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Mathematical Modeling of Kidney Transport

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Abstract

In addition to metabolic waste and toxin excretion, the kidney also plays an indispensable role in regulating the balance of water, electrolytes, nitrogen, and acid-base. In this review, we describe representative mathematical models that have been developed to better understand kidney physiology and pathophysiology, including the regulation of glomerular filtration, the regulation of renal blood flow by means of the tubuloglomerular feedback mechanisms and of the myogenic mechanism, the urine concentrating mechanism, epithelial transport, and regulation of renal oxygen transport. We discuss the extent to which these modeling efforts have expanded our understanding of renal function in both health and disease.

Keywords

mathematical models; urine concentrating mechanism; glomerular filtration; renal hemodynamics; oxygen

1 Introduction

The kidneys are commonly known to function as filters, removing metabolic wastes and toxins from the blood and excreting them through the urine. But, through various regulatory mechanisms, the kidneys also help maintain the body's water balance, electrolyte balance, nitrogen balance, and acid-base balance. Additionally, the kidneys produce or activate hormones that are involved in erythrogenesis, calcium metabolism, and the regulation of blood pressure and blood flow.

Despite decades of experimental efforts, some aspects of the fundamental kidney functions remain yet to be fully unexplained. For example, the processes by which a concentrated urine is produced by the mammalian kidney (or, more specifically, the production of a substantial concentrating effect in the inner medulla) when the animal is deprived of water remains one of the longest-standing mysteries in traditional physiology. In conjunction with experimental work, mathematical models have helped to test, confirm, refute, or suggest a number of hypotheses related to the urine concentrating mechanism (79).

This review will describe modeling efforts that have sought to better understand kidney physiology and pathophysiology, including the regulation of glomerular filtration, the regulation of renal blood flow by means of the tubuloglomerular feedback mechanisms and of the myogenic mechanism, the urine concentrating mechanism, epithelial transport, and regulation of renal oxygen transport.

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2 Glomerular Filtration

Most mammalian kidneys have three major sections: the cortex, the outer medulla, and the inner medulla. The outer and inner medulla are collectively referred to as the medulla. The outer medulla may be divided into the outer stripe and the inner stripe.

The functional unit of the kidney is the nephron; see Fig. 1. Each rat kidney (which is the most well-studied mammalian kidney) is populated by about 38,000 nephrons; each human kidney consists of about a million nephrons. Each nephron consists of an initial filtering component called the renal corpuscle and a renal tubule specialized for reabsorption and secretion. The renal corpuscle is composed of a glomerulus and the Bowman's capsule. A glomerulus is a tuft of capillaries arising from the afferent arterioles. Some of the water and solutes in the blood supplied by the afferent arteriole are driven by a pressure gradient into the space formed by the Bowman's capsule. The remainder of the blood flows into the efferent arteriole.

The most notable models of filtration of blood by glomerular capillaries are by Deen and coworkers (16, 7, 14, 27, 17, 19, 20, 15). Most glomerular filtration models idealize the tortuous capillaries as a network of identical, parallel, rigid cylinders with homogeneous properties. Model equations typically consist of a system of coupled ODEs expressing fluid and solute conservation:

$$\frac{\partial}{\partial x}Q = -\frac{S}{L}J_{\nu} \quad (1)$$
$$\frac{\partial}{\partial x}(QC_{k}) = -\frac{S}{L}J_{k} \quad (2)$$
$$\frac{\partial}{\partial x}(QC_{pr}) = 0 \quad (3)$$

where Q denotes plasma flow rate, S and L denote the surface area and length of the capillary, J_v and J_k denote the fluid and solute fluxes, C_k denotes the total plasma concentration (free and bound states) of solute k, the subscript pr denotes protein, and x denotes the position along the capillary. Boundary conditions are given for Q, C_k , and C_{pr} at the afferent end of the capillary. Volume flux is assumed to be driven by hydrostatic and oncotic pressure differences, and fluxes for small solutes (smaller than proteins) are assumed to be both advective and diffusive, through the fenestrated capillary walls.

Early models represent the capillary wall as an isoporous membrane formed of parallel, cylindrical pores of uniform radius (14). The isoporous model has the advantage of being relatively easy to formulate and to implement, and has successfully predicted clearance data in a few cases, such as in normal and nephritic rats. However, isoporous model predictions are incompatible with experimental results in quite a few human diseases, such as diabetic nephropathy and glomerulonephritis. Deen and collaborators were thus motivated to develop models that assume that the glomerular barrier can be represented by a distribution of pore sizes, which better approximates the actual glomerular structure. Those "heteroporous models" yield much improved clearance data in nephrotic humans when compared to isoporous models. In later studies, Deen and collaborators sought to relate the permeability properties of the wall to its unique cellular, and even molecular, characteristics, and they developed new models of glomerular filtration based on the specific ultrastructure of the capillary wall (20, 17, 15).

