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Mathematical model for ionic exchanges in renal tubules: the role of epithelium.

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*"A Decadência é a perda total da inconsciência;
porque a inconsciência é o fundamento da vida.
O coração, se pudesse pensar, pararia."*

My thesis was under the supervision of Professor Bruno Franchi (from Department of Mathematics, University of Bologna, Italy) and Professor Nicolas Vauchelet (LAGA - Laboratoire Analyse, Géométrie et Applications, Université Paris 13, Villetaneuse, France). Vuk Milišić collaborated with us during my research period in Paris and we had helpful discussions about the biological aspects with Aurélie Edwards (Department of Biomedical Engineering, Boston University, Massachusetts, USA).

Mathematical model for ionic exchanges in renal tubules: the role of epithelium.

Abstract

This thesis deals with a mathematical model for a particular component of the kidney, the loop of Henle. We focus our attention on the ionic exchanges that take place in the tubules of the nephron, the functional unit of this organ. The model explicitly takes into account the epithelial layer at the interface between the tubular lumen and the surrounding environment (interstitium) where the tubules are immersed.
The main purpose of this work is to understand the impact of the epithelium (cell membrane) on the mathematical model, how its role influences it and whether it provides more information on the concentration gradient, an essential determinant of the urinary concentrating capacity.
In the first part of this transcript, we describe a simplified model for sodium exchanges in the loop of Henle, and we show the well-posedness of problem proving the existence, uniqueness and positivity of the solution. This model is an hyperbolic system 5×5 with constant speeds, a 'source' term and specific boundary conditions.
We present a rigorous passage to the limit for this system 5×5 to a system of equations 3×3, representing the model without epithelial layers, in order to clarify the link between them.
In the second part, thanks to the analysis of asymptotic behaviour, we show that our dynamic model converges towards the stationary system with an exponential rate for large time. In order to prove rigorously this global asymptotic stability result, we study eigen-elements of an auxiliary linear operator and its dual. We also perform numerical simulations on the stationary system solution to understand the physiological behaviour of ions concentrations.

Keywords: Counter-current, transport equation, characteristics, ionic exchanges, stationary system, eigenproblem, long-time asymptotics.

Mathematical model for ionic exchanges in renal tubules: the role of epithelium.

Résumé

Cette thèse est consacrée à plusieurs études reliant un modèle mathématique pour une composante particulière du rein, l'anse de Henle. L'accent est mis sur les échanges ioniques qui ont lieu dans les tubules du néphron, unité fonctionnelle de cet organe. Le modèle prend explicitement en compte la couche épithéliale à l'interface entre la composante tubulaire et le milieu environnant (interstice) où les tubules se plongent.
Le but principal de cette thèse est de comprendre si l'épithélium (membrane cellulaire) a un impact sur le modèle mathématique, comment son rôle l'influence et s'il offre plus d'informations sur le gradient de concentration, un facteur déterminant pour la capacité de concentration de l'urine.
Dans une première partie du manuscrit, nous décrivons un modèle simplifié pour les échanges de sodium dans l'anse de Henle, et nous montrons que c'est un problème bien posé en montrant l'existence, l'unicité et la positivité de la solution. Il s'agit d'un système hyperbolique 5×5 avec des vitesses constantes, un terme 'source' et des conditions spécifiques au bord. Ensuite nous présentons un passage rigoureuse à la limite pour ce système 5×5 vers un système d'équations 3×3, représentant le modèle sans couche épithéliale, pour clarifier le lien entre les deux modèles.
Dans la deuxième partie, grâce à une analyse du comportement asymptotique, nous montrons que notre modèle dynamique converge vers le système stationnaire avec un taux de convergence exponentiel en temps grand. Afin de démontrer rigoureusement ce résultat global de stabilité asymptotique, nous étudions les éléments propres d'un système auxiliaire avec un opérateur linéaire et son duale associé. Nous présentons également des simulations numériques sur la solution liée au système stationnaire pour comprendre le comportement des concentrations d'ions même au niveau physiologique.

Mots-clés : Contre-courant, équation de transport, caractéristiques, échanges ioniques, système stationnaire, problème éléments spectraux, comportement asymptotique.

Mathematical model for ionic exchanges in renal tubules: the role of epithelium.

Sommario

Questa tesi riguarda lo studio di un modello matematico per una particolare componente del rene, l'ansa di Henle. L'attenzione è rivolta agli scambi ionici che avvengono nei tubuli del nefrone, unità funzionale di questo organo. Il modello prende in considerazione esplicitamente lo strato epiteliale nell'interfaccia tra il lume tubolare e l'ambiente circostante (interstizio) dove sono immersi i tubuli.
Lo scopo principale di questo studio è capire se l'epitelio (membrana cellulare) ha un impatto sul modello matematico, come il ruolo di questo lo influenza e se fornisce maggiori informazioni sul gradiente di concentrazione, un fattore determinante della capacità di concentrazione urinaria.
Nella prima parte di questa tesi descriviamo un modello semplificato per gli scambi di sodio nell'ansa di Henle e dimostriamo che è un problema ben posto, mostrando l'esistenza, l'unicità e la positività della soluzione. Questo è un sistema 5×5 di tipo iperbolico con velocità costanti, un termine 'sorgente' e delle specifiche condizioni al bordo. Successivamente presentiamo un passaggio al limite rigoroso per questo sistema 5×5 verso un sistema di equazioni di 3×3, rappresentante il modello senza strato epiteliale, per chiarire il legame tra i due modelli.
Nella seconda parte, grazie ad un'analisi sul comportamento asintotico, dimostriamo che per tempi grandi il nostro modello dinamico converge verso il sistema stazionario con un rate esponenziale. Al fine di provare rigorosamente questo risultato globale di stabilità asintotica, studiamo gli auto elementi di un sistema ausiliario con un operatore lineare e il suo duale associato. Presentiamo inoltre delle simulazioni numeriche sulla soluzione relativa al sistema stazionario per comprendere il comportamento delle concentrazioni ioniche anche a livello fisiologico.

Parole chiave : Controcorrente, equazione di trasporto, scambio ionico, sistema stazionario, problema auto funzioni, comportamento asintotico.

Contents

Chapter 1

Introduction

My thesis deals with the study of a mathematical model for a particular component of the kidney. We will focus attention on the ionic exchanges within the nephron tubules, the functional unit of this organ. In recent years many mathematical models have been used to solve and reconsider questions posed by medicine and biology. This model would give a contribution in the field of physiological renal transport model. It could be a good starting point to explain and to understand some mechanisms underlying certain renal pathologies or diseases, caused by the abnormal transport of ions in the kidney and to elucidate some mechanisms underlying concentrating mechanism. The goal of this Chapter is not to provide an exhaustive presentation of the whole architecture of the kidney, but it is to introduce relevant parts and implicated quantities, emphasizing the important features for mathematical modelling. It will be briefly described the structure of kidney and its principal functions to have a biological background and to give a presentation of elements implied in our mathematical model. In this way, a biological motivation also for the choice of the parameters inside the model is justified.

1.1 Kidney and nephron: biological background

One of the main functions of the kidneys is to filter metabolic wastes and toxins from blood plasma and excrete them in urine. The kidneys also play a key role in regulating the balance of water and electrolytes, long-term blood pressure, as well as acid-base equilibrium. In fact, the cells of the human body in order to survive have to live in an environment with constant physiological electro-chemical conditions. It means that some quantities such as temperature, glycemia (blood sugar), concentration of certain ions have to respect and stay in some interval values. They should not undergo significant changes beyond their optimal value over time. The external alteration, in particular due to the food contribution, can cause perturbations of this equilibrium in addition to others factors such as the hour of day, the season, some pathologies or renal stress. Sometimes this organ could not always guarantee these functions, leading to some malfunctions and certain diseases. For example, the poor ion transport inside the kidney could bring about nephrocalcinosis. In renal pathology, this disease is mainly due to the presence of calcium deposits in the renal parenchyma, as result of an abnormal increase in blood calcium

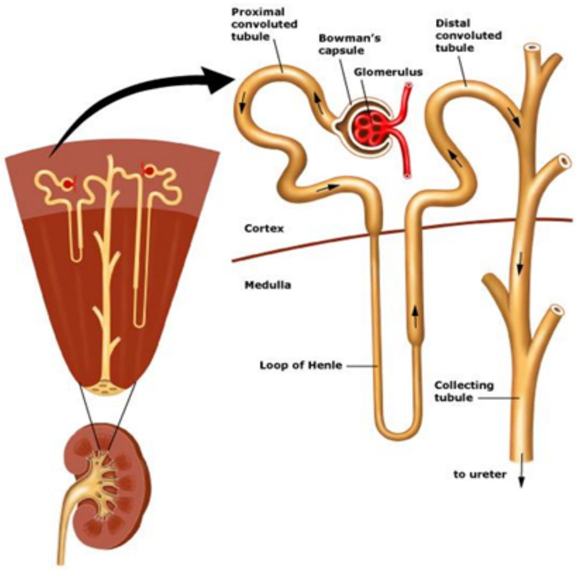


Figure 1.1: Kidney and nephron schematic diagram

concentration (hypercalciuria), which often evolves to "kidney failure", [1]. This is just a little example but clearly and unfortunately, there are many renal diseases related to dysfunction of ion channels, [19].

On average the kidneys filter about 180 litres of blood a day. Most of them are rejected in the body, and the remaining part (about 1,5 litres) is excreted in the urine. The kidneys ensure and partly provide the physiological balance and the blood homostasis. An external or outer region and an inner region (in depth), respectively the cortex and the medulla, make up the kidney structure. The cortex contains glomeruli, which are like a capillaries tuft, and convoluted segments of tubules, whereas the medulla contains tubules and vessels arranged roughly in parallel, [20]. Approximately the 20% of cardiac blood output is sent to the kidneys to be filtered. Then, for example, if the blood that arrives is too concentrated in sodium, the kidney will produce a more concentrated filtrate in sodium than the incoming blood and after it will reject into the general blood circulation a filtrate less concentrated in sodium. This process has been called urinary concentration mechanism.

The structural and functional units of the kidney are called nephrons, which number about 1 million in each human kidney, [3]. Blood is first filtered by glomerular capillaries and then the composition of the filtrate varies as it flows along the different segments of the nephron : the proximal tubule, the loop of Henle which is formed by a descending limb and an ascending limb, the distal tubule, and the collecting duct. The reabsorption of water and solutes from the tubules into the surrounding interstitium (or secretion in the opposite direction) allows the kidneys to combine urinary excretion to dietary intake, [36]. The main function of the renal tubules is also to recover most of the glomerular filtrate. 'Otherwise, we would lose all our blood plasma in less than half an hour!', citing [20]. The loop of Henle and its architecture play

an important role in the concentrated or diluted urine formation.
Despite the development of sophisticated models about water and electrolyte transport in the kidney, some aspects of the fundamental functions of this organ remain yet to be fully unexplained, [20]. For example, how a concentrated urine can be produced by the mammalian kidney when the animal is deprived of water remains not entirely clear. The previous work of M. Tournus ([46], Chapter 2) confirms the importance of counter-current arrangement of tubules and it illustrates how this architecture enhances the axial concentration gradient, favouring the production of highly concentrated urine.
In order to explain how an animal or an human being can produce a concentrated urine and from what this mechanism depends on, it needs to spend few words on counter-current transport in the 'ascending' and 'descending' tubules, in which the exchanges between the cell membrane and the environment where tubules are immersed, take place.

1.1.1 Countercurrent Multiplication mechanism

Starting from the work presented in [46], the main purpose of this thesis is to understand how the role of the epithelium (cell membrane) of renal tubules influences the mathematical modelling and whether it provides more information on the concentration gradient formation. We want to track the ionic or molecular concentrations in the tubules and in the interstitium (this term indicates all the space/environment that surrounds the tubules and blood vessels). Sometimes we will indicate as **lumen** the considered limb and as **tubule** the segment with its epithelial layer. In physiological common language, the term 'tubule' refers to the cavity of lumen together with its related epithelial layer (membrane) as part of it.

The first models about nephron and kidney were developed in the 1950s with the purpose of explaining the concentration gradient, [12] (or see also [20] in Chap.3). The original reference of [12] is in German, but a translation of their fundamental article appeared recently. In their attempt, the authors describe for the first time the urinary concentration mechanism as a consequence of countercurrent transport in the tubules. This mechanism occurs in the loop of Henle which consists of two parallel limbs running in opposite directions, as already mentioned in the descending and ascending limb, separated by the interstitial space of the renal medulla.

As explained in [22], an osmolality gradient could be generated along parallel but with opposite flows in tubules that are connected by a hair-pin turn. We briefly explain below what means the countercurrent multiplication mechanism in the nephron, [43]. The movement of a solute from one tubule to another (called a *single* effect) amplifies (*multiplies* or reinforces) the axial osmolality gradient in the parallel flow. In fact, thanks to this arrangement, a small single effect will be multiplied into a much larger osmolality difference along the axis of tubular flow, [44]. In the Hargitay and Kuhn's model presented in [12], the driving force for the single effect was the hydrostatic pressure applied to the central ionic channel which produces an osmotic pressure. However, the authors recognized that the pressures were not high enough to drive such a process in the kidney. The idea concerning the "hairpin" counterflow system in the loop of Henle provides an arrangement whereby a small "single effect" could be repeatedly "multiplied" to produce a large gradient along the axis parallel to the direction of flow. Despite that and considering the general architecture of the kidney, the point of view gets started to change around the end of 1980s, [24]. In this study, a simple mathematical model for a single nephron

developed by C.S. Peskin (unpublished manuscript) has been introduced and described. The author explains how the tubules distribution and partition may enhance urine concentrating capability, playing a significant role also in establishing the concentration gradient. Moreover, it concludes that just the passive concentrating mechanism can not improve the concentrating capability of a single-nephron model. Furthermore, in the work of J.L. Stephenson [44] it turns out that the formation of a large axial concentration gradient in the kidney depends mainly on the different permeabilities in the tubules and on their counterflow arrangement.
In our study it will be described a mathematical model that represents a loop with a descending limb and an ascending limb and it takes into account passive and active transport mechanisms. It is possible to find an historical excursus and how these types of models have been developed, referring to [44]. In order to have a more specific and meticulous introduction to mathematical models in renal physiology we refers to [20]. In the next paragraph it will be given more details about different type of membrane transport.

1.1.2 Biological membrane transport

The membrane transport is the property that allows the movement of molecules or ions between two compartments through a plasma membrane. We briefly describe the various forms of membrane transport as well as their mechanisms, helpful later in the setting-up of our mathematical model.
Concerning the passive transport, there are different types of movement through cell membrane such as *diffusion, osmosis, electro-diffusion* or also known as *facilitated diffusion*. They are the simplest ways of transport across membrane and in these cases there is not energy consumption by the cells. On the other hand, the active transport uses energy to pump or transport substances across a membrane. The movement of ions in the kidney is a phenomenon of tubular reabsorption and it can be observed in nephrons, [16], [41].

Passive transport

An example of passive transport is the osmosis, the diffusion of water through a semi-permeable membrane. It is defined as the number of moles of particles in solution that contains 1 litre of solution. The water transport is driven by the difference of osmotic pressure of one side to another.

$$Osm = \sum_{i=solutes} \Phi_i u_i$$

where u_i is the molar concentration of the solute, Φ_i is the osmotic coefficient of the solute i which measure the amount of particles that a solute will give to the solution. Φ_i is a constant between 0 and 1, where 1 indicates maximum dissociation. In fact, it can be considered as the degree of dissociation of the solute. For example, the urea does not dissociate in water then it has osmotic coefficient equal to 1.
Concerning our mathematical model, we want to focus our attention just to the transepithelial diffusion process, when the membrane is permeable to a solute. We refer to **diffusion** as the biological process in which a substance tends to move from an area of high concentration to an area of low concentration, [41]. As described also in [46], the diffusive solute flux from

compartment 1 to compartment 2 (expressed in $[mol.m^{-1}.s^{-1}]$) is given by:

$$J_{\text{diffusion}} = P\ell(u_2 - u_1),$$

where P $[m.s^{-1}]$ is the permeability of the membrane to the considered solute, ℓ the perimeter of the membrane, and u_1 and u_2 are the respective concentrations of the solute in compartments 1 and 2, divided by membrane.

Active transport

The Na^+/K^+ pump is an important ion pump existing in the membrane of many types of cells, for instance in the nerve cells to assure the electrical gradient and potential across their cell membranes. The active solute transport could be described by Michaelis-Menten kinetics which relates the speed of a chemical reaction to the concentration of considered substance, [31]:

$$J_{pompe} = V_m\Big(\frac{u}{K_m + u}\Big),$$

with V_m maximum active transport rate and the concentration of the substrate at which the rate of transport is at half the maximum rate K_m, or also known as Michaelis constant. The active transport flow generated by this pump allows a displacement of molecules against the concentration gradient that require energy consumption (hence the *active* name) [20], [41].

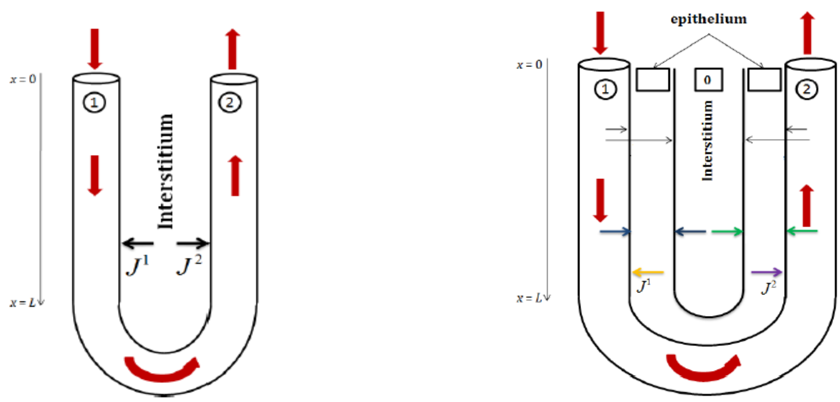
1.2 Mathematical modelling

The main topic of this thesis is the modelling of water and solutes exchange in the kidney. For the development of a multi-scale physiological model of renal tubules transport, this basic model represents an essential step to understand the mechanisms underlying certain pathologies. In a simplified approach and in order to introduce our mathematical model, we start from the systems described in the Ph.D. thesis of Magali Tournus [46], where a macroscopic model integrating molecular and cellular transport processes was developed. In one of her works, it has been considered an architecture of the kidney consisting of five tubules (three of them represent the nephron while others represent the vas-recta). All of the tubules are immersed in a common interstitium and water and solute are exchanged through it. We consider a simplified system for the nephron, functional unit of the kidney. In this simplified version, the nephron is modelled by two tubules with the same radius (loop of Henle, countercurrent arrangement). We model the dynamics of a solute (here, sodium) by the dynamics of its concentration in each tubule. The lumen of the tubules is separated from the external medium (the interstitium) by a layer of epithelial cells.

In general, for these types of model it is possible to consider different architectures, for example, taking into account epithelium or not. For the last option, the ion exchange is modelled by 3 equations (system of PDEs) with constant velocity transport, for example as done in [47]. With regard to the architecture with the epithelium, the number of equations to describe this phenomenon depends also on the number of ions to be considered. For the base model 5 equations has needed, 7 for the non-constant speed model and 10 for the two-ion model, Na^+

(sodium) and K^+ (potassium). We present and study a 5×5 semi-linear hyperbolic system, accounting for the presence of epithelium layers, but composed only of two tubules and it will be the main object of the following results.
The first spontaneous question that it has been posed concerns the link and the relation in terms of mathematical properties between the basic model with epithelium (Figure (1.2b)) and without it (Figure (1.2a)). Supposing these two new epithelial layers, we add two additional unknown concentrations in the basic system. Therefore, we try to deduce the impact of this epithelial layer, i.e. of the cell membrane, on the system. In Figure (1.2) we give a representation of what was mentioned above.

Simplified system and epithelium system



(a) Basic scheme for reduced or simplified system.

(b) Basic scheme for system with epithelial layer.

Figure 1.2: Different schematic representations of the loop of Henle.

The model is one-dimensional, with respect to space $x \in [0, L]$. The main parameters and variables are being described :

- r_i : denote the radius for the tubule i ($[m]$),
- $r_{i,e}$: denote the radius for the tubule i with accounted epithelial layer,
- $P_i^j(x)$: permeability to solute j between the lumen i and the epithelium ($[m.s^{-1}]$),
- $P_{i,e}^j(x)$: permeability between the epithelium of lumen i and the interstitium,
- α_i : volumetric flow rate (flow of water) $[m^3.s^{-1}]$,
- $J_i^j(t, x)$: flow of solute j entering in the tubule i, $[mol/m.s]$.

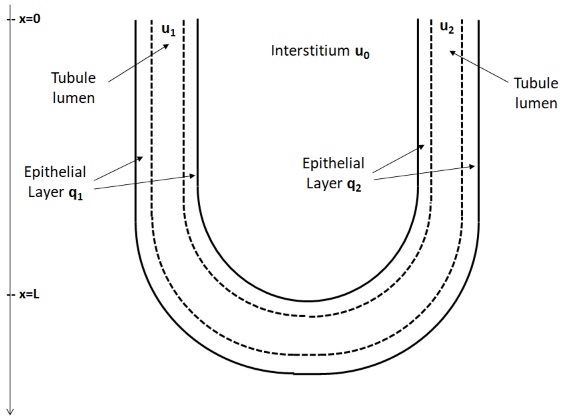


Figure 1.3: Simplified model of loop of Henle.

The unknowns represent ionic concentrations, i.e. $u_i^j(t,x)$ solute j in the tubule or compartment i ($[mol/m^3]$), $q_i^j(t,x)$ solute j in the epithelium 'near' tubule i and $u_0(t,x)$ in the interstitium. In the first two Chapters we only consider one generic uncharged solute in two tubules, for this reason afterwards we will neglect the superscript j.
Now we present a simplified mathematical model of solute transport in the loop of Henle. Previous mathematical models developed and discussed in [46] and in [48] were based on a simple renal architecture that did not consider explicitly the epithelial layer separating the tubule lumen from the surrounding interstitium, and that represented the barrier as a single membrane. The present model accounts for ion transport between the lumen and the epithelial cells, and between the cells and the interstitium. The principal aim of this work is to examine the impact of explicitly considering the epithelium on solute concentration in the loop of Henle. In our simplified approach, the loop of Henle is represented as two tubules in a counter-current arrangement, and the descending and ascending limb are considered to be rigid cylinders of length L lined by a layer of epithelial cells. Water and solute re-absorption from the luminal fluid into the interstitium proceeds in two steps: water and solutes cross first the apical membrane (which refers to the cell membrane oriented *towards* the lumen) at the lumen-cytosol interface and then the basolateral membrane (which is oriented *away* from the lumen of the tubule) at the cytosol-interstitium interface. A schematic representation of the model is given in Figure 1.3.

The energy that drives tubular transport is provided by a Na^+/K^+-ATPase, an enzyme that couples the hydrolysis of ATP to the pumping of sodium (Na^+) ions out of the cell and potassium (K^+) ions into the cell, across the basolateral membrane. The electrochemical potential gradients resulting from this active transport mechanism in turn drive the passive transport of ions across other transporters, via diffusion or coupled transport. We assume that the volumetric flow rate in the luminal fluid (denoted by α) remains constant, i.e. there is no transepithelial water transport. Actually the descending limb is permeable to water, but we will make this simplifying assumption in order to facilitate the mathematical analysis in our hyperbolic system. Given the counter-current tubular architecture, this flow rate will have a negative value in the ascending limb. As noted in [20], since the thick ascending limb is water impermeable, it is coherent to assume α constant but, for example, it may vary in time in other models.

The following model focuses on tubular Na^+ transport. The concentration of Na^+ ($[mol.m^{-3}]$) is denoted by u_1 and u_2, respectively, in the descending and ascending limb lumen, by q_1 and q_2 in the epithelial cells of the descending and ascending limbs, respectively, and by u_0 in the interstitium. The permeability to Na^+ of the membrane separating the lumen and the epithelial cell of the descending and ascending limb is denoted by P_1 and P_2, respectively. $P_{1,e}$ denotes the permeability to Na^+ of the membrane separating the epithelial cell of the descending limb and the interstitium; the Na^+ permeability at the interface between the epithelial cell of the ascending limb and the interstitium is taken to be negligible.

The concentrations depend on the time t and the spatial position $x \in [0, L]$. The dynamics of Na^+ concentration is given by the following model on $(0, +\infty) \times (0, L)$

$$a_1 \frac{\partial u_1}{\partial t} + \alpha \frac{\partial u_1}{\partial x} = J_1, \quad a_2 \frac{\partial u_2}{\partial t} - \alpha \frac{\partial u_2}{\partial x} = J_2, \tag{1.1}$$

$$a_3 \frac{\partial q_1}{\partial t} = J_3, \quad a_4 \frac{\partial q_2}{\partial t} = J_4, \quad a_0 \frac{\partial u_0}{\partial t} = J_0. \tag{1.2}$$

The parameters a_i, for $i = 0, 1, 2, 3, 4$, denote positive constants defined as:

$$a_1 = \pi(r_1)^2,\ a_2 = \pi(r_2)^2,\ a_3 = \pi(r_{1,e}^2 - r_1^2),\ a_4 = \pi(r_{2,e}^2 - r_2^2),\ a_0 = \pi\Big(\frac{r_{1,e}^2 + r_{2,e}^2}{2}\Big).$$

In these equations, r_i, with $i = 1, 2$, denotes the inner radius of tubule i, whereas $r_{i,e}$ denotes the outer radius of tubule i, which includes the epithelial layer. The fluxes J_i describe the ionic exchanges between the different domains. They are modeled in the following way:

Lumen. In the lumen, we consider the diffusion of Na^+ towards the epithelium. Then, as mentioned before we are taking into account the difference between concentration in epithelial layer and in lumen, multiplied by the perimeter of the membrane and respectively permeabilities,

$$J_1 = 2\pi r_1 P_1(q_1 - u_1), \quad J_2 = 2\pi r_2 P_2(q_2 - u_2).$$

Epithelium. We take into account the diffusion of Na^+ from the descending limb epithelium towards both the lumen and the interstitium,

$$J_3 = 2\pi r_1 P_1(u_1 - q_1) + 2\pi r_{1,e} P_{1,e}(u_0 - q_1).$$

In the ascending limb (tubule 2), we also consider the active reabsorption that is mediated by Na^+/K^+-ATPase, which pumps 3 Na^+ ions out of the cell in exchange for 2 K^+ ions.

The net flux into the ascending tubule is given by the sum of the diffusive flux from the lumen and the export across the pump, which is described using Michaelis-Menten kinetics:

$$J_4 = 2\pi r_2 P_2(u_2 - q_2) + 2\pi r_{2,e} P_{2,e}(u_0 - q_2) - 2\pi r_{2,e} G(q_2),$$

where

$$G(q_2) = V_m \left[\frac{q_2}{K_{M,2} + q_2} \right]^3. \tag{1.3}$$

The exponent of G is related to the number of exchanged sodium ions. The affinity of the pump $K_{M,2}$, and its maximum velocity V_m, are given positive numbers. We notice that when $q_2 \to +\infty$, then $G(q_2) \to V_m$ which is in accordance with the biological observation that the pump can be saturated since the number of carriers is limited. As explained in [20], the Michaelis-Menten kinetics is one of the simplest and best-known models of enzyme kinetics. V_m represents the maximum transport rate achieved by the system at solute concentration q_2, and the Michaelis constant $K_{M,2}$ is the solute concentration at which the reaction rate is half of V_m. The transport rate increases as q_2 increases, but it levels off and approaches V_m as q_2 approaches infinity.

Interstitium.

$$J_0 = 2\pi r_{1,e} P_{1,e}(q_1 - u_0) + 2\pi r_{2,e} P_{2,e}(q_2 - u_0) + 2\pi r_{2,e} G(q_2).$$

Afterwards the constant $2\pi r_{2,e}$ will be included in the parameter V_m and replace the parameter V_m with $V_{m,2} := 2\pi r_{2,e} V_m$.
We model the dynamics of a solute by the evolution of its concentration in each tubule. Then the transport of solute and its exchange are modelled by a hyperbolic PDE system at constant speed with a non-linear transport term and with specific boundary conditions which make the model interesting. To sum up, the dynamics of the ionic concentrations is given by the following model :

$$\begin{cases} a_1 \partial_t u_1(t,x) + \alpha \partial_x u_1(t,x) = J_1(t,x) \\ a_2 \partial_t u_2(t,x) - \alpha \partial_x u_2(t,x) = J_2(t,x) \\ a_3 \partial_t q_1(t,x) = J_3(t,x) \\ a_4 \partial_t q_2(t,x) = J_4(t,x) \\ a_0 \partial_t u_0(t,x) = J_0(t,x) \\ \\ u_1(t,0) = u_b(t); \quad u_1(t,L) = u_2(t,L) \quad t > 0 \\ u_1(0,x) = u_1^0(x); \quad u_2(0,x) = u_2^0(x); \quad u_0(0,x) = u_0^0(x); \\ q_1(0,x) = q_1^0(x); \quad q_2(0,x) = q_2^0(x). \end{cases} \tag{1.4}$$

The simplified model without epithelium is similar but there are not two epithelial layers and then the two additional unknown concentrations q_1, q_2 :

$$\begin{cases} a_1 \partial_t u_1(t,x) + \alpha \partial_x u_1(t,x) = 2\pi r_1 P_1 (u_0 - u_1) \\ a_2 \partial_t u_2(t,x) - \alpha \partial_x u_2(t,x) = 2\pi r_2 P_2 (u_0 - u_2) - G(u_2) \\ a_0 \partial_t u_0(t,x) = 2\pi r_1 P_1 (u_1 - u_0) + 2\pi r_2 P_2 (u_2 - u_0) + G(u_2). \end{cases} \tag{1.5}$$

After introducing these models, one of the objectives is to understand if there is a link between the two models and to answer the question: what is it the role of the epithelial layer?

