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Feedback-Mediated Dynamics in a Model of a Compliant Thick Ascending Limb

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Abstract

The tubuloglomerular feedback (TGF) system in the kidney, which is a key regulator of filtration rate, has been shown in physiologic experiments in rats to mediate oscillations in tubular fluid pressure and flow, and in NaCl concentration in the tubular fluid of the thick ascending limb (TAL). In this study, we developed a mathematical model of the TGF system that represents NaCl transport along a TAL with compliant walls. The model was used to investigate the dynamic behaviors of the TGF system. A bifurcation analysis of the TGF model equations was performed by deriving and finding roots of the characteristic equation, which arises from a linearization of the model equations. Numerical simulations of the full model equations were conducted to assist in the interpretation of the bifurcation analysis. These techniques revealed a complex parameter region that allows a variety of qualitatively different model solutions: a regime having one stable, time-independent steady-state solution; regimes having one stable oscillatory solution only; and regimes having multiple possible stable oscillatory solutions. Model results suggest that the compliance of the TAL walls increases the tendency of the model TGF system to oscillate.

Keywords

renal hemodynamic control; negative feedback loop; delay differential equation; nonlinear dynamics

1. Introduction

The mammalian kidneys are vital organs whose many functions include regulation of acid-base and electrolyte balance, excretion of metabolic waste products, gluconeogenesis, secretion of hormones, as well as the regulation of blood pressure and the maintenance of steady whole-organism water volume [1].

The functional unit of the kidney is the nephron, which consists of a bundle of capillaries, called a glomerulus, and a tubule having walls made up of a single layer of epithelial cells, each with its basement membrane. Forced by blood pressure from the glomerulus, a filtrate of blood plasma enters the tubule, which begins the transformation of this filtrate of blood plasma into urine. Along the tubule, the 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 loop of Henle, actively transports NaCl from tubular fluid into the interstitium, thereby diluting the tubular fluid. (In a rat kidney, there are ~38,000

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loops of Henle [2].) A negative feedback mechanism, called tubuloglomerular feedback (TGF), attempts to maintain the NaCl concentration of the fluid exiting the TAL near a target level by varying the tubular fluid flow rate in the TAL.

The TGF response is mediated by a change in chloride concentration in tubular fluid flowing past the macula densa (MD), a cluster of specialized cells located in the renal tubule wall near the end of the TAL. An elevated chloride concentration in tubular fluid at the MD reduces filtration rate and decreases TAL fluid flow, which allows more time for dilution of the tubular fluid. Conversely, a low chloride concentration at the MD increases tubular fluid flow and raises the chloride concentration at the MD back to its normal target value. By these means, TGF stabilizes the fluid and solute delivery into the distal portion of the loop of Henle, and prevents large imbalances in the rate of filtration relative to the capacity for tubular absorption.

Mathematical models of the TGF system have suggested that, depending on the physical and transport characteristics of the TAL, renal tubular fluid flow and related variables may exhibit regular oscillations or may reach a time-independent steady state after a transient perturbation [3,4]. Our model studies predict that key parameters such as the feedback loop gain, delay, and the luminal volume of the TAL may be crucial bifurcation parameters [5,6,3,4].

Our previous mathematical model of the TGF system consists of simple components that have been individually well-characterized in our publications [3,5,7]. In particular, the TAL is represented by a rigid tube with plug flow that carries only the chloride ion. *In vivo*, however, the TAL likely expands and contracts as luminal fluid flow rate changes, although the wall movements may be hindered by surrounding TALs and connecting tissues. Using a more detailed mathematical model of the nephron that represents hydrodynamic pressure and compliant tubular walls [8,9,10], Marsh and collaborators predicted that a compliant renal tubule will tend to function as a low-pass filter with respect to pressure oscillations. Because our previous rigid tubule model does not compute hydrodynamic pressure but instead prescribes flow rate as a function of predicted single-nephron glomerular filtration rate (SNGFR) [11], one may wonder if the high degree of nonlinearity exhibited by our model may be an artifact of the rigid tubule formulation and that if, instead, our model represented pressure-driven flow in conjunction with compliant TAL walls, then some of our model's predictions might be rendered null and void.

To address these concerns, we developed a TGF model that represents a TAL having pressure-driven flow and compliant walls. To investigate and predict the impact of tubular wall compliance on TGF-mediated dynamics *in vivo*, we have analyzed the model by means of linearization and numerical simulations.

2. Mathematical Model

2.1. Model Equations and Parameters

We describe a mathematical model of a TGF system that represents a TAL with compliant walls. The model is formulated as a boundary value problem, and predicts tubular fluid, fluid pressure, and tubular radius as functions of time and space. At the entrance to the TAL, tubular fluid pressure is given by the TGF response. At the end of the TAL, pressure is assumed to be known *a priori*. However, tubular fluid pressure at the MD is not well-characterized. To avoid that uncertainty, we model a longer tubule: the model represents the portion of a short-loop nephron that extends in space from $x = 0$ at loop bend to $x = L_0$ at the end of the collecting duct, where fluid pressure in rat can be inferred to be 1–3 mmHg, based on measurements in the interstitia, vessels, and the pelvic space [12,13,14]. The tubular

walls are assumed to be compliant, with a radius that depends on transmural pressure gradient. We represent chloride ion (Cl^-), the concentration of which alongside the MD is believed to be the principal tubular fluid signaling agent for TGF activation. Cl^- concentration is represented only along the TAL, which extends in space from $x = 0$ at loop bend to $x = L$ at the MD ($L \leq L_0$). A schematic diagram for the model TGF system is given in Fig. 1.

Fluid motion along the model nephron is modeled as the flow of an incompressible fluid along a narrow compliant tube. Intratubular fluid flow and pressure are described by the coupled partial differential equations

$$\frac{\partial}{\partial x} P(x, t) = - \frac{8\mu}{\pi R(x, t)^4} Q(x, t) \quad (1)$$

$$\frac{\partial}{\partial x} Q(x, t) = - \left(2\pi R(x, t) \frac{\partial R}{\partial P} \right) \frac{\partial}{\partial t} P(x, t) \quad (2)$$

where x is axial position along the nephron ($0 \leq x \leq L_0$), t is time, $P(x, t)$ is the tubular fluid pressure, $Q(x, t)$ is the tubular volume flow, and $R(x, t)$ is the tubular radius. As given by Eq. (1), which represents Poiseuille flow along a narrow tubule in the zero Reynold's number limit, fluid flow along the model nephron is driven by axial pressure gradient. Equation (2) represents the incompressibility constraint or continuity of mass. Equations (1) and (2) are justified in the APPENDIX. The inflow pressure $P_0(t) = P(0, t)$ is given by the TGF response (see below), and the outflow pressure $P_1 = P(L_0, t)$ is considered fixed.

