Time Delays in Neural Systems

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1 Introduction

In this chapter I will give a overview of the role of time delays in understanding neural systems. The main focus will be on models of neural systems in terms of delay differential equations. Later in this section, I will discuss how such models arise. The goal of the chapter is two-fold: (1) to give the reader an introduction and guide to some methods available for understanding the dynamics of delay differential equations and (2) to review some of the literature documenting how including time delays in neural models can have a profound effect on the behaviour of those models.

1.1 Modelling delay in neural systems

To begin, we will formulate a general model for a network of neurons and then determine how delays may occur in this model. Consider a network of n neurons modelled by the equations

$$\dot{\mathbf{x}}_i(t) = \mathbf{f}_i(\mathbf{x}_i(t)) + \sum_{j=1}^{n} f_{ij}(\mathbf{x}_i(t), \mathbf{x}_j(t)), \ i = 1, \ldots, n. \tag{1}$$

The variable $\mathbf{x}_i$ represents all the variables describing the physical state of the cell body of the i^{th} neuron in the network. For example, in the standard Hodgkin-Huxley model, it would represent the membrane voltage and gating variables: $\mathbf{x}_i = (V_i, m_i, n_i, h_i)$. The function $\mathbf{f}_i$ represents the intrinsic dynamics of the i^{th} neuron and the function f_{ij}, often called the coupling function, represents the input to the i^{th} neuron from the j^{th} neuron.

If the j^{th} neuron is connected to the i^{th} via a chemical synapse, then the coupling function usually represented as

$$f_{ij}(\mathbf{x}_i(t), \mathbf{x}_j(t)) = c_{ij} g_{ij}(\mathbf{x}_j(t)) h_{ij}(\mathbf{x}_i(t)). \tag{2}$$

Here g_{ij} is a sigmoidal function, usually chosen to have maximum value 1, so that c_{ij} represents the maximum coupling strength (synaptic conductance) and h_{ij} is typically a linear function (e.g. for Hodgkin Huxley type neurons, $h_{ij}(\mathbf{x}_i(t)) = V_i(t) - K_{ij}$, where K_{ij} is a constant). Some models set $\mathbf{h}_{ij} = 1$, eliminating the dependence on the post-synaptic neuron. This is commonly called **sigmoidal coupling**.

If the neurons are connected via a gap junction, then the coupling function is usually represented as

$$f_{ij}(\mathbf{x}_i(t), \mathbf{x}_j(t)) = c_{ij}(\mathbf{x}_i(t) - \mathbf{x}_j(t)). \tag{3}$$

There are several sources of delay in a neural system. Consider first the delay due to propagation of action potentials along the axon. In the model above, when an action potential is generated in the cell body of neuron j, it is immediately felt by all other neurons to which it is connected. However, in reality, the action potential must travel along the axon of neuron j to the synapse or gap junction. Conduction velocities can range from the order of 1 m/sec along unmyelinated axons to more than 100 m/sec along myelinated axons [16, 55]. This can lead to significant time delays in certain brain structures. There are several ways to incorporate this into the model, such as including spatial dependence of the variables or multiple compartments representing different parts of the neuron [37]. However, if we are primarily interested in the effect of the action potential when it reaches the end of the axon (will it cause an action potential in another neuron?), then a simpler approach is to include a time delay in the coupling term. In this case the general coupling term becomes

$$f_{ij}(\mathbf{x}_i(t), \mathbf{x}_j(t - \tau_{ij})) \tag{4}$$

where $\tau_{ij} > 0$ represents the time taken for the action potential to propagate along the axon connecting neuron j (the pre-synaptic neuron) to neuron i (the post-synaptic neuron).

The above assumes that the axon of neuron j connects on or close to the cell body of neuron i. Some cells may have synapses or gap junctions on dendrites far from the cell body. In this case, there can also be a delay associated with propagation of the action potential along the dendrite. This will introduce an additional time delay, viz.,

$$f_{ij}(\mathbf{x}_i(t - \tau_{ij}^d), \mathbf{x}_j(t - \tau_{ij}^d - \tau_{ij}^a)) \tag{5}$$

where τ_{ij}^a and τ_{ij}^d represent the time delays due to the propagation of the action potential along the axon and dendrite, respectively.

Another delay can occur in the transmission of the electrical signal across the synapse. That is, once the action potential from neuron j reaches the synapse, there is some time before an action potential is initiated in neuron i. A common way to model this is to augment the model equations above by equations modelling the chemical kinetics of the synapse [36, 37]. Alternatively, this can be incorporated into (4) just by increasing the delay τ_{ij}. I

will focus on the latter approach, but in section 3 will review some literature that indicates the qualitative effect on the dynamics can be quite similar using both approaches. Clearly, the latter approach will yield a simpler model if one also wants to include the effect of axonal delay.

Equations (4) and (5) assume that the time delays are fixed. In reality, the delay will likely vary slightly each time an action potential is propagated from neuron j to neuron i. This may be incorporated into the model putting time dependence into the delay: $\tau_{ij}(t)$. Many of the methods outlined in section may be extended to this case, by assuming the delay satisfies some constraints $\bar{\tau}_{ij} \leq \tau_{ij}(t) \leq 0$. Alternatively, one might consider adding some noise to the delay. Unfortunately, there is very little theory know for such stochastic delay differential equations.

An alternative approach is to incorporate a distribution of delays, representing the situation where the delay occurs in some range of values with some associated probability distribution. In this case, coupling term (4) becomes

$$\int_0^\infty f_{ij}(\mathbf{x}_i(t), \mathbf{x}_j(t-\sigma))g(\sigma)\, d\sigma. \tag{6}$$