Potential future extensions to glomerular filtration models include representation of charge selectivity, which remains somewhat controversial, particularly concerning the selectivity of the barrier to albumin and the origin of protenuria. A rigorious theoretical approach for incorporating the effect of proteins on sieving coefficients would also be worthwhile.

3 Two Mechanisms for Renal Autoregulation

Normal renal function requires that the fluid flow through the glomerulus and nephron be kept within a narrow range. When tubular flow rate falls outside of that range, the ability of the nephron to maintain salt and water balance may be compromised. Tubular flow rate depends, in large part, on glomerular filtration rate, which is regulated by several mechanisms, including the tubuloglomerular feedback (TGF) and the myogenic mechanism.

3.1 Tubuloglomerular feedback

The delivery of water and electrolytes to the distal nephron is regulated by TGF (81). The TGF response is initiated by changes in tubular fluid chloride concentration near the macula densa, which is a cluster of specialized cells, located in the renal tubule wall near the end of the thick ascending limb of the loop of Henle. If the macula densa chloride concentration is too low, TGF acts to restore it to target by increasing tubular fluid flow rate. This is accomplished by a dilation of the afferent arteriole, which increases glomerular filtration pressure and consequently single nephron filtration rate (SNGFR). The opposite happens if the macula densa chloride concentration is too high. Most experimental TGF studies were done on the superficial nephrons, which give rise to the short loops of Henle. Because the juxtamedullary nephrons, which give rise to long loops of Henle, are inaccessible, their TGF properties are not well characterized.

The thick ascending limb actively pumps out NaCl from tubular fluid into the interstitium. Because the thick ascending limb walls are water impermeable, the active reabsorption of NaCl is not accompanied by water loss, and the tubular fluid NaCl concentration progressively decreases along the thick ascending limb. Thus, the thick ascending limb is an important segment of the TGF system, and its transport properties allow it to act as a key operator of the TGF system. Typically, TGF models represent the conservation of chloride ion, the concentration of which is believed to be the principal tubular fluid signal for the TGF response (82):

$$\frac{\partial}{\partial t}(\pi R^2 C) = -\frac{\partial}{\partial x}(QC) - 2\pi R_{ss} \left(\frac{V_{\max}C}{K_M + C} + \kappa(C - C_e)\right) \quad (4)$$

where *C* is the tubular fluid chloride concentration, C_e is the time-independent extratubular (interstitial) chloride concentration which is assumed to be fixed. The second component on the right-hand side of the equation represents an axial advective chloride transport at the intratubular flow rate *Q*. The two terms inside the large pair of parentheses corresponds to active solute transport characterized by Michaelis-Menten-like kinetics (with maximum Cl⁻ transport rate V_{max} and Michaelis constant K_M) and transpithelial Cl⁻ diffusion (with backleak permeability κ). A schematic diagram of the TGF model in Ref. (77) is shown in Fig. 2 as an example.

Additional model equations are needed to describe tubular fluid dynamics. Some models assume that the renal tubule is a rigid tube with plug flow (e.g., Refs. (59, 61, 60, 52)), whereas other represent pressure-drive fluid flow along compliant tubules (e.g., Refs. (30, 78, 107)); see discussion below. Together with a representation of the TGF response (see below), the model equations can be solved to yield tubular fluid flow and chloride concentration as functions of time and space.

Model studies predict that, for some system parameters, the TGF system can exhibit oscillatory behavior (30) By linearizing the model equations, Layton et al. (59) derived a characteristic equation that predicts the appearance of TGF-mediated oscillations for different model parameter values within a two-dimensional $(\tau - \gamma)$ parameter space; see Fig. 3. The first parameter, τ , is simply the signal delay from macula densa to afferent arteriole. The parameter γ is the product of two terms: (a) the steady-state strength of the macula densa signal on thick ascending limb fluid flow, and (b) the axial concentration gradient of salt along the ascending limb at the macula densa. This latter term determines how variations in ascending limb flow will be perceived at the macula densa as variations in luminal concentration. These modeling efforts have yielded the conclusion that TGF-mediated oscillations arise from a bifurcation: the dynamic behaviors of the system depend on the feedback-loop gain, which is a function of how much output is fed back to the input, or, more specifically, how much SNGFR is changed given a deviation in macula densa chloride concentration. If feedback-loop gain is sufficiently large, then the stable state of the system is a regular oscillation and not a time-independent steady state (30, 52, 59, 76).