Solute conservation in the TAL's tubular fluid is represented by a hyperbolic partial differential equation

$$\pi R(x, t)^2 \frac{\partial}{\partial t} C(x, t) = -2\pi R(x, t) C(x, t) \frac{\partial}{\partial t} R(x, t) - Q(x, t) \frac{\partial}{\partial x} C(x, t) - 2\pi R_o \left(\frac{V_{\max} C(x, t)}{K_M + C(x, t)} + \kappa (C(x, t) - C_e(x)) \right), \quad (3)$$

where $0 \leq x \leq L$, $C(x, t)$ is TAL tubular fluid chloride concentration, $C_e(x)$ is the extratubular (interstitial) chloride concentration, and R_o is the steady-state TAL radius. The two terms inside the large pair of parentheses on the right-hand side correspond to active solute transport characterized by Michaelis-Menten-like kinetics (characterized by maximum transport rate $V_{\max}$ and Michaelis constant K_M) and transepithelial diffusion (characterized by backleak permeability κ). The boundary condition $C_o = C(0, t)$ is considered fixed.

To represent a compliant tube, the tubular luminal radius is allowed to vary as a function of transmural pressure difference:

$$R(x, t) = \alpha (P(x, t) - P_e(x)) + \beta(x) \quad (4)$$

where $P_e(x)$ is the extratubular (interstitial) pressure, α specifies the degree of tubular compliance, and $\beta(x)$ is the unpressurized tubular radius (see below).

The feedback-mediated loop-bend pressure is given by

$$P_0(t) = P_0 + K_1 \tanh(K_2(C_{op} - C(L, t - \tau))), \quad (5)$$

where K_1 denotes half of the range of pressure variation around its reference value P_0 ; K_2 quantifies TGF sensitivity; the target concentration C_{op} is the time-independent steady-state TAL tubular fluid chloride concentration alongside the MD when $P(0, t) = P_0$; and $C(L, t - \tau)$ is the chloride concentration alongside the MD at the time $t - \tau$ (which is τ seconds before time t), where τ is the TGF delay.

Parameters—Base-case values for model parameters are given in Table 1. The luminal radius parameter $\beta(x)$ is given (in μm) by the piecewise function:

$$\beta(x) = \begin{cases} \beta_0 & 0 \leq x \leq 1.5 \times L \\ \beta_1(x) & 1.5 \times L \leq x \leq L_0 \end{cases} \quad (6)$$

where $\beta_1(x)$ is a cubic polynomial such that $\beta_1(x = 1.5 \times L) = \beta_0$ and $\beta_1(x = L_0) = \beta_2$ [15]. The values β_0 and β_2 are chosen such that at steady state (i.e., with Q assumed constant) the model yields a target average TAL radius and a target outflow pressure $P(L_0)$.

Extracellular concentration is specified by $C_e(x) = C_o(A_1 \exp(-A_3(x/L)) + A_2)$, where $A_1 = (1 - C_e(L)/C_o)/(1 - \exp(-A_3))$, $A_2 = 1 - A_1$, and $A_3 = 2$, and where $C_e(L)$ corresponds to a cortical interstitial concentration of 150 mM. Graphs for $C_e(x)$ and the steady-state profile $C(x, \cdot)$ were given in Figure 1 of Ref. [3].

Numerical method—To compute an approximation for the tubular fluid motions, we take the spatial derivative of Eq. (1) and use the resulting equation to eliminate the fluid flow gradient term $\partial Q / \partial x$ from Eq. (2). That yields an advection-diffusion equation for the pressure P

$$\frac{\partial}{\partial t} P(x, t) - \frac{R(x, t)^2}{4\mu \frac{\partial R}{\partial P}} \frac{\partial}{\partial x} R(x, t) \frac{\partial}{\partial x} P(x, t) = \frac{R(x, t)^3}{16\mu \frac{\partial R}{\partial P}} \frac{\partial^2}{\partial x^2} P(x, t), \quad (7)$$

subject to the boundary conditions $P(0, t) = P_0(t)$ and $P(L, t) = P_1$.

Equation (7) was integrated in time by means of a numerical method that is second order in space and time. Let Δx denote the spatial mesh interval, and let Δt denote the time step interval. We denote $P(j\Delta x, n\Delta t)$ by P_j^n ; analogous notation is used for other functions of x and t . To advance P by one time step, we discretized Eq. (7), and we solved for P_j^{n+1} .

The discretized version of Eq. (7), was given by

$$\begin{aligned}
& \left(\frac{P_j^{n+1} - P_j^{n-1}}{2\Delta t} \right) \\
& - \left(\frac{(R_j^n)^2}{4\mu\alpha} \right) \left(\frac{R_{j+1}^n - R_{j-1}^n}{2\Delta x} \right) \left(\frac{(P_{j+1}^n + \Delta P_{j+1}^n) - (P_j^n + \Delta P_j^n)}{\Delta x} \right) \\
& = \frac{(R_j^n)^3}{2 \cdot 16\mu\alpha} \left(\frac{P_{j+1}^{n+1} - 2P_j^{n+1} + P_{j-1}^{n+1}}{(\Delta x)^2} + \frac{P_{j+1}^{n-1} - 2P_j^{n-1} + \Delta P_{j-1}^{n-1}}{(\Delta x)^2} \right),
\end{aligned} \tag{8}$$

where

$$\Delta P_j^n = \frac{1}{2} (\text{sign}(P_{j+1}^n - P_j^n) + \text{sign}(P_j^n - P_{j-1}^n)) \times \frac{1}{2} \min(|P_{j+1}^n - P_j^n|, |P_j^n - P_{j-1}^n|) \tag{9}$$

with

$$\text{sign}(x) = \begin{cases} 0, & \text{if } x \leq 0, \\ 1, & \text{otherwise} \end{cases}; \tag{10}$$

and where $\frac{\partial R}{\partial P}$ in Eq. (7) was replaced by α (from Eq. (4)). Equations (8)–(10) yield a system of coupled linear equations, which were solved at each time step n .

