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A TEST PROBLEM FOR MODELS OF THE URINE CONCENTRATING MECHANISM

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Abstract. The kidney is one of the most important organs in our body and is responsible for: regulating the volume and composition of the extracellular fluid; excreting metabolic waste (as urine) and foreign substances; and also producing some hormones. The mechanism by which the osmotic gradient is created within the inner medulla still has no satisfactory explanation that accounts for measured permeabilities and other active transport issues. The main goal of this project is to extend the steady state WKM ([3]) model, where anatomical features such as the radial organization of the medulla are included, to a transient version that will include more recent discoveries and issues (glycolysis [1],[2], prebend transitions, etc). The complexity of this kind of model suggests that first we build a simpler test model where the issues mentioned above can be checked in advance. This paper presents a test model where steady state and transient versions are solved.

1 The kidney

In a normal human adult (Figure 1), each kidney is about 11 *cm* long and about 5 *cm* thick, weighing 150 grams. If the kidney is bisected from top to bottom, the two major regions that can be visualized are the outer *cortex* and the inner region referred as the *medulla*, where we can also distinguish two regions, the *outer medulla* (OM) and the *inner medulla*(IM).

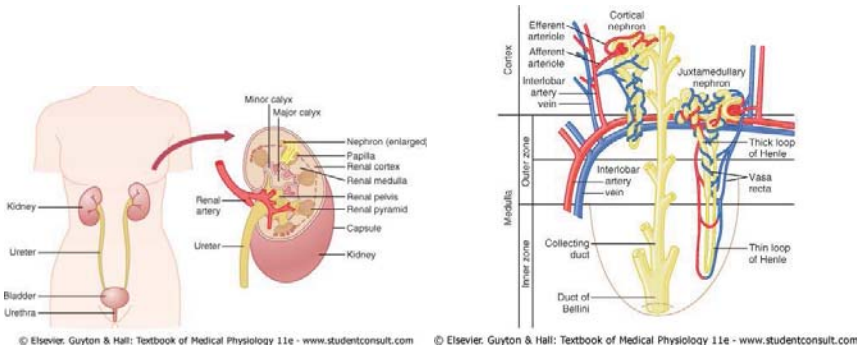

Figure 1: Left:Urinary system and the kidney. Right: Nephron within the blood supply system ([5])

The nephron (Figure 1) is the functional unit of the kidney. There are more than a million in each normal adult human kidney. Each nephron contains a tuft of capillaries called the *glomerulus* , through which large amounts of fluid are filtered from the blood, and a long *tubule* in which the filtered fluid is converted into urine on its way to the pelvis of the kidney.

In the blood supply of the kidney, the vasa recta (VR)(Figure 1) forms a series of straight capillaries that descend from the cortex into the medulla. These vessels branch off the efferent arterioles of juxtamedullary nephrons (those nephrons closest to the medulla), enter the medulla, and surround the loop of Henle.

2 The model

2.1 Description

The model described here contains the VR considered as a tube with a turning point at the bottom of the medulla and also the collecting duct (CD), a straight tube open at the bottom of the medulla where fluid leaves the nephron on its way to the bladder. The VR has two branches, the descending vasa recta (DVR) and the ascending vasa recta (AVR), the latter also considered as playing the role of the interstitium. For simplicity only one solute is considered and also each type of tube represents a single structure. Medullary depth (x) is set as 1 *mm*.

2.2 Equations

The system of equations describing the model is based on water and solute conservation within the tubes (DVR and CD) and also on conservation of mass for the medulla as a whole (AVR). System variables are the axial tubular

flows of water and concentrations. The usual convention that descending tubule flows are positive and ascending flows are negative is adopted.

For the descending vasa recta and collecting duct, conservation of volume within the tube gives:

$$\frac{\partial F_v^j}{\partial x} = -J_v^j \tag{1}$$

Conservation of mass within the tube gives ([4])

$$\frac{\partial C^j}{\partial t} = \frac{1}{A^j}(-\frac{\partial F_s^j}{\partial x} - J_s^j) \tag{2}$$

where C represents the concentration of solute at each tubule j, F_v^j and F_s^j are tubular flows of volume and solute, different J^j represents transmural fluxes due to membrane transport (osmosis, diffusion, solvent drag and active transport) and A^j represents the cross-sectional area of each tube j. Boundary conditions are known at $x = 0$ for volume flows and concentrations entering the descending structures, and for $x = L$ (where L represents the papillary tip of the medulla) continuity conditions are imposed. Concentration of solute in tubes j are calculated from the ratio of solute flow to volume flow $C^j = \frac{F_s^j}{F_v^j}$

