Modeling the Effects of Positive and Negative Feedback in Kidney Blood Flow Control

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Abstract

Blood flow in the mammalian kidney is tightly autoregulated. One of the important autoregulation mechanisms is the myogenic response, which is activated by perturbations in blood pressure along the afferent arteriole. Another is the tubuloglomerular feedback, which is a *negative* feedback that responds to variations in tubular fluid $[Cl^-]$ at the macula densa¹. When initiated, both the myogenic response and the tubuloglomerular feedback adjust the afferent arteriole muscle tone. A third mechanism is the connecting tubule glomerular feedback, which is a *positive* feedback mechanism located at the connecting tubule, downstream of the macula densa. The connecting tubule glomerular feedback is much less well studied. The goal of this study is to investigate the interactions among these feedback mechanisms and to better understand the effects of their interactions. To that end, we have developed a mathematical model of solute transport and blood flow control in the rat kidney. The model represents the myogenic response, tubuloglomerular feedback, and connecting tubule glomerular feedback. By conducting a bifurcation analysis, we studied the stability of the system under a range of physiologically-relevant parameters. The bifurcation results were confirmed by means of a comparison with numerical simulations. Additionally, we conducted numerical simulations to test the hypothesis that the interactions between the tubuloglomerular feedback and the connecting tubule glomerular feedback may give rise to a yet-to-be-explained low-frequency oscillation

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¹The macula densa is a cluster of specialized cells lining the wall of the cortical thick ascending limb at the transition to the distal convoluted tubule.

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that has been observed in experimental records.

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1. Introduction

The kidney performs the essential physiological functions of regulating the balance of water, salt, and blood pressure. This is accomplished by filtering, reabsorbing, and secreting controlled amounts of solute and water along its functional unit called the nephron (Eaton and Pooler, 2013). A nephron consists of the glomerulus, made up of a bundle of capillaries, and a renal tubule, which is lined by a single layer of epithelial cells. The rat kidney contains $\sim 40,000$ nephrons (Pennell et al., 1974), whereas the human kidney contains ~ 1 million nephrons. Blood is delivered by the afferent arteriole to the glomerulus, where the filtration process allows only fluid and small solutes to enter the nephron, while keeping the larger blood cells and proteins in the bloodstream. The filtrate, having entered the nephron, begins the process of being transformed into urine. The amount of filtrate entering the nephron (called glomerular filtration rate (GFR)) has a significant impact on the delivery of water and electrolytes to the distal nephron segments and thus on renal function.

Single-nephron GFR (SNGFR) is determined, in large part, by blood pressure. In this study, we will consider autoregulatory mechanisms that control SNGFR by adjusting the muscle tone of the afferent arteriole (Layton, 2015). When the afferent arteriole constricts, vascular resistance increases, resulting in lower blood pressure downstream and reduced SNGFR. Conversely, vasodilation elevates SNGFR. One of the key regulators of GFR is the myogenic response, which induces vasoconstriction in response to elevations in blood pressure.

A second key regulator of GFR is tubuloglomerular feedback (TGF). TGF is activated by the perturbations in the $[\text{Cl}^-]$ in the tubular fluid flowing past the macula densa, which is a cluster of specialized cells located in the renal tubule wall near the end of the thick ascending limb (TAL) of the loop of Henle (Schnermann and Briggs, 2012). If the macula densa $[\text{Cl}^-]$ falls below its target value, TGF acts to restore equilibrium by inducing a vasodilation of the afferent arteriole to increase SNGFR. The resulting higher tubular flow and shorter tubular fluid transit time decreases NaCl reabsorption along the

Figure 1: A schematic of the model feedback systems. The two arrows represent signals from tubuloglomerular feedback (TGF, at $x = L_{TGF}$) and connecting tubule glomerular feedback (CTGF, at $x = L_{CTGF}$).

TAL and elevates macula densa $[Cl^-]$.

A third autoregulatory feedback mechanism is associated with the connecting tubule, which is a nephron segment downstream of the TAL (see Fig. 1). It has been observed experimentally that increasing NaCl delivery to the connecting tubule dilates the afferent arteriole, in a process known as the connecting tubule glomerular feedback (CTGF) (Ren et al., 2007, 2010). The mediators and the functional roles of the CTGF have remained controversial.

It is well known in dynamical systems that whether a negative feedback mechanism, following a transient perturbation, gives rise to a time-independent steady-state solution or limit-cycle oscillations may depend on the feedback delay and feedback gain. In the context of TGF, the feedback delay is associated with the time lag between the perturbation of the tubular fluid $[Cl^-]$ at the macula densa and the resulting full constriction or dilation of the afferent arteriole. It has been demonstrated both in biological experiments and mathematical modeling studies that, given a sufficiently long feedback delay and a sufficiently large feedback gain, the TGF system

Figure 2: Experimental pressure record from proximal tubule of Wistar-Kyoto (WKY) rat showing a spontaneous limit-cycle oscillation (panel a) and the power spectrum for that limit cycle oscillation, in arbitrary units, showing relative strength of frequency components (panel b). Figure adapted from Holstein-Rathlou and Leyssac (1986) with permission.

may give rise to oscillations in SNGFR, tubular flow, and tubular fluid $[Cl^-]$ (Layton and Edwards, 2014). These TGF-mediated oscillations exhibit a fundamental frequency of $\sim 25\text{--}40$ mHz; see Fig. 2. Interestingly, experimental records have also revealed the imprint of a much slower, and somewhat weaker, oscillation, at a low frequency of < 10 mHz (Holstein-Rathlou and Leyssac, 1986); that slow mode cannot be explained solely by TGF. The mediators of this slow oscillation have yet to be identified.

In this study, we investigate our hypothesis that the interactions of TGF and CTGF may generate oscillations having a frequency substantially lower than the fundamental TGF frequency. The fundamental frequency of a feedback-mediated limit-cycle oscillation is determined, in large part, by the signal transit time. In the context of renal hemodynamics, this transit time

corresponds to the time it takes for a fluid packet to travel from the glomerulus to the site where the signal is sensed. For TGF, that signal sensing site is the macula densa; for CTGF, it is the connecting tubule. Because the connecting tubule is located downstream of the macula densa (see Fig. 1), the transit time associated with the CTGF is larger than that of the TGF. Thus, if CTGF were to generate oscillations, those oscillations are expected to exhibit a fundamental frequency lower than that of TGF. However, normally positive feedback like CTGF does not, by itself, generate oscillations. Now because the TGF and CTGF share the same activator in the afferent arteriole, the CTGF-induced changes in SNGFR can be viewed as perturbations to TGF. That is, the interactions between TGF and CTGF may yield limit-cycle oscillations that exhibit two major frequencies, one that corresponds to the TGF fundamental frequency ($\sim 25\text{--}40$ mHz), and another that corresponds to the lower CTGF fundamental frequency.

