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Delay-induced destabilization of entrainment of nerve impulses on ephaptically coupled nerve fibers

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We study the effect of delay on the synchronization of two nerve impulses traveling along two ephaptically coupled, unmyelinated nerve fibers. The system is modeled as a pair of delay-coupled Fitzhugh-Nagumo equations. A multiple-scale perturbation approach is used for the analysis of these equations in the limit of weak coupling. In the absence of delay, two pulses with identical speeds are shown to be entrained precisely. However, as the delay is increased beyond a critical value, we show that this precise entrainment becomes unstable. We make quantitative estimates for the actual values of delay at which this can occur in the case of squid giant axons and compare them with the relevant time scales involved.

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I. INTRODUCTION

Ephaptic coupling refers to interactions between nerve fibers mediated by current flow through the extracellular space without any specialized connecting regions such as synapses for chemical transmission or electronic gap junctions. These interactions occur due to physical proximity of axons, especially those lacking an insulating myelin sheath around them. The mammalian olfactory nerve in which unmyelinated axons are arranged in densely packed fascicles (see Fig. 1 in [1]) is an example of a brain region that may favor ephaptic interactions.

Experimentally, ephaptic coupling can be detected by observing several phenomena. One such phenomenon is when an action potential on one nerve fiber changes the excitability of the neighboring fibers, and in some cases, evokes action potentials on them. In the second case, adjacent nerve fibers can synchronize their firing patterns, i.e., the action potentials traveling along them can travel at the same speeds and get phase locked. These observations were recorded by Katz and Schmitt in 1940 [2] in the case of crab motoneurons by placing two axons in a medium with reduced extracellular conductance. Similar experiments to detect ephaptic coupling have been done using squid giant axons by Arvanitaki [3] and Ramon and Moore [4], active single nerve fibers in the spinal nerve roots of dystrophic mice by Rasminsky [5] and algal strands by Tabata [6]. Early theoretical studies of ephaptic coupling between unmyelinated nerve fibers were done by Markin [7,8], Luzader and Scott [9], and Barr and Plonsey [10]. More recently, Bokil *et al.* [1] tested the hypothesis that ephaptic interactions occur in a mammalian olfactory nerve by considering the Hodgkin-Huxley model of impulse propagation and showed that an action potential in a single axon can evoke an action potential in all other axons in the fascicle and that the action potentials in neighboring nerve fibers can synchronize. Ephaptic coupling between myelinated nerve fibers whose membrane is covered by a fatty insulating myelin sheath except for some regions called the active nodes, has been studied by Binczak *et al.* [11] and Reutskiy *et al.* [12] and Bateman and Van Vleck [13].

Since these interactions occur via the spread of ionic currents, it is reasonable to expect transmission time delays in these processes, due to finite times of propagation for these currents. Most experimental papers [3–5] on ephaptic transmission mention that an action potential on one fiber evokes an action potential on an adjacent fiber after a certain time-delay often referred to as the ephaptic transmission time. Ramon and Moore [4] found that this time varied from 200 to 400 μs in the case of squid giant axons. Rasmisky [5] measured an ephaptic transmission time of 100–240 μs in the case of single nerve fibers in the spinal nerve roots of dystrophic mice. While, to our knowledge, there are no experimental measurements of the speeds of the ion currents involved in ephaptic transmission, the observations by Ramon and Moore and Rasminsky strongly suggest the presence of time-delays in ephaptic interactions. Since delays are ubiquitous in dynamical systems and may have profound effects related to stability and the onset of complex behavior [14–17], understanding the impact of ephaptic transmission time delays on the stability of the entrained state of nerve impulses could be of wider interest.

In this article, we study the effect of delay on the entrainment of pulses on two ephaptically coupled, unmyelinated nerve fibers. Our approach is an extension of some old work of Luzader and Scott [9] who developed an analytical model of the ephaptic coupling between two parallel, unmyelinated nerve fibers, representing giant axons of squid. Each individual fiber was expressed mathematically by the piecewise-linear Fitzhugh-Nagumo equations. By using a perturbation expansion of the velocities of the impulses on two fibers in terms of the coupling parameter they showed that in the limit of weak coupling, the two coupled pulses can be entrained to leading order. Eilbeck *et al.* [18] integrated these equations numerically and confirmed this result. These, as well as all the previous studies assumed instantaneous transmission with no delays.

We show that, when delay is included in the Luzader and Scott model this precisely entrained state is destabilized as the delay increases beyond a critical value and the pulses maintain a stable, nonzero phase difference between them. We calculate an estimate of this critical value of delay in the case of squid giant axons and show that it is comparable to the ephaptic transmission times measured by Ramon and Moore [4] and Rasminsky [5]. Since the piecewise-linear form of Fitzhugh-Nagumo equations captures the essential features of impulse generation and propagation on nerve fibers exhibited by more complex models such as the Hodgkin-Huxley or the Fitzhugh-Nagumo with cubic nonlinearity, this destabilization of precise entrainment due to delay is expected to be generic, independent of the precise nonlinearity in the equations. Thus, careful experiments could be carried out to measure phase differences between entrained pulses which, in turn, can be used to estimate the ephaptic transmission times.

