Mathematical Modelling and Numerical Simulations in Nerve Conduction

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Abstract: In this paper we are concerned with the numerical solution of the discrete FitzHugh-Nagumo equation. This equation describes the propagation of impulses across a myelinated axon. We analyse the asymptotic behaviour of the solutions of the considered equation and numerical approximations are computed by a new algorithm, based on a finite difference scheme and on the Newton method. The efficiency of the method is discussed and its performance is illustrated by a set of numerical examples.

1 INTRODUCTION

In the present work we analyse a functional-differential equation, sometimes known as the discrete FitzHugh-Nagumo equation, arising in nerve conduction theory. The history of this equation began in 1952, when A. Hodgkin and A. Huxley (Hodgkin and Huxley, 1952) introduced a mathematical model that describes the excitation and flow of electrical current through the surface of a giant nerve fibre from a squid. This investigation was continued in the works of FitzHugh (FitzHugh, 1960), (FitzHugh, 1962) and Nagumo (Nagumo et al., 1962).

During its evolution the FitzHugh-Nagumo equation has taken different forms. The case of myelinated axons deserves special attention.

In a myelinated nerve axon the myelin completely insulates the membrane, so that the potential change jumps from node to node (pure saltatory condition).

According to Bell (Bell, 1984) two basic properties of the myelinated axon are the following:

- it possesses threshold behaviour; this means that there are conditions which guarantee either the decay of a solution (subthreshold response) or non-decay of a solution (suprathreshold response);
- it is able to conduct pulses.

On the other hand, with the purpose of obtaining a mathematical model that can be analysed and lead to numerical solutions, some theoretical assumptions have been imposed: a) the axon is infinite in extent, b) the Ranvier nodes are identical and uniformly spaced; c) the electric signals propagate with constant speed. These assumptions make sense when considering the propagation of signals not at the central, but at the peripheral nervous system.

The mathematical model for myelinated axons developed in (Chi et al., 1986), based on these assumptions, leads to the discrete FitzHugh-Nagumo equations:

$$v'(t) = v(t+\tau) - 2v(t) + v(t-\tau) + bv(t)(v(t)-1)(\alpha - v(t)), \quad (1)$$

where $v(t)$ represents the potential at a Ranvier node of the axon at the moment t (in this case, the potential at the neighbouring nodes is denoted by $v(t-\tau)$ and $v(t+\tau)$; the constant τ is the time that a signal takes to be transmitted from a node to the neighbouring one (in other words, τ is inversely proportional to the propagation speed of the signal). The constant b reflects the resistance and the conductance in the nerve axon, while α is the threshold potential.

From a mathematical point of view, an important feature of equation (1) is that it contains both negative and positive deviations of the argument (delayed and advanced terms); this is the reason why it is called a mixed type functional differential equation (or an advance-delay-differential equation). Important contributions to the analysis of this type of equation have been introduced in the literature in the last two decades of the past century, by Rustichini (Rustichini, 1989), Mallet-Paret and Verduyn-

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Lunel (Mallet-Paret, 1999). More recently, Hupkes and Verduyn-Lunel studied the behaviour of solutions to nonlinear autonomous MTFDEs in the neighbourhood of an equilibrium solution (Hupkes and Verduyn-Lunel, 2007). Concerning boundary value problems for MTFDEs, contributions to their analysis and numerical methods for their solution have been introduced in (Ford and Lumb, 2009), (Lima et al., 2010) and (Ford et al., 2010). Computational methods for nonlinear MFTDEs, which includes equations of the form (1), were introduced by Abell et al. (Abell et al., 2005) and then by the authors of the present paper in (Lima et al., 2013) and (Ford et al., 2014). Comparing with previous contributions, the present paper describes more robust and efficient methods, which are able to produce accurate results for a wider choice of the input parameters. The outline of this paper is as follows. In section 2 we investigate the asymptotic behaviour of solutions at infinity. In section 3 we describe some computational methods used for numerical approximation. In section 4 we provide some numerical results and we finish with some conclusions in section 5.

