Appl. Math. Lett. Vol. 6, No. 2, pp. 83–87, 1993
Printed in Great Britain.

0893-9659/93 $6.00 + 0.00

A MATHEMATICAL MODELING TECHNIQUE FOR RENAL COUNTERFLOW SYSTEMS

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Dedicated to Professor Dr. Dr.h.c. Roland Bulirsch on the occasion of his 60^{th} birthday

(Received and accepted December 1992)

Abstract—Realistic and comprehensive mathematical models of the renal concentrating mechanism lead to large systems of nonlinear differential equations. Their complexity can be considerably reduced by combining like tubules into common structures. Then the different lengths of the combined tubules have to be modeled by the *shunt flow technique*. The present paper investigates the validity of this methodology.

1. INTRODUCTION

The main structures in the renal medulla are the *loops of Henle*. It is common to model a single loop in the steady state by the following five ordinary differential equations and the corresponding boundary conditions. Throughout this paper it is assumed that the concentrations in the surrounding space (*interstitium*) are given.

The inflow of water, salt and urea into the descending limb is prescribed by three boundary conditions: $F_{v,d}(0) = F_{v,0}$, $F_{s,d}(0) = F_{s,0}$, $F_{u,d}(0) = F_{u,0}$. The symbols $F_{v,\cdot}$, $F_{s,\cdot}$, $F_{u,\cdot}$ refer to axial flow rates of water, salt, urea, respectively, and the independent variable z denotes the distance into the medulla. The differential equations for the descending limb are

$$\frac{dF_{v,d}}{dz} = -J_{v,d}, \qquad \frac{dF_{s,d}}{dz} = -J_{s,d}, \qquad \frac{dF_{u,d}}{dz} = -J_{u,d}. \tag{1}$$

These equations reflect the local conservation of mass. The transmural fluxes $J_{v,d}$, $J_{s,d}$, $J_{u,d}$ are functions of the tubular concentrations $C_{s,d}$, $C_{u,d}$ as well as the interstitial concentrations $C_{s,\text{int}}$, $C_{u,\text{int}}$ (for details see e.g. [1–4]:

$$J_{\cdot,d} = J_{\cdot,d}(C_{s,d}, C_{u,d}, C_{s,\text{int}}, C_{u,\text{int}}), \qquad C_{s,d} = \frac{F_{s,d}}{F_{v,d}}, \qquad C_{u,d} = \frac{F_{u,d}}{F_{v,d}}. \tag{2}$$

Let $z = b$ be the level where the loop of Henle turns. In the ascending limb, the water flow rate $F_{v,a}$ is assumed to be constant:

$$F_{v,a}(z) \equiv -F_{v,d}(b). \tag{3}$$

This equation and the following two boundary conditions reflect the turn of the loop:

$$F_{s,a}(b) = -F_{s,d}(b), \qquad F_{u,a}(b) = -F_{u,d}(b). \tag{4}$$

The differential equations for the ascending limb are

$$\frac{dF_{s,a}}{dz} = -J_{s,a}, \qquad \frac{dF_{u,a}}{dz} = -J_{u,a}. \tag{5}$$

The loops of Henle turn at different levels of the renal medulla. One possibility to take this fact into consideration is to choose a population of loops of different lengths and to model each of these loops separately just in the manner described above. It is obvious that the number of differential equations increases considerably by this procedure. Nevertheless, several authors have used this approach (e.g. [1,3,5,6]). Numerical techniques to handle the large systems of differential equations have been developed in [1,3,5–8].

An alternative is to combine like tubules into common structures. This approach has been suggested in [9] and has been used subsequently in several articles [2,4,10–14]. The procedure to produce the combined structure is described in the next section with the help of a simple example. This example also shows that the combined structure is not mathematically equivalent to the corresponding population of single loops. Until now, there exists no study that investigates how much the numerical results for the combined structure deviate from those for the original problem. It is the aim of this paper to close this gap. In particular, a recent model [13,14] is investigated.

