Bifurcation Analysis of the Tubular Fluid Oscillations Mediated by Tubuloglomerular Feedback in a Loop of Henle

Hwayeon Ryu[1] and Anita T. Layton[1]
[1]Department of Mathematics, Duke University

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 tubular fluid of the loop of Henle. In this study, we developed a mathematical model of the TGF system that represents NaCl transport along a short loop of Henle with compliant walls. The proximal tubule and the outer-stripe segment of the descending limb are assumed to be highly water permeable; the thick ascending limb is assumed to be water impermeable and have active NaCl transport. 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. The analysis revealed a complex parameter region that allows a variety of qualitatively different model equations: 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 proximal tubule, descending limb, and thick ascending limb walls increases the tendency of the model TGF system to oscillate.
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Introduction

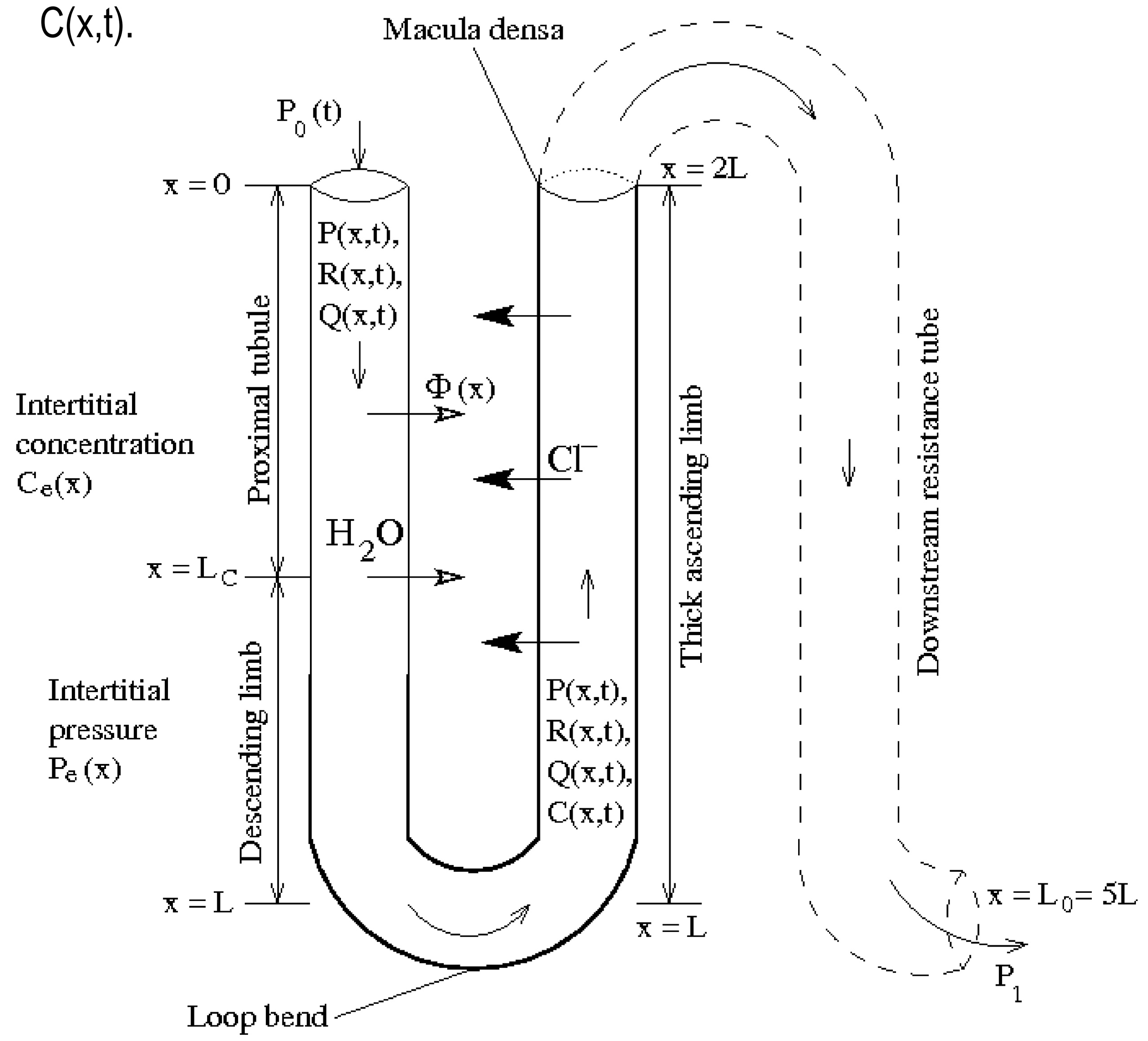
The tubuloglomerular feedback (TGF) system is a key regulator of SNGFR and of water and electrolyte delivery to the distal nephron. In the 1980's, experiments in rats by Leyssac and colleagues demonstrated that nephron flow and related variables may exhibit regular oscillations with a period of ~30 s [4]. Mathematical models have indicated that these regular oscillations are TGF- mediated and that they arise from a bifurcation: if feedback-loop gain is sufficiently large, and if the delay in TGF signal transmission at the juxtaglomerular apparatus (JGA) is sufficiently long, then the stable state of the system is a regular oscillation, not a time-independent steady state [1-3].

