A schematic model of passive urine concentrating mechanism

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1 Introduction

Concentration gradient in the renal medullary interstitium is responsible for concentrating urine. It is well-understood that the active reabsorption of NaCl from the thick ascending tubules, together with the counter-current multiplication, establish this concentration gradient in the outer medulla. For the inner medulla, where there is no such an active transport, it is the passive reabsorption of NaCl and urea that take over; this is the widely accepted passive mechanism hypothesis of urine concentration. To have the passive mechanism working, we need to have relatively high tubular concentration of NaCl at the turning of loops of Henle, and of urea in the collecting tubules. A common explanation is that the net water and NaCl reabsorption preceding the inner medulla collecting tubules concentrate the urea enough that it diffuses out in the inner medulla. This in turn increases osmolality in the interstitium that drives the water reabsorption from the thin descending limbs, concentrating NaCl in the process.

The aim of this document is to provide a clean picture of the passive mechanism through a relatively simple model. We derive a schematic model of inner medulla with a central core configuration and containing only two solute species: salt and urea. We show that the model can be reduced to a system of 4 ordinary differential equations. Finally, we perform numerical simulations to examine factors that contribute to the passive mechanism.

2 Model derivation

We consider a steady-state model of the inner medulla. We use k to identify the compartments in the inner medulla: the central core ($k = 0$), descending tubules ($k = \mathrm{D}$), ascending tubules ($k = \mathrm{A}$), and the collecting tubules ($k = \mathrm{C}$). Each compartment is described in a 1-dimensional spatial domain $x \in (0, 1)$ where $x = 0$ represents the outer-inner medullary junction, and $x = 1$ the renal papilla.

We denote by s_k, u_k and q_k, as a function of x, the salt and urea concentration and the axial water flow in the compartment k respectively. For simplicity, we will assume that the urea content in the descending tubule and the salt content in the collecting tubule are negligible, i.e., $u_{\mathrm{D}} = s_{\mathrm{C}} \equiv 0$. Thus, there are total of 9 unknowns in the model: the water flow $q_{\mathrm{D}}, q_{\mathrm{A}}, q_{\mathrm{C}}, q_0$ and the solute concentrations $s_{\mathrm{D}}, s_{\mathrm{A}}, s_0, u_{\mathrm{C}}, u_0$.

We assume that the transmural water fluxes are allowed only for the descending tubules and the collecting tubules into the interstitium, and these are formally described as $w_{\mathrm{D}} := \zeta_{\mathrm{D}}(2s_0 + u_0 - s_{\mathrm{D}})$ and $w_{\mathrm{C}} := \zeta_{\mathrm{C}}(2s_0 + u_0 - u_{\mathrm{C}})$ where $\zeta_k > 0$ is the water permeability, i.e., the fluxes are proportional to the osmolarity differences. Note that the osmolarity of salt is twice the concentration. By mass balance, we require that

$$\frac{dq_{\mathrm{D}}}{dx} = -\zeta_{\mathrm{D}}\left(2s_0 + u_0 - 2s_{\mathrm{D}}\right) = -w_{\mathrm{D}}, \tag{2.1}$$

$$\frac{dq_{\mathrm{A}}}{dx} = 0, \tag{2.2}$$

$$\frac{dq_{\mathrm{C}}}{dx} = -\zeta_{\mathrm{C}}\left(2s_0 + u_0 - u_{\mathrm{C}}\right) = -w_{\mathrm{C}}, \tag{2.3}$$

$$\frac{dq_0}{dx} = w_{\mathrm{D}} + w_{\mathrm{C}}. \tag{2.4}$$

These equations are accompanied by 4 boundary conditions:

$$q_{\mathrm{D}}(0) = \frac{2S}{C}, \quad q_{\mathrm{A}}(1) = -q_{\mathrm{D}}(1), \quad q_{\mathrm{C}}(0) = \frac{U}{C}, \quad q(1) = 0. \tag{2.5}$$

Here, we assume that the initial osmolarity at the beginning (outer-inner medullary junction) of the descending and the collecting tubule is C, and the initial salt and urea flow are S and U respectively. The second equality represents the turning of the loop of Henle, and we have no-flux boundary at the papillary interstitium for the last equality.