2 BOUNDARY CONDITIONS AND ASYMPTOTIC ANALYSIS

Let us rewrite equation (1) in the following form:

$$v'(t) = f(v(t)) + v(t-\tau) - 2v(t) + v(t+\tau), \quad (2)$$

where

$$f(v) = bv(v-\alpha)(1-v); \quad (3)$$

this function is the nonlinear part of (2) and is called the current voltage function. Due to the form of f, given by (3), equation (2) has two stable equilibrium points: $v = 0$ (resting potential) and $v = 1$ (fully activated potential). Therefore, we are interested in a solution of (2), increasing on $]-\infty,\infty[$, which satisfies the boundary conditions

$$\lim_{t\to-\infty} v(t) = 0, \qquad \lim_{t\to+\infty} v(t) = 1. \quad (4)$$

These conditions will be satisfied by the potential at any node. In order to guarantee uniqueness of solution, we add the condition

$$v(0) = 1/2. \quad (5)$$

We are interested in a **monotone** solution of problem (2)-(5), that is, we assume that once the signal starts propagating, the potential will increase at every node, tending to its maximal value ($v(t) = 1$). Such a solution exists for a certain value of τ, which must be computed. An extensive analysis of this behaviour has been provided in (Chi et al., 1986), so here we will just recall the main results from that paper. Based on the Taylor expansion of f, as v tends to 0, we assume that v has the form

$$v_-(t) = \varepsilon_- e^{\lambda(t+L)}, \quad (6)$$

where L is a sufficiently large parameter and ε_- is an estimate for $v_-(-L)$. In this way we obtain the equation

$$\lambda + 2 - f'(0) - 2\cosh(\lambda\tau) = 0. \quad (7)$$

This equation has two real roots; since we are interested in a function v_- that tends to 0 at $-\infty$, we choose the positive one, which we denote by λ_+.

The case where $t \to \infty$ can be handled in an analogous way. In this case, we assume that v has the form

$$v_+(t) = 1 - \varepsilon_+ e^{\lambda(t-L)}, \quad (8)$$

where ε_+ is an estimate of $1 - v_+(L)$. In this way we obtain the characteristic equation

$$\lambda + 2 - f'(1) - 2\cosh(\lambda\tau) = 0 \quad (9)$$

Here we choose the negative root of the characteristic equation, which we will denote by λ_-, in order to have $v_+(t) \to 1$, as $t \to +\infty$.

Now we have obtained two representations for the solution of our problem, (6) and (8), which we shall use to approximate the solution, for $t < -L$ and $t > L$, respectively, where L is a sufficiently large number. According to the form of equation (2), L must be a multiple of the delay τ; in our computations we have used $L = k\tau$, where $2 \le k \le 9$, depending on the specific problem (as discussed in Sec. 4).

These representations of the solution are used in the computational methods to replace the boundary conditions (4). In the next section we will show how this can be achieved.

3 COMPUTATIONAL METHODS

In this section we will describe and compare some computational methods that can be applied to obtain approximate solutions of the problem (2), (4), (5). Since the problem is nonlinear, some of the methods considered require initial approximations, which must be sufficiently close to the true solution, to guarantee the convergence of the iterative process. Thus we begin by presenting some preliminary results, which can help us to build a rough approximation of the solution.

3.1 Finding an Initial Approximation

We now present an approach that results from approximating the solution by a piecewise differentiable

function. In this case, we search for an approximate solution of the considered problem in the form

$$v_0(t)=\begin{cases}\varepsilon_- e^{\lambda_+(t+2\tau)}, & if \quad t<-2\tau;\\ a_0+a_1t+a_2t^2, & if \quad -2\tau\le t<-\tau;\\ \frac{1}{2}+b_1t+b_2t^2+b_3t^3, & if \quad -\tau\le t<0;\\ \frac{1}{2}+c_1t+c_2t^2+c_3t^3 & if \quad 0<t<\tau;\\ d_0+d_1t+d_2t^2, & if \quad \tau\le t<2\tau;\\ 1-\varepsilon_+ e^{\lambda_-(t-2\tau)}, & if \quad t\ge 2\tau;\end{cases} \tag{10}$$

From the form of v_0 if follows that this function satisfies the boundary conditions (4) and (5). We easily see that v_0 depends on 17 parameters: τ,ε_-, ε_+,λ_-,λ_+, a_0,a_1,a_2,b_1,b_2,b_3,c_1,c_2,c_3,d_0,d_1, d_2. These coefficients are computed from a system of 17 equations. (for details, see (Ford et al., 2014)). The nonlinear system of equations can be solved by the Newton method. Note that in this case the number of equations in the system is not so high as when we apply the finite difference method, and therefore it is not so difficult to find an initial approximation for the Newton method. For example, if we know the solution for a cetain set of values a,b, we can use this soution as initial approximation to solve the system and find the solution for close values of a,b. The estimates for λ_-,λ_+ and τ from above can be used as initial approximations. As follows easily from the construction, $v_0\in C^1(I\!R)$. Some examples of application of this approximation will also be given in section 4. As we shall see, though these results have relative errors which may attain 0.1, the corresponding approximate solutions have the correct qualitative behaviour and this explains that they provide good initial approximations for the more refined method we describe in the next subsection.