II. EPHAPTIC COUPLING WITH DELAY

In order to study the effect of delay on the synchronization of pulses on two ephaptically coupled, unmyelinated nerve fibers, we employ the model equations used by Luzader and Scott [9] and include the delay in the coupling terms. Thus the equations have the following dimensionless form:

$$V_{1,t}(x,t) = (1-\alpha)V_{1,xx}(x,t) - \alpha V_{2,xx}(x,(t-\delta)) - F(V_1(x,t)) - R_1(x,t), \tag{1}$$

$$R_{1,t}(x,t) = \epsilon(V_1(x,t) - bR_1(x,t)), \tag{2}$$

$$V_{2,t}(x,t) = (1-\alpha)V_{2,xx}(x,t) - \alpha V_{1,xx}(x,(t-\delta)) - F(V_2(x,t)) - R_2(x,t), \tag{3}$$

$$R_{2,t}(x,t) = \epsilon[V_2(x,t) - bR_2(x,t)]. \tag{4}$$

Here V denotes the normalized trans-membrane potential across each fiber and R is the recovery variable which roughly represents the turn-on of potassium permeability. Thus the individual fibers are modeled using the Fitzhugh-Nagumo set of two coupled equations [19] that capture the essential features of action potential generation and propagation of a four dimensional description given by Hodgkin and Huxley [20]. The independent variables x and t are scaled in the units of $1/\sqrt{rg}$ and g/c, respectively, with g, r, and c being the trans-membrane conductance (in mhos/cm), resistance (in ohm/cm), and capacitance (in F/cm) per unit length, respectively. ε can be considered to represent any of a number of debilitating effects such as temperature or narcotic concentration, etc. [9], and δ represents the time-delay involved in ephaptic transmission. The nonlinear function for the potential, $F(V)$, is approximated by a piecewise linear form considered originally by McKean [21]:

$$\tilde{F}(\tilde{V}) = \tilde{V} - V_+ H(\tilde{V} - \tilde{a}) \tag{5}$$

with $H(\tilde{V}-\tilde{a})$ being the Heavyside unit step function, $\tilde{a}$ being the threshold for the generation of an action potential, and V_+ the peak value of the membrane potential. We introduce dimensionless variables V,a,R by normalizing with V_+: $\tilde{V}=V_+V$, $\tilde{R}=V_+R$ and $\tilde{a}=V_+a$ so that the dimensionless nonlinear potential function that appears in the Eqs. (1) and (3) has the form $F(V)=V-H(V-a)$, whose largest zero is unity.

For a single fiber, integration of the corresponding Fitzhugh-Nagumo equations yields a family of traveling wave solutions parametrized by velocity $u(\varepsilon)$. Rinzel and Keller [22] assumed $b=0$ and showed that, for each value of ε below a critical value ε_c, there exists a stable pulse solution of higher velocity and an unstable pulse solution of lower velocity.

Luzader and Scott [9] assume $b=0$ and consider two pulses traveling with the same velocity on identical fibers coupled ephaptically. They assume instantaneous coupling and hence set $\delta=0$. The coupling parameter α is equal to the ratio of external to internal resistance/length and is considered small. They assume the following expansions for the potential and the velocity of the pulse on each fiber in terms of α:

$$V_i = V_{i0} + \alpha V_{i1} + \cdots; \quad i=1,2,$$

$$u_i = u_0 + \alpha u_1^{(i)} + \cdots; \quad i=1,2$$

and solve for the first order corrections in the velocities $u_1^{(i)}$ as a function of the phase difference between the pulses. Requiring $u_1^{(1)}=u_1^{(2)}$, they show that the phase difference of zero between the pulses is stable, implying that the two pulses can be entrained if they start with a sufficiently small phase difference initially. We introduce a slow time scale in the problem owing to the smallness of the coupling constant and study the entrainment of the pulses in slow time scale as a function of the time delay δ.

Assuming $b=0$, Eqs. (1)–(4) can be written as

$$V_{1,tt}(x,t) = (1-\alpha)V_{1,xxt}(x,t) - \alpha V_{2,xxt}(x,(t-\delta)) - F'(V_1)V_{1,t}(x,t) - \epsilon V_1(x,t), \tag{6}$$

$$V_{2,tt}(x,t) = (1-\alpha)V_{2,xxt}(x,t) - \alpha V_{1,xxt}(x,(t-\delta)) - F'(V_2)V_{2,t}(x,t) - \epsilon V_2(x,t). \tag{7}$$

We assume

$$V_i(\xi,\tau;\alpha) = V_{i0}(\xi,\tau) + \alpha V_{i1}(\xi,\tau) + O(\alpha^2), \tag{8}$$

where $\xi=x-ut$ is the traveling wave coordinate and u is the speed with which each pulse travels down the axon. $\tau=\alpha t$ is a slow time variable:

$$\frac{\partial}{\partial t} = -u\frac{\partial}{\partial \xi} + \alpha\frac{\partial}{\partial \tau},$$

$$\frac{\partial}{\partial x} = \frac{\partial}{\partial \xi}.$$

Thus for $i=1,2$ we get

$$V_{i,x} = V_{i0,\xi} + \alpha V_{i1,\xi} + O(\alpha^2),$$

$$V_{i,t} = -uV_{i0,\xi} + \alpha[V_{i0,\tau} - uV_{i1,\xi}] + O(\alpha^2),$$

$$V_{i,tt} = u^2 V_{i0,\xi\xi} + \alpha[u^2 V_{i1,\xi\xi} - 2uV_{i0,\xi\tau}] + O(\alpha^2),$$

$$V_{i,xx} = V_{i0,\xi\xi} + \alpha V_{i1,\xi\xi} + O(\alpha^2),$$

$$V_{i,xxt} = -uV_{i0,\xi\xi\xi} + \alpha[-uV_{i1,\xi\xi\xi} + V_{i0,\xi\xi\tau}] + O(\alpha^2),$$

$$-\alpha V_{i,xxt} = \alpha u V_{i0,\xi\xi\xi} + O(\alpha^2),$$

$$-\epsilon V_1 = -\epsilon V_{i0} + \alpha(-\epsilon V_{i1}) + O(\alpha^2),$$

$$-F'(V_i)V_{i,t} = uV_{i0,\xi}F'(V_{i0}) + \alpha[F'(V_{i0})(uV_{i1,\xi} - V_{i0,\tau}) + uV_{i1}V_{i0,\xi}F''(V_{i0})] + O(\alpha^2).$$

Substituting these expressions in Eqs. (6) and (7) we get the leading order equations for $i=1,2$:

$$u^2V_{i0,\xi\xi} + uV_{i0,\xi\xi\xi} - uF'(V_{i0})V_{i0,\xi} + \epsilon V_{i0} = 0. \qquad (9)$$

