Multidomain model of kidney

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This is a reformulation of Alan Weinstein's kidney model as of 2022 in the framework of multidomain model. In the process, we point out the necessary assumptions, in addition to those of multidomain model, needed to be made in order to derive the kidney model. Then, we give the steady state model used in Alan Weinstein's recent papers. This is in hope that we have a clear overall picture which will ease us in the analysis of the model.

1 Model derivation

Consider a one-dimensional domain $\Omega = (-2, 7)$ which represents the radial coordinate of the kidney tissue from the superficial to the deeper layers; here, we assume that there is no variation across the kidney tissue of the same depth. Specifically, $(-2, 0)$ represents medullary ray, and $[0, 7)$ represents renal medulla. The domain is multiphasic in the sense that multiple radially aligned compartments of the kidney — which include the lumina, tubular cells and their intercellular space (also called lateral interspace) of different tubular segments (except convoluted tubules and connecting tubules), interstitia of medulla together with medullary ray, and vasa recta — are formally described within the same region, Ω.

Anatomically speaking, the renal cortex also share the same region $(-2, 0)$ as medullary ray. However, since the geometry of the convoluted tubules and connecting tubules, which are contained in the renal cortex, are difficult to describe, the spatial variations within the interstitium and the capillary plexus of the renal cortex are ignored. Therefore, we treat the tubules within the cortex as separated systems with their own one-dimensional domain which are coupled to components in Ω via their boundary and the cortical interstitium; we will come back to this later.

1.1 The renal medulla and medullary ray

We will use the label $k = 0$ for the interstitium of medullary ray and the renal medulla. It is important to note that, in this model, we do not make a distinction between the actual interstitium and the capillary plexus present in the renal cortex and medullary ray. Suppose there are N distinct types of

nephrons. For each type of nephron there are 2 components contained in Ω: the descending and the ascending parts, each of which are divided into the lumen, the intracellular space (ICS), and the lateral intercellular space (LIS). For the n^{th} type nephron, $1 \le n \le N$, we label by $k = \pm n$, $k = \pm(N+n)$, and $k = \pm(2N+n)$ the descending (positive) and the ascending (negative) parts of the lumen, the ICS, and the LIS respectively. Similarly, for P distinct types of vasa recta, the capillaries of the renal medulla running in opposition, we label by $k = \pm(3N+j)$, for $j = 1, \dots, P$, the descending and the ascending vasa recta. Finally, there are 3 distinct types of collecting tubular cells: principal cell, α-cell, and β-cell; the functions of the two additional cell types are urine acidification by α-intercalated cell and urine alkalinization by β-intercalated cell, and hence the necessity of assigning a distinct compartment for each of them. We assign $k = K, K+1, K+2, K+3, K+4$, where $K := 3N+P+1$ the lumen, the ICS of principal, α- and β-intercalted cells, and the LIS of the collecting tubules respectively.

We describe the occupied volume of each k^{th} compartment, $-3N-P \le k \le 3N+P+3$, in Ω by the volume per unit depth $\alpha_k : \Omega_k \times [0,\tau) \to \mathbb{R}_+$, where $0 < \tau \le \infty$ and $\Omega_k \subset \Omega$ is an open interval with $\Omega_n \supset \Omega_{N'+n} = \Omega_{2N'+n}$ and $\inf \Omega_n = \inf \Omega_{N'+n} \le 0$ for $n = \pm 1, \cdots \pm N$ where we denote $N'+n := \operatorname{sign}(n)N + n$ and $2N'+n := 2\operatorname{sign}(n)N + n$. The sets $\Omega_n \setminus \Omega_{N'+n}$ are where the thin loops of Henle located. Additionally, each loop of vasa recta begins at and returns to the cortex-medullary junction at $x = 0$, i.e., $\inf \Omega_{3N+j} = \inf \Omega_{-3N-j} = 0$, for $j = 1, \dots, P$. Moreover, we must have the turning points of the loops of Henle and vasa recta at the end and the beginning of their corresponding descending and the ascending compartments, i.e., $\sup \Omega_k = \sup \Omega_{-k}$ for $k = 1, \dots, N, 3N+1, \dots, 3N+P$. For collecting tubules, we have $\Omega_{3N+P+1} = \Omega_{3N+P+2} = \Omega_{3N+P+3} = \Omega$. We require that, by setting $\alpha_k = 0$ in $\Omega \setminus \Omega_k$, we must have

$$\sum_{k=-3N-P}^{3N+P+3} \alpha_k = \alpha \tag{1}$$

for a given volume density function $\alpha : \overline{\Omega} \to \mathbb{R}_+$. That is, we assume that the total volume of the medullary tissue is constant. Note that, in the steady state model of kidney, α_k is only dependent on the depth $x \in \Omega_k$.