Numerical solutions to the solute conservation equation (3) were found as previously described [16, 17]: a spatially second-order ENO method was used in conjunction with Heun's method to obtain a method that was second-order in both space and time. A time step of $\Delta t = 1/320$ s was applied on a spatial grid of 1280 subintervals, which yielded a space step of $\Delta x = L_0/1280 = 2/1280$ cm.

3. The Characteristic Equation

Renal blood pressure undergoes almost constant fluctuations, caused by the animal's respiration, heart beat, or change in posture. Following a perturbation, tubular fluid pressure (or flow) may tend to an approximation of a time-independent steady state, or it may evolve into a regular, sustained, stable oscillation, i.e., a limit-cycle oscillation (LCO). Given a set of model parameters, one may predict the asymptotic behavior of the *in vivo* tubular fluid dynamics that occurs in response to a perturbation by means of a direct computation of the numerical solution to the model equations Eqs. (3) and (7). However, such computations can be time-consuming, and may not be feasible if one wishes to attain a thorough understanding of the systematic dependence of model behavior on the parameter values that fall within the physiologic range. Thus, as an alternative, we derived and analyzed a characteristic equation from a linearization of the model equations.

We first nondimensionalize Eqs. (7) and (3) by letting $\tilde{x} = x/L$, $\tilde{t} = t/T_o$, $\tilde{\tau} = \tau/T_o$, $\tilde{c}_{A_o} = c_{A_o}/c_{A_o}$ (where $c_{A_o} = 2\pi R_o$), $\tilde{C} = C/C_o$, $\tilde{C}_e = C_e/C_o$, $\tilde{Q} = Q/Q_o$, $\tilde{V}_{\max} = V_{\max}/(C_o Q_o/(c_{A_o} L))$, $\tilde{K}_M = K_M/C_o$, $\tilde{\kappa} = \kappa/(Q_o/(c_{A_o} L))$, $\tilde{P} = P/P_o$, $\tilde{R} = R/R_o$, $\tilde{\mu} = \mu/(\pi P_o R_o^4/Q_o L)$, where $T_o = \pi R_o^2 L/Q_o$. Then, expressing Eqs. (7) and (3) in terms of nondimensional variables, simplifying, and dropping the tildes, we obtain

$$\frac{\partial}{\partial t}P - \frac{R^2}{4\mu\alpha} \frac{\partial}{\partial x}R \frac{\partial}{\partial x}P = \frac{R^3}{16\mu\alpha} \frac{\partial^2}{\partial x^2}P, \quad (11)$$

$$R^2 \frac{\partial}{\partial t}C = -2RC \frac{\partial}{\partial t}R - Q \frac{\partial}{\partial x}C - \left(\frac{V_{\max}C}{K_M + C} + \kappa(C - C_e) \right). \quad (12)$$

In the derivation of the characteristic equation, we make the simplifying assumption that, at steady state, the tubular fluid pressure is linear and the radius parameter $\beta(x)$ is chosen such that tubular radius is constant. Given these assumptions, we first linearize Eq. (11) by assuming infinitesimal perturbations in C , P , and R :

$$C(x, t) = C_{ss}(x) + \varepsilon C_\varepsilon(x, t) \quad (13)$$

$$P(x, t) = P_{ss}(x) + \varepsilon P_\varepsilon(x, t), \quad (14)$$

$$R(x, t) = 1 + \varepsilon R_\varepsilon(x, t), \quad (15)$$

where $\varepsilon \ll 1$, and $C_{ss}(x)$ and $P_{ss}(x)$ denote the steady-state Cl^- concentration and pressure, respectively. Steady-state tubular radius is assumed to be normalized to 1. Note that from Eq. (1),

$$\frac{\partial}{\partial x}P_{ss}(x) = -8\mu, \quad (16)$$

in nondimensional form, with steady-state tubular flow rate normalized to 1. Note that the π factor does not appear in Eq. (16) because it has been incorporated in the nondimensionalization of μ . Also, from the pressure-radius relationship (4), one can show that

$$\varepsilon R_\varepsilon(x, t) = \alpha(P(x, t) - P_{ss}(x)) = \varepsilon \alpha P_\varepsilon(x, t) \quad (17)$$

Substituting Eqs. (14) and (15) into Eq. (11), we obtain

$$\frac{\partial}{\partial t}(P_{ss} + \varepsilon P_\varepsilon) - \frac{(1 + \varepsilon R_\varepsilon)^2}{4\mu\alpha} \left(\varepsilon \frac{\partial R_\varepsilon}{\partial x} \right) \frac{\partial}{\partial x}(P_{ss} + \varepsilon P_\varepsilon) = \frac{(1 + \varepsilon R_\varepsilon)^3}{16\mu\alpha} \frac{\partial^2}{\partial x^2}(P_{ss} + \varepsilon P_\varepsilon) \quad (18)$$

Keeping only the $\mathcal{O}(\varepsilon)$ terms and simplifying, we obtain the following linear advection-diffusion equation for P_ε

$$\frac{\partial}{\partial t}P_{\varepsilon}+2\frac{\partial}{\partial x}P_{\varepsilon}=\frac{1}{16\mu\alpha}\frac{\partial^2}{\partial x^2}P_{\varepsilon} \quad (19)$$

subject to the boundary conditions:

$$P_{\varepsilon}(0,t)=P'(C_{op})C_{\varepsilon}(1,t-\tau), \quad (20)$$

$$P_{\varepsilon}(L_0,t)=0. \quad (21)$$

The boundary condition at $x = 0$ (i.e., Eq. (20)) specifies the change in P_0 in response to a deviation in MD Cl^- concentration; that response has a delay of τ . The other boundary condition (Eq. (21)) imposes a fixed pressure value at $x = L_0$.

