A Transient Model of the Renal Medulla

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Abstract

The kidney is one of the most important organs in the body, responsible for regulating the volume and composition of the extracellular fluid; excreting metabolic waste (as urine) and foreign substances; and also producing some hormones. Through its functional unit, the nephron, blood is filtered and along the course of the different segments reabsorption and secretion takes place until the final product leaves the collecting duct as urine.

This thesis focuses on the urine concentrating mechanism, presenting a transient shunt model of the renal medulla where a population of nephrons is merged into a common structure. The model, consisting of a coupled system of PDEs-ODEs describing concentrations and volume flows through the loop of Henle, collecting duct, and vasa recta, is solved by the numerical Method of Lines.

For the first time in the case of a shunt model, the prebend transition occurring at a fixed distance before the turn at the tip of the descending loop of Henle is included. The hypothesis considering glycolysis as a source of external osmoles is presented in a model of the vasa recta, where a new numerical approach based on the software package Chebfun is considered. Later, this process is included in a full model of the renal medulla. Several results from the transient analysis are also presented, such as the time that it takes to wash out the gradient if an increase of blood flow occurs and the time that the gradient takes to build up for the different solutes.
Para todos aquellos que me han apoyado y han creído en mí.

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# Contents

List of Figures v

List of Tables xiii

1 Introduction 1

2 The kidney and the urine concentrating mechanism 7
   2.1 Anatomy 7
   2.2 Functions 9
   2.3 Nephron 10
      2.3.1 Types of nephrons 12
      2.3.2 Renal blood supply 12
   2.4 Tubular transport 14
      2.4.1 Diffusion 15
         2.4.1.1 Fick’s first law 15
      2.4.2 Osmosis across selectively permeable membranes 16
      2.4.3 Active transport 17
   2.5 The urine concentrating mechanism 19
      2.5.1 The countercurrent mechanism 22

3 Modelling the Urine Concentrating Mechanism 29
   3.1 General considerations 29
   3.2 Mass balance equations 30
   3.3 Transmural fluxes 32
   3.4 Modelling a population of nephrons 35
      3.4.1 Multinephron-weighted-type model 35
# CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.4.2</td>
<td>Shunt models</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>3.4.2.1 Exponential decay</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>3.4.2.2 Interstitium/AVR</td>
<td>40</td>
</tr>
<tr>
<td>3.5</td>
<td>Boundary conditions and initial conditions</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>Numerical method</td>
<td>43</td>
</tr>
<tr>
<td>4.1</td>
<td>Introduction</td>
<td>43</td>
</tr>
<tr>
<td>4.2</td>
<td>Analytical base case</td>
<td>43</td>
</tr>
<tr>
<td>4.3</td>
<td>Numerical approach: The Method of Lines</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>4.3.1 Background</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>4.3.2 Method description</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>4.3.2.1 First order differences</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>4.3.2.2 Collocation</td>
<td>57</td>
</tr>
<tr>
<td>4.3.3</td>
<td>Numerical results</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>4.3.3.1 Approximation using Chevyshev Points: Chebfun</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>4.3.3.2 Conclusions</td>
<td>63</td>
</tr>
<tr>
<td>5</td>
<td>Inclusion of Pre-bend Transitions in Shunt Models</td>
<td>65</td>
</tr>
<tr>
<td>5.1</td>
<td>Introduction</td>
<td>65</td>
</tr>
<tr>
<td>5.2</td>
<td>The use of a virtual tube</td>
<td>66</td>
</tr>
<tr>
<td>5.3</td>
<td>Derivation of equations for the number of tubes</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>5.3.1 Number of LDLs</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>5.3.2 Equations describing the changes in the number of tubes</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>5.3.2.1 LAL</td>
<td>72</td>
</tr>
<tr>
<td>5.3.3</td>
<td>Mass conservation equations</td>
<td>73</td>
</tr>
<tr>
<td>5.4</td>
<td>Multinephron vs Shunt Model with prebend transitions</td>
<td>74</td>
</tr>
<tr>
<td>5.4.1</td>
<td>General considerations</td>
<td>74</td>
</tr>
<tr>
<td>5.4.2</td>
<td>The Multinephron Model</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>5.4.2.1 Anatomy considerations</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>5.4.2.2 Numerical solution</td>
<td>77</td>
</tr>
<tr>
<td>5.4.3</td>
<td>Shunt Model</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>5.4.3.1 Numerical solution</td>
<td>80</td>
</tr>
<tr>
<td>5.4.4</td>
<td>Comparison</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>5.4.4.1 Number of tubes</td>
<td>80</td>
</tr>
</tbody>
</table>
5.4.4.2 Osmolality profiles and concentration: The effect of the prebend transition 82

6 Glycolysis: a source of external osmoles 87
6.1 Introduction 87
6.2 Glycolysis 87
6.3 The Vasa Recta Model 89
   6.3.1 Model description 89
   6.3.2 Equations 89
      6.3.2.1 Volume flow equations 89
      6.3.2.2 Solute equations 90
6.4 Numerical solution: Chebfun 92
6.5 Results 94
   6.5.1 Glycolytic rate 94
   6.5.2 Effect of decreasing inner medullary blood flow 98
   6.5.3 Effect of increasing inner medullary blood flow 100
   6.5.4 Effect of varying nephrons uptake 102

7 Full dynamic renal model including glycolysis and prebend transitions 105
7.1 Introduction 105
7.2 Anatomical considerations 105
   7.2.1 Boundary conditions and membrane parameters 106
   7.2.2 Number of tubes 108
7.3 System of equations 113
7.4 Numerical simulations 116
   7.4.1 Baseline case 116
   7.4.2 Effect of the prebend transition 119
   7.4.3 Gradient washout 121
   7.4.4 Conclusions 125

8 Conclusion 127

Bibliography 129
## List of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>The kidney and its functional unit.</td>
<td>2</td>
</tr>
<tr>
<td>1.2</td>
<td>Parts of the nephron included in a model of the UCM.</td>
<td>2</td>
</tr>
<tr>
<td>2.1</td>
<td>Urinary system and the kidney.</td>
<td>8</td>
</tr>
<tr>
<td>2.2</td>
<td>Section of the human kidney.</td>
<td>8</td>
</tr>
<tr>
<td>2.3</td>
<td>Parts of the nephron</td>
<td>12</td>
</tr>
<tr>
<td>2.4</td>
<td>Renal blood supply and types of nephrons[12].</td>
<td>13</td>
</tr>
<tr>
<td>2.5</td>
<td>Nephron blood supply</td>
<td>14</td>
</tr>
<tr>
<td>2.6</td>
<td>Passive transport and active transport</td>
<td>14</td>
</tr>
<tr>
<td>2.7</td>
<td>Process of osmosis taking place when a solution of sodium chloride and water are placed on the two sides of a membrane</td>
<td>17</td>
</tr>
<tr>
<td>2.8</td>
<td>Transport of sodium and potassium ions by active pumps.</td>
<td>19</td>
</tr>
<tr>
<td>2.9</td>
<td>Summary of forces involved in glomerular filtration with values shown belonging to estimates for healthy humans</td>
<td>20</td>
</tr>
<tr>
<td>2.10</td>
<td>Reabsorption of filtered water and solutes from the tubular lumen across epithelial cells back into the blood.</td>
<td>21</td>
</tr>
<tr>
<td>2.11</td>
<td>Changes in osmolality along the nephron.</td>
<td>23</td>
</tr>
<tr>
<td>2.12</td>
<td>Left: Parallel structures with fluid flowing in opposite directions.</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Red indicates a higher concentration if this is the transferred property considered. Double arrows indicate the exchange between both structures. Right: The Loop of Henle as a countercurrent exchanger.</td>
<td></td>
</tr>
<tr>
<td>2.13</td>
<td>General HCC assumptions</td>
<td>25</td>
</tr>
<tr>
<td>2.14</td>
<td>HCC main steps</td>
<td>25</td>
</tr>
<tr>
<td>2.15</td>
<td>Mechanism involved in the passive hypothesis</td>
<td>26</td>
</tr>
</tbody>
</table>
LIST OF FIGURES

3.1 Section of tube ................................................. 30
3.2 Scheme of model configuration shown in [43]. The arrows indicate
the direction of the flow and as Equation (3.16) shows, the Central
Core (CC) is considered closed at the tip (x = L) ................. 36
3.3 Composite tube representing the Loop of Henle .............. 38
3.4 Left: Schematic illustration of loop structure with shunt return,
for flux calculations ([87]). Right: Section of a tubule representing
the new term added to equation (3.27) ......................... 39
3.5 Boundary conditions applied to the composite structures .... 41
4.1 Number of tubes decreasing exponentially with depth .......... 45
4.2 Schematic showing assumptions made and boundary conditions.
Dashed lined walls show infinite permeability to water while solid
lined walls show impermeability to water. Red arrows indicate
transmural solute exchange ..................................... 52
4.3 Analytical concentration for LDL and LAL .................. 53
4.4 Analytical volume flows for LDL, LAL, DVR, AVR and CD (scaled
by the number of tubes at x = 0) ............................. 53
4.5 Method of lines approach .................................... 55
4.6 Concentration of LDL ......................................... 59
4.7 Concentration of LAL ......................................... 59
4.8 Plot of the chebfun representation of sin(5x) including Chebyshev
points ......................................................... 63
5.1 Left: Representation of the IM from [69] where prebend transitions
are represented by the color transition from yellow to green. Right:
Inner medullary loop of Henle where the change of radius at the
prebend transition can be seen. .............................. 65
5.2 Volume and solute flows through the different structures considered
in the Loop of Henle .................................. 66
5.3 Schematic drawing where a discrete population is represented to
distinguish important regions that should be considered. Blue lines
represent LDL properties and red lines LAL. Dashed curves indi-
cate the shunts between structures ......................... 67
5.4 Loss to LAL ......................................................... 69
5.5 Top: Number of LDLs with depth. Bottom: Number of virtual LDLs. ........................................................................... 71
5.6 Virtual and non virtual structures add up the expected number of LDLs ................................................................. 72
5.7 Number of tubes of each type in every region ............................... 72
5.8 Multinephron model structure. Number of each structures is indicated in brackets. In the case of the nephrons: Continuous black lines indicate the section of the descending limb before reaching the prebend transition; Light dashed black curves indicate IM ascending limb properties; and heavy dashed curves indicating OM ascending limbs. The 256 collecting ducts in the outer medulla converge by pairs eight times in the inner medulla to terminate as a single terminal collecting duct. Vasa recta is represented as a single structure with 5 discrete shunts. ........................................ 78
5.9 Schematic of the shunt model with the different structures considered ................................................................................. 79
5.10 Dashed line showing the decay on the number of tubes for the multinephron case. The decay starts at $x = 5.25$ as the first turn does not appear right after the $OM/IM$ border as it is assumed in the Shunt Model (continuous line) (and as also happens in a real case scenario). ........................................................................ 81
5.11 Dashed line showing the eight coalescences considered in the multinephron model; Continuous line showing a CD with continuous coalescences ........................................................................ 81
5.12 Dashed line showing five discrete shunts in the case of the Multinephron model, while shunting in the Shunt model happens continuously and starts at the $OM/IM$ border (continuous line) . . . 82
5.13 Left: Osmolality profiles achieved by the shunt model. Right: Osmolality profiles in the multinephron case ......................... 83
5.14 Inner medullary HL osmolality for both shunt (solid lines) and multinephron (dashed lines). .................................................. 83
5.15 Long loops flow comparison .......................................................... 84
LIST OF FIGURES

5.16 Salt concentration profiles through the medulla. Long loops urea comparison. .................................................. 84
5.17 Top: Concentration profiles at the IM region. Bottom: A closer look to the IM region surrounding the last prebend transition . . 85
6.1 Aerobic and anaerobic glycolysis pathways ............................. 88
6.2 Process of glycolysis in the IM cells ................................. 89
6.3 Single volume flow in \textit{nl/min}, solid curve shows values for DVR, dashed curve for AVR. Outflow from AVR is 30\% higher than DVR inflow, due to assumed volume uptake from nephrons ............. 93
6.4 Glucose and lactate concentration profiles for no glycolysis and glycolysis at 10\% .................................................. 95
6.5 Glucose and lactate concentration profiles for glycolysis at 15\% and 20\% ............................................................. 96
6.6 Glucose and lactate concentration profiles for glycolysis at 30\% and 40\% ............................................................. 97
6.7 Lactate concentration profiles when reducing IMBF ................. 99
6.8 Lactate concentration profiles when IMBF is increased ............ 101
6.9 Lactate concentration profiles when varying volume reabsorption from nephrons ................................................. 103
7.1 Schematic of tubes and regions considered, together with the boundary conditions. For simplicity picture merges LDL and LDLV in a single structure. .................................................. 110
7.2 Number of vasa recta, collecting ducts and long Loops of Henle. Note that the number of Loops of Henle and Collecting Ducts reaching the papillary tip is equal to one. ................................. 111
7.3 Solute contribution to interstitial osmolality without (left) and with glycolysis (right). .................................................. 118
7.4 Build up of salt and lactate gradients in the interstitium from a non-glycolysis state. .................................................. 118
7.5 Effect of doubling the IMBF on the different solutes present at the different structures at the papillary tip. .......................... 122
<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.6</td>
<td>Effect of doubling the IMBF on the different solutes present at the different tubes at the OM/IM border.</td>
<td>123</td>
</tr>
<tr>
<td>7.7</td>
<td>Effect of doubling the IMBF on the total osmolality at the papillary tip.</td>
<td>124</td>
</tr>
<tr>
<td>7.8</td>
<td>Effect of doubling the IMBF on the total osmolality at the OM/IM border.</td>
<td>124</td>
</tr>
<tr>
<td>7.9</td>
<td>Interstitial osmolality at the quasi-steady state: before and after the increase in medullary blood flow.</td>
<td>125</td>
</tr>
</tbody>
</table>
LIST OF FIGURES
List of Tables

4.1 MOLFIRST global spatial convergence results computed for $C_{LDL}$ 60
4.2 PDECOL global spatial convergence results computed for $C_{LDL}$ with a choice of $KORD = 3$ ................................. 61
4.3 PDECOL global spatial convergence results computed for $C_{LDL}$ with a choice of $KORD = 4$ ................................. 61
4.4 PDECOL global spatial convergence results computed for $C_{LDL}$ with a choice of $KORD = 6$ ................................. 61

5.1 Transport parameters and radius. $L_p RT$ measured in $10^{-4} \text{mm}/(s \text{mosm/l})$. Permeabilities measured in $10^{-4} \text{mm/s}$. Radius measured in $\mu m$ and $V_m$ measured in $nmol/(mm^2 \cdot s^{-1})$. .............................. 75

6.1 Baseline values, parameters and boundary conditions ................. 93
6.2 Concentration of lactate building up for various times when glycolysis is set at 20% .......................................................... 94
6.3 Concentration of lactate building up for various times after IMBF decreases by 50% ............................................................ 98
6.4 Concentration of lactate when IMBF is increased by 50% for various times. ............................................................................ 100
6.5 Concentration of lactate when the absorption rate is decreased to 10%. .............................................................................. 102

7.1 Concentrations and volume flows entering LDL, SDL and DVR . . 108
7.2 Baseline parameters .................................................................. 109
7.3 Number of tubes at each depth ............................................... 112
7.4 VR concentrations .................................................................... 117
LIST OF TABLES

7.5 Interstitial concentration without and with prebend . . . . . . . 119
7.6 Long descending limb salt concentrations and osmolality with and
without prebend . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 120
1

Introduction

The kidney is one of the most important organs in our body, responsible for regulating the volume and composition of the extracellular fluid, excreting metabolic waste and foreign substances and also producing some hormones. But it is also involved in more complex processes and diseases, as for example common types of hypertension.

Understanding the functioning of the kidney requires a combination of experimental techniques such as microperfusion (see Microperfusion, [76]) and micropuncture (see Micropuncture, [24]) at cortical and papillary tip levels (but not within the kidney itself) and mathematical modelling, that allows the verification of complicated hypotheses about the “in vivo” functioning of this organ that cannot be verified rigorously without the use of modelling tools.

A kidney contains about one million nephrons, the functional units of the kidney, and each of these consist of a renal corpuscle and a renal tubule. The nephron is responsible for the production of urine, a process that starts with the filtration of blood taking place at the glomerulus. After this first stage, the filtrate continues through the different segments (proximal tubule, loop of Henle and distal tubule) where reabsorption and secretion take place, keeping the amount of water and ion concentrations in the body balanced.
1. INTRODUCTION

The legacy of mathematical models in the kidney study is extensive, including: (1) Tubulo-glomerular feedback models ([4], [32], [44], [71]), that study and model the glomerulus (filtration unit of the kidney) and the filtration of the blood prior the formation of urine; (2) Tubular transport models, usually focused on the modelling of epithelial cell transport and commonly modelling sections such as the proximal and the distal tubule ([9], [10] [26], [27], [99], [101], [102]); (3) Microcirculation Models ([18], [106], [97]); and (4) UCM (urine concentrating mechanism) models ([31], [45], [61], [104]).

This thesis focuses on these later models that study the functioning of the loop of Henle and the collecting ducts, including sometimes the vasculature surrounding these segments. Appropriate boundary conditions are included to account for the non-modelled structures.

Figure 1.1: The kidney and its functional unit.

Figure 1.2: Parts of the nephron included in a model of the UCM.
Outline of Chapters

Chapter 2

Since modelling the kidney requires a basic understanding of its anatomy and main functions, Chapter 2 in this thesis presents a review of the basics of renal physiology and the notation that will be assumed in future chapters. The main parts of the kidney and its functional unit (the nephron) are explained together with the main functions and processes taking place in this organ.

Chapter 3

Modelling the urine concentrating mechanism requires to model a population of nephrons. During Chapter 3 the main two approaches to modelling a population of nephrons are discussed and compared. While some authors model nephrons as individual structures ([46], [86]) in what is called a Multinephron model, others ([31], [104]) consider a population of nephrons merged into a single structure in what is called a Shunt model. The inclusion of the vasculature surrounding these units is also studied and the main advantages and disadvantages of the two models presented.

Chapter 4

Throughout the history of the modelling of the nephron, the majority of models ([87], [104]) have required the solution of a coupled boundary value problem describing steady state flows of volume and solute; however, some transient issues observed in experimental studies ([2]) and others of interest to the physiological community cannot be addressed if a transient model is not considered. A transient model of the kidney implies the solution of a coupled system of PDEs and ODEs describing concentrations and volume flows ([21], [45], [61]). It is known, as is discussed in Chapter 4, that the numerical simulation of kidney models implies the solution of stiff systems in both steady state and transient cases, due to anatomical configurations and abrupt changes in some of the membrane properties, such as permeabilities to some solutes or also the change in radius through the course of a tubule.
1. INTRODUCTION

Considering several assumptions and only one solute, a shunt model with analytical steady solutions is derived in the first part of Chapter 4. This is used in the second part of the chapter to test the performance of two different numerical approaches based on the numerical Method of Lines for the solution of a transient shunt model.

Chapter 5

As was mentioned before, membrane properties and radius can change abruptly in some sections of the tube. A special case of these sudden changes is the prebend segment, a section of the descending branch of the loop of Henle starting at a fixed distance before the loop turns. In this portion of the tube the descending branch assimilates properties as the ascending one ([69]) becoming completely impermeable to water and also changing radius. The modelling of this segment has been considered before in multinephron models ([45]) but implies a considerable challenge in shunt models, where several tubes are merged into a single one, making this transition complicated to locate. In Chapter 5, an approach to prebend transitions in shunt models by using an auxiliary structure is presented and its performance is compared with a multinephron model based on the one presented at [86], where the prebend transition is explicitly included in each tube.

Chapter 6

As is explained in Chapter 2, the mechanism responsible for the high osmolarities found in the inner region of the kidney (the inner medulla) is yet not completely understood. Several hypotheses have been proposed since the nineteen-fifties ([89]), some of which have been proved to be not possible. It is believed ([90]) that a combination of different processes could be the key to finding a final answer to the remaining questions. Such processes include: (1) renal pelvis contractions ([25]); (2) special tubes exchange arrangements ([69], [104]); (3) contribution of external osmoles ([62], [92]).

In Chapter 6, the hypothesis that considers the process of glycolysis taking place in the inner medullary cells as a contributor to the increase of the inner medullary gradient is modelled using a transient version of the previous work.
presented in [88]. This only models the vasculature (vasa recta) surrounding the loop of Henle that extends deep into the medulla. Although time scales might differ from a more complete model of the renal medulla where more solutes interact and the nephrons are included, transient findings help to quantify the difference between the build up and washout of the concentration gradients. Together with the model, the efficiency and future use of the software package Chebfun ([5]) based on spectral collocation at Chevyshev points is explored.

Chapter 7

In Chapter 7 the model presented in Chapter 5 is merged with the glycolysis hypothesis from Chapter 6 resulting in a more complex model where a total of five solutes (NaCl, urea, glucose, lactate and KCl) interact in a system of eight different structures. Time dependent results testing similar ideas to those in Chapter 6 are presented as well as the time taken for each individual solute gradient to build up. The effect of the prebend transition in the process of glycolysis is also discussed.

Chapter 8

Finally Chapter 8 presents an overall conclusion and highlights the main issues to consider in order to improve the full transient problem presented in Chapter 7.
1. INTRODUCTION
The kidney and the urine concentrating mechanism

The following chapter is an introduction to the basics of kidney physiology based mainly on [14], [20], [28], [60], [63], [77] and [105].

2.1 Anatomy

In a normal human adult, each kidney is about 11 cm long and about 5 cm thick, weighing about 150 grams. The kidneys are bean-shaped organs that lie on the posterior wall of the abdomen, outside the peritoneal cavity (Figure 2.1). The medial side of each kidney contains an indented region called the hilum through which pass the renal artery and vein, lymphatics (see Lymphatics), the nerve supply, and the ureter, which carries the final urine from the kidney to the bladder. The kidney is surrounded by a tough, fibrous capsule that protects its delicate inner structures.

If the kidney is bisected from top to bottom (Figure 2.2), the two major regions that can be visualized are the outer cortex and the inner region referred to as the medulla. The medulla is divided into multiple cone-shaped masses of tissue called renal pyramids. The base of each pyramid originates at the border between the cortex and medulla and terminates in the papilla, which projects into the space of the renal pelvis, a funnel-shaped continuation of the upper end of the ureter. The outer border of the pelvis is divided into open-ended pouches
2. THE KIDNEY AND THE URINE CONCENTRATING MECHANISM

called major calyces that extend downward and are in turn divided into minor calyces, which collect urine from the tubules of each papilla. The walls of calyces, pelvis and ureter contain contractile elements that propel the urine toward the bladder.

Figure 2.1: Urinary system and the kidney.

Figure 2.2: Section of the human kidney.
2.2 Functions

As will be explained in the next sections, the best known function of the kidney is its responsibility for ridding the body of waste materials that are either ingested or produced by the metabolism. However, the kidney is responsible for many other functions such as regulation of water and electrolyte balances, regulation of arterial pressure, regulation of acid base balance, regulation of erythrocyte production and glucose synthesis.

Excretion of Metabolic Waste Products, Foreign Chemicals, Drugs and Hormone Metabolites. The kidneys are the primary means for eliminating waste products of the metabolism that are no longer needed by the body. These products include urea (from the metabolism of amino acids (see Amino acids)), creatinine (from muscle creatine (see Creatine)), uric acid (from nucleic acids), end products of hemoglobin breakdown, and metabolites (see Metabolites) of various hormones (see Hormone). These waste products must be eliminated by the body as rapidly as they are produced since most of them are toxic.

Regulation of Water and Electrolyte Balance. Homeostasis (see Homeostasis) requires that excretion of water and electrolytes (see Electrolytes) must precisely match intake. Intake of water and many electrolytes is governed mainly by eating and drinking habits, thus requiring the kidneys to adjust their excretion rates.

Regulation of arterial pressure. The kidneys play an important role in long-term regulation of arterial pressure by excreting variable amounts of sodium and water. The kidneys also contribute to short-term arterial pressure regulation by secreting vasoactive (see Vasoactive) factors or substances which are responsible for causing constriction or dilation of blood vessels.

Regulation of Acid Base Balance. The kidneys contribute to acid-base regulation, along with the lungs, by excreting acids. The kidneys are the only means of eliminating from the body certain types of acids such as sulphuric acid and
phosphoric acid, which are generated by the metabolism of proteins.

Regulation of erythrocyte production. An erythrocyte (red blood cell) in the circulation cannot reproduce, as it lacks a nucleus. Erythropoiesis is the production of new red cells, replacing the worn-out cells in the circulation. The number of erythrocytes normally remains constant: cell production equals cell death. However, a low level of oxygen delivery to the tissues stimulates an increased rate of erythropoiesis. This is controlled by erythropoietin, a hormone produced by the kidneys.

Glucose synthesis. Gluconeogenesis, the synthesis of glucose from amino acids and other precursors, occurs in the kidney. Under normal conditions this is a minor function but during prolonged fasting the kidney can become a major source of blood glucose producing about one fifth as much glucose as the liver. Organic nutrients such as glucose and amino acids are normally maximally conserved by the kidney. They are actively reabsorbed against steep concentration gradients (see Concentration gradient) and normally their urinary excretion is essentially zero.

2.3 Nephron

The nephron is the functional unit of the kidney. There are more than a million in each normal adult human kidney. Its chief function is to regulate water and soluble substances by filtering them from the blood, reabsorbing what is needed and excreting the rest as urine. Its functions are vital to life and are regulated by the endocrine system and by hormones such as antidiuretic hormone (see Antidiuretic hormone), aldosterone (see Aldosterone), and parathyroid hormone (see Parathyroid hormone).