For time-dependent model and $n = \pm 1, \dots, \pm N$, we have the equations for the tubular compartments:

$$\frac{\partial \alpha_n}{\partial t} + \frac{\partial}{\partial x}(\alpha_n u_n) = -\gamma_1^n w_1^n - \gamma_2^n w_2^n \qquad \text{in} \quad \Omega_n, \tag{2}$$

$$\frac{\partial \alpha_{N'+n}}{\partial t} = \gamma_1^n w_1^n - \beta_1^n v_1^n - \lambda_n \ell_0^n \quad \text{in} \quad \Omega_{N'+n}, \tag{3}$$

$$\frac{\partial \alpha_{2N'+n}}{\partial t} = \gamma_2^n w_2^n - \beta_2^n v_2^n + \lambda_n \ell_0^n \quad \text{in} \quad \Omega_{2N'+n} = \Omega_{N'+n}, \tag{4}$$

$$\gamma_m^n w_m^n = \beta_m^n v_m^n, \quad m = 1, 2, \quad \text{in} \quad \Omega_n \setminus \Omega_{N'+n}. \tag{5}$$

Here, u_n is the flow velocity of the water in the lumen; $\gamma_m^n, \beta_m^n, \lambda_n : \overline{\Omega_n} \to \mathbb{R}_+$ represent the area per unit depth of the luminal membrane, the basement mem-

brane, and the cell membrane between the ICS and the LIS; w_m^n, v_m^n are the water flux (per unit depth) from the lumen and into the interstitium respectively with the subscript $m = 1, 2$ represents into or from the ICS and the LIS respectively, and ℓ_0^n is the water flux from the ICS into LIS. We will give the equations for u_n, v_n, w_n, ℓ_0^n later.

Similarly, for the collecting tubules ($k = K, K+1, K+2$, $K := N + P + 1$):

$$\frac{\partial \alpha_K}{\partial t} + \frac{\partial}{\partial x}(\alpha_K u_K) = -\sum_{m=1}^{4} \gamma_m^K w_m^K \qquad \text{in} \quad \Omega, \tag{6}$$

$$\frac{\partial \alpha_{K+m}}{\partial t} = \gamma_m^K w_m^K - \beta_m^K v_m^K - \lambda_m^K \ell_0^{K,m} \qquad \text{in} \quad \Omega, \tag{7}$$

$$\frac{\partial \alpha_{K+4}}{\partial t} = \gamma_4^K w_4^K - \beta_4^K v_4^K + \sum_{m=1}^{3} \lambda_m^K \ell_0^{K,m} \quad \text{in} \quad \Omega, \tag{8}$$

where $u_K, \gamma_K, \beta_K, \lambda_K, w_1^K, w_2^K, v_1^K, v_2^K, \ell_0^K$ are interpreted the same as previously.

For vasa recta ($k = 3N' + j := 3\,\mathrm{sign}(j)N + j$, $j = \pm 1, \ldots, \pm P$) and the interstitium ($k = 0$), we have:

$$\frac{\partial \alpha_{3N'+j}}{\partial t} + \frac{\partial}{\partial x}(\alpha_{3N'+j} u_{3N'+j}) = -\eta_j \omega_j \qquad \text{in} \quad \Omega_{3N'+j}, \tag{9}$$

$$\frac{\partial \alpha_0}{\partial t} + \frac{\partial}{\partial x}(\alpha_0 u_0) = \sum_{\substack{1 \le |n| \le N \\ \text{or } n = K}} \beta_n (v_1^n + v_2^n) + \sum_{|j| \le P+1} \eta_j \omega_j \quad \text{in} \quad \Omega. \tag{10}$$

Here, $u_0, u_{3N'+j}$ are also the flow velocity, ω_j is the water flux from the vessel ($j = \pm 1, \ldots, \pm P$), the cortex ($j = 0$) into the interstitium, and the input and output ($j = \pm(P+1)$) into and from the capillary plexus of medullary ray. For convenience, we set $\omega_j = 0$ in $\Omega \setminus \Omega_{3N'+j}$, $j = \pm 1, \ldots, \pm P$, and $v_1^n, v_2^n = 0$ in $\Omega \setminus \Omega_n$. In Alan Weinstein's steady state model, $\eta_{P+1}\omega_{P+1}$ is given and $\eta_{-P-1}\omega_{-P-1}$ is computed so that the balance equation is satisfied, but more generally, we can have them depending on pressures which we will describe later. The parameter $\eta_j : \overline{\Omega_{3N'+j}} \to \mathbb{R}_+$, $j = \pm 1, \ldots, \pm P$, are the area per unit depth of the wall of vasa recta. Note also that, in Alan Weinstein's steady state model the left-hand side of (10) is zero by an assumption that u_0 is identically zero in Ω. Additionally, it is also assumed that $\omega_0 \equiv 0$ in his model, i.e., the interstitia of the cortex and medullary ray are completely separated.