As in previous studies [3,17,18,7], we assume that $C_{\varepsilon}(x, t)$ can be written as $C_{\varepsilon}(x, t) = f(x)e^{\lambda t}$, for some function $f(x)$ and a constant λ . Thus,

$$P_{\varepsilon}(0,t)=P'(C_{op})f(1)e^{\lambda(t-\tau)} \quad (22)$$

Assuming that the solution to Eqs. (19)–(21) takes the form

$$P_{\varepsilon}(x,t)=P'(C_{op})f(1)g(x)e^{\lambda(t-\tau)} \quad (23)$$

we obtain that

$$g(x)=c_+e^{k_+x}+c_-e^{k_-x} \quad (24)$$

where

$$k=16\mu\alpha \pm \sqrt{(16\mu\alpha)^2+16\mu\alpha\lambda}, \quad (25)$$

$$c^{\pm}=\pm \frac{e^{k_{\mp}L_0}}{e^{k_-L_0}-e^{k_+L_0}}. \quad (26)$$

Note that in the rigid-tube limit, i.e., $\alpha \rightarrow 0$, $k^+ - k^- \rightarrow 0$ and $g(x)$ approaches a linear function, thereby approximating the behavior of a rigid tube. Also, when the solution (23) is substituted into (19), the factor $f(1)$ cancels on both sides of the equation; thus, the value of $f(1)$ is not needed in the analysis.

We then linearize the solute conservation equation by substituting Eqs. (13)–(15) and the normalized form of Eq. (1) into Eq. (12):

$$\begin{aligned}
 (1+\varepsilon R_\varepsilon)^2 \frac{\partial}{\partial t} (C_{ss} + \varepsilon C_\varepsilon) &= -2(1 + \varepsilon R_\varepsilon)(C_{ss} + \varepsilon C_\varepsilon) \frac{\partial}{\partial t} (1 + \varepsilon R_\varepsilon) \\
 &+ \frac{(1+\varepsilon R_\varepsilon)^4}{8\mu} \frac{\partial}{\partial x} (P_{ss} + \varepsilon P_\varepsilon) \frac{\partial}{\partial x} (C_{ss} + \varepsilon C_\varepsilon) \\
 &- \left(\frac{V_{\max}(C_{ss} + \varepsilon C_\varepsilon)}{K_M + C_{ss} + \varepsilon C_\varepsilon} + \kappa(C_{ss} + \varepsilon C_\varepsilon - C_e) \right)
 \end{aligned} \quad (27)$$

To simplify notations, we denote the active transport term by $K(C) = V_{\max}C/(K_M + C)$. Thus, at steady state, where the time-derivatives vanish, one obtains that

$$\frac{1}{8\mu} \frac{\partial}{\partial x} P_{ss} \frac{\partial}{\partial x} C_{ss} = K(C_{ss}) + \kappa(C_{ss} - C_e) \quad (28)$$

Keeping only the $\mathcal{O}(\varepsilon)$ terms in (27), and using the relation $\partial R_\varepsilon / \partial t = \alpha \partial P_\varepsilon / \partial t$ from (17), we arrive at the evolution equation for C_ε

$$\frac{\partial}{\partial t} C_\varepsilon = -2\alpha C_{ss} \frac{\partial}{\partial t} P_\varepsilon + \frac{1}{8\mu} \left(4R_\varepsilon \frac{\partial}{\partial x} P_{ss} \frac{\partial}{\partial x} C_{ss} + \frac{\partial}{\partial x} P_{ss} \frac{\partial}{\partial x} C_\varepsilon + \frac{\partial}{\partial x} P_\varepsilon \frac{\partial}{\partial x} C_{ss} \right) - (K'(C_{ss}) + \kappa) C_\varepsilon \quad (29)$$

Substituting $C_\varepsilon(x, t) = f(x)e^{\lambda t}$, $P_\varepsilon(x, t) = P'(C_{op})f(1)g(x)e^{\lambda(t-\tau)}$, and $R_\varepsilon(x, t) = \alpha P_\varepsilon(x, t)$ into the above equation, we obtain

$$\begin{aligned}
 \lambda f(x)e^{\lambda t} &= \frac{1}{8\mu} (C'_{ss} P'(C_{op})f(1)g'(x)e^{\lambda(t-\tau)} \\
 &+ P'_{ss} f'(x)e^{\lambda t} \\
 &+ 4\alpha C'_{ss} P'_{ss} P'(C_{op})f(1)g(x)e^{\lambda(t-\tau)} \\
 &- 2\alpha C_{ss} \lambda P'(C_{op})f(1)g(x)e^{\lambda(t-\tau)} \\
 &- (K'(C_{ss}) + \kappa)f(x)e^{\lambda t}
 \end{aligned} \quad (30)$$

Applying (16), canceling out $e^{\lambda t}$, and rearranging,

$$f'(x) + (\lambda + K'(C_{ss}) + \kappa)f(x) = e^{-\lambda \tau} P'(C_{op})f(1) \left(\frac{1}{8\mu} C'_{ss}(x) g'(x) - 2\alpha g(x) (\lambda C_{ss}(x) + 2C'_{ss}(x)) \right) \quad (31)$$

Recall that Cl^- concentration at the loop bend (i.e., entrance to the TAL) is assumed fixed, so $C_e(0) = f(0)e^{\lambda t} = 0$, which implies that $f(0) = 0$. Hence, we obtain the following solution for (31):

$$f(s) = \exp\left(-\int_0^s (\lambda + K'(C_{ss}) + \kappa) dy\right) P'(C_{op})f(1) \times \int_0^s e^{-\lambda \tau} \left(\frac{1}{8\mu} C'_{ss} g' - 2\alpha g (\lambda C_{ss} + 2C'_{ss}) \right) \exp\left(\int_0^x (\lambda + K'(C_{ss}) + \kappa) dy\right) dx \quad (32)$$

Setting $s = 1$ and canceling the factor $f(1)$,

$$1 = e^{-\lambda \tau} P'(C_{op}) \int_0^1 \left(\frac{1}{8\mu} C'_{ss} g' - 2\alpha g (\lambda C_{ss} + 2C'_{ss}) \right) \exp\left(-\int_x^1 (\lambda + K'(C_{ss}) + \kappa) dy\right) dx \quad (33)$$

