International Conference on Bioinspired Systems and Signal Processing, Lisbon, 12-15 January 2015.

MATHEMATICAL MODELLING AND NUMERICAL SIMULATIONS IN NERVE CONDUCTION

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INTRODUCTION

In the first models of nerve excitation and propagation of electronic impulses, nerves were considered as electric cables, through which electric current flows. This is the case for the squid nerve, studied by Hodgkin and Huxley [3], but in other animals (like frogs, for example) nerve axons have a different structure. The nerve membrane is insulated by a substance called myelin (see Fig. 1). According to Bell [1], myelination of an axon allows it to conduct neuroelectric signals by exciting only a small portion of membrane exposed to the extracellular medium at the nodes of Ranvier. This permits transmission at greatly reduced energy expenditure and higher speeds than comparably sized unmyelinated axons. In models of myelinated axons, the following hypothesis is assumed: the myelin has such high resistance and low capacitance that it completely insulates the membrane (pure saltatory condition).

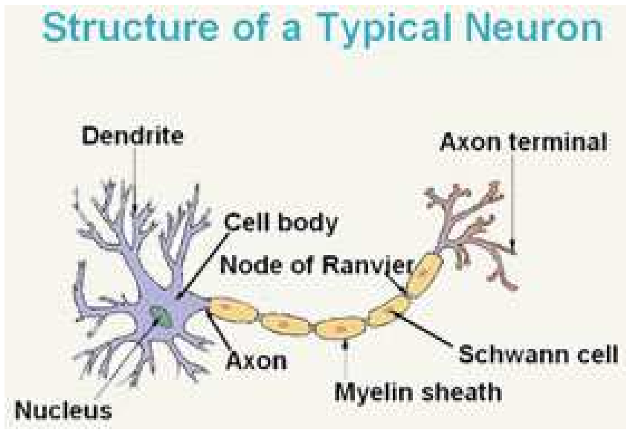

Fig.1 Neuron and myelinated axon

With the purpose of obtaining a mathematical model of myelinated axons 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 [2], based on these assumptions, leads to the discrete FitzHugh-Nagumo equations:

$$\begin{aligned} v'(t) &= v(t+\tau) - 2v(t) + v(t-\tau) + \\ &\quad bv(t)(v(t)-1)(\alpha - v(t)), \end{aligned} \tag{1}$$

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.

BOUNDARY CONDITIONS AND ASYMPTOTIC ANALYSIS

Equation (1) has two stable equilibrium points: $v = 0$ (resting potential) and $v = 1$ (fully activated potential). We are interested in a solution of (1), increasing on $]-\infty, \infty[$, which satisfies the boundary conditions

$$\lim_{t\to-\infty} v(t) = 0, \qquad \lim_{t\to+\infty} v(t) = 1. \tag{2}$$

In order to guarantee uniqueness of solution, we add the condition

$$v(0) = 1/2. \tag{3}$$

We are interested in a monotone solution of problem (1)-(3), 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 [2]. Based on the Taylor expansion of f, as v tends to 0, we assume that v has the form

$$v_-(t) = \epsilon_- e^{\lambda(t+L)}, \tag{4}$$

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

$$\lambda + 2 - f'(0) - 2\cosh(\lambda\tau) = 0. \tag{5}$$

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

$$v_+(t) = 1 - \epsilon_+ e^{\lambda(t-L)}, \tag{6}$$

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

$$\lambda + 2 - f'(1) - 2\cosh(\lambda\tau) = 0 \tag{7}$$

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, (4) and (6), 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 (1), L must be a multiple of the delay τ; in our computations we have used $L = k\tau$, where $2 \leqslant k \leqslant 9$, depending on the specific problem. These representations of the solution are used in the computational methods to replace the boundary conditions (2).

COMPUTATIONAL METHODS

Finding an Initial Approximation A rough approximation of the solution of problem (1)-(3) may be obtained by representing it in the form of a piecewise differentiable function v_0. More precisely, we split the real axis into 6 subsets :

$I_0 = [-\infty, -2\tau]$, $I_1 = [-2\tau, -\tau]$, $I_2 = [-\tau, 0]$, $I_3 = [0, \tau]$, $I_4 = [\tau, 2\tau]$, $I_5 = [2\tau, \infty]$. In I_0 and I_5, according to (4) and (6), the solution is sought in the form of an exponential function. In each of the intervals I_1, I_2,I_3 and I_4, it takes the form of a quadratic or cubic polynomial. The coefficients of these polynomials are computed from a system of 17 nonlinear equations, resulting from equation (1);from the characteristic equations (5) and (7); from the continuity of v_0 and its first two derivatives. The approximation v_0 can then be used as an initial guess for the application of more sophisticated numerical methods.