The solution to this equation $V_{i0}(\xi)$ is the traveling pulse on each fiber (if they are uncoupled) with a speed u. We assume that the solutions to Eq. (9) have the form

$$V_{i0} \equiv V_{i0}(\xi + \psi_i(\tau)). \qquad (10)$$

Thus,

$$V_{i0,\xi} = V_{i0,\xi},$$

$$V_{i0,\tau} = \psi_{i,\tau}V_{i0,\xi},$$

$$V_{i0,\xi\tau} = \psi_{i,\tau}V_{i0,\xi\xi},$$

$$V_{i0,\xi\xi\tau} = \psi_{i,\tau}V_{i0,\xi\xi\xi}.$$

Using the above expressions and Eq. (9), $O(\alpha)$ equations can be written as

$$uV_{i1,\xi\xi\xi} + u^2V_{i1,\xi\xi} - uF'(V_{i0})V_{i1,\xi} - V_{i1}[uF''(V_{i0})V_{i0,\xi} - \epsilon] = \psi_{i,\tau}\left[uV_{i0,\xi\xi}(\xi'_i) - \frac{\epsilon}{u}V_{i0}(\xi'_i)\right] + uV_{j0,\xi\xi\xi}(\xi'_i + \eta) + uV_{i0,\xi\xi\xi}(\xi'_i) \qquad (11)$$

Here, $i, j=1,2$; $i \neq j$, $\xi'_i = \xi + \psi_i(\tau)$ and $\eta = u\delta$. Equations (11) are linear and hence, for $i=1,2$, each can be written as

$$L_iV_{i1} = f_i \qquad (12)$$

for which a solvability condition is

$$(w_i, L_iV_{i1}) = (w_i, f_i) = 0, \qquad (13)$$

where w_i is the solution of

$$L_i^\dagger w_i = 0.$$

Here, $L_i^\dagger$ is the adjoint of L_i under the inner product employed in Eq. (13). Here we use the conventional definition for the inner product

$$(v,w) \equiv \int_{-\infty}^{\infty} v(\xi)w(\xi)d\xi. \qquad (14)$$

Integrating Eq. (13) by parts, we get

$$L_i^\dagger w_i = uw_{i,\xi\xi\xi} - u^2w_{i,\xi\xi} - uF'(V_{i0})w_{i,\xi} - \epsilon w_i = 0. \qquad (15)$$

Then for $i=1,2$, $(w_i, f_i)=0$ implies

$$\psi_{1,\tau}\int_{-\infty}^{\infty} w_1(\xi'_1)\left[\frac{\epsilon}{u^2}V_{10}(\xi'_1) - V_{10,\xi\xi}(\xi'_1)\right]d\xi = \int_{-\infty}^{\infty} w_1(\xi'_1)V_{10,\xi\xi\xi}(\xi'_1)d\xi + \int_{-\infty}^{\infty} w_1(\xi'_1)V_{20,\xi\xi\xi}(\xi'_2 + \eta)d\xi,$$

$$\psi_{2,\tau}\int_{-\infty}^{\infty} w_2(\xi'_2)\left[\frac{\epsilon}{u^2}V_{20}(\xi'_2) - V_{20,\xi\xi}(\xi'_2)\right]d\xi = \int_{-\infty}^{\infty} w_2(\xi'_2)V_{20,\xi\xi\xi}(\xi'_2)d\xi + \int_{-\infty}^{\infty} w_2(\xi'_2)V_{10,\xi\xi\xi}(\xi'_1 + \eta)d\xi.$$

These two equations can be solved for the change in the phase difference between two pulses as a function of the slow time variable τ, if we know the functional form of V_{i0} and w_i which are the solutions to Eqs. (9) and (15), respectively. Solving these equations is straightforward and is done in the Appendix.

Now the first integrals on the right hand sides of above equations are independent of ψ_1 and ψ_2 and when integrated from $-\infty$ to ∞, they are equal to constants. Similarly, the coefficients of $\psi_{1,\tau}$ and $\psi_{2,\tau}$ on the left hand sides of the equations are independent of ψ_1 and ψ_2 and when integrated from $-\infty$ to ∞, they are also equal to each other and constants. Thus we can write

$$\int_{-\infty}^{\infty} w_1V_{10,\xi\xi\xi}d\xi = \int_{-\infty}^{\infty} w_2V_{20,\xi\xi\xi}d\xi = H_1,$$

$$\int_{-\infty}^{\infty} w_i\left[\frac{\epsilon}{u^2}V_{i0} - V_{i0,\xi\xi}\right]d\xi = H_2 \cdots i = 1,2.$$

Hence the equation for the rate of change of the phase difference between the two pulses with respect to τ becomes

$$\frac{d\Delta\psi}{d\tau} = \frac{[I_{\eta-\Delta\psi} - I_{\eta+\Delta\psi}]}{H_2}, \qquad (16)$$

where $\Delta\psi = \psi_2 - \psi_1$, H_2 is as defined before, and

$$I_{\eta\pm\Delta\psi} = \int_{-\infty}^{\infty} w(\xi)V_0'''(\xi + \eta \pm \Delta\psi)d\xi. \qquad (17)$$