Similarly, we only allow passive transmural fluxes of salt from the ascending tubule and of urea from the collecting tubules. The fluxes are given by $\gamma_s(s_{\mathrm{A}} - s_0)$ and $\gamma_u(u_{\mathrm{C}} - u_0)$ respectively, where γ_s is the ascending tubule salt permeability and γ_u is the collecting tubule urea permeability. Further, we assume that the axial solute flows are purely advective, i.e., the salt and urea flows are $s_k q_k$ and $u_k q_k$. As earlier, we have balance equations for salt and urea:

$$\frac{d}{dx}(s_{\mathrm{D}} q_{\mathrm{D}}) = 0, \tag{2.6}$$

$$\frac{d}{dx}(s_{\mathrm{A}} q_{\mathrm{A}}) = -\gamma_s(s_{\mathrm{A}} - s_0), \tag{2.7}$$

$$\frac{d}{dx}(s_0 q_0) = \gamma_s(s_{\mathrm{A}} - s_0), \tag{2.8}$$

$$\frac{d}{dx}(u_{\mathrm{C}} q_{\mathrm{C}}) = -\gamma_u(u_{\mathrm{C}} - u_0), \tag{2.9}$$

$$\frac{d}{dx}(u_0 q_0) = \gamma_u(u_{\mathrm{C}} - u_0). \tag{2.10}$$

The equations (2.6) and (2.9) are subject to boundary conditions:

$$2s_{\mathrm{D}}(0) = u_{\mathrm{C}}(0) = C, \tag{2.11}$$

which describe the initial osmolarity of the descending and the collecting tubules.

Since we have nine ODEs, we need 3 more boundary conditions. These are obtained by the conservation of water, salt and urea:

$$\frac{2S}{C} + q_0(0) + q_{\mathrm{A}} + \frac{U}{C} = q_{\mathrm{C}}(1), \tag{2.12}$$

$$S + q_{\mathrm{A}}(0)s_{\mathrm{A}}(0) + s_0(0)q_0(0) = 0, \tag{2.13}$$

$$U + u_0(0)q_0(0) = u_{\mathrm{C}}(1)q_{\mathrm{C}}(1). \tag{2.14}$$

The system of nine ordinary differential equations we just obtained can be simplified even further. First, we can turn the differential equation describing the salt concentration in the descending tubules (2.6) into an algebraic equation. With the boundary condition $s_{\mathrm{D}}(0)q_{\mathrm{D}}(0) = S$, integrating (2.6) yields

$$s_{\mathrm{D}} = \frac{S}{q_{\mathrm{D}}}. \tag{2.15}$$

For the ascending tubule, in place of the water balance equation (2.2), we simply have q_A being constant. With the salt conservation (2.13) and (2.15), summing (2.7) and (2.8) and taking integral gives

$$S + s_{\mathrm{A}}q_{\mathrm{A}} + s_0q_0 = s_{\mathrm{D}}q_{\mathrm{D}} + s_{\mathrm{A}}q_{\mathrm{A}} + s_0q_0 = 0. \tag{2.16}$$

Note the second equality of (2.16) and the boundary condition $q_{\mathrm{A}}(1) = -q_{\mathrm{D}}(1)$ imply that $s_{\mathrm{D}}(1) = s_{\mathrm{A}}(1)$. Consequently, by integrating (2.2) we obtain an equation for q_A:

$$q_{\mathrm{A}} = -q_{\mathrm{D}}(1). \tag{2.17}$$

Now, we solve the equations for the central core (2.4), (2.8), and (2.10). Similarly to how we obtain (2.16), using the urea conservation (2.14), we have by summing (2.9) and (2.10) and integrating

$$u_{\mathrm{C}}q_{\mathrm{C}} + u_0q_0 = u_{\mathrm{C}}(1)q_{\mathrm{C}}(1). \tag{2.18}$$

