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Water transport through the kidney

J B van den Berg, J R King, S J Franks, H J Mason

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Abstract

In occupational medicine, measurements of levels within the urine of toxic chemicals, or their metabolites, are used to indicate the level of exposure of workers to chemicals. In a worker's body the kidney is the main organ taking care of the excretion of unwanted/toxic chemicals and the recovery of useful ones, via three mechanisms: filtration, reabsorption and secretion. We model these processes, taking the fairly complicated geometry of the kidney into account, and study how the flow rate of urine influences the concentration of certain drugs/toxins in a urine sample.

1 Introduction

In occupational medicine, urine measurements of toxic chemicals, or their metabolites, are used to indicate the level of exposure of workers to chemicals. International regulatory guidelines and limit values are assigned to urine concentrations of specific chemicals/metabolites which can have significant implications for the factory or individual worker. The practical difficulties of collecting accurately timed and complete urine collections are well known and, in practice, measurements are undertaken on single 'spot' urine samples from workers at the end of a work-shift.

The measure of the body burden of a chemical has traditionally been attempted by expressing the excretion of chemical as mass per unit time, averaged over a significant timeframe. This is done to lessen the influence of fluctuations in urine flow rate on the measured excretion of the chemical. It has been common practice to ratio the urine concentration of the chemical to that of creatinine, which is a substance produced at a relatively constant rate by the body and with relatively little tubular secretion or absorption (i.e. the excretion rate of creatinine is relatively constant and its concentration reflects urine flow rate). If such a correction were not done, the measured concentration of chemical in urine might reflect urine production rate rather than the body burden of the chemical. However creatinine is not a perfect chemical for this purpose as elements of tubular secretion of creatinine can be found at extremes of urine flow rates and total creatinine production in the body depends on muscle mass and is therefore variable between subjects.

The kidney is a major organ for the excretion of unwanted/toxic chemicals and the recovery of useful ones. It carries out three main functions: filtration, reabsorption and

secretion. It is also a key organ in homeostasis, including the control of water balance in the body. The kidney comprises about a million individual units (nephrons), each with a blood filtration unit (glomerulus) and the capability to re-absorb wanted chemicals or actively secrete various unwanted chemicals in the tubules post-filtration. The kidney's ability to control water balance is evident from the fact that a normal kidney can filter about 125 ml/min of blood, whilst only excreting (on average) about 1ml/min of urine. However, the kidney is quite capable of giving, over short periods of time, 20-30 fold differences in the urine flow rate (as ardent beer drinkers or those visiting hot countries can testify). The tubules in the kidney, both proximal and distal, have important roles in controlling these acute changes in rate of fluid excretion. The bladder (which comes after the kidney in the urinary tract) can largely be considered as an impermeable bag with a maximum volume capacity. Usually when the bladder gets towards full, the brain is signalled about the need to urinate, so the time between micturition is also dependent on the urine flow rate.

Complications may arise because the excretion of some chemicals is not just determined by the glomerular filtration of blood, but is also strongly influenced by secretion and/or reabsorption in the tubules (e.g. ethanol passively diffuses into urine across cell walls in the tubule and therefore the rate of urine excretion of ethanol is independent on flow rate and the body burden can be simply reflected by urine ethanol concentration). However, many toxic chemicals do largely enter urine through glomerular filtration with relatively little tubular absorption or excretion, leading to the chemical's excretion being urine flow rate dependent. Typically these results are normalised against creatinine excretion to overcome the concentration/dilution effects that may be caused by the kidney's key role in ensuring water balance. The interpretation of urine measurements of chemicals and the value of creatinine correction would therefore be greatly improved by a mathematical model for

- water handling in the kidney, incorporating induced temporal physiological changes and associated control mechanisms;
- creatinine handling in the kidney, including variation (intra and inter-individual) in production;
- handling of specific toxic chemicals or metabolites (class categorization) by the kidney.

The main questions addressed in this study group report are related to (a) how the flow rate of urine influences the concentration of certain drugs/toxins in a urine sample and (b) how the intake of these drugs/toxins influences the flow rate. These mechanisms may depend upon the particular substance under scrutiny, so we consider a generic substance in this report.