The expressions for V_{i0} and w_i can be divided into three regions defined by L, the range of ξ for which the potential is above the threshold, as follows. Region I: $\xi < -L$; $V_{i0} \leqslant a$, region II: $-L < \xi < 0$; $V_{i0} \geqslant a$, region III: $\xi > 0$; $V_{i0} \leqslant a$. Then, as done in the Appendix, the functional forms of V_0 and w in these three regions can be written as given below. (We drop the symbol i as the leading order expressions for the solution and the adjoint are identical on both fibers.) Thus, for $\xi < -L$,

$$V_0(\xi) \equiv V_1(\xi) = A_1e^{k_1\xi} + A_2e^{k_2\xi}, \qquad (18)$$

$$w(\xi) \equiv w_1(\xi) = A'e^{-k_3\xi}. \qquad (19)$$

For $-L < \xi < 0$,

$$V_0(\xi) \equiv V_2(\xi) = B_1e^{k_1\xi} + B_2e^{k_2\xi} + B_3e^{k_3\xi}, \qquad (20)$$

$$w(\xi) \equiv w_2(\xi) = B_1' e^{-k_1 \xi} + B_2' e^{-k_2 \xi} + B_3' e^{-k_3 \xi} \tag{21}$$

and for $\xi > 0$,

$$V_0(\xi) \equiv V_3(\xi) = C e^{k_3 \xi}, \tag{22}$$

$$w(\xi) \equiv w_3(\xi) = C_1' e^{-k_1 \xi} + C_2' e^{-k_2 \xi} \tag{23}$$

with k_1, $k_2 > 0$ and $k_3 < 0$. Next, we want to find expressions for $I_{\eta+\Delta\psi}$ and $I_{\eta-\Delta\psi}$ in terms of $\Delta\psi$. Since $V_0''(\xi)$ is discontinuous at $\xi = -L$ and $\xi = 0$, we can write

$$\begin{aligned} V_0''(\xi_\pm) = {} & V_1''(\xi_\pm) + [V_2''(\xi_\pm) - V_1''(\xi_\pm)]H[\xi_\pm - (-L)] \\ & + [V_3''(\xi_\pm) - V_2''(\xi_\pm)]H(\xi_\pm - 0). \end{aligned}$$

Here, $\xi_\pm = \xi + \eta \pm \Delta\psi$ and $H(\xi)$ is the Heaviside step function. Hence,

$$\begin{aligned} V_0'''(\xi_\pm) = {} & V_1'''(\xi_\pm) + [V_2'''(\xi_\pm) - V_1'''(\xi_\pm)]H[\xi_\pm - (-L)] \\ & + [V_2''(\xi_\pm) - V_1''(\xi_\pm)]\delta[\xi_\pm - (-L)] \\ & + [V_3'''(\xi_\pm) - V_2'''(\xi_\pm)]H(\xi_\pm) \\ & + [V_3''(\xi_\pm) - V_2''(\xi_\pm)]\delta(\xi_\pm). \end{aligned} \tag{24}$$

Thus,

$$\begin{aligned} & \int_{-\infty}^{\infty} w(\xi) V_0'''(\xi_\pm) d\xi \\ & = \int_{-\infty}^{-L_\pm} w(\xi) V_1'''(\xi_\pm) d\xi + \int_{-L_\pm}^{-\eta_\pm} w(\xi) V_2'''(\xi_\pm) d\xi \\ & \quad + \int_{-\eta_\pm}^{\infty} w(\xi) V_3'''(\xi_\pm) d\xi + w(-L_\pm)[V_2''(-L) - V_1''(-L)] \\ & \quad + w(-\eta_\pm)[V_3''(0) - V_2''(0)], \end{aligned} \tag{25}$$

where $L_\pm = L + \eta \pm \Delta\psi$ and $\eta_\pm = \eta \pm \Delta\psi$. Now, integrating each of the first three integrals on the right-hand side of Eq. (25) by parts, we see that the last two terms on the right-hand side of above equation, will cancel with the contributions from the values of the integrands in the first three integrals at the limits of the integration. Hence we obtain

$$\begin{aligned} & \int_{-\infty}^{\infty} w(\xi) V_0'''(\xi_\pm) d\xi \\ & = - \int_{-\infty}^{-L_\pm} w'(\xi) V_1''(\xi_\pm) d\xi - \int_{-L_\pm}^{-\eta_\pm} w'(\xi) V_2''(\xi_\pm) d\xi \\ & \quad - \int_{-\eta_\pm}^{\infty} w'(\xi) V_3''(\xi_\pm) d\xi. \end{aligned}$$

However since $w'(\xi)$ has different functional forms in different regions of ξ, each of the three integrals on the right-hand side of the above equation needs to be divided differently for different ranges of values of $\Delta\psi$. Here, then, are the different cases and the various integrals involved in the calculation of $I_{\eta+\Delta\psi}$.

Case I: $\Delta\psi = 0$. There is nothing to learn in this case as the right-hand side of the Eq. (16) equals zero, hence, $\Delta\psi_{,\tau} = 0$ as well and this just implies that $\Delta\psi = 0$ is a fixed point of Eq. (16) irrespective of the value of η or the delay in ephaptic coupling.

Case II: $0 < \Delta\psi \leqslant L - \eta$.

$$\begin{aligned} & \int_{-\infty}^{\infty} w(\xi) V_0'''(\xi_+) d\xi \\ & = - \int_{-\infty}^{-L_+} w_1'(\xi) V_1''(\xi_+) d\xi - \int_{-L_+}^{-L} w_1'(\xi) V_2''(\xi_+) d\xi \\ & \quad - \int_{-L}^{-\eta_+} w_2'(\xi) V_2''(\xi_+) d\xi - \int_{-\eta_+}^{0} w_2'(\xi) V_3''(\xi_+) d\xi \\ & \quad - \int_{0}^{\infty} w_3'(\xi) V_3''(\xi_+) d\xi. \end{aligned}$$

Case III: $-L - \eta \leqslant \Delta\psi < 0$.

$$\begin{aligned} & \int_{-\infty}^{\infty} w(\xi) V_0'''(\xi_+) d\xi \\ & = - \int_{-\infty}^{-L} w_1'(\xi) V_1''(\xi_+) d\xi - \int_{-L}^{-L_+} w_2'(\xi) V_1''(\xi_+) d\xi \\ & \quad - \int_{-L_+}^{0} w_2'(\xi) V_2''(\xi_+) d\xi - \int_{0}^{-\eta_+} w_3'(\xi) V_2''(\xi_+) d\xi \\ & \quad - \int_{-\eta_+}^{\infty} w_3'(\xi) V_3''(\xi_+) d\xi. \end{aligned}$$

Case IV: $L - \eta \leqslant \Delta\psi < \infty$.

