COUPLED MACROMODELS FOR THE SIMULATION OF THE SALTATORY CONDUCTION

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The saltatory conduction is the way the action potential is transmitted along a myelinated axon. The potential diffuses along the myelinated compartments and is regenerated in the Ranvier nodes due to the ionic channels that allow the flow of ions across the membrane. For an efficient simulation of large-scale neuronal networks, it is important to develop low-order models – especially for myelinated compartments where the potential satisfies PDEs – and have control over the accuracy of the reduced models and access to the inner parameters. The paper proposes two coupled macromodels for the simulation of the saltatory conduction in myelinated axons, one as circuits, implemented in a circuit simulator (Spice), and the second as systems, implemented in Simulink. In both formulations, the global model is obtained by concatenating reduced order models of 1D myelinated compartments with nonlinear 0D models of the Ranvier nodes.

Keywords: multiscale, myelinated axons, model order reduction, saltatory conduction, coupled models

1. Introduction

The main function of a neuronal axon is the transmission of information, in the form of action potentials. These are rapid rises and falls of the membrane potential of a specific axon location. The triggering of the action potential depends on the fact that the electric potential's magnitude reaches a threshold. The transmission speed of the action potential in myelinated axons is much higher than in unmyelinated axons. The myelinated axons consist of alternating sequencies of Ranvier nodes and myelinated compartments (also called internodes) (Fig. 1). Myelin is a protein-rich fat substance acting like an insulating layer and therefore reducing the energy loss across the membrane. This has two effects: the transmission speed of the action potential along the compartment is high, and its amplitude decreases. The signal is regenerated in the Ranvier nodes, which are gaps in the myelin layer and therefore uninsulated,

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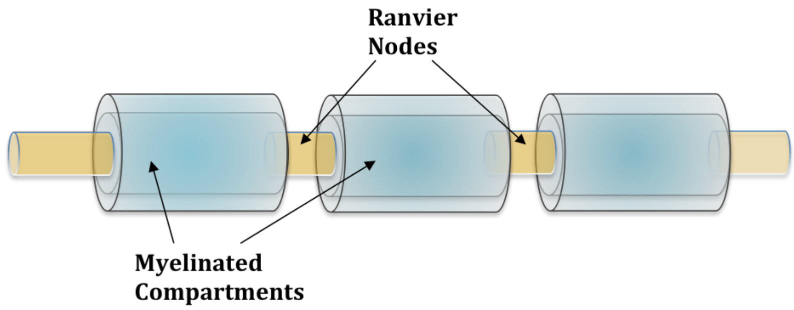

Fig. 1. Simplified geometrical model of a myelinated axon, as a chain of myelinated compartments and Ranvier nodes.

allowing the exchange of ions across the membrane. Hence the myelinated axons can be very long, provided that the length of the myelinated compartments is not greater than the maximum transmission length [1], so that the signal is strong enough to reach the threshold when entering a Ranvier node.

Due to this behavior, the electric potential seems to jump from one Ranvier node to another in myelinated axons, being called "saltatory conduction" [2]. Since it has been experimentally observed, the phenomenon of saltatory conduction has been described [3], [4] and modeled in the literature on several occasions [5] - [8]. However, for an efficient simulation of impulse neural circuits, which are very complex circuits in the central and peripheral nervous system, the axons should be described by reduced order models, able to accurately reproduce the saltatory conduction in low simulation times.

The purpose of this paper is to propose various coupled macromodels for the simulation of the saltatory conduction in myelinated axons with acceptable accuracy, but also to obtain the most appropriate global modal so that it can be included in large scale neuronal circuits. The global model is obtained by concatenating low-order models of myelinated compartments with nonlinear models of the Ranvier nodes. The global reduced order model grasps both phenomena, the one occurring in the myelinated compartments (linear models with spatially distributed parameters) and the one in the Ranvier nodes (nonlinear, compact models).

2. Modeling of components

The standard approach currently used to simulate the saltatory conduction [3], [6], [7] is based on compartmental modeling and is implemented in most neural simulators (GENESIS, NEURON) [10], [11]. The method used here (Fig. 2) replaces the myelinated compartments with reduced order models and concatenates them with 0D models of Ranvier nodes, with accuracy control. Two coupled macromodels are extracted, one as circuits and one as systems. Each of the two formulations for the coupled macromodels implies a specific formulation for the constitutive models.