The first goal of this work is to study the effects of epithelium region in the mathematical model. We notice with a formal computation that if the value of permeability grows, the model "behaves" in the same way as the system without epithelium.
We neglect for a moment the constants a_i, with $i = 0, 1, 2, 3, 4$, and we consider the case where the permeability between the lumen and the epithelium is large. We simplify the notation $2\pi r_{i,e} P_{i,e} = K_i$ with $i = 1, 2$ and $2\pi r_1 P_1 = k_1 = 2\pi r_2 P_2 = k_2$ and we set $k = k_1 = k_2 \to \infty$, i.e. when $P_i \to \infty$, with $i = 1, 2$. For this purpose we set $k = k_1 = k_2 = \frac{1}{\varepsilon}$ and we let ε go to 0. We introduce formally this limit using the parameter ε :

$$\partial_t u_1^\varepsilon + \alpha \partial_x u_1^\varepsilon = k(q_1^\varepsilon - u_1^\varepsilon) \tag{1.6a}$$

$$\partial_t u_2^\varepsilon - \alpha \partial_x u_2^\varepsilon = k(q_2^\varepsilon - u_2^\varepsilon) \tag{1.6b}$$

$$\partial_t q_1^\varepsilon = k(u_1^\varepsilon - q_1^\varepsilon) + K_1(u_0^\varepsilon - q_1^\varepsilon) \tag{1.6c}$$

$$\partial_t q_2^\varepsilon = k(u_2^\varepsilon - q_2^\varepsilon) + K_2(u_0^\varepsilon - q_2^\varepsilon) - G(q_2^\varepsilon) \tag{1.6d}$$

$$\partial_t u_0^\varepsilon = K_1(q_1^\varepsilon - u_0^\varepsilon) + K_2(q_2^\varepsilon - u_0^\varepsilon) + G(q_2^\varepsilon). \tag{1.6e}$$

Formally when $P_i \longrightarrow \infty$, we expect the concentrations u_1^ε and q_1^ε to converge to the same concentration. Physically, this means fusing the epithelial layer with the lumen. The same happens for $u_2^\varepsilon \to u_2$ and $q_2^\varepsilon \to u_2$. We denote u_1, respectively u_2, the limit of $(u_1^\varepsilon)_\varepsilon$ and $(q_1^\varepsilon)_\varepsilon$, respectively $(u_2^\varepsilon)_\varepsilon$ and $(q_2^\varepsilon)_\varepsilon$. Adding equations (1.6a) and (1.6c) of system and adding equations (1.6b) and (1.6d), we obtain the system

$$\begin{aligned}
\partial_t u_1^\varepsilon + \partial_t q_1^\varepsilon + \alpha \partial_x u_1^\varepsilon &= K_1(u_0^\varepsilon - q_1^\varepsilon) \\
\partial_t u_2^\varepsilon + \partial_t q_2^\varepsilon - \alpha \partial_x u_2^\varepsilon &= K_2(u_0^\varepsilon - q_2^\varepsilon) - G(q_2^\varepsilon).
\end{aligned}$$

Passing formally to the limit $P_i \to \infty$, we arrive at

$$2\partial_t u_1 + \alpha \partial_x u_1 = K_1(u_0 - u_1) \tag{1.7}$$

$$2\partial_t u_2 - \alpha \partial_x u_2 = K_2(u_0 - u_2) - G(u_2), \tag{1.8}$$

coupled to the equation for the concentration in the interstitium obtained by passing into the limit in equation (1.6e)

$$\partial_t u_0 = K_1(u_1 - u_0) + K_2(u_0 - u_2) + G(u_2). \tag{1.9}$$

In the first part of this thesis we are going to study the semi-linear first order system depending on the parameter $\varepsilon > 0$. In order to connect the problem (1.6) with the reduced or limit system, we will have to make some assumptions about the non linear term $G(q_2)$ and boundary conditions.
What does it mean that the model "behaves" in the same way as the system without epithelium? First of all, we need to define in some sense a solution of system (1.6).
In the framework of non linear hyperbolic systems and of conservation laws, a weak solution, in the sense of distributions, does not guarantee the uniqueness of the solution and therefore also the well-posedness of problem, [42]. In our case, the hyperbolic system is semi-linear with a

linear operator and a source term, then it is not necessary to introduce an entropic formulation and the concept of entropy solutions, [18]. In Chapter 2 it has been showed that the weak solution of model without epithelium can be rigorously derived by assuming that permeabilities between the lumen region and the epithelium are large ($P_1, P_2 \to \infty$) in the epithelium model. The equations (1.7), (1.8), (1.9) describe the same concentrations dynamics in the system without epithelium which is similar to that previously studied in [46] and [47]. Then, this 3×3 system (1.5) may be considered as a good approximation of the larger system.
In this setting our problem and the used techniques could be inserted in some way in the context of relaxation problem. The semi-linear relaxation where the principal part of considered operator is linear and with constant coefficients, was introduced by Jin and Xin [15], with the propose of building robust numerical schemes. The authors construct a linear hyperbolic system to approximate the original non linear system with a small dissipative correction. They take into account a Cauchy problem 1-D of the form: $\frac{\partial}{\partial t} u + \frac{\partial}{\partial x} f(u) = 0, \quad (t, x) \in \mathbb{R}^+ \times \mathbb{R}$ with initial data $u(0, x) = u^0(x)$ and then a linear system (relaxation system) as :

$$\partial_t u + \partial_x v = 0;$$
$$\partial_t v + a\partial_x u = -\frac{1}{\varepsilon}(v - f(u))$$

with a positive constant and choosing initial data as $u(0, x) = u^0(x), \quad v(0, x) = v^0(x) = f(u^0(x))$. This particular choice of initial condition avoids to introduce an initial layer through the relaxation system. The initial condition is said to be 'well-prepared', i.e. the state is already in the equilibrium state at the beginning. The same approach could be used to prevent a boundary layer in case of boundary-value problems even if sometimes this choice is not consistent with the physical aspects of model. Some examples of boundary value problems for systems with relaxation are discussed in [33], [35]. In [49] is given an important contribution to the study of relaxation approximations for boundary value problems but in the general entropy formulation. A general overview for mathematical results on hyperbolic relaxation problems can be found in [32].

In the second part of this transcript we focus on the analysis of solutions to stationary problem related to (1.6). We show that the dynamic system converges as time goes to infinity to the steady state solution. Thanks to spectral theory arguments, we can also prove convergence with an exponential rate.
Here, we give just a workflow idea used to prove the above-mentioned result, following the same approach in [37] and [39]. We will introduce a 'toy equation' with u solution of dynamic 'model' and $\bar{u}$ solution of stationary:

$$\begin{cases} \partial_t u(t, x) + \alpha\partial_x u(t, x) = q(t, x) - u(t, x) \\ \qquad +\alpha\partial_x \bar{u}(x) = \bar{q}(x) - \bar{u}(x). \end{cases} \tag{1.10}$$

In order to have a exponential rate convergence we are going to look for

$$|u(t, x) - \bar{u}(x)| \sim e^{-\lambda t} N(x), \qquad |q(t, x) - \bar{q}(x)| \sim e^{-\lambda t} Q(x), \quad \lambda \in \mathbb{R}^+.$$

It will allow us to say that $|u(t,x) - \bar{u}(x)| \to 0$ when $t \to \infty$ in some norm and space defined at later stage.

Then, if we subtract the first line with the second of (1.10), we formally can compute and obtain:

$$\partial_t(e^{-\lambda t}N(x)) + \alpha\partial_x(e^{-\lambda t}N(x)) = e^{-\lambda t}Q(x) - e^{-\lambda t}N(x)$$
$$-\lambda e^{-\lambda t}N(x) + \alpha e^{-\lambda t}\partial_x N(x) = e^{-\lambda t}Q(x) - e^{-\lambda t}N(x)$$
$$\alpha\partial_x N(x) = \lambda N(x) + Q(x) - N(x)$$
$$\alpha\partial_x N(x) - (Q(x) - N(x)) = \lambda N(x).$$

Setting $\mathcal{L}N(x) = \alpha\partial_x N(x) - (Q(x) - N(x))$ this means that we are going to search the eigenfunctions and eigenvalues of linear operator $\mathcal{L}$, i.e. $\mathcal{L}N = \lambda N$.
We use a similar approach for 5×5 system (3.4) in Chapter 3 introducing an auxiliary linear operator related to our system with its boundary and initial conditions. Let us introduce the eigen-problem of an auxiliary stationary linear system and its dual,

$$\begin{bmatrix} \partial_x U_1(x) \\ -\partial_x U_2(x) \\ 0 \\ 0 \\ 0 \end{bmatrix} = \lambda\mathcal{U}(x) + A\mathcal{U}(x); \qquad \mathcal{U}(x) = \begin{bmatrix} U_1 \\ U_2 \\ Q_1 \\ Q_2 \\ U_0 \end{bmatrix} \tag{1.11}$$

$$\begin{bmatrix} -\partial_x \varphi_1(x) \\ \partial_x \varphi_2(x) \\ 0 \\ 0 \\ 0 \end{bmatrix} = \lambda\Phi(x) + {}^tA\Phi(x); \qquad \Phi(x) = \begin{bmatrix} \varphi_1 \\ \varphi_2 \\ \phi_1 \\ \phi_2 \\ \varphi_0 \end{bmatrix} \tag{1.12}$$

with related matrix defined by

$$A = \begin{bmatrix} -k & 0 & k & 0 & 0 \\ 0 & -k & 0 & k & 0 \\ k & 0 & -k-K_1 & 0 & K_1 \\ 0 & k & 0 & -k-g & 0 \\ 0 & 0 & K_1 & g & -K_1 \end{bmatrix}.$$

The constants k, K_1 have already been defined and the constant $g > 0$ will be chosen later. For a given λ, the function $\mathcal{U}$ is the right eigenvector solving (1.11) and Φ is the left one, associated with the dual operator and solving (1.12). Roughly speaking, the system (1.11) is in some sort, a linearised version of the starting stationary system where the derivative of the non-linearity is replaced by a positive constant g. Moreover, the systems are complemented with boundary and a normalization conditions as will be clarified in (B.2.2). The normalization condition $\int_0^L (U_1 + U_2 + Q_1 + Q_2 + U_0)\ dx = 1$, will ensure the uniqueness of the solution $\mathcal{U}$. Then, one of the main tool to study the asymptotic behaviour of our dynamic system concentrations $\mathbf{u} = (u_1, u_2, q_1, q_2, u_0)$ when $t \to \infty$ is the existence of these eigenelements $(\lambda, \mathcal{U}, \Phi)$ solutions of above-defined auxiliary system. We report the most significant result of Chapter 3 :

Theorem 1.2.1 (Long time behaviour)**.** *The solution to the dynamical problem denoted by* $\mathbf{u}(t,x) = (u_1, u_2, q_1, q_2, u_0)$ *converges as time* t *goes to* $+\infty$ *towards* $\bar{\mathbf{u}}(x) = (\bar{u}_1, \bar{u}_2, \bar{q}_1, \bar{q}_2, \bar{u}_0)$*, the unique solution to the related stationary problem, in the following sense*

$$\lim_{t\to+\infty} \|\mathbf{u}(t) - \bar{\mathbf{u}}\|_{L^1(\Phi)} = 0,$$

with the space

$$L^1(\Phi) = \Big\{\mathbf{u} : [0,L] \to \mathbb{R}^5; \quad \|\mathbf{u}\|_{L^1(\Phi)} := \int_0^L |\mathbf{u}(x)| \cdot \Phi(x)\ dx < \infty\Big\},$$

where $\Phi = (\varphi_1, \varphi_2, \phi_1, \phi_2, \varphi_0)$ *is defined in Proposition 1.2.1 below.*

Moreover, if we assume that there exist $\mu_0 > 0$ *and* C_0 *such that* $|u_b(t) - \bar{u}_b| \le C_0 e^{-\mu_0 t}$ *for all* $t > 0$*, then there exist* $\mu > 0$ *and* $C > 0$ *such that we have the convergence with an exponential rate*

$$\|\mathbf{u}(t) - \bar{\mathbf{u}}\|_{L^1(\Phi)} \le Ce^{-\mu t}. \tag{1.13}$$

The scalar product used in this latter claim means :

$$\int_0^L |\mathbf{u}(x)| \cdot \Phi(x)\ dx =$$
$$\int_0^L \big(|u_1|\varphi_1(x) + |u_2|\varphi_2(x) + |q_1|\phi_1(x) + |q_2|\phi_2(x) + |u_0|\varphi_0(x)\big)\ dx.$$

Proposition 1.2.1. *Let* $g > 0$ *be a constant. There exists a unique* $(\lambda, \mathcal{U}, \Phi)$*, with* $\lambda \in (0, \lambda_-)$*, solution to the eigenproblem* (1.11)–(1.12) *where*

$$\lambda_- = \frac{(2K_1 + k) - \sqrt{4K_1^2 + k^2}}{2}.$$

Moreover, we have $\mathcal{U}(x) > 0$*,* $\Phi(x) > 0$ *on* $(0, L)$ *and* $\phi_2 < \varphi_0$*.*

The definition of the left eigenvector Φ and its role will be better clarified later.

1.3 Thesis structure

We will present a general overview of the main objectives that have been pursued in this thesis and the main results obtained in each chapter.
The transcript is divided into three chapters and two appendices.
In the first Chapter the mathematical model has been introduced, explaining briefly the biological processes that the system describes.
The Chapter 2 deals entirely with the rigorous passage to the limit in semi-linear hyperbolic 5×5 system, accounting for the presence of epithelium layers, towards a system of 3 equations, related to sodium exchanges in a kidney nephron. In this simplified version, the nephron is modelled by a counter-current architecture of two tubules and the ionic exchanges occur in the interface between the tubules and the epithelium and in the interface between the epithelium

and the interstitium. In order to clarify the link between both models, we show that model without epithelium can be rigorously derived by assuming that the permeabilities between the lumen region and the epithelium are large. A priori estimates with respect to parameter ε (accounting for permeability) and a L^∞ bound need to prove this result, investigated in [27]. In addition, the estimates on time derivatives are necessary with a more subtle approach due to boundary conditions (3.17) of system and to take care of the initial layers. The dynamic problem is well-posed proving the existence and uniqueness of the weak solution. The Chapter 2 is currently being elaborated into a draft paper.

In the Chapter 3, we still study a mathematical model describing the transport of sodium in a fluid circulating in a counter-current tubular architecture, which constitutes a simplified model of the loop of Henle in a kidney nephron. We present the stationary system solution and we explore numerical simulations to describe the results dealing with a particular choice of parameters. Our dynamic model for $t \to +\infty$, converges towards the stationary system with an exponential rate. In order to prove rigorously this convergence, we study the eigenelements of an auxiliary linear operator and its dual. The solution related to the stationary system has been explicitly presented and numerical simulations have been performed to understand also the physiological behaviour of the system.

At the end, some mathematical tools and theorems utilized in the proofs have been included in the Appendices.

Chapter 2

Reduction of a model for ionic exchanges in kidney nephron

This chapter refers to the working paper [27], in collaboration with Nicolas Vauchelet and Vuk Milišić.

2.1 Introduction

We consider a simplified model for ionic exchange in the kidney nephron. In this simplified version, we focus on the mechanisms involved in the loop of Henle, a component of nephron. The ionic exchanges occur at the interface between the tubules and the epithelium and at the interface between the epithelium and the interstitium. A schematic representation for the model is given in Figure 2.1.
We present the following semi-linear hyperbolic system with $(t,x) \in (0,+\infty) \times (0,L)$:

$$\begin{cases} \partial_t u_1 + \alpha \partial_x u_1 = J_1 = 2\pi r_1 P_1 (q_1 - u_1) \\ \partial_t u_2 - \alpha \partial_x u_2 = J_2 = 2\pi r_2 P_2 (q_2 - u_2) \\ \partial_t q_1 = J_{1,e} = 2\pi r_1 P_1 (u_1 - q_1) + 2\pi r_{1,e} P_{1,e} (u_0 - q_1) \\ \partial_t q_2 = J_{2,e} = 2\pi r_2 P_2 (u_2 - q_2) + 2\pi r_{2,e} P_{2,e} (u_0 - q_2) - G(q_2) \\ \partial_t u_0 = J_0 = 2\pi r_{1,e} P_{1,e} (q_1 - u_0) + 2\pi r_{2,e} P_{2,e} (q_2 - u_0) + G(q_2) \\ u_1(t,0) = u_b(t); \quad u_1(t,L) = u_2(t,L) \quad t > 0 \\ u_1(0,x) = u_1^0(x); \quad u_2(0,x) = u_2^0(x); \quad u_0(0,x) = u_0^0(x); \\ q_1(0,x) = q_1^0(x); \quad q_2(0,x) = q_2^0(x) \end{cases} \tag{2.1}$$

We recall and describe used frequently symbols below :

- r_i : denote the radius for the lumen i ($[m]$).
- $r_{i,e}$: denote the radius for the tubule i with epithelium layer.
- Ionic concentrations ($[mol/m^3]$) :
  $u_i(t,x)$: solute in the lumen i,
  $q_i(t,x)$: solute in the epithelium 'near' lumen i
  $u_0(t,x)$: solute in the interstitium.
- Permeabilities ($[m/s]$):
  P_i : between the lumen and the epithelium,
  $P_{i,e}$: between the epithelium and the interstitium.

The non-linear term representing active transport is usually described using Michaelis-Menten kinetics:

$$G(q_2) = V_{m,2} \left(\frac{q_2}{k_{M,2} + q_2} \right)^3 \quad k_{M,2}, V_{m,2} \in \mathbb{R}^+. \tag{2.2}$$

In the tubule 2, the transport of solute both by the passive diffusion and the active reabsorption uses Na^+/K^+-ATPases pumps, which exchange 3 Na^+ ions for 2 K^+ ions.
In each tube, the fluid (mostly water) is assumed to flow at constant rate α and here we only consider one generic uncharged solute in two tubules as in Figure 2.1.

We consider the following assumptions :

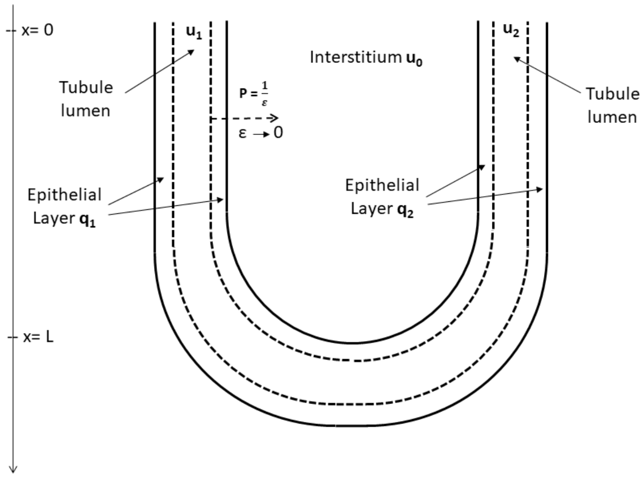


Figure 2.1: Schematic representation of the loop of Henle model.

Assumption 1: We assume that the initial solute concentrations are non-negative and uniformly bounded in $L^\infty(0, L)$ and in total variation :

$$0 \leq u_1^0, u_2^0, q_1^0, q_2^0, u_0^0 \in BV(0, L) \cap L^\infty(0, L). \tag{2.3}$$

Assumption 2: Boundary conditions of system are the following:

$$0 \leq u_b \in BV(0, T) \cap L^\infty(0, T). \tag{2.4}$$

The space BV is the space of the bounded variation functions, notice that such functions have a trace on the boundary (see e.g. [7]). Hence the boundary condition $u_2(t, L) = u_1(t, L)$ is well-defined.

Assumption 3: Regularity and boundedness of G. We assume that the non-linear function modelling active transport in the ascending limb (tubule 2) is an odd and Lipschitz-continuous function with respect to its argument :

$$\forall\, x \geq 0, \quad G(-x) = -G(x), \quad G(x) \leq \|G\|_\infty, \quad 0 \leq G'(x) \leq \|G'\|_\infty. \tag{2.5}$$

We notice that the function G defined on $\mathbb{R}^+$ by the expression in (2.2) may be straightforwardly extended by symmetry on $\mathbb{R}$ by a function satisfying (2.5). We know by classical results [7] that a Lipschitz function is almost everywhere differentiable, then it allows us to use the notation G'. The pump described with this term carries the solute from the lumen of the thick ascending limb toward the interstitium. It has been justified the biological meaning of its mathematical assumptions with the fact that the pump can be saturated because the number of transporters is limited. Moreover, we notice that $G(0) = 0$ which means that there is no transport in the absence of solute, that is reasonable.

To simplify our notation in (2.1), we set $2\pi r_{i,e}P_{i,e} = K_i$, $i = 1, 2$ and $2\pi r_i P_i = k_i$, $i = 1, 2$. The orders of magnitude of k_1, k_2 are the same even if their values are not definitely equal, we may assume to further simplify the analysis that $k_1 = k_2 = k$. We consider the case where the permeability between the lumen and the epithelium is large and we set, $k_1 = k_2 = \frac{1}{\varepsilon}$ for $\varepsilon \ll 1$. Then, we investigate the limit $\varepsilon \to 0$ in the following system :

$$\partial_t u_1^\varepsilon + \alpha \partial_x u_1^\varepsilon = \frac{1}{\varepsilon}(q_1^\varepsilon - u_1^\varepsilon) \tag{2.6a}$$

$$\partial_t u_2^\varepsilon - \alpha \partial_x u_2^\varepsilon = \frac{1}{\varepsilon}(q_2^\varepsilon - u_2^\varepsilon) \tag{2.6b}$$

$$\partial_t q_1^\varepsilon = \frac{1}{\varepsilon}(u_1^\varepsilon - q_1^\varepsilon) + K_1(u_0^\varepsilon - q_1^\varepsilon) \tag{2.6c}$$

$$\partial_t q_2^\varepsilon = \frac{1}{\varepsilon}(u_2^\varepsilon - q_2^\varepsilon) + K_2(u_0^\varepsilon - q_2^\varepsilon) - G(q_2^\varepsilon) \tag{2.6d}$$

$$\partial_t u_0^\varepsilon = K_1(q_1^\varepsilon - u_0^\varepsilon) + K_2(q_2^\varepsilon - u_0^\varepsilon) + G(q_2^\varepsilon). \tag{2.6e}$$

Formally, when $\varepsilon \to 0$, we expect the concentrations u_1^ε and q_1^ε to converge to the same concentration. The same happens for $u_2^\varepsilon \to u_2$ and $q_2^\varepsilon \to u_2$. We denote u_1, respectively u_2, the limit of $(u_1^\varepsilon)_\varepsilon$ and $(q_1^\varepsilon)_\varepsilon$, respectively $(u_2^\varepsilon)_\varepsilon$ and $(q_2^\varepsilon)_\varepsilon$. Adding equations (2.6a) and (2.6c) of system (2.6) and adding equations (2.6b) and (2.6d), we obtain the system

$$\begin{aligned} \partial_t u_1^\varepsilon + \partial_t q_1^\varepsilon + \alpha \partial_x u_1^\varepsilon &= K_1(u_0^\varepsilon - q_1^\varepsilon) \\ \partial_t u_2^\varepsilon + \partial_t q_2^\varepsilon - \alpha \partial_x u_2^\varepsilon &= K_2(u_0^\varepsilon - q_2^\varepsilon) - G(q_2^\varepsilon). \end{aligned}$$

Passing formally to the limit $\varepsilon \to 0$, we arrive at

$$2\partial_t u_1 + \alpha \partial_x u_1 = K_1(u_0 - u_1) \tag{2.7}$$

$$2\partial_t u_2 - \alpha \partial_x u_2 = K_2(u_0 - u_2) - G(u_2), \tag{2.8}$$

coupled to the equation for the concentration in the interstitium obtained by passing into the limit in equation (2.6e)

$$\partial_t u_0 = K_1(u_1 - u_0) + K_2(u_2 - u_0) + G(u_2). \tag{2.9}$$

This system is complemented with the initial and boundary conditions

$$u_1(0, x) = u_1^0 + q_1^0, \quad u_2(0, x) = u_2^0 + q_2^0, \quad u_0(0, x) = u_0^0(x), \tag{2.10}$$

$$u_1(t, 0) = u_b(t), \quad u_2(t, L) = u_1(t, L). \tag{2.11}$$

Finally, we recover a simplified system for only three unknowns. From a physical point of view this means fusing the epithelial layer with the lumen. When we consider the limit of infinite permeability it turns out to merge the lumen and the epithelium into a single domain. The main purpose of this work is to make this formal computation rigorous. More precisely, the main result reads,

Theorem 2.1.1. *Let $T > 0$ and $L > 0$. We assume that initial data and boundary conditions satisfying assumptions* (2.3), (2.4), (2.5).
Then, the weak solution $(u_1^\varepsilon, u_2^\varepsilon, q_1^\varepsilon, q_2^\varepsilon, u_0^\varepsilon)$ of system (2.6) *converges, as ε goes to zero, to the weak solution of reduced (or limit) problem* (2.7)–(2.9) *complemented with* (2.10)–(2.11). *More precisely,*

$$u_i^\varepsilon \xrightarrow[\varepsilon\to 0]{} u_i \quad i = 0, 1, 2, \qquad \textit{strongly in } L^1([0, T] \times [0, L]),$$
$$q_j^\varepsilon \xrightarrow[\varepsilon\to 0]{} u_j \quad j = 1, 2, \qquad \textit{strongly in } L^1([0, T] \times [0, L]),$$

where (u_1, u_2, u_0) is the unique weak solution of limit problem (2.7)–(2.9).

The aim of this Chapter is to clarify the link between both models. In particular, we show that when the permeability between the epithelium and the lumen is large, then system 3×3 of (2.7), (2.8), (2.9) may be considered as a good approximation of the larger system (2.1). The system can be seen as a particular case of the above-mentioned model introduced and studied in [46] and [47].

Definition 2.1.1. Let $u_1^0(x), u_2^0(x), q_1^0(x), q_2^0(x), u_0^0(x) \in BV(0, L) \cap L^\infty(0, L)$ and $u_1(t, 0) = u_b(t) \in BV(0, T) \cap L^\infty(0, T)$.
We define $U(t, x) = (u_1(t, x), u_2(t, x), q_1(t, x), q_2(t, x), u_0(t, x))$ weak solution of system (2.6) for each fixed $\varepsilon > 0$ if

1. for all $\varphi_i, \psi_j \in \mathcal{S}$ with $i = 0, 1, 2$ $j = 1, 2$ and with

$$\mathcal{S} = \{\phi \in C^1([0, T] \times [0, L]), \quad \phi(T, x) = 0\}$$

it satisfies:

$$
\begin{cases}
\displaystyle\int_0^T\int_0^L u_1^\varepsilon(\partial_t\varphi_1+\alpha\partial_x\varphi_1)+\frac{1}{\varepsilon}(q_1^\varepsilon-u_1^\varepsilon)\varphi_1\ dxdt+ \\
\qquad\displaystyle+\int_0^T(u_b^\varepsilon(t)\varphi_1(t,0)-u_1^\varepsilon(t,L)\varphi_1(t,L))\ dt+\int_0^L u_1^\varepsilon(0,x)\varphi_1(0,x)\ dx=0 \\
\displaystyle\int_0^T\int_0^L u_2^\varepsilon(\partial_t\varphi_2-\alpha\partial_x\varphi_2)+\frac{1}{\varepsilon}(q_2^\varepsilon-u_2^\varepsilon)\varphi_2\ dxdt+ \\
\qquad\displaystyle+\int_0^T(u_2^\varepsilon(t,0)\varphi_2(t,0)-u_2^\varepsilon(t,L)\varphi_2(t,L))\ dt+\int_0^L u_2^\varepsilon(0,x)\varphi_2(0,x)\ dx=0 \\
\displaystyle\int_0^T\int_0^L q_1^\varepsilon(\partial_t\psi_1)+K_1(u_0^\varepsilon-q_1^\varepsilon)\psi_1-\frac{1}{\varepsilon}(q_1^\varepsilon-u_1^\varepsilon)\psi_1\ dxdt+ \\
\qquad\displaystyle+\int_0^L q_1^\varepsilon(0,x)\psi_1(0,x)\ dx=0 \\
\displaystyle\int_0^T\int_0^L q_2^\varepsilon(\partial_t\psi_2)+K_2(u_0^\varepsilon-q_2^\varepsilon)\psi_2-\frac{1}{\varepsilon}(q_2^\varepsilon-u_2^\varepsilon)\psi_2-G(q_2^\varepsilon)\psi_2\ dxdt+ \\
\qquad\displaystyle+\int_0^L q_2^\varepsilon(0,x)\psi_2(0,x)\ dx=0 \\
\displaystyle\int_0^T\int_0^L u_0^\varepsilon(\partial_t\varphi_0)+K_1(q_1^\varepsilon-u_0^\varepsilon)\varphi_0+K_2(q_2^\varepsilon-u_0^\varepsilon)\varphi_0+G(q_2^\varepsilon)\varphi_0\ dxdt+ \\
\qquad\displaystyle+\int_0^L u_0^\varepsilon(0,x)\varphi_0(0,x)\ dx=0.
\end{cases}
\tag{2.12}
$$

With regard to existence and uniqueness of the solution, in [47] and [46], the authors propose a semi-discrete scheme related to numerical algorithm with a priori bounds to show the existence of solution in $[0, L]$. We propose the standard approach based on fixed point theorem and we consider the system with fixed $\varepsilon > 0$. We report the following existence theorem:

Theorem 2.1.2 (Existence)**.** *With previous assumptions* (2.3)*,* (2.4)*,* (2.5) *and for every fixed* $\varepsilon > 0$*, there is a unique weak solution in* $(L^\infty([0,T]; L^1(0,L)\cap L^\infty(0,L)))^5$ *to the problem* (2.6)*.*

2.2 Existence and uniqueness

We report our system as the following:

$$
\partial_t U + A\partial_x U = BU + C; \qquad C = \begin{bmatrix} 0 \\ 0 \\ 0 \\ -G(q_2) \\ G(q_2) \end{bmatrix}, \tag{2.13}
$$

$$B = \begin{bmatrix} -\frac{1}{\varepsilon} & 0 & \frac{1}{\varepsilon} & 0 & 0 \\ 0 & -\frac{1}{\varepsilon} & 0 & \frac{1}{\varepsilon} & 0 \\ \frac{1}{\varepsilon} & 0 & -\frac{1}{\varepsilon} - K_1 & 0 & K_1 \\ 0 & \frac{1}{\varepsilon} & 0 & -\frac{1}{\varepsilon} - K_2 & K_2 \\ 0 & 0 & K_1 & K_2 & -K_1 - K_2 \end{bmatrix}, \quad U = \begin{bmatrix} u_1 \\ u_2 \\ q_1 \\ q_2 \\ u_0 \end{bmatrix}, \tag{2.14}$$

with coefficient $A = diag(\alpha, -\alpha, 0, 0, 0)$.
We prove the existence using the Banach-Picard fixed point theorem. We consider a small $T > 0$ (to be chosen later) and the map $\mathcal{T} : E \to E$ with $E = L^\infty([0,T], B)$ Banach space and $B = L^1(0,L)^5$. For a given function $\widetilde{U} \in E$, with $\widetilde{U} = (\tilde{u}_1, \tilde{u}_2, \tilde{q}_1, \tilde{q}_2, \tilde{u}_0)$, we define $U := \mathcal{T}(\widetilde{U})$ solution of the following problem:

$$\begin{cases} \partial_t u_1 + \alpha \partial_x u_1 = \frac{1}{\varepsilon}(\tilde{q}_1 - u_1) \quad x \in (0,L),\ t > 0 \\ \partial_t u_2 - \alpha \partial_x u_2 = \frac{1}{\varepsilon}(\tilde{q}_2 - u_2) \\ \partial_t q_1 = \frac{1}{\varepsilon}(\tilde{u}_1 - q_1) + K_1(\tilde{u}_0 - q_1) \\ \partial_t q_2 = \frac{1}{\varepsilon}(\tilde{u}_2 - q_2) + K_2(\tilde{u}_0 - q_2) - G(\tilde{q}_2) \\ \partial_t u_0 = K_1(\tilde{q}_1 - u_0) + K_2(\tilde{q}_2 - u_0) + G(\tilde{q}_2) \\ \\ u_1^0(x), u_2^0(x), q_1^0(x), q_2^0(x), u_0^0(x) \in BV(0,L) \cap L^\infty(0,L) \\ u_1(t,0) = u_b(t) \geq 0 \quad \in BV(0,T) \cap L^\infty(0,T); \\ u_2(t,L) = u_1(t,L) \quad t > 0 \end{cases} \tag{2.15}$$

For every fixed $\varepsilon > 0$, it is possible to define u_1 and u_2 with the method of characteristics. For instance, $u_1(t,x)$ satisfies:

$$u_1(t,x) = \begin{cases} u_1^0(x - \alpha t) e^{-\frac{t}{\varepsilon}} + \dfrac{1}{\varepsilon} \displaystyle\int_0^t e^{-\frac{t-s}{\varepsilon}} \tilde{q}_1(x - \alpha(t-s), s)\, ds, \quad x > \alpha t \\ u_b\left(t - \dfrac{x}{\alpha}\right) e^{-\frac{x}{\varepsilon\alpha}} + \dfrac{1}{\alpha\varepsilon} \displaystyle\int_0^x e^{-\frac{1}{\alpha\varepsilon}(x-y)} \tilde{q}_1\left(t - \dfrac{x-y}{\alpha}, y\right) dy, \quad x < \alpha t \end{cases} \tag{2.16}$$

with $u_1^0(x), u_b(t)$ initial and boundary condition. It is possible to built $u_2(t,x)$ in the same way using $u_2^0(x)$ and the boundary condition $u_2(t,L) = u_1(t,L)$ that it is well-defined thanks to (2.16).
In addition, it is possible also define easily the other quantities satisfying :

$$q_1(t,x) = q_1^0(x) e^{-(\frac{1}{\varepsilon} + K_1)t} + \int_0^t e^{-(\frac{1}{\varepsilon}+K_1)(t-s)} \Big(\frac{1}{\varepsilon}\tilde{u}_1 + K_1 \tilde{u}_0\Big)(s,x)\, ds,$$

$$q_2(t,x) = q_2^0(x) e^{-(\frac{1}{\varepsilon} + K_2)t} + \int_0^t e^{-(\frac{1}{\varepsilon}+K_2)(t-s)} \Big(\frac{1}{\varepsilon}\tilde{u}_2 + K_1 \tilde{u}_0 - G(\tilde{q}_2)\Big)(s,x)\, ds,$$

$$u_0(t,x) = u_0^0(x) e^{-(K_1+K_2)t} + \int_0^t e^{-(K_1+K_2)(t-s)} \Big(K_1 \tilde{q}_1 + K_2 \tilde{q}_2 + G(\tilde{q}_2)\Big)(s,x)\, ds.$$

Thanks to previous assumptions, the map $\mathcal{T}$ is an endomorphism of E.