$$\begin{aligned} & \int_{-\infty}^{\infty} w(\xi) V_0'''(\xi_+) d\xi \\ & = - \int_{-\infty}^{-L_+} w_1'(\xi) V_1''(\xi_+) d\xi \\ & \quad - \int_{-L_+}^{-\eta_+} w_1'(\xi) V_2''(\xi_+) d\xi - \int_{-\eta_+}^{-L} w_1'(\xi) V_3''(\xi_+) d\xi \\ & \quad - \int_{-L}^{0} w_2'(\xi) V_3''(\xi_+) d\xi - \int_{0}^{\infty} w_3'(\xi) V_3''(\xi_+) d\xi. \end{aligned}$$

Case V: $-\infty < \Delta\psi \leqslant -L - \eta$.

$$\begin{aligned} & \int_{-\infty}^{\infty} w(\xi) V_0'''(\xi_+) d\xi \\ & = - \int_{-\infty}^{-L} w_1'(\xi) V_1''(\xi_+) d\xi - \int_{-L}^{0} w_2'(\xi) V_1''(\xi_+) d\xi \\ & \quad - \int_{0}^{-L_+} w_3'(\xi) V_1''(\xi_+) d\xi - \int_{-L_+}^{-\eta_+} w_3'(\xi) V_2''(\xi_+) d\xi \\ & \quad - \int_{-\eta_+}^{\infty} w_3'(\xi) V_3''(\xi_+) d\xi. \end{aligned}$$

These integrals can be done analytically or numerically, given the functional forms of V_{i0} and w_i, for particular values of ε and a, and hence $I_{\eta+\Delta\psi}$ can be calculated for a given

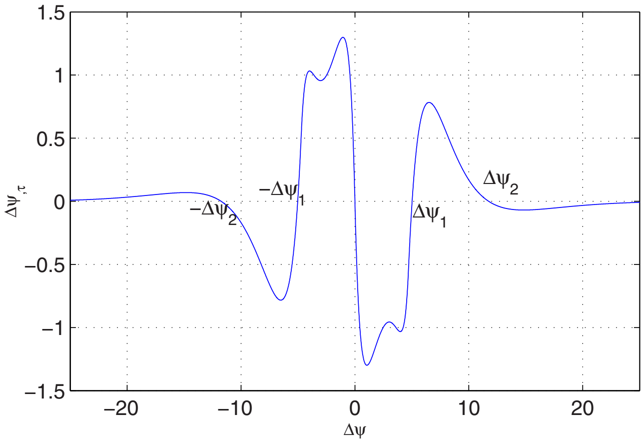

FIG. 1. (Color online) The Luzader-Scott result: a plot of the right-hand side of Eq. (16) for the zero delay case ($\eta=0$) [9] showing five fixed points with 0 and $\pm\Delta\psi_2$ being the stable fixed points. (Here $a=0.3$, $\varepsilon=0.1$ and both x and y axes are plotted in units of traveling wave coordinate ξ.)

value of η. $I_{\eta-\Delta\psi}$ can be calculated in a similar fashion and hence the vector field in Eq. (16) can be found as a function of $\Delta\psi$.

In the case considered by Luzader and Scott [9], i.e., when the coupling is instantaneous and hence $\eta=0$, there are five fixed points with 0, $\Delta\psi_2$ and $-\Delta\psi_2$ being the stable fixed points while $\Delta\psi_1$ and $-\Delta\psi_1$ being the unstable fixed points, as shown in Fig. 1. Since $\Delta\psi=0$ is a stable fixed point, the two pulses will get entrained with no phase difference between them, if they start with a small initial phase difference, as was shown by Luzader and Scott.

However, as the value of the delay is increased from zero, while $\Delta\psi=0$ remains a fixed point, it undergoes a pitchfork bifurcation giving rise to two new fixed points. These new fixed points are stable while 0 becomes unstable, in turn destroying the precise entrainment of the two pulses. This, nonzero stable phase difference between the two pulses increases as the delay increases further. The other nonzero fixed points ($\pm\Delta\psi_1$ and $\pm\Delta\psi_2$ in Fig. 1) present in the zero delay case also increase in magnitude but do not change their stability. These effects of a higher-than-critical value of the delay can be seen in Fig. 2(c) [with a closer look near $\Delta\psi=0$ in Fig. 2(d)] while Fig. 2(a) [with a closer look near $\Delta\psi=0$ in Fig. 2(b)] shows that, for a lower-than-critical value of the delay, the locations as well as the nature of stability of all the fixed points in the zero delay case (Fig. 1) remain unchanged; the only difference is in the value of the slope at $\Delta\psi=0$.

As mentioned in the last section, Rinzel and Keller [22] showed that for a given value of the threshold potential a, there are several values of $\varepsilon<\varepsilon_c$ for which the Fitzhugh-Nagumo equations for a single nerve fiber admit stable pulse solutions. We calculated the critical values of the delay, at which the precise entrainment between the two pulses is destabilized, for several such values of ε. As shown in Fig. 3, the critical value of the delay increases as ε increases. It indicates that for slower recovery (i.e., smaller values of ε), the threshold values of the delay in ephaptic transmission beyond which the pulses will maintain a stable, nonzero phase difference between them, is smaller than those for quicker recovery. In other words, shorter pulses (i.e., those having quick recovery) can maintain precise entrainment for comparatively higher values of the delay in ephaptic transmission than longer ones.

