

Modeling the Saltatory Conduction in Myelinated Axons by Order Reduction

Ruxandra Barbulescu, Daniel Ioan, Gabriela Ciuprina

Abstract—The saltatory conduction is the way the action potential is transmitted along a myelinated axon. The potential diffuses along the myelinated compartments and it is regenerated in the Ranvier nodes due to the ion channels allowing the flow across the membrane. For an efficient simulation of populations of neurons, it is important to use reduced order models both for myelinated compartments and for Ranvier nodes and to have control over their accuracy and inner parameters. The paper presents a reduced order model of this neural system which allows an efficient simulation method for the saltatory conduction in myelinated axons. This model is obtained by concatenating reduced order linear models of 1D myelinated compartments and nonlinear 0D models of Ranvier nodes. The models for the myelinated compartments are selected from a series of spatially distributed models developed and hierarchized according to their modeling errors. The extracted model described by a nonlinear PDE of hyperbolic type is able to reproduce the saltatory conduction with acceptable accuracy and takes into account the finite propagation speed of potential. Finally, this model is again reduced in order to make it suitable for the inclusion in large-scale neural circuits.

Keywords—Saltatory conduction, action potential, myelinated compartments, nonlinear, Ranvier nodes, reduced order models, POD.

I. INTRODUCTION

THE myelinated axons have alternating sequences of myelin covered compartments and Ranvier nodes (Fig. 1). The myelin sheath surrounding the axon made of glial cells works like an insulating layer, increasing the transmission speed of the action potential along the axon and reducing the energy loss across the membrane. However, the diffusion of potential in this section decreases its magnitude at the far end. If the axon were long enough, the signal at the end would not be strong enough to reach the threshold and to trigger an action potential in the next myelinated compartment. The Ranvier nodes are evenly spaced gaps in the myelin sheath, therefore uninsulated and highly rich in ion channels, allowing the exchange of ions required to regenerate the action potential.

This optimal design allows the axons to be no matter how long, provided that the myelinated compartments length is not greater than the maximum transmission length [1], so that the potential is eligible for regeneration when entering a Ranvier node. The transmission of action potential in myelinated axons is called saltatory conduction [2] (from the Latin word *saltare*, which means to hop), because the potential seems to jump from one Ranvier node to another. Since it has been experimentally observed, the phenomenon of saltatory

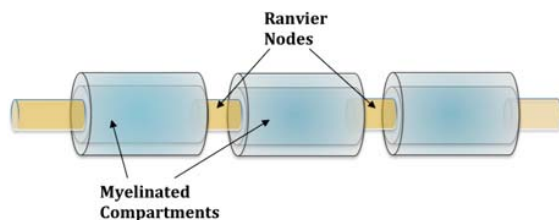


Fig. 1 Simplified geometrical model of a myelinated axon, consisting of a chain of myelinated compartments and Ranvier nodes

conduction has been described [3], [4] and modeled in the literature on several occasions [5]- [7]. However, for the efficient simulation of impulse neural circuits, which are very complex circuits in the central and peripheral nervous system, reduced order models should be developed, able to accurately reproduce the saltatory conduction in low simulation times.

The purpose of this paper is to create a numerical model of myelinated axons, having a minimal order for a reasonable accuracy. The global model is obtained by concatenating reduced order models of myelinated compartments with nonlinear models of Ranvier nodes. A final reduction of the resulting nonlinear system is carried out.

The global reduced order model grasps both phenomena, the one occurring in the myelinated compartments (linear and spatially distributed) and the one in the Ranvier nodes (nonlinear, compact). Due to its low order the simulation times of the containing large-scale neural circuits are improved.

II. AXON MODELING

The standard approach currently used to simulate the saltatory conduction [3], [6], [7] is based on compartmental modeling. This approach, where the myelinated segments are compartmentalized and replaced with the simplest models, then linked with nonlinear 0D models of Ranvier nodes [8] is implemented in most neural simulators (GENESIS, NEURON) [9], [10].

