ANALYSIS OF FEEDBACK-MEDIATED DYNAMICS IN TWO COUPLED NEPHRONS

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Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Mathematics in the Graduate School of Duke University

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Abstract

This dissertation examines the effects of inter-nephron coupling by means of mathematical models of the tubuloglomerular feedback (TGF) system in two short-looped nephrons. The TGF system is known to spontaneously transition from time-independent steady states to regular, sustained oscillations in nephron flow (i.e., limit cycle oscillations, or LCO). By means of analytical and numerical investigation of an existing mathematical model of TGF, this study identifies the surfaces in various parameter spaces where these bifurcations from stable steady state to LCO occur, determines the different qualitative behaviors that are exhibited by the model system and the regions of parameter space where these behaviors are observed, and determines the characteristics of these qualitatively differing behaviors. In addition, the numerical methods used in this study are described and shown to have a global truncation error of order $(\Delta t)^2$. The physiological implications of these results are discussed.
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First and foremost, I would like to thank my advisor, Harold Layton for unending patience, good advice, and meticulous attention to detail. Without his support I never would have made it to this point. I would also like to thank Charles MacCluer, for having confidence in me when I didn’t and an amazing amount of good advice, some of which I even followed; Patrick Dugan, for unfailing support when a needed it most and a willingness to listen anytime day or night; fellow graduate students Aaron Cinzori (who hasn’t been a graduate student for quite a while), Colleen Mitchell, Michael Kozdron, Laura Taalman, Phillip Riley, Carl Emery Ryan Haskett, Chris Hale, Tim Lucas, David Anderson, Ted Welsh, Michael Gratton, Melanie Bain, Greg Firestone, Janice McCarthy, William LeFew, Michael Nicholas, Ryan Deering, Ben Cooke, James Michael, John Cain, Darren Oldson, and many others, for the exchange of enthusiasm and ideas; Ed, Ben, Jeff, and Brit for distracting me from time to time; and lastly, my parents, George and Nancy Kesseler, without whom this dissertation would not be possible.

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Chapter 1

Introduction

1.1 Overview

This dissertation examines the role of coupling in the behavior of a feedback-mediated oscillatory system that occurs in the kidney. In particular, the system under consideration is a negative-feedback controller of the rate at which fluid enters a nephron (the nephron is the functional unit of the kidney).

First, the relevant physiology will be presented in order to understand the physiological mechanisms being studied. This includes the physiology of the kidney and a description of the processes that are being considered.

Then, to place this study in its appropriate context, a brief survey of the literature relating to this system will be presented. This will show how understanding of this feedback system has developed from a basic understanding of the physiology to mathematical models of the process and finally to the study presented in this dissertation.

Next the mathematical model used in this study will be introduced in a general
formulation. This model will be reduced to the non-dimensionalized form that is used in the remainder of the study. It will be shown how two of these non-dimensionalized models may be coupled to simulate the physiology of the coupling being investigated.

It will be shown how this model may be linearized about a steady-state solution in order to produce a characteristic equation for the single-nephron model. This characteristic equation will be analyzed to yield its implications for the behavior of the model. Then the characteristic equation for two coupled nephrons will be presented along with the concept of spectral splitting, a phenomenon that occurs when oscillatory systems are coupled. An analysis of the characteristic equation for coupled nephrons follows, yielding some insight into how behavior is changed by coupling.

To further understand the behavior of the coupled system, results from the numerical simulation of the coupled nephron model will be examined. Starting with the different types of waveforms generated by numerical simulation of the model, this study will consider what qualitative types of behavior are possible over various choices of parameter planes. Analysis of these possible behaviors will be furthered by consideration of power spectra of the simulated waveforms. A depiction of these spectra over a range of parameter values yields insight into the behavior of the model.

In addition, the numerical methods used in simulating this model will be described. Further, proofs relating to estimates used in this numerical method and convergence of the method will be given.

Finally, to show the relevance of this study to current physiological inquiry, the physiological significance of this study will be discussed. How this investigation fits
into the physiological study of this feedback system and the implications of this investigation to the physiology will be considered.

1.2 Physiology of the Kidney

This dissertation is centered on the investigation of a mathematical model of a feedback system that regulates the rate of filtration in nephrons.

The nephron is the functional unit of the kidney, the organ responsible for separating waste products from the blood and regulating the level of electrolytes (including NaCl) and other molecules in the blood. In an adult human male, the kidney processes roughly 20 to 25 percent of cardiac output [25]. The blood flow into the renal artery splits into progressively smaller arteries before entering the cortical radial artery (CRA) from which it flows into a nephron through an afferent arteriole (AA). Blood flows through the AA into a capillary bundle known as the glomerulus. The glomerulus is enclosed by a structure known as the Bowman’s Capsule. The wall of the Bowman’s Capsule allows the smaller molecules of the blood to filter into the proximal tubule of the nephron. About 20 percent of the plasma is filtered out of the bloodstream and into the proximal tubule [25]. This tubular fluid (nearly identical to blood plasma) then flows through the tubular portion of the nephron while the remaining blood plasma and large molecules leave the glomerulus through the efferent arteriole after the capillaries recombine. This is the only place in the body where an arteriole splits into capillaries and then recombines into an arteriole again (instead of a vein). The efferent arteriole then breaks into capillaries again which supply the structures of the kidney with blood.
In the proximal tubule glucose, sodium chloride, and other solutes are reclaimed into the local vasculature from the tubular fluid via active transporters in the cells lining the tubule. The proximal tubule is water permeable, thus water is also passively reclaimed through absorption down the osmotic gradient. From the proximal tubule the remaining fluid enters the loop of Henle, which consists of the descending limb and the thick ascending limb (TAL). It should be noted that the description given here is for a short-looped nephron—in long-looped nephrons there is a thin ascending limb as well as a TAL. The mathematical model that is the basis of this research is primarily a model of the TAL.

The TAL is water impermeable so changes in the tubular fluid as it flows through the TAL are primarily due to the active transport of Na\(^+\) (via the K\(^+\)-Na\(^+\)-ATPase transporters in the walls of the TAL) and the associated passive transport of Cl\(^-\) down the electrochemical gradient which is created. There is also a secondary effect of backleak of NaCl into the lumen through the tight junctions between the cells which comprise the walls of the TAL. At the end of the TAL is a plaque of cells in the wall of the tubule known as the macula densa (MD).

The MD is adjacent to the glomerulus (every loop of Henle returns to its own glomerulus) and plays an important role in the regulation of the filtration rate (and hence the rate of fluid flow through the nephron). Chloride concentration is sensed by the MD which in turn (through a process incompletely understood) leads to a signal reaching the AA and causing it to contract (in the case that the chloride concentration at the MD is too high) or relax (in the case the chloride concentration is too low). Once this signal reaches the distal end of the AA it is propagated up
the length of the AA and some portion of the associated vasculature by electrotonic conduction.

This process is known as tubuloglomerular feedback (TGF). TGF is the key moment-to-moment controller of the rate of fluid filtration in the glomerulus. It takes some time (about 3-5 seconds) between a change in $\text{Cl}^-$ concentration in TAL tubular fluid at the MD and the associated change in the diameter of the AA [4]. Partially due to this delay, it is possible for the TGF system to exhibit limit cycle oscillations (LCO) in the fluid flow rate through the nephron and in the chloride concentration at the MD. This has been both observed in vivo [6] and predicted in dynamic mathematical models of the TGF system [16, 8, 10, 21].

1.3 **Physiology of Coupled Nephrons**

In the kidney, some branches off of the CRA lead to a connecting artery that subdivides into two (or more) AA, instead of just one. According to [3] over 50% of nephrons are paired in this manner. Furthermore, studies have shown that these pairs of nephrons exhibit coupling in their TGF systems [5, 6, 13]. Figure 1.1 shows a schematic view of two coupled nephrons.

1.4 **Summary of TGF Modeling History**

In 1983 *in vivo* experimental studies were performed on rats using halothane as an anesthetic [17]. These studies gave the first reports of LCO due to TGF. Because prior studies had used barbiturate anesthetics which are now known to impede LCO,
Figure 1.1: A schematic of two coupled nephrons. The labeled structures are the cortical radial artery (CRA), the afferent arteriole (AA), the glomerulus (G), the proximal tubule (PT), the descending limb (DL) and thick ascending limb (TAL) of the loop of Henle, the macula densa (MD), and the distal convoluted tubule (DCT). Figure from [22].

this phenomenon had not been reported before this time.

Once the TGF system became known, dynamic mathematical models describing this system were created [2, 8, 9, 15, 21]. Through modeling, numerical simulation, and experimental studies it came to be understood that spontaneous oscillations in both glomerular filtration rate (GFR) and the Cl\(^-\) concentration profile in the TAL could occur in the normal functioning of the nephron. Several studies [2, 15, 8, 10] have predicted that the TGF system undergoes a bifurcation from a stable, time-independent steady-state to stable LCO when the TGF gain magnitude or time delay parameters become sufficiently large. Furthermore, it has been shown experimentally that LCO in nearby nephrons may become synchronized [6]. Yip et al. [26] have shown that experimental data exhibits some of the characteristics of deterministic
chaos, specifically, experimentally measured single nephron glomerular filtration rate (SNGFR) from spontaneously hypertensive rats shows waveforms similar to systems exhibiting deterministic chaos.

