Multidomain model of kidney

Chanoknun Sintavanuruk

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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.

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.

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 medullary ray (and the renal cortex.) 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-intercalated cell, and β-intercalated 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 $K := 3N+P+1$, for 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, $-3N-P \le k \le 3N+P+5 = K+4$, 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

(i) $\Omega_0 = \Omega$,

(ii) $\Omega_{N'+n} = \Omega_{2N'+n} \subset \Omega_n$, 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 $2N' + n := 2\operatorname{sign}(n)N + n$,

(iii) $\inf \Omega_{3N+j} = \inf \Omega_{-3N-j} = 0$ for $j = 1, \dots, P$,

(iv) $\sup \Omega_k = \sup \Omega_{-k}$ for $k = 1, \dots, N, 3N+1, \dots, 3N+P$,

(v) $\Omega_K = \Omega_{K+1} = \Omega_{K+4} = \Omega$, and $\Omega_{K+2} = \Omega_{K+3} = (-2, 0)$.

We can readily see from (i) that the interstitium is defined everywhere. In (ii), the sets $\Omega_n \setminus \Omega_{N'+n}$ contains the thin loops of Henle, the ICS and the LIS of which are not defined. Further, in (iii), each loop of vasa recta begins at and returns to the cortex-medullary junction at $x = 0$. Moreover, we must have turning points of the loops of Henle and vasa recta at the end and the beginning of their corresponding descending and the ascending compartments. Finally, the last condition tell us that α- and β-intercalted cells can be found only in the cortical collecting duct (CCD), which is in medullary ray.

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

$$\frac{\partial \alpha_n}{\partial t} + \frac{\partial}{\partial x}(\alpha_n u_n) = -\gamma_1^n w_1^n - \gamma_2^n w_2^n \qquad \text{in} \quad \Omega_n, \tag{1}$$

$$\frac{\partial \alpha_{N'+n}}{\partial t} = \gamma_1^n w_1^n - \beta_1^n v_1^n - \lambda_n \ell_0^n \quad \text{in} \quad \Omega_{N'+n}, \tag{2}$$

$$\frac{\partial \alpha_{2N'+n}}{\partial t} = \gamma_2^n w_2^n - \beta_2^n v_2^n + \lambda_n \ell_0^n \quad \text{in} \quad \Omega_{2N'+n} = \Omega_{N'+n}, \tag{3}$$

$$\gamma_m^n w_m^n = \beta_m^n v_m^n, \quad m = 1, 2, \qquad \text{in} \quad \Omega_n \setminus \Omega_{N'+n}. \tag{4}$$

Here, $u_n : \overline{\Omega_n} \times [0,\tau) \to \mathbb{R}$; $\gamma_m^n, \beta_m^n : \Omega_n \to \mathbb{R}_+$, $m = 1, 2$ represent the area per unit depth at the luminal membrane the basement membrane of the

ICS ($m = 1$) and the LIS ($m = 2$), and $\lambda_n : \Omega_{N'+n} \to \mathbb{R}_+$ is that of the cell membrane between the ICS and the LIS; $w_m^n, v_m^n : \Omega_n \times [0,\tau) \to \mathbb{R}$ 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; and $\ell_0^n : \Omega_{N'+n} \times [0,\tau) \to \mathbb{R}$ is the water flux from the ICS into LIS. We will give the equations for $u_m^n, v_m^n, w_m^n, \ell_0^n$ later.

Similarly, for the collecting tubules ($k = K, \ldots, K+4$):

$$\frac{\partial \alpha_K}{\partial t} + \frac{\partial}{\partial x}(\alpha_K u_K) = -\sum_{m=1}^{4} \gamma_m^K w_m^K \qquad \text{in} \quad \Omega, \tag{5}$$

$$\frac{\partial \alpha_{K+m}}{\partial t} = \gamma_m^K w_m^K - \beta_m^K v_m^K - \lambda_m^K \ell_0^{K,m}, \quad m = 1,2,3, \qquad \text{in} \quad \Omega_{K+m}, \tag{6}$$

$$\frac{\partial \alpha_{K+4}}{\partial t} = \gamma_4^K w_4^K - \beta_4^K v_4^K + \sum_{m=1}^{3} \lambda_m^K \ell_0^{K,m} \qquad \text{in} \quad \Omega, \tag{7}$$

where $u_K : \overline{\Omega} \times [0,\tau) \to \mathbb{R}$, $w_m^K, v_m^K, \ell_0^{K,m} : \Omega_{K+m} \times [0,\tau) \to \mathbb{R}$ and $\gamma_m^K, \beta_m^K, \lambda_m^K : \Omega_{K+m} \to \mathbb{R}_+$ are interpreted the same as previously. By convention, these functions are set to 0 outside their defined domain.

