An optimization study of a mathematical model of the urine concentrating mechanism of the rat kidney

Milagros Loreto
Dept. of Computer Science and Mathematics, Florida Memorial University, Miami G., FL, USA
and
Anita Layton
Department of Mathematics, Duke University, Durham, NC, USA

1 Introduction

In the present study, we applied and optimization technique to the urine concentrating mechanism (UCM) model of the rat renal medulla [2]. We considered three measures of UCM effectiveness:

1. The urine-to-plasma osmolality $(U/P)_\rho$ ratio that maintains a urine flow rate within a plausible physiological range.
2. The ratio of (U/P) to TAT (total active transport).
3. Free water absorption rate (FWA).

Using the parameter values identified by the optimization procedure, model effectiveness is significantly improved above base-case, with the corresponding urine flow rate and the concentrations of NaCL and urea, all within or near the reported experimental ranges.

2 Mathematical Model

The rat renal medulla model used in this work (Figure 1) is based on the central core (CC) formulation [5] and incorporates a hypothesis for the inner medulla (IM) UCM by Layton *et al.* [2].

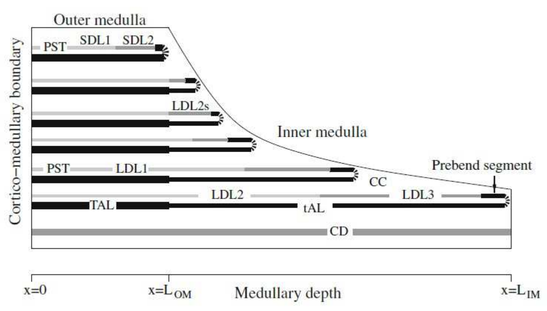

Figure 1: Schematic diagram of central core model with six loops of Henle and composite collecting duct. PST, proximal straight tubule, terminates at the outer-inner stripe boundary. SDL2, terminal water-impermeable segment of a SDL. LDL2$_s$, the upper 40% of the IM portion of a LDL that reaches beyond the first millimeter of the IM; LDL3, the remaining 60% which corresponds to the aquaporin-1-null segment of the LDL; the first segment of a LDL that turns within the first millimeter of the IM.

Model assumptions:

1. The vasculature, interstitial fluid and interstitial cells are merged into a single compartment, the Central Core (CC).

2. The Descending Limb (DL), Ascending Limb (AL), Collecting Duct (CD) and Central Core (CC) are represented by rigid tubules index by $i = 1, 2, 3$ and 4, these are oriented along the cortico-medullary axis, which extends from $x = 0$ at the cortico medullary boundary to $x = L$.

3. The DL, AL and CD exchange water and solute with the CC.

4. It is assumed that 38,000 loops of Henle and 7,300 CDs extend into the medulla .

5. The model is formulated for three solutes: NaCl, urea and non-reabsorbable solute (NR) (only represented at CD) denoted by $k = 1, 2, 3$.

6. Loops of Henle are of different lengths and turn back at different levels along the medulla. This configuration can be represented by means of continuously distributed model loops.

Model equations:

The model equations are based on conservation of solute and water in the renal medulla.

Water Conservation in a descending or ascending limb:

$$\frac{\partial}{\partial x} F_{iV}(x, y, t) = J_{iV}(x, y, t)$$

Solute Conservation in a descending or ascending limb:

$$\frac{\partial}{\partial t} C_{ik}(x, y, t) = \frac{1}{A_i}(-F_{iV}(x, y, t)\frac{\partial}{\partial x} C_{ik}(x, y, t) + J_{ik}(x, y, t) - C_{ik}(x, y, t) J_{iV}(x, y, t)$$

The water and solute conservation equations for CD and CC are obtained by omitting the argument y and letting $0 \le x \le L$. A derivation of the equations can be found in [3] and the complete model parameters can be found in [4].

Notation: $F_{iV}(x, y, t)$ represents water flow rate at time t in a descending or ascending limb of a loop of Henle reaching to level y; $J_{iV}(x, y, t)$: transmural water line flux; $C_{ik}(x, y, t)$: concentration of solute k; $A_i(x, y)$: the cross-sectional area of the limb; $J_{ik}(x, y, t)$: transmural line flux of solute k.

