

Numerical Solution of a Kidney Model by Multiple Shooting

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ABSTRACT

The mathematical modeling of the renal counterflow system involves a two-point boundary-value problem for a system of nonlinear differential equations. In this paper the multiple shooting technique is used for the numerical solution of this problem. This method ensures highly precise and reliable computations. Special consideration is given to the treatment of the border between outer and inner medulla for various widths of the outer zone.

1. INTRODUCTION

The mathematical models of the mechanism for urine concentration in the kidney contribute towards a better understanding of the renal function. The work presented in this paper deals with a six-tube model of the medullary counterflow system. The model includes provisions for all the tubes present in the renal medulla and was suggested by Stephenson, Tewarson, and Mejia [1]. The mathematical description involves a two-point boundary-value problem for a system of nonlinear differential equations.

For the numerical solution of this problem the multiple shooting technique is used in this paper. This method is described in detail in Bulirsch, Stoer, and Deuffhard [2], Stoer and Bulirsch [3], and Keller [4]. It ensures highly precise and reliable computations. Special consideration is given to the treatment of the border between outer and inner medulla for various widths of the outer zone.

The paper is structured as follows: In Sec. 2 the mathematical model is outlined. Section 3 contains a description of the multiple shooting method for the solution of two-point boundary-value problems. In Sec. 4 the numerical results are presented.

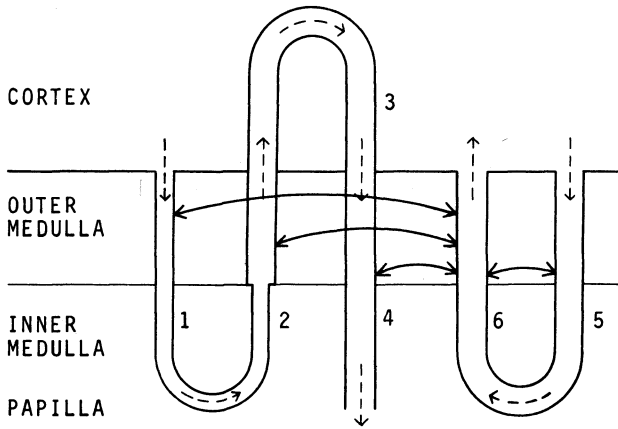


FIG. 1. The six-tube model of the medullary counterflow system with the axial flows (dashed arrows) and the transmembrane fluxes (solid arrows).

2. THE MATHEMATICAL MODEL

In the six-tube model of the medullary counterflow system (Fig. 1), fluid from the proximal tubule enters tube 1 (the descending Henle's limb—DHL). Then it flows through tube 2 (the ascending Henle's limb—AHL), tube 3 (the distal nephron—DN), and tube 4 (the collecting duct—CD) in sequence to emerge from tube 4 as final urine. Blood enters tube 5 (the descending vasa recta—DVR) and leaves from tube 6 (the ascending vasa recta—AVR). Tube 3 exchanges solutes and water with the cortical interstitium—a bath of uniform solute concentrations. All the other tubes exchange with tube 6 as shown in Fig. 1.

This model can be described by the following boundary-value problem. A physiological interpretation of the differential equations is given in [1]. The parameters are chosen according to Farahzad and Tewarson [5].

Differential equations:

$$\frac{dF_{1v}}{dx} = -J_{1v}, \quad J_{1v} = 10[(c_{61} - c_{11}) + (c_{62} - c_{12})],$$

$$\frac{dF_{2v}}{dx} = 0,$$

$$\frac{dF_{3v}}{dx} = -J_{3v}, \quad J_{3v} = (1 - c_{31}) + (0.05 - c_{32}),$$

$$\frac{dF_{4v}}{dx} = -J_{4v}, \quad J_{4v} = 10[(c_{61} - c_{41}) + (c_{62} - c_{42})],$$