Each nephron contains a tuft of capillaries called the glomerulus, through which large amounts of fluid are filtered from the blood, and a long tubule in which the filtered fluid is converted into urine on its way to the pelvis of the kidney (see Figure 2.3).
The glomerulus contains a network of branching and anastomosing (see Anastomosis) glomerular capillaries that, compared with other capillaries, have high hydrostatic pressure (about 60 mm Hg, see Hydrostatic pressure). The glomerular capillaries are covered by epithelial cells, and the total glomerulus is encased in the Bowman’s Capsule (see Bowman’s Capsule). Fluid filtered from the glomerular capillaries flows into the Bowman’s capsule and then into the proximal tubule, which lies in the cortex of the kidney. The proximal tubule is a leaky epithelium with high reabsorption of water and solutes but low capacity to create concentration gradients.

From the proximal tubule, fluid flows into the loop of Henle, which dips into the inner medulla. The loop of Henle is divided into three sections: (1) the descending limb, (2) the thin ascending limb (located at the inner medulla) and (3) the thick ascending limb (located at the outer medulla). The descending limb is a thin tubule leading from the proximal tubule and extending into the renal medula. At the tip of the loop the tubule reverses direction, becoming the thin ascending limb, which extends towards the cortex. As the tubule approaches the cortex, it widens into the thick ascending limb. A fixed distance before the tip of the loop (165 µm), the descending limb presents a segment, structurally and functionally identical to the ascending limb called prebend enlargement or prebend segment.

At the end of the thick ascending limb there is a short segment, which is actually a plaque in its wall, known as the macula densa (as it will be explained in Section 2.5). The macula densa plays an important role in controlling nephron function. Beyond the macula densa the fluid enters the distal tubule, which, like the proximal tubule, lies in the renal cortex. This is followed by the cortical collecting duct; the initial parts of 8 to 10 cortical collecting ducts join to form a single larger collecting duct that runs downward into the medulla and becomes the medullary collecting duct. The collecting ducts merge to form progressively larger ducts that eventually empty into the renal pelvis through the tips of the renal papillae. In each human kidney there are about 250 of the very large collecting ducts, each of which collect urine from about 4000 nephrons.
2. THE KIDNEY AND THE URINE CONCENTRATING MECHANISM

2.3.1 Types of nephrons

Although each nephron has all the components described earlier, there are some differences, depending on how deep the nephron lies within the kidney mass.

Two different types of nephrons can be distinguished (see Figure 2.5):

_Cortical nephrons_: have glomeruli in the outer two-thirds of the cortex with lower filtration rate and short loops of Henle that just dip into the outer medulla.

_Juxtamedullary nephrons_: have glomeruli in the inner cortex with higher filtration rate and long loops of Henle that plunge deep into the medulla, some as far as the tips of the papillae.

2.3.2 Renal blood supply

Blood flow to the kidneys (see Figure 2.4) is normally about 22% of the cardiac output. The renal artery enters the kidney through the hilum and then branches into _segmental arteries_, which branch into a number of smaller _interlobar arteries_ that feed into another set of arteries called _arcuate arteries_. The arcuate
2.3 Nephron

arteries then branch into the *interlobular arteries*, from which blood is carried to individual nephrons by the *afferent arterioles*, which lead into the *glomerular capillary beds*, where large amounts of fluid and solutes are filtered to begin urine formation.

Coming off each of the glomerular capillary beds is the *efferent arteriole*, which then gives rise to one of two types of capillary beds: *peritubular capillaries*, which branch from the efferent arterioles of cortical nephrons and are located close to the renal tubules, and *vasa recta* (see Figure 2.5), which branch from the efferent arterioles of juxtamedullary nephrons and are networks of blood vessels forming hairpin loops that run along the loops of Henle and collecting ducts, dipping deep into the renal medulla.

The peritubular capillaries and vasa recta empty into the vessels of the venous system and progressively form the *interlobular veins*, from where blood is carried away from nephrons by the *arcuate vein, intalobar vein*, which run parallel to their respective arterial counterparts, eventually draining into the *renal vein*, which leaves the kidney beside the renal artery and ureter.

![Renal blood supply and types of nephrons](image)

**Figure 2.4:** Renal blood supply and types of nephrons[12].
2.4 Tubular transport

The process in the tubules involves transport of substances across the tubular walls, which are composed of epithelial cells.

Transport through the cell membrane occurs by one of two basic processes: diffusion or active transport (see Figure 2.7). Diffusion, also called passive transport, requires no energy from the cell, while active transport requires the cell to expend energy, usually in the form of ATP (see Adenosine Triphosphate).
2.4 Tubular transport

2.4.1 Diffusion

Diffusion is the movement of solutes where thermic agitation and difference in concentration is the driving force: material moves from an area of high concentration of that material to an area of lower concentration. The difference in concentration between the two areas is termed as the concentration gradient, and diffusion will continue until this gradient has been eliminated. Since diffusion moves material from areas of higher concentration to areas of lower concentration, it is described as moving solutes “down the concentration gradient”.

2.4.1.1 Fick’s first law

The diffusion velocity of particles was formulated in 1855 by the physiologist Adolf E. Fick and is known as Fick’s Law (see [34]). The simplified version of it is used in steady-state diffusion when the concentration within the diffusion volume does not change with respect to time. In one (spatial) dimension, this is:

\[ J = -D \frac{\partial C}{\partial x}, \]  

(2.1)

where

- \( J \) is the diffusion flux (\([\text{amount of substance}]L^{-2}T^{-1}\)).
- \( D \) is the diffusion coefficient or diffusivity (\(L^2T^{-1}\)).
- \( C \) is the concentration of a given solute (\([\text{amount of substance}]L^{-3}\)).
- \( x \) is the position (\(L\)).

The negative sign indicates that the particles move from the highest concentrated region to the lowest concentrated.

If a membrane of thickness \( \Delta x \) is considered and the difference between the two compartments separated by the membrane is constant \( \Delta C = C_2 - C_1 \), then a discrete version of the first Fick’s Law is

\[ J = -D \frac{\Delta C}{\Delta x}, \]  

(2.2)
2. THE KIDNEY AND THE URINE CONCENTRATING MECHANISM

Considering the membrane’s permeability coefficient \( P = \frac{D}{\Delta x} \), then Equation (2.2) gives rise to the formula commonly used in biology models:

\[
J = -P\Delta C
\]  

(2.3)

where \( P \) is the permeability, an experimentally determined membrane “conductance” for a given substance at a given temperature.

Considering \( C_1 \) and \( C_2 \) the concentrations at each side of the membrane

\[
J = -P(C_2 - C_1)
\]  

(2.4)

which will be used in the following chapters.

2.4.2 Osmosis across selectively permeable membranes

By far the most abundant substance that diffuses through the cell membrane is water. Normally, the amount that diffuses in the two directions through the cell membrane is balanced so precisely that zero net movement of water occurs. Therefore, the volume of the cells remain constant. However, under certain conditions, a concentration difference for water can develop across a membrane. When this happens, net movement of water does occur across the cell membrane, causing the cell either to swell or to shrink, depending on the direction of the water movement. This process of net movement of water caused by a concentration difference of water is called osmosis (Figure 2.7).

Van’t Hoff ([96]) showed that every dilute solution follows mathematical laws analogous to those describing the behaviour of ideal gases; so volume flux due to osmosis can be written as (see [77])

\[
J_v = L_p \sigma RT \Delta C
\]  

(2.5)

where \( L_p \) is the hydraulic conductivity of the membrane. The ability of the barrier to discriminate between the solute and water can be described by a reflection coefficient \( \sigma \) (also known as Staverman’s coefficient). The expression \( \sigma RT \Delta C \) represents the effective osmotic pressure. The value of \( \sigma \) can vary from 0 to 1. When the membrane is impermeable to the solute \( \sigma = 1 \) and when it is equally
permeable to solute and water $\sigma = 0$. $R$ represents the ideal gas constant, $T$ is (absolute) temperature and $\Delta C$ is the concentration difference between the two sides of the membrane.

As water moves across the tight junctions (see Tight junction) by osmosis, it can also carry with it some of the solutes (assuming that the reflection coefficient is not 1), a process referred to as solvent drag $J_{sd}$. The expression for flux due to solvent drag is given by (see [77]):

$$J_{sd} = (1 - \sigma)\bar{C}J_v$$  \hspace{1cm} (2.6)

where $\bar{C}$ is usually taken as the mean between concentrations on each side of the membrane.

### 2.4.3 Active transport

At times, a large concentration of a substance is required in the intracellular fluid even though the extracellular fluid contains only a small concentration. When a cell membrane moves molecules or ions “uphill” against a concentration gradient, the process is called active transport. Active transport is the mediated transport of biochemicals, and other atomic/molecular substances, across membranes. Unlike passive transport, this process requires chemical energy in the form of
adenosine triphosphate (ATP). In this form of transport, molecules move against either an electrical or concentration gradient.

Different substances that are actively transported through at least some cell membranes include sodium ions, potassium ions, calcium ions, iron ions, hydrogen ions, chloride ions, urate ions, several different sugars, and most of the amino acids.

There are two main types of active transport: primary and secondary. In primary transport, energy is directly coupled to the movement of a desired substance across a membrane independent of any other species. Secondary transport concerns the diffusion of one species across a membrane to drive the transport of another.

Among the substances that are transported by primary active transport are sodium, potassium, calcium, hydrogen, chloride and a few other ions. The active transport mechanism that has been studied in greatest detail is the sodium-potassium pump, present in cells of the outer medullary ascending limb of Henle and also in the collecting duct. This transport process pumps sodium ions outward through the cell membrane and at the same time pumps potassium ions from the outside to the inside. As seen in Figure 2.8ⁱ three sodium ions from inside the cell first bind to the transport protein. Then a phosphate group is transferred from ATP to the transport protein causing it to change shape and release the sodium ions outside the cell. Then two potassium ions from outside the cell bind to the transport protein and as the phosphate is removed, the protein assumes its original shape and releases the potassium ions inside the cell.

Detailed models of active transport require some insight into the mechanisms involved and give rise to complicated functional forms for the relevant reaction rates, with the consequent estimation of a number of parameters. In models of the urine concentrating mechanism active transport is approximated by a saturable expression having the form of Michaelis Menten kinetics (see [34], [77]).

¹Pictures created by Dr. Kaiser at http://student.cebcmd.edu/gkaiser/goshp.html.
2.5 The urine concentrating mechanism

As has already been discussed, urine formation begins with the process of filtration, which goes on continually in the renal corpuscles. The glomerular filtrate consists primarily of water, sugar, salts and nitrogenous waste products (such as urea, creatinine and uric acid). Larger substances such as proteins and blood cells, cannot pass through the glomerular walls; they remain in the blood.

Urea is formed in the body to eliminate the very toxic ammonia (see Ammonia) products that are formed in the liver from amino acids. Since humans cannot excrete ammonia, it is converted to the less dangerous urea and then filtered out of the blood. Urea is the most abundant of the waste products that must be excreted by the kidneys.

The total rate of glomerular filtration (glomerular filtration rate or GFR) for the whole body (i.e., for all of the nephrons in both kidneys) is normally about 125 ml per minute or 180 l/day. The GFR is determined by the sum of hydrostatic and colloid osmotic forces across the glomerular membrane (see Colloid, Oncotic pressure and Hydrostatic pressure), which gives the net filtration pressure (Figure 2.9). Therefore it can be expressed as:

\[
GFR = K_f \times \text{Net filtration pressure}
\]
where $K_f$ represents the glomerular capillary filtration coefficient and Net filtration rate is given by:

$$\text{Net filtration pressure} = P_G - P_B - \pi_G + \pi_B$$  \hspace{1cm} (2.8)

where

- $P_G$ is the hydrostatic pressure inside the glomerular capillaries, which promotes filtration.
- $P_B$ is the hydrostatic pressure of Bowman’s capsule outside the capillaries, which opposes to filtration.
- $\pi_G$ is the colloid osmotic pressure of the glomerular capillary proteins, which opposes to filtration.
- $\pi_B$ is the colloid pressure of the proteins in Bowman’s capsule, which promotes filtration (protein concentration in the glomerular filtrate is so low that this is usually considered zero).

### Feedback mechanisms

Feedback mechanisms intrinsic to kidneys normally keep the renal blood flow and GFR relatively constant. This relative constancy of GFR and renal blood flow is referred to as *autorregulation*. To perform the function of autorregulation,
2.5 The urine concentrating mechanism

The kidneys have a feedback mechanism that links changes in the sodium chloride concentration at the macula densa with the control of renal arteriolar resistance (see Vascular Resistance). This feedback helps ensure a relatively constant delivery of sodium chloride to the distal tubule and helps prevent spurious fluctuation in renal excretion.

Reabsorption is the second process after glomerular filtration takes place. Reabsorption, by definition, is the movement of substances out of the renal tubules back into the blood capillaries located around the tubules (called the peritubular capillaries) as shown in Figure 2.10. It is a highly selective process. Some substances such as glucose and amino acids are almost completely reabsorbed from the tubules. Other substances such as many of the ions in plasma (sodium, chloride and bicarbonate) can have different rates of reabsorption depending on the needs of the body. Reabsorption begins in the proximal convoluted tubules and continues in the loop of Henle, distal convoluted tubules, and collecting tubules.

![Figure 2.10: Reabsorption of filtered water and solutes from the tubular lumen across epithelial cells back into the blood.](image)

Secretion is the third important process in the formation of urine. Secretion is the process by which substances move into the distal and collecting tubules from blood in the capillaries around these tubules. In this respect, secretion is reabsorption in reverse. Whereas reabsorption moves substances out of the tubules and into the blood, secretion moves substances out of the blood and into the tubules where they mix with the water and other wastes and are converted
2. THE KIDNEY AND THE URINE CONCENTRATING MECHANISM

into urine. These substances are secreted through either an active transport mechanism or as a result of diffusion across the membrane. Substances secreted are hydrogen ions ($H^+$), potassium ions ($K^+$), ammonia ($NH_3$), and certain drugs. Kidney tubule secretion plays a crucial role in maintaining the body’s acid-base balance, another example of an important bodily function in which the kidney participates.

2.5.1 The countercurrent mechanism

The renal medulla is characteristic of higher vertebrates, and the inner medulla (i.e., long limbs of Henle within epithelia) exists only in mammals. They have the ability to excrete urine at osmolalities significantly above their blood osmolality ($270-300 \text{ mOsmols}$) (see Figure 2.11), which is essential for the survival of those that live on land (as explained below). The human kidney can produce a maximal urinary concentration of 1400 $\text{mOsmol/l}$, almost five times the osmolality of plasma.

Water is continuously lost from the body through various routes. Fluid intake is required to match this loss, but the ability of the kidney to form a small volume of concentrated urine minimizes the intake of fluid required for homeostasis, a function that is especially important when water is in short supply. The basic requirements for forming a concentrated urine are ([28]): (1) a high level of $ADH$, which increases the permeability of the distal tubules and collecting ducts, thereby allowing these tubular segments to avidly reabsorb water, and (2) a high osmolality of the renal medullary interstitial fluid, which provides the osmotic gradient necessary for water reabsorption to occur in the presence of high levels of $ADH$.

Although it is clear that the creation and maintenance of a steep corticopapillary gradient is fundamental to the kidney’s concentrating ability, intriguing questions remain unanswered concerning how the interstitial fluid becomes hyperosmotic in the renal medulla. In 1951 Hargitay and Kuhn [38] were the first to propose an explanation for the creation of hyperosmotic urine in the mammalian kidney, based on the operation of the countercurrent mechanism.
Countercurrent exchange (see Figure 2.12) comprises the mechanisms used to transfer some property of a fluid from one flowing current of fluid to another across a semipermeable membrane or thermally-conductive material between them. The property transferred could be heat, concentration of a chemical substance, or others. With a working physical model Hargitay and Kuhn [38] showed how this principle could be applied to the hairpin configuration of the loop of Henle and vasa recta in a mammalian kidney, since the loop of Henle (and also the vasa recta) consists of two parallel limbs (descending and ascending) arranged so that the tubular fluid flows in opposite directions, or countercurrent (see Figure 2.12). They called it The Hairpin Counter Current Hypothesis (HCC).

According to the HCC hypothesis the large axial gradient, which serves to concentrate the urine in the collecting ducts as it passes through on their way to the bladder, is established by multiplication of a small osmotic effort (called the “single effect”) at each medullary level by countercurrent exchange between the ascending and descending limbs of Henle. That is, although the difference in osmolality between adjacent limbs will be very small, the multiplication of this difference by the countercurrent system could build an axial gradient with theoretically unlimited osmolalities which would contribute to concentrating collecting duct fluid on its way to the bladder.
2. THE KIDNEY AND THE URINE CONCENTRATING MECHANISM

**Figure 2.12:** Left: Parallel structures with fluid flowing in opposite directions. Red indicates a higher concentration if this is the transferred property considered. Double arrows indicate the exchange between both structures. Right: The Loop of Henle as a countercurrent exchanger.

Although the nature of the single effect (at the inner medullary level) is not yet completely understood, the countercurrent multiplier hypothesis is often explained by using active transport of sodium chloride in the ascending limbs as the source that originates this single effect as in Figure 2.13. The different steps that by multiplication increase the osmotic gradient in the inner medulla are represented in Figure 2.14:  

a) Before the vertical gradient is established the medullary interstitial fluid concentration is uniformly 300 mOsmol/l as the remainder of the body fluids;  
b) The active salt pump in the AHL is able to transport out of the lumen until the surrounding interstitial fluid is 200 mOsmol/l higher than the fluid in the limbs;  
c) As an effect of the pump, the interstitial fluid becomes hypertonic causing the net diffusion of water from the descending limb into the interstitium until the DHL and interstitium are in osmotic equilibrium;  
d) More fluid enters the tubule pushing higher osmolarity by bulk flow;  
e) Again pumps at the AHL transport salt to the interstitium causing water to diffuse by osmosis from the DHL (as in steps b) and c));  
f) As more fluid enters the tubule the process continues achieving (by multiplication of the single effect) higher osmolalities until a steady state is reached and the osmotic gradient has been established.
2.5 The urine concentrating mechanism

Figure 2.13: General HCC assumptions

(a) Initial Scene  (b) Pump begins  (c) Passive water movement from DHL

(d) New flow entrance  (e) b) and c) are repeated increasing the gradient

(f) Continuous flow entrance and multiplication of the single effect raises concentration

Figure 2.14: HCC main steps
2. THE KIDNEY AND THE URINE CONCENTRATING MECHANISM

Even though micropuncture (see Micropuncture) data has confirmed the predictions of the countercurrent hypothesis ([15], [24], [33], [39]), the nature of the single effect remains open. As mentioned before, active salt transport in the ascending limbs was the first idea proposed in 1959 by Kuhn ([38], [37]) but in the late sixties it became clear that there was no evidence of active transport in the inner medulla ([58]). After the lack of active transport in the inner medulla was shown, simultaneously (1972) Stephenson [80] and Kokko [36] proposed “The passive hypothesis”, based on the idea that the energy expended in the OM on active transport can be transferred to the IM by recycling of two solutes (NaCl and urea). The passive mechanism (see Figure 2.15) assumes that the interstitium has a much higher urea concentration than NaCl concentration, and that fluid in Henle’s loops has a much higher NaCl concentration than urea concentration. If the AHL has a sufficiently high permeability to NaCl, and a sufficiently low permeability to urea, then much NaCl will diffuse (passively) from the AHL lumen into the interstitium, while little urea will diffuse from the interstitium into the thin limb lumen. If the concentration differences can be sustained, the interstitial fluid will be concentrated while the luminal fluid of the loop of Henle is being diluted.

![Diagram](image_url)

**Figure 2.15:** Mechanism involved in the passive hypothesis

(a) Active transport in OM
(b) Terminal CD dumps urea
(c) Passive transport of NaCl

2.5 The urine concentrating mechanism

With the development of the in vitro microperfusion technique (see Microperfusion) ([7]), it was proved ([50], [103]) that the values in the inner medulla are incompatible with this hypothesis: the descending thin limb of animals that concentrate better have higher urea permeabilities, which contradicts the predictions of the passive hypothesis.

Thus, there is still no adequate explanation for the steep cortico-papillary gradient of osmolality in the IM. Lately several authors ([90]) have proposed that a full explanation might need to include several features such as: (1) Transport heterogeneity along descending limbs of long loops of Henle. The recent finding by Dantzler and collaborators ([40], [66], [65]) have provided new insights into the transport properties of the long descending limb, which have been found to present segments of considerable length which present limited water permeability; (2) Papillary peristalsis (see Peristalsis). Ureteral peristalsis can be considered as a series of compressive zones, corresponding to waves of active muscular contraction, that move at near-constant speed along the ureter towards the bladder. Reinking and Schmidt-Nielson ([72]) were one of the first to hypothesize that peristalsis plays a fundamental role in the UCM. However, up to date, and even though some studies ([70], [72], [75]) have found that disabled peristalsis results in a reduction of urine osmolalities ([11], [78]), the crucial role of peristalsis in the concentrating mechanism has failed to be supported ([64]); (3) Inner medullary metabolic osmole production. This idea proposes that the energy for the buildup of the IM gradient could be due to some “external osmoles” instead of NaCl and urea and was initially proposed by Niesel and Röskenbleck ([62]) in 1963. The idea that the lactate produced during the anaerobic glycolysis taking place in the inner medulla could provide the “external” osmoles mentioned before was briefly considered at [73] but abandoned in favour of the active salt transport (later proved not to be feasible in that region). This idea was reconsidered again by Thomas and colleagues at [31], [88], [90] and [106] where it has been shown that an osmole production in the range of 20 – 100 mOsm/l could suffice for lactate to play a significant role in the concentrating ability.

Some of the proposed features are based on well-established experimental findings but they also contradict at some level certain generally accepted principles or pose other problems of a thermodynamic or biophysical nature that remain to be
resolved. The combination of such features, together with the fact that different tube segments are more likely to exchange with neighbouring ones ([53],[103]) and also some other perhaps presently unidentified factors could help explain some of the remaining mysteries of the concentrating mechanism.
3

Modelling the Urine
Concentrating Mechanism

3.1 General considerations

Following the anatomy of the kidney described in Chapter 2 it is reasonable to think that a full model of the renal medulla will include the two main medullary regions, outer medulla (OM) and inner medulla (IM) as well as the two types of nephrons (cortical and juxtamedullary nephrons) and their different segments.

The main segments of the nephron, either short or long, included in a model of the urine concentrating mechanism are: the loop of Henle (descending and ascending limbs), the collecting duct and also the interstitium (explicitly including the vasa recta or including a central core). Appropriate boundary conditions are used to represent the missing segments such as the proximal or distal tubules, as well as the glomerulus.

The inclusion of the vasculature has divided the community of modellers over the past few years. While some authors consider essential the explicit inclusion of the vasculature (e.g. [31], [61], [86], [103]), others prefer to consider both the descending and the ascending vasa recta as a single compartment (Central Core) (e.g. [45], [40], [46], [85], [80]), ignoring the effect that medullary blood flow could have on the concentrating ability.

The following sections describe the mass balance equations considered in such models and also the two main types of approach taken for this purpose in the
3. MODELLING THE URINE CONCENTRATING MECHANISM

existing literature: Multinephron and Shunt models. Major differences between the models only arise in the treatment of the inner medulla (IM), therefore only this region is discussed here. A description of the outer medullary region will be given in detail in future chapters where this is included as part of the model.

3.2 Mass balance equations

All models published to date (e.g., [45],[52], [90],[103]) on the mammalian concentrating mechanism are based on the conservation equations that describe solute and water flow in the medullary counterflow system (consisting of nephrons and capillaries) as follows.

**Figure 3.1:** Section of tube

Local mass balance within tubes (see Section of a tube in Figure 3.1) requires that the \( k \)th solute in the \( i \)th flow tube, obeys the conservation equation ([81]):

\[
\frac{\partial (A^i C^i_k)}{\partial t} = - \frac{\partial F^i_k}{\partial x} + A^i s^i_k - J^i_k
\]  

(3.1)

where \( F^i_k \) is the axial flow of the \( k \)th solute in the \( i \)th flow tube (\( nmol \ s^{-1} \)); \( A^i \) (\( mm^2 \)) is the cross sectional area of the tube; \( s^i_k \) is the average net rate per unit volume at which material is being produced or destroyed by chemical or physical reaction (\( nmol \ mm^{-3} \ s^{-1} \)); \( J^i_k \) (\( nmol \ mm^{-1} \ s^{-1} \)) is net outward transmural flux
3.2 Mass balance equations

per unit length; \( C^i_k \ (mmol \ l^{-1} = mmol \ mm^{-3}) \) is the concentration of the solute \( k \) in the \( i \)th tube; \( x \) is axial distance along the tube \( (mm) \); and \( t \) is time \( (s) \).

The corresponding equation for volume flows is:

\[
\frac{\partial A^i_i}{\partial t} = -\frac{\partial F^i_v}{\partial x} - J^i_v
\]  

(3.2)

where \( F^i_v \ (mm^3 \ s^{-1}) \) is the axial volume flow and \( J^i_v \) represents the net outward transmural volume flux per unit length \( (mm^2 \ s^{-1}) \).

In most existing models, the cross-sectional area does not vary with time, as the medulla, nephrons and capillaries are considered non-compliant. Also, for now, the term \( s^i_k \) is considered to be zero. It will be introduced later for the inclusion of processes such as glycolysis [88].