The method proposed (Fig. 2) concatenates reduced models of myelinated compartments with 0D models of Ranvier nodes, with accuracy control.

A. Modeling of Myelinated Compartments

The myelinated compartments are replaced with a reduced model from a hierarchical series of models developed before [11]. This series contains 9 types of models, of three spatial geometry classes: 2.5D, 1D and 0D. In each class there are three categories of models: analytical, numerical and reduced

R. Barbulescu is with the Numerical Methods Laboratory, at University Politehnica of Bucharest, Bucharest, Romania (e-mail: ruxi@lmn.pub.ro).

D. Ioan and G. Ciuprina are with the Numerical Methods Laboratory, at University Politehnica of Bucharest, Bucharest, Romania.

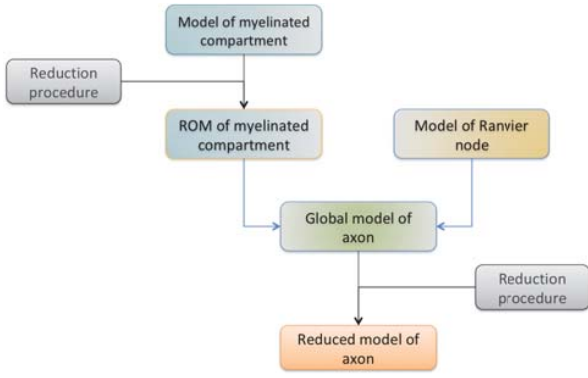


Fig. 2 The procedure proposed for the extraction of a reduced axon model: reduced models of myelinated compartments are connected with models of Ranvier nodes and the global model thus obtained is again reduced

order models. The series is hierarchized based on modeling errors, which are closely related to the complexity of the models.

The best model from this series proved to be the analytical 1D model reduced with the vector fitting (VF) technique [12]. 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). Figure 3 shows the electric potential 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, $\tau_1 = 1$ ms, $\tau_2 = 0.9$ ms. The potential decreases in amplitude as it diffuses along the insulated compartment.

VF is able to reproduce this variation with very small errors. Fig. 4 shows the relative errors of the reduced 1D analytical model (a multipolar Electric Circuit Element – ECE [13] 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. A circuit realizing the rational expression provided by VF is built as described in [14]. The compartment model used in what follows corresponds to length λ_0 and order 3.

B. 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 OD models, of which the most commonly used are: FitzHugh-Nagumo (FHN) [5], Frankenhaeuser-Huxley (FH) [15], Izhikevich (Iz) [16]. These models can be regarded as low-order approximations of the highly nonlinear HodgkinHuxley (HH) model [17], 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.

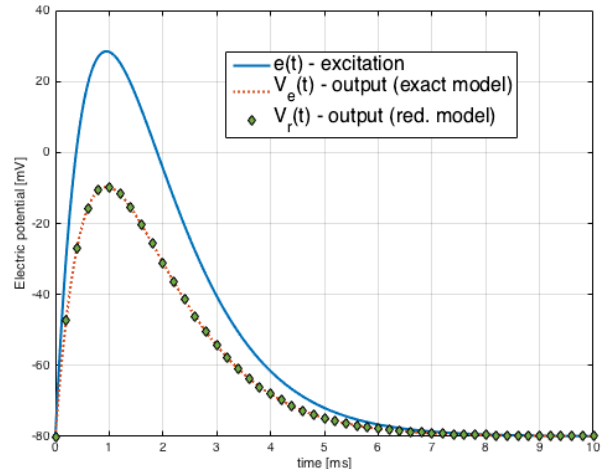


Fig. 3 The electric potential of a myelinated compartment: excitation, at far end before the reduction, at far end after the reduction