As was stated in the previous section, physiological studies have shown that many branches off of the CRA lead to two or more AAs and that nephrons arising from the same CRA may exhibit synchronous LCO. Furthermore, whole kidney data from conscious dogs [12] display oscillations at the frequency characteristic of TGF, suggesting that large-scale coupling of nephrons may occur.
Chapter 2

Mathematical Model

2.1 Single-Nephron Model

2.1.1 Full Model

Before describing the two-nephron model, we summarize the single-nephron model; additional detail can be found in Layton et al. [15]. A schematic of the coupled model is shown in Figure 2.1. We represent the TAL of a short loop of Henle as a rigid tube of radius $R$. The variable $x$ denotes axial position along the TAL, with $x = 0$ at the loop bend and $x = L$ at the macula densa (MD). Although the sodium-potassium pumps (Na$^+$-K$^+$-ATPase) in the TAL epithelium transport sodium across the tubular wall, and chloride transport is secondary to sodium, we have chosen to represent the chloride concentration because chloride concentration in the TAL luminal fluid adjacent to the MD is thought to primarily mediate TGF response [24]. The luminal fluid chloride concentration in the TAL is given by $C(x, t)$, where $t$ is time. The transepithelial chloride flux $J(C(x, t), C_e(x))$ from the TAL depends on both $C(x, t)$ and the interstitial chloride concentration $C_e(x)$, with $J > 0$ for chloride
efflux from the TAL. The luminal fluid flow rate $F$ along the TAL depends on the chloride concentration at the MD. With this notation and these assumptions, one obtains an equation for chloride conservation in the TAL:

$$\frac{\partial}{\partial t} C(x, t) + \frac{F}{\pi R^2} \frac{\partial}{\partial x} C(x, t) = -2J(C(x, t), C_e(x)) / R. \quad (2.1)$$

The flow rate $F(C(L, t - \tau))$ is given by $F(C_{MD}) = \alpha Q(C_{MD})$ where

$$Q(C_{MD}) = Q_{op} + \frac{\Delta Q}{2} \tanh \left( \frac{k}{2} (C_{op} - C_{MD}) \right), \quad (2.2)$$

and the source term $J(C(x, t), C_e(x))$ is given by

$$J(C, C_e) = -\frac{V_{max} C}{K_M + C} - P(C - C_e). \quad (2.3)$$

In these equations $Q$ is the SNGFR, $k$ is a measure of TGF sensitivity, $V_{max}$ is the maximum transport rate of $\text{Cl}^-$ out of the TAL lumen, and $K_M$ is the Michaelis constant for the transport. Although it is $\text{Na}^+$ that is actively transported out of the tubule, we have chosen to model the $\text{Cl}^-$ concentration because $\text{Cl}^-$ is thought to stimulate the TGF response [24]. If the time derivative in equation (2.1) is set to zero, an ODE for the time-independent TAL concentration profile is given by

$$\frac{d}{dx} S(x) = -\frac{2\pi R}{F_{op}} J(S(x), C_e(x)), \quad (2.4)$$
where \( S(x) \) is the steady-state concentration corresponding to the time-dependent concentration \( C(x, t) \), and \( F_{op} \) is the steady-state operating fluid flow rate along the TAL.

To nondimensionalize equations (2.1) and (2.4), we normalize variables and parameters by setting \( \tilde{x} = x/L \), \( \tilde{t} = t/t_o \), \( \tilde{A} = \pi R^2/A_o \), \( \tilde{C}(\tilde{x}, \tilde{t}) = C(x, t)/C_o \), \( \tilde{S}(\tilde{x}) = S(x)/C_o \), \( \tilde{C}_e(\tilde{x}) = C_e(x)/C_o \), \( \tilde{F} = F/F_o \), \( \tilde{F}_{op} = F_{op}/F_o \), and \( \tilde{J}(\tilde{C}, \tilde{C}_e) = J(C, C_e)/J_o \), where the quantities subscripted with a “o” are reference values that can be computed from the model parameters, and where \( A_o = \pi R^2 \), \( t_o = A_o L/F_o \) (the time required for a molecule traveling with the flow to traverse the TAL at the reference flow rate \( F_o \)), and \( J_o = F_o C_o / 2\pi RL \). This summary of the model is taken from [22].

### 2.1.2 Non-Dimensionalized Model

The model has been put into a dimensionless form to simplify mathematical analysis. The concentration of \( \text{Cl}^- \) (0 ≤ \( C(x, t) \) ≤ 1 in the dimensionless form of the model) at position \( x \) (0 ≤ \( x \) ≤ 1) and at dimensionless time \( t \) in the model TAL is given by

\[
\frac{\partial}{\partial t} C(x, t) + F \frac{\partial}{\partial x} C(x, t) = -J(C(x, t), C_e(x)) .
\]

(2.5)

In this equation the source term \( J(C, C_e) \) is given by

\[
J(C, C_e) = -\frac{V_{max} C}{K_M + C} + P(C - C_e) ,
\]

(2.6)

which represents the transepithelial transport of \( \text{Cl}^- \) along the TAL. The first term on the right hand side of equation 2.6 represents the active transport of chloride—a
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$</td>
<td>0.200 (dimensionless)</td>
</tr>
<tr>
<td>$C_0$</td>
<td>275 mM</td>
</tr>
<tr>
<td>$L$</td>
<td>0.500 cm</td>
</tr>
<tr>
<td>$Q_{op}$</td>
<td>30.0 nl/min</td>
</tr>
<tr>
<td>$\Delta Q$</td>
<td>18.0 nl/min</td>
</tr>
<tr>
<td>$R$</td>
<td>10.0 $\mu$m</td>
</tr>
<tr>
<td>$t_o$</td>
<td>5$\pi$ s</td>
</tr>
<tr>
<td>$\tau$</td>
<td>3.50 s</td>
</tr>
<tr>
<td>$K_M$</td>
<td>140 mM</td>
</tr>
<tr>
<td>$V_{max}$</td>
<td>17.3 nmole/(cm$^2 \cdot$ s)</td>
</tr>
<tr>
<td>$C_{op}$</td>
<td>32.12 mM</td>
</tr>
</tbody>
</table>

**Table 2.1:** Base case parameter values for dimensional model.

A model similar to Michaelis-Menton kinetics—whereas the second term on the right hand side represents the backleak of Cl$^-$ into the lumen. The equation

$$F(C(1, t - \tau)) = 1 + K_1 \tanh \left( K_2 (C_{op} - C(1, t - \tau)) \right)$$

(2.7)

gives the flow rate of fluid through the TAL, which depends on the concentration at the MD ($x = 1$) at a previous time. In these equations, $C(x, t)$ is the Cl$^-$ concentration in the TAL of a nephron, $\tau$ is the time delay in the feedback mechanism in non-dimensional units (1 non-dimensional time unit = 5$\pi$ seconds, the time it takes for the TAL to be washed out at the steady-state flow rate), $K_1$ and $K_2$ are parameters relating to the gain of the feedback, and $V_{max}$, $K_M$, $C_e(x)$, $P$, and $C_{op}$ are all fixed (See Table 2.1 for parameter values).
2.1.3 Single-Nephron Characteristic Equation

By setting the time derivative to zero in equation (2.5), the following equation for the steady-state concentration profile of the TAL $S(x)$ is obtained

$$\frac{d}{dx}S(x) = -\frac{J(S(x), C_e(x))}{F_{op}}$$

(2.8)

where $F_{op}$ is the flow rate corresponding to the steady state concentration at the MD, $S(1)$. By linearizing about this steady-state solution, the characteristic equation

$$\frac{\lambda}{\gamma e^{-\lambda t}(1 - e^{-\lambda})} + 1 = 0$$

(2.9)

may be obtained [15]. In this equation, $\gamma$, the magnitude of the TGF gain, is given by

$$\gamma = -S'(1)K_1K_2$$

(2.10)

where $S'(1)$ is the derivative of the steady-state Cl$^-$ concentration alongside the MD.

2.2 Coupled-Nephron Model

2.2.1 Coupling Non-Dimensionalized Models

Experimental evidence suggests that the TGF mechanisms of nephrons that branch off of the same CRA are coupled [6]. When two AAs share the same branch off of the CRA, the TGF signal from the MD of one nephron is thought to be spread by electrotonic conduction along the AA to the shared connecting artery, thus affecting
the pressure in the flow of blood into the glomerulus of the other nephron. In this way TGF in the two nephrons may be coupled. A schematic drawing of the coupled-nephron model can be seen in Figure 2.1. To include coupling in the model equations, changes must be made to the model. The Cl\(^{-}\) conservation equation becomes

\[
\frac{\partial}{\partial t} C_i(x, t) + F_i \frac{\partial}{\partial x} C_i(x, t) = -\frac{V_{\text{max}} C_i(x, t)}{K_M + C_i(x, t)},
\]  

(2.11)

for \(i = 1\) or \(2\) with the flow rate \(F_i\) given by

\[
F_i(C_i, C_j) = F_i(C_i(1, t - \tau_i)) + \phi(F_j(C_j(1, t - \tau_j)) - 1), \quad j \neq i,
\]  

(2.12)

where \(\phi\) is a parameter that specifies the strength of the coupling [22].

### 2.2.2 Coupled-Nephron Characteristic Equation

In this case of coupled nephrons, it has been shown [22] that the characteristic equation is given by

\[
\left(\frac{\lambda}{\gamma_1 e^{-\lambda \tau_1}(1 - e^{-\lambda})} + 1\right) \left(\frac{\lambda}{\gamma_2 e^{-\lambda \tau_2}(1 - e^{-\lambda})} + 1\right) = \phi^2,
\]  

(2.13)

where \(\gamma_1\) and \(\gamma_2\) are TGF gain magnitudes for nephrons 1 and 2 respectively, \(\tau_1\) and \(\tau_2\) are the time delays (the time it takes for a change in Cl\(^{-}\) concentration at the MD to be reflected in the flow rate of blood through the AA), and \(\phi\) is a parameter specifying the strength of the coupling. The derivation for this characteristic equation is given in appendix A.
Figure 2.1: A schematic of the coupled-nephron model showing two ascending limbs, delays at MD, TGF response and key model parameters.
Figure 2.2: This figure shows the surfaces where the real part of lambda is zero for some eigenvalue lambda. The left panel depicts the $\tau_1 - \tau_2$ plane. In this figure the fixed parameters are $\gamma_1 = \gamma_2 = 2.25$ and $\phi = 0.1$. The right panel depicts the $\gamma_1 - \gamma_2$ plane, with the solid lines indicating the curves where $\text{Re}\lambda = 0$ and the dashed lines indicating the asymptotes of the hyperbola. The fixed parameters are $\tau_1 = \tau_2 = 0.2$ and $\phi = 0.1$.

2.3 Summary of Prior Analysis of Coupled System

In [22] equation (2.13) was analyzed in two special cases, the case of equal gains, $\gamma_1 = \gamma_2$, and the case of equal time delays, $\tau_1 = \tau_2$. In both of these cases, the curves where an eigenvalue crossed the imaginary axis were analytically determined and from this the loci at which the system underwent a bifurcation from a stable steady state to stable LCO were determined.

In the case of equal time delays, solving the characteristic equation (2.13) with the condition $\lambda = i\omega$ yields a hyperbola with asymptotes at $\gamma_1 = \gamma_{\text{crit}}$ and $\gamma_2 = \gamma_{\text{crit}}$ where $\gamma_{\text{crit}}$ is the value of $\gamma$ at which bifurcation from stable steady state to LCO occurs in a single uncoupled nephron. An example of these curves for selected values of the parameters can be seen in Figure 2.2. The bifurcation surface in this case is the lower left branch of the hyperbola, since even though an eigenvalue changes sign as the parameters cross the upper right branch of the hyperbola, LCO
are stable for parameter values in the neighborhood of this hyperbola, so there is no bifurcation across this curve. Although the bifurcation curve is the only qualitative change in asymptotic behavior of the system, if oscillations are started with an out-of-phase perturbation, the out-of-phase oscillations will continue substantially longer when $\gamma_1 = \gamma_2$ than they will otherwise. This phenomenon is investigated further in Chapter 4.