3 Optimization Problems

Let us consider the nonlinear optimization problem:

$$\begin{array}{ll} \max & E(z) \\ \text{s.t.} & z_l \le z \le z_u \end{array} \quad (1)$$

Where E is equal to $E_{(U/P)_\rho}$ or $E_{(U/P)/TAT}$ or E_{FWA}.

3.1 Effectiveness functions

(1) Urine-to-plasma osmolality ratio, $(U/P)_\rho$:

$$E_{(U/P)_\rho}(z) = \begin{cases} (U/P)(z) - \rho(F_{3v}(L; z) - F^E_{3v})^2 & \text{if } F_{3v}(L; z) < F^E_{3v} \\ (U/P)(z) - \frac{\rho}{3}(F_{3v}(L; z) - F^E_{3v})^2 & \text{otherwise} \end{cases}$$

Where $F_{3v}(L; z)$ is the model urine flow, F^E_{3v} is an experimental value of the urine flow, ρ is the penalty scaling parameter for the urine flow. The (U/P) ratio is given by:

$$(U/P)(z) = \frac{\sum_{k=1}^{3} C_{3k}(L; z)}{\sum_{k=1}^{3} C_{3k}(0)}$$

(2) Ratio of $(U/P)_\rho$ to total active transport(TAT), $(U/P)/TAT$: We take into account the active transport of NaCl.

$$TAT(z) = \int_0^L (J^A_1(x; z) + J^A_2(x; z) + J^A_3(x; z))dx$$

Where $J^A_i(x; z)$ for $i = 1, 2$ denotes the aggregate active transport from distributed tubules i at level x, given parameter values z. With this notations, model efficiency E is given by:

$$E_{(U/P)/TAT}(z) = \frac{(U/P)_\rho(z)}{TAT(z)}$$

(3) Free-water absorption rate, FWA: FWA is the hypothetical volume of plasma, per unit time, that can be considered completely cleared of solute by the production of urine that has a higher osmolality than blood plasma.

$$E_{FWA}(z) = F_{3v}(L; z)((U/P)_\rho(z) - 1)$$

3.2 Optimization algorithm

To solve the optimization problem (1), we use a version of the spectral projected gradient (SPG) by Birgin *et al.* combined with the stepwise Newton method by Layton [1] to evaluate the UCM effectiveness function E. The SPG algorithm needs the function E and its gradient denoted as g, which is approximated using finite differences. Our integration of the direct problem and SPG can be described in two steps:

***SPG* Algorithm:**

Given the current vector of parameters z at the iteration q, P(z) is the projection of z on the region of experimental ranges (z_l, z_u), α_q is the spectral step, μ is the momentum term and $m_0 = 0$.

- Step 1. Compute the search direction:

$$m_q = \alpha_q g_q + \mu m_{q-1}$$
$$d_q = P(z_q + m_q) - z_q$$

- 1.1 Set $\tau = 1$, $\eta_q = \frac{\eta_0}{q^{1.1}}$ and $z_+ = z_q + \tau d_q$

$$\text{While } \; E(z_+) \ge \max_{0 \le j \le \min\{q, M-1\}} E(z_{q-j}) + \gamma(z_+ - z_q)^t g_q + \eta_q$$

$$\text{Choose } \; \tau_{new}$$

$$\text{Set } \; \tau = \tau_{new}\tau$$

$$z_+ = z_q + \tau d_q$$

- Step 1.2

$$z_{q+1} = z_+$$

- Step 2.- Compute the spectral step α_{q+1}.

3.3 Optimization Results

A selected set of model parameters were varied by ±15% relative to the corresponding base-case values (see Table 1, the column labeled "Varied parameters"). The parameter values that optimize $E_{(U/P)_\rho}$, $E_{(U/P)/TAT}$ and E_{FWA} are exhibited in Table 1, and simulation values in Table 2.