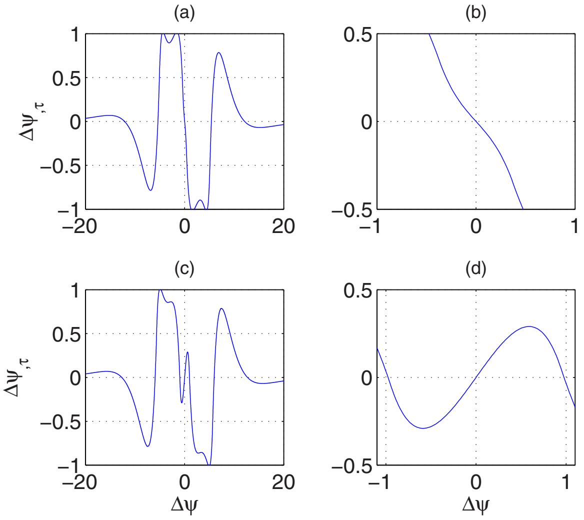

FIG. 2. (Color online) Plots of the right-hand side of Eq. (16) for two values of the delay showing the change of stability for the precisely entrained state. (a) and (b): $\eta=0.08L\approx0.38$ ($\delta\approx7.4$ μs for squid axons); $\Delta\psi=0$ is stable. (c) and (d): $\eta=0.16L\approx0.76$ ($\delta\approx14.7$ μs for squid axons); $\Delta\psi=0$ is clearly unstable while two new fixed points at $\Delta\psi\approx\pm0.98$ (19 μs for squid axons) are now stable. The value of this new, nonzero, stable phase difference increases as the delay increases further. Here $\varepsilon=0.1$ and $a=0.3$ and both x and y axes are plotted in units of traveling wave coordinate ξ.

III. DISCUSSION

Ephaptic interactions happen between neurons that are in close proximity of each other, through spread of ionic cur-

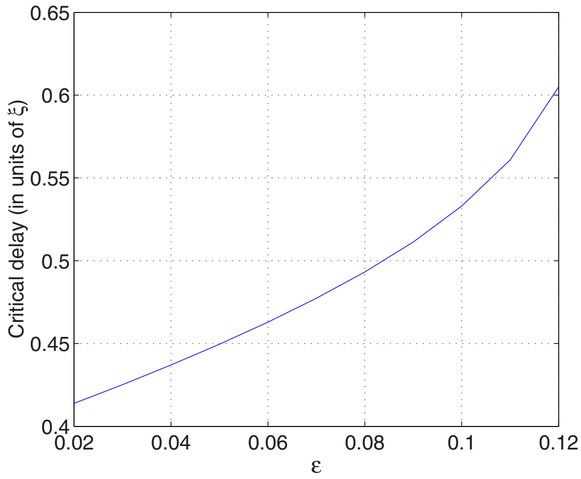

FIG. 3. (Color online) Figure shows the plot of the critical values of delay at which the phase difference of zero between the pulses on neighboring fibers loses stability, as a function of the recovery parameter ε for $a=0.3$.

rent. It is reasonable to expect that they occur with some delay due to finite time of propagation of these currents. In this article, we showed theoretically, that if the delay is sufficiently large, then it can destabilize the precise entrainment between impulses traveling down two identical, parallel nerve fibers. We now make a rough estimate of the actual value of this critical delay, in the case of squid giant axons.

For $\varepsilon=0.1$ and $a=0.3$, the value of η at which $\Delta\psi=0$ bifurcates, turns out to be $\approx 0.11L$ where L, in the units of the traveling-wave coordinate ξ, is ≈ 4.72. Now $\eta=u\delta$, where u, the dimensionless velocity of each pulse, is ≈ 0.71. This gives the value of δ, but since the original equations (1)–(4) are dimensionless themselves, the actual value of delay is obtained by multiplying δ by g/c, the relevant time scale in the problem. For the giant axon of squid the typical values of g and c are 0.0108 mhos/cm and 1.5×10^{-7} F/cm, respectively [23]. Thus the value of the transmission delay at which the pulses are desynchronized, turns out to be ≈ 10.1 μs. The time interval between the arrival of the action potential at the preephaptic fiber and the firing of the postephaptic fiber was found to be, in the range of 200–400 μs by Ramon and Moore [4] in the case of squid giant axons and, in the range of 100–240 μs by Rasminsky [5] in the case of spinal nerve roots of dystrophic mice. Considering that the processes involved in generation of an action potential on a resting fiber by an active adjacent fiber are more complex and time consuming than the case when both fibers have action potentials traveling along them, our estimate of the time delay responsible for the destabilization of precise entrainment between the two impulses seems quite reasonable and relevant. Thus our results suggest that careful experiments could be carried out to measure the stable, nonzero phase difference between the pulses thereby calculating the transmission time delay. On the other hand, if the pulses get entrained precisely, with zero phase difference between them, our result gives an upper limit for the time delays involved in ephaptic transmission.

In this article we demonstrated the effect of finite ephaptic transmission time (delay) qualitatively and gave an estimate of the critical delay for loss of synchrony between two fibers. Extending this work to study the effect of time delay on the synchronization of a collection of ephaptically coupled fibers would be of considerable biological interest.

APPENDIX: CALCULATION OF V_{i0} AND w_i

The equations for the leading order solution V_{i0} and its adjoint w_i are as follows:

$$V_{i0,\xi\xi\xi}+uV_{i0,\xi\xi}-F'(V_{i0})V_{i0,\xi}+\frac{\epsilon}{u}V_{i0}=0, \tag{A1}$$

$$w_{i,\xi\xi\xi}-uw_{i,\xi\xi}-F'(V_{i0})w_{i,\xi}-\frac{\epsilon}{u}w_i=0. \tag{A2}$$

Let us take Eq. (A1) first. This has a pulse solution, which when plotted as a function of ξ, can be divided into three regions. Region I: $\xi<-L$; $V_{i0}\leqslant a$, region II: $-L<\xi<0$; $V_{i0}\geqslant a$, region III: $\xi>0$; $V_{i0}\leqslant a$. We can write a general form of the solution in all three regions as

$$\begin{aligned}V_{i0}&=A_1\exp(k_1\xi)+A_2\exp(k_2\xi)+A_3\exp(k_3\xi);\ \text{in I},\\&=B_1\exp(k_1\xi)+B_2\exp(k_2\xi)+B_3\exp(k_3\xi);\ \text{in II},\\&=C_1\exp(k_1\xi)+C_2\exp(k_2\xi)+C_3\exp(k_3\xi);\ \text{in III}.\end{aligned}$$

