

Recent Advances in the Modelling of Renal Function

Peter Lory

Department of Computer Science and Mathematics, FH München
Lothstrasse 34, D-8000 München 2, Germany

ABSTRACT: Differential equation models have become an indispensable tool in the effort towards a complete understanding of hypertonic urine formation. Recent advances in this field include the treatment of a kidney model as an inverse problem, the modelling of the three-dimensional organization of the renal medulla, and dynamic models for the tubuloglomerular feedback mechanism. The latter make use of techniques from bifurcation and chaos theory.

I. INTRODUCTION

The kidney consists of thousands of basic functional units, the nephrons. The vasa recta form the vascular system associated with the nephrons (Fig. 1).

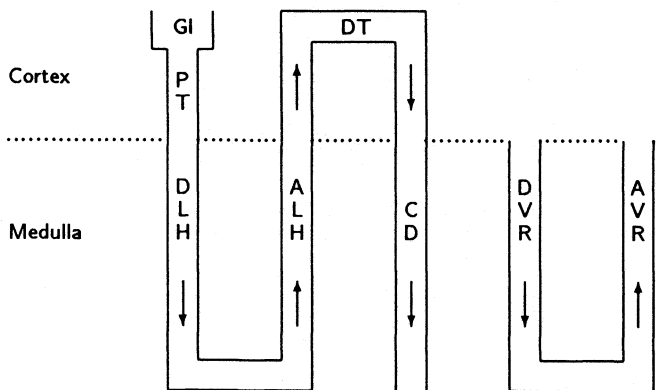


Fig. 1. Nephron and vas rectum (schematic).

Each nephron originates in the renal cortex, where blood plasma (minus large proteins) enters the nephron through the walls of a tuft of capillaries, called glomerulus (GI). The fluid then flows in sequence through the various tubular segments of the nephron: proximal tubule (PT), descending and ascending limb of Henle's loop (DLH and ALH), distal tubule (DT), and collecting duct (CD). At the end of the CD the fluid empties into the renal pelvis. The arrows in Fig. 1 indicate the directions of axial flows. Closely coupled to the counterflow system of the nephron is the parallel counterflow system of the blood vessels called vasa recta (DVR, AVR: descending and ascending vas rectum, respectively). Nephrons and vasa recta are embedded in a common surrounding space, called interstitium. The various tubule epithelia have

different permeability and active transport characteristics, which in concert enable the kidney to produce concentrated urine. A detailed understanding of this process requires the use of complex mathematical models. These are multi-point boundary value problems for ordinary differential equations in the steady-state case and initial-boundary value problems for partial differential equations in the dynamic case (see e. g. [2], [9], [12], [13]).

II. INVERSE APPROACH

Naturally, the above mentioned boundary-value problems depend on many geometric and thermodynamic parameters, like solute permeabilities of the membranes in the various tubular segments. For a realistic kidney model, both these parameters as the input and the predicted concentration profiles as the output must be consistent with experimental results. Because of their biological nature, most of these input data can be measured only with considerable uncertainty. Hence, the inverse approach in [2] allows these input parameters to vary within their ranges of measurements. Within these bounds it determines a set of parameters, for which the resulting concentration profiles optimally agree with tissue-slice measurements. This goal is achieved in a systematic way: The boundary value problem is discretized. Thus, the original inverse problem is reduced to a nonlinear optimization problem with equality and inequality constraints. This can be solved effectively by the sequential quadratic programming method.

This inverse approach allows the rigorous judgement of the potential of a given modelling technique. A parameter set could be found, for which the computed concentrations for both salt and urea increase considerably along the depth of the medulla. However, these results are consistent only with the flattest measured medullary concentration profiles. The situation with respect to salt improves drastically, if a "salt transport cascade" is included in the model. Morphological observations that support the existence of active salt secretion into the tubular fluid in certain portions of the DLHs have been given in [6]. In the same article, a hypothesis is presented how this active transport in concert with certain characteristics of the medullary architecture can produce a transport cascade towards the lower portions of the medulla, thus supporting the accumulation of salt in this region. Computer simulations in [9] have demonstrated the effectiveness of the hypothesized mechanism. Computations based on an inverse approach and including a transport cascade [1] have determined a parameter set, for which the model has a very high concentra-

tion capability for salt. Nevertheless, that for urea remains only moderate.

III. THREE-DIMENSIONAL ANATOMY

Commonly, models for the renal counterflow system treat the interstitial space as a well mixed compartment. Concentration gradients are present only in the axial direction along the depth of the medulla. However, careful anatomic studies in [8] and related papers have revealed a three-dimensional architectural organization of the medulla. Additionally, the functional consequences of this pattern are discussed in this article. Broadly speaking, they appear to facilitate salt and urea trapping in the lower portions of the medulla.

To a certain extent, a three-dimensional anatomy of the medulla is modelled in [14], [15]. Indeed, the model predicts concentration profiles that are consistent with experiments. However, the high complexity of the problem has forced the authors to simplifications in their simulation strategy: The non-axial direction is not modelled by differential equations. Rather, several new compartments are introduced and the interactions between these compartments are modelled with the help of parameters that are not fully accessible to measurements. Nevertheless, the model gives valuable first insights into the functional consequences of a three-dimensional anatomy. For an investigation of the "shunt flow technique", on which this model heavily relies, the reader is referred to [10].