The TGF system includes the glomerulus, proximal tubule, and loop of Henle, along with a feedback signal from macula densa to afferent arteriole. Different TGF models represent each component with different degrees of detail. For example, the action of the afferent arteriole is explicitly represented in Refs. (33, 34), but implicitly through the tubular fluid flow rate or pressure in Refs. (52, 59, 62, 76). A simple model that represents plug flow in rigid tubes may describe the TGF response by assuming the boundary inflow Q(0, t) as a function of time-delayed macula densa chloride concentration C_{MD} :

$$Q(0,t) = Q_o + K_1 \tanh \left(K_2(C_{\rm op} - C_{\rm MD}(t-\tau)) \right)$$
 (5)

In the above equation, K_1 denotes half of the range of flow variation around its reference value Q_o ; K_2 quantifies TGF sensitivity; the target concentration C_{op} is the time-independent steady-state TAL tubular fluid chloride concentration alongside the macula densa when $Q(0, t) = Q_o$ (i.e., when $C_{op} = C_{MD}$); and $C_{MD}(t - \tau)$ is the chloride concentration alongside the macula densa at the time $t - \tau$, where τ represents the TGF delay. The TGF response curve assumed in Ref. (59) is shown in Fig. 4 as an example.

In many TGF models (e.g., Refs. (30, 43, 59, 62, 71)) the thick ascending limb is represented in detail, because model investigations have indicated that the transduction process in the thick ascending limb exhibits a number of features, such as the generation of harmonics that transform sinusoidal waves into waves that are periodic but nonsinusoidal, that may help explain phenomena found in regular and irregular oscillations that are mediated by TGF (52, 60, 61). Thus, these models solved the hyperbolic partial differential equation that explicitly represents the advective transport of solute and its coupling with transepithelial active and diffusive transport (e.g., Eq. 4). In contrast, other components of the TGF loop were represented in those TGF models by means of simple, phenomenological representations: the actions of the proximal tubule and descending limb of a short-looped nephron were modeled by a linear function that represents glomerular-tubular balance in proximal tubule and water absorption from the descending limb (59). Other TGF models include more detailed representation of the proximal tubular and descending limb (30, 77). Other models employ simple, non-spatially distributed formulations to represent the TAL and its delays-e.g., a linear system of three first-order ordinary differential equations in Ref. (2).

TGF systems in neighboring nephrons are known to be coupled, via electrotonic conduction along the pre-glomerular vasculature (29, 35, 106). A schematic diagram of two short-

looped nephrons coupled through their afferent arterioles is shown in Fig. 5. Thus, for two nephrons having afferent arterioles that are nearby on the cortical radial artery, the contraction of one nephron's afferent arteriole tends to result in the contraction of the other nephron's afferent arteriole. To represent a system of *n* coupled nephrons, the flow equation (5) can be modified to include the influences of neighboring nephrons:

$$Q_{i}(0,t) = Q_{i,o} + K_{1,i} \tanh\left(K_{2,i}(C_{op} - C_{MD}(t-\tau_{i}))\right) + \sum_{j \neq i} \varphi_{ij}(Q_{j}(0,t) - Q_{o,i}), \quad (6)$$

where φ_{ii} denotes the coupling strength between nephrons *i* and *j*.

Modeling investigations of coupled nephrons (75, 53, 52) have shown that differing gain parameters and time delays between coupled nephrons, which merely reflect differences in nephron dimensions and TGF gains, can introduce doublet and triplet spectral peaks into the power spectrum, and generate irregular flow oscillations and complex power spectra similar to those observed in spontaneously hypertensive rats. Other studies suggest that internephron coupling may induce synchronization, quasiperiodicity, and perhaps chaos in a nephron tree (42, 68).

3.2 Myogenic mechanism

The afferent arteriole exhibits an intrinsic property that induces a compensatory vasoconstriction of the afferent arteriole when the vessel is presented with an increase in transmural pressure. Measurements by Loutzenhiser et al. of afferent arteriolar diameter at different perfused pressures are exhibited in Fig. 6. This phenomenon, in which vascular smooth muscle responds to increased stretch with active force development, is termed the myogenic response. This response enables arterial blood vessels to constrict as intraluminal pressure increases under physiological conditions. In the arteriolar system, myogenic responses is thought to be important for local autoregulation of blood flow and regulation of capillary pressure.

Based on the kinetic attributes of the afferent arteriole myogenic response and the steadystate pressure and afferent arteriole diameters, Loutzenhiser et al. (64) developed a mathematical model of renal autoregulation. That model is a phenomenological one that predicts vascular responses in terms of arteriolar diameter only, and those appear to be consistent with the dynamic features of renal autoregulation observed in the intact kidney. In a follow-up study, Williamson et al. (105) developed a more extensive systems model to examine the impact of systolic-pressure sensitivity on renal autoregulation. Their results show that the asymmetry in time delays in the myogenic response is more important than differences in the time constants of vasoconstriction versus vasodilation in accounting for the sensitivity to systolic pressure in the hydronephrotic kidney.