To assess the validity of the aforementioned hypothesis and to better understand the effects of the interactions between TGF and CTGF, we have extended a previously-applied model of the TGF system (Arciero et al., 2015) to include CTGF. We then conduct a bifurcation analysis on this new model to examine the effects of key parameters such as feedback loop sensitivity, feedback delay, and time constants for the response of the diameter and smooth muscle tone of the afferent arteriole. Model results suggest that the interactions between TGF and CTGF indeed produce a slow oscillation, although that oscillation appears to be transient.

2. Model Equations

The mathematical model we use to investigate the interactions between TGF and CTGF is based on a recently published model of TGF (Arciero et al., 2015; Ford Versypt et al., 2015). Briefly, the model describes flow dynamics along a superficial nephron² in a rat kidney by coupling partial differential equations (PDEs) describing $[\text{Cl}^-]$ transport along the nephron with a system of ordinary differential equations (ODEs) describing the vessel

²In a rat kidney, nephrons can be classified as superficial or juxtamedullary. The glomeruli of the superficial nephrons are located near the surface of the cortex, and their loops of Henle turn at the outer-inner medullary boundary. The glomeruli of the juxtamedullary nephrons are located close to the corticomedullary boundary, and their loops of Henle reach into the inner medulla (Eaton and Pooler, 2013).

wall mechanics of the afferent arteriole. The updated system includes the effects of the myogenic responses, TGF and CTGF.

Via Na-K-ATPase, the TAL actively reabsorbs Na^+ from tubular fluid into the general circulation; Cl^- reabsorption follows via a favorable transmural electrochemical gradient. Because the TAL walls are nearly water impermeable, NaCl transport is not accompanied by water loss, and the tubular fluid $[\text{Cl}^-]$ concentration progressively decreases along the TAL. Thus, the TAL is an important segment of the TGF system, and its transport properties allow it to act as a key operator of the TGF system. The model explicitly represents the TAL and the contiguous distal convoluted tubule. The model TAL extends from its connection to the upstream descending limb (at $x = 0$) to the site of the macula densa ($x = L_{\text{TGF}}$), where the TGF signal is sensed. The model distal tubule extends from $x = L_{\text{TGF}}$, its connection to the TAL, to $x = L_{\text{CTGF}}$, where the CTGF signal is sensed. Below we describe the system of equations that represent tubular fluid and solute transport. $C(x, t)$ is the tubule fluid chloride concentration at time t and position x (see Fig. 1). The PDEs describing Cl^- conservation (Eqs. 1 and 2) are coupled to a system of ODEs governing the diameter $D(t)$ and the smooth muscle activation $A(t)$ of the afferent arteriole (Eq. 3 and 4).

$$\begin{aligned} \pi r^2 \frac{\partial}{\partial t} C(x, t) = & -\frac{\partial}{\partial x} [F_{\text{TAL}}(D(t)) C(x, t)] \\ & - 2\pi r \left(\frac{V_{\text{max}, \text{TAL}} C(x, t)}{K_{m, \text{TAL}} + C(x, t)} + p(C(x, t) - C_e(x)) \right) \end{aligned} \quad 0 \leq x \leq L_{\text{TGF}} \quad (1)$$

$$\begin{aligned} \pi r^2 \frac{\partial}{\partial t} C(x, t) = & -\frac{\partial}{\partial x} [F_{\text{DT}}(D(t), x) C(x, t)] - 2\pi r \left(\frac{V_{\text{max}, \text{DT}} C(x, t)}{K_{m, \text{DT}} + C(x, t)} \right) \end{aligned} \quad L_{\text{TGF}} < x \leq L_{\text{CTGF}} \quad (2)$$

$$\frac{d}{dt} D(t) = \frac{1}{t_d} \frac{2}{P_{\text{avg}, c}} \left(\frac{P_{\text{avg}} D(t)}{2} - T_{\text{total}}(D(t), A(t)) \right) \quad (3)$$

$$\frac{d}{dt} A(t) = \frac{1}{t_a} \left(A_{\text{total}}(C(L_{\text{TGF}}, t - \tau_{\text{TGF}}), C(L_{\text{CTGF}}, t - \tau_{\text{CTGF}}), D(t)) - A(t) \right) \quad (4)$$

The PDE for $C(x, t)$ is defined in a piecewise manner: as previously noted, $0 \leq x \leq L_{\text{TGF}}$ corresponds to the TAL, whereas $L_{\text{TGF}} < x \leq L_{\text{CTGF}}$

corresponds to the distal tubule (DT). Along both segments, the first term on the right-hand-side of each of Eqs. 1 and 2 represents advective transport; the second term describes transmural solute transport by means of Michaelis-Menten kinetics and, in Eq. 1, also by passive diffusion with tubular permeability p . For simplicity, the model assumes that transmural Cl^- transport along the distal tubule is entirely by active transport. In Eq. 1, $C_e(x)$ denotes extratubular (interstitial) $[\text{Cl}^-]$, which exhibits a decreasing axial gradient because the active NaCl reabsorption from the TAL elevates interstitial $[\text{Cl}^-]$ towards the loop bend ($x = 0$):

$$C_e = C_0(Be^{-2x/L_{\text{TGF}}} + (1 - B)), \quad 0 \leq x \leq L_{\text{TGF}} \quad (5)$$

where B is

$$B = (1 - C_{e,\text{MD}}/C_0)/(1 - e^{-2}) \quad (6)$$

B is defined so that at the macula densa, $C_e(L_{\text{TGF}}) = C_{e,\text{MD}} = 150$ mM. We assume that the intra- and extratubular $[\text{Cl}^-]$ at the bend of the loop of Henle (i.e., $x = 0$) are both taken to be $C_0 = C(0, t) = 275$ mM.

