\) conductivity of fibre cell membrane was 2.2 mS/m$^2$ and the K\(^+\) conductivity of the surface membrane was 2.1 S/m$^2$; these were spatially constant. These values are the same as those used in the analytic model developed by
Mathias (1985b). Further work is needed to include the observed spatial variation of the membrane conductivity, which would have a significant influence on the solute and fluid transport, in the model.

### 6.2.3 Na/K Pumps

Gao et al. (2000) studied the function and distribution of specific isoforms of the Na/K pumps in the frog epithelium. The cells from the epithelial layer were isolated and divided into anterior and equatorial cells. They used RNase protection assays to measure the amount of $\alpha_1$-, $\alpha_2$-, and $\alpha_3$-isoforms of the Na/K pumps. At the equator, 92% of the Na*/K* pumps were the $\alpha_1$-isoform, 8% were the $\alpha_2$-isoform, and there were no $\alpha_3$-isoforms. At the anterior surface, 23% of the Na*/K* pumps were the $\alpha_1$-isoform, 77% were the $\alpha_2$-isoform, and there were no $\alpha_3$-isoforms. They performed whole cell patch clamp experiments to measure the dependence of the pump current to external Ca$^{2+}$, ouabain, internal Na$^+$, external K$^+$ and external H$^+$. The pump current did not depend on external Ca$^{2+}$ concentration.

Using these results, Gao et al. (2000) derived equations describing the current through the $\alpha_1$ and $\alpha_2$ Na*/K* pump isoforms,

\[
I_{p1} = I_{\text{max}1} \left( \frac{[Na^+]_i}{[Na^+]_i + K_{Na1}} \right)^3 \left( \frac{[K^+]_o}{[K^+]_o + K_{K1}} \right)^2 \left( \frac{K_H}{K_H + [H^+]_o} \right) \tag{6.5}
\]

\[
I_{p2} = I_{\text{max}2} \left( \frac{[Na^+]_i}{[Na^+]_i + K_{Na2}} \right)^3 \left( \frac{[K^+]_o}{[K^+]_o + K_{K2}} \right)^2 \tag{6.6}
\]

Since the concentration of H$^+$ is not modelled, a modified form of the Na*/K* pump models is used in the lens model. The contribution from the Hill function term involving the H$^+$ concentration in Equation (6.5) is included in the maximum current parameter ($I_{\text{max}}$). Therefore, the models for the $\alpha_1$ and $\alpha_2$ isoforms of the Na*/K* pumps are$^1$,

\[
I_{p1} = I_{\text{max}1} \left( \frac{C_{Na}}{C_{Na} + K_{Na1}} \right)^3 \left( \frac{C_{Ko}}{C_{Ko} + K_{K1}} \right)^2 \tag{6.7}
\]

\[
I_{p2} = I_{\text{max}2} \left( \frac{C_{Na}}{C_{Na} + K_{Na2}} \right)^3 \left( \frac{C_{Ko}}{C_{Ko} + K_{K2}} \right)^2 \tag{6.8}
\]

$^1$Same as Equations (3.21) and (3.22)
where the subscripts 1 and 2 associate the parameters with the $\alpha_1$ and $\alpha_2$ isoforms of the Na$^+$/K$^+$ pumps, respectively, and $I_{max}$ is the maximum current rates through the pumps. The $K$ values are given by,

$$K_{Na1} = (\sqrt{2} - 1)K_{\frac{1}{2}Na1} \quad K_{Na2} = (\sqrt{2} - 1)K_{\frac{1}{2}Na2}$$
$$K_{K1} = (\sqrt{2} - 1)K_{\frac{1}{2}K1} \quad K_{K2} = (\sqrt{2} - 1)K_{\frac{1}{2}K2}$$

$K_{\frac{1}{2}Na}$ and $K_{\frac{1}{2}K}$ are the Na$^+$ and K$^+$ concentrations at which the pump current is half the maximum current ($I_{max}$).

**Table 6.2: Properties of the Na$^+$/K$^+$ pumps.**

<table>
<thead>
<tr>
<th>Isoforms</th>
<th>$\alpha_1$</th>
<th>$\alpha_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_{\frac{1}{2}Na}$</td>
<td>9 mM</td>
<td>9 mM</td>
</tr>
<tr>
<td>$K_{\frac{1}{2}K}$</td>
<td>3.9 mM</td>
<td>0.4 mM</td>
</tr>
</tbody>
</table>

For the lens model, the values of $I_{max1}$ and $I_{max2}$ were determined by fitting Equations (6.7) and (6.8) to the data presented in Gao et al. (2000). The half-maximal concentration values are listed Table 6.2. For the Na$^+$ dependence fit, the outside K$^+$ concentration was assumed to be fixed at 7.5 mM, and for the K$^+$ dependence fit, the intracellular Na$^+$ concentration was assumed to be fixed at 15 mM. At the equator, the fitted $I_{max1}$ value was 0.48 A/m$^2$ and the fitted $I_{max2}$ value was $65\times10^{-3}$ A/m$^2$; the fitted model and data are shown in Figure 6.9. At the anterior pole, the fitted $I_{max1}$ value was $7.38\times10^{-3}$ A/m$^2$ and fitted $I_{max2}$ value was 0.13 A/m$^2$; the fitted model and data are shown in Figure 6.10.

![Figure 6.9: The fitted Na$^+$/K$^+$ pump model against the Na$^+$ and K$^+$ dependence data (Gao et al. 2000) at the equator.](image-url)
Model Properties

Figure 6.10: The fitted Na⁺/K⁺ pump model against the Na⁺ and K⁺ dependence data (Gao et al. 2000) at the anterior pole.

Figure 6.11 shows the assumed distribution of \( I_{\text{max}1} \) and \( I_{\text{max}2} \) at the surface the lens. The equatorial values of \( I_{\text{max}1} \) and \( I_{\text{max}2} \) are assumed to constant between 70° and 110°. Between 0° and 70°, \( I_{\text{max}1} \) and \( I_{\text{max}2} \) are assumed to linearly vary between the fitted values at the anterior pole and the equator. Between 110° and 150°, \( I_{\text{max}1} \) and \( I_{\text{max}2} \) are assumed to decline linearly to zero, indicating the there are no Na⁺/K⁺ pumps at the posterior surface.

Figure 6.11: Maximum pump rates at the lens surface for the \( \alpha_1 \) and \( \alpha_2 \) isoforms of the Na⁺/K⁺ pumps.
6.3 Fluid Transport

The fluid transport equations for the lens are derived in Chapter 4. From these equations, the key fluid transport properties are the:

- membrane hydraulic permeability \((L_m, L_p, L_s)\)
- membrane reflectance \((\sigma)\)
- fluid viscosity \((\mu)\)
- zeta potential \((\zeta)\)
- Debye length \((\lambda_D)\)
- hydraulic conductivity \((K_{i,f}, \tilde{K}_e)\) - calculated
- electro-osmotic coefficient \((\tilde{k}_e)\) - calculated

The hydraulic permeability of the cell membrane in the lens is much higher than the solute permeability (Mathias et al. 1997). Therefore, the membrane reflectance is assumed to be 1; this is the same value used in the analytic model (Mathias 1985b). A sensitivity analysis may be performed to determine its importance to solute and fluid flow in the lens. If it does have a significant influence on fluid transport then a more accurate value should be sourced.

Inside the fibre cells, there exists a high inhomogeneous concentration of crystallin proteins. This may have an influence on the value and spatial distribution of the intracellular fluid viscosity. For the lens model, both the intracellular and extracellular fluid viscosity are assumed to be the same as for water \((\mu = 0.7 \times 10^{-3} \text{ Pa s at 310 K})\). Further work is needed to assess the influence of the fluid viscosity on the transport in the lens.

The zeta potential \((\zeta)\) used in the lens models was sourced from Mathias (1985b) and Debye length \((\lambda_D)\) from McLaughlin & Mathias (1985). These parameters were not investigated further.

The derivation of the hydraulic conductivity and electro-osmotic coefficient is described in Chapter 4. In the intracellular space, the hydraulic conductivity along the fibre cell is given by Equation (4.41). The effective hydraulic conductivity in the cross-fibre direction is given by the product of the fibre cell width \((b)\) and intercellular membrane hydraulic permeability \((L_p)\), i.e., \(K_{i,c} = b L_p\) (see Equation (4.44)). In the extracellular space, the hydraulic conductivity is given by Equation (4.56) and electro-osmotic coefficient is given by Equation (4.57).
6.3.1 Membrane Hydraulic Permeability

Water is transported across the cell membrane primarily by aquaporin water channels. The lens expresses two forms of aquaporin channels: AQP0 and AQP1 (see Figure 6.12). AQP0 is localised to the fibre cell membrane and AQP1 to the epithelial cell membrane.

![Figure 6.12: The immunostaining of AQP0 and AQP1 in the mouse lens. (Reproduced from Varadaraj et al. (2005))](image)

Varadaraj et al. (2005) studied the Ca\(^{2+}\) and pH-mediated regulation of membrane water permeability of AQP0 in lens fibre cells and AQP1 in lens epithelial cells. The membrane water permeability (\(\mu m/s\)) was measured in rabbit, mouse and frog fibre and epithelial cells by changing the osmolarity (325mOsM to 488mOsM) of the solution surrounding the cell and measuring the rate of charge of the cell volume. A summary of the control experiments results are listed in Table 6.3.

The rate of change of the water content inside the cell at time \(t\), is described by (Varadaraj et al. 1999),

\[
C_{H_2O} \frac{dV_i(t)}{dt} = S_m p_{H_2O} (C_i(t) - C_o)
\]

(6.9)

where \(V_i\) is the volume of the cell, \(C_{H_2O}\) is the concentration of water, \(C_i\) and \(C_o\) is the osmolarity inside and outside the cell, \(p_{H_2O}\) is the membrane water permeability and \(S_m\) is the surface area of
the cell.

The rate of change of the cell volume is given by

\[ \frac{dV_i(t)}{dt} = u_m(t) S_m \]  \hspace{1cm} (6.10)

where \( u_m \) is the membrane fluid velocity.

The fluid velocity through a membrane due to a concentration or osmotic gradient is given by (Benedek & Villas 2000c)

\[ u_m(t) = L_p RT (C_i(t) - C_o) \]  \hspace{1cm} (6.11)

where \( L_p \) is the hydraulic conductivity, \( R \) is the gas constant and \( T \) is the temperature.

Substituting Equations (6.10) and (6.11) into Equation (6.9) gives the relationship between the hydraulic conductivity and membrane water permeability,

\[ L_p = \frac{p_{H_2O}}{RT C_{H_2O}} \]  \hspace{1cm} (6.12)

where \( R = 8.314 \text{ J/(K mol)} \), \( T = 310 \text{ K} \) and \( C_{H_2O} \approx 55 \text{ M} \). This equation is used to calculate the hydraulic conductivity of the rabbit, mouse and frog fibre and epithelial cells membranes, which are listed in Table 6.3.

<table>
<thead>
<tr>
<th>Species</th>
<th>Permeability (( \mu m/s ))</th>
<th>Hydraulic Conductivity (m/(Pa s))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Membrane</td>
<td>AQP</td>
</tr>
<tr>
<td>Mouse fibre cell (AQP0)</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>Rabbit fibre cell (AQP0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Frog fibre cell (AQP0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rabbit epithelial cell (AQP1)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

The membrane hydraulic conductivity for the frog fibre cell \( (1.34x10^{-13} \text{ m/(Pa s)}) \) is used for the fibre hydraulic conductivity \( (L_f) \) and the membrane hydraulic conductivity for the rabbit epithelial cell \( (8.89x10^{-13} \text{ m/(Pa s)}) \) is used for the surface membrane permeability \( (L_s) \) in the lens models. These parameters are assumed to be spatially constant.
The intercellular membrane has a high density of gap junctions, which allow water to pass between adjacent cells, but there is a lack data on the water permeability of gap junctions in the lens. Therefore, the intercellular hydraulic conductivity ($L_p$) is calculated using Equation (4.39). The structure of a gap junction is shown in Figure 6.13. The mean pore radius is $1\text{nm}$ and mean pore length is $10\text{nm}$ (Unger, Kumar, Gilula & Yeager 1999). The ratio of gap junction pore area to membrane area is $0.025$ (Cannell et al. 2004). Given these properties, the estimate of the hydraulic conductivity of the intercellular membrane ($L_p$) is $4.46 \times 10^{-10} \text{m}/(\text{Pa s})$. This is assumed to be spatially constant in the lens models.

![Figure 6.13: The structure of gap junctions. (Reproduced from Unger et al. (1999))](image)

### 6.4 Lens Physiological Properties

#### 6.4.1 Electrical Potential

The intracellular and extracellular potential in the lens varies with location in the lens, with age and between species. Table 6.4 list the potential measured from frog and human lenses.

Figure 6.14 shows the spatial variation of the intracellular and extracellular potential as a function of the depth into the lens. Mathias & Rae (1985) measured the potential in the frog lens by plunging
Table 6.4: Measured potentials in the frog and human lenses.

<table>
<thead>
<tr>
<th>Species</th>
<th>Potential (mV)</th>
<th>Study</th>
</tr>
</thead>
</table>
| Frog    | Extra: \(\sim-30\)  
          | Intra: \(\sim-70\) | Delamere & Paterson (1979): Measured by inserting two electrodes into the posterior cortex, one about 100 \(\mu m\) deep, the other 200 – 300 \(\mu m\) deep. They were able to measure potentials between -85 and -20 mV. |
| Frog    | Extra: 0 to -36  
          | Intra: -70 to -50 (Poles to Nucleus) | Mathias & Rae (1985): Measured using plunge electrode along pole axis |
| Human   | -50 to -20 (ages 14 to 90) | Duncan, Hightower, Gandolfi, Tomlinson & Maraini (1989): Measured using microelectrodes inserted the posterior capsule |

an electrode along the anterior-posterior axis. The potential would oscillate between \(\sim 20\) mV and \(\sim 60\) mV as the electrode moved between the extracellular and intracellular space. There was little data for the extracellular space due to its small volume. The profile of the potential was found to be symmetric about the center of the lens. The smooth curve in Figure 6.14 is the theoretical potential that was calculated using an equivalent circuit model of the lens. The resistance and membrane conductance values used in the model were measured from the frog lens in the same study. These required little adjustment to obtain a good fit between the calculated and measured potentials.

Duncan et al. (1989) collate a number studies on human lenses that measured the age-related change in the membrane potential concentration of Na\(^+\), K\(^+\) and Ca\(^{2+}\), the relative permeability between Na\(^+\) and K\(^+\) \((P_{Na}/P_K)\), and the optical density. Their results showed a decrease in membrane potential and an increase in the concentration of Na\(^+\) and Ca\(^{2+}\), the relative permeability \((P_{Na}/P_K)\) and the optical density with age. The concentration of K\(^+\) remained relatively constant. The membrane potential changed significantly from around -50 mV to -20 mV over a 80 year period (see Figure 6.15).
Figure 6.14: The intracellular and extracellular potentials in the frog lens. The oscillating curves are the potentials measured by plunging an electrode into the lens. The smooth curves are the potentials predicted by an analytic model. (Reproduced from Mathias et al. (1997))

Figure 6.15: Graph of the age-related intracellular potential for human lenses. The open symbols represent cataractous lenses. (Reproduced from Duncan et al. (1989))
6.4.2 Solute Concentrations

Early studies on the ion concentrations in the lens measured the ion concentration in the whole lens and expressed the concentration in units of \( mEq/kg \) lens or \( mEq/ml \) lens. The units can be converted to \( mol/l \) by

\[
C = \frac{N}{z}
\]

(6.13)

where \( C \) is the molarity \([mol/l]\), \( N \) is the normality \([Eq/l]\), and \( z \) is the valency of the ion. Therefore, for monovalent ions, like \( Na^+ \), \( K^+ \), and \( Cl^- \), \( 1 \) \( Eq/l \) is equivalent to \( 1 \) \([mol/l]\).

The measured concentration for the whole lens was converted to an intracellular concentration by

\[
C_i = \frac{C_L - C_e \Lambda_e}{\Lambda_i}
\]

(6.14)

where \( C_L \), \( C_i \) and \( C_e \) are the total lens, intracellular and extracellular concentrations \([mol/l]\), and \( \Lambda_i \) and \( \Lambda_e \) are the intracellular and extracellular volume fractions. Usually, an estimate is used for the extracellular volume fraction \( \Lambda_e \) and the intracellular volume fraction is give by \( \Lambda_i = 1 - \Lambda_e \). The extracellular volume faction \( (\Lambda_e) \) was typically estimated to be between 1% and 5%. Also, it was common to assume that the extracellular concentration was equal to the concentration outside the lens.

Delamere & Duncan (1977) compared the ion concentrations, potentials and conductances of amphibian, bovine and cephalopod lenses. A summary of the total ion concentrations measured in the whole lens is given in Table 6.5. They then computed the ion concentration in the intracellular space by assuming the extracellular space occupied 5% of the total lens volume. The computed values are summarised in Table 6.5.

<table>
<thead>
<tr>
<th>Species</th>
<th>([Na^+]_i) (mM)</th>
<th>([K^+]_i) (mM)</th>
<th>([Cl^-]_i) (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frog</td>
<td>9.4 (14.7 ± 1.1)</td>
<td>94.9 (90.3 ± 3.1)</td>
<td>12.8 (17.7 ± 2.0)</td>
</tr>
<tr>
<td>Sepiola</td>
<td>39.9 (62.4 ± 2.9)</td>
<td>131.0 (124.9 ± 2.8)</td>
<td>219.3 (235.1 ± 5.6)</td>
</tr>
<tr>
<td>Bovine</td>
<td>24.7 (30.0 ± 3.1)</td>
<td>149.0 (142.0 ± 3.4)</td>
<td>26.9 (32.8 ± 2.1)</td>
</tr>
</tbody>
</table>

Guerschanik, Reinach & Candia (1977) measured the intracellular chloride concentration and chloride permeability of the frog lens. For ten lenses, they measured a chloride concentration of
13.3 ± 3.5 mM.

Duncan (1970) measured the movement of sodium and chloride in toad lenses. In this study, the measured total lens sodium concentration was 22.5 mM and the computed nucleus and cortex sodium concentrations were 17 ± 4 mM (n=4) and 20 ± 4 mM (n=4).

The solute concentrations in the extracellular space are assumed to be the same as outside the lens. However, the extracellular $K^+$ concentration predicted by the analytic model developed by Mathias (1985b), varied between 3 mM at the surface to 21 mM at the nucleus (see Figure 6.16). This result suggests the concentration of other solutes may vary between the surface and nucleus.