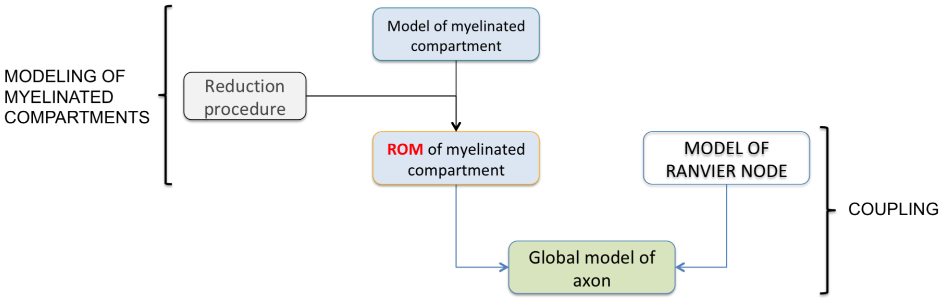

FIG. 2. The procedure proposed for the extraction of a reduced axon model: reduced models of myelinated compartments are coupled with models of Ranvier nodes.

2.1. Modeling of Myelinated Compartments

The reduced models for the myelinated compartments are chosen from a hierarchical series of models previously developed [12]. This series contains models of three spatial geometry classes: 2.5D, 1D and 0D. In each class there are three categories of models: analytical, numerical and reduced order models, hierarchized based on modeling errors, closely related to models' complexity.

Different lengths were considered for the myelinated compartment: $0.25\lambda_0$, λ_0, $2.5\lambda_0$, with $\lambda_0 = 0.215$ mm representing the characteristic length (the length constant of the line). The best model from this series proved to be the analytical 1D model reduced with the vector fitting (VF) technique [13]. Figure 3 (left) shows the electric potential at the beginning (excitation) and at the end of the compartment of length λ_0 before and after reduction (order 3). The excitation potential $e(t)$ is approximated with an expression of two exponentials $e(t) = V_0 + V_m(e^{-t/\tau_1} - e^{-t/\tau_2})$, with $V_0 = -80$ mV, $V_m = 2800$ mV, $\tau_1 = 1$

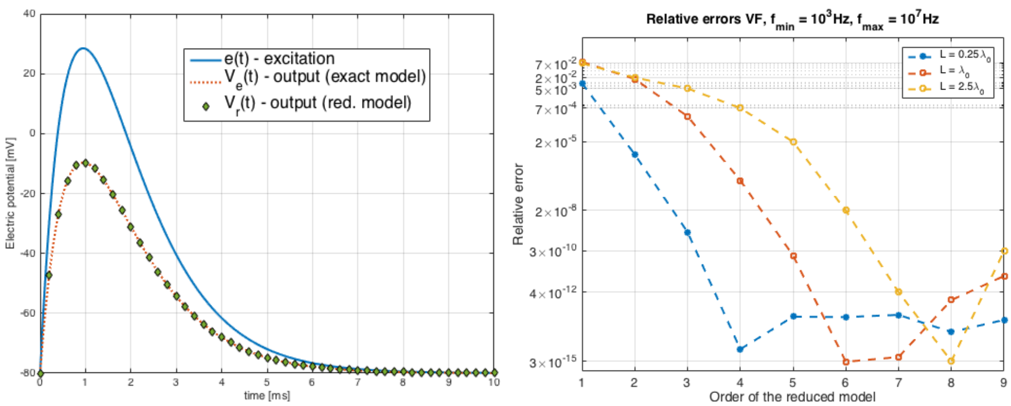

FIG. 3. Left: the electric potential of a myelinated compartment: excitation, at far end before and after the reduction; right: the relative errors of the reduced model with vector fitting.

ms, $\tau_2 = 0.9$ ms. The potential diffuses along the insulated compartment as its amplitude decreases.