The function g is called the kernel of the distribution and represents the probability density function of the time delay. Since g is a pdf it is normalized so that $\int_0^\infty g(\sigma)\, d\sigma = 1$. Although distributions of delays are not commonly used in neural network models, they have been extensively used in models from population biology [15, 42]. In this literature, the most commonly used distributions are the uniform distribution:

$$g(\sigma) = \begin{cases} 0 & 0 \leq \sigma < \tau_{\min} \\ \frac{1}{\delta} & \tau_{\min} \leq \sigma \leq \tau_{\min} + \delta \\ 0 & \tau_{\min} < \sigma \end{cases}, \tag{7}$$

and the gamma distribution:

$$g(\sigma) = \begin{cases} 0 & 0 \leq \sigma < \tau_{\min} \\ \frac{a^m}{\Gamma(m)}(\sigma - \tau_{\min})^{m-1} e^{-a(\sigma - \tau_{\min})} & \tau_{\min} \leq \sigma \end{cases}, \tag{8}$$

where $a, m \geq 0$ are parameters. Γ is the gamma function defined by $\Gamma(0) = 1$ and $\Gamma(m+1) = m\Gamma(m)$. Both these distributions can be shown to approach a Dirac distribution in the appropriate limits ($\delta \to 0$ for the uniform distribution and $m \to \infty$ for the gamma distribution), which leads to a discrete delay in the coupling term. It is usual in the population biology literature ([15, 42]) to take $\tau_{min} = 0$. In this case the gamma distribution can be shown to be equivalent to a system of m ordinary differential equations, which is amenable to the analysis described in elsewhere in this volume [6]. However, as pointed out by Bernard et al. [5], it makes more biological sense to take $\tau_{\min} > 0$, since the probability of having zero delay is effectively zero in most applications. In this case, the gamma distribution is equivalent to a system of $m-1$ ordinary differential equations and one discrete delay differential equation.

In the next section we will review some tools for analyzing delay differential equations. To make the theory concrete, we will apply it to a particular example. Consider the following representation of the Fitzhugh-Nagumo model for a neuron [25, 45]

$$\begin{aligned} \dot{v}(t) &= -v^3 + (a+1)v^2 - av - w + I \\ \dot{w}(t) &= bv - \gamma w \end{aligned}. \tag{9}$$

Assume that the parameters are such that there is just one equilibrium point $(\bar{v}, \bar{w})$ of this equation, where $\bar{v}, \bar{w}$ satisfy

$$\bar{v}^3 - (a+1)\bar{v}^2 + (a + \frac{b}{\gamma})\bar{v} + I = 0 \tag{10}$$

$$\bar{w} = \frac{b}{\gamma}\bar{v} \tag{11}$$

We shall consider the situation when two of these neurons are joined with delayed sigmoidal coupling in the following way

$$\begin{aligned} \dot{v}_1(t) &= -v_1^3 + (a+1)v_1^2 - av_1 - w_1 + I + c\tanh(v_2(t-\tau) - \bar{v}) \\ \dot{w}_1(t) &= bv_1 - \gamma w_1 \\ \dot{v}_2(t) &= -v_2^3 + (a+1)v_2^2 - av_2 - w_2 + I + c\tanh(v_1(t-\tau) - \bar{v}) \\ \dot{w}_2(t) &= bv_2 - \gamma w_2 \end{aligned} \tag{12}$$

This setup is due to [7]. We will sometimes write (12) in the condensed form

$$\dot{\mathbf{x}} = f(\mathbf{x}(t), \mathbf{x}(t-\tau)), \tag{13}$$

where $\mathbf{x} = (v_1, w_1, v_2, w_2)$.

We will focus on equations with a single discrete delay. The approach is similar for multiple delays the analysis may just becomes more complicated. We will discuss some of the differences that arise for distributed delays in the final section.

There is a very large literature on the effect of time delays on artificial neural networks (ANNs). An example of such a network is the additive (also called Hopfield) neural network with delays. This is usually written in the following form

$$\dot{x}_i(t) = -k_i x_i(t) + \sum_{j=1}^{n} f_{ij}(x_j(t-\tau_{ij}).$$

I will not attempt to review all the material related to such equations, but will try to highlight those results I feel may have implications for biological neural networks. In particular, networks of the following form

$$\dot{x}_i(t) = -k_i x_i(t) + f_{ii}(x(t-\tau_1)) + \sum_{j\neq i}^{n} f_{ij}(x_j(t-\tau_2), \tag{14}$$

have some parallels with biological neural networks, since the uncoupled units may behave as type II oscillators [13].

2 Tools for Analysis

The main tools for studying the behaviour of delay differential equations are extensions of those for ordinary differential equations which are discussed elsewhere in this volume [6]. Some familiarity with these tools will be helpful in reading this section.

To improve the flow of the text, I will not give references for all the standard results for delay differential equations that I use. For more information on these, I refer the reader to the fairly accessible books of Kolmanovskii and Nosov [38] and Stépán [56] which cover the results of section 2 or the books of Hale and Lunel [31] and Diekmann et al. [18] which give complete, although not so accessible, accounts of the theory of delay differential equations.

To begin our discussion, consider the types of solutions which occur most often in neural systems. These are equilibrium solutions ($\mathbf{x}(t) = \bar{\mathbf{v}}$, for some constant $\bar{\mathbf{v}}$) and periodic solutions ($\mathbf{x}(t) = \mathbf{x}(t+T)$ for some $T > 0$). The fundamental questions we would like to answer in order to understand the behaviour of a model with time delays are the following

1. *What equilibrium solutions occur in the system?*
2. *What periodic solutions occur in the system?*
3. *Are these stable or unstable? That is, do we expect to observe them in experiments and numerical simulations?*
4. *How do the answers to these questions change as parameters are varied?*

Question 1 is easily answered: the equilibrium solutions of a system with time delays are the same as those of the corresponding system with zero delay. Thus for (13) these correspond to constant vectors $\bar{\mathbf{x}}$ such that $\mathbf{f}(\bar{\mathbf{x}}, \bar{\mathbf{x}}) = 0$.

Example. For system (12) the equilibrium points are given by $(v_1, w_1, v_2, w_2) = (\bar{v}_1, \bar{w}_1, \bar{v}_2, \bar{w}_2)$ where $\bar{v}_j, \bar{w}_j$ are constants, found by solving the following equations

$$\begin{aligned} 0 &= -\bar{v}_1^3 + (a+1)\bar{v}_1^2 - a\bar{v}_1 - \bar{w}_1 + I + c\tanh(\bar{v}_2 - \bar{v}) \\ 0 &= b\bar{v}_1 - \gamma\bar{w}_1 \\ 0 &= -\bar{v}_2^3 + (a+1)\bar{v}_2^2 - a\bar{v}_2 - \bar{w}_2 + I + c\tanh(\bar{v}_1 - \bar{v})) \\ 0 &= b\bar{v}_2 - \gamma\bar{w}_2 \end{aligned} \tag{15}$$

It is easy to check that one solution of these equations is $(\bar{v}_1, \bar{w}_1, \bar{v}_2, \bar{w}_2) = (\bar{v}, \bar{w}, \bar{v}, \bar{w})$. We will focus on this solution as we pursue this example further.