To facilitate a comparison of (33) with the characteristic equation derived for a rigid TAL [3], we use the relation

$$\frac{d}{dx} C_{ss}(x) = -K(C_{ss}) - \kappa(C_{ss}(x) - C_e(x)), \quad (34)$$

which can be obtained from (12) by eliminating all the time-derivatives and setting $Q_{ss} = 1$. Upon differentiation, (33) yields

$$C''_{ss}(x) = -K'(C_{ss})C'_{ss}(x) - \kappa(C'_{ss}(x) - C'_e(x)) \quad (35)$$

$$\Rightarrow K'(C_{ss}) + \kappa = \frac{\kappa C''_e}{C'_{ss}} - \frac{C''_{ss}}{C'_{ss}} \quad (36)$$

Now substituting (36) into (33), we get

$$1 = \gamma e^{-\lambda \tau} \int_0^1 e^{-\lambda(1-x)} \left(\frac{1}{8\mu} g' - 2\alpha g \left(\lambda \frac{C_{ss}}{C'_{ss}} + 2 \right) \right) \exp\left(-\int_x^1 \frac{\kappa C'_e}{C'_{ss}} dy\right) dx, \quad (37)$$

where $\gamma \equiv P'(C_{op})C'_{ss}(1)$ is the TGF gain. The gain γ can be related to the parameters K_1 and K_2 in the pressure response function (5). Differentiating Eq. (5) with respect to C and setting C to C_{op} , we obtain that $P'(C_{op}) = K_1 K_2$; thus

$$\gamma = -K_1 K_2 C'_{ss}(1) \quad (38)$$

In the rigid-tube limit, where $\alpha \rightarrow 0$, $g' \rightarrow -1/L_0$; thus, (37) reduces to

$$1 = -\frac{\gamma}{8\mu L_0} e^{-\lambda\tau} \int_0^1 e^{-\lambda(1-x)} \exp\left(-\int_x^1 \frac{\kappa C'_e}{C'_{ss}} dy\right) dx, \quad (39)$$

From [3], the characteristic equation for a TGF model with a rigid TAL is given by

$$1 = -\gamma_{\text{rigid}} e^{-\lambda\tau} \int_0^1 e^{-\lambda(1-x)} \exp\left(-\int_x^1 \frac{\kappa C'_e}{C'_{ss}} dy\right) dx. \quad (40)$$

Comparing (39) and (40), we see that in the limit $\alpha \rightarrow 0$, the gain factors γ for the rigid and compliant TAL models are related by

$$\gamma = 8\mu L_0 \gamma_{\text{rigid}} \quad (41)$$

4. Model Results

To better understand the impacts of the compliance of TAL walls on the dynamics of the TGF system, we conducted a bifurcation analysis for parameter regimes having physiologic relevance. We first used the model's characteristic equation (37) to predict, based on a linearization of the model, parameter boundaries that separate differing behaviors. We then used numerical solutions of the full (nonlinear) model (Eqs. (3)–(7)) to supplement the information provided by the characteristic equation.

A solution to the characteristic equation (37) 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 are indicators of the strength and frequency, respectively, of a solution to the model equations. We determined parameter regions that correspond to differing combinations of signs of $\text{Re}(\lambda_n)$ by computing values of γ – τ pairs that are encompassed within the physiologic range and that correspond to $\text{Re}(\lambda_n) = 0$, roots that may indicate a solution bifurcation or transition between stable solution behaviors. These γ – τ pairs, which form curves in the γ – τ plane, were obtained for two cases: (1) the rigid TAL case, i.e., $\alpha = 0$; (2) the compliant TAL case with baseline compliance $\alpha = 1.33 \times 10^{-5} \text{ cm-mmHg}^{-1}$. The results are shown in Fig. 2, panels A1 and B1, respectively.

For the rigid TAL case, sufficiently small values of γ or τ , i.e., for points (γ, τ) that fall below all curves $\text{Re}(\lambda_n) = 0$, any initial solution, or any transient perturbation of a steady-state solution, results in a solution that converges to the time-independent steady-state solution; that solution, indicated by “Steady State,” is the only stable solution. But for $\tau > 0$ and for values of γ such that the points (γ, τ) are above the curve $\text{Re}(\lambda_n) = 0$ for some n , a

perturbation of the steady-state solution results in a LCO. Previously we also noted that the crossing of the root curves gives rise to new parameter regimes, such as one where $\text{Re}(\lambda_2) > 0$ and $\text{Re}(\lambda_1) < 0$ [5,7], and where a LCO of a frequency corresponding to either $\text{Im}(\lambda_1)$ or $\text{Im}(\lambda_2)$ can be elicited. In other words, model solutions can exhibit multiple stable dynamic modes, i.e., multistability [7].

When TAL tubular wall compliance is introduced, oscillatory states become attainable at notably lower gain values, inasmuch as compliance lowers the root curves, as shown by comparison of Fig. 2A1 and Fig. 2B1. Indeed, the linearized model predicts that for a TGF delay of 3.5 s, which corresponding to a nondimensional value of $\tau = 0.2228$, a LCO can be obtained for a gain value of as low as $\gamma = 1.37$, which seems to be substantially lower than most experimental observations [19]. The degree to which the compliant-TAL model agrees with experimental records will be addressed in the discussion.

We then investigated actual model behaviors, without the linearization that was applied to derive the characteristic equation (37). Numerical solutions were computed for the full, nonlinear model equations (Eqs. (3)–(7)), as a function of selected values of gain γ and delay τ . The results, which were obtained for the rigid-TAL case and for the baseline-compliance case, are summarized in Fig. 2, panels A2 and B2. In the regions marked “Steady State,” $\rho_n < 0$, where $\rho \equiv \text{Re}(\lambda)$, and the only stable solution is the time-independent steady state. In the regions marked “ f_n ,” ($n = 1, 2, 3$ or 4) the only stable solutions elicited by a transient perturbation are LCO-solutions having a frequency f that approximates that corresponding to $\text{Im}(\lambda_n)/(2\pi)$. In some regions, two or more stable LCO, of differing frequencies, can be elicited, depending on initial conditions. For example, in the region marked “ f_1, f_2 ,” one of these corresponds to the f_1 -LCO, and the other to the f_2 -LCO. This parameter region, where the real parts of both λ_1 and λ_2 are both positive, and where the amplitude of $\text{Re } \lambda_2$ is sufficiently large relative to $\text{Re } \lambda_1$, exhibits bistability with respect to model solutions.