$$\begin{aligned}
 \frac{dF_{5v}}{dx} &= 0, \\
 \frac{dF_{6v}}{dx} &= J_{1v} + J_{4v}, \\
 \frac{dF_{11}}{dx} &= 0, \\
 \frac{dF_{21}}{dx} &= -J_{21}, \quad J_{21} = \begin{cases} 1.8, & 0.0 \leq x < \gamma, \\ 10(c_{21} - c_{61}), & \gamma \leq x \leq 1.0 \end{cases} \\
 \frac{dF_{31}}{dx} &= -J_{31}, \quad J_{31} = \frac{0.75c_{31}}{1 + c_{31}}, \\
 \frac{dF_{41}}{dx} &= 0, \\
 \frac{dF_{51}}{dx} &= -J_{51}, \quad J_{51} = 1000(c_{51} - c_{61}), \\
 \frac{dF_{61}}{dx} &= J_{21} + J_{51}, \\
 \frac{dF_{12}}{dx} &= 0, \\
 \frac{dF_{22}}{dx} &= 0, \\
 \frac{dF_{32}}{dx} &= 0, \\
 \frac{dF_{42}}{dx} &= -J_{42}, \quad J_{42} = \begin{cases} 0.0 & 0.0 \leq x < \gamma, \\ 0.01(c_{42} - c_{62}) & \gamma \leq x \leq 1.0, \end{cases} \\
 \frac{dF_{52}}{dx} &= -J_{52}, \quad J_{52} = 1000(c_{52} - c_{62}), \\
 \frac{dF_{62}}{dx} &= J_{42} + J_{52}.
 \end{aligned} \tag{2.1.a}$$

F_{ik} , F_{io} , and c_{ik} are related by the equation

$$F_{ik} = F_{io}c_{ik} \quad (i = 1, \dots, 6; \quad k = 1, 2). \tag{2.1.b}$$

Boundary conditions:

$$\begin{aligned}
 F_{1v}(0) &= 1, & F_{5v}(0) &= 5, \\
 c_{11}(0) &= 1, & c_{51}(0) &= 1, \\
 c_{12}(0) &= 0.05, & c_{52}(0) &= 0.05, \\
 \\
 F_{1v}(1) &= -F_{2v}(1), & F_{5v}(1) &= -F_{6v}(1), \\
 c_{11}(1) &= c_{21}(1), & c_{51}(1) &= c_{61}(1), \\
 c_{12}(1) &= c_{22}(1), & c_{52}(1) &= c_{62}(1), \\
 \\
 F_{2v}(0) &= -F_{3v}(0), & F_{3v}(1) &= F_{4v}(0), \\
 c_{21}(0) &= c_{31}(0), & c_{31}(1) &= c_{41}(0), \\
 c_{22}(0) &= c_{32}(0), & c_{32}(1) &= c_{42}(0).
 \end{aligned} \tag{2.1.c}$$

List of symbols used:

- x Independent variable—distance into medulla from corticomedullary border,
 γ Border between outer and inner medulla,
 k Solutes: $k=1$ is salt; $k=2$ is urea,
 F_{iv} Axial volume flow in tube i ,
 F_{ik} Axial flow of solute k in tube i ,
 c_{ik} Concentration of solute k in tube i ,
 J_{iv} Outward transmural volume flux from tube i ,
 J_{ik} Outward transmural flux of solute k from tube i .

For tube 3 (the DN), x is measured along the tube so that $x=0$ and $x=1$ correspond to its junctions with tube 2 (AHL) and tube 4 (CD), respectively. The flows and concentrations are normalized in that $c_{ik}=1 \simeq 300$ mOsm/l and $F_{iv}=1 \simeq 34$ nl/min.

The transition from the outer to the inner medulla occurs at the junction of the thin AHL with the thick. Currently, there are two hypothesized mechanisms for urine concentration in the inner medulla, one involving active transport of salt out of the thin AHL ("active model"), the second relying on an entirely passive movement of solutes in the inner zone ("passive model"). In both cases, salt is actively transported across the wall of the thick AHL. The boundary-value problem (2.1) describes a passive model.

An analysis of the ultrastructure of a single loop of Henle in the rabbit kidney demonstrates that a thin AHL makes its transition to its thick part within about 2/1000 of the total medullary thickness (Kaissling and Kriz [6,

Fig. 28]). Similarly, investigations of the rat kidney show that these transitions occur nearly on the same level (Kriz [7, p. 513]). Therefore, the division between outer and inner medulla is fairly sharp. This coincides with direct measurements of sodium and chloride concentrations in tissue slices of the medulla. Recent electron-probe microanalysis demonstrates a marked change in concentration profiles at the boundary between outer and inner medulla (Lechene and Bonventre [8]). In order to simulate this biological fact in the model, the transmural flux of salt out of tube 2 is assumed to change abruptly at the border $x = \gamma$. This is reflected in a discontinuity in J_{21} and, similarly, in J_{42} .

