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► **To cite this version:**

S Randall Thomas. Mathematical models for kidney function focusing on clinical interest. *Morphologie*, 2019, 103 (343), pp.161-168. 10.1016/j.morpho.2019.10.043 . hal-02393817

HAL Id: hal-02393817

<https://univ-rennes.hal.science/hal-02393817v1>

Submitted on 11 Dec 2019

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Mathematical models for kidney function focusing on clinical interest

(and in French: Modèles mathématiques du rein dans l'intérêt du clinicien)

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Abstract (<= 250 words)

We give an overview of mathematical models of renal physiology and anatomy with the clinician in mind. Beyond the past focus on issues of local transport mechanisms along the nephron and the urine concentrating mechanism, recent models have brought insight into difficult problems such as renal ischemia (oxygen and CO₂ diffusion in the medulla) or calcium and potassium homeostasis. They have also provided revealing 3D reconstructions of the full trajectories of families of nephrons and collecting ducts through cortex and medulla. The recent appearance of sophisticated whole-kidney models representing nephrons and their associated renal vasculature promises more realistic simulation of renal pathologies and pharmacological treatments in the foreseeable future.

Keywords: VPH, Mathematical models, kidney anatomy, renal physiology, electrolyte metabolism, renal epithelial transport

Résumé

Nous présentons un compte rendu de modèles mathématiques de la physiologie et de l'anatomie rénales qui peuvent intéresser le clinicien. Au-delà du penchant historique à traiter le mécanisme de concentration de l'urine et les mécanismes de transport « locaux » le long du néphron, des modèles récents s'efforcent d'éclaircir des problèmes difficiles tels que l'ischémie rénale (e.g., diffusion d'oxygène et CO₂ dans la médullaire) ou l'homéostasie du calcium et du potassium. D'autres ont fourni des reconstructions 3D des trajectoires complets de familles de néphrons et canaux collecteurs à travers le cortex et la médullaire. La publication récente de modèles sophistiqués du rein entier, qui incluent à la fois les néphrons et les vaisseaux sanguins associés, promet des simulations plus réalistes de pathologies rénales et traitements pharmacologiques dans un avenir proche.

Mots clés : VPH, Modèles mathématiques, anatomie rénale, physiologie rénale, métabolisme des électrolytes, transport épithélial rénal

Introduction

In this review, we summarize mathematical modelling studies of kidney physiology and anatomy that have relevance for the clinician. We make no pretense of giving the detailed contributions or modeling techniques of the mentioned modeling studies, but rather point to the relevant studies for those interested in particular issues. For more general reviews of renal modelling, we refer the reader to the following papers:

- on the urine concentrating mechanism, see Stephenson [49] for a thorough, technically detailed history starting with Hargitay & Kuhn [21,22], and see Pannabecker and colleagues for more recent developments that take advantage of imaging studies and 3D reconstruction of medullary nephron-vascular anatomy [8,43,48];
- for reviews and models of tubular function and tubule-specific transporters, see Weinstein [59-61,65-68]; and
- for more general reviews of renal modelling at several scales, see Edwards [9], Thomas et al. [54], and Thomas [53].

We also point out that experimenters and clinicians are well advised to read the modelling literature — the models are often the best sort of critical review of the experimental literature, since they must establish a coherent set of model parameters based on experimental measurements made under a variety of conditions using a number of experimental techniques and often in several different species.

Models of whole-kidney function

Among the earliest models of whole-kidney function are the treatments by Guyton and colleagues. Developed as part of the classic Guyton model of cardiovascular function [16,17], these were not stand-alone kidney models and they gave a rather simple input-output description of kidney function with scant internal detail, but they were developed with the clinic in mind by Guyton and his colleagues and established their conviction that the kidney plays a central role in blood pressure regulation. This work was of central importance for research into the mechanisms of blood pressure regulation, though a recent paper [29] has cast doubt on the validity of the predictions of both the classic Guyton model and its more recent descendants [1,24] under conditions of salt loading. Hallow and colleagues [18-20] have updated and improved on the Guyton “platform”, taking advantage of Karaaslan’s improved version [26,27] of the Guyton kidney. Moss et al. [40] presented a scenario for future individualized, “virtual patient” models of whole-body physiology based on an extension of the classic Guyton model.