![Figure 6.16: The extracellular potassium concentration predicted by the analytic model (Reproduced from Mathias (1985)).](image)

### 6.4.3 Solute Fluxes

Three key studies measured the currents at the surface of the lens: Robinson & Patterson (1983); Parmelee (1986); and Candia & Zamudio (2002). The results from these studies, which are plotted in Figure 6.17, are compared with the surface currents predicted by the lens models. Robinson & Patterson (1983) and Parmelee (1986) used the vibrating probe technique to measure the currents at the surface of the rat and frog lens, respectively. Candia & Zamudio (2002) tried to use the
same technique on the rabbit lens, but found the technique to be unreliable, hence they used a three-chambered Ussing apparatus.

![Figure 6.17: Measured currents at the surface.](image)

### 6.4.4 Fluid Flow

There are limited studies on the transport of water in the lens:
- Fowlks (1973) observed the secretion of water on the surface of the rabbit and human lens.
- Fischbarg et al. (1999) measured the mass flow across isolated surfaces of the rabbit lens.
- Mathias (1985b) developed an analytical model that predicted the fluid flow in the frog lens.

These studies are covered below in chronological order and summarised in Table 6.6.

The fluid flow in the following studies are presented in terms of mass flow \( \dot{m} \). This is the volume of fluid transported across a surface in an interval of time. From the mass flow, the surface velocity \( u_s \) can be calculated by

\[
    u_s = \frac{\dot{m}}{A} \tag{6.15}
\]

where \( A \) is the area of the surface.
Fowlks (1973) observed water moving from the posterior to the anterior surface of the rabbit and human lens. In this study, Fowlks dried the surface of the lenses and observed a secretion of fluid on only the anterior surface of the lens. Furthermore, if a source of fluid was placed on the posterior surface, then fluid, which was roughly a similar shape, would appear at the same location on the anterior surface. This suggests a directed path between the posterior and anterior surfaces. These fluid movements were found to be independent of the direction of gravity.

Mathias (1985b) developed an analytic model of the current and fluid flow in the frog lens. Figure 6.18 shows the extracellular pressure and fluid flow predicted by the model.

The model predicted a mass flow of $0.36 \mu l/hr$ ($100 \mu l/s$) through the surface of the lens via the extracellular space, and an extracellular hydrostatic pressure of 52 mmHg (6.9 kPa) at the center of the lens. Using Equation (6.15), where the surface area was assumed to be that of a sphere with a radius of 1.6 mm ($A = 4\pi r^2$), the surface velocity ($u_s$) was calculated to be 3.10 nm/s.

Fischbarg et al. (1999) used an Ussing-chamber to isolate the anterior and posterior surfaces of the rabbit lens and measure the fluid flow from one chamber to the other (see Figure 6.19). The lenses placed in the chamber experienced a pressure head of 3 cmH$_2$O on the top surface, hence the lenses were placed "upright" or "inverted" to ensure fluid flow was not driven solely by the pressure head. The "upright" lenses had their anterior surface facing the top chamber and the "inverted" lenses had their posterior surface facing the top chamber.
The measured flow was directed from the anterior to the posterior surface for all lenses. The flow through the anterior and posterior surface for the "upright" lenses was $12.5 \pm 1.1 \text{ ul/hr/lens (} n = 6 \text{)}$ and for the "inverted" lenses was $10.3 \pm 0.62 \text{ ul/hr/lens (} n = 5 \text{)}$. Given this flow rate, Fischborg et al. (1999) calculated the lens could recycle the fluid in the extracellular space in two hours. They also found that the flow ceased when ouabain was applied to the epithelial layer on the anterior surface. Given the epithelial area was $1.2 \text{ cm}^2$, the surface velocity was calculated as $24 - 28 \text{ nm/s}$.

Fischborg et al. (1999) also measured the hydraulic conductivity in excised sections of the rabbit lens. They measured a value of $0.76 \text{ nm/(Pa.s)}$, which compared well to the theoretically calculated value of $0.122 \text{ nm/(Pa.s)}$.

Candia & Gerometta (2003) used a novel Ussing-type chamber (see Figure 6.20) to measure the fluid movement across the anterior, posterior and equatorial surfaces of bovine lenses. The chamber isolated the surface of bovine lens, which had an average diameter of 18 mm, into three regions by clamping the lens between two O-rings that were 8 mm in diameter. For 40% of the lenses, the fluid movement was measured to exit the equatorial surface at $3.0 \pm 1.5 \mu\text{l/hr (} n=15 \text{)}$. For the remaining 60% of the lenses, the measurement were either unreliable or there was no measurable fluid movement.

The diameter of the bovine lens at the equator was 18 mm. For a 17 mm diameter bovine lens, the anterior thickness is 4.25 mm and the posterior thickness is 6.90 mm (Kuszak, Zoltoski & Sivertson 2004). Scaling the 17 mm lens to 18 mm would give a anterior and posterior thickness of 4.5 mm and 7.3 mm, respectively. Given these dimensions and assuming the anterior and posterior halves of the lens form an ellipsoid, the isolated equatorial, anterior, and posterior surfaces have an area of 695 mm$^2$, 51 mm$^2$, and 52 mm$^2$. Given the mass flow through and the area of the equatorial region, the mean fluid velocity through the equatorial surface is $1.20 \text{ nm/s}$. 

**Figure 6.19**: Ussing-chamber used by Fischborg et al. (1999) to measure the fluid movement in the rabbit lens.
Later, Candia (2004) reported further, more reliable, experimental data from the setup used by Candia & Gerometta (2003). At the anterior surface, the fluid entered the lens at approximately 1.84 $\mu$l/hr, and at the equatorial and posterior surfaces, fluid exited the lens at 1.60 $\mu$l/hr and 0.29 $\mu$l/hr, respectively. The surface velocity for the anterior, equatorial and posterior surfaces are $-10$ nm/s, 0.64 nm/s and 1.55 nm/s, respectively, where a positive velocity is fluid exiting the lens.

A summary of these fluid flow studies is shown in Table 6.6.

The lens properties covered in this chapter are used to develop the one- and two-dimensional models, which are described in the next two chapters. These models are solved and the predictions are compared with the experimentally measured and theoretically predicted results described in Section 6.4.
### Table 6.6: Summary of fluid flow studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Species</th>
<th>Surface Velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fowlks (1973)</td>
<td>rabbit, human</td>
<td></td>
</tr>
<tr>
<td>Mathias (1985b)</td>
<td>frog model</td>
<td>$u = 3.1 \text{ nm/s}$</td>
</tr>
<tr>
<td>Fischbarg et al. (1999)</td>
<td>rabbit</td>
<td>$u = -26 \text{ nm/s}$</td>
</tr>
<tr>
<td>Candia &amp; Gerometta (2003)</td>
<td>bovine</td>
<td>$u = 1.2 \text{ nm/s}$</td>
</tr>
<tr>
<td>Candia (2004)</td>
<td>bovine</td>
<td>$u = 0.64 \text{ nm/s}$ and $u = 1.55 \text{ nm/s}$</td>
</tr>
</tbody>
</table>
The main purpose of this one-dimensional model is to ensure the modelling framework is capable of simulating the transport of solutes and fluid in the lens. The numerical model is an extension of the analytic model of the lens developed by Mathias (1985b). If the results from the one-dimensional numerical model compare well with the results from the analytical model and experimentally measured values, then we can be satisfied with the numerical modelling framework. The model parameters are not adjusted to obtain a better match between the model results and experimental data since this is an involved process and is better performed with a more advanced model, such as a two-dimensional model.

The one-dimensional numerical model represents a wedge that extends from the center to the equatorial surface of the lens (see Figure 7.1). This model assumes symmetry about the $x$-axis and in the angular direction between the anterior and posterior poles. In this case, the transport of solutes and fluid is limited to the radial direction, which is the cross-fibre direction, with no transport through the sides of the wedge.
This chapter will give a brief description of the model, which includes the mesh in Section 7.1 and the governing equations in Section 7.2. This description is brief since these parts of the model are covered in earlier chapters, Chapter 3 covers the solute transport equations, Chapter 4 covers the fluid transport equations and Chapter 5 covers the mesh generation, finite volume methods and solution algorithm. The results from the model are discussed in Section 7.3 and summarised in Section 7.4.

7.1 Mesh

The mesh representing the model of the wedge in the lens is generated by Gmsh using the script listed in Appendix D (Figure 7.2a). This mesh is extruded about the $x$-axis to obtain the three-dimensional mesh (Figure 7.2b) representing the wedge shown in Figure 7.1. The methods used to extrude the mesh are covered in Section 5.1. Notice that the element widths at the surface are smaller than those at the center since the largest gradient occurs near the surface. The parameters used to generate the mesh are listed in Table 7.1.

The one-dimensional model is a bidomain model. The bidomain properties, such as the membrane density and volume fractions, are calculated from the tissue properties (see Table 7.2).
7.2 Governing Equations

The governing equations for the solute and fluid transport in the lens are covered in Sections 3.5 and 4.8 respectively. This section will discuss the components of the model and the governing equations and parameters used within it. For a concise and complete list of equations and parameters see Appendix A.

Figure 7.3 shows the dependent variables \( (C, \phi, p) \), solute fluxes \( (j) \), and fluid velocities \( (u) \) included in the model. Since the model represents a wedge that extends from the nucleus to the surface of the lens, the flux and velocity equations represent the transport in the cross-fibre direction. The transport equations in the fibre direction are assumed to be zero.

The model has ten dependent variables:

- \( C_{Na_i}, C_{K_i}, C_{Cl_i} \) – intracellular \( \mathrm{Na}^+, \mathrm{K}^+ \) and \( \mathrm{Cl}^- \) concentrations
- \( C_{Na_e}, C_{K_e}, C_{Cl_e} \) – extracellular \( \mathrm{Na}^+, \mathrm{K}^+ \) and \( \mathrm{Cl}^- \) concentrations
- \( \phi_i \) – intracellular potential
- \( \phi_e \) – extracellular potential
- \( p_i \) – intracellular pressure
- \( p_e \) – extracellular pressure

The ion concentrations \( (C_{Na_o}, C_{K_o}, C_{Cl_o}) \), electrical potential \( (\phi_o) \) and hydraulic pressure \( (p_o) \) outside the lens act as boundary conditions to the surface and extracellular flux equations. The solute
7.2.1 Solute Fluxes

The intracellular and extracellular Na\(^+\), K\(^+\) and Cl\(^-\) fluxes are governed by the advective-Nernst-Plank equation. The intracellular fluxes are given by Equation (3.18) and the extracellular fluxes are given by Equation (3.30).

The surface fluxes are composed of Na\(^+\) and K\(^+\) fluxes which are transported between the intracellular space and the outside of the lens by Na\(^+\)/K\(^+\) pumps and K\(^+\) channels. There are no Cl\(^-\) transporters at the surface, hence there is no Cl\(^-\) flux. The surface fluxes are given by

\[
\begin{align*}
\dot{j}_{Na,s} &= 3 \frac{I_{p1} + I_{p2}}{F} \\
\dot{j}_{K,s} &= -2 \frac{I_{p1} + I_{p2}}{F} + \dot{j}_{K,ic}
\end{align*}
\]

where \(I_{p1}\) is given by Equation (3.21), \(I_{p2}\) is given by Equation (3.22), and \(\dot{j}_{K,ic}\) is given by Equa-
tion (3.19). These fluxes act as boundary conditions for the intracellular fluxes.

The transmembrane fluxes are composed of Na\(^+\) and Cl\(^-\) fluxes which are transported between the intracellular and extracellular space by Na\(^+\) and K\(^+\) channels embedded in the fibre cell membrane. There are no K\(^+\) transporters, hence there is no K\(^+\) flux. The transmembrane fluxes are given by,

\[
\begin{align*}
\dot{j}_{Na,m} &= \dot{j}_{Na,ic} \\
\dot{j}_{Cl,m} &= \dot{j}_{Cl,ic}
\end{align*}
\]

where \(\dot{j}_{Na,ic}\) and \(\dot{j}_{Cl,ic}\) are given by Equation (3.8). These fluxes are transmembrane fluxes but are treated as solute sources since the lens model is a bidomain model.

The solute transport parameters defined for the above equations are listed in Table 7.3. The intracellular diffusion coefficients for Na\(^+\), K\(^+\) and Cl\(^-\) \((D_{\alpha i,c})\) in the cross-fibre direction are estimated to be 1\% of the diffusion coefficients in the cytoplasm (Cannell et al. 2004) as discussed in Section 6.2.1. The diffusion coefficient for small ions in the cytoplasm is assumed to be the same as in free solution. This assumption is valid if there is no significant interaction between the ions and the cell membrane or large molecules. Similarly, the extracellular diffusion coefficients for Na\(^+\), K\(^+\) and Cl\(^-\) \((D_{\alpha e,c})\) are assumed to be the same as in free solution. These values are scaled by the \(\tau_c\) (see Table 7.2) to account for the tortuosity of the extracellular cleft. The conductivities for the Na\(^+\), K\(^+\) and Cl\(^-\) channels are the same as those used in the analytic model and are assumed to spatially uniform. The model for the Na\(^+\)/K\(^+\) pumps is a modified form of the model presented by Gao et al. (2000) as discussed in Section 3.5.2.

### 7.2.2 Fluid Velocities

The intracellular fluid flow is driven by hydrostatic and osmotic pressures where the velocity is governed by Equation (4.44). The fluid flow along the extracellular cleft is driven by the hydrostatic pressure and electro-osmotic forces, where the fluid velocity is given by Equation (4.59).

At the surface, of the lens fluid is transported between the intracellular space and outside of the lens via AQP1 channels in the surface membrane. The fluid flow through the surface membrane is modelled as transmembrane flow where the velocity is given by Equation (4.45). This equation acts as a boundary condition to the intracellular fluid flow.
Inside the lens, fluid is transported between the intracellular space and outside of the lens via AQP0 channels in the fibre cell membrane. The fluid flow through the fibre cell membrane is modelled as transmembrane flow where the velocity is given by Equation (4.47).

The parameter values for these velocity equations are listed in Table 7.4. Most of the parameters are similar to the parameters used in the analytic model. A comparison of the parameters between the analytic model and numerical models is listed in Appendix A. The most significant change between the analytic and numerical models is the intercellular, surface and fibre cell hydraulic conductivities, where more recent values are used (see Section 6.3.1).


<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T$</td>
<td>Temperature</td>
<td>310 K</td>
</tr>
<tr>
<td>$k_B$</td>
<td>Boltzmann constant</td>
<td>$1.380 \times 10^{-11}$ pJ/K</td>
</tr>
<tr>
<td>$e$</td>
<td>Electron charge</td>
<td>$1.6 \times 10^{-10}$ nC</td>
</tr>
<tr>
<td>$F$</td>
<td>Faraday constant</td>
<td>$9.648 \times 10^4$ nC/nmol</td>
</tr>
<tr>
<td>$D_{Na}$</td>
<td>Free solution/cytoplasm Na(^+) diffusion(^1)</td>
<td>$1.39 \times 10^{-3}$ mm(^2)/s</td>
</tr>
<tr>
<td>$D_K$</td>
<td>Free solution/cytoplasm K(^+) diffusion(^1)</td>
<td>$2.04 \times 10^{-3}$ mm(^2)/s</td>
</tr>
<tr>
<td>$D_{Cl}$</td>
<td>Free solution/cytoplasm Cl(^-) diffusion(^1)</td>
<td>$2.12 \times 10^{-3}$ mm(^2)/s</td>
</tr>
<tr>
<td>$D_{Na\text{,i,c}}$</td>
<td>Intracellular Na(^+) diffusion</td>
<td>$1.39 \times 10^{-5}$ mm(^2)/s</td>
</tr>
<tr>
<td>$D_{K\text{,i,c}}$</td>
<td>Intracellular K(^+) diffusion</td>
<td>$2.04 \times 10^{-5}$ mm(^2)/s</td>
</tr>
<tr>
<td>$D_{Cl\text{,i,c}}$</td>
<td>Intracellular Cl(^-) diffusion</td>
<td>$2.12 \times 10^{-5}$ mm(^2)/s</td>
</tr>
<tr>
<td>$D_{Na\text{,e,c}}$</td>
<td>Extracellular Na(^+) diffusion</td>
<td>$1.39 \times 10^{-3}$ mm(^2)/s</td>
</tr>
<tr>
<td>$D_{K\text{,e,c}}$</td>
<td>Extracellular K(^+) diffusion</td>
<td>$2.04 \times 10^{-3}$ mm(^2)/s</td>
</tr>
<tr>
<td>$D_{Cl\text{,e,c}}$</td>
<td>Extracellular Cl(^-) diffusion</td>
<td>$2.12 \times 10^{-3}$ mm(^2)/s</td>
</tr>
<tr>
<td>$g_{Na}$</td>
<td>Na(^+) fibre cell membrane conductivity(^2)</td>
<td>2.2 mS/m(^2)</td>
</tr>
<tr>
<td>$g_{Cl}$</td>
<td>Cl(^-) fibre cell membrane conductivity(^2)</td>
<td>2.2 mS/m(^2)</td>
</tr>
<tr>
<td>$g_{K}$</td>
<td>K(^+) surface membrane conductivity(^2)</td>
<td>2.1 S/m(^2)</td>
</tr>
<tr>
<td>$I_{max1}$</td>
<td>Na(^+)/K(^+) pump max. pump rate</td>
<td>0.478 A/m(^2)</td>
</tr>
<tr>
<td>$I_{max2}$</td>
<td>Na(^+)/K(^+) pump max. pump rate</td>
<td>0.065 A/m(^2)</td>
</tr>
<tr>
<td>$K_{Na1}$</td>
<td>Na(^+)/K(^+) pump (\frac{1}{2}) max Na(^+) concentration</td>
<td>9 mM</td>
</tr>
<tr>
<td>$K_{Na2}$</td>
<td>Na(^+)/K(^+) pump (\frac{1}{2}) max Na(^+) concentration</td>
<td>9 mM</td>
</tr>
<tr>
<td>$K_{K1}$</td>
<td>Na(^+)/K(^+) pump (\frac{1}{2}) max K(^+) concentration</td>
<td>3.9 mM</td>
</tr>
<tr>
<td>$K_{K2}$</td>
<td>Na(^+)/K(^+) pump (\frac{1}{2}) max K(^+) concentration</td>
<td>0.4 mM</td>
</tr>
</tbody>
</table>
7.2 Governing Equations


<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( R ) Gas constant</td>
<td>( 8.314 \times 10^3 ) pJ/(nmol.K)</td>
</tr>
<tr>
<td>( \varepsilon_0 ) Permittivity of vacuum</td>
<td>( 8.854 ) pF/m</td>
</tr>
<tr>
<td>( \varepsilon_r ) Dielectric constant (water)</td>
<td>( 80.4 )</td>
</tr>
<tr>
<td>( \tilde{h} ) Extracellular cleft width</td>
<td>( 40 ) nm</td>
</tr>
<tr>
<td>( \mu ) Fluid viscosity</td>
<td>( 700 ) mPa ms</td>
</tr>
<tr>
<td>( \zeta ) Zeta potential</td>
<td>( -15 ) mV</td>
</tr>
<tr>
<td>( \lambda_D ) Debye length</td>
<td>( 1 ) nm</td>
</tr>
<tr>
<td>( L_p ) Intercellular hydraulic permeability</td>
<td>( 4.46 \times 10^{-10} ) m/(Pa s)</td>
</tr>
<tr>
<td>( L_f ) Fibre cell membrane hydraulic permeability</td>
<td>( 1.34 \times 10^{-13} ) m/(Pa s)</td>
</tr>
<tr>
<td>( L_s ) Surface hydraulic permeability</td>
<td>( 8.89 \times 10^{-13} ) m/(Pa s)</td>
</tr>
<tr>
<td>( \sigma ) Intercellular membrane reflectance</td>
<td>1</td>
</tr>
<tr>
<td>( \tilde{K}_e ) Extracellular hydraulic conductivity</td>
<td>( 3.05 \times 10^{-14} ) m²/(Pa s)</td>
</tr>
<tr>
<td>( \tilde{k}_e ) Extracellular electro-osmotic coefficient</td>
<td>( 1.45 \times 10^{-8} ) m²/(V s)</td>
</tr>
</tbody>
</table>

7.2.3 Conservation Equations

The amount of solute, the net charge and the volume of fluid must be conserved in the lens model. The conservation of the amount of solute is governed by the rate of change of the concentration equations (Equations (3.34) and (3.35)). The net charge is conserved by satisfying the weak form of the electroneutrality condition (Equations (3.31) and (3.32)). The volume of fluid is conserved by the conservation of mass equations (Equations (4.65) and (4.66)).