Now, let there be M mobile solute species, e.g., Na^+, K^+, Cl^-, glucose, CO_2, etc., which are labeled by $i = 1, \ldots, M$. We denote by $c_i^k : \overline{\Omega_k} \times [0, \tau) \to \mathbb{R}_+$ the concentration of the i^{th} solute in the k^{th} compartment, and by $a_i^k := \alpha_k c_i^k$ the solute amount of i in k per unit depth. We have the equations for the solutes

in nephron compartments, with $n = \pm 1, \ldots, \pm N$ and $i = 1, \ldots, M$:

$$\frac{\partial}{\partial t}(\alpha_n c_i^n) = -\frac{\partial f_i^n}{\partial x} - \gamma_n(g_i^{n,1} + g_i^{n,2}) + s_i^n \qquad \text{in} \quad \Omega_n, \tag{11}$$

$$\frac{\partial}{\partial t}(\alpha_{N'+n} c_i^{N'+n}) = \gamma_n g_i^{n,1} - \beta_n q_i^{n,1} - \lambda_n \ell_i^n + s_i^{N'+n} \quad \text{in} \quad \Omega_{N'+n}, \tag{12}$$

$$\frac{\partial}{\partial t}(\alpha_{2N'+n} c_i^{2N'+n}) = \gamma_n g_i^{n,2} - \beta_n q_i^{n,2} + \lambda_n \ell_i^n + s_i^{2N'+n} \quad \text{in} \quad \Omega_{N'+n}, \tag{13}$$

$$\gamma_n g_i^{n,m} = \beta_n q_i^{n,m}, \quad m = 1, 2, \qquad \text{in} \quad \Omega_n \setminus \Omega_{N'+n}, \tag{14}$$

where $g_i^{n,m}, q_i^{n,m}$ are the solute flux (per unit depth) from the lumen and into the interstitium with the superscript $m = 1, 2$ represents into or from the ICS and the LIS respectively, ℓ_i^n is the solute flux from the ICS into LIS, and s_i^k is the generation of the solute i in the k^{th} compartment. Similarly, for collecting tubules, we also have

$$\frac{\partial}{\partial t}(\alpha_K c_i^K) = -\frac{\partial f_i^K}{\partial x} - \gamma_K(g_i^{n,1} + g_i^{n,2}) + s_i^K \qquad \text{in} \quad \Omega, \tag{15}$$

$$\frac{\partial}{\partial t}(\alpha_{K+1} c_i^{K+1}) = \gamma_K g_i^{n,1} - \beta_K q_i^{n,1} - \lambda_K \ell_i^K + s_i^{K+1} \quad \text{in} \quad \Omega, \tag{16}$$

$$\frac{\partial}{\partial t}(\alpha_{K+2} c_i^{K+2}) = \gamma_K g_i^{n,2} - \beta_K q_i^{n,2} + \lambda_K \ell_i^K + s_i^{K+2} \quad \text{in} \quad \Omega. \tag{17}$$

We will use $i = M$ to represent CO_2 and write $\mathbf{s}_k = (s_1^k, \ldots, s_M^k)^\top$ for all tubular compartments $k = \pm 1, \ldots, \pm 3N$, $3N + P + 1$, $3N + P + 2$, $3N + P + 3$. We describe the tubular solute generation by an invertible reaction matrix $R \in \mathbb{Z}^{M \times M}$ and the metabolic generation $\mathbf{r}_k$, whose value is in $\mathbb{R}^M$ so that we have

$$R\mathbf{s}_k = \alpha_k \mathbf{r}_k. \tag{18}$$

The trivial case of R would be $R = I$, the identity matrix, and $\mathbf{r}_k = \mathbf{0}$. In case that there are buffer reactions, R represents both mass conservation and the reaction kinetics captured by $\mathbf{r}_k$. For example, when the solutes are Na^+, Cl^-, H^+, $HCO_3{}^-$, H_2CO_3, and CO_2, with a reaction $H^+ + HCO_3{}^- \rightleftharpoons H_2CO_3 \rightleftharpoons H_2O + CO_2$ we might have