According to these considerations, equations (3.1) and (3.2) can be rewritten as

\[
\frac{\partial C^i_k}{\partial t} = \frac{1}{A^i} \left( -\frac{\partial F^i_k}{\partial x} - J^i_k \right)
\]  

(3.3)

\[
\frac{\partial F^i_v}{\partial x} = -J^i_v
\]  

(3.4)

Relationship between volume flows, solute flows and concentration is described by the Nernst Planck equation ([17],[34],[77]) which considers the motion of particles due to diffusion, convection and also attraction or repulsion to give, for any tube \( i \) and any solute \( k \), the following relationship:

\[
F^i_k = -A^i D^i_k \frac{\partial C^i_k}{\partial x} + F^i_v C^i_k - A^i u^i_k C^i_k \frac{\partial \psi}{\partial x}
\]  

(3.5)

where \( D^i_k \) is the diffusion coefficient of the \( k \)th solute, \( u^i_k \) is the ionic mobility, and \( \psi \) is electrical potential in the tube.

In the majority of Renal Models (e.g. [40], [45], [16], [87], [88], [90], [92], [98], [103]) diffusive and mobility terms are assumed to be negligible relative to convective flows\(^1\) ([52]) and therefore solute flows and volume flows are considered to be related as follows

\[
F^i_k = F^i_v C^i_k
\]  

(3.6)

\(^1\)Because renal tubules have small diameters and are long relative to their diameters, it is usually assumed that transverse intratubular solute diffusion is instantaneous and that axial diffusion is orders of magnitude slower than axial convection.
3. MODELLING THE URINE CONCENTRATING MECHANISM

Then equations (3.3), (3.4) and (3.6) can be combined to give

\[
\frac{\partial C_i^k}{\partial t} = \frac{1}{A_i} (-F_v \frac{\partial C_i^k}{\partial x} + C_i^k J_v^i - J_k^i)
\]  

(3.7)

The pair of equations (3.4) and (3.7) give the coupled system of ODEs and PDEs that will be used in the models presented in the following chapters.

3.3 Transmural fluxes

Transmural fluxes of both water and solutes involve cellular and paracellular pathways (as seen in Chapter 2). Also, at a particular medullary level, and depending on relative spatial placement of the individual tubes, a given tube maybe be contiguous with, and thus able to exchange with several other tubes, a factor which has been found to affect the concentrating ability ([104]). However, the following expressions will consider all tubes exchanging with only one structure, the interstitium, which it is considered here to be a well-mixed compartment with no lateral gradients.

Tubules and ascending vessels are assumed to transport fluid by osmosis and solute by combinations of processes that include membrane diffusion, solvent drag and coupled or active transport described by Michaelis-Menten saturable kinetics. The transmural fluid flux across tubule \(i\), \(J_v^i\) (\(mm^2\ s^{-1}\)), following (2.5), is governed by

\[
J_v^i = 2\pi r_i^i L_p^i RT \sum_{k=1}^j \sigma_k^i \phi_k^i (C_{k}^{\text{int}} - C_k^i)
\]  

(3.8)

where \(j\) denotes the total number of solutes in tubule \(i\); \(r_i^i\) (\(mm\)) represents the radius of the tube; \(L_p^i\) (\(mm\ s^{-1}\ mosM^{-1}\)) corresponds to the hydraulic permeability (usually including RT, the universal gas constant times temperature \((0.02545\ atm\ mosm/l)\) at \(37^\circ\)); \(\sigma_k^i\) (dimensionless) is the Staverman reflection coefficient and \(\phi_k^i\) (\(mosm/mM\)) represents the osmotic coefficient, usually 1.82 for salts and 1 for nonelectrolytes ([31]). \(C_k^{\text{int}}\) represents the concentration of a solute \(k\) in the interstitium.

An analogous expression for (3.8) is given in terms of the osmotic water permeability [40]. The relation between hydraulic permeability and osmotic water

32
3.3 Transmural fluxes

Permeability is given by

\[ P_i^f = \frac{I_p^i RT}{V_w^i} \]  \hspace{1cm} (3.9)

where \( V_w \) is the partial molar volume of water (0.018136 \( cm^3 \) \( mmol \)).

Therefore Equation (3.8) can also be written as

\[ J_v^i = 2\pi r_i P_i^f \bar{V}_w \sum_{k=1}^{j} \sigma_k^i \phi_k^i (C_{int}^k - C_k^i) \]  \hspace{1cm} (3.10)

The transmural flux of the \( k \)th solute in the \( i \)th tube \( J_k^i \) (\( nmol \) \( mm^{-1} \) \( s^{-1} \)) is given by

\[ J_k^i = 2\pi r_i P_k^i (C_k^i - C_{int}^i) + (1 - \sigma_k^i) J_v^i \bar{C}_k^i + 2\pi r_i \frac{V_m C_k^i}{K_m + C_k^i} \]  \hspace{1cm} (3.11)

where the first term refers to linear diffusion (Equation (2.4)), with \( P_k^i \) (\( cm \) \( s^{-1} \)) indicating solute permeability; the second term refers to solvent drag (Equation (2.6)), where \( \bar{C}_k^i \) is usually the arithmetic average between the concentration in the \( ith \) tube and concentration in the interstitium ([91]); and the last term refers to active salt transport and is assumed to obey approximate Michaelis Menten kinetics, where \( V_m \) (\( nmol \) \( cm^{-2} \) \( s^{-1} \)) is the maximum rate of transport and \( K_m \) (\( mM \)) is the Michaelis constant (equal to the concentration at half-maximal transport rate).

As is shown in [81], each positive outward component of \( J_k^i \) is a negative outward component of some other flux, and likewise for the \( J_v^i \). Therefore, the sum for all tubes of transmural transport of a given solute (or water) satisfies

\[ \sum_i J_v^i = \sum_i J_k^i = 0 \]  \hspace{1cm} (3.12)

If Equation (3.4) is summed over all tubes, then

\[ \sum_i \frac{\partial F_v^i}{\partial x} = - \sum_i J_v^i \Rightarrow \sum_i \frac{\partial F_v^i}{\partial x} = 0 \]  \hspace{1cm} (3.13)

Integration of Equation (3.13) gives that the sum of all volume flows at level \( x \) is constant

\[ \sum_i F_v^i(x) = B \]  \hspace{1cm} (3.14)
### 3. MODELLING THE URINE CONCENTRATING MECHANISM

At \( x = L \) (bottom of the medulla), for looped tubes such as the loop of Henle or the vasa recta the following boundary conditions can be considered:

\[
F_{v}^{AH}(L) = -F_{v}^{DH}(L) \\
F_{v}^{AV}(L) = -F_{v}^{DV}(L)
\] (3.15)

In the case of using a central core approach rather than including vasculature, the central core is considered closed at the papillary tip, therefore volume flow in the central core \( F_{v}^{CC} \) at \( x = L \) satisfies

\[
F_{v}^{CC}(L) = 0
\] (3.16)

Thus, using Equation (3.15) (and for CC models Equation (3.16)) at \( x = L \)

\[
\sum_{i} F_{v}^{i}(L) = F_{v}^{CD}(L)
\] (3.17)

and so Equation (3.14) becomes

\[
\sum_{i} F_{v}^{i}(x) = F_{v}^{CD}(L)
\] (3.18)

Thus both in the transient (with a non-compliant medulla) and steady state cases, axial volume flow in all tubes must sum to the final urine flow at every medullary level.

In a similar way, considering \( \sum_{i} J_{k}^{i} = 0 \), Equation (3.3) can be summed over all tubes to give

\[
\sum_{i} \frac{\partial(A^{i}C_{k}^{i})}{\partial t} = -\sum_{i} \frac{\partial F_{k}^{i}}{\partial x}
\] (3.19)

which on integration yields

\[
\int_{x}^{L} \sum_{i} \frac{\partial(A^{i}C_{k}^{i})}{\partial t} \, dz = -\int_{x}^{L} \sum_{i} \frac{\partial F_{k}^{i}}{\partial z} \, dz \Rightarrow
\]

\[
\sum_{i} F_{k}^{i}(x) = \int_{x}^{L} \sum_{i} \frac{\partial(A^{i}C_{k}^{i})}{\partial t} \, dz + F_{k}^{CD}(L)
\] (3.20)

where analogous assumptions for solute flows as the ones described in (3.15) have been made.

Equation (3.20) states the intuitively obvious fact that at any medullary level net inflow of any solute must equal urinary outflow of the solute plus the rate of accumulation ([81]).
3.4 Modelling a population of nephrons

All equations described previously are equations that consider each tube as a single structure, but in order to properly represent the concentrating ability, the fact that the kidney contains thousands of nephrons with different lengths has to be included somehow.

Two main different approaches for modelling this fact are present in the literature: Multinephron [45], [86] and Shunt models [88], [103]. The first approach, mainly used by A. Layton and H.Layton ([45],[40]) considers a discrete number of Loops of Henle (see Figure 3.2) turning at specific depths (each one can at the same time represent a certain number of identical tubes). Shunt models, first introduced in a “3D” model by Wexler ([103]), and further developed by Thomas ([89], [92]), consider a single composite structure that represents a population of nephrons turning back continuously (see Figure 3.3), which considerably reduces the number of equations in the model. Both volume and solute equations add an “extra” term in looped tubes that represents the flow in the descending limb that turns at each depth to return to the ascending limb; this is known as the “shunt” term. Both Multinephron and Shunt models make use of a single composite structure to represent the collecting ducts.

3.4.1 Multinephron-weighted-type model

The model described in this section corresponds to the Central Core Multinephron approach used by A. Layton and H. Layton in [40], [43], [45],[46] and [47]. It is a more accurate and complete multinephron model compared with those of previous authors ([86],[98]) as it includes a significant number of discrete nephrons. A recent paper [53] has considered it to be a Vasa Recta model where vasculature is included explicitly (as expected the inclusion of the Vasa Recta has reduced the concentrating ability of the models presented in previous papers [46]).

The major difference between a Shunt model and a Multinephron model is the treatment of the Loop of Henle. Here each Loop of Henle is treated as a single structure (not composite). The advantage of such an approach is that, since there is one equation for each nephron turning at level “y”, the radius and several other parameters (or tubular characteristics) do not necessarily have to
be the same for all nephrons (as they must be when they are merged into only one structure). However, the fact of not having a single equation for a population of tubes considerably increases the number of equations in the system.

The equations described in the previous section (see Equations (3.4) and (3.7)) for single structures are slightly modified in the case of the Loop of Henle on a Multinephron model due to the inclusion of an “extra” variable not present in other structures, “y”, introduced in order to indicate when a tube turns. According to this, and by using the subindex $i$ for both Long Descending Limb (LDL) and Long Ascending Limb (LAL), equations (3.4) and (3.7) describing volume and solute flow can be rewritten as follows

$$\frac{\partial}{\partial x} F_v^i(x, y, t) = -J_v^i(x, y, t)$$  \hspace{1cm} (3.21)

$$\frac{\partial}{\partial t} C_k^i(x, y, t) = \frac{1}{A_v} (-F_v^i \frac{\partial}{\partial x} C_k^i(x, y, t) + C_k^i(x, y, t)J_v^i(x, y, t) - J_k^i(x, y, t))$$  \hspace{1cm} (3.22)

where $0 \leq x \leq y \leq L$ and $L$ denotes the length of the papilla. The population of collecting ducts is merged (as is done in Shunt models) in a single composite
3.4 Modelling a population of nephrons

structure with decreasing total cross-sectional area. Equations for both the collecting duct and central core (in the case of a CC approach) are identical to those given in (3.4) and (3.7).

In the case of the loops of Henle, transmural fluxes must be weighted according to the loop distribution $\omega(y)$, which is the fraction of loops reaching to level $y$.

The total transmural water flux $\bar{J}_v^{LDL}(x,t)$ from the descending limbs (as ascending limbs are impermeable to water) at level $x$ is given by an integral of the fluxes from loops turning at level $x$ or beyond, weighted by $-\omega'(y) \equiv -d\omega(y)/dy$ [43]:

$$\bar{J}_v^{LDL}(x,t) = \int_x^L J_v^{LDL}(x,y,t)(-\omega'(y))dy$$  \hspace{1cm} (3.23)

The equation of transmural water flux for the central core (CC), which arises from the weighted fluxes into the loops (LDL) and into the collecting duct (CD) (following (3.12)) is given by

$$J_v^{CC}(x,t) = -\bar{J}_v^{LDL}(x,t) - n_{cd} J_v^{CD}(x,t)$$  \hspace{1cm} (3.24)

where $n_{cd}$ is the ratio of the total number of collecting ducts to loops of Henle at $x = 0$, and $J_v^{LDL}(x,t)$ is the total transmural water flux from all tubules per loop. A similar approach is taken for the transmural flux of solutes at the loop of Henle, the collecting duct and the central core.

The luminal area of the central core is assumed to equal that of a tubule and is scaled with the collecting duct population in the inner medulla.

3.4.2 Shunt models

In Shunt models, as mentioned above, all structures are treated as composite structures representing a population of tubules at a time (as in Figure 3.3). Due to the merging into a single structure, membrane properties and parameters will be the same for each type of structure. Although Stephenson has published papers considering a Shunt model with a central core approach ([84],[83]), the majority of Shunt models in the literature (e.g. [31],[87],[88], [92]) use a vasa recta approach, where the vasculature is explicitly included and not merged into a common bath. Throughout this section and in future chapters a vasa recta approach will be considered when modelling a population of nephrons.
3. MODELLING THE URINE CONCENTRATING MECHANISM

Figure 3.3: Composite tube representing the Loop of Henle

3.4.2.1 Exponential decay

The number of renal tubules are known ([29], [35]) to follow an exponential decay towards the papillary tip. Considering this, the number of tubes of any type (loop of Henle, collecting duct or vasa recta) at any depth $x$ within the IM is given by

$$N^i(x) = N_0^i \exp(-k_{sh}^i x)$$  \hspace{1cm} (3.25)

where $x$ is the depth of the inner medulla, $N_0^i$ is the number of tubes of type $i$ entering at the OM/IM border and $k_{sh}^i$ is the shunt factor which is adjusted in order to get the desired fraction of loops, collecting duct or vasa recta reaching the papillary tip.

The decrease of the total number of loops and vasa recta toward the papilla, and therefore the “loss” of flow at every $x$ level, is represented by shunting flow at every $x$ level at which a tube turns (see Figure 3.4).

Shunt flows (solute and volume) from a descending tube $d^i$ to the corresponding ascending tube at depth $x$ are given by (single tube flow times the number of tubes turning at that level):

$$F_{sh}^i = \frac{F_{di}^i(x) dN^i(x)}{N^i(x) dx}$$  \hspace{1cm} (3.26)
3.4 Modelling a population of nephrons

Figure 3.4: Left: Schematic illustration of loop structure with shunt return, for flux calculations ([87]). Right: Section of a tubule representing the new term added to equation (3.27).

According to this and considering equations (3.3) and (3.4), the new conservation equations including shunt flows are (for the loop of Henle and vasa recta)

\[
\frac{\partial C^i_k}{\partial t} = \frac{1}{A^i} \left( - \frac{\partial F^i_k}{\partial x} - J^i_k \pm F^i_{sh,k} \right) \tag{3.27}
\]

\[
\frac{\partial F^i_v}{\partial x} = - J^i_v \pm F^i_{sh,v} \tag{3.28}
\]

where the ± indicates a plus for long descending limbs of Henle (LDL) or descending vasa recta (DVR) and a minus for long ascending limbs of Henle (LAL) or ascending vasa recta (AVR), respectively. Note that cross-sectional areas are assumed circular: \( A^i = \pi (r_i)^2 N^i \) (same below for collecting duct).

For the CD, the equations remain the same as (3.4) and (3.7)

\[
\frac{\partial F^{CD}_v}{\partial x} = - J^{CD}_v \tag{3.29}
\]

\[
\frac{\partial C^{CD}_k}{\partial t} = \frac{1}{A^{CD}} \left( - \frac{\partial F^{CD}_k}{\partial x} - J^{CD}_k \right) \tag{3.30}
\]

Since all tubes are composite structures, the expressions for the transmural fluxes have to account for this fact, thus expressions (3.8) and (3.11) are modified.
as follows to include the total surface area

\[ J_v^i = 2\pi r^i N^i L^i_p RT \sum_{k=1}^{j} \sigma_k^i \phi_k^i (C_{k}^{\text{int}} - C^i_k) \]  

\[ J_k^i = 2\pi r^i N^i P_k^i (C_k^i - C_{k}^{\text{int}}) + (1 - \sigma_k^i) J_v^i \bar{C}_k^i + 2\pi r^i N^i \frac{V_m C_k^i}{K_m + C_k^i} \]  

where \( i \) indicates LDL, LAL, CD or DVR.

### 3.4.2.2 Interstitium/AVR

As has been mentioned before, the majority of Shunt models do include the vasculature explicitly. As the ascending vasa recta is an open epithelium, this is combined with the interstitium ([31],[88]). If all tubes are considered to exchange with the interstitium, the transmural fluxes in the case of the AVR can be calculated following equation (3.12)

\[ J_{AVR}^v = -J_{v}^{\text{LDL}} - J_{v}^{\text{CD}} - J_{v}^{\text{DVR}} \]  

\[ J_{AVR}^k = -J_{k}^{\text{LDL}} - J_{k}^{\text{LAL}} - J_{k}^{\text{CD}} - J_{k}^{\text{DVR}} \]  

Note that, in the case of volume flows, Equation (3.33) needs not be used as volume flows at the AVR can be calculated by applying the conservation condition (3.18). Similarly in a steady state model, equation (3.34) can also be replaced by the analogous conservation condition for solute flows ([31]).

### 3.5 Boundary conditions and initial conditions

In a model of the inner medulla, volume flow and concentrations are considered to be known at any time at the OM/IM border (in the case of an inner medullary model) or at the cortex (in the case of a full medullary model) for descending structures such as the descending limb, descending vasa recta and collecting duct, while for ascending tubes such as the ascending loop of Henle and the ascending vasa recta the continuity condition is applied at the papillary tip (\( x = L \)) (see Figure 3.5).
3.5 Boundary conditions and initial conditions

In the case of volume flows boundary conditions are set as follows:

\[
\begin{align*}
F_{vLDL}(0, t) &= F_{vLDL}^{0} \\
F_{vDVR}(0, t) &= F_{vDVR}^{0} \\
F_{vCD}(0, t) &= F_{vCD}^{0} \\
F_{vLAL}(L, t) &= -F_{vLDL}(L, t) \\
F_{vAVR}(L, t) &= -F_{vDVR}(L, t)
\end{align*}
\]  

(3.35)

Note that flow in the ascending tubes is considered negative as it flows in the opposite direction as to that in descending structures.

For concentrations boundary conditions are considered:

\[
\begin{align*}
C_{kLDL}(0, t) &= C_{kLDL}^{0} \\
C_{kDVR}(0, t) &= C_{kDVR}^{0} \\
C_{kCD}(0, t) &= C_{kCD}^{0} \\
C_{kLAL}(L, t) &= C_{kLDL}(L, t) \\
C_{kAVR}(L, t) &= C_{kDVR}(L, t)
\end{align*}
\]  

(3.36)

Figure 3.5: Boundary conditions applied to the composite structures
3. MODELLING THE URINE CONCENTRATING MECHANISM

Due to the lack of a feasible initial condition, usually the system of PDEs is started by considering concentrations constant along tubes matching those entering the descending structures at \( x = 0 \).

So at \( t = 0 \)

\[
\begin{align*}
C_k^{LDL}(x, 0) & = C_k^{LDL} \\
C_k^{LAL}(x, 0) & = C_k^{LDL} \\
C_k^{DVR}(x, 0) & = C_k^{DVR} \\
C_k^{AVR}(x, 0) & = C_k^{DVR} \\
C_k^{CD}(x, 0) & = C_k^{CD}
\end{align*}
\] (3.37)

The system is then started from a non-realistic steady state until a proper one is reached and then this is used as an initial condition to study nephron response to changes in membrane parameters and medullary blood inflow.
Numerical method

4.1 Introduction
The following chapter describes the numerical approach that will be used in future chapters to solve the coupled system of ODEs-PDEs describing volume flows and concentrations.

The numerical Method of Lines is considered here with two different approaches for the spatial discretisation. The first one uses a first order approximation in space (backward differences) following the natural flow in the nephron. The second one explores the use of collocation in a similar way as was done for the steady state case in [92].

Also, a third approach based on Chebyshev polynomials (Chebfun) is described at the end of the chapter but will only be applied in Chapter 6 for a model where the ODE-PDE system of equations is not coupled.

Both techniques using the numerical Method of Lines approach are compared and validated on a simplified (one solute) model of the renal inner medulla where analytical solutions can be derived for the steady-state case.

4.2 Analytical base case
Since this research considers the shunted approach following the work of Thomas ([31], [92], [88]), all the equations in this and coming chapters are based on those
4. NUMERICAL METHOD

described in equations (3.27)-(3.30).

A simplified Shunt model which has an analytical solution for the steady state case is considered here so the efficiencies of the numerical methods used can be compared.

Only the inner medullary region is considered and the model includes long loops of Henle (both descending and ascending limbs), the vasa recta (descending and ascending) and also the collecting duct. Inner medullary length is taken to be 4 mm as in [88]. Also this is considered to be a one-solute model; more precisely this solute will be considered to be NaCl.

In order to derive an analytical solution a few assumptions, following those made in the multinephron case presented in [45] (Figure 4.2), need to be made to obtain a more simplified model:

1. Long descending limbs (LDL), collecting duct (CD) and the vasa recta (DVR and AVR) are assumed to be infinitely permeable to water.

2. Long ascending limb (LAL) is completely impermeable to water and therefore $J_{v}^{LAL} = 0$.

With this, $C(x)$ can be defined to be the concentration of LDL, DVR, CD and AVR at any papillary depth, as they will be in osmotic equilibrium.

The rate of solute advection (“solute flow”) is defined as $F_{i}^{t}(x) \equiv F_{i}^{v}(x)C_{i}^{t}(x)$ (Equation (3.6)) for any tubule of type $i$, with $k = NaCl$ in this one-solute model.

As described in Chapter 3, the loops of Henle, vasa recta and collecting duct are considered to decrease exponentially (see Figure 4.1) according to:

$$N^{HL}(x) = N_{0}^{LDL} \exp (-k_{sh}^{LDL}x)$$  \hspace{1cm} (4.1)

$$N^{VR}(x) = N_{0}^{DVR} \exp (-k_{sh}^{DVR}x)$$  \hspace{1cm} (4.2)

$$N^{CD}(x) = N_{0}^{CD} \exp (-k_{sh}^{CD}x)$$  \hspace{1cm} (4.3)

where $N_{0}^{CD} = 64, N_{0}^{LDL} = 2N_{0}^{CD}$ and $N_{0}^{DVR} = 4N_{0}^{CD}$ as in [31]. The calculation of the shunt factor is done by considering that the fraction of vasa recta and loops of Henle reaching the papillary tip is 1/128 for an inner medullary thickness of 4 mm, and over the same distance, 64 collecting ducts converge to a single exiting collecting duct (see [31]).
4.2 Analytical base case

Figure 4.1: Number of tubes decreasing exponentially with depth

In the following calculations $k_{sh}^{HL} = k_{sh}^{VR} = k_{sh}$ while for the collecting duct the shunt factor is labelled as $k_{sh}^{CD}$.