Secomb and co-workers developed a model of blood flow regulation (4, 1). Their model's representations of the active contractile force and resulting muscle mechanics are similar to the model by Lush and Fray (65), but the model by Secomb and co-workers represents also metabolic vasoactive and shear stress-dependent responses. Their model was formulated for both large and small arterioles, each with a different set of parameters.

Layton and collaborators (11, 83) developed a mathematical model of the myogenic response of the afferent arteriole, based on an arteriole model by Gonzalez-Fernandez and Ermentrout (26). The model incorporates ionic transport, cell membrane potential, contraction of the arteriolar smooth muscle cell, and the mechanics of a thick-walled cylinder. The model's representation of the myogenic response is based on the hypothesis that changes in hydrostatic pressure induce changes in the activity of non-selective cation

channels. The resulting changes in membrane potential then affect calcium influx through changes in the activity of the voltage-gated calcium channels, so that vessel diameter decreases with increasing pressure values. Model results suggest that the interaction of Ca²⁺ and K^+ fluxes mediated by voltage-gated and voltage-calcium-gated channels, respectively, gives rise to periodicity in the transport of the two ions. This results in a time-periodic cytoplasmic calcium concentration, myosin light chain phosphorylation, and crossbridges formation with the attending muscle stress. A flow chart the illustrates the step by which periodic oscillations in cytosolic calcium concentration gives rise to spontaneous vasomotion of the model afferent arteriole is shown in Fig. 7, top-left panel; oscillations in key model variables are shown in Fig. 7, bottom panels. Further, the model predicts myogenic responses that agree with experimental observations (see Fig. 7, top-right panel), most notably those which demonstrate that the renal AA constricts in response to increases in both steady and systolic blood pressures (11). Model simulation of vasoconstriction initiated from local stimulation also agrees well with findings in the experimental literature, notably those of Steinhausen et al. (84), which indicated that conduction of vasoconstrictive response decays more rapidly in the upstream flow direction than downstream. Marsh et al. (67) also adopted the smooth muscle cell model of Gonzalez-Fernandez and Ermentrout (26) to study the interactions between afferent arteriole myogenic response and TGF.

4 Urine Concentration

When deprived of water, the kidney of a mammal can conserve water by increasing the solute concentration (or, osmolality) in the urine to a level well above that of the blood. This process of urine concentration occurs in the renal medulla, and has the effect of stabilizing the osmolality of blood plasma. Such urine, which is said to be hypertonic, is concentrated in the final stages of urine production: water is absorbed, in excess of solute, from the collecting ducts and into the vasculature of the medulla, thus increasing the osmolality of the collecting duct fluid—fluid that is called urine after it emerges from the collecting ducts.

The highest human urine osmolality was measured to be 1,430 mosm/(kg H₂O), which is ~4.8 times above blood plasma (300 mosm/(kg H₂O)). Note that that is the *maximum* value ever measured, so it is fair to say that most of us don't do that well. That human maximum urine osmolality value is also the reason that one should refrain from drinking sea water to quench thirst, given that sea water osmolality ranges from 2,000–2,400 mosm/kg H₂O. Some mammals can do much better. A rat kidney can produce a urine (in units of mosm/(kg H₂O)) as concentrated as 2,849; mouse, 2,950; chinchilla, 7,599 (3). The kidney of an Australian hopping mouse, which lives in the desert, can produce an amazingly concentrated urine that has an osmolality >30 times that of blood plasma at 9,374.

In the outer medulla of the rat kidney, water absorption from collecting ducts is driven by active transepithelial transport of NaCl from the water-impermeable thick ascending limbs into the surrounding interstitium, where the NaCl promotes, via osmosis, water absorption from collecting ducts, descending limbs, and some blood vessels. Although this concentrating mechanism is well-established in the outer medulla—by both physiological experiments and theoretical investigation—the nature of the concentrating mechanism in the inner medulla, where the concentrating effect is the largest in some mammals, remains to be elucidated. For details on current understanding of the mammalian urine concentrating mechanism, see reviews (51, 80, 13).

Steady-state urine concentrating mechanism models typically consist of ODEs that describe water and solute conservation:

$$\frac{\partial}{\partial x}Q(x) = J_{\nu}(x) \quad (7)$$
$$\frac{\partial}{\partial x}(Q(x)C_{k}(x)) = J_{k}(x) \quad (8)$$

where Q denotes tubular water flow rate, J_v denotes water flux through the tubular walls, taken positive into the tubules, C_k denotes the concentration of the k-th solute, J_k denotes its transmural flux, and x denotes the medullary depth.