IV. TUBULOGLOMERULAR FEEDBACK AND CHAOS

Blood to and from the glomerulus is conducted by the afferent and efferent arterioles, respectively. There is strong experimental evidence that the afferent arteriolar resistance adjusts in response to the concentration of salt in the cortical ALH, decreasing if the salt concentration is too low and increasing if the salt concentration is too high. Thus, the glomerular filtration rate and the pressure in the PT is regulated. This feedback loop is called tubuloglomerular feedback (TGF).

Recent experimental results in [16] and related papers have revealed that pressure and flow oscillate in the PT of normotensive rats. These oscillations have a frequency of 30–40 mHz and are mediated by the TGF system. Instead of oscillations, spontaneously hypertensive rats have aperiodic tubular pressure fluctuations. The spectral analysis and the graphic presentation of the data in the phase space are suggestive of deterministic chaos. In addition, the correlation dimension of the phase space attractor is estimated at 2.7 ± 0.1 . The largest Lyapunov exponent is positive, indicating sensitivity to initial conditions.

There have been several attempts to model these experimental results. The model in [3] is able to predict oscillations with approximately the same frequencies and phase relationships among the oscillating variables as have been found experimentally. Hopf bifurcations from stable steady-state solutions to stable limit cycles are studied numerically. The model [7] is a "minimal" model, in that it includes only those features necessary for the model to attain a reasonable degree of structural isomorphism with the TGF system. The relative simplicity of the model allows an analytic Hopf bifurcation analysis and interesting parameter studies. However, these models (and [11]) fail to predict chaotic behavior.

Chaos could be simulated in [4] and [5], the latter model being

an extension of the single nephron model [4] to a system of interacting nephrons. Here, the modelling technique is less detailed than in the examples mentioned above. In particular, the loop of Henle is modelled rather crudely.

REFERENCES

- [1] M. Breinbauer: Das Nierenmodell als inverses Problem, Diplomarbeit, Mathematisches Institut der TU München, 1988.
- [2] M. Breinbauer, P. Lory: The kidney model as an inverse problem, *Applied Mathematics and Computation* 44, pp. 195-223, 1991.
- [3] N.-H. Holstein-Rathlou, D. Marsh, A dynamic model of the tubuloglomerular feedback mechanism. *American J. of Physiology* 258, pp. F1448-F1459, 1990.
- [4] K. Jensen, E. Mosekilde, N.-H. Holstein-Rathlou, Self-sustained oscillations and chaotic behaviour in kidney pressure regulation, *Mondes Dev.* 54, pp. 91-109, 1986.
- [5] K. Jensen, N.-H. Holstein-Rathlou, P. Leyssac, E. Mosekilde, D. Rasmussen, Chaos in a system of interacting nephrons, H. Degn, A. Holden, L. Olsen (eds.), *Chaos in Biological systems*, pp. 23-32, 1987.
- [6] W. Kriz, Structural organization of the renal medullary counterflow system. *Federation Proc.* 42, pp. 2379-2385, 1983.
- [7] H. Layton, E. Pitman, L. Moore, Bifurcation analysis of TGF-mediated oscillations in SNGFR, *American J. of Physiology* 261, pp. F904-F919, 1991.
- [8] K. Lemley, W. Kriz, Cycles and separations: the histotopography of the urinary concentrating process, *Kidney Internat.* 31, pp. 538-548, 1987.
- [9] P. Lory, Effectiveness of a salt transport cascade in the renal medulla: Computer simulations, *American J. of Physiology* 252, pp. F1095-F1102, 1987.
- [10] P. Lory, On a mathematical modelling technique for renal counterflow systems, *Applied Mathematics Letters*, in press.
- [11] E. Pitman, H. Layton, Tubuloglomerular feedback in a dynamic nephron, *Communications on Pure and Applied Mathematics* 42, pp. 759-787, 1989.
- [12] J. Stephenson, R. Tewarson, R. Mejia, Quantitative analysis of mass and energy balance in non-ideal models of the renal counterflow system, *Proc. Nat. Acad. Sci. U.S.A.* 71, pp. 1618-1622, 1974.
- [13] J. Stephenson, R. Mejia, R. Tewarson, Model of solute and water movement in the kidney, *Proc. Nat. Acad. Sci. U.S.A.* 73, pp. 252-256, 1976.
- [14] A. Wexler, R. Kalaba, D. Marsh, Three-dimensional anatomy and renal concentrating mechanism. I. Modeling results, *American J. of Physiology* 260, pp. F368-F383, 1991.
- [15] A. Wexler, R. Kalaba, D. Marsh, Three-dimensional anatomy and renal concentrating mechanism. II. Sensitivity analysis, *American J. of Physiology* 260, pp. F384-F394, 1991.
- [16] K.-P. Yip, N.-H. Holstein-Rathlou, D. Marsh, Chaos in blood flow control in genetic and renovascular hypertensive rats. *American J. of Physiology* 261, pp. F400-F408, 1991.