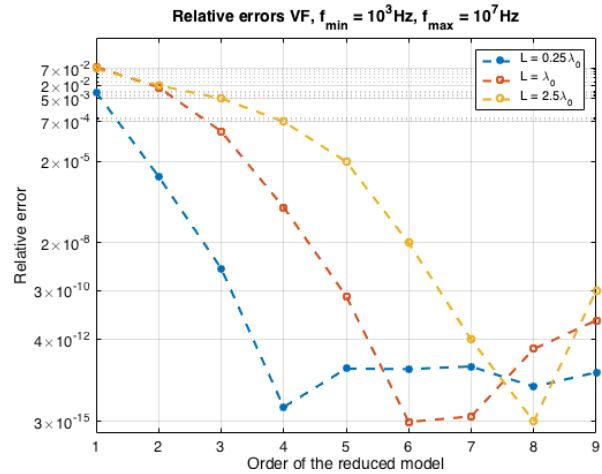


Fig. 4 The relative errors of the reduced model with vector fitting

The mathematical HH model consists of four nonlinear ODEs, in which one describes a linear capacitive effect, having as state quantity the membrane voltage V , and the other three characterize the voltage-gated channels opening, by the state variables n , m and h . They are dimensionless quantities between 0 and 1 that describe the potassium channel activation (n), sodium channel activation (m) and sodium channel inactivation (h).

III. COUPLING

The coupling is carried out in a circuit simulator as shown in Fig. 5. We generate a chain of sections $N \times L_x$ and the model is completed with a nonlinear bloc. The electric potential at the output of every nonlinear node for a 13 sections ($N \times L_x$) interconnection is shown in Fig. 6 describing the saltatory conduction obtained when the left end of the axon is excited with an impulse current of 20 nA, having a width of 5 ms.

IV. REDUCTION OF THE AXON MODEL

The model reduction uses Proper Orthogonal Decomposition (POD), a data-oriented reduction method

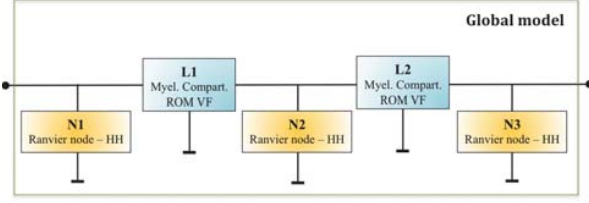


Fig. 5 The coupling of models in the global axon model is carried out in a circuit simulator. The blocks represent sub-circuits

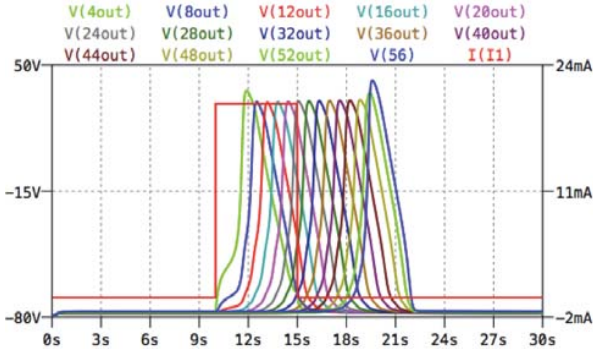


Fig. 6 The electric potential at the output of every nonlinear node for an axon with 13 sections Nx-Lx. The quantities are scaled: the time is in [ms], the potentials are in [mV] and the current in [nA]

based on processing solution samples at different time moments. This approach does not analyze the system in depth, but only some of its characteristics, reflected in its behavior towards a particular input signal. This gives POD the extra advantage of being suitable to nonlinear systems as well.