Proof. The proof relies on a fixed point argument inspired by [29] and it is a straightforward adaptation from [37]. The map $\mathcal{T}$ is well defined thanks to the method of characteristics and also the trace $u_2(t,L)$ is well-defined in $L^1(0,L)$ thanks to $u_1(t,x)$ definition above. Before proving that the map $\mathcal{T}$ is a contractive map in the following Banach space

$$E = L^\infty([0,T],B) \quad ||\cdot||_E = \sup_{t\in(0,T)} ||\cdot||_B,$$

we report a simple a priori bounds result for the solution.

- Multiplying formally by sgn each function of system (2.15) we get :

$$\begin{cases} \partial_t|u_1| + \alpha\partial_x|u_1| \le \frac{1}{\varepsilon}(|\tilde{q}_1| - |u_1|) \\ \partial_t|u_2| - \alpha\partial_x|u_2| \le \frac{1}{\varepsilon}(|\tilde{q}_2| - |u_2|) \\ \partial_t|q_1| \le \frac{1}{\varepsilon}(|\tilde{u}_1| - |q_1|) + K_1(|\tilde{u}_0| - |q_1|) \\ \partial_t|q_2| \le \frac{1}{\varepsilon}(|\tilde{u}_2| - |q_2|) + K_2(|\tilde{u}_0| - |q_2|) + |G(\tilde{q}_2)| \\ \partial_t|u_0| \le K_1(|\tilde{q}_1| - |u_0|) + K_2(|\tilde{q}_2| - |u_0|) + |G(\tilde{q}_2)| \end{cases} \tag{2.17}$$

because by the 4th equation of system and since $sgn(G(\tilde{q}_2)) = sgn(\tilde{q}_2)$ by definition, we have $-G(\tilde{q}_2)sgn(\tilde{q}_2) = -|G(\tilde{q}_2)|$ and for the last one we have $G(\tilde{q}_2)sgn(u_0) \le |G(\tilde{q}_2)|$.
Adding all equations of system above and integrating in $[0,L]$, we obtain:

$$\frac{d}{dt}\int_0^L (|u_1| + |u_2| + |u_0| + |q_1| + |q_2|) \le \alpha|u_1(t,0)| + \frac{1}{\varepsilon}\int_0^L (|\tilde{u}_1| + |\tilde{u}_2| + |\tilde{q}_1| + |\tilde{q}_2|)\, dx + \\ (K_1+K_2)\int_0^L |\tilde{u}_0|\, dx + K_1\int_0^L |\tilde{q}_1|\, dx + K_2\int_0^L |\tilde{q}_2|\, dx + 2\mu\int_0^L |\tilde{q}_2|\, dx, \tag{2.18}$$

since $u_1(t,L) = u_2(t,L)$ and non-linear term assumption (2.5) with $\mu = ||G||_\infty$.
Setting $||U(t,x)||_{L^1} = \int_0^L (|u_1| + |u_2| + |q_1| + |q_2| + |u_0|)(t,x)\, dx$ and integrating with respect to time, we obtain:

$$||U(t,x)||_{L^1} \le ||U(0,x)||_{L^1} + \alpha\int_0^T |u_b(s)|\, ds + \eta\int_0^T ||\widetilde{U}(t,x)||_{L^1}\, dt, \tag{2.19}$$

with $\eta = K_1 + K_2 + 2\mu + \frac{1}{\varepsilon} > 0$, constant.

- Then, for given function $(\widetilde{U},\widetilde{W}) \in E^2$, we define $U := \mathcal{T}(\widetilde{U}),\ W := \mathcal{T}(\widetilde{W})$ and the function $\mathcal{U} = U - W$ satisfies for $\widetilde{\mathcal{U}} = \widetilde{U} - \widetilde{W}$:

$$||\mathcal{T}(\widetilde{U}) - \mathcal{T}(\widetilde{W})||_{L^1(0,L)} = ||U - W||_{L^1(0,L)} \le \eta\int_0^T ||\widetilde{U} - \widetilde{W}||_{L^1(0,L)}. \tag{2.20}$$

Then, we get :

$$||\mathcal{U}||_E \le \eta T ||\widetilde{\mathcal{U}}||_E, \tag{2.21}$$

which means that as soon as $T < 1/\eta$, $\mathcal{T}$ is a strict contraction in the Banach space E and this proves the existence of a unique fixed point. We can iterate the operator on $[T,2T], [2T,3T]\ldots$, since the condition on T does not depend on the iteration. With this iteration process, we have built a solution to (2.13).

2.3 Uniform a priori estimates

In order to show the principal result of this Chapter we need to establish some uniform a priori estimates. The strategy of the proof of Theorem 2.1.1 relies on a compactness argument. In this Section we will omit the exponent ε in all quantities to simplify the notation.

2.3.1 Non-negativity and $L^1 \cap L^\infty$ estimates

The following lemma establishes that all concentrations of system are non-negative and this is consistent with the biological interpretation. For the sake of simplicity, in this section we obmit ε in the system (2.6).

Lemma 2.3.1 (Nonnegativity)**.** *Let $U(t,x)$ be a weak solution of system* (3.4) *such that the assumptions* (2.3)*,* (2.4)*,* (2.5) *hold. Then for all $(t,x) \in (0,T) \times (0,L)$, $U(t,x)$ is non-negative, i.e. $u_1(t,x), u_2(t,x), q_1(t,x), q_2(t,x), u_0(t,x) \geq 0$.*

Proof. We are going to prove that the negative part of our functions vanishes. Using Stampacchia method and following the same approach of [38], we formally multiply each equation of system (2.6) by corresponding indicator function as follows:

$$\begin{cases} (\partial_t u_1 + \alpha \partial_x u_1)\mathbf{1}_{\{u_1<0\}} = \frac{1}{\varepsilon}(q_1 - u_1)\mathbf{1}_{\{u_1<0\}} \\ (\partial_t u_2 - \alpha \partial_x u_2)\mathbf{1}_{\{u_2<0\}} = \frac{1}{\varepsilon}(q_2 - u_2)\mathbf{1}_{\{u_2<0\}} \\ (\partial_t q_1)\mathbf{1}_{\{q_1<0\}} = \frac{1}{\varepsilon}(u_1 - q_1)\mathbf{1}_{\{q_1<0\}} + K_1(u_0 - q_1)\mathbf{1}_{\{q_1<0\}} \\ (\partial_t q_2)\mathbf{1}_{\{q_2<0\}} = \frac{1}{\varepsilon}(u_2 - q_2)\mathbf{1}_{\{q_2<0\}} + K_2(u_0 - q_2)\mathbf{1}_{\{q_2<0\}} - G(q_2)\mathbf{1}_{\{q_2<0\}} \\ (\partial_t u_0)\mathbf{1}_{\{u_0<0\}} = K_1(q_1 - u_0)\mathbf{1}_{\{u_0<0\}} + K_2(q_2 - u_0)\mathbf{1}_{\{u_0<0\}} + G(q_2)\mathbf{1}_{\{u_0<0\}}. \end{cases}$$

We remember that for each function u we can define positive and negative part as $u^+ = \max(u,0)$, $u^- = \max(-u,0)$. It is possible also to write in the distribution sense:

$$u_i^- = -u_i \mathbf{1}_{\{u_i<0\}} \quad \partial_t u_i^- = -\partial_t u_i \mathbf{1}_{\{u_i<0\}}, \quad i = 0,1,2.$$

The same is true for other functions q_j with $j = 1,2$.

Taking into account the fact that:

$$q_i \mathbf{1}_{\{u_i<0\}} = (q_i^+ - q_i^-)\mathbf{1}_{\{u_i<0\}} \geq -q_i^-, \quad i = 1,2,$$

since $q_i^- \mathbf{1}_{\{u_i<0\}}$ is zero or positive by definition of negative part, we obtain :

$$\begin{cases} \partial_t u_1^- + \alpha \partial_x u_1^- \leq \frac{1}{\varepsilon}(q_1^- - u_1^-) \\ \partial_t u_2^- - \alpha \partial_x u_2^- \leq \frac{1}{\varepsilon}(q_2^- - u_2^-) \\ \partial_t q_1^- \leq \frac{1}{\varepsilon}(u_1^- - q_1^-) + K_1(u_0^- - q_1^-) \\ \partial_t q_2^- \leq \frac{1}{\varepsilon}(u_2^- - q_2^-) + K_2(u_0^- - q_2^-) + G(q_2)\mathbf{1}_{\{q_2<0\}} \\ \partial_t u_0^- \leq K_1(q_1^- - u_0^-) + K_2(q_2^- - u_0^-) - G(q_2)\mathbf{1}_{\{u_0<0\}}. \end{cases}$$

Adding all equations, the inequality reads

$$\partial_t(u_1^- + q_1^- + q_2^- + u_2^- + u_0^-) + \alpha \partial_x(u_1^- - u_2^-) \leq G(q_2)(\mathbf{1}_{\{q_2<0\}} - \mathbf{1}_{\{u_0<0\}}). \qquad (2.22)$$

By assumption (2.5), we have $sgn(G(q_2)) = sgn(q_2)$ with $[G(q_2)]^+ = G(q_2^+)$ and $[G(q_2)]^- = G(q_2^-)$. Thus,

$$[G(q_2)]^- = G(q_2)\mathbf{1}_{\{G(q_2)<0\}} = G(q_2)\mathbf{1}_{\{q_2<0\}}, \qquad G(q_2)\mathbf{1}_{\{u_0<0\}} \geq -G(q_2^-).$$

With these relations we can conclude $G(q_2)(\mathbf{1}_{\{q_2<0\}} - \mathbf{1}_{\{u_0<0\}}) \leq 0$.
Then integrating (2.22) on interval $[0, L]$, we get:

$$\frac{d}{dt}\int_0^L (u_1^- + q_1^- + q_2^- + u_2^- + u_0^-)(t,x)\, dx \leq \alpha(u_2^-(t,L) - u_2^-(t,0) - u_1^-(t,L) + u_1^-(t,0)).$$

Since $u_1^-(t,L) = u_2^-(t,L)$ thanks to condition (2.4), it follows:

$$\frac{d}{dt}\int_0^L (u_1^- + q_1^- + q_2^- + u_2^- + u_0^-)(t,x)\, dx \leq \alpha u_1^-(t,0) = \alpha u_b^-(t).$$

As supposed in (2.4), the negative part of u_b is zero and as supposed in (2.3) also initial condition are non negative, then $u_1^-(0,x), q_1^-(0,x), q_2^-(0,x)u_2^-(0,x), u_0^-(0,x)$ should be necessarily equal to zero.
We can deduce the non-negativity of solutions and it concludes the proof. □

Lemma 2.3.2 (L^∞ bound)**.** *Let $(u_1, u_2, q_1, q_2, u_0)$ be a solution in $\big(L^\infty([0,T];(L^1\cap L^\infty)(0,L))\big)^5$ to (2.6). Assume that (2.3), (2.4), (2.5) hold, then the solution satisfies: for a.e. $(t,x) \in (0,T)\times(0,L)$,*

$$0 \leq u_0 \leq \kappa(1+t), \quad 0 \leq u_i \leq \kappa(1+t), \quad 0 \leq q_i \leq \kappa(1+t), \quad i = 1,2,$$

$$0 \leq u_2(t,0) \leq \kappa(1+t), \quad 0 \leq u_1(t,L) \leq \kappa(1+t),$$

where the constant $\kappa \geq \max\big\{\|G\|_\infty, \|u_b\|_\infty, \|u_0^0\|_\infty, \|u_i^0\|_\infty, \|q_i^0\|_\infty,\ i \in \{1,2\}\big\}$.

Proof. We use the same method as in previous Lemma but now for the functions

$$w_i = (u_i - \kappa(1+t)), \quad i = 0,1,2, \quad z_j = (q_j - \kappa(1+t)), \quad j = 1,2.$$

We can also rewrite positive part of functions w_i, z_j as:

$$w_i^+ := (u_i - \kappa(1+t))^+ = (u_i - \kappa(1+t))\mathbf{1}_{\{w_i\geq 0\}} = (u_i - \kappa(1+t))\mathbf{1}_{\{u_i\geq\kappa(1+t)\}},$$

$$z_j^+ := (q_j - \kappa(1+t))^+ = (q_j - \kappa(1+t))\mathbf{1}_{\{z_j\geq 0\}} = (q_j - \kappa(1+t))\mathbf{1}_{\{q_j\geq\kappa(1+t)\}}.$$

From system (2.6) and using the fact that

$$z_j\mathbf{1}_{\{w_i\geq 0\}} = z_j^+\mathbf{1}_{\{w_i\geq 0\}} - z_j^-\mathbf{1}_{\{w_i\geq 0\}} \leq z_j^+, \qquad w_i\mathbf{1}_{\{z_j\geq 0\}} \leq w_i^+,$$

we get

$$\begin{cases} \partial_t w_1^+ + \kappa\mathbf{1}_{\{w_1\geq 0\}} + \alpha\partial_x w_1^+ \leq \frac{1}{\varepsilon}(z_1^+ - w_1^+) \\ \partial_t w_2^+ + \kappa\mathbf{1}_{\{w_2\geq 0\}} - \alpha\partial_x w_2^+ \leq \frac{1}{\varepsilon}(z_2^+ - w_2^+) \\ \partial_t z_1^+ + \kappa\mathbf{1}_{\{z_1\geq 0\}} \leq \frac{1}{\varepsilon}(w_1^+ - z_1^+) + K_1(w_0^+ - z_1^+) \\ \partial_t z_2^+ + \kappa\mathbf{1}_{\{z_2\geq 0\}} \leq \frac{1}{\varepsilon}(w_2^+ - z_2^+) + K_2(w_0^+ - z_2^+) - G(q_2)\mathbf{1}_{\{z_2\geq 0\}} \\ \partial_t w_0^+ + \kappa\mathbf{1}_{\{w_0\geq 0\}} \leq K_1(z_1^+ - w_0^+) + K_2(z_2^+ - w_0^+) + G(q_2)\mathbf{1}_{\{w_0\geq 0\}}. \end{cases} \tag{2.23}$$

Adding all equations, we deduce

$$\partial_t(w_1^+ + w_2^+ + z_1^+ + z_2^+) + \alpha\partial_x(w_1^+ - w_2^+) \leq \; -\kappa\mathbf{1}_{\{w_0\geq 0\}} + G(q_2)(\mathbf{1}_{\{w_0\geq 0\}} - \mathbf{1}_{\{z_2\geq 0\}}).$$

Integrating with respect to x yields

$$\frac{d}{dt}\int_0^L (w_1^+ + w_2^+ + z_1^+ + z_2^+ + w_0^+)(t,x)\,dx$$
$$\leq \alpha(w_2^+(t,L) - w_2^+(t,0) - w_1^+(t,L) + w_1^+(t,0)) + \int_0^L (G(q_2) - \kappa)\mathbf{1}_{\{w_0\geq 0\}}\,dx,$$

where we use the fact that $G(q_2) \geq 0$ from assumption (2.5) since $q_2 \geq 0$ from previous Lemma. From the boundary conditions in (2.1), we have for all $t \geq 0$, $w_2^+(L) = [u_2(L) - \kappa(1+t)]^+ = [u_1(L) - \kappa(1+t)]^+ = w_1^+(L)$. Then,

$$\frac{d}{dt}\int_0^L (w_1^+ + w_2^+ + z_1^+ + z_2^+ + w_0^+)(t,x)\,dx + \alpha w_2^+(t,0)$$
$$\leq \alpha(u_b(t) - \kappa(1+t))^+ + (\|G\|_\infty - \kappa)\int_0^L \mathbf{1}_{\{w_0\geq 0\}}\,dx.$$

If we choose arbitrary constant $\kappa \geq \max\{\|G\|_\infty, \|u_b\|_\infty\}$, it implies:

$$\frac{d}{dt}\int_0^L (w_1^+ + w_2^+ + z_1^+ + z_2^+ + w_0^+)(t,x)\,dx + \alpha w_2^+(t,0) \leq 0,$$

which allows us to obtain the estimates provided κ large enough. In this case it has been showed the vanishing of positive part to conclude in other words that:

$$u_i - \kappa(1+t) \leq 0, \quad i = 0,1,2; \quad q_j - \kappa(1+t) \leq 0, \quad j = 1,2.$$

For the last estimate on $u_1(t,L)$, we add the first and the third inequalities in system (2.23) and integrate on $(0,L)$,

$$\frac{d}{dt}\int_0^L (w_1^+ + z_1^+)\,dx + \alpha w_1^+(t,L) \leq \alpha w_1^+(t,0) + K_1\int_0^L (w_0^+ - z_1^+)\,dx$$
$$- \kappa\int_0^L (\mathbf{1}_{\{w_1\geq 0\}} + \mathbf{1}_{\{z_1\geq 0\}})\,dx.$$

Integrating on $(0,T)$ and since we have proved above that $w_0^+ = 0$ and $z_1^+ = 0$, we arrive at

$$\alpha\int_0^T w_1^+(t,L)\,dt \leq \alpha\int_0^T w_1^+(t,0)\,dt = 0,$$

for $\kappa \geq \|u_b\|_\infty$. □

Lemma 2.3.3 (L^1 estimate)**.** *Let $T > 0$ and let $(u_1, u_2, q_1, q_2, u_0)$ be a weak solution of system* (3.4) *in* $\left(L^\infty([0,T];(L^1 \cap L^\infty)(0,L))\right)^5$. *We define:*

$$\mathcal{H}(t) = \int_0^L (|u_1| + |u_2| + |u_0| + |q_1| + |q_2|)(t,x)\ dx.$$

Then, under hypothesis (2.3), (2.4), (2.5) *the following a priori estimate, uniform in $\varepsilon > 0$, holds:*

$$\mathcal{H}(t) \le \alpha \|u_b\|_{L^1(0,T)} + \mathcal{H}(0), \quad \forall t > 0.$$

Moreover the following inequalities hold:

$$\int_0^T |u_2(t,0)|\, dt \le \|u_b\|_{L^1(0,T)} + \frac{1}{\alpha}\mathcal{H}(0),$$

and

$$\int_0^T |u_1(t,L)|\, dt \le \int_0^L (|u_1^0(x)| + |q_1^0(x)|)\, dx + CT$$

with $C > 0$ constant.

Proof. Since from Lemma 2.3.1 all concentrations are non-negative, we may formally write from system (2.6)

$$\begin{cases} \partial_t |u_1| + \alpha \partial_x |u_1| = \frac{1}{\varepsilon}(|q_1| - |u_1|) \\ \partial_t |u_2| - \alpha \partial_x |u_2| = \frac{1}{\varepsilon}(|q_2| - |u_2|) \\ \partial_t |q_1| = \frac{1}{\varepsilon}(|u_1| - |q_1|) + K_1(|u_0| - |q_1|) \\ \partial_t |q_2| = \frac{1}{\varepsilon}(|u_2| - |q_2|) + K_2(|u_0| - |q_2|) - |G(q_2)| \\ \partial_t |u_0| = K_1(|q_1| - |u_0|) + K_2(|q_2| - |u_0|) + |G(q_2)|. \end{cases} \tag{2.24}$$

Otherwise, to obtain the absolute value without having non-negativity of functions, we should have formally multiplied by the sign of each concentrations respectively. Adding all equations in (2.24) and integrating on $(0, L)$, we get, recalling the boundary condition $u_1(t,L) = u_2(t,L)$,

$$\frac{d}{dt}\mathcal{H}(t) + \alpha |u_2(t,0)| = \alpha |u_1(t,0)| = \alpha |u_b(t)|. \tag{2.25}$$

Integrating now with respect to time, we obtain:

$$\mathcal{H}(t) + \alpha \int_0^t |u_2(s,0)|\, ds \le \alpha \int_0^t |u_b(s)|\ ds + \mathcal{H}(0). \tag{2.26}$$

with $\mathcal{H}(t)$ previously defined. It gives the first two estimates of the Lemma. Finally, to obtain the last inequality, we add equations (2.6a) and (2.6c) and integrate on $(0, L)$ to get

$$\frac{d}{dt}\int_0^L (|u_1| + |q_1|)\ dx + \alpha |u_1(t,L)| \le \alpha |u_b(t)| + K_1 \int_0^L |u_0|\ dx.$$

Since we have shown that $\int_0^L |u_0|\ dx \le \mathcal{H}(t) < \infty$, we can conclude after integrating with respect to time. □

2.3.2 Time derivatives estimates

The estimates about time derivatives are more subtle due to boundary conditions. In order to take care of the initial layers, we introduce an auxiliary system. When $\varepsilon \to 0$ the concentrations u_1, q_1 and u_2, q_2 approach very quickly each other becoming roughly speaking the same. Introducing this following system we can evaluate this 'difference' between them. It follows,

$$\begin{cases} \partial_t \tilde{u}_1 = \tilde{q}_1 - \tilde{u}_1 \\ \partial_t \tilde{u}_2 = \tilde{q}_2 - \tilde{u}_2 \\ \partial_t \tilde{q}_1 = \tilde{u}_1 - \tilde{q}_1 \\ \partial_t \tilde{q}_2 = \tilde{u}_2 - \tilde{q}_2, \end{cases} \tag{2.27}$$

with initial conditions

$$\tilde{u}_1(0,x) = q_1^0 - u_1^0, \quad \tilde{u}_2(0,x) = q_2^0 - u_2^0, \quad \tilde{q}_1(0,x) = 0, \quad \tilde{q}_2(0,x) = 0.$$

Actually, this system may be solved explicitly and we obtain

$$\tilde{u}_i(t) = \frac{1}{2}(q_i^0 - u_i^0)(1 + e^{-2t}); \quad \tilde{q}_i(t) = \frac{1}{2}(q_i^0 - u_i^0)(1 - e^{-2t}), \quad i = 1, 2. \tag{2.28}$$

In addition, we introduce the following quantities

$$\begin{cases} U_1 = u_1 + \tilde{u}_1(\frac{t}{\varepsilon}, x) \\ U_2 = u_2 + \tilde{u}_2(\frac{t}{\varepsilon}, x) \\ Q_1 = q_1 + \tilde{q}_1(\frac{t}{\varepsilon}, x) \\ Q_2 = q_2 + \tilde{q}_2(\frac{t}{\varepsilon}, x) \\ U_0 = u_0. \end{cases} \tag{2.29}$$

The next purpose will be to prove the uniform bounds on the time derivatives of these functions with the following arguments,

Proposition 2.3.1. *Let $T > 0$. Under hypothesis* (2.3), (2.4), (2.5), *we set:*

$$\tilde{\mathcal{H}}_t(t) = \int_0^L \big(|\partial_t U_1| + |\partial_t U_2| + |\partial_t Q_1| + |\partial_t Q_2| + |\partial_t U_0|\big)(t,x)\, dx,$$

with functions U_1, U_2, U_0, Q_1, Q_2 as defined in (2.29)*. Then, it holds:*

$$\int_0^T \tilde{\mathcal{H}}_t(t)\, dt + \int_0^T |\partial_t U_2(t,0)|\, dt \le C.$$

Moreover, we have

$$\int_0^T |\partial_t U_1(t,L)|\, dt \le C. \tag{2.30}$$

As a consequence, we deduce the following estimates on the time derivatives:

Corollary 2.3.1 (Time derivatives estimates). *Let $T > 0$, under above assumptions, there exists a constant $C_T > 0$ such that we have the following uniform estimates :*

$$\int_0^L (|\partial_t u_1| + |\partial_t u_2| + |\partial_t u_0| + |\partial_t q_1| + |\partial_t q_2|)(t,x)\,dx \leq C_T \tag{2.31}$$

$$\int_0^T |u_{2,t}(t,0)|\;dt \leq C_T, \tag{2.32}$$

$$\int_0^T |u_{1,t}(t,L)|\;dt \leq C_T. \tag{2.33}$$

Proof of Proposition 2.3.1. From system (2.6) and the functions defined in (2.29), we deduce

$$\begin{cases} \partial_t U_1 + \partial_x U_1 = \frac{1}{\varepsilon}(Q_1 - U_1) + \partial_x \tilde{u}_1(\frac{t}{\varepsilon}, x) \\ \partial_t U_2 - \partial_x U_2 = \frac{1}{\varepsilon}(Q_2 - U_2) - \partial_x \tilde{u}_2(\frac{t}{\varepsilon}, x) \\ \partial_t Q_1 = \frac{1}{\varepsilon}(U_1 - Q_1) + K_1(u_0 - Q_1) + K_1\tilde{q}_1(\frac{t}{\varepsilon}, x) \\ \partial_t Q_2 = \frac{1}{\varepsilon}(U_2 - Q_2) + K_2(u_0 - Q_2) + K_2\tilde{q}_2(\frac{t}{\varepsilon}, x) - G(q_2) \\ \partial_t u_0 = K_1(Q_1 - u_0) + K_2(Q_2 - u_0) - K_1\tilde{q}_1(\frac{t}{\varepsilon}, x) - K_2\tilde{q}_2(\frac{t}{\varepsilon}, x) + G(q_2) \end{cases} \tag{2.34}$$

with following initial and boundary conditions:

$$\begin{array}{ll} U_1(t,0) = u_1(t,0) + \tilde{u}_1(t,0) = u_b(t) + \tilde{u}_1(\frac{t}{\varepsilon}, 0), & t \in (0,T), \\ U_2(t,L) = U_2(t,L) + \tilde{u}_2(\frac{t}{\varepsilon}, L), & t \in (0,T), \\ U_1(0,x) = u_1(0,x) + \tilde{u}_1(0,x) = q_1^0(x), & x \in (0,L), \\ U_2(0,x) = u_2(0,x) + \tilde{u}_2(0,x) = q_2^0(x), & \\ Q_1(0,x) = q_1(0,x) + \tilde{q}_1(0,x) = q_1^0(x), & \\ Q_2(0,x) = q_2(0,x) + \tilde{q}_2(0,x) = q_2^0(x). & \end{array} \tag{2.35}$$

Taking the derivative with respect to time in system (2.34), we compute

$$\begin{cases} \partial_t U_{1,t} + \partial_x U_{1,t} = \frac{1}{\varepsilon}(Q_{1,t} - U_{1,t}) + \frac{1}{\varepsilon}\partial_x \tilde{u}_{1,t} \\ \partial_t U_{2,t} - \partial_x U_{2,t} = \frac{1}{\varepsilon}(Q_{2,t} - U_{2,t}) - \frac{1}{\varepsilon}\partial_x \tilde{u}_{2,t} \\ \partial_t Q_{1,t} = \frac{1}{\varepsilon}(U_{1,t} - Q_{1,t}) + K_1(u_{0,t} - Q_{1,t}) + \frac{1}{\varepsilon}K_1\tilde{q}_{1,t} \\ \partial_t Q_{2,t} = \frac{1}{\varepsilon}(U_{2,t} - Q_{2,t}) + K_2(u_{0,t} - Q_{2,t}) + \frac{1}{\varepsilon}K_2\tilde{q}_{2,t} - G'(q_2)q_{2,t} \\ \partial_t u_{0,t} = K_1(Q_{1,t} - u_{0,t}) + K_2(Q_{2,t} - u_{0,t}) - \frac{1}{\varepsilon}K_1\tilde{q}_{1,t} - \frac{1}{\varepsilon}K_2\tilde{q}_{2,t} + G'(q_2)q_{2,t}. \end{cases}$$

We can formally multiply each equation respectively by $sgn(U_{i,t})$ and $sgn(Q_{j,t})$, with $i = 1, 2, 0$ and $j = 1, 2$, as in [33]. It implies

$$\begin{cases} \partial_t|U_{1,t}| + \partial_x|U_{1,t}| \leq \frac{1}{\varepsilon}(|Q_{1,t}| - |U_{1,t}|) + |\frac{1}{\varepsilon}\partial_x\tilde{u}_{1,t}| \\ \partial_t|U_{2,t}| - \partial_x|U_{2,t}| \leq \frac{1}{\varepsilon}(|Q_{2,t}| - |U_{2,t}|) + |\frac{1}{\varepsilon}\partial_x\tilde{u}_{2,t}| \\ \partial_t|Q_{1,t}| \leq \frac{1}{\varepsilon}(|U_{1,t}| - |Q_{1,t}|) + K_1(|U_{0,t}| - |Q_{1,t}|) + |\frac{1}{\varepsilon}K_1\tilde{q}_{1,t}| \\ \partial_t|Q_{2,t}| \leq \frac{1}{\varepsilon}(|U_{2,t}| - |Q_{2,t}|) + K_2(|U_{0,t}| - |Q_{2,t}|) + |\frac{1}{\varepsilon}K_2\tilde{q}_{2,t}| \\ \qquad\qquad + |G'(q_2)\frac{1}{\varepsilon}\tilde{q}_{2,t}| - G'(q_2)|Q_{2,t}| \\ \partial_t|U_{0,t}| \leq K_1(|Q_{1,t}| - |U_{0,t}|) + K_2(|Q_{2,t}| - |U_{0,t}|) + |\frac{1}{\varepsilon}K_1\tilde{q}_{1,t}| \\ \qquad\qquad + |\frac{1}{\varepsilon}K_2\tilde{q}_{2,t}| + |G'(q_2)\frac{1}{\varepsilon}\tilde{q}_{2,t}| + G'(q_2)|Q_{2,t}|. \end{cases} \tag{2.36}$$

Indeed, we justify $4th$ and $5th$ inequalities of previous system with underlying arguments. On the one hand, we have

$$\begin{aligned}-G'(q_2)q_{2,t}sgn(Q_{2,t}) &= -G'(q_2)\Big(Q_{2,t}(t,x) - \frac{1}{\varepsilon}\tilde{q}_{2,t}(\frac{t}{\varepsilon},x)\Big)sgn(Q_{2,t})\\ &= -G'(q_2)|Q_{2,t}(t,x)| + G'(q_2)\frac{1}{\varepsilon}\tilde{q}_{2,t}(\frac{t}{\varepsilon},x)sgn(Q_{2,t})\\ &\le -G'(q_2)|Q_{2,t}| + \frac{1}{\varepsilon}|G'(q_2)\tilde{q}_{2,t}|.\end{aligned}$$

On the other hand

$$\begin{aligned}-G'(q_2)q_{2,t}\mathrm{sgn}(U_{0,t}) &= -G'(q_2)\Big(Q_{2,t}(t,x) - \frac{1}{\varepsilon}\tilde{q}_{2,t}(\frac{t}{\varepsilon},x)\Big)sgn(U_{0,t})\\ &\le G'(q_2)|Q_{2,t}| + \frac{1}{\varepsilon}|G'(q_2)\tilde{q}_{2,t}|,\end{aligned}$$

where we use for the last inequality that G is non-decreasing from assumption (2.5). Summing all equations and integrating on $(0,L)$, we obtain

$$\frac{d}{dt}\tilde{\mathcal{H}}_t(t) + |U_{2,t}(t,0)| \le F_1(t) + F_2(t) + F_3(t) + F_4(t), \tag{2.37}$$

where

$$\begin{aligned}F_1(t) &= |U_{2,t}(t,L)| - |U_{1,t}(t,L)|; \quad F_2(t) = |U_{1,t}(t,0)|;\\ F_3(t) &= \int_0^L \Big|\frac{1}{\varepsilon}\partial_x\tilde{u}_{2,t}(\frac{t}{\varepsilon},x)\Big|\,dx + \int_0^L \Big|\frac{1}{\varepsilon}\partial_x\tilde{u}_{1,t}(\frac{t}{\varepsilon},x)\Big|\,dx;\\ F_4(t) &= 2K_1\int_0^L \Big|\frac{1}{\varepsilon}\tilde{q}_{1,t}(\frac{t}{\varepsilon},x)\Big|\,dx + 2(\|G'\|_\infty + K_2)\int_0^L \Big|\frac{1}{\varepsilon}\tilde{q}_{2,t}(\frac{t}{\varepsilon},x)\Big|\,dx.\end{aligned}$$

Integrating (2.37) in time, we get

$$\tilde{\mathcal{H}}_t(t) + \int_0^T |U_{2,t}(t,0)|\,dt \le \int_0^T (F_1(t) + F_2(t) + F_3(t) + F_4(t))\,dt + \tilde{\mathcal{H}}_t(0). \tag{2.38}$$

Let us consider each term of the right hand side of (2.38) separately:

- F_1: Because of boundary condition $u_{2,t}(t,L) = u_{1,t}(t,L)$ and

$$\tilde{u}_{1,t}(t) = e^{-2t}(u_1^0 - q_1^0), \quad \tilde{u}_{2,t}(t) = e^{-2t}(u_2^0 - q_2^0), \tag{2.39}$$

(see (2.28)), we can conclude by definition (2.29) and the change of variable $\tau = \frac{t}{\varepsilon}$ that

$$\begin{aligned}\int_0^T (|U_{2,t}(t,L)| - |U_{1,t}(t,L)|)\,dt &\le \int_0^T \Big|\frac{1}{\varepsilon}(\tilde{u}_{2,t} - \tilde{u}_{1,t})(\frac{t}{\varepsilon},L)\Big|\,dt\\ &\le \int_0^{\frac{T}{\varepsilon}} |(\tilde{u}_{2,t} - \tilde{u}_{1,t})(\tau,L)|\,d\tau\\ &\le \frac{1}{2}\big(\|u_1^0 - q_1^0\|_\infty + \|u_2^0 - q_2^0\|_\infty\big).\end{aligned}$$

- F_2: Thanks to assumptions (2.3) and since

$$\int_0^T \left|\frac{1}{\varepsilon}\tilde{u}_{1,t}(\frac{t}{\varepsilon},x)\right| dt = \int_0^{\frac{T}{\varepsilon}} |(u_1^0(x) - q_1^0(x))e^{-2\tau}|\ d\tau,$$

from the expression of $\tilde{u}_{1,t}$ in (2.39) and the change of variable $\tau = \frac{t}{\varepsilon}$, we get

$$\begin{aligned}\int_0^T |U_{1,t}(t,0)|\ dt &\leq \int_0^T |u_b'(s)|\, ds + \int_0^{\frac{T}{\varepsilon}} |(u_1^0(x) - q_1^0(x))e^{-2\tau}|\ d\tau \\ &\leq \int_0^T |u_b'(s)|\, ds + \frac{1}{2}\|u_1^0 - q_1^0\|_\infty.\end{aligned}$$

- F_3: With the change of variable $\tau = \frac{t}{\varepsilon}$, we have, using again (2.39),

$$\begin{aligned}\int_0^T\int_0^L \left|\frac{1}{\varepsilon}\partial_x\tilde{u}_{i,t}(\frac{t}{\varepsilon},x)\right| dxdt &= \int_0^{\frac{T}{\varepsilon}}\int_0^L |\partial_x\tilde{u}_{i,t}(\tau,x)|\, dxd\tau \\ &\leq \frac{1}{2}\|\partial_x(u_i^0 - q_i^0)\|_{L^1(0,L)},\end{aligned}$$

which is uniformly bounded thanks to assumption on the initial data in (2.3).