2 The model

A kidney consists of many (about a million) nephrons working in parallel. The action of a nephron begins in the glomerulus, where the blood plasma is filtrated. The filtrate contains

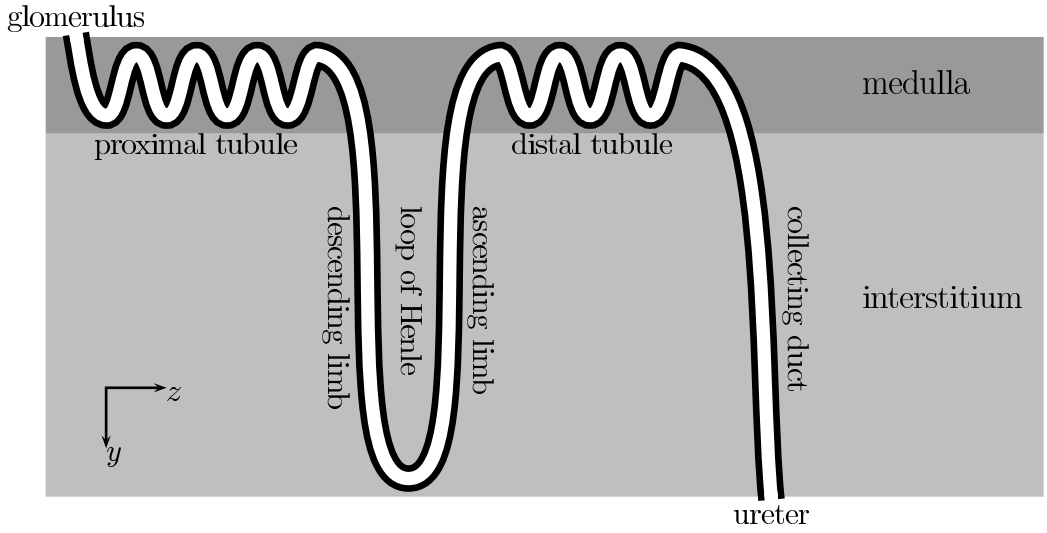

Figure 1: Schematic picture of the sections of the tubule in a nephron.

no proteins, but is otherwise identical to the plasma, i.e. all substances of small molecular weight pass the filter. Nearly all of the fluid that passes this filter gets re-absorbed in the subsequent concentration process, which takes place in a long tubule. We model the flow through this tubule and the concentration/diluting process by distinguishing between five distinct *sections* in the tubule:

- proximal tubule, denoted by p;
- descending limb of the loop of Henle, denoted by d;
- ascending limb of the loop of Henle, denoted by a;
- distal tubule, denoted by d;
- collecting duct, denoted by c.

For a schematic picture of the geometry, see Figure 1.

We also distinguish between two spatially separated types of surrounding tissue: the proximal and distal tubules lie in the medulla (denoted by m), while the other three sections are surrounded by interstitial tissue (denoted by s), as shown in Figure 1

There are two mechanism for exchanging sodium with the surrounding tissue, diffusion through the permeable walls and active transport out of the tubule by ATPase pumps.

Table 1 summarises the types of exchange in each of the sections. The permeabilities of the walls are denoted by K_i, with $i = p, d, a, l, c$, where $K_a = 0$ since the walls of the ascending limb are impermeable. We note that the permeability K_c of the collecting duct depends crucially on the antidiuretic hormone (ADH) concentration. The pituitary gland secretes ADH and the ADH concentration determines whether the urine will be diluted or concentrated. When ADH is absent, the walls of the distal tubule and of the collecting

Section	notation	permeable	active transport
Proximal tube	p	yes	yes
Descending limb	d	yes	no
Ascending limb	a	no	yes
Distal tube	l	yes	yes
Collecting duct	c	yes	no