Steady state equations describing solute flows are obtained by letting $\frac{\partial C}{\partial t} = 0$ in Equation (3.27), where the shunt term has been simplified as follows:

$$F_{sh}^i = \frac{F_d^i(x)}{N^i(x)} \frac{dN^i(x)}{dx} = -k_{sh}F_d^i(x) \quad (4.4)$$

Thus, one obtains the following set of ordinary differential equations for solute flows:

$$
\begin{align*}
(F_k^{LDL})' &= -J_s^{LDL} - k_{sh}F_k^{LDL} \quad (4.5) \\
(F_k^{LAL})' &= -J_s^{LAL} + k_{sh}F_k^{LDL} \quad (4.6) \\
(F_k^{DVR})' &= -J_s^{DVR} - k_{sh}F_k^{DVR} \quad (4.7) \\
(F_k^{AVR})' &= -J_s^{AVR} + k_{sh}F_k^{DVR} \quad (4.8) \\
(F_k^{CD})' &= -J_s^{CD} \quad (4.9)
\end{align*}
$$
4. NUMERICAL METHOD

Similarly for volume flows, following Equations (3.28) and (3.29):

\[
(F_v^{LDL})' = -J_v^{LDL} - k_{sh} F_v^{LDL} \quad (4.10)
\]

\[
(F_v^{LAL})' = -J_v^{LAL} + k_{sh} F_v^{LDL} \quad (4.11)
\]

\[
(F_v^{DVR})' = -J_v^{DVR} - k_{sh} F_v^{DVR} \quad (4.12)
\]

\[
(F_v^{AVR})' = -J_v^{AVR} + k_{sh} F_v^{DVR} \quad (4.13)
\]

\[
(F_v^{CD})' = -J_v^{CD} \quad (4.14)
\]

with boundary conditions:

\[
F_v^{LDL}(0) = F_v^{LDL}
\]

\[
F_v^{DVR}(0) = F_v^{DVR}
\]

\[
F_v^{CD}(0) = F_v^{CD}
\]

\[
F_v^{LAL}(L) = -F_v^{LDL}(L)
\]

\[
F_v^{AVR}(L) = -F_v^{DVR}(L)
\]

\[
F_k^{LDL}(0) = F_k^{LDL}
\]

\[
F_k^{DVR}(0) = F_k^{DVR}
\]

\[
F_k^{CD}(0) = F_k^{CD}
\]

\[
F_k^{LAL}(L) = -F_k^{LDL}(L)
\]

\[
F_k^{AVR}(L) = -F_k^{DVR}(L)
\]

Considering that \( C \) is the concentration in osmotic equilibrium, the solute flow at \( LDL \) can be rewritten as \( F_k^{LDL} = F_v^{LDL} C \) and so:

\[
F_k^{LDL} = (F_v^{LDL} C)' = F_v^{LDL} C' + F_v^{LDL} C'' \quad (4.17)
\]

Then Equation (4.5) becomes

\[
(F_v^{LDL})' C + F_v^{LDL} C' = -J_s^{LDL} - k_{sh} F_k^{LDL} \quad (4.18)
\]

Substituting (4.10) into (4.18)

\[
(-J_v^{LDL} - k_{sh} F_v^{LDL}) C + F_v^{LDL} C' = -J_s^{LDL} - k_{sh} F_k^{LDL} \quad (4.19)
\]
4.2 Analytical base case

which gives

$$F_v^{LDL} C' = -J_s^{LDL} + CJ_v^{LDL}$$  \hspace{1cm} (4.20)

Similarly for CD, DVR and AVR:

$$F_v^{CD} C' = -J_s^{CD} + CJ_v^{CD}$$  \hspace{1cm} (4.21)

$$F_v^{DVR} C' = -J_s^{DVR} + CJ_v^{DVR}$$  \hspace{1cm} (4.22)

$$F_v^{AVR} C' = -J_s^{AVR} + CJ_v^{AVR}$$  \hspace{1cm} (4.23)

Adding (4.20)-(4.23):

$$C'(F_v^{LDL} + F_v^{CD} + F_v^{DVR} + F_v^{AVR}) = -(J_s^{LDL} + J_s^{CD} + J_s^{DVR} + J_s^{AVR})$$

$$+ C(J_v^{LDL} + J_v^{CD} + J_v^{DVR} + J_v^{AVR})$$  \hspace{1cm} (4.24)

Since $J_v^{LAL} = 0$, following the conservation Equation (3.12)

$$J_v^{LDL} + J_v^{CD} + J_v^{DVR} + J_v^{AVR} = 0$$  \hspace{1cm} (4.25)

and

$$J_s^{LDL} + J_s^{CD} + J_s^{DVR} + J_s^{AVR} = -J_s^{LAL}$$  \hspace{1cm} (4.26)

Then Equation (4.24) becomes

$$C'(F_v^{LDL} + F_v^{CD} + F_v^{DVR} + F_v^{AVR}) = J_s^{LAL}$$  \hspace{1cm} (4.27)

As $F_v = F_k/C$

$$\frac{C'}{C} = \frac{J_s^{LAL}}{(F_k^{LDL} + F_k^{CD} + F_k^{DVR} + F_k^{AVR})}$$  \hspace{1cm} (4.28)

In order to solve Equation (4.28) above solute flows for LDL, DVR, AVR and CD need to be calculated first.

Integrating (4.9), the rate of solute advection along the collecting duct at a level $x$ is given by

$$F_k^{CD}(x) = F_k^{CD}(L) + \int_x^L J_s^{CD}(s)ds$$  \hspace{1cm} (4.29)

The rate of solute advection for the DVR at a level $x$ is (Equation (4.7))

$$F_k^{DVR}(x) = -J_s^{DVR}(x) - k_{sh}F_k^{DVR}(x)$$  \hspace{1cm} (4.30)
4. NUMERICAL METHOD

Solving analytically,

\[
F_{k}^{DVR}(x) = \exp(-k_{sh}x)\left(F_{k}^{DVR}(0) + \int_{0}^{x} -J_{s}^{DVR}(s) \exp(k_{sh}s) ds \right) \tag{4.31}
\]

The rate of solute advection for the AVR at a level \(x\) is (Equation (4.8))

\[
F_{k}^{AVR}(x) = -J_{s}^{AVR}(x) + k_{sh}F_{k}^{DVR}(x). \tag{4.32}
\]

Integrating and using (4.31)

\[
F_{k}^{AVR}(x) = F_{k}^{AVR}(L) + \int_{x}^{L} J_{s}^{AVR}(s) ds - \int_{x}^{L} k_{sh}F_{k}^{DVR}(0) \exp(-k_{sh}s) ds \\
+ \int_{x}^{L} \left( k_{sh} \exp(-k_{sh}s) \int_{0}^{s} J_{s}^{DVR}(r) \exp(k_{sh}r) dr \right) ds \tag{4.33}
\]

Applying the continuity condition at the bottom of the vasa recta (Equation (3.15)) the equation above can be written as

\[
F_{k}^{AVR}(x) = -F_{k}^{DVR}(L) + \int_{x}^{L} J_{s}^{AVR}(s) ds - \int_{x}^{L} k_{sh}F_{k}^{DVR}(0) \exp(-k_{sh}s) ds \\
+ \int_{x}^{L} \left( k_{sh} \exp(-k_{sh}s) \int_{0}^{s} J_{s}^{DVR}(r) \exp(k_{sh}r) dr \right) ds \tag{4.34}
\]

Using (4.26)

\[
F_{k}^{AVR}(x) = -F_{k}^{DVR}(L) + \int_{x}^{L} \left( -J_{s}^{LDL}(s) - J_{s}^{LAL}(s) - J_{s}^{CD}(s) - J_{s}^{DVR}(s) \right) ds \\
- \int_{x}^{L} k_{sh}F_{k}^{DVR}(0) \exp(-k_{sh}s) ds \\
+ \int_{x}^{L} \left( k_{sh} \exp(-k_{sh}s) \int_{0}^{s} J_{s}^{DVR}(r) \exp(k_{sh}r) dr \right) ds \tag{4.35}
\]
4.2 Analytical base case

Summing up Equations (4.29), (4.31) and (4.35)

\[ F_{CD}^k(x) + F_{DV R}^k(x) + F_{AV R}^k(x) = F_{CD}^k(L) + \int_x^L \dot{J}_{CD}^s ds \]

\[ + \exp(-k_{sh}x) \left( F_{DV R}^k(0) + \int_0^x \dot{J}_{DV R}^s \exp(k_{sh}s) ds \right) \]

\[ - F_{DV R}^k(L) + \int_x^L \left( -J_{LDL}^s - J_{LAL}^s - J_{CD}^s - J_{DV R}^s \right) ds \]

\[ - \int_x^L k_{sh} F_{DV R}^k(0) \exp(-k_{sh}s) ds \]

\[ + \int_x^L \left( k_{sh} \exp(-k_{sh}r) \int_0^r J_{DV R}^s \exp(k_{sh}r) dr \right) ds \]

(4.36)

If it is further assumed that no solute is transported by the tubular walls of LDL, CD and DVR (\( J_{CD}^s = J_{LDL}^s = J_{DV R}^s = 0 \)), then Equation (4.36) simplifies to give

\[ F_{CD}^k(x) + F_{DV R}^k(x) + F_{AV R}^k(x) = F_{CD}^k(L) - F_{DV R}^k(L) - \int_x^L (J_{LAL}^s) ds \]

(4.37)

Rearranging and considering that \( F_{DV R}^k(L) = \exp(-k_{sh}L)F_{DV R}^k(0) \)

\[ F_{CD}^k(x) + F_{DV R}^k(x) + F_{AV R}^k(x) = F_{CD}^k(L) - \int_x^L J_{LAL}^s ds \]

(4.38)

Substituting back into (4.28)

\[ \frac{C'(x)}{C(x)} = \frac{J_{LAL}^s}{F_{LDL}^k(x) + \int_x^L (-J_{LAL}^s) ds + F_{CD}^k(L)} \]

(4.39)

If transport in the distal tubule is considered then solute leaving the CD can be written as a fraction \( \epsilon \) of the solute entering LDL

\[ F_{CD}^k(L) = \epsilon F_{LDL}^k(0) \]

(4.40)

then Equation (4.39) gives

\[ \frac{C'(x)}{C(x)} = \frac{J_{LAL}^s}{F_{LDL}^k(0) \exp(-k_{sh}x) - \int_x^L J_{LAL}^s ds + \epsilon F_{LDL}^k(0)} \]

(4.41)
4. NUMERICAL METHOD

Solving the differential equation

\[
\frac{C(x)}{C(0)} = \exp\left(\int_0^x \frac{J_{s}^{LAL}(y)}{F_k^{LDL}(0) \exp(-k_{sh}s) - \int_y^L J_{s}^{LAL}(s)ds + \epsilon F_k^{LDL}(0)} dy\right)
\]

(4.42)

In order to give a more explicit solution of Equation (4.42), solute transport across the walls of LAL (\(J_{s}^{LAL}\)) needs to be specified. In the present model this is taken to be an explicit fraction \(\bar{v}\) of the entering flow (at LDL) distributed over the length of the inner medulla in proportion with the number of tubes [88]:

\[
J_{s}^{LAL}(x) = \frac{\bar{v}F_k^{LDL}(0)}{\gamma_1} N_{s}^{LAL}(x) = \gamma \exp(-k_{sh}x)
\]

(4.43)

where \(\gamma = \frac{\bar{v}F_k^{LDL}(0)}{L}\)

Then, going back to (4.42)

\[
\frac{C(x)}{C(0)} = \exp\left(\int_0^x \frac{\gamma \exp(-k_{sh}s)}{\int_y^L (\gamma \exp(-k_{sh}s))ds + F_k^{LDL}(0) \exp(-k_{sh}s) + \epsilon F_k^{LDL}(0)} dy\right)
\]

(4.44)

\[
\frac{C(x)}{C(0)} = \exp\left(\int_0^x \frac{\gamma \exp(-k_{sh}s)}{\frac{1}{k_{sh}} (\exp(-k_{sh}s) - \exp(-k_{sh}L)) + F_k^{LDL}(0) \exp(-k_{sh}s) + \epsilon F_k^{LDL}(0)} dy\right)
\]

(4.45)

Defining \(\gamma_1 = F_k^{LDL}(0) - \frac{\gamma}{k_{sh}}\) and \(\gamma_2 = \frac{\gamma}{k_{sh}} (\exp(-k_{sh}L) + \epsilon F_k^{LDL}(0)\) then:

\[
\frac{C(x)}{C(0)} = \exp\left(\int_0^x \frac{\gamma \exp(-k_{sh}s)}{\gamma_1 (\exp(-k_{sh}s)) + \gamma_2} dy\right)
\]

(4.46)

Integrating,

\[
C(x) = C(0) \left\{\frac{\gamma_1 (\exp(-k_{sh}s)) + \gamma_2}{\gamma_1 + \gamma_2}\right\} \left(\frac{k_{sh}^{-1}}{\gamma_{1/2}}\right)
\]

(4.47)
which is the concentration in the LDL, DVR, CD and AVR at a medullary depth $x$.

With the assumptions made during the calculations to obtain $C(x)$, equations (4.31), (4.29) and (4.30) give respectively

$$F_{k}^{LDL}(x) = F_{k}^{LDL}(0) \exp(-k_{sh}x)$$  
$$F_{k}^{CD}(x) = F_{k}^{CD}(L) = \epsilon(F_{k}^{LDL}(0))$$  
$$F_{k}^{DVR}(x) = F_{k}^{DVR}(0) \exp(-k_{sh}x)$$

And finally for the AVR equation (4.35) gives

$$F_{k}^{AVR}(x) = -F_{k}^{DVR}(L) + \int_{x}^{L} (-J_{s}^{LAL}(s))ds$$

$$= \frac{\gamma}{k_{sh}} \exp(-k_{sh}L) - \left(\frac{\gamma}{k_{sh}} + F_{k}^{DVR}(0)\right) \exp(-k_{sh}x)$$  

In the case of the LAL:

$$F_{k}^{LAL}(x) = -F_{k}^{LDL}(L) - \frac{\gamma - k_{sh}F_{k}^{LDL}(0)}{k_{sh}} (\exp(-k_{sh}L) - \exp(-k_{sh}x))$$

$$= -\frac{\gamma}{k_{sh}} \exp(-k_{sh}L) + \left(\frac{\gamma}{k_{sh}} - F_{k}^{LDL}(0)\right) \exp(-k_{sh}x)$$

And for volume flow

$$F_{v}^{LAL}(x) = k_{sh}F_{v}^{LDL}(x)$$

Considering $F_{v} = \frac{F_{k}}{C}$

$$F_{v}^{LAL}(x) = k_{sh}F_{k}^{LDL}(0) \exp(-k_{sh}x) \left(\frac{\gamma_{1}(\exp(-k_{sh}x)) + \gamma_{2}}{\gamma_{1} + \gamma_{2}}\right)$$  

$$\left(\frac{1}{k_{sh}\gamma_{1}}\right)$$
4. NUMERICAL METHOD

Letting $\gamma_3 = k_{sh} \frac{F_{LDL}(0)}{C(0)}$

$$F_v^{LAL}(x) = \gamma_3 \exp(-k_{sh} x) \left( \frac{\gamma_1(\exp(-k_{sh} x)) + \gamma_2}{\gamma_1 + \gamma_2} \right) \left( \frac{1}{k_{sh} \gamma_1} \right)$$  (4.56)

Integrating and simplifying

$$F_v^{LAL}(x) = \frac{\epsilon F_k^{LDL}(0) - F_k^{LDL}(0)(\epsilon + \exp(-k_{sh} x)) + \frac{\gamma_2}{k_{sh}}(\exp(-k_{sh} L) - \exp(-k_{sh} x))}{C(x)}$$  (4.57)

By using the relationship between solute flows and volume flows $C = F_k/F_v$, an expression for the concentration in the LAL and expressions for volume flows in the LDL, DVR, AVR and CD can be easily obtained in order to complete the set of solutions of the model presented here.

![Figure 4.2: Schematic showing assumptions made and boundary conditions. Dashed lined walls show infinite permeability to water while solid lined walls show impermeability to water. Red arrows indicate transmural solute exchange.](image_url)

The solutions shown in Figure 4.3 and 4.4 have considered all radii as $r = 10 \mu m$. The following boundary concentrations and water flows are specified for LDL, DVR and CD: $C_{LDL}(0) = C_{DVR}(0) = C_{CD}(0) = 200 \text{ mM} = \text{nmol} \cdot \text{mm}^{-3}$, $F_v^{LDL}(0) = F_v^{DVR}(0) = 10 \text{ nl/min/tube}$ (10$^{-3}$/60 mm$^3$ · s$^{-1}$) and $F_v^{CD}(0) = 5 \text{ nl/min}^{-1} \cdot \text{tube}^{-1}$ (see Figure 4.2). Because the ratio between the number of CD and the number of LDL is 0.5 then $\epsilon = 0.25$. 

52
4.2 Analytical base case

Figure 4.3: Analytical concentration for LDL and LAL.

Figure 4.4: Analytical volume flows for LDL, LAL, DVR, AVR and CD (scaled by the number of tubes at $x = 0$)
4. NUMERICAL METHOD

4.3 Numerical approach: The Method of Lines

4.3.1 Background

A steady-state Urine Concentrating Mechanism (UCM) model typically consists of a system of coupled, nonlinear (primarily because the concentrations of solutes are inversely proportional to the volume flow rate) ordinary differential equations. Frequently they have been solved by adaptations of Newton’s Method ([56] [83] [85]) or a combination of this with other techniques such as quasilinearisation ([103]) or collocation ([98]). In [98] Wexler et al replaced the quasilinearisation technique described in [103] by the collocation routine COLNEW (COLSYS) developed by Ascher et al [1], which resulted in a faster and more stable method than that previously used. The use of such a technique has been further applied also by other authors ([87], [92] [87]).

While steady-state approaches are more common in the history of UCM models, dynamic formulations of the model equations, which consist of a system of coupled, nonlinear, hyperbolic partial differential equations (PDEs) and ODEs, have also been considered, although usually only with the intention of reaching the steady state. A variety of numerical methods has been applied to the transient model including the numerical Method of Lines [61], the ENO method [49] [52] and more recently a Semi-Lagrangian method ([40], [42], [45], [46], [53]), where, in order to reach a desirable steady state, this method is combined with a Newton type solver once the dynamic solution is close enough to the steady state solution to be a good initial guess.

In steady state models, the difficulty of finding a good initial guess has been an ever present issue especially when using Newton type methods, as this approach has to contend with numerical instabilities unless initial conditions that are sufficiently close to the steady-state solutions are specified.

It is well known that due to the high water permeabilities of some of the renal tubules, the system of equations describing such models is stiff (see [34]). Another contributor to the stiffness in the case of a Shunt model is the exponential decay of the number of tubules along the corticomedullary axis as solute and volume flows change by orders of magnitude as the structures traverse the medulla.

In transient simulations the lack of realistic initial conditions can lead in some cases to flow reversal at early time steps ([43], [42], [47], [48]) which can also
happen in a steady state model, if one considers the successive approximations to the steady state numerical solution as time steps of a quasidynamic problem.

### 4.3.2 Method description

In this section, the test case described in section 4.2 is solved numerically following its dynamic formulation (Equations (3.27) and (3.28)).

The system of PDEs describing concentrations is solved by using the numerical Method of Lines (MOL). The essence of the MOL is to semi-discretise the PDEs, i.e., discretise the space derivatives so that one obtains a system of ODEs (for each PDE) and then solve the system by using a standard ODE integrator (see Figure 4.5). As the resulting problem is likely to be stiff, this is integrated in time by using Gear’s Method: as in *Ode15s* (Matlab routine) and *PDECOL* (Fortran routine) described later.

![Figure 4.5: Method of lines approach](image)

The general approach taken for the solution of the dynamic model solves the coupled system of ODEs-PDEs decoupled, so volume flows are integrated at every time step by using known concentrations (concentrations at previous time steps).

#### 4.3.2.1 First order differences

Considering the case of hyperbolic PDEs, the approximation of first order terms plays a crucial role. To avoid undesirable oscillations in the solution profile, it
4. NUMERICAL METHOD

is generally necessary to resort to upwind spatial approximations. Here, a finite difference approximation is considered, more specifically a first order backward difference approximation, that subtracts the upstream concentration from the concentration at the point where the derivative is to be evaluated following the natural flow in the nephron is taken.

\[ C_x \approx \frac{C_i - C_{i-1}}{\Delta x} \]  \hspace{1cm} (4.58)

where \( i \) is the index designating a position along a grid in \( x \) and \( \Delta x \) is the spacing in \( x \) along the grid, assumed constant for the time being.

Considering that solute flows can be written in terms of volume flows and concentrations \( F_k = CF_v \), Equation (3.27) can be rewritten as

\[
\frac{\partial C^i_k}{\partial t} = \frac{1}{A^i} \left( -F^i_v \frac{\partial C^i_k}{\partial x} - C^i_k \frac{\partial F^i_v}{\partial x} - J^i_k \mp F^i_{sh,k} \right) \quad (4.59)
\]

Substituting the expression for \( \frac{\partial F_v}{\partial x} \) by Equation (3.28)

\[
\frac{\partial C^i_k}{\partial t} = \frac{1}{A^i} \left( -F^i_v \frac{\partial C^i_k}{\partial x} - C^i_k \left( -J^i_v \mp F^i_{sh,v} \right) - J^i_k \mp F^i_{sh,k} \right) \quad (4.60)
\]

Applying (4.58) to spatial derivatives, for each node \( x_j \), the following ODE in time is obtained (note that \( j \) denotes now the grid point \( x_j \) and subindexes and superindexes have been ignored)

\[
\frac{\partial C_j}{\partial t} = \frac{1}{A} \left( -F_{v,j} \frac{C_j - C_{j-1}}{\Delta x} - C_j \left( -J_{v,j} \mp F_{sh,v,j} \right) - J_{k,j} \pm F_{sh,k,j} \right) \quad (4.61)
\]

The system of ODEs above together with the boundary conditions described in (3.37) give a differential algebraic system of equations describing the problem, that is integrated in time by the Matlab solver \textit{ode15s}.
4.3 Numerical approach: The Method of Lines

*Ode15s*

The Matlab ODE solver *ode15s* is based on the multi-step method known as Backward Differentiation Formulas or Gear’s formulas. In contrast with the single-step methods such as Euler’s method, these formulas give an approximation to a derivative of a variable at a time $t_n$ in terms of its function values $y(t)$ at earlier times (hence the “backward” in the name). They are derived by forming the $k$th degree interpolating polynomial approximating the function $y(t)$ using $y(t_n), y(t_{n-1}), \ldots, y(t_{n-k})$, differentiating it, and evaluating it at $t_n$ (see [79]).

In general Matlab ODE solvers deal with systems of differential equations given in the form:

$$M(t, y)y' = f(t, y)$$  \hspace{1cm} (4.62)

where $M$ denotes the mass matrix. *Ode15s* allows the mass matrix to be singular, which it is in the case of the Differential Algebraic problem described here where the mass matrix is the identity matrix with the exception of the rows defining the boundary conditions where all entries are zero.

For simplicity MOL-FIRST will be used to refer to all simulations that use the technique described above.

4.3.2.2 Collocation

In this section a higher order space approximation is explored based on the collocation approach taken in [87], [92], [98] in order to solve the steady state problem of the concentrating mechanism.

The system of PDEs is solved in Fortran 90 (due to the lack of an equivalent routine in Matlab) by the package PDECOL [57] using a piecewise polynomial space of order three (default value of $KORD$). Note that in the case of *Ode15s* the system of discretised ODEs has to be provided by the user while in the case of PDECOL the discretisation based on collocation is done by the solver; therefore the user has to specify the system of PDEs to solve.
4. NUMERICAL METHOD

The basic assumption made when using collocation over piecewise polynomials is that at any given time \( t \), each approximate solution component \( u_k \) is a piecewise polynomial on the specified space and hence can be written in terms of the B-spline basis functions as:

\[
u_k(t, x) = \sum_{i=1}^{n} c_{i,k}(t) \Phi_{i,k}(x) \quad k = 1, 2, ..., npde \quad (4.63)
\]

where \( npde \) is the number of partial differential equations. The unknown coefficients \( c_{i,k} \) depend only on the time \( t \), and the known basis functions \( \Phi_i \) depend on \( x \). The semidiscrete ordinary differential equations which determine these coefficients \( c_{i,k} \) for \( i = 1, 2, ..., ncpts \) and \( k = 1, 2, ..., npde \) are obtained by requiring the approximate \( u_k(t, x) \) to satisfy the system of PDEs and the boundary conditions exactly at the set of collocation points \( (ncpts) \). Required inputs for the solver are: the function defining the PDEs, the function defining the boundary conditions as well as the function that defines the initial conditions.

For simplicity PDECOL will be used to refer to all simulations that use the technique described above.

4.3.3 Numerical results

Here, the steady state analytical solution obtained in Section 4.2 is compared with the steady state solution computed with the transient formulation of the problem using the two numerical approaches described earlier. Comparison with the analytical solutions requires to set values for water permeabilities at LDL, CD and DVR to be set sufficiently high to match the infinite permeability assumption made earlier.

Figures 4.6 and 4.7 show the concentration profiles for both LDL and LAL computed with PDECOL for 80 subintervals and also the solution obtained for different number of subintervals in the case of MOL-FIRST. In the case of MOL-FIRST and as was expected due to the first order approximation, a larger number of subintervals (around three times the number of subintervals for PDECOL) is required for the computation of an accurate solution.
4.3 Numerical approach: The Method of Lines

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**Figure 4.6:** Concentration of LDL

**Figure 4.7:** Concentration of LAL
4. NUMERICAL METHOD

Considering the following norms for a given vector $x$:

\[
\|x\|_1 = |x_1| + \ldots + |x_n| \tag{4.64}
\]

\[
\|x\|_2 = (|x_1|^2 + \ldots + |x_n|^2)^{\frac{1}{2}} \tag{4.65}
\]

\[
\|x\|_\infty = \max(|x_1|, \ldots, |x_n|) \tag{4.66}
\]

If $\hat{x}$ is the approximated solution vector to $x$, then the relative error $r_q$ with respect to a vector norm $q$ can be defined as:

\[
r_q = \frac{\|\hat{x} - x\|_q}{\|x\|_q} \tag{4.67}
\]

With the relative errors defined, the order of convergence can be calculated for the solutions computed on grids $N/2$ and $N$ as follows:

\[
p_q = \frac{\ln(r_{q/2}^N)}{\ln 2} \tag{4.68}
\]

Tables 4.1 shows the comparison between the analytical solution and the solution computed by MOL-FIRT for different numbers of subintervals in the case of the concentration in the LDL.