At the other extreme of detail are models treating solute and water transport along all the nephrons in the whole kidney or in the whole medulla. Following Weinstein [68], one can distinguish *nephron models* from *kidney models* — in a nephron model, peritubular or interstitial conditions are specified (i.e., they are boundary conditions, not variables), whereas in a kidney model, transport by tubules and blood vessels determine the peritubular environment. Of kidney models, Weinstein’s recent model [68] is the most detailed, since it is the first to include the vasculature (vasa recta) in a model that treats epithelial transport of a rich set of ions and buffer systems along each nephron segment in the whole population of short and long nephrons in both cortex and medulla. This is clearly the most complete whole-kidney model to date, and it is replete with cogent reflection on many issues of clinical relevance. The whole-kidney model by Moss & Thomas [41] also includes both nephrons and vasculature but treats tubular epithelia as a simple barrier; their

model was the first to explicitly couple glomerulovascular and medullary dynamics and aims to serve as a platform for simulation of pathophysiological conditions and pharmacological interventions. The Moss & Thomas [41] model was also conceived to be embedded in whole body physiological models for exploration of the relationship between the extrarenal environment and renal excretory function in physiological and pathophysiological contexts.

The three previous families of kidney models treated nephron-vascular exchanges of only salt and urea and were focused on the still open question of the origin of the cortico-medullary gradient of osmolality and the urine concentrating mechanism (see below). These three families of models were those by Stephenson and colleagues [49,50], by Layton and Layton [32,33], and that of Wexler and colleagues [70], advanced by Thomas [23,51,55,58].

Future modeling work will profit from new insights from experimental manipulations, such as recent work on “anomalous” tubuloglomerular feedback (TGF) in rats fed a high sodium diet, such that stimulation of TGF increases rather than decreases single nephron GFR, thereby favoring excretion of a high sodium load rather than stabilization of GFR [3,56].

Renal epithelia and specificities of tubular function

Transport along each segment of the nephron is specific to the functions local to the given segment, and each segment has specific membrane transporters and epithelial permeability properties. Unraveling the specific roles of these transporters and the pathologies arising from transporter defects has profited greatly from give and take between experimental and modeling studies. These epithelial and tubular models [59-62, 65,66, 2,9-11,34] have provided much clinical insight and are generally motivated not by a desire to simply simulate published experimental results but rather to resolve conflicting interpretations of experimental data or address open questions and clinical conundrums.

Potassium handling

Plasma potassium concentration ($[K^+]$) must be strictly regulated, since even slight elevation above normal levels incurs serious cardiac and neurological disorders. The kidney is the principal regulator of K^+ homeostasis [38], and the site of this regulation is the distal nephron, where K^+ secretion is managed. Several modeling studies [31,62,64,68,71] have addressed questions of renal potassium handling. In a model of epithelial transport along the full distal nephron, Weinstein considers the question of independent regulation of Na^+ and K^+ excretion, focusing on familial hyperkalemic hypertension (FHH), concluding that there must be two distinct distal nephron signals. The recent whole-kidney model of Weinstein [68] (see above) provides the most complete context for quantitative speculation about the renal responses to perturbations of (among other things) electrolyte balance. In this paper, one issue explored in some depth is the cascade of effects on transport of sodium and potassium in proximal tubule, ascending Henle's limb, and distal tubule resulting from mild hyperkalemia (plasma K^+ was raised from 5.0 to 5.5 mM) — the model identifies a 3.3% decrease of proximal tubule Na^+ reabsorption as the source of the predicted 2.3-fold increase in Na^+ excretion (K^+ excretion increases by 1.3-fold). Layton, Edwards, & Vallon [31], in their whole-nephron model (but with no explicit vasculature), directly addressed renal adaptations to increases of K^+ load under normal conditions or following reduced renal function. They quantitatively evaluated the limits to excretion of an acute or chronic potassium load in simulations of nephrectomized rats.