Simulated oscillations in SNGFR and tubular fluid Cl^- concentration at the MD were computed for four points, labeled **W**, **X**, **Y**, and **Z** in Fig. 3A. These points correspond to the following pairs of delays and gains: $(\tau_W, \gamma_W) = (0.2, 1.0)$, $(\tau_X, \gamma_X) = (0.4, 3.0)$, $(\tau_Y, \gamma_Y) = (0.2, 3.0)$, and $(\tau_Z, \gamma_Z) = (0.1, 5.0)$. The MD $[\text{Cl}^-]$ profiles corresponding to these points are shown in Figs. 3W–3Z. Point **W**, which lies within the “Steady State” regime, corresponds to a time-independent steady state. Points **X**, **Y**, and **Z**, which lie in the f_1, f_2 , and f_3 regions, respectively, correspond to oscillatory solutions, with LCO frequencies $f_1 = 31.7$, $f_2 = 75.6$, and $f_3 = 125.7$.

In our previous TGF models [7,3], in which the TAL is represented by a rigid tube, the LCO frequencies have been found in good (although not precise) agreement with the frequencies predicted by an approximate formula (derived based, in part, on the assumption that the TAL backleak permeability is zero)

$$f_n \approx \frac{n}{t_o(1+2\tau)}, \quad (42)$$

where τ is in nondimensional form and t_o is the dimensional steady-state transit time. Thus, in those rigid-TAL models, we have, approximately, that $f_2 \approx 2f_1$ and $f_3 \approx 3f_1$. In contrast, the compliant TAL used in this study predicted, for the points considered above, ratios of $f_2/f_1 = 2.385$ and $f_3/f_1 = 3.902$, which deviate substantially from 2 and 3, respectively. That discrepancy is attributable, in most part, to the compliance of the model TAL tubular walls, inasmuch as the TAL was assumed to be rigid in the derivation of the formula (42). Indeed,

as suggested by our results below, our model predicts LCO frequencies that are better approximated by Eq. (42) when the TAL compliance α is reduced.

A comparison between the root curves obtained for the characterization equation corresponding to the *rigid*-TAL model (see Fig. 2A1) and the bifurcation curves obtained for the full model (see Fig. 2A2) indicates that, for the rigid-TAL case, the linearized model and the full, nonlinear model give approximately identical predictions for the boundary between steady-state solutions (marked “ $\text{Re}(\lambda_n) < 0$ ” in Fig. 2A1 and “Steady State” in Fig. 2A2) and oscillatory solutions. This result, obtained for the rigid-tube model, is consistent with the Hartman-Grobman Theorem [20], which concerns the local behavior of dynamic systems in the neighborhood of a hyperbolic fixed point, and, straightly speaking, does not apply to the rigid-tube model equations which comprise of partial differential equations. Our result is also consistent our previous studies of the rigid-tube TGF system [3,5,7]. However, for the basecase *compliant*-TAL case, there is substantial difference between the boundaries between steady-state and oscillatory solutions predicted by the linearized model and by the full model (compare Fig. 2, panels B1 and B2). That discrepancy suggests that certain assumption or assumptions that were made in the derivation of the characteristic equation could be violated in the full model.

One possible source of discrepancy is the assumption of a constant steady-state TAL luminal radius in the derivation of the characteristic equation (see text below Eq. (12)); that assumption was made to keep the derivation tractable. In the full model, however, steady-state TAL luminal radius was allowed to vary in space (see Eq. (6)) so that at a given flow rate Q the model yields a target outflow pressure $P(L_0)$. To assess the extent to which the violation of the constant radius assumption is responsible for the discrepancy between the linearized and full models, we computed numerical solutions for a full model that has a constant steady-state radius. That is accomplished by setting $\beta(x) = R_0 - \alpha(P_{SS}(x) - P_e(x))$.

To apply the same end-tubule pressure $P(L_0)$, we used a longer tube $L'_0 = 2.9075 L_0 = 11.63L$. The value of L'_0 was chosen so that the steady-state pressure P_{SS} satisfies the boundary conditions at $x = 0$ and $x = L_0$ for a constant R_{SS} . The length of the TAL was kept at the basecase value L . This model will be referred to as the “extended-tube model.”

Solution behaviors of the extended-tube model are summarized in Fig. 4. Comparison among the linearized model (Fig. 2B1), the base-case full model (Fig. 2B2), and the extended-tube model (Fig. 4) indicates that steady-state regime predicted by the extended-tube model is smaller compared to the base-case full model, and is, in fact, in better agreement with the linearized model. For example, at $\tau = 0.2$, the linearized model and the extended-tube model predict oscillatory solutions for $\gamma \geq 1.39$ and 1.50 , respectively, a 7.9% difference, whereas the base-case full model predicts oscillatory solutions for $\gamma \geq 1.85$, a critical gain that is 33% higher than that predicted by the linearized model.

Comparing the rigid- and compliant-TAL results in Fig. 2, we again note that, for a given nonzero τ value, oscillatory states are attainable in the compliant-TAL case at substantially lower gain values. These results, which are consistent with the predictions of the linearized models, suggest that TAL compliance increases the tendency of the model TGF system to oscillate.

To further assess the effect of TAL compliance on model stability, we computed numerical solutions for the full model equations for selected values of γ and τ , for the case where TAL compliance is double that of basecase value, i.e., $\alpha = 2.67 \times 10^{-5} \text{ cm}\cdot\text{mmHg}^{-1}$. The results, summarized in Fig. 5, show that doubling TAL compliance further lowered the gain values at which oscillatory states are attainable. For example, for $\tau = 0.2228$, oscillatory states are attainable for $\gamma > 1.80$ for the basecase compliance α . When α is doubled, oscillatory states

are attainable for a lower critical gain value of $\gamma > 1.15$. In contrast, for the rigid-TAL case, a much higher TGF gain is required ($\gamma > 3.15$) for the model to exhibit oscillatory solutions.