Figure 3 (right) shows the relative errors of the reduced 1D analytical model (a multipolar Electric Circuit Element – ECE [14] with three terminals – one ground and the other voltage controlled – with admittances Y_{11} and Y_{12}) with VF, for different line lengths and different orders q. Extremely small errors are obtained for orders ranging from 4 to 8; for larger lengths higher orders q are recommended, but for practical applications a order $q = 3 \div 5$ provides acceptable accuracy. The compartment model used in what follows corresponds to length λ_0 and order 3.

2.2. Modeling of the Ranvier Node

The simplified modeling of the Ranvier nodes membrane has had an intense scientific interest, so that there are several non-linear 0D models, of which the most commonly used are: FitzHugh-Nagumo (FHN) [5], Frankenhaeuser-Huxley (FH) [16], Izhikevich (Iz) [17]. These models can be regarded as low-order approximations of the highly nonlinear Hodgkin–Huxley (HH) model [18], and are preferred in theoretical studies, precisely because of their relative simplicity. However, these non-dimensional reduced models are not able to retain the physical and biological significance of the inner parameters. For this reason, the Ranvier nodes in this study are modeled with the HH model.

The equivalent circuit described by four nonlinear ODEs (1) is shown in Fig. 4. The outside of the cell is considered to have null potential, therefore the state variables are the potential inside the cell and three *gating variables* (characterizing the degree of voltage-gated ion channels opening): n (activation variable for the potassium channel), m (activation variable for the sodium channel) and h (inactivation variable for the sodium channel).

$$\begin{cases} C\frac{\mathrm{d}V}{dt} = -G_K(V - E_K) + -G_{Na}(V - E_{Na}) + i(t) \\ \frac{\mathrm{d}n}{\mathrm{d}t} = \alpha_n(V)(1-n) - \beta_n(V)n \\ \frac{\mathrm{d}m}{\mathrm{d}t} = \alpha_m(V)(1-m) - \beta_m(V)m \\ \frac{\mathrm{d}h}{\mathrm{d}t} = \alpha_h(V)(1-h) - \beta_h(V)h \end{cases} \tag{1}$$

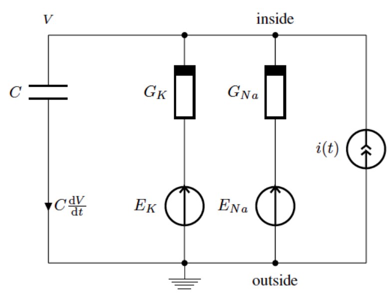

FIG. 4. Equivalent circuit of the HH model for a Ranvier node.

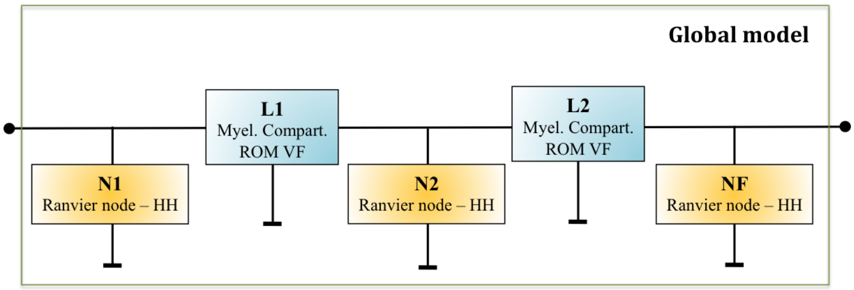

FIG. 5. The coupling of models in the global axon model. A number of Nx–Lx sections are interconnected and the model is completed with a nonlinear block. The figure represents the interconnection of 2 sections Nx–Lx.

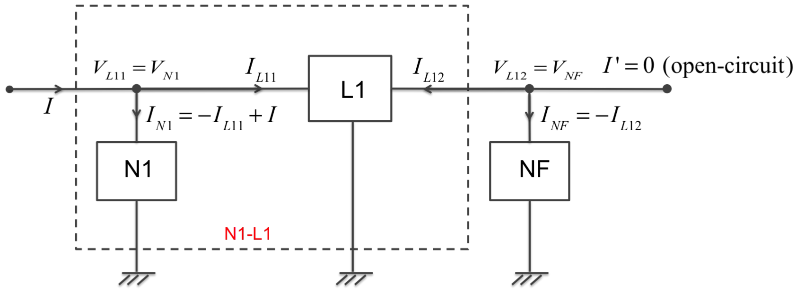

FIG. 6. The macromodel obtained by coupling circuits: N1–L1–NF.