3. COMPUTATION BY MULTIPLE SHOOTING

For the numerical solution of the two-point boundary-value problem (2.1) the axial flows F_{iv} and F_{ik} are computed in this paper ($i = 1, \dots, 6$; $k = 1, 2$). Thus, the concentrations c_{ik} on the right-hand sides of the differential equations must be replaced by the quotients F_{ik}/F_{iv} according to (2.1.b). The trivial differential equations together with the appropriate boundary conditions immediately yield the following identities:

$$F_{5v} \equiv 5, \quad F_{11} \equiv 1, \quad F_{12} \equiv 0.05, \quad F_{22} \equiv -0.05, \quad F_{32} \equiv 0.05.$$

In this manner, the number of differential equations is reduced to 13. Denoting the vector

$$(F_{1v}, F_{2v}, F_{3v}, F_{4v}, F_{6v}, F_{21}, F_{31}, F_{41}, F_{51}, F_{61}, F_{42}, F_{52}, F_{62})^T$$

by y , the resulting two-point boundary-value problem may be written in the following compact form ($N = 13$):

$$y' = g(x, y), \tag{3.1.a}$$

$$A \cdot y(0) + B \cdot y(1) = r. \tag{3.1.b}$$

Here $g(x, y)$ is vector-valued with components $g_k(x, y)$ ($k = 1, 2, \dots, N$), which are functions of the $N + 1$ variables (x, y) . A and B are constant square matrices of order N , and r is a vector. They are chosen so that (3.1.b) is equivalent to the boundary conditions (2.1.c).

The reduction of the system (2.1) to a system of 13 unknowns makes use of the trivial differential equations. If the number of vanishing right-hand sides in (2.1.a) is reduced (e.g. in order to investigate salt recycling in DHL in the model), the size N of the system (3.1) increases. A simple change of the input parameters of the multiple-shooting routine allows the treatment of such a modification.

The multiple-shooting method for the solution of a two-point boundary-value problem of the form (3.1) is described in [3], [4], and realized in the code [2]. It has been extensively tested in actual computations (see e.g. Diekhoff et al. [9]). Here the interval $0 \leq x \leq 1$ is suitably subdivided:

$$0 = x_1 < x_2 < \cdots < x_{M-1} < x_M = 1 \quad (M \text{ nodes}). \quad (3.2)$$

Let $y(x; x_j, s_j)$ ($j = 1, \dots, M-1$) denote the solution of the initial-value problem

$$y' = g(x, y), \quad y(x_j) = s_j, \quad x_j \leq x \leq x_{j+1}. \quad (3.3)$$

Then the N -dimensional vectors s_j have to be determined so that the following conditions hold:

continuity conditions (for $M > 2$):

$$G_j(s_j, s_{j+1}) := y(x_{j+1}; x_j, s_j) - s_{j+1} = 0, \quad j = 1, \dots, M-2, \quad (3.4.a)$$

boundary conditions:

$$G_{M-1}(s_1, s_{M-1}) := A \cdot s_1 + B \cdot y(x_M; x_{M-1}, s_{M-1}) - r = 0. \quad (3.4.b)$$

The conditions (3.4) define a system of nonlinear equations

$$G(s) := \begin{bmatrix} G_1(s_1, s_2) \\ \vdots \\ G_{M-2}(s_{M-2}, s_{M-1}) \\ G_{M-1}(s_1, s_{M-1}) \end{bmatrix} = 0 \quad \text{with} \quad s := \begin{bmatrix} s_1 \\ \vdots \\ s_{M-1} \end{bmatrix}. \quad (3.5)$$

This system is solved numerically by the modified Newton method:

$$s^{k+1} = s^k + \lambda_k \Delta s^k, \quad 0 < \lambda_k \leq 1, \quad (3.6.a)$$

$$\Delta s^k = -DG(s^k)^{-1} G(s^k) \quad (3.6.b)$$

($DG(s)$ denotes the Jacobian matrix).