Varied parameters	Base-case	Optimal parameter values for: $E_{(U/P)_\rho}$	$E_{(U/P)/TAT}$	E_{FWA}	Range (z_l, z_u)
Cortico-medullary boundary values					
CD C_{Na+}	63.8	54.3	54.23	73.37	(54.23,73.37)
CD C_{NR}	10	8.5	8.5	11.5	(8.5,11.5)
CD Transport parameters					
OM CD P_{urea}	1×10^{-5}	8.5×10^{-6}	8.5×10^{-6}	8.5×10^{-6}	$(85.0,1.15)\times10^{-5}$
Initial IM CD V_{max,Na^+}	5	5.3118	5.262	4.4	(4.4,5.6)
Late IM CD V_{max,Na^+}	5	4.4	4.4	4.4	(4.4,5.6)
Initial IM CD P_{urea}	1×10^{-5}	8.5×10^{-6}	8.5×10^{-6}	8.5×10^{-6}	$(85.0,1.15)\times10^{-5}$
Late IM CD P_{urea}	80×10^{-5}	68×10^{-5}	68×10^{-5}	68×10^{-5}	$(68,92)\times10^{-5}$
Initial IM CD P_{water}	450	382.5	382.5	517.5	(382.5,517.5)
Late IM CD P_{water}	450	382.5	382.5	517.5	(382.5,517.5)
Location where CD P_{urea} changes	0.45	0.3852	0.3852	0.5175	(0.3852,0.5175)
Loop transport parameters					
OS TAL V_{max,Na^+}	8	9.2	9.2	6.8	(6.8,9.2)
IS TAL V_{max,Na^+}	17	19.55	18.11	19.55	(14.45,19.55)

Table 1: Optimization study-parameters

Most of the parameters that optimize the effectiveness functions: $E_{(U/P)_\rho}$; $E_{(U/P)/TAT}$ and E_{FWA} assumed optimal values at the extreme of their prescribed ranges (Table 1).

Simulation Values	Base-case	Optimal simulation values for: $E_{(U/P)_\rho}$	$E_{(U/P)/TAT}$	E_{FWA}
Urine				
Osmolality (mOsm/kg H_2O)	1517	2357	2192	1127
Na^+ concentration (mM)	302	498	387	251
Urea concentration (mM)	780	1143	1197	601
NR concentration (mM)	222	361	347	88.3
Flow rate (nl/min/nephron)	0.0520	0.0271	0.0282	0.150
Flow rate (nl/day/animal)	5.69	2.97	3.09	16.4
CD tubular fluid values at outer-inner medullary boundary				
Osmolality (mOsm/kg H_2O)	821	1152	1003	814
Na^+ concentration (mM)	193	233	202	214
Urea concentration (mM)	452	713	622	402
NR concentration (mM)	29.7	35.5	30.8	33.0
Flow rate (nl/min/nephron)	0.388	0.276	0.318	0.563

Table 2: Optimization study-simulation values

For $E_{(U/P)_\rho}$ from Table 2, the optimal parameters yielded a urine osmolality of 2357, mOsm/kg H_2O, urine Na^+, urea and NR concentrations of 498, 1143 and 361 mM respectively, at urine flow rate of 0.0271 nl/min/nephron. That correspond to a 55.4% increase in urine osmolality, compared to the base-case. The optimal parameters increase the relative OM concentrating capability by 64% and relative IM concentrating capability by 73.1% (given by increase CD tubular fluid osmolality along the OM and IM), relative to base-case. Similar analysis for the other two functions can be found in [4].