Finite Difference Method 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 $\epsilon_1 = v(-K\tau)$ is comparable with h^2. As in [2], the first derivative is approximated by a 4-th order finite difference:

$$\begin{aligned} v'(t_i) &\approx L_h(v)_i = \\ &\frac{1}{h}\left(\frac{2}{3}(v(t_{i+1}) - v(t_{i-1})) - \frac{1}{12}(v(t_{i+2}) - v(t_{i-2}))\right). \end{aligned} \tag{8}$$

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

$$L_h(v)_i = v(t_i + \tau) + v(t_i - \tau) - 2v(t_i) + f(v(t_i)) + r_i^h, \tag{9}$$

where $\|r_h^i\| = O(h^4)$. Note that for $t_i > (K-1)\tau$ and $t_i < -(K-1)\tau$ equation (9) 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 (2) are applied, by considering the fact that v satisfies (4) or (6), when $v < -K\tau$ or $v > K\tau$, respectively. This gives a system of $2KN + 1$ equations, which is then completed with the equation $v_{KN} = 1/2$, resulting from (3). Moreover, we have the characteristic equations (5) and (7), 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.

NUMERICAL RESULTS

In Tables 1 and 2 numerical approximations for $v'(0)$, obtained by the two methods considered, are given for a set of values of a and b. Even for $a > 0.3$ or $b > 21$, the differences between the two values are not greater than 5 per cent.

Table 1. 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 2. 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 Fig. 2.

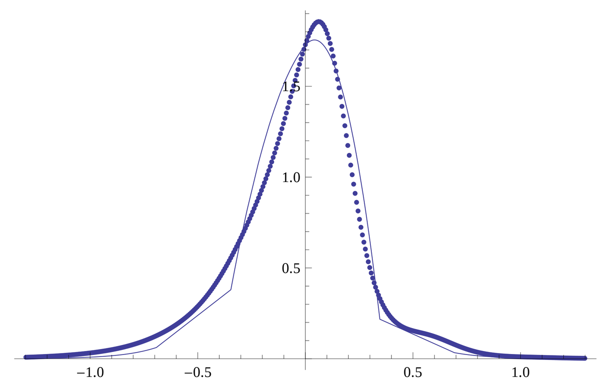

Fig. 2: Approximation of $v'(t)$: by the finite difference method (thick line); using v_0 (thin line).

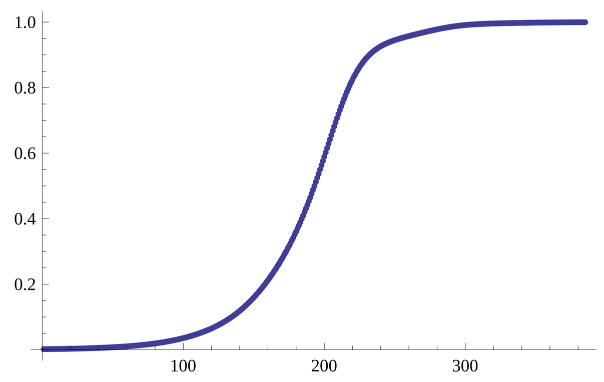

Fig. 3: Graphic of the numerical solution $v(t)$ obtained by the finite difference method, with $N = 64$, in the case $a = 0.1$, $b = 15$.

CONCLUSIONS AND FUTURE WORK

- The finite difference 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 $0 \leqslant a < 0.3$ and $5 \leqslant b \leqslant 51$.
- Another simple method method was discussed, based on piecewise polynomial approximation. 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 mathematical model considered. In particular, it was observed that the propagation speed $(1/\tau)$ increases as the threshold potential a decreases and as the intensity of the ionic currents (represented by b) increases.
- The typical S-shaped form of the solution graphic (illustrated by Fig. 3) 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 1 and 2).
- In conclusion, we can see that the results of the simulations match the observed behaviour from experiments, which means that predictions can be made using the simulations through the numerical schemes and these can be reasonably reliable and reduce experimental costs and delays.
- 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

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