A strategy for choosing the λ_k has been developed and thoroughly tested by Deuffhard [10]. In order to start the process (3.6) the following initial data must be available:

$$s_j^0 = \begin{bmatrix} s_{1j}^0 \\ \vdots \\ s_{Nj}^0 \end{bmatrix}, \quad j = 1, \dots, M-1. \quad (3.7)$$

With the abbreviations

$$H_j := \frac{\partial y(x_{j+1}; x_j, s_j)}{\partial s_j}, \quad j = 1, \dots, M-1,$$

(3.6.b) can be written in more detail (the k -index is omitted):

$$\begin{bmatrix} H_1 & -I & & & & \\ & H_2 & -I & & & \\ & & \ddots & \ddots & & \\ & & & \ddots & \ddots & \\ & 0 & & & H_{M-2} & -I \\ A & & & & & BH_{M-1} \end{bmatrix} \begin{bmatrix} \Delta s_1 \\ \Delta s_2 \\ \vdots \\ \Delta s_{M-2} \\ \Delta s_{M-1} \end{bmatrix} = - \begin{bmatrix} G_1 \\ G_2 \\ \vdots \\ G_{M-2} \\ G_{M-1} \end{bmatrix}. \tag{3.6.b'}$$

The Δs_j allow a recursive determination by

$$\begin{aligned} \Delta s_1 &= E^{-1}w, \\ \Delta s_j &= H_{j-1}\Delta s_{j-1} + G_{j-1}, \quad j = 2, \dots, M-1, \end{aligned}$$

with

$$\begin{aligned} E &:= A + BH_{M-1}H_{M-2}\dots H_1, \\ w &:= -(G_{M-1} + BH_{M-1}G_{M-2} + \dots + BH_{M-1}\dots H_2G_1). \end{aligned}$$

At the solution point, the algorithm computes a special norm of the matrix E , called norm (E) (cf. [2]). norm (E) represents the sensitivity of the problem relative to the variation of s_1 .

CONSISTENT TREATMENT OF THE DISCONTINUITY

For the numerical solution of the initial-value problems (3.3), two integration routines were used:

- DIFSY1: Bulirsch-Gragg-Stoer extrapolation method (Bulirsch and Stoer [11]) with the stepsize control described in Hussels [12].
- RKF7: Runge-Kutta-Fehlberg method of seventh order (Fehlberg [13]).

Both routines control the integration stepsizes automatically according to the prescribed tolerance.¹ To work well, they require a high order of differentiability on the right-hand side of (3.1.a). $g(x,y)$, however, is of the form [cf. (2.1.a)]

$$g(x,y) = \begin{cases} g_1(x,y), & 0.0 \leq x < \gamma, \\ g_2(x,y), & \gamma \leq x \leq 1.0. \end{cases}$$

¹This control of the stepsizes is based on built-in estimators of the truncation error.

Because of this discontinuity $x_k = \gamma$ was chosen as one of the nodes in (3.2). For the numerical solution of the initial-value problem (3.3) in the interval $x_{k-1} \leq x \leq x_k$, the continuous extension of $g_1(x, y)$ to the interval $0 \leq x \leq \gamma$ has to be used. Then on both sides of $x_k = \gamma$ the differential equation is correctly computed. The continuous junction of both parts of the solution curve at $x_k = \gamma$ is guaranteed by (3.4.a).

STORAGE REQUIREMENTS

The storage requirements of the multiple-shooting algorithm are very low. Most of the storage is needed by the $M-1$ $N \times N$ matrices H_j . $M \approx 10$ is sufficient for nearly all purposes. In contrast to finite-difference methods it is not necessary to increase M if higher accuracy is required. In the actual computation of the kidney model $M=12$ and the following nodes in (3.2) were chosen:

$$0.0, 0.1, 0.2, 0.3, 0.4, 0.45, \\ 0.5, 0.6, 0.7, 0.8, 0.9, 1.0.$$

The tolerance for the integration routines was prescribed as $1_{10}-15$. In this case, the stepsizes selected by the RKF7 algorithm varied between $0.55_{10}-4$ and $0.42_{10}-3$. It seems impossible to achieve the same accuracy by finite-difference methods. Indeed, recalling that RKF7 is of order 7, a finite-difference approximation of order 2 would need a net spacing

$$h \approx (1_{10}-4)^{7/2} = 1 \cdot 10^{-14}$$

in order to yield comparable results. Thus the most economical sparse-matrix method (cf. Table 1 in [5]) would require a storage of approximately $(2 \times 1_{10}14)^2 = 4_{10}28$.