As previously noted, the TAL is water impermeable; thus, its tubular fluid flow F_{TAL} is constant in space and depends only on the afferent arteriole diameter $D(t)$. In contrast, the distal tubule is water permeable; thus, its tubular fluid flow F_{DT} not only depends on $D(t)$ but varies in space as well. For simplicity, we assume that water absorption is constant through the distal tubule; thus, F_{DT} decreases linearly. The equations that describe F_{TAL} and F_{DT} are given by

$$F_{\text{TAL}}(D(t)) = \alpha Q_A = \alpha \frac{\pi D(t)^4 \Delta P}{128 \mu l} \quad (7)$$

$$F_{\text{DT}}(D(t), x) = F_{\text{TAL}}(D(t)) - \frac{x - L_{\text{TGF}}}{L_{\text{CTGF}} - L_{\text{TGF}}} J F_{\text{TAL}}(D(t)) \quad (8)$$

Q_A is the afferent arteriole flow rate which follows Poiseuille's Law and depends on: arteriolar diameter $D(t)$, pressure drop ΔP along the afferent arteriole, blood viscosity μ , and afferent arteriole segment length l . α is the fraction of the afferent arteriole flow that enters the TAL. J denotes fractional water reabsorption along the distal tubule.

In Eq. 3, T_{total} denotes tension in the afferent arteriole smooth muscle wall, and is a sum of passive and active components (denoted T_{pass} and $T_{\text{act}}^{\text{max}}$)

respectively):

$$T_{total}(D(t), A(t)) = T_{pass}(D(t)) + A(t)T_{act}^{max}(D(t)) \quad (9)$$

$$T_{pass}(D(t)) = c_{pass} \exp(c_{pass,1}(D(t)/D_0 - 1)) \quad (10)$$

$$T_{act}^{max} = c_{act} \exp \left[- \left(\frac{D(t)/D_0 - c_{act,1}}{c_{act,2}} \right)^2 \right] \quad (11)$$

Finally, Eq. 4 describes the overall feedback response of the afferent arteriole, driven by variations in $[Cl^-]$ at the macula densa (TGF) and at the distal tubule exit (CTGF), with feedback delays τ_{TGF} and τ_{CTGF} , respectively. To represent both TGF and CTGF, the target activation A_{total} is given by

$$A_{total} = \frac{1}{1 + \exp \left[- S_{tone} \left(C(L_{TGF}, t - \tau_{TGF}), C(L_{CTGF}, t - \tau_{CTGF}), D(t) \right) \right]} \quad (12)$$

where S_{tone} is given by

$$S_{tone} = c_{myo} \frac{P_{avg} D(t)}{2} + \frac{c_2}{1 + \exp[-c_{TGF}(C(L_{TGF}, t - \tau_{TGF}) - C_{TGF,op})]} - \frac{c_3}{1 + \exp[-c_{CTGF}(C(L_{CTGF}, t - \tau_{CTGF}) - C_{CTGF,op})]} - c_{tone} \quad (13)$$

Parameter values are summarized in Table 1. Justification for key parameters for TGF and myogenic response can be found in our previous studies (Arciero et al., 2015; Ford Versypt et al., 2015). The new CTGF parameters are not well characterized. We set c_{CTGF} to the same value as c_{TGF} , and set c_3 to a value similar to (but different from) c_2 so that in the base case the model predicts oscillations.

3. Results

3.1. Derivation of the Characteristic Equation

An animal's breathing, heart beat, movement, and other physical activities may cause a transient perturbation in renal blood pressure. Following a transient perturbation, nephron fluid pressure or flow may tend to an approximation of a time-independent steady state, or it may evolve into a limit-cycle

oscillation. To predict the asymptotic behavior of the *in vivo* tubular fluid dynamics that occurs in response to a transient perturbation, one may perform direct computations of the numerical solution to the model equations (Eqs. 1–4) for a given set of model parameter values. However, such computations involve long-time integration of a system of coupled PDEs, and can thus be time-consuming. Furthermore, because the model involves a large number of parameters, and thus an even larger number of parameter combinations, the PDE solution approach is particularly unfeasible if one wishes to attain a thorough understanding of the systemic dependence of model behavior on the parameter values that fall within the physiologic ranges. Therefore, as an alternative, we have derived and analyzed a characteristic equation from a linearization of the model equations. To that end, we first rewrite Eqs. 1–4 as

$$\frac{\partial}{\partial t}C_1(x, t) = F^{(0)}(D(t))\frac{\partial}{\partial x}C_1(x, t) + F^{(1)}(C_1(x, t)) \quad 0 \leq x \leq L_{\text{TGF}} \quad (14)$$

$$\frac{\partial}{\partial t}C_2(x, t) = \frac{\partial}{\partial x}[F^{(a)}(D(t), x)C_2(x, t)] + F^{(b)}(C_2(x, t)) \quad 0 \leq x \leq L_{\text{DT}} \quad (15)$$

$$\frac{d}{dt}D(t) = F^{(2)}(D(t), A(t)) \quad (16)$$

$$\frac{d}{dt}A(t) = F^{(3)}(D(t), A(t), C_1(L_{\text{TGF}}, t - \tau_{\text{TGF}}), C_2(L_{\text{CTGF}}, t - \tau_{\text{CTGF}})) \quad (17)$$

We have split the piecewise equations 1 and 2 into two variables, C_1 and C_2 , in order to simplify the algebraic manipulation. But the equations remain coupled inasmuch as we require that $C_1(L_{\text{TGF}}) = C_2(0)$ to ensure continuity between the TAL and the distal tubule. By comparing Eqs. 1–4 and Eqs. 14–17, one sees that $F^{(0)}$ and $F^{(a)}$ stand for the fluid flow equations, $F^{(1)}$ and $F^{(b)}$ denote the Cl^- transport terms, and $F^{(2)}$ and $F^{(3)}$ represent factors determining changes in afferent arteriole and muscle activation, respectively. L_{DT} is defined as $L_{\text{CTGF}} - L_{\text{TGF}}$, the length of the distal tubule. We then linearize these equations about a steady state (denoted by $\bar{C}_1(x)$, $\bar{C}_2(x)$, $\bar{D}$, and $\bar{A}$), and assume a solution of the form

$$\begin{pmatrix} C_1(x, t) \\ C_2(x, t) \\ D(t) \\ A(t) \end{pmatrix} = \begin{pmatrix} \bar{C}_1(x) \\ \bar{C}_2(x) \\ \bar{D} \\ \bar{A} \end{pmatrix} + \begin{pmatrix} f_1(x) \\ f_2(x) \\ b_1 \\ b_2 \end{pmatrix} e^{\lambda t} \quad (18)$$

