CHAPTER 43

Solution of Differential-Algebraic Equations for Renal Acid-Base Balance

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Abstract. Domain decomposition with parameter continuation is used to solve a system of differential-algebraic equations that includes convection-reaction-diffusion equations that describe acid-base transport in the mammalian kidney. A sparse decomposition with fourth-order accurate space discretization is described, and a sample problem that analyzes parameter sensitivity is solved. Performance parameters for a solution algorithm are given.

1. Introduction. The process of urine formation by mammals has been studied by renal physiologists (see [11] and [3] for references to the physiological literature) and mathematical modelers for some time. The differential equations that describe the concentration of solutes by the kidney for excretion in the urine have been solved using both domain decomposition [8] and parameter continuation [9]. Previously, several models, for example [12], [16] and [4], had used the structure of the kidney to advantage and had exploited the connectivity of the renal tubules to reduce the size of the system of discretized equations that describe a steady state. Recently, continuation of solutions as a function of physiological parameters has been used both to study the transition of solutions from one steady state to another, and to reduce the labor required to obtain a solution for a desired set of transport parameters [9], [6]. In addition, charged species have been considered in [13] and [14] to study the concentrating mechanism, and in [7] to investigate acid-base transport in a perfused tubule [2].

We describe a mixed system of differential and algebraic equations for acid-base balance in the mammalian kidney that includes both reactive and non-reactive species, and we show a method of solution. Fig. 1 shows schematically a model with two nephron populations. The first consists of long nephrons that originate near the cortico-medullary border and extend into the inner medulla to the papilla. The second population consists of short nephrons that originate higher in the cortical labyrinth and extend to the junction of the inner and outer medulla. In addition to axial flow

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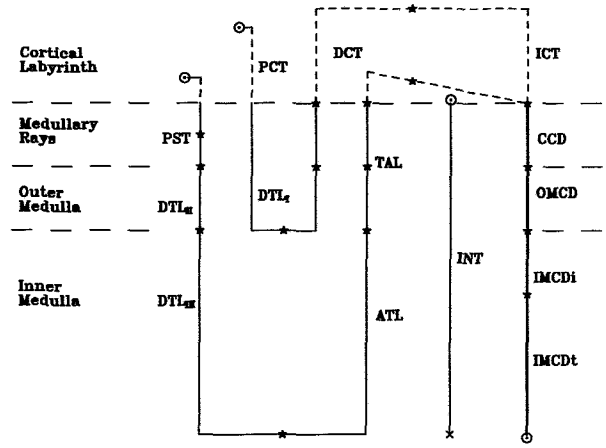

Fig. 1. Schematic diagram showing two nephron populations of the mammalian kidney. Boundary data are prescribed at ⊙; matching boundary conditions at ⋆; the closed end of the interstitium (*INT*) at the papilla is marked by a ×. *PCT* = proximal convoluted tubule; *PST* = proximal straight tubule; *DTL* = descending limb of Henle's loop; *ATL* = ascending thin limb; *TAL* = thick ascending limb; *DCT* = distal convoluted tubule; *ICT* = initial collecting tubule; *CCD* = cortical collecting duct; *OMCD* = outer medullary collecting duct; $IMCD_i$ and $IMCD_t$ are initial and terminal segments of the inner medullary collecting duct, respectively. Nephron segments in the cortical labyrinth that are not modeled are shown as – – lines.

in the tubular segments, transmembrane flux between structures takes place via an interstitium that is represented in Fig. 1 as a tube closed at the papilla and open at the cortico-medullary border. Differential equations describe conservation of solute species and water as well as hydrostatic pressure along the nephrons and intersitium. Algebraic equations describe equilibrium reactions and electrical potential.