Our previous mathematical model of the TGF consists of simple components; the thick ascending limb (TAL) is represented by a rigid tube with plug flow that carries only the Cl^- ion, and the actions of proximal tubule and descending limb were modeled by a linear function that represents glomerular-tubular balance in proximal tubule and water absorption from descending limb.

In this study, we aim to investigate the role of the proximal tubule and descending limb on TGF dynamics, and to assess the extent to which the high degree of nonlinearity exhibited by our model may be an artifact of the rigid tubule formulation. We developed a TGF model that represent a short loop of Henle having pressure-driven flow and compliant walls, and we analyzed the model by means of linearization and numerical computations.

Model Formulation

Schematic representation of model loop of Henle. Hydrodynamic pressure, which is determined by the TGF response, drives flow into loop entrance (x=0). Oscillations is pressure result in oscillations in loop flow Q(x,t), radius R(x,t), and tubular fluid chloride concentration C(x,t).



Fluid flow through the AA lumen is represented by Poiseuille flow:

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

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

Chloride conservation along the loop is given by:

$$\pi R(x,t)^2\frac{\partial}{\partial t}C(x,t) = -2\pi R(x,t)C(x,t)\frac{\partial}{\partial t}R(x,t)$$
$$-Q(x,t)\frac{\partial}{\partial x}C(x,t) + C(x,t)\Phi(x)$$
$$-2\pi R_0(x)\left(\frac{V_{max}(x)C(x,t)}{K_M + C(x,t)} + \kappa(x)\big(C(x,t) - C_e(x)\big)\right)$$