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:

$$\frac{\partial \alpha_{3N'+j}}{\partial t} + \frac{\partial}{\partial x}(\alpha_{3N'+j} u_{3N'+j}) = -\eta_j \omega_j \qquad \text{in} \quad \Omega_{3N'+j}, \tag{8}$$

$$\frac{\partial \alpha_0}{\partial t} + \frac{\partial}{\partial x}(\alpha_0 u_0) = \sum_{\substack{1 \le |n| \le N \\ \text{or } n = K}} \sum_m \beta_m^n v_m^n + \sum_{|j| \le P+1} \eta_j \omega_j \quad \text{in} \quad \Omega. \tag{9}$$

Here, $u_0 : \overline{\Omega} \times (0,\tau] \to \mathbb{R}$ and $u_{3N'+j} : \overline{\Omega_{3N'+j}} \times (0,\tau] \to \mathbb{R}$ are the water flow velocity, $\omega_j : \Omega_{3N'+j} \times [0,\tau) \to \mathbb{R}$, $j = \pm 1, \ldots, \pm P$, is the water flux from the vessel. Likewise, $\omega_0, \omega_{\pm(P+1)} : (-2,0) \times [0,\tau) \to \mathbb{R}$ the cortex ($j = 0$) into the interstitium, and the input and output ($j = \pm(P+1)$) *into* the capillary plexus of medullary ray. Again, for convenience, these are set to 0 outside their domain. 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. Similarly, $\omega_0, \omega_{\pm(P+1)} : (-2,0) \to \mathbb{R}$ are those of the cortex-medullary ray junction and the vessels supplying the capillary plexus.

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 $i = 1, \ldots, M$:

$$\frac{\partial}{\partial t}(\alpha_n c_i^n) = -\frac{\partial f_i^n}{\partial x} - \gamma_1^n g_i^{n,1} - \gamma_2^n g_i^{n,2} + s_i^n \qquad \text{in} \quad \Omega_n, \tag{10}$$

$$\frac{\partial}{\partial t}(\alpha_{N'+n} c_i^{N'+n}) = \gamma_1^n g_i^{n,1} - \beta_1^n q_i^{n,1} - \lambda_n \ell_i^n + s_i^{N'+n} \quad \text{in} \quad \Omega_{N'+n}, \tag{11}$$

$$\frac{\partial}{\partial t}(\alpha_{2N'+n} c_i^{2N'+n}) = \gamma_2^n g_i^{n,2} - \beta_2^n q_i^{n,2} + \lambda_n \ell_i^n + s_i^{2N'+n} \quad \text{in} \quad \Omega_{N'+n}, \tag{12}$$

$$\gamma_m^n g_i^{n,m} = \beta_m^n q_i^{n,m}, \quad m = 1, 2, \qquad \text{in} \quad \Omega_n \setminus \Omega_{N'+n}, \tag{13}$$

where $g_i^{n,m}, q_i^{n,m} : \Omega_n \times [0, \tau) \to \mathbb{R}$ 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, $\ell_i^n : \Omega_{N'+n} \to \mathbb{R}$ is the solute flux from the ICS into LIS, and $s_i^k : \Omega_k \times [0, \tau) \to \mathbb{R}$ is the generation of the solute i in the k^{th} compartment. Similarly, for collecting tubules, we also have

$$\frac{\partial}{\partial t}(\alpha_K c_i^K) = -\frac{\partial f_i^K}{\partial x} - \sum_{m=1}^{4} \gamma_m^K g_i^{K,m} + s_i^K \qquad \text{in} \quad \Omega, \tag{14}$$

$$\frac{\partial}{\partial t}(\alpha_{K+m} c_i^{K+m}) = \gamma_m^K g_i^{K,m} - \beta_m^K q_i^{K,m} - \lambda_m^K \ell_i^{K,m} + s_i^{K+m} \qquad \text{in} \quad \Omega_{K+m}, \tag{15}$$

$$\frac{\partial}{\partial t}(\alpha_{K+2} c_i^{K+2}) = \gamma_4^K g_i^{K,4} - \beta_4^K q_i^{K,4} + \sum_{m=1}^{3} \lambda_m^K \ell_i^{K,m} + s_i^{K+4} \quad \text{in} \quad \Omega. \tag{16}$$