Urine concentrating mechanism models typically assume single-barrier transport. Water flux into a renal tubule can be described by

$$J_{\nu}(x) = 2\pi r(x) L_{p}(\Delta P + RT \sum_{k} \varphi_{k} \left(C_{k}(x) - C_{k}^{e}(x) \right))$$
(9)

where L_p is the water permeability of the tubule, ΔP denotes the hydrostatic pressure gradient, φ_k denotes the osmotic coefficient, and $C_k^e(x)$ denotes the interstitial concentration of the *k*-th solute.

A typical model describes two pathways by which a solute may be transported across renal tubular walls, passive and active:

$$J_k(x) = 2\pi r(x) \left(-\frac{V_{\max}(x)C_k(x)}{K_M + C_k(x)} + P_k(x) \left(C_k^e(x) - C_k(x) \right) \right).$$
(10)

The first term on the right represents active solute transport, which is characterized by Michaelis-Menten kinetics, with maximum transport rate V_{max} and Michaelis constant K_M . The second term represents transmural diffusion, with solute permeability P_k .

Hoppensteadt and Peskin (31) presented a simple model of the loop of Henle that exemplified the countercurrent multiplication that may take place between the descending and ascending limbs of the loop. Their model assumes that NaCl is actively pumped out of the ascending limb, and water is reabsorbed from the water-permeable descending limb. The limbs interact through an external compartment, which represents the peritubular capillaries. The model assumes that the reabsorbate (i.e., NaCl from the ascending limb and water from the descending limb) is picked up locally, i.e., axial flow is not allowed in this compartment. The collecting duct is not represented in this model, although an extension to include a collecting duct is straightforward. Owing to the simplicity of this model, analytical solution can be derived to relate the concentrating effect (loop-bend concentration) to active NaCl transport rate or loop length.

Because the Hoppensteadt and Peskin model (31) assumes that there is no axial flow outside of the loop, water and solute absorbed from tubules into the interstitium enter the peritubular capillaries directly, at each medullary level, and afterward, that absorbate was assumed to have no further interaction with the medulla. Consequently, relatively concentrated ascending fluid does not equilibrate with progressively less concentrated surrounding interstitium. And as a result, that model may be unrealistically dissipative of the axial osmolality gradient. An alternative model formulation is the *central core assumption*, developed by Stephenson (85). In the central core formulation, blood vessels, the interstitial cells, and the interstitial spaces are merged into a single tubular compartment, in which the loops of Henle and collecting ducts interact. Axial flow is allowed within the central core. The central core formulation assumes maximum countercurrent exchange by the vasculature, and is thought to be least dissipative of the axial osmolality gradient. A schematic diagram of the central core model is shown in Fig. 8.

The central core formulation was used in urine concentrating mechanism models of the rat kidney (e.g., (54, 55, 58, 86)) and of the avian (quail) kidney (57, 66). While birds and mammals can regulate blood plasma osmolality by producing a concentrated urine when deprived of water, the avian kidney differs from the mammalian one in that all the ascending limbs of the avian loop of Henle have active transepithelial transport of NaCl, whereas only the thick ascending limbs in the outer medulla of the mammalian kidney have significant active NaCl transport. Thus, the avian urine concentrating mechanism is relatively well understood, and the mathematical models (57, 66) predicted tubular fluid concentrations that are consistent with experimental measurements in Gambel's quail. In contrast, the thin ascending limbs found in the inner medulla have no significant active transport coupled with countercurrent flow does not explain the concentrating process in this region, where the steepest osmotic gradient is generated.

The most influential theory for the generation of the inner medullary osmolality gradient has been the "passive mechanism" hypothesis, proposed independently in 1972 by Kokko and Rector (37) and by Stephenson (85). The passive mechanism depends on the assumption that the interstitium has a much higher urea concentration than NaCl concentration, and that fluid in the ascending limbs has a much higher NaCl concentration than urea concentration. If the ascending thin limb has a sufficiently high permeability to NaCl, and a sufficiently low permeability to urea, then much NaCl will diffuse (passively) from the ascending thin limb lumen into the interstitium, while simultaneously little urea will diffuse from the interstitium into the thin limb lumen. If the transepithelial concentration differences are sustained, the interstitial fluid will be concentrated while the luminal fluid is being diluted. The passive mechanism hypothesis assumes that the concentrations are sustained by continuous diffusion of urea from the collecting duct lumen and by continuous delivery of tubular fluid having a high NaCl concentration to the ascending thin limb; this delivery depends on the descending thin limb having sufficiently low NaCl and urea permeabilities that transepithelial concentration gradients are not dissipated along the course of the descending thin limbs. Thus, the passive mechanism is critically dependent on specific loop-of-Henle permeabilities to NaCl and urea.