Table 1: The five sections of the tubule

duct are impermeable to water, so in this case the volume of urine is essentially that of the fluid that leaves the top of the ascending limb of Henle's loop. In this case the kidney excretes a large volume of dilute urine. However, when ADH is present, the walls of the distal tubule and the collecting duct become permeable to water. In the distal tubule enough water is withdrawn (osmotically) to bring the concentration of solutes back up to the level of the blood plasma. Then as the tubular fluid descends to the collecting duct, enough water is withdrawn to equilibrate with the local interstitial concentration at each level. Thus, the urine ends up with a solute concentration equal to that at the bottom of Henle's loop, a concentration much higher than that of the blood plasma. Moreover, because this high concentration is achieved by withdrawal of water, the volume of urine excreted per unit time is much lower than if ADH had not been present. Hence, an increase in ADH concentration leads to a higher permeability of the collecting duct. The active transport of the solute across the tubule walls is modelled via Michaelis-Menten kinetics:

$$\sigma_i(c) = \sigma_{0i}\frac{c}{1 + c/\kappa_i}, \tag{1}$$

with κ_i the carrying capacity, σ_{0i} the rate constant (units m^2/s), and c the sodium concentration. Since there is no active transport in the descending limb and the collecting duct, $\sigma_{0d} = \sigma_{0l} = 0$.

The lengths of the sections are denoted by L_i, and the geometry prescribes that $L_d = L_a = L_c$. It is convenient also to introduce the lengths $\ell_1, \ldots, \ell_5$, where ℓ_j is the total length of the first j sections (e.g. $\ell_3 = L_p + L_d + L_a$). We choose a coordinate x along the tubule. The coordinates in the reference frame are y and z. To distinguish the five pieces we write the sodium concentration $c(t, x)$ as

$$c(t,x) = \begin{cases} c_p(t,x) & x \in [0, \ell_1], \\ c_d(t, x-\ell_1) & x \in [\ell_1, \ell_2], \\ c_a(t, x-\ell_2) & x \in [\ell_2, \ell_3], \\ c_l(t, x-\ell_3) & x \in [\ell_3, \ell_4], \\ c_c(t, x-\ell_4) & x \in [\ell_4, \ell_5]. \end{cases} \tag{2}$$

where $c_i(t, x)$ is defined for $x \in [0, L_i]$. Similar notation is used for the flow velocity $q(t, x)$ along the tube (i.e. in the x-direction) and the pressure $p(t, x)$. All three dependent variables are continuous along the tubule leading to straightforward continuity equations on the boundaries between different sections.

The flow and concentrations in each section are governed by conservation laws for the sodium, i.e., for $i = p, d, a, l, c$ and $x \in (0, L_i)$.

$$\frac{\partial}{\partial t}(A_i c_i) + \frac{\partial}{\partial x}(q_i c_i) = -\sigma_i(c_i) \tag{3}$$

where A_i is the cross sectional area of the tubule, q_i is the flow rate (the volume flux of liquid), and σ_i is the Michaelis-Menten reaction term introduced above. The flow of water across the membrane is controlled by the pressure difference, so that the conservation law for the water leads to

$$\frac{\partial q_i}{\partial x} = K_i[p_{s,m} - p_i + \lambda(c_i - c_{s,m}) - \pi_{s,m}], \tag{4}$$

with K_i the permeability of the walls of the tubule. One should read this equation as follows: select subscript s (interstitium) for $i = d, a, c$, and subscript m (medulla) for $i = p, l$. The pressure consists of the hydrostatic pressure difference $p_{s,m} - p_i$, the osmotic pressure difference due to the difference in sodium concentration (with proportionality constant λ) and an additional osmotic pressure $\pi_{s,m}$ due to the presence of other chemicals (we will assume $p_{s,m} - \pi_{s,m}$ are known constants). Finally, the pressure in the tubule is related to the flow via Darcy's law (since we may assume there is a Poiseuille flow in the long, thin tubule), with resistances R_i,

$$\frac{\partial p_i}{\partial x} = -R_i q_i. \tag{5}$$

To close the system we need equations for the sodium concentrations in the surrounding tissues: $c_s(t, y)$ and $c_m(t)$. In particular, these concentration are assumed to be uniform in the z-coordinate (cf. Figure 1). A relation for c_s is provided by the overall conservation law in the interstitium

$$A_s \frac{\partial c_s}{\partial t} = \sigma_a(\overline{c_a}) + \Big(\frac{\partial q_d}{\partial x} + \frac{\partial q_c}{\partial x}\Big) c_s \tag{6}$$

where, as follows from the geometry, $\overline{c_a}(t, x) = c_a(t, L_a - x)$. The final terms in (6) describe the flow of liquid from the descending limb to the interstitium, and similarly for the collecting duct.