$$\begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 1 & 1 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} s^k_{\mathrm{Na}^+} \\ s^k_{\mathrm{Cl}^-} \\ s^k_{\mathrm{H}^+} \\ s^k_{\mathrm{HCO_3}^-} \\ s^k_{\mathrm{H_2CO_3}} \\ s^k_{\mathrm{CO_2}} \end{pmatrix} = \alpha_k \begin{pmatrix} 0 \\ 0 \\ 0 \\ m_k \\ k_1^+ c^k_{\mathrm{HCO_3}^-} c^k_{\mathrm{H}^+} - k_1^- c^k_{\mathrm{H_2CO_3}} \\ k_2^+ c^k_{\mathrm{H_2CO_3}} - k_2^- c^k_{\mathrm{CO_2}} + m_k \end{pmatrix}$$

where $k_1^+, k_1^-, k_2^+, k_2^-$ are reaction rate constants and m_k is the rate of oxidative metabolism generating CO_2. In general, $\mathbf{r}_k$ is a function depending on $\mathbf{c}_k := (c_1^k, \ldots, c_M^k)^\top$, and the fluxes of active membrane transports when k is a cellular compartment which generates CO_2 via oxidative metabolism.

Alternatively, we can take an approximation that some reaction is instantaneous, i.e., the reaction is always at the equilibrium. In this case, R is not invertible. Specifically, the rank of R is now deficient by the number of the reactions assumed to be instantaneous. However, the equation (18) can still determine $\mathbf{s}_k$ since $\mathbf{r}_k$ on the right-hand side now supplement the 'missing' equation(s). For instance, if we assumed that the reaction $\mathrm{H}^+ + \mathrm{HCO_3}^- \rightleftharpoons \mathrm{H_2CO_3}$ in the previous example is instantaneous, now we would have

$$\begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} s^k_{\mathrm{Na}^+} \\ s^k_{\mathrm{Cl}^-} \\ s^k_{\mathrm{H}^+} \\ s^k_{\mathrm{HCO_3}^-} \\ s^k_{\mathrm{H_2CO_3}} \\ s^k_{\mathrm{CO_2}} \end{pmatrix} = \alpha_k \begin{pmatrix} 0 \\ 0 \\ 0 \\ m_k \\ k_1^+ c^k_{\mathrm{HCO_3}^-} c^k_{\mathrm{H}^+} - k_1^- c^k_{\mathrm{H_2CO_3}} \\ k_2^+ c^k_{\mathrm{H_2CO_3}} - k_2^- c^k_{\mathrm{CO_2}} + m_k \end{pmatrix}$$

from which we have $c^k_{\mathrm{H_2CO_3}}/(c^k_{\mathrm{HCO_3}^-} c^k_{\mathrm{H}^+}) = k_1^+/k_1^-$ which, together with the balance equation, determines $s^k_{\mathrm{H_2CO_3}}$.

For vasa recta ($k = 3N' + j$, $j = \pm 1, \ldots, \pm P$) and the interstitium ($k = 0$) — recall that we treat the interstitium and the plasma of the capillary plexus of medullary ray as a single compartment, there are additional solute species, namely hemoglobin buffer species which we label by $i = M+1, \ldots, M+B$. These additional solute species provide additional buffering for H^+, and $\mathrm{CO_2}$. For the hemoglobin buffer species, we have $c_i^k : \overline{\Omega_k} \times [0, \tau)$, $i = M+1, \ldots, M+B$, for $k = 3N' + j$ and with $c_i^0 : [-2, 0] \times [0, \tau) \to \mathbb{R}_+$, be the concentration with respect to the total blood volume per unit depth, not just plasma. In other words, we have $a_i^k = \tilde{\alpha}_k c_i^k$ for $i = M+1, \ldots, M+B$ where $\tilde{\alpha}_k := \alpha_k + \alpha_k^{\mathrm{b}}$ with $\alpha_k^{\mathrm{b}} : \overline{\Omega_k} \to \mathbb{R}_+$ being the volume distribution of the red blood cells, which are fixed. We have the solute equations, with $i = 1, \ldots, M$, for vasa recta:

$$\frac{\partial}{\partial t}(\alpha_{3N'+j} c_i^{3N'+j}) = -\frac{\partial f_i^{3N'+j}}{\partial x} - \eta_j \vartheta_i^j + s_i^{3N'+j} \qquad \text{in} \quad \Omega_{3N'+j} \tag{19}$$

and for $i = M+1, \ldots, M+B$:

$$\frac{\partial}{\partial t}(\tilde{\alpha}_{3N'+j} c_i^{3N'+j}) = -\frac{\partial f_i^{3N'+j}}{\partial x} + s_i^{3N'+j} \qquad \text{in} \quad \Omega_{3N'+j} \tag{20}$$