However, mathematical models using measured values of urea permeability have generally been unable to predict a significant axial osmolality gradient (80). Indeed, unless idealized tubular transport properties are used, central core models of the rat kidney fail to produce substantial concentrating effect (58, 102). The inconsistency between measured urine osmolalities and the predictions of mathematical models has motivated the formulation of a number of alternative hypotheses, extensively reviewed in Ref. (56).

One attempt to salvage the passive hypothesis is by means of representation of the preferential interactions that arise from three-dimensional medullary structure (87, 103). Both the Hoppensteadt and Peskin model (31) and the central core model (85) assume that solute concentrations are uniform at each medullary level, i.e., tubules (and blood vessels, if represented) were assumed to interact with each other through a common surrounding medium in which solute concentrations varied only along the corticomedullary axis. However, this assumption appears to be inconsistent with anatomical studies. A number of investigators, notably Kriz and colleagues, have reported that the medullary organization of

tubules and vessels is highly structured in a number of mammals (40) including rats and mice (39, 41, 108). Descending and ascending vasa recta form tightly-packed vascular bundles that appear to dominate the histotopography of the outer medulla, especially in the inner stripe. Throughout the outer medulla, collecting ducts are found distant from vascular bundles, whereas the loops of Henle are positioned nearer the bundles. Recent anatomic studies of three-dimensional architecture of rat inner medulla and expression of membrane proteins associated with fluid and solute transport in nephrons and vasculature have revealed transport and structural properties that likely impact the inner medullary urine concentrating mechanism in the rat kidney. These studies have shown that the inner medullary-portion of the descending limbs have at least two or three functionally distinct subsegments, and that clusters of collecting ducts form the organizing motif through the first 3-3.5 mm of the inner medulla (72, 73, 74). Schematic diagrams of tubular organization in the rat renal medulla are shown in Fig. 9 for the inner stripe and upper inner medulla. The structural organization is believed to result in preferential interactions among tubules and vasa recta, interactions that may contribute to more efficient countercurrent exchange or multiplication, to urea cycling and inner medullary urea accumulation, and to sequestration of urea or NaCl in particular tubular or vascular segments (63, 87).

Several investigators have sought to represent aspects of three-dimensional medullary structure in mathematical models of the urine concentrating mechanism (e.g., Ref. (5, 36)) Notably, Wexler, Kalaba, and Marsh (103, 104) developed a model (the "WKM" model) that represented a very substantial degree of structural organization by means of weighted connections between tubules and vessels. Although the WKM model was formulated primarily to investigate the concentrating mechanism of the inner medulla, outer medullary function played a large role in both the original (103) and subsequent WKM studies (87, 89).

More recently, Layton and co-workers developed high-detailed mathematical models for the rat kidney's concentrating mechanism. To represent the radial distribution of tubules and vasa recta, with respect to the vascular bundle, the model separate the medulla into "regions" (see Fig. 10), with radial structure incorporated by assigning appropriate tubules and vasa recta to each region. The region-based approached was used to first develop a model of the rat outer medulla (48, 49, 50), and then used in a series of models of the rat renal medulla (44, 45, 46). These models predicted moderately concentrated urine at flow rates consistent with experimental measurements, but were unable to predict highly concentrated urine. Further progress may be contingent upon new experimental data, especially on the transport properties of the tubules, some of which remain poorly characterized.

5 Epithelial Transport

As the tubular fluid flows along the nephron, its composition is constantly modified as water and solutes are secreted or reabsorbed, based on the animal's daily intake. The secretion or reabsorption of water and solutes is mediated by epithelial transport processes. Transpithelial transport can proceed via transcellular and/or paracellular pathways. Transport pathways across the apical and basolateral cell membranes of the rat proximal convoluted tubule cell, shown in Fig. 11, include Na⁺-glucose cotransporter, Na⁺-H⁺ antiporter, H⁺-pump, K⁺-Cl⁻ cotranspoter, ionic channels, and many more. Given the many different types of pathways that are present in a given cell, mathematical models of epithelial transport are useful for understanding how Na⁺, K⁺, Cl⁻, and acid-base fluxes are coupled, and how overll cell function is regulated.