COMMENT

It is shown in [3] that quasilinearization (cf. Bellman and Kalaba [14]) can be obtained from multiple shooting by a limiting process $M \rightarrow \infty$. This method was used by Foster, Jacquez, and Daniels [15] for the computation of a three-tube model of the renal medulla (central-core model).

4. COMPUTATIONAL RESULTS

All computations were performed in FORTRAN double precision (96-bit mantissa) on the CDC Cyber 175 of the Leibniz-Rechenzentrum der Bayerischen Akademie der Wissenschaften. The initial data (3.7) were obtained by means of a homotopy method (or continuation method). The use of this technique may be motivated by theoretical investigations (for

TABLE 1

	Results of multiple shooting for $\gamma =$		
	0.4	0.45	0.5
$F_{1v}(1)^a$	0.5674811 ₁₀ +00	0.4178138 ₁₀ +00	0.3642430 ₁₀ +00
$c_{11}(1)$	0.1762173 ₁₀ +01	0.2393411 ₁₀ +01	0.2745420 ₁₀ +01
$c_{12}(1)$	0.8810866 ₁₀ -01	0.1196705 ₁₀ +00	0.1372710 ₁₀ +00
$F_{4v}(1)^a$	0.6176376 ₁₀ -01	0.1509508 ₁₀ -01	0.1280209 ₁₀ -01
$c_{41}(1)$	0.1107612 ₁₀ +01	0.2256045 ₁₀ -01	0.3000758 ₁₀ -03
$c_{42}(1)$	0.7425895 ₁₀ +00	0.2491849 ₁₀ +01	0.2882899 ₁₀ +01
$F_{6v}(0)^a$	-0.5542662 ₁₀ +01	-0.5615708 ₁₀ +01	-0.5670587 ₁₀ +01
$c_{61}(0)$	0.1025019 ₁₀ +01	0.1044662 ₁₀ +01	0.1049184 ₁₀ +01
$c_{62}(0)$	0.4585070 ₁₀ -01	0.4672346 ₁₀ -01	0.4639606 ₁₀ -01

^aSince the axial flows form a countercurrent system, any flow from the corticomedullary border to the papilla is positive, whereas the opposite flow direction must be negative in the model.

details see [16]). The modified Newton iteration (3.6) of the multiple-shooting algorithm was terminated when the solution had achieved a relative precision² of $1_{10}-12$. An important check on the final results is the conservation of mass over the medulla. In these computations the mass inflow agreed with the mass outflow to a relative accuracy of at least $1_{10}-20$ for both water and the two solutes.

As in Sec. 2, γ may denote the border between the outer and inner medulla. In Table 1 (truncated) results for various values of γ ($\gamma=0.4, 0.45,$ and 0.5) are given. For these values of γ , norm (E) (cf. Sec. 3) was computed as $3_{10}13, 1_{10}13,$ and $4_{10}12$. This indicates how extremely sensitive the problem is. Therefore, a careful computation in double precision is necessary in order to get reliable results for this challenging boundary-value problem. Figures 2 and 3 show the computed total solute concentrations in tubes 1-4 for $\gamma=0.5$.

COMMENT

In comparison with measured salt concentrations in the final urine, the computed values of $c_{41}(1)$ for $\gamma=0.45$ or 0.5 are too low. $c_{41}(1)\approx 1$ would be closer to reality. The reason for this discrepancy is as follows: In order to concentrate the urine in the inner medulla with the passive mechanism, it was necessary in [1] and [5] to maximize the urea load entering the CD. As

²When the algorithm had reached this precision it performed an additional Newton step. So, due to the quadratic convergence, the continuity and boundary conditions are satisfied with an accuracy of about $1_{10}-30$ in these computations.