It is desirable to solve the differential and algebraic equations in their semi-explicit form [1] for several reasons. First of all, we wish to retain the physiological significance of the variables and parameters in order to facilitate the interpretation of solutions. Secondly, it is advantageous to consider mass balance of certain chemical constituents (for example, total acid and total phosphate) rather than individual chemical species such as HPO_4^{2-} and $H_2PO_4^-$. A third consideration is the treatment of stiffness by separating fast and slow chemical reactions. An important consideration in the formulation of the model for solution is the need to exploit the connectivity of the

renal structures to reduce the computational labor and make the problem tractable.

2. Model. Equations that describe solute and fluid conservation and equations of motion in each segment of the kidney are

$$\begin{aligned} \partial_t(A\mathbf{C}) + \partial_x\mathbf{F} &= -\mathbf{J} + A\mathbf{S}, \\ \partial_t A + \partial_x F_v &= -J_v, \\ \partial_x P &= -R_v F_v, \end{aligned} \tag{2.1}$$

where by the Nernst-Planck equation mass flow

$$\mathbf{F} = F_v\mathbf{C} - A(\mathbf{D}'\partial_x\mathbf{C} + \mathbf{u}'\mathbf{C}\partial_x\psi);$$

x is distance along the cortico-papillary axis; t is time; A is the cross-sectional area of the segment; $\mathbf{C}$ is a vector of concentrations; F_v is volume flow; $\mathbf{D}$ is a vector of diffusion coefficients; ψ is the electrical potential; $\mathbf{J}$ is solute flux (positive defined to be out of the lumen), and $\mathbf{S}$ is the production or consumption of species due to chemical reaction. The k^{th} element of the vector $\mathbf{u}$ of species mobilities is related to the diffusivity by $u_k = D_k z_k \mathcal{F}/RT$, where z_k is the valence of the k^{th} species; $\mathcal{F}$ is Faraday's constant; R is the gas constant, and T is the absolute temperature. J_v is volume flux out of the lumen. P is hydrostatic pressure, and R_v is resistance to flow.

Algebraic equations that determine buffer balance and electroneutrality are

$$\begin{aligned} pH &= pK_B + log(C_{B^-}/C_{HB}), \\ < \mathbf{z}, \mathbf{C} > &= - < \mathbf{z}, \mathbf{J} - A\mathbf{S} > = 0, \end{aligned} \tag{2.2}$$

where $pH = -logC_{H^+}$; $pK_B = -logK_B$; the dissociation constant K_B is the proton concentration at half neutralization; subscripts B^- and HB designate the base and protonated forms of buffer pair B, respectively. $\mathbf{z}$ is the vector of valences for all species.

Transmural water flux is given by

$$J_v = -2\pi\rho P_f V_w \sum_k \sigma_k \Delta C_k, \tag{2.3}$$

where ρ is the radius of the tubule; P_f is the water permeability; V_w is the partial molar volume of water; σ_k is the reflection coefficient of the k^{th} species; and $\Delta C_k = C_k - C_{*k}$, where C_k and C_{*k} are the concentration of the k^{th} species in the lumen and interstitium, respectively.

Transmural solute flux is given by

$$\begin{aligned} J_k &= 2\pi\rho P_k \Delta C_k + (1-\sigma_k)\underline{C_k}J_v + J_k^a \quad \text{if } z_k = 0, \\ J_k &= 2\pi\rho P_k z_k q \left[\frac{C_k - C_{*k}e^{-z_k q}}{1 - e^{-z_k q}}\right] + (1-\sigma_k)\underline{C_k}J_v + J_k^a \quad \text{if } z_k \neq 0, \end{aligned} \tag{2.4}$$

where P_k is the solute permeability of the k^{th} species; $\underline{C_k} = (C_k + C_{*k})/2$, and $q = \mathcal{F}\Delta\psi/RT$, where $\Delta\psi = \psi - \psi_*$ with ψ and ψ_* the electrical potential in the lumen and interstitium, respectively. Active transport of the k^{th} species is given by

$$\begin{aligned} J_k^a &= \frac{V_{mk}C_k}{K_{mk}+C_k} \quad \text{if } k \neq H^+, \\ &= \frac{V_{mk}K_{mk}}{K_{mk}+[H^+]} \quad \text{if } k = H^+, \end{aligned} \tag{2.5}$$

where V_{mk} is the maximum rate of active transport, and K_{mk} is the Michaelis constant.