7.2.4 Initial Conditions

It is important to choose the appropriate initial concentrations when solving the model. Choosing concentrations that result in large osmotic pressures across the fibre cell membrane will lead to large transmembrane, intracellular and extracellular fluid velocities that may cause instabilities. The initial concentrations listed in Table 7.5 were chosen, in order of importance, to be electrically neutral, to minimise the osmotic pressure across the fibre cell membrane and to be close to the expected steady-state concentrations.
Table 7.5: Initial conditions.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{Nat}$</td>
<td>Intracellular Na$^+$ concentration</td>
<td>29.5 mM</td>
</tr>
<tr>
<td>$C_{K_i}$</td>
<td>Intracellular K$^+$ concentration</td>
<td>100 mM</td>
</tr>
<tr>
<td>$C_{Cl_i}$</td>
<td>Intracellular Cl$^-$ concentration</td>
<td>12.5 mM</td>
</tr>
<tr>
<td>$C_{Nat}$</td>
<td>Extracellular Na$^+$ concentration</td>
<td>107 mM</td>
</tr>
<tr>
<td>$C_{K_e}$</td>
<td>Extracellular K$^+$ concentration</td>
<td>3 mM</td>
</tr>
<tr>
<td>$C_{Cl_e}$</td>
<td>Extracellular Cl$^-$ concentration</td>
<td>110 mM</td>
</tr>
</tbody>
</table>

7.3 Results and Discussion

The one-dimensional model took 3-4 hours to solve. A mesh convergence analysis was performed by comparing the results from a 4, 8, 12 and 16 element model to the results from a 20 element model (see Figure 7.4).

![Figure 7.4](image)

*Figure 7.4: Convergence of model results with increased mesh resolution. The results from models with 4, 8, 12 and 16 elements were compared with results from a model with 20 elements.*

Most model results, except the intracellular Na$^+$ concentration, have converged to within a RMS difference of 2% for models with 8 or more elements. However, visually, the intracellular Na$^+$ concentration appears to be converged in models with 8 or more elements (see Figure 7.5).

7.3.1 Electrical Potential

Mathias & Rae (1985) measured the potential in frog lenses by plunging an electrode along the anterior-posterior pole axis of the lens. Figure 7.6 show the potential predicted by the model and
the experimentally measured potential – the modelled potential shows reasonable agreement with the measured potential. The curvature of the predicted potentials are similar but the values are slightly offset. The modelled extracellular potential is $5 - 10$ mV more positive and the modelled intracellular potential is approximately $10$ mV more negative than the measured potential. These differences can be reduced by adjusting the model parameters, particularly the transmembrane ion conductivities and the Na$^+$/K$^+$ pump currents.

### 7.3.2 Solute Concentrations

Figure 7.7 shows the intracellular and extracellular ion concentrations predicted by the numerical model. The mean concentration of each solute in each domain was calculated using

$$\bar{C} = \frac{\sum_k C_\alpha(k) V(k)}{\sum_k V(k)}$$

where $\alpha$ is the species and $k$ is the element number. The mean intracellular concentrations from the model along with values from the literature for the frog lens (see Section 6.4.2 for details on these studies) are listed in Table 7.6. The predicted mean Na$^+$ concentrations are within the measured values by Delamere & Duncan (1977) and Duncan (1970) but are high compared to recent values measured by Mathias (see Figure 8.14 in Section 8.4.2). The modelled mean K$^+$ concentration is 20 mM (20 %) above and the modelled mean Cl$^-$ concentration is 3-8 mM (26-46 %) below the measured values. The mean K$^+$ concentration can be reduced by reducing the Na$^+$/K$^+$ pump rate.
**Figure 7.6:** The modelled and measured steady-state intracellular and extracellular potential. Mathias & Rae (1985) measured the potential in frog lenses by plunging electrodes along the optical axis of the lens. The oscillations are due to the electrode moving between the intracellular and extracellular space as it is plunged into the lens.

**Table 7.6:** The mean concentrations predicted by the model and experimentally measured. The measured values were calculated using Equation (6.14) with a 1% extracellular volume fraction and extracellular concentrations of 107 mM for Na⁺, 3 mM for K⁺, and 110 mM for Cl⁻. References: 1. Delamere & Duncan (1977); 2. Duncan (1970); 3. Guerschanik et al. (1977).

<table>
<thead>
<tr>
<th></th>
<th>Modelled</th>
<th>Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Na⁺]_i</td>
<td>15.1 mM</td>
<td>13.8 mM [1] 21.5 mM [2]</td>
</tr>
<tr>
<td>[K⁺]_i</td>
<td>111.0 mM</td>
<td>91.2 mM [1]</td>
</tr>
<tr>
<td>[Cl⁻]_i</td>
<td>9.1 mM</td>
<td>16.8 mM [1]     12.3 mM [3]</td>
</tr>
</tbody>
</table>

The modelled mean extracellular concentrations were 102.1 mM for Na⁺, 6.6 mM for K⁺, and 108.6 mM for Cl⁻. In experimental studies, it is common to assume the extracellular concentrations are the same as the concentrations outside the lens. But it is reasonable to expect some concentration changes within the extracellular space due to potential gradients and fluid flow. Between the surface and the nucleus, the model predicted a 13 mM decrease for the sodium concentration, a 13 mM increase in the potassium concentration and a minor change for the chloride concentration.

The analytic model predicted a 18 mM increase in the K⁺ concentration (see Figure 6.16) and a 18 mM decrease in the Na⁺ concentration. There is a 27 % difference between the numerical and analytic prediction but they display the same trend. These results cannot be discussed further since there are no experimentally measured values for the extracellular concentrations.
7.3 Results and Discussion

Figure 7.7: The intracellular and extracellular concentrations that were predicted by the numerical model.

7.3.3 Solute Fluxes

Figure 7.8 shows the steady-state extracellular Na\(^+\) and Cl\(^-\) fluxes predicted by the numerical model. The sodium enters the lens via the extracellular space, crosses the fibre cell membrane into the intracellular space, and exits the lens via the intracellular space. There is a small chloride circulation that is localised to the interior of the lens. It travels towards the center of the lens via the extracellular space, crosses the fibre cell membrane into the intracellular space, travels towards the surface via intracellular space, and crosses the fibre cell membrane back into the extracellular space. At steady-state, the net extracellular potassium flux is zero but there exists a circulating flux between the intracellular space and the outside of the lens at the surface via K\(^+\) channels and Na\(^+\)/K\(^+\) pumps. The zero K\(^+\) flux is unrealistic since a circulation between the pole and the equator that is localised to either the intracellular or extracellular space can exist. This circulation has
been measured by Candia & Zamudio (2002) and is predicted by the two-dimensional model (see Section 8.4.3).

To ensure continuity at steady-state, the solute flow \( (J = j A) \), where \( J \) is the solute flow, \( j \) is the solute flux, and \( A \) is the area normal to the flux vector) in the intracellular space must be equal and opposite to the solute flow in the extracellular space. Since the cross-sectional area of the intracellular space is 99 times greater than that of the extracellular space, the intracellular fluxes are 99 times smaller than the extracellular fluxes but in the opposite direction.

The circulation of \( \text{Na}^+ \), \( \text{K}^+ \) and \( \text{Cl}^- \) predicted by the numerical model are consistent with those predicted by the analytic model. The analytic model predicted 22 pmol/s of \( \text{Na}^+ \) entering the whole lens surface via the extracellular space. The surface area \( (S) \) of the whole lens is given by \( S = 4 \pi r^2 \), where \( r \) is the radius of the lens. Given a radius of 1.6 mm, the surface area is 32.2 mm\(^2\). The extracellular space occupies 1\% of the surface area, which is 0.32 mm\(^2\). The flux predicted by the analytic model is given by dividing the \( \text{Na}^+ \) flowing into the extracellular space by the extracellular surface area, hence the extracellular flux predicted by the analytic model is \(-6.8 \times 10^{-5}\) nmol/(mm\(^2\) ms). The numerical model predicted an extracellular \( \text{Na}^+ \) flux of \(-7.43 \times 10^{-5}\) nmol/(mm\(^2\) ms). The small difference is due to the higher \( \text{Na}^+/\text{K}^+ \) pump rate in the numerical model.

The fluxes are consistent with the general hypothesis of a circulating current, where \( \text{Na}^+ \) enters via the extracellular space, crosses the fibre cell membrane and exits via the intracellular space.
The Na\(^+\) and K\(^+\) fluxes are comparable to those listed in literature but this is expected since the circulation is driven by the Na\(^+\)/K\(^+\) pumps and the pump rate is based on experimentally measured values from the literature. The one-dimensional model is unable to simulate the angular dependence of the circulating current, a limitation that is addressed by the two-dimensional model.

### 7.3.4 Fluid Flow

Figure 7.9 shows the predicted intracellular, extracellular and transmembrane fluid flow velocity in the lens. The fluid enters the lens via the extracellular space, crosses the fibre cell membrane and exits via the intracellular space. This is consistent with the hypothesised fluid circulation in the lens.

![Steady-state Fluid Velocities](image)

**Figure 7.9:** The intracellular, extracellular and transmembrane fluid flow velocity predicted by the one-dimensional numerical model.
The mass flow entering the extracellular space is equal to the mass flow exiting the intracellular space, indicating that the mass in the model is conserved. These velocity profiles and values are similar to those predicted by the analytical model (see Figure 6.18 in Section 6.4.4).

If we consider the extracellular fluid flow only, in other word, we assume that the fluid entering only the extracellular space at the surface is measured, the extracellular velocity \( (u_e) \), which is the mass flow per cross-sectional area of the extracellular cleft, is \( 0.4 \times 10^{-3} \) mm/s. The surface velocity \( (u_s) \), which is the mass flow per lens surface area, is given by \( u_s = \Lambda_e u_e \), where \( \Lambda_e \) is the extracellular volume fraction. Given a extracellular volume fraction of 1%, the surface velocity is 4 nm/s, which is similar to the surface velocity of 3.1 nm/s predicted by the analytic model (see Section 6.4.4). A significant factor contributing to the slightly higher surface velocity in the numerical model is the higher steady-state Na\(^+\)/K\(^+\) pump current and the smaller extracellular volume fraction. The surface velocity predicted by the numerical model is within an order of magnitude of the spread of measured values, which are 26 nm/s by Fischbarg et al. (1999), 1.2 nm/s by Candia & Gerometta (2003), and −10 nm/s, 0.64 nm/s, and −1.55 nm/s by Candia (2004). These studies are covered in Section 6.4.4.

### 7.3.5 Hydrostatic Pressure

Figure 7.10 shows the intracellular and extracellular hydraulic pressure predicted by the numerical model. The extracellular pressure, which ranged between 0 kPa at the surface and 7.5 kPa at the...
center, compared well with the extracellular pressure predicted by analytic model, which ranged between 0 kPa at the surface and -5.6 kPa (-42 mmHg) at the center (see Figure 6.18). For the analytic model, the intracellular pressure was assumed to be spatially constant at a value of 0 kPa in order to render the analytic equations solvable. The numerical model did not have to make this assumption and predicted an intracellular pressure that ranged between $-16.3$ kPa at the surface and $-8.0$ kPa at the center. Since experimentally measured values of the pressure in the lens are not available from the literature, these results are not discussed.

7.4 Summary

The one-dimensional numerical model was consistent with the analytical model. These results assure us that the modelling framework is capable of modelling the solute and fluid transport in the lens. There were small differences between the model results that can be accounted for by the differences in the modelling approaches and parameters. The key differences in the modelling approach include: the use of the advective-Nernst-Plank equation to model individual solutes instead of using Ohms law to model a current that represents all solutes; and allowing the intracellular variables (concentrations, pressure, and voltage) to spatially vary. Two slight changes in parameters include the 17% decrease in the extracellular volume fraction and the 4% increase in the Na$^+/K^+$ pump rate.

In order to solve the equations in the analytic model, the intracellular voltage, concentrations, hydrostatic pressure, Nernst potentials and membrane conductances were assumed to be spatially uniform. For the numerical model, the intracellular voltage, concentrations and hydrostatic pressure are unconstrained dependent variables and the membrane conductances need not be spatially uniform, although they were in this model. These improvements allow us to develop a two-dimensional model that accounts for the radial and angular dependence of properties, ion fluxes, fluid flow, concentrations, potentials and hydrostatic pressures.

This one-dimensional numerical model leads on to the development of the two-dimensional numerical model, which is discussed in the next chapter.
The Two-Dimensional Model

8.1 Introduction

The one-dimensional model captures the key features of the transport of solutes and fluid in the lens that compared well with experimental measurements. However, this model is limited to radial transport and fails to account for the experimentally measured circulation of solutes and fluid between the poles and the equator. The development from a one-dimensional to a two-dimensional model is the next logical step to overcome this limitation. In addition to modelling the the angular transport of solutes and fluid in the lens, the two-dimensional model can capture the angular variation of lens properties which itself has a significant influence on the solute and fluid transport.

The two-dimensional model represents an axial slice in the lens (see Figure 8.1). This model assumes symmetry about the $x$-axis, which is a reasonable assumption since the only asymmetry about the $x$-axis is the twist of the fibre cell orientation (Kuszak, Zolotski & Sivertson 2004) and the structure of the sutures.

This chapter covers the development of two two-dimensional models, which are referred to as ”Model A” and ”Model B”. Model A is based on the simple extension of the one-dimensional model to two dimensions. All model parameters in Model A are spatially uniform except for the fibre angles, which are perpendicular to the radial direction, and the Na$^+$/K$^+$ pump current, which varies between the equator and poles. Model B extends Model A to incorporate the spatial variation of two structural properties, the tapering of the fibre cell between the equator and poles, and the variation of the extracellular cleft width between the equator, poles and center of the lens. The variation of the cleft width was specifically chosen to represent the sutures in order to investigate the influence of the sutures on solute and fluid transport in the lens.
To demonstrate the application of the lens model, the age-related change in ion concentrations and potential were modelled by changing the radius of the model to mimic the growth of the lens with age. The results were compared to age-related changes observed by Duncan et al. (1989).

This chapter begins by discussing the mesh, governing equations and model parameters for Model A and Model B. The results from both models are presented in Section 8.4 and discussed in Section 8.5. The application of the model to simulate the age-related changes in lens physiology is covered in Section 8.6.

### 8.2 Mesh

Figure 8.2 shows the mesh representing the model of the axial slice. This is generated by Gmsh using the script listed in Appendix D. This mesh is extruded about the $x$-axis by an angle $\Delta \theta_{eq}$ to obtain the three-dimensional properties of the mesh – Figure 8.2b shows the extruded three-dimensional mesh. The methods used to extrude the mesh are covered in Section 5.1. The element widths at the surface are smaller than those at the center since the largest gradient occurs near the surface. The parameters used to generate the mesh are listed in Table 8.1.


<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R$</td>
<td>Radius</td>
<td>1.60 mm</td>
</tr>
<tr>
<td>$\Delta \eta_{c0}$</td>
<td>Center element width</td>
<td>0.60 mm</td>
</tr>
<tr>
<td>$\Delta \eta_{c1}$</td>
<td>Surface element width</td>
<td>0.06 mm</td>
</tr>
<tr>
<td>$\Delta \theta_{eq}$</td>
<td>Sweep angle (equator)</td>
<td>0.1 radians</td>
</tr>
<tr>
<td>$N_E$</td>
<td>Number of elements</td>
<td>108</td>
</tr>
</tbody>
</table>
Figure 8.2: The mesh (a), which is generated by Gmsh, is extruded about the \( x \)-axis to obtain the three-dimensional mesh (b) that represents the slice being modelled.

Figure 8.3 shows the spatial variation of the fibre angle. The fibre angles are perpendicular to the radial direction. These fibre angles are idealised but provide a reasonable approximation for the bulk of the lens. The fibre angles fail to capture the fibre cell twist between the poles (Kuszak, Zoltoski & Sivertson 2004) but a three-dimensional model would be required to capture this. The fibre angles ignore the omega-shaped fibre angles near the sutures (Zampighi et al. 2000).

The two-dimensional model is a bidomain model. The bidomain properties shown in Table 8.2 are calculated from the tissue properties.

In Model B, the fibre cell height and extracellular cleft width is spatially varied. The cell height is varied between the equator and the poles, where the cell height at the poles is a third the cell height at the equator (Figure 8.4a).

The extracellular cleft width is interpolated between the equator (40 nm), poles (60 nm) and the center (10 nm) of the lens using Hill functions (Figure 8.4b). The values at the landmarks and the
interpolation profiles between the landmarks were chosen to reflect some observations of the lens documented in the literature. The cleft width dilates within $30^\circ$ of the poles and linearly constricts between the polar surface and the center in order to represent the sutures. An extracellular diffusion barrier, which is impenetrable to macromolecules, has been observed in the lens by Moffat & Pope (2002) and Grey et al. (2003). This is represented by a rapid constriction of the extracellular cleft about $400 \, \mu m$ into the lens between the equator and center. The cleft width at the equator is based on the value used by Mathias (1985b) in the analytic model. The cleft width at the poles is based on values measured Zampighi et al. (2000) for the Type 0 cells, and the cleft width at the center is an estimate based on observations of the diffusion barrier.

The spatial variation of the cell height and cleft width has a flow-on effect on the membrane density (Figure 8.5), and the intracellular and extracellular volume fractions (Figure 8.6). The membrane density is calculated using Equation (6.2), which assumes the cell width and tortuosity is spatially constant. The intracellular and extracellular volume fractions are calculated using Equations (6.3) and (6.4).
8.3 Governing Equations

The governing equations for the solute and fluid transport in the lens are covered in Sections 3.5 and 4.8, respectively. This section will discuss the components of the model and the governing equations and parameters used within it. For a concise and complete list of equations and parameters see Appendix A.