Calcium handling

As reviewed by Friedman [12,13] and Moor & Bonny [39], overall calcium reabsorption in the kidney proceeds in parallel with sodium reabsorption, especially in the proximal tubule and loop of Henle (with different cellular mechanisms). However, hormonal and pharmacological regulation of renal calcium balance is situated in the distal nephron, where, under the influence of PTH and calcitonin and other factors, sodium and calcium transport can be dissociated and are inversely related. The channels and transporters involved in the various cell types along the nephron have (largely) been worked out, including identification of the mutations responsible for inherited disorders of distal calcium absorption such as Bartter's and Gitelman's syndromes. Nonetheless, questions remain, and mathematical models are needed to understand quantitatively the details of the kidney's handling of calcium transport as a function of hormonal signals, blood calcium and phosphate levels, and the various factors that perturb these.

To this purpose, recent mathematical models of calcium transport along the proximal tubule [11] and along the late nephron [2,10] (thick ascending limb, distal tubule, cortical and medullary collecting ducts) have contributed quantitative and qualitative substance to these issues. In particular, building on a model of distal tubule calcium transport [2] and an integrated epithelial model of ion transport from the thick ascending limb through the inner medullary collecting duct [63], Edwards [10] was the first to include calcium transport in a detailed model of epithelial transport from the medullary thick ascending limb through the inner medullary collecting duct. Her model focused especially on the role of calcium-sensing mechanisms (e.g., CaSR, the calcium-sensing receptor). For calcium transport in the proximal convoluted tubule (PCT), a recent model by Edwards & Bonny [11] confirmed quantitatively that the generally accepted discursive model of transcellular and paracellular calcium transport is consistent with available experimental data (principally from micropuncture studies in rodents), and provided detailed predictions of the expected impact of PTH, $1,25(\text{OH})_2\text{D}_3$, and calcitonin or perturbations of cell membrane transporters (NHE3 for protons and sodium, SGLT2 for sodium-glucose) or tight-junction permeabilities.

As pointed out by Weinstein [69], the models of Edwards and Bonny [2,10,11] provide the key components for an eventual overall treatment of renal calcium and phosphate handling. The next step would be to combine them into an integrated model (more complete and detailed than the one by Granjon et al. [15]) that would include PCT, short and long loops of Henle, and distal nephrons of both superficial and juxtamedullary nephrons to enable simulation of acute changes in kidney function, blood composition, or diuretic administration.

Oxygen delivery/consumption in cortex and medulla...

The kidney should be the organ that is least susceptible to hypoperfusion and ischemia since it has by far the highest rate of blood flow per gram of tissue (420 ml/min/100g in kidney, but 54 ml/min/100g in brain and 84 ml/min/100g in heart) and its ratio of O_2 consumption/ O_2 delivery is only about 8%, which is lower than that for any other organ (cf. 34% for brain and skeletal muscle and 65% for heart) (values in humans, from Table 1 of Brezis et al. [4]). Nonetheless, the kidney suffers the most severe hypoperfusion damage in patients with acute renal failure (ARF). The explanation for this seeming paradox is two-fold. First, oxygenation and blood flow are heterogeneous within the kidney due to the essentially separate irrigation of cortex, outer medulla, and inner medulla and also to the special hairpin-turn configuration of nephrons and vessels (and consequent recycling and counter-

current exchange of solutes and water). And secondly, transepithelial solute transport consumes a high amount of energy, particularly in the mTAL (medullary thick ascending limb), situated in the relatively hypoxic region of the outer medulla outside the vascular bundles — for outer medulla, the ratio of O_2 consumption/ O_2 delivery is at least 79% (rat kidney, Table 1 of Brezis et al. [4]). As Brezis et al. [4] also pointed out, decreased urine concentrating ability (which depends on mTAL active transport) is the most consistent defect in ARF (acute renal failure), is a very early sign of impending ARF, and is exquisitely sensitive to brief periods of experimental renal hypoxia induced by cyanide or mild renal ischemia even in the absence of ARF.