Likewise, c_m is determined by a conservation law in the medulla:

$$V_m \frac{\partial c_m}{\partial t} = \int_0^{L_p} \sigma_p(c_p)dx + \int_0^{L_l} \sigma_l(c_l)dx + \big[q_p(L_p) - q_p(0) + q_l(L_1) - q_l(0)\big] c_m. \tag{7}$$

Here A_s and V_m are active area (that is, the horizontal cross-sectional area occupied by tubules) and volume of the interstitium tubules and the medulla, respectively.

At the glomerulus we have "upstream" boundary conditions for c and q, while at the ureter we have a "downstream" boundary condition for the pressure p:

$$q(t, 0) = q_0, \tag{8}$$

$$c(t, 0) = c_0, \tag{9}$$

$$p(t, \ell_5) = p_1. \tag{10}$$

As noted before, these boundary conditions are supplemented with 12 continuity equations for c, q and p at the boundaries ($x = \ell_i$, $i = 1, 2, 3, 4$) between the different sections of the tubule. We thus have a system of 17 equations. The equations for q_i and p_i are time-independent and form a set of five elliptic equations. The remaining five equations for the sodium concentration c_i in the tubule are of hyperbolic nature, while the equations for $c_{s,m}$ are ODEs in time (in particular, there are no spatial derivatives of c_s in (6)). This is of course a rough division, because the equations are coupled.

3 Numerical results

The hyperbolic-elliptic system was solved numerically to get an idea about the properties of the model and the extent to which it is able to predict the relevant phenomena. A simple forward-difference scheme was used for the hyperbolic part (3), while the elliptic part, i.e. equations (4) and (5), was solved, at each time step, by a boundary value solver (the matlab function `bvp4c`). To speed up the calculations one may decide to update the solutions q_i and p_i of the elliptic part after a few time steps instead of after each time step. Of course one needs to take care that the time step is sufficiently small compared to the spatial discretisation to prevent numerical instabilities. At the initial stage a first guess for a solution of the elliptic part is needed. This is obtained by assuming that the initial concentrations $c_i(0, x)$ are constant (per section) and then solving the system of linear equations analytically (if the initial concentrations are not piecewise constant, one may average over sections and use the result as an initial guess).

For choosing the parameters we use the following criteria: simplicity, information provided in [1], and the general goal of obtaining reasonable answers. While the equations are stated above in dimensional terms, for the purposes of the illustrative numerical simulations we treat the parameters as dimensionless but do not need to elaborate here on the choice of non-dimensionalisation. Unless mentioned otherwise, the parameters used are lengths $L_i = 1$; permeabilities $K_{p,d,l} = 1$, $K_a = 0$, $K_c = 5$; Michaelis-Menten reactions constants $\sigma_{0p} = 0.6$, $\sigma_{0a} = 0.15$, $\sigma_{0l} = 0.02$, $\sigma_{d,c} = 0$ with carrying capacities $\kappa_i = 20$ (so that σ_i is almost linear for the concentrations considered); resistances $R_i = 1$; cross sections $A_i = 1$, and active area/volume $A_m = V_s = 30$; pressures $p_{s,m} - \pi_{s,m} = 0.1$ and proportionality constant $\lambda = 0.001$; finally, the boundary conditions are $c_0 = 1$, $q_0 = 1$ and $p_1 = 0.1$.

For initial data $c(0, x) = 1$, the solution is shown in Figure 2. The dynamics show a wave of sodium concentration moving downstream from the glomerulus to the ureter. The wave propagates slower as it gets closer to the ureter, because the flow velocity decreases further away from the glomerulus, expected. The flow velocity quickly decreases along the tubule, and it changes only marginally over time. In equilibrium, the sodium flux is constant in the descending limb, as well as in the collecting duct, since there is no active sodium transport through the walls of those sections. On the other hand, in the ascending limb the flow velocity is seen to be constant, since the wall in that section of the tubule is impermeable. The final (almost) equilibrium profile shows two peaks in the sodium