The parameters of the equations have been fitted from experimental data. The model parameters used in this study are from [20].

- The quantity C is a constant value representing the capacitance of the node, the corresponding capacitor being initially charged at a resting potential of a typical value of -62.5 mV.
- $i(t)$ is the input signal that travels and reaches the node.
- G_K and G_{Na} are the conductances of the potassium and sodium channels respectively and they depend nonlinearly with respect to the node potential and the gating variables: $G_K = \bar{G_K} n^4$, $G_{Na} = \bar{G_{Na}} m^3 h$, where $\bar{G_K}$ and $\bar{G_{Na}}$ are constants.
- The gating variables n, m and h are dimensionless quantities between 0 and 1 that describe the potassium channel activation (n), sodium channel activation (m) and sodium channel inactivation (h). The initial values of the gating variables are also known, they correspond to a resting state of the node, in which no signal is traveling: $n_0 = 0.317$, $m_0 = 0.052$, $h_0 = 0.596$.
- Coefficients α and β have known dependencies with respect to the node voltage.
- Each ion species has a equilibrium potential known as batery potential and denoted by E_K and E_{Na} in (1).

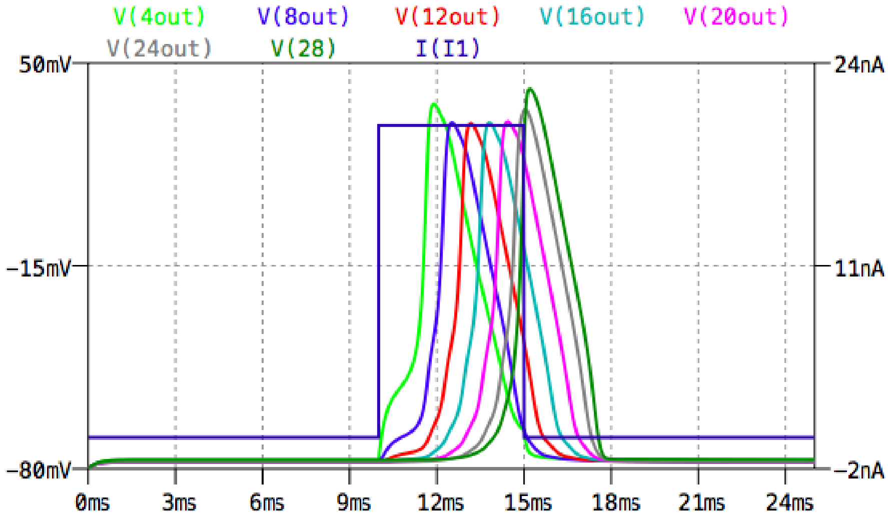

FIG. 7. Circuit macromodel: the electric potential at the output of every nonlinear node for 6 sections Nx–Lx.

The node is thus described by a compact 0D model, it involves no space variables.

3. Coupling formulations

The saltatory conduction implies the simulation of a nonlinear system obtained by coupling linear models of myelinated compartments with nonlinear models of the Ranvier nodes. For an efficient simulation, model reduction is compulsory. The simulation can be done either by coupling reduced models or by formulating the problem with full models and reduce the coupled system. For both alternatives, the components can be described either as circuit netlists (and use circuit simulators, such as Spice) or by using a systemic approach (which can be described in Simulink). In our procedure, we generate a chain of sections Nx-Lx and the model is completed with a nonlinear bloc.