Thus, given that the special problems of renal oxygenation are intimately tied up with the complex structure of the kidney, and despite the technical difficulties (high diffusion rates, complex buffering relations, limited experimental measurements of certain important parameters, etc.), a number of mathematical models of renal oxygen transport and metabolism have been realized, ranging in complexity from a simple but clinically motivated Matlab model [5] to sophisticated medullary [6,14,74] or even whole kidney 3D models [34,36] of oxygen delivery, distribution, and consumption under normal and disturbed conditions. These modeling studies and related experimental studies firmly establish the delicate balance maintained by the kidney between, on one hand, minimizing medullary blood flow in order to favor increased concentrating ability, and on the other hand, increasing medullary blood flow to deliver sufficient oxygen for the metabolically expensive transport processes of the mTAL and the medullary CD. These models also explore various questions relating to hypothesized tradeoffs between aerobic and anaerobic modes of transport within the low PO_2 environments of outer and inner medulla.

Urine concentrating mechanism

As pointed out above, abnormal dilution or concentrating ability of the urine is often an early sign of renal pathologies, and while the main principles of the concentrating mechanism are well understood for the outer medulla (see, e.g., [30,35,53]), the origin of the steep osmotic gradient in the inner medulla remains one of the central mysteries of renal physiology. For example, it remains unknown how the kidney is able to concentrate urine to the degree that is evident in antidiuresis, and so this cannot be modeled mechanistically without hypothesizing an extra driving force such as metabolic osmole production in the medullary interstitium (perhaps lactate production by anaerobic glycolysis [23, 25, 52, 55]) or some other mechanism [28, 30]. This ongoing story is too involved to relate here, but has been described in a number of reviews [8,9,47,49,52,53], and most recently by Nawata & Pannabecker [42], who relate in particular the collaborative contributions of anatomical and functional modeling.

Models of renal anatomy

Most mathematical models of renal anatomy have been reconstructions from serial sections, focused on the medulla or on the glomerulus. Nordsletten [46] gave a 3D reconstruction (see Figure [1]) of arterial and venous vessels of the whole rat kidney down to 30 μm in diameter and made the 3D dataset available for download for reconstruction and morphologically based blood flow analysis.