Figure 8.7 shows the dependent variables \((C, \phi, p)\), solute fluxes \((j)\), and fluid velocities \((u)\) included in the model. Since the model represents an axial slice of the lens, the flux and velocity vectors exist in both the fibre and cross-fibre direction.
Like the one-dimensional model, the two-dimensional model has ten dependent variables (see Section 7.2):

- $C_{Na_i}, C_{K_i}, C_{Cl_i}$ – intracellular Na$^+$, K$^+$ and Cl$^-$ concentrations
- $C_{Na_e}, C_{K_e}, C_{Cl_e}$ – extracellular Na$^+$, K$^+$ and Cl$^-$ concentrations
- $\phi_i$ – intracellular potential
- $\phi_e$ – extracellular potential
- $p_i$ – intracellular pressure
- $p_e$ – extracellular pressure

The ion concentrations ($C_{Na_o}, C_{K_o}, C_{Cl_o}$), electrical potential ($\phi_o$) and hydraulic pressure ($p_o$) outside the lens act as boundary conditions to the surface and extracellular flux equations in the cross-fibre direction. The solute fluxes can be categorised into intracellular fluxes ($j_{ai,f}, j_{ai,c}$), extracellular fluxes ($j_{ae,f}, j_{ae,c}$), surface fluxes ($j_{a,s}$), and transmembrane fluxes ($j_{a,m}$). Similarly, the fluid velocities can be categorised into the intracellular velocity ($u_{ai,f}, u_{ai,c}$), extracellular velocity ($u_{ae,f}, u_{ae,c}$), surface velocity ($u_{a,s}$), and transmembrane velocity ($u_{a,m}$).

### 8.3.1 Solute Fluxes

The intracellular and extracellular Na$^+$, K$^+$ and Cl$^-$ fluxes are governed by the advective-Nernst-Plank equation. The intracellular fluxes in the fibre and cross-fibre directions are given by Equa-
tions (3.17) and (3.18) and the extracellular fluxes in the fibre and cross-fibre directions are given by Equations (3.29) and (3.30).

The surface fluxes consist of Na\(^+\) and K\(^+\) fluxes which are transported between the intracellular space and the outside of the lens by Na\(^+\)/K\(^+\) pumps and K\(^+\) channels. There are no Cl\(^-\) transporters at the surface, hence there is no Cl\(^-\) flux. The surface fluxes are given by

\[
\begin{align*}
  j_{Na,s} &= 3 \frac{I_{p1} + I_{p2}}{F} \\
  j_{K,s} &= -2 \frac{I_{p1} + I_{p2}}{F} + j_{K,ic}
\end{align*}
\]

where \(I_{p1}\) is given by Equation (3.21), \(I_{p2}\) by Equation (3.22), and \(j_{K,ic}\) by Equation (3.19). These fluxes act as boundary conditions for the intracellular fluxes.

The transmembrane fluxes are composed of Na\(^+\) and Cl\(^-\) fluxes which are transported between the intracellular and extracellular space by Na\(^+\) and K\(^+\) channels embedded in the fibre cell membrane. There are no K\(^+\) transporters, hence there is no K\(^+\) flux. The transmembrane fluxes are given by,

\[
\begin{align*}
  j_{Na,m} &= j_{Na,ic} \\
  j_{Cl,m} &= j_{Cl,ic}
\end{align*}
\]

where \(j_{Na,ic}\) and \(j_{Cl,ic}\) are given by Equation (3.8). Although these fluxes are transmembrane fluxes, since the lens model is a bidomain model they are treated as solute sources.

The solute transport parameters defined for the above equations are listed in Table 8.3. The parameters are the same for Model A and Model B since they are not dependent on cell height or extracellular cleft width.

The diffusion coefficient for Na\(^+\), K\(^+\) and Cl\(^-\) in the cytoplasm of the fibre cell is assumed to be the same as in free solution. This assumption is valid if there is no significant interaction between the ions and the cell membrane or large molecules. Therefore, the diffusion coefficients in the fibre direction (\(D_{\alpha i,f}\)) are the same as in free solution. The intracellular diffusion coefficients for Na\(^+\), K\(^+\) and Cl\(^-\) (\(D_{\alpha i,c}\)) in the cross-fibre direction are estimated to be 1% of the diffusion coefficients in the cytoplasm (Cannell et al. 2004) as discussed in Section 6.2.1.

The extracellular diffusion coefficients for Na\(^+\), K\(^+\) and Cl\(^-\) in the both fibre and cross-fibre direc-
of the maximum pump current over the lens surface for the $\alpha$ form of the model presented by Gao et al. (2000) as discussed in Section 3.5.2. The distributions $D_{\alpha e,f}$ are assumed to be the same as in free solution. The diffusion coefficients in the cross-fibre direction are scaled by $\tau_c$ (see Table 8.2) to account for the tortuosity of the extracellular cleft. There is no tortuosity in the fibre direction.

The conductivities for the Na$^+$, K$^+$ and Cl$^-$ channels are the same as those used in the analytic model and are assumed to be spatially uniform. The model for the Na$^+/K^+$ pumps is a modified form of the model presented by Gao et al. (2000) as discussed in Section 3.5.2. The distributions of the maximum pump current over the lens surface for the $\alpha 1$ and $\alpha 2$ isoforms of the Na$^+/K^+$ are shown Figure 8.8.


| $T$ | Temperature | 310 K |
| $k_B$ | Boltzmann constant | 1.380×10$^{-11}$ pJ/K |
| $e$ | Electron charge | 1.6×10$^{-10}$ nC |
| $F$ | Faraday constant | 9.648×10$^4$ nC/nmol |
| $D_{Na}$ | Free solution/cytoplasm Na$^+$ diffusion$^1$ | 1.39×10$^{-3}$ mm$^2$/s |
| $D_K$ | Free solution/cytoplasm K$^+$ diffusion$^1$ | 2.04×10$^{-3}$ mm$^2$/s |
| $D_{Cl}$ | Free solution/cytoplasm Cl$^-$ diffusion$^1$ | 2.12×10$^{-3}$ mm$^2$/s |
| $D_{Na,f}$ | Intracellular Na$^+$ diffusion (fibre) | 1.39×10$^{-3}$ mm$^2$/s |
| $D_{K,f}$ | Intracellular K$^+$ diffusion (fibre) | 2.04×10$^{-3}$ mm$^2$/s |
| $D_{Cl,f}$ | Intracellular Cl$^-$ diffusion (fibre) | 2.12×10$^{-3}$ mm$^2$/s |
| $D_{Na,c}$ | Intracellular Na$^+$ diffusion (cross-fibre) | 1.39×10$^{-5}$ mm$^2$/s |
| $D_{K,c}$ | Intracellular K$^+$ diffusion (cross-fibre) | 2.04×10$^{-5}$ mm$^2$/s |
| $D_{Cl,c}$ | Intracellular Cl$^-$ diffusion (cross-fibre) | 2.12×10$^{-5}$ mm$^2$/s |
| $D_{Na,e,c}$ | Extracellular Na$^+$ diffusion (fibre) | 1.39×10$^{-3}$ mm$^2$/s |
| $D_{K,e,f}$ | Extracellular K$^+$ diffusion (fibre) | 2.04×10$^{-3}$ mm$^2$/s |
| $D_{Cl,e,f}$ | Extracellular Cl$^-$ diffusion (fibre) | 2.12×10$^{-3}$ mm$^2$/s |
| $D_{Na,e,c}$ | Extracellular Na$^+$ diffusion (cross-fibre) | 1.39×10$^{-3}$ mm$^2$/s |
| $D_{K,e,c}$ | Extracellular K$^+$ diffusion (cross-fibre) | 2.04×10$^{-3}$ mm$^2$/s |
| $D_{Cl,e,c}$ | Extracellular Cl$^-$ diffusion (cross-fibre) | 2.12×10$^{-3}$ mm$^2$/s |
| $\tau_c$ | Tortuosity$^2$ | 0.16 |
| $g_{Na}$ | Na$^+$ fibre cell membrane conductivity$^2$ | 2.2 mS/m$^2$ |
| $g_{Cl}$ | Cl$^-$ fibre cell membrane conductivity$^2$ | 2.2 mS/m$^2$ |
| $g_K$ | K$^+$ surface membrane conductivity$^2$ | 2.1 S/m$^2$ |
| $I_{max1}$ | Na$^+/K^+$ pump max. pump rate | 0.478 A/m$^2$ |
| $I_{max2}$ | Na$^+/K^+$ pump max. pump rate | 0.065 A/m$^2$ |
| $K_{1/2 Na1}$ | Na$^+/K^+$ $\alpha_1$ pump $1/2$ max Na$^+$ concentration | 9 mM |
| $K_{1/2 Na2}$ | Na$^+/K^+$ $\alpha_2$ pump $1/2$ max Na$^+$ concentration | 9 mM |
| $K_{1/2 K1}$ | Na$^+/K^+$ $\alpha_1$ pump $1/2$ max K$^+$ concentration | 3.9 mM |
| $K_{1/2 K2}$ | Na$^+/K^+$ $\alpha_2$ pump $1/2$ max K$^+$ concentration | 0.4 mM |
8.3 Governing Equations

Figure 8.8: Maximum pump rates at the lens surface for the $\alpha_1$ and $\alpha_2$ isoforms of the Na$^+$/K$^+$ pumps. Note: this figure is a copy of Figure 6.11, reproduced for convenience.

8.3.2 Fluid Velocities

The intracellular fluid flow is driven by hydrostatic and osmotic pressures where the velocity in the fibre and cross-fibre directions are governed by Equations (4.40) and (4.44). The fluid flow along the extracellular cleft is driven by the hydrostatic pressure and electro-osmotic forces where the fluid velocity in the fibre and cross-fibre directions are given by Equations (4.58) and (4.59).

At the surface of the lens, fluid is transported between the intracellular space and outside of the lens via AQP1 channels in the surface membrane. The fluid flow through the surface membrane is modelled as transmembrane flow where the velocity is given by Equation (4.45). This equation acts as a boundary condition to the intracellular fluid flow in the cross-fibre direction.

Inside the lens, fluid is transported between the intracellular space and outside of the lens via AQP0 channels in the fibre cell membrane. The fluid flow through the fibre cell membrane is modelled as transmembrane flow where the velocity is given by Equation (4.47).

The parameter values for these velocity equations are listed in Table 8.4. Most of the parameters are the same as the ones used in the one-dimensional numerical model. The parameters that change are the intracellular hydraulic conductivity along the fibre cells and the extracellular hydraulic conductivity and electro-osmotic coefficient. A full comparison of the parameters values between the analytic model and numerical models is listed in Appendix A.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R$ Gas constant</td>
<td>$8.314 \times 10^3$ pJ/(nmol.K)</td>
</tr>
<tr>
<td>$\varepsilon_0$ Permittivity of vacuum$^4$</td>
<td>8.854 pF/m</td>
</tr>
<tr>
<td>$\varepsilon_r$ Dielectric constant (water)$^6$</td>
<td>80.4</td>
</tr>
<tr>
<td>$h$ Extracellular cleft width$^2$</td>
<td>40 nm</td>
</tr>
<tr>
<td>$\mu$ Fluid viscosity</td>
<td>700 mPa.ms</td>
</tr>
<tr>
<td>$\zeta$ Zeta potential$^1$</td>
<td>$-15$ mV</td>
</tr>
<tr>
<td>$\lambda_D$ Debye length$^2$</td>
<td>1 nm</td>
</tr>
<tr>
<td>$L_p$ Intercellular hydraulic permeability$^3$</td>
<td>$4.46 \times 10^{-10}$ m/(Pa s)</td>
</tr>
<tr>
<td>$L_f$ Fibre cell membrane hydraulic permeability$^3$</td>
<td>$1.34 \times 10^{-13}$ m/(Pa s)</td>
</tr>
<tr>
<td>$L_s$ Surface hydraulic permeability$^3$</td>
<td>$8.89 \times 10^{-13}$ m/(Pa s)</td>
</tr>
<tr>
<td>$\sigma$ Intercellular membrane reflectance$^1$</td>
<td>$1$</td>
</tr>
<tr>
<td>$\tilde{K}_i$ Intracellular hydraulic conductivity</td>
<td>$7.37 \times 10^{-10}$ m$^2$/(Pa s)</td>
</tr>
<tr>
<td>$\tilde{K}_e$ Extracellular hydraulic conductivity</td>
<td>$1.90 \times 10^{-13}$ m$^2$/(Pa s)</td>
</tr>
<tr>
<td>$\tilde{k}_e$ Extracellular electro-osmotic coefficient</td>
<td>$1.45 \times 10^{-8}$ m$^2$/(V s)</td>
</tr>
</tbody>
</table>

The spatial variation of cell height effects the spatial variation of intracellular hydraulic conductivity (Figure 8.9) along the fibre cell through Equation (4.41). The spatial variation of extracellular cleft width effects the spatial variation of extracellular hydraulic conductivity (Figure 8.10a) and electro-osmotic coefficient (Figure 8.10b) through Equations (4.56) and (4.57), respectively.

Figure 8.9: Spatial variation of the intracellular hydraulic conductivity in the fibre direction.

Figure 8.10: Spatial variation of the extracellular hydraulic conductivity (a) and electro-osmotic coefficient (b).
8.3.3 Conservation Equations

The concentration of solutes in the lens is governed by Equations (3.34) and (3.35). The volume of fluid in the lens is conserved by the conservation of mass equations (Equations (4.65) and (4.66)). To satisfy the electro-neutrality condition, the net charge at any point must be zero. The charge balance in the lens is maintained by satisfying the weak form of the electroneutrality condition (Equations (3.31) and (3.32)).

8.3.4 Initial Conditions

It is important to choose the appropriate initial concentrations when solving the model. Choosing concentrations that result in large osmotic pressures across the fibre cell membrane will lead to large transmembrane, intracellular and extracellular fluid velocities that may cause instabilities. The initial concentrations listed in Table 8.5 were chosen, in order of importance, to be electrically neutral, to minimise the osmotic pressure across the fibre cell membrane and to be close to the expected steady-state concentrations.

| \( C_{Na_i} \) | Intracellular \( Na^+ \) concentration | 29.5 mM |
| \( C_{K_i} \) | Intracellular \( K^+ \) concentration | 100 mM |
| \( C_{Cl_i} \) | Intracellular \( Cl^- \) concentration | 12.5 mM |
| \( C_{Na_e} \) | Extracellular \( Na^+ \) concentration | 107 mM |
| \( C_{K_e} \) | Extracellular \( K^+ \) concentration | 3 mM |
| \( C_{Cl_e} \) | Extracellular \( Cl^- \) concentration | 110 mM |
8.4 Results and Discussion

Model A took five days to solve and Model B just over a day, on a computer with two Dual Core AMD Opteron 2.2 GHz processors and 8 GB of shared memory. Although the computer had four processors, only one was used to solve each model. Parallelisation of the modelling code to use multiple processors is discussed in Chapter 9 as future work.

The time required to solve a model depends on the number of dependent variables and elements. Between Model A and Model B, the number of dependent variables and elements are the same, yet the solution time of Model A is five times that of Model B. The only difference between the two models is the spatial distribution of model parameters. Therefore, it appears the model parameters have a significant influence on the solution time of the model. In Model B, the spatial variation of the extracellular cleft width and the tapering of the fibre cells leads to an increase in coupling between the surface and center of the lens and between the intracellular and extracellular space. This increase in coupling allows the model to reach steady-state faster.

A proper convergence analysis could not be performed on the two-dimensional model (without further development of parallel processing algorithms and more efficient solution methods) due to the unrealistic solution time required. In one case, the outer layer of elements were refined in the radial direction and the model results were essentially the same. However, there are 6 element in the radial direction of the mesh, therefore, from the mesh convergence data from the one-dimensional model, we expect the RMS difference for most fields to be less than 2%.

8.4.1 Electrical Potential

Figure 8.11 shows the predicted electrical potential predicted by Model A and Model B. Table 8.6 lists the mean potentials predicted by Model A and Model B. Figure 8.12 shows the radial profile of the modelled potential in the anterior pole, equatorial, and posterior pole directions for Model B and the frog potentials measured by Mathias & Rae (1985).

<table>
<thead>
<tr>
<th></th>
<th>1D Model</th>
<th>Model A</th>
<th>Model B</th>
<th>Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\phi_i$</td>
<td>-75.1 mV</td>
<td>-73.6 mV</td>
<td>-70.2 mV</td>
<td>-70 mV$^{[1]}$; -70 to -50 mV$^{[2]}$</td>
</tr>
<tr>
<td>$\phi_e$</td>
<td>-8.9 mV</td>
<td>-4.2 mV</td>
<td>-4.5 mV</td>
<td>-30 mV$^{[1]}$; -0 to -36 mV$^{[2]}$</td>
</tr>
</tbody>
</table>

Table 8.6: Mean potentials predicted by the models and experimentally measured values. References: 1. Delamere & Paterson (1979); 2. Mathias & Rae (1985).
There is little difference in the spatial distribution of the potential between Model A and Model B, but there is a small difference in the mean and range of potentials. The modelled intracellular potential, $-68.5$ to $-72.2$ mV, compares well with the potentials measured by Delamere & Paterson (1979) ($\sim-70$ mV) and Mathias & Rae (1985) ($-50$ to $-70$ mV), but the modelled extracellular potential is between one third to a half of the measured potential.

Mathias & Rae (1985) measured the potential along the anterior and posterior pole axes and noted the symmetry between the poles. The two-dimensional model predicts this symmetry where the radial profile is constant in the angular direction (see Figure 8.12). Although, there is a small variation in the modelled potential, it is within the noise range of the measured potential.
Figure 8.11: Intracellular and extracellular potential predicted by Model A (left) and Model B (right).

Figure 8.12: The potential profiles along the anterior, equatorial and posterior radials predicted by Model B with the experimentally measured values by Mathias & Rae (1985).
8.4.2 Solute Concentrations

Figure 8.13 shows the Na\(^+\), K\(^+\) and Cl\(^-\) concentrations predicted by Model A and Model B and Table 8.7 lists the mean concentrations predicted by Model A and Model B, and the experimentally measured values. The concentration field difference between the one-dimensional model, Model A and Model B is minor, therefore we will only discuss Model B in comparison to measured data.

