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. 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.

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 also 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, we label by $k = \pm(3N+j)$, for $j = 1, \dots, P$, the descending and the ascending vasa recta. Finally, the lumen, the ICS, and the LIS of the collecting tubules are labeled by $k = 3N+P+1, 3N+P+2, 3N+P+3$ 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:

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

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

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

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

Here, u_n is the flow velocity of the water in the lumen; $\gamma_n, \beta_n, \lambda_n : \overline{\Omega_n} \to \mathbb{R}_+$ represent the area per unit depth of the luminal membrane, the basement membrane, 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 ($k = K, K+1, K+2$, $K := N+P+1$):

$$\frac{\partial \alpha_K}{\partial t} + \frac{\partial}{\partial x}(\alpha_K u_K) = -\gamma_K (w_1^K + w_2^K) \quad \text{in} \quad \Omega, \tag{6}$$

$$\frac{\partial \alpha_{K+1}}{\partial t} = \gamma_K w_1^K - \beta_K v_1^K - \lambda_K \ell_0^K \quad \text{in} \quad \Omega, \tag{7}$$

$$\frac{\partial \alpha_{K+2}}{\partial t} = \gamma_K w_2^K - \beta_K v_2^K + \lambda_K \ell_0^K \quad \text{in} \quad \Omega, \tag{8}$$

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:

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

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

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 or 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 $c_i^k : \Omega_k \times [0, T) \to \mathbb{R}_+$ 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 $i = 1, \ldots, M$:

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

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

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

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

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

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

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 equilibria of reactions whose kinetics are assumed to be instantaneous; otherwise, the reaction kinetics will be captured by $\mathbf{r}_k$. 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.

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 capillary plexus of medullary ray as a single compartment, there are additional solute species, namely impermeable proteins and Hemoglobin buffer species which we label by $i = M+1, \ldots, M+B$. We have the solute equations, with $i = 1, \ldots, M+B$, for vasa recta:

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

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

$$\frac{\partial}{\partial t}(\alpha_0 c_i^0) = -\frac{\partial f_i^0}{\partial x} + \sum_{\substack{1\le|n|\le N \\ \text{or } n=K}} \beta_n(q_1^n + q_2^n) + \sum_{|j|\le P+1} \eta_j \vartheta_i^j + s_i^0 \quad \text{in} \quad \Omega, \tag{20}$$

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

$$\frac{\partial}{\partial t}(\alpha_0 c_i^0) = -\frac{\partial f_i^0}{\partial x} + \sum_{j=\pm(P+1)} \eta_j \vartheta_i^j + s_i^0 \quad \text{in} \quad (-2, 0). \tag{21}$$

Here, ϑ_i^j is the solute flux from vasa recta ($j = \pm 1, \ldots, \pm P$) and the renal cortex ($j = 0$) into the interstitium, and the input and output ($j = \pm(P+1)$) into or

from the capillary plexus of medullary ray. 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 $\Omega \setminus \Omega_n$. Note that it is assumed $f_i^0 \equiv 0$ and $\vartheta_i^j \equiv 0$ 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.

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 invertible matrix $R' \in \mathbb{R}^{(M+B)\times(M+B)}$ and $\mathbf{r}_k$ has value in $\mathbb{R}^{M+B}$, i.e.,

$$R'\mathbf{s}_k = \mathbf{r}_k, \quad k = 0, \pm(3N+1), \ldots, \pm(3N+P). \tag{22}$$

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 $f_i^0 = u_0 = 0$ for all i. For $k = \pm 1, \ldots, \pm N, \pm(3N+1), \ldots, \pm(3N+P), K, K+1, K+2$, the water flow is given by Poisseuille's equation $\rho_k \alpha_k u_k = -\partial p_k / \partial x$, where $\rho_k \alpha_k$ is the hydrolic resistivity with ρ_k constant and p_k is the hydrostatic pressure, and the corresponding solute flows f_i^k 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:

$$f_i^k = -D_i^k \left(\frac{\partial c_i^k}{\partial x} + \frac{z_i F c_i^k}{RT} \frac{\partial \phi_k}{\partial x} \right) + \alpha_k u_k c_i^k, \tag{23}$$

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; and the water flow velocity u_k is determined by the compartmental pressure field and driven by electrostatic force:

$$\rho_k \alpha_k u_k = -\frac{\partial \tilde{p}_k}{\partial x} - \sum_{i=1}^{M'} z_i F c_i^k \frac{\partial \phi_k}{\partial x}, \tag{24}$$

$$M' = \begin{cases} M & \text{if} \quad k = \pm 1, \ldots, \pm N, K, K+1, K+2, \\ M+B & \text{if} \quad k = 0, \pm(3N+1), \ldots, \pm(3N+P), \end{cases}$$

where $\tilde{p}_k := p_k - RTa_k/\alpha_k$ is the compartmental pressure with a_k being the amount per unit depth of immobile solute. Finally, the solute and water flows at the turning points of loops of Henle and vasa recta must match, i.e.,

$$\alpha_k u_k = -\alpha_{-k} u_{-k}, \quad \text{on} \quad \sup \Omega_k, \quad k = 1, \ldots N, 3N+1, \ldots, 3N+P, \tag{25}$$

$$f_i^k = -f_i^{-k}, \quad \text{on} \quad \sup \Omega_k, \quad k = 1, \ldots N, 3N+1, \ldots, 3N+P. \tag{26}$$

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

$$0 = z_0^k F a_k + \sum_{i=1}^{M'} z_i F \alpha_k c_i^k, \tag{27}$$

and the pressure balance between compartments is described by compliances ν_k, $k = \pm 1, \ldots, \pm N, \pm(3N+1), \ldots, \pm(3N+P), K, K+1, K+2$:

$$\nu_k(p_k - p_0) = \frac{\alpha_k}{\alpha_k^0} - 1, \tag{28}$$

where α_k^0 is the baseline volume in which the pressure on both sides are equal. For the ICS and ECS compartments, we set, for $n = \pm 1, \ldots, \pm N$:

$$p_{N'+n} = p_n, \tag{29}$$

$$p_K = p_{K+1}, \tag{30}$$

$$p_{2N'+n} = p_0 = p_{K+2}. \tag{31}$$

Note that, in Alan Weinstein's model, the hydrostatic pressures of vasa recta and interstitium are computed from the balance equation, since the volume densities of vasa recta and interstitium are fixed. These conditions are functionally equivalent to our equation (1).