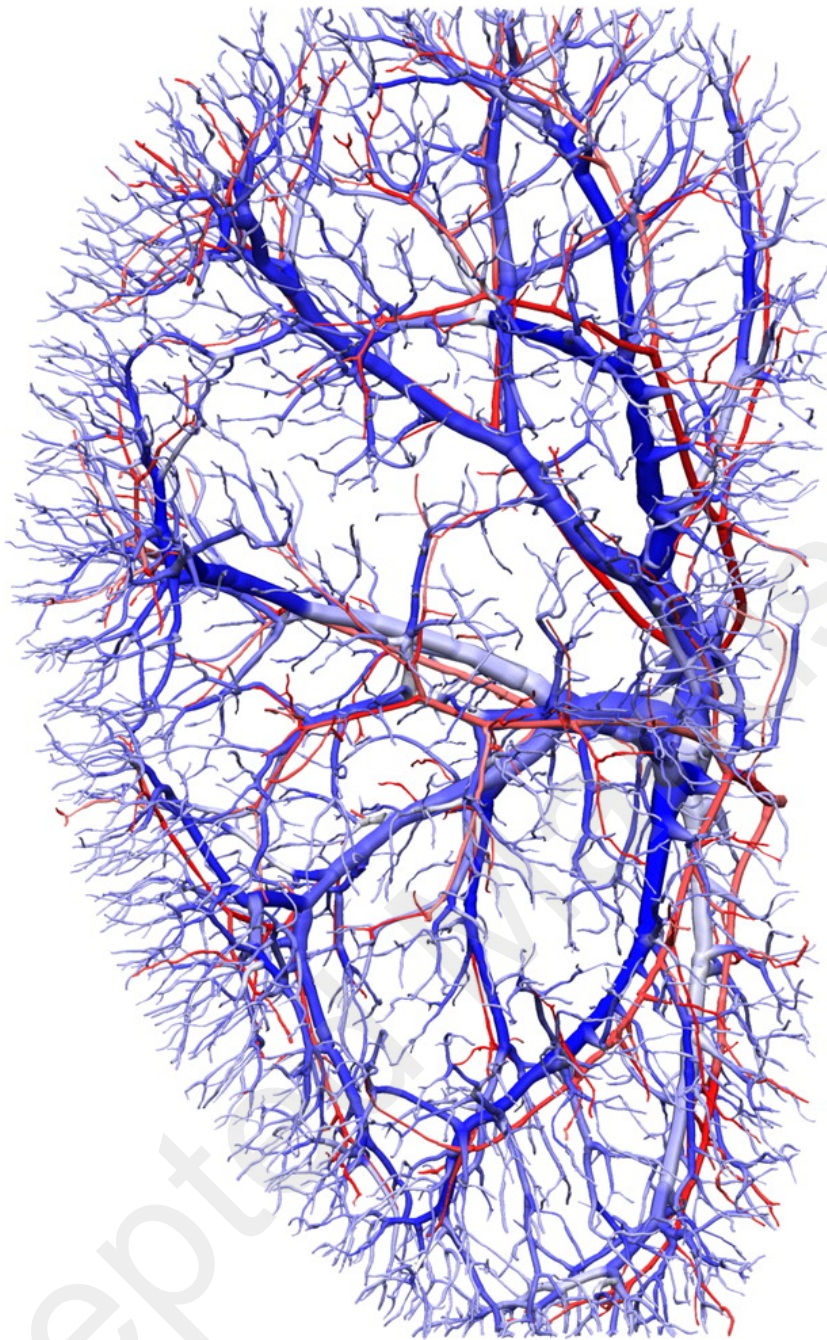


Fig. 1. Side view of rat renal vasculature with vessel thickness proportional to a quarter the true radial value. Color of the arterial tree indicates vessel order stability, white giving $\{\rho\}_s = 0$ and red giving $\{\rho\}_s = 1$. The venous tree exhibits the same information on a fading blue scale. (from reference [46]: Nordsletten et al. 2006).

Pannabecker and colleagues have published a number of studies reconstructing nephrons and collecting ducts in the rat medulla (for example, Figure [2]); these are reviewed by Newata & Pannabecker [42] in the context of recent advances towards understanding the urine concentrating mechanism.