Consider the nonlinear system described by:

$$\dot{\mathbf{x}} = f(\mathbf{x}(t), u(t))$$

$$\text{and } \mathbf{X} = [\mathbf{x}(t_1), \mathbf{x}(t_2), \dots, \mathbf{x}(t_N)] \in \mathbb{R}^{M \times N} \quad (1)$$

a collection of solution samples $\mathbf{x} \in \mathbb{R}^M$ (the state variables at different moments in time $t_j, j = 1, \dots, N$). The samples matrix is decomposed in singular values (SVD):

$$\mathbf{X} = \mathbf{U}\mathbf{\Sigma}\mathbf{V}^* \quad (2)$$

where the matrices $\mathbf{U}$, $\mathbf{U}\mathbf{U}^* = \mathbf{I}_M$ and $\mathbf{V}$, $\mathbf{V}\mathbf{V}^* = \mathbf{I}_N$ are orthogonal, their columns being the left and right singular vectors of $\mathbf{X}$ and $\mathbf{\Sigma}$ is a diagonal matrix of the singular values of $\mathbf{X}$.

The singular values give information on the linearly independent character of matrix $\mathbf{X}$, thus implicitly on the rank of the matrix. If $\sigma_r > 0$ and $\sigma_{r+1} = 0$, then the rank of matrix $\mathbf{X}$ is r . The SVD factorization expresses $\mathbf{X}$ as a sum of dyadic products $\mathbf{X} = \sigma_1 \mathbf{u}_1 \mathbf{v}_1^* + \sigma_2 \mathbf{u}_2 \mathbf{v}_2^* + \dots + \sigma_r \mathbf{u}_r \mathbf{v}_r^*$.

The decomposition is then truncated by keeping only the first $k \ll r$ most important singular values. SVD allows the identification and elimination of the "almost singular" part of the matrix, that is the lines that are almost linearly dependent. The low-rank approximation matrix $\tilde{\mathbf{X}} = \mathbf{U}_k \mathbf{\Sigma}_k \mathbf{V}_k^*$ has the same size as $\mathbf{X}$ and the rank k .

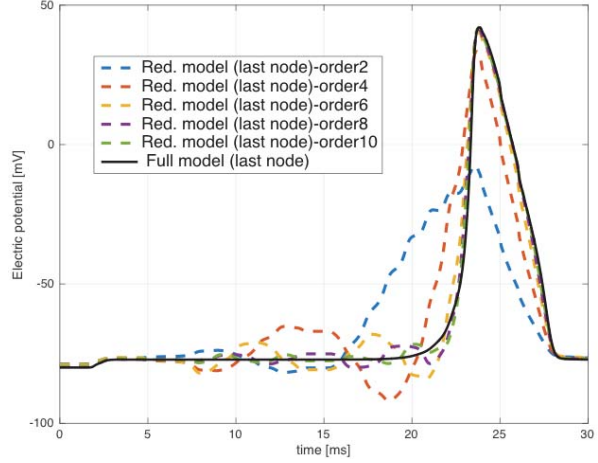


Fig. 7 The response of the full and reduced models of orders 1 ÷ 10. The displayed voltage corresponds to the last Ranvier node in the chain (the 14th)

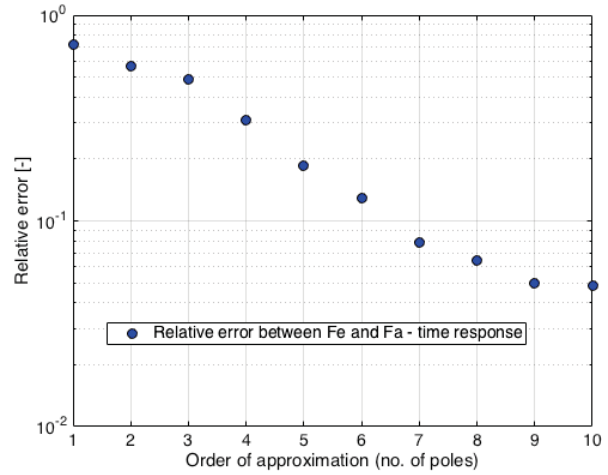


Fig. 8 The relative error of the full and reduced models of orders 1 ÷ 10

The deviation norm between the initial matrix and the truncated matrix satisfies the inequality:

$$\sigma_{k+1}(\mathbf{X}) < \|\mathbf{X} - \tilde{\mathbf{X}}\|_2 < \sigma_k(\mathbf{X}) \quad (3)$$

In this way a subspace is identified from the state space where the solution's time dependency path is located. The other directions of the state space are basically linear combinations of elements in the selected subspace, so they can be approximated with directions from this space.