The other situation that was considered in the prior study was the case of equal gain magnitudes ($\gamma_1 = \gamma_2$). In this case the curves where an eigenvalue crosses the imaginary axis are given in Figure 2.2. As in the preceding case, the bifurcation locus is limited to the first curves encountered as one increases the time delay from zero. There are, however, other loci at which the qualitative behavior of the system changes; these loci will be described in Chapter 4.
Chapter 3

Investigation of Characteristic Equation

In this chapter, the characteristic equations resulting from linearization of the single-nephron model equations (2.5 and 2.6) and the coupled-nephron model equations (2.11 and 2.12) are analyzed.

The eigenvalues (solutions to one of the characteristic equations) were obtained by using Newton’s method for finding roots of equations. As can be seen in Figure 3.1, the basins of attraction of Newton’s method for the characteristic equations has a fractal structure, making the determination of eigenvalues difficult due to the intertwined basins of attraction of the eigenvalues. To locate all of the desired eigenvalues (generally, the two to eight eigenvalues with the smallest positive imaginary part), Newton’s method was performed over a $50 \times 50$ grid of starting values in the complex plane for each choice of the parameters $\tau_1, \tau_2, \gamma_1, \gamma_2,$ and $\phi$. 
Figure 3.1: Newton’s method basins of attraction for two nephron characteristic equation. Each pixel is colored according to the eigenvalue that Newton’s method converges to when it is used on the characteristic equation (3.4) and started at the complex value corresponding to the pixel. The figure shows that the basins of attraction for Newton’s method have a complex fractal structure and demonstrates that care must be taken when computing eigenvalues.
3.1 Validity of the Linearization

As the general theory of linear stability analysis was not developed with delay differential equations such as the model equations (2.5, 2.6, and 2.7) in mind, it is reasonable to ask whether the application of this method is a valid technique in this case. Although numerical evidence provides substantial support to the assumption that the linear stability analysis of this model is valid, a more rigorous argument is desirable.

In his Ph.D. dissertation, Darren Oldson provides evidence for the validity of the linearization of this model [19]. Working from (almost) the same model presented in Chapter 2, Oldson showed that the model equations can be represented as

\[ \frac{d\omega}{dt} = A\omega \]  

for an appropriately defined operator \( A \). It is then shown that the stability of the solution \( \omega \equiv 0 \) of equation (3.1) is completely determined by the spectrum of the operator \( A \) which, in turn, is approximated by solutions to the characteristic equation obtained by the linear stability analysis discussed in the previous chapter.

3.2 Spectrum of Single-Nephron Characteristic Equation

It is shown in [15] and [22] that by writing the solutions as a perturbation of the steady-state solution and linearizing the result, the characteristic equations (3.2 and 3.4) may be obtained. In the case of the single-nephron model, the characteristic
equation is given by

\[ \frac{\lambda}{\gamma e^{-\lambda \tau} (1 - e^{-\lambda})} + 1 = 0, \quad (3.2) \]

as was given in section 2.1.3, equation (2.9).

3.2.1 Form of Spectrum

For fixed values of the gain magnitude parameter \( \gamma \) (hereafter referred to simply as gain) and time delay parameter \( \tau \), the set of complex numbers \( \lambda \) that satisfy equation (3.2) appear to consist of an infinite number of points with no accumulation points as shown in figure 3.2. Furthermore, equation (3.2) and equation (3.4) have the property that if a value \( \lambda \) satisfies the equation, then its complex conjugate will also satisfy it. Another property of this spectrum is that if Re(\( \lambda_1 \)) < 0 then Re(\( \lambda \)) < 0 for all eigenvalues \( \lambda \) (i.e., if an eigenvalue has positive real part, then all of the eigenvalues closer to the real axis will also have positive real parts), although if Re(\( \lambda_1 \)) > 0, it may be the case that other eigenvalues have greater real part. This can be seen if the curves in the \( \tau-\gamma \) parameter plane where Re(\( \lambda \)) = 0 for some eigenvalue \( \lambda \) are plotted. Figure 3.3 is such a plot of the \( \tau-\gamma \) plane, and it can be observed that all of the curves in the figure are bounded away from the neighborhood of the origin (where all eigenvalues have negative real part) by a single curve which is associated with \( \lambda_1 \). However, as is shown in [14], if the backleak of chloride into the lumen is allowed then there are parameter values for which the higher frequency LCO emerge as the stable ones.

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Figure 3.2: Example spectra from single nephron and coupled nephron characteristic equations. The left panel shows solutions to the single-nephron characteristic equation for parameter values $\tau = 0.3$ and $\gamma = 3.0$. The right panel show solutions to the two-nephron characteristic equation for parameter values $\tau_1 = \tau_2 = 0.3$, $\gamma_1 = \gamma_2 = 3.0$, and $\phi = 0.3$.

### 3.2.2 Significant Eigenvalues

To more clearly describe the spectrum, we order the eigenvalues by their distance from the real axis and label them accordingly, e.g., the (conjugate pair) of eigenvalues with imaginary part of smallest magnitude will be labeled $\lambda_1^+$ and $\lambda_2^-$, respectively. Since, as discussed in the section above, if any eigenvalue has positive real part then $\lambda_1$ also has positive real part (here $\lambda_1$ refers to both $\lambda_1^+$ and $\lambda_2^-$), this eigenvalue is the one that controls the behavior of the model. By taking the discrete Fourier transform of the flow rate LCOs it is shown that the frequencies that are prevalent in this waveform correspond to the imaginary part of $\lambda_1$ eigenvalue and its harmonics (for evidence of this phenomenon, see section 4.2). The frequencies corresponding to other eigenvalues, even other eigenvalues with positive real part, are not seen to be present in the LCOs. Although it is possible to set up transient LCO having higher fundamental frequencies, these oscillations will eventually decay into LCO at
the frequency corresponding to eigenvalue $\lambda_1$.

### 3.2.3 $\tau-\gamma$ Plane Eigenvalues

**Re($\lambda$) = 0 Curves**

The curves for which Re($\lambda$) = 0 for some eigenvalue $\lambda$ have been plotted in Figure 3.3. A similar figure has previously appeared in Layton et al., [15], where the equations for the curves shown are given as

$$
\gamma = (-1)^{n+1} \frac{n\pi}{2} \frac{1}{\sin\left(\frac{n\pi}{2}/(\tau + \frac{1}{2})\right)}, \quad n = 1, 2, 3, ..., \quad (3.3)
$$

However the curves shown in Figure 3.3 were generated by finding the Re($\lambda$) = 0 level curves in eigenvalue data obtained by the method described at the beginning of this chapter. In the region to the lower left of this figure, no eigenvalues have positive real part and any perturbations will decay to the stable steady-state asymptotically.

**Bifurcation Curves**

As the parameter values cross from a region where no eigenvalues have positive real part into a region where one (or more) eigenvalues are positive, the steady-state solution loses stability and LCO arise as the stable solution. It is important to note that although there are several curves where an eigenvalue crosses the imaginary axis, only the curve that bounds the region where no eigenvalues have positive real part is a bifurcation boundary, because LCO are stable on both sides of the other curves.
Figure 3.3: $\text{Re}(\lambda) = 0$ curves in $\tau-\gamma$ plane. Because this is a diagram for the single-nephron case, there are no fixed parameters—$\tau$ and $\gamma$ are the only parameters in this case.
3.3 Spectrum of Coupled-Nephron Characteristic Equation

As in the single-nephron case, analyzing the coupled-nephron model using its characteristic equation (2.13) provides insight into the behavior of the model. In the case of two coupled nephrons, it is shown in Appendix A that the coupled-nephron characteristic equation is given by

\[
\left( \frac{\lambda}{\gamma_1 e^{-\lambda \tau_1} (1 - e^{-\lambda})} + 1 \right) \left( \frac{\lambda}{\gamma_2 e^{-\lambda \tau_2} (1 - e^{-\lambda})} + 1 \right) = \phi^2, \tag{3.4}
\]

where \( \phi \) is a constant that represents the strength of the coupling.

3.3.1 Spectral Splitting

The case of two coupled nephrons (equation (3.4)) is more complicated than the single-nephron case. Due to “spectral splitting,” when we change from the single-nephron case to the coupled-nephron case, the spectrum “splits,” with each eigenvalue becoming a pair of eigenvalues near the location of the original (single-nephron) eigenvalue. An example of this phenomenon is shown in Figure 3.4. In this figure, the left panel shows eigenvalues of the single-nephron characteristic equation and the right panel show eigenvalues of the coupled-nephron characteristic equation (3.4) for several values of the coupling parameter \( \phi \) ranging from 0.0 to 0.3 (the other parameters are all fixed at the values stated in the caption of the figure). The bigger the dot representing the eigenvalue, the bigger the value of \( \phi \) in the figure.

We will label the eigenvalues \( \lambda_{na} \) and \( \lambda_{nb} \) in order of increasing imaginary part,
Figure 3.4: A depiction of how the solutions to the characteristic equation change as $\phi$ increases from zero. The left panel shows the spectrum for the case where $\phi = 0$. The right panel shows how the spectrum changes as $\phi$ is increased from zero to 0.3 by increasing the size of the point used to mark each eigenvalue as the parameter $\phi$ increases. The other parameters were fixed at $\tau_1 = \tau_2 = 0.3$ and $\gamma_1 = \gamma_2 = 3.0$ i.e., $\text{Im}(\lambda_{1a}) \leq \text{Im}(\lambda_{1b}) \leq \text{Im}\lambda_{2a}$, etc. For simplicity of discussion we will only refer to the eigenvalues having positive imaginary part. Figure 3.2 shows sample spectra of the single-nephron (left panel) and coupled-nephron (right panel) models for generic sets of values of the parameters.

3.3.2 Significant Eigenvalues

As in the single-nephron case, the eigenvalues form a countably infinite set, but only the $\lambda_1$ eigenvalues play a significant role in determining the system’s behavior. In the case of two coupled nephrons, there are four significant eigenvalues (two conjugate pairs). This is due to spectral splitting, which causes the single conjugate pair of significant eigenvalues to split into two conjugate pairs of eigenvalues that determine the stable state of the system. In all of the regimes in which other eigenvalues have positive real part, these eigenvalues ($\lambda^+_{1a}$, $\lambda^-_{1a}$, $\lambda^+_{1b}$, and $\lambda^-_{1b}$) also have positive real part.
and the oscillatory frequencies present correspond to combinations of the imaginary parts of the $\lambda_1$ group of eigenvalues.