Since $V_{i0}\to 0$ as $\xi\to\pm\infty$, we get

$$V_{i0}=A_1\exp(k_1\xi)+A_2\exp(k_2\xi);\ \text{in I}, \tag{A3}$$

$$=B_1\exp(k_1\xi)+B_2\exp(k_2\xi)+B_3\exp(k_3\xi);\ \text{in II}, \tag{A4}$$

$$=C\exp(k_3\xi);\ \text{in III}. \tag{A5}$$

k_1, $k_2>0$, and $k_3<0$ are the roots of the characteristic equation obtained from Eq. (A1):

$$k^3+uk^2-k+\frac{\epsilon}{u}=0. \tag{A6}$$

Thus k_1, k_2, k_3 are functions of ε and u. Now we use the continuity of the solution and its first derivative and the discontinuity in the second derivative at $\xi=0$ and $\xi=-L$ to solve for the constants in Eqs. (A3)–(A5) and also for L. The discontinuity in the second derivative comes from the form of the function $F(V)$ and is expressed as follows:

$$(V''_{i0})_{\mathrm{II}}-(V''_{i0})_{\mathrm{I}}=-1,$$

$$(V''_{i0})_{\mathrm{III}}-(V''_{i0})_{\mathrm{II}}=1.$$

Thus using these matching conditions at $\xi=0$ we get three equations that can be written in a compact form as follows:

$$k_3^mC=\sum_{i=1}^{3}k_i^mB_i+\delta_{m2}\cdots m=0,1,2 \tag{A7}$$

and at $\xi=-L$,

$$\sum_{i=1}^{2}k_i^mA_ie^{-k_iL}=\sum_{j=1}^{3}k_j^mB_je^{-k_jL}+\delta_{m2}\cdots m=0,1,2, \tag{A8}$$

where δ_{m2} is the Kronecker delta. There are two additional conditions

$$V_{i0}(\xi=0)=V_{i0}(\xi=-L)=a \tag{A9}$$

which along with Eq. (A7) imply $C=a$. Then we can solve for B_1, B_2, and B_3 in terms of k_1, k_2, and k_3:

$$B_1=\frac{(k_2-k_3)}{D}, \tag{A10}$$

$$B_2=\frac{k_3-k_1}{D}, \tag{A11}$$

$$B_3=\frac{k_1-k_2}{D}+a \tag{A12}$$

with $D=k_2k_3(k_3-k_2)+k_1k_3(k_1-k_3)+k_1k_2(k_2-k_1)$. We can then solve for L:

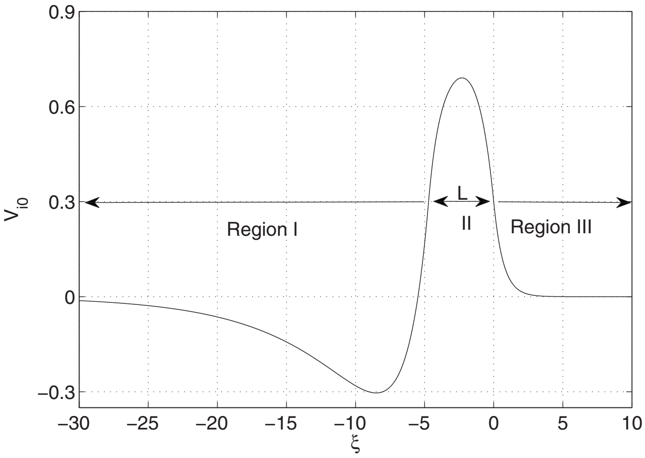

FIG. 4. Functional form of V_{i0} as a function of ξ—a stable pulse solution for the Fitzhugh-Nagumo equation with $\varepsilon=0.1$ and $a=0.3$.

$$L = \frac{-1}{k_3} ln\,\eta. \tag{A13}$$

Here,

$$\eta(k_1,k_2,k_3,a) = 1 - \frac{a}{B_3} = \frac{k_1-k_2}{(k_1-k_2)+aD}. \tag{A14}$$

We can then solve for A_1 and A_2:

$$A_1 = B_1[1-\eta^{-k_1/k_3}], \tag{A15}$$

$$A_2 = B_2[1-\eta^{-k_2/k_3}]. \tag{A16}$$

Now using the final condition, i.e., $V_{i0}(\xi{=}-L)=a$ we get

$$B_1\eta^{k_1/k_3} + B_2\eta^{k_2/k_3} + B_3 = 2a. \tag{A17}$$

This is an equation in terms of k_1, k_2, k_3 which are in turn in terms of u, the velocity. Thus we can solve this equation for u for particular values of ε and a. Once we know u, we can calculate k_1, k_2, k_3 from which we can know A_1, A_2, B_1, B_2, B_3, and L and hence the functional form of V_{i0}. The plot of V_{i0} is given in Fig. 4 and it matches the plot in the article by Luzader and Scott [9].

The functional form of w_i would be similar since the differential equation for the adjoint, Eq. (A2) is similar to Eq. (A1) although a main difference is that Eq. (A2) is linear. The only change would be in the signs of k_1, k_2, k_3 as the characteristic equation corresponding to Eq. (A2) can be obtained from that for Eq. (A1) by replacing k by $-k$. A general form of the solution to Eq. (A2), in all the three regions defined before, can be written as

$$w_i = A_1'\exp(k_1'\xi) + A_2'\exp(k_2'\xi) + A_3'\exp(k_3'\xi);\ \text{in I},$$

$$= B_1'\exp(k_1'\xi) + B_2'\exp(k_2'\xi) + B_3'\exp(k_3'\xi);\ \text{in II},$$

$$= C_1'\exp(k_1'\xi) + C_2'\exp(k_2'\xi) + C_3'\exp(k_3'\xi);\ \text{in III},$$

where k_1', k_2', k_3' are the roots of the characteristic equation

$$k^3 - uk^2 - k - \frac{\epsilon}{u} = 0. \tag{A18}$$

Comparing this equation with Eq. (A6) we see that $k_1'{=}-k_1$, $k_2'{=}-k_2$, and $k_3'{=}-k_3$ which implies that $k_1'<0$, $k_2'<0$, $k_3'>0$. Hence the functional form of w_i becomes