The base-case TAL tubular wall compliance was used by Marsh and coworkers [10] and was based on measurements in isolated tubule studies. However, using that compliance value, the base-case model (and to an even larger extent, the model that uses twice that compliance value) predicts oscillatory solutions at gain values that appear to be significantly lower than values suggested by experimental measurements [19]. That discrepancy may be attributed to the likelihood that the effective compliance of the TAL tubular walls may be lowered *in vivo* by the stiffness of the interstitial matrix, and by the resistance exerted by neighboring TALs whose tubular fluid may be oscillating in sync. To estimate the effective TAL compliance *in vivo*, we computed numerical solutions for the full model using a TAL compliance that is 1/5 of basecase value, i.e., $\alpha = 2.67 \times 10^{-6} \text{ cm-mmHg}^{-1}$. The results are summarized in Fig. 5B. With this lower compliance value, substantially higher gain values are needed to produce oscillatory solutions (compare Fig. 5B with base-case results in Fig. 2B2). Indeed, the predictions of the lower-compliance model approximate those of the rigid-tube model (Fig. 2A2), although the former predicts higher-mode oscillations (i.e., f_2 and f_3 -LCO) at lower gain values. (Note, for example, that f_3 -LCO can be obtained in the lower-compliance model for γ as low as 7.8, whereas f_3 -LCO cannot be obtained in the rigid-tube model for γ lower than 9.)

5. Discussion

We have developed a mathematical model of the TGF system in the rat kidney. The model represents hydrodynamic pressure in TAL tubular fluid and compliant TAL walls. Using that model, we have identified a variety of dynamic behaviors that can arise for parameters within normal and pathophysiologic parameter regimes. These behaviors, which include limit-cycle oscillations and solution multistability, were identified and characterized by means of an analysis of the characteristic equation that arises from a linearization of the model equations and of extensive numerical simulations of the solutions for the full model equations,

The model describes fluid dynamics along the TAL by means of model equations that are based on the Stokes equations. To reduce the problem to one spatial dimension along the TAL axis, simplifying assumptions were made, although we believe that any error thus introduced relative to a full three-dimensional formulation is negligible. Solute advection along the tubule also depends only on the spatial variable along the TAL, and both axial and radial diffusion are ignored. These assumptions, which have been standard for sufficiently long tubular segments, have been previously justified [21].

A goal of this study is to derive a characteristic equation for a TGF model that represents a compliant TAL. (In previous studies, characteristic equations were derived for rigid-tube models [3,7].) The characteristic equation, which was obtained from a linearization of the model equations about its steady state, can provide a useful guide for locating bifurcations in parameter space and characterizing those solutions. The characteristic equation is useful not only in identifying bifurcations from the stable time-independent steady-state solution to a region exhibiting a LCO (f_1 -, f_2 -, or f_3 -LCO) but also in identifying bifurcations from a region exhibiting such an LCO to a multistable f_1 , f_2 -LCO or to another LCO (i.e., an f_1 -LCO to an f_2 -LCO, or an f_2 -LCO to an f_3 -LCO).

For our previous TGF model which represents the TAL as a rigid tube, the characteristic equation and the full, nonlinear model yield approximately identical predictions for the boundary between time-independent steady-state solutions and oscillatory solutions. In

contrast, significant discrepancy was revealed in the corresponding predictions in the compliant-TAL model. That discrepancy can be attributed to the assumption, which was made to facilitate the derivation of the characteristic equation for the compliant-TAL model, that at steady state the TAL radius is constant in space. That assumption is inconsistent with the terminal segment of the model tube in the full model, where the steady-state radius is set to decrease so as to attain a target outflow fluid pressure (see Eq. (6)).

Despite that discrepancy, results of both the bifurcation analysis and simulations of the full model suggest revealed that oscillatory states are attainable in the compliant-TAL model at gain values that are substantially lower in the rigid-TAL model. That is, TAL compliance increases the tendency of the TGF system to oscillate. These results are consistent with the predictions of our previous study [22], in which we used a model of a compliant-TAL to analyze the signal transduction properties of the model TAL. That model exhibited essentially the same nonlinear phenomena as the rigid-tubule model, and those results indicate that the high degree of nonlinearity exhibited by our previous rigid-tubule model is not an artifact of the rigid-tubule formulation. In fact, some of those phenomena are more marked in the more inclusive model than in the rigid-tubule model.

The compliant-tube TGF model predicts oscillatory states for very low TGF gain values. It also predicts that oscillations with frequency as high as five times that of the fundamental frequency can be attained at physiologic delay and gain values. These predictions appear to be inconsistent with micropuncture experiments, which suggest that nephron flow and related variables may be in an approximate steady state, or may exhibit regular oscillations with a period of about 30 s [19], which corresponds to the fundamental frequency. To our knowledge, oscillations more than twice the fundamental frequency have not been reported. Moreover, for the TGF gain of a normotensive rat, which is ~ 3.5 [23], the compliant-tube TGF model predicts that nephron flow is always in an oscillatory state, which is inconsistent with experimental observations [19]. To reconcile the above discrepancy, we note that the *in situ* compliance of the TAL walls depends on a number of factors: the inherent elasticity of the epithelium; possible tethering to other tubules via the interstitial matrix; possible synchronization of the oscillations in tubular fluid pressure and flows, and thus of the distension of the tubular walls, among neighboring tubules; and the renal capsule, which contains the kidney and may limit the distension of tubules and vessels. The base-case TAL compliance of our model was based on measurements in isolated tubules, which, owing to the above factors, may be substantially larger than the *in situ* compliance of the TAL. Indeed, the agreement of the predictions of our previous rigid-TAL model with experimental measurements [3,5] suggests that the *in situ* compliance of the TAL may be sufficiently low that the rigid-tube formulation does not render the model's predictions null and void.