3.3.3 EIGENVALUES IN THE $\gamma_1-\gamma_2$ PLANE

Consider first the case of equal delay times ($\tau_1 = \tau_2$). In the paper by Pitman et al. [22] the characteristic equation 3.4 is studied in the case where $\tau_1 = \tau_2$ to determine the bifurcation curves. It is shown that in this case the characteristic equation and the condition $\text{Re}(\lambda) = 0$ yield the equations

\[
\omega^2 + 2\omega(\gamma_1 + \gamma_2) \left( \sin \frac{\omega}{2} \right) \left( \cos \frac{\omega(2\tau + 1)}{2} \right) + 4(1 - \phi^2) \gamma_1 \gamma_2 \left( \sin \frac{\omega}{2} \right) \left( \cos \omega(2\tau + 1) \right) = 0
\]  

(3.5)

and

\[
\left( \sin \frac{\omega}{2} \right) \left( \sin \frac{\omega(2\tau + 1)}{2} \right) \left( 2\omega(\gamma_1 + \gamma_2) + 4(1 - \phi^2) \gamma_1 \gamma_2 \left( \sin \frac{\omega}{2} \right) \left( \cos \frac{\omega(2\tau + 1)}{2} \right) \right) = 0.
\]  

(3.6)

Furthermore, by setting the second factor in equation (3.6) to zero (setting the other factors equal to zero yield only trivial solutions) the condition

\[
\sin \frac{\omega(2\tau + 1)}{2} = 0,
\]  

(3.7)
is obtained, which implies that $\omega$ can take on only the values

$$
\omega_n(\tau) = \frac{2\pi n}{1+2\tau}, \quad n = 0, \pm 1, \pm 2, \pm 3, \ldots.
$$

(3.8)

Substitution of equation (3.8) into equation (3.5) leads to

$$
\left( \frac{\gamma_1}{\xi_n(\tau)} - \frac{1}{1 - \phi^2} \right) \left( \frac{\gamma_2}{\xi_n(\tau)} - \frac{1}{1 - \phi^2} \right) = \frac{\phi^2}{(1 - \phi^2)^2},
$$

(3.9)

where

$$
\xi_n(\tau) = (-1)^{n+1} \frac{\omega_n(\tau)/2}{\sin(\omega_n(\tau)/2)}.
$$

(3.10)

The analysis in [22] is restricted to the case where $n = 1$ in Equation (3.8). There are, however, additional curves for which $\text{Re}(\lambda) = 0$ in the $\gamma_1-\gamma_2$ plane if $n$ is allowed to take on other values in this equation.

**Re($\lambda$) = 0 Curves**

For every integer $n$, the solutions to Equation (3.9) are given by a hyperbola in the $\gamma_1-\gamma_2$ plane with asymptotes given by
\[ \gamma_i = \frac{\xi_n(\tau)}{1 - \phi^2}. \tag{3.11} \]

This gives us a family of hyperbolas with asymptotes which intersect along the curve \( \gamma_1 = \gamma_2 \). Each of these hyperbolas correspond to two conjugate pairs of eigenvalues each of which has \( \text{Re}(\lambda) = 0 \) along one branch of the hyperbola (for more information on the structure of the set of eigenvalues refer to Section 3.3.1 on spectral splitting).

For each hyperbola the associated eigenvalues have negative real part in the region containing the origin (in this region there are no LCOs, so no eigenvalues have positive real part), thus the only bifurcation curve (where the system changes from a stable steady state solution to a stable LCO solution) is the curve associated with \( n = 1 \). (Technically speaking, the \( n = 2 \) curve is also a bifurcation surface, but because this hyperbola does not intersect the first quadrant, it can be safely ignored because negative values of \( \gamma \) are not physiologically significant.) In addition, there is no evidence from numerical experiments to indicate that the stable solution to the mathematical model undergoes any qualitative change when the parameters cross any of the hyperbolas associated with \( n > 1 \).

**Bifurcation Curves**

If attention is restricted to physically significant gain values (\( \gamma_i > 0 \)), then only the lower left branch of the first hyperbola (\( n = 1 \)) is a bifurcation curve. Figure 3.5 shows both branches of the first hyperbola with its asymptotes as dashed lines.
Figure 3.5: $\text{Re}(\lambda) = 0$ curves in the $\gamma_1$–$\gamma_2$ plane. The dashed lines are the asymptotes of the hyperbolae. The fixed parameter values are $\tau_1 = \tau_2 = 0.2$ and $\phi = 0.1$. 
Figure 3.6: Re(\(\lambda\)) = 0 curves in the \(\tau_1-\gamma_1\) plane. The fixed parameter values are \(\tau_2 = 0.2\), \(\gamma_2 = 4.0\), and \(\phi = 0.1\). None of these curves are bifurcation loci because at least one eigenvalue has positive real part for all values of \(\tau_1\) and \(\gamma_2\).

3.3.4 \(\tau_1-\gamma_1\) Plane Eigenvalues

Re(\(\lambda\)) = 0 Curves

In the case where the time delay and gain for one model nephron are fixed and the parameters for the other nephron are allowed to vary, the Re(\(\lambda\)) = 0 curves are similar to the single nephron case (as shown in Figure 3.6).
BIFURCATION CURVES

If \( \tau_2 \) and \( \gamma_2 \) are sufficiently small (small enough that the steady state is stable for small values of \( \tau_1 \) and \( \gamma_1 \)), this case is similar to the single nephron case in that the bifurcation curve is the curve in the lower left (see Figure 3.3). If \( \tau_2 \) and \( \gamma_2 \) are sufficiently large (roughly, large enough that, uncoupled, nephron 2 will exhibit LCO), then there are technically no bifurcation curves in the \( \tau_1 - \gamma_1 \) plane as there is at least one conjugate pair of eigenvalues with positive real part everywhere. It should also be noted that the “straight” curves seen in Figure 3.6 are curves where two conjugate pairs of eigenvalues cross the imaginary axis at the same time in opposite directions, thus there are the same number of eigenvalues with positive real part on both sides of these curves.

3.3.5 \( \tau_1 - \tau_2 \) PLANE EIGENVALUES

Re(\( \lambda \)) = 0 Curves

BIFURCATION CURVES

As demonstrated in [22], the surfaces where Re(\( \lambda \)) = 0 are shown in the left panel of Figure 3.8 in bold. It is important to note that all of these curves are not bifurcation surfaces as in some cases even though one eigenvalue changes from positive to negative real part as the parameter values cross the curve, there is another eigenvalue which has positive real part the throughout. Furthermore, as will be shown later, the curves where the real part of an eigenvalue changes sign are not the only places where a qualitative difference in behavior can be observed. In this case, there is also an observable change in behavior when the parameters cross the curves where
Figure 3.7: This figure shows the level curves of $\text{Im}(\lambda_{1a})$ in the $\tau_1-\tau_2$ plane (left panel) and the level curves of $|\text{Im}(\lambda_{1b} - \lambda_{1a})|$ in the $\tau_1-\tau_2$ plane (right panel). The fixed parameter values for these figures are $\gamma_1 = \gamma_2 = 2.25$ and $\phi = 0.1$.

Figure 3.8: This figure shows the level curves of $\text{Re}(\lambda_{1a})$ in the $\tau_1-\tau_2$ plane (left panel) and the level curves of $|\text{Re}(\lambda_{1b} - \lambda_{1a})|$ in the $\tau_1-\tau_2$ plane (right panel). The fixed parameter values for these figures are $\gamma_1 = \gamma_2 = 2.25$ and $\phi = 0.1$. 

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Figure 3.9: This figure shows the Re(λ) = 0 curves (bold) and the curves where Re(λ_{1a}) = Re(λ_{1b}) (dashed) in the τ_{1}–τ_{2} plane. The fixed parameter values for this figure are γ_{1} = γ_{2} = 2.25 and φ = 0.1.

Re(λ_{1a}) = Re(λ_{1b}). These curves are shown in the right panel of Figure 3.8 in bold and in Figure 3.9 as dashed lines.
Chapter 4

Investigation of Numerical Solutions

4.1 Numerical Simulations

The numerical simulations conducted for this chapter were all done using the model described in Chapter 2 and the numerical method described in Chapter 5. Unless otherwise noted, the simulations were started with a flow history perturbed by $10^{-3}$ (i.e. the non-dimensional flow rate was 1.001 for the entire flow history) and allowed to run until the waveforms reached maturity, at which time the data was taken as described below. In the case of out-of-phase perturbations, one nephron was given a flow history of 1.001 and the other nephron a was given a flow history of 0.999. The out-of-phase simulations were also run for shorter times in order to capture transient phenomena. The discrete Fourier transforms (DFTs) were performed on the flow rate data using code for the fast Fourier transform obtained from *Numerical Recipes in Fortran* [18]. Instead of subtracting the average from each value, the steady-state flow rate of 1.0 was subtracted. Welch windowing was used on the data, then a DFT was applied to 8 overlapping data sets of 2048 values. The results of these DFTs
4.1.1 Types of Behavior Exhibited by Model Systems

To better understand the effects of coupling we determine the behaviors that the system exhibits and the regions for which these behaviors are observed. By means of extensive numerical simulation, four qualitatively different behaviors have been identified in the coupled-nephron system. Typical examples of SNGFR waveforms and their PSDs are given in Figure 4.2 and the parameter values for each of the points are depicted in Figure 4.1.

- **Type I**: This type of behavior occurs when all eigenvalues have negative real part and the time-independent steady-state is stable. Although this region could be separated into two parts along the curves where \( \text{Im}(\lambda_{1a}) = \text{Im}(\lambda_{1b}) \) based on whether the oscillations were synchronized or not, we do not make this distinction because any oscillations ultimately decay as \( t \to \infty \).