In our case the matrix $\mathbf{X}$ contains samples for every state variable (V, n, m, h) from the initial model at different time moments, resulting in a dimension of 56×556 and rank 56. The full model is reduced to models of orders 1 to 10; the responses are shown in Fig. 7 for a simulation time of 30 ms. The relative error (Fig. 8) is computed as follows:

$$\varepsilon_{rel} = \frac{\varepsilon_{abs}}{|\max(F_e)|} = \frac{1}{|\max(F_e)|} \sqrt{\frac{\sum_k |F_{e_k} - F_{a_k}|^2}{N}}, \quad (4)$$

where F_e and F_a represent the responses before (exact) and after (approximated) truncation, respectively. The error drops

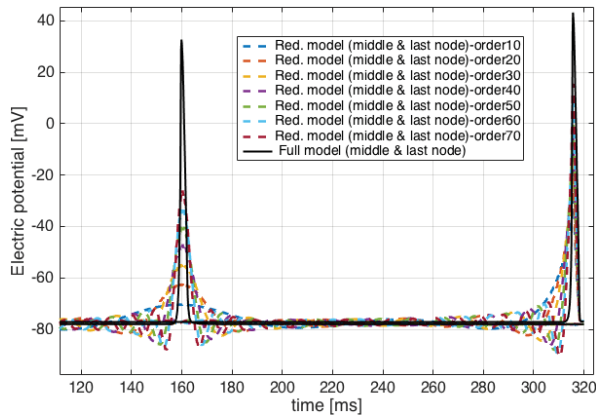


Fig. 9 The response of the full (500 sections Nx-Lx) and reduced models of orders 1 ÷ 70. The displayed voltages correspond to the middle and the last Ranvier node in the chain (the 250th and the 501st)

under 10% from order 7 (relative error of 7.88%).

The exact same results are obtained for all reduction orders for a matrix containing only the electric potential V samples, meaning a matrix X of size 14×556 . This suggests that a proper reduction can be performed without needing information about all the state variables from the initial model, which is advantageous for longer axons, with a larger number of Ranvier nodes.

A real axon can however reach a length of 1 meter and the myelinated compartments have around 2 mm [18]- [20]. Neglecting the length of the nonlinear node leads to axons with up to 500 Nx-Lx sections. The reduction details for models with 100 and 500 Nx-Lx sections are given in Table I. The simulation of 320 ms for the model with 500 sections took 15 minutes on a two-core 3GHz, 2GB of RAM, whereas the reduction of this global model to a model of order 70 needed under 30 seconds. The time responses are shown in Fig. 9. Errors smaller than 10% are obtained from order 10 for the 100 sections chain and from order 63 for the 500 sections chain. The results improve if the period simulated, from which the samples matrix is extracted, is larger.

V. CONCLUSION

The main function of an axon is the transmission of information. The saltatory conduction is a proof for the optimality of the myelinated fiber. In order to efficiently simulate complex circuits, it is important to find the equilibrium between the complexity and the accuracy of the comprised models. The extracted model is able to reproduce the saltatory conduction with controlled accuracy. The myelinated compartments are selected from the series based on the imposed modeling error and the Ranvier nodes are modeled with HH zero-dimensional nonlinear model. The hierarchy of myelinated compartments ordered by their modeling error allows the control of accuracy, which is closely related to the models complexity. The 0D nonlinear models are able to regenerate the signal, so that the resulting reduced model gives control on the inner model parameters (geometrical data, material constants, excitation type and

TABLE I
DETAILS OF THE MODEL REDUCTION FOR GLOBAL MODELS OF 100 AND 500 SECTIONS

Nx-Lx sections	Period simulated	Size of X	Rank of X	Order at which errors drop below 10%
100	250 ms	101×1648	100	10
500	320 ms	501×2049	500	63

value, 0D system parameters). This model is a basis for more complex simulations, of the electric potential measured in the extracellular 3D space of axons and neural circuits.