2. THE SHUNT FLOW TECHNIQUE

For the sake of simplicity, only water and salt are present in the example of this section. The transmural fluxes are modeled very simply, too:

$$J_{v,d} = -10(C_{s,d} - C_{s,\mathrm{int}}), \qquad J_{s,d} = 8(C_{s,d} - C_{s,\mathrm{int}}), \tag{6}$$

$$J_{s,a} = P_{s,a}(C_{s,a} - C_{s,\mathrm{int}}), \tag{7}$$

where

$$P_{s,a} = \begin{cases} 6, & \text{for } 0.0 \le z \le 0.5 \\ 1, & \text{for } 0.5 < z \le 1.0. \end{cases} \tag{8}$$

The interstitial concentration is defined as

$$C_{s,\mathrm{int}}(z) = \begin{cases} 1 + 2z, & \text{for } 0.0 \le z \le 0.5 \\ 2 + 20(z - 0.5), & \text{for } 0.5 < z \le 1.0. \end{cases} \tag{9}$$

The inflows into a single descending limb are assumed to be $F_{v,0} = F_{s,0} = 12$. The parameters of this model are chosen mainly for demonstration purposes. Please note that in the medullary segment under consideration no active transport is present and the differential equation (5) for the salt flow rate in the ascending limb is linear. Figure 1 shows a population of two loops with lengths 0.5 and 1.0, respectively, and the corresponding composite structure.

The symbol $\mathcal{F}$ refers to flow rates in the composite structure. The differential equations for the descending composite structure in the interval [0.0,0.5] are

$$\frac{d\mathcal{F}_{v,d}}{dz} = 2 \cdot 10 \left(\frac{\mathcal{F}_{s,d}}{\mathcal{F}_{v,d}} - C_{s,\mathrm{int}} \right), \qquad \frac{d\mathcal{F}_{s,d}}{dz} = -2 \cdot 8 \left(\frac{\mathcal{F}_{s,d}}{\mathcal{F}_{v,d}} - C_{s,\mathrm{int}} \right). \tag{10}$$

The corresponding initial conditions are $\mathcal{F}_{v,d}(0) = 2 \cdot F_{v,0}$, $\mathcal{F}_{s,d}(0) = 2 \cdot F_{s,0}$. Obviously, this initial value problem is equivalent to the corresponding initial value problem for a single descending limb via the scaling

$$\mathcal{F}_{v,d} = 2 \cdot F_{v,d}, \qquad \mathcal{F}_{s,d} = 2 \cdot F_{s,d}. \tag{11}$$

The turn of the short loop at $z = 0.5$ is reflected in the composite structure in the following way. Flow rates $\mathcal{F}_{v,d}(0.5)/2$, $\mathcal{F}_{s,d}(0.5)/2$ are shunted from the descending structure to the ascending one (***shunt flow technique***). Consequently, the remaining flow rates, which enter the descending composite structure at $z = 0.5$, are the same as in a single loop. In the interval (0.5, 1.0] the equations for both the descending and the ascending composite structure are identical to those for a single loop, too.

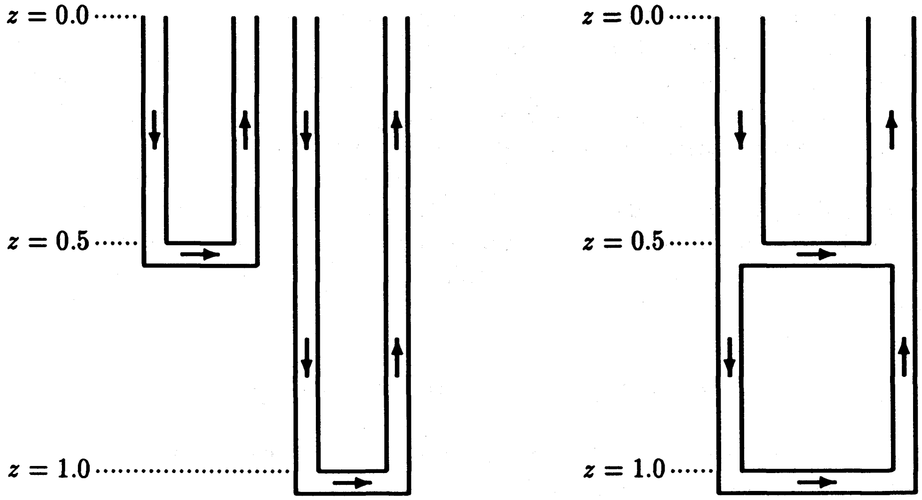

Figure 1. Separate loops (*left*) and corresponding composite structure (*right*). Arrows indicate the directions of axial flows.