For the interstitium, we have the equations for $i = 1, \ldots, M$:

$$\frac{\partial}{\partial t}(\alpha_0 c_i^0) = -\frac{\partial f_i^0}{\partial x} + \sum_{\substack{1 \le |n| \le N \\ \text{or } n = K}} \beta_n (q_1^n + q_2^n) + \sum_{|j| \le P+1} \eta_j \vartheta_i^j + s_i^0 \quad \text{in} \quad \Omega, \tag{21}$$

and for $i = M+1, \ldots, M+B$:

$$\frac{\partial}{\partial t}(\tilde{\alpha}_0 c_i^0) = \eta_{P+1} \vartheta_i^{P+1} + \eta_{-P-1} \vartheta_i^{-P-1} + s_i^0 \quad \text{in} \quad (-2, 0). \tag{22}$$

Here, $\vartheta_i^j : \Omega_{3N'+j} \to \mathbb{R}$, $j = \pm 1, \ldots, \pm P$, and $\vartheta_i^j : (0,2) \to \mathbb{R}$, $j = 0, \pm(P+1)$, are the solute fluxes from vasa recta ($j = \pm 1, \ldots, \pm P$) and the renal cortex ($j = 0$) into the interstitium, and the vascular input and output ($j = \pm(P+1)$) into or from the capillary plexus of medullary ray. In the equation (21), we also set $\vartheta_i^j = 0$ in $\Omega \setminus \Omega_{3N'+j}$ for $j = \pm 1, \ldots, \pm P$, and $q_1^n, q_2^n = 0$ in $\Omega \setminus \Omega_n$; similarly, $\vartheta_i^{\pm(P+1)} = 0$ in $[0,7)$. Note that it is assumed $f_i^0 \equiv 0$ and $\vartheta_i^0 \equiv 0$ in Alan Weinstein's model. Moreover, since there is no need to explicitly describe ϑ_i^j, $j = \pm(P+1)$, in the steady state model, ϑ_i^{P+1} is given and ϑ_i^{-P-1} is a model unknown in such a case; we need to have equations for these for the time-dependent model. Note that, since we need to account for the total blood volume for the hemoglobin buffer species, the axial flux $f_i^{3N'+j}$ in the equation (20) are slightly different from that when $i = 1, \ldots, M$. That is, the convection need to account for the total blood flow instead of the plasma flow.

The reaction terms s_i^k, $k = 0, \pm(3N+1), \ldots, \pm(3N+P)$, also have similar equations as (18), but now with $\mathbf{s}_k := (s_1^k, \ldots, s_M^k, s_{M+1}^k, \ldots, s_{M+B}^k)$, R is replaced by another non-invertible matrix $R' \in \mathbb{R}^{(M+B)\times(M+B)}$ and $\mathbf{r}_k$ has value in $\mathbb{R}^{M+B}$, i.e.,

$$R'\mathbf{s}_k = \mathrm{diag}(\underbrace{\alpha_k, \ldots}_{M}, \underbrace{\tilde{\alpha}_k, \ldots}_{B})\mathbf{r}_k, \quad k = 0, \pm(3N+1), \ldots, \pm(3N+P) \tag{23}$$

with $\mathbf{r}_k$ depending on $\mathbf{c}_k := (c_1^k, \ldots, c_{M+B}^k)^\top$ which provides the 'missing' equations, as before.

Now, we describe the water flow velocity, u_k and the solute flow within each compartment f_i^k. In Alan Weinstein's steady state model, there is no axial flow in the interstitium ($k = 0$) — that is $u_0 \equiv 0$ and $f_i^0 \equiv 0$ for all i. For $k = \pm 1, \ldots, \pm N, \pm(3N+1), \ldots, \pm(3N+P), K$, the water flow is given by Poisseuille's equations

$$\frac{\rho_k u_k}{\alpha_k} = -\frac{\partial p}{\partial x}, \quad k = \pm 1, \ldots, \pm N, K, \tag{24}$$

$$\frac{\rho_k u_k}{\tilde{\alpha}_k} = -\frac{\partial p}{\partial x}, \quad k = \pm(3N+1), \ldots, \pm(3N+P), \tag{25}$$