<table>
<thead>
<tr>
<th></th>
<th>1D Model</th>
<th>Model A</th>
<th>Model B</th>
<th>Measured†</th>
</tr>
</thead>
<tbody>
<tr>
<td>([\text{Na}^+]_i)</td>
<td>15.1 mM</td>
<td>16.4 mM</td>
<td>18.8 mM</td>
<td>13.8 mM(^{[1]}); 21.5 mM(^{[2]})</td>
</tr>
<tr>
<td>([\text{K}^+]_i)</td>
<td>111.0 mM</td>
<td>108.7 mM</td>
<td>107.5 mM</td>
<td>91.2 mM(^{[1]})</td>
</tr>
<tr>
<td>([\text{Cl}^-]_i)</td>
<td>9.1 mM</td>
<td>8.1 mM</td>
<td>9.3 mM</td>
<td>16.8 mM(^{[1]}); 12.3 mM(^{[3]})</td>
</tr>
<tr>
<td>([\text{Na}^+]_e)</td>
<td>102.0 mM</td>
<td>104.9 mM</td>
<td>104.3 mM</td>
<td></td>
</tr>
<tr>
<td>([\text{K}^+]_e)</td>
<td>6.5 mM</td>
<td>4.2 mM</td>
<td>4.4 mM</td>
<td></td>
</tr>
<tr>
<td>([\text{Cl}^-]_e)</td>
<td>108.2 mM</td>
<td>109.1 mM</td>
<td>108.7 mM</td>
<td></td>
</tr>
</tbody>
</table>

† The measured concentration values were calculated using Equation (6.14) with a 1% extracellular volume fraction and extracellular concentrations of 107 mM for Na\(^+\), 3 mM for K\(^+\), and 110 mM for Cl\(^-\).

The extracellular concentration field along the sutures are flatter due to the higher coupling along the sutures, but this effect is not reflected in the intracellular space. Instead, the intracellular concentration field reflects the action of the Na\(^+\)/K\(^+\) pumps. The radial profile of the intracellular concentrations between the center and the anterior or equatorial surface shows the depletion of Na\(^+\) and the accumulation of K\(^+\) due to the Na\(^+\)/K\(^+\) pumps, but the radial profile between the center and the posterior surface shows a flatter profile (see Figure 8.14).

Although the mean intracellular Na\(^+\) concentration predicted by Model B (19.1 mM) is within the values reported by Delamere & Duncan (1977) (13.8 mM) and Duncan (1970) (21.5 mM), the concentration profile is about twice the recent values measured by Mathias (see Figure 8.14). There is a 18% difference between the mean intracellular K\(^+\) concentration predicted by the Model B (107.3 mM) and the value reported by Delamere & Duncan (1977) (91.2 mM). There is a 44% and 24% difference between the mean intracellular concentration predicted by Model B (9.4 mM) and the values reported by Delamere & Duncan (1977) (16.8 mM) and Guerschanik et al. (1977) (12.3 mM).
Figure 8.13: Intracellular and extracellular Na⁺, K⁺ and Cl⁻ concentrations predicted by Model A (left) and Model B (right).
These are quite significant differences so further development of the model is needed to improve the prediction of the concentration fields. For example, a more accurate description of the spatial variation of the membrane conductances of Na\(^+\), K\(^+\) and Cl\(^-\) (\(g_{Na}, g_{K}, g_{Cl}\)) may improve the accuracy of the predicted concentration profiles (Mathias 1985b).

**Figure 8.14:** Radial profile of the intracellular Na\(^+\) concentration predicted by Model B and that measured by Mathias. Reproduced with permission from Mathias, R.T. (Unpublished).

### 8.4.3 Solute Fluxes

**Intracellular and Extracellular Fluxes**

Figure 8.15 shows the intracellular and extracellular Na\(^+\), K\(^+\) and Cl\(^-\) fluxes predicted by Model A and Model B.

In both Model A and Model B, the Na\(^+\) fluxes enter the lens via the extracellular space, cross the fibre cell membrane and exit via the intracellular space. The intracellular Na\(^+\) fluxes have a slight polarisation towards the equatorial surface.

The intracellular K\(^+\) flux is independent of the extracellular K\(^+\) flux since there is no K\(^+\) transport across the fibre cell membrane. In both Model A and Model B, the intracellular K\(^+\) fluxes enters via the anterior and equatorial surfaces and exit via the posterior surface. The extracellular K\(^+\) flux in Model A is essentially zero, where the residual fluxes seen in Figure 8.15 are small and at the resolution of numerical errors. In contrast, the extracellular K\(^+\) flux in Model B enters at the anterior and posterior poles and exits at the equator where the streamlines reach the nucleus of the
lens.

The Cl\(^{-}\) fluxes show the influence of representing the sutures in the model. In Model A, the Cl\(^{-}\) fluxes are internalised, meaning there is no Cl\(^{-}\) flux through the surface of the lens (this is clear in the net surface flux graphs in Figure 8.17). The internal Cl\(^{-}\) flux generates a radial circulation that flows towards the nucleus in the extracellular space and flows towards the surface in the intracellular space. This radial Cl\(^{-}\) flux is the same as the Cl\(^{-}\) fluxes predicted by the one-dimensional numerical model.

In Model B, the Cl\(^{-}\) flux flow is more complex. Cl\(^{-}\) enters the extracellular space at the poles and flows towards the nucleus. A small amount of Cl\(^{-}\) crosses the fibre cell membrane into the intracellular space but most remains in the extracellular space and flows towards the equatorial surface where it exits the lens. The Cl\(^{-}\) that crosses into the intracellular space flows towards the equator where it is diverted via the outer cortex towards the poles. At the poles, Cl\(^{-}\) is transported into the extracellular space where it joins the extracellular Cl\(^{-}\) flow towards the nucleus. The net flux is the sum of a circulation between the poles and equator and a small internalised circulation.

In general, there is a significant change in the flow patterns of the extracellular K\(^{+}\) and intracellular and extracellular Cl\(^{-}\) between Model A and Model B, but only a minor change in the extracellular Na\(^{+}\) flow patterns. In addition to the change in flow patterns, the representation of the sutures in Model B results in a large increase in the extracellular solute fluxes along the sutures. The maximum extracellular flux along the sutures increases from 36 \(\mu\text{mol}/(\text{m}^2\text{s})\) to 57 \(\mu\text{mol}/(\text{m}^2\text{s})\) for Na\(^{+}\), from almost zero to 1.25 \(\mu\text{mol}/(\text{m}^2\text{s})\) for K\(^{+}\), and from 0.77 \(\mu\text{mol}/(\text{m}^2\text{s})\) to 27.7 \(\mu\text{mol}/(\text{m}^2\text{s})\) for Cl\(^{-}\). There is a 42\% increase in the maximum intracellular Cl\(^{-}\) flux between Model A and Model B, but the increase is less for the maximum intracellular Na\(^{+}\) and K\(^{+}\) fluxes, 12\% and 10\%, respectively.

From these results, it appears the Na\(^{+}\)/K\(^{+}\) pumps dominate the transport of the intracellular Na\(^{+}\) and K\(^{+}\) such that the influence of the sutures is not noticeable. The sutures, on the other hand, influence the extracellular solute fluxes and the intracellular flux of non-actively transported solutes, namely Cl\(^{-}\).
Figure 8.15: The intracellular and extracellular Na⁺, K⁺ and Cl⁻ fluxes predicted by Model A (left) and Model B (right).
Net Fluxes

The net flux in the lens is given by

$$j_\alpha = \frac{j_{\alpha i} A_i + j_{\alpha e} A_e}{A_i + A_e}$$

(8.1)

where the subscript $\alpha$ indicates the solute species, $j_\alpha$ is the net flux, $j_{\alpha i}$ and $j_{\alpha e}$ are the intracellular and extracellular fluxes, and $A_i$ and $A_e$ are the intracellular and extracellular cross-sectional area normal to the flux vector. The net flow is given by scaling the net flux vector by the circumference at the location of the flux vector,

$$J_\alpha = 2\pi y j_\alpha$$

(8.2)

where $J$ is the flow vector, $j_{Na}$ is the net flux vector and $y$ is the distance the flux vector is from the $x$-axis (the anterior-posterior pole axis). The flow vector accounts for the increasing cross-sectional area of the slice away from the $x$-axis and gives a better indication of the amount of ions flowing through the region.

It is important to realise that the net flux and net flow fields do not indicate the penetration of a solute into the lens, instead they indicate the angular flow of the solute, which is the circulation between regions on the surface of the lens. To explain further, consider an intracellular and extracellular flow field that is symmetric, such as the Cl$^-$ fluxes for Model A shown in Figure 8.15. The extracellular Cl$^-$ flowing into the lens equals the intracellular Cl$^-$ flowing out of the lens, resulting in a net flow of zero. We will look at the penetration of solutes into the lens using another method (see Penetration section below).

Figure 8.16 shows the net Na$^+$, K$^+$ and Cl$^-$ fluxes and flows predicted by Model A and Model B and Figure 8.17 shows the net Na$^+$, K$^+$ and Cl$^-$ fluxes at the surface of the lens predicted by Model A and Model B.

Although there appears to be no significant difference in the intracellular and extracellular Na$^+$ fluxes between Model A and Model B (see Figure 8.15), there is a significant difference in the net Na$^+$ flux. In Model A, Na$^+$ enters at the posterior surface, flows across the lens and exits at the equatorial surface. At the anterior surface, the Na$^+$ flux is close to zero since Na$^+$ enters via the extracellular space, crosses into the intracellular space and exits through the same surface it entered. In Model B, Na$^+$ enters the lens at the anterior and posterior surfaces and exits at the
equatorial surface. The net Na$^+$ flux into the lens at the anterior surface is increased from zero and the net flux at the posterior and equatorial surfaces is increased by two to three fold.

The magnitude and path of the net K$^+$ flux through the lens and the net surface K$^+$ flux are similar in Model A and Model B.

Even though the streamlines show a circulation of the net Cl$^-$ flux, these fluxes are essentially zero, which is expected since the intracellular and extracellular Cl$^-$ fluxes are radially symmetric and internalised. The residual fluxes shown in Figure 8.16 are small and at the resolution of the numerical error. In Model B, the net Cl$^-$ flux shows a similar pattern to the net Na$^+$ flux, Cl$^-$ enters at the pole and exits at the equator. The Cl$^-$ flux at the anterior and posterior surface is 0.40-0.45 $\mu$mol/(m$^2$s), which is about a quarter to a third of the Na$^+$ flux at the anterior and posterior surfaces. The Cl$^-$ flux at the equatorial surface is about a tenth of the Na$^+$ flux at the equatorial surface, but it is more evenly spread across the equatorial surface. These are significant fluxes for an ion that is not actively transported.
Figure 8.16: Net Na⁺, K⁺ and Cl⁻ fluxes and flows predicted by Model A (left) and Model B (right).
Figure 8.17: Surface Na⁺, K⁺ and Cl⁻ flux predicted by Model A and Model B.
Penetration

As mentioned previously, the net flux and net flow fields do not indicate the penetration of a solute into the lens, instead they indicate the angular flow of a solute. To calculate the penetration of a solute into the lens, consider a spherical shell that has a smaller radius than the lens and is concentric with the lens. The integral of the amount of intracellular and extracellular solute flowing inwards through the surface of the shell would give a measure of the amount of solute penetrating the shell. If this calculation was repeated for shells of various radii, then we can get an idea of the amount and depth of the solute penetration.

Figure 8.18 shows the penetration of Na$^+$, K$^+$ and Cl$^-$ into the lens predicted by Model A and Model B. In the outer 400 $\mu$m of the lens, the penetration of Na$^+$ increases by 12-13% and the penetration of K$^+$ increases by 12-20% between Model A and Model B. In contrast, there is a three to four fold increase in the amount Cl$^-$ penetrating the lens in Model B compared to Model A. Furthermore, Cl$^-$ penetrates the lens surface in Model B but does not in Model A. This means the Cl$^-$ is being replaced in Model B, whereas it is stagnant in Model A.

The large increase in Cl$^-$ penetration suggests the sutures significantly improve the passive transport of charged solutes. Further investigation is required to determine the relative contribution of diffusion, electro-diffusion and advection to the increase in penetration seen in Model B, and also, whether the effect seen here influences the penetration of uncharged solutes.

The penetration results also indicate the relative amount of a solute entering the lens. Of the total amount of solute entering the lens in Model A, 94% is Na$^+$, 6% is K$^+$ and 0% is Cl$^-$. Of the solutes entering the lens in Model B, 91.5% is Na$^+$, 6% is K$^+$ and 2.5% is Cl$^-$. Therefore, Na$^+$ accounts for the majority of the solute flow in the lens.
Figure 8.18: Na⁺, K⁺ and Cl⁻ penetration predicted by Model A and Model B.
8.4.4 Current Density

The current density is the sum of the charge fluxes carried by the ions in the model. Therefore, the intracellular and extracellular current densities are given by

\[
i_i = (j_{Na}^i + j_{K^+}^i - j_{Cl^-}^i) F
\]
\[
i_e = (j_{Na}^e + j_{K^+}^e - j_{Cl^-}^e) F
\]

where \(i\) is the current density vector \([A/m^2]\), \(j\) is the solute flux vector \([mol/(m^2 s)]\) and \(F\) is the Faraday constant \((F = 9.65 \times 10^4 C/mol)\).

Figure 8.19 shows the intracellular and extracellular current densities predicted by Model A and Model B. In both models, the charge enters the lens via the extracellular space, crosses the fibre cell membrane and exits via the intracellular space.

In Model A, the intracellular and extracellular current densities are radially symmetric with the intracellular current density having a slight polarisation towards the equator.

In Model B, the extracellular current density is radially symmetric but the intracellular current density is more polarised towards the equators. The charge entering the intracellular space from the extracellular space near the anterior and posterior poles exits via the anterior and posterior surfaces, respectively, and the charge entering the intracellular space at the nucleus of the lens, exits via the equatorial surface.

The range of current density values between Model A and Model B are similar, but the spatial distribution of the magnitude of the current density is different. The current density in extracellular space of Model A decreases steadily towards the center of the lens, whereas in Model B it is maintained at around 150-250 \(\mu A/cm^2\).

Figure 8.20 shows the net current density and net charge flow predicted by Model A and Model B. In Model A, the charge enters the lens at the posterior pole and exits at the equator, the net charge entering the anterior surface is essentially zero. In Model B, charge enters at the anterior and posterior poles and exits at the equator. These results suggest that the sutures have a significant influence on the circulation of current between the poles and the equator. The sutures also influence the path of the charge between the pole and the equator. The maximum current density is near the surface in Model A, whereas the maximum current density is along the sutures in Model B.
8.4 Results and Discussion

Figure 8.19: Intracellular and extracellular current density predicted by Model A (left) and Model B (right).

Figure 8.20: Net current density and flow predicted by Model A (left) and Model B (right).

Studies by Robinson & Patterson (1983), Parmelee (1986) and Candia & Zamudio (2002) have measured the current density at the surface of rat, frog and rabbit lens, respectively. Their results are plotted in Figure 8.21 along with the surface current density predicted by Model A and Model B. Compared to Model A, Model B predicts a surface current density that is more consistent with the measured data, therefore only Model B is discussed further.
The circulation between the poles and equator predicted by the model is consistent with the circulation measured by Robinson & Patterson (1983) and Parmelee (1986), but less so with the circulation measured by Candia & Zamudio (2002), where the outward current is skewed more towards the anterior surface.

The predicted current density at the anterior pole, equator and posterior pole are approximately a third, a tenth and a quarter the values measured by Robinson & Patterson (1983) and Parmelee (1986). The current density at the surface is dependent on the Na$^+$/K$^+$ pump currents, the membrane conductances, and the coupling between the poles and equator. The results from modelling the sutures, which increases the coupling between the poles and equator, have shown the increase in circulation between the poles and equator and the increase in surface current density. Further work is required to investigate the influence of the Na$^+$/K$^+$ pumps and membrane conductances.

In summary, modelling the sutures increases the circulation of current between the poles and the equator. Compared to Model A, the surface current density predicted by Model B is more consistent with measured data, but the measured surface current density is over three times larger than the predicted surface current density.
8.4.5 Hydrostatic Pressure

Figure 8.22 shows the hydrostatic pressure and Table 8.8 lists the mean pressures, predicted by Model A and Model B. These pressures are difficult to discuss in terms of the real lens due to a lack of experimental data in the literature.

Figure 8.22: Intracellular and extracellular hydrostatic pressure predicted by Model A (left) and Model B (right).

However, we can discuss the differences between Model A and Model B due to the sutures. The intracellular pressure difference between the anterior and equatorial surfaces and the center of the lens is similar in Model A and Model B, 3.1 kPa and 5.1 kPa, respectively, but the mean pressure in Model A is 40% larger than in Model B. The intracellular pressure field reflects the influence of the Na⁺/K⁺ pumps on the anterior and equatorial surfaces, which are also seen in the intracellular potential (Figure 8.11) and concentration (Figure 8.13) fields.

Table 8.8: Mean hydraulic pressure predicted by Model A and Model B

<table>
<thead>
<tr>
<th></th>
<th>1D Model</th>
<th>Model A</th>
<th>Model B</th>
<th>Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p_i$</td>
<td>-13.7 kPa</td>
<td>-19.4 kPa</td>
<td>-13.3 kPa</td>
<td></td>
</tr>
<tr>
<td>$p_e$</td>
<td>-3.1 kPa</td>
<td>-1.4 kPa</td>
<td>-3.4 kPa</td>
<td></td>
</tr>
</tbody>
</table>
There is a significant difference in the extracellular pressure drop between the surface and the center of the lens, 2.9 kPa in Model A compared to 17.2 kPa in Model B. Furthermore, the symmetric extracellular pressure field seen in Model A is disrupted by the inclusion of the sutures in Model B.

### 8.4.6 Fluid Flow

Figure 8.23 shows the fluid velocity predicted by Model A and Model B. In both models, the fluid enters the lens via the extracellular space, crosses the fibre cell membrane and exits the lens via the intracellular space. The intracellular fluid flow in Model B is more polarised towards the equator. The fluid that enters the intracellular space near the poles exits via the polar surfaces and the fluid that enters the intracellular space at the nucleus exits via the equatorial surface.

![Figure 8.23: Intracellular and extracellular fluid velocity predicted by Model A (left) and Model B (right).](image)

The fluid flow in Model A is highly symmetry, but the inclusion of sutures in Model B disrupts this symmetry. Furthermore, it increases the maximum fluid velocity between the polar surfaces and the nucleus by 2-3 times.

Figure 8.24 shows the net fluid velocity predicted by Model A and Model B and Figure 8.25 shows
the net surface fluid velocity predicted Model A and Model B. Like the solute fluxes, the inclusion of sutures in the model increases the circulation of the fluid between the poles and equator. The circulation predicted by Model A is close to zero. The residual velocities shown in Figure 8.24 are at the resolution of the numerical error.

Figure 8.24: Intracellular and extracellular net fluid velocity and flow predicted by Model A (left) and (b) Model B (right).

Figure 8.25: Fluid velocity at the lens surface predicted by Model A and Model B.