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 $k = \pm 1, \ldots, \pm 3N$, $K, \ldots, K+4$. 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 for $k = \pm 1, \ldots, \pm 3N$, $K, \ldots, K+4$:

$$R\mathbf{s}_k = \alpha_k \mathbf{r}_k \quad \text{in} \quad \Omega_k. \tag{17}$$

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 (17) 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 $H^+ + HCO_3{}^- \rightleftharpoons H_2CO_3$ in the previous example is instantaneous, now we would have

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

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

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 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 $\alpha_k^{\mathrm{b}} : \overline{\Omega_k} \to \mathbb{R}_+$, $k = 3N' + j$, and $\alpha_0^{\mathrm{b}} : (-2, 0) \to \mathbb{R}_+$ being the volume distribution of the red blood cells. We have the solute equations, with $i = 1, \ldots, M$, for vasa recta:

$$\frac{\partial}{\partial t}(\alpha_{3N'+j} c_i^{3N'+j}) = -\frac{\partial f_i^{3N'+j}}{\partial x} - \eta_j \vartheta_i^j + s_i^{3N'+j} \qquad \text{in} \quad \Omega_{3N'+j} \tag{18}$$

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

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

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

$$\frac{\partial}{\partial t}(\alpha_0 c_i^0) = -\frac{\partial f_i^0}{\partial x} + \sum_{\substack{1 \le |n| \le N \\ \text{or } n = K}} \sum_m \beta_m^n q_m^n + \sum_{|j| \le P+1} \eta_j \vartheta_i^j + s_i^0 \quad \text{in} \quad \Omega, \tag{20}$$

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

$$\frac{\partial}{\partial t}(\tilde{\alpha}_0 c_i^0) = \eta_{P+1} \vartheta_i^{P+1} + \eta_{-P-1} \vartheta_i^{-P-1} + s_i^0 \quad \text{in} \quad (-2, 0). \tag{21}$$

Here, $\vartheta_i^j : \Omega_{3N'+j} \times [0,\tau) \to \mathbb{R}$, $j = \pm 1, \ldots, \pm P$, and $\vartheta_i^j : (0,2) \times [0,\tau) \to \mathbb{R}$, $j = 0, \pm(P+1)$, 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* the capillary plexus of medullary ray. In the equation (20), 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 $(0,2)$.

The reaction terms s_i^k, $k = 0, \pm(3N+1), \ldots, \pm(3N+P)$, also have similar equations as (17), 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., for $k = 0, \pm(3N+1), \ldots, \pm(3N+P)$,

$$R'\mathbf{s}_k = \mathrm{diag}(\underbrace{\alpha_k, ...}_{M}, \underbrace{\tilde{\alpha}_k, \ldots}_{B})\mathbf{r}_k, \quad \text{in} \quad \Omega_k \tag{22}$$

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. Note that, in Alan Weinstein's steady state model, there is no radial flow in the interstitium ($k = 0$) — that is

$$u_0 \equiv 0. \tag{23}$$

For $k = \pm 1, \ldots, \pm N, \pm(3N+1), \ldots, \pm(3N+P), K$, the water flow is given by Poisseuille's equations

$$\frac{\rho_n u_n}{\alpha_n} = -\frac{\partial p_n}{\partial x}, \quad n = \pm 1, \ldots, \pm N, K, \qquad \text{in} \quad \Omega_n \tag{24}$$

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

where ρ_k/α_k and $\rho_k/\tilde{\alpha}_k$ are the hydraulic resistivity with ρ_k constant and $p_k : \overline{\Omega_k} \times [0,\tau) \to \mathbb{R}_+$ is the hydrostatic pressure, and the solute flows f_i^k, $i = 1, \ldots, M$, are assumed to be purely advective, i.e., $f_i^k = \alpha_k u_k c_i^k$. In general, f_i^k can be generalized into Nernst-Planck equation: for $i = 1, \ldots, M$ and $k = 0, \pm 1, \ldots, \pm N, \pm(3N+1), \ldots, \pm(3N+P), K$,