- F_4: as above, we have

$$\begin{aligned}\int_0^T\int_0^L \left|\frac{1}{\varepsilon}\tilde{q}_{i,t}(\frac{t}{\varepsilon},x)\right| dxdt &= \int_0^{\frac{T}{\varepsilon}}\int_0^L |\tilde{q}_{i,t}(\tau,x)|\ dxd\tau \\ &\leq \frac{1}{2}\|q_i^0 - u_i^0)\|_{L^1(0,L)},\end{aligned}$$

thanks to the fact that $\partial_t\tilde{q}_i(\tau,x) = (q_i^0(x) - u_i^0(x))e^{-2\tau}$ with $i = 1, 2$.

We still have to control the term $\tilde{\mathcal{H}}_t(0)$ in (2.38), where

$$\tilde{\mathcal{H}}_t(0) = \int_0^L (|U_{1,t}(0,x)| + |U_{2,t}(0,x)| + |Q_{1,t}(0,x)| + |Q_{2,t}(0,x)| + |U_{0,t}(0,x)|)\, dx.$$

Therefore, we bound each term of the right-hand side separately.

- For the first term, we use the first equation of (2.34) to write

$$\partial_t U_1(0,x) = \frac{1}{\varepsilon}(Q_1(0,x) - U_1(0,x)) + \partial_x\tilde{u}_1(0,x) - \partial_x U_1(0,x).$$

Recalling that $Q_1(0,x) = q_1^0(x)$ and $U_1(0,x) = q_1^0(x)$ as defined in (2.35) we get: $\partial_t U_1(0,x) = \partial_x(q_1^0(x) - u_1^0(x)) - \partial_x U_1(0,x) = -\partial_x u_1^0(x)$, then

$$\int_0^L |\partial_t U_1(0,x)|\ dx \leq \int_0^L |\partial_x u_1^0(x)|\ dx < \infty,$$

since $u_1^0(x)$ belongs to $BV(0,L)$ (see assumption (2.3)).

- For the second term, by $2nd$ equation of system (2.34) with initial condition in (2.35), we get
$$\partial_t U_2(0,x) = \frac{1}{\varepsilon}(Q_2(0,x) - U_2(0,x)) + \partial_x \tilde{u}_2(0,x) + \partial_x U_2(0,x).$$
As above, recalling that $Q_2(0,x) = q_1^0(x)$ and $U_2(0,x) = q_2^0(x)$, it implies
$$\int_0^L |\partial_t U_2(0,x)|\, dx \leq \int_0^L |\partial_x u_2^0(x)|\, dx.$$

- For the third term, by $3rd$ equation of system (2.34), we have
$$\partial_t Q_1(0,x) = \frac{1}{\varepsilon}(U_1(0,x) - Q_1(0,x)) + K_1(u_0(0,x) - Q_1(0,x)) + K_1\tilde{q}_1(0,x),$$
Then with the initial conditions chosen for $\tilde{u}_i$ and $\tilde{q}_i$, we get
$$\int_0^L |\partial_t Q_1(0,x)|\; dx \leq K_1 \int_0^L |(u_0^0(x) - q_1^0(x))|\; dx < \infty.$$

- From the $4th$ equation of system (2.34), we have $\partial_t Q_2(0,x) = \frac{1}{\varepsilon}(U_2(0,x) - Q_2(0,x)) + K_2(u_0(0,x) - Q_2(0,x)) + K_2\tilde{q}_2(0,x) - G(q_2)$, which implies
$$\int_0^L |\partial_t Q_2(0,x)|\; dx \leq K_2 \int_0^L |(u_0^0(x) - q_2^0(x))|\; dx + \|G\|_\infty.$$

- Finally, with the last equation in (2.34) we get $\partial_t U_0(0,x) = K_1(Q_1(0,x) - U_0(0,x)) + K_2(Q_2(0,x) - u_0(0,x)) - K_1\tilde{q}_1(0,x) - K_2\tilde{q}_2(0,x) + G(q_2)$. It implies
$$\int_0^L |\partial_t U_0(0,x)|\; dx \leq K_1\|q_1^0 - u_0^0\|_{L^1(0,L)} + K_2\|q_2^0 - u_0^0\|_{L^1(0,L)} + \|G\|_\infty.$$

We conclude from (2.38) and the above calculations that
$$\tilde{\mathcal{H}}_t(t) + \int_0^T |U_{2,t}(t,0)|\, dt \leq \tilde{\mathcal{H}}_t(0) + \int_0^t (F_1 + F_2 + F_3 + F_4)(s)\; ds < \infty.$$

Finally, to recover (2.30) we add the $1st$ and $3rd$ inequalities in (2.36) and integrate on $(0,T) \times (0,L)$,
$$\begin{aligned}
&\int_0^L (|U_{1,t}(T,x)| - |U_{1,t}(0,x)|)\, dx + \int_0^L (|Q_{1,t}(T,x)| - |Q_{1,t}(0,x)|)\, dx \\
&+ \int_0^T (|U_{1,t}(t,L)| - |U_{1,t}(t,0)|)\, dt \leq \\
&\leq \int_0^T \int_0^L \left(K_1(|U_{0,t}(t,x)| - |Q_{1,t}(t,x)|) + \frac{K_1}{\varepsilon}|\tilde{q}_{1,t}(t,x)| + \frac{1}{\varepsilon}|\partial_x \tilde{u}_{1,t}(t,x)| \right) dxdt.
\end{aligned}$$

Then, we get

$$\begin{aligned}
&\int_0^L (|U_{1,t}(T,x)| + |Q_{1,t}(T,x)|)\, dx + \int_0^T |U_{1,t}(t,L)|\, dt \\
&\le \int_0^T |U_{1,t}(t,0)|\, dt + \int_0^L (|U_{1,t}(0,x)| + |Q_{1,t}(0,x)|)\, dx \\
&\quad + \int_0^T \int_0^L \left(K_1 |U_{0,t}(t,x)| + \frac{K_1}{\varepsilon} |\tilde{q}_{1,t}(t,x)| + \frac{1}{\varepsilon} |\partial_x \tilde{u}_{1,t}(t,x)| \right) dxdt.
\end{aligned}$$

We have already proved that the second term of the right-hand side is bounded. It has also been showed above that $U_{0,t}$ is uniformly bounded in $L^1((0,T)\times(0,L))$.
From (2.35), we have $U_{1,t}(t,0) = u_b'(t) + \frac{1}{\varepsilon}\tilde{u}_{1,t}(\frac{t}{\varepsilon}, 0)$, see also in term F_2. As above, we use $\tilde{u}_1$ and $\tilde{q}_1$ expressions and a change of variable to bound each term of the right hand side. It concludes the proof of Proposition 2.3.1. □

Proof of Corollary 2.3.1. We recall the expressions

$$U_1 = u_1 + \tilde{u}_1, \quad U_2 = u_2 + \tilde{u}_2, \quad U_0 = u_0, \quad Q_1 = q_1 + \tilde{q}_1, \quad Q_2 = q_2 + \tilde{q}_2.$$

By triangle inequality we have for $i = 1, 2$,

$$\begin{aligned}
\|\partial_t u_i\|_{L^1([0,T]\times[0,L])} &\le \|\partial_t U_i\|_{L^1([0,T]\times[0,L])} + \frac{1}{\varepsilon}\|\partial_t \tilde{u}_i(t/\varepsilon, x)\|_{L^1([0,T]\times[0,L])}, \\
\|\partial_t q_i\|_{L^1([0,T]\times[0,L])} &\le \|\partial_t Q_i\|_{L^1([0,T]\times[0,L])} + \frac{1}{\varepsilon}\|\partial_t \tilde{q}_i(t/\varepsilon, x)\|_{L^1([0,T]\times[0,L])}.
\end{aligned}$$

The first terms of the right hand side are bounded from Proposition 2.3.1. For the second terms, we have, as above,

$$\begin{aligned}
\int_0^T \int_0^L \frac{1}{\varepsilon}\Big|\partial_t \tilde{q}_i(\frac{t}{\varepsilon}, x)\Big|\, dxdt &= \int_0^T \int_0^L \Big|\frac{1}{\varepsilon}(q_i^0(x) - u_i^0(x))e^{-2\frac{t}{\varepsilon}}\Big|\, dxdt < \infty, \\
\int_0^T \int_0^L \frac{1}{\varepsilon}\Big|\partial_t \tilde{u}_i(\frac{t}{\varepsilon}, x)\Big|\, dxdt &= \int_0^T \int_0^L \Big|\frac{1}{\varepsilon}(u_i^0(x) - q_i^0(x))e^{-2\frac{t}{\varepsilon}}\Big|\, dxdt < \infty.
\end{aligned}$$

Furthermore, the expression in (2.38) leads us to

$$\int_0^T |U_{2,t}(t,0)|\, dt \le C_T.$$

By triangle inequality, it implies (2.32).

To recover (2.33), we notice that by definition of U_1 and using again triangle inequality, we get

$$|u_{1,t}(t,L)| \le |U_{1,t}(t,L)| + \frac{1}{\varepsilon}|\tilde{u}_{1,t}(\frac{t}{\varepsilon}, L)| \le |U_{1,t}(t,L)| + \frac{1}{\varepsilon}e^{-\frac{2t}{\varepsilon}}\|q_1^0 - u_1^0\|_{L^\infty}.$$

Integrating with respect to time as previously done in similar term and using (2.30) allows us to conclude the proof. □

Lemma 2.3.4 (Space derivatives estimates). *Let $T > 0$. Let us assume that* (2.3), (2.4), (2.5) *hold. Then, the space derivatives of functions u_1, u_2 satisfy the following uniform in ε estimate :*

$$\int_0^L (|\partial_x u_1(t,x)| + |\partial_x u_2(t,x)|)\, dxdt \leq C_T,$$

for some nonnegative constant C_T.

Proof. Adding equation (2.6a) with (2.6c) and also (2.6b) with (2.6d) we get

$$\alpha\partial_x u_1 = K_1(u_0 - q_1) - \partial_t u_1 - \partial_t q_1,$$
$$-\alpha\partial_x u_2 = K_2(u_0 - q_2) - \partial_t u_2 - \partial_t q_2 - G(q_2).$$

Using Corollary 2.3.1 and (2.5), the right hand sides are uniformly bounded in $L^1([0,L] \times [0,T])$. □

2.4 Convergence

In this section, we prove the main result of this Chapter.

Proof of Theorem 2.1.1. The proof is divided into several steps.

1st step. Convergence.
From Lemma 2.3.2, Lemma 2.3.3 and Corollary (2.3.1), we deduce that the sequences $(u_1^\varepsilon)_\varepsilon$ and $(u_2^\varepsilon)_\varepsilon$ are uniformly bounded in $L^\infty \cap BV((0,T) \times (0,L))$. Thanks to the Helly's theorem (see [5], [25] or also [14]), we deduce that, up to extraction of a subsequence,

$$u_1^\varepsilon \underset{\varepsilon\to 0}{\longrightarrow} u_1 \text{ strongly in } L^1([0,T] \times [0,L]),$$
$$u_2^\varepsilon \underset{\varepsilon\to 0}{\longrightarrow} u_2 \text{ strongly in } L^1([0,T] \times [0,L]),$$

with limit function $u_1, u_2 \in L^\infty \cap BV((0,T) \times (0,L))$.

By equations (2.6a), we know that:

$$\|q_1^\varepsilon - u_1^\varepsilon\|_{L^1} \leq C\varepsilon(\|\partial_t u_1^\varepsilon\|_{L^1} + \|\partial_x u_1^\varepsilon\|_{L^1}),$$

which tends to zero as ε goes to 0 thanks to the bounds in Corollary 2.3.1 and Lemma 2.3.4. Therefore, $q_1^\varepsilon \underset{\varepsilon\to 0}{\longrightarrow} u_1$ strongly in $L^1((0,T) \times (0,L))$ (up to an extraction). Basically,

$$||q_1^\varepsilon - u_1||_{L^1} = ||q_1^\varepsilon - u_1^\varepsilon + u_1^\varepsilon - u_1||_{L^1} \leq ||q_1^\varepsilon - u_1^\varepsilon||_{L^1} + ||u_1^\varepsilon - u_1||_{L^1}.$$

By the same token, we can deduce $q_2^\varepsilon \underset{\varepsilon\to 0}{\longrightarrow} u_2$ strongly in $L^1((0,T)\times(0,L))$ (up to an extraction). Moreover, since G is Lipschitz-continuous, when ε goes to zero, we have

$$\|G(q_2^\varepsilon) - G(u_2)\|_{L^1((0,T)\times(0,L))} \longrightarrow 0.$$

For the convergence of u_0^ε, let us first denote u_0 a solution to the equation

$$\partial_t u_0 = K_1(u_1 - u_0) + K_2(u_2 - u_0) + G(u_2).$$

We recall that $sgn(u^\varepsilon - u_0)\partial_t(u_0^\varepsilon - u_0) = \partial_t|u_0^\varepsilon - u_0|$ in the sense of distributions. Then, taking the last equation of system (2.6), subtracting by this latter equation and multiplying by $sgn(u_0^\varepsilon - u_0)$, we get

$$\begin{aligned}\partial_t|u_0^\varepsilon - u_0| &\leq K_1|q_1^\varepsilon - u_1| + K_2|q_2^\varepsilon - u_2| + (K_1+K_2)|u_0 - u_0^\varepsilon| + |G(q_2^\varepsilon) - G(u_2)| \\ &\leq K_1|q_1^\varepsilon - u_1| + K_2|q_2^\varepsilon - u_2| + (K_1+K_2)|u_0 - u_0^\varepsilon| + \|G'\|_\infty|q_2^\varepsilon - u_2|.\end{aligned}$$

Using a Grönwall Lemma, we get, after an integration on $[0, L]$,

$$\begin{aligned}\int_0^L |u_0^\varepsilon - u_0|(t,x)\,dx \leq &\int_0^L e^{(K_1+K_2)t}|u_0 - u_0^\varepsilon|(0,x)\,dx \\ &+ K_1\int_0^L\int_0^T e^{(K_1+K_2)(t-s)}|q_1^\varepsilon - u_1|(s,x)\,dsdx \\ &+ (\|G'\|_\infty + K_2)\int_0^L\int_0^T e^{(K_1+K_2)(t-s)}|q_2^\varepsilon - u_2|(s,x)\,dsdx.\end{aligned}$$

By previous arguments, we conclude that

$$u_0^\varepsilon \xrightarrow[\varepsilon\to 0]{} u_0 \text{ strongly in } L^1((0,T)\times(0,L)).$$

For the boundary terms, we deduce from (2.32) and (2.33) and Lemma 2.3.2 and Lemma 2.3.3, that the sequences $(u_1^\varepsilon(t,L))_\varepsilon$ and $(u_2^\varepsilon(t,0))_\varepsilon$ are uniformly bounded in $L^\infty \cap BV(0,T)$. Hence, by Helly's compactness theorem, we may extract subsequence, still denoted $(u_1^\varepsilon(t,L))_\varepsilon$ and $(u_2^\varepsilon(t,0))_\varepsilon$, which converge strongly in $L^1(0,T)$. We denote by $\overline{u_1}^L$ and $\overline{u_2}^0$ their respective limits.

2nd step. Limiting system.
We pass to the limit into the weak formulation of system (2.6). Let φ_1 and ψ_1 be two test functions such that $\varphi_1(T) = \psi_1(T) = 0$. For the first and the third equation in system (2.6), we have

$$\begin{aligned}-\int_0^T\int_0^L u_1^\varepsilon(\partial_t\varphi_1 + \alpha\partial_x\varphi_1)\,dxdt = &\int_0^T (u_b(t)\varphi_1(t,0) - u_1^\varepsilon(t,L)\varphi_1(t,L))\,dt \\ &+ \int_0^L u_1^0(x)\varphi_1(0,x)\,dx + \int_0^T\int_0^L \frac{1}{\varepsilon}(q_1^\varepsilon - u_1^\varepsilon)\varphi_1\,dxdt, \\ -\int_0^T\int_0^L q_1^\varepsilon\partial_t\psi_1\,dxdt = &\int_0^L q_1^0(x)\psi_1(0,x)\,dx - \int_0^T\int_0^L \frac{1}{\varepsilon}(q_1^\varepsilon - u_1^\varepsilon)\psi_1\,dxdt \\ &+K_1\int_0^T\int_0^L (u_0^\varepsilon - q_1^\varepsilon)\psi_1\,dxdt.\end{aligned}$$

Taking $\varphi_1 = \psi_1$ and adding the two equations,

$$\begin{aligned}-\int_0^T\int_0^L (\,(u_1^\varepsilon + q_1^\varepsilon)\partial_t\varphi_1 + u_1^\varepsilon\alpha\partial_x\varphi_1)\,dxdt = &\int_0^T (u_b(t)\varphi_1(t,0) - u_1^\varepsilon(t,L)\varphi_1(t,L))\,dt \\ + \int_0^L u_1^0(x)\varphi_1(0,x)\,dx + \int_0^L q_1^0(x)\varphi_1(0,x)\,dx &+ K_1\int_0^T\int_0^L (u_0^\varepsilon - q_1^\varepsilon)\varphi_1\,dxdt,\end{aligned}$$

then we may pass to the limit $\varepsilon \to 0$ in the resulting identity thanks to the above results of convergence and we obtain

$$
\begin{aligned}
-\int_0^T\int_0^L u_1(2\partial_t\varphi_1 + \alpha\partial_x\varphi_1)\,dxdt &= \int_0^T (u_b(t)\varphi_1(t,0) - \overline{u_1}^L(t)\varphi_1(t,L))\,dt \\
&+ \int_0^L (u_1^0(x) + q_1^0(x))\varphi_1(0,x)\,dx + K_1\int_0^T\int_0^L (u_0 - q_1)\varphi_1\,dxdt.
\end{aligned}
$$

This is the weak formulation of solution to system (2.7) with initial condition (2.10) and boundary condition $u_1(t,L) = \overline{u_1}^L$.

By the same token for the second and fourth equations in the weak formulation of system (2.6), for any test functions φ_2 and ψ_2 such that $\varphi_2(T) = \psi_2(T) = 0$, we have

$$
\begin{aligned}
-\int_0^T\int_0^L u_2^\varepsilon(\partial_t\varphi_2 + \alpha\partial_x\varphi_2)\,dxdt &= \int_0^T (u_2^\varepsilon(t,0)\varphi_2(t,0) - u_1^\varepsilon(t,L)\varphi_2(t,L))\,dt \\
&+ \int_0^L u_2^0(x)\varphi_2(0,x)\,dx + \int_0^T\int_0^L \frac{1}{\varepsilon}(q_2^\varepsilon - u_2^\varepsilon)\varphi_2\,dxdt, \\
-\int_0^T\int_0^L q_2^\varepsilon\partial_t\psi_2\,dxdt &= \int_0^L q_2^0(x)\psi_2(0,x)\,dx - \int_0^T\int_0^L \frac{1}{\varepsilon}(q_2^\varepsilon - u_2^\varepsilon)\psi_2\,dxdt \\
&+ K_2\int_0^T\int_0^L (u_0^\varepsilon - q_2^\varepsilon)\psi_2\,dxdt - \int_0^T\int_0^L G(q_2^\varepsilon)\psi_2\,dxdt.
\end{aligned}
$$

Taking $\varphi_2 = \psi_2$ and adding the two equations, we may pass to the limit $\varepsilon \to 0$ in the resulting identity thanks to the above results of convergence, we obtain

$$
\begin{aligned}
-\int_0^T\int_0^L u_2(2\partial_t\varphi_2 + \alpha\partial_x\varphi_2)\,dxdt &= \int_0^T (\overline{u_2}^0(t)\varphi_2(t,0) - \overline{u_1}^L(t)\varphi_2(t,L))\,dt \\
&+ \int_0^L (u_2^0(x) + q_2^0(x))\varphi_2(0,x)\,dx + K_2\int_0^T\int_0^L (u_0 - q_2)\varphi_2\,dxdt \\
&- \int_0^T\int_0^L G(q_2)\varphi_2\,dxdt.
\end{aligned}
$$

This is the weak formulation of (2.8) with initial conditions (2.10) and boundary conditions $u_2(t,L) = \overline{u_1}^L$. Passing to the limit in the weak formulation of the equation for u_0^ε is straightforward. Therefore, we recover (2.7)-(2.8) with initial and boundary conditions (2.10)-(2.11). Finally, since the solution to this latter system is unique, we deduce that the whole sequence converges. It concludes the proof of Theorem 2.1.1. □

Chapter 3

On the role of the epithelium in a model of sodium exchange in renal tubules

The results presented in this Chapter follow by the collaboration with Aurélie Edwards, Vuk Milišić and Nicolas Vauchelet, [26].

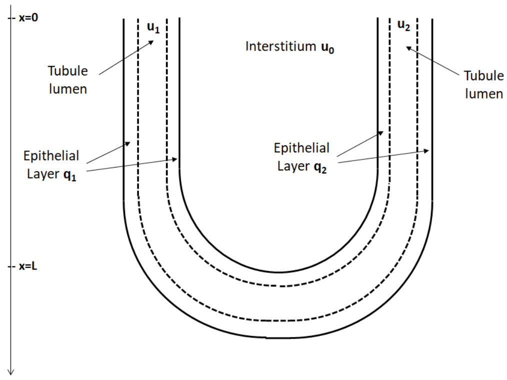


Figure 3.1: Simplified model of loop of Henle. q_1/q_2 and u_1/u_2 denote solute concentration in the epithelial layer and lumen of the descending/ascending limb, respectively.

3.1 Introduction

As already explained in the Introduction, one of the main functions of the kidneys is to filter metabolic wastes and toxins from plasma and excrete them in urine. The kidneys also play a key role in regulating the balance of water and electrolytes, long-term blood pressure, as well as acid-base equilibrium. The structural and functional units of the kidney are called nephrons, which number about 1 million in each human kidney [3].

Blood is first filtered by glomerular capillaries and then the composition of the filtrate varies as it flows along different segments of the nephron : the proximal tubule, Henle's loop (which is formed by a descending limb and an ascending limb), the distal tubule, and the collecting duct. In this study we present a simplified mathematical model of solute transport in Henle's loop. In our simplified approach, the loop of Henle is represented as two tubules in a counter-current arrangement, the descending and ascending limb are considered to be rigid cylinders of length L lined by a layer of epithelial cells. Water and solute reabsorption from the luminal fluid into the interstitium proceeds in two steps : water and solutes cross first the apical membrane at the lumen-cytosol interface and then the basolateral membrane at the cytosol-interstitium interface, [52]. A schematic representation of the model is given in Figure 3.1.

The energy that drives tubular transport is provided by Na^+/K^+-ATPase, an enzyme that couples the hydrolysis of ATP to the pumping of sodium (Na^+) ions out of the cell and potassium (K^+) ions into the cell, across the basolateral membrane. The electrochemical potential gradients resulting from this active transport mechanism in turn drive the passive transport of ions across other transporters, via diffusion or coupled transport. We refer to diffusion as the biological process in which a substance tends to move from an area of high concentration to an area of low concentration [41, 45]. As described in the Introduction 1, in the absence of electrical forces, the diffusive solute flux from compartment 1 to compartment 2 (expressed in $[mol.m^{-1}.s^{-1}]$) is given by:

$$J_{\text{diffusion}} = P\ell(u_2 - u_1),$$

where P $[m.s^{-1}]$ is the permeability of the membrane to the considered solute, ℓ the perimeter of the membrane, and u_1 and u_2 are the respective concentrations of the solute in compartments 1 and 2.

We assume that the volumetric flow rate in the luminal fluid (denoted by $\alpha > 0$) remains constant, i.e. there is no transepithelial water transport. The present model focuses on tubular Na^+ transport. We recall the main variables and parameters:

- u_1 and u_2, denote respectively the concentration of Na^+ ($[mol.m^{-3}]$) in the lumen of the descending and ascending limb,
- q_1 and q_2 are the concentration of Na^+ respectively in the epithelial cells of the descending and ascending limbs
- u_0 in the interstitium,
- P_1 and P_2 denote respectively the permeability to Na^+ of the membrane separating the lumen and the epithelial cell of the descending and ascending limb,
- $P_{1,e}$ denotes the permeability to Na^+ of the membrane separating the epithelial cell of the descending limb and the interstitium.

In this study the Na^+ permeability at the interface between the epithelial cell of the ascending limb and the interstitium is taken to be negligible, i.e. $P_{2,e} = 0$. The re-absorption or secretion of ions generates electrical potential differences across membranes but here the impact of transmembrane potentials on Na^+ transport is not taken into account.

The concentrations depend on the time t and the spatial position $x \in [0, L]$. The dynamics of Na^+ concentration is given by the following model on $(0, +\infty) \times (0, L)$

$$a_1 \frac{\partial u_1}{\partial t} + \alpha \frac{\partial u_1}{\partial x} = J_1, \quad a_2 \frac{\partial u_2}{\partial t} - \alpha \frac{\partial u_2}{\partial x} = J_2, \tag{3.1}$$

$$a_3 \frac{\partial q_1}{\partial t} = J_3, \quad a_4 \frac{\partial q_2}{\partial t} = J_4, \quad a_0 \frac{\partial u_0}{\partial t} = J_0. \tag{3.2}$$

The parameters a_i, for $i = 0, 1, 2, 3, 4$, denote positive constants defined as:

$$a_1 = \pi r_1^2,\ a_2 = \pi r_2^2,\ a_3 = \pi(r_{1,e}^2 - r_1^2),\ a_4 = \pi(r_{2,e}^2 - r_2^2),\ a_0 = \pi\Big(\frac{r_{1,e}^2 + r_{2,e}^2}{2}\Big). \tag{3.3}$$

In these equations, r_i, $i = 1, 2$, denotes the inner radius of tubule i, whereas $r_{i,e}$ denotes the outer radius of tubule i, which includes the epithelial layer. The fluxes J_i describe the ionic exchanges between the different domains modeled in the following way:

$$J_1 = 2\pi r_1 P_1 (q_1 - u_1), \quad J_2 = 2\pi r_2 P_2 (q_2 - u_2),$$

$$J_3 = 2\pi r_1 P_1 (u_1 - q_1) + 2\pi r_{1,e} P_{1,e} (u_0 - q_1),$$

$$J_4 = 2\pi r_2 P_2 (u_2 - q_2) - 2\pi r_{2,e} G(q_2),$$

$$J_0 = 2\pi r_1 P_{1,e} (q_1 - u_0) + 2\pi r_{2,e} G(q_2).$$

In the ascending limb (tubule 2), we also consider the active reabsorption that is mediated by Na^+/K^+-ATPase, which pumps 3 Na^+ ions out of the cell in exchange for 2 K^+ ions. The pump is described using the Michaelis-Menten kinetics, [16]:

$$G(q_2) = V_m \left[\frac{q_2}{K_{M,2} + q_2} \right]^3 .$$

The dynamics of ionic concentrations is given by the following model:

$$\begin{cases} a_1 \partial_t u_1(t,x) + \alpha \partial_x u_1(t,x) = J_1(t,x) \\ a_2 \partial_t u_2(t,x) - \alpha \partial_x u_2(t,x) = J_2(t,x) \\ a_3 \partial_t q_1(t,x) = J_3(t,x) \\ a_4 \partial_t q_2(t,x) = J_4(t,x) \\ a_0 \partial_t u_0(t,x) = J_0(t,x). \end{cases} \tag{3.4}$$

We set the boundary conditions :

$$u_1(t,0) = u_b(t), \quad u_2(t,L) = u_1(t,L), \quad t > 0, \tag{3.5}$$

where u_b is a given function in $L^\infty(\mathbb{R}^+) \cap L^1_{loc}(\mathbb{R}^+)$, which is such that $\lim_{t\to\infty} u_b(t) = \bar{u}_b$ for some positive constant $\bar{u}_b > 0$.