Table 6.6 shows a summary of the fluid flow results from experimental studies. Although the results from these studies have limited data points at the surface they can still give an idea of the general direction and magnitude of the flow. One could argue that the results from Fischbarg et al. (1999),
Candia & Gerometta (2003), and Candia (2004) suggest that fluid enters the lens at the anterior pole and exits at the equator and to a lesser extent the posterior pole. The magnitude of the measured velocities range between 0.64 nm/s and 26 nm/s. The surface velocities predicted by Model A are too small compared to the measured values and show no circulation. The velocities predicted by Model B show a better correlation, where the fluid enters at the poles and exit at the equator and the magnitude of the velocity is approximately 1 nm/s at the equator and 7-9 nm/s at the poles.

Figure 8.26 shows the penetration of fluid into the lens predicted by Model A and Model B. In the outer 400 µm of the lens, the penetration of fluid increases by 12-14 % between Model A and Model B.

8.5 Discussion

The potential and concentration fields predicted by the two-dimensional models are comparable to measured data, although more accurate predictions may be obtained by improving the model parameters.

The main component of solute fluxes through the lens is Na\(^+\). Of the total solute flowing into the lens, over 90 % is Na\(^+\), 6 % is K\(^+\) and less than 3 % is Cl\(^-\). The direction of the predicted Na\(^+\) and K\(^+\) circulation is consistent with observations from literature.

The predicted charge flow is consistent with the direction of the measured current, but the magni-
tudes of the measured surface currents are more than three times larger than those predicted by the model.

The fluid flow results predicted a flow rate of $0.15 \times 10^{-3}$ mm$^3$/s (150 pl/s) into the lens. Given the volume of the lens is 17.2 mm$^3$ ($V = \frac{4}{3} \pi r^3$, where $r = 1.6$ mm) and assuming the fluid flow into the lens is evenly distributed, it would take 32 hours to replace the entire fluid content of the lens. This is clearly too long for a mechanism to deliver nutrient into and remove waste from the lens. However, it is possible that directed fluid flow pathways exist. For example, the maximum fluid velocity in Model B was along the sutures, in this case the sutures may act as a shuttling path for nutrients to the nucleus where they are consumed or transported by diffusion or advection to another regions in the lens. The outer cortex may rely on both diffusion and advection to deliver nutrients. Further investigation, using the lens model, is required to study these theories.

Modelling the sutures increased solute flux, current density and fluid velocity along the sutures. Modelling the sutures also increased the circulation of Na$^+$, charge, and fluid between the poles and equator and increased the penetration of Na$^+$, K$^+$ and fluid into the lens. However, the most significant effect of the sutures is to generate Cl$^-$ circulation between the pole and equator and increase the penetration of Cl$^-$ by 300-400%. This is significant since Cl$^-$ is not an actively transported solute.

These results highlight the strong structure-function relationship and importance of spatial variation of lens properties. In light of these results, one has to question the importance of the values, the kinetics and spatial variation of other lens properties. For example, the spatial variation and pH sensitivity of Cx46 gap junctions.

The next logical step is to use the model to perform a sensitivity analysis on the values and spatial distribution of model parameters. This will identify the important parameters in the model, allowing their accuracy to be improved, thus improving the accuracy of the model.
8.6 Age-Related Changes in Lens Properties

The aim of this section is to demonstrate the application of the model to replicating the age-related changes in the lens observed by Duncan et al. (1989). Duncan et al. (1989) collated a number of studies on human lenses that measured the age-related change in the membrane potential concentration of Na\(^+\), K\(^+\) and Ca\(^{2+}\), the relative permeability between Na\(^+\) and K\(^+\) (\(P_{Na}/P_{K}\)), and the optical density. Their results showed that with age, the membrane potential decreased (see Figure 8.27a), the concentration of K\(^+\) remained constant (see Figure 8.27b), and the concentration of Na\(^+\) (see Figure 8.27b) and Ca\(^{2+}\), the relative permeability (\(P_{Na}/P_{K}\)) and the optical density all increased.

![Figure 8.27: The age-related change in (a) intracellular potential and (b) Na\(^+\) (filled symbols) and K\(^+\) (open symbols) concentrations in the human lens (Duncan et al. 1989).](a) (b)

To mimic the age related growth of the lens, the radius of Model B of the lens model was increased from 1.0 mm to 2.2 in 0.2 mm steps - a 120 % increase. The radius of frog lenses are reported as 1.6 mm (Mathias 1985b) and 1.9 mm (Kuszak et al. 2006). Strenk, Semmlow, Strenk, Munoz, Gronlund-Jacob & DeMarco (1999) measured the profile of the human lens in situ using MRI. They reported a range of lens thickness between 3.1 mm and 5.3 mm, a 60 % increase, and a lens radius between 4.28 mm and 4.93 mm, a 15 % increase, for human lenses between the ages of 22 and 83. Kuszak, Al-Ghoul, Novak, Peterson, Herbert & Sivak (1999) presented CAD representations of the development of sutures in rat lenses. Their rendered lenses showed an 85 % increase in the equatorial diameter between a 2 and 15 month old rat lens.

All other properties for the lens model were maintained. The models were solved to steady-state for lens radius value. The mean intracellular potential (Figure 8.28) and mean intracellular Na\(^+\), K\(^+\) and Cl\(^-\) concentrations (Figure 8.29) were plotted with respect to the equatorial radius.
The model was able to predict the same trends for the intracellular potential, an increase with age or lens size, and Na\(^+\) concentration, an increase with age or lens size. This is as far as one can compare these results since they are across different species and the age-related change is mimicked by an increase in lens size. The model predicted a decrease in the intracellular K\(^+\) concentration with age or lens size, which was reported by Duncan et al. (1989) as being constant with age. The model also predicted an increase in intracellular Cl\(^-\) concentration. The modelled change in the extracellular Na\(^+\), K\(^+\) and Cl\(^-\) concentrations were less than 2 mM.

Duncan et al. (1989) proposed that the increase of the permeability ratio \((P_{Na}/P_{K})\) was due to a relative increase in the permeability of Na\(^+\). In the lens model, the Na\(^+\) channels are localised to the fibre cell membrane, hence the total Na\(^+\) permeability depends on the volume of the lens. The
K⁺ channels and Na⁺/K⁺ pumps are localised to the surface membrane of the lens, hence the K⁺ permeability and rate that Na⁺ and K⁺ are pumped out of the lens would depend on the surface area of the lens.

The size of the lens increases with age. Therefore, if the radius of the lens is increased, the surface area of the lens increases at roughly the radius squared and the volume increases at roughly the radius cubed. This means the permeability of Na⁺ would increase faster than the permeability of K⁺, hence the ratio of the permeability (P_{Na}/P_{K}) would increase. Furthermore, the surface area of the Na⁺/K⁺ pumps increases slower than the volume of lens being served by the pumps. This means less Na⁺ can be pumped out of the lens, increasing the intracellular Na⁺ concentration, and less K⁺ is being pumped into the lens, decreasing the intracellular K⁺ concentration.

Although, the explanation above explains the changes in the lens physiology with an increase in lens size, it is unlikely to be complete since changes in the lens can be much more complex. For example, the dynamics of the Na⁺/K⁺ pumps depends on intracellular Na⁺ which in turn depends on lens size and the model does not include the spatial variation of the Na⁺ conductivity of the fibre cell membrane. Further development of the lens model should give greater confidence that the experimental observations and the model observations stem from the same physical processes.
Conclusions &
Future Developments

9.1 Conclusions

A framework, based on finite volume methods, was developed to model the structure and function on the ocular lens. This framework was used to simulate the solute ($\text{Na}^+$, $\text{K}^+$ and $\text{Cl}^-$) and fluid transport in one-dimensional and two-dimensional models of the lens. The one-dimensional model took 3-4 hours to solve and the two-dimensional model 1-5 days, where solution time depended on the number of elements in the model and on the model parameters. A three-dimensional model could not be solved using this framework (without further development of parallel processing algorithms and more efficient solution methods) due to the unrealistic solution time required. A three-dimensional model would be useful in assessing the influence of the twist in fibre cell and the structure of sutures.

The results from the one-dimensional model were consistent with results from the analytical model developed by Mathias (1985b) and with experimentally measured data. There were minor differences between the one-dimensional numerical model and analytic model which were due to the differences in the modelling approach and model parameters.

The initial two-dimensional model was based on the one-dimensional numerical model, where all model parameters were spatially uniform, except for the fibre angles and $\text{Na}^+$/K$^+$ pump currents. The model predicted radial flow patterns that were similar to those predicted by the one-dimensional model but there was little circulation between the poles and equator which is inconsistent with measured data.

The two-dimensional model was improved by spatially varying the extracellular cleft width and
fibre cell height in order to represent the sutures and extracellular diffusion barrier. This model predicted an increase in the solute flux and fluid velocity along the sutures, an increase in the Na\(^+\), Cl\(^-\) and fluid circulation between the poles and equator, and an increase in the amount of solute and fluid penetrating the lens. The amount of Na\(^+\), K\(^+\) and fluid penetrating the lens increased by 12-20\% and the amount Cl\(^-\) penetrating the lens increased by 300-400\%.

One of the more significant predictions was the generation of a Cl\(^-\) circulation between the poles and equator, which was not predicted by the initial two-dimensional model, and the increase in Cl\(^-\) penetration, especially since Cl\(^-\) is not an actively transported solute. In the first version of the two-dimensional model, the Cl\(^-\) circulated within the lens and there was no Cl\(^-\) flux through the lens surface, meaning the Cl\(^-\) inside the lens was stagnant. In the second version of the two-dimensional model, Cl\(^-\) circulated through the lens and was exchanged through the lens surface.

The direction of the surface current predicted by the second two-dimensional model was consistent with the measured surface current but the magnitude was between a tenth and a third of the measured values.

These results highlight the structure-function relationship in the lens as well as the need for accurate spatial descriptions of parameter values. It is anticipated that by improving the accuracy of the spatial description of the model parameters, the correlation between the model and measured data will improve.

Finally, the application of the model was demonstrated by modelling the age-related change in lens physiology. The growth of the lens with age was simulated by increasing the radius of the lens. The model predicted an increase in the intracellular Na\(^+\) concentration, Cl\(^-\) concentration and potential with age, which correlated with observed trends by Duncan et al. (1989). The model predicted a decrease in the intracellular K\(^+\) concentration with age whereas the data in the literature showed no change.
9.2 Future Developments

The two-dimensional model forms a foundation for future developments and applications, including:

1) improvements to the modelling framework
2) improvements to and applications of the lens model
3) application of the modelling framework to other biological systems

9.2.1 Modelling Framework

Reducing the Solution Time

The one-dimensional model took 3-4 hours to solve and the two-dimensional models 1-5 days. In order to solve models with higher resolution meshes, more complexity from added transport protein models and extra solute species, and that are three-dimensional, the solution time of the models must be reduced. This can be achieved by implementing more efficient solution algorithms and modifying the modelling code to solve a model across multiple processors (parallelisation).

Fortunately, many solution algorithms are available in libraries that can be easily linked into existing code, and some of these are parallelised. Many solution algorithms are required since different solution algorithms suit different models.

Today there are supercomputers with over ten thousand processors and desktops are starting to emerge with two to four processors. Analysts predict that in a few years time, desktops with tens to hundreds of processors would be common. To take advantage of these advances, the modelling code should be parallelised. It should be relatively easy to parallelise the existing modelling code and gain major benefits.

Accuracy of the Modelling Techniques

The development of the modelling framework began with the most basic techniques, which are sufficient for modelling the lens, but many improvements could be made to increase the accuracy and possibly reduce the solution time of the model. It is difficult to access the accuracy of the model since refining the mesh to check the convergence of the solution would require unrealistic
solution times. However, the results from the model appeared reasonable.

There are many ways to improve the accuracy of the model: higher resolution and higher order meshes; higher order interpolation and approximation methods; advanced solution techniques, such as implicit, semi-implicit and nonlinear solution methods; and other modelling approaches, such as finite element methods, the lattice-Boltzmann method or hybrid methods. Ferziger & Peric (1997) covers a number of possible methods and provides references to more advanced methods.

**User Interface**

I believe this model has much potential in the hands of others, such as physiologists, but the user-friendliness of the model would have to be improved. The most significant improvement would be the development of a graphical user interface (GUI). This would allow only the key modelling components to be presented to the user and many modelling processes that can be automated through scripts to be hidden. Some examples of key modelling components are: adding and removing solute species and transport proteins; changing the spatial distribution of parameter values; and importing experimental data to be displayed with model results.

Another consideration for the user interface is where the model is solved. The model may be a stand-alone software package that runs on the users local computer. Alternatively, the GUI may be an interface to a remote computer where the model is modified through the interface but is solved on the remote computer. Each have their advantages and disadvantages which need to be considered.

CellML is an xml language designed to store and exchange computer-based mathematical models (www.cellml.org). CellML offers significant advantages to a modelling framework, for example, models defined in CellML can be interpreted into code, compiled, and executed. This feature would provide a convenient method of adding models of transport proteins to a lens model without editing the core modelling code. This would improve the ability of a user to interface with the model without having to get into low level language programming.
9.2.2 Modelling the Lens

Certainly the lens model is nowhere near complete: the geometry of the lens is idealised; the description of the cellular structure is simple; many parameters are assumed to spatially constant when evidence suggests they are not; many solutes, cellular processes, and proteins are missing; and more physical processes, such as volume regulation, can be added. And then there are the age-related changes and the variations between species. The lens model developed in this project provides the foundations for further development.

Model Parameters

The result from the two-dimensional model showed the importance of the spatial distribution of parameter values. Based of these results the next logical step is to improve the model parameters.

Fortunately, the lens model can be used to identify the important model parameters by performing a sensitivity analysis. A sensitivity analysis is performed by perturbing a parameter in the lens model, solving the model and analysing the change in key properties. A more advanced sensitivity analysis involves spatially perturbing a parameter or perturbing multiple parameters. Having identified the important parameters action can be taken to source more accurate values.

The two-dimensional model also highlighted the strong structure-function relationship in the lens. The geometry of the lens, the fibre cell angles and the suture structure were somewhat idealised, yet it would be relatively simple to improve these properties. It would be worthwhile developing species specific models based on the comprehensive work by Kuszak and colleagues.

Model Complexity

The complexity of the model can be increased by adding more solute species, more transport protein models, and other physical processes, such as volume regulation and mechanics. Volume regulation would be required to model the formation of cataracts.

A time-dependent model would be required to simulate the temporal changes in lens physiology. A steady-state model is sufficient for modelling the function of the normal lens but a temporal model is required to simulate some experiments and to model the dysfunction of the lens, such as the
formation of cataracts.

Although the two-dimensional model captures most processes in the lens, a three-dimensional model is required to study the influence of the structure of the sutures, i.e., the line, 'Y' and star shapes of the sutures, and the twist of the fibre cell out of the axial plane as it spans between the poles. The solution time of the models would need to be reduced in order to solve a three-dimensional model. It may turn out that the three-dimensional influence of the sutures and fibre cell twist can be homogenised into a two-dimensional representation.

**Application of the Lens Model**

The modelling framework can be applied to other aspects of lens physiology. For example, the lens model may be able to simulate and help interpret experimental results. Simulating experiments would validate the model as well as improve our understanding of the processes in the lens. Three studies where this may be possible are: Delamere & Paterson (1979), Duncan et al. (1989) and Fischbarg et al. (1999).

The work by Duncan et al. (1989) on age-related changes in lens physiology was used to demonstrate the application of the two-dimensional model in Section 8.6.

Fischbarg et al. (1999) derived the theoretical hydraulic conductivity of the lens by assuming an idealised cell structure. The model can be used to calculate the bulk hydraulic conductivity where the shape of the lens, the intracellular and extracellular space, and the spatial variation of structural properties are accounted for. By applying a pressure drop across the anterior and posterior surface, the model will predict a fluid velocity through the lens. Using the integrated fluid velocity and the pressure drop, the bulk hydraulic permeability can be estimated by using a simple Darcy flow relationship.

Delamere & Paterson (1979) raised the $K^+$ concentration outside the frog lens from 2.5mM to 25mM and measured an intracellular and extracellular change in potential from -70 mV to -43 mV and from -30 mV to -12 mV, respectively. It would be interesting to see if the two-dimensional model would simulate these changes.
9.2.3 Modelling Other Biological Systems

The modelling framework used for the lens can be applied to other biological systems. Local to the lens is the ciliary body, aqueous and vitreous humors, the iris and the cornea. There are many studies that investigate the transport in the ciliary body and the cornea. Applying this modelling framework to these systems would validate the modelling framework against other models, as well as investigate the system. Furthermore, the models of these systems can be merged to form an integrated model of the anterior eye.

There are many biological systems outside the eye where a model of the transport would be beneficial. Two possible models where the modelling framework could be applied to are by Lindemann (2001) and Yi, Fogelson, Keener & Peskin (2003). Lindemann (2001) developed a model that predicted the steady-state ion concentrations in olfactory cilia and Yi et al. (2003) developed a compartment model of volume shifts and solute transport in ischemic and hypoxic cardiac tissue. The modelling framework would improve the cardiac model by adding a spatial dimension, but a volume regulation model would have to be added. Therefore, this cardiac tissue model would be an ideal test case for volume regulation, which will be required for modelling the formation of cataracts. Modelling these systems will validate the modelling framework as well as open opportunities for future research in other areas.
This appendix summarises (for reference purposes) the equations and model parameters used in the one- and two-dimensional lens models presented in this thesis.