- **Type II**: When this behavior is observed, one of the significant eigenvalues has positive real part and the other one has negative real part. This causes the nephron with the larger time delay (or gain) to oscillate strongly, while the other nephron is entrained into these strong oscillations. This type of behavior is shown in panels A1 and A2 of Figure 4.2, with the clean peaks in the PSD showing the synchrony of the oscillations and the noise in the troughs showing that other frequencies are present, although these frequencies are not very
Figure 4.1: Location of parameters and bifurcation curves in the $\tau_1$–$\tau_2$ plane. The points for which waveforms and PSDs in Figure 4.2 are labeled A, B, and C. The regions labeled I, II, III, and IV correspond to where the associated type of behavior described in Section 4.1.1 may be found. The fixed parameters for this figure are $\gamma_1 = \gamma_2 = 2.25$ and $\phi = 0.1$. 
Figure 4.2: SNGFR Waveforms (panels A1, B1, and C1) and PSD (panels A2, B2, and C2) for selected parameters in the $\tau_1$–$\tau_2$ plane. The frequencies for selected peaks in the PSDs are given next to the appropriate peak in panels A2, B2, and C2. The fixed parameters for this figure are $\gamma_1 = \gamma_2 = 2.25$ and $\phi = 0.1$. 

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strong.

- **Type III**: This type of behavior occurs when both significant eigenvalues having positive real parts and sufficiently similar imaginary parts. In this case the natural frequencies of the two nephrons are close enough that they oscillate synchronously. The frequency of this oscillation is given by the imaginary part of the eigenvalues ($\text{Im}\lambda_{1a}$ and $\text{Im}\lambda_{1b}$ are nearly equal in this case). This type of behavior is shown in panels **C1** and **C2** of Figure 4.2, with the very well-defined clean peaks with little noise in the PSD indicating the synchrony of the waveforms. The phase shift in the waveforms is due to a difference in time delays, if the were adjusted to account for the difference in time delays, the waveforms would be identical.

- **Type IV**: As with Type III behavior, both significant eigenvalues have positive real part when Type IV occurs, however, the imaginary parts are sufficiently different that the nephrons cannot oscillate synchronously. The result of this is that the two oscillations interfere with each other, producing an interference pattern of frequencies. This type of behavior is shown in panels **B1** and **B2** of Figure 4.2 with the asynchronous oscillations in panel **B1** and the complicated PSD in panel **B2**.
4.1.2 Coloring Algorithm for Numerical Simulations

To determine how several different parameter planes may be divided into regions where one of these four types of behavior is exhibited, a series of numerical experiments were performed on a grid of values for each parameter plane. After the simulation had run sufficiently long to be indistinguishable from its asymptotic state, the arrays of flow rate versus time for each model nephron are considered and the amplitude of oscillations in flow for each model nephron are measured. Using the data of flow rate vs. time for each simulation ($F_i(n)$, where $n$ is an integer ranging between 1 and 5000). Let

$$F_{i,\text{min}} = \min_n F_i(n)$$  \hspace{1cm} (4.1)

and

$$F_{i,\text{max}} = \max_n F_i(n) .$$  \hspace{1cm} (4.2)

Then the amplitude of the flow oscillation of each model nephron ($A_i$) is given by

$$A_i = F_{i,\text{max}} - F_{i,\text{min}} .$$  \hspace{1cm} (4.3)

The normalized flow waveform of each nephron $\tilde{F}_i(n)$ is then computed using the equation

$$\tilde{F}_i(n) = \frac{F_i(n) - F_{i,\text{min}}}{A_i} ,$$  \hspace{1cm} (4.4)
thus scaling it to amplitude 1. The degree of synchronization $A_s$ of the two nephrons is then determined by taking the difference of these normalized waveforms ($F_s(n)$) and computing the amplitude of the result using the following equations:

$$F_s(n) = \tilde{F}_1(n) - \tilde{F}_2(n),$$  \hspace{1cm} (4.5)

$$A_s = \max_n F_s(n) - \min_n F_s(n).$$  \hspace{1cm} (4.6)

Each point on the plane was then assigned a color according to the following algorithm: The color of the pixel is then set by making the intensity of red in the pixel $A_1$ (see, for instance, the upper right panel of Figure 4.9), the intensity of green in the pixel $A_2$ (upper left panel of Figure 4.9), and the intensity of blue in the pixel $A_s$ (lower left panel of Figure 4.9). Under this scheme the pixels corresponding to parameter values for which the system exhibits Type I behavior are colored blue or black; pixels corresponding to parameter values for which the system exhibits Type II behavior are colored red or green; and pixels corresponding to parameter values for which the system exhibits Type III behavior are colored yellow. Pixels corresponding to parameter values for which the system exhibits Type IV behavior do not have a characteristic color because the red, green and blue values change as the waveforms slide in and out of phase with each other. Instead, regions that exhibit Type IV behavior show a striation pattern.

Using this coloration method on numerical simulations run over a grid of parameter values from different parameter planes, the parameter planes can be divided into regions over which the behavior is defined by a single type. Extensive evidence
Figure 4.3: Re($\lambda$) = 0 curves for the $\tau$–$\gamma$ (upper left panel), $\tau_1$–$\gamma_1$ (upper right panel), $\gamma_1$–$\gamma_2$ (lower left panel), and $\tau_1$–$\tau_2$ (lower right panel) parameter planes. The fixed parameters for all of these figures are given where the figures appear independently.

from numerical experiments indicates that the results described in this chapter are qualitatively unchanged by varying the “fixed” parameters (the parameters not being varied in a numerical experiment) within physiologically significant regimes.

4.1.3 Numerical Simulations of the single-nephron model

First the consistency of the numerical simulation of the mathematical model was verified by checking that the predictions made by analyzing the characteristic equa-
tion agree with the results of the numerical simulations. In Figure 4.3 we see the \( \text{Re}(\lambda) = 0 \) curves for the \( \tau-\gamma \) plane (single-nephron case), the \( \tau_2-\gamma_2 \) plane (coupled-nephron case), the \( \tau_1-\tau_2 \) plane, and the \( \gamma_2-\gamma_2 \) plane. Starting with the single-nephron case, we demonstrate that the bifurcation curve previously identified [15] agrees with the results of the numerical simulation. In the single-nephron case, the only stable, long-term behaviors that are observed are the time-independent steady-state and stable LCO. The bifurcation from steady-state to LCO occurs along the curve identified in Section 3.2.3.

4.1.4 Numerical Simulations in the \( \tau_1-\tau_2 \) Plane

In the \( \tau_1-\tau_2 \) plane all four of the behavior types described above can be observed. The numerical experiments allow the classification of this plane into regions with the characteristic behavior of that region as shown in Figure 4.4. The boundary between the regions exhibiting Type III behavior and the regions exhibiting Type IV behavior is of interest. These curves appear to coincide with the level curves where \( \text{Im}(\lambda_{1a}) = \text{Im}(\lambda_{1b}) \), rather than curves where \( \text{Re}(\lambda) = 0 \). Figure 4.5 shows the results of numerical simulations of coupled nephrons on a grid of values in the \( \tau_1-\tau_2 \) parameter plane. The composite image, Figure 4.6, shows how the images decompose into component parts. The other composite image, Figure 4.7, shows changes as the parameter \( \gamma (= \gamma_1 = \gamma_2) \) varies.

4.1.5 Numerical Simulations in the \( \tau_1-\gamma_1 \) Plane

The types of behavior found in the \( \tau_1-\gamma_1 \) plane depend on the fixed values of \( \gamma_2 \) and \( \tau_2 \). If \( \gamma_2 \) and \( \tau_2 \) are sufficiently large, behavior types II, III, and IV are observed as
Figure 4.4: This figure shows the $\text{Re}(\lambda) = 0$ curves (bold) and the curves where $\text{Re}(\lambda_1) = \text{Re}(\lambda_2)$ (dashed) in the $\tau_1 - \tau_2$ plane. The regions labeled I, II, III, and IV correspond to where the associated type of behavior described in Section 4.1.1 may be found. The fixed parameter values for this figure are $\gamma_1 = \gamma_2 = 2.25$ and $\phi = 0.1$. 
Figure 4.5: The amplitude of oscillations and the degree of synchronization of oscillations in numerical solutions to the coupled nephron model for parameter values ranging over the $\tau_1 - \tau_2$ plane are represented by the color of pixels in this figure. Refer to Section 4.1.2 for the coloring algorithm. Fixed parameter values are $\gamma_1 = \gamma_2 = 0.25$ and $\phi = 0.1$. 
Figure 4.6: A composite figure depicting the elements of construction of Figure 4.5. The upper left panel shows the $\text{Re}(\lambda) = 0$ curves for the $\tau_1-\tau_2$ plane, the upper right panel shows the red and green components of the image, the lower left panel shows the blue component of the image and the lower right panel shows the complete image. The coloring is according to the algorithm described in Section 4.1.2.
Figure 4.7: A composite figure showing images similar to Figure 4.5 for three different values of the parameter $\gamma (= \gamma_1 = \gamma_2)$; $\gamma = 4.0$ (upper right), $\gamma = 3.5$ (lower right), and $\gamma = 3.0$ (lower left). The upper left panel shows the $\text{Re}(\lambda) = 0$ curves for $\gamma = 2.25$ for comparison. $\phi = 0.1$ for all three images. The images are colored using the scheme described in Section 4.1.2.
shown in Figure 4.8. Behavior type $I$ is not seen as nephron 2’s parameters are in a regime where the nephron displays LCO even if uncoupled. If $\gamma_2$ and $\tau_2$ are not sufficiently large, only behavior types $I$ and $II$ will occur because behavior types $III$ and $IV$ generally occur only when both nephrons would exhibit LCO if uncoupled. Figure 4.10 shows the case of small $\tau_2$ and $\gamma_2$.

4.1.6 Numerical Simulations in the $\gamma_1-\gamma_2$ Plane

In the $\gamma_1-\gamma_2$ plane ($\tau_1 = \tau_2 = \text{constant}$) only Type $I$, Type $II$, and Type $III$ behavior is observed. Type $IV$ behavior occurs when $\tau_1$ and $\tau_2$ differ and thus is never observed in this case. As is observed in the lower right panel of Figure 4.13 the bifurcation curve identified in Section 3.3.3 separates the $\gamma_1-\gamma_2$ plane into 2 regions, the region in the lower left corner of the plane where Type $I$ behavior is observed and the remainder of the plane where Type $II$ and Type $III$ behavior are observed.