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

where $D_i^k : \Omega_k \to \mathbb{R}_+$ 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:

$$0 = z_0^k F a_0^k + \sum_{i=1}^{M'} z_i F \alpha_k c_i^k, \quad k = -3N - P, \ldots, K + 4, \quad \text{in} \quad \Omega_k \tag{29}$$

and the pressure balance between compartments are described by compliances ν_k. We can have all luminal compartments be compliant structure, i.e., for $k = \pm 1, \ldots, \pm N,$:

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

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

$$p_{N'+n} = p_n, \qquad \text{in} \quad \Omega_{N'+n} \tag{31}$$

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

$$p_K = p_{K+1} = p_{K+2} = p_{K+3} \quad \text{in} \quad (-2, 0), \tag{33}$$

$$\nu_{K+4}(p_{K+4} - p_K) = \frac{\alpha_{K+4}}{\alpha_{K+4}^0} - 1 \qquad \text{in} \quad (-2, 0), \tag{34}$$

where α_k^0 are the baseline volumes in which the pressure on both sides are equal. For the collecting ducts and vasa recta, we could have the same equations as (30), (31), and (32). However, in Alan Weinstein's model, the lumina of vasa recta and collecting ducts are not compliant. Instead, we have for $k = \pm(3N + 1), \ldots, \pm(3N + p), K$:

$$\frac{\partial \alpha_k}{\partial t} \equiv 0 \tag{35}$$

$$p_k(0) = p_k^0 \tag{36}$$

where $p_k^0 : [0, \tau) \to \mathbb{R}_+$ is given for $k = \pm(3N + 1), \ldots, \pm(3N + P)$ and depending on the terminal flow of the connecting tubule in the renal cortex when $k = K$. The interstitial pressure is determined so that a condition for tissue volume is satisfied. In Alan Weinstein's model, such a condition is that the interstitial volume is constant in time. Alternatively, we can still have α_0 be time-dependent by having another condition such that the sum of the volume of all compartments is constant in time. In other words, we choose either

$$\frac{\partial \alpha_0}{\partial t} \equiv 0 \quad \text{or} \quad \sum_{k=-3N-P}^{3N+P+3} \alpha_k = \alpha \quad \text{(choose only one)} \tag{37}$$

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.

Now, we describe the rest of 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:

$$\left.\begin{aligned} \alpha_n u_n &= \bar{\alpha}_n(L_n,\cdot)\bar{u}_n(L_n,\cdot), \\ f_i^n &= \bar{f}_i^n(L_n,\cdot), \end{aligned}\right\} \quad \text{on} \quad \inf\Omega_n, \quad n=1,\dots,N,K, \tag{38}$$

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 ($n = 1,\dots,N$) 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:

$$\left.\begin{aligned} \alpha_k u_k &= \bar{u}_k, \\ f_i^k &= \bar{f}_i^k, \end{aligned}\right\} \quad \text{on} \quad \inf\Omega_k = 0, \quad k = 3N+1,\dots,3N+P, \tag{39}$$

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.,

$$\left.\begin{aligned} \alpha_k u_k &= -\alpha_{-k} u_{-k}, \\ f_i^k &= -f_i^{-k}, \end{aligned}\right\} \quad \text{on} \quad \sup\Omega_k, \quad k = 1,\dots N, 3N+1,\dots,3N+P. \tag{40}$$

(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:

$$u_0(-2,\cdot) = u_0(7,\cdot) = 0, \tag{41}$$

$$f_i^0(-2,\cdot) = f_i^0(7,\cdot) = 0. \tag{42}$$

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 of PCT (positive) and DCT (negative) labeled by $k = \pm(N+1), \dots, \pm 3N$. Lastly, the CNT, which receives flows from all types of nephrons is labeled by $k = K, \dots, K+4$, corresponding to the lumen, the ICS of principal cells, α- and β-intercalated cells of the CNT, 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. Here, we use the notation $\xi \in (0, L_n)$, instead of x, for the spatial variable of each tubule. We have equations for the compartment volumes, for $n = \pm 1, \dots, \pm N$:

$$\frac{\partial \bar{\alpha}_n}{\partial t} + \frac{\partial}{\partial \xi}(\bar{\alpha}_n \bar{u}_n) = -\bar{\gamma}_1^n \bar{w}_1^n + \bar{\gamma}_2^n \bar{w}_2^n \qquad \text{in} \quad (0, L_n), \tag{43}$$