Chemical sources for carbonic acid and carbon dioxide are given by

$$S_{H_2CO_3} = k_1 CO_2 - k_{-1} H_2CO_3 = -S_{CO_2}, \tag{2.6}$$

where k_1 is the hydration rate constant of CO_2, and k_{-1} is the dehydration rate constant of H_2CO_3.

Water and mass conservation require that

$$\begin{aligned} J_{*v}(x) &= -\sum_i J_{iv}(x), \\ J_{*k}(x) &= -\sum_i J_{ik}(x), \end{aligned} \tag{2.7}$$

where subscript $*$ represents the medullary interstitium, and summation is over all tube segments i that extend to medullary depth x.

The interstitum is treated as a tube open at the border of the cortical labyrinth and the medullary rays and closed at the papilla. Thus equations (2.1) and (2.2) hold, and boundary conditions for $t \geq 0$ are

$$\begin{aligned} A_*(L)\partial_t \mathbf{C}_*(L,t) &= \mathbf{C}_*(L,t)J_{*v}(L,t) - \mathbf{J}_*(L,t) + A_*\mathbf{S}_*(L,t), \\ F_{*v}(L,t) &= \mathbf{F}_*(L,t) = 0, \\ P_*(0,t) &= P_*^c, \end{aligned} \tag{2.8}$$

where L is the depth of the medulla. Boundary conditions for each nephron population are given by

$$\mathbf{C}_1(0,t) = \mathbf{C}_1^0, \quad F_{1v}(0,t) = F_{1v}^0, \tag{2.9}$$

$$P_I(L,t) = P_b, \tag{2.10}$$

where subscripts 1 and I refer to the first and last tube segment of each nephron population, respectively, and P_b is the bladder pressure. Intermediate boundary data are obtained by matching the value entering a tube segment to that leaving the previous segment as shown in Fig. 1.

Initial conditions at each axial position x and time $t = 0$ in the lumen and interstitium are given by

$$\mathbf{C}(x,0) = \mathbf{C}^0, \quad F_v(x,0) = F_v^0, \quad P(x,0) = P^0. \tag{2.11}$$

Table 1
Tubule Parameters

Segment	Length (mm)	Radius (μm)	P_f ($\mu m/s$)
$PST2$	1.0	10	3000
$PST3$	0.7	10	3000
DTL_{II}	1.5	9	2430
DTL_{III}	6.0	8	2430–100
Buffer			pK
HCO_3^-/CO_2			6.08
H_2CO_3/HCO_3^-			3.57
NH_4^+/NH_3			9.03
$H_2PO_4^-/HPO_4^{2-}$			6.80
Reaction Rate (s^{-1})			
carbonic anhydrase		k_{-1}	k_1
present		4.9×10^4	1.459×10^2
absent		4.9×10^1	1.459×10^{-1}

3. Solution Algorithm. Given a set of initial values (2.11) and boundary values (2.9)–(2.10) proceed to solve equations (2.1) and (2.2) with transmural fluxes (2.3)–(2.5) and (2.7) and sources (2.6) as follows:

A. Use the continuation program CONKUB [5] to obtain a steady-state solution as a function of a model parameter. CONKUB will call a subroutine supplied by the user and named FCTN.

B. FCTN uses the interstitial, boundary and initial data to evaluate equations (2.1) for each nephron segment as follows:
   1. Solve equations (2.2) at the current segment and axial position, j.
   2. Use Hermite interpolation and solve (2.2) to obtain $\mathbf{C}(x_{j+1/2}, t)$.
   3. Use Simpson's rule to solve (2.1) at $j+1$.
   4. Iterate steps 1–3 to convergence.
   5. Increment j and repeat steps 1–4 until the current tube segment is completed.
   6. Proceed to the next segment and repeat steps 1–5 until all nephron segments are completed.