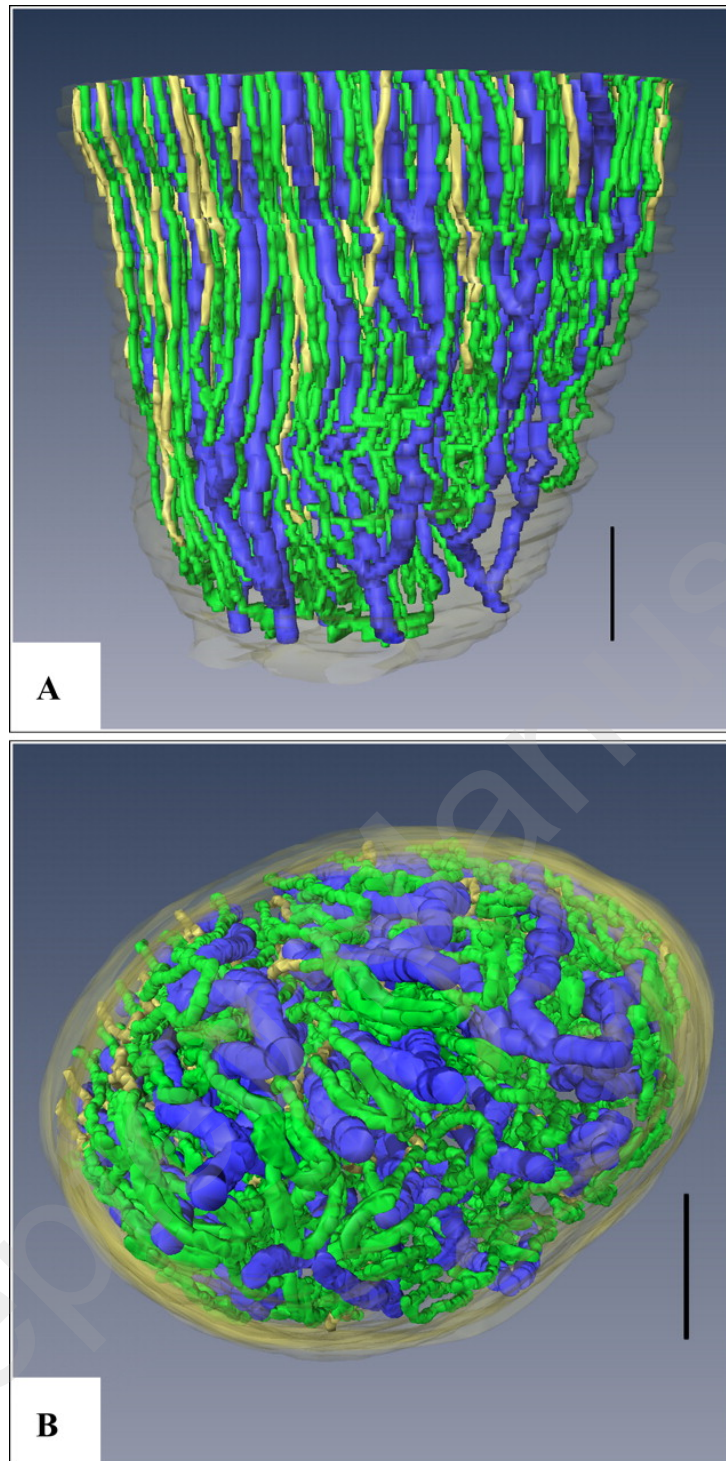


Fig. 2. Three-dimensional reconstruction of all papillary CDs (AQP2, blue), ATLs (CIC-K1, green), and DTLs (α B-crystallin, yellow) from a single kidney. Papillary surface epithelium is shown in gray. A: lateral view. B: axial view from papilla tip. Scale bars = 100 μ m. See Supplemental Video 2 for additional details. (from reference [47], Pannabecker and Dantzler 2007.)

Zhai, Christensen, and colleagues published wonderfully revealing reconstructions of the paths of multiple families of nephrons and vessels in mouse [37,72,73] and rat [7, 37]

kidneys, with great relevance for issues of nephron-vascular exchange and the urine concentrating mechanism.