In addition to this classification of the long-term behavior of systems in this parameter plane, differences in transient behavior occur. If a simulation is initiated with out-of-phase perturbations the model system will oscillate out-of-phase transiently before the out-of-phase oscillations collapse and in-phase oscillations arise. If the duration for which the out-of-phase oscillations persist is measured, it is found that the out-of-phase oscillations persist significantly longer along the line where $\gamma_1 = \gamma_2$ than for other values of the parameters. This can be seen in graphically in Figure 4.12, which shows the results of numerical simulations colored according to the scheme described above; the variable along the horizontal axis is $\gamma_1$, $\gamma_2 = 10 - \gamma_1$, and time is measured along the vertical axis. Figure 4.1.6 shows the results of a numerical
Figure 4.8: Amplitude and synchronization of oscillations in the $\tau_1-\gamma_1$ plane. This figure shows the types of behavior (described in Section 4.1.1) exhibited in the $\tau_1-\gamma_1$ plane for sufficiently large values of $\gamma_2$ and $\tau_2$. The image is colored using the algorithm described in Section 4.1.2. Fixed parameter values are $\tau_2 = 0.2$, $\gamma_2 = 4.0$, and $\phi = 0.1$. 
Figure 4.9: The red (upper right), green (upper left), and blue (lower left) components of Figure 4.8 are shown in this figure along with a copy of Figure 4.8 (lower right).
Figure 4.10: Amplitude and synchronization of oscillations in the $\tau_1$-$\gamma_1$ plane. This figure shows the types of behavior exhibited in the $\tau_1$-$\gamma_1$ plane for sufficiently small values of $\gamma_2$ and $\tau_2$ (lower right) as well as the decomposition of the image into red (upper right), green (upper left), and blue (lower left) components. The pixels are colored by the scheme described in Section 4.1.2. Fixed parameter values are $\tau_2 = 0.11$, $\gamma_2 = 2.0$, and $\phi = 0.1$. 
Figure 4.11: Waveforms from selected parameters in the $\gamma_1-\gamma_2$ plane. The parameter values used to obtain the waveforms in panels B, C, and D are indicated on panel A.

Experiment in the $\tau_1-\tau_2$ plain with oscillations initiated by out-of-phase perturbations. As can be seen in this figure, the out-of-phase oscillations persist along the line $\tau_1 = \tau_2$, which agrees with the observations in this section. Some examples of SNGFR waveforms initiated with out-of-phase oscillations are given in Figure 4.11.
Figure 4.12: Persistence of out-of-phase oscillations in $\gamma_1-\gamma_2$ plane. This figure shows the duration that out-of-phase oscillations persist at different parameter values in the $\gamma_1-\gamma_2$ plane. $\gamma_1$ varies along the horizontal axis and time varies along the vertical axis. The figure is colored using the algorithm from Section 4.1.2. The sharp peak in the center of the figure shows that for $\gamma_1 \approx \gamma_2$ out-of-phase oscillations persist significantly longer. For this figure the parameter values are $\gamma_2 = 10 - \gamma_1$, $\tau_1 = \tau_2 = 0.2$, and $\phi = 0.1$. 
Figure 4.13: Behavior of simulations in $\gamma_1$–$\gamma_2$ plane. Simulations initiated with out-of-phase oscillations. The upper left panel shows the $\text{Re}(\lambda) = 0$ curves for this case, the upper right panel shows the red and green components of the figure, the lower left panel shows the blue component of the figure and the lower right panel shows the combination of all three color components (in accordance with Section 4.1.2). The persistence of out-of-phase oscillations is observed along the line $\gamma_1 = \gamma_2$ in all three color figures. Fixed parameter values are $\tau_1 = \tau_2 = 0.2$ and $\phi = 0.1$. 
Figure 4.14: A figure generated by methods identical to Figure 4.5 except for the numerical simulations being started with symmetric out-of-phase perturbations. This figure provides further evidence of the persistence of out-of-phase oscillations when gains and time delays are equal. This figure is colored using the algorithm from Section 4.1.2. Fixed parameters values are $\gamma_1 = \gamma_2 = 4.0$ and $\phi = 0.1$. 
4.2 Time Series Analysis Using Discrete Fourier Transforms

To better understand how the behavior of the system and the PSDs change as parameters change an analysis of this system via the discrete Fourier transform on the data of flow rate versus time for a varying parameter value was employed. Figure 4.16 shows the results of spectral analysis of numerical simulations. For this figure numerical simulations were conducted with $\tau_2$ fixed at 0.8 and $\tau_1$ varying between 0.1 and 0.8 along the horizontal axis. The vertical axis corresponds to the frequency of the oscillations in the flow rate of the simulation at its asymptotic state. Pixels thus correspond to a specific frequency and parameter value. The pixels are colored according to the value of the power spectral density for the corresponding simulation at the specified frequency. The color scale is given at the right of the figure. Figure 4.16 shows the evolution from a single fundamental frequency and its harmonics (left) into a complex pattern that then coalesces back into a single frequency and its harmonics (right). The peak values labeled “A” correspond to the eigenvalue frequency (imaginary component) which has positive real part for all values of the parameter $\tau_1$ and its harmonics (integer multiples of this frequency). The peak labeled “B” corresponds to the eigenvalue frequency which crosses the imaginary axis at approximately $\tau_1 = 2.8$. The peak labeled “C” corresponds to twice the first eigenvalue frequency plus the difference between the two eigenvalue frequencies. Similarly, the peaks labeled “D” correspond to an integer multiple of the first eigenvalue frequency minus the difference between the two eigenvalue frequencies. We see this pattern repeated in progressively fainter peaks at values corresponding to $\text{Im}(n\lambda_1 \pm m(\lambda_2 - \lambda_1))$.
where $m$ and $n$ are integers.

To establish that these frequencies correspond to combinations of only the first two eigenvalues, two figures have been produced (Figures 4.17 and 4.18) in which the frequencies corresponding to all of the eigenvalues within the frequency range have been plotted (in black) in addition to the power spectra. In Figure 4.17, the lines corresponding to the imaginary parts of the first two eigenvalues match exactly with the peaks they were claimed to represent whereas none of the other eigenvalues match peaks in the figure. In Figure 4.18, only one peak is a match as the second eigenvalue has negative real part.

The remaining figures (Figures 4.19, 4.20, 4.21, and 4.22) all show spectrum plots made for parameters varying over the $\tau_1-\gamma_1$ plane. These figures show patterns similar to Figures 4.15 and 4.16, although Figure 4.19 has some characteristics that are not currently explained—on the left side of the figure there is a complicated pattern at relatively low power (the green lines on blue) and as the system transitions from the interaction of two frequencies (on the right) to a single frequency and its harmonics (on the left), the frequencies do not fully coalesce as they do in the other figures.
Figure 4.15: The magnitude of the PSD obtained from numerical experiments for varying $\tau_1$ and fixed $\tau_2 = 0.3$, $\gamma_1 = \gamma_2 = 2.25$, and $\phi = 0.1$. 
Figure 4.16: The magnitude of the PSD obtained from numerical experiments for varying $\tau_1$ and fixed $\tau_2 = 0.8$, $\gamma_1 = \gamma_2 = 2.25$, and $\phi = 0.1$. The peaks labeled A have frequencies corresponding to integer multiples of the imaginary part of the first eigenvalue. The peak labeled B has a frequency corresponding to the imaginary part of the second eigenvalue. The peak labeled C has a frequency corresponding to the imaginary part of twice the first eigenvalue plus the second eigenvalue. The peaks labeled D have frequencies corresponding to the imaginary part of an integer multiple of the first eigenvalue minus the difference between the two eigenvalues.
Figure 4.17: Magnitude of PSD with frequencies corresponding to eigenvalues plotted. The black curves correspond to the imaginary part of the eigenvalues of the system. Fixed values are $\tau_2 = 0.8$, $\gamma_1 = \gamma_2 = 2.25$, and $\phi = 0.1$. 
Figure 4.18: Magnitude of PSD with frequencies corresponding to eigenvalues plotted. The black curves correspond to the imaginary part of the eigenvalues of the system. The time delays are specified by $\tau_1 + \tau_2 = 0.558$. Fixed values are $\gamma_1 = \gamma_2 = 2.25$ and $\phi = 0.1$. 
Figure 4.19: Magnitude of PSD for parameters varying in $\tau_1-\gamma_1$ plane. Both $\gamma_1$ and $\tau_1$ vary in this simulation, satisfying the relationship $10\tau_1 = 0.7\gamma_1 + 1$. The patterns in blue and green when $\tau_1 < 2.7$ and the lack of the frequencies coalescing as $\tau_1$ decreases through 2.7 are currently unexplained phenomena. The fixed parameters are $\tau_2 = 0.2$, $\gamma_2 = 4.0$ and $\phi = 0.1$. 
Figure 4.20: Magnitude of PSD for parameters varying in $\tau_1-\gamma_1$ plane. The fixed parameters are $\tau_2 = 0.2$, $\gamma_1 = 2.0$, $\gamma_2 = 9.0$, and $\phi = 0.1$. 
Figure 4.21: Magnitude of PSD for parameters varying in $\tau_1$–$\gamma_1$ plane. Both $\gamma_1$ and $\tau_1$ vary in this simulation, satisfying the relationship $10\tau_1 + 0.7\gamma_1=7$. The fixed parameters are $\tau_2 = 0.2$, $\gamma_2 = 4.0$ and $\phi = 0.1$. 
Figure 4.22: Magnitude of PSD for parameters varying in $\tau_1-\gamma_1$ plane. The simple structure seen in this figure is due to the fact that only one eigenvalue has positive real part in the entire parameter range represented in the figure. The fixed parameters are $\tau_2 = 0.1$, $\gamma_1 = 2.0$, $\gamma_2 = 5.0$ and $\phi = 0.1$. 
Chapter 5

Numerical Methods

5.1 Introduction

To conduct rapid numerical simulations using the coupled two-nephron model, an integral numerical method based on the method of characteristics was developed. The implementation of this method requires only $O(n)$ operations to calculate $n$ time steps. This method requires the estimation of a limit of integration in an integral equation (vide infra equation (5.1)). The technique for this approximation is described below and the error is shown to be less than $O((\Delta t)^3)$ where $\Delta t$ is the step size used in the numerical integration. Furthermore, the global truncation error in the numerical method is less than $O((\Delta t)^2)$.

5.1.1 Description of Method

Before describing the numerical method, two mathematical preliminaries are appropriate. First consider the distance traveled by the fluid currently at the MD ($x = 1$). This fluid has traveled the length of the TAL (1 non-dimensional length unit), and
by integrating its velocity (equivalent to the non-dimensional flow rate \( F(C(1,t)) \)), the distance traveled is obtained. Setting the distance equal to 1 and the upper bound of integration to the time the fluid reaches the MD, \( t_{end} \), gives an equation that defines the lower bound of integration, the time at which the fluid entered the TAL, \( t_{end} - T(t_{end}) \),

\[
1 = \int_{t_{end} - T(t_{end})}^{t_{end}} G(s) \, ds, \tag{5.1}
\]

where \( T(t_{end}) \) is the time that fluid arriving at the MD at time \( t_{end} \) has taken to traverse the TAL, and where \( G(t) = F(C(1,t)) \).