$$\frac{\partial \bar{\alpha}_{N'+n}}{\partial t} = \bar{\gamma}_1^n \bar{w}_1^n - \bar{\beta}_1^n \bar{v}_1^n - \bar{\lambda}_n \bar{\ell}_0^n \qquad \text{in} \quad (0, L_n), \tag{44}$$

$$\frac{\partial \bar{\alpha}_{2N'+n}}{\partial t} = \bar{\gamma}_2^n \bar{w}_2^n - \bar{\beta}_2^n \bar{v}_2^n + \bar{\lambda}_n \bar{\ell}_0^n \qquad \text{in} \quad (0, L_n), \tag{45}$$

$$\frac{\partial \bar{\alpha}_K}{\partial t} + \frac{\partial}{\partial \xi}(\bar{\alpha}_K \bar{u}_K) = -\sum_{m=1}^{4} \bar{\gamma}_m^K \bar{w}_m^K \qquad \text{in} \quad (0, L_K), \tag{46}$$

$$\frac{\partial \bar{\alpha}_{K+m}}{\partial t} = \bar{\gamma}_m^K \bar{w}_m^K - \bar{\beta}_m^K \bar{v}_m^K - \bar{\lambda}_m^K \bar{\ell}_0^{K,m}, \quad m = 1, 2, 3, \qquad \text{in} \quad (0, L_K), \tag{47}$$

$$\frac{\partial \bar{\alpha}_{K+4}}{\partial t} = \bar{\gamma}_4^K \bar{w}_4^K - \bar{\beta}_4^K \bar{v}_4^K + \sum_{m=1}^{3} \bar{\lambda}_m^K \bar{\ell}_0^{K,m} \qquad \text{in} \quad (0, L_K), \tag{48}$$

$$\frac{d\bar{\alpha}_0}{dt} = \sum_{\substack{1 \le |n| \le N \\ \text{or } n = K}} \sum_m \int_0^{L_n} \bar{\beta}_m^K \bar{v}_m^K \, d\xi + \eta_+ \omega_+ + \eta_- \omega_- - \eta_0 \omega_0. \tag{49}$$

Further, we have solutes $i = 1, \dots, M$ for the tubular compartments and $i = 1, \dots, M + B$ for the cortical interstitium. The concentrations of the solutes

$i = 1, \ldots, M$ in the tubular components are given below:

$$\frac{\partial}{\partial t}(\bar{\alpha}_n \bar{c}_i^n) = -\frac{\partial \bar{f}_i^n}{\partial \xi} - \bar{\gamma}_1^n \bar{g}_i^{n,1} + \bar{\gamma}_2^n \bar{g}_i^{n,2} + \bar{s}_i^n \tag{50}$$

$$\frac{\partial}{\partial t}(\bar{\alpha}_{N'+n} \bar{c}_i^{N'+n}) = \bar{\gamma}_1^n \bar{g}_i^{n,1} - \bar{\beta}_1^n \bar{q}_i^{n,1} - \bar{\lambda}_n \bar{\ell}_i^n + \bar{s}_i^{N'+n} \tag{51}$$

$$\frac{\partial}{\partial t}(\bar{\alpha}_{2N'+n} \bar{c}_i^{2N'+n}) = \bar{\gamma}_2^n \bar{g}_i^{n,2} - \bar{\beta}_2^n \bar{q}_i^{n,2} + \bar{\lambda}_n \bar{\ell}_i^n + \bar{s}_i^{2N'+n} \tag{52}$$

$$\frac{\partial}{\partial t}(\bar{\alpha}_K \bar{c}_i^K) = -\frac{\partial \bar{f}_i^K}{\partial \xi} - \sum_{m=1}^{4} \bar{\gamma}_m^K \bar{g}_i^{K,m} + \bar{s}_i^K \tag{53}$$

$$\frac{\partial}{\partial t}(\bar{\alpha}_{K+m} \bar{c}_i^{K+m}) = \bar{\gamma}_m^K \bar{g}_i^{K,m} - \bar{\beta}_K \bar{q}_i^{K,m} - \bar{\lambda}_m^K \bar{\ell}_i^{K,m} + \bar{s}_i^{K+m} \tag{54}$$

$$\frac{\partial}{\partial t}(\bar{\alpha}_{K+4} \bar{c}_i^{K+4}) = \bar{\gamma}_4^K \bar{g}_i^{K,4} - \bar{\beta}_4^K \bar{q}_i^{n,4} + \sum_{m=1}^{3} \bar{\lambda}_m^K \bar{\ell}_i^{K,m} + \bar{s}_i^{K+4} \tag{55}$$