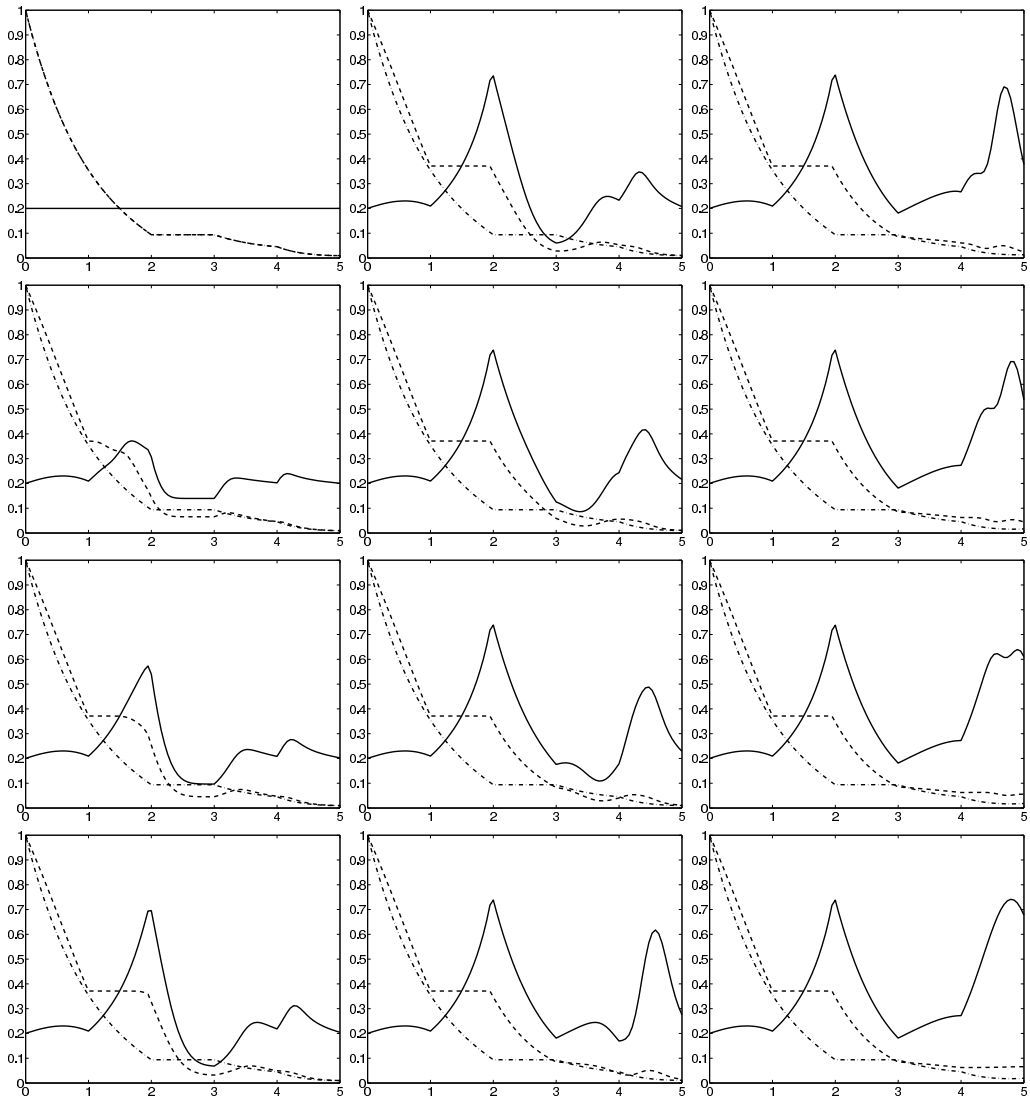

Figure 2: The evolution of the sodium concentration (solid line), the sodium flux (dashed) and the flow (dash-dot). Note that the depicted sodium concentration is scaled by a factor 0.2 to have all quantities on comparable scales. The boundary condition is $c_0 = 1$. The horizontal axis represents the x-variable (distance along the tubule). The times depicted are, from top to bottom and from left to right (i.e. the left column first), $t = 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 10$.