Question 2 is difficult to answer with any completeness analytically. A partial answer can be obtained by determining the bifurcations that occur in the system which lead to the creation of periodic solutions. More detail can be found in subsection 2.2. This question can also be addressed through the use of numerical tools, which are discussed in subsection 2.5.

For equilibrium solutions, question 3 can be addressed via linear stability analysis (see subsection 2.1) and via Lyapunov theory (see subsection 2.3). For periodic solutions this question generally must be answered using numerical tools, as discussed in subsection 2.5.

Answering question 4 is the main goal of bifurcation theory. Analytical methods for studying bifurcations will be discussed in subsection 2.2 and numerical methods in subsection 2.5.

2.1 Linear stability

One way to study the stability of an equilibrium solution is through linearization. This is constructed in a similar way as for ordinary differential equations. The **linearization** of (13) about $\bar{\mathbf{x}}$ is given by

$$\dot{\mathbf{x}}(t) = A\mathbf{x}(t) + B\mathbf{x}(t-\tau) \tag{16}$$

where A is a the Jacobian matrix of $f(y,z)$ with respect to y, i.e. the matrix with entries $a_{ij} = \frac{\partial f_i}{\partial y_j}$, and B is the Jacobian matrix of $f(y,z)$ with respect to z. If the system has multiple delays, then there will be a term in the linearization corresponding to each delay.

It can be shown that, under the right conditions, equation (16) describes the behaviour of solutions close to $\bar{\mathbf{x}}$. This will in turn determine the the stability of $\bar{\mathbf{x}}$. To study this behaviour, we assume that there are solutions of (16) of the form $\mathbf{x}(t) = e^{\lambda t}\mathbf{k}$ where λ is a complex number and $\mathbf{k}$ is an n-vector of complex numbers, to be determined. Substituting this into (16) we obtain

$$\left[-\lambda I + A + Be^{-\lambda\tau}\right]\mathbf{k} = 0. \tag{17}$$

For solutions with $\mathbf{k} \neq 0$ to exist, we require

$$\det[-\lambda I + A + Be^{-\lambda\tau}] = 0. \tag{18}$$

If (13) is an n-dimensional system, then (18) can be written in the form

$$\Delta(\lambda) = \lambda^n + \lambda^{n-1}(\delta_{n-1,0} + \delta_{n-1,1}e^{-\lambda\tau}) + \cdots + \lambda\sum_{j=0}^{n-1}\delta_{1,j}e^{-j\lambda\tau} + \sum_{j=0}^{n}\delta_{0,j}e^{-j\lambda\tau} = 0, \tag{19}$$

where the $\delta_{i,j}$ depend on the elements of the matrices A and B.

Equation (19) is called the **characteristic equation** of the linearization of (13) about $\bar{\mathbf{x}}$. Any complex number λ which satisfies (19) will give rise to a solution of (16) ($\mathbf{k}$ is found by solving (17) with the particular value of λ substituted in). In practice, we are mostly concerned with the λ values for the reasons outlined below.

Example: For our coupled Fitzhugh-Nagumo model (12) the linearization about the equilibrium point $(\bar{v}, \bar{w}, \bar{v}, \bar{w})$ is given by (16) where

$$A = \begin{bmatrix} \alpha & -1 & 0 & 0 \\ b & -\gamma & 0 & 0 \\ 0 & 0 & \alpha & -1 \\ 0 & 0 & b & -\gamma \end{bmatrix} \text{ with } \alpha = -3\bar{v}^2 + 2(a+1)\bar{v} - a, \text{ and } B = \begin{bmatrix} 0 & 0 & c & 0 \\ 0 & 0 & 0 & 0 \\ c & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}.$$

Note that α depends on all the intrinsic neuron parameters (a, b, γ, I), since $\bar{v}$ is a solution of (10). It follows that the characteristic equation for this example is

$$\Delta_+(\lambda)\Delta_-(\lambda) = 0 \tag{20}$$

where

$$\Delta_\pm(\lambda) = (\lambda + \gamma)(\lambda - \alpha \pm ce^{-\lambda\tau}) + b.$$

Fact: If all the roots of the characteristic equation of the linearization of (13) about $\bar{\mathbf{x}}$ have negative real part, then $\bar{\mathbf{x}}$ is stable in the sense that all solutions which start sufficiently near to $\bar{\mathbf{x}}$ will tend toward it as t increases.

Fact: If at least on root of the characteristic equation of the linearization of (13) about $\bar{\mathbf{x}}$ has positive real part, then $\bar{\mathbf{x}}$ is unstable in the sense that some solutions which start near to $\bar{\mathbf{x}}$ will tend away from it as t increases.

So we see that to determine the stability of an equilibrium point we need to determine the roots, λ of the characteristic equation (19). These are often called the **eigenvalues** of the equilibrium point. For ordinary differential equations, the characteristic equation is a polynomial in λ and hence there are a finite number of solutions all of which may be calculated or numerically approximated. For delay differential equations, however, the presence of the $e^{-\lambda\tau}$ terms means that there are an *infinite* number of solutions of the characteristic equation. This means we must rely on other methods to determine whether an equilibrium point is stable. Several methods are outlined in the book of Kolmanovskii and Nosov [38], here we will focus a particular one which relies on the following result.

Fact: The zeros of $\Delta(\lambda)$ depend continuously on τ and the $\delta i, j$, and hence on the elements of A and B. Thus as any of these parameters is varied, the number of zeros of $\Delta(\lambda)$ with positive real part can only change if a root passes through the imaginary axis.

The most common way of using this fact in coupled neural systems, is outlined in the following procedure.

1. Set the delay, τ, equal to zero. This will change the delay differential equation into an ordinary differential equation with the same equilibrium points as the delay differential equation.
2. Determine the stability of an equilibrium point for the ODE system, i.e. determine the number of eigenvalues with positive real parts.
3. Determine the values of the delay, $\tau_1 < \tau_2 < \cdots$ for which the characteristic equation (19) has eigenvalues with zero real parts. These are the values of the delay where the stability of the equilibrium point may change.
4. Calculate the rate of change of the real part of an eigenvalue with respect to τ when τ is equal to one of the critical values found in the previous step, i.e., calculate

$$\left.\frac{dRe(\lambda)}{d\tau}\right|_{\tau=\tau_k} = -\,Re\left(\frac{\partial\Delta}{\partial\tau}\Big/\frac{\partial\Delta}{\partial\lambda}\right)\Bigg|_{\tau=\tau_k}.$$

If $\frac{dRe(\lambda)}{d\tau} > 0$, then the number of roots with positive real parts is increasing, if it is negative, then the number of roots is decreasing.