3.1. Circuit coupling

The blocks in Fig. 5 represent sub-circuits. The circuit describing the linear blocks is extracted from the VF reduction procedure and the nonlinear circuit for the Ranvier nodes is the one in Fig. 4. The coupling is illustrated in Fig. 6. The electric potential at the output of every nonlinear node for a 6 sections (Nx-Lx) interconnection is shown in Fig. 7, when the left end of the axon is excited with an impulse current of 20 nA, having a width of 5 ms. We use a circuit macromodel with scaled quantities, this having the advantage of being more numerically stable than a non-scaled model. The solution was obtained using the second-order implicit modified trapezoidal integration method, with a relative tolerance of 0.001. The simulation of 25

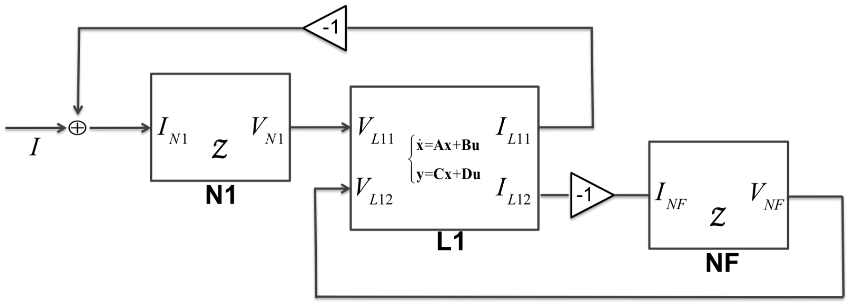

FIG. 8. The systemic coupling for blocks N1–L1–NF.

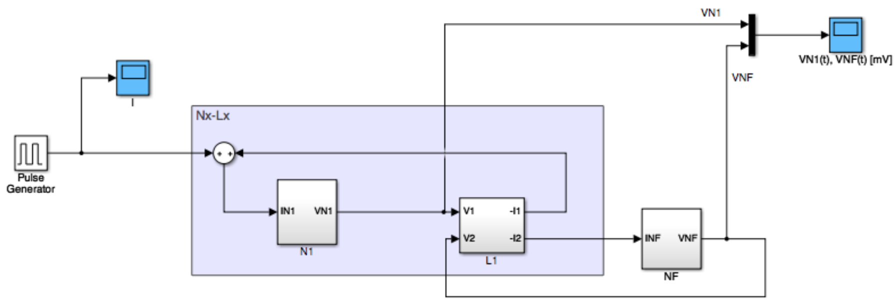

FIG. 9. The coupled model in Simulink: N1–L1–NF.

ms for the circuit corresponding to 6 Nx-Lx sections took 0.35 sec in SPICE. Note that the potential is delayed at every nonlinear node. This behavior describes the phenomena of saltatory conduction and is validated with the literature [19].

3.2. Systemic coupling

The nonlinear circuit can be defined as a nonlinear SISO system having as input the current and the output the electric potential V_N, described by:

$$V_N = \mathbf{Z}(I_N) \tag{2}$$

where **Z** is a nonlinear operator.

The linear block is a state space system, with the state space matrices (A, B, C and D) extracted from the VF reduction procedure.

The coupling of a N1–L1 section (nonlinear system–linear system) with a final nonlinear block NF is illustrated in Fig. 8. The coupling conditions are:

- For the interconnection N1–L1:

$$\begin{cases} V_{L1,1} = V_{N1} \\ I_{N1} = -I_{L1,1} + I \end{cases}$$

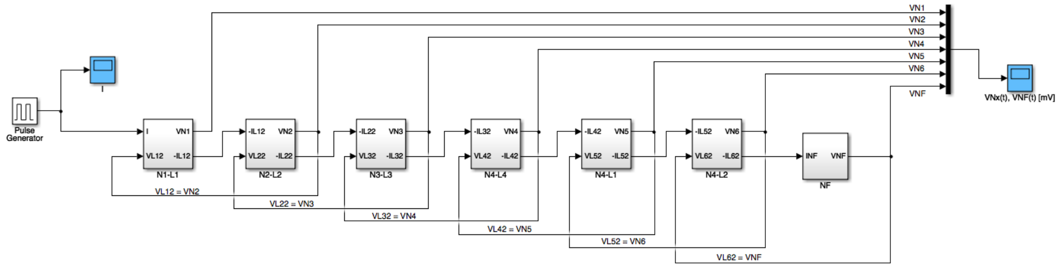

FIG. 10. The model in Simulink, with 6 coupled sections: (6× Nx–Lx)–NF.