Modeling of renal epithelial transport has been pioneered by Weinstein, whose early work was dedicated to the proximal tubule (90, 91, 93, 38), focusing on the forces and route of

water transport and subsequently ion transport through the paracellular pathway. An early model (91) of the proximal tubule predicted that solute-solvent coupling represents a major force for water reabsorption, which implies that the observed epithelial water permeability obtained in osmotic experiment is significantly less than the water permeability of the tight junction and cell in parallel. Another interesting aspect of proximal tubular transport considered is the nature of the mechanisms underlying perfusion-absorption balance, which was initially at odds with model predictions (92). To address that discrepancy, Guo et al. (28) hypothesized that proximal tubule brush-border microvilli may serve as mechanosensors that activate luminal transporters or insert membrane transporters in response to changes in tubular fluid flow rate. Du et al. (18) later provided experimental confirmation of the hypothesis that, indeed, Na⁺ and HCO₃ reabsorption varies proportionally with the torque exerted on the microvilli.

Mathematical models have also been developed for other segments of the nephroh, but owing to space constraint those models will only be mentioned briefly. Chang and Fujita developed the first model of the distal tubule (6). Almost a decade later, Weinstein constructed a more comprehensive model (98), and used that model to understand the distribution of K^+ secretion, which was predicted to occur primarily along the connecting tubule. Models of the collecting duct (94, 95, 96, 97) were used to study urinary acidification and other aspects of collecting duct transport, whereas models of the thick ascending limb (70, 69, 99, 100, 101), were used to study transporter function and fluid dilution.

6 Regulation of Oxygen

While oxygen is relatively abundant in the cortex of the rat kidney (\sim 40–50 mmHg), it becomes quite low in the medulla, from \sim 20 mmHg in the outer medulla to \sim 10 mmHg in the inner medulla. That low medullary oxygen availability is in large part a consequence of the high metabolic requirements of medullary thick ascending limbs, which consumes oxygen and energy to actively pump NaCl against a concentration gradient, and the low medullary blood flow (IM blood flow is < 1% of total renal blood flow (12)).

Evans et al. (23) recently argued that arterial-to-venous (AV) oxygen shunting could play an important role in the dynamic regulation of kidney oxygenation as well as the development of renal hypoxia in kidney disease. They proposed that blood flow-dependent changes in AV oxygen shunting may explain why renal oxygen tension is stable when renal blood flow is varied within physiological ranges ($\pm 30\%$ relative to basal levels) and oxygen consumption does not vary significantly. They developed models of oxygen transport in the renal cortex (24, 25), which predict that cortical AV oxygen shunting limits the change in oxygen delivery to cortical tissue and stabilizes tissue oxygen tension when arterial oxygen tension changes, but renders the cortex and perhaps also the medulla susceptible to hypoxia when oxygen delivery falls or consumption increases.

Detailed models of oxygen transport in the outer medulla by Edwards and co-workers (10, 9, 8, 109) have confirmed the suggestion that the countercurrent arrangement of decending and ascending vasa recta in the medulla results in oxygen shunting from descending vasa recta to ascending vasa recta (109), similar to AV oxygen shunting in the cortex, and significantly limits oxygen delivery to the deep medulla. Also, the segregation of descending vasa recta, the main supply of oxygen, at the center and immediate periphery of the vascular bundles limits oxygen reabsorption from descending vasa recta that reach into the inner medulla, thereby preserving oxygen delivery to the inner medulla but severely restricting oxygen distribution to the interbundle region where thick ascending limbs are located. The model predicts that, as a result, the concentrating capacity of the outer medulla is significantly

reduced. The validity of the predicted impact on the concentrating effect depends on the model assumption that medullary thick ascending limbs active Na⁺ transport is supported solely by aerobic metabolism. That assumption, which is based on the observation that the amount of ATP produced by glycolysis in thick ascending limbs is a small proportion of that produced by aerobic metabolism (88), but should perhaps be more thoroughly verified. The oxygen transport models were subsequently extended to represent nitric oxide and its scavenger superoxide (22, 21), both of which modulate renal medullary vascular and tubular function, albeit in opposite ways.

7 Conclusions

Mathematical models of renal transport and dynamics have shed light into various aspects of kidney function and dysfunction. Together with advances in experimental techniques, modeling efforts have the potential of bringing further progress in the understanding of renal function. Indeed, further progress in many modeling areas now depends on new experimental advances, such as *in vivo* and *in vitro* measurements. Thus, it is imperative that modelers ensure that their work is accessible to physiologists and is widely disseminated among the renal community.

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Figure 2.

Schematic representation model TGF system. Hydrodynamic pressure $P_o(t) = P(0, t)$ drives flow into loop entrance (x = 0) at time t. Oscillations in pressure result in oscillations in loop pressure P(x, t), flow rate Q(x, t), radius R(x, t), and tubular fluid chloride concentration C(x, t). Reprinted from Ref. (77).



Figure 3.