The second term on the right is the deviation from steady state. In accordance with our coupling of C_1 and C_2 , we require that $f_2(0) = f_1(L_{\text{TGF}})$. Also, $f_1(0) = 0$ so that $C_1(0, t) = \bar{C}_1(0)$. Then after much algebraic manipulation (see appendix) we arrive at a characteristic equation that relates λ to all the other parameters:

$$1 = -(K_1 + K_2) \left(\frac{F_D^{(0)}(\bar{D})}{F^{(0)}(\bar{D})} \right) \int_0^{L_{\text{TGF}}} \bar{C}_1(z) e^{\lambda(L_{\text{TGF}}-z)/F^{(0)}(\bar{D})} \exp \left(- \int_z^{L_{\text{TGF}}} \left(\frac{F_{C_1}^{(1)}(\bar{C}_1(y))}{F^{(0)}(\bar{D})} \right) dy \right) dz \\ - K_2 \int_0^{L_{\text{DT}}} \left(\frac{\frac{\partial}{\partial z}(F_D^{(a)}(\bar{D}, z) \bar{C}_2(z))}{F^{(a)}(\bar{D}, z)} \right) \exp \left(\int_z^{L_{\text{DT}}} \left(\frac{\lambda - \frac{\partial}{\partial y} F^{(a)}(\bar{D}, y) - F_{C_2}^{(b)}(\bar{C}_2(y))}{F^{(a)}(\bar{D}, y)} \right) dy \right) dz \quad (19)$$

where K_1 and K_2 are

$$K_1 = \frac{F_A^{(2)} F_{C_1}^{(3)} e^{-\lambda \tau_{\text{TGF}}}}{(\lambda - F_A^{(3)})(\lambda - F_D^{(2)}) - F_A^{(2)} F_D^{(3)}} \quad (20)$$

$$K_2 = \frac{F_A^{(2)} F_{C_2}^{(3)} e^{-\lambda \tau_{\text{CTGF}}}}{(\lambda - F_A^{(3)})(\lambda - F_D^{(2)}) - F_A^{(2)} F_D^{(3)}} \quad (21)$$

and each F^i is evaluated at its appropriate steady state. Finally, define the TGF gain as:

$$\gamma_{\text{TGF}} = \frac{\bar{C}_1'(L_{\text{TGF}}) F_D^{(0)}(\bar{D}) F_A^{(2)}(\bar{D}, \bar{A}) F_{C_1}^{(3)}(\bar{D}, \bar{A}, \bar{C}_1, \bar{C}_2)}{F^{(0)}(\bar{D})} \quad (22)$$

and the CTGF gain as:

$$\gamma_{\text{CTGF}} = \frac{\bar{C}_2'(L_{\text{DT}}) F_D^{(a)}(\bar{D}, L_{\text{DT}}) F_A^{(2)}(\bar{D}, \bar{A}) F_{C_2}^{(3)}(\bar{D}, \bar{A}, \bar{C}_1, \bar{C}_2)}{F^{(a)}(\bar{D}, L_{\text{DT}})} \quad (23)$$

These feedback gain parameters incorporate all of the factors that determine the closed loop feedback loop performance of TGF and CTGF at steady state, including a measure of the sensitivity of the flow rate with respect to changes in afferent arteriolar diameter, a measure of the sensitivity of the arteriolar diameter to activation, and a measure of the arteriolar activation to changes in the appropriate tubular fluid $[\text{Cl}^-]$. In Eq. 22, the product $F_D^{(0)} F_A^{(2)} F_{C_1}^{(3)}$ describes the response of the flow $F^{(0)}$ at L_{TGF} to a perturbation in $[\text{Cl}^-]$

at the MD. Analogously, in Eq. 23, the product $F_D^{(a)} F_A^{(2)} F_{C_2}^{(3)}$ describes the response of the flow $F^{(a)}$ at L_{DT} to a perturbation in $[Cl^-]$ at the end of the distal tubule. We also assume that the fluid is incompressible and thus an increase (or decrease) in flow will result in an instantaneous translation of the concentration profile, so the terms $\bar{C}_1'(L_{TGF})$ and $\bar{C}_2'(L_{DT})$ describe this change. The $F^{(0)}(\bar{D}, L_{TGF})$ and $F^{(a)}(\bar{D}, L_{DT})$ terms in the denominators are the nondimensionalizing constants. The TGF gain takes on positive values, while the CTGF gain has negative values. The opposite signs for the two gains can be attributable to the $F_{C_1}^{(3)}$ and $F_{C_2}^{(3)}$ terms in the numerator. Note that the derivatives are taken with respect to C_1 (for γ_{TGF}) and C_2 (for γ_{CTGF}), which have opposite effects on afferent arteriole. For both gains, a larger absolute value corresponds to a greater sensitivity.

We seek to substitute γ_{TGF} and γ_{CTGF} into the characteristic equation. Notationally, let INT_1 be the integral in the first term of Eq. 19, and INT_2 be the second integral; i.e.,

$$INT_1 = \int_0^{L_{TGF}} \bar{C}_1(z) e^{\lambda(L_{TGF}-z)/F^{(0)}(\bar{D})} \exp\left(-\int_z^{L_{TGF}} \left(\frac{F_{C_1}^{(1)}(\bar{C}_1(y))}{F^{(0)}(\bar{D})}\right) dy\right) dz \quad (24)$$

$$INT_2 = \int_0^{L_{DT}} \left(\frac{\frac{\partial}{\partial z}(F_D^{(a)}(\bar{D}, z)\bar{C}_2(z))}{F^{(a)}(\bar{D}, z)}\right) \exp\left(\int_z^{L_{DT}} \left(\frac{\lambda - \frac{\partial}{\partial y} F^{(a)}(\bar{D}, y) - F_{C_2}^{(b)}(\bar{C}_2(y))}{F^{(a)}(\bar{D}, y)}\right) dy\right) dz \quad (25)$$

Also let

$$K_{denom} = (\lambda - F_A^{(3)})(\lambda - F_D^{(2)}) - F_A^{(2)} F_D^{(3)} \quad (26)$$

With these notations, we rewrite the characteristic equation 19 as

$$1 = -\frac{\gamma_{TGF} e^{-\lambda \tau_{TGF}}}{K_{denom} \bar{C}_1'(L_{TGF})} (INT_1) - \frac{\gamma_{CTGF} e^{-\lambda \tau_{CTGF}}}{K_{denom} \bar{C}_2'(L_{DT})} \left(\frac{F_D^{(0)}(\bar{D})}{F^{(0)}(\bar{D})}\right) \left(\frac{F^{(a)}(\bar{D}, L_{DT})}{F_D^{(a)}(\bar{D}, L_{DT})}\right) (INT_1) \\ - \frac{\gamma_{CTGF} e^{-\lambda \tau_{CTGF}}}{K_{denom} \bar{C}_2'(L_{DT})} \left(\frac{F^{(a)}(\bar{D}, L_{DT})}{F_D^{(a)}(\bar{D}, L_{DT})}\right) (INT_2) \quad (27)$$