where ρ_k/α_k and $\rho_k/\tilde{\alpha}_k$ are the hydraulic resistivity with ρ_k constant and p_k is the hydrostatic pressure, and the solute flows f_i^k, $i = 1, \ldots, M$, are assumed to be purely convective, i.e., $f_i^k = \alpha_k u_k c_i^k$. In general, f_i^k can be generalized into Nernst-Planck equation:

$$f_i^k = -D_i^k \left(\frac{\partial c_i^k}{\partial x} + \frac{z_i F c_i^k}{RT} \frac{\partial \phi_k}{\partial x} \right) + \alpha_k u_k c_i^k, \quad i = 1, \ldots, M, \tag{26}$$

where D_i^k is the diffusion coefficient, z_i is the valence of the solute i, F/RT is a constant, ϕ_k is the electrical potential in compartment k. For the hemoglobin buffer species ($i = M+1, \ldots, M+B$), the flows are given (only in vasa recta) by

$$f_i^k = \tilde{\alpha}_k u_k c_i^k \quad \text{in} \quad \Omega_k, \quad \text{for} \quad k = \pm(3N+1), \ldots, \pm(3N+P), \tag{27}$$

where $\tilde{\alpha}_k u_k$ is the *blood flow* which must satisfy the incompressibility of the red blood cell, $\partial(\alpha_k^{\mathrm{b}} u_k)/\partial x = 0$, or equivalently:

$$\frac{\partial}{\partial x}\left(\tilde{\alpha}_k u_k\right) = \frac{\partial}{\partial x}\left(\alpha_k u_k\right). \tag{28}$$

To determine the electrical potential ϕ_k and the hydrostatic pressure in each compartment, we have an electroneutrality approximation:

$$0 = z_0^k F a_k + \sum_{i=1}^{M'} z_i F \alpha_k c_i^k, \quad k = -3N - P, \ldots, K+2, \tag{29}$$

and the pressure balance between compartments are described by compliances ν_k. For the luminal compartments ($k = \pm 1, \ldots, \pm N, \pm(3N+1), \ldots, \pm(3N+p), K$), we have:

$$\nu_k(p_k - p_0) = \frac{\alpha_k}{\alpha_k^0} - 1. \tag{30}$$

and for the ICS and LCS, with $n = \pm 1, \ldots, \pm N$:

$$p_{N'+n} = p_n, \tag{31}$$

$$\nu_{2N'+n}(p_{2N'+n} - p_{N'+n}) = \frac{\alpha_{2N'+n}}{\alpha_{2N'+n}^0} - 1, \tag{32}$$

where α_k^0 are the baseline volumes in which the pressure on both sides are equal. Note that the interstitial pressure is determined so that the equation (1) is satisfied.

Now, we describe the boundary conditions for the time-dependent model which include those of hydrostatic pressures, water flow velocities, and solute flows. The water and solute flows at the beginning of the descending tubules, including the collecting tubules, are determined by those at the ending point of the proximal convoluted tubule (PCT) or the connecting tubules (CNT) in the renal cortex:

$$\left.\begin{aligned} \alpha_n u_n &= \bar{\alpha}_n(L_n, \cdot)\bar{u}_n(L_n, \cdot), \\ f_i^n &= \bar{f}_i^n(L_n, \cdot), \end{aligned}\right\} \quad \text{on} \quad \inf \Omega_n, \quad n = 1, \ldots, N, K, \tag{33}$$

where $\bar{\alpha}_n, \bar{u}_n, \bar{f}_i^n, \bar{p}_n : [0, L_n] \times [0, \tau) \to \mathbb{R}_+$ are the cross-sectional area of the PCT ($n = 1, \ldots, N$) and the CNT ($n = K$) of length $L_n > 0$, the water flow velocity, the solute flow, and the hydrostatic pressure inside the lumen respectively. For the descending vasa recta, the water and solute flows are given at the begining:

$$\left.\begin{aligned} \alpha_k u_k &= \bar{u}_k, \\ f_i^k &= \bar{f}_i^k, \end{aligned}\right\} \quad \text{on} \quad \inf \Omega_k = 0, \quad k = 3N+1, \ldots, 3N+P, \tag{34}$$

where $\bar{\alpha}_k, \bar{u}_k, \bar{f}_i^k, \bar{p}_k : [0,\tau) \to \mathbb{R}_+$ are given. Further, the solute and water flows and hydrostatic pressure at the turning points of loops of Henle and vasa recta must match, i.e.,

$$\left.\begin{aligned} \alpha_k u_k &= -\alpha_{-k} u_{-k}, \\ f_i^k &= -f_i^{-k}, \end{aligned}\right\} \quad \text{on} \quad \sup \Omega_k, \quad k = 1, \dots N, 3N+1, \dots, 3N+P. \tag{35}$$

(Do the above boundary conditions, together with the continuity at the turning point of the initial conditions of concentrations, electrical potentials, and hydrostatic pressures, imply continuity at the turning point for all time? Would it be redundant to include such continuity conditions into the boundary conditions?) Finally, we have no-flux boundary conditions for the interstitium:

$$u_0(-2,\cdot) = u_0(7,\cdot) = 0, \tag{36}$$

$$f_i^0(-2,\cdot) = f_i^0(7,\cdot) = 0. \tag{37}$$

We are now left with the description of the renal cortex and its coupling with the renal medulla and medullary ray.