5. Due to the fact above, the number of roots of the characteristic equation with positive real part will be constant for $0 \le \tau < \tau_1$ and equal to the number found in step 2. For each subsequent interval, $\tau_k < \tau < \tau_{k+1}$, the number can be determined from the number in the previous interval $\tau_{k-1} < \tau < \tau_k$, the number of roots with zero real part at τ_k and the rate of change calculated in step 4.

Example. Consider our coupled Fitzhugh-Nagumo model (12). We will follow the procedure outlined above.

1. When $\tau = 0$ the factors of the characteristic equation (20) become
$$\Delta_\pm = \lambda^2 + \lambda(\gamma - \alpha \pm c) + \gamma(-\alpha \pm c) + b.$$
2. By analyzing the roots of this equation, it can be shown that if $\gamma^2 < b$ the trivial solution is stable for $|c| < \gamma - \alpha \stackrel{def}{=} c_H$, and for c outside this region the equilibrium point has two complex conjugate eigenvalues with positive real part, i.e. it is unstable. (In fact the two points $c = \pm c_H$ are Hopf bifurcation points for the system with zero delay.)
3. To find the parameter values where the characteristic equation (20) has eigenvalues with zero real part, we substitute $\lambda = i\omega$ into (20) and separate into real and imaginary parts. This yields
$$-\alpha + \frac{b\gamma}{\gamma^2 + \omega^2} \pm c\cos\omega\tau = 0$$
$$\omega\left(1 - \frac{b}{\gamma^2 + \omega^2}\right) \mp c\sin\omega\tau = 0.$$
Note that we choose the $+$ in the first equation and $-$ in the second for the parameter values for Δ_+ to have a pair of complex conjugate roots and the opposite for Δ_-. Some rearrangement of these equations gives
$$(b\gamma - \alpha(\gamma^2 + \omega^2))^2 + \omega^2(\gamma^2 + \omega^2 - b)^2 - c^2(\gamma^2 + \omega^2)^2 = 0 \qquad (21)$$
and
$$\tan\omega\tau = \frac{\omega(\gamma^2 + \omega^2 - b)}{b\gamma - \alpha(\gamma^2 + \omega^2)}. \qquad (22)$$
Thus, for given values of the parameters a, b, γ, I (which determine α) and c one can find ω from the first equation and the corresponding τ values from the second equation. Alternatively, we can think of these two equations as defining the coupling parameters τ and c in terms of the intrinsic neuron parameters and ω. Then these equations define curves in the c, τ parameter plane. These curves are shown in Figure 1 for a specific set of intrinsic parameter values.

4. Taking the appropriate derivatives, we find

$$\frac{d\lambda}{d\tau} = \frac{\pm\lambda c e^{-\lambda\tau}}{1 \mp \tau c e^{-\lambda\tau} - \frac{b}{(\lambda+\gamma)^2}}.$$

5. Putting together the results of all steps, allows us to fill in the number of eigenvalues with positive real part in each of the subregions of the c, τ plane as shown in Figure 1.

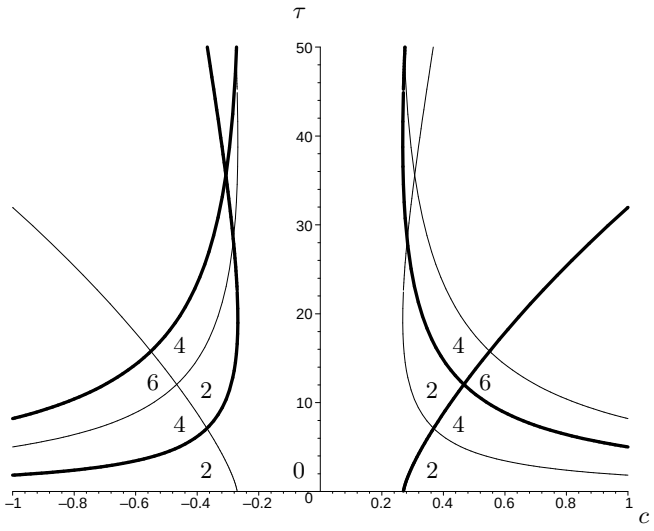

Fig. 1. Illustration of the stability and bifurcation results for the example of equation (12). The equilibrium solution is stable in the region contiguous with the τ axis. The number of eigenvalues with positive real part is shown in each subregion of the plane. Thick/thin curves correspond to Hopf bifurcations giving rise to synchronous/anti-phase oscillation

An alternative way to use the procedure outlined above is to set the coupling coefficient (c in (12)) to zero in step 1 and follow the procedure but varying the coupling coefficient instead of the delay. In systems with multiple delays, the procedure can be followed by setting one of the delays to zero (see e.g. [12, 13] for examples of this.

To close, we note the work of Olgac and Sipahi [46, 47] who have found a way to automate this procedure using a transformation of the characteristic equation.

2.2 Bifurcations

As noted in the previous subsection, points in parameter space where the characteristic equation has an eigenvalue with zero real part are points where the stability of an equilibrium point may change. These are places where a bifurcation may occur. As discussed in [6], bifurcations may lead to the creation of other equilibrium points or of a periodic orbit.

Recall that the equilibrium points of (13) with $\tau > 0$ are the same as those with $\tau = 0$. Thus for the neural model (13) with $\tau > 0$, the bifurcations involving only equilibrium points (saddle-node, pitchfork, transcritical) will be the same as those for (13) with $\tau = 0$.

There are two main bifurcations involving periodic orbits. Consider first the Hopf bifurcation, which involves the creation of a periodic orbit as an equilibrium point changes stability. There are simple criteria to check to determine if a Hopf bifurcation occurs in a delay differential equation at a particular parameter value, say $\tau = \tau_c$.

Hopf Bifurcation Test
Assume that system (13) has an equilibrium point $\bar{\mathbf{x}}$. If the following are satisfied, then system (13) undergoes a Hopf bifurcation at $\bar{\mathbf{x}}$ as τ passes through τ_c.