3.2. Results of the Bifurcation Analysis

The characteristic equation (Eq. 27) allows us to identify parameter regimes that yield qualitatively different model behaviors. A solution to Eq. 27 is a

number in an infinite series $\lambda_1, \lambda_2, \dots$, where $\lambda_n \in \mathbb{C}$. The real and imaginary parts of λ_n correspond to the strength and frequency, respectively, of a model solution. Specifically, the $\text{Re}(\lambda_n) < 0$ and $\text{Re}(\lambda_n) > 0$ regimes correspond to parameters that yield a time-independent steady state and a limit-cycle oscillation, respectively, following a transient perturbation. Given a 2D parameter space (e.g., corresponding to τ_{TGF} and γ_{TGF}), we identify parameter regions that have different combinations of signs of $\text{Re}(\lambda_n)$. This is done by computing values of parameter pairs that yield $\text{Re}(\lambda_n) = 0$, which indicate a solution bifurcation or transition between stable solution behaviors.

We first consider the effect of TGF parameters on overall system dynamics. Figure 3 shows the root curves ($\text{Re}(\lambda_n) = 0$) obtained for paired values of TGF delay τ_{TGF} and TGF gain γ_{TGF} , chosen within their physiological ranges. Unless explicitly stated otherwise, model parameters are taken from Table 1. Model dynamics exhibit Hopf bifurcations, where model solution changes abruptly from a stable steady state to limit cycles. These results indicate that for sufficiently low TGF gain (i.e., for γ_{TGF} values below both curves), the only stable solution is a time-independent steady state. A typical solution is shown in Fig. 3(a). That solution was obtained via a numerical solution of the system of coupled differential equations 1–4: the PDEs (Eqs. 1 and 2) are first discretized in space to yield a system of coupled ODEs, which are then advanced in time.

Above the curve labeled “ $\text{Re}(\lambda_1) = 0$ ”, a limit-cycle oscillation is a stable solution; a full (PDE) model solution is shown in Fig. 3(b). A fast Fourier transform of the solution yields a frequency of ~ 40 mHz (Fig. 3(d)), which corresponds to the fundamental frequency of TGF. Above the other curve labeled “ $\text{Re}(\lambda_2) = 0$ ”, the stable limit-cycle oscillation has a higher frequency of ~ 100 mHz (Fig. 3(e)). These results are consistent with previous modeling studies (Ford Versypt et al., 2015; Layton et al., 1991, 2006; Ryu and Layton, 2012; Layton et al., 2012).

We then consider the effect of the CTGF on the model’s dynamic behaviors. Figure 4 maps out the qualitatively different behaviors for a range of physiologically relevant TGF delay (τ_{TGF}) and CTGF gain (γ_{CTGF}). We observe that in general, the strength of the positive feedback must be lower than some critical value (γ_{CTGF} less negative) in order to observe limit cycles (Fig. 4 (b)). Below the root curve, i.e., for sufficiently strong positive feedback, renal blood flow deviates sufficiently far from its operating point that limit cycles are no longer possible, resulting in a time-independent steady state (Fig. 4 (a)). Moreover, for a given γ_{CTGF} , the model predicts limit cy-

Figure 3: Bifurcation results for τ_{TGF} versus γ_{TGF} . Simulation results for afferent arteriole diameter following a transient perturbation are shown in (a), (b), and (c) obtained for parameter pairs labeled in the bifurcation diagram. Power spectra corresponding to (b) and (c) are shown in (d) and (e), respectively.

Figure 4: Bifurcation results for τ_{TGF} versus γ_{CTGF} . Panel (a), simulations results showing afferent arteriole diameter approaching a time-independent steady state following a transient perturbation, obtained for $(\tau_{TGF}, \gamma_{CTGF}) = (2.0, -0.3827)$. Panel (b), analogous results showing a limit-cycle oscillation, obtained for $(\tau_{TGF}, \gamma_{CTGF}) = (2.5, -0.1094)$.

cles for sufficiently long TGF delay τ_{TGF} , similar to results discussed above (Fig. 3).

The effects of the CTGF parameters (delay τ_{CTGF} and gain γ_{CTGF}) on system dynamics are exhibited in Fig. 5. These results, similar to those in Fig. 4, indicate that oscillatory solutions are permitted for sufficiently weak CTGF gain (less negative γ_{CTGF}). Interestingly, these results suggest that CTGF delay τ_{CTGF} has only minimal effects on the qualitative behavior of the system.

We then investigate the effects of the time constants in the afferent arteriole response (t_d and t_a in Eqs. 3 and 4) on the stability of the model solution.

Figure 5: Bifurcation results for τ_{TGF} versus γ_{CTGF} . Panel (a), simulations results showing afferent arteriole diameter approaching a time-independent steady state following a transient perturbation, obtained for $(\tau_{CTGF}, \gamma_{CTGF}) = (4.0, -0.4922)$. Panel (b), analogous results showing a limit-cycle oscillation, obtained for $(\tau_{CTGF}, \gamma_{CTGF}) = (4, -0.2734)$.

We computed root curves for parameter pairs t_a - τ_{TGF} and for t_d - τ_{TGF} ; see Fig. 6a. Below the root curves, the only stable solution is a time-independent steady state; above the root curves, limit cycles are predicted. Thus, these results indicate that oscillatory solutions can be obtained for sufficiently large TGF delay, consistent with results above, or sufficiently slow afferent arteriole activation response (t_a or t_d).

3.3. Slow oscillations

As previously noted, modeling studies have demonstrated that for some parameters a model of TGF may yield sustained oscillations in tubular fluid

Figure 6: Panel (a), bifurcation diagram for τ_{TGF} versus t_a . Panel (b), bifurcation diagram for τ_{TGF} versus t_d . LCO, limit-cycle oscillations. * indicates base-case parameter values.

and related variables, following a transient perturbation. For an isolated nephron, these TGF-mediated oscillations exhibit a fundamental frequency (30–40 mHz) and/or its harmonics (see Fig. 3). In the next set of simulations, we seek to identify model parameters that give rise to oscillations having also the slower (~ 10 mHz) frequency observed in experimental records (Holstein-Rathlou and Leyssac, 1986).

