

# 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.

However, the passive mechanism remains poorly understood. Many modeling studies incorporating the idea were only partially successful in producing significant concentration gradient in the inner medulla. The ones that yield desirable results need nephrons require parameters far from those experimentally measured.

The aim of this document is to generate a clearer picture of the passive mechanism. 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, with a few additional assumptions, the model can be reduced to a system of 3 ordinary differential equations. The hope is that, in this simplified model, we can better understand and identify factors that contribute to the passive mechanism.

## 2 Model derivation

The key idea behind the construction of this model is to qualitatively reproduce the explanation of the passive mechanism that passive urea reabsorption from the collecting tubules drives descending tubules water and ascending tubules NaCl reabsorption. Any assumption we made in the process will be in the favor of this explanation.

We will 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 ( $k = D$ ), ascending tubules ( $k = A$ ), and the collecting tubules ( $k = C$ ). 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.,  $u_D = s_C \equiv 0$ . Thus, there are total of 9 unknowns in the model: the water flow  $q_D, q_A, q_C, q_0$  and the solute concentrations  $s_D, s_A, s_0, u_C, u_0$ .

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  $w_D := \zeta_D(2s_0 + u_0 - s_D)$  and  $w_C := \zeta_C(2s_0 + u_0 - u_C)$  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

$$\frac{dq_D}{dx} = -\zeta_D(2s_0 + u_0 - s_D) = -w_D, \quad (2.1)$$

$$\frac{dq_A}{dx} = 0, \quad (2.2)$$

$$\frac{dq_C}{dx} = -\zeta_C(2s_0 + u_0 - u_C) = -w_C, \quad (2.3)$$

$$\frac{dq_0}{dx} = w_D + w_C. \quad (2.4)$$

These equations are accompanied by 4 boundary conditions:

$$q_D(0) = \frac{2S}{C}, \quad q_A(1) = -q_D(1), \quad q_C(0) = \frac{U}{C}, \quad q(1) = 0. \quad (2.5)$$

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

$\gamma_s(s_A - s_0)$  and  $\gamma_u(u_C - u_0)$  respectively, where  $\gamma_s$  is the ascending tubule salt permeability and  $\gamma_u$  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:

$$\frac{d}{dx}(s_D q_D) = 0, \quad (2.6)$$

$$\frac{d}{dx}(s_A q_A) = -\gamma_s(s_A - s_0), \quad (2.7)$$

$$\frac{d}{dx}(s_0 q_0) = \gamma_s(s_A - s_0), \quad (2.8)$$

$$\frac{d}{dx}(u_C q_C) = -\gamma_u(u_C - u_0), \quad (2.9)$$

$$\frac{d}{dx}(u_0 q_0) = \gamma_u(u_C - u_0). \quad (2.10)$$

The equations (??) and (??) are subject to boundary conditions:

$$2s_D(0) = u_C(0) = C, \quad (2.11)$$

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:

$$\frac{2S}{C} + q_0(0) + q_A + \frac{U}{C} = q_C(1), \quad (2.12)$$

$$S + q_A(0)s_A(0) + s_0(0)q_0(0) = 0, \quad (2.13)$$

$$U + u_0(0)q_0(0) = u_C(1)q_C(1). \quad (2.14)$$

The system of nine ordinary differential equations we just obtained can be simplified even further. First, we can turn the differential equations describing the descending tubules, (??) and (??), into algebraic equations. By assuming that the water permeability in the descending tubule is large, we approximate the equation(??) by taking the limit  $\zeta_D \rightarrow \infty$  which results in

$$s_D = s_0 + \frac{u_0}{2}. \quad (2.15)$$

With the boundary condition  $s_D(0)q_D(0) = S$  and (??), integrating (??) yields

$$q_D = \frac{S}{s_D} = \frac{2S}{2s_0 + u_0}. \quad (2.16)$$

For the ascending tubule, in place of the water balance equation (??), we simply have  $q_A$  being constant. With the salt conservation (??) and the first equality of (??), summing (??) and (??) and taking integral gives

$$S + s_A q_A + s_0 q_0 = s_D q_D + s_A q_A + s_0 q_0 = 0. \quad (2.17)$$

Note the second equality of (??) and the boundary condition  $q_A(1) = -q_D(1)$  imply that  $s_D(1) = s_A(1)$ . Consequently, by integrating (??) we obtain an equation for  $q_A$ :

$$q_A = -q_D(1) = -\frac{S}{s_D(1)} = -\frac{S}{s_A(1)}. \quad (2.18)$$

The salt concentration  $s_A$  is still governed by the same equation (??), with a boundary condition (??).