**Table 4.1:** MOLFIRST global spatial convergence results computed for $C^{LDL}$

<table>
<thead>
<tr>
<th>N</th>
<th>$r_1$</th>
<th>$p_1$</th>
<th>$r_2$</th>
<th>$p_2$</th>
<th>$r_\infty$</th>
<th>$p_\infty$</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>0.036384283</td>
<td>0.040644153</td>
<td>0.023470298</td>
<td>0.016299065</td>
<td>0.008455090</td>
<td>0.946897109</td>
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<tr>
<td>16</td>
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<td>0.011417606</td>
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<tr>
<td>32</td>
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<td>0.004340105</td>
<td>0.962090174</td>
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<td></td>
</tr>
</tbody>
</table>

Table 4.2-4.4 show the comparison between the analytical solution and the solution computed by PDECOL for different number of subintervals. Relative errors and order of convergence are worked as in table 4.1 but this time the solution is computed for different orders of the piecewise polynomial space. $KORD$ is chosen to be 3, 4 and 6 so the polynomials are of order 2, 3 and 5 respectively.
### 4.3 Numerical approach: The Method of Lines

**Table 4.2:** PDECOL global spatial convergence results computed for $C^{LDL}$ with a choice of $KORD = 3$

<table>
<thead>
<tr>
<th>N</th>
<th>$r_1$</th>
<th>$p_1$</th>
<th>$r_2$</th>
<th>$p_2$</th>
<th>$r_{\infty}$</th>
<th>$p_{\infty}$</th>
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<td>0.000271545</td>
<td>2.167644672</td>
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</tr>
</tbody>
</table>

**Table 4.3:** PDECOL global spatial convergence results computed for $C^{LDL}$ with a choice of $KORD = 4$

<table>
<thead>
<tr>
<th>N</th>
<th>$r_1$</th>
<th>$p_1$</th>
<th>$r_2$</th>
<th>$p_2$</th>
<th>$r_{\infty}$</th>
<th>$p_{\infty}$</th>
</tr>
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<tr>
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<tr>
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<td>2.377216051</td>
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</tr>
<tr>
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<td>0.000951828</td>
<td>2.269818786</td>
<td>0.000217337</td>
<td>2.375487658</td>
<td></td>
</tr>
<tr>
<td>128</td>
<td>0.000190561</td>
<td>0.000197367</td>
<td>2.267257168</td>
<td>0.000174926</td>
<td>2.418850683</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4.4:** PDECOL global spatial convergence results computed for $C^{LDL}$ with a choice of $KORD = 6$

<table>
<thead>
<tr>
<th>N</th>
<th>$r_1$</th>
<th>$p_1$</th>
<th>$r_2$</th>
<th>$p_2$</th>
<th>$r_{\infty}$</th>
<th>$p_{\infty}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>0.010621442</td>
<td>0.01193435</td>
<td>0.433710687</td>
<td>0.015229464</td>
<td></td>
<td>0.448569467</td>
</tr>
<tr>
<td>16</td>
<td>0.007980192</td>
<td>0.412484285</td>
<td>0.906851899</td>
<td>0.00583012</td>
<td>0.938458281</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>0.004299739</td>
<td>0.892174528</td>
<td>2.28987029</td>
<td>0.001134527</td>
<td>2.359675146</td>
<td></td>
</tr>
<tr>
<td>64</td>
<td>0.000893161</td>
<td>2.267257168</td>
<td>2.461768494</td>
<td>0.000209367</td>
<td>2.50137926</td>
<td></td>
</tr>
<tr>
<td>128</td>
<td>0.000167026</td>
<td>2.418850683</td>
<td>2.461768494</td>
<td>0.000209367</td>
<td>2.50137926</td>
<td></td>
</tr>
</tbody>
</table>
4. NUMERICAL METHOD

4.3.3.1 Approximation using Chevyshev Points: Chebfun

In this section the “chebfun” software system ([93]) developed by Zachary Battles and Lloyd N. Trefethen ([5]) (version 3.0) is introduced as a future possible technique to solve problems such as the one mentioned in this chapter. However, and for the moment this will only be applied in Chapter 6 as, although a newer version has been released, the solution of coupled ODEs-PDEs systems is still not possible with the subroutine pde15s (an adaptation of the already mentioned ode15s).

Chebfun, in object-oriented MATLAB, extends many MATLAB operations on vectors and matrices to functions and operators based on Chebyshev expansions, combining the feeling of symbolic computation with the speed of numerics ([95]).

A chebfun object represents a function $f$ by interpolants in suitably rescaled Chebyshev points. Thus the central principle of the chebfun system is to evaluate functions in sufficiently many Chebyshev points for a polynomial interpolant to be accurate to machine precision ([94]). As an example of the structure of a chebfun, the following command creates a chefun object for the function $y = \sin(5x)$:

```matlab
>> f=chebfun('(sin(5*x))',[0,4*pi])
```

```
f =
    chebfun column (1 smooth piece)
      interval    length    endpoint values
        (   0,    13)    66       0  -2.4e-015 vertical scale

= 1
```

A chebfun can have more than one column, in which case this structure is know as a quasimatrix, a matrix where one of the dimensions is discrete but the other is continuous.

Chebfun can deal with both ordinary differential equations as well as partial differential equations involving one space and one time variable. In this case the Chebfun tool called chebop ([16]) is used to represent a differential or integral operator that acts on chebfuns (such technique is known as Spectral collocation).
4.3 Numerical approach: The Method of Lines

4.3.3.2 Conclusions

Comparison between the two numerical approaches taken shows that in order to achieve more accurate results a significant number of nodes have to be considered in the case of MOL-FIRST, as expected by the use of a first order method. However MOL-FIRST offers the flexibility to include features in the model such as the prebend transition (Chapter 5) as the user specifies the system of ODEs to solve in time already discretised. Also, as Ode15s provides the approximate solutions at each time step it is possible to solve the set of ODEs describing volume flow at each time step within the routine, obtaining accurate volume flows to be used in the concentration equations.

On the other hand, while PDECOL offers more accurate results, it complicates the inclusion of features such as the one described in Chapter 5 as well as the solution of accurate volume flows. In the case of the PDECOL routine, this returns the basis function coefficients in equation (4.63) and not the actual approximate solution values, therefore volume flows can only be computed after a full call to PDECOL has been performed and the approximate solutions have
been evaluated (by the *values* subroutine) which requires to perform several calls to PDECOL rather than performing the integration in the desired interval in a single call.

The Chebfun package, the performance of which is evaluated in Chapter 6 could offer an alternative numerical approach that combines the collocation techniques (proven successful in the steady state case [87], [92], [98]) with the familiarity and easy programming of Matlab.
5

Inclusion of Pre-bend Transitions in Shunt Models

5.1 Introduction

As was mentioned in Chapter 2, along the course of a renal tubule, cell type - and thus transmural transport properties - change abruptly at the pre-bend transition of the long Henle’s loop (Figure 5.1): a fixed point (165µm) before the turn below, where the descending limb of Henle (LDL) has properties (including radius) as those of the ascending limb (LAL).

Figure 5.1: Left: Representation of the IM from [69] where prebend transitions are represented by the color transition from yellow to green. Right: Inner medullary loop of Henle where the change of radius at the prebend transition can be seen.

Prebend transitions have been included in multinephron models ([45]), where, as each equation represents a single nephron, the matter of locating the prebend transitions does not represent a problem. However, the abrupt change of radius
5. INCLUSION OF PRE-BEND TRANSITIONS IN SHUNT MODELS

within the same equation seems to cause numerical problems as the area of the tubes experiences a non-smooth sudden change ([45]).

Up to date, none of the shunt models present in the literature has included the prebend transition. The inclusion of prebend transitions in shunt models represents a challenge as the use of a single composite structure where tubes turn continuously makes this point difficult to locate.

5.2 The use of a virtual tube

This chapter presents an approach to prebend transitions in shunt models ([22], [23]). In order to account for the prebend segment, an additional descending structure is created, called a virtual descending limb (LDLV) \(^1\). The virtual LDL will have identical properties to the LAL. A similar technique to the one usually used for representing the turns by using shunts is applied in this approach to incorporate the prebend transition.

Volume and solutes flowing through the LDL are “shunted” to the virtual LDL when a prebend point is reached (see Figure 5.2(a)). Flow then remains in the virtual LDL until the tip of the loop is reached (Figure 5.2(b)) , where regular “shunts” will bring it to the LAL (Figure 5.2(c)).

---

\(^1\)Inspired by unpublished work of Thomas and Wexler in 1994 (personal communication from S.R. Thomas.)
The introduction of a new structure implies the addition of new equations describing volume and solute flows in the virtual descending limb and also the inclusion of new shunt terms. In order to do so the number of tubes of each structure described in (3.25) needs to be redefined.

Considering the length of the prebend segment to be represented by $P_b$, to calculate the number of tubes present at each depth for each type of tubule, different regions (Figure 5.3) have to be considered depending on some important locations:

1. Distance from the corticomedullary border to the first prebend transition $dx_1$.

2. Distance from the corticomedullary border to the first turn $dx_1 + P_b$ which occurs at the border between the OM and the IM ($x_{OM/IM}$).

3. Distance from the corticomedullary border to the last prebend transition reached $L - P_b$.

Figure 5.3: Schematic drawing where a discrete population is represented to distinguish important regions that should be considered. Blue lines represent LDL properties and red lines LAL. Dashed curves indicate the shunts between structures.
5. INCLUSION OF PRE-BEND TRANSITIONS IN SHUNT MODELS

5.3 Derivation of equations for the number of tubes

During the following calculations and throughout this chapter the renal medulla will be assumed to include both parts: outer and inner medullary regions (OM and IM). In order to derive the new equations describing the number of tubes at each depth for both LDL and LDLV calculations will be based on Equation (3.25) with the exception that this time \( x \) is considered to be the depth of the whole renal medulla and not just the inner medullary region (therefore \( x = 0 \) represents the corticomedullary border)

5.3.1 Number of LDLs

To describe the change in the number of the long descending limbs three main regions will be distinguished based on the locations defined earlier.

- \( 0 \leq x \leq d_1 \)

  In this region none of the LDLs have yet reached the prebend transition, so the number of LDLs is the same as the number of entering LDLs that started at \( x = 0 \), therefore the number of tubes remains constant \( N_0 \).

  \[
  N_{LDL}(x) = N_0
  \] (5.1)

- \( d_1 < x \leq L - P_b \)

  LDLs start reaching the prebend transition so their number will start decreasing following an exponential decay analogous to that described in Chapter 3.

  \[
  N_{LDL}(x) = N_0 e^{-k_{sb}(x-d_1)}
  \] (5.2)

- \( L - P_b < x \leq L \)

  Last LDLs have reached the prebend transition so at this region there are be no LDLs left.

  \[
  N_{LDL}(x) = 0
  \] (5.3)
5.3 Derivation of equations for the number of tubes

5.3.2 Equations describing the changes in the number of tubes

To calculate the number of LDLVs at each level, the following differential equation describing the change in the number of tubes is considered

\[
\frac{dN_{LDLV}}{dx} = \text{Gain from LDL} - \text{Loss to LAL} \tag{5.4}
\]

where

\[
\text{Gain from LDL} = -\frac{dN_{LDL}}{dx} \tag{5.5}
\]

and \text{Loss to LAL} is calculated considering that the number of LDLVs leaving to LALs is the same as the number that has just shunted from the LDL at a distance \(x - P_b\) (see Figure (5.4))

\[
\text{Loss to LAL} = \left(\frac{dN_{LDL}}{dx}\right)_{x-P_b} \tag{5.6}
\]

Then Equation (5.4) can be rewritten as:

\[
\frac{dN_{LDLV}(x)}{dx} = -\frac{dN_{LDL}(x)}{dx} + \frac{dN_{LDL}(x - P_b)}{dx} \tag{5.7}
\]

Equation (5.7) is integrated in the following regions for the number of LDLVs (for regions see Figure (5.3)):

- \(0 < x \leq dx_1\): As first LDL has not reached the first prebend then the number of LDLVs has to be zero.

\[
N_{LDLV}(x) = 0 \tag{5.8}
\]
5. INCLUSION OF PRE-BEND TRANSITIONS IN SHUNT MODELS

- $dx_1 < x \leq dx_1 + P_b$: LDLs start reaching the prebend transition, but still the first one has not reached the turn, therefore Loss to LAL = 0

$$\int_{dx_1}^{x} \frac{dN_{LDLV}(t)}{dt} dt = - \int_{dx_1}^{x} \frac{dN_{LDL}(t)}{dt} dt$$  \hspace{1cm} (5.9)

which gives

$$N_{LDLV}(x) - N_{LDLV}(dx_1) = -N_{LDL}(x) + N_{LDL}(dx_1)$$  \hspace{1cm} (5.10)

Considering that $N_{LDL}(dx_1) = N_0$ and $N_{LDLV}(dx_1) = 0$, then

$$N_{LDLV}(x) = -N_{LDL}(x) + N_0$$  \hspace{1cm} (5.11)

- $dx_1 + P_b < x \leq L - P_b$: From here until the next region some tubes reach their prebend at the same time as others reach their turn.

$$\int_{dx_1 + P_b}^{x} \frac{dN_{LDLV}(t)}{dt} dt = - \int_{dx_1 + P_b}^{x} \frac{dN_{LDL}(t)}{dt} dt + \int_{dx_1 + P_b}^{x} \frac{dN_{LDL}(t - P_b)}{dt} dt$$  \hspace{1cm} (5.12)

which gives

$$N_{LDLV}(x) - N_{LDLV}(dx_1 + P_b) = -N_{LDL}(x) + N_{LDL}(dx_1 + P_b)$$

$$+ N_{LDL}(x - P_b) - N_{LDL}(dx_1)$$  \hspace{1cm} (5.13)

From (5.11) $N_{LDLV}(dx_1 + P_b) = -N_{LDL}(dx_1 + P_b) + N_0$, and also $N_{LDL}(dx_1) = N_0$, then

$$N_{LDLV}(x) = -N_{LDL}(x) + N_{LDL}(x - P_b)$$  \hspace{1cm} (5.14)

- $L - P_b < x \leq L$: LDLs disappear as they have all reached the prebend transition.

$$\int_{L - P_b}^{x} \frac{dN_{LDLV}(t)}{dt} dt = - \int_{L - P_b}^{x} \frac{dN_{LDL}(t)}{dt} dt + \int_{L - P_b}^{x} \left( \frac{dN_{LDL}(t - P_b)}{dt} \right) dt$$  \hspace{1cm} (5.15)

which gives

$$N_{LDLV}(x) - N_{LDLV}(L - P_b) = -N_{LDL}(x) + N_{LDL}(L - P_b)$$

$$+ N_{LDL}(x - P_b) - N_{LDL}(L - 2P_b)$$  \hspace{1cm} (5.16)
5.3 Derivation of equations for the number of tubes

Using equation (5.14) \( N_{LDLV}(L - P_b) = -N_{LDL}(L - P_b) + N_{LDL}(L - 2P_b) \)
and substituting back we get

\[
N_{LDLV}(x) = N_{LDL}(x - P_b) \quad (5.17)
\]

Figure 5.5 shows the number of LDLs (top) and LDLVs (bottom) with depth. The plot shows a medullary length of 4 mm. The first prebend transition has been placed at a distance \( dx_1 = 0.150 \) mm from the border \( (x = 0) \). The shunt factor has been taken to give a single LDL reaching the last prebend for a better visualization.

Figure 5.5: Top: Number of LDLs with depth. Bottom: Number of virtual LDLs.
5. INCLUSION OF PRE-BEND TRANSITIONS IN SHUNT MODELS

Figure 5.6 shows both virtual and non-virtual descending limbs adding up to the expected number of LDLs.

Figure 5.6: Virtual and non virtual structures add up the expected number of LDLs

5.3.2.1 LAL

Then the number of LALs has to match the sum of both LDL and LDLV. Figure 5.7 gives the summary of the number of tubes per region

Figure 5.7: Number of tubes of each type in every region
5.3 Derivation of equations for the number of tubes

5.3.3 Mass conservation equations

Following Equation (3.26) the shunt terms for both LDL and LDLV can be described by:

\[
F_{sh,k}^{LDL} = \frac{F_k^{LDL}}{N_{LDL}} \left( \frac{dN_{LDL}}{dx} \right) \tag{5.18}
\]

\[
F_{sh,k}^{LDLV} = \frac{F_k^{LDLV}}{N_{LDLV}} \left( \frac{dN_{LDLV}}{dx} \right) (x-P_b) \tag{5.18}
\]

So the system of ODEs and PDEs for the Loop of Henle described in Chapter 3 in Equations (3.27) and (3.28) is modified as follows to include the virtual descending limb:

\[
\frac{\partial F_v^{LDL}}{\partial x} = -J_v^{LDL} + F_{sh,v}^{LDL} \tag{5.19}
\]

\[
\frac{\partial F_v^{LDLV}}{\partial x} = -J_v^{LDLV} - F_{sh,v}^{LDLV} + F_{sh,v}^{LDL} \tag{5.19}
\]

\[
\frac{\partial F_v^{LAL}}{\partial x} = -J_v^{LAL} - F_{sh,v}^{LAL} \tag{5.19}
\]

For concentration (of each solute present k):

\[
\frac{\partial C_k^{LDL}}{\partial t} = \frac{1}{A_{LDL}} \left( -\frac{\partial F_k^{LDL}}{\partial x} - J_s^{LDL} + F_{sh,k}^{LDL} \right) \tag{5.20}
\]

\[
\frac{\partial C_k^{LDLV}}{\partial t} = \frac{1}{A_{LDLV}} \left( -\frac{\partial F_k^{LDLV}}{\partial x} - J_s^{LDLV} - F_{sh,k}^{LDLV} + F_{sh,k}^{LDL} \right) \tag{5.20}
\]

\[
\frac{\partial C_k^{LAL}}{\partial t} = \frac{1}{A_{LAL}} \left( -\frac{\partial F_k^{LAL}}{\partial x} - J_s^{LAL} - F_{sh,k}^{LAL} \right) \tag{5.20}
\]
5. INCLUSION OF PRE-BEND TRANSITIONS IN SHUNT MODELS

with boundary conditions:

\[ F^{LDL}_v(0, t) = F^{LDL}_{v,0} \]
\[ F^{LDLV}_v(0, t) = 0 \]
\[ F^{LAL}_v(L, t) = -F^{LDLV}_v(L, t) \]
\[ C^{LDL}_k(0, t) = C^{LDL}_{k,0} \]
\[ C^{LDLV}_k(0, t) = 0 \]
\[ C^{LAL}_k(L, t) = C^{LDLV}_k(L, t) \] (5.21)

Note that only equations for the Loop of Henle have been considered in this section, as the prebend transition is located only there and therefore the equations for the rest of the tubes remain the same as in Chapter 3.

5.4 Multinephron vs Shunt Model with prebend transitions

The following section validates the inclusion of the prebend transition in shunt models by using the auxiliary structure explained above.

In order to do so, the main two approaches described in Chapter 3 including the prebend transition are compared here: A modified version of the steady state Multinephron model presented in [86] is compared with a Shunt Model (transient formulation) with virtual descending limb.

In order to have a better understanding of both models and the main differences between them, a detailed description of each one is provided before comparing any results.

5.4.1 General considerations

As the comparison of the new Shunt model with prebend transitions is done by using a modified version of the model presented in [86], the same anatomical considerations will be assumed.

Papillary length is taken as 10.5 mm this being divided into two regions: Outer medulla with length 4.5 mm and inner medulla with length 6 mm.
5.4 Multinephron vs Shunt Model with prebend transitions

The inclusion of the outer medulla implies the inclusion of the short loops of Henle which have been ignored until now as all models presented earlier were inner medullary models.

As in [86] solutes considered are NaCl and urea. Volume flows entering SDL, LDL, DVR and CD are 10, 10, 4 and 7.06 nl min\(^{-1}\) respectively. Concentration for salt entering SDL, LDL and DVR is taken to be 140 mM while for CD, salt concentration entering is taken as 123.8 mM. Concentration for urea entering SDL, LDL and DVR is taken to be 5 mM while urea concentration entering CD is taken as 23.7 mM. Note that the input values for CD are obtained from the exiting values of the distal tubules in the Multinephron model and these are used as the boundary conditions for the Shunt model.

Table 5.1 shows the transport parameters as well as tube radius used in the models that will be described later.

**Table 5.1**: Transport parameters and radius. \(L_p RT\) measured in \(10^{-4} \text{ mm/(s mosm/l)}\). Permeabilities measured in \(10^{-4} \text{ mm/s}\). Radius measured in \(\mu\text{m}\) and \(V_m\) measured in \(\text{nmol/(mm}^2 \cdot \text{s}^{-1})\).

<table>
<thead>
<tr>
<th>TUBE</th>
<th>(L_p RT \times 10^{-4})</th>
<th>(P_s)</th>
<th>(P_u)</th>
<th>(\sigma_s)</th>
<th>(\sigma_u)</th>
<th>radius</th>
<th>(V_m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDL</td>
<td>0.4117</td>
<td>2.8</td>
<td>5.5</td>
<td>0.96</td>
<td>1</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>LDL Om</td>
<td>0.4117</td>
<td>41</td>
<td>1.7</td>
<td>0.96</td>
<td>1</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>LDL Im</td>
<td>0.4117</td>
<td>2.4</td>
<td>7.9</td>
<td>0.96</td>
<td>1</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>LAL Im</td>
<td></td>
<td>0</td>
<td>25</td>
<td>6.27</td>
<td>1</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>LAL Om and SAL</td>
<td></td>
<td>0</td>
<td>6.27</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>CD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(x = 0 - 4.5)</td>
<td>0.08067</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>(x = 4.5 - 5.25)</td>
<td>0.05</td>
<td>0</td>
<td>0.12</td>
<td>1</td>
<td>0.74</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>(x = 5.25 - 6.0)</td>
<td>0.05</td>
<td>0</td>
<td>0.24</td>
<td>1</td>
<td>0.74</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>(x = 6.0 - 6.75)</td>
<td>0.05</td>
<td>0</td>
<td>0.48</td>
<td>1</td>
<td>0.74</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>(x = 6.75 - 7.5)</td>
<td>0.05</td>
<td>0</td>
<td>0.96</td>
<td>1</td>
<td>0.74</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>(x = 7.5 - 8.25)</td>
<td>0.05</td>
<td>0</td>
<td>1.44</td>
<td>1</td>
<td>0.74</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>(x = 8.25 - 9.0)</td>
<td>0.05</td>
<td>0</td>
<td>35</td>
<td>1</td>
<td>0.74</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>(x = 9.0 - 9.75)</td>
<td>0.05</td>
<td>0</td>
<td>70</td>
<td>1</td>
<td>0.74</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>(x = 9.75 - 10.5)</td>
<td>0.05</td>
<td>0</td>
<td>70</td>
<td>1</td>
<td>0.74</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>DVR</td>
<td>0.316692</td>
<td>39</td>
<td>39</td>
<td>1</td>
<td>0.2</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>AVR</td>
<td>0</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5. INCLUSION OF PRE-BEND TRANSITIONS IN SHUNT MODELS

5.4.2 The Multinephron Model

5.4.2.1 Anatomy considerations

The Multinephron model described in [86] consists of a model of six nephrons (see Figure 5.8): a short Loop of Henle and 5 long Loops of Henle together with a collecting duct and a composite vasa recta. The structure representing the short loops accounts for 1024 short nephrons. The different 5 long structures considered represent nephrons turning at depths equal to 5.25, 6.0, 6.75, 8.25 and 10.5 (note first turn does not appear until a distance of 0.75 mm after crossing the OM/IM border). Each of these structures represents at the same time 256, 128, 64, 32 and 32 nephrons each respectively. A total of 512 long nephrons is thus represented.

Short and Long vasa recta are merged into a single structure that represents at the start 1536 vasa recta and that presents discrete shunts in order to account for the turn of each population of nephrons.

The collecting duct is also represented as a composite structure which merges 8 times from 256 collecting ducts to give a single one at the papillary tip. The permeability of urea changes at each coalescence.

The model presented in this paper includes structures that represent the distal tubules. Therefore boundary conditions for the CD are calculated from the exiting flows of the DT.

In order to model the prebend transition a change in transport properties is included in each long structure at a distance of 0.150 mm before the turn of the tube. According to table 5.1 this segment will assume the properties of the inner medullary ascending limb. In this specific model, the first prebend actually takes place in the IM.

Equations describing volume and concentrations in the loops of Henle (short and Long), vasa recta and collecting duct are identical to those described in Equation (3.27) and Equation (3.28) with no shunts as this is not a shunt model.
5.4 Multinephron vs Shunt Model with prebend transitions

As this model solves the steady state case, the term $\frac{\partial C}{\partial t}$ in Equation (3.27) is taken as zero, giving the following system of differential equations:

$$\frac{\partial F^i_k}{\partial x} = -J^i_k$$  \hspace{1cm} (5.22)

$$\frac{\partial F^i_v}{\partial x} = -J^i_v$$  \hspace{1cm} (5.23)

where $i =$ SDL, SAL, LDL (5), LAL (5), DVR, AVR, CD and $k =$NaCl, Urea.

5.4.2.2 Numerical solution

As in [86], the steady state boundary value problem described by the system of equations (5.22) and (5.23) is solved by approximating each equation by using finite differences: Backward differences are used to approximate spatial derivatives and then transmural fluxes are evaluated at the midpoint of the interval by assuming concentrations at the midpoint of the interval are the arithmetic average between concentrations at $j$ and $j-1$.

$$\frac{F^i_v(j) - F^i_v(j-1)}{\Delta x} = -\frac{J^i_v(j) + J^i_v(j-1)}{2}$$  \hspace{1cm} (5.24)

$$\frac{F^i_k(j) - F^i_k(j-1)}{\Delta x} = -\frac{J^i_k(j) + J^i_k(j-1)}{2}$$  \hspace{1cm} (5.25)

In order to solve the above system an initial guess is made for the AVR concentrations and then assuming these as fixed, each tube is integrated by using an analytical Jacobian applying Newton’s Method locally. The approximation obtained for each tube is then used together with the conservation of mass condition described in equation (3.18) and also in equation (3.20) by letting $\frac{\partial (AC)}{\partial t}$ be zero to correct the AVR guesses by using Newton’s method globally and a numerically generated Jacobian.
Figure 5.8: Multinephron model structure. Number of each structures is indicated in brackets. In the case of the nephrons: Continuous black lines indicate the section of the descending limb before reaching the prebend transition; Light dashed black curves indicate IM ascending limb properties; and heavy dashed curves indicating OM ascending limbs. The 256 collecting ducts in the outer medulla converge by pairs eight times in the inner medulla to terminate as a single terminal collecting duct. Vasa recta is represented as a single structure with 5 discrete shunts.
5.4 Multinephron vs Shunt Model with prebend transitions

5.4.3 Shunt Model

The main difference from the previous multinephron model described is that, in the shunted approach, all long nephrons are merged into a single composite structure, where tubes will be turning continuously (see Figure 5.9).