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Glossary

Parameters

α	TAL compliance ($\text{cm}\cdot\text{mmHg}^{-1}$)
C_o	$[\text{Cl}^-]$ at TAL entrance (mM)
κ	TAL chloride permeability (cm/s)
K_1	K_2 , parameters for TGF response

K_M	Michaelis constant (mM)
L_0	length of model nephron (cm)
L	length of TAL (cm)
μ	fluid viscosity ($\text{cm}\cdot\text{s}^{-1}$)
P_1	pressure at end of nephron (mmHg)
T_o	base-case steady-state TAL transit time (s)
$V_{\max}$	maximum transport rate of chloride ($\text{nmole}\cdot\text{cm}^{-2}\cdot\text{s}^{-1}$)

Independent Variables

t	time (s)
x	axial position along nephron (cm)

Specified Functions

β	(x), unpressurized TAL radius (μm)
$C_e(x)$	extratubular $[\text{Cl}^-]$ (mM)
$P_0(t)$	pressure at loop bend (mmHg)
$P_e(x)$	extratubular pressure (mmHg)

Dependent Variables

C	(x, t), TAL $[\text{Cl}^-]$ (mM)
$P(x, t)$	)Tubular fluid pressure (mmHg)
$Q(x, t)$	)Tubular fluid flow ($\text{nl}\cdot\text{min}^{-1}$)
$R(x, t)$	)luminal radius (μm)

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Appendix: Derivation of the Fluid Equations

The model TAL and contiguous resistance tubule is represented as a cylindrical, low-compliance tube. Fluid flow within the tube is assumed to be laminar flow. Because the Reynolds number for the model tubule is sufficiently low, tubular flow can be approximated by Poiseuille flow [10], which describes the laminar flow of a viscous, incompressible, Newtonian fluid through a cylindrical tube:

$$\frac{\partial}{\partial x}P(x, t) = - \frac{8\mu}{\pi R^4(x, t)}Q(x, t). \quad (\text{A1})$$

(In this equation, the nature of the dependence of R on space and time remains unspecified.) To maintain mass conservation, the radial and axial fluid velocities, denoted V_r and V_x , respectively, are related [24] by

$$\frac{1}{r} \frac{\partial}{\partial r}(rV_r(r, x, t)) + \frac{\partial}{\partial x}V_x(r, x, t) = 0. \quad (\text{A2})$$

Because we assume cylindrical symmetry, V_r and V_x do not depend on the angular coordinate θ . To relate Eq. (A2) to fluid pressure P and volumetric flow Q , we observe that $Q(x, t) = A(x, t) \bar{V}_x(x, t)$, where $A(x, t) = \pi R^2(x, t)$ is the cross-sectional area of the tubule, and $\bar{V}_x(x, t)$ is the axial velocity averaged over that cross-sectional area, i.e.,

$$\bar{V}_x(x, t) = \frac{1}{A(x, t)} \int_0^{2\pi} \int_0^{R(x, t)} V_x(r, x, t) r dr d\theta. \quad (\text{A3})$$

By integrating Eq. (A2) over the cross-sectional area, one obtains

$$2\pi R(x, t) V_r(R, x, t) + \frac{\partial}{\partial x} Q(x, t) = 0. \quad (\text{A4})$$

At $r = R$, V_r is the rate at which the tubular radius R changes, i.e.,

$$V_r(R, x, t) = \frac{\partial}{\partial t} R(x, t). \quad (\text{A5})$$

Because the radius $R(x, t)$ is assumed in our model to be a function of tubular fluid pressure $P(x, t)$ (i.e., $R(x, t) = F(P(x, t))$, for an appropriate F ; see Eq. (4), we replace the notation $R(x, t)$ with $R(P(x, t))$, so that the dependence of R on x and t is made explicit through Eq. (4). By means of the chain rule, we can write

$$\frac{\partial}{\partial t} R(P(x, t)) = \left(\frac{\partial R}{\partial P}(x, t) \right) \left(\frac{\partial}{\partial t} P(x, t) \right). \quad (\text{A6})$$

Therefore, Eq. (A4) can be expressed as

$$2\pi R(x, t) \left(\frac{\partial R}{\partial P}(x, t) \right) \left(\frac{\partial}{\partial t} P(x, t) \right) + \frac{\partial}{\partial x} Q(x, t) = 0, \quad (\text{A7})$$

which is equivalent to Eq. (2).

Figure 1.

Model represents three essential elements of the TGF pathway: thick ascending limb (cylinder), delay at the MD (box at right), and TGF response function (box at left). Symbols are identified in the *Glossary*. Perturbations enter as adjustments to hydrodynamic pressure $P(0, t)$ that drives flow into TAL entrance ($x = 0$) at time t . Oscillations in pressure result in oscillations in TAL flow $Q(x, t)$, radius $R(x, t)$, and tubular fluid chloride concentration $C(x, t)$.

Figure 2.

A1: root loci, for $\rho \equiv \text{Re}(\lambda) = 0$, of the characteristic equation for a rigid TAL, as a function of gain γ and delay τ . B1: root loci for a TAL with basecase compliance. A2 and B2: behaviors of model solutions, based on numerical simulations using full model equations.

Figure 3.

A, behaviors of model solutions, based on numerical simulations using full model equations using basecase compliance. Sample solutions for points (**W**: $\gamma = 1$, $\tau = 0.2$) (**X**: $\gamma = 3$, $\tau = 0.4$), (**Y**: $\gamma = 3$, $\tau = 0.2$), and (**Z**: $\gamma = 5$, $\tau = 0.1$), are shown in panels W, X, Y, and Z, respectively.

Figure 4.
Behaviors of model solutions, based on numerical simulations using full model equations using basecase compliance and a tube that of 2.9075 times longer than base case.

Figure 5. Behaviors of model solutions, based on numerical simulations using full model equations using TAL compliance that is (A) double that of base case, and (B) one-fifth that of base case.

Table 1

Base-case parameter values.

Parameter	Dimensional Value
<i>Independent Parameters</i>	
α	$1.33 \times 10^{-5} \text{ cm} \cdot \text{mmHg}^{-1}$
β_0	$9.380 \text{ } \mu\text{m}$
β_2	$5.693 \text{ } \mu\text{m}$
C_o	275 mM
κ	$1.50 \times 10^{-5} \text{ cm/s}$
K_M	70.0 mM
L_0	2.00 cm
L	0.500 cm
μ	$7.2 \times 10^{-3} \text{ g}/(\text{cm s})$
P_e	5.00 mmHg
P_0	10.00 mmHg
P_1	2.00 mmHg
Q_o	6 nl/min
R_o	$10.0 \text{ } \mu\text{m}$
T_o	15.708 s
$V_{\max}$	$14.5 \text{ nmole} \cdot \text{cm}^{-2} \cdot \text{s}^{-1}$