C. Solve equations (2.1) and (2.2) for the interstitial unknowns and satisfy boundary condition (2.10).

D. For solution of the time-dependent problem, use a centered trapezoidal approximation for the time derivatives, and iterate steps B–C to convergence.

Some comments about the solution algorithm are in order. We use CONKUB for several reasons. First of all, it provides an interactive means of solving the discretized differential equations with continuation on one or more parameters of the model. Secondly, continuation is performed using a subsystem of equations (2.1) and (2.2), namely, the interstitial equations in this model. Thus, we reduce the computer time required to obtain a steady-state solution for a target set of model parameters. A

Table 2
Transport Coefficients

Species	P_k $cm/s \times 10^5$		V_{mk} $pmol/mm/min$		K_{mk} mM
	PST	*DTL*	*PST*	*DTL*	*PST*
HCO_3^-	0.1	4, 9–15	0	0	
NH_4^+	4.5	50,5–0	0	0	
NH_3	1600	2000	0	0	
$H_2PO_4^-$	0.1	42.5	0	0	
HPO_4^{2-}	0.1	42.5	0,6	0	1×10^{-3}
H^+	100	100	-42,-10	0	1×10^{-5}
H_2CO_3	100	10	0	0	
Na^+	2.6	26,29–75	108,46	0	50
K^+	1.4	85	-20,-2	0	50
Cl^-	7.3	11,25–41	54,23	0	50
$Urea$	1.5	3,17–48	0	0	
CO_2	10^4	10^4	0	0	

similar solution approach that uses continuation techniques has been suggested in [10] for a class of algebraically incomplete systems. In addition, FCTN is used to solve both the steady-state and time dependent problems by placing a coefficient, which is set to either 0 or 1, before the approximation to the time derivative.

Simpson's rule, as opposed to an adaptive, variable-step method, is used to approximate the space derivatives. This provides an $O(\Delta x^4)$ rate of convergence and permits one to use a priori information about the transmembrane flux to distribute the mesh nodes. We thus obtain high-order convergence with a variable selected grid, and avoid the need to recompute the interstitial variables as the mesh size is changed [15]. This makes it is feasible to solve the tube equations as a sequence of initial value problems and the others as a boundary value problem.

Equations (2.2) are solved using a quasi-Newton method (ROOTS). Once the inverse of a Jacobian matrix is available, ROOTS continues to use it as long as the sup norm of the residual is reduced by a specified amount. If this criterion is not met, a rank-1 update is performed. If the criterion is still not satisfied, a secant approximation [9] may be performed, or the Jacobian is computed.

4. Example. Consider a model of a single long nephron population with parameters derived from in vitro rat data. Tubule parameters are shown in Table 1, and transport coefficients are shown in Table 2. All reflection coefficients are taken equal to one except in *DTL*, where $\sigma_{Na} = 0.83$ and $\sigma_K = 0.81$. Where two values separated by commas appear in a table, they apply to the first and second segment of that tubule, respectively. Where a range of values is shown, a linear profile from the proximal to the distal terminus of the segment is used for the parameter. Boundary and initial data are shown in Table 3 for the proximal straight tubule and for the

Table 3
Boundary and Initial Data

Species	Concentration (mM)		
	$PST2$	*Interstitium*	
		Cortex	Papilla
$NaCl$	136.6	113.0	541.0
$NaHCO_3$	8.0	25.0	25.0
NH_4Cl	0.4	0.2	10.0
K_2HPO_4	2.5	2.5	2.5
$Urea$	9.0	5.0	300.0
CO_2	1.2	1.2	1.2
$mOsm$	304.6	289.1	1470.9
pH	6.9	7.4	7.4
F_v^0 (nl/min)	20.0	– –	0.0
ψ (mV)	0.0	0.0	-5.0
P^0 (atm)	0.0	0.0	0.0

intersititium.