From the first equality of (2.16) and (2.17), we can write

$$q_0 = \frac{s_{\mathrm{A}}q_{\mathrm{D}}(1) - S}{s_0}. \tag{2.19}$$

Substituting q_0 into (2.18) yields

$$s_0\left(u_{\mathrm{C}}(1)q_{\mathrm{C}}(1) - u_{\mathrm{C}}q_{\mathrm{C}}\right) + u_0\left(s_{\mathrm{A}}q_{\mathrm{D}}(1) - S\right) = 0. \tag{2.20}$$

We can do the same for the water conservation as well. Summing (2.1), (2.2), (2.3) and (2.4) and integrating, we have $q_{\mathrm{D}} + q_{\mathrm{A}} + q_{\mathrm{C}} + q_0 = q_{\mathrm{C}}(1)$. By substituting q_{A}, q_0 from (2.17) and (2.19), we obtain

$$q_{\mathrm{D}} - q_{\mathrm{D}}(1) + q_{\mathrm{C}} + \frac{s_{\mathrm{A}} q_{\mathrm{D}}(1) - S}{s_0} = q_{\mathrm{C}}(1). \tag{2.21}$$

We can now solve (2.20) and (2.21) for s_0 and u_0 in terms of s_A, u_{C} and q_{C}:

$$s_0 = \frac{S - s_{\mathrm{A}} q_{\mathrm{D}}(1)}{q_{\mathrm{D}} - q_{\mathrm{D}}(1) + q_{\mathrm{C}} - q_{\mathrm{C}}(1)}, \quad u_0 = \frac{u_{\mathrm{C}} q_{\mathrm{C}} - u_{\mathrm{C}}(1) q_{\mathrm{C}}(1)}{q_{\mathrm{D}} - q_{\mathrm{D}}(1) + q_{\mathrm{C}} - q_{\mathrm{C}}(1)}. \tag{2.22}$$

With all the 5 unknowns solved, the problem is reduced to a system of ODEs with 4 differential equations:

$$\frac{dq_{\mathrm{D}}}{dx} = -\zeta_{\mathrm{D}} \left(2s_0 + u_0 - \frac{2S}{q_{\mathrm{D}}} \right) \tag{2.23}$$

$$\frac{ds_{\mathrm{A}}}{dx} = -\frac{\gamma_s}{q_{\mathrm{A}}}(s_{\mathrm{A}} - s_0), \tag{2.24}$$

$$\frac{dq_{\mathrm{C}}}{dx} = -\zeta_{\mathrm{C}}(2s_0 + u_0 - u_{\mathrm{C}}), \tag{2.25}$$

$$\frac{du_{\mathrm{C}}}{dx} = \frac{1}{q_{\mathrm{C}}} \left(\zeta_{\mathrm{C}} u_{\mathrm{C}} (2s_0 + u_0 - u_{\mathrm{C}}) - \gamma_u (u_{\mathrm{C}} - u_0) \right), \tag{2.26}$$

