Efficient model reduction of myelinated compartments as port-Hamiltonian systems

Ruxandra Barbulescu, Gabriela Ciuprina, Tudor Ionescu, Daniel Ioan, and Luis Miguel Silveira

Abstract The information is transmitted in neurons through axons, many of whom have myelin-covered sections, whose main purpose is to increase the speed of electrical signal transmission. Modeling the myelinated axons in a realistic way, by maintaining the physical meaning of components may lead to complex systems, described by high-dimensional systems of PDEs, whose solution is computationally demanding. Analysis of larger neuronal circuits including multiple myelinated axons therefore requires the generation of equivalent low-order models to control complexity. Such models must preserve the physical interpretation and properties of the original system including its passivity and stability. The axons port-based structure makes them suitable to be modeled as port-Hamiltonian systems. This paper uses a structure-preserving reduction method for port-Hamiltonian systems to reduce the description of a myelinated compartment into a model with comparable accuracy with the previously used vector fitting technique. The reduced system is synthesized into an equivalent passive circuit with no controlled sources and only positive parameters, amenable for inclusion in standard neuronal simulators.

1 Introduction

A myelinated axon (Fig. 1) consists of myelinated sections through which the signal dissipates, which alternate with Ranvier nodes where the signal is regenerated ("saltatory conduction"). To model the transmission of signals through this chain, the phenomena occurring in the Ranvier *nodes* have to be coupled with those in the

Ruxandra Barbulescu, Luis Miguel Silveira
INESC ID/IST Tecnico Lisboa, Universidade de Lisboa, Rua Alves Redol 9, 1000 Lisboa, Portugal, e-mail: ruxi@inesc-id.pt, lms@inesc-id.pt

Gabriela Ciuprina, Daniel Ioan, Tudor Ionescu
Politehnica University of Bucharest, Spl. Independentei 313, 060042, Bucharest, Romania, e-mail: gabriela@lmn.pub.ro, daniel@lmn.pub.ro, tudor.ionescu@acse.pub.ro

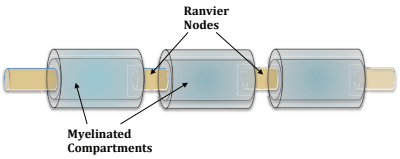

Fig. 1 Simplified geometrical model of a myelinated axon, as a chain of myelinated compartments and Ranvier nodes.

myelinated sections (*internodes*). The underlying mechanisms of a Ranvier node are well described by the Hodgkin & Huxley model [10], or its reduced versions [3].

The most popular approach to model the internodes is represented by the "cable model", described by parabolic 1D PDEs [14], i.e. the RC transmission line equation. In a previous work [11], the authors reduced the internode model with different methods, resulting in a hierarchical series of models of three spatial geometry classes: 2.5D, 1D and 0D and three categories of models: analytical, numerical and reduced order models. The most accurate model proved to be the analytical 1D model reduced with the vector fitting (VF) technique. In [11] the error is computed using a weighted norm, where the weights associated to frequencies are extracted from the spectrum of the standard neuronal signal. This error is suitable to estimate the global accuracy of neuronal signals, since in the typical neuronal spectrum the low frequency components are much more significant than the high frequency ones. The accuracy of the current reduction method is compared with the results in [11].

For the simulation of the saltatory conduction in a whole axon, the internodes were replaced in [4] with the differential equation macromodel extracted from VF, so the equivalent circuit had many controlled sources. This is acceptable when there is no constraint on the reduced circuit, but in some environments dedicated to neuronal simulations, such as NEURON [6], one can only create a circuit with no controlled sources (or a small amount of controlled sources, modeled using Op-Amps) and with positive parameters. In this work we synthesize the reduced system into an equivalent circuit with only positive RLCs and no controlled sources (we call this circuit **ECi+**). We now start from the numerical model, discretizing the transmission line into several segments, each being minimally modeled with lumped parameters (Fig. 2). The resulting circuit is a long network of RC sections having resistive parameters describing longitudinal electrical conduction phenomena through axoplasm, and capacitive and transverse conductive effects through the cell membrane.

This particular model of a myelinated compartment, as a chain of RC cells, is suitable for port-based network modeling, more precisely in the port-Hamiltonian framework. Port-Hamiltonian (pH) systems are widely used in modeling, analysis and control of (multi-)physical systems [16]. Extensive research is done on model order reduction with preservation of properties and/or port-Hamiltonian structure for linear [1], [12] and nonlinear systems [7], [15]. Among these techniques, the time-domain moment-matching procedure is an efficient tool [2], [12]. The reduced model is obtained by constructing a lower degree rational function that approximates the given transfer function and matches it at various interpolation points in the complex plane. This formulation is preferred to the direct reduction of the number of cells of the segmented numerical model, which already is a reduced model.