ACKNOWLEDGMENT

This work has been funded by University Politehnica of Bucharest, through the Excellence Research Grants Program, UPB GEX 2017. Ctr. No. 05/25.09.2017.

REFERENCES

- [1] R. Barbulescu, D. Ioan and J. Ciurea, *Simple 1D models for neuro-signals transmission along axons*, 2016 International Conference and Exposition on Electrical and Power Engineering (EPE), 2016: 313-319.
- [2] A. Huxley and R. Stampeli, *Evidence for saltatory conduction in peripheral myelinated nerve fibres*, The Journal of physiology 108(3), 1949: 315-339.
- [3] R. FitzHugh, *Computation of impulse initiation and saltatory conduction in a myelinated nerve fiber*, Biophysical journal 2.1, 1962: 11.
- [4] I. Tasaki, *Physiology and Electrochemistry of Nerve Fibers*, Academic Press, New York, 1982.
- [5] R. FitzHugh, *Mathematical models of excitation and propagation in nerve*, Chapter 1 (pp. 185 in H.P. Schwan, ed. Biological Engineering, McGrawHill Book Co., N.Y.), 1969.
- [6] F. Rattay et al., *Impact of morphometry, myelination and synaptic current strength on spike conduction in human and cat spiral ganglion neurons*, PloS one 8.11, 2013: e79256.
- [7] A. M. Brown and M. Hamann, *Computational modeling of the effects of auditory nerve dysmyelination*, Frontiers in neuroanatomy 8, 2014.
- [8] J. P. Keener and J. Sneyd, *Mathematical physiology*, Vol.1, New York: Springer, 1998, 2nd ed., 2009.
- [9] J. M. Bower and D. Beeman, *The Book of GENESIS: Exploring Realistic Neural Models with the GENeralNEuralSimulation System*, Second edition, Springer-Verlag, New York, 1998.
- [10] N. T. Carnevale and M. L. Hines, *The NEURON book*, Cambridge University Press, 2006.
- [11] D. Ioan, R. Barbulescu, L. M. Silveira and G. Ciuprina, *Reduced Order Models of Myelinated Axonal Compartments*, 2018, under review.
- [12] B. Gustavsen and A. Semlyen, *Rational approximation of frequency domain responses by vector fitting*, IEEE Transactions on power delivery 14(3), 1999: 1052-1061.
- [13] D. Ioan and I. Munteanu, *Missing link rediscovered: The electromagnetic circuit element concept*, JSAEM Studies in Applied Electromagnetics and Mechanics 8, 1999: 302-320.
- [14] G. Ciuprina et al., *Parameterized model order reduction*, Coupled Multiscale Simulation and Optimization in Nanoelectronics. Springer, Berlin, Heidelberg, 2015: 267-359.
- [15] B. Frankenhaeuser and A. F. Huxley, *The action potential in the myelinated nerve fibre of Xenopus laevis as computed on the basis of voltage clamp data*, The Journal of Physiology 171.2, 1964: 302.
- [16] E. M. Izhikevich, *Simple model of spiking neurons*, IEEE Transactions on neural networks 14.6, 2003: 1569-1572.
- [17] A. L. Hodgkin and A. F. Huxley, *A quantitative description of membrane current and its application to conduction and excitation in nerve*, The Journal of physiology, 117(4), 1952: 500-44.
- [18] M. C. Ford et al., *Tuning of Ranvier node and internode properties in myelinated axons to adjust action potential timing*, Nature communications 6, 2015: 8073.
- [19] S. Grissmer, *Properties of potassium and sodium channels in frog internode*, J Physiol, vol. 381, 1986:119-34.
- [20] N. A. Angel, *Equivalent circuit implementation of demyelinated human neuron in spice*, Master's Thesis, 2011.