and we have the solute generation

$$R\bar{\mathbf{s}}_k = \bar{\alpha}_k \mathbf{r}_k. \tag{56}$$

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

$$\frac{d}{dt}(\bar{\alpha}_0 \bar{c}_i^0) = \sum_{\substack{1 \le |n| \le N \\ \text{or } n=K}} \sum_m \int_0^{L_n} \bar{\beta}_m^n \bar{q}_1^n \, d\xi + \eta_+ \vartheta_i^+ + \eta_- \vartheta_i^- - \eta_0 \vartheta_i^0 + \bar{s}_i^0. \tag{57}$$

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

$$\frac{d}{dt}(\tilde{\bar{\alpha}}_0 \bar{c}_i^0) = \eta_+ \vartheta_i^+ + \eta_- \vartheta_i^- + \bar{s}_i^0. \tag{58}$$

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

$$R'\bar{\mathbf{s}}_0 = \mathrm{diag}(\underbrace{\bar{\alpha}_0, ..., }_{M} \underbrace{\tilde{\bar{\alpha}}_0, \ldots}_{B})\mathbf{r}_0. \tag{59}$$

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

$$0 = z_0^k F \bar{a}_0^k + \sum_{i=1}^{M'} z_i F \bar{\alpha}_k \bar{c}_i^k \tag{60}$$

and

$$\bar{\nu}_n(\bar{p}_n - \bar{p}_0) = \frac{\bar{\alpha}_n}{\bar{\alpha}_n^0} - 1 \quad \text{in} \quad (0, L_n), \quad n = \pm 1, \ldots, \pm N, \tag{61}$$

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

$$\bar{p}_{N'+n} = \bar{p}_n, \qquad \text{in} \quad (0, L_n) \tag{62}$$

$$\bar{\nu}_{2N'+n}(\bar{p}_{2N'+n} - \bar{p}_{N'+n}) = \frac{\bar{\alpha}_{2N'+n}}{\bar{\alpha}^0_{2N'+n}} - 1 \qquad \text{in} \quad (0, L_n), \tag{63}$$

$$\bar{p}_K = \bar{p}_{K+1} = \bar{p}_{K+2} = \bar{p}_{K+3} \quad \text{in} \quad (0, L_K), \tag{64}$$

$$\bar{\nu}_{K+4}(\bar{p}_{K+4} - \bar{p}_K) = \frac{\bar{\alpha}_{K+4}}{\bar{\alpha}^0_{K+4}} - 1 \qquad \text{in} \quad (0, L_K). \tag{65}$$

Also, the CNT is not compliant, i.e.,

$$\frac{\partial \bar{\alpha}_K}{\partial t} \equiv 0, \tag{66}$$

$$p_K(0) = p^0_K \tag{67}$$

and the cortical interstitial volume is fixed, i.e.,

$$\frac{d\bar{\alpha}_0}{dt} = 0. \tag{68}$$

Finally, 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, for $n = 1, \ldots, N \quad n = 1, \ldots, N$:

$$\bar{\alpha}_n(0,t)\bar{u}_n(0,t) = \mathrm{SNGFR}\left(\mathbf{c}_{-n}\left(\inf \Omega_{-n}, t\right)\right), \tag{69}$$

$$\bar{f}^n_i(0,t) = \bar{\alpha}_n(0,t)\bar{u}_n(0,t)\bar{c}^{n,0}_i, \tag{70}$$

$$\bar{\alpha}_{-n}(0,t)\bar{u}_{-n}(0,t) = \alpha_{-n}(\sup \Omega_{-n}, t)u_{-n}(\sup \Omega_{-n}, t) \tag{71}$$

$$\bar{f}^{-n}_i(0,t) = f^{-n}_i(\sup \Omega_{-n}, t) \tag{72}$$

$$\bar{\alpha}_K(0,t)\bar{u}_K(0,t) = \sum_{n=1}^{N} \bar{\alpha}_{-n}(L_n, t)\bar{u}_{-n}(L_n, t) \tag{73}$$

$$\bar{f}^K_i(0,t) = \sum_{n=1}^{N} \bar{f}^{-n}_i(L_n, t). \tag{74}$$

Note that the first equation above characterize the Tubuloglomerular Feedback (TGF).

2 Steady state model