1.2 The renal cortex

Within the cortex, we have the cortical interstitium, the proximal convoluted tubules (PCT), the distal convoluted tubules (DCT), and the connecting tubules (CNT). We use the same convention to label these compartments. We have $k = 0$ for the cortical interstitium together with the plasma of the capillary plexus. However, unlike the medullary ray, we shall treat this compartment as a homogeneous compartment with no spatial variation. For N types of nephrons, the lumen of PCT are labeled by $k = 1, \dots, N$ and that of the DCT by $k = -1, \dots, -N$, with $k = \pm n$ belongs to the n^{th} type nephron. As before, we also have the ICS and the LIS labeled by $k = \pm(N+1), \dots, \pm 3N$. Lastly, the CNT, which receives flows from all types of nephrons is labeled by $k = K, K+1, K+2$, corresponding to the lumen, the ICS, and the LIS respectively.

We describe the volume of the cortical interstitium by $\bar{\alpha}_0 : [0,\tau) \to \mathbb{R}_+$, and the cross-sectional area of each tubular components by $\bar{\alpha}_n, \bar{\alpha}_{N'+n}, \bar{\alpha}_{2N'+n} : (0, L_n) \to \mathbb{R}_+$, for $n = \pm 1, \dots, \pm N$ and $\bar{\alpha}_K, \bar{\alpha}_{K+1}, \bar{\alpha}_{K+2} : (0, L_K) \to \mathbb{R}_+$, where $L_n > 0$, $n = \pm 1, \dots, \pm N, K$ are the length of the PCT, the DCT, and the CNT.

We have equations for the compartment volumes, for $n = \pm 1, \ldots, \pm N$:

$$\frac{\partial \bar{\alpha}_n}{\partial t} + \frac{\partial}{\partial x}(\bar{\alpha}_n \bar{u}_n) = -\bar{\gamma}_n(\bar{w}_1^n + \bar{w}_2^n) \quad \text{in} \quad (0, L_n), \tag{38}$$

$$\frac{\partial \bar{\alpha}_{N'+n}}{\partial t} = \bar{\gamma}_n \bar{w}_1^n - \bar{\beta}_n \bar{v}_1^n - \bar{\lambda}_n \bar{\ell}_0^n \quad \text{in} \quad (0, L_n), \tag{39}$$

$$\frac{\partial \bar{\alpha}_{2N'+n}}{\partial t} = \bar{\gamma}_n \bar{w}_2^n - \bar{\beta}_n \bar{v}_2^n + \bar{\lambda}_n \bar{\ell}_0^n \quad \text{in} \quad (0, L_n), \tag{40}$$

$$\frac{\partial \bar{\alpha}_K}{\partial t} + \frac{\partial}{\partial x}(\bar{\alpha}_K \bar{u}_K) = -\bar{\gamma}_K(\bar{w}_1^K + \bar{w}_2^K) \quad \text{in} \quad (0, L_K), \tag{41}$$

$$\frac{\partial \bar{\alpha}_{K+1}}{\partial t} = \bar{\gamma}_n \bar{w}_1^K - \bar{\beta}_K \bar{v}_1^K - \bar{\lambda}_K \bar{\ell}_0^K \quad \text{in} \quad (0, L_K), \tag{42}$$

$$\frac{\partial \bar{\alpha}_{K+2}}{\partial t} = \bar{\gamma}_n \bar{w}_2^K - \bar{\beta}_K \bar{v}_2^K + \bar{\lambda}_K \bar{\ell}_0^K \quad \text{in} \quad (0, L_K), \tag{43}$$

$$\frac{d\bar{\alpha}_0}{dt} = \sum_{\substack{1 \le |n| \le N \\ \text{or } n=K}} \int_0^{L_n} \bar{\beta}_n(\bar{v}_1^n + \bar{v}_2^n)\, d\xi + \eta_+ \omega_+ + \eta_- \omega_- - \eta_0 \omega_0. \tag{44}$$