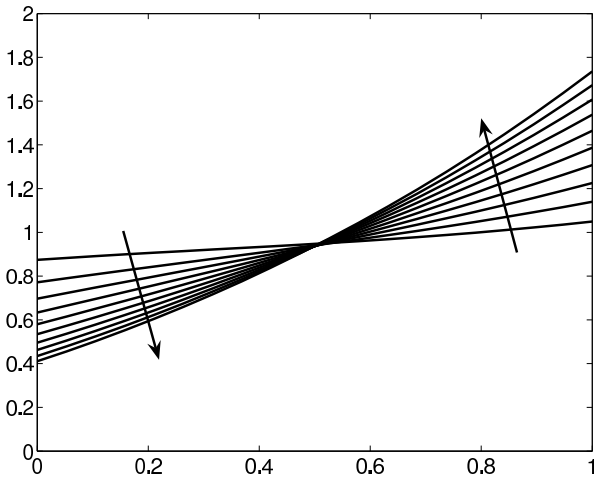

Figure 3: Time development (shown by arrows) of the sodium concentration in the interstitium. The steepest gradient corresponds to the final picture in Figure 2. The horizontal axis represents the y-variable, see Figure 1.

concentration, the first near the turning point in the loop of Henle, the second at the exit of the nephron towards the ureter. In Figure 3 we see the build-up of a sodium gradient in the interstitium. This sodium gradient is ultimately responsible for the efficient concentration of salts in the urine, and leads to the peaks in sodium concentration mentioned above.

Once the dynamics has settled in an equilibrium we decrease the concentration at the glomerulus by 50% ($c_0 = 0.5$), and we can see how this change gradually propagates, see Figure 4. Obviously this leads to a lower sodium flux at the ureter. Finally, we perform the same calculation again, but now for $K_c = 5/3$, simulating a decrease of ADH. In Figure 5 we compare the final state to that without a decrease of ADH ($K_c = 5$). We see that a decrease of ADH leads to a larger flow rate at the ureter and a lower sodium concentration. The model thus correctly displays the fact that the body can use this mechanism to increase urine production (and thereby dilute it).

4 Further developments

In this report we have shown how a simple model can be derived to reflect the physiological and temporal changes of water flow through the kidney. However, the incorporation of toxins and creatinine production into the model needs to be considered before meaningful interpretations can be drawn and the results presented herein are to be regarded as a promising preliminary study. Subsequent models can be developed to include the renal handling of specific toxic chemicals and the influence of the bladder.