Now, we solve the equations for the central core (??), (??), and (??). Similarly to how we obtain (??), using the urea conservation (??), we have by summing (??) and (??) and integrating

$$u_C q_C + u_0 q_0 = u_C(1) q_C(1). \quad (2.19)$$

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

$$q_0 = -\frac{s_A q_A + S}{s_0} = -\frac{S}{s_0} \left( 1 - \frac{s_A}{s_A(1)} \right). \quad (2.20)$$

Substituting  $q_0$  into (??) yields

$$s_0 (u_C(1) q_C(1) - u_C q_C) + u_0 S \left( 1 - \frac{s_A}{s_A(1)} \right) = 0. \quad (2.21)$$

We can do the same for the water conservation as well. Summing (??), (??), (??) and (??) and integrating, we have  $q_D + q_A + q_C + q_0 = q_C(1)$ . By substituting  $q_D$ ,  $q_A$ ,  $q_0$  from (??), (??) and (??), we obtain

$$\frac{2S}{2s_0 + u_0} - \frac{S}{s_D(1)} + q_C - \frac{S}{s_0} \left( 1 - \frac{s_A}{s_A(1)} \right) = q_C(1). \quad (2.22)$$

We can now solve (??) and (??) for  $s_0$  and  $u_0$  in terms of  $s_A$ ,  $u_C$  and  $q_C$ :

$$u_0 = R s_0, \quad s_0 = S \left( \frac{1 - \frac{s_A}{s_A(1)} - \frac{2}{2+R}}{q_C - q_C(1) - \frac{S}{s_A(1)}} \right), \quad (2.23)$$

$$R := \frac{u_C q_C - u_C(1) q_C(1)}{S \left( 1 - \frac{s_A}{s_A(1)} \right)} \quad (2.24)$$

With all the 6 unknowns solved, the problem is reduced to a system of ODEs with only 3 differential equations:

$$\frac{ds_A}{dx} = -\frac{\gamma_s}{q_A} (s_A - s_0), \quad (2.25)$$

$$\frac{dq_C}{dx} = -\zeta_C (2s_0 + u_0 - u_C), \quad (2.26)$$

$$\frac{du_C}{dx} = \frac{1}{q_C} (\zeta_C u_C (2s_0 + u_0 - u_C) - \gamma_u (u_C - u_0)), \quad (2.27)$$

with boundary conditions

$$\begin{aligned} s_A(0) &= s_0(0) + s_A(1) \left( 1 - \frac{s_0(0)}{S} \left( \frac{2S+U}{C} - q_C(1) \right) \right), \\ q_C(0) &= \frac{U}{C}, \quad u_C(0) = C, \end{aligned} \quad (2.28)$$

where  $q_A = -S/s_A(1)$ , and  $s_0, u_0$  are given in (??). The model parameters are the ascending tubule salt permeability  $\gamma_s$ , the ADH dependent urea permeability  $\gamma_u$  and water permeability  $\zeta_C$ , the salt and urea input  $S, U$ , and  $C$  the osmolarity of the descending and the collecting tubules at the outer-inner medullary junction.

### 3 Numerical method

We use a finite difference method with forward difference approximation of derivatives to solve the system of ODEs. Let  $N$  be the number of grid on the spatial domain  $(0, 1)$  and the grid size is  $\delta x = 1/N$ . We denote by  $s^n, q^n, u^n, s_0^n, q_0^n$ , for  $n = 0, 1, \dots, N$ , the approximation of  $s_A, q_C, u_C, s_0, q_0$  on the grid point  $x = n\delta x$ . Further, we define the backward difference operator

$$(\mathcal{D}y)^n := \frac{y^{n+1} - y^n}{\delta t}, \quad n = 0, \dots, N-1, \quad (3.1)$$

where  $y^n$  is a discretized unknown.

We write the finite difference scheme for the system (??) - (??) as

$$(\mathcal{D}s)^n = -\frac{\gamma_s s^N}{S} (s^n - s_0^n) \quad (3.2)$$

$$(\mathcal{D}q)^n = -\zeta (2s_0^n + u_0^n - u^n), \quad (3.3)$$

$$(\mathcal{D}u)^n = \frac{1}{q^n} (\zeta u^n (2s_0^n + u_0^n - u^n) - \gamma_u (u^n - u_0^n)), \quad (3.4)$$

for  $n = 1, \dots, N$ . Moreover, we have the boundary conditions:

$$s^0 = s^N \left( 1 + \frac{s_0^0 q_0^0}{S} \right), \quad q^0 = \frac{U}{C}, \quad u^0 = U. \quad (3.5)$$

Here,  $s_0^n, q_0^n$ ,  $n = 0, \dots, N-1$ , are given by

$$u_0^n = R^n s_0^n, \quad s_0^n = S \left( \frac{1 - \frac{s^n}{s^N} - \frac{2}{2+R^n}}{q^n - q^N - \frac{S}{s^N}} \right), \quad R^n := \frac{u^n q^n - u^N q^N}{S \left( 1 - \frac{s^n}{s^N} \right)}. \quad (3.6)$$

The above system of equations is to be solved using an iterative method.