3.2 A Finite Difference Approach

In this section we describe a finite difference scheme for the solution of problem (2), (4), (5). This scheme has some common features with the one described in (Chi et al., 1986), but it has the advantage that it can be easily solved by the Newton iterative method, without using the continuation algorithm. As an initial approximation for the Newton method we have used the function v_0, defined by (10).

In order to approximate the solution we introduce on $[-K\tau,K\tau]$ a uniform mesh with stepsize $h=\tau/N$. Let $t_i=-K\tau+ih$, $i=0,...,2KN$ be the nodes of this mesh. Here K is a sufficiently large integer so that $\varepsilon_1=v(-K\tau)$ is comparable with h^2 (the reason for this choice will be explained below). As in (Chi et al., 1986), the first derivative is approximated by a 4-th order finite difference:

$$v'(t_i)\approx L_h(v)_i=\\ \frac{1}{h}\left(\frac{2}{3}(v(t_{i+1})-v(t_{i-1}))-\frac{1}{12}(v(t_{i+2})-v(t_{i-2}))\right). \tag{11}$$

By using this approximation at each node t_i we obtain $2KN+1$ equations of the form:

$$L_h(v)_i=v(t_i+\tau)+v(t_i-\tau)-2v(t_i)+f(v(t_i))+r_i^h, \tag{12}$$

where $\|r_h^i\|=O(h^4)$. Note that for $t_i>(K-1)\tau$ and $t_i<-(K-1)\tau$ equation (12) involves the value of v at one or more points that do not belong to the interval $[-K\tau,K\tau]$. In this case the boundary conditions (4) are applied, by considering the fact that v satisfies (6) or (8), when $v<-K\tau$ or $v>K\tau$, respectively. In this way, we write

$$v(-K\tau-x)=v(-K\tau)e^{-\lambda_+x}, \qquad (x>0), \tag{13}$$

$$1-v(K\tau+x)=(1-v(K\tau))e^{-\lambda_-x}, \qquad (x>0). \tag{14}$$

Finally, by ignoring r_i^h in (12), we obtain $(2K-2)N$ finite difference equations of the form:

$$L_h(v)_i=v_{i+N}+v_{i-N}-2v_i+f(v_i), \tag{15}$$

$$i=N+1,...,(2K-1)N+1.$$

Here as usual v_i represents the approximate value of $v(t_i)$. For $0\le i<N+1$ and $(2K-1)N+1<i\le 2KN+1$, we have modifications of equation (15) which result from applying formulae (13) or (14), respectively. This gives a system of $2KN+1$ equations, which is then completed with the equation $v_{KN}=1/2$, resulting from (5). Moreover, we have the characteristic equations (7) and (9), making a total of $2KN+4$ equations. Note that the number of unknowns is also $2KN+4$: $2KN+1$ entries of the vector $v=(v_0,...,v_{2KN})$, λ_-, λ_+ and τ.

This nonlinear system is then solved by the Newton method.

4 NUMERICAL RESULTS

We first compare the estimates of τ, λ_-, and λ_+, obtained by the two methods described in Sec. 3. In both cases we consider the problem (2), (4), (5). We denote by τ_0 the estimate of τ obtained when using the approximating function v_0, defined by (10); τ_1 stands for the value obtained by the finite difference method with $N=64$. Table 1 contains the values of τ_0 and τ_1, for $b=15$, with different values of a. The values of τ_0 and τ_1, obtained in the case $a=0.05$, for different values of b, are displayed in Table 2.