The second preliminary is to develop a relationship between the transit time of fluid through the TAL and the concentration of chloride at the MD. To obtain the desired relationship, apply the method of characteristics to equation (2.5) with no backleak \((P = 0 \text{ in equation (2.6)})\). Along a characteristic curve \( x(t) \), equation (2.5) becomes

\[
\frac{d}{dt} C(x(t), t) = \frac{-V_{max}C(x(t), t)}{K_M + C(x(t), t)}, \tag{5.2}
\]

for \( t_{end} \geq t \geq t_{end} - T(t_{end}) \) with boundary condition \( C(x(0), 0) = 1 \). Solving equation (5.2) with these conditions yields the desired relationship between concentration and transit time, which is

\[
C(1, t_{end})^{K_m} e^{C(1,t_{end})} = e^{1-V_{max}T(t_{end})}. \tag{5.3}
\]

Equation (5.3) shows that the concentration depends only on the transit time, \( T \).
To numerically approximate solutions to this model, begin with a flow history $G(t) = F(C(1, t))$ for $t \in [-\tau_{\text{max}} - T_{\text{max}}, 0]$, where $\tau_{\text{max}}$ and $T_{\text{max}}$ are the maximum time delay and the maximum transit time, respectively. Then calculate $G(t + \Delta t)$ as follows:

i. Set $t_{\text{end}} = t + \Delta t - \tau$.

ii. Define the transit time ($T(t_{\text{end}})$) for the fluid arriving at $x = 1$ at time $t_{\text{end}}$ by equation (5.1).

iii. Approximate $T(t_{\text{end}})$ by numerical integration and interpolation of the integral (equation (5.1)).

iv. Approximate $C(1, t_{\text{end}})$ by using Newton’s method to numerically solve the equation obtained by the method of characteristics, equation (5.3).

v. Evaluate $G(t + \Delta t) = F(C(1, t_{\text{end}}))$ using equation (2.7).

This numerical method may be modified to couple two single-nephron models by replacing $F(C(1, t_{\text{end}}))$ in each model with its coupled counterpart:

$$\mathcal{F}_i(C_i, C_j) = F_i(C_i(1, t - \tau_i)) + \phi(F_j(C_j(1, t - \tau_j)) - 1). \quad (5.4)$$

This modification allows two copies of the single nephron model to be coupled.
At the heart of this method is the approximation of \( T(t_{\text{end}}) \) via numerical integration of equation (5.1). Approximating \( T(t_{\text{end}}) \) is equivalent to solving the equation

\[
1 = \int_{0}^{t^*} f(s) \, ds \quad (5.5)
\]

for \( t^* \) given the values of a function \( f \) at discrete values. This may be accomplished by using Simpson’s rule to evaluate the integral in equation (5.5) numerically until the first value of \( t \) for which the integral exceeds 1 is found. Call this value \( t_1 \). Then if one considers the function

\[
x(t) = \int_{0}^{t} f(s) \, ds \quad (5.6)
\]

at the points \( t_1, t_1 - \Delta t, \) and \( t_1 - 2\Delta t \), a quadratic interpolation of the function \( x(t) \) can be determined. This quadratic function \( \tilde{x}(t) \) may now be used to solve the equation \( \tilde{x}(t) = 1 \) for \( t \), yielding an approximation to \( t^* \).

### 5.1.2 Accuracy of the Numerical Method

In this section it will be shown that the truncation error in each time step in the numerical method is \( O(\Delta t^3) \) and hence the method converges to the true solution at rate \( O(\Delta t^2) \).

To calculate the order of the method one must first consider the error involved in solving equation (5.5) numerically for \( t^* \). This equation is solved by using the following numerical method. Approximate the integral in equation (5.5) step by step using Simpson’s rule until the approximated value is greater than one. Take the final three values of the approximation (call them \( x_{-1}, x_0 \) and \( x_1 \)—they correspond
to approximations at times $t_{-1}, t_0, \text{ and } t_1$, respectively) and find the quadratic polynomial interpolating the above approximation of equation (5.5) at times $t_{-1}, t_0, \text{ and } t_1$, $q(t)$. Define $\bar{t}$ by the equation $q(\bar{t}) = 1$. Then $\bar{t}$ approximates $t^\ast$.

Let $S(t, \Delta t)$ be the Simpson’s rule approximation to $\int_0^t f(s) \, ds$ for step size $\Delta t$. (Here $\Delta t$ is taken to be the distance between successive values of the function being integrated numerically, each Simpson’s rule step will cover $2(\Delta t)$.) Given $\Delta t$, define $t_i$ for $i = -1, 0, 1$ such that $t_0 = 2n\Delta t$ for some integer $n$, $t_i - t_{i-1} = 2\Delta t$ and $S(t_0, \Delta t) \leq 1 < S(t_1, \Delta t)$. Let $x_i = S(t_i, \Delta t)$ and $\hat{x}_i = \int_{t_i}^t f(s) \, ds$. Then $q(t) = a(t - t_0)^2 + b(t - t_0) + c$ where

$$a = \frac{x_1 - 2x_0 + x_{-1}}{8\Delta t^2} \quad (5.7)$$

$$b = \frac{x_1 - x_{-1}}{4\Delta t} \quad (5.8)$$

$$c = x_0 \quad (5.9)$$

Let $\hat{q}(t) = \hat{a}(t - t_0)^2 + \hat{b}(t - t_0) + \hat{c}$, where $\hat{a}$, $\hat{b}$ and $\hat{c}$ are defined by taking the definitions of $a$, $b$ and $c$ and replacing the $x_i$’s with $\hat{x}_i$’s. Define $\hat{t}$ such that $\hat{q}(\hat{t}) = 1$.

**Lemma 6.1:** $\bar{t} \to t^\ast$ at $3^{rd}$ order in the step size used in the Simpson’s rule.

**Proof:**

Define $f_{max}^{(i)}$ for $i = 1, 2, \ldots$ by

$$f_{max}^{(i)} = \max_{t_{i-1} \leq t \leq t_i} |f^{(i)}(t)| \quad (5.10)$$
where \( f^{(i)} \) denotes the \( i \)th derivative of \( f \). Then for \(-2\Delta t \leq t \leq 2\Delta t\):

\[
|q(t) - \hat{q}(t)| = |(a - \hat{a})(t - t_0)^2 + (b - \hat{b})(t - t_0) + (c - \hat{c})| = \frac{|(x_1 - \hat{x}_1) - 2(x_0 - \hat{x}_0) + (x_{-1} - \hat{x}_{-1})|}{8(\Delta t)^2} (t - t_0)^2 + \frac{|(x_1 - \hat{x}_1) - (x_{-1} - \hat{x}_{-1})|}{4\Delta t} + x_0 - \hat{x}_0| (5.11)
\]

\[
\leq \frac{t_1 - t_0}{45} \Delta t^4 f_{max}^{(4)} (5.12)
\]

where equation (5.13) follows from the fact that \( x_i - \hat{x}_i = \frac{t_i}{180} \Delta t^4 f^{(4)}(\xi_i) \) where \( 0 \leq \xi_i \leq t_i \). This comes from the error in using Simpson’s rule to approximate an integral [1].

If \( p(t) \) is the quadratic interpolation of \( f(t) \) such that \( p(t) = f(t) \) for \( t = -2\Delta t, 0, 2\Delta t \) then for \(-2\Delta t \leq t \leq 2\Delta t\), there exists a \( \xi, -2\Delta t \leq \xi \leq 2\Delta t \), such that

\[
|f(t) - p(t)| = \left| t(t - 2\Delta t)(t + 2\Delta t) \frac{f^{(3)}(\xi)}{3!} \right| (5.14)
\]

\[
\leq \frac{8 f_{max}^{(3)}}{3\sqrt{3}} \Delta t^3 (5.15)
\]

where the right hand side of equation (5.14) is the error in a quadratic interpolation and equation (5.15) results from maximizing equation (5.14) over the interval \( t_0 \leq t \leq t_1 \).
Define $f_{\text{min}}$ to be the minimum flow rate through the TAL. By the definition of the flow rate function for the non-dimensionalized model, equation (2.7) $f_{\text{min}} = 1 - K_1 > 0$. Now consider the following:

$$|\bar{t} - t^*| \leq \frac{1}{f_{\text{min}}} \left| \int_{\bar{t}}^{t^*} f(s)ds \right|$$ (5.16)

$$\leq \frac{1}{f_{\text{min}}} \left( \left| \int_{\bar{t}}^{t^*} f(s)ds \right| + \left| \int_{\bar{t}}^{t^*} f(s)ds \right| \right)$$ (5.17)

$$\leq \frac{1}{f_{\text{min}}} \left( \left| \int_{0}^{\bar{t}} f(s)ds - \int_{0}^{\bar{t}} f(s)ds \right| + \left| \int_{0}^{\bar{t}} f(s)ds - \int_{0}^{\bar{t}} f(s)ds \right| \right)$$ (5.18)

$$\leq \frac{1}{f_{\text{min}}} \left( \left| \int_{0}^{\bar{t}} f(s)ds - \hat{q}(\bar{t}) - \int_{0}^{\bar{t}} f(s)ds + q(\bar{t}) \right| \right)$$

$$\leq \frac{1}{f_{\text{min}}} \left( \left| 1 - \int_{0}^{\bar{t}} f(s)ds \right| \right)$$ (5.19)

$$\leq \frac{1}{f_{\text{min}}} \left( \left| \int_{0}^{\bar{t}} f(s)ds - \hat{q}(\bar{t}) \right| + \left| \int_{0}^{\bar{t}} f(s)ds - q(\bar{t}) \right| \right)$$

$$\leq \frac{1}{f_{\text{min}}} \left( \frac{8}{3\sqrt{3}} \Delta t^3 f_{\text{max}}^{(2)} + \left| \int_{0}^{\bar{t}} f(s)ds - \hat{q}(\bar{t}) + \hat{q}(\bar{t}) - q(\bar{t}) \right| \right)$$

$$+ \frac{1}{f_{\text{min}}} \left( \frac{8}{3\sqrt{3}} \Delta t^3 f_{\text{max}}^{(2)} \right)$$ (5.21)

$$\leq \frac{1}{f_{\text{min}}} \left( \frac{16}{3\sqrt{3}} \Delta t^3 f_{\text{max}}^{(2)} + \left| \int_{0}^{\bar{t}} f(s)ds - \hat{q}(\bar{t}) \right| + |\hat{q}(\bar{t}) - q(\bar{t})| \right)$$ (5.22)
Equation (5.19) follows from equation (5.18) because 
\[ \hat{q}(\hat{t}) = q(\bar{t}) = \int_{0}^{t^{*}} f(s)ds = 1. \]
The first and last terms in equation (5.20) are the difference between an exact integral and a Simpson’s rule approximation of the same interval (an interpolating function is exact on the points it is interpolating) and as such may be replaced by the Simpson’s error estimate. The middle term in equation (5.22) is also a Simpson’s rule approximation and the error estimate on the last term of equation (5.22) comes from equation (5.15).

q.e.d.