Finally, the system is complemented with initial conditions

$$\begin{aligned} &u_1(0,x) = u_1^0(x), \quad u_2(0,x) = u_2^0(x), \quad u_0(0,x) = u_0^0(x), \\ &q_1(0,x) = q_1^0(x), \quad q_2(0,x) = q_2^0(x). \end{aligned}$$

We simplify the notation as already explained and we will refer to this as the dynamic system and then (3.4) reads :

$$a_1 \partial_t u_1 + \alpha \partial_x u_1 = k(q_1 - u_1) \tag{3.6a}$$

$$a_2 \partial_t u_2 - \alpha \partial_x u_2 = k(q_2 - u_2) \tag{3.6b}$$

$$a_3 \partial_t q_1 = k(u_1 - q_1) + K_1(u_0 - q_1) \tag{3.6c}$$

$$a_4 \partial_t q_2 = k(u_2 - q_2) - G(q_2) \tag{3.6d}$$

$$a_0 \partial_t u_0 = K_1(q_1 - u_0) + G(q_2). \tag{3.6e}$$

with

$$G(q_2) = V_{m,2} \left[\frac{q_2}{K_{M,2} + q_2} \right]^3, \quad V_{m,2} := 2\pi r_{2,e} V_m. \tag{3.7}$$

The existence and uniqueness of vector solution $\mathbf{u} = (u_1, u_2, q_1, q_2, u_0)$ to this system are investigated in the Chapter 2 and in [27]. Several previous works have neglected the epithelium region (see e.g. [47, 46]). The first goal of this work is to study the effects of this region in the mathematical model. The main indicator quantifying these effects is the parameter k which accounts for the permeability between the lumen and the epithelium. Then, we analyse the dependency between the concentrations and k. In the absence of physiological perturbations, the concentrations are very close to the steady state, thus it seems reasonable to consider solutions of (3.6) at equilibrium, which leads us to study the system :

$$\begin{cases} +\alpha\partial_x \bar{u}_1 = k(\bar{q}_1 - \bar{u}_1) \\ -\alpha\partial_x \bar{u}_2 = k(\bar{q}_2 - \bar{u}_2) \\ 0 = k(\bar{u}_1 - \bar{q}_1) + K_1(\bar{u}_0 - \bar{q}_1) \\ 0 = k(\bar{q}_2 - \bar{u}_2) - G(\bar{q}_2) \\ 0 = K_1(\bar{q}_1 - \bar{u}_0) + G(\bar{q}_2) \\ \bar{u}_1(L) = \bar{u}_2(L), \quad \bar{u}_1(0) = \bar{u}_b. \end{cases} \tag{3.8}$$

Section 3.2 concerns the analysis of solutions to stationary system (3.8). In particular, we study their qualitative behaviour and their dependency with respect to the parameter k. Our mathematical observations are illustrated by some numerical computations.

The second aim of the paper is to study the asymptotic behaviour of the solutions of (3.6). In Theorem 3.3.1, we show that they converge as t goes to $+\infty$ to the steady state solutions solving (3.8). Section 3.3 is devoted to the statement and the proof of this convergence result. Finally, an Appendix provides some useful technical lemmas.

3.2 Stationary system

In this section, after proving basic existence and uniqueness results, we investigate how solutions of (3.8) depend upon the parameter k. We recall that it includes also the permeability parameter as $k = k_i$ with $k_i := 2\pi r_i P_i$, $i = 1, 2$. In order to study the qualitative behaviour of these solutions, we then perform some numerical simulations.

3.2.1 Stationary solution

We first show existence and uniqueness of solutions to the stationary system:

Lemma 3.2.1. *Let $\bar{u}_b > 0$. Let G be a C^2 function, uniformly Lipschitz, such that G'' is uniformly bounded and $G(0) = 0$ (e.g. the function defined in* (3.7)*). Then, there exists an unique vector solution to the stationary problem* (3.8)*.*

Moreover, if we assume that $G > 0$ on $\mathbb{R}^+$, then we have the following relation

$$\bar{q}_2 < \bar{u} < \bar{q}_1 < \bar{u}_0.$$

Proof. Summing up all the equations of system (3.8), we deduce that $\alpha(\partial_x \bar{u}_1 - \partial_x \bar{u}_2) = 0$. From the boundary condition $\bar{u}_1(L) = \bar{u}_2(L)$, we obtain $\bar{u}_1 = \bar{u}_2 = \bar{u}$. Therefore, we may simplify system (3.8) in

$$\begin{cases} \alpha\partial_x \bar{u} = k(\bar{u} - \bar{q}_2) \\ 2\bar{u} = \bar{q}_1 + \bar{q}_2 \\ 0 = k(\bar{u} - \bar{q}_1) + K_1(\bar{u}_0 - \bar{q}_1) \\ 0 = k(\bar{u} - \bar{q}_2) - G(\bar{q}_2) \\ 0 = K_1(\bar{q}_1 - \bar{u}_0) + G(\bar{q}_2). \end{cases} \tag{3.9}$$

Parameters	Description	Values
L	Length of tubules	$2 \cdot 10^{-3}$ $[m]$
α	Water flow in the tubules	10^{-13} $[m^3/s]$
r_i	Radius of tubule $i = 1, 2$	10^{-5} $[m]$
$r_{i,e}$	Radius of epithelium layer $i = 1, 2$	$1.5 \cdot 10^{-5}$ $[m]$
K_1	$2\pi r_{1,e} P_{1,e}$	$\sim 2\pi \cdot 10^{-11}$ $[m^2/s]$
$k = k_i$	$2\pi r_i P_i,\ i = 1, 2$	changeable $[m^2/s]$
$V_{m,2}$	Rate of active transport	$\sim 2\pi r_{2,e} 10^{-5}$ $[mol.m^{-1}.s^{-1}]$
$K_{M,2}$	Pump affinity for sodium (Na^+)	$3,5$ $[mol/m^3]$
$\bar{u}_b$	Initial concentration in tubule 1	140 $[mol/m^3]$

Table 3.1: Frequently used parameters

By the fourth equation of (3.9), $\bar{u} = \bar{q}_2 + \frac{G(\bar{q}_2)}{k}$, inserted into the first equation, it gives $\partial_x \bar{u} = \frac{G(\bar{q}_2)}{\alpha}$. We obtain a differential equation satisfied by $\bar{q}_2$,

$$\partial_x \bar{q}_2 = \frac{G(\bar{q}_2)}{\left(\alpha + \frac{\alpha}{k} G'(\bar{q}_2)\right)}, \tag{3.10}$$

with α, k positive constants and provided with the condition $\bar{q}_2(0)$ that satisfies

$$\bar{q}_2(0) + \frac{G(\bar{q}_2(0))}{k} = \bar{u}_b. \tag{3.11}$$

We first remark that $\bar{q}_2(0) \mapsto \bar{q}_2(0) + \frac{G(\bar{q}_2(0))}{k}$ is a C^2 increasing function which takes the value 0 at 0 and goes to $+\infty$ at $+\infty$. Thus, for any $\bar{u}_b > 0$ there exists a unique $\bar{q}_2(0) > 0$ solving (3.11).

By assumption, G' and G'' are uniformly bounded, thus we check easily that the right-hand side of (3.10) is uniformly Lipschitz. Therefore, the Cauchy problem (3.10)–(3.11) admits a unique solution, which is positive (by uniqueness since 0 is a solution).

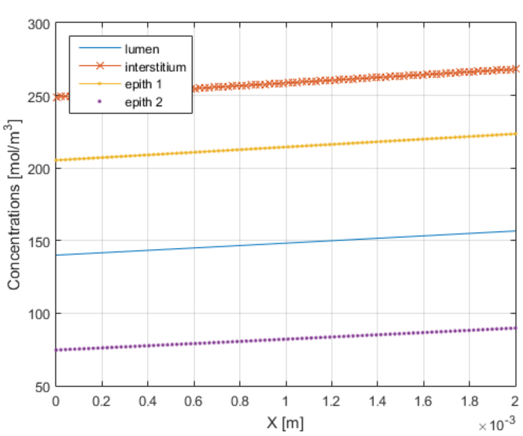
Then, other quantities are computed thanks to the relations:

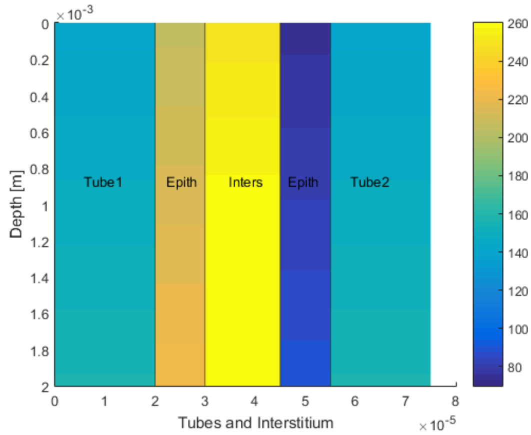
$$\bar{u} = \bar{q}_2 + \frac{G(\bar{q}_2)}{k}, \quad \bar{q}_1 = \bar{q}_2 + \frac{2G(\bar{q}_2)}{k}, \quad \bar{u}_0 = \left(\frac{1}{K_1} + \frac{2}{k}\right) G(\bar{q}_2) + \bar{q}_2. \tag{3.12}$$

Moreover, by the fourth and fifth equations of system (3.9) and since $G(\bar{q}_2) > 0$, we immediately deduce that $\bar{q}_2 < \bar{u}$ and $\bar{q}_1 < \bar{u}_0$. Using the second equation of (3.9), we obtain the claim. $\square$

3.2.2 Numerical simulations of stationary solutions

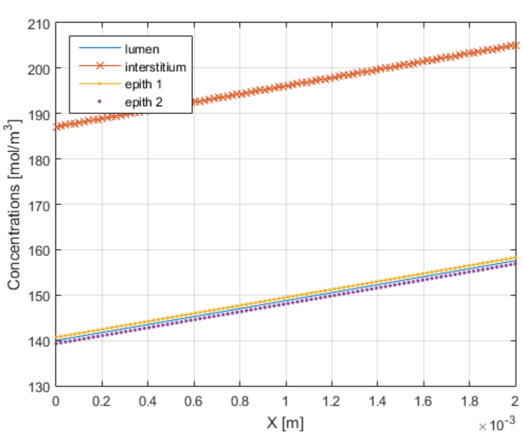
We approximate numerically solutions of (3.9). Numerical values of the parameters (cf Table 3.1) are extracted from Table 2 in [13] and Table 1 in [23]. Taking into account these quantities allow us to have the numerical ranges of the constants and the solution results in a biologically realistic framework. Following the proof of Lemma 3.2.1, we first solve (3.11) thanks to a Newton method. Then, we solve (3.10) with a fourth order Runge-Kutta method. Finally, we deduce other concentrations u, q_1, u_0 using (3.12).

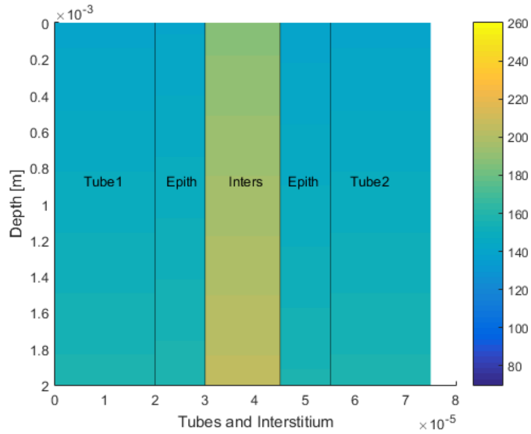




(a) Concentration profiles with permeability $P_i = 2 \cdot 10^{-7}$ [m/s].

(b) Concentrations in 2D with $P_i = 2 \cdot 10^{-7}$. Length of lumen on vertical axis.





(c) Concentration profiles with permeability $P_i = 2 \cdot 10^{-5}$ [m/s].

(d) Concentrations in 2D with $P_i = 2 \cdot 10^{-5}$. Length of lumen on vertical axis.

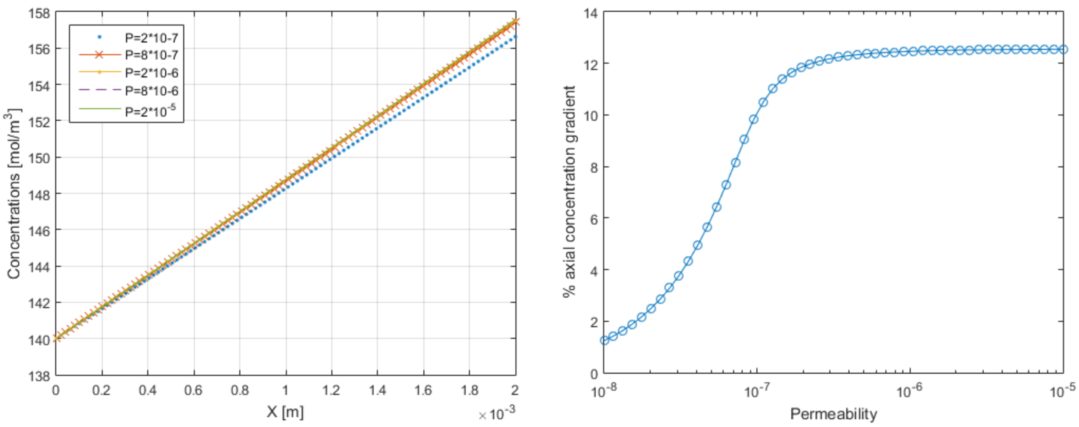
Figure 3.2: Concentration profiles for $V_{m,2} = 2\pi r_{2,e} 10^{-5}$ and different permeability values.

Results from Figures 3.2a and 3.2c show that in all compartments, concentrations increase as a function of depth (x-axis). Physiologically, this means that the fluid is more concentrated towards the hairpin turn ($x = L$) than near $x = 0$, because of active transport in the ascending limb. It can also be seen that Na^+ concentration is higher in the central layer of interstitium and lower in the ascending limb epithelium owing to active Na^+ transport from the latter to the central compartment, described by the non-linear term $G(q_2)$. Furthermore, Figure 3.2b and Figure 3.2d highlight that increasing the permeability value homogenizes the concentrations in the tubules and in the epithelium region. Taking a very large permeability value is equivalent to fusing the epithelial layer with the adjacent lumen, such that luminal and epithelial concentrations become equal. It is proved rigorously in Chapter 2 that this occurs in the dynamic system (3.6). This is derived and explained formally also in Appendix B.1.

Figures 3.3 and 3.4 depict the impact of permeability $P_1 = P_2 = P$ on concentration profiles for various pump rates $V_{m,2}$. Axial profiles of luminal concentrations are shown in Figures 3.3a and 3.4a, considering different values of the permeability between the lumen and the epithelium. The fractional increase in concentration (FIC) is shown in Figures 3.3b and 3.4b : for each permeability value (plotted on the horizontal axis), we compute the following ratio (shown on the vertical axis):

$$\text{FIC}(\bar{u}) := 100\frac{\bar{u}(L) - \bar{u}(0)}{\bar{u}(0)}, \tag{3.13}$$

where $\bar{u}(L)$ is the concentration in the tubular lumen $1, 2$ at $x = L$ and $\bar{u}(0)$ the concentration at $x = 0$. This illustrates the impact of permeability on the axial concentration gradient. We observe that this ratio depends also strongly on the value of $V_{m,2}$.



(a) Axial concentrations in the lumen for different values of permeability.

(b) Fractional increase in concentration as a function of permeability.

Figure 3.3: Concentration profiles for $V_{m,2} = 2\pi r_{2,e} \cdot 10^{-5}$ $[mol.m^{-1}.s^{-1}]$.

The permeability range (numerically $P \in [10^{-8}, 10^{-5}]$, equispaced 50 values between these) encompasses the physiological value which should be around 10^{-7} m/s. As shown in Figures 3.3b and 3.4b, the FIC increases significantly with P until it reaches a plateau : indeed, as diffusion becomes more rapid than active transport (that is, pumping by Na^+/ K^+-ATPase), the permeability ceases to be rate-limiting. As shown by comparing Figures 3.3b and 3.4b, the FIC is strongly determined by the pump rate $V_{m,2}$: if $P \in [10^{-8}, 10^{-6}]$, Na^+ concentration along the lumen increases by less than 12% if $V_{m,2} = 2\pi r_{2,e}10^{-5}$, and may reach 120% if $V_{m,2} = 2\pi r_{2,e}10^{-4}$. This raise is expected since concentration differences are generated by active transport ; the higher the rate of active transport, the more significant these differences. Conversely, in the absence of pumping, concentrations would equilibrate everywhere. In regards to the axial gradient, the interesting numerical results are in Figure (3.4a) and (3.4b). We observe that the axial gradient increases with increasing permeability when the latter is varied within the chosen range. Therefore this indicates that taking into account the epithelial layer in the model has a significant influence on the axial concentration gradient.

Moreover, numerical results also confirm that : $\bar{u}_1 = \bar{u}_2 = u < \bar{q}_1 < \bar{u}_0$ as reported in Lemma 3.2.1. We recall that we assume a constant water flow α which allows us to deduce $\bar{u}_1 = \bar{u}_2$. As noted above, the descending limb is in fact very permeable to water and α should decrease significantly in this tubule, such that $\bar{u}_1$ differs from $\bar{u}_2$, except at the hairpin turn at $x = L$. On the other hand, the last equation of system (3.9) implies that $\bar{q}_1 < \bar{u}_0$, meaning that the concentration of Na^+ is lower in the epithelial cell than in the interstitium, as observed in vivo, [2].

With the expression of G in (3.7), equation (3.11) reads

$$\bar{q}_2(0) + \frac{V_{m,2}}{k}\left(\frac{\bar{q}_2(0)}{K_{M,2} + \bar{q}_2(0)}\right)^3 = \bar{u}_b. \tag{3.14}$$

In order to better understand the behaviour of the axial concentration gradient shown in Figures (3.3b), (3.4b), we compute the derivative of (3.14) with respect to the parameter V_m and with respect to k respectively:

$$\frac{\partial \bar{q}_2(0)}{\partial V_m} + \frac{1}{k}G'(\bar{q}_2(0))\frac{\partial \bar{q}_2(0)}{\partial V_m} + \frac{1}{k}\left(\frac{\bar{q}_2(0)}{K_{M,2} + \bar{q}_2(0)}\right)^3 = 0,$$

$$\frac{\partial \bar{q}_2(0)}{\partial k} + \frac{1}{k}G'(\bar{q}_2(0))\frac{\partial \bar{q}_2(0)}{\partial k} - \frac{1}{k^2}G(\bar{q}_2(0)) = 0.$$

Then, we get

$$\frac{\partial \bar{q}_2(0)}{\partial V_m} = \frac{-\frac{1}{k}}{1 + \frac{1}{k}G'(\bar{q}_2(0))}\left(\frac{\bar{q}_2(0)}{k_M + \bar{q}_2(0)}\right)^3 \leq 0,$$

$$\frac{\partial \bar{q}_2(0)}{\partial k} = \frac{\frac{1}{k^2}G(\bar{q}_2(0))}{1 + \frac{1}{k}G'(\bar{q}_2(0))} \geq 0,$$

because G is a monotone non-decreasing function and $q_2(0)$ is positive.

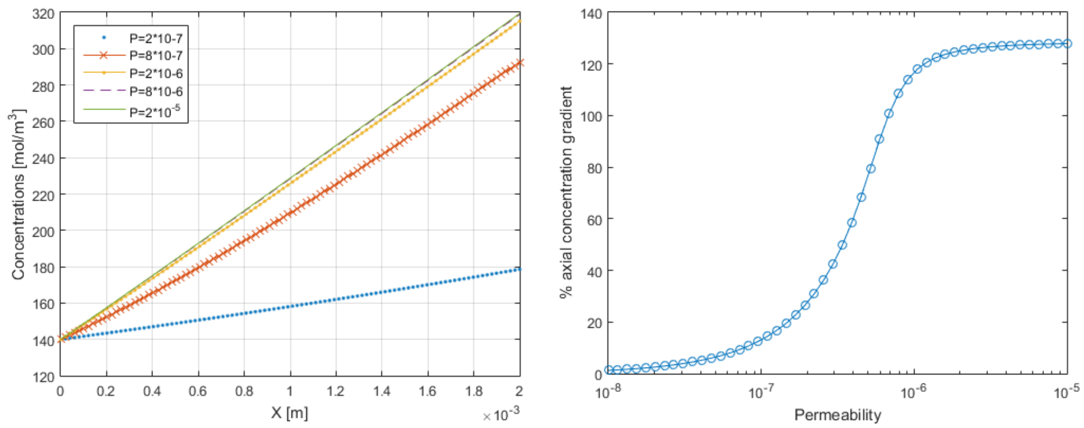
We observe from numerical results (see Figures 3.2a, 3.2c, 3.3a, and 3.4a) that the gradient of u is almost constant. Thus, we may make the approximation

$$\partial_x \bar{u} \sim \partial_x \bar{u}(0) = \frac{G(\bar{q}_2(0))}{\alpha}. \tag{3.15}$$

Its derivatives with respect to $V_{m,2}$ and k are both non negative :

$$\frac{\partial}{\partial k}[\partial_x \bar{u}] \sim \frac{G'(\bar{q}_2(0))}{\alpha}\left(\frac{\frac{G(\bar{q}_2(0))}{k^2}}{1 + \frac{1}{k}G'(\bar{q}_2(0))}\right) \geq 0,$$

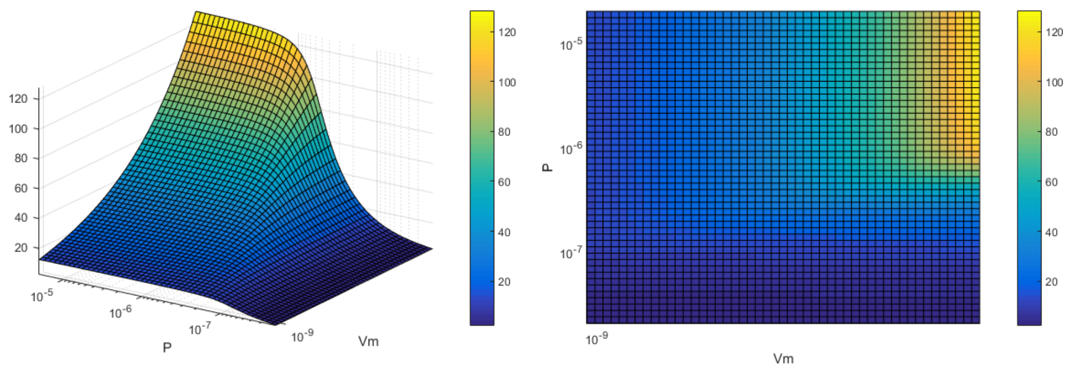
$$\frac{\partial}{\partial V_m}[\partial_x \bar{u}] \sim \frac{1}{\alpha}\left(\frac{\bar{q}_2(0)}{K_M + \bar{q}_2(0)}\right)^3\left(\frac{1}{1 + \frac{1}{k}G'(\bar{q}_2(0))}\right) \geq 0.$$



(a) Axial concentrations in the lumen for different values of permeability.

(b) Percentage of concentration gradient as a function of permeability.

Figure 3.4: Concentration profiles for $V_{m,2} = 2\pi r_{2,e} \cdot 10^{-4}$ $[mol.m^{-1}.s^{-1}]$



(a) Percentage of concentration gradient 2D in tubules

(b) Percentage of concentration gradient projection

Figure 3.5: Percentage of concentration gradient 2D with range $V_{m,2} \in 2\pi r_{2,e} \cdot (10^{-5}, 10^{-4})$ $[mol.m^{-1}.s^{-1}]$ ($x-$axis) and $P \in 2 \cdot (10^{-8}, 10^{-5})$ ($y-$axis)

It means that the axial concentration gradient is an increasing function both with respect to the rate of active transport $V_{m,2}$ and to the permeability k.

Indeed in Fig. 3.5, we perform numerical simulations varying both P and $V_{m,2}$ and observe that the ratio (3.13) increases monotonically with respect to both parameters.

3.2.3 Limiting cases: $k \to \infty$, and $k \to 0$

Numerical results show that above a certain high value of permeability, the epithelial concentration in tubule 2 seems to reach a plateau (see Figures 3.3b and 3.4b). There are two different regimes : one for large values of permeabilities, one for small values of permeabilities, and a fast transition between them.

In the large permeabilities asymptotic, we may approximate system (3.9) by the limiting model $k = +\infty$. In this case, (3.12) reduces to

$$\bar{u} = \bar{q}_2, \quad \bar{q}_1 = \bar{q}_2, \quad \bar{u}_0 = \frac{G(\bar{q}_2)}{K_1} + \bar{q}_2.$$

for all $x \in (0, L)$. This is understandable from a formal point of view, also taking into account computations in Appendix (B.1) for the stationary system (3.8). In this case, the gradient concentration is directly proportional to $V_{m,2}$:

$$\partial_x \bar{q}_2 = \frac{G(\bar{q}_2)}{\alpha + \frac{\alpha}{k} G'(\bar{q}_2)} \underset{k \to +\infty}{\longrightarrow} \frac{G(\bar{q}_2)}{\alpha} = \partial_x \bar{u}.$$

From (3.10), the Cauchy problem reduces to

$$\partial_x \bar{q}_2(x) = \frac{G(\bar{q}_2)}{\alpha}, \quad \bar{q}_2(0) = \bar{u}_b.$$

Additionally, it is clear that the higher pump value, the more the FIC will increase, as observed in Figure 3.4b.

On the other hand for small values of permeability, we obtain formally

$$\partial_x \bar{q}_2 \underset{k \to 0}{\longrightarrow} 0, \qquad \partial_x \bar{u} = \frac{G(\bar{q}_2)}{\alpha}.$$

Therefore in a neighbourhood of the value $P \sim 10^{-8}$, the concentration gradient tends to be constant and for this reason we notice a plateau.

3.3 Long time behaviour

This section is devoted to the main mathematical result of this paper concerning the long time asymptotics of solutions to (3.6) towards solutions to the stationary system (3.8) as time goes to $+\infty$. We first state the main result and the assumptions needed. Then, we introduce eigenelements of an auxiliary linear system and its dual problem. Using these auxiliary functions, we are able to show the convergence when the time variable goes to $+\infty$. A similar approach was considered in [47] following ideas from [39].

3.3.1 Statement of the main result

Before stating the main result, we provide and recall the mathematical assumptions (2.3), (2.4), (2.5) on the initial and boundary data

Assumption 3.3.1. We assume that the initial solute concentrations are non-negative and uniformly bounded in $L^\infty(0, L)$ and in the total variation :

$$0 \leq u_1^0, u_2^0, q_1^0, q_2^0, u_0^0 \in BV(0, L) \cap L^\infty(0, L). \tag{3.16}$$

Assumption 3.3.2. The boundary condition of system (3.6) is such that

$$0 \leq u_b \in L^\infty(\mathbb{R}^+) \cap L^1_{loc}(\mathbb{R}^+), \quad \lim_{t\to+\infty} |u_b - \bar{u}_b| = 0, \tag{3.17}$$

for some constant $\bar{u}_b > 0$.

BV is the space of functions with bounded variation, we notice that such functions have a trace on the boundary (see e.g. [7]); hence the boundary condition $u_2(t, L) = u_1(t, L)$ is well-defined.

Assumption 3.3.3. Regularity and boundedness of G. We assume that the non-linear function modelling active transport in the ascending limb (tube 2) is a bounded and Lipschitz-continuous function on $\mathbb{R}^+$:

$$\forall x \in \mathbb{R}^+, \quad 0 \leq G(q_2) \leq \|G\|_\infty, \quad 0 \leq G'(q_2) \leq \|G'\|_\infty. \tag{3.18}$$

We notice that G defined by (3.7) satisfies straightforwardly (3.18).

We now state the main result.

Theorem 3.3.1 (Long time behavior). *Under above-mentioned Assumptions 3.3.1, 3.3.2 and 3.3.3, the solution to the dynamical problem* (3.6) *denoted by* $\mathbf{u}(t, x) = (u_1, u_2, q_1, q_2, u_0)$ *converges as time t goes to $+\infty$ towards $\bar{\mathbf{u}}(x)$, the unique solution to the stationary problem* (3.8)*, in the following sense*

$$\lim_{t\to+\infty} \|\mathbf{u}(t) - \bar{\mathbf{u}}\|_{L^1(\Phi)} = 0,$$

with the space

$$L^1(\Phi) = \Big\{\mathbf{u} : [0, L] \to \mathbb{R}^5; \quad \|\mathbf{u}\|_{L^1(\Phi)} := \int_0^L |\mathbf{u}(x)| \cdot \Phi(x)\, dx < \infty\Big\},$$

where $\Phi = (\varphi_1, \varphi_2, \phi_1, \phi_2, \varphi_0)$ is defined in Proposition 3.3.1 below.

Moreover, if we assume that there exists $\mu_0 > 0$ and C_0 such that $|u_b(t) - \bar{u}_b| \leq C_0 e^{-\mu_0 t}$ for all $t > 0$, then there exist $\mu > 0$ and $C > 0$ such that we have the convergence with an exponential rate

$$\|\mathbf{u}(t) - \bar{\mathbf{u}}\|_{L^1(\Phi)} \leq Ce^{-\mu t}. \tag{3.19}$$

The scalar product used in the latter claim means :

$$\int_0^L |\mathbf{u}(x)| \cdot \Phi(x)\, dx =$$
$$\int_0^L \big(|u_1|\varphi_1(x) + |u_2|\varphi_2(x) + |q_1|\phi_1(x) + |q_2|\phi_2(x) + |u_0|\varphi_0(x)\big)\, dx.$$

The definition of the left eigenvector Φ and its role are given hereafter.

3.3.2 The eigen-problem

In order to study the long time asymptotics of the time dependent system (3.6), we consider the eigen-problem associated with a specific linear system [37, 47]. This system is, in some sort, a linearized version of the stationary system (3.8) where the derivative of the non-linearity is replaced by a constant g. When these eigenelements $(\lambda, \mathcal{U}, \Phi)$ exist, the asymptotic growth rate in time for a solution $\mathbf{u}$ of (3.6) is given by the first positive eigenvalue λ and the asymptotic shape is given by the corresponding eigenfunction $\mathcal{U}$.

Let us introduce the eigenelements of an auxiliary stationary linear system

$$\begin{cases} \partial_x U_1 = \lambda U_1 + k(Q_1 - U_1) \\ -\partial_x U_2 = \lambda U_2 + k(Q_2 - U_2) \\ 0 = \lambda Q_1 + k(U_1 - Q_1) + K_1(U_0 - Q_1) \\ 0 = \lambda Q_2 + k(U_2 - Q_2) - gQ_2 \\ 0 = \lambda U_0 + K_1(Q_1 - U_0) + gQ_2, \end{cases} \tag{3.20}$$

where g is a positive constant which will be fixed later. This system is complemented with boundary and a normalization condition :

$$U_1(0) = 0, \quad U_1(L) = U_2(L), \quad \int_0^L (U_1 + U_2 + Q_1 + Q_2 + U_0)\, dx = 1. \tag{3.21}$$

We also consider the related dual system :

$$\begin{cases} -\partial_x \varphi_1 = \lambda \varphi_1 + k(\phi_1 - \varphi_1) \\ \partial_x \varphi_2 = \lambda \varphi_2 + k(\phi_2 - \varphi_2) \\ 0 = \lambda \phi_1 + k(\varphi_1 - \phi_1) + K_1(\varphi_0 - \phi_1) \\ 0 = \lambda \phi_2 + k(\varphi_2 - \phi_2) + g(\varphi_0 - \phi_2) \\ 0 = \lambda \varphi_0 + K_1(\phi_1 - \varphi_0), \end{cases} \tag{3.22}$$

with following conditions :

$$\varphi_1(L) = \varphi_2(L), \quad \varphi_2(0) = 0, \quad \int_0^L (U_1\varphi_1 + U_2\varphi_2 + Q_1\phi_1 + Q_2\phi_2 + U_0\varphi_0)\, dx = 1. \tag{3.23}$$

For a given λ, the function $\mathcal{U} := (U_1, U_2, Q_1, Q_2, U_0)$ is the right eigenvector solving (3.20), while $\Phi := (\varphi_1, \varphi_2, \phi_1, \phi_2, \varphi_0)$ is the left one, associated with the adjoint operator. The following result shows the existence of a positive eigenvalue and some properties of eigenelements. We underline that in order to make the proof easier, we consider the case $k = k_1 = k_2$ but the same result could be extended to the more general case where $k_1 \neq k_2$.

Proposition 3.3.1. *Let $g > 0$ be a constant. There exists a unique $(\lambda, \mathcal{U}, \Phi)$ with $\lambda \in (0, \lambda_-)$ solution to the eigenproblem (3.20)–(3.23), where*

$$\lambda_- = \frac{(2K_1 + k) - \sqrt{4K_1^2 + k^2}}{2}.$$

Moreover, we have $\mathcal{U}(x) > 0$, $\Phi(x) > 0$ on $(0, L)$ and $\phi_2 < \varphi_0$.

In order to prove this result, we will divide the proof in two steps : Lemmas 3.3.1 and 3.3.2 respectively. Proposition 3.3.1 is a direct consequence of these two Lemmas. We start with the direct problem :

Lemma 3.3.1 (The direct problem)**.** *There exists a unique* $\lambda > 0$ *such that the direct problem* (3.20)-(3.21) *admits a unique positive solution* $\mathcal{U} = (U_1, U_2, Q_1, Q_2, U_0)$ *on* $(0, L)$*, and* $0 < \lambda < \lambda_-$.