1. The characteristic equation (19) of the linearization of (13) about $\bar{\mathbf{x}}$ has a pair of pure imaginary eigenvalues, $\pm i\omega$ when $\tau = \tau_c$, that is,
$$\Delta(\pm i\omega)|_{\tau=\tau_c} = 0.$$
2. As τ passes through τ_c the rate of change of the real part of this eigenvalue(s) is nonzero, that is, $\frac{dRe(\lambda)}{d\tau} \neq 0$.
3. The characteristic equation (19) of the linearization of (13) about $\bar{\mathbf{x}}$ has no other eigenvalues with zero real part.

Other than some exceptional cases, this is enough to guarantee that a periodic orbit is created as τ passes through τ_c.

Whether the periodic orbit is stable or unstable depends on the nonlinear terms in the equation. There are two main approaches for determining this analytically, both of which require intensive computations and are best done with a symbolic algebra package such as Maple. The centre manifold construction reduces the system of delay differential equations to a system of two ordinary differential equations from which the stability of the periodic orbit (for τ close to τ_c) may be deduced. See [4, 66, 67] for examples of how this is done. Perturbation methods, such as averaging and the method of multiple scales, find an approximate expression for the periodic solution and for the corresponding Floquet exponents. See [12, 29, 65] for examples of how this is done.

Example. Applying this test to our coupled Fitzhugh-Nagumo model shows that the system has a Hopf bifurcation along each of the curves where the pair of pure imaginary eigenvalues. That is along the curves defined by

(21)–(22) and shown in Figure 1. By analyzing the solutions of the linearization (16) that correspond the roots, one can show that some of the Hopf bifurcations give rise to synchronous or in-phase oscillations (i.e. $v_1(t) = v_2(t)$ and $w_1(t) = w_2(t)$ for all t) and some to anti-phase solutions (i.e. the spikes in v_1 and v_2 are half a period apart and similarly for w_1 and w_2).

One important thing to note about Hopf bifurcation in systems of delay differential equations is the there are always multiple branches of Hopf bifurcation. This can be seen in our example. The τ value where a Hopf bifurcation occurs corresponds to a τ value satisfying (22). Clearly if a given value of τ satisfies this equation, then so does $\tau + k\pi,\ k = \pm 1, \pm 2, \ldots$.

Another bifurcation commonly associated with the creation of periodic orbits in neural systems, is the infinite period bifurcation. As described in [6] this bifurcation occurs when a saddle-node bifurcation occurs on an invariant circle. As indicated above, the conditions for the saddle-node bifurcation to occur are the same as for the corresponding system with no delay. Whether or not this bifurcation occurs on a limit cycle is not easily determined analytically (even without delays), thus these bifurcations are often investigated using numerical tools (see below).

2.3 Lyapunov Theory

The basic idea of Lyapunov theory is to use an auxiliary function to determine the dynamics of a nonlinear system. A very simple example is the total energy in a mechanical system with damping, such as the pendulum model:

$$\ddot{\theta} + \gamma\theta + \frac{g}{l}\sin\theta = 0.$$

The total energy of this system is

$$E(\theta, \dot{\theta}) = \frac{1}{2}\dot{\theta}^2 + gl(1 - \cos\theta).$$

A simple calculation, keeping in mind that θ and $\dot{\theta}$ depend on t, show that $\frac{dE}{dt} < 0$. This means that as t increases, E must tend to a minimum value. This in turn determines what the solutions of the nonlinear model can do. In particular, one can show that this implies that all solutions must tend to one of the equilibrium points $(\theta, \dot{\theta}) = (2k\pi, 0),\ k \in \mathbb{Z}$ as $t \to \infty$, i.e. the pendulum swings with smaller and amplitude until it is hanging straight down. Lyapunov theory generalizes this idea, to arbitrary auxiliary functions which have similar properties to the energy function in the above example. These properties are:

1. $V(x) > 0,\ x \neq 0; V(0) = 0$ (V positive definite)
2. $\frac{dV}{dt} < 0,\ x \neq 0$ ($\frac{dV}{dt}$ negative definite).

These properties can be used to show that the equilibrium point $x = 0$ is asymptotically stable. By modifying the properties above, one can also use

Lyapunov functions to show that an equilibrium point is unstable, that all solutions are bounded or that all solutions synchronize as $t \to \infty$.

There are two ways of extending the Lyapunov theory for ordinary differential equations to delay differential equations such as (13). **Lyapunov functionals** are auxiliary functions which depend on the value of the state over an interval in time: $x_t(\theta) = x(t+\theta),\ -\tau \le \theta \le 0$. The conditions for showing an equilibrium point is stable are basically the same as those outlined for the ODE case, above. The main difference comes in showing those conditions are satisfied, which can be more complicated. The **Razumikhin approach** uses an auxiliary *function* $V(x(t))$, but the second condition is relaxed to $\frac{dV}{dt} < 0$ whenever $x(t) > x(t+\theta),\ -\tau \le \theta \le 0$. Essentially this just requires that V not increase for time intervals longer than the delay.

2.4 Phase Models

Many of the analytical tools I have discussed so far are useful for studying the stability of equilibrium points and the creation of oscillatory solutions as parameters are varied. These can be very useful for studying systems where the individual neurons do not exhibit oscillatory behaviour when they are uncoupled. For systems which are inherently oscillatory, i.e. systems where the individual neurons exhibit oscillatory behaviour when they are uncoupled, one of the primary tools available is the phase model. The basic idea of this approach is that for a group of oscillating neurons with small coupling between them, the the key variable of importance in understanding how the neurons affect each other is the phase of the oscillator associated with each neuron. Thus a system of k model neurons, each represented by an n-dimensional system of differential equations, can be reduced to a system of k equations for the phases of the k oscillators. Typically these are in the form

$$\dot{\theta}_i(t) = \Omega + h_i(\phi_1(t), \phi_2(t), \ldots, \phi_{k-1}(t))$$

where Ω is the network frequency and $\phi_i = \theta_i - \theta_{i-1}$ is the i^{th} *phase difference*.

The procedure to calculate the phase model for a particular differential equation is described in [32]. In most cases it is not possible to carry out this procedure analytically, however, a numerical implementation is available in the package XPPAUT [23] and described in the book of Ermentrout [22]. The numerical implementation yields a numerical approximation of the functions h_i. A Fourier series representation of these functions can also be calculated.