Figure 7 shows afferent arteriole diameter, macula densa tubular fluid $[\text{Cl}^-]$, and distal tubule fluid $[\text{Cl}^-]$ as functions of time, obtained for two sets of parameters: for results shown in panels (a) and (c), we set $\tau_{\text{TGF}} = 2$, $\tau_{\text{CTGF}} = 8$, $t_d = 2.4$, $t_a = 10$; and for panels (b) and (d), we set $\tau_{\text{TGF}} = 3.5$, $\tau_{\text{CTGF}} = 8$, $t_d = 2$, $t_a = 3.5$. Both sets of simulations exhibit TGF-mediated oscillations that are either sustained (panels (a) and (c)) or transient (panels (b) and (d)). Additionally, a slower oscillation at a frequency of ~ 10 mHz can be observed in the first 800 s. Afterward, that slower mode disappears. Note that for other parameter sets the slow mode may not be present at all; see, e.g., Figs. 4 and 5.

To understand the mechanism leading to the transient nature of the slow oscillations, we examine the behaviors of the tubular fluid $[\text{Cl}^-]$ of the distal tubule outflow. As can be seen in Fig. 7, panels (c) and (d), as long as the distal tubule outflow $[\text{Cl}^-]$ hovers around its operating point, the system's oscillations include a slow mode. However, because the distal tubule feedback is a positive one, once its $[\text{Cl}^-]$ deviates sufficiently far from its operating point, it diverges. As a result, the distal tubule feedback signal becomes

Figure 7: Two simulations showing the imprint of a slow oscillation. Panels (a) and (b), afferent arteriole diameter as a function of time; panels (c) and (d), corresponding $[\text{Cl}^-]$ at the macula densa (blue curves) and at the distal tubule outlet (red curves). In one case (left column), a limit-cycle oscillation is predicted; in the other case (right column), the solution converges to a time-independent steady state. In both cases, the slow mode appears to be transient. Horizontal lines in panels (c) and (d) denote TGF and CTGF $[\text{Cl}^-]$ operating points. See text for parameters.

sustained, not oscillatory, and the slow oscillations disappear.

4. Discussion

The goal of this study is to investigate the effects of the connecting tubule glomerular feedback (CTGF) and its interactions with the tubuloglomerular feedback (TGF) on the dynamic behaviors of tubular flow in the rat kidney. CTGF is a positive feedback mechanism, whereas TGF is a negative feedback.

Negative feedback in biological systems helps maintain homeostasis. For instance, TGF is responsible for balancing salt load and the reabsorptive capacity of the thick ascending limbs. Other biological negative feedback systems include body temperature regulation by the hypothalamus, blood pressure regulation signals, blood sugar regulation via insulin, etc. Indeed, the importance of biological negative feedback is well known. In contrast, biological positive feedbacks are less well studied, although there are classic examples including the lambda phage lysis-lysogeny switch and the bacterial lac operon (Angeli et al., 2004; Gouzé, 1998; DeAngelis et al., 2012; Plahte et al., 1995; Snoussi, 1998; Thieffry, 2007).

To understand the effects and interactions of positive and negative feedback in renal autoregulation, we have extended a previously-applied TGF model (Arciero et al., 2015) to represent the distal tubular segments and the CTGF. TGF and CTGF interact via their common effector, the afferent arteriole. We have conducted a bifurcation analysis of that model, which reveals that, even in the presence of a positive feedback mechanism, the model can generate a number of parameter regions having the potential for different stable dynamic states: a region having one stable, time-independent steady-state solution; a region having one stable oscillatory solution with fundamental frequency; and additional regions having stable oscillatory solutions with higher frequencies. Numerical solutions of the full equations similarly exhibit a variety of behaviors in these regions. Model results suggest that CTGF lowers the stability of the system at low TGF delay values (i.e., oscillatory solutions can be obtained at lower TGF gain values) but increases its stability at higher TGF delays (see Fig. 8).

The fundamental frequency of the TGF is $\sim 30\text{--}40$ mHz. Experimental records (Holstein-Rathlou and Leyssac, 1986) have revealed a ~ 10 mHz tubular flow oscillation that cannot be mediated solely by TGF. The origin of that slow oscillation has yet to be identified. Thus, another goal of this study is to determine the extent to which the interactions between TGF and CTGF can generate a slow oscillation. Our hypothesis is that the positive feedback signals from the CTGF can be viewed as perturbations on the TGF system, and owing to the substantially longer CTGF transit time (compared to TGF), any resulting oscillations would have a much lower fundamental frequency. Our simulation results indicate that, for some parameters, the TGF-CTGF model can indeed produce a slow oscillation in addition to the regular TGF-mediated oscillation (see Fig. 7). However, that slow oscillation is significantly weaker compared to experimental records (compare Fig. 2 and

Figure 8: Bifurcation diagram in the $\tau_{\text{TGF}}-\gamma_{\text{TGF}}$ plane, obtained with CTGF (dashed lines) and without CTGF (solid lines).

Fig. 7), and is transient.

A closer look at the simulation results has revealed the reason behind the transience of the slow oscillations: the interactions between TGF and CTGF perturb tubular flow and fluid concentration, including the $[\text{Cl}^-]$ at the distal tubule outflow. When the deviation of distal $[\text{Cl}^-]$ from its operating point becomes sufficiently large, the positive feedback signal from the CTGF drives it further away. Consequently, the CTGF signal becomes sustained rather than oscillatory, resulting in the disappearance of the CTGF-mediated slow oscillation.

The large deviation of distal $[\text{Cl}^-]$ from its operating point (as large as > 15 mM in Fig. 7(c)) may not be physical, due to a feedback mechanism underlying tubular water reabsorption. When tubular fluid osmolality becomes high, water is secreted into the tubule, provided that the tubular epithelium is water permeable, which is true for the distal convoluted tubule. That water entry would lower tubular fluid $[\text{Cl}^-]$, bringing it closer to the operating point. Conversely, when distal tubular fluid $[\text{Cl}^-]$ decreases (as in Fig. 7(d)), water is reabsorbed from the tubule, raising its $[\text{Cl}^-]$. That is, water transport should depend on tubular fluid $[\text{Cl}^-]$ in a way that keeps it close to the operating point. However, our model assumes that water transport is known *a priori* and independent of tubular fluid $[\text{Cl}^-]$. That simplifying assumption is necessary because the model represents only Cl^- , whereas tubular water transport depends on many other solutes such as Na^+ , K^+ , urea, etc. Indeed,

a more realistic model may predict a sustained slow oscillation. Nonetheless, given that an animal's blood pressure is under almost constant perturbations (from breathing, heart beats, etc.), even a transient slow oscillation may well persist long enough to be observed in experimental records.