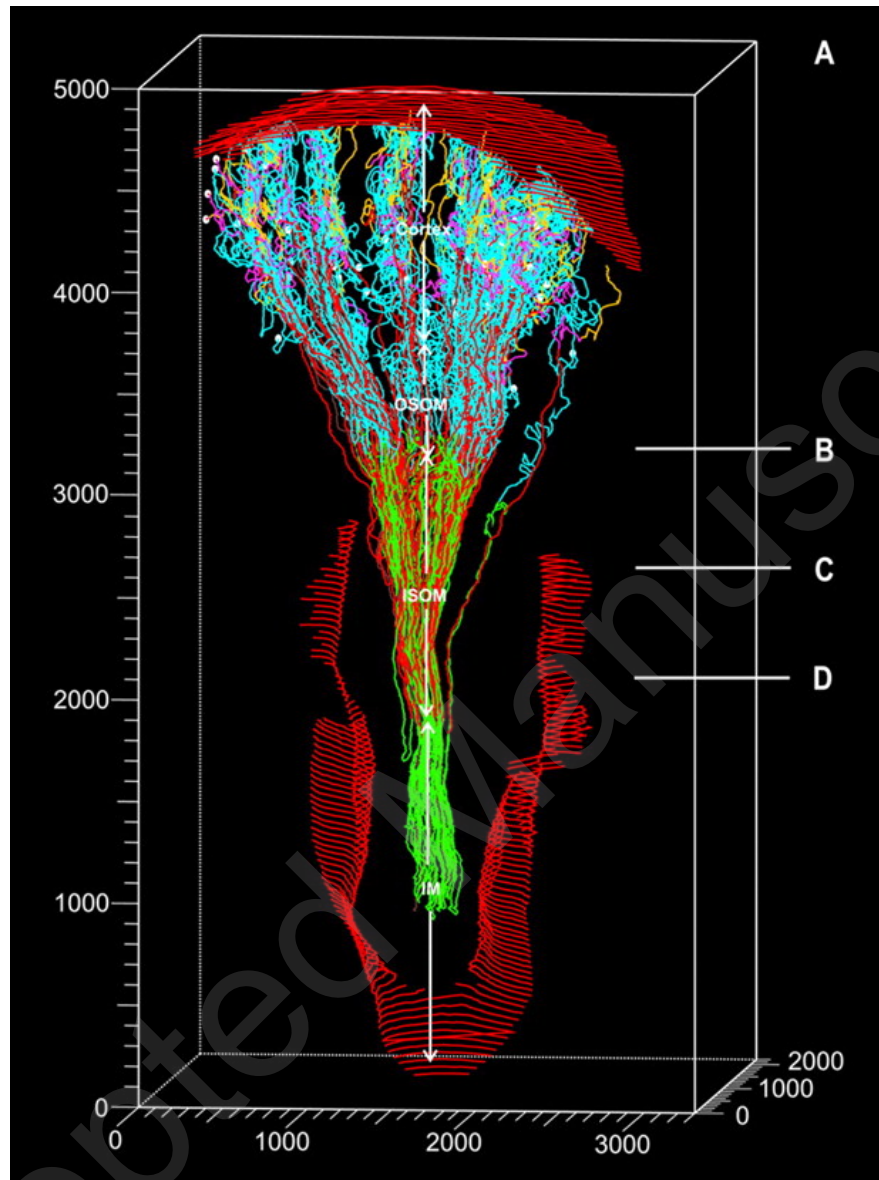


Figure 3 near here

Fig. 3. All SLN, LLN, and CD traced within one kidney. The red lines represent the renal capsule and the papilla. The white dots represent glomeruli (not actual size). Tubule segments are represented in different colors: PT, blue; thin limbs (TL), green; TAL, red; DCT, purple; connecting tubules (CNT), orange; and CD, brown. (B) Level of the OSOM (approximately 1570 μm from the renal surface). (C) Level of the initial part of the ISOM (approximately 1925 μm). (D) Level of the middle to lower ISOM (approximately 2585 μm). White circles highlight the same vascular bundles. . Scale = 50 μm . (from Zhai et al. 2006, reference [72])

These have provided great insight into the intimate details of the relative placement of long and short nephrons and vasculature (vasa recta, in particular), relevant especially for questions of salt and urea recycling in studies of the urine concentrating mechanism.

Neal et al. [43-45] published 3D reconstructions of glomeruli, not only in the rat but also in human kidneys. They were the first to show [44] that Bowman's Space is actually three functionally distinct spaces. They describe [43] the functional implications of the difference in scale between rodent and human kidneys. Their most recent studies have clarified the roles of these spaces in glomerular filtration and point to possible correlations with glomerular pathologies.

Other models of practical clinical use

Other "models", which may not qualify as models of the kidney, can be useful didactic tools for clinical procedures. An example is Walther et al. [57], which provides two spreadsheet calculators for prediction of solute clearances and solute concentrations during renal replacement therapy — these are useful for teaching but not for clinical application, since they have not been clinically tested or FDA approved. The first calculates clearance values from inputs including blood flow, hematocrit, ultrafiltration rate, dialysate flow rate, as well as the reflection coefficient and the mass transfer area coefficient for the solute of interest, and the free fraction if the solute is protein bound. The second program calculates plasma solute concentrations from the clearance values obtained by the first program and from additional input values including the number of treatments per week, the duration of the treatments, and the solute's production rate and volumes of distribution. The program calculates the time-averaged solute concentration and provides a graphic display of the solute concentration profile through a week-long interval.

Conclusions

Given its unique triple role of maintaining water balance, salt balance, and nitrogen balance, the mammalian kidney fulfills such a multitude of functions that it would be vain to expect any single mathematical model to capture them all. As shown here, many sorts of models have been published, from simple black-box treatments of overall renal input-output relations to extremely sophisticated models of water and electrolyte transport across the epithelia of all nephrons and vessels. Certainly, the great majority of these models treat the rat kidney, since it is for rats and mice that there is the most complete set of experimental measurements. Nonetheless, the motivation for most of these studies is to further the understanding of human kidney function, and in general they carefully relate the model results to issues of human physiology and pathophysiology. One can therefore wholeheartedly encourage the clinician to delve into the modeling literature despite its necessarily technical nature — each mathematical modeling paper is a carefully reasoned review of the relevant experimental literature (two outstanding examples are Moss & Thomas [41] and Weinstein [68]).

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgements

The author is grateful to the CNRS for continuing support during his emeritus period.

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