There are two main results concerning phase models for equations such as (13) which have an explicit time delay in the coupling. The analysis of Ermentrout [21, 39] indicates that explicit time delays will produce phase shifts in the corresponding phase models provided that the delay is not a multiple of the oscillation period. In particular, the models will have the form

$$\dot{\theta}_i(t) = \Omega + h_i(\phi_1(t) - \psi, \phi_2(t) - \psi, \ldots, \phi_{k-1}(t) - \psi),$$

where $\psi = \tau\Omega \bmod 2\pi$.

Izhikevich [33] has refined this analysis. He has shown that while Ermentrout's analysis holds for delays as large as the order of the oscillation period, for larger delays, i.e. on the order of $1/\epsilon$ where $0 < \epsilon \ll 1$ is the size of the coupling, an explicit delay will also occur in the phase model. In this case the phase model will consist of a set of $k-1$ delay differential equations of the form

$$\dot{\theta}_i(t) = \Omega + h_i(\phi_1(t-\zeta) - \psi, \phi_2(t-\zeta) - \psi, \ldots, \phi_{k-1}(t-\zeta) - \psi),$$

where $\zeta = \epsilon\tau$.

For equations with a distributed delay in the coupling, Ermentrout [21, 39] has shown that the phase model will be of the form

$$\dot{\theta}_i(t) = \Omega + \int_0^\infty g(s) h_i(\phi_1(t-s), \phi_2(t-s), \ldots, \phi_{k-1}(t-s))\, ds.$$

2.5 Numerical Tools

There are two basic numerical tools which can aid in the study of delay differential equations such as (13): numerical simulation and numerical bifurcation analysis.

In numerical simulation one attempts to determine an approximate solution of a differential equation given a particular initial state. Note that to solve such a problem for a delay differential equation such as (13), one needs to specify the value of the variable $\mathbf{x}$ not just at the start time $t = 0$, but for the whole interval $[-\tau, 0]$. Thus an initial condition for (13) is

$$\mathbf{x}(t) = \phi(t), \ -\tau \le t \le 0.$$

Typically ϕ is taken to be a constant, i.e.,

$$\mathbf{x}(t) = \mathbf{x}_0, \ -\tau \le t \le 0,$$

which is reasonable for most experimental systems. It should be noted that only solutions which are asymptotically stable can be accurately approximated using numerical integration.

There are two main programs available for the numerical integration of delay differential equations. The widely-used (and free) package XPPAUT [23] can perform numerical integration using a variety of fixed step numerical methods, including Runge-Kutta. It has a good graphical user interface for visualizing the results. Perhaps the most useful aspect of this program is the ease with which parameters and initial conditions can be changed. The recent book of Ermentrout [22] gives a overview of the package including many examples. Information on how to download the package as well as documentation and tutorials are available at `www.math.pitt.edu/~bard/xpp/xpp.html`.

Within Matlab there is the function DDE23 [53] which is a variable step size numerical integration routine for delay differential equations. A tutorial is on this routine available at `www.mathworks.com/dde_tutorial`. Results maybe visualized using the extensive graphing tools of Matlab.

Numerical bifurcation analysis consists of two parts, the approximation of a solution and the calculation of the stability of this solution. The approximation of a solution in a numerical bifurcation package is not done using numerical integration, but rather using numerical continuation. Numerical continuation uses a given solution for a particular parameter value to find a solution for a different (but close) parameter value. This is most useful for studying equilibrium and periodic solutions. Both stable and unstable solutions can be found. Once an equilibrium solution is found to a desired accuracy, a finite set of the eigenvalues with the largest real part can be determined, which will determine the stability of the equilibrium point. The stability of periodic orbits can be numerically determined in a similar way. Numerical bifurcation packages generally track the stability of equilibrium points and periodic orbits, indicating where bifurcations occur.

There is one package available that does numerical bifurcation analysis for delay differential equations, DDE-BIFTOOL [20]. This package runs on Matlab. An overview of the numerical methods used in this package and some examples applications can be found in the paper of Engelborghs et al. [19]. The user manual and information on how to download the package are available at `www.cs.kuleuven.ac.be/cwis/research/twr/research/software/delay/`

3 Effects of delay

In this section we will try to outline some of the effects of delay that have been documented in the literature.

3.1 Creation of Oscillations

Time delays are commonly associated with type II oscillations, i.e. oscillations created by a Hopf bifurcation [6], for the following reason. There are many examples of system that have a stable equilibrium point if the time delay is zero (or sufficiently small), but have oscillatory behaviour if the delay is large enough. In these systems, the oscillation is created via a Hopf bifurcation at a critical value of the delay. This is sometimes referred to as a *delay-induced oscillation*. One of the simplest example of this is the following model for recurrent inhibition due to Plant [48]:

$$\begin{aligned}\dot{v}(t) &= v(t) - \frac{1}{3}v^3(t) - w(t) + c(v(t-\tau) - v_0)\\ \dot{w}(t) &= \rho(v(t) + a - bw(t)).\end{aligned}$$

This is a Fitzhugh-Nagumo model neuron with a delayed term which represents recurrent feedback. Plant considered parameters such that the system with no feedback has a stable equilibrium point and showed that this stability is maintained for the system with feedback and sufficiently small delay. He then showed that when $c < 0$ (i.e. the recurrent feedback is inhibitory), there is a Hopf bifurcation at a critical value of the delay, leading to oscillations.

3.2 Oscillator Death

One of the most publicized [57] effects of time delays is the fact that the presence of time delays in the coupling between oscillators can destroy the oscillations. This phenomenon, usually called *oscillator death* or *amplitude death* was first noted by Ramana Reddy et al. [49], in their analysis of a simple model of type II oscillators with gap junctional coupling. They subsequently [51] observed this phenomenon experimentally in a system of two intrinsically oscillating circuits with the same type of coupling. There are many papers related to delay induced oscillator death in the coupled oscillator literature, which I will not attempt to review here. Instead I will focus the discussion on results relevant to neural models.

The work of Ramana Reddy et al. [49, 50] shows that when two or more intrinsically oscillating elements are connected with gap junctional coupling of sufficient strength with a sufficiently large delay then the oscillations may be destroyed. Their work focussed on systems where the elements were identical except for the frequency of the intrinsic oscillations and the coupling was all-to-all and symmetric (all the coupling coefficients were the same). Their model oscillator was just the normal form for the Hopf bifurcation. This behaviour has also been seen for a delayed, linearly coupled (i.e. (3) with no $\mathbf{x}_i(t)$ term) pair of van der Pol oscillators [65], which are similar to Fitzhugh- Nagumo oscillators. To my knowledge this has yet to be observed for other biophysical models of neural oscillators, however, it may be expected to occur for most type II oscillators. Atay [2] extended these results to a network of weakly nonlinear oscillators with a symmetric connection matrix. He shows that if the intrinsic frequency of the oscillations is sufficiently similar then oscillator death can still occur.