Further, we have solutes $i = 1, \ldots, M$ for the tubular compartments and $i = 1, \ldots, M + B$ for the cortical interstitium. The concentrations of the solutes $i = 1, \ldots, M$ in the tubular components are given below:

$$\frac{\partial}{\partial t}(\bar{\alpha}_n \bar{c}_i^n) = -\frac{\partial \bar{f}_i^n}{\partial \xi} - \bar{\gamma}_n(\bar{g}_i^{n,1} + \bar{g}_i^{n,2}) + \bar{s}_i^n \quad \text{in} \quad (0, L_n), \tag{45}$$

$$\frac{\partial}{\partial t}(\bar{\alpha}_{N'+n} \bar{c}_i^{N'+n}) = \bar{\gamma}_n \bar{g}_i^{n,1} - \bar{\beta}_n \bar{q}_i^{n,1} - \bar{\lambda}_n \bar{\ell}_i^n + \bar{s}_i^{N'+n} \quad \text{in} \quad (0, L_n), \tag{46}$$

$$\frac{\partial}{\partial t}(\bar{\alpha}_{2N'+n} \bar{c}_i^{2N'+n}) = \bar{\gamma}_n \bar{g}_i^{n,2} - \bar{\beta}_n \bar{q}_i^{n,2} + \bar{\lambda}_n \bar{\ell}_i^n + \bar{s}_i^{2N'+n} \quad \text{in} \quad (0, L_n), \tag{47}$$

$$\frac{\partial}{\partial t}(\bar{\alpha}_K \bar{c}_i^K) = -\frac{\partial \bar{f}_i^K}{\partial \xi} - \bar{\gamma}_K(\bar{g}_i^{K,1} + \bar{g}_i^{K,2}) + \bar{s}_i^n \quad \text{in} \quad (0, L_K), \tag{48}$$

$$\frac{\partial}{\partial t}(\bar{\alpha}_{K+1} \bar{c}_i^{K+1}) = \bar{\gamma}_n \bar{g}_i^{K,1} - \bar{\beta}_K \bar{q}_i^{K,1} - \bar{\lambda}_K \bar{\ell}_i^K + \bar{s}_i^{K+1} \quad \text{in} \quad (0, L_K), \tag{49}$$

$$\frac{\partial}{\partial t}(\bar{\alpha}_{K+2} \bar{c}_i^{K+2}) = \bar{\gamma}_n \bar{g}_i^{K,2} - \bar{\beta}_K \bar{q}_i^{n,2} + \bar{\lambda}_K \bar{\ell}_i^K + \bar{s}_i^{K+2} \quad \text{in} \quad (0, L_K), \tag{50}$$

and we have the solute generation

$$R\bar{\mathbf{s}}_k = \bar{\alpha}_k \mathbf{r}_k. \tag{51}$$

For the interstitial concentration when $i = 1, \ldots, M$ we have

$$\frac{d}{dt}(\bar{\alpha}_0 \bar{c}_i^0) = \sum_{\substack{1 \le |n| \le N \\ \text{or } n=K}} \int_0^{L_n} \bar{\beta}_n(\bar{q}_1^n + \bar{q}_2^n)\, d\xi + \eta_+ \vartheta_i^+ + \eta_- \vartheta_i^- - \eta_0 \vartheta_i^0 + \bar{s}_i^0. \tag{52}$$

For the hemoglobin buffer species, $i = M + 1, \ldots, M + B$, we have

$$\frac{d}{dt}(\tilde{\bar{\alpha}}_0 \bar{c}_i^0) = \eta_+ \vartheta_i^+ + \eta_- \vartheta_i^- + \bar{s}_i^0. \tag{53}$$

The solute generations in the cortical interstitium and capillary plexus are given by

$$R'\bar{\mathbf{s}}_0 = \mathrm{diag}(\underbrace{\bar{\alpha}_0, ...}_{M}, \underbrace{\tilde{\bar{\alpha}}_0, \dots}_{B})\mathbf{r}_0. \tag{54}$$

We also have the electroneutrality approximation and the compliance of the tubular structures determining the hydrostatic pressure in each compartment.

The model renal cortex is completed with three conditions of the single nephron glomerular filtration rate (SNGFR), which gives the flow at the beginning of the PCT of each nephron, and the CNT end pressure which depends on the terminal flow in the lumen:

$$\bar{\alpha}_n(0,t)\bar{u}_n(0,t) = \mathrm{SNGFR}\left(\mathbf{c}_{-n}\left(\inf \Omega_{-n}, t\right)\right), \quad n = 1, \dots, N \tag{55}$$

2 Steady state model