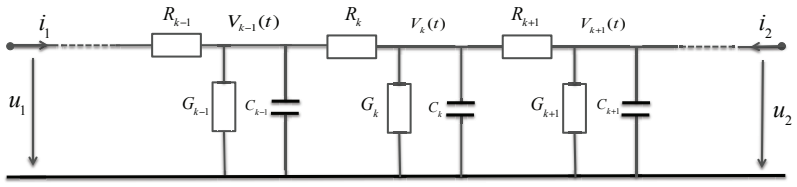

Fig. 2 The segmented model of an internode, a network of RC cells. The companion circuit is generated by the spatial discretization with centered differences of the transmission line equation.

2 Port-Hamiltonian formulation and reduction

The pH representation is based on the energy state space, which represents a natural state space for the equations composing the mathematical models of physical systems. The Hamiltonian gives the total stored energy of the system, whereas the system has boundary ports to interact with the environment, through the exchange of energy. The mathematical representation of a pH system is:

$$\begin{cases} \dot{\mathbf{x}} = (\mathbf{J}-\mathbf{R})\nabla_{\mathrm{x}}\mathrm{H}(\mathrm{x}) + \mathbf{B}u(t) \\ \mathbf{y} = \mathbf{B}^{\mathrm{T}}\nabla_{\mathrm{x}}\mathrm{H}(\mathrm{x}) \end{cases} \tag{1}$$

where $\mathbf{x} \in \mathbb{R}^n$ is the state vector; $\mathrm{H} : \mathbb{R}^n \to [0,\infty]$ is continuously differentiable – the Hamiltonian, describing the internal energy of the system as a function of state; $\mathbf{J} = -\mathbf{J}^{\mathrm{T}} \in \mathbb{R}^{n\times n}$ is the structure matrix (skew-symmetric) describing the interconnection of energy storage elements in the system; $\mathbf{R} = \mathbf{R}^{\mathrm{T}} \geq 0$ is the dissipation matrix describing the energy loss in the system; and $\mathbf{B} \in \mathbb{R}^{n\times m}$ is the port matrix describing how energy enters and exits the system through the m terminals.

Our approach is based on describing the myelinated compartment in Fig. 2 as a pH system (1) and reducing the overall model with structure-preserving moment-matching. We start from the circuit description of the original model (a SPICE netlist) and generate the pH form of this system. Next, the system is reduced by moment-matching. Finally, the equivalent reduced circuit is synthesized from the state-space representation of the reduced system.

We consider the network in Fig 2 as a 2x2 system with input $u = \left[\frac{u_1(t)}{R_1} \;\; i_2(t)\right]^{\mathrm{T}}$ and output $y = [V_1(t) \;\; u_2(t)]^{\mathrm{T}}$. The state space vector consists of the charges of the capacitors $\mathbf{x} = [q_1, q_2, \ldots, q_n]^{\mathrm{T}}$, thus its derivative $\dot{\mathbf{x}} = [i_{C_1}, i_{C_2}, \ldots, i_{C_n}]^{\mathrm{T}}$ is composed of the currents through the capacitors. The Hamiltonian is defined as $\mathrm{H}(\mathrm{x}) = \frac{1}{2}\sum_{k=1}^{n}\frac{1}{C_k}q_k^2 = \frac{1}{2}\mathbf{x}^{\mathrm{T}}\mathbf{Q}\mathbf{x}$ and its derivative with respect to the state variables is a vector of voltages: $\nabla_{\mathrm{x}}\mathrm{H}(\mathrm{x}) = [u_{C_1}, u_{C_2}, \ldots, u_{C_n}]^{\mathrm{T}} = \mathbf{Q}\mathbf{x}$.

In this formulation, $\mathbf{Q}$ is a diagonal matrix $\mathbf{Q} = \mathrm{diag}\left(\frac{1}{C_k}\right)$, the structure matrix $\mathbf{J} = \mathbf{0}$ and the dissipative matrix $\mathbf{R}$ is tridiagonal, having on line k the elements $-\frac{1}{R_k}$, $\frac{1}{R_k} + \frac{1}{R_{k+1}} + G_k$ and $-\frac{1}{R_k}$. The port matrix is $\mathbf{B} = \begin{bmatrix} 1 & 0 & \ldots & 0 \\ 0 & \ldots & 0 & 1 \end{bmatrix}^{\mathrm{T}}$.