In order to reproduce the Multinephron case scenario the number of long loops of Henle, collecting duct and vasa recta will be fitted into the exponential decay definition presented in Equation (3.25).

According to the multinephron model, 32 long nephrons reach the papillary tip of the 512 that started at the OM. Therefore in Equation (5.2), the shunt factor $k_{sh}$ is defined to give 32 loops of Henle at $L - P_b$ ($N(L - P_b) = 32$).

\[ N(L - P_b) = N_0 \exp(-k_{sh}(L - P_b - dx_1)) \Rightarrow \]

\[ k_{sh} = -\frac{\ln(N(L - P_b)/N_0)}{L - P_b - dx_1} \quad (5.26) \]

Figure 5.9: Schematic of the shunt model with the different structures considered
5. INCLUSION OF PRE-BEND TRANSITIONS IN SHUNT MODELS

In the case of the collecting ducts these are considered to coalesce continuously rather than only 8 times. Then the shunt factor \( k_{sh} \) is calculated to give a single CD for the 256 that started at the outer medulla.

As has been mentioned before, distal tubules are not included in this model, and for the simulations shown later boundary conditions at \( x = 0 \) for the CD have been taken from the ones obtained by the outputs of the distal tubules in the multinephron model.

5.4.3.1 Numerical solution

The numerical solution of the shunt model is computed using the MOL described in Chapter 4. Some modifications have to be made in order to ensure that the points where a transition between the regions described in Figure 5.7 are reached.

In the case of the volume flow equations each tube is broken into several IVP problems whose boundaries match with the mentioned regions. As at the point \( L - P_b \) the function \( N(x) \) is not a differentiable function (as LDLs are forced to disappear after that point), an inner boundary condition is applied at LDLV to ensure that all flow left at LDL is shunted to LDLV.

5.4.4 Comparison

5.4.4.1 Number of tubes

Figures 5.10, 5.11 and 5.12 show the main differences in the number of tubes profile presented in both models. It is important to note that, as the first turn in the Multinephron model occurs at a distance of \( x = 5.25 \ mm \), the first prebend starts within the inner medulla. However, as shunts start at the \( OM/IM \) border for the Shunt model (which is also true for a real population of nephrons), the first prebend transition takes place at the \( OM \). This explains the shift seen at Figure 5.10 between the dashed (Multinephron model) and the continuous lines (Shunt model).
5.4 Multinephron vs Shunt Model with prebend transitions

![Graph showing decay on number of tubes for multinephron case](image1)

**Figure 5.10:** Dashed line showing the decay on the number of tubes for the multinephron case. The decay starts at $x = 5.25$ as the first turn does not appear right after the $OM/IM$ border as it is assumed in the Shunt Model (continuous line) (and as also happens in a real case scenario).

![Graph showing eight coalescences](image2)

**Figure 5.11:** Dashed line showing the eight coalescences considered in the multinephron model; Continuous line showing a CD with continuous coalescences
5. INCLUSION OF PRE-BEND TRANSITIONS IN SHUNT MODELS

Figure 5.12: Dashed line showing five discrete shunts in the case of the Multi-nephron model, while shunting in the Shunt model happens continuously and starts at the OM/IM border (continuous line)

5.4.4.2 Osmolality profiles and concentration: The effect of the prebend transition

Figure 5.13 shows the osmolality profiles achieved in each structure by the two different models. A closer look at the inner medullary region (Figure 5.14) clarifies how the osmolality profile for the Loop of Henle is slightly higher in the case of the multinephron model, explained by the early appearance of the prebend transition and a higher number of those in the shunted model. Since the prebend segment presents properties identical to those in the LAL it is expected that the impermeability to water will cause osmolalities to decrease, as it can clearly be observed when the last prebend transition appears (Figure 5.14).
5.4 Multinephron vs Shunt Model with prebend transitions

Figure 5.13: Left: Osmolality profiles achieved by the shunt model. Right: Osmolality profiles in the multinephron case

Figure 5.14: Inner medullary HL osmolality for both shunt (solid lines) and multinephron (dashed lines).
5. INCLUSION OF PRE-BEND TRANSITIONS IN SHUNT MODELS

Figures 5.15 and 5.16 show the volume flow and the salt and urea concentration profiles for both Shunt and Multinephron model. In Figure 5.15 a shift can be observed between the two solutions, which can be explained by the later appearance of the first shunt in the Multinephron model.

Salt and urea concentration profiles for both models are compared in Figure 5.16, the non-smooth concentration profiles for the multinephron case being explained by the presence of 5 discrete structures. Concentration is obtained by averaging the values obtained for each different tubule.

Figure 5.15: Long loops flow comparison

Figure 5.16: Salt concentration profiles through the medulla. Long loops urea comparison.
5.4 Multinephron vs Shunt Model with prebend transitions

Figure 5.17 shows salt concentration profiles at the IM for both models; a closer look (bottom picture) shows the lowering concentration effect of the prebend transition, more evident when the last one is reached.

**Figure 5.17:** Top: Concentration profiles at the IM region. Bottom: A closer look to the IM region surrounding the last prebend transition.

Despite the differences described in this chapter between the two model approaches, results in this section confirm the virtual tube structure as a way to include the prebend transition in a continuous shunted model.
5. INCLUSION OF PRE-BEND TRANSITIONS IN SHUNT MODELS
6

Glycolysis: a source of external osmoles

6.1 Introduction

As was already mentioned in Chapter 2, the mechanisms that contribute to the concentration of urine at the inner medulla are not completely understood. This chapter is based on the hypothesis proposed by Thomas in [88] that glycolysis as a source of external osmoles could contribute to the urine concentrating mechanism. Based on the steady state model developed by Thomas and also on the model developed by Zhang and Edwards [106] (a model focused on microcirculation), this chapter describes a time-dependent model of the vasa recta where, besides verifying some of the steady state results of [88], also some time dependent issues, such as the time that it will take to wash out the gradient created by glycolysis if an increase in blood inflow occurs, are studied.

6.2 Glycolysis

Oxidation of glucose is known as glycolysis. Glucose is oxidized to either lactate or pyruvate. Under aerobic conditions, the dominant product in most tissues is pyruvate and the pathway is known as aerobic glycolysis. When oxygen is depleted, the dominant glycolytic product in many tissues is lactate and the process is known as anaerobic glycolysis (Figure 6.1).
It has been suggested (see [19]) that the renal medulla can operate an anaerobic metabolism under conditions which approach those present in vivo during antidiuresis, since it is known that anaerobic glycolysis is the main source of ATP in the relatively hypoxic (see Hypoxia) inner medulla.

Results from [74] suggest that the transport of sodium in the loop of Henle may be linked to glycolytic metabolic pathways responsible for the high amount of lactate found in the inner medulla of mammalian kidney.

Since anaerobic glycolysis generates two lactate molecules per molecule of glucose consumed, it increases the amount of interstitial solute providing a source of external osmoles that could contribute to the concentration mechanism ([62], [92]).
6.3 The Vasa Recta Model

6.3.1 Model description

As shown in Figure 6.2, the model described in this section considers the inner medullary renal region (as this is the region where glycolysis takes place) and includes only the vasa recta (see Vasa Recta location in Figure 2.5).

![Figure 6.2: Process of glycolysis in the IM cells](image)

As in previous chapters, the population of vasa recta is represented by a single composite structure with shunts, assumed to diminish exponentially in number along the IM toward the tip of the papilla according to the same relation as in earlier models and in conformity with reported rat anatomy:

\[ N(x) = N(0)e^{-k_{sh}x} \]  

(6.1)

where \( N(0) \), number of VR at the OM/IM border, is considered 128, which will give a system with a single vasa recta at the papillary tip if \( k_{sh} \) is 1.213 \( mm^{-1} \). Medullary depth in this model is taken as \( L = 4 \ mm \).

6.3.2 Equations

6.3.2.1 Volume flow equations

Equations describing volume flow in the descending and ascending vasa recta are analogous to Equation (3.28) with the difference that this time, and as no
nephrons are explicitly included in the model, an extra term accounting for net volume reabsorption into the AVR from LDL and CD, designated as $J_v^{ABS}$, is added.

$$\frac{dF^{DVR}_v}{dx} = -J^{DVR}_v + F^{DVR}_{sh,v} \quad (6.2)$$

$$\frac{dF^{AVR}_v}{dx} = J^{DVR}_v - F^{DVR}_{sh,v} + J^{ABS}_v \quad (6.3)$$

As $J_v$ depends on forces not represented in this model, this is taken as an explicit fraction ($\bar{v}$) of the entering flow.

$$J^{DVR}_v(x) = \bar{v} F^{DVR}_v(0) N(0) L N(x) \quad (6.4)$$

where $F^{DVR}_v(0)$ is the single volume flow entering the OM/IM border.

The term representing the net volume reabsorption into the AVR from LDL and CD $J^{ABS}_v$ is taken in proportion to the number of VR present with depth as

$$J^{ABS}_v = k_v N(x) \quad (6.5)$$

where the expression of $k_v$ can be obtained by analogy with the treatment of glycolytic $V_{max}$ (see deduction of Equation (6.14)). Total IM volume absorption is expressed as a proportion ($v_{abs}$) of entering blood flow ($J^{ABS}_v)^{TOT} = v_{abs} F^{DVR}_v(0)$

$$k_v = \frac{k_{sh} (J^{ABS}_v)^{TOT}}{N(0)(1 - e^{-k_{sh}L})} = \frac{k_{sh}}{N(0)(1 - e^{-k_{sh}L})} v_{abs} F^{DVR}_v(0) \quad (6.6)$$

### 6.3.2.2 Solute equations

In the case of the system of PDEs describing glucose and lactate concentrations, analogous equations to (3.27) are used with the inclusion, this time, of the term describing glycolysis in the AVR. As two molecules of lactate are obtained per each molecule of glucose consumed, the glycolysis term is subtracted from the right hand side of Equation (6.8) and added twice to the right hand side of Equation (6.10).
6.3 The Vasa Recta Model

\[
\frac{\partial C^{\text{DV R}}_{\text{glu}}}{\partial t} = \frac{1}{A^{\text{DV R}}} \left( -\frac{\partial F^{\text{DV R}}_{\text{glu}}}{\partial x} - J^{\text{DV R}}_{\text{glu}} - F_{\text{sh,glu}}^{\text{DV R}} \right) \tag{6.7}
\]

\[
\frac{\partial C^{\text{AV R}}_{\text{glu}}}{\partial t} = \frac{1}{A^{\text{AV R}}} \left( -\frac{\partial F^{\text{AV R}}_{\text{glu}}}{\partial x} - J^{\text{AV R}}_{\text{glu}} + F_{\text{sh,glu}}^{\text{DV R}} - J_{\text{gly}} \right) \tag{6.8}
\]

\[
\frac{\partial C^{\text{DV R}}_{\text{lac}}}{\partial t} = \frac{1}{A^{\text{DV R}}} \left( -\frac{\partial F^{\text{DV R}}_{\text{lac}}}{\partial x} - J^{\text{DV R}}_{\text{lac}} - F_{\text{sh,lac}}^{\text{DV R}} \right) \tag{6.9}
\]

\[
\frac{\partial C^{\text{AV R}}_{\text{lac}}}{\partial t} = \frac{1}{A^{\text{AV R}}} \left( -\frac{\partial F^{\text{AV R}}_{\text{lac}}}{\partial x} - J^{\text{AV R}}_{\text{lac}} + F_{\text{sh,lac}}^{\text{DV R}} + 2J_{\text{gly}} \right) \tag{6.10}
\]

where \( J_{\text{gly}} \), the glycolytic rate is described simply with a first degree Michaelis-Menten equation saturable as a function of AVR glucose consumption

\[
J_{\text{gly}}(x,t) = N(x) \frac{V_{\text{max}} C^{\text{AV R}}_{\text{glu}}(x,t)}{K_m + C^{\text{AV R}}_{\text{glu}}(x,t)} \tag{6.11}
\]

In practice, for exploration of model behaviour, values for \( V_{\text{max}} \) that would result in specified fractions of total glucose consumption need to be specified. With this purpose and assuming \( K_m \ll C^{\text{AV R}}_{\text{glu}} \) for all \( x \), substituting the expression of \( N(x) \) from equation (6.1) gives

\[
J_{\text{gly}}(x,t) = N(x) \frac{V_{\text{max}} C^{\text{AV R}}_{\text{glu}}(x,t)}{K_m + C^{\text{AV R}}_{\text{glu}}(x,t)} \approx N(x)V_{\text{max}} = N(0)e^{-k_{\text{sh}}x}V_{\text{max}} \tag{6.12}
\]

and integrating over the whole IM (\( L \) represents length), total glucose consumption is

\[
J_{\text{gly}}^{\text{TOT}}(x,t) = V_{\text{max}}N(0) \int_0^L e^{-k_{\text{sh}}x} = V_{\text{max}}N(0) \frac{1-e^{-k_{\text{sh}}L}}{k_{\text{sh}}} \tag{6.13}
\]

Solving this for \( V_{\text{max}} \) and expressing \( J_{\text{gly}}^{\text{TOT}} \) as a fraction \( v_{\text{gly}} \) of total baseline glucose delivery, \( F_{\text{glu}}^{\text{DV R}}(0) \) the following is obtained:

\[
V_{\text{max}} = \frac{k_{\text{sh}}J_{\text{gly}}^{\text{TOT}}}{N(0)(1-e^{-k_{\text{sh}}L})} = \frac{k_{\text{sh}}}{N(0)(1-e^{-k_{\text{sh}}L})} v_{\text{gly}} F_{\text{glu}}^{\text{DV R}}(0,t) \tag{6.14}
\]
6. GLYCOLYSIS: A SOURCE OF EXTERNAL OSMOLES

6.4 Numerical solution: Chebfun

Since transmural flux of volume at (6.4) is independent of solute concentrations, the volume flow equations in (6.2) and (6.3) can be solved analytically, taking the volume flow entering the DVR , \( F_{v}^{DVR}(0) \), to be 3.75 \( nl \ min^{-1} \ tube^{-1} \) (see Figure 6.3).

As explained in Chapter 4 Section 4.3.3.1, the system of partial differential equations describing concentrations of glucose and lactate along the vasa recta (Equations (6.7)-(6.10)) is solved in this chapter by the Chebfun Package.

The solution of a system of PDEs is accomplished in Chebfun by the routine called \textit{pde15s} which uses a MOL approach by using Chebyshev spectral discretization in space and solves the resulting system of ODEs in time by using the Matlab routine (already mentioned in Chapter 4) \textit{ode15s}.

The solution process for the problem occurs as follows (the code solving the baseline case can be found in Appendix A):

1. Set model parameters
2. Set time and space intervals
3. Compute volume flows at the desired nodes
4. Solve the system of PDEs
   - Define the domain object:
     \[
     [d \ x]=\text{domain}(0,L);
     \]
   - Define the initial conditions:
     \[
     C_{\text{glu}}_0=C_{\text{glu}}0;
     C_{\text{aglu}}_0=C_{\text{glu}}0;
     C_{\text{dlac}}_0=C_{\text{lac}}0;
     C_{\text{alac}}_0=C_{\text{lac}}0;
     \]
   - Define boundary conditions as a function (chebfun):
     \[
     \text{bc.left} = @(C_{\text{glu}},C_{\text{aglu}},C_{\text{dlac}},C_{\text{alac}},t,x,D) \ [C_{\text{glu}}-C_{\text{glu}}0, C_{\text{dlac}}-C_{\text{lac}}0];
     \text{bc.right} = @(C_{\text{glu}},C_{\text{aglu}},C_{\text{dlac}},C_{\text{alac}},t,x,D) \ [C_{\text{glu}}-C_{\text{aglu}},C_{\text{dlac}}-C_{\text{alac}}];
     \]
   - Define the function defining the RHS of the PDEs
   - Call \textit{pde15s} for solving the system with initial and boundary conditions described before:
     \[
     [tt uu] = \text{pde15s}(f,\text{time},[\text{chebfun}(C_{\text{glu}}_0,d) C_{\text{aglu}}_0 C_{\text{dlac}}_0 C_{\text{alac}}_0],\text{bc});
     \]
   - The solution \( uu \) is returned as a cell array of quasimatries at times given by \( tt \).
     \[
     uu = [0x4 \text{ chebfun}] \ [0x4 \text{ chebfun}] \ [0x4 \text{ chebfun}] \ [0x4 \text{ chebfun}]
     \]

92
Figure 6.3: Single volume flow in $nl/min$, solid curve shows values for DVR, dashed curve for AVR. Outflow from AVR is 30% higher than DVR inflow, due to assumed volume uptake from nephrons.

Tube parameters and boundary conditions are given in Table 6.1. During all simulations parameters not indicated are set as their baseline values: a 20% consumption is adopted as the baseline value for glycolysis in all simulations when this is not tested. $J^{ABS}_v$ and $J_v$ baseline values are set at 30%.

Table 6.1: Baseline values, parameters and boundary conditions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$r$</td>
<td>9 $\mu$m</td>
</tr>
<tr>
<td>$F^DVR_v(0,t)$</td>
<td>3.75 $nl \cdot min^{-1} \cdot tube^{-1}$</td>
</tr>
<tr>
<td>$C^{DVR}_{glu}(0,t)$</td>
<td>10 mM</td>
</tr>
<tr>
<td>$C_{lac}^{DVR}(0,t)$</td>
<td>2 mM</td>
</tr>
<tr>
<td>$P^{DVR}_{glu}$</td>
<td>$4 \times 10^{-4} mm/s$</td>
</tr>
<tr>
<td>$P_{lac}^{DVR}$</td>
<td>$100 \times 10^{-4} mm/s$</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>0.5</td>
</tr>
</tbody>
</table>
6. GLYCOLYSIS: A SOURCE OF EXTERNAL OSMOLES

6.5 Results

6.5.1 Glycolytic rate

Figures 6.4 to 6.6 show the baseline model behavior for different glycolytic consumptions for both glucose and lactate profiles. Notice that as was shown in [92], 20 – 100 mOsmols of external osmoles could suffice to improve the concentrating ability in the IM. As glucose consumption is increased glucose concentrations falls as lactate rises.

Figures 6.4(a) and 6.4(b) show concentration profiles when no glucose consumption takes place; even with no glycolysis, glucose concentration falls, that is due to incoming volume from the nephrons. A constant initial condition matching values entering the descending vasa recta has been used in Figures 6.4(a) and 6.4(b), while from Figures 6.4(c) to 6.6(d) the non-glycolysis case is used as an initial condition.

Table 6.2 shows the concentration of lactate for various times when 20% of glucose is consume, the lactate gradient quickly builds up during the first 100 sec taking 500 sec to reach its final steady state.

<table>
<thead>
<tr>
<th>Depth (mm)</th>
<th>0</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>80</th>
<th>100</th>
<th>200</th>
<th>300</th>
<th>400</th>
<th>500</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0.54376</td>
<td>4.7743</td>
<td>6.888</td>
<td>8.0982</td>
<td>8.8277</td>
<td>9.2786</td>
<td>9.9779</td>
<td>10.056</td>
<td>10.066</td>
<td>10.067</td>
</tr>
<tr>
<td>4</td>
<td>0.0020859</td>
<td>3.9393</td>
<td>6.9314</td>
<td>8.9616</td>
<td>10.325</td>
<td>11.238</td>
<td>12.82</td>
<td>13.022</td>
<td>13.048</td>
<td>13.051</td>
</tr>
</tbody>
</table>

Table 6.2: Concentration of lactate building up for various times when glycolysis is set at 20%
Figure 6.4: Glucose and lactate concentration profiles for no glycolysis and glycolysis at 10%
Figure 6.5: Glucose and lactate concentration profiles for glycolysis at 15% and 20%
6.5 Results

![Graphs of glycolysis at 30% and 40%]

(a) Glycolysis at 30%
(b) Glycolysis at 30%
(c) Glycolysis at 40%
(d) Glycolysis at 40%

**Figure 6.6:** Glucose and lactate concentration profiles for glycolysis at 30% and 40%
6. GLYCOLYSIS: A SOURCE OF EXTERNAL OSMOLES

6.5.2 Effect of decreasing inner medullary blood flow

Under the assumption that tissue glucose consumption is not affected by the change of blood flow, lactate accumulation (Figure 6.7) is seen to dramatically increase as IMBF falls to 50% of its baseline value, as may occur in antidiuresis (see Antidiuresis). The predicted lactate profiles suggest that IMBF may play an important role in the extent of lactate accumulation.

Table 6.3 shows the build up of the gradient after IMBF is decreased to 50% (Figure 6.7(d)). During the first 100 sec the gradient doubles and, as shown in Table 6.2, the final gradient will take another 400 sec until it stabilizes completely.

Table 6.3: Concentration of lactate building up for various times after IMBF decreases by 50%

<table>
<thead>
<tr>
<th>Depth (mm)</th>
<th>0</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>80</th>
<th>100</th>
<th>200</th>
<th>300</th>
<th>400</th>
<th>500</th>
</tr>
</thead>
</table>
Figure 6.7: Lactate concentration profiles when reducing IMBF
6. GLYCOLYSIS: A SOURCE OF EXTERNAL OSMOLES

6.5.3 Effect of increasing inner medullary blood flow

Figure 6.8 shows the wash out effect that a sudden increase of IMBF would make in the gradient built by glycolysis.

Table 6.3 shows the concentration along the AVR for various times after IMBF is increased by 50% (Figure 6.8(b)), after 500 sec only half of the gradient created remains.

**Table 6.4:** Concentration of lactate when IMBF is increased by 50% for various times.

<table>
<thead>
<tr>
<th>Depth (mm)</th>
<th>0</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>80</th>
<th>100</th>
<th>200</th>
<th>300</th>
<th>400</th>
<th>500</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>10.233</td>
<td>8.0873</td>
<td>7.0121</td>
<td>6.3955</td>
<td>6.0234</td>
<td>5.7932</td>
<td>5.4357</td>
<td>5.3955</td>
<td>5.3907</td>
<td>5.3901</td>
</tr>
</tbody>
</table>
6.5 Results

![Graphs showing lactate concentration profiles for various IMBF percentages.](image)

(a) IMBF 100%
(b) IMBF 150%
(c) IMBF 200%
(d) IMBF 300%

**Figure 6.8:** Lactate concentration profiles when IMBF is increased
6. GLYCOLYSIS: A SOURCE OF EXTERNAL OSMOLES

6.5.4 Effect of varying nephrons uptake

The effect of varying $J_{\text{ABS}}^{\text{v}}$ is shown in Figure 6.9. Absorption rates of 10%, 50% and 90% of DVR inflow are shown here. Increasing volume reabsorption affects significantly lactate accumulation. Table 6.5 shows the build up of the lactate gradient when the absorption rate is decreased to 10% from the baseline case, it can be observed that the build up process is slower for low absorption rates, taking around 400 sec to reach almost three times of its initial value.

**Table 6.5:** Concentration of lactate when the absorption rate is decreased to 10%.

<table>
<thead>
<tr>
<th>Depth (mm)</th>
<th>Time in seconds</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>4.6097</td>
</tr>
</tbody>
</table>
Figure 6.9: Lactate concentration profiles when varying volume reabsorption from nephrons
6. GLYCOLYSIS: A SOURCE OF EXTERNAL OSMOLES
7

Full dynamic renal model including glycolysis and prebend transitions

7.1 Introduction

After validating the virtual tube performance to model the prebend transition with the multinephron model presented in Chapter 5, and in order to incorporate the process of glycolysis taking place in the IM cells (as explained in Chapter 6), the shunted model presented in Chapter 5 is modified to incorporate three more solutes: Glucose, Lactate and $KCl$ (the latter one only present in the CD).

7.2 Anatomical considerations

The model in this chapter will consider a medullary length of 6 $mm$, this being divided into: (1) Outer medulla, with a total length of 2 $mm$ divided into two regions: the outer stripe (with length 0.7 $mm$) and the inner stripe (with length 1.3 $mm$); (2) Inner medulla, with a total length of 4 $mm$ where the inner medulla is divided in two sections labelled as inner upper and inner lower medulla, each with a length of 2 $mm$.

A total number of 8 different structures is considered: LDL, LDLV, LAL, CD, DVR, AVR, SDL and SAL where each at the same time will represent a
population of individual structures with the same characteristics.

This time, and as in [31], a total of five solutes are incorporated in the model. As usual \( NaCl \) and urea are present in all tubes but also glucose, lactate and \( KCl \) are included. Glucose and lactate are considered to be present at low concentrations in the loops of Henle, both short and long (as generally reported after the end of the proximal tubule) and are used to represent the nonreabsorbable solutes present in the nephron. In the case of \( KCl \), and as this is only present in considerable amounts in the collecting duct, its concentration in the rest of the structures will be considered as zero ([51]).

7.2.1 Boundary conditions and membrane parameters

Volume flows and concentrations entering the collecting duct are calculated in this model by applying the virtual distal tubule condition, as described in [31]. Usually models of the renal medulla do not include explicitly tube sections such as the distal tubule, as microperfusion data at this level are accurate enough to describe appropriate boundary conditions to simulate the entering values in the CD as a function of exiting flows of the AHLs.

The entry to the collecting ducts is calculated from flow and concentrations at the top of the SAL and LAL together with the following assumptions:

- Fluid entering the outer medullary collecting duct (OMCD) is isosmotic to plasma and is assigned the value 263 mosM \( (Osm_{CD}^{0} = 263) \).