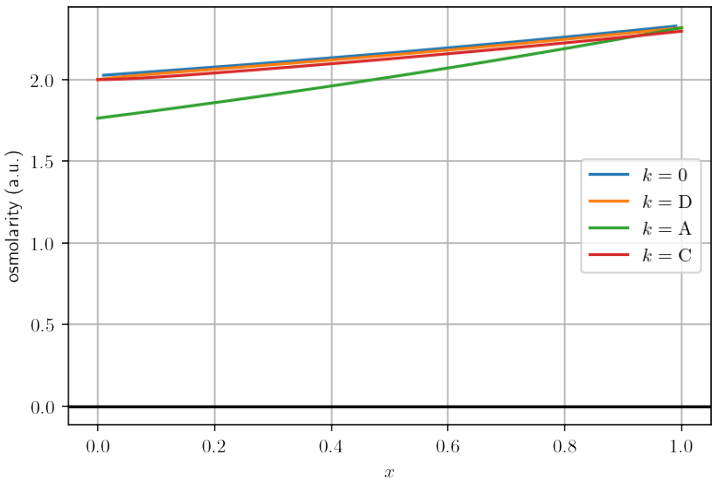
with boundary conditions

$$q_{\mathrm{D}}(0) = \frac{2S}{C}, \quad s_{\mathrm{A}}(1) = S/q_{\mathrm{D}}(1), \quad q_{\mathrm{C}}(0) = \frac{U}{C}, \quad u_{\mathrm{C}}(0) = C, \tag{2.27}$$

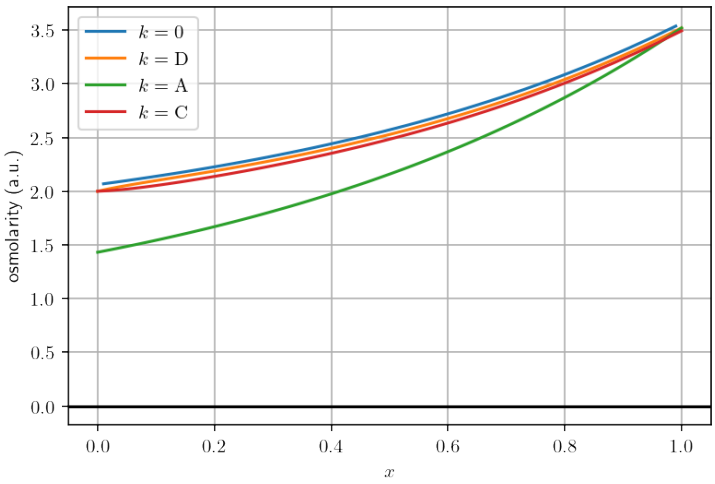
where $q_{\mathrm{A}} = -q_{\mathrm{D}}(1)$, and s_0, u_0 are given in (2.22). The model parameters are the ascending tubule salt and urea permeability γ_s, γ_u, water permeability $\zeta_{\mathrm{D}}, \zeta_{\mathrm{C}}$, salt and urea input S, U, and the osmolarity C of the descending and the collecting tubules at the outer-inner medullary junction.

3 Passive mechanism

We numerically solve the system of ODEs (2.23) - (2.26) with boundary conditions (2.27) using central difference approximation of the derivative and the discretized variables are computed using an iterative method. The resulting osmolarity in each compartment is increasing along the depth of the inner medulla with osmolarity in the central core slightly above those of the descending tubule and the collecting tubule at the inner-outer medullary junction, as shown in the Figure 1. What we see is that the fluid in the collecting and the descending tubule is concentrated by water extraction which is driven by the relatively high osmolarity in the central core. At the same time, urea and salt are reabsorbed into the core from the collecting and the ascending tubule, establishing the interstitial concentration gradient. Since the ascending tubule is water impermeable,