The errors of τ_0 can be obtained by comparing these estimates with τ_1, which can be considered as

Table 1: Estimates of τ, λ_- and λ_+ for different values of a, with $b = 15$.

a	τ_0	τ_1	λ_-	λ_+
0	0.3101	0.38029	−6.22752	5.1007
0.05	0.3461	0.43511	−5.44866	4.5111
0.1	0.3910	0.5056	−4.6909	3.9297
0.15	0.4485	0.5993	−3.95523	3.3586
0.2	0.5250	0.73001	−3.32594	2.6073
0.25	0.6318	0.92525	−2.55197	2.2691
0.3	0.7916	1.2515	−1.88069	1.66568
0.35	1.0575	1.9371	−1.2111	1.08772

Table 2: Estimates of τ, λ_- and λ_+ for different values of b, with $a = 0.05$.

b	τ_0	τ_1	λ_-	λ_+
1	1.652	1.6250	−0.4333	0.4096
5	0.6639	0.7229	−2.0677	1.8678
11	0.4325	0.5008	−4.1869	3.5574
16	0.3296	0.4227	−5.7499	4.7354
21	0.2656	0.3744	−7.1795	5.7840
51	0.1216	0.1200	−14.0692	10.6338

the most accurate value for this purpose. Notice that the presented values of τ_1 coincide with those obtained in (Chi et al., 1986), within the given precision.

The approximate values of λ_- and λ_+ obtained by the finite difference method, with $N = 64$, are given in the two last columns of the mentioned tables.

All the estimates preserve the main characteristics of τ, as a function of a and b: they increase with a and decrease as b increases. This behaviour agrees with the physical meaning of the variables. Since a is the threshold potential, the propagation speed is supposed to decrease as a increases, and therefore we observe τ increasing. On the other hand, increasing b means a higher potential at the nodes and this leads to a greater propagation speed and the decreasing of τ.

It is worth remarking that for values of a, greater than 0.3 large discrepancies between the different estimates arise. This is connected with the numerical instability of the different methods which is observed for the values of a we considered. In particular, in the case $a \geq 0.3$, the value τ obtained by the finite difference method seems to have a larger error than the other approximations (and this does not arise elsewhere). The explanation for this may be the instability which is also visible in the graph of Figure 3. Note that according to the available theoretical results, existence of a solution can be proved only for $a < 0.5$. The accuracy of the results is also reduced for values of b, greater than 21.

According to Keener (Keener, 1987), the discrete Nagumo equation has a "propagation failure" for sufficiently small coupling coefficient. When the equation is written in the form (2), a small coupling corresponds to high values of b. Thus when b is large the problem (2),(4),(5) becomes unsolvable. This explains why for high values of b estimates obtained by different methods differ signifficantly.

In Tables 3 and 4 numerical approximations for $v'(0)$, obtained by the two considered methods, are given for a set of values of a and b. In agreement with the notation used in Tables 1 and 2, we denote by $v'_0(0)$ (resp. $v'_1(0)$) the estimate obtained by the method, corresponding to τ_0 (resp. τ_1). In this case the differences between the estimates obtained by different methods are not so large as in the case of the evaluation of τ. Even for $a > 0.3$ or $b > 21$, these differences are not greater than 5 per cent. This suggests that the gradient of the solution at the origin is not so sensitive to computational errors as the value of τ.

Table 3: Estimates of $v'(0)$ for different values of b, with $a = 0.05$.

b	$v'_0(0)$	$v'_1(0)$
1	0.1224	0.112695
5	0.6045	0.58339
11	1.2821	1.2774
16	1.83603	1.84116
21	2.39174	2.40116
51	5.7504	5.76174

Table 4: Estimates of $v'(0)$ for different values of a, with $b = 15$.

a	$v'_0(0)$	$v'_1(0)$
0	1.9171	1.9181
0.05	1.72515	1.72889
0.1	1.53326	1.53918
0.15	1.34141	1.34891
0.2	1.1496	1.1580
0.25	0.957907	0.96647
0.3	0.76624	0.774237
0.35	0.57463	0.58131

Note that, for all the approximations, the largest errors occur close to $t = 0$, where the solution changes faster. In this region the error can reach about 10 per cent of the solution value.

We remark that by differentiating v_0 we obtain a reasonable approximations of v'. The derivatives of v_0 and v_1 are plotted in Figure 1.