3 System reduction

The reduction is based on a moment-matching technique, part of the family of interpolatory methods [2]. A system described by the state matrices $(\mathbf{A},\mathbf{B},\mathbf{C})$ has the transfer function $K(s)=\mathbf{C}(s\mathbf{I}-\mathbf{A})^{-1}\mathbf{B},\ \ K:\mathbb{C}\to\mathbb{C}$. Consider a point in the complex plane that is not in the spectrum of $\mathbf{A}$. The k-order moment of the system with the transfer function K at $s^*\in\mathbb{C}-\sigma(\mathbf{A})$ is defined as:

$$\eta_k(s^*)=\frac{(-1)^k}{k!}\left[\frac{\mathrm{d}^k K(s)}{\mathrm{d}s^k}\right]_{s=s^*}. \tag{2}$$

For a fixed point s^*, a reduced-order system described by the transfer function $\hat{K}$ with the corresponding moments $\hat{\eta}_k(s^*)$ matches the first n^* moments of K if $\eta_k(s^*)=\hat{\eta}_k(s^*),k=\overline{1,n^*}$, which in fact means it matches the coefficients of n^* terms of the Taylor expansion of K [9]. The selection of the interpolation points is important. Whereas selecting n^* moments at a fixed s^* may improve the approximation accuracy, selecting $s_1,\ldots,s_r$ points for a reduced order r and matching the 0-order moments at these points better preserves input-output behaviours. Customary, $s=0$ is chosen to preserve the step response of the given system.

For SISO systems the interpolation conditions are enforced pointwise, but in the MIMO case – where $K(s)$ is a $m\times m$ matrix-valued rational function – full matrix interpolation would translate into $m\times m$ conditions at every interpolation point s^*. This would result in an actual larger order of the reduced system than the initially imposed r. Instead we only interpolate along certain directions $\mathbf{b_k}$ ("right tangential interpolation"). This relaxed notion of interpolation is adequate for an optimal approximation [5]. For an imposed reduced order r we compute the matrix

$$\mathbf{\Pi}=\left[(s_1\mathbf{I}-\mathbf{A})^{-1}\mathbf{B}\mathbf{b}_1\ \ (s_2\mathbf{I}-\mathbf{A})^{-1}\mathbf{B}\mathbf{b}_2\ \ldots\ (s_r\mathbf{I}-\mathbf{A})^{-1}\mathbf{B}\mathbf{b}_r\right]$$

where the vectors $\mathbf{b_1},\mathbf{b_2},\ldots,\mathbf{b_r}$ represent the tangential directions of interpolation.

Since the interpolation points s_k and the tangential directions $\mathbf{b_k}$ are dependent on the reduced model, we use an iterative process to correct the interpolation points and tangential directions until the interpolation conditions are met [7] .

The reduced matrices are computed as in [12]:

$$\mathbf{J}_r=\mathbf{\Pi}^{\mathrm{T}}\mathbf{Q}\mathbf{J}\mathbf{Q}\mathbf{\Pi}\qquad\qquad \mathbf{Q}_r=\left(\mathbf{\Pi}^{\mathrm{T}}\mathbf{Q}\mathbf{\Pi}\right)^{-1}$$
$$\mathbf{R}_r=\mathbf{\Pi}^{\mathrm{T}}\mathbf{Q}\mathbf{R}\mathbf{Q}\mathbf{\Pi}\qquad\qquad \mathbf{B}_r=\mathbf{\Pi}^{\mathrm{T}}\mathbf{Q}\mathbf{B}$$

and they are used to construct the reduced system in the port-Hamiltonian form:

$$\begin{cases}\dot{\mathbf{x}}_r=(\mathbf{J}_r-\mathbf{R}_r)\mathbf{Q}_r\mathbf{x}_r+\mathbf{B}_r u(t)\\ \mathbf{y}=\mathbf{B}_r^{\mathrm{T}}\mathbf{Q}_r\mathbf{x}_r\end{cases}. \tag{3}$$

Such reduced order system matches the 0-order moments of the original system at the chosen interpolation points [13]. The reduction procedure is structure-preserving, in the sense that the reduced system is still in the port-Hamiltonian form, but the matrices have lost some of their properties, for instance $\mathbf{Q}_r$ is not diagonal anymore, $\mathbf{R}_r$ is not tridiagonal, but is still symmetric and positive definite, $\mathbf{B}_r$ is now likely full.