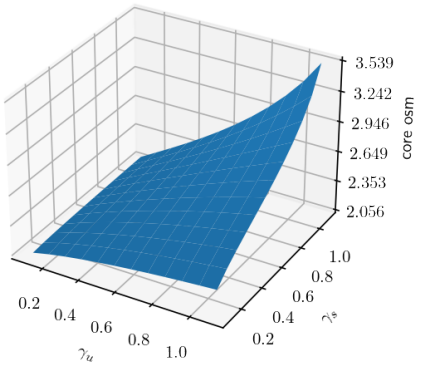


(a) $\gamma_u = \gamma_s = 0.1$

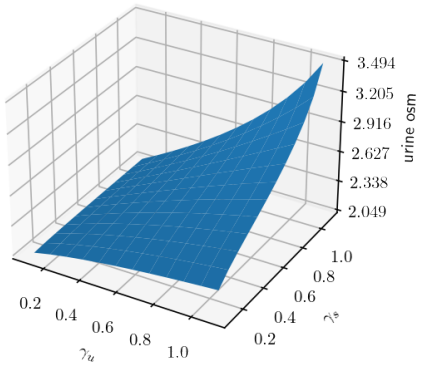


(b) $\gamma_u = \gamma_s = 1.2$

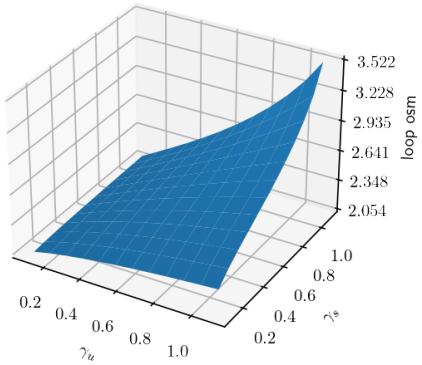
Figure 1: $\zeta_{\mathrm{D}} = \zeta_{\mathrm{C}} = 10$, $S = 1$, $U = 2$, $C = 2$



(a) papillary core osmolarity



(b) urine osmolarity



(c) osmolarity at the turning of Henle's loop

Figure 2: $\zeta_D = \zeta_C = 10$, $S = 1$, $U = 2$, $C = 2$

we clearly see the decreasing osmolarity in the ascending tubule as the flow goes upward.

We can also see that the concentration gradient is increased when the solute permeability is higher (Figure 1b). This is not so surprising; the more solute reabsorption, the more osmotic drive to concentrate the urine. To understand the distinct roles between that of salt and urea, we plot the osmolarity at the papillary end as a function of solute permeabilities (Figure 2). We see that, as γ_u vanishes, the osmolarity at the papillary end of each compartment becomes closer to the osmolarity at the inner-outer medullary junction. Under such a condition, increasing the ascending tubule salt permeability has very little effect to the concentration gradient. Therefore, urea is an 'enabler' of salt reabsorption, while both salt and urea act as sources of osmotic drive.

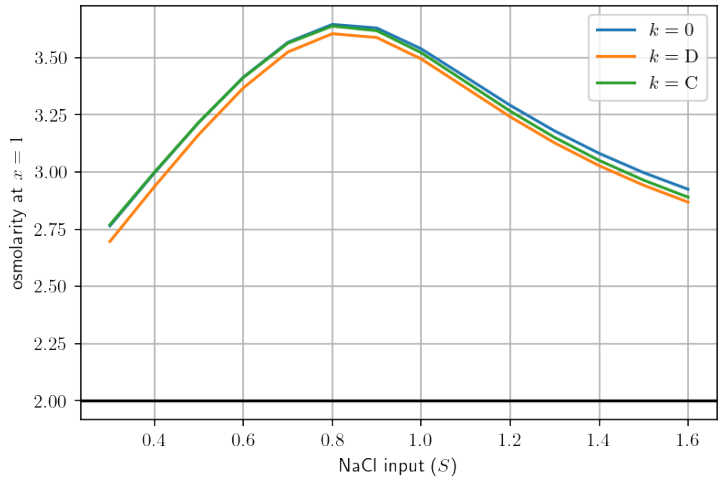


Figure 3: $\zeta_{\mathrm{D}} = \zeta_{\mathrm{C}} = 10$, $\gamma_u = \gamma_s = 1.2$, $U = 2$, $C = 2$

There is yet another factor that can further enhance the effectiveness of the passive mechanism: the proportion of long-loop nephrons. The initial salt flux S is proportional to the number of loops of nephron that descend pass the inner-outer medullary junction. We see in the Figure 3 that the osmolarity at the papillary end is maximized at a certain value of S. The rationale for this is that if there are less loops in the inner medulla, the salt load will not be enough to create a concentration gradient in the vascular core and the collecting tubule. On the other hand, if there are too many loops, the water inside the descending tubule cannot be reabsorbed to the extent that heighten the salt concentration at the loop turning enough to effectively drive the salt reabsorption.