The ascending composite structure for $0.0 \leq z \leq 0.5$ is modeled by the initial condition

$$\mathcal{F}_{s,a}(0.5) = \frac{-\mathcal{F}_{s,d}(0.5)}{2 + \mathcal{F}_{s,a}(0.5)}, \tag{12}$$

the differential equation

$$\frac{d\mathcal{F}_{s,a}}{dz} = -2 \cdot P_{s,a} \left(\frac{\mathcal{F}_{s,a}}{\mathcal{F}_{v,a}} - C_{s,\text{int}} \right), \tag{13}$$

and the definition of the (constant) water flow rate

$$\mathcal{F}_{v,a}(z) \equiv \frac{-\mathcal{F}_{v,d}(0.5)}{2 - \mathcal{F}_{v,d}(1.0)}. \tag{14}$$

It cannot be expected that this part of the composite structure is equivalent to the corresponding pair of single loops. Indeed, the results for the present example differ substantially: integrating the descending limb numerically yields $F_{v,d}(0.5) = 10.0745, F_{v,d}(1.0) = 1.72677$, $F_{s,d}(0.5) = 13.5404, F_{s,d}(1.0) = 20.2186$. With these data the ascending structures can be integrated analytically. The results are summarized in Table 1.

Table 1. Computed results at the top of the ascending structures ($z = 0$). In the right column, "*flow rate*" means the sum of the flow rates in the single tubules and "*concentration*" the corresponding quotient of these sums.

	composite structure	pair of single tubules
water flow rate	−11.8013	−11.8013
salt flow rate	−25.8685	−18.9988
salt concentration	2.19200	1.60989

REMARK. In realistic kidney models, the populations of loops and the functions for the transmural fluxes are much more complex than in the preceding example. Using a transformation like (11), it is easy to see that the *descending* part of the composite structure is equivalent to the corresponding separate structure in these cases, too. This is also valid for continuously defined populations (cf. [2,4,11–14]).

3. A REALISTIC PROBLEM

In this section, a recent kidney model [13,14] is used as a test problem for the shunt flow technique. A population of long loops reaching various depths in the inner medulla (ranging from $z = 0.2\,\mathrm{cm}$ to $z = 0.6\,\mathrm{cm}$) is an essential part of this model. The function $n(z) = 2\exp[-12.13(z-0.2)]$ describes the fraction of loops reaching level z. A comparison of the corresponding separate and composite structures requires a discretization of this function:

$$\hat{n}(z) = 2\exp[-.1213(i-1)] \qquad \text{if } .2 + .01(i-1) < z \leq .2 + .01i, \qquad i = 1, \ldots, 40.$$

This means that a population of 40 loops is present. In [14] ascending vasa recta and interstitial capillary nodes play the role of the interstitial space. The results for these components (see Table 3 of [14]) have been taken to construct functions $C_{\cdot,\mathrm{int}}$ via interpolation. The shape of the urea concentration in the upper inner medullary NLAL motivates the use of rational interpolation [15,16]. In all other cases, polynomial interpolation has been used. The numerical integration was performed by a stiff integrator [17] for the descending structures and by a non-stiff integrator [18] for the ascending ones. The computed results are given in Table 2. Please note that at the papillary tip ($z = 0.6\,\mathrm{cm}$) only one nephron is present. Hence, the results for both cases are identical there and are not listed in Table 2.

Table 2. Computed results for the ascending structures. In the right column, "*flow rate*" means the sum of the flow rates in the single tubules and "*concentration*" the corresponding quotient of these sums.

	$z =$	composite structure	population of single tubules
salt flow rate in	.20	−2804	−2807
10^{-9} mM/min	.33	−448.6	−451.8
urea flow rate in	.20	−551.2	−512.3
10^{-9} mM/min	.33	−471.5	−467.9
salt conc. in	.20	323.3	323.8
mM/l	.33	323.5	325.7
urea conc. in	.20	63.57	59.08
mM/l	.33	339.9	337.3

4. CONCLUSION

The descending part of the composite structure is equivalent to the corresponding population of single descending limbs, whereas the results for the ascending composite structure may deviate substantially from those for the original problem. In Table 1, differences up to 36% are to be observed; however, these numbers result from a model with rather artificial parameters. For the realistic model the agreement is quite satisfactory (Table 2). The deviations are less than 7.6%. Similarly, the differences in the total transmural fluxes of both salt and urea from the upper and lower inner medullary structures are less than 12.3%. This shows that the composite structure approximation influences the interstitial concentrations only moderately. However, a general guarantee that the shunt flow technique will always give results of acceptable quality is lacking.

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