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Bifurcation study of blood flow control in the kidney

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ABSTRACT

Renal blood flow is maintained within a narrow window by a set of intrinsic autoregulatory mechanisms. Here, a mathematical model of renal hemodynamics control in the rat kidney is used to understand the interactions between two major renal autoregulatory mechanisms: the myogenic response and tubuloglomerular feedback. A bifurcation analysis of the model equations is performed to assess the effects of the delay and sensitivity of the feedback system and the time constants governing the response of vessel diameter and smooth muscle tone. The results of the bifurcation analysis are verified using numerical simulations of the full nonlinear model. Both the analytical and numerical results predict the generation of limit cycle oscillations under certain physiologically relevant conditions, as observed *in vivo*.

1. Introduction

Many biological systems exhibit spontaneous limit cycle oscillations. The mechanisms that give rise to such biological oscillators are intrinsically nonlinear; indeed, no linear system has robust limit cycle behavior. One example of biological limit cycle oscillations occurs in the kidney [1,2]. The kidney regulates the balance of water, salt, and blood pressure via filtration, reabsorption, and secretion of the appropriate amounts of water and solutes across the epithelia of renal tubules known as nephrons. A nephron consists of a glomerulus, which is a bundle of capillaries, and a tubule whose walls consist of a single layer of epithelial cells. Blood is delivered via the afferent arteriole to the glomerulus, where the filtration process begins. Blood cells and large plasma proteins are retained in the blood stream, while fluid and smaller solutes (now called filtrate) are forced out into Bowman's capsule, the entrance of the tubule. The resulting filtrate travels through the tubule, where the transformation of the filtrate into urine is initiated. Along the tubule, the filtrate (tubular fluid) composition is altered by transport processes in the epithelial cells of the renal tubule. In particular, the thick ascending limb (TAL), a water-impermeable portion of the tubule in a zone called the loop of Henle, actively and passively transports sodium chloride from tubular fluid into the interstitium outside of the tubule where molecules and ions can be reabsorbed by the bloodstream through nearby capillaries.

To maintain normal renal function, fluid flow through the nephron must be kept within a narrow range. This is accomplished primarily by two physiological regulatory mechanisms: the myogenic response and tubuloglomerular feedback (TGF). The myogenic response induces vasoconstriction in response to increases in blood pressure. In TGF, changes in the chloride ion concentration in the TAL are detected by a collection of epithelial cells at the exit of the TAL called the macula densa (MD). This generates feedback signals that alter the afferent arteriolar smooth muscle tone in order to regulate the glomerular filtration rate. Fig. 1 is a schematic diagram illustrating the anatomy involved in these regulatory mechanisms. The reader may also refer to [3] for additional detail on kidney physiology.

Spontaneous fluctuations of fluid flow and oscillating intratubular pressure have been observed in the rat kidney [1,2,4–8]. Mathematical models of the TGF mechanism have successfully simulated these phenomena [9–12], and sensitivity analysis of these models has suggested the oscillatory or steady state behavior depends on physical and transport characteristics of the TAL. We have recently developed a renal hemodynamics model that combines both the myogenic and TGF mechanisms and used the model to study renal autoregulation [13]. In the present study, we use this model to explore the influence of key bifurcation parameters, including the feedback loop sensitivity, delay, and time constants that govern changes in the diameter and smooth muscle tone of the afferent arteriole. Frequencies of

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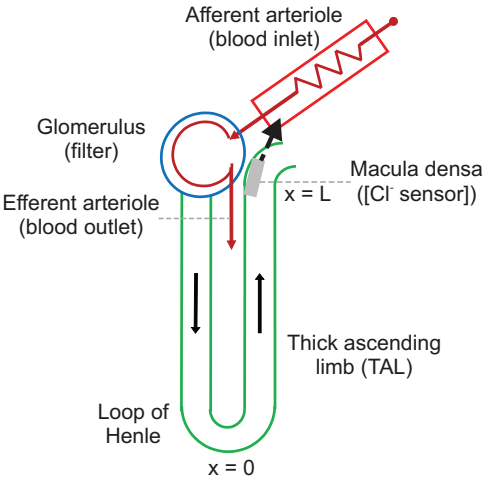

Fig. 1. Schematic diagram of the major components of a kidney nephron. As detailed in Section 2, the present model includes a partial differential equation (PDE) for the chloride ion concentration in the thick ascending limb (TAL), and ordinary differential equations (ODEs) for the afferent arteriolar diameter and smooth muscle tone. The chloride concentration at the end of the TAL is sensed by the macula densa (MD), causing adjustments in the afferent arteriolar diameter and tone, which in turn impact the chloride ion concentration by changing the flow rate entering the TAL.

periodic solutions simulated from our model are in agreement with those observed in the literature [14].

We present the details of the first analytical bifurcation analysis on the renal hemodynamics model with both autoregulatory mechanisms. We compare the bifurcation results to the full numerical simulations of the mathematical model for certain parameter values. The bifurcation analysis allows us to understand the global behaviors of the model (i.e., its behaviors over a very large range of parameters), as opposed to direct numerical simulations, which typically cover only a small range of parameters and must be repeated for each combination of parameter values. The major contribution of the present work is the mathematical formulation for the bifurcation analysis that facilitates the exploration of the parameter space in a way that augments the current experimental capabilities for determining the physiological responses in different parameter ranges.