We will now focus on the numerical results for the problem (2)-(5), obtained by the finite difference method. We have tested numerically the convergence order of the method. When the exact solution is not known, an estimate of the convergence order can be obtained from three finite difference solutions, ob-

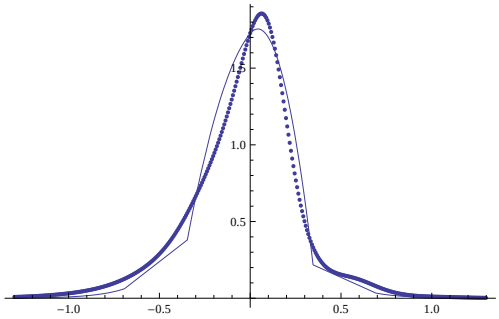

Figure 1: Approximation of the solution derivative: by the finite difference method (thick line); using v_0 (thin line).

tained with different stepsizes: $v_{2h}, v_h, v_{h/2}$, where $h > 0$. The estimate of the convergence order is then given by

$$p = \log_2 \frac{\|v_h - v_{2h}\|}{\|v_h - v_{h/2}\|},$$

where the maximum norm is used. The numerical results displayed in Tables 5,6,7 suggest that the method has 4-th order of convergence, as could be expected.

Table 5: Estimates of convergence order in the case $a = 0.05, b = 5$, with $K = 9$.

h	$\|v_h - v_{2h}\|$	p
$\tau/2^4$	$1.51E-5$	6.22
$\tau/2^5$	$2.03E-7$	3.981
$\tau/2^6$	$1.29E-8$	3.994
$\tau/2^7$	$0.07E-10$	3.998
$\tau/2^8$	$5.05E-11$	

Table 6: Estimates of convergence order in the case $a = 0.05, b = 15$, with $K = 6$.

h	$\|v_h - v_{2h}\|$	p
$\tau/2^4$	0.015	7.42
$\tau/2^5$	$8.80E-5$	5.11
$\tau/2^6$	$2.55E-6$	3.97
$\tau/2^7$	$1.63E-7$	3.99
$\tau/2^8$	$1.02E-8$	

Table 7: Estimates of convergence order in the case $a = 0.05, b = 21$, with $K = 6$.

h	$\|v_h - v_{2h}\|$	p
$\tau/2^4$	0.00041	6.518
$\tau/2^5$	$4.48E-6$	3.973
$\tau/2^6$	$2.85E-7$	3.992
$\tau/2^7$	$1.79E-8$	3.998
$\tau/2^8$	$1.12E-9$	

The large differences between the estimates of τ, obtained by the two methods, for certain values of a and b, suggest that some of the computational methods may become unstable for such values, in particular, when a is close to 0.5 or b is large. This is true, in particular, in the case of the finite difference method, as is shown by the graphs of the approximate solutions plotted in Figures 2 and 3.

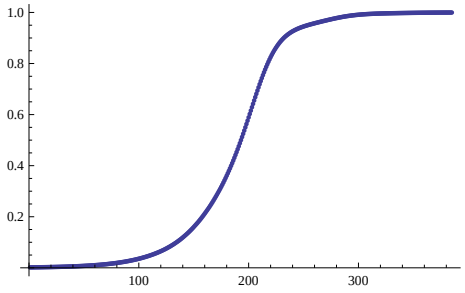

Figure 2: Graph of the numerical solution obtained by the finite difference method with $N = 64$, in the case $a = 0.1, b = 15$. Here the numerical solution preserves the smoothness of the true solution.

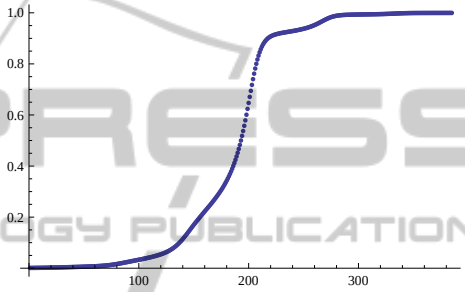

Figure 3: Graph of numerical solutions obtained by the finite difference method with $N = 64$, in the cases $a = 0.35, b = 15$ (right side). Here the effect of numerical instability is even mor evident than in the previous figure.

As mentioned in subsection 3.2, the finite difference method developed in this work was inspired by the method described in (Chi et al., 1986) . However, the algorithm described in that work relies on the continuation method, that is, a numerical solution is first computed for a test problem and then, by a continuous change of a parameter, a sequence of auxiliary equations is solved, until reaching the target problem. Possibly following on from this, the results reported in (Chi et al., 1986) are limited to the cases where $a \leq 0.2$ and $b \leq 20$. In our numerical experiments, the initial approximations for the Newton method were obtained by the numerical method described in subsection 3.1; this enabled us to solve the problem for a wider range of values of a and b. Moreover, our algorithm worked with stepsizes as small as 0.001, while in the case of the numerical results reported in (Chi et al., 1986) the typical stepsize was $h = 0.05$.