Then, we can write the conservation equation as

$$\frac{\partial C^j}{\partial t} = \frac{1}{A^j}(-F_v^j \frac{\partial C^j}{\partial x} + C^j J_v^j - J_s^j) \tag{3}$$

For the ascending vasa recta, conservation of mass for the medulla as a whole says simply that, at any depth x, the algebraic sum of flows in all tubes j (taking flows to be positive toward and negative away from the papilla) must equal the exit rate of flow from the terminal collecting duct, considering that no material is being produced or destroyed by chemical or physical reactions.

$$\sum_j F_v^j(x) = F_v^{CD}(L) \tag{4}$$
$$\sum_j F_s^j(x) = F_s^{CD}(L)$$

Differentiating both equations two new ODEs are obtained

$$\frac{\partial F_v^{AVR}}{\partial x} = J_v^{CD} + J_v^{DVR} \tag{5}$$

$$\frac{\partial C^{AVR}}{\partial x} = \frac{1}{F_v^{AVR}}(J_s^{CD} + J_s^{DVR} - C^{AVR}(J_v^{CD} + J_v^{DVR})) \tag{6}$$

Transmural fluxes due to membrane transport are given by

$$J_v^j = 2\pi r^j L_p R T^j \sigma^j (C^{AVR} - C^j) \tag{7}$$

where J_v represents transport by osmosis, where L_p is the hydraulic permeability, and σ is the reflection coefficient.

$$J_s^j = 2\pi r^j P^j (C^j - C^{AVR}) + (1-\sigma^j) J_v^j \frac{C^j + C^{AVR}}{2} + 2\pi r^j \frac{V_m^j C^j}{K_m^j + C^j} \tag{8}$$

where the first term refers to linear diffusion (P represents permeability and r radius of each tube), the second term describes solvent drag and third term indicates active transport, where a simple Michaelis-Menten type relation is assumed for the active solute pumps, saturable as a function of solute concentration, with a maximum rate V_m and a half maximal concentration K_m.

From the above transient equations, steady state ones can be easily derived by setting time derivatives to zero.

2.3 Boundary conditions and parameters

Volume flow into DVR is 4 $nl\ min^{-1}$ and into CD is 10 $nl\ min^{-1}$. Input concentrations are 150 mM and 35 mM for DVR and CD. Continuity at the papillary tip is expressed as

$$F_v^{AVR}(L) = -F_v^{DVR}(L) \tag{9}$$
$$C^{AVR}(L) = C^{DVR}(L)$$

Initial conditions are taken constant along the tube as values entering the descending structures.

3 Numerical simulations

3.1 Steady state solution

The boundary value problem resulting from the steady state formulation of the problem is solved by collocation (*bvp*4*c Matlab* routine). Figure 2 shows concentration profiles for the VR. Figure 3 shows the same profiles for the CD.

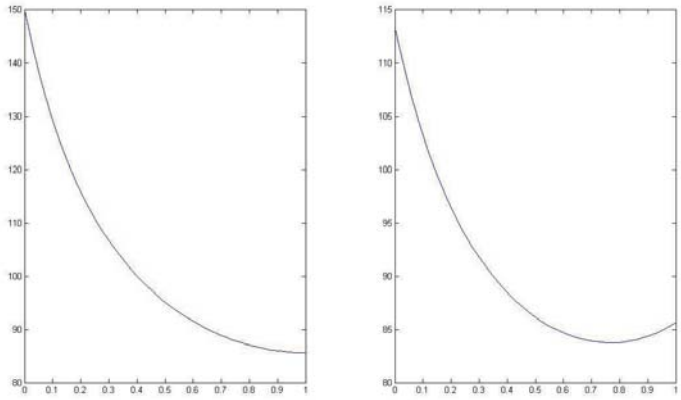

Figure 2: Left:Steady state concentration profile at the DVR. Right: Steady state concentration profile at the AVR. Medullary depth(x) in *mm* Vs Concentration (*mM*).

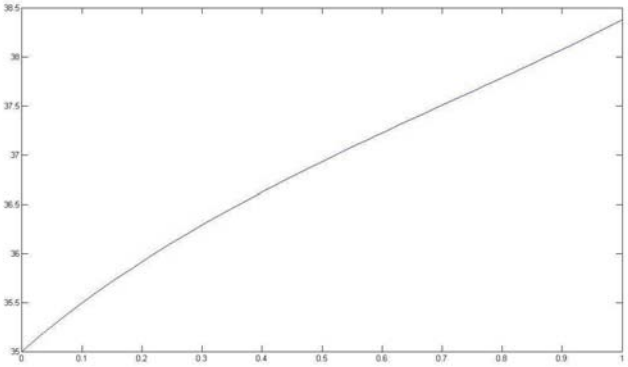

Figure 3: Steady state concentration profile at the CD. Medullary depth(x) in *mm* Vs Concentration (*mM*)