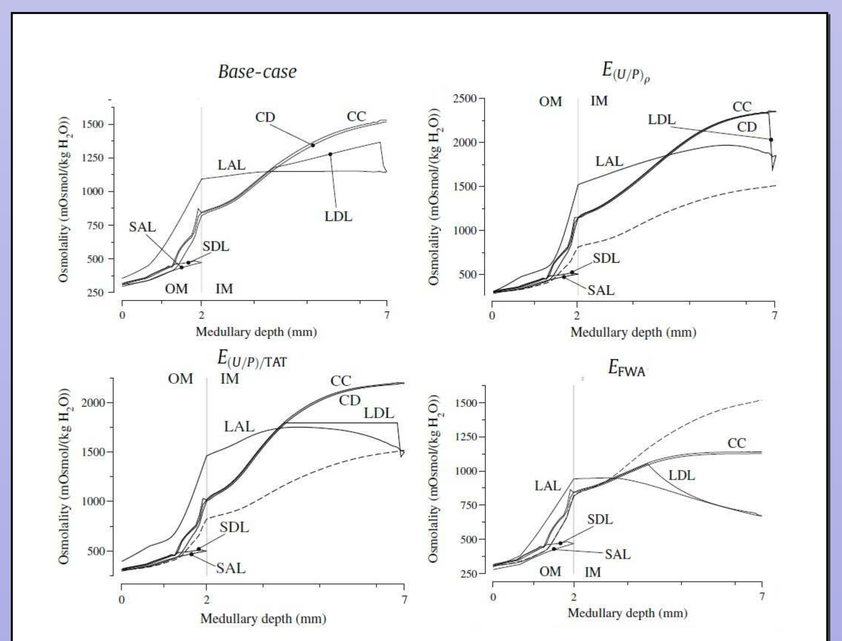

Figure 2: Profiles for fluid osmolality for Base-case, $E_{(U/P)_\rho}$, $E_{(U/P)/TAT}$ and E_{FWA}.

Figure 2 base-case shows that osmolality increased, with increasing medullary depth in the CD, short loop of Henle, the longest loop of Henle (except near the OM-IM boundary and along the prebend segment), and interstitium. For $E_{(U/P)_\rho}$, $E_{(U/P)/TAT}$ also the osmolality increased. It is above the base-case (dotted line). For E_{FWA} the osmolality was lower than the base-case (dotted line) since the optimization procedure selected parameters that maximize E_{FWA} by increasing urine flow rate, even at expense of a lower urine osmolality.

3.4 Discussion of the optimization results

- The optimization of (U/P) corresponds to the situation where the animal is deprived of water. When (U/P) is maximized in isolation, a highly concentrated urine may be produced at an unrealistically low flow rate, because of that $(U/P)_\rho$ is maximized.
- When $E_{(U/P)_\rho}$ was optimized the model produced a urine osmolality of 2357 in (mOsmol/kg H_2O) which is above 55.4% the base-case.
- When $E_{(U/P)/TAT}$ was optimized energy efficiency was taken into account. In this case the model produced a urine osmolality of 2192 in (mOsmol/kg H_2O) which is above 44.5% the base-case. These results suggest that a rat may be able to attain a substantially higher concentrating capability by relatively small changes in morphological and transport properties.
- For FWA the optimization algorithm selected parameters that maximize E_{FWA} by increasing urine flow rate.

Final Remarks: Because the optimization approach used in this study takes into account the potential for the nonlinear interactions when a larger set of parameters are simultaneously varied, this study offers the potential for a better understanding of the integrated function in the rat and other mammalian UCM. The optimization results support the conclusion of this study: that by means of modest changes in parameters, the UCM can improve its efficiency and respond to different physiologic needs.

References

[1] A. T. LAYTON and H. E. LAYTON. A efficient numerical method for distributed-loop models of the urine concentrating mechanism. *Math Biosci*, 45:549–567, 2002.

[2] A. T. LAYTON, T. L. PANNABECKER, W. H. DANTZLER, and H. E. LAYTON. Two modes for concentrating urine in rat inner medulla. *American Journal of Physiology - Renal Physiology 287*, 56:816–839, 2004.

[3] H. E. LAYTON, E. B. PITMAN, and M. A. KNEPPER. A dynamic numerical method for models of the urine concentrating mechanism. *SIAM J. Appl. Math*, 55:1390, 1995.

[4] M. LORETO and A. T. LAYTON. An optimization study of a mathematical model of the urine concentrating mechanism of the rat kidney. *Math. Biosci*, 223:66, 2010.

[5] J.L. STEPHENSON. Central core model of the renalcounterflow system. *Kidney Int.*, 2:85, 1972.