**Theorem 6.2**: The error in approximating \( F(t) \) is of order \( \Delta t^3 \).

**Proof**:

Let \( \tilde{F}(t) \) be the approximation of \( F(t) \) and \( \tilde{C}(x, t) \) be the approximation of \( C(x, t) \) using this method. Then, by equation 2.7,

\[
|\tilde{F}(t) - F(t)| \leq |\tilde{C}(1, t - \tau) - C(1, t - \tau)|\kappa_1,
\]

where \( \kappa_1 \) is a bound on the derivative of (2.7). This shows that the error in approximating the flow rate is of the same order as the error in approximating the concentration. Now define \( T(t) \) as the transit time of fluid arriving at the MD at
time $t$ and $\tilde{T}(t)$ as the approximation of the transit time using the numerical method. By equation (5.3),

$$|\tilde{C}(1, t - \tau) - C(1, t - \tau)| \leq |\tilde{T}(t) - T(t)|\kappa_2,$$

(5.26)

where $\kappa_2$ is a bound on the derivative of equation (5.3) in the allowed domain of $T$.

Now, by Lemma 6.1,

$$|\tilde{T}(t) - T(t)| \leq \Delta t^3 \left( \frac{8}{\sqrt{3}} f_{max}^{(2)} + \frac{t_1}{45} \Delta t f_{max}^{(4)} \right),$$

(5.27)

which implies that

$$|\tilde{F}(t) - F(t)| \leq \kappa_3 (\Delta t)^3,$$

(5.28)

where

$$\kappa_3 = \frac{\kappa_1 \kappa_2}{f_{min}} \left( \frac{8}{\sqrt{3}} f_{max}^{(2)} + \frac{t_1}{45} \Delta t f_{max}^{(4)} \right).$$

(5.29)

Since the single step error is of order $(\Delta t)^3$ for step size $\Delta t$, the global truncation error is of order $(\Delta t)^2$, thus establishing the theorem.

q.e.d.

5.1.3 INCLUSION OF BACKLEAK INTO THE METHOD

The method describe above may be modified to include backleak of chloride ($P \neq 0$ in equation (2.6)). In the case of backleak, the method requires $O(n^2)$ operations.
to calculate \( n \) time steps. To accomplish this, step iv must be modified because equation (5.3) is only valid in the case where backleak is set to 0. In the case \( P \neq 0 \) there is no explicit functional relationship between transit time through the TAL and concentration at the MD. The lack of a usable relationship between transit time and concentration in this case may be solved by making use of the characteristic curves of equation (2.5). By defining

\[
x(t) = \int_{t_{end}-T(t_{end})}^{t} G(s) \, ds
\]

(5.30)

and substituting equation (5.30) into equation (2.6) one obtains the ordinary differential equation (ODE)

\[
\frac{d}{dt}(C(x(t), t))) = -J(C(x(t), t), C_{e}(x(t))).
\]

(5.31)

with boundary condition \( C(0, t) = 1 \) \( \forall t \). This ODE may then be solved from \( t = t_{end} - T(t_{end}) \) to \( t = t_{end} \) using standard techniques (i.e., a Runge-Kutta method) in order to approximate \( C(1, t_{end}) \) which may then be used to calculate the flow rate in step v.
Chapter 6

Physiological Significance

The study of TGF is an active area of physiological research [24]. Previous modeling studies have predicted that LCO increase sodium delivery to the distal portion of the nephron, suggesting that LCO in TGF may lead to increased sodium excretion [16, 20]. This hypothesis, if correct, would demonstrate an important role for TGF-mediated LCO physiologically. A previous study of two coupled nephrons predicted that coupled nephrons are more likely to exhibit LCO than uncoupled nephrons [22]. In the present study, that model of TGF in two coupled nephrons was examined to determine how coupling affects the types of qualitative behavior exhibited by the model. This understanding may lead to a greater understanding of the physiological system and what types of behaviors might be expected therein.

It has been shown here that four types of behavior are exhibited by the system of coupled models over the physiologically significant portion of the parameter space (consisting of the physiologically reasonable values $0.1 \leq \tau_1, \tau_2 \leq 0.3$ [4], $1 \leq \gamma_1, \gamma_2 \leq 10$ [7], and $0.1 \leq \phi \leq 0.3$ [13, 22]). The physiologic parameter space has regions
that correspond to four qualitatively different model behaviors:

- a time-independent steady state in both nephrons;
- sustained synchronous oscillations in both nephrons with small amplitude in one nephron and large amplitude in the other;
- sustained large-amplitude oscillations in both nephrons with interacting inherent frequencies resulting in asynchronous waveforms; and
- sustained large-amplitude synchronous oscillations in both nephrons at a fundamental frequency and its harmonics.

This study describes where each of these behaviors is seen in various planes in the parameter space as well as the boundaries between these behaviors.

Although the physiological system is substantially more complex than the pair of model coupled nephrons in this study, insight into the physiology may still be gained. In particular, numerical simulations of the model predict that strong synchronous oscillations indicate that the nephrons have similar time delays in their TGF loops, whereas asynchronous waveforms result when time delays differ. The analysis of experimentally obtained time series using power spectra is a widely-used tool in the physiology of renal hemodynamics [6, 12, 26]. The interaction of frequencies inherent in asynchronous waveforms may contribute to the complex power spectra observed in physiological experiments [26], which have been attributed to deterministic chaos. Thus this modeling study may help explain complicated power spectra based on time series obtained from physiological experiments [26].
Appendix A

Derivation of Coupled-Nephron Characteristic Equation

The first step in developing the characteristic equation for two coupled nephrons is to consider the time-independent steady-state solution to equation (2.8) \( S(x) \). (In this analysis it is assumed that the steady-state solution is identical for both model nephrons.) By making the approximation

\[
C_i(x, t) = S(x) + \epsilon D_i(x, t), \tag{A.1}
\]

substituting equation (A.1) into equation (2.11), linearizing the resulting equation in \( \epsilon \), and canceling terms of order \( \epsilon^2 \) or less the equation

\[
\frac{\partial}{\partial t} D_i(x, t) + \frac{\partial}{\partial x} D_i(x, t) = -J'(S(x))D_i(x, t) - F_i'(C_{i,op})S_i'(x) \\
\times D_i(1, t - \tau_i) - \phi F_j'(C_{j,op})S_j'(x) \\
\times D_j(1, t - \tau_j) \tag{A.2}
\]
is obtained. By assuming that \( D_i(x,t) \) is of the form \( D_i(x,t) = f_i(x)e^{\lambda t} \), we can obtain from equation (A.2) the following system of two linear ODEs for \( f_i(x) \), \((i,j) = (1,2) \) or \((2,1)\):

\[
f_i'(x) + (\lambda + J'(S(x))) f_i(x), = -F'_i(C_{op})S'(x)f_i(1)e^{-\lambda \tau_i} - \phi F'_j(C_{op})S'(x)f_j(1)e^{\lambda \tau_j}
\]

(A.3)

where we have made use of the assumption that \( S_1(x) = S_2(x) = S(x) \) and hence \( C_{i,op} = C_{j,op} = C_{op} \). This system must have boundary condition \( f_i(0) = 0 \) in order to satisfy the condition \( C(0,t) = 1 \) because \( S(0) = 1 \). Following the method used by Layton et al. [15] in the single nephron case, use the integrating factor

\[
\mu_i(x) = e^{\int (\lambda - \frac{S''(x)}{S'(x)}) dx} = \frac{e^{\lambda x}}{S'(x)}.
\]

(A.4)

for both instances of equation (A.3). By using this integrating factor we find that the solution to equation (A.3) is given by

\[
f_i(x) = S'(x) \left( e^{-\lambda x} - 1 \right) \frac{1}{\lambda} \left( F'_i(C_{op})f_i(1)e^{-\lambda \tau_i} + \phi F'_j(C_{op})f_j(1)e^{\lambda \tau_j} \right).
\]

(A.5)

Evaluating this equation at \( x = 1 \) and making the substitution \( \gamma_i = F'(C_{op})S' \) (an equivalent form of equation (2.10)), we find that

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\[ f_i(1) = \frac{e^{-\lambda} - 1}{\lambda} \left( \gamma_i f_i(1) e^{\lambda \tau_i} + \phi \gamma_j f_j(1) e^{-\lambda \tau_j} \right). \quad (A.6) \]

Solving for \( f_i(1) \) yields

\[ f_i(1) = \frac{\phi \gamma_j e^{-\lambda \tau_j}}{\frac{\lambda}{e^{\lambda} - 1} - \gamma_i e^{-\lambda \tau_i}} f_j(1). \quad (A.7) \]

By substituting the expression for \( f_2(1) \) from equation (A.7) into the expression for \( f_1(1) \) from equation (A.7) we find that

\[ f_1(1) = \frac{\phi \gamma_2 e^{-\lambda \tau_2}}{\frac{\lambda}{e^{\lambda} - 1} - \gamma_1 e^{-\lambda \tau_1}} \cdot \frac{\phi \gamma_1 e^{-\lambda \tau_1}}{\frac{\lambda}{e^{\lambda} - 1} - \gamma_2 e^{-\lambda \tau_2}} \cdot f_1(1). \quad (A.8) \]

Canceling \( f_1(1) \) from both sides and rearranging we find that equation (A.8) is equivalent to equation (2.13).
Bibliography


Biography

Kevin Jay Kesseler was born on March 3, 1969 in Eaton Rapids, Michigan. He received his B.S. from Michigan State University in 1991, his M.S. from Michigan State University in 1995, and his M.A from Duke University in 2002. His father, George, is a retired entrepreneur and his mother, Nancy is a retired elementary school teacher. His sister, Karyen Lipscomb, lives in Cary, North Carolina with her husband, George, a commercial pilot and their three children, Alexia, Lea, and Steven.

Kevin’s interests include tai chi chuan, poker, and basketball. As a “Cameron Crazie” for his 6 years at Duke University he became a well-known face in the crowd at home basketball games. He currently resides in Durham, North Carolina.