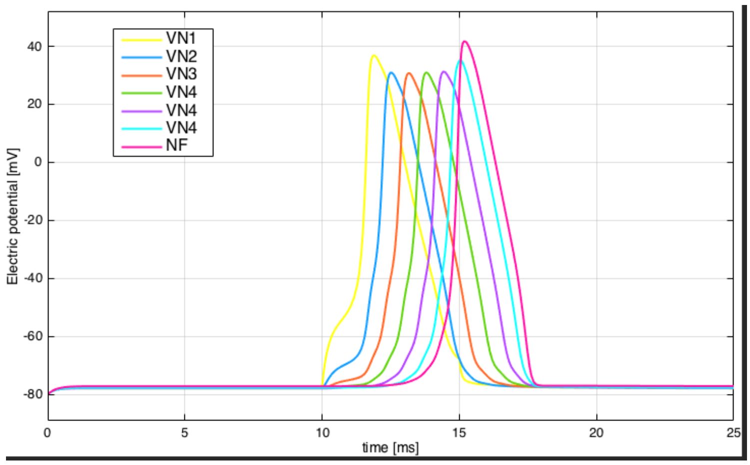

FIG. 11. Systemic macromodel: the electric potential at the output of every nonlinear node for 6 sections Nx–Lx.

- For the interconnection L1–NF:

$$\begin{cases} V_{L1,2} = V_{NF} \\ I_{NF} = -I_{L1,2} \end{cases}$$

The global system obtained has as input the current I and as output the electric potential V_{NF}, while we are also interested in the electric potential at the output of every nonlinear node V_{Nx}. This system, implemented in Simulink/Matlab is shown in Fig. 9. The blocks are sub-systems, where Nx are modeled as nonlinear systems and the time integration is performed in a Matlab procedure and L1 is described by the state space matrices of the reduced order model extracted from VF.

This coupling formulation can be generalized for a chain of many Nx–Lx sections connected with a final NF system. Then for an inner node k the coupling conditions are:

$$\begin{cases} V_{L(k-1),2} = V_{Lk,1} = V_{Nk} \\ I_{Nk} = -I_{L(k-1),2} - I_{k,1} \end{cases}$$

to which the coupling conditions at the beginning and end of the chain are added:

$$\begin{cases} V_{L1,1} = V_{N1} \\ I_{N1} = -I_{L1,1} + I \\ V_{Lx,2} = V_{NF} \\ I_{NF} = -I_{Lx,2} \end{cases}$$

The model with 6 sections Nx–Lx implemented in Simulink is shown in Fig. 10. The electric potentials at the output of every nonlinear block (including the last) are shown in Fig. 11. The solver used is ode15s from Matlab, with variable-step and a relative tolerance of 0.001. The execution time for the simulation of 25 ms for the systemic macromodel with 6 Nx-Lx sections, reported by Simulink is 0.75 sec.

4. **Conclusions**

This paper explores two formulations for the modeling and simulation of the saltatory conduction in myelinated axons, where the global model is obtained by concatenating reduced order models of the myelinated compartments with nonlinear models of the Ranvier nodes. The two models proposed give very similar results. The absolute differences between the maximal values of the seven signals represented in Fig. 7 and Fig. 11 is less than 0.06 mV, corresponding to a relative error of max. 0.2% between the two macromodels. The last node reaches its peak at 15.189 ms for the circuit macromodel and at 15.2 ms for the systemic macromodel.

In the first case, the equivalent circuit for the linear blocks has to be generated by the reduction procedure. Chains with a large number of sections can be easily generated afterwards, with the help of short codes. Yet the success of the solving method for the global model is restricted by the facilities offered by the circuit simulator. Even so, the circuit macromodel simulation can be two times faster than for the systemic model implemented in Simulink.

The systemic formulation can be more advantageous because one could use directly the reduced order models obtained from the model order reduction procedure, without the need to realize them as circuits and thus artificially increase the degrees of freedom of the circuit model, as usually this realisation includes a lot of controlled sources. Moreover, in such an approach the user has direct access to the library of available robust nonlinear ODE solvers. However, in this approach procedures to couple the models are required and they have to be tailored for the specific significance of the input/output signals that are considered for each constitutive part. Also, the lack of code generation procedures makes this model hard to scale up to tens or hundreds of Nx-Lx sections.

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