Several studies have shown that the type of oscillator death described above does not occur for type II oscillators with sigmoidal coupling [8, 10, 54]. However, a different type of oscillator death can occur [8, 7, 10, 54]: for elements which are intrinsically excitable (i.e. not oscillating when decoupled), oscillations induced by instantaneous coupling may be lost if a time delay is introduced.

The work of Burić et al. [7] has shown that for the type I oscillator of [58], there is no oscillator death of this latter type with either gap junctional or sigmoidal coupling. Their work also suggests that delay induced oscillator death of the first type is not possible.

The study of type II oscillator death in coupled neural systems combines various techniques of section 2. Oscillator death can occur when increasing the time delay causes the *stabilization* of an equilibrium point. Values of the delay where this occurs will correspond to places where the characteristic equation (19) has an eigenvalue with zero real part and $\frac{dRe(\lambda)}{d\tau} < 0$. To have oscillator death, however, one must also show that the periodic orbit is eliminated. This means that at the value of τ where the equilibrium point stabilizes, there is a "reverse" Hopf bifurcation destroying the stable limit cycle. This may be checked via numerical simulations or numerical continuations (see subsection 2.5), or by showing, as outlined in subsection 2.2, that the Hopf bifurcation is subcritical. Burić et al. [7, 8, 9] have shown that for excitable Fitzhugh-Nagumo neurons, the restabilization of the equilibrium point is not always accompanied by oscillator death. In the case that the Hopf bifurcation is subcritical, the stable oscillator may persist with the stable equilibrium point giving a region of bistability. In their model, for larger values of τ the periodic orbit is eliminated in a saddle-node bifurcation of limit cycles, leading to oscillator death.

The results of Burić et al. on type I oscillator death are primarily based on numerical simulations. To my knowledge there has been virtually no mathematical study of this situation. Recall that type I oscillators are those where the oscillation is created by an infinite period bifurcation [6]. If such a bifurcation takes place in the coupled system with no time delay, introducing a time delay will not change the presence of the saddle-node bifurcation, however, it may affect whether this bifurcation occurs on an invariant circle. Continuity arguments would suggest that for sufficiently small delay, the saddle-node bifurcation will still occur on the invariant circle, leading to the creation of a periodic orbit a exactly the same bifurcation point as for the undelayed system. What happens for large delay remains to be investigated.

3.3 Attractor switching and multistability

A significant observation about ANNs of the form (14), is that many intersections between different Hopf bifurcation curves and between Hopf bifurcation curves and pitchfork bifurcation curves can occur [4, 54, 68]. Figure 1 shows that this occurs in our coupled Fitzhugh-Nagumo model as well. These intersection points are called **codimension two bifurcation points**. Such points can lead to more complicated dynamics including: the existence of solutions with multiple frequencies (quasiperiodicity), the coexistence of more than one stable solution (multistability) or the switching of the system from one type of solution to another as a parameter is varied [30, Chapter 7], [41, Chapter 8]. In ordinary differential equation models, such points are quite rare. In delay differential equations such points are more common as the time delay forces there to be multiple branches of Hopf bifurcation.

In the ANN models, the following behaviour associated with the codimension two points has been observed [4, 13, 54, 68]: (i) multistability between a

periodic solution and one or more equibrium points; (ii) bistability between two periodic solutions (both synchronous or one synchronous and one asynchronous); and (iii) switching from one stable solutions to another as the delay is changed for a fixed coupling strength or as the coupling strength is changed for a fixed delay. The switching may take place through a region of bistability or a region where the trivial solution is stable. Note that the first situation leads to a different type of oscillator death than that discussed in the previous subsection: a slight perturbation can cause the system to switch from the stable oscillatory solution to the stable equilibrium solution, with *no change* in the parameter values.

Some of this behaviour has been confirmed for networks consisting of two relaxation oscillators with delayed coupling. In an experimental circuit system, Ramana Reddy et al. [51] have observed the sequence: in-phase oscillations $\rightarrow$ no oscillations $\rightarrow$ anti-phase oscillations as the time delay in the (gap-junctional) coupling is increased. Rand et al. have both numerically observed [52] and analytically proven [65] the sequence in-phase oscillations $\rightarrow$ bistability between in-phase and anti-phase oscillations $\rightarrow$ anti-phase oscillation as the time delay is increased. They also observed the reverse sequence for different values of the coupling strength. In these articles, the coupling was linear (i.e. (3) with no $\mathbf{x}_i(t)$ term).

In their studies of rings of Fitzhugh-Nagumo oscillators with time delayed gap-junctional or sigmoidal coupling, Burić et al. [8, 7] have documented almost all the behaviour observed in the ANN models including switching between different oscillation patterns and bistability between different oscillation patterns.

Finally we note that bistability between different types of travelling pulses has been observed in certain integrate-and-fire networks with delayed excitatory synaptic connections [27, 28]. In particular, they observe a switch from continuous travelling pulses to lurching travelling pulses as the time delay is increased with a transition region where there is bistability between the two types. This behaviour does not seem to be associated with a co-dimension two bifurcation point, but rather a subcritical Hopf bifurcation.

3.4 Synchronization

There are several approaches to studying synchronization. I will not review the details here, but give some indication which of these have been extended to delay differential equations and what the results are.

There is a very large literature on synchronization in artificial neural networks, some of which addresses systems with time delays [12, 67, 68, 69, 70]. Most of these papers use Lyapunov functionals to show that the all solutions synchronize as $t \rightarrow \infty$, for the appropriate parameter values. Although the equations of the individual elements are not relevant for modelling biophysical neurons, the techniques of analysis may be carried over to neural systems. A common conclusion in many of these papers is that if the strength of the

coupling is small enough, one can achieve synchronization for all $\tau \geq 0$. However, synchronization may mean that all elements asymptotically approach the same equilibrium point.