Despite its limitations, the current model has revealed, *for the first time*, the potential of CTGF as the mediator, or one of the mediators, of the slow oscillation in tubular flow variables, and its role may be revisited using a more comprehensive model.

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Appendix A. Derivation of Characteristic Equation

We linearize Eqs. 14–17 about the steady state $(\bar{C}_1, \bar{C}_2, \bar{D}, \bar{A})$ and drop the steady-state terms to obtain

$$\frac{\partial}{\partial t} \begin{pmatrix} C_1(x, t) \\ C_2(x, t) \\ D(t) \\ A(t) \end{pmatrix} = \begin{pmatrix} F^{(0)}(\bar{D}) \frac{\partial}{\partial x} + F_{C_1}^{(1)}(\bar{C}_1(x)) & 0 \\ 0 & \frac{\partial}{\partial x} F^{(a)}(\bar{D}, x) + F^{(a)}(\bar{D}, x) \frac{\partial}{\partial x} + F_{C_2}^{(b)}(\bar{C}_2(x)) \\ 0 & 0 \\ F_{C_1}^{(3)}(\bar{D}, \bar{A}, \bar{C}_1(L_{\text{TGF}}), \bar{C}_2(L_{\text{DT}})) \mathcal{L}_1 & F_{C_2}^{(3)}(\bar{D}, \bar{A}, \bar{C}_1(L_{\text{TGF}}), \bar{C}_2(L_{\text{DT}})) \mathcal{L}_2 \end{pmatrix} \begin{pmatrix} F_D^{(0)}(\bar{D}) \frac{\partial}{\partial x} \bar{C}_1(x) & 0 \\ \frac{\partial}{\partial x} F_D^{(a)}(\bar{D}, x) \bar{C}_2(x) + F_D^{(a)}(\bar{D}, x) \frac{\partial}{\partial x} \bar{C}_2(x) & 0 \\ F_D^{(2)}(\bar{D}, \bar{A}) & F_A^{(2)}(\bar{D}, \bar{A}) \\ F_D^{(3)}(\bar{D}, \bar{A}, \bar{C}_1(L_{\text{TGF}}), \bar{C}_2(L_{\text{DT}})) & F_A^{(3)}(\bar{D}, \bar{A}, \bar{C}_1(L_{\text{TGF}}), \bar{C}_2(L_{\text{DT}})) \end{pmatrix} \begin{pmatrix} C_1(x, t) \\ C_2(x, t) \\ D(t) \\ A(t) \end{pmatrix} \quad (\text{A.1})$$

where $\mathcal{L}_1 C_1(x, t) := C_1(L_{\text{TGF}}, t - \tau_{\text{TGF}})$ and $\mathcal{L}_2 C_2(x, t) := C_2(L_{\text{DT}}, t - \tau_{\text{CTGF}})$. We then substitute into Eq. A.1 the solution given in Eq. 18 to obtain

$$\lambda \begin{pmatrix} f_1(x) \\ f_2(x) \\ b_1 \\ b_2 \end{pmatrix} = \begin{pmatrix} F^{(0)}(\bar{D}) f_1'(x) + F_{C_1}^{(1)}(\bar{C}_1(x)) f_1(x) + F_D^{(0)}(\bar{D}) \frac{\partial}{\partial x} \bar{C}_1(x) b_1 \\ \frac{\partial}{\partial x} F^{(a)}(\bar{D}, x) f_2(x) + F^{(a)}(\bar{D}, x) f_2'(x) + F_{C_2}^{(b)}(\bar{C}_2(x)) f_2(x) + \frac{\partial}{\partial x} F_D^{(a)}(\bar{D}, x) \bar{C}_2(x) b_1 + F_D^{(a)}(\bar{D}, x) \frac{\partial}{\partial x} \bar{C}_2(x) b_1 \\ F_D^{(2)}(\bar{D}, \bar{A}) b_1 + F_A^{(2)}(\bar{D}, \bar{A}) b_2 \\ F_{C_1}^{(3)}(\bar{D}, \bar{A}, \bar{C}_1(L_{\text{TGF}}), \bar{C}_2(L_{\text{DT}})) f_1(L_{\text{TGF}}) e^{-\lambda \tau_{\text{TGF}}} + F_{C_2}^{(3)}(\bar{D}, \bar{A}, \bar{C}_1(L_{\text{TGF}}), \bar{C}_2(L_{\text{DT}})) f_2(L_{\text{DT}}) e^{-\lambda \tau_{\text{CTGF}}} \dots \\ + F_D^{(3)}(\bar{D}, \bar{A}, \bar{C}_1(L_{\text{TGF}}), \bar{C}_2(L_{\text{DT}})) b_1 + F_A^{(3)}(\bar{D}, \bar{A}, \bar{C}_1(L_{\text{TGF}}), \bar{C}_2(L_{\text{DT}})) b_2 \end{pmatrix} \quad (\text{A.2})$$

From the last row, we solve for b_2 :

$$b_2 = \frac{F_{C_1}^{(3)} f_1(L_{\text{TGF}}) e^{-\lambda \tau_{\text{TGF}}} + F_{C_2}^{(3)} f_2(L_{\text{DT}}) e^{-\lambda \tau_{\text{CTGF}}} + F_D^{(3)} b_1}{\lambda - F_A^{(3)}} \quad (\text{A.3})$$

and substituting this into the equation given by the third row, we obtain an expression for b_1

$$b_1 = \frac{F_A^{(2)} F_{C_1}^{(3)} f_1(L_{\text{TGF}}) e^{-\lambda \tau_{\text{TGF}}} + F_A^{(2)} F_{C_2}^{(3)} f_2(L_{\text{DT}}) e^{-\lambda \tau_{\text{CTGF}}}}{(\lambda - F_A^{(3)})(\lambda - F_D^{(2)} - F_A^{(2)} F_D^{(3)})} \quad (\text{A.4})$$

From the first row, we have the following differential equation:

$$f_1'(x) = \left(\frac{\lambda - F_{C_1}^{(1)}(\bar{C}_1(x))}{F^{(0)}(\bar{D})} \right) f_1(x) - \left(\frac{F_D^{(0)}(\bar{D}) \bar{C}_1'(x)}{F^{(0)}(\bar{D})} \right) b_1 \quad (\text{A.5})$$