Proof. Summing all equations in (3.20) we find that :

$$U_1' - U_2' = \lambda(U_1 + U_2 + Q_1 + Q_2 + U_0). \tag{3.24}$$

Integrating with respect to x and using condition (3.21), we obtain $U_2(0) = \lambda$. By the fourth equation in (3.20), we find directly:

$$Q_2(x) = \frac{kU_2(x)}{k + g - \lambda} = \frac{U_2(x)}{1 + \frac{1}{k}(g - \lambda)}. \tag{3.25}$$

Putting this expression into the second equation in (3.20), we find

$$-U_2' = U_2 \left(\lambda + \frac{\lambda - g}{1 + \frac{1}{k}(g - \lambda)} \right),$$

Solving the latter equation, we deduce that

$$\begin{aligned} U_2(x) &= U_2(0) e^{-\lambda x + \int_0^x \frac{-\lambda + g}{1 + \frac{1}{k}(g - \lambda)} \, dy} = \lambda e^{(-\lambda + \eta(\lambda))x}; \\ \text{with } \eta(\lambda) &:= \frac{-\lambda + g}{1 + \frac{1}{k}(g - \lambda)}. \end{aligned} \tag{3.26}$$

Using the fifth equation of system (3.20) we recover

$$U_0(x) = \frac{K_1}{K_1 - \lambda} Q_1(x) + \frac{g}{K_1 - \lambda} Q_2(x).$$

We inject this into the third equation to obtain

$$Q_1(x) \left(k - \lambda - \frac{K_1 \lambda}{K_1 - \lambda} \right) = \frac{gK_1}{K_1 - \lambda} Q_2(x) + kU_1(x).$$

Thanks to (3.25) we write also:

$$Q_1(x) \left(k - \lambda - \frac{K_1 \lambda}{K_1 - \lambda} \right) = \frac{K_1 g}{K_1 - \lambda} \frac{1}{(1 + \frac{1}{k}(g - \lambda))} U_2(x) + kU_1(x).$$

Taking into account the first equation of system (3.20), we obtain :

$$U_1'(x) = c_\lambda U_1(x) + k_\lambda \frac{g}{1 + \frac{1}{k}(g - \lambda)} U_2(x), \tag{3.27}$$

where we simplify notations by introducing :

$$k_\lambda := \frac{k\frac{K_1}{K_1-\lambda}}{k-\lambda-\frac{K_1\lambda}{K_1-\lambda}}, \quad c_\lambda := \lambda + \frac{k(\lambda+\frac{K_1\lambda}{K_1-\lambda})}{k-\lambda-\frac{K_1\lambda}{K_1-\lambda}}. \tag{3.28}$$

The denominator $k-\lambda-\frac{K_1\lambda}{K_1-\lambda}$ vanishes for

$$\lambda_\pm = \frac{(2K_1+k)\pm\sqrt{4K_1^2+k^2}}{2}.$$

Obviously $\lim_{\lambda\to\lambda_-} k_\lambda = +\infty$ and we also have that $0 < \lambda_- < \min(K_1, k)$.

Now we solve directly the ODE (3.27) with its initial condition, we get

$$U_1(x) = \frac{\lambda g k_\lambda}{1+\frac{1}{k}(g-\lambda)} \frac{e^{c_\lambda x} - e^{(\eta(\lambda)-\lambda)x}}{c_\lambda+\lambda-\eta(\lambda)}.$$

We are looking for a $\lambda > 0$ such that boundary condition $U_1(L) = U_2(L)$ is satisfied, in other words $\frac{U_1(L)}{U_2(L)} = 1$, namely

$$F(\lambda) := \frac{g k_\lambda}{1+\frac{1}{k}(g-\lambda)} \left(\frac{e^{(c_\lambda+\lambda-\eta(\lambda))L}-1}{c_\lambda+\lambda-\eta(\lambda)}\right) = 1, \tag{3.29}$$

where we recall that k_λ, c_λ are defined in (3.28) and $\eta(\lambda)$ in (3.26). We remark immediately that for $\lambda = 0$ in (3.28), we have $k_0 = 1$, $c_0 = 0$. Then,

$$F(0) = 1 - \exp\Big(-\frac{gL}{1+\frac{g}{k}}\Big) < 1.$$

We notice that for $k_\lambda, c_\lambda > 0$, $F(\lambda)$ is a continuous increasing function with respect to λ since the product of increasing and positive functions is still increasing (see Appendix (B.2.1) for more details). Moreover $\lim_{\lambda\to\lambda_-} F(\lambda) = +\infty$. Then it exists a unique $\lambda \in (0, \lambda_-)$ such that $F(\lambda) = 1$. Moreover, for $0 < \lambda < \lambda_- < \min(k, K_1)$, the functions U_1, U_2, Q_1, Q_2, U_0 are positive on $[0, L]$.

□

Lemma 3.3.2 (The dual problem)**.** *Let λ and $\mathcal{U}$ be as in Lemma* (3.3.1)*. Then, there exists $\Phi := (\varphi_1, \varphi_2, \phi_1, \phi_2, \varphi_0)$, the unique solution of dual problem* (3.22)*–*(3.23) *with $\varphi_1, \varphi_2, \phi_1, \phi_2, \varphi_0 > 0$. Moreover, we have $\phi_2 < \varphi_0$.*

Proof. By the fifth equation of system (3.22) we have directly :

$$\varphi_0 = \frac{K_1}{K_1-\lambda}\phi_1.$$

Replacing this expression in the third equation we obtain

$$(k-\lambda-\frac{K_1\lambda}{K_1-\lambda})\phi_1 = k\varphi_1.$$

Then,

$$\varphi_0(x) = \frac{k\frac{K_1}{K_1-\lambda}}{k-\lambda-\frac{K_1\lambda}{K_1-\lambda}}\varphi_1(x) = k_\lambda\varphi_1(x),$$

where k_λ is defined in (3.28). Using the first equation of (3.22), we have

$$-\varphi_1' = \varphi_1\left(\lambda + k\left(\frac{\lambda+\frac{K_1\lambda}{K_1-\lambda}}{k-\lambda-\frac{K_1\lambda}{K_1-\lambda}}\right)\right).$$

Integrating, we obtain

$$\varphi_1(x) = \varphi_1(0)e^{-\lambda x}e^{-\beta x}, \quad \beta = \beta_\lambda = \frac{\lambda k(2K_1-\lambda)}{\lambda^2-2K_1\lambda-\lambda k+K_1k}. \tag{3.30}$$

We easily check that $\beta > 0$ if $0 < \lambda < \lambda_- < K_1$.

As shown in details in the Appendix B.2.2, for all $x \in (0, L)$, $(U_1\varphi_1)' - (U_2\varphi_2)' = 0$. Integrating, we get $U_1(x)\varphi_1(x) - U_2(x)\varphi_2(x) = U_1(0)\varphi_1(0) - U_2(0)\varphi_2(0) = 0$, thanks to boundary conditions $U_1(0) = 0$ and $\varphi_2(0) = 0$. (Notice also that taking $x = L$ in this latter relation, and using the boundary condition $U_1(L) = U_2(L) \neq 0$, we recover $\varphi_1(L) = \varphi_2(L)$.) Therefore, we get

$$\varphi_2(x) = \frac{U_1(x)}{U_2(x)}\varphi_1(x) \quad \forall x \in [0, L]. \tag{3.31}$$

Using the fourth equation in (3.22) and thanks to (3.31), we obtain

$$0 = \lambda\phi_2 + k\frac{U_1}{U_2}\varphi_1 - k\phi_2 + g\varphi_1\left(\frac{K_1}{K_1-\lambda}\cdot\frac{k}{k-\lambda-\frac{K_1\lambda}{K_1-\lambda}}\right),$$

which allows to compute ϕ_2 :

$$\phi_2(x) = \frac{k\frac{U_1(x)}{U_2(x)}\varphi_1(x)}{k-\lambda+g} + \frac{g}{k-\lambda+g}k_\lambda\varphi_1(x).$$

Each function depends on the first component of Φ, i.e. $\varphi_1(x)$, and to sum up, the following relation has been obtained:

$$\begin{cases}\varphi_1(x) = \varphi_1(0)e^{-\lambda x}e^{-\beta x}\\ \varphi_2(x) = \frac{U_1(x)}{U_2(x)}\varphi_1(x)\\ \phi_1(x) = \varphi_1(x)\left(\frac{k}{k-\lambda-\frac{K_1\lambda}{K_1-\lambda}}\right)\\ \phi_2(x) = \frac{1}{k-\lambda+g}\left(k\frac{U_1(x)}{U_2(x)} + gk_\lambda\right)\varphi_1(x)\\ \varphi_0(x) = k_\lambda\varphi_1(x),\end{cases} \tag{3.32}$$

where k_λ, β are defined in (3.28) and (3.30). Hence the sign of Φ depends on the sign of $\varphi_1(0)$, the other quantities and constants being positive for $\lambda \in (0, \lambda_-)$ and $g > 0$ by assumption.

Then, we use the normalization condition (3.23) and (3.32) in order to show the positivity of $\varphi_1(0)$. It implies that

$$\varphi_1(0)\int_0^L e^{-\lambda x}e^{-\beta x}\left[2U_1(x)+Q_1(x)\left(\frac{k}{k-\lambda-\frac{K_1\lambda}{K_1-\lambda}}\right)+\right.$$
$$\left.+\frac{Q_2(x)}{k+g+\lambda}\left(k\frac{U_1(x)}{U_2(x)}+gk_\lambda\right)+k_\lambda U_0(x)\right]\,dx=1.$$

The integral on the left hand side is positive, thanks to properties of functions previously defined. Given that $\varphi_1(0)$ is constant and all other quantities positive, we can conclude that $\varphi_1(0)>0$.

We are left to prove that the quantity $\phi_2-\varphi_0$ is negative. Using (3.32), we rewrite :

$$\phi_2-\varphi_0=\frac{kk_\lambda\varphi_1(x)}{k-\lambda+g}\left(\frac{1}{k_\lambda}\frac{U_1}{U_2}+\frac{\lambda}{k}-1\right).$$

From the explicit expression of U_1 and U_2, we have

$$\begin{aligned}\phi_2-\varphi_0&=\frac{k_\lambda\varphi_1(x)}{1+\frac{1}{k}(g-\lambda)}\left[\frac{\int_0^x\frac{g}{1+\frac{1}{k}(g-\lambda)}e^{-c_\lambda(y-x)}e^{(-\lambda+\eta(\lambda))y}\,dy}{e^{(-\lambda+\eta(\lambda))x}}+\frac{\lambda}{k}-1\right]\\&=\frac{k_\lambda\varphi_1(x)}{1+\frac{1}{k}(g-\lambda)}\left[\frac{g}{1+\frac{1}{k}(g-\lambda)}\left[\frac{1-e^{-c_\lambda x-\lambda x+\eta(\lambda)x}}{c_\lambda+\lambda-\eta}\right]+\frac{\lambda}{k}-1\right],\end{aligned}$$

where we recall the notation $\eta(\lambda)=\frac{-\lambda+g}{1+\frac{1}{k}(g-\lambda)}$. We set

$$H(x):=\frac{g}{1+\frac{1}{k}(g-\lambda)}\left[\frac{1-e^{-c_\lambda x-\lambda x+\eta(\lambda)x}}{c_\lambda+\lambda-\eta(\lambda)}\right].\tag{3.33}$$

We have

$$\phi_2-\varphi_0<0\iff H(x)+\frac{\lambda}{k}-1<0.$$

We observe that $H(0)=0$ and $H(L)=\frac{1}{k_\lambda}$ thanks to (3.29). Moreover, $H(L)<1-\frac{\lambda}{k}$ for $\lambda\in(0,\lambda_-)$. Indeed, we have

$$\lambda<k-\frac{k}{k_\lambda},$$

which holds if and only if $\frac{\lambda^2-K_1\lambda-k\lambda}{K_1}<0$ which is true on $(0,\lambda_-)$, since $\lambda_-<k$ by definition. Moreover, it is clear that H is an increasing function on $[0,L]$ for $\lambda\in(0,\lambda_-)$. Then $H(x)\le H(L)<1-\frac{\lambda}{k}$. This concludes the proof. □

3.3.3 Proof of Theorem 3.3.1

Now we are ready to prove Theorem 3.3.1. We set $d_i(t,x):=|u_i(t,x)-\bar{u}_i(x)|$ $i=0,1,2$ and $\delta_j:=|q_j(t,x)-\bar{q}_j(x)|$, $j=1,2$ with $\bar{u}_i,\bar{q}_i$ satisfying (3.8) and u_i,q_i solving (3.6).

We subtract component-wise (3.6) to (3.8). Then we multiply each of the entries by $sign(u_i - \bar{u}_i)$ or $sign(q_j - \bar{q}_j)$ respectively. We obtain the following inequalities :

$$\begin{cases} a_1\partial_t d_1 + \alpha\partial_x d_1 \leq k(\delta_1 - d_1) \\ a_2\partial_t d_2 - \alpha\partial_x d_2 \leq k(\delta_2 - d_2) \\ a_3\partial_t \delta_1 \leq k(d_1 - \delta_1) + K_1(d_0 - \delta_1) \\ a_4\partial_t \delta_2 \leq k(d_2 - \delta_2) - \hat{G} \\ a_0\partial_t d_0 \leq K_1(\delta_1 - d_0) + \hat{G}, \end{cases} \tag{3.34}$$

with $\hat{G} := |G(q_2) - G(\bar{q}_2)|$. We have used also the monotonicity of G (see (3.18)). We set

$$M(t) := \int_0^L (a_1 d_1 \varphi_1 + a_2 d_2 \varphi_2 + a_3 \delta_1 \phi_1 + a_4 \delta_2 \phi_2 + a_0 d_0 \varphi_0)\, dx,$$

with a_1, a_2, a_3, a_4, a_5 positive constants as defined in (3.3). Multiplying each equation of (3.34) by the corresponding dual function φ_i, ϕ_i, adding all equations and integrating with respect to x, we obtain :

$$\begin{aligned} \frac{d}{dt}M(t) \leq \int_0^L \Big(& k(\delta_1 - d_1)\varphi_1 + k(\delta_2 - d_2)\varphi_2 + k(d_1 - \delta_1)\phi_1 + K_1(d_0 - \delta_1)\phi_1 \\ & + k(\delta_2 - d_2)\phi_2 - \hat{G}\phi_2 + K_1(\delta_1 - d_0)\varphi_0 + \hat{G}\varphi_0 \Big)\, dx + \alpha \int_0^L (\partial_x d_2 \varphi_2 - \partial_x d_1 \varphi_1)\, dx. \end{aligned}$$

Integrating by parts the last integral, we can simplify the latter inequality into

$$\begin{aligned} \frac{d}{dt}M(t) \leq {} & \alpha\Big(d_2(t,L)\varphi_2(L) - d_2(t,0)\varphi_2(0) + \int_0^L d_2(t,x)(\partial_x\varphi_2)\, dx \Big) + \\ & - \alpha\Big(d_1(t,L)\varphi_1(L) - d_1(t,0)\varphi_1(0) - \int_0^L d_1(t,x)(\partial_x\varphi_1)\, dx \Big) + \\ & + \int_0^L \Big(k(\delta_1 - d_1)\varphi_1 + k(\delta_2 - d_2)\varphi_2 + k(d_1 - \delta_1)\phi_1 + K_1(d_0 - \delta_1)\phi_1 \\ & \qquad + k(\delta_2 - d_2)\phi_2 - \hat{G}\phi_2 + K_1(\delta_1 - d_0)\varphi_0 + \hat{G}\varphi_0 \Big)\, dx. \end{aligned}$$

We now use the dual system (3.22) as $\partial_x\varphi_1 = -\lambda\varphi_1 + k(\varphi_1 - \phi_1)$, $\partial_x\varphi_2 = \lambda\varphi_2 + k(\phi_2 - \varphi_2)$ and we recall below the last three equations of system (3.22) with changed sign and multiplied respectively by δ_1, δ_2, d_0, such as :

$$\begin{aligned} 0 &= -\lambda\phi_1\delta_1 - k(\varphi_1 - \phi_1)\delta_1 - K_1(\varphi_0 - \phi_1)\delta_1 \\ 0 &= -\lambda\phi_2\delta_2 - k(\varphi_2 - \phi_2)\delta_2 - g(\varphi_0 - \phi_2)\delta_2 \\ 0 &= -\lambda\varphi_0 d_0 - K_1(\phi_1 - \varphi_0)d_0. \end{aligned}$$

The latter inequality becomes

$$\frac{d}{dt}M(t) \leq -\lambda \int_0^L (d_1\varphi_1 + d_2\varphi_2 + \delta_1\phi_1 + \delta_2\phi_2 + d_0\varphi_0)\, dx + d_2(L)\varphi_2(L) - d_1(L)\varphi_1(L)$$

$$+ d_1(0)\varphi_1(0) - d_2(0)\varphi_2(0) + \int_0^L -\hat{G}(\phi_2 - \varphi_0)\, dx + \int_0^L k(\delta_1 - d_1)\varphi_1\, dx + \int_0^L k(\delta_2 - d_2)\varphi_2\, dx$$

$$+ \int_0^L k(d_1 - \delta_1)\phi_1\, dx + \int_0^L K_1(d_0 - \delta_1)\phi_1\, dx + \int_0^L k(\delta_2 - d_2)\phi_2\, dx + \int_0^L K_1(\delta_1 - d_0)\varphi_0\, dx$$

$$+ \int_0^L k(\phi_1 - \varphi_1)\delta_1 + K_1(\phi_1 - \varphi_0)\delta_1\, dx + \int_0^L k(\phi_2 - \varphi_2)\delta_2 + g(\phi_2 - \varphi_0)\delta_2\, dx + \int_0^L K_1(\varphi_0 - \phi_1)d_0\, dx.$$

Using the conditions in (3.21) and in (3.23), we obtain

$$\frac{d}{dt}M(t) \leq \frac{-\lambda}{\max\{a_1, a_2, a_3, a_4, a_0\}} M(t) + d_1(t,0)\varphi_1(0) + \int_0^L (g\delta_2 - \hat{G})(\phi_2 - \varphi_0)\, dx.$$

To simplify the notation we set $\bar{\lambda} = \frac{-\lambda}{\max\{a_1,a_2,a_3,a_4,a_0\}}$.
Since G is Lipschitz-continuous and by assumption (3.18), $\hat{G} \leq g\delta_2$ with $g = \|G'\|_\infty$. With this choice of g, we apply Proposition 3.3.1 and deduce that the quantity $(\phi_2 - \varphi_0)$ is negative. Then,

$$\frac{d}{dt}M(t) + \bar{\lambda}M(t) \leq d_1(t,0)\varphi_1(0).$$

Thanks to (3.17) and applying Gronwall's lemma, we conclude that

$$M(t) \leq M(0)e^{-\bar{\lambda}t} + \varphi_1(0) \int_0^t d_1(s,0)e^{\bar{\lambda}(s-t)}\, ds. \tag{3.35}$$

Moreover, from (3.17), we have $d_1(s,0) = |u_b(t) - \bar{u}_b| \to 0$ as $t \to +\infty$. Then, for every $\varepsilon > 0$, it exists $\bar{t} > 0$ such that $d_1(s,0) < \varepsilon$ for each $s > \bar{t}$. Then for every $t \geq \bar{t}$, we have

$$\begin{aligned}\int_0^t d_1(s,0)e^{\bar{\lambda}(s-t)}\, ds &\leq \int_0^{\bar{t}} d_1(s,0)e^{\bar{\lambda}(s-t)}\, ds + \varepsilon \int_{\bar{t}}^t e^{\bar{\lambda}(s-t)}\, ds \\ &\leq e^{\bar{\lambda}(\bar{t}-t)} \int_0^{\bar{t}} d_1(s,0)\, ds + \frac{\varepsilon}{\bar{\lambda}}.\end{aligned}$$

The first term of the right hand side is arbitrarily small at t goes to $+\infty$. Hence, we have proved that for any $\varepsilon > 0$ there exists τ large enough such that for every $t \geq \tau$,

$$M(t) \leq M(0)e^{-\bar{\lambda}t} + C\varepsilon.$$

Since $M(t) = \|\mathbf{u}(t) - \bar{\mathbf{u}}\|_{L^1(\Phi)}$, it proves the convergence as stated in Theorem 3.3.1.

Finally, if we assume that there exists positive constants μ_0 and C_0 such that $|u_b(t) - \bar{u}_b| \leq C_0 e^{-\mu_0 t}$, then from (3.35) we deduce

$$M(t) \leq M(0)e^{-\bar{\lambda}t} + C_0\varphi_1(0)\frac{e^{-\mu_0 t} - e^{-\bar{\lambda}t}}{\bar{\lambda} - \mu_0} \leq Ce^{-\min\{\bar{\lambda},\mu_0\}t}.$$

□

3.3.4 Comments

In the proof just concluded, it should be pointed out an interesting property of the system: the coupling of the equations in the model. Without this kind of structural symmetry, it would be difficult to draw the same conclusions. This property is reflected also in the eigen-problem of the auxiliary linear system and in the specific boundary conditions (3.5). Thanks to this coupling structure, for example, we can conclude for eigenelements of dual problem (3.22)-(3.23) that $\phi_2 - \varphi_0 < 0$, then $\phi_2 < \varphi_0$ which is not due and expected in general. This feature of model (*'couplage'*) allows us to eliminate in the calculus certain terms paired with each other and then to conclude with the reached inequality (3.35).
As stated in [20] Chap.3, the water and solute flows are tightly coupled in the kidney. The transepithelial solute fluxes may be driven by electrochemical potential gradients, by pumps (i.e., active transport), or via coupled transport systems, both in the case of single-barrier modelling assumption and in that of a two-membrane representation. Therefore this choice of modelling is also closely related to the ionic exchange mechanisms within the nephron and to the homeostatic functions to maintain a certain balance in the cells environment, which is the key role of the kidneys.

Chapter 4

Study of a two-ion model

"All models, no matter how realistic, are always 'wrong' in that they are less complex than the real system. Failure of the model to explain observed results forces us to further refine the model and teaches us something more about the system."
[17]

The Na/K-ATPase is a transmembrane enzyme that moves 3 Na^+ ions out of the cell for every 2 K^+ ions pumped into the cell spending energy. The cells would not be able to maintain high intracellular levels of Na^+ and low levels of Na^+ without this active transport pump. In this study we try to make a little more realistic the mathematical model by 'enriching' it.
In the previous Chapters only one uncharged solute has been considered in two tubules, here we take into account simplified system at equilibrium with epithelium layer and 2 ions, Na (sodium) and K (potassium). For this reason we are going to present a system accounting for two solutes adding five equations of previous studied system. As suggested in [20] Chap. 8, the flux of Na^+ ions across the pump can be expressed as:

$$J_{Na}^{NaK} = V_m \left(\frac{q_2^{Na}}{k_s + q_2^{Na}} \right)^3 \left(\frac{u_0^K}{k_p + u_0^K} \right)^2,$$

where the constant V_m is the maximum flux of sodium ions at steady state and k_s, k_p are related to the association and dissociation kinetic constants for enzymatic reaction, i.e. the affinity of the pumps. The intracellular/epithelial concentrations are described by q_i with $i = 1, 2$ and the u_0 refers to extracellular/interstitial solute concentration in the fluid. Whereas for K^+ ions the flux can be expressed as:

$$J_K^{NaK} = -\frac{2}{3} J_{Na}^{NaK}.$$

4.1 Sodium-potassium system

The following system describes the sodium and potassium exchanges in the loop of Henle through transport mechanisms in the renal tubules. In the absence of physiological perturbations, the concentrations are very close to the steady state of the system, then also in this case we are going to consider solutions at equilibrium :

$$\begin{cases} +\alpha\partial_x u_1^{Na} = 2\pi r_1 P_1^{Na}(q_1^{Na} - u_1^{Na}) \\ -\alpha\partial_x u_2^{Na} = 2\pi r_2 P_2^{Na}(q_2^{Na} - u_2^{Na}) \\ 0 = 2\pi r_1 P_1^{Na}(u_1^{Na} - q_1^{Na}) + 2\pi r_{1,e} P_{1,e}^{Na}(u_0^{Na} - q_1^{Na}) \\ 0 = 2\pi r_2 P_2^{Na}(u_2^{Na} - q_2^{Na}) + 2\pi r_{2,e} P_{2,e}^{Na}(u_0^{Na} - q_2^{Na}) - G(q_2^{Na}, u_0^K) \\ 0 = 2\pi r_{1,e} P_{1,e}^{Na}(q_1^{Na} - u_0^{Na}) + 2\pi r_{2,e} P_{2,e}^{Na}(q_2^{Na} - u_0^{Na}) + G(q_2^{Na}, u_0^K) \\ +\alpha\partial_x u_1^K = 2\pi r_1 P_1^K(q_1^K - u_1^K) \\ -\alpha\partial_x u_2^K = 2\pi r_2 P_2^K(q_2^K - u_2^K) \\ 0 = 2\pi r_1 P_1^K(u_1^K - q_1^K) + 2\pi r_{1,e} P_{1,e}^K(u_0^K - q_1^K) \\ 0 = 2\pi r_2 P_2^K(u_2^K - q_2^K) + 2\pi r_{2,e} P_{2,e}^K(u_0^K - q_2^K) + \frac{2}{3}G(q_2^{Na}, u_0^K) \\ 0 = 2\pi r_{1,e} P_{1,e}^K(q_1^K - u_0^K) + 2\pi r_{2,e} P_{2,e}^K(q_2^K - u_0^K) - \frac{2}{3}G(q_2^{Na}, u_0^K) \\ u_1^{Na}(L) = u_2^{Na}(L), \quad u_1^K(L) = u_2^K(L), \\ u_1^{Na}(0) = \bar{u}^{Na}, \quad u_1^K(0) = \bar{u}^K \end{cases} \tag{4.1}$$

At equilibrium we will consider $P_{2,e}^K = 0$, $P_{2,e}^{Na} = 0$ which means to ignore the diffusion of Na^+ and K^+ from the ascending limb epithelium towards interstitium which is negligible according to physiological behaviour. In order to simplify the notation, we set $K = 2\pi r_i, i = 1, 2, \quad K_e = 2\pi r_{i,e} P_{i,e}$ and $P_1^{Na} = P_2^K = P$. It should be noted that also in this case we consider the radius of tube being the same since the orders of magnitude are the same. It leads us to study the behaviour of concentrations satisfying these equations:

$$\begin{cases} +\alpha\partial_x u_1^{Na} = KP(q_1^{Na} - u_1^{Na}) \\ -\alpha\partial_x u_2^{Na} = KP(q_2^{Na} - u_2^{Na}) \\ 0 = KP(u_1^{Na} - q_1^{Na}) + K_e^{Na}(u_0^{Na} - q_1^{Na}) \\ 0 = KP(u_2^{Na} - q_2^{Na}) - G(q_2^{Na}, u_0^K) \\ 0 = K_e^{Na}(q_1^{Na} - u_0^{Na}) + G(q_2^{Na}, u_0^K) \\ \\ +\alpha\partial_x u_1^K = KP(q_1^K - u_1^K) \\ -\alpha\partial_x u_2^K = KP(q_2^K - u_2^K) \\ 0 = KP(u_1^K - q_1^K) + K_e^K(u_0^K - q_1^K) \\ 0 = KP(u_2^K - q_2^K) + \frac{2}{3}G(q_2^{Na}, u_0^K) \\ 0 = K_e^K(q_1^K - u_0^K) - \frac{2}{3}G(q_2^{Na}, u_0^K) \end{cases} \tag{4.2}$$

with the non linear term related to active transport defined as:

$$G(q_2^{Na}, u_0^K) = V_m \left(\frac{q_2^{Na}}{k_s + q_2^{Na}} \right)^3 \left(\frac{u_0^K}{k_p + u_0^K} \right)^2. \tag{4.3}$$

The exponent 3 is related to the number of exchanged sodium ions, whereas the exponent 2 relates to the exchanged potassium ions. In this case the source term (4.3) accounting for

the active transport in the system links the sodium epithelial concentration in the ascending limb with the potassium concentration in the interstitum. It is noteworthy that the function $G(q_2^{Na}, u_0^K)$ realise the coupling in the two-ion model. Therefore it follows that without this coupling term, the problem (4.1) would reduce to two independent and equal models for a single ion species with the same structural feature as (3.8), in Chap. 3 of this thesis.
The unknowns of system depend on (t, x) and the model is one-dimensional with respect to the space $x \in [0, L]$. The unknowns represent ionic concentrations of sodium and potassium in different compartments as showed in Figure (3.1). We summarize them hereafter :

$u_i^{Na}(t, x)$: Na in the tubule or compartment i, with $i = 1, 2$
$q_i^{Na}(t, x)$: Na in the epithelium 'near' tubule i
$u_0^{Na}(t, x)$: Na in the interstitium
$u_i^K(t, x)$: K in the tubule i
$q_i^K(t, x)$: K in the epithelium 'near' tubule i
$u_0^K(t, x)$: K in the interstitium.

Lemma 4.1.1. *Let be $u^{Na}, u^K > 0$. Let G be a C^2 function, uniformly Lipschitz and $G(0) = 0$ (as defined in* (4.3)*.) Then there exists an unique vector solution to the stationary problem* (4.5)*. Moreover, assuming that $G > 0$ the following relations hold*

$$q_2^{Na} < u^{Na} < q_1^{Na} < u_0^{Na} \qquad q_2^K > u^K, \qquad q_1^K > u_0^K, \qquad q_2^K > u_0^K. \tag{4.4}$$

Proof. Summing the first five equations of system (4.5a)-(4.5e) and then the others (4.5f)-(4.5j), we deduce that : $\alpha(\partial_x u_1^{Na} - \partial_x u_2^{Na}) = 0$ and $\alpha(\partial_x u_1^K = \partial_x u_2^K)$. Recalling the conditions $u_1^{Na}(L) = u_2^{Na}(L)$ and $u_1^K(L) = u_2^K(L)$, we obtain $u_1^{Na} = u_2^{Na} = u^{Na}$ and $u_1^K = u_2^K = u^K$. We may simplify system as previously done for stationary model in Section 3.2.1. It follows,

$$2u^{Na} = q_1^{Na} + q_2^{Na} \tag{4.5a}$$

$$\alpha \partial_x u^{Na} = \frac{K}{\varepsilon}(u_2^{Na} - q_2^{Na}) \tag{4.5b}$$

$$0 = \frac{K}{\varepsilon}(u^{Na} - q_1^{Na}) + K_e^{Na}(u_0^{Na} - q_1^{Na}) \tag{4.5c}$$

$$0 = \frac{K}{\varepsilon}(u^{Na} - q_2^{Na}) - G(q_2^{Na}, u_0^K) \tag{4.5d}$$

$$0 = K_e^{Na}(q_1^{Na} - u_0^{Na}) + G(q_2^{Na}, u_0^K) \tag{4.5e}$$

$$+ \alpha \partial_x u_1^K = \frac{K}{\varepsilon}(q_1^K - u_1^K) \tag{4.5f}$$

$$- \alpha \partial_x u_2^K = \frac{K}{\varepsilon}(q_2^K - u_2^K) \tag{4.5g}$$

$$0 = \frac{K}{\varepsilon}(u_1^K - q_1^K) + K_e^K(u_0^K - q_1^K) \tag{4.5h}$$

$$0 = \frac{K}{\varepsilon}(u_2^K - q_2^K) + \frac{2}{3}G(q_2^{Na}, u_0^K) \tag{4.5i}$$

$$0 = K_e^K(q_1^K - u_0^K) - \frac{2}{3}G(q_2^{Na}, u_0^K). \tag{4.5j}$$

In the above-mentioned system we consider the permeabilities $P_i^j = P$ as $\frac{1}{\varepsilon}$, with $i = 1, 2$ and $j = Na, K$.