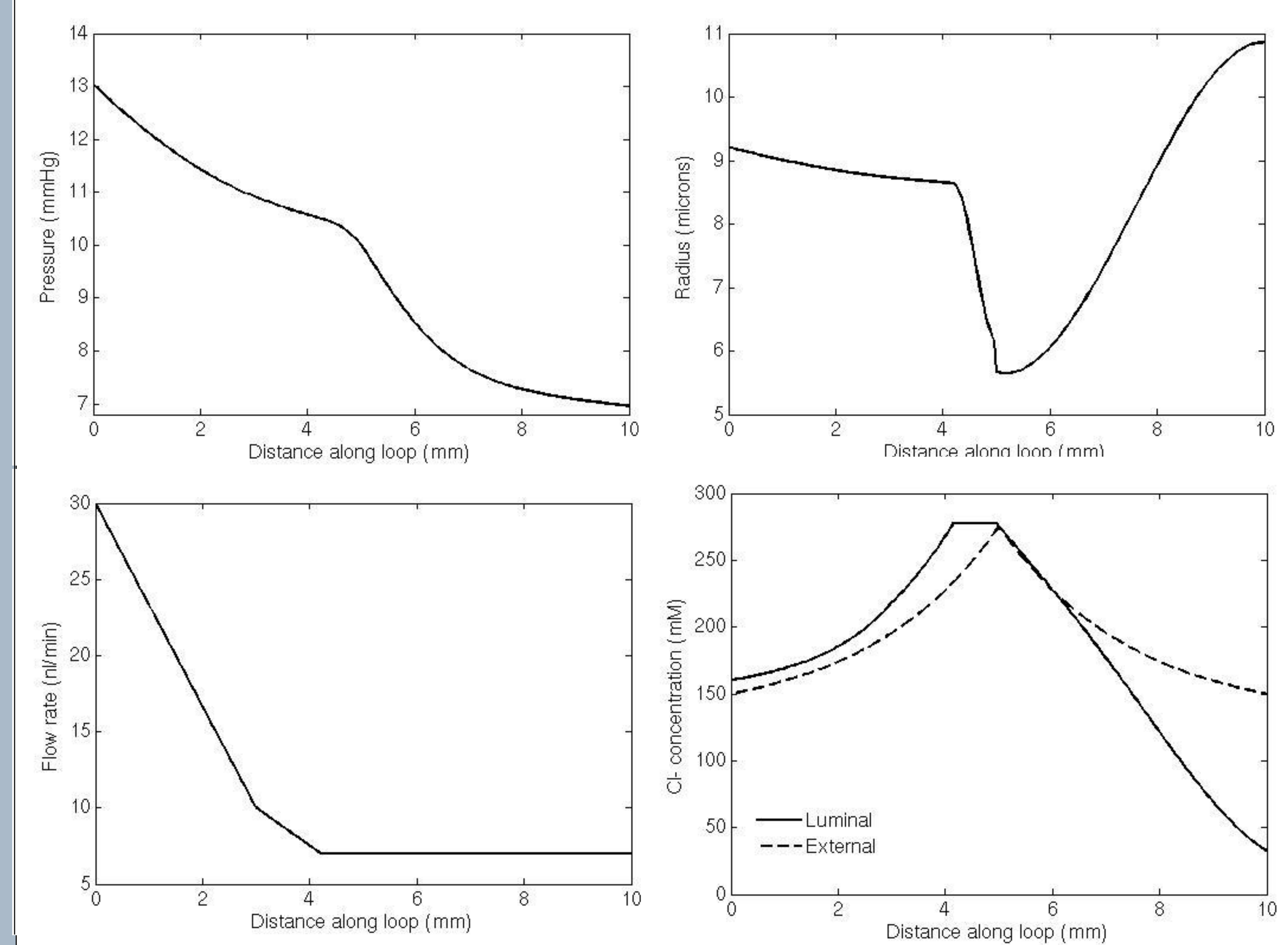
Tubular radius is assumed to depend on transmural pressure gradient:

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

By means of linearization, we derived the characteristic equation:

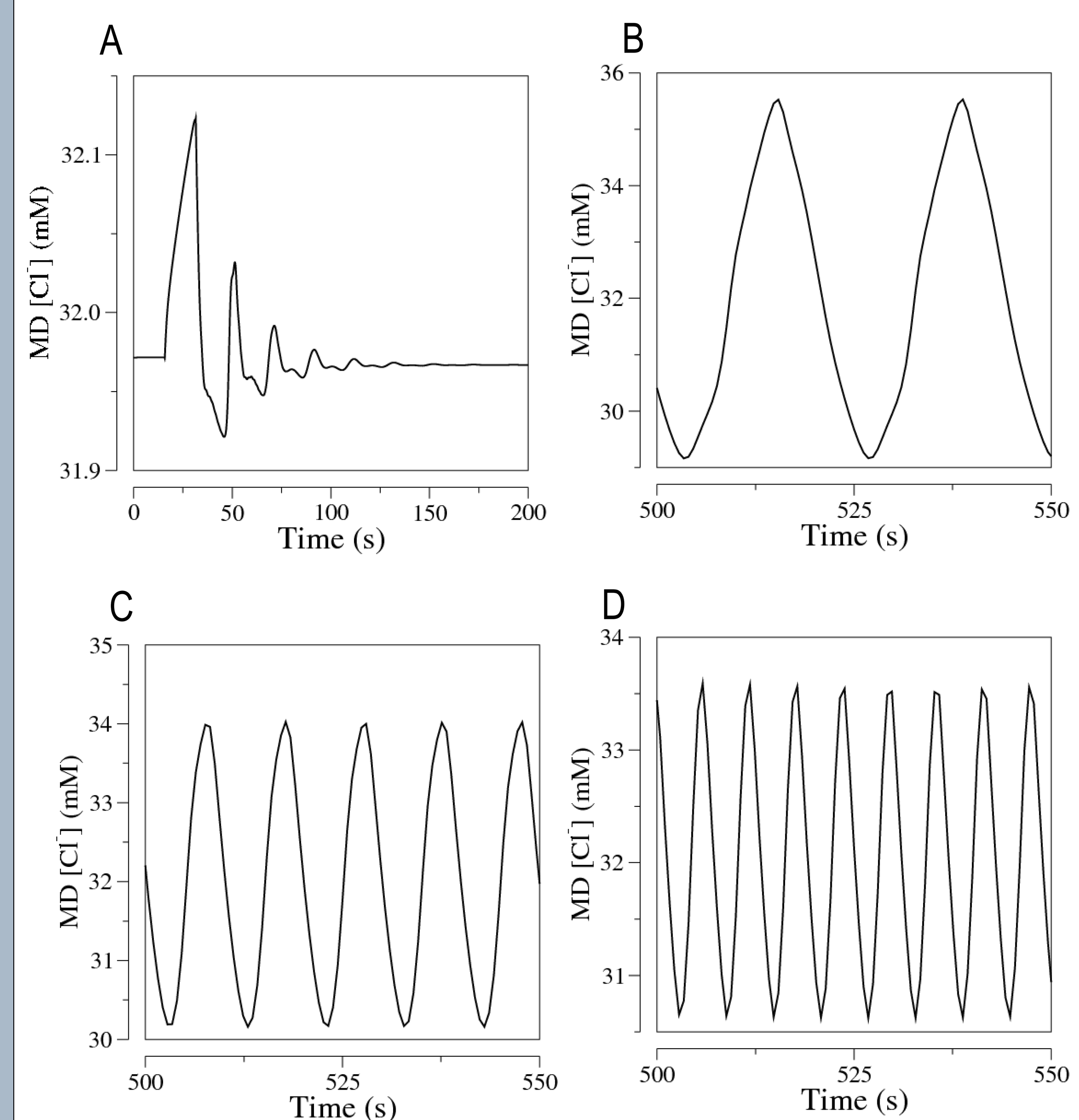
$$1 = \gamma\exp(-\lambda\tau)\frac{Q_{ss}(2L)}{R_{ss}(2L)}\int_0^{2L}\frac{\frac{R_{ss}^5}{8\mu}g' - 2\alpha g\left(\lambda R_{ss}^5\frac{C_{ss}}{C_{ss}'} + 2Q_{ss}\right)}{Q_{ss}^2}$$
$$\times\exp\left(\int_0^{2L}\frac{\frac{\kappa C_{ss}'}{C_{ss}'}R_{ss} + \lambda R_{ss}^2 - c\Phi\frac{C_{ss}}{C_{ss}'}\frac{R_{ss}'}{R_{ss}}}{Q_{ss}}dy\right)dx$$

Model Results: Base-case Steady-state Profiles



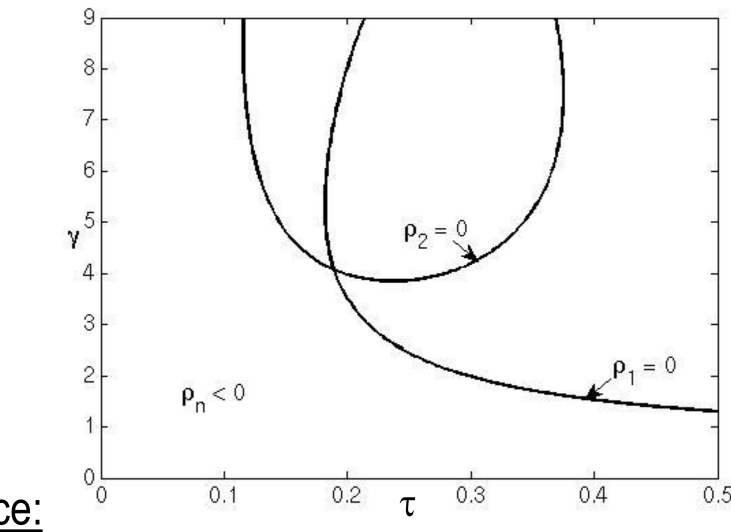
Model Results: MD [Cl-] Oscillatory Behaviors