5 CONCLUSIONS

We have applied two computational approaches to the solution of the problem (2)-(4), analysed and compared the numerical results. The more accurate results are obtained by the finite difference method, described in Sec. 3.2. The numerical results suggest that this method has fourth order of convergence, as it could be expected. Highly accurate results can be obtained, within a reasonable computational effort, when the parameters satisfy $0 \leq a < 0.3$ and $5 \leq b \leq 51$. However, for other values of the parameters computational instability arises.

Another approximation method was discussed in Sec. 3.1 . The computational effort required by this method is very small and the algorithms are very simple. Although its accuracy is reduced, it can provide good initial approximations for the finite difference method.

The numerical results obtained in our paper confirm the main features of the considered mathematical model. In particular, it was observed that the propagation speed $(1/\tau)$ increases as the threshold potential a decreases (see table 1) and as the intensity of the ionic currents (represented by b) increases (see table 2). The typical S-shaped form of the solution graphic (illustrated by figure 2) means that the potential value changes slowly when it is close to its resting or fully activated value; and changes fast, when it is close to the average value. As a consequence, the solution derivative takes its highest values when t is close to 0, and these values are particularly high when a is small and b is large (as it follows from tables 3 and 4). In conclusion, the numerical results obtained by the described methods can be useful for applications, because they help to interpret experimental results on the propagation of nervous signals through axons.

The proposed numerical techniques can be easily extended to more general forms of the Fitzhugh-Nagumo equations, in particular, systems of differential-difference equations describing other physical variables than the membrane potential (Bell, 1984). This will be the subject of future work.

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REFERENCES

Abell, K., Elmer, C., Humphries, A., and Vleck, E. V. (2005). Computation of mixed type functional differential boundary value problems. *SIAM J. Appl. Dyn. Syst.*, 4:755–781.

Bell, J. (1984). Behaviour of some models of myelinated axons. *IMA Journal of Mathematics Applied in Medicine and Biology*, 1:149–167.

Chi, H., Bell, J., and B.Hassard (1986). Numerical solution of a nonlinear advance-delay-differential equation from nerve conduction theory. *J. Math. Biol*, 24:583–601.

FitzHugh, R. (1960). Impulses and physiological states in theoretical models of nerve membrane. *Biophysical J.*, 1:445–466.

FitzHugh, R. (1962). Computation of impulse initiation and saltatory condition in a myelinated nerve fiber. *Biophysical J.*, 2:11–21.

Ford, N., Lima, P., and Lumb, P. (2014). Computational methods for a mathematical model of propagation of nerve impulses in myelinated axons. *Appl. Num. Math.*, 85:38–53.

Ford, N. and Lumb, P. (2009). Mixed-type functional differental equations: a numerical approach. *J. Comput. Appl. Math.*, 229:471–479.

Ford, N., Lumb, P., Lima, P., and Teodoro, M. (2010). The numerical solution of forward-backward equations: decomposition and related issues. *J. Comput. Appl. Math.*, 234:2745–2756.

Hodgkin, A. and Huxley, A. (1952). A quantitative description of nerve current and its application to conduction and excitation in nerve. *J. Phisiology*, 117:500–544.

Hupkes, H. and Verduyn-Lunel, S. (2007). Center manifold theory for functional differential equations of mixed type. *J. Dyn. Diff. Eq.*, 19:497–560.

Keener, J. (1987). Propagation and its failure in coupled systems of discrete excitable cells. *SIAM J. Appl. Math.*, 47:556–572.

Lima, P., Teodoro, M., Ford, N., and Lumb, P. (2010). Analytical and numerical investigation of mixed-type functional differential equations. *J. Comput. Appl. Math.*, 234:2826–2837.

Lima, P., Teodoro, M., Ford, N., and Lumb, P. (2013). Analysis and computational approximation of a forward-backward equation arising in nerve conduction. In *Differential and Difference Equations with Applications*, pages 475–483. Springer.

Mallet-Paret, J. (1999). The fredholm alternative for functional differential equations of mixed type,. *J. Dyn. Diff. Eq.*, 11:1–47.

Nagumo, J., Arimoto, S., and Yoshizawa, S. (1962). An active pulse transmission line simulating nerve axon. *Proceedings of the IRE*, 50:2051–2070.

Rustichini, A. (1989). Functional differential equations of mixed type: the linear autonomous case. *J. Dyn. Diff. Eq.*, 1:121–143.