2. Model formulation

The mathematical model used in this study to investigate potential bifurcation parameters was recently described [13]. Briefly, the model captures the flow dynamics along a short loop of Henle in a rat kidney by coupling a partial differential equation (PDE) describing chloride ion transport along the TAL of a short-loop nephron with a system of ordinary differential equations (ODEs) describing vessel wall mechanics of the afferent arteriole. The resulting system includes the effects of both the myogenic and TGF responses. The model takes the form

$$\frac{\partial}{\partial t}C(x,t) = -\left(\frac{1}{\pi r^2}\right)F(D(t))\frac{\partial}{\partial x}C(x,t) - \frac{2}{r}\left(\frac{V_{\max}C(x,t)}{K_m + C(x,t)} + p\left(C(x,t) - C_e(x)\right)\right), \tag{2.1}$$

$$\frac{d}{dt}D(t) = \frac{1}{t_d}\frac{2}{P_{\text{avg},c}}\left(\frac{P_{\text{avg}}D(t)}{2} - T_{\text{total}}(D(t),A(t))\right), \tag{2.2}$$

$$\frac{d}{dt}A(t) = \frac{1}{t_a}\left(A_{\text{total}}(C(L,t-\tau),D(t)) - A(t)\right), \tag{2.3}$$

where $C(x,t)$ is the concentration of chloride ions in the TAL at position x and time t, with $x = 0$ at the bend in the loop of Henle and $x = L$ at the upper end of the TAL at the MD, while $D(t)$ and $A(t)$ are the diameter and smooth muscle tone (activation), respectively, of the afferent arteriole. The functional forms of $F(D(t))$ and $C_e(x)$ are given in Eqs. (2.4)–(2.6). As given explicitly in Eqs. (2.7)–(2.11), T_{total} is a function of $D(t)$ and $A(t)$, while A_{total} is a function of $D(t)$ and $C(L,t-\tau)$. The parameter τ gives the time required for transmitting the signal of the chloride ion concentration sensed in the MD to the afferent arteriole, including any associated lag in response; thus the system is properly one of delay differential equations (DDEs) with time delay τ. Values for all parameters appearing in Eqs. (2.1)–(2.3), as well as parameters appearing in the subsidiary functions detailed below, are given in Table 1. We refer to these as reference values, and to the resulting model solution as the reference state.

The PDE (2.1) represents axial advective chloride ion transport, outward-directed active solute transport, and transepithelial chloride ion diffusion. The flow rate, $F(D(t))$, appearing in the advective term of Eq. (2.1) has the explicit form

$$F(D(t)) = \alpha\beta Q_A = \alpha\beta\frac{\pi D(t)^4\Delta P}{128\,\mu l}. \tag{2.4}$$

Here Q_A is the afferent arteriole flow rate which, in accordance with Poiseuille's law, depends on diameter, $D(t)$; pressure drop along the afferent arteriole, ΔP; viscosity, μ; and afferent arteriole segment length, l. The parameter β represents the fraction of the afferent arteriole flow entering the loop of Henle. The quantity $Q = \beta Q_A$ is commonly referred to as the single nephron glomerular filtration rate (SNGFR), and α is the portion of the SNGFR that is not reabsorbed along the proximal tubule or the descending limb of the loop of Henle before entering the TAL. Note that the TAL is assumed to be water impermeable, so that fluid flow along the TAL is constant in space, although it may vary in time.

The second term in Eq. (2.1) represents active NaCl reabsorption and is assumed to follow standard Michaelis–Menten kinetics. The last term describes chloride ion diffusion across the TAL with permeability p, while $C_e(x)$ is the extratubular chloride ion concentration, which is assumed to be time independent. $C_e(x)$ is given as [11]

$$C_e(x) = C_0(Be^{-2x/L} + (1-B)), \tag{2.5}$$

where

$$B = \frac{1 - C_e(L)/C_0}{1 - e^{-2}}. \tag{2.6}$$

The extra- and intratubular chloride ion concentrations are assumed to be equal at the bend of the loop of Henle, so that the boundary condition for chloride ion concentration is given by a constant: $C(0,t) = C_0 = 275$ mM [11].

We use a previously developed vessel wall mechanics model [22,23] to predict changes in the diameter and smooth muscle tone of the afferent arteriole according to the myogenic and TGF mechanisms. The quantities P_{avg} and $P_{\text{avg},c}$ appearing in Eq. (2.2) refer to midpoint pressures in the afferent arteriole; these are determined by the incoming pressure and pressure drop, i.e., $P_{\text{avg}} = P - \Delta P/2$, where P is the intraluminal pressure entering the afferent arteriole. $P_{\text{avg},c}$ is the midpoint pressure with the control (baseline) incoming pressure of 100 mmHg, whereas P_{avg} may vary. In the present study, the pressure P is fixed at 100 mmHg so that P_{avg} does not change and the dynamics over a wide parameter range can be assessed. In our previous work [13], we explored the effects of pressure change on the system by varying afferent arterial pressure between 60 and 180 mmHg. Future studies will combine both investigations to assess simultaneously the effect of varying parameter values and average pressure values on the appearance of limit cycle oscillations.

The total tension in the afferent arteriole wall is expressed as a sum of passive and active components:

$$T_{\text{total}}(D(t),A(t)) = T_{\text{pass}}(D(t)) + A(t)T_{\text{act}}^{\max}(D(t)), \tag{2.7}$$