- A specified fraction, 85%, of urea is delivered to OMCD (i.e., distal tubules reabsorb 15% of the urea delivered to the early distal tubules).

- \( NaCl \) concentration entering the OMCD has a fixed value of 35 mM \( (C_{s,0}^{CD}) \).

- Glucose and Lactate flows are conserved along the virtual distal tubules, i.e., their flows into OMCD equal the sum of their flows out of the LAL and SAL.

- \( KCl \) enters the OMCD at a concentration of 20 mM \( (C_{KCl,0}^{CD}) \) and no transport across the walls occurs.
7.2 Anatomical considerations

Given the osmotic coefficient of the solute \( j \) considered \( \phi_j \), the osmolality of a given tube \( i \) is given by

\[
Osm^i = \sum_{j=1}^{\text{totsol}} \phi_j C^i_j
\]  
(7.1)

where the osmotic coefficient is considered 1.82 for NaCl and KCl and 1 for the rest of the solutes ([98]).

Based on Equation (7.1) volume flow entering the CD (\( F^\text{CD}_{v,0} \)) at any time \( t \) can be calculated as follows

\[
Osm^\text{CD}_{0} = 1.82(C^\text{CD}_{s,0} + C^\text{CD}_{\text{KCl},0}) + C^\text{CD}_{u,0} + C^\text{CD}_{g,0} + C^\text{CD}_{l,0}
\]  
(7.2)

where \( C^\text{CD}_{u,0} \), \( C^\text{CD}_{g,0} \) and \( C^\text{CD}_{l,0} \) are calculated from outflow of the ascending limbs to give:

\[
Osm^\text{CD}_{0} = 1.82(C^\text{CD}_{s,0} + C^\text{CD}_{\text{KCl},0}) + 0.85(F^\text{LAL}_{u,0} + F^\text{SAL}_{u,0}) + (F^\text{LAL}_{g,0} + F^\text{SAL}_{g,0}) + (F^\text{LAL}_{l,0} + F^\text{SAL}_{l,0})
\]  
(7.3)

Then volume flow entering the CD is given by

\[
F^\text{CD}_{v,0} = \frac{0.85(F^\text{LAL}_{u,0} + F^\text{SAL}_{u,0}) + (F^\text{LAL}_{g,0} + F^\text{SAL}_{g,0}) + (F^\text{LAL}_{l,0} + F^\text{SAL}_{l,0})}{Osm^\text{CD} - 1.82(C^\text{CD}_{s,0} + C^\text{CD}_{\text{KCl},0})}
\]  
(7.4)

Following the relationship between solute and volume flows (Equation (3.6)) one can obtain the remaining boundary conditions:

\[
C^\text{CD}_{u,0} = \frac{0.85(F^\text{LAL}_{u,0} + F^\text{SAL}_{u,0})}{F^\text{CD}_{v,0}}
\]  
(7.5)

\[
C^\text{CD}_{g,0} = \frac{F^\text{LAL}_{g,0} + F^\text{SAL}_{g,0}}{F^\text{CD}_{v,0}}
\]  
(7.6)

\[
C^\text{CD}_{l,0} = \frac{F^\text{LAL}_{l,0} + F^\text{SAL}_{l,0}}{F^\text{CD}_{v,0}}
\]  
(7.7)

Table 7.1 shows the concentrations of glucose, lactate and urea entering LDL, SDL and DVR as well as the volume flows entering these structures ([31]).
Table 7.1: Concentrations and volume flows entering LDL, SDL and DVR

<table>
<thead>
<tr>
<th>Tube</th>
<th>LDL</th>
<th>SDL</th>
<th>DVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume flow (nl/min)</td>
<td>10</td>
<td>10</td>
<td>3.75</td>
</tr>
<tr>
<td>Glucose (mM)</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>NRS (mM)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lactate (mM)</td>
<td>10^{-3}</td>
<td>10^{-3}</td>
<td>1</td>
</tr>
<tr>
<td>Urea (mM)</td>
<td>10</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

Assuming an osmolality of 263 mosM at the cortex \( (Osm_0^i) \), entering salt concentrations are calculated from the above for LDL, SDL and DVR as follows:

\[
C_{s,0}^i = \frac{Osm_0^i - (C_{u,0}^i + C_{g,0}^i + C_{i,0}^i)}{1.82}
\]

(7.9)

where \( i = LDL, SDL, CD \).

7.2.2 Number of tubes

As in Chapter 5 the number of long loops of Henle, vasa recta and collecting ducts will be considered to decrease exponentially within the inner medulla. But, in the case of the vasa recta, and as was previously considered in [103] and [31], two thirds of the number at cortical level will turn within the inner stripe, representing the population of short descending vasa recta (SDV) that are not modelled individually.

\(^1\)Note this value has been corrected from [31] since the real value of the results shown use an inflow corresponding to half of the one indicated in the paper.

\(^2\)NRS at the loops of Henle and collecting duct are represented by glucose.
### Table 7.2: Baseline parameters

<table>
<thead>
<tr>
<th>Tube</th>
<th>Region</th>
<th>Radius $\mu m$</th>
<th>$Lp_{10^{-6}mm\cdot s^{-1}\cdot mosM^1}$</th>
<th>$P_u$ $10^{-4}mm\cdot s^{-1}$</th>
<th>$P_s$</th>
<th>$P_g$</th>
<th>$P_l$</th>
<th>$\sigma_u$</th>
<th>$\sigma_s$</th>
<th>$\sigma_g$</th>
<th>$\sigma_l$</th>
<th>$V_m$ $nmol\cdot mm^{-2}\cdot s^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>OS</td>
<td>10</td>
<td>66.6</td>
<td>2</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.9</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>IS</td>
<td></td>
<td>10</td>
<td>62.5</td>
<td>2</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>IU</td>
<td></td>
<td>10</td>
<td>58.3</td>
<td>12</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>IL</td>
<td></td>
<td>10</td>
<td>58.3</td>
<td>12</td>
<td>0.5</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>LAL</td>
<td>OS</td>
<td>10</td>
<td>0</td>
<td>4.5</td>
<td>2</td>
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<td>0</td>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>IS</td>
<td></td>
<td>10</td>
<td>0</td>
<td>4.5</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<td>1</td>
</tr>
<tr>
<td>IU</td>
<td></td>
<td>10</td>
<td>0</td>
<td>23</td>
<td>80</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
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<td>10</td>
<td>0</td>
<td>23</td>
<td>80</td>
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<td>1</td>
</tr>
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<td>CD</td>
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<td>1</td>
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</tr>
<tr>
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<td></td>
<td>15</td>
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</tr>
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</tr>
<tr>
<td>DV</td>
<td>OS</td>
<td>9</td>
<td>66.6</td>
<td>360</td>
<td>80</td>
<td>0.78</td>
<td>39</td>
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<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
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<td>360</td>
<td>80</td>
<td>0.78</td>
<td>39</td>
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<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>IU</td>
<td></td>
<td>9</td>
<td>33.3</td>
<td>120</td>
<td>80</td>
<td>0.78</td>
<td>39</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>IL</td>
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<td>9</td>
<td>33.3</td>
<td>120</td>
<td>80</td>
<td>0.78</td>
<td>39</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>SDL</td>
<td>OS</td>
<td>11</td>
<td>58.3</td>
<td>8.5</td>
<td>2.3</td>
<td>0</td>
<td>0</td>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
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<td>11</td>
<td>50</td>
<td>8.5</td>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>SAL</td>
<td>OS</td>
<td>10</td>
<td>0</td>
<td>4.5</td>
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<td>0</td>
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<td>1</td>
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<td>1</td>
<td>1</td>
</tr>
<tr>
<td>IS</td>
<td></td>
<td>10</td>
<td>0</td>
<td>4.5</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
7. FULL DYNAMIC RENAL MODEL INCLUDING GLYCOLYSIS AND PREBEND TRANSITIONS

**Figure 7.1:** Schematic of tubes and regions considered, together with the boundary conditions. For simplicity picture merges LDL and LDLV in a single structure.
7.2 Anatomical considerations

Table 7.3 shows then the number of tubes in each region, the number of SAL and AVR being equal to the number of SDL and DVR respectively, where

\[ N^{LDL}(x) = N_{0}^{LDL}e^{k_{sh}(x-(x_{OM/IM}-P_b))} \]  
(7.10)

\[ N^{SDV}(x) = N_{0}^{SDV} \left( 1 - \frac{x-x_{OS/IS}}{x_{OM/IM}-x_{OS/IS}} \right) \]  
(7.11)

\[ N^{LDV}(x) = N_{0}^{LDV}e^{k_{sh}(x-x_{OM/IM})} \]  
(7.12)

\[ N^{CD}(x) = N_{0}^{CD}e^{k_{sh}(x-x_{OM/IM})} \]  
(7.13)

where \( x_{OM/IM} \) denotes the outer/inner medullary border occurring at a distance of 2 mm and \( x_{OS/IS} \) denotes the border between the outer and inner stripe at a distance of 0.7 mm. Shunt factors \( k_{sh} \) are calculated so the fraction of vasa recta and Henle’s loops reaching the papillary tip is 1/128 for an IM thickness of 4 mm and, over the same distance, 64 CDs converge to a single exiting collecting duct.

The number of structures that extends to the inner medulla (long Henle’s loop, vasa recta and collecting duct) can also be seen in Figure 7.2.

![Figure 7.2: Number of vasa recta, collecting ducts and long Loops of Henle. Note that the number of Loops of Henle and Collecting Ducts reaching the papillary tip is equal to one.](image)

111
Table 7.3: Number of tubes at each depth

<table>
<thead>
<tr>
<th>Tube</th>
<th>OS</th>
<th>IS₁</th>
<th>IS₂</th>
<th>IM₁</th>
<th>IM₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDL</td>
<td>$N_{0}^{SDL}$</td>
<td>$N_{0}^{SDL}$</td>
<td>$N_{0}^{SDL}$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LDL</td>
<td>$N_{0}^{LDL}$</td>
<td>$N_{0}^{LDL}$</td>
<td>$N_{0}^{LDL}(x)$</td>
<td>$N_{0}^{LDL}(x)$</td>
<td>0</td>
</tr>
<tr>
<td>LDLV</td>
<td>0</td>
<td>0</td>
<td>$-N_{0}^{LDL}(x) + N_{0}^{LDL}$</td>
<td>$-N_{0}^{LDL}(x) + N_{0}^{LDL}(x - P_b)$</td>
<td>$N_{0}^{LDL}(x - P_b)$</td>
</tr>
<tr>
<td>LAL</td>
<td>$N_{0}^{LDL}$</td>
<td>$N_{0}^{LDL}$</td>
<td>$N_{0}^{LDL}$</td>
<td>$N_{0}^{LDL}(x - P_b)$</td>
<td>$N_{0}^{LDL}(x - P_b)$</td>
</tr>
<tr>
<td>CD</td>
<td>$N_{0}^{CD}$</td>
<td>$N_{0}^{CD}$</td>
<td>$N_{0}^{CD}$</td>
<td>$N_{0}^{CD}(x)$</td>
<td>$N_{0}^{CD}(x)$</td>
</tr>
<tr>
<td>DVR</td>
<td>$N_{0}^{SDV} + N_{0}^{LDV}$</td>
<td>$N_{0}^{SDV}(x) + N_{0}^{LDV}$</td>
<td>$N_{0}^{SDV}(x) + N_{0}^{LDV}$</td>
<td>$N_{0}^{LDV}(x)$</td>
<td>$N_{0}^{LDV}(x)$</td>
</tr>
</tbody>
</table>

IS₁ refers to the length of the IS until the first prebend transition while IS₂ is the distance between the first prebend transition and the OM/IM border. Similarly IM₁ corresponds with the distance until the last prebend and IM₂ is the distance from the last prebend until the papillary tip. Considering the number of CDs entering the cortico-medullary border as $N_{0}^{CD} = 64$ then: $N_{0}^{SDL} = 4N_{0}^{CD}$, $N_{0}^{LDL} = 2N_{0}^{CD}$, $N_{0}^{SDV} = 8N_{0}^{CD}$ and $N_{0}^{LDV} = 4N_{0}^{CD}$.
7.3 System of equations

As seen before, the system of coupled ODEs and PDEs describing volume flow and concentrations is based on Equations (3.27) and (3.28), where shunt terms are only considered in the long loops of Henle and vasa recta. Since the model in this chapter contains the prebend transition, the equations for the long loops of Henle are modified to account for the new structure incorporated (LDLV) and the new shunt terms following Equations (7.21) and (5.21). Following the notation for all shunt terms as in Equation (3.26), the system of equations for volume flows and concentration is as follows:

**Volume flows**

\[
\frac{\partial F_{v}^{SDL}}{\partial x} = -J_{v}^{LDL} \tag{7.14}
\]
\[
\frac{\partial F_{v}^{SAL}}{\partial x} = 0 \tag{7.15}
\]
\[
\frac{\partial F_{v}^{LDL}}{\partial x} = -J_{v}^{LDL} + F_{sh,v}^{LDL} \tag{7.16}
\]
\[
\frac{\partial F_{v}^{LDLV}}{\partial x} = -J_{v}^{LDLV} - F_{sh,v}^{LDLV} \tag{7.17}
\]
\[
\frac{\partial F_{v}^{LAL}}{\partial x} = -F_{sh,v}^{LDLV} \tag{7.18}
\]
\[
\frac{\partial F_{v}^{DVR}}{\partial x} = -J_{v}^{DVR} + F_{sh,v}^{DVR} \tag{7.19}
\]
\[
\frac{\partial F_{v}^{AVR}}{\partial x} = -J_{v}^{AVR} - F_{sh,v}^{DVR} \tag{7.20}
\]
\[
\frac{\partial F_{v}^{CD}}{\partial x} = -J_{v}^{CD} \tag{7.21}
\]
Salt and Urea

If $j = \text{salt, urea}

\frac{\partial C_{SDL}^j}{\partial t} = \frac{1}{A_{SDL}} \left( - \frac{\partial F_{SDL}^j}{\partial x} - J_{SDL}^j \right) \quad (7.22)

\frac{\partial C_{SAL}^j}{\partial t} = \frac{1}{A_{SAL}} \left( - \frac{\partial F_{SAL}^j}{\partial x} - J_{SAL}^j \right) \quad (7.23)

\frac{\partial C_{LDL}^j}{\partial t} = \frac{1}{A_{LDL}} \left( - \frac{\partial F_{LDL}^j}{\partial x} - J_{LDL}^j + F_{sh;LDL}^j \right) \quad (7.24)

\frac{\partial C_{LDLV}^j}{\partial t} = \frac{1}{A_{LDLV}} \left( \frac{\partial F_{LDLV}^j}{\partial x} - J_{LDLV}^j - F_{sh;LDL}^j + F_{sh;LDLV}^j \right) \quad (7.25)

\frac{\partial C_{LAL}^j}{\partial t} = \frac{1}{A_{LAL}} \left( - \frac{\partial F_{LAL}^j}{\partial x} - J_{LAL}^j - F_{sh;LAL}^j \right) \quad (7.26)

\frac{\partial C_{DVR}^j}{\partial t} = \frac{1}{A_{DVR}} \left( - \frac{\partial F_{DVR}^j}{\partial x} - J_{DVR}^j + F_{sh;DVR}^j \right) \quad (7.27)

\frac{\partial C_{AVR}^j}{\partial t} = \frac{1}{A_{AVR}} \left( - \frac{\partial F_{AVR}^j}{\partial x} - J_{AVR}^j - F_{sh;AVR}^j \right) \quad (7.28)

\frac{\partial C_{CD}^j}{\partial t} = \frac{1}{A_{CD}} \left( - \frac{\partial F_{CD}^j}{\partial x} - J_{CD}^j \right) \quad (7.29)

KCl

As KCl is only present in reasonable amounts in the CD it will be considered 0 in the rest of the tubes and therefore only one PDE is needed to describe its concentration.

\frac{\partial C_{KCl}^CD}{\partial t} = \frac{1}{A_{CD}} \left( - \frac{\partial F_{KCl}^CD}{\partial x} \right) \quad (7.30)
7.3 System of equations

**Glucose and Lactate**

If \( j = \text{Glucose, lactate} \)

\[
\frac{\partial C_j^{SDL}}{\partial t} = \frac{1}{A^{SDL}} \left(- \frac{\partial F_j^{SDL}}{\partial x} + 1 \right) \quad (7.31)
\]

\[
\frac{\partial C_j^{SAL}}{\partial t} = \frac{1}{A^{SAL}} \left(- \frac{\partial F_j^{SAL}}{\partial x} + 1 \right) \quad (7.32)
\]

\[
\frac{\partial C_j^{LDL}}{\partial t} = \frac{1}{A^{LDL}} \left(- \frac{\partial F_j^{LDL}}{\partial x} - J_j^{LDL} + F_j^{LDL} + F_{sh,j}^{LDL} \right) \quad (7.33)
\]

\[
\frac{\partial C_j^{LDLV}}{\partial t} = \frac{1}{A^{LDLV}} \left(- \frac{\partial F_j^{LDLV}}{\partial x} - F_j^{LDLV} + F_{sh,j}^{LDLV} \right) \quad (7.34)
\]

\[
\frac{\partial C_j^{LAL}}{\partial t} = \frac{1}{A^{LAL}} \left(- \frac{\partial F_j^{LAL}}{\partial x} - F_j^{LAL} + F_{sh,j}^{LAL} \right) \quad (7.35)
\]

\[
\frac{\partial C_j^{DVR}}{\partial t} = \frac{1}{A^{DVR}} \left(- \frac{\partial F_j^{DVR}}{\partial x} - J_j^{DVR} + F_j^{DVR} + F_{sh,j}^{DVR} + k_j J_{gly} \right) \quad (7.36)
\]

\[
\frac{\partial C_j^{AVR}}{\partial t} = \frac{1}{A^{AVR}} \left(- \frac{\partial F_j^{AVR}}{\partial x} - J_j^{AVR} + F_j^{AVR} + F_{sh,j}^{AVR} + k_j J_{gly} \right) \quad (7.37)
\]

\[
\frac{\partial C_j^{CD}}{\partial t} = \frac{1}{A^{CD}} \left(- \frac{\partial F_j^{CD}}{\partial x} + 1 \right) \quad (7.38)
\]

where \( k_j \) is \(-1\) for glucose and \( 2 \) for lactate and \( J_{gly} \) refers to the Michaelis-Menten term described in Equation 6.11 this time with a glycolysis rate corresponding to approximately 20%. 
7. FULL DYNAMIC RENAL MODEL INCLUDING GLYCOLYSIS AND PREBEND TRANSITIONS

7.4 Numerical simulations

As in Chapter 5, the model is solved by the numerical Method of Lines using a first order approximation for the spatial derivatives. During the solution of such a model, several restrictions have been encountered, one of them being the number of spatial nodes to use. For all the simulations shown in the following sections ∆x has been chosen to be 0.1 mm giving a total of 61 nodes. To ensure that first and last prebend transition points are reached, the length of the prebend segment has been increased slightly and considered now to be 0.2 mm in contrast with the 0.15 mm used in Chapter 5.

Attempts to decrease ∆x have led to several issues due to matrix memory storage problems within Ode15s (Matlab subroutine in Section 4.3.2.1), therefore for the moment the number of spatial nodes cannot be increased.

The stiffness mentioned in Chapter 4 is more evident in this model, specially with the incorporation of the glycolysis process.

7.4.1 Baseline case

Following the membrane parameters and boundary conditions presented in Tables 7.1 and 7.2 the system of equations in Section 7.3 is solved until a quasi-steady state is reached. The glycolysis rate is such that approximately 20% of glucose is consumed. Transient results for the vasa recta are presented in Table 7.4 where t = 0 is considered the initial state before glycolysis is activated. After 30 min the system reaches what may be considered as a quasi-steady state since, although concentrations and volume flows change, the order of magnitude of these changes do not predict physiologically significant changes regarding osmolalities achieved.

As in [31] the main effect of lactate accumulation is seen in the NaCl gradient although urea accumulation is also increased. Comparison with [31] shows that in the model presented here lactate accumulation does not reach values as highs as presented there, therefore having a smaller effect on the build up of salt gradients.

\footnote{Although experimental transient data is not available, personal communication with S.R Thomas suggest that such processes could take days/weeks to reach a real steady state.}
### Table 7.4: VR concentrations

<table>
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<tr>
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<th></th>
<th></th>
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<th></th>
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<td>0.00</td>
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</tr>
</tbody>
</table>

Note: The values are given in millimolar (mM) concentrations for each substance at various depths.
7. FULL DYNAMIC RENAL MODEL INCLUDING GLYCOLYSIS AND PREBEND TRANSITIONS

Figure 7.3 shows the interstitial osmolality profiles without glycolysis ($t = 0$ in Table 7.4) and after half an hour of the activation of glycolysis ($t = 30 \text{ min}$ in Table 7.4) where the individual contribution of each solutes is differentiated.

**Figure 7.3:** Solute contribution to interstitial osmolality without (left) and with glycolysis (right).

Figure 7.4 shows the time taken for salt, urea and lactate gradients to build up. As suggested $^1$, the lactate gradient develops ahead of the salt gradient and the latter keeps building up once the lactate gradient has been established.

**Figure 7.4:** Build up of salt and lactate gradients in the interstitium from a non-glycolysis state.

$^1$Personal communication by S.R Thomas
7.4 Numerical simulations

7.4.2 Effect of the prebend transition

As mentioned in Chapter 5, the existence of the prebend transition is included in this work for the first time in a shunt model. The effect that the prebend transition may have on the process of the build up of the lactate and salt gradients is not known: whether it contributes in a positive or negative way or make no major differences is checked in this section by comparing the results of the described model against a model where the prebend transition has assumed the same properties as the long descending limb (as is the case in [31]).

Table 7.6 shows the concentration of salt and the final osmolality at the long descending limb of Henle in both models without (as the model presented in [31]) and with prebend. As seen in Chapter 5 Figure 5.17, the prebend transition dilutes the content at the descending limb therefore lowering the salt concentration at this tube. The effect is more obvious when the last prebend occurs (highlighted in Table 7.6) when the solution has reached a quasi-steady state. However, comparison between both scenarios shows that this gradient difference is really small causing no major effect on interstitial osmolalities (see Table 7.5).

Table 7.5: Interstitial concentration without and with prebend

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<th>Prebend 30 min</th>
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</table>
7. FULL DYNAMIC RENAL MODEL INCLUDING GLYCOLYSIS AND PREBEND TRANSITIONS

Table 7.6: Long descending limb salt concentrations and osmolality with and without prebend

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7.4 Numerical simulations

7.4.3 Gradient washout

As was done in Section 6.5.3 the effect of a sudden increase in medullary blood flow is shown in Figures 7.5 and 7.6. After the quasi-steady state described in Section 7.4.1 has been reached, the volume flow entering the descending vasa recta ($F_{v}^{DVR}(0)$) is increased by 100% (7.5 nl/min). Its effect on the different solute gradients is shown in Figure 7.5 at the papillary tip ($x = L$) for the long loops of Henle, vasa recta and collecting ducts. The same is shown at Figure 7.6 but this time at the OM/IM border ($x = OM/IM$).

Total osmolality washout can be observed in Figures 7.7 and 7.8 at the papillary tip and OM/IM border respectively. Results at the papillary tip show a slight increase of osmolality (see Figure 7.7) during the first 100 seconds, that is due to the increase of urea concentration seen at Figure 7.5 which seems not to be affected by changes on medullary blood flow.

Figure 7.9 shows the interstitial osmolality at the quasi-steady state along the renal medulla achieved for the baseline case and after increasing medullary blood flow. The most significant effect happens at the OM level since, the increment on osmolality achieved by glycolysis at the inner medullary level is approximately 240 mM in both cases.
Figure 7.5: Effect of doubling the IMBF on the different solutes present at the different structures at the papillary tip.
Figure 7.6: Effect of doubling the IMBF on the different solutes present at the different tubes at the OM/IM border.
7. FULL DYNAMIC RENAL MODEL INCLUDING GLYCOLYSIS AND PREBEND TRANSITIONS

Figure 7.7: Effect of doubling the IMBF on the total osmolality at the papillary tip.

Figure 7.8: Effect of doubling the IMBF on the total osmolality at the OM/IM border.
7.4 Numerical simulations

7.4.4 Conclusions

After comparing the results obtained in section 7.4.1 with those presented in [31], it is obvious that lactate gradients are much lower in the transient model than they are in the steady state model in [31].

Since, it has been seen that the prebend slightly dilutes the content of the loop of Henle but without having much impact in the overall interstitial osmolality, the main difference and therefore source of potential differences in results lies in the treatment of the glycolysis term. In the model presented in this chapter the process of glycolysis is included specifically in the system of equations following a Michaelis-Menten term (in a similar way as it was done in [21] and [88], while at [31] concentrations at the AVR (assimilated with the interstitium) are calculated following the conservation condition shown at (3.20) with no time derivatives and considering the rate at which glucose is destroyed and lactate created as follows:

$$\sum_i F_i(x) = F_{CD}^i(L) - \int_x^L \sum S_i dz$$

(7.39)

The calculation of $V_{max}$ values in this work has followed the same approach as used in [31], however and after analysing the results obtained it seems reasonable to question whether the assumption used in a steady state case are transferable to a transient scenario, being this left as the major issue for future studies.
7. FULL DYNAMIC RENAL MODEL INCLUDING GLYCOLYSIS AND PREBEND TRANSITIONS
Conclusion

Several issues have been discussed and addressed during the main chapters of this thesis, the major three concerning: (1) Numerical approach; (2) Presence, effect and simulation of the prebend transition in shunt models and; (3) Glycolysis as a source of external osmoles in a dynamic model.