The object of the example is to study the sensitivity of the model to the phosphate permeability of DTL_{III} for a fixed interstitial profile. The steady-state concentration of total phosphate is shown in Fig. 2 for two values of the permeability. At a permeability of 42.5×10^{-5} cm/s and higher, the phosphate concentration in the lumen essentially equilibrates with the interstitium, while for a permeability of 42×10^{-5} cm/s the phosphate concentration increases rapidly in DTL_{III} to 10 mM, which would precipitate in the lumen.

Table 4 shows performance parameters for the model. The convergence criteria ϵ_1 and ϵ_2 were chosen to reduce the residual to machine precision on a Convex 240 in single precision (64 bit word). The program, written in FORTRAN and optimized at level O1 (including vectorization), has an execution time of 0.015 seconds per discretization interval, for a total execution time of 6.3 seconds. Subscripts 1 and 2 in the table represent parameters associated with the solution of equations (2.1) and (2.2), respectively. For example, ϵ_1 is the criterion used in step B.3 of the algorithm, ϵ_2 is used in steps B.1 and B.2. $\mathcal{I}$ is the number of iterations required for convergence. h is a factor used to compute difference quotients to obtain the elements of a Jacobian matrix. For example, given matrix G and variable γ

$$\frac{dG}{d\gamma} = \frac{G(\gamma + h \times \gamma + h^n) - G(\gamma)}{h \times \gamma + h^n},$$

where ROOTS uses $n = 4$.

5. Conclusions. We have shown the formulation and method of solution of differential and algebraic equations that describe a convection-reaction-diffusion system for renal acid-base balance. The algorithm solves a series of initial value problems

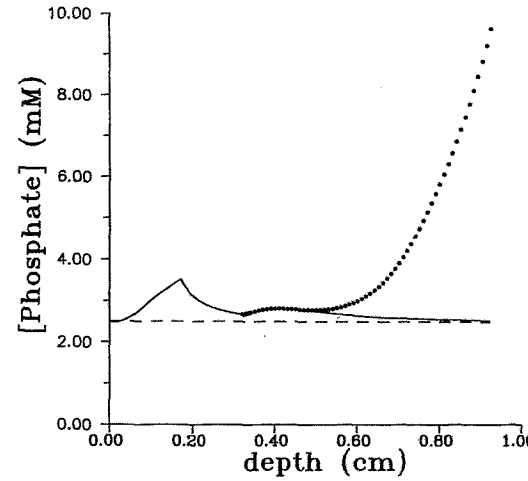

Fig. 2. Concentration of total phosphate versus medullary depth for two values of the phosphate permeability of DTL_{III}. Solid line shows the solution for a permeability of 42.5×10^{-5} cm/s; • shows the solution for 42×10^{-5} cm/s, and – – shows the concentration in the intersitium.

Table 4
Performance Parameters

ϵ_1	h_1	min Δx	min $\mathcal{I}_1$	min $\mathcal{I}_2$
10^{-19}	10^{-4}	10^{-5}	2	0
ϵ_2	h_2	max Δx	max $\mathcal{I}_1$	max $\mathcal{I}_2$
10^{-20}	10^{-5}	10^{-2}	6	6

and a boundary value problem, both with nonlinear algebraic constraints. As the number of nephron populations considered is increased, the algorithm can be readily parallelized.

The sample problem shows the sensitivity of the model to a parameter that requires measurement in a perfused tubule experiment [2]. The model of the entire kidney will make it possible to formulate and test various hypotheses about urine formation, suggest laboratory experiments to obtain the necessary parameters, and help integrate experimental measurements into a theory of systemic acid-base balance.

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