Sample solutions, based on numerical simulations using full model equations, obtained for different TGF gains and delays. Results show that long-term model solutions can be a time-independent steady state (A), or limit-cycle oscillations at different frequencies (B-D)



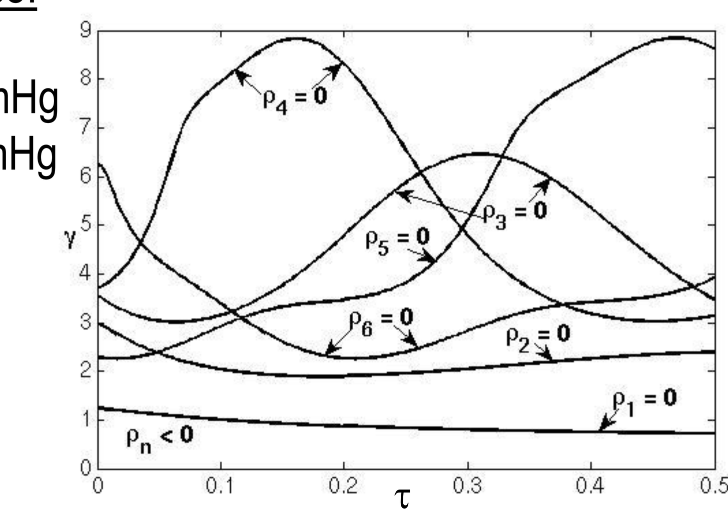
Model Results: Bifurcation Analysis

Rigid tubule:

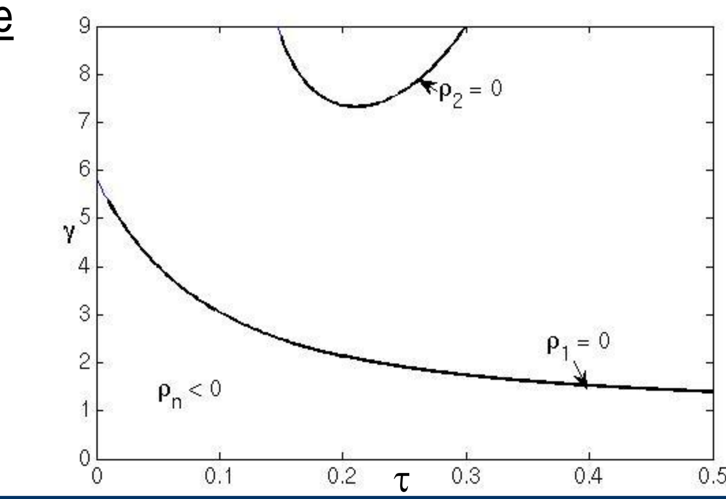


Basecase compliance:

α_{DL} = 1.33E-5 cm/mmHg
α_{TAL} = 2.25E-5 cm/mmHg



Reduced compliance (1/5 of base case):



Summary

1. We have developed a mathematical model of the TGF system in the rat kidney.
2. The model represents a short loop of Henle. Fluid dynamics along the loop is described by means of Poiseuille flow.
3. We derived a characteristic equation for the TGF model by linearizing the model equations about its steady state. The characteristic equation can provide a useful guide for locating bifurcations in parameter space and characterizing those solutions.
4. Analysis of the characteristic equation suggests that tubular compliance substantially increases the tendency of the TGF system to oscillate, consistent with previous modeling results [3].

References

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