Left: Bifurcation diagrams indicating observed behavior of TGF model solutions. Four qualitatively different model solutions are possible: (1) a regime having one stable, time-independent steady-state solution (labelled "Steady State"); (2) a regime having one stable oscillatory solution only, with fundamental frequency f(``1-fLCO"); (3) a regime having one stable oscillatory solution only, with frequency $\sim 2f(``2-fLCO")$ and (4) a regime having two possible stable oscillatory solutions, of frequencies $\sim f$ and $\sim 2f(``1,2-fLCO")$. Reprinted from Ref. (52). Right: Oscillations in SNGFR and TAL tubular fluid Cl⁻ concentration and at the macula densa obtained using τ and γ values denoted by the point **B3**.

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Figure 4. Typical TGF response, with operating point (Q, C_{MD}) = (30, 32)

Figure 5.

A schematic drawing of two short-looped nephrons and their afferent arterioles (AA). The arterioles branch from a small connecting artery (unlabeled), which arises from a cortical radial artery (CRA). The nephron consists of the glomerulus (G) and a tubule having several segments, including: the proximal tubule (PT), the descending limb (DL), the thick ascending limb (TAL), and the distal convoluted tubule (DCT). Each nephron has its glomerulus in the renal cortex, and each short-looped rat nephron has a loop that that extends into the outer medulla of the kidney. The axis on the TAL of the lower nephron corresponds to the spatial axis used in the model (vide infra, Section 2.1); in this figure distance is indicated in terms of fractional (nondimensional) TAL length. Tubular fluid from the DL flows into the TAL lumen at x = 0; the chloride concentration of TAL luminal fluid is sensed by the macula densa (MD) at x = 1. The MD, a localized plaque of specialized cells, forms a portion of the TAL wall that is separated from the AA by a few layers of extraglomerular mesangial cells; in this figure, the MD is part of the short TAL segment that passes behind the AA. Fluid from the DCT enters the collecting duct system (not shown), from which urine ultimately emerges. Structures labeled on one nephron apply to both nephrons. (Figure and legend adapted from Ref. (75).)

Figure 6.

A: Steady-state diameter at renal arteriolar pressure of 60 to 180 mmHg. B: Percent change from basal (60 mmHg) diameter, fitted using a simple quadratic equation. Reprinted from Ref. (64).

Figure 7.

Top-left: A flow chart that illustrates the steps by which periodic oscillations in cytosolic calcium concentration give rise to spontaneous vasomotion of the model afferent arteriole in Refs. (11, 83). Top-right: Average vessel inner diameter as a function of steady-state transmural pressure, with and without a myogenic response. A: Oscillations in Ca²⁺ and K⁺ currents (denoted I_{Ca} and I_{K} , respectively) and membrane potential v. D: Oscillations in intracellular arteriolar inner diameter. Reprinted from Ref. (11).

Figure 8.

Schematic diagram of the central core model. Panel A, tubules along spatial axis. DL, descending limb; AL, ascending limb; CD, collecting duct; CC, central core. Arrows, steady-state flow directions. Heavy lines, water-impermeable boundaries. Panel B, cross-section showing connectivity between CC and other tubules. Modified from Ref. (47).

Figure 9.

Schematic diagrams of tubular organization in the rat renal medulla. A: cross section through the inner stripe of outer medulla, where tubules appear to be organized around a vascular bundle. B: cross section through the upper inner medulla, where tubules and vessels are organized around a collecting duct cluster. Inset: schematic configuration of a collecting duct, ascending vasa recta (AVR), an ascending thin limb, and a nodal space. Reprinted from Ref. (51).

Figure 10.

Schematic diagram of a cross section through the outer stripe, inner stripe, upper inner medulla (IM), mid-IM, and deep IM, showing regions and relative positions of tubules and vessels. Decimal numbers in panel A indicate relative interaction weightings with regions. R1, R2, R3, and R4, regions in the outer medulla; R5, R6, and R7, regions in the IM. SDL, descending limbs of short loops of Henle. SAL, ascending limbs of long loops of Henle. LDL, descending limb of long loop of Henle. LAL, ascending limb of long loop of Henle. Subscripts 'S,' 'M,' and 'L' associated with a LDL or LAL denote limbs that turn with the first mm of the IM (S), within the mid-IM (M), or reach into the deep IM (L). CD, collecting duct. SDV, short descending vasa recta. SAV3 and SAV4, two populations of short ascending vasa recta. LDV, long descending vasa recturn. LAV1, LAV2, ..., LAV7, populations of long ascending vasa recta. Reprinted from Ref. (45).

Figure 11.

Transport pathways across apical and basolateral membranes of the proximal convoluted cell of the rat. Reprinted from Ref. (93).