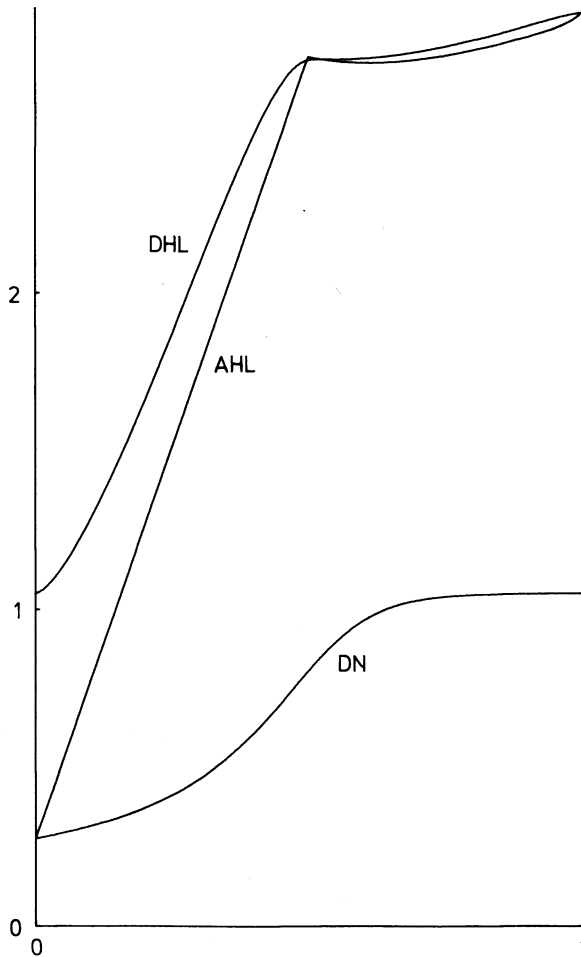


FIG. 2. Total concentrations in DHL ($c_{11} + c_{12}$), AHL ($c_{21} + c_{22}$), and DN ($c_{31} + c_{32}$) for $\gamma = 0.5$.

a consequence, the salt concentration at the end of the DN had to be assumed very low to achieve the biologically correct total concentration in the final urine. Therefore, these articles and the present paper use somewhat artificial parameters in the DN.

To compare the results of [1] and [5] with those presented here it is necessary to know that in these papers a somewhat different problem is solved. The computed values of these articles belong to a model with a linear transition zone between the outer and inner medulla such that, for

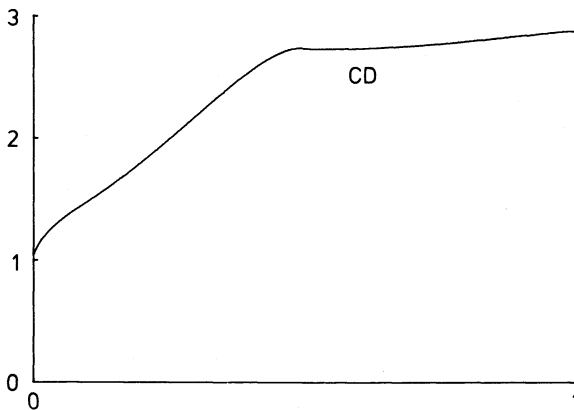


FIG. 3. Total concentration in CD ($c_{41} + c_{42}$) for $\gamma = 0.5$.

example,

$$J_{21}(x) = \begin{cases} 1.8, & 0.0 \leq x < 0.4, \\ 1.8 + m \cdot (x - 0.4), & 0.4 \leq x \leq 0.5, \\ 10(c_{21} - c_{61}), & 0.5 < x \leq 1.0, \end{cases}$$

where $m = 10 \{ 10 [c_{21}(x) - c_{61}(x)] - 1.8 \}$. A computation of this problem by the multiple-shooting algorithm yielded the following results:

$$F_{1v}(1) = 0.4283387_{10} + 00,$$

$$c_{11}(1) = 0.2334601_{10} + 01,$$

$$c_{12}(1) = 0.1167301_{10} + 00,$$

$$F_{4v}(1) = 0.1580020_{10} - 01,$$

$$c_{41}(1) = 0.4669535_{10} - 01,$$

$$c_{42}(1) = 0.2406077_{10} + 01,$$

$$F_{6v}(0) = -0.5605542_{10} + 01,$$

$$c_{61}(0) = 0.1043765_{10} + 01,$$

$$c_{62}(0) = 0.4673652_{10} - 01.$$

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