As was mentioned in Chapter 4, models of the urine concentrating mechanism are often stiff due in part to anatomical configurations but also due to sudden changes in membrane properties along the course of the tubes. It has also been mentioned (Chapter 7), that it is possible too, that real situations could take several days or weeks to reach steady state, so it remains to be studied whether the current method is equipped to deal with this. The MOL presented in Chapter 4 and further used in Chapters 5 and 7 has proved to be a successful and manageable way of dealing with the prebend transition problem described in Chapter 5 but restricts the number of nodes therefore increasing the spatial error of the final solutions. Since collocation has worked effectively in the case of steady state models, the Chebfun package described in Chapter 4 and developed in Chapter 7 could be a good option in the case of a dynamic formulation. However, before this package can be used for such a purpose, the subroutine solving the system of PDEs (Pde15s) needs to be updated to deal with coupled systems of PDEs and ODEs as Ode15s does for DAE systems with the use of a mass matrix (currently under revision by the Chebfun team).

Although the inclusion of the prebend transition has been proven successful following the technique of using an auxiliary structure, it can be legitimately
questioned whether its inclusion in a shunt model makes the problem unnecessarily more complicated without having so much physiological effect on the final results. It may be more efficient and easy to consider a multinephron model if changes like that and other later findings ([40]) which could be more relevant, need to be included. However this technique could be of interest for other potential applications in situations not necessarily related with kidney modelling issues.

As seen in Chapter 2, a satisfactory explanation for the build up of the inner medullary gradient has not been found yet but it could involve different factors. Since flat models, like the one presented in Chapter 7, where the tubes only exchange with the interstitium, do not satisfactorily explain the urea gradient, it will be of interest to try to formulate a dynamic model following that in [104] where anatomical configurations such as those found in [67], [68], [69], and [66] can be included, allowing tubes to exchange with neighbouring structures.

However, and as mentioned in Chapter 7, before moving any further, a closer look at the inclusion of the glycolysis process in a transient formulation of the problem is needed to ensure that the assumptions made are not only valid in a steady state scenario but also during the transient stages of the problem. Even without a full match to the results shown in [31], the transient findings regarding times of build up and washout of the gradient offer new insight on other potential issues that could be tested and probably suggest new experimental tests.
Bibliography


BIBLIOGRAPHY


Appendix A

Vasa Recta Chebfun Code

%%% Vasa recta transient model
%%% Maria Gonzalez, 09 March 2011
%%% The following codes corresponds to the solution of the transient vasa
%%% recta model presented at chapter thesis
%%% The system solved for this particular problem consist on a set of 4 ODE’s
%%% describing volume flow equations which can be solved analytically and
%%% then, a set pf 4 coupled hyperbolic PDEs that will be solved using the CHEBFUN
%%% package.
%%%***********************************************
%%% Parameters (baseline)
***********************************************
L=4; % mm length of the renal medulla
vbar=0.3; % percentage of transmural volume flow 30%
IMBF=1.0; % factor to increase or decrease inner medullary blood flow
N0=128; % number of tubes entering the IM
FvdvrI=(((3.75*10^-3)/(60))*N0); % dvr inflow in mm^3/s
Fvdvr0=FvdvrI;
ksh=1.213; % shunt factor
vabs=0.3; % percentage of nephron reabs baseline value 30%
kv=(ksh*(Fvdvr0)*vabs)/(N0*(1-exp(-ksh*L))); % reabsorption from nephrons
Pglu=4*10^-4; % permeability of glucose
Plac=100*10^-4; % permeability of lactate
sigma=0.5; % reflection coefficient equal for both lactate and glucose
rad=9*10^-3; % avr/dvr radius
Cglu0=10; % entering glucose concentration
Clac0=2; % entering lactate concentration
A. VASA RECTA CHEBFUN CODE

% Analytical solution of ODE's: Variables Fvdvr, Fvavr
% Constants defined in Chapter thesis
A_1=(vbar*(Fvdvr0/N0))/(N0*L);
A_2=kv*N0;

% time vector:
time=0:20:500;

% ***************** ******************************************************
% ODE: solved analytically by the command below
% ******************************************************
Fvdvr=inline('-(A_1*A_2+Fvdvr0)*exp(-ksh*x)');
Fvavr=inline('-(Fvdvr0-1/ksh*A_2+A_1*x)*exp(-ksh*x)*exp(-ksh*L)*A_2/ksh');

% % derivatives (to be used in the PDEs)
dFvdvr=inline('A_1*A_2*exp(-ksh*x)*ksh*(-(A_1*A_2+Fvdvr0)*exp(-ksh*x)*A_2*exp(-ksh*x))');
dFvavr=inline('A_1*A_2*exp(-ksh*x)*ksh*(-(A_1*A_2+Fvdvr0)*exp(-ksh*x)*A_2*exp(-ksh*x))');

% Plot volume flow
node=0:0.1:4;
plot(node, Fvdvr(A_1,Fvdvr0,ksh,node)*(60/10ˆ(-3))/N0, 'blue');
hold on
plot(node, -Fvavr(A_1,A_2,Fvdvr0,L,ksh,node)*(60/10ˆ(-3))/N0, 'blue');
AX=legend('DVR', 'AVR');
LEG=findobj(AX, 'type', 'text');
set(LEG, 'Fontsize', 7);
xlabel('papillary depth mm', 'fontsize', 11)
ylabel('Single volume flow in nl/min', 'fontsize', 11)
saveas(gcf, 'flows.fig');
close all

% ********************** ***********************************************
% PDES
% Partial differential equations
% variables Cdglu, Cdlac, Caglu, Calac

% Cdglu_t=(1/Area)*(-FdFvvd+Cdglu_x-dFvvd+Cdglu-ksh*Fvdvr*Cdglu-Jsglu)
% Caglu_t=(1/Area)*(-FdFvvd+Caglu_x-dFvvd+Caglu+ksh*Fvdvr+Caglu-Jsglu+Jgly)
% Cdlac_t=(1/Area)*(-FdFvvd+Cdlac_x-dFvvd+Cdlac-ksh*Fvdvr+Cdlac-Jslac)
% Calac_t=(1/Area)*(-FdFvvd+Calac_x-dFvvd+Calac+ksh*Fvdvr+Calac+Jslac+2*Jgly)
% where Jsglu and Jslac represent transmural fluxes across the walls
% Jsglu= 2 pi rad N(x) Pglu (Cdglu-Caglu)+(1-sigma)Jv*0.5*(Cdglu+Caglu);
\[
\text{J}_{\text{lac}} = 2 \pi \text{ rad}
\]
\[
\text{N}(x) \text{ Plac (C}_{\text{dlac}} - \text{Calac}) + (1 - \sigma) \text{J}_v \times 0.5 \times (\text{C}_{\text{dlac}} + \text{Calac});
\]
\[
\text{J}_v \text{ is the transmural flux of volume and is given by}
\]
\[
\text{Area} = 2 \pi \text{ rad}^2 \text{N}(x) = 2 \pi \text{ rad}^2 \text{N} \exp(-k_{\text{sh}} \times x)
\]
\[
\text{J}_{\text{gly}} \text{ Michaelis menten expression describing glycolysis}
\]
\[
\text{vgly} = 0.0; \text{ no glycolysis case}
\]
\[
\text{V}_{\text{maxgly}} = \frac{(k_{\text{sh}})}{\text{N} \exp(-k_{\text{sh}} \times L)};
\]
\[
\text{V}_{\text{maxgly}} = \text{V}_{\text{maxgly}} \times \text{vgly} \times \text{F}_{\text{vdv}} \times \text{C}_{\text{glu}};
\]
\[
\text{K}_{\text{mgly}} = 0.01;
\]
\[
\text{domain of computation}
\]
\[
[d \ x] = \text{domain}(0, L);
\]
\[
\text{IC}
\]
\[
\text{Constant along the tube matching boundary conditions}
\]
\[
\text{Cd}_{\text{glu}} = \text{C}_{\text{glu}};
\]
\[
\text{C}_{\text{aglu}} = \text{C}_{\text{glu}};
\]
\[
\text{C}_{\text{dlac}} = \text{C}_{\text{lac}};
\]
\[
\text{Calac} = \text{C}_{\text{lac}};
\]
\[
\text{bc.left} = \text{@(Cd}_{\text{glu}}, \text{C}_{\text{aglu}}, \text{C}_{\text{dlac}}, \text{Calac}, t, x, D) \left[ \text{Cd}_{\text{glu}} - \text{C}_{\text{glu}}, \text{C}_{\text{dlac}} - \text{C}_{\text{lac}} \right];
\]
\[
\text{bc.right} = \text{@(Cd}_{\text{glu}}, \text{C}_{\text{aglu}}, \text{C}_{\text{dlac}}, \text{Calac}, t, x, D) \left[ \text{Cd}_{\text{glu}} - \text{C}_{\text{aglu}}, \text{C}_{\text{dlac}} - \text{C}_{\text{lac}} \right];
\]
\[
\text{RIGHT HAND SIDE PDES}
\]
\[
\text{Replace all Js and Jv by their expressions to avoid calling my own functions}
\]
\[
\text{increasing}
\]
A. VASA RECTA CHEBFUN CODE

%% solve first without varying and then read from that
f = @(Cdglu,Caglu,Cdlac,Calac,t,x,D)
%(1./(2*pi*radˆ2*N0*exp(-ksh*x))).*(−Fvdvr(A₁,Fvdvr0,ksh,x).*D(Cdglu,1)...
−dFvdvr(A₁,Fvdvr0,ksh,x).*Cdglu−ksh*Fvdvr(A₁,Fvdvr0,ksh,x).*Cdglu...
−(2*pi*rad*N0*exp(-ksh*x))*Pglu.*((Cdglu−Caglu)...
+(1−sigma)*A₁*exp(-ksh*x)*0.5.*(Cdglu+Caglu))) ... % end PDE glu dvr
(1./(2*pi*rad*2*N0*exp(-ksh*x))).*(−Fvavr(A₁,A₂,Fvdvr0,L,ksh,x).*D(Caglu,1)...
−dFvavr(A₁,A₂,Fvdvr0,L,ksh,x).*Caglu+ksh*Fvdvr(A₁,Fvdvr0,ksh,x).*Cdglu...
+(2*pi*rad*N0*exp(-ksh*x))*Pglu.*((Cdglu−Caglu)...
+(1−sigma)*A₁*exp(-ksh*x)*0.5.*(Cdglu+Caglu)))...
−N0*exp(-ksh*x).*((Vmaxgly.*Caglu)./(Kmgly+Caglu)) ... % end PDE glu avr
(1./(2*pi*rad*2*N0*exp(-ksh*x))).*(−Fvavr(A₁,A₂,Fvdvr0,L,ksh,x).*D(Cdlac,1)...
−dFvavr(A₁,A₂,Fvdvr0,L,ksh,x).*Cdglu+ksh*Fvdvr(A₁,Fvdvr0,ksh,x).*Cdglac...
−(2*pi*rad*N0*exp(-ksh*x))*Plac.*((Cdlac−Calac)...
+(1−sigma)*A₁*exp(-ksh*x)*0.5.*(Cdlac+Calac))) ... % end PDE lac dvr
(1./(2*pi*rad*2*N0*exp(-ksh*x))).*(−Fvavr(A₁,A₂,Fvdvr0,L,ksh,x).*D(Cdlac,1)...
−dFvavr(A₁,A₂,Fvdvr0,L,ksh,x).*Calac +ksh*Fvdvr(A₁,Fvdvr0,ksh,x).*Cdglac...
+(2*pi*rad*N0*exp(-ksh*x))*Plac.*((Cdlac−Calac)...
+(1−sigma)*A₁*exp(-ksh*x)*0.5.*(Cdlac+Calac)))...
+2*N0*exp(-ksh*x).*((Vmaxgly.*Caglu)./(Kmgly+Caglu)))
%
%% % Solve the system
[tt uu] = pde15s(f,time,[chebfun(Cdglu_0,d) Caglu_0 Cdlac_0 Calac_0],bc);
%
[s1,s2]=size(uu{4});
u=uu{1};
v=uu{2};
w=uu{3};
r=uu{4};
%
% Save solution to be used as IC for following calls
u0=u(:,s2);
v0=v(:,s2);
w0=w(:,s2);
r0=r(:,s2);
%
%****************************************************************************%
% CONCENTRATION PLOTS
%****************************************************************************
% Plotting
cols = get(0,'DefaultAxesColorOrder');
plot3(0,0,NaN,0,0,NaN,0,0,NaN), hold on % Used for legend entries
legend('Calac')
close all
% Glu dvr
figure
surf{uu{1},tt,'EdgeColor',[0.50196 0.50196 0.50196])
colormap hsv
```matlab
% Glu avr
figure
surf(uu{2},tt,'EdgeColor',[0.50196 0.50196 0.50196])
colormap hsv
colorbar
grid on
xlabel('Papillary depth');
ylabel('Time in seconds')
zlabel('Concentration of Lactate')
saveas(gcf,['Surf_CgluAvr_gly_0'],'fig');

% Lac dvr
figure
surf(uu{3},tt,'EdgeColor',[0.50196 0.50196 0.50196])
colormap hsv
colorbar
grid on
xlabel('Papillary depth');
ylabel('Time in seconds')
zlabel('Concentration of Lactate')
saveas(gcf,['Surf_ClacDvr_gly_0'],'fig');

% Lac avr
figure
surf(uu{4},tt,'EdgeColor',[0.50196 0.50196 0.50196])
colormap hsv
colorbar
grid on
xlabel('Papillary depth');
ylabel('Time in seconds')
zlabel('Concentration of Lactate')
saveas(gcf,['Surf_ClacAvr_gly_0'],'fig');
```
A. VASA RECTA CHEBFUN CODE
Appendix B

Notation

Variables and equation terms

- \( A^i \) Cross-sectional area of tube \( i \) \( \text{mm}^2 \)
- \( C_k \) Concentration of solute \( k \) \( \text{mM} \) or \( \text{nmol} \cdot \text{mm}^{-3} \)
- \( F_k \) Axial flow of solute \( k \) \( \text{nmol} \cdot \text{s}^{-1} \)
- \( F_v \) Axial flow of volume \( \text{nl} \cdot \text{min}^{-1} \) or \( \text{mm}^3 \cdot \text{s}^{-1} \)
- \( J_k \) Transmural flux of solute \( k \) \( \text{nmol} \cdot \text{mm}^{-1} \cdot \text{s}^{-1} \)
- \( J_v \) Transmural flux of volume \( \text{mm}^2 \cdot \text{s}^{-1} \)
- \( x \) Papillary Depth \( \text{mm} \)

Parameters

- \( K_m \) Michaelis constant \( \text{mM} \)
- \( L_p \) Hydraulic permeability \( \text{mm} \cdot \text{s}^{-1} \cdot \text{mosM}^{-1} \)
- \( P_k \) Permeability of solute \( k \) \( \text{mm} \cdot \text{s}^{-1} \)
- \( r \) radius \( \text{mm} \)
- \( V_{max} \) Maximum rate of transport \( \text{nmol} \cdot \text{cm}^{-2} \cdot \text{s}^{-1} \)
## B. NOTATION

### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH</td>
<td>Anidiuretic Hormone</td>
</tr>
<tr>
<td>AHL</td>
<td>Ascending Henle’s Loop</td>
</tr>
<tr>
<td>AVR</td>
<td>Ascending Vasa Recta</td>
</tr>
<tr>
<td>CC</td>
<td>Central Core</td>
</tr>
<tr>
<td>CD</td>
<td>Collecting Duct</td>
</tr>
<tr>
<td>DHL</td>
<td>Descending Henle’s Loop</td>
</tr>
<tr>
<td>DV</td>
<td>Descending Vasa Recta (DVR)</td>
</tr>
<tr>
<td>DT</td>
<td>Distal Tubule</td>
</tr>
<tr>
<td>DVR</td>
<td>Descending Vasa Recta</td>
</tr>
<tr>
<td>HL</td>
<td>Henle’s Loop</td>
</tr>
<tr>
<td>IL</td>
<td>Inner Lower Medulla</td>
</tr>
<tr>
<td>IM</td>
<td>Inner Medulla</td>
</tr>
<tr>
<td>IS</td>
<td>Inner Stripe</td>
</tr>
<tr>
<td>IU</td>
<td>Inner Upper Medulla</td>
</tr>
<tr>
<td>IMBF</td>
<td>Inner Medullary Blood Flow</td>
</tr>
<tr>
<td>LAL</td>
<td>Long Ascending Limb of Henle</td>
</tr>
<tr>
<td>LDL</td>
<td>Long Descending Limb of Henle</td>
</tr>
<tr>
<td>LDLV</td>
<td>Virtual Long Descending Limb of Henle</td>
</tr>
<tr>
<td>NRS</td>
<td>Nonreabsorbable solutes OM</td>
</tr>
<tr>
<td>OMCD</td>
<td>Outer Medullary Collecting Duct</td>
</tr>
<tr>
<td>OS</td>
<td>Outer Stripe</td>
</tr>
<tr>
<td>PT</td>
<td>Proximal tubule</td>
</tr>
<tr>
<td>SAL</td>
<td>Short Ascending Limb of Henle</td>
</tr>
<tr>
<td>SDL</td>
<td>Short Descending Limb of Henle</td>
</tr>
<tr>
<td>SDV</td>
<td>Short Descending Vasa Recta</td>
</tr>
<tr>
<td>UCM</td>
<td>Urine Concentrating Mechanism</td>
</tr>
<tr>
<td>VR</td>
<td>Vasa Recta</td>
</tr>
</tbody>
</table>
Glossary

A

**Adenosine Triphosphate**  An important carrier of energy in cells in the body and a compound that is important in the synthesis (the making) of RNA. Adenosine triphosphate (ATP) is a nucleotide (a building block of a nucleic acid such as RNA). The body produces ATP from food and then ATP produces energy as needed by the body, p. 14.

**Affinity**  An attractive force between substances or particles that causes them to enter into and remain in chemical combination.

**Aldosterone**  A hormone produced by the adrenal glands that controls excretion of sodium by the kidneys and thereby maintains the balance of salt and water in the body fluids., p. 10.

**Amino acids**  Any of a group of water-soluble organic compounds that possess both a carboxyl group (\(-\text{COOH}\)) and an amino \((-\text{NH}_2\)) group both attaced to the same carbon atom, p. 9.

**Ammonia**  Colourless gas, \(\text{NH}_3\) produced produced by the deamination of excess amino acids in the lover, p. 19.

**Anastomosis**  communication between vessels by collateral channels, p. 11.

**Antidiuresis**  The reduction of urinary volume, p. 98.
GLOSSARY

**Antidiuretic hormone**  Commonly known as ADH, a hormone secreted by the posterior pituitary gland, that stimulates reabsorption of water by the kidneys and thus controls the concentration of body fluids, p. 10.

**B**

**Basement membrane**  A thin membrane upon which is posed a single layer of cells. The basement membrane is made up of proteins held together by type IV collagen.

**Boltzmann’s constant**  The Boltzmann constant (k or kB) is the physical constant relating temperature to energy, \(1.3806504(24) \times 10^{-23} \, JK^{-1}\).

**Bowman’s Capsule**  A membranous, double-walled capsule surrounding a glomerulus of a nephron. Named after Sir William Bowman (1816-192), English surgeon., p. 11.

**C**

**Colloid**  Colloids is a term used to collectively refer to the large molecular weight particles present in a solution. In normal plasma, the plasma proteins are the major colloids present. As the colloids are solutes they contribute to the total osmotic pressure of the solution. This component due to the colloids is typically quite a small percent of the total osmotic pressure. It is referred to as colloid osmotic pressure (or sometimes as the oncotic pressure), p. 19.

**Concentration gradient**  The graduated difference in concentration of a solute per unit distance through a solution, p. 10.

**Creatine**  A compound, synthesized from amino acids, that occurs in muscle. It is an important reserve of energy for muscle concentration, which is released when creatine phosphate loses its phosphate and is converted to creatinine, which is excreted in the urine (at a rate of 1.2-1.5 g/day in humans), p. 9.
GLOSSARY

D

Diuresis  Excretion of an unusually large quantity of urine.

E

Electrolytes  A liquid that conducts electricity as a result of the presence of positive or negative ions, p. 9.

H

Homeostasis  Homeostasis is the property of either an open system or a closed system, especially a living organism, that regulates its internal environment so as to maintain a stable, constant condition, p. 9.

Hormone  A substance that is manufactured and secreted in very small quantities into the bloodstream by an endocrine gland or a specialized nerve cell and regulates the growth or functioning of specific tissue or organ in a distant part of the body, p. 9.

Hydrostatic pressure  The pressure in the circulatory system exerted by the volume of blood when it is confined in a blood vessel. The hydrostatic pressure, coupled with the osmotic pressure within a capillary is opposed by the hydrostatic and osmotic pressure of the surrounding tissues. Fluids flow from the higher pressure areas to the lower pressure areas. This pressure is highest at the arteriolar end of the capillary and lowest at the venular end. Depending upon the organ, the pressure may drop along the length of the capillary (axial pressure gradient) by 15 – 30 mmHg, p. 11.

Hypertonic solution  A solution that contains a high concentration of solute relative to another solution (e.g. the cell’s cytoplasm). When a cell is placed in a hypertonic solution, the water diffuses out of the cell, causing the cell to shrivel.

Hypoxia  Hypoxia, or hypoxiation, is a pathological condition in which the body
as a whole (generalized hypoxia) or a region of the body (tissue hypoxia) is deprived of adequate oxygen supply., p. 88.

I

Isosmotic Having the same concentration of solutes as the blood.

L

Lipids substances such as a fat, oil or wax that dissolves in alcohol but not in water. Lipids contain carbon, hydrogen and oxygen but have far less oxygen proportionally than carbohydrates. Lipids are an important part of living cells. Together with carbohydrates and proteins, lipids are the main constituents of plant and animal cells.

Lumen The inner open space or cavity of a tubular organ, such as a blood vessel or an intestine.

Lymphatics Small thin channels similar to blood vessels that do not carry blood, but collect and carry tissue fluid (called lymph) from the body to ultimately drain back into the blood stream, p. 7.

M

Metabolites The various compounds that take part in all the chemical reactions that occur within living organisms, p. 9.

Microperfusion A technique used in renal physiology which consist of injecting some liquid with a known composition at a chosen point along the nephron, then taking a microsample from another point and comparing the compositions are compare to study how things have changed in that segment of the tube, p. 1.

Micropuncture The micropuncture technique consist of introducing a quartz capillary micropipette in the nephron guided by microscopes and special micromanipulators, to obtain microsamples of the glomerular
filtrate or tubular content to be analysed afterwards by microscope, p. 1.

**Mole**  
The mole is the SI base unit that measures an amount of substance. The mole is a counting unit. One mole contains Avogadro’s number (approximately $6.02214 \cdot 10^{23}$) entities (atoms, molecules, elemental particles).

**N**

**Negative feedback**  
When a change occurs in the body, negative feedback responds in such a way as to reverse the direction of change.

**Nucleotide**  
A subunit of DNA or RNA. To form a DNA or RNA molecule, thousands of nucleotides are joined in a long chain.

**O**

**Oncotic pressure**  
The difference between the osmotic pressure exerted by plasma proteins (colloidal osmotic pressure) in blood plasma and that exerted by tissue fluid proteins is the oncotic pressure. Because large plasma proteins cannot easily cross through the capillary walls, their effect on the osmotic pressure of the capillary interiors will, to some extent, balance out the tendency for fluid to leak out of the capillaries, p. 19.

**Osmolality**  
The osmolal concentration of a solution is called osmolality when the concentration is expressed as osmoles per kilogram of water. Osmolality is $mmol/l$ of dissolved particles, thus it depends on the osmotic coefficient.

**Osmolarity**  
The osmolal concentration of a solution is called osmolarity when is expressed as osmoles per liter of solution.

**Osmoles**  
The total number of particles in a solution is measured in osmoles. A solution containing 1 mole of glucose in each litre has a concentration of 1 osm/l. If a molecule dissociates into two ions (giving two particles)
then a solution containing 1 mol/l will have an osmolar concentration of 2 osm/l.

P

Paracellular route  The route between cells. For example, substances can travel through epithelia by paracellular pathways if the tight junctions between constituent cells are not fully continuous. Paracellular pathways lack any means of active transport, and substances can only move passively by simple diffusion.

Parathyroid hormone  An hormone secreted by the parathyroid gland in response to low levels of calcium in the blood. Increases the reabsorption of calcium and magnesium ions in the nephrons, p. 10.

Peristalsis  The progressive wave of contraction and relaxation of a tubular muscular system., p. 27.

Plasma  Blood plasma is the yellow-colored liquid component of blood, in which blood cells are suspended.

Positive feedback  This means that if a change occurs in some variable, the response is to change that variable even more in the same direction. This has a de-stabilizing effect, so it does not result in homeostasis. Positive feedback is used in certain situations where rapid change is desirable.

T

Tight junction  The region between the plasma membrane of two adjacent cells that are so closely positioned that there is no intercellular space between them. This type of junction fuses cells together and provides a selective barrier to the diffusion of substances between cells, p. 17.

V

Vasa Recta  Name used for blood vessels within the medulla.
**GLOSSARY**

**Vascular Resistance**  Impediment to blood flow in a vessel., p. 21.

**Vasoactive**  Causing constriction or dilation of blood vessels, p. 9.
I herewith declare that I have produced this thesis without the prohibited assistance of third parties and without making use of aids other than those specified; notions taken over directly or indirectly from other sources have been identified as such. This thesis has not previously been presented in identical or similar form to any other Irish or foreign examination board.

María T. González Cerverón

Limerick 2011