If we insert the 4^{th} equation of system (4.5) , $u_2^{Na} = q_2^{Na} + \frac{\varepsilon}{K}G(q_2^{Na}, u_0^K)$, in 2^{nd} equation (4.5b), it gives :

$$\alpha\partial_x\left(q_2^{Na} + \frac{\varepsilon}{K}G(q_2^{Na}, u_0^K)\right) = G(q_2^{Na}, u_0^K).$$

Since

$$\partial_x G(q_2^{Na}, u_0^K) = \frac{\partial G}{\partial q_2^{Na}}\partial_x q_2^{Na} + \frac{\partial G}{\partial u_0^K}\partial_x u_0^k,$$

we obtain the following equation:

$$\partial_x q_2^{Na}\left(\alpha + \frac{\varepsilon\alpha}{K}\frac{\partial G}{\partial q_2^{Na}}\right) + \partial_x u_0^K\left(\frac{\varepsilon\alpha}{K}\frac{\partial G}{\partial u_0^K}\right) = G(q_2^{Na}, u_0^K). \tag{4.6}$$

We consider now the part of system where the potassium concentrations are involved (4.5f)-(4.5j) to get a second relation between $\partial_x q_2$ and $\partial_x u_0$ in order to reduce our problem to a non-linear 2×2 system of ODEs. By (4.5j) we recover directly $q_1^K = u_0^K + \frac{2}{3K_{1,e}}G(q_2^{Na}, u_0^K)$. As already mentioned, $u_1^K = u_2^K = u^K$ and then

$$2u^K = q_1^K + q_2^K. \tag{4.7}$$

Since (4.5i) we know also that $u^K = q_2^K - \frac{2\varepsilon}{3K}G(q_2^{Na}, u_0^K)$. We can rewrite $q_2^K = q_1^K + \frac{4\varepsilon}{3K}G(q_2^{Na}, u_0^K)$ and inject here the previous expression of q_1^K. We can recover the following relation,

$$q_2^K = u_0^K + (\frac{2}{3K_{1,e}} + \frac{4\varepsilon}{3K})G(q_2^{Na}, u_0^K).$$

We replace these two expressions, q_1^K, q_2^K in (4.7) to get

$$u^K = u_0^K + (\frac{2}{3K_{1,e}} + \frac{2\varepsilon}{3K})G(q_2^{Na}, u_0^K). \tag{4.8}$$

Summing (4.5f), (4.5h), (4.5j) we obtain : $\alpha\partial_x u^K = -\frac{2}{3}G(q_2^{Na}, u_0^K)$ and finally

$$\partial_x q_2^{Na}\left(\gamma\alpha\frac{\partial G}{\partial q_2^{Na}}\right) + \partial_x u_0^K\left(\gamma\alpha\frac{\partial G}{\partial u_0^K} + \alpha\right) = -\frac{2}{3}G(q_2^{Na}, u_0^K), \tag{4.9}$$

with positive constant $\gamma = \dfrac{2}{3K_{1,e}} + \dfrac{2\varepsilon}{3K}$.

Combining equations (4.6), (4.9), the problem is reduced to solve this non-linear system of ODEs:

$$M\begin{bmatrix}\partial_x q_2^{Na}\\ \partial_x u_0^K\end{bmatrix} = \begin{bmatrix}G(q_2^{Na}, u_0^K)\\ -\frac{2}{3}G(q_2^{Na}, u_0^K)\end{bmatrix}, \qquad M = \begin{bmatrix}\alpha + \frac{\alpha\varepsilon}{K}\frac{\partial G}{\partial q_2^{Na}} & \frac{\alpha\varepsilon}{K}\frac{\partial G}{\partial u_0^K}\\ \alpha\gamma\frac{\partial G}{\partial q_2^{Na}} & \alpha + \alpha\gamma\frac{\partial G}{\partial u_0^K}\end{bmatrix}$$

with $det(M) = \alpha^2 \left(1 + \gamma \frac{\partial G}{\partial u_0^K} + \frac{\varepsilon}{K} \frac{\partial G}{\partial q_2^{Na}}\right) \neq 0$ and provided with the initial condition for $q_2^{Na}(0)$ and $u_0^K(0)$ that satisfy :

$$q_2^{Na}(0) + \frac{\varepsilon}{K} G(q_2^{Na}(0), u_0^K(0)) - u_2^{Na}(0) = 0, \tag{4.12}$$

$$u_0^K(0) + \gamma G(q_2^{Na}, u_0^K) - u_1^K(0) = 0. \tag{4.13}$$

We are going to solve :

$$\begin{bmatrix} \partial_x q_2^{Na} \\ \partial_x u_0^K \end{bmatrix} = M^{-1} \begin{bmatrix} G(q_2^{Na}, u_0^K) \\ -\frac{2}{3} G(q_2^{Na}, u_0^K) \end{bmatrix}$$

which it reads

$$\begin{cases} \partial_x q_2^{Na} = \dfrac{G(q_2^{Na}, u_0^K) \left((\gamma + \frac{2\varepsilon}{3K}) \frac{\partial G}{\partial u_0^K} + 1\right)}{\alpha \left(1 + \gamma \frac{\partial G}{\partial u_0^K} + \frac{\varepsilon}{K} \frac{\partial G}{\partial q_2^{Na}}\right)} \\ \\ \partial_x u_0^K = \dfrac{-G(q_2^{Na}, u_0^K) \left((\gamma + \frac{2\varepsilon}{3K}) \frac{\partial G}{\partial q_2^{Na}} + \frac{2}{3}\right)}{\alpha \left(1 + \gamma \frac{\partial G}{\partial u_0^K} + \frac{\varepsilon}{K} \frac{\partial G}{\partial q_2^{Na}}\right)} \end{cases} \tag{4.14}$$

with $\frac{\partial G}{\partial q_2^{Na}}$ and $\frac{\partial G}{\partial q_2^K}$ defined below:

$$\frac{\partial G}{\partial q_2^{Na}} = 3V_m k_s \left(\frac{(q_2^{Na})^2}{(k_s + q_2^{Na})^4}\right) \left(\frac{u_0^K}{k_p + u_0^K}\right)^2,$$

$$\frac{\partial G}{\partial u_0^K} = 2V_m k_p \left(\frac{u_0^K}{(k_p + u_0^K)^3}\right) \left(\frac{q_2^{Na}}{k_s + q_2^{Na}}\right)^3.$$

Moreover, by the equations (4.5d), (4.5e) and (4.5i), (4.5j) of system and since $G > 0$, we immediately deduce the relation between concentrations as (4.4) in the claim and to conclude. □

Parameters	Description	Values
L	Length of tubules	$2 \cdot 10^{-3}[m]$
α	Water flow in the tubules	$10^{-13}[m^3/s]$
r_i	Radius of tubule $i = 1, 2$	$10^{-5}[m]$
$K = k_1 = k_2$	$2\pi r_i,\ i = 1, 2$	$2\pi 10^{-5}[m]$
$r_{i,e}$	Radius of epithelium layer $i = 1, 2$	$1.5 \cdot 10^{-5}[m]$
$k_e = K_e^{Na} = K_e^K$	$2\pi r_{1,e} P_{1,e}^{Na} = 2\pi r_{1,e} P_{1,e}^K$	$\sim 10^{-11}[m/s]$
$k_M^{Na} = k_s$	Pump affinity for sodium (Na)	$3,5[mol/m^3]$
$k_M^K = k_p$	Pump affinity for potassium (K)	$1[mol/m^3]$
$u_1^{Na}(0)$	Na initial concentration in tubule 1	$140[mol/m^3]$
$u_1^K(0)$	K initial concentration in tubule 1	$10[mol/m^3]$
$V_{m,2}$	Rate of active transport	changeable
$P_{2,e}^{Na} = P_{2,e}^K$	Permeability between the epithelium 2 and the interstitium	$0[m/s]$

Table 4.1: Frequently used parameters in two-ion model

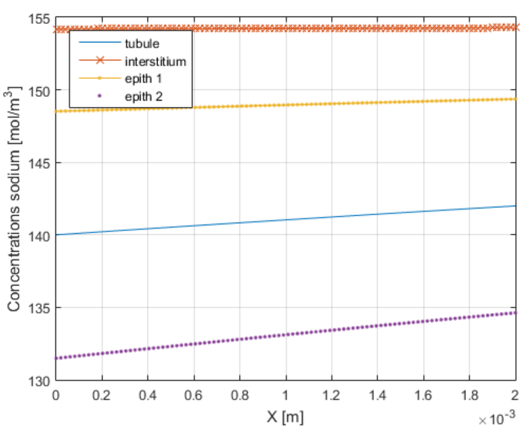
4.1.1 Numerical results

We approximate numerically concentrations of (4.5) starting from looking for the solution of (4.14). Numerical values of the parameters (cf Table 4.1) are extracted from Table 2 in [13] and Table 1 in [23], as in previous Chapter. Taking into account these quantities allow us to have the numerical ranges of the constants and the solution results in a biologically realistic framework. Following the previous computations, we first solve (4.12) and (4.13) thanks to a Newton method. Then, we solve (4.14) with a fourth order Runge-Kutta method. Finally, we deduce other concentrations about sodium $u^{Na}, q_1^{Na}, u_0^{Na}$ and potassium u^K, q_1^K, q_2^K using their above expressions depending respectively on q_2^{Na} and u_0^K.

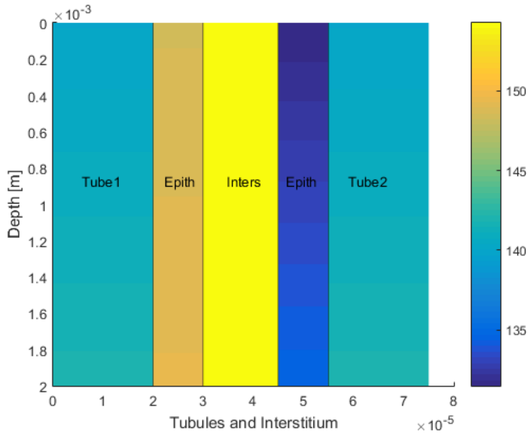
Results from Figures 4.1a and 4.1b show that in all compartments, Na concentrations increase as a function of depth (x-axis). It means that the sodium fluid is more concentrated towards the hairpin turn ($x = L$) than near $x = 0$. Whereas in Figures 4.1c and 4.1d we observe an opposite behaviour for the potassium. We can note that also in this two-ion model the Na$^+$ concentration is higher in the central layer of interstitium and lower in the ascending limb epithelium owing to active Na$^+$ transport from the latter to the central compartment, described by the non-linear term G. Furthermore, also in this larger system it should be highlighted that increasing the permeability value homogenizes the sodium concentrations in the tubules and in the epithelium region. It could be easily verified by formal computation in the concentrations expressions defined before. Moreover, numerical results also confirm the relations :

$$q_2^{Na} < u^{Na} < q_1^{Na} < u_0^{Na}, \qquad q_2^K > u^K, \qquad q_1^K > u_0^K, \qquad q_2^K > u_0^K.$$

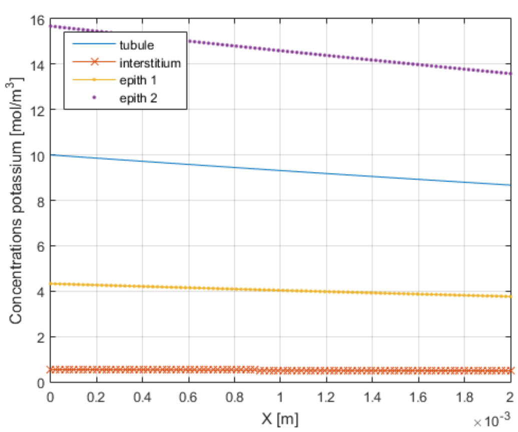
as reported in Lemma 4.1.1. The Na/K pump spends energy to pump potassium into their cells and sodium out. The Na$^+$ concentration inside the cells (epithelial membrane/epithelium)



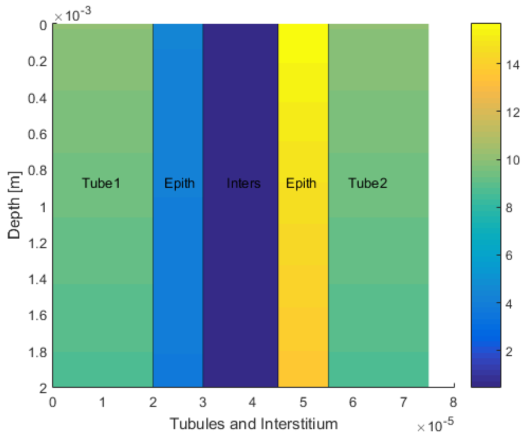
(a) Sodium concentration profiles with permeability $P_i = 2 \cdot 10^{-7}$ [m/s].



(b) Concentrations in 2D with $P_i = 2 \cdot 10^{-7}$. Length of lumen on vertical axis.



(c) Potassium concentration profiles with permeability $P_i = 2 \cdot 10^{-7}$ [m/s].



(d) Concentrations in 2D with $P_i = 2 \cdot 10^{-7}$. Length of lumen on vertical axis.

Figure 4.1: Concentration profiles with $V_{m,2} = 2\pi r_{2,e} 10^{-5}$ for sodium and potassium concentrations

is much lower than in the extracellular (luminal/interstitial) fluid, whereas it is the opposite behaviour for K^+. We would like the concentrations to be of the following orders of magnitude:

- $u_1^{Na}, u_2^{Na}, u_0^{Na}$ (extracellular fluid/tubules and interstitial sodium fluid respectively) should be of the order of 140 mM,
- q_1^{Na}, q_2^{Na} (intracellular fluid/epithelial fluid) should be of the order of 10 mM,
- the opposite behaviour, with respect to sodium, in potassium concentrations, u_1^K, u_2^K, u_0^K should be of the order of 10mM,
- q_1^K, q_2^K (intracellular fluid/epithelial potassium fluid) should be of the order of 140 mM.

This relation in our model does not occur, as showed in the results of Figure (4.1). It means that we can not draw more conclusions with respect to a biologically consistent framework and coherent with a physiological point of view.

4.2 Comments and remarks

This chapter does not aim to add remarkable results from a mathematical point of view but to show some numerical simulations carried out for a slightly more enlarged system and to suggest some changes to improve the model. In fact, it helps to highlight some weaknesses of the model and its limits. Adding another solute does not really help to approach the real physiological behaviour. Taking into account the same boundary conditions and studying the stationary system, we point out, also in this case, that the concentrations in the two tubules are the same. Actually, the concentrations in tubule 1 and 2 must have a difference, i.e. $u_1^{Na} \neq u_2^{Na}$, $u_1^K \neq u_2^K$. It would be more appropriate to choose two values of parameters (for example $\alpha_1 \neq \alpha_2$ for sodium and $\alpha_1^K \neq \alpha_2^K$ for potassium), both constant, or to set this parameters depending on space and time variable. One of these attempts in this direction, i.e. in different setting of α was presented by [48] and reported in [46].
Taking into account the physiological explanations in [20], a possible more complete description for a one-ion model without epithelium could be,

$$\begin{cases} a_i \frac{\partial}{\partial t} u_i(t,x) + \frac{\partial}{\partial x}(\alpha_i(t,x) u_i(t,x)) = J_i(t,x) \\ a_0 \frac{\partial}{\partial t} u_0(t,x) = J_0(t,x) \\ \frac{\partial}{\partial x} \alpha_i(t,x) = J_i^V(t,x), \end{cases} \tag{4.15}$$

where $J_i^V(t,x)$ refers to the water flow through tubule i and for the parameters and the variables we refer to Section 1.2. As explained in [20] Chap. 3, the water flow in a renal tubule i depends on the osmotic pressure and osmosis; in particular for a only one solute represented in the model, it could be expressed as follows,

$$J_i^V(t,x) = 2\pi r_i L_{i,p} RT \sigma_i \phi_i (u_i - u_0)$$

where $2\pi r_i$ is the length of membrane related to tubule of radius i, $L_{i,p}RT\sigma_i(u_i - u_0)$ is the osmotic pressure with $(u_i - u_0)$ the difference in concentration of the considered solute between the two sides of the membrane and $L_{i,p}$ is the membrane permeability of tubule i to water.
In general, if we consider a membrane that is permeable to water but impermeable to a given solute, the osmotic pressure exerted by that solute can be approximated by $RT\sigma_i(u_i - u_0)$ where R is the universal gas constant ($62.36 \cdot 10^{-3}\ mmHg \cdot K^{-1} \cdot mM^{-1}$) and T is the absolute temperature. A small concentration gradient can still exert a substantial osmotic pressure. Given the above considerations, a possible model in the counter-current mechanism and counter-flows description could be

$$\begin{cases} a_1 \frac{\partial}{\partial t} u_1(t,x) + \frac{\partial}{\partial x}(\alpha_1(t,x) u_1(t,x)) = 2\pi r_1 (u_0 - u_1) \\ a_2 \frac{\partial}{\partial t} u_2(t,x) - \frac{\partial}{\partial x}(\alpha_2(t,x) u_2(t,x)) = 2\pi r_2 (u_0 - u_2) - G(u_2) \\ a_0 \frac{\partial}{\partial t} u_0(t,x) = 2\pi r_1 (u_1 - u_0) + 2\pi r_2 (u_2 - u_0) + G(u_2) \\ \frac{\partial}{\partial x} \alpha_1(t,x) = 2\pi r_1 L_{1,p} RT \sigma_1 \phi_1 (u_1 - u_0) \\ \frac{\partial}{\partial x} \alpha_2(t,x) = 0, \end{cases} \tag{4.16}$$

The last equation is due to the fact that the tubule 1 is highly permeable to water and tubule 2 is impermeable to water, that means $L_{2,p} = 0$ and consequently $J_2^V(t,x) = 0$. In general, the solute flow (for uncharged solute) should take into account diffusion, active transport but also convection. In these solute fluxes J_1, J_2, the simpler case was considered. A possible subject of future and in-depth studies could be the model accounting for charged solutes and electrical forces.

Chapter 5

Conclusion and outlook

In this thesis we present a simplified mathematical model of solutes transport in Henle's loop. The model accounts for ion transport between the lumen and the epithelial cells, and between the cells and the interstitium. The aim of this work is to evaluate the impact of explicitly considering the epithelium on predicted solute concentration gradients in the loop of Henle and to examine this impact on solute concentrations. In the last years, several research groups have developed sophisticated models of water and electrolyte transport in the kidney. We can broadly divide these models in two categories: (a) detailed cell-based models that incorporate cell-specific transporters and predict the function of small populations of nephrons at steady-state ([34]; [50]; [21]; [51]; [6]), and (b) macroscale models that describe the integrated function of nephrons and renal blood vessels but without accounting for cell-specific transport mechanisms ([46], [47]; [48]; [30]; [8]; [4]; [11]; [10]). These latter models do not consider explicitly the epithelial layer separating the tubule lumen from the surrounding interstitium, and represent the barrier as a single membrane.

In the second Chapter, after introducing the biological background, the mathematical aspects and difficulties to explore, we present a rigorous passage to the limit for $P \to +\infty$. Physically, studying this limit means studying what happens to the model by 'removing' the epithelial layer, assuming that the tubules are directly in contact with the surrounding environment (interstitium). This result ensures the consistency between the 'reduced' model (3-eq. system) and the 'epithelial' model (5-eq. system), but also rigorously explains and makes explicit the link between two possible descriptions of the same physical phenomenon with different levels of complexity.

On the other hand, the model we have been studying is quite far from how the kidneys actually work. For this reason it is not reasonable to conclude that the 5-equation model is sufficient to describe the sodium fluxes and the counter-current mechanism, very important for the urinary concentration capacity in mammals, [22]. Furthermore, based on this study, it could be reckless any other suggestions on the order of magnitude of permeability, for example for a comparison between the 'normal/healthy' cases and the pathological ones in kidneys. In fact, the 3 equation system had already given a proper representation of the counter-current mechanism, but it is not sufficient to give other suggestions about sodium fluxes in clinical cases and for the description of the entire phenomenon. In order to look after a more appropriate analysis that could be explicitly applied to physiological conditions, the first step would be to take into account the water flow and the fluid reabsorption in the descending tubule. Then, the second one would have to consider the electrical forces that apply to ions such as sodium and potassium, and that modulate the flows (in other words, the flows depend not only on concentration gradients but also on electrical potential).

In the third Chapter, we recall the model describing the transport of sodium in a simplified version of the Henle's loop in a kidney nephron. From a modelling point of view, it seems important to take into account the epithelium in the counter-current tubular architecture since we observe that it may strongly affect the solute concentration profiles in a specific range of permeabilities and parameters.

It turns out that the main limitation of the model is to not consider the re-absorption of water in descending limb. Indeed, in Section 3.2, we study the steady state solution and the assumption of a constant rate α and the boundary conditions lead to $\bar{u}_1(x) = \bar{u}_2(x)$, i.e. the luminal concentrations of sodium are the same in both tubules for every $x \in (0, L)$. Conversely, in vivo, the concentrations in lumen 1 and 2 are different due to the constitutive differences between the segments and presence of membrane channel proteins, for example the aquaporins. The thin descending limb of Henle's loop has low permeability to ions and urea, while being highly permeable to water. The thick ascending limb is impermeable to water, but it is permeable to ions. For this reason, a possible extension of the model shall assume that α is not constant but space-dependent. A first step could be, for instance, to take two different values of α for the first and second equation of the model (3.6), α_1 and α_2. From the mathematical viewpoint, this choice slightly changes the structure of the hyperbolic system : for example, conservation of certain quantities should not be that easy to prove. As noted in [20] and already underlined in the Introduction, since the thick ascending limb is water impermeable, it is coherent to assume α constant but in other models it may vary in time.

Furthermore, this assumption about α has a relevant influence on other factors. As already pointed out, the relation between $\bar{q}_1$ and $\bar{u}_0$ is biologically correct and consistent, this means that in vivo the concentration of Na^+ in the epithelial cell (intracellular) is lower than in interstitium. The intracellular concentrations (epithelium, $\bar{q}_1$ and $\bar{q}_2$) are usually of the order of 10mM whereas the extracellular ones (therefore in the lumen and in the interstitium) are of the order of 140mM.

There are also other types of source terms in the interstitium that could be added, accounting for blood vessels and/or collecting ducts. In this case, the last equation (3.6e) of the dynamic system should include a term that accounts for interstitium concentration storage or accumulation and for secretion-reabsorption of water and solutes, but the impact of adding such complex mechanisms in the model remains to be assessed.

In the study presented in Chap.3 of this thesis, we focused our attention on the axial concentration gradient and the FIC, previously defined in Section (3.2), which are significant factors in the urinary concentration mechanism, [22, 20]. The axial gradient is an important determinant of urinary concentration capacity. When water intake is limited, mammals can conserve water in body fluids by excreting solutes in a reduced volume of water, that is, by producing a concentrated urine. The thick ascending limb plays an essential role in urine concentration and dilution, [40] : the active reabsorption of sodium without parallel reabsorption of water

generates an interstitial concentration gradient in the outer medulla that in turn drives water reabsorption by the collecting ducts, thereby regulating the concentration of final urine.
In summary, our model confirms that the active trans-epithelial transport of sodium from the ascending limbs into the surrounding environment is able to generate an osmolality gradient. Our model indicates that explicitly accounting for the 2-step transport across the epithelium significantly impacts the axial concentration gradient within the physiological range of parameters values considered here. Thus, representing the epithelial layer as two membrane in series, as opposed to a single-barrier representation, may provide a more accurate understanding of the forces that contribute to the urinary concentrating mechanism. Therefore, the system gives a contribution in the field of physiological renal transport model and it could be a good starting point to elucidate and to better understand some mechanisms underlying concentrating mechanism and related to the normal or abnormal ions transport in the kidney.

Appendix A

Chapter 2 tools

"I hate T.V. I hate it as much as peanuts.
But I can't stop eating peanuts ."
[14]

A.1 Preliminaries and general notation

There are several definitions of the functions with bounded variation, especially in the one-dimensional case, we report here just some of these referring to [9] and [25].

Definition A.1.1. Let be $\Omega \subset \mathbb{R}^N$ be an open set and let $u \in L^1(\Omega)$. Define

$$\int_\Omega |Du| = sup \left\{ \int_\Omega u \; div(g) \; dx : g \in C_0^1(\Omega; R^n); |g(x)| \leq 1; \quad x \in \Omega \right\}$$

Definition A.1.2. A function $u \in L^1(\Omega)$ is said to have bounded variation in Ω if $\int_\Omega |Du| < \infty$. We define $BV(\Omega)$ as the space of all functions in $L^1(\Omega)$ with bounded variation.

Definition A.1.3. Let $u \in L^1(\Omega)$; we say that u is a function of bounded variation in Ω if the distributional derivative of u is representable by a finite Radon measure in Ω, i.e. if:

$$\int_\Omega u \frac{\partial \varphi}{\partial_{x_i}} \; dx = - \int_\Omega \varphi \; dD_i u = - \int_\Omega \varphi \; d\lambda_i \quad \forall \varphi \in C_c^\infty(\Omega) \quad i = 1, .., N$$

The vector space of all functions of bounded variation in Ω is denoted by $BV(\Omega)$.

Definition A.1.4. Let (a, b) be a bounded or unbounded interval. A map $u : (a, b) \to \mathbb{R}^N$ defined at every point $x \in (a, b)$ is called a function with bounded variation in one variable if its total variation is finite:

$$TV(u; (a, b)) = \sup\{\sum_{k=1}^{q} |u(x_k) - u(x_{k-1})|; a \leq x_0 < x_1 .. < x_q \leq b\} < \infty.$$

An equivalent definition is given as follows. A function $u : (a, b) \to \mathbb{R}^N$ defined almost everywhere for the Lebesgue measure, belongs to $BV((a, b); R^N)$ if its distributional derivative $\partial_x u$ is a bounded measure, the total variation of u being then:

$$TV(u; (a, b)) = \sup_{\varphi \in C_c^1(a,b)} \frac{\int_a^b u \partial_x \varphi \, dx}{\|\varphi\|_{L^\infty}}$$

A.2 Tools

All computations done in this paper may be done rigorously thanks to a regularization process, as explained for example in [28]. We recall that if u is a $BV(0, L)$ function, we can define its truncature for instance as: $u^\delta = u(1 - \chi_\delta) + c\chi_\delta$ with χ_δ which takes value 1 in $x \in [0, \delta]$ and c real constant. Then, we can also define:

$$u^{\delta,\nu} = (u(1 - \chi_\delta) + c\chi_\delta) * \phi_\nu, \tag{A.1}$$

with ϕ_ν standard regularizing convolution kernel. Furthermore, a standard property of the BV function (see [7] or [53]) allows us to write that:

$$\|u * \phi_\nu\|_{BV} \leq \|u\|_{BV},$$

for all sufficiently small $\nu > 0$ and $u \in BV$, the regularization does not increase the norm. We also recall following result in [28] describing the behaviour of BV-norm for truncated and regularized function of BV space:

$$\forall \gamma > 0 \; \exists \beta_\gamma \; s.t. \; \forall \delta < \beta_\gamma, \quad TV(u^\delta) \leq TV(u) + |u(0) - c| + \gamma.$$

We want pass to the limit in the regularization parameter with uniform estimates to prove that the obtained estimates hold uniformly respect to the regularization and truncation procedure and therefore, fulfil the previous results.

We consider the regularized and truncated initial data of the problem (3.6):

$$u_1^{\delta,\nu}(0, x), u_2^{\delta,\nu}(0, x), q_1^{\delta,\nu}(0, x), q_2^{\delta,\nu}(0, x), u_0^{\delta,\nu}(0, x),$$

and $u_b^{\delta,\nu}(t)$, all defined as in (A.1).
The system (3.6) admits a unique smooth solution when the initial data is regularized and truncated, i.e. $\exists \; (u_1^{\delta,\nu}, u_2^{\delta,\nu}, q_1^{\delta,\nu}, q_2^{\delta,\nu}, u_0^{\delta,\nu})_{\delta,\nu>0}$ approximating family which solves (3.6) with corresponding and regular initial and boundary data.

We notice that the previous (a priori) estimates still hold true passing to the limit uniformly in δ and ν.

Lemma A.2.1. *For truncated and regularized functions $u_1^{\delta,\nu}(0, x)$, $u_2^{\delta,\nu}(0, x)$, $q_1^{\delta,\nu}(0, x)$, $q_2^{\delta,\nu}(0, x)$, $u_0^{\delta,\nu}(0, x)$, and $u_b^{\delta,\nu}(t)$ and for every fixed $\varepsilon > 0$ there exists a unique vector solution $U^{\delta,\nu}$ solution to (3.6) and $U^{\delta,\nu} \in C^\infty$. Moreover, if U is a weak solution associated to the data $u_1(0, x), u_2(0, x), q_1(0, x), q_2(0, x), u_0(0, x)$, and $u_b(t)$, then we have $U^{\delta,\nu} \to U$ in L^1 when $\delta, \nu \to 0$.*

A.2.1 Contraction property

We will present briefly the contraction property, using the notation $d_i(t,x) = |u_1 - \bar{u}_1|, i = 0,1,2$ and $\delta_j(t,x) = |q_j - \tilde{q}_j|$, $j = 1,2$. We subtract line i of system (3.4) for u_i, q_j and $\bar{u}_i, \bar{q}_j$ and we multiply by $sgn(u_i - \bar{u}_i)$ and in line j we multiply by $sgn(q_j - \bar{q}_j)$ respectively, [37]. We obtain the following inequalities :

$$\begin{cases} \partial_t d_1 + \alpha \partial_x d_1 \leq k(\delta_1 - d_1) \\ \partial_t d_2 - \alpha \partial_x d_2 \leq k(\delta_2 - d_2) \\ \partial_t \delta_1 \leq k(d_1 - \delta_1) + K_1(d_0 - \delta_1) \\ \partial_t \delta_2 \leq k(d_2 - \delta_2) + K_2(d_0 - \delta_2) - g\delta_2 \\ \partial_t d_0 \leq K_1(\delta_1 - d_0) + K_2(\delta_2 - d_0) + g\delta_2. \end{cases} \tag{A.2}$$

In the last and the 4th equation of system, we use that $-G(q_2)sgn(q_2) = -|G(q_2)|$ (since for assumption on the non-linear term $sgn(G(q_2)) = sgn(q_2)$. For the last one we recall $G(q_2)sgn(u_0) \leq |G(q_2)|$ and $g\delta_2 = g|q_2 - \bar{q}_2|$. G is nondecreasing in q_2 and it holds,

$$sgn(G(q_2(t,x)) - G(\bar{q}_2(t,x)))[G(q_2(t,x)) - G(\bar{q}_2(t,x))] = |G(q_2) - G(\bar{q}_2)| \leq g\delta_2(t,x).$$

Adding all equations of system above, we obtain:

$$\partial_t(d_1 + d_2 + d_0 + \delta_1 + \delta_2) \leq \alpha(\partial_x d_2 - \partial_x d_1).$$

Integrating in the space $[0, L]$:

$$\frac{d}{dt}\int_0^L (d_1 + d_2 + d_0 + \delta_1 + \delta_2)(t,x)\ dx \leq \alpha(d_2(t,L) - d_2(t,0) - d_1(t,L) + d_1(t,0)).$$

Since $u_1(t,L) = u_2(t,L)$, we can simplify and get:

$$\frac{d}{dt}\int_0^L (d_1 + d_2 + d_0 + \delta_1 + \delta_2)(t,x)\ dx \leq \alpha d_1(t,0) - \alpha d_2(t,0). \tag{A.3}$$

It implies:

$$\frac{d}{dt}\int_0^L (d_1 + d_2 + d_0 + \delta_1 + \delta_2)(t,x)\ dx \leq \alpha d_1(t,0).$$

Integrating now with respect to time, we obtain:

$$\int_0^L (d_1(t,x) + d_2(t,x) + d_0(t,x) + \delta_1(t,x) + \delta_2(t,x))\ dx \leq \alpha \int_0^T d_1(t,0)\ dt + \int_0^L (d_1(0,x) + d_2(0,x) + d_0(0,x) + \delta_1(0,x) + \delta_2(0,x))\ dx,$$

which implies,

$$\int_0^L (|u_1 - \bar{u}_1| + |u_2 - \bar{u}_2| + |u_0 - \bar{u}_0| + |q_1 - \bar{q}_1| + |q_2 - \bar{q}_2|)(t,x)\ dx \leq \alpha \int_0^T |(u_1 - \bar{u}_1)|(t,0)\ dt + \\ + \int_0^L (|u_1 - \bar{u}_1| + |u_2 - \bar{u}_2| + |u_0 - \bar{u}_0| + |q_1 - \bar{q}_1| + |q_2 - \bar{q}_2|)(0,x)\ dx. \tag{A.4}$$

A.3 Definition of weak solutions: 3×3 system

We recall the 3×3 system with simplified notation $k_1 = 2\pi r_1 P_1$ and $k_2 = 2\pi r_2 P_2$, constants related to biological parameters:

$$\begin{cases} \partial_t u_1 + \alpha \partial_x u_1 = k_1(u_0 - u_1) \\ \partial_t u_2 - \alpha \partial_x u_2 = k_2(u_0 - u_2) - G(u_2) \\ \partial_t u_0 = k_1(u_1 - u_0) + k_2(u_2 - u_0) + G(u_2), \end{cases} \tag{A.5}$$

with related initial and boundary conditions:

$$u_1(t,0) = u_b(t); \quad u_1(t,L) = u_2(t,L) \quad t \geq 0,$$

$$u_1(0,x) = u_1^0(x); \quad u_2(0,x) = u_2^0(x); \quad u_0(0,x) = u_0^0(x).$$

Definition A.3.1. We call $U(t,x) = (u_1, u_2, u_0)$ weak solution of system (A.5), if for all $\varphi_1, \varphi_2, \varphi_0 \in \mathcal{S}$ with $\mathcal{S} = \{\varphi \in C^1([0,T] \times [0,L]), \quad \varphi(T,x) = 0\}$, it satisfies following equalities:

$$\begin{cases} \int_0^T \int_0^L u_1(\partial_t \varphi_1 + \alpha \partial_x \varphi_1)\ dxdt + \int_0^T \int_0^L k_1(u_0 - u_1)\varphi_1\ dxdt + \\ + \int_0^T u_b(t)\varphi_1(t,0) - u_1(t,L)\varphi_1(t,L)\ dt + \int_0^L u_1(0,x)\varphi_1(0,x)\ dx = 0, \\ \int_0^T \int_0^L u_2(\partial_t \varphi_2 - \alpha \partial_x \varphi_2)\ dxdt + \int_0^T \int_0^L k_2(u_0 - u_2)\varphi_2\ dxdt + \\ + \int_0^T u_2(t,0)\varphi_2(t,0) - u_2(t,L)\varphi_2(t,L)\ dt + \int_0^L u_2(0,x)\varphi_2(0,x)\ dx - \int_0^T \int_0^L G(u_2)\varphi_2\ dxdt = 0, \\ \int_0^T \int_0^L u_0(\partial_t \varphi_0)\ dxdt - \int_0^T \int_0^L k_1(u_0 - u_1)\varphi_0\ dxdt - \int_0^T \int_0^L k_2(u_0 - u_2)\varphi_0\ dxdt + \\ + \int_0^L u_0(0,x)\varphi_0(0,x)\ dx + \int_0^T \int_0^L G(u_2)\varphi_0\ dxdt = 0. \end{cases} \tag{A.6}$$

Appendix B

Chapter 3 tools

B.1 Large permeability asymptotic

In this section we consider the case where the permeability between the lumen and the epithelium is large, i.e. when $P_i \to \infty$, with $i = 1, 2$ in the definition of constants k_1 and k_2. For this purpose, we set $k = k_1 = k_2 = \frac{1}{\varepsilon}$ and we let ε go to 0. Physically, this means fusing the epithelial layer with the lumen.