A.1 Model Equations

A.1.1 Tissue Properties

Membrane Density:
\[ \rho_m = \frac{2 \xi_c}{a} \]

\[ \xi_c = \sqrt{\frac{1}{\tau_c}} \]

Intracellular Volume Fraction:
\[ \Lambda_i = 1 - \frac{h \rho_m}{2} \]

Extracellular Volume Fraction:
\[ \Lambda_e = \frac{h \rho_m}{2} \]

A.1.2 Solute Fluxes

Intracellular Fluxes

Fibre Flux:
\[ j_{\alpha i, f} = -D_{\alpha i, f} \frac{dC_{\alpha i}}{d\eta_f} - z_{\alpha e} e \frac{D_{\alpha i, f}}{k_B T} \frac{d\phi_i}{d\eta_f} C_{\alpha i} + u_{i, f} C_{\alpha i} \]
Cross-fibre Flux

\[ j_{\alpha_1, \alpha_2} = -D_{\alpha_1, \alpha_2} \frac{dC_{\alpha_1}}{d\eta} - z_{\alpha_1} e D_{\alpha_1, \alpha_2} \frac{d\phi}{d\eta} C_{\alpha_1} + u_{i, \alpha} C_{\alpha_1} \]

\[ \alpha = \text{Na, K, Cl} \]

**Surface Fluxes**

Na\(^+\) Flux:

\[ j_{\text{Na}, i, s} = 3 \frac{I_{p_1} + I_{p_2}}{F} \]

K\(^+\) Flux:

\[ j_{\text{K}, i, s} = -2 \frac{I_{p_1} + I_{p_2}}{F} + j_{\text{K}, ic} \]

Cl\(^-\) Flux:

\[ j_{\text{Cl}, i, s} = 0 \]

Na\(^+\)/K\(^+\) Pumps (\(\alpha_1\) isoform):

\[ I_{p_1} = I_{\text{max} 1} \left( \frac{C_{\text{Na}_1}}{C_{\text{Na}_1} + K_{\text{Na}_1}} \right)^3 \left( \frac{C_{\text{Ko}}}{C_{\text{Ko}} + K_{\text{Ko}}} \right)^2 \]

\[ K_{\text{Na}_1} = (\sqrt{2} - 1)K_{0.5\text{Na}_1} \]

\[ K_{\text{K}_1} = (\sqrt{2} - 1)K_{0.5\text{K}_1} \]

Na\(^+\)/K\(^+\) Pumps (\(\alpha_2\) isoform):

\[ I_{p_2} = I_{\text{max} 2} \left( \frac{C_{\text{Na}_2}}{C_{\text{Na}_2} + K_{\text{Na}_2}} \right)^3 \left( \frac{C_{\text{Ko}}}{C_{\text{Ko}} + K_{\text{Ko}}} \right)^2 \]

\[ K_{\text{Na}_2} = (\sqrt{2} - 1)K_{0.5\text{Na}_2} \]

\[ K_{\text{K}_2} = (\sqrt{2} - 1)K_{0.5\text{K}_2} \]

K\(^+\) Channels:

\[ j_{\text{K}, ic} = \frac{g_K}{F} (V_m - E_K) \]

\[ V_m = \phi_0 - \phi_i \]

\[ E_K = \frac{k_B T}{z_K e} \ln \left( \frac{C_{\text{Ko}}}{C_{\text{K}_1}} \right) \]

**Transmembrane Fluxes**

Na\(^+\) flux:

\[ j_{\text{Na}, m} = j_{\text{Na}, ic} \]

K\(^+\) flux:

\[ j_{\text{K}, m} = 0 \]
A.1 Model Equations

\textbf{Cl}⁻ flux: \[ j_{Cl,m} = j_{Cl,ic} \]

\textbf{Na}⁺ Channels: \[ j_{Na,ic} = \frac{g_{Na}}{F} (V_m - E_{Na}) \]

\( V_m = \phi_e - \phi_i \)

\[ E_{Na} = \frac{k_B T}{z_{Na} e} \ln \left( \frac{C_{Na,e}}{C_{Na,i}} \right) \]

\textbf{Cl}⁻ Channels: \[ j_{Cl,ic} = \frac{g_{Cl}}{F} (V_m - E_{Cl}) \]

\( V_m = \phi_e - \phi_i \)

\[ E_{Cl} = \frac{k_B T}{z_{Cl} e} \ln \left( \frac{C_{Cl,e}}{C_{Cl,i}} \right) \]

\textbf{Solute Sources}

\textbf{Intracellular:} \[ s_{\alpha,i} = \frac{j_{\alpha,m} \rho_m}{\Lambda_i} \]

\textbf{Extracellular:} \[ s_{\alpha,e} = \frac{j_{\alpha,m} \rho_m}{\Lambda_e} \]

\( \alpha = \text{Na, K, Cl} \)

\textbf{Extracellular Fluxes}

\textbf{Fibre Flux:} \[ j_{\alpha,e,f} = -D_{\alpha,e,f} \frac{dC_{ae}}{dh} - z_{\alpha} e D_{ae,f} \frac{d\phi_e}{dh} C_{ae} + u_{e,f} C_{ae} \]

\textbf{Cross-fibre Flux:} \[ j_{\alpha,e,c} = -D_{\alpha,e,c} \tau_c \frac{dC_{ae}}{dh} - z_{\alpha} e D_{ae,c} \tau_c \frac{d\phi_e}{dh} C_{ae} + u_{e,c} C_{ae} \]

\( \alpha = \text{Na, K, Cl} \)

\textbf{A.1.3 Rate of Change of Concentration}

\textbf{Intracellular:} \[ \int_{V_i} \frac{dC_{\alpha}}{dt} dV_i = -\int_{V_i} \nabla j_{\alpha,i} dV_i + \int_{V_i} s_{\alpha,i} dV_i \]
Extracellular: \[ \int_{V_e} \frac{dC_{ae}}{dt} dV_e = -\int_{V_e} \nabla j_{ae} dV_e + \int_{V_e} s_{ae} dV_e \]

A.1.4 Electroneutrality

Intracellular: \[ \int_{V_i} \sum_{\alpha} z_{\alpha} \frac{dC_{ai}}{dt} dV_i = 0 \]

Extracellular: \[ \int_{V_e} \sum_{\alpha} z_{\alpha} \frac{dC_{ae}}{dt} dV_e = 0 \]

A.1.5 Fluid Velocity

Intracellular Velocity

Fibre Velocity: \[ u_{i,f} = -K_{i,f} \frac{\partial p_i}{\partial \eta_f} \]

\[ K_{i,f} = \frac{1}{16\mu a^2 + b^2} \]

Cross-Fibre Velocity: \[ u_{i,c} = - b L_p \frac{dP_i}{d\eta_c} - \sigma b L_p R T_i \frac{dO_{si}}{d\eta_c} \]

\[ O_{si} = C_{Nai} + C_{Ki} + C_{Cl_i} + C_{Ai} \]

Surface Velocity

Fibre Velocity: \[ u_{i,s} = -L_s (p_o - p_i) + \sigma R T L_s (O_{so} - O_{si}) \]

\[ O_{so} = C_{Nao} + C_{Ko} + C_{Clo} \]

\[ O_{si} = C_{Nai} + C_{Ki} + C_{Cl_i} + C_{Ai} \]

Transmembrane Velocity

\[ u_m = -L_m (p_i - p_e) + \sigma R T L_m (O_{si} - O_{se}) \]
\[ Os_i = C_{Nai} + C_{K_i} + C_{Cl_i} + C_{A_i} \]
\[ Os_e = C_{Nae} + C_{K_e} + C_{Cl_e} \]

**Fluid Sources**

Intracellular:
\[ s_i = -\frac{u_m \rho_m}{\Lambda_i} \]

Extracellular:
\[ s_e = \frac{u_m \rho_m}{\Lambda_e} \]

**Extracellular Velocity**

Fibre Velocity:
\[ u_{e,f} = -\tilde{K}_e \frac{dp_e}{d\eta_f} + \tilde{k}_e \frac{d\phi_e}{d\eta_f} \]

Cross-Fibre Velocity:
\[ u_{e,c} = -\tilde{K}_e \tau_c \frac{dp_e}{d\eta_c} + \tilde{k}_e \tau_c \frac{d\phi_e}{d\eta_c} \]
\[ \tilde{K}_e = \frac{\tilde{h}^2}{12\mu} \]
\[ \tilde{k}_e = \frac{\varepsilon_r \varepsilon_0 \zeta}{\mu} \left( \coth\left(\frac{\tilde{h}}{2\lambda_D}\right) - \frac{2\lambda_D}{\tilde{h}} \right) \]

**A.1.6 Conservation of Mass**

Intracellular:
\[ \int_{V_i} \nabla u_i \, dV_i = \int_{V_i} s_i \, dV_i \]

Extracellular:
\[ \int_{V_e} \nabla u_e \, dV_e = \int_{V_e} s_e \, dV_e \]
## A.2 Model Parameters

<table>
<thead>
<tr>
<th>Common Properties</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$T$</td>
<td>Temperature</td>
</tr>
<tr>
<td>$k_B$</td>
<td>Boltzmann constant</td>
</tr>
<tr>
<td>$R$</td>
<td>Gas constant</td>
</tr>
<tr>
<td>$e$</td>
<td>Electron charge</td>
</tr>
<tr>
<td>$F$</td>
<td>Faraday constant</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Fluid viscosity</td>
</tr>
<tr>
<td>$\zeta$</td>
<td>Zeta potential</td>
</tr>
<tr>
<td>$\lambda_D$</td>
<td>Debye length</td>
</tr>
<tr>
<td>$\varepsilon_0$</td>
<td>Permittivity of vacuum</td>
</tr>
<tr>
<td>$\varepsilon_r$</td>
<td>Dielectric constant</td>
</tr>
<tr>
<td>$z_{Na}^+$</td>
<td>Na$^+$ valence</td>
</tr>
<tr>
<td>$z_K^+$</td>
<td>K$^+$ valence</td>
</tr>
<tr>
<td>$z_{Cl}^-$</td>
<td>Cl$^-$ valence</td>
</tr>
<tr>
<td>$z_{A^-}$</td>
<td>A$^-$ valence</td>
</tr>
<tr>
<td>$C_{A^-}$</td>
<td>Intracellular A$^-$ concentration</td>
</tr>
<tr>
<td>$C_{Na_o}$</td>
<td>Outside Na$^+$ concentration</td>
</tr>
<tr>
<td>$C_{K_o}$</td>
<td>Outside K$^+$ concentration</td>
</tr>
<tr>
<td>$C_{Cl_o}$</td>
<td>Outside Cl$^-$ concentration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tissue Properties</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$a$</td>
<td>Lens Radius</td>
<td>1.6</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>$h$</td>
<td>Extracellular cleft width</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>$r$</td>
<td>Cell height</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>$b$</td>
<td>Cell width</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>$\tau$</td>
<td>Tortuosity</td>
<td>0.16</td>
<td>0.16</td>
<td>0.16</td>
</tr>
<tr>
<td>$\rho_m$</td>
<td>Membrane density</td>
<td>600</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>$\Lambda_{in}$</td>
<td>Intracellular volume fraction</td>
<td>0.988</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>$\Lambda_{ex}$</td>
<td>Extracellular volume fraction</td>
<td>0.012</td>
<td>0.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>
### A.2 Model Parameters

#### Solute Transport Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Analytic</th>
<th>1D</th>
<th>2D v1</th>
<th>2D v2</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_i$</td>
<td>Intracellular Resistance</td>
<td>9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$R_e$</td>
<td>Extracellular Resistance</td>
<td>47</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$D_{Na_i,f}$</td>
<td>Intracellular Na⁺ diffusion</td>
<td>-</td>
<td>-</td>
<td>1.39×10⁻³</td>
</tr>
<tr>
<td>$D_{K_i,f}$</td>
<td>Intracellular K⁺ diffusion</td>
<td>-</td>
<td>-</td>
<td>2.04×10⁻³</td>
</tr>
<tr>
<td>$D_{Cl_i,f}$</td>
<td>Intracellular Cl⁻ diffusion</td>
<td>-</td>
<td>-</td>
<td>2.12×10⁻³</td>
</tr>
<tr>
<td>$D_{Na_e,c}$</td>
<td>Extracellular Na⁺ diffusion</td>
<td>-</td>
<td>-</td>
<td>1.39×10⁻⁵</td>
</tr>
<tr>
<td>$D_{K_e,f}$</td>
<td>Extracellular K⁺ diffusion</td>
<td>-</td>
<td>-</td>
<td>2.04×10⁻⁵</td>
</tr>
<tr>
<td>$D_{Cl_e,f}$</td>
<td>Extracellular Cl⁻ diffusion</td>
<td>-</td>
<td>-</td>
<td>2.12×10⁻⁵</td>
</tr>
<tr>
<td>$g_{Na}$</td>
<td>Na⁺ fibre cell membrane conductivity</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>$g_{Cl}$</td>
<td>Cl⁻ fibre cell membrane conductivity</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>$g_K$</td>
<td>K⁺ surface membrane conductivity</td>
<td>2.1</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>$I_{max}$</td>
<td>Na⁺/K⁺ pump max. pump rate</td>
<td>0.023</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$I_{max1}$</td>
<td>Na⁺/K⁺ pump max. pump rate</td>
<td>-</td>
<td>0.478</td>
<td>Figure A.5</td>
</tr>
<tr>
<td>$I_{max2}$</td>
<td>Na⁺/K⁺ pump max. pump rate</td>
<td>-</td>
<td>0.065</td>
<td>Figure A.5</td>
</tr>
<tr>
<td>$K_{Na_1}$</td>
<td>Na⁺/K⁺ α₁ pump max Na⁺ concentration</td>
<td>-</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>$K_{Na_2}$</td>
<td>Na⁺/K⁺ α₂ pump max Na⁺ concentration</td>
<td>-</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>$K_{K_1}$</td>
<td>Na⁺/K⁺ α₁ pump max K⁺ concentration</td>
<td>-</td>
<td>3.9</td>
<td>3.9</td>
</tr>
<tr>
<td>$K_{K_2}$</td>
<td>Na⁺/K⁺ α₂ pump max K⁺ concentration</td>
<td>-</td>
<td>0.4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

#### Fluid Transport Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Analytic</th>
<th>1D</th>
<th>2D v1</th>
<th>2D v2</th>
</tr>
</thead>
<tbody>
<tr>
<td>$L_p$</td>
<td>Intercellular hydraulic permeability</td>
<td>0</td>
<td>4.46×10⁻¹⁰</td>
<td>4.46×10⁻¹⁰</td>
</tr>
<tr>
<td>$L_a$</td>
<td>Surface hydraulic permeability</td>
<td>3.75×10⁻¹³</td>
<td>8.89×10⁻¹³</td>
<td>8.89×10⁻¹³</td>
</tr>
<tr>
<td>$L_f$</td>
<td>Fibre cell membrane hydraulic permeability</td>
<td>3.75×10⁻¹³</td>
<td>1.34×10⁻¹³</td>
<td>1.34×10⁻¹³</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>Intracellular membrane reflectance</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>$K_i$</td>
<td>Hydraulic conductivity</td>
<td>-</td>
<td>7.37×10⁻¹⁰</td>
<td>Figure A.6</td>
</tr>
<tr>
<td>$K_e$</td>
<td>Hydraulic conductivity</td>
<td>1.63×10⁻¹³</td>
<td>1.90×10⁻¹³</td>
<td>1.90×10⁻¹³</td>
</tr>
<tr>
<td>$k_e$</td>
<td>Electro-osmotic coefficient</td>
<td>1.72×10⁻⁸</td>
<td>1.45×10⁻⁸</td>
<td>1.45×10⁻⁸</td>
</tr>
</tbody>
</table>

---

**Figure A.1:** The fibre angle in Model A and B of the two-dimensional model.
**Figure A.2:** The extracellular cleft width (left) and cell height (right) used in Model B of the two-dimensional model.

**Figure A.3:** The membrane density used in Model B of the two-dimensional model.

**Figure A.4:** The intracellular (left) and extracellular (right) volume fractions used in Model B of the two-dimensional model.
Figure A.5: The maximum pump rates at the lens surface for the $\alpha_1$ and $\alpha_2$ isoforms of the Na$^+/K^+$ pumps.

Figure A.6: The intracellular hydraulic conductivity in the fibre direction used in Model B of the two-dimensional model.

Figure A.7: The extracellular hydraulic permeability (left) and electro-osmotic coefficient (right) used in Model B of the two-dimensional model.
Mathias (1985a) simplified the Navier-Stokes equations user to model the fluid flow in the lens by exploiting the smallness of the ratio between the width and length of the extracellular space. This section applies the same analysis to the three-dimensional fluid flow in the extracellular cleft (see Figure B.1). For simplicity, we will analyse the flow in a single extracellular cleft and assume it has a constant width and is non-tortuous - we will include tortuosity later.

\[ \epsilon = \frac{h}{r} \]  

(B.1)

Consider the value of \( \epsilon \) for a frog lens - the width of the cleft is approximately 40 nm and the length, which is defined as the radius of the lens, is about 1.6 mm, therefore \( \epsilon = (2.5) \times 10^{-5} \). This
exemplifies the smallness of $\epsilon$.

In order to simplify the dimensionless analysis, a single extracellular cleft will be analysed. Furthermore, the tortuosity of the cleft will be ignored by assuming the radius of curvature of the tortuous path is much less than the cleft width. In this case, the extracellular cleft is assumed to be the space between two parallel discs which are separated by a distance $h$ and have a radius $r$ (Figure B.2).

**Figure B.2:** An exaggerated view of the extracellular cleft in the lens which is approximated as the space between two parallel discs (a). The characteristic velocity ($u_c$) at the surface of the discs, characteristic pressure ($p_c$) at the center of the discs, and the spatially uniform transmembrane velocity ($u_m$) (b).

### Governing Equations

The Stokes flow equations describe the fluid flow in the extracellular cleft (Equations (4.5) and (4.6)):

1. \[
\frac{\partial u}{\partial x} + \frac{\partial v}{\partial y} + \frac{\partial w}{\partial z} = s \tag{B.2}
\]
2. \[
\nu \frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \nu \frac{\partial^2 u}{\partial z^2} = \frac{1}{\rho} \frac{dp}{dx} - f_x \tag{B.3}
\]
3. \[
\nu \frac{\partial^2 v}{\partial x^2} + \frac{\partial^2 v}{\partial y^2} + \nu \frac{\partial^2 v}{\partial z^2} = \frac{1}{\rho} \frac{dp}{dy} - f_y \tag{B.4}
\]
4. \[
\nu \frac{\partial^2 w}{\partial x^2} + \frac{\partial^2 w}{\partial y^2} + \nu \frac{\partial^2 w}{\partial z^2} = \frac{1}{\rho} \frac{dp}{dz} \tag{B.5}
\]

The body forces, which represent the electro-osmotic forces, do not act in the $z$-direction, therefore $f_z$ is neglected.

The $x$ and $y$ variables are normalised by the radius $r$, and the $z$ variable is normalised by the width
of the cleft $h$, therefore,

$$X = \frac{x}{r}, \quad Y = \frac{y}{r}, \quad \text{and} \quad Z = \frac{z}{h} \tag{B.6}$$

The velocities, source, pressure and body forces are normalised by a characteristic velocity $u_c$, source $s_c$, pressure $p_c$, and body force $f_c$. Therefore, the normalised dependent variables, which are denoted by a superscript $\ast$, are

$$u^\ast = \frac{u}{u_c}, \quad v^\ast = \frac{v}{u_c}, \quad w^\ast = \frac{w}{u_c}, \quad s^\ast = \frac{s}{s_c}, \tag{B.7}$$

$$p^\ast = \frac{p}{p_c}, \quad f_x^\ast = \frac{f_x}{f_c}, \quad f_y^\ast = \frac{f_y}{f_c}. \tag{B.8}$$

**Characteristic Velocity**

Let the characteristic velocity ($u_c$) be the velocity of the fluid entering cleft at the edge of the discs. If all fluid that entering the cleft is assumed to exits through the discs into what would be assumed to be the the intracellular space, then we can derive an expression for the characteristic source ($s_c$) and pressure ($p_c$). Consider the exaggerated section of the cleft that spans from the equator to the center of the lens shown in Figure B.2b. The fluid enters the cleft with a velocity $u_c$, and the fluid exits the cleft via the discs with a spatially uniform velocity $u_m$.