As I have mentioned elsewhere in this chapter, a basic principle of delay differential equations such as (13) is that the behaviour of the system for small delay is often qualitatively similar to that for zero delay. Thus if the neurons are synchronized for a given value of the coupling with zero delay they should remain synchronized for small enough delays in the coupling. Unfortunately, quantifying "small enough" may be difficult and will generally depend on the particular neural model involved. Recall the example illustrated in Figure 1. We showed that for $c > 0$ large enough (sufficiently large excitatory coupling) the undelayed system exhibits synchronized oscillations. We expect these oscillations to persist for $\tau > 0$ at least until one reaches the first thick Hopf bifurcation curve where synchronous oscillations are destroyed. (If the Hopf bifurcation is subcritical, the oscillations may persist above the curve). Thus, for this particular example, the Hopf bifurcation curve gives a lower bound on "how small" the delay must be to preserve the synchronization found for zero delay. Note that this does not preclude synchronization occurring for larger values of the delay, which is the case in this example. A similar situation is seen for coupled van der Pol oscillators in [65]. Another example is the work of Fox et al. [26] who study relaxation oscillators with excitatory time delayed coupling. They show that synchrony achieved for zero delay is preserved for delays up to about 10% of the period of the oscillation, for a variety of different models. The one exception is when the right hand side of the is not a differentiable function, in which case synchronization is lost for $\tau > 0$. Crook et al. [14] observed a similar phenomenon for a continuum model of the cortex, with excitatory coupling and distance dependent delays. Namely, they found for small enough delay the synchronous oscillation is stable, but for larger delays this oscillation loses stability to a travelling wave.

More complicated situations occur when both excitatory and inhibitory connections exist. Ermentrout, Kopell and co-authors [24, 40, 35] have studied a model for hippocampal networks of excitatory and inhibitory neurons where two types of synchronous oscillation are possible. They show that persistence of the synchronous oscillations with delays depends subtly on the currents present in the cells and the connections present between cells.

So far I have discussed synchronization *in spite of* delays. I now move on to the more interesting case of synchronization *because of* delays. This situation can occur when there are inhibitory synaptic connections in the network. This has been extensively documented and studied when the delay is modelled by slow kinetics of the synaptic gating variable [60, 61, 62, 63, 64]. Further, Maex and De Schutter [44] suggest that the type of delay is not important, just the fact that it leads to a separation in time between when the pre-synaptic neuron generates an action potential and the post-synaptic neuron receives it. They confirm this for a network of multi-compartment model neurons with fast synaptic kinetics and a discrete conduction delay. This idea is further sup-

ported by the observation of synchronization via discrete delayed inhibition in a number of artificial neural network models [10, 13, 54]. Finally we illustrate this with our coupled Fitzhugh-Nagumo model. Consider the part of Figure 1 with $c < 0$ (inhibitory coupling). For sufficiently large coupling strength and zero delay the system tends to an asynchronous phase-locked state. This state persists for $\tau > 0$ sufficiently small, however, for τ large enough a stable synchronous state may be created in the Hopf bifurcation corresponding to the thin curve.

Only a few studies have looked at synchronization with time delayed gap-junctional coupling. One example is the work of Dhamala et al. [17] which shows that for two gap junctional coupled Hindmarsh-Rose neurons synchronization is achieved for smaller coupling strengths if there is a nonzero time delay in the coupling. Another is the work of Burić et al. [7].

4 Distributed Delays

There are very few results concerning neural systems with distributed delays, thus I will review some general results, mostly from the population biology literature, which should carry over to neural systems. What has emerged from this literature is a general principle *that a system with a distribution of delays is inherently more stable than the same system with a discrete delay.* Some specific results to support this are described below.

Bernard et al. [5] analyzed the linear stability of a scalar system with one and two delays in terms of generic properties of the distribution g, such as the mean, variance and skewness. For the uniform and continuous distributions, they have shown that stability regions are larger than those with a discrete delay.

Jirsa and Ding [34] have analyzed an $n \times n$ linear system with linear decay and arbitrary connections with a common delay. They have shown, under some mild assumptions, that the stability region of the trivial solution for any distribution of delays is larger than and contains the stability region for a discrete delay.

Campbell and Ncube [11] have shown that it is more difficult to get delay induced oscillations with distributions of delays of the form (6) with $\tau_m = 0$. For large variance ($m = 1$) delay induced instability is impossible and for smaller variance ($m > 1$) the mean delay needed for instability is much larger than the discrete delay value. They have also shown that sufficiently small variance in the distribution is needed to get the bifurcation interactions which may lead to multistability, oscillator death and attractor switching discussed above.

Atay [1, 3] has studied the same model as [49] only with distributed delays of the form (6) with g given by (7). He shows it is easier to destroy oscillations with a distribution of delays than with a discrete delay, in the sense that there is a larger region of oscillator death in the parameter space consisting

of the mean delay and the strength of the coupling. As the variance of the distribution increases the size of this region increases.

Thiel et al. [59] studied a scalar equation representing a mean field approximation for a population pyramidal cells with recurrent feedback, first formulated by Mackey and and der Heiden [43]. They show that having a uniform distribution of delays simplifies the dynamics of the system. The size of the stability region of the equilibrium point is larger and larger mean delays are needed to induce oscillations. More complex phenomena such as chaos is less likely to occur, or totally precluded if the variance of the distribution is sufficiently large. The model with a distribution of delays better explains the appearance of periodic bursts of activity when penicillin is added to a hippocampal slice preparation (which reduces the coupling strength).

5 Summary and Future Directions

In this chapter I showed how time delays due to conduction along the axon or dendrite or due to transmission across the synapse could be modelled with delay differential equations. I outlined some of the tools available for analyzing such equations and reviewed some of the literature about such models. Some key observations are:

- Time delays can lead to the creation of type II oscillations, especially in systems with delayed inhibitory coupling.
- Time delays can destroy type II oscillations in a network of intrinsically oscillatory neurons with gap junctional coupling.
- If a system has a stable synchronous oscillation when there is no delay in the coupling, the solution remains stable for small enough delay, but may lose stability for larger delay.
- A system with inhibitory coupling which does not have a stable synchronous oscillation for zero delay, may have one if the delay is large enough.
- Time delays may lead to bistability between different type II oscillatory solutions (e.g. synchronous and anti-phase) or switching between different type II oscillatory solutions.

There are a number of problems which still require further study. These include: determining the effect of delay on the generation and destruction of type I oscillations (infinite period bifurcations), applying and/or extending the methods used to study synchronization in artificial neural networks to biophysical neural networks, and studying the effect of distributions of delays on biophysical neural networks.

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