$$w_i = A'\exp(-k_3\xi);\ \text{in I}, \tag{A19}$$

$$= \sum_{i=1}^{3} B_i'\exp(-k_i\xi);\ \text{in II}, \tag{A20}$$

$$= C_1'\exp(-k_1\xi) + C_2'\exp(-k_2\xi);\ \text{in III}. \tag{A21}$$

Now we use the continuity of the solution and its first derivative and the discontinuity in the second derivative at $\xi{=}0$ and $\xi{=}-L$ to solve for the constants in Eqs. (A19)–(A21). The discontinuity in the second derivative comes from the form of the function $F(V)$ and is expressed as follows:

$$(w_i'')_{\text{II}} - (w_i'')_{\text{I}} = \frac{-w_i'(-L)}{V_{i0}'(-L)}, \tag{A22}$$

$$(w_i'')_{\text{III}} - (w_i'')_{\text{II}} = \frac{w_i'(0)}{V_{i0}'(0)}. \tag{A23}$$

Thus using these matching conditions at $\xi{=}0$ we get the following set of equations:

$$\sum_{i=1}^{2} k_i^m C_i' = \sum_{i=1}^{3} k_i^m B_i' \cdots m = 0,1, \tag{A24}$$

$$\sum_{i=1}^{2} k_i^2 C_i' = \sum_{i=1}^{3} k_i^m B_i' + \frac{k_1C_1' + k_2C_2'}{k_3C} \tag{A25}$$

and at $\xi{=}-L$,

$$k_3^m A' e^{k_3L} = \sum_{i=1}^{3} k_i^m B_i' e^{k_iL} \cdots m = 0,1, \tag{A26}$$

$$k_3^2 A' e^{k_3L} = \sum_{i=1}^{3} k_i^2 B_i' e^{k_iL} - \frac{k_3A'e^{k_3L}}{\Sigma_{j=1}^{2} k_jA_je^{-k_jL}}. \tag{A27}$$

Eliminating B_1', B_2', B_3' leads to the following three equations for C_1', C_2', and A':

$$(1+c_{11})C_1' + c_{12}C_2' - a_{11}A' = 0, \tag{A28}$$

$$c_{12}C_1' + (1+c_{22})C_2' - a_{12}A' = 0, \tag{A29}$$

$$c_{13}C_1' + c_{23}C_2' - (1+a_{13})A' = 0, \tag{A30}$$

where

$$c_{11} = -\frac{k_1B_1}{k_3C}, \quad c_{12} = -\frac{k_1B_2}{k_3C}, \quad c_{13} = -\frac{k_1(B_3-C)}{k_3C},$$

$$c_{21} = -\frac{k_2B_1}{k_3C}, \; c_{22} = -\frac{k_2B_2}{k_3C}, \quad c_{23} = -\frac{k_2(B_3 - C)}{k_3C},$$

$$a_{11} = -\frac{k_3\beta_1 e^{(k_3L)}}{k_1\alpha_1 + k_2\alpha_2}, \quad a_{12} = -\frac{k_3\beta_2 e^{(k_3L)}}{k_1\alpha_1 + k_2\alpha_2},$$

$$a_{13} = -\frac{k_3\beta_3}{k_1\alpha_1 + k_2\alpha_2},$$

where $\alpha_i = A_i e^{(-k_iL)}$, $i=1,2$, $\beta_j = B_j e^{(-k_jL)}$, $j=1,2,3$ and A_i, B_j, and C are the coefficients in the functional form of V_{i0}. The above relations can be obtained from the expressions (A10)–(A12) for these coefficients and using the condition for the discontinuity in the second order derivative of w_i—Eqs. (A22) and (A23). It can be easily proved that two of the three equations (A28)–(A30) are redundant and hence we can solve for two of three coefficients C_1', C_2', and A' in terms of the third one. Hence we solve for C_1' and A' in terms of C_2', which then yields all the coefficients in the functional form of w_i:

$$C_1' = \left[\frac{a_{11}(1 + c_{22}) - a_{12}c_{21}}{a_{12}(1 + c_{11}) - a_{11}c_{12}}\right] C_2', \tag{A31}$$

$$A' = \frac{c_{13}C_1' + c_{23}C_2'}{(a_{13} + 1)}, \tag{A32}$$

$$B_1' = a_{11}A', \tag{A33}$$

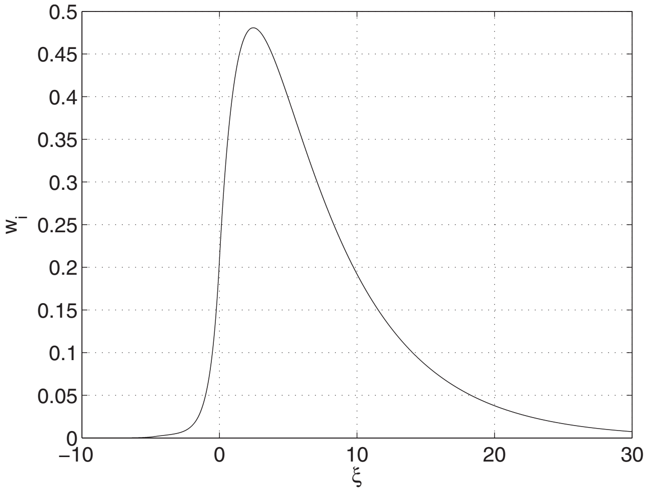

FIG. 5. A solution of the adjoint homogeneous equation that corresponds to the pulse shown in the above figure. The ordinate scale is arbitrary (a=0.3, ε=0.1).

$$B_2' = a_{12}A', \tag{A34}$$

$$B_3' = (a_{13} + 1)A'. \tag{A35}$$

With these coefficients, we now plot w_i as functions of ξ for a=0.3 and ε=0.1 in Fig. 5 and it matches with the one given in Ref. [9].

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