3.2 Transient solution

The system described by Equations (1) and (4) is solved by the numerical Method of Lines (previously applied by Moore and Marsh [6]); i.e., the part of the equations involving the space variables is discretised. In this particular problem the medulla is divided into n different regions: $i = 1$ corresponds to the corticomedullary border ($x = 0$) and $i = n$ corresponds to the papillary tip ($x = L$). Finite difference approximations for each of the partial derivatives with respect to the distance along the corticopapillary axis are used. In particular backward differencing (Equation 13) is used: one subtracts the upstream concentration from the concentration at the point where the derivative is to be evaluated following the natural flow in the nephron.

$$C_x \approx \frac{C_i - C_{i-1}}{h} \tag{10}$$

This approach gives a system of ODEs approximating the PDE arising from conservation of solute and a system of algebraic equations from conservation of volume. The resulting DAE system is solved by the Matlab ODE solver *ode*15*s*.

Figure 4 shows concentration profile at the CD at various different times; note that at the steady state the graph is the same as that shown in Figure 3.

Figure 5 shows the case where, rather than representing a single structure, each structure represents a whole population of tubes with the same characteristics. The VR and CD are assumed to diminish exponentially in number along the medulla toward the tip of the papilla according to the same relation as earlier models and in conformity with reported rat anatomy:

$$N^j = N^j(0)e^{-k_{sh}^j x} \tag{11}$$

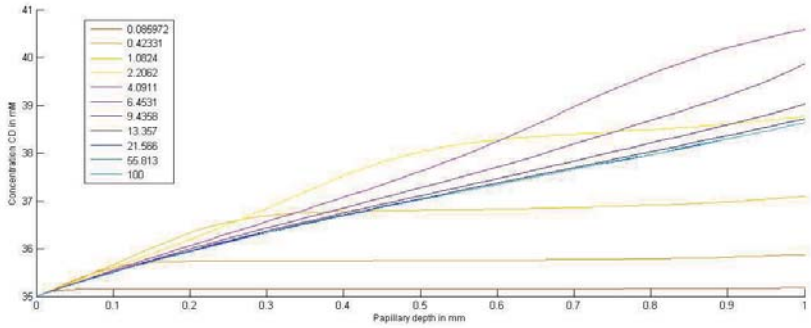

Figure 4: Concentration profiles at the CD for different times (in s).

where the number of tubes at $x = 0$ is 64 for the CD and $N^{DVR}(0) = 4N^{CD}(0)$. The factor describing the decrease is taken as 1.213 mm^{-1} for the DVR and 1.04 mm^{-1} for the CD.

The issue of a tube representing more than one structure makes it necessary to take into account the amount of flow that leaves the descending branch of the VR at each depth due to a loop turning. That requires a new term in the conservation equations for the DVR and AVR which is denoted as F_{shunt} and is described in [1] and [2].

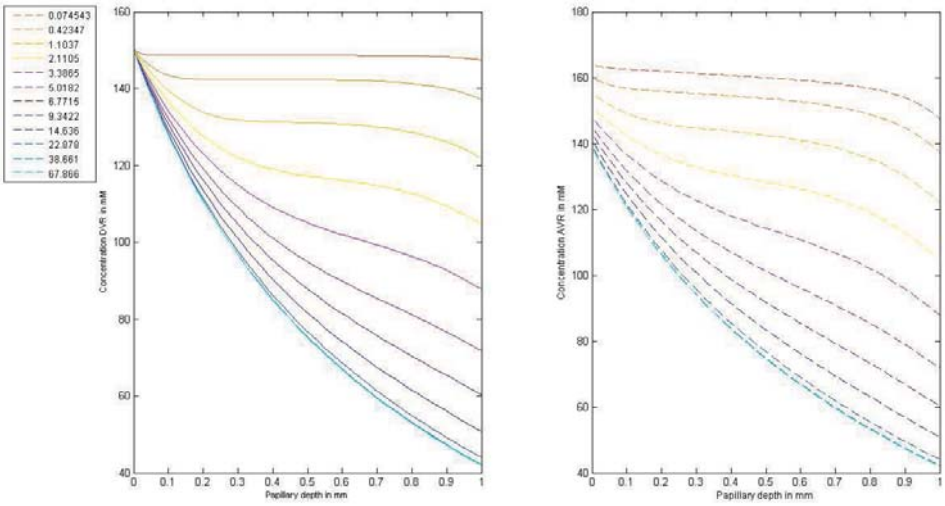

Figure 5: Concentration profiles through time for the VR (DVR left and AVR right)

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