**Characteristic Source**

The characteristic source term is defined by,

$$s_c = u_m \rho_m \tag{B.9}$$

where $u_m$ is the mean transmembrane velocity [m/s] and $\rho_m$ is the membrane area per unit volume [m$^{-1}$]. For the discs shown in Figure B.2b, the membrane density ($\rho_m$) is given by,

$$\rho_m = \frac{A}{V} = \frac{2 \pi r^2}{\pi r^2 h} = \frac{2}{h} \tag{B.10}$$
To ensure mass is conserved, the fluid entering the extracellular space must equal the fluid exiting,

\[ u_m (2 \pi r^2) = u_c (2 \pi r h) \]  \hspace{1cm} (B.11)

Therefore, the mean transmembrane velocity is given by

\[ u_m = \frac{u_c h}{r} \]  \hspace{1cm} (B.12)

By substituting Equations (B.10) and (B.12) into the characteristic source term (Equation (B.9)) gives,

\[ s_c = \frac{2 u_c}{r} \]  \hspace{1cm} (B.13)

**Characteristic Pressure**

The characteristic pressure is defined as the pressure at the center of the lens, where the largest pressure difference with the surface exists. The pressure is due to drag from the cleft walls and electro-osmotic forces. In order to get an expression for the characteristic pressure we will ignore electro-osmotic forces. The fluid flow in the cleft is assumed to be Couette flow therefore,

\[ u(x) = -\frac{h^2}{12 \mu} \frac{dp}{dx} \]  \hspace{1cm} (B.14)

where \( x = 0 \) at the center and \( x = r \) at the surface of the discs. If the transmembrane velocity is constant then the cleft velocity must reduce linearly between the \( u_c \) at the surface and 0 at the center,

\[ u(x) = \frac{u_c}{r} x \]  \hspace{1cm} (B.15)

Equation (B.15) can be substituted into Equation (B.14) and rearranged to get an expression for the pressure gradient,

\[ \frac{dp}{dx} = -\frac{12 \mu u_c}{h^2 r} x \]  \hspace{1cm} (B.16)
The pressure difference between the center and surface can be calculated by integrating the pressure gradient between $x = 0$ and $x = r$,

$$\Delta p = \int_{0}^{r} -\frac{12\mu u_c}{h^2 r} x \, dx = -\frac{6\mu r}{h^2} u_c$$  \hspace{1cm} (B.17)$$

Therefore, the pressure at the center of the lens and thus the characteristic pressure is,

$$p_c = p_s - \Delta p = \frac{6\mu r}{h^2} u_c$$  \hspace{1cm} (B.18)$$
since the pressure at the surface ($p_s$) is defined as zero. This can be rearranged to give the characteristic velocity as a function of the characteristic pressure,

$$u_c = \frac{h^2}{6\mu r} p_c$$  \hspace{1cm} (B.19)$$

**Dimensionless Derivatives**

The first and second order derivatives of scalar and vector fields need to be normalised. As an example of the normalisation, consider the derivatives of the $x$-velocity ($u$),

$$\frac{\partial u}{\partial x} = \frac{\partial (u_c u^*)}{\partial X} \frac{\partial X}{\partial x} = \frac{u_c \partial u^*}{r \partial X} \text{ since } \frac{\partial X}{\partial x} = \frac{1}{r}$$  \hspace{1cm} (B.20)$$

and,

$$\frac{\partial^2 u}{\partial x^2} = \frac{\partial}{\partial X} \left( \frac{\partial (u_c u^*)}{\partial X} \frac{\partial X}{\partial x} \right) \frac{\partial X}{\partial x} = \frac{u_c \partial^2 u^*}{r^2 \partial X^2}$$  \hspace{1cm} (B.21)$$

Similarly, the derivatives for the $y$- and $z$-velocities and pressure can be derived.

**Dimensionless Continuity Equation**

Substituting the normalised parameters into the continuity equation (Equation (B.2)) gives,

$$\frac{u_c}{r} \frac{\partial u^*}{\partial X} + \frac{u_c}{r} \frac{\partial v^*}{\partial Y} + \frac{u_c}{h} \frac{\partial w^*}{\partial Z} = s_c s^*$$  \hspace{1cm} (B.22)$$
Multiplying through by $h/u_c$ gives

$$\epsilon \frac{\partial u^*}{\partial X} + \epsilon \frac{\partial v^*}{\partial Y} + \frac{\partial w^*}{\partial Z} = \frac{hs}{u_c}s^* \quad \text{where} \quad \epsilon = \frac{h}{r} \quad (B.23)$$

Substituting the characteristic source (Equation (B.13)) into Equation (B.23) gives,

$$\epsilon \frac{\partial u^*}{\partial X} + \epsilon \frac{\partial v^*}{\partial Y} + \frac{\partial w^*}{\partial Z} = 2\epsilon s^* \quad (B.24)$$

**Dimensionless $x$ and $y$ Momentum Equations**

Substituting the normalised variables into the $x$-momentum equation gives,

$$\nu \frac{u_c}{r^2} \frac{\partial^2 u^*}{\partial X^2} + \nu \frac{u_c}{r^2} \frac{\partial^2 u^*}{\partial Y^2} + \frac{u_c}{h^2} \frac{\partial^2 u^*}{\partial Z^2} = \frac{p_c}{\rho r} \frac{\partial p^*}{\partial X} - \frac{f_c}{f_x} \frac{x}{(B.25)}$$

Multiplying by $h^2/(\nu u_c)$ gives

$$\epsilon^2 \frac{\partial^2 u^*}{\partial X^2} + \epsilon^2 \frac{\partial^2 u^*}{\partial Y^2} + \frac{\partial^2 u^*}{\partial Z^2} = \frac{p_c}{\nu p u_c r} \frac{\partial p^*}{\partial X} - \frac{h^2 f_c}{\nu u_c} f_x^* \quad (B.26)$$

Substituting the characteristic pressure (Equation (B.18)) gives

$$\epsilon^2 \frac{\partial^2 u^*}{\partial X^2} + \epsilon^2 \frac{\partial^2 u^*}{\partial Y^2} + \frac{\partial^2 u^*}{\partial Z^2} = 6 \frac{\partial p^*}{\partial X} - \frac{h^2 f_c}{\nu u_c} f_x^* \quad (B.27)$$

Similarly, substituting the normalised into the $y$-momentum equation gives,

$$\epsilon^2 \frac{\partial^2 v^*}{\partial X^2} + \epsilon^2 \frac{\partial^2 v^*}{\partial Y^2} + \frac{\partial^2 v^*}{\partial Z^2} = 6 \frac{\partial p^*}{\partial Y} - \frac{h^2 f_c}{\nu u_c} f_y^* \quad (B.28)$$

**Dimensionless $z$ Momentum Equation**

Substituting the normalised variables into the $z$-momentum equation gives

$$\nu \frac{u_c}{r^2} \frac{\partial^2 w^*}{\partial X^2} + \nu \frac{u_c}{r^2} \frac{\partial^2 w^*}{\partial Y^2} + \frac{u_c}{h^2} \frac{\partial^2 w^*}{\partial Z^2} = \frac{p_c}{\rho h} \frac{\partial p^*}{\partial Z} \quad (B.29)$$
Multiplying by $h^2/\nu u_c$ gives
\begin{equation}
\frac{h^2}{\nu^2} \frac{\partial^2 w^*}{\partial X^2} + \frac{h^2}{\nu^2} \frac{\partial^2 w^*}{\partial Y^2} + \frac{\partial^2 w^*}{\partial Z^2} = \frac{h p_c}{\nu u_c} \frac{\partial p^*}{\partial Z} \tag{B.30}
\end{equation}

Substituting the characteristic pressure (Equation (B.18)) gives
\begin{equation}
\epsilon^2 \frac{\partial^2 w^*}{\partial X^2} + \epsilon^2 \frac{\partial^2 w^*}{\partial Y^2} + \frac{\partial^2 w^*}{\partial Z^2} = \frac{12}{\epsilon} \frac{\partial p^*}{\partial Z} \tag{B.31}
\end{equation}

Multiplying by $\epsilon$ gives,
\begin{equation}
\epsilon^3 \frac{\partial^2 w^*}{\partial X^2} + \epsilon^3 \frac{\partial^2 w^*}{\partial Y^2} + \epsilon \frac{\partial^2 w^*}{\partial Z^2} = 6 \frac{\partial p^*}{\partial Z} \tag{B.32}
\end{equation}

**Reduced Dimensionless Equations**

We have shown that $\epsilon$ is small for the frog lens - around $10^{-5}$. If we assume $\epsilon$ is zero for any lens, then the dimensionless Stokes flow equations (Equations (B.24), (B.27), (B.28), and (B.32)) reduce to,
\begin{align}
\frac{\partial w^*}{\partial Z} & \approx 0 \tag{B.33} \\
\frac{\partial^2 u^*}{\partial Z^2} & \approx 6 \frac{\partial p^*}{\partial X} - \frac{h^2 f_c}{\nu u_c} f_x^* \tag{B.34} \\
\frac{\partial^2 v^*}{\partial Z^2} & \approx 6 \frac{\partial p^*}{\partial Y} - \frac{h^2 f_c}{\nu u_c} f_y^* \tag{B.35} \\
\frac{\partial p^*}{\partial Z} & \approx 0 \tag{B.36}
\end{align}

In this case, we have made no assumptions about the size of the body forces compared to the pressure forces. McLaughlin & Mathias (1985) developed a one-dimensional model of the fluid flow in the renal proximal tubules which included electro-osmosis. They concluded that electro-osmotic forces were significant in narrow clefts like the extracellular cleft of the lens, hence we have left the normalised forces in the above equations.

The main result of the dimensionless analysis is the reduction of both the $x$ and $y$ momentum equations where only the $z$-diffusion terms ($\partial^2 u/\partial z^2$ and $\partial^2 v/\partial z^2$), pressure and body force terms are left. This result suggests the forces acting on the extracellular fluid is dominated by the shearing forces applied by the membranes and body forces such as electro-osmotic forces. The reduced $x$
and $y$ momentum equations can be solved in the same way the Couette and Poiseuille flow equations are solved to obtain expressions for the mean $x$ and $x$ velocities in the cleft.
C Analytic Models

The following models were solved and compared to their analytic solutions to test the integrity of the modelling framework. Three models were developed to test the physical processes in the modelling framework. These processes include ion fluxes, fluid flow, and the conservation of charge and mass. In addition to these test models, the integrity of any model could be observed by ensuring mass and charge are conserved to within the numerical error of the computation.

C.1 Cell Model

A passive biological cell will settle to an equilibrium state known as the Donnan equilibrium. This equilibrium state will depend on the concentration of ions outside the cell, the transport proteins embedded in the cell membrane and the concentration of impermeant ions inside the cell. The convergence of a cell to the Donnan equilibrium is used to test the ion flux and conservation of charge processes in the modelling framework.

Figure C.1 shows the Donnan equilibrium state of the cell in the test model, which is based on the example given by Benedek & Villas (2000a, p473). The cell membrane contains Na\(^+\), K\(^+\) and Cl\(^-\) channels but no Na\(^+\)/K\(^+\) pumps. The impermeant ion concentration is fixed at 125mM inside the cell and 0mM outside the cell. The ion concentrations outside the cell are fixed at 140mM for Na\(^+\), 10mM for K\(^+\) and 150mM for Cl\(^-\). The potential outside the cell is fixed at 0mV.

Given these conditions (with T=310 K), the cell will settle to an equilibrium state described by the Donnan condition. At equilibrium, the intracellular ion concentrations would be 210mM for Na\(^+\), 100mM for Cl\(^-\) and 15mM for K\(^+\), and the transmembrane potential would be -10.85mV. This cell model was simulated using the modelling framework, which predicted the correct Donnan
equilibrium state of the cell.

C.2 Heat Conduction Model

This test model is based on the steady-state heat conduction example in Hunter & Pullan (2005, p23). Heat conduction is modelled using the same equations as diffusion, hence this model can be used to test the diffusion component of the modelling framework. The governing equation for heat conduction in one-dimension is

\[
\frac{d}{dx} \left( -k \frac{dT(x)}{dx} \right) + q(T, x) = 0
\]

where \( T \) is temperature (°C), \( q \) the heat sink, and \( k \) the thermal conductivity [W/(m °C)].

Consider the case where the heat sink proportional to the temperature (\( q = T \)), the thermal conductivity (\( k \)) is spatially constant, and the boundary conditions are \( T(0) = 0° \)C and \( T(1) = 1° \)C. In this case, Equation (C.1) becomes

\[
-k \frac{d^2 T(x)}{dx^2} + T(x) = 0 \quad \text{for} \quad 0 < x < 1
\]

For the case where \( k = 1 \), the exact solution for Equation (C.2) is

\[
T(x) = \frac{e}{e^x - e^{-x}}
\]
The equivalent heat conduction equations solved by the modelling framework are

\[ \frac{dT(x)}{dt} = -\nabla \cdot j(x) - T(x) \quad \text{for} \quad 0 < x < 1, \]

\[ j(x) = -k \frac{dT(x)}{dx} \tag{C.4} \]

subject to the boundary conditions: \( T(0) = 0^\circ C \) and \( T(1) = 1^\circ C \).

This problem was modelled as a transient heat conduction model on a 16 element mesh and solved to steady-state using the adaptive-Euler method described in Section 5.4. Figure C.2 shows the analytic and modelled results, which compare well. The RMS error between the analytic and modelled solutions is \( 2.5 \times 10^{-4}^\circ C \), or 0.05\% of the maximum temperature.

![Concentration Profiles: Modelled and Analytic Solutions](image)

**Figure C.2:** Analytic and modelled solutions for the heat conduction problem.

### C.3 Fluid Flow Model

This test model simulates the fluid flow in a long narrow tube where the left end of the tube is closed and fluid is entering the tube through the walls (see Figure C.3). This model tests the fluid flow component of the modelling framework, which includes flow driven by pressure gradients and the conservation of mass. The tube has a length \( (L) \) of 1m and radius \( (r) \) of 1mm. The viscosity \( (\mu) \) of the fluid is 0.7mPas and velocity \( (u_w) \) of the fluid flowing through the walls is given by \( u_w(x) = 0.1x \text{mm/s} \). The boundary conditions are \( u(0) = 0 \text{m/s} \) and \( p(L) = 0 \text{Pa} \).
The fluid velocity in the tube is assumed to be Poiseuille flow, where the velocity is given by

\[ u(x) = -K \frac{dp(x)}{dx} \]  

(C.5)

where \( K = \frac{r^2}{(8 \mu)} \), is the hydraulic conductivity of the tube.

The fluid entering the tube via the walls can be described by a volume source term \( s \), which is the volume of fluid entering the tube per unit length of tube,

\[ s = \frac{u_w A_w}{V} = \frac{u_w 2 \pi r \Delta x}{\pi r^2 \Delta x} = \frac{2 u_w}{r} \]  

(C.6)

where \( u_w \) is the velocity of the fluid flowing through the tube wall, \( A_w \) is the wall area per unit length and \( V \) is the volume per unit length.

The conservation of mass equation for a one-dimensional problem is

\[ \frac{du(x)}{dx} = s \]  

(C.7)

where the source term \( s \), describes the fluid entering the tube via the walls.

Substituting Equation (C.6) into Equation (C.7), integrating the result, and applying the velocity boundary condition gives the analytic solution for the velocity profile,

\[ u(x) = \frac{s x^2}{2} \]  

(C.8)

Substituting Equation (C.8) into Equation (C.5), integrating the result, and applying the pressure
boundary condition gives the analytic solution for the pressure profile,

\[ p(x) = -\frac{s}{6K} x^3 + \frac{sL^3}{6K} \]  \hspace{1cm} (C.9)

This fluid flow was modelled as a static problem (see Section 5.3) on a 32 element mesh. Figures C.4 and C.5 show the analytic and modelled results for the velocity and pressure in the tube. The modelled results compare well with the analytic solutions. The RMS error for the pressure was 0.11 Pa, or 0.06% of maximum pressure, and the RMS error for the velocity was negligible at \(5.0 \times 10^{-17}\) m/s.

\[\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{vel.png}
\caption{Analytic and modelled velocity profiles for the fluid flow in a tube.}
\end{figure}\]

\[\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{press.png}
\caption{Analytic and modelled pressure profiles for the fluid flow in a tube.}
\end{figure}\]
The Gmsh .geo file used to generate the mesh for one-dimensional model.

\[
\begin{align*}
R &= 1.6; & \text{ // Radius of the lens} \\
lc0 &= 0.20; & \text{ // Nucleus characteristic length} \\
lc1 &= 0.02; & \text{ // Surface characteristic length} \\
\theta &= 0.1; & \text{ // Angle of rotation} \\
\text{Point}(1) &= (0,0,0,lc0); \\
\text{Point}(2) &= \{R+\cos(\theta/2),-R+\sin(\theta/2),0,lc1\}; \\
\text{Line}(1) &= \{1,2\}; & \text{// Extrude line 1 about nucleus} \\
\text{Extrude} \{\{0,0,1\},\{0,0,0\}\} \{ \text{Line} \{1\}; \text{Layers} \{\{1\},\{1.0\}\}; \text{Recombine}; \} \\
\text{// Tagging faces and elements} \\
\text{Physical Line}(1) &= \{1,2\}; & \text{// Sides (no flux through these faces)} \\
\text{Physical Line}(2) &= \{3\}; & \text{// Surface face} \\
\text{Physical Surface}(3) &= \{4\}; & \text{// Interior faces and elements}
\end{align*}
\]

The Gmsh .geo file used to generate the mesh for the two-dimensional model.

\[
\begin{align*}
R &= 1.6; & \text{ // Radius of the lens} \\
lc0 &= 0.6; & \text{ // Nucleus characteristic length} \\
lc1 &= 0.06; & \text{ // Surface characteristic length} \\
\text{Point}(1) &= (0,0,0,lc0); \\
\text{Point}(2) &= \{R,0,0,lc1\}; \\
\text{Line}(1) &= \{1,2\}; & \text{// Extrude Line 1 about the nucleus in three steps} \\
\text{Extrude} \{\{0,0,1\},\{0,0,0\}\} \{ \text{Line} \{1\}; \text{Layers} \{\{2.2,2.0,0.5,1.0\}\}; \text{Recombine}; \} \\
\text{Extrude} \{\{0.0,1\},\{0,0,0\}\} \{ \text{Line} \{2\}; \text{Layers} \{\{6\},\{1\}\}; \text{Recombine}; \} \\
\text{Extrude} \{\{0.0,1\},\{0,0,0\}\} \{ \text{Line} \{5\}; \text{Layers} \{\{2.5,2.2,0.5,0.8,1.0\}\}; \text{Recombine}; \} \\
\text{// Tagging faces and elements} \\
\text{Physical Line}(1) &= \{1,8\}; & \text{// Faces through the pole axis} \\
\text{Physical Line}(2) &= \{3,6,9\}; & \text{// Surface faces} \\
\text{Physical Surface}(3) &= \{4,7,10\}; & \text{// Interior faces and elements}
\end{align*}
\]
References


REFERENCES


REFERENCES