And from the second row, the following differential equation results:

$$f_2'(x) = \left(\frac{\lambda - \frac{\partial}{\partial x} F^{(a)}(\bar{D}, x) - F_{C_2}^{(b)}(\bar{C}_2(x))}{F^{(a)}(\bar{D}, x)} \right) f_2(x) - \left(\frac{\frac{\partial}{\partial x} (F_D^{(a)}(\bar{D}, x) \bar{C}_2(x))}{F^{(a)}(\bar{D}, x)} \right) b_1 \quad (\text{A.6})$$

Solving the ODE for f_1 , we obtain

$$f_1(x) = - \left(\frac{F_D^{(0)}(\bar{D})}{F^{(0)}(\bar{D})} \right) b_1 \exp \left(\int_0^x \left(\frac{\lambda - F_{C_1}^{(1)}(\bar{C}_1(y))}{F^{(0)}(\bar{D})} \right) dy \right) \times \int_0^x \bar{C}_1'(z) \exp \left(- \int_0^z \left(\frac{\lambda - F_{C_1}^{(1)}(\bar{C}_1(y))}{F^{(0)}(\bar{D})} \right) dy \right) dz \quad (\text{A.7})$$

Evaluating at $x = L_{\text{TGF}}$, we obtain

$$f_1(L_{\text{TGF}}) = - \left(\frac{F_D^{(0)}(\bar{D})}{F^{(0)}(\bar{D})} \right) b_1 \int_0^{L_{\text{TGF}}} \bar{C}_1'(z) e^{\lambda(L_{\text{TGF}}-z)/F^{(0)}(\bar{D})} \exp \left(- \int_z^{L_{\text{TGF}}} \left(\frac{F_{C_1}^{(1)}(\bar{C}_1(y))}{F^{(0)}(\bar{D})} \right) dy \right) dz \quad (\text{A.8})$$

Recall that our initial condition enforces $f_2(0) = f_1(L_{\text{TGF}})$. Thus, the ODE for f_2 gives

$$f_2(x) = -b_1 \exp \left(\int_0^x \left(\frac{\lambda - \frac{\partial}{\partial y} F^{(a)}(\bar{D}, y) - F_{C_2}^{(b)}(\bar{C}_2(y))}{F^{(a)}(\bar{D}, y)} \right) dy \right) \int_0^x \left(\frac{\frac{\partial}{\partial z} (F_D^{(a)}(\bar{D}, z) \bar{C}_2(z))}{F^{(a)}(\bar{D}, z)} \right) \times$$

$$\exp \left(- \int_0^z \left(\frac{\lambda - \frac{\partial}{\partial y} F^{(a)}(\bar{D}, y) - F_{C_2}^{(b)}(\bar{C}_2(y))}{F^{(a)}(\bar{D}, y)} \right) dy \right) dz + f_1(L_{\text{TGF}}) \quad (\text{A.9})$$

Evaluating this at $x = L_{\text{DT}}$, we get

$$f_2(L_{\text{DT}}) = -b_1 \int_0^{L_{\text{DT}}} \left(\frac{\frac{\partial}{\partial z} (F_D^{(a)}(\bar{D}, z) \bar{C}_2(z))}{F^{(a)}(\bar{D}, z)} \right) \times \exp \left(\int_z^{L_{\text{DT}}} \left(\frac{\lambda - \frac{\partial}{\partial y} F^{(a)}(\bar{D}, y) - F_{C_2}^{(b)}(\bar{C}_2(y))}{F^{(a)}(\bar{D}, y)} \right) dy \right) dz + f_1(L_{\text{TGF}}) \quad (\text{A.10})$$

We combine the expressions for $f_2(L_{\text{DT}})$, $f_1(L_{\text{TGF}})$, and b_1 to obtain the characteristic equation (Eq. 19).

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Table 1: Glossary. AA, afferent arteriole. CTGF, connecting tubule glomerular feedback. DT, distal convoluted tubular. MD, macula densa. TAL, thick ascending limb. TGF, tubuloglomerular feedback. VSM, vascular smooth muscle.

Symbol	Description	Units	Value
α	Fraction of arteriolar flow entering TAL	-	0.0168
C_0	Tubular fluid $[\text{Cl}^-]$ at TAL entrance	mM	275
c_2	VSM TGF sensitivity	cm/dyn	1.80
c_3	VSM CTGF sensitivity	cm/dyn	1.40
c_{act}	VSM peak tension	dyn/cm	274.19
$c_{act,1}$	VSM length dependence	-	0.75
$c_{act,2}$	VSM tension range	-	0.38
c_{CTGF}	VSM $[\text{Cl}^-]$ sensitivity in distal tubule	cm/dyn	3×10^5
c_{TGF}	VSM $[\text{Cl}^-]$ sensitivity in TAL	cm/dyn	3×10^5
$C_{CTGF,op}$	CTGF operating $[\text{Cl}^-]$	mM	21.24
$C_{TGF,op}$	TGF operating $[\text{Cl}^-]$	mM	32.32
$C_{e,MD}$	Interstitial $[\text{Cl}^-]$ at MD	mM	150
c_{myo}	VSM tension sensitivity	cm/dyn	0.159
c_{pass}	Passive tension strength	dyn/cm	220
$c_{pass,1}$	Passive tension sensitivity	-	11.47
c_{tone}	VSM constant	-	13.29
D_0	passive AA diameter	μm	33
J	Fraction of water reabsorbed along DT	-	0.835
$K_{m,DT}$	Michaelis-Menten constant for DT	mM	40.0
$K_{m,TAL}$	Michaelis-Menten constant for TAL	mM	70.0
l	length of AA	cm	0.031
L_{CTGF}	Combined length of TAL & distal tubule	cm	2.5
L_{DT}	Length of distal tubule	cm	2
L_{TGF}	Length of TAL	cm	0.5
p	TAL Cl^- permeability	cm/s	1.5×10^{-5}
P	Tubular fluid pressure at TAL entrance	mmHg	100
ΔP	Pressure drop	mmHg	50
P_{avg}	Midpoint pressure in AA, specified	mmHg	75
$P_{avg,c}$	Midpoint pressure in AA, control state	mmHg	75
Q_A	AA blood flow rate	nl/min	355.4
r	TAL luminal radius	cm	1.0×10^{-3}
τ_{CTGF}	time delay, connecting tubule to AA response	s	8
τ_{TGF}	time delay, MD to AA response	s	4
t_a	time constant for AA activation response	s	10
t_d	time constant for AA diameter response	s	1
μ	Blood viscosity	cP	4.14
$V_{max,DT}$	Maximum active transport rate in DT	mol/(cm ² ·s)	55×10^{-8}
$V_{max,TAL}$	Maximum active transport rate in TAL	mol/(cm ² ·s)	14.5×10^{-9}