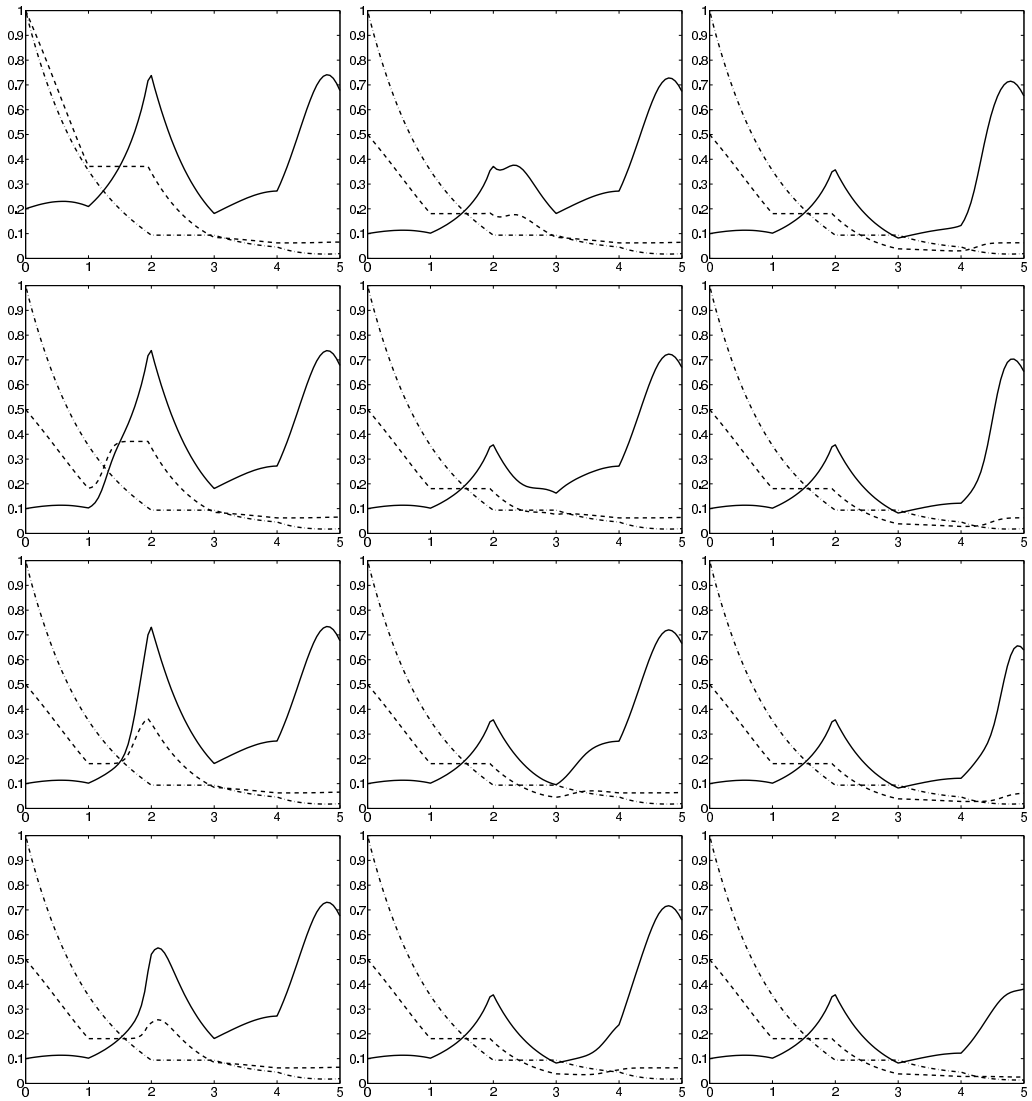

Figure 4: The evolution of the sodium concentration (solid line), the sodium flux (dashed) and the flow (dashed-dot). Note that the depicted sodium concentration is scaled by a factor 0.2 to have all quantities on comparable scales. The boundary condition is $c_0 = 0.5$ and the initial data is the final situation in Figure 2. The horizontal axis represents the x-variable (distance along the tubule). The times depicted are the same as in Figure 2.

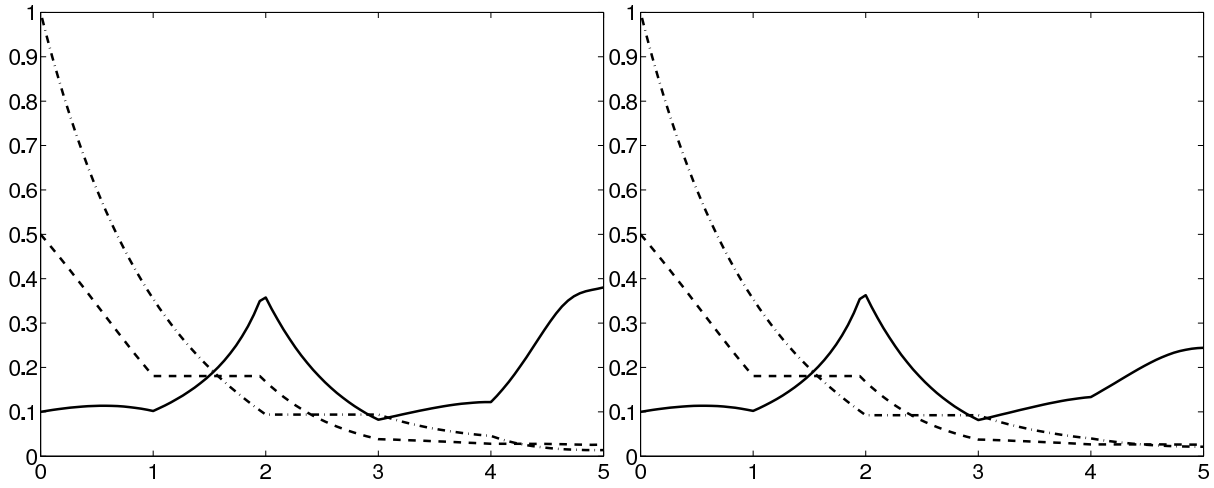

Figure 5: Comparison of the equilibrium state with a higher and (left) and lower (right) ADH concentration.

5 Participants

The following people were involved with this problem during the study group: JB van den Berg, JR King, SJ Franks, HJ Mason and S McKee.

References

[1] James Keener and James Sneyd. *Mathematical physiology*, volume 8 of *Interdisciplinary Applied Mathematics*. Springer-Verlag, New York, 1998.