Rewriting (3.6) in this perspective gives

$$\partial_t u_1^\varepsilon + \alpha \partial_x u_1^\varepsilon = \frac{1}{\varepsilon}(q_1^\varepsilon - u_1^\varepsilon) \tag{B.1a}$$

$$\partial_t u_2^\varepsilon - \alpha \partial_x u_2^\varepsilon = \frac{1}{\varepsilon}(q_2^\varepsilon - u_2^\varepsilon) \tag{B.1b}$$

$$\partial_t q_1^\varepsilon = \frac{1}{\varepsilon}(u_1^\varepsilon - q_1^\varepsilon) + K_1(u_0^\varepsilon - q_1^\varepsilon) \tag{B.1c}$$

$$\partial_t q_2^\varepsilon = \frac{1}{\varepsilon}(u_2^\varepsilon - q_2^\varepsilon) - G(q_2^\varepsilon) \tag{B.1d}$$

$$\partial_t u_0^\varepsilon = K_1(q_1^\varepsilon - u_0^\varepsilon) + G(q_2^\varepsilon). \tag{B.1e}$$

We expect the concentrations u_1^ε and q_1^ε to converge to the same quantity. The same happens for $u_2^\varepsilon \to u_2$ and $q_2^\varepsilon \to u_2$. We denote u_1, respectively u_2, the limit of u_1^ε and q_1^ε, respectively u_2^ε and q_2^ε. Adding (1.6a) to (B.1c) and (B.1b) to (B.1d), we obtain

$$\begin{aligned} \partial_t u_1^\varepsilon + \partial_t q_1^\varepsilon + \alpha \partial_x u_1^\varepsilon &= K_1(u_0^\varepsilon - q_1^\varepsilon) \\ \partial_t u_2^\varepsilon + \partial_t q_2^\varepsilon - \alpha \partial_x u_2^\varepsilon &= -G(q_2^\varepsilon). \end{aligned}$$

Passing formally to the limit $\varepsilon \to 0$, we arrive at

$$2\partial_t u_1 + \alpha \partial_x u_1 = K_1(u_0 - u_1) \tag{B.2}$$

$$2\partial_t u_2 - \alpha \partial_x u_2 = -G(u_2), \tag{B.3}$$

coupled to the equation for the concentration in the interstitium obtained by passing into the limit in equation (B.1e)

$$\partial_t u_0 = K_1(u_1 - u_0) + G(u_2). \tag{B.4}$$

The equations (B.2), (B.3), (B.4) describe the same concentration dynamics in a system without epithelium, previously studied in [46] and [47]. The formal computation above shows that this 3×3 system may be considered as a good approximation of the larger system (3.6) for large permeabilities.

Such a convergence result may be proved rigorously and it is investigated in Chapter 2. It relies on specific *a priori* estimates and the introduction of an initial layer.

B.2 Technical results

B.2.1 Function $F(\lambda)$

In this subsection we prove that the function $F(\lambda)$ which appears in the proof of Lemma 3.3.1 is a monotonic function. First let's recall it

$$F(\lambda) := \frac{gk_\lambda}{1 + \frac{1}{k}(g-\lambda)} \left(\frac{e^{(c_\lambda + \lambda - \eta(\lambda))L} - 1}{c_\lambda + \lambda - \eta(\lambda)} \right). \tag{B.5}$$

Lemma B.2.1. *The function F defined by* (B.5) *is monotonically increasing on* $(0, \lambda_-)$.

Proof. The product of positive increasing functions is increasing.

- $\lambda \mapsto k_\lambda = \frac{K_1 k}{\lambda^2 - 2K_1\lambda - k\lambda + kK_1}$ is a positive and increasing function if $\lambda \in (0, \lambda_-)$. Indeed $\frac{\partial k_\lambda}{\partial \lambda} = \frac{-2\lambda k K_1 + 2kK_1^2 + k^2 K_1}{(\lambda^2 - 2K_1\lambda - k\lambda + kK_1)^2}$ is positive for $0 < \lambda < K_1 + \frac{k}{2}$ and $\lambda_- < K_1$ by definition.
- We set $f_1(\lambda) := \frac{g}{1 + \frac{1}{k}(g-\lambda)}$; if $\lambda < g + k$ the function f_1 is positive since $g > 0$ by hypothesis and it is also increasing since $\frac{\partial}{\partial_\lambda} f_1(\lambda) = \frac{\frac{g}{k}}{(1 + \frac{1}{k}(g(y) - \lambda))^2} > 0$, and $\lambda_- \le \frac{k}{2}$.
- The function $x \mapsto \frac{e^x - 1}{x}$ is increasing on $\mathbb{R}^+$ and the function $\lambda \mapsto c_\lambda + \lambda - \eta(\lambda)$ is increasing on $(0, \lambda_-)$. Indeed, we have straightforwardly

$$c_\lambda + \lambda - \eta(\lambda) = 2\lambda + 2k + \frac{k^2}{k - \lambda - \frac{K_1\lambda}{K_1 - \lambda}} + \frac{k^2}{k + g - \lambda}.$$

□

B.2.2 Relation between direct and dual system

We recall the eigenelements problem written as below:

$$\begin{bmatrix} \partial_x U_1(x) \\ -\partial_x U_2(x) \\ 0 \\ 0 \\ 0 \end{bmatrix} = \lambda \mathcal{U}(x) + A\mathcal{U}(x); \qquad \mathcal{U}(x) = \begin{bmatrix} U_1 \\ U_2 \\ Q_1 \\ Q_2 \\ U_0 \end{bmatrix} \tag{B.6}$$

$$\begin{bmatrix} -\partial_x \varphi_1(x) \\ \partial_x \varphi_2(x) \\ 0 \\ 0 \\ 0 \end{bmatrix} = \lambda \Phi(x) + {}^t A \Phi(x); \qquad \Phi(x) = \begin{bmatrix} \varphi_1 \\ \varphi_2 \\ \phi_1 \\ \phi_2 \\ \varphi_0 \end{bmatrix} \tag{B.7}$$

with related matrix defined by

$$A = \begin{bmatrix} -k & 0 & k & 0 & 0 \\ 0 & -k & 0 & k & 0 \\ k & 0 & -k-K_1 & 0 & K_1 \\ 0 & k & 0 & -k-g & 0 \\ 0 & 0 & K_1 & g & -K_1 \end{bmatrix}.$$

Multiplying (B.6) on the left by ${}^t\Phi$, we deduce

$$\varphi_1 \partial_x U_1 - \varphi_2 \partial_x U_2 = \lambda^t \Phi \mathcal{U} + {}^t \Phi A \mathcal{U}.$$

Taking the transpose of (B.20) and multiplying on the right by $\mathcal{U}$, we also have

$$-\partial_x \varphi_1 U_1 + \partial_x \varphi_2 U_2 = \lambda^t \Phi \mathcal{U} + {}^t \Phi A \mathcal{U}.$$

As a consequence, we deduce the relation

$$(U_1 \varphi_1)' - (U_2 \varphi_2)' = 0, \quad \forall x \in [0, L]. \tag{B.8}$$

Since $U_1(L) = U_2(L)$ in (3.21) and by initial conditions $U_1(0) = 0$, $\varphi_2(0) = 0$, then also $\varphi_1(L) = \varphi_2(L)$, as set in (3.23). It means that $(U_1 \varphi_1) = (U_2 \varphi_2)$ $\forall x \in [0, L]$. Thanks to this relation, we can consider in our previous computation:

$$\varphi_2(x) = \frac{U_1(x)}{U_2(x)} \varphi_1(x), \quad \forall x \in [0, L].$$

B.3 A simpler case: 3×3 system without epithelium.

In this section we introduce a simpler system 3×3 describing a countercorrent architecture but without taking into account the epithelial layers and the ionic exchanges through them.

Then we will introduce the eigenelements problem related to the non linear stationary problem:

$$\begin{bmatrix} \partial_x N_1(x) \\ -\partial_x N_2(x) \\ 0 \end{bmatrix} - AN(x) = \lambda N(x); \qquad N(x) = \begin{bmatrix} N_1 \\ N_2 \\ N_0 \end{bmatrix} \tag{B.9}$$

$$\begin{bmatrix} -\partial_x \varphi_1(x) \\ \partial_x \varphi_2(x) \\ 0 \end{bmatrix} - {}^t A \Phi(x) = \lambda \Phi(x); \qquad \Phi(x) = \begin{bmatrix} \varphi_1 \\ \varphi_2 \\ \varphi_0 \end{bmatrix} \tag{B.10}$$

with related matrix defined as:

$$A = \begin{bmatrix} k_1 & 0 & -k_1 \\ 0 & k_2 + g(x) & -k_2 \\ -k_1 & -k_2 - g(x) & k_1 + k_2 \end{bmatrix}, \; {}^tA = \begin{bmatrix} k_1 & 0 & -k_1 \\ 0 & k_2 + g(x) & -k_2 - g(x) \\ -k_1 & -k_2 & k_1 + k_2 \end{bmatrix} \tag{B.11}$$

It is easy to verify that following relation between "direct" and "dual" system holds:

$$\begin{bmatrix} \partial_x N_1(x) \\ -\partial_x N_2(x) \\ 0 \end{bmatrix} \cdot \begin{bmatrix} \varphi_1 \\ \varphi_2 \\ \varphi_0 \end{bmatrix} - \begin{bmatrix} -\partial_x \varphi_1(x) \\ \partial_x \varphi_2(x) \\ 0 \end{bmatrix} \cdot \begin{bmatrix} N_1 \\ N_2 \\ N_0 \end{bmatrix} = 0 \tag{B.12}$$

If we set

$$D = \begin{bmatrix} \partial_x N_1(x) \\ -\partial_x N_2(x) \\ 0 \end{bmatrix}, \quad D^* = \begin{bmatrix} -\partial_x \varphi_1(x) \\ \partial_x \varphi_2(x) \\ 0 \end{bmatrix},$$

we can rewrite

$$DU - AU - \lambda U = 0, \qquad D^*\Phi - {}^tA - \lambda \Phi = 0.$$

Multiplying the first by U and the second by Φ,

$$DU \cdot \Phi - AU \cdot \Phi - \lambda U \cdot \Phi = D^*\Phi U - {}^tA\Phi \cdot U - \lambda \Phi \cdot U$$

we verify the following relation,

$$DU \cdot \Phi - D^*\Phi \cdot U = AU \cdot \Phi - A^*\Phi \cdot U = U \cdot A^*\Phi - A^*\Phi \cdot U = 0$$

B.3.1 Existence of eigenelements: case 3×3

We consider the non linear stationary problem:

$$\begin{cases} \partial_x \bar{u}_1 = k_1(\bar{u}_0 - \bar{u}_1) \\ -\partial_x \bar{u}_2 = k_2(\bar{u}_0 - \bar{u}_2) - G(\bar{u}_2) \\ 0 = k_1(\bar{u}_1 - \bar{u}_0) + k_2(\bar{u}_2 - \bar{u}_0) + G(\bar{u}_2) \\ \bar{u}_1(0) = u_1^0 \quad \bar{u}_1(L) = \bar{u}_2(L) \end{cases} \tag{B.13}$$

We state the first eigenelement problem for a given continuous function $g(x) > 0$:

$$\begin{cases} \partial_x N_1 = \lambda N_1 + k_1(N_0 - N_1) \\ -\partial_x N_2 = \lambda N_2 + k_2(N_0 - N_2) - g(x)N_2 \\ 0 = \lambda N_0 + k_1(N_1 - N_0) + k_2(N_2 - N_0) + g(x)N_2 \end{cases} \tag{B.14}$$

wtih following conditions:

$$N_1(0) = 0; \quad N_1(L) = N_2(L); \quad \int_0^L (N_1(x) + N_2(x) + N_0(x)) \, dx = 1 \tag{B.15}$$

In case $k_2 = 0$:

$$\begin{cases} \partial_x N_1 = \lambda N_1 + k_1(N_0 - N_1) \\ -\partial_x N_2 = \lambda N_2 - g(x) N_2 \\ 0 = \lambda N_0 + k_1(N_1 - N_0) + g(x) N_2 \end{cases} \tag{B.16}$$

We sum all equations:

$$N_1' - N_2' = \lambda(N_1 + N_2 + N_0).$$

Integrating with respect to x, since (B.15) holds, we obtain that $\lambda = N_2(0)$.

By $2nd$ equation we get immediately:

$$N_2(x) = N_2(0) e^{-\int_0^x (\lambda - g(\sigma)\ ) d\sigma}.$$

By $3rd$ equation we get:

- if $\lambda = k_1$, then $N_1 = -\frac{g(x)}{k_1} N_2$,
- if $\lambda \neq k_1$ then $N_0(x) = \frac{g(x)}{k_1 - \lambda} N_2(x) + \frac{k_1}{k_1 - \lambda} N_1$

Putting the last expression in the $1st$ equation, we get:

$$N_1' - \frac{2k_1 - \lambda}{k_1 - \lambda} = \frac{k_1 g(x)}{k_1 - \lambda} N_2(x),$$

$$N_1(x) = \frac{k_1 \lambda}{k_1 - \lambda} \int_0^x e^{\frac{2k_1 - \lambda}{k_1 - \lambda} \lambda (x - y)} g(y) e^{-\lambda y + \int_0^y g(\sigma)\ d\sigma}. \tag{B.17}$$

We recall the fact that $N_1(L) = N_2(L)$. We have to check that the boundary condition is satisfied, i.e. $\frac{N_1(L)}{N_2(L)} = 1$:

$$F(\lambda) = \frac{k_1}{k_1 - \lambda} \int_0^L e^{(\frac{2k_1 - \lambda}{k_1 - \lambda}) \lambda (L - y)} g(y) e^{\lambda (L - y) - \int_y^L g(\sigma)\ d\sigma}\ dy = 1. \tag{B.18}$$

With $\lambda = 0$, $F(0) = \int_0^L g(y) e^{-\int_y^L g(\sigma)\ d\sigma}\ dy < 1$, because of:

$$0 < F(0) = \left[e^{\int_y^L g(\sigma)\ d\sigma} \right]_0^L = 1 - e^{-\int_0^L g(\sigma)\ d\sigma} < 1.$$

For $\lambda < k_1$, it easy to verify that $F(\lambda) > 0$ and increasing continuos function. Since the product of positive increasing function is still increasing, we can study each component in the integral as function of λ and conclude. Moreover $\lim_{\lambda \to k_1} F(\lambda) = +\infty$. Then, there $\exists$ a unique $\lambda \in (0, k_1)$ which fulfills $F(\lambda) = 1$. In addition, it exists $N_1, N_2, N_0 \geq 0$ unique solution of system (B.16).

Relation between direct and dual system

We recall the eigenelements problem written as below:

$$\begin{bmatrix} \partial_x N_1(x) \\ -\partial_x N_2(x) \\ 0 \end{bmatrix} = \lambda N(x) + AN(x); \qquad N(x) = \begin{bmatrix} N_1 \\ N_2 \\ N_0 \end{bmatrix} \tag{B.19}$$

$$\begin{bmatrix} -\partial_x \varphi_1(x) \\ \partial_x \varphi_2(x) \\ 0 \end{bmatrix} = \lambda \Phi(x) + {}^t A\Phi(x); \qquad \Phi(x) = \begin{bmatrix} \varphi_1 \\ \varphi_2 \\ \varphi_0 \end{bmatrix} \tag{B.20}$$

with related matrix defined as:

$$A = \begin{bmatrix} -k_1 & 0 & k_1 \\ 0 & -k_2 - g(x) & k_2 \\ k_1 & k_2 + g(x) & -k_1 - k_2 \end{bmatrix}, \; {}^t A = \begin{bmatrix} -k_1 & 0 & k_1 \\ 0 & -k_2 - g(x) & k_2 + g(x) \\ k_1 & k_2 & -k_1 - k_2 \end{bmatrix} \tag{B.21}$$

$$\begin{bmatrix} \partial_x N_1(x) \\ -\partial_x N_2(x) \\ 0 \end{bmatrix} \cdot \begin{bmatrix} \varphi_1 \\ \varphi_2 \\ \varphi_0 \end{bmatrix} - \begin{bmatrix} -\partial_x \varphi_1(x) \\ \partial_x \varphi_2(x) \\ 0 \end{bmatrix} \cdot \begin{bmatrix} N_1 \\ N_2 \\ N_0 \end{bmatrix} = 0 \tag{B.22}$$

The previous relation leads us to: $N_1'\varphi_1 - N_2'\varphi_2 + \varphi_1' N_1 - \varphi_2' N_2 = 0$,, that implies $(N_1\varphi_1)' = (N_2\varphi_2)'$. Since $N_1(L) = N_2(L)$ (B.15) and by initial conditions $N_1(0) = 0,\ \varphi_2(0) = 0$, then also $\varphi_1(L) = \varphi_2(L)$. It means that $(N_1\varphi_1) = (N_2\varphi_2)\ \forall x \in [0, L]$. Thanks to this relation, we can consider:

$$\varphi_2(x) = \frac{N_1(x)}{N_2(x)}\varphi_1(x).$$

In the case 5×5 investigated in this work, the same relation reads:

$$\lambda \Phi U + {}^t M \Phi U = \lambda U \Phi + MU\Phi, \tag{B.23}$$

$$(U_1\varphi_1)' - (U_2\varphi_2)' = 0 \quad \forall x \in [0, L], \tag{B.24}$$

with $U = (u_1, u_2, q_1, q_2, u_0),\ \Phi = (\varphi_1, \varphi_2, \phi_1, \phi_2, \varphi_0)$ and

$$M = \begin{bmatrix} \lambda - k_1 & 0 & k_1 & 0 & 0 \\ 0 & \lambda - k_2 & 0 & k_2 & 0 \\ k_1 & 0 & \lambda - k_1 - K_1 & 0 & K_1 \\ 0 & k_2 & 0 & \lambda - k_2 - g & 0 \\ 0 & 0 & K_1 & g & \lambda - K_1 \end{bmatrix}, \tag{B.25}$$

$${}^t M = \begin{bmatrix} \lambda - k_1 & 0 & k_1 & 0 & 0 \\ 0 & \lambda - k_2 & 0 & k_2 & 0 \\ k_1 & 0 & \lambda - k_1 - K_1 & 0 & K_1 \\ 0 & k_2 & 0 & \lambda - k - g & g \\ 0 & 0 & K_1 & g & \lambda - K_1 \end{bmatrix}. \tag{B.26}$$

Dual problem: case 3×3

We consider now dual system associated to (B.16) with $g > 0$ continuous function and $k_2 = 0$ case:

$$\begin{cases} -\partial_x \varphi_1 = \lambda\varphi_1 + k_1(\varphi_0 - \varphi_1) \\ \partial_x \varphi_2 = \lambda\varphi_2 + g(x)(\varphi_0 - \varphi_2) \\ 0 = \lambda\varphi_0 + k_1(\varphi_1 - \varphi_0) \end{cases} \tag{B.27}$$

with following condition:

$$\varphi_2(0) = 0, \quad \varphi_1(L) = \varphi_2(L) \quad \int_0^L (N_1\varphi_1 + N_2\varphi_2 + N_0\varphi_0)\ dx = 1.$$

By $3rd$ equation of (B.27) : $\varphi_0(x) = \frac{k_1}{k_1-\lambda}\varphi_1(x)$.

Putting the expression for φ_0 in the $1st$ of (B.27), we obtain:

$$-\varphi_1'(x) = \left(\frac{k_1\lambda}{k_1 - \lambda} + \lambda\right)\varphi_1(x).$$

Then,

$$\varphi_1(x) = \varphi_1(0)e^{-\left(\frac{k_1\lambda}{k_1-\lambda}+\lambda\right)x}. \tag{B.28}$$

All functions depend on $\varphi_1(x)$:

$$\begin{aligned} \varphi_1(x) &= \varphi_1(0)e^{-\left(\frac{\lambda k_1}{k_1-\lambda}+\lambda\right)x} \\ \varphi_2(x) &= \frac{N_1(x)}{N_2(x)}\varphi_1(x) \\ \varphi_0(x) &= \frac{k_1}{k_1 - \lambda}\varphi_1(x) \end{aligned}$$

To prove their positivity, we need to know the sign of $\varphi_1(0)$. We use the normalization condition and previous expressions:

$\int_0^L 2N_1(x)\varphi_1(x) + N_0(x)\varphi_0(x)\ dx = 1,$

$$\int_0^L \varphi_1(0)\left(2N_1 + N_0\frac{k_1}{k_1 - \lambda}\right)e^{-(\frac{\lambda k_1}{k_1-\lambda}+\lambda)x}\ dx = 1. \tag{B.29}$$

All quantities are positive for $\lambda < k_1$, then the constant $\varphi_1(0) > 0$.

Now we are ready to prove long time behaviour Theorem for this 3×3 case. We set $d_i(t,x) := |u_i(t,x) - \bar{u}_i(x)|\ i = 0,1,2$ with $\bar{u}_i$ satisfying stationary system (B.30) and u_i solving the dynamic system (B.31).

$$\begin{cases} \alpha\partial_x\bar{u}_1 = k_1(\bar{u}_0 - \bar{u}_1) \\ -\alpha\partial_x\bar{u}_2 = k_2(\bar{u}_0 - \bar{u}_2) - G(\bar{u}_2) \\ 0 = k_1(\bar{u}_1 - \bar{u}_0) + k_2(\bar{u}_2 - \bar{u}_0) + G(\bar{u}_2) \\ \bar{u}_1(0) = u_1^0 \quad \bar{u}_1(L) = \bar{u}_2(L) \end{cases} \tag{B.30}$$

$$\begin{cases} a_1\partial_t u_1 + \alpha\partial_x u_1 = k_1 u_0 - u_1) \\ a_2\partial_t u_2 - \alpha\partial_x u_2 = k_2(u_0 - u_2) - G(u_2) \\ a_0\partial_t = k_1(u_1 - u_0) + k_2(u_2 - u_0) + G(u_2) \\ u_1(0,x) = u_1^0(x) \quad u_1(t,L) = u_2(t,L) \quad u(t,0) = u_b(t) \end{cases} \tag{B.31}$$

We subtract component-wise (B.31) to (B.30). Then we multiply each of the entries by $sign(u_i - \bar{u}_i)$ respectively. We obtain the following inequalities :

$$\begin{cases} a_1\partial_t d_1 + \alpha\partial_x d_1 \le k_1(d_0 - d_1) \\ a_2\partial_t d_2 - \alpha\partial_x d_2 \le k_2(d_2 - d_0) - \hat{G} \\ a_0\partial_t d_0 \le k_1(d_1 - d_0) + \hat{G}, \end{cases} \tag{B.32}$$

with $\hat{G} := |G(u_2) - G(\bar{u}_2)|$. We have used also the monotonicity of G (by definition). We recall that a_1, a_2, a_0, α are positive constants. We set

$$M(t) := \int_0^L (a_1|u_1 - \bar{u}_1|\varphi_1 + a_2|u_2 - \bar{u}_2|\varphi_2 + a_0|u_0 - \bar{u}_0|\varphi_0)\,dx.$$

In the case $k_2 = 0$, multiplying each equation of (B.32) by the corresponding dual function φ_i, adding all equations and integrating with respect to x, we obtain :

$$\frac{d}{dt}M(t) \le \alpha\int_0^L (\partial_x d_2\varphi_2 - \partial_x d_1\varphi_1)\,dx + \int_0^L \Big(k_1(d_0 - d_1)\varphi_1 + k_1(d_1 - d_0)\varphi_0 - \hat{G}\varphi_2 + \hat{G}\varphi_0\Big)\,dx.$$

Integrating by parts the first integral, we can simplify the latter inequality into

$$\begin{aligned} \frac{d}{dt}M(t) \le \alpha\Big(d_2(t,L)\varphi_2(L) - d_2(t,0)\varphi_2(0) + \int_0^L d_2(t,x)(\partial_x\varphi_2)\;dx\Big) + \\ - \alpha\Big(d_1(t,L)\varphi_1(L) - d_1(t,0)\varphi_1(0) - \int_0^L d_1(t,x)(\partial_x\varphi_1)\;dx\Big) + \\ + \int_0^L \Big(k_1(d_0 - d_1)\varphi_1 + k_1(d_1 - d_0)\varphi_0 - \hat{G}\varphi_2 + \hat{G}\varphi_0\Big)\;dx. \end{aligned}$$

then, using the dual system equations in (B.27) and the boundary condition $d_1(t,L) = d_2(t,L)\;\forall t > 0$

$$\begin{aligned} \frac{d}{dt}M(t) \le \alpha\int_0^L d_2(t,x)(\lambda\varphi_2 + g(\varphi_0 - \varphi_2))\;dx + \alpha d_1(t,0)\varphi_1(0) + \\ + \alpha\int_0^L d_1(t,x)(-\lambda\varphi_1 - k_1(\varphi_0 - \varphi_1))\;dx + \int_0^L \alpha\; d_0(t,x)(-\lambda\varphi_0 - k_1(\varphi_1 - \varphi_0))\;dx. \end{aligned}$$

since $\alpha d_0(t,x)(-\lambda\varphi_0 - k_1(\varphi_1 - \varphi_0)) = 0$, thanks to the last equation of (B.27) and since $d_1(t,L)\varphi_1(L) = d_2(t,L)\varphi_2(L)$ thanks to the boundary condition on u_1, u_2 and relation between direct and dual system.

$$\frac{1}{\alpha}\frac{d}{dt}M(t) \leq -\lambda \int_0^L (d_1\varphi_1 + d_2\varphi_2 + d_0\varphi_0)\ dx + d_1(t,0)\varphi_1(0) + \int_0^L (gd_2 - \hat{G})(\varphi_2 - \varphi_0)\ dx.$$

Then, we obtain

$$\frac{1}{\alpha}\frac{d}{dt}M(t) \leq -\lambda M(t) + d_1(t,0)\varphi_1(0) + \int_0^L (gd_0 - \hat{G})(\varphi_2 - \varphi_0)\ dx.$$

Since G is Lipschitz-continuous and by assumption and definition of it, $\hat{G} \leq gd_0$ with $g = \|G'\|_\infty$. With this choice of g and we deduce also the negativity of quantity $(\varphi_2 - \varphi_0)$.

$$\frac{1}{\alpha}\frac{d}{dt}M(t) \leq -\frac{\lambda}{\max\{a_1, a_2, a_0\}}M(t) + d_1(t,0)\varphi_1(0) + \int_0^L (gd_0 - \hat{G})(\varphi_2 - \varphi_0)\ dx.$$

Then, with $\bar{\lambda} = \frac{\lambda}{\max\{a_1,a_2,a_0\}}$,

$$\frac{1}{\alpha}\frac{d}{dt}M(t) + \bar{\lambda}M(t) \leq d_1(t,0)\varphi_1(0).$$

Thanks to (3.17) and applying Gronwall's lemma, we conclude that

$$M(t) \leq \alpha M(0)e^{-\bar{\lambda}t} + \alpha\varphi_1(0)\int_0^t d_1(s,0)e^{\bar{\lambda}(s-t)}\,ds. \tag{B.33}$$

Moreover, as in (3.17), we are supposing also in this case $d_1(s,0) = |u_b(t) - \bar{u}_b| \to 0$ as $t \to +\infty$. Then, for every $\varepsilon > 0$, it exists $\bar{t} > 0$ such that $d_1(s,0) < \varepsilon$ for each $s > \bar{t}$. Then for every $t \geq \bar{t}$, we have

$$\begin{aligned}\int_0^t d_1(s,0)e^{\bar{\lambda}(s-t)}\ ds &\leq \int_0^{\bar{t}} d_1(s,0)e^{\bar{\lambda}(s-t)}\ ds + \varepsilon\int_{\bar{t}}^t e^{\bar{\lambda}(s-t)}\,ds \\ &\leq e^{\bar{\lambda}(\bar{t}-t)}\int_0^{\bar{t}} d_1(s,0)\ ds + \frac{\varepsilon}{\bar{\lambda}}.\end{aligned}$$

The first term of the right hand side is arbitrarily small at t goes to $+\infty$. Hence, we have proved that for any $\varepsilon > 0$ there exists τ large enough such that for every $t \geq \tau$,

$$M(t) \leq M(0)e^{-\bar{\lambda}t} + C\varepsilon.$$

Since $M(t) = \|\mathbf{u}(t) - \bar{\mathbf{u}}\|_{L^1(\Phi)}$, it proves the convergence as stated in Theorem 3.3.1. Finally, if we assume that there exists positive constants μ_0 and C_0 such that $|u_b(t) - \bar{u}_b| \leq C_0e^{-\mu_0 t}$, then from (B.33) we deduce

$$M(t) \leq M(0)e^{-\bar{\lambda}t} + C_0\varphi_1(0)\frac{e^{-\mu_0 t} - e^{-\bar{\lambda}t}}{\bar{\lambda} - \mu_0} \leq Ce^{-\min\{\bar{\lambda},\mu_0\}t}.$$

$\square$

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