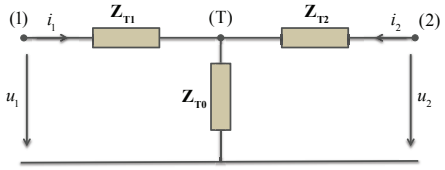

Fig. 3 The circuit realization T scheme for a 2×2 system.

4 Synthesis of equivalent reduced circuit

There is extensive research on circuit realization of systems, either by direct interpretation of the mathematical model or from the state-space form or the system's transfer function [17]. However, in most approaches the resulting circuit is not guaranteed to contain only physically-meaningful elements, due to the presence of negative R, L or C elements or it has a large number of controlled sources.

The transfer function of the reduced system is actually a 2×2 symmetrical matrix of impedances. A possible circuit realization for this is a star (Fig. 3), where the impedances of the subcircuits result directly from either the transfer function components or the state-space matrices of the reduced system.

Each impedance $\mathbf{Z}_{T0}$, $\mathbf{Z}_{T1}$ and $\mathbf{Z}_{T2}$ can be realized through a pole-residue decomposition as the sum of the impedances of r cells connected in series, each composed of a capacitor in parallel with a conductance: $\mathbf{Z}_{xx} = \sum_{k=1}^{r} 1/(C_k s + G_k)$.

The standard general state-space representation of the reduced system (3) is:

$$\begin{cases} \mathbf{C}\dot{\mathbf{x}}_r = -\mathbf{G}\mathbf{x}_r + \mathbf{B}u(t) \\ \mathbf{y} = \mathbf{E}\mathbf{x}_r \end{cases}.$$

The reduced states are the capacitors' voltages in the reduced circuit. To simplify realization, each state should be involved in only one equation. To that end, matrices $\mathbf{C}$ and $\mathbf{G}$ are diagonalized to allow the equations to be separated. Their diagonalization impacts the matrices $\mathbf{B}$ and $\mathbf{E}$, which become full (likely already the case here). In the reduced system this would translate into the circuit as controlled sources. To avoid that, the two matrices are scaled so that all their values are either 1 or -1 and consequently the outputs will be algebraic sums of all the states.

The computations lead to the following relations for the components $\mathbf{Z}_{xx}$, where c_{kk} and g_{kk} ($k = \overline{1,r}$) are the diagonal values of $\mathbf{C}$ and $\mathbf{G}$ (after diagonalization) and the denominator actually represents the scaling of $\mathbf{B}$ and $\mathbf{E}$:

$$\mathbf{Z_{T0}}: \begin{cases} C_k = \frac{c_{kk}}{e_{1k} b_{k2}} \\ G_k = \frac{g_{kk}}{e_{1k} b_{k2}} \end{cases} \quad \mathbf{Z_{T1}}: \begin{cases} C_k = \frac{c_{kk}}{e_{1k}(b_{k1} - b_{k2})} \\ G_k = \frac{g_{kk}}{e_{1k}(b_{k1} - b_{k2})} \end{cases} \quad \mathbf{Z_{T2}}: \begin{cases} C_k = \frac{c_{kk}}{e_{2k}(b_{k2} - b_{k1})} \\ G_k = \frac{g_{kk}}{e_{2k}(b_{k2} - b_{k1})} \end{cases}.$$

In theory the capacitance C_k and the conductance G_k of a cell may have any sign. But the CG pair signs differ only by the signs of the diagonal values of the matrices $\mathbf{C}$ and $\mathbf{G}$. Here $\mathbf{C}$ is the identity matrix, so clearly positive definite. $\mathbf{G}$ is a diagonal matrix that comes from the original system matrix $\mathbf{RQ}$, which is positive definite. Since the reduction procedure guarantees passivity, it will preserve the definiteness

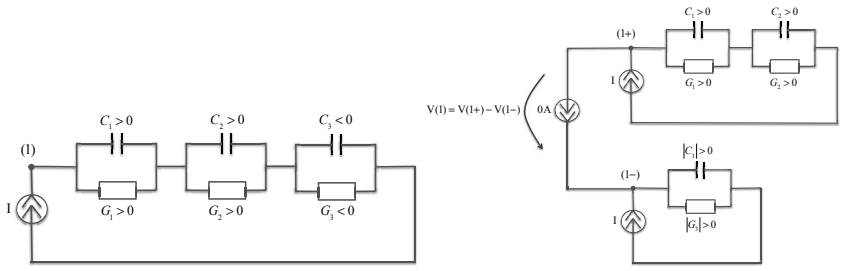

Fig. 4 Synthesis of a component $\mathbf{Z}_{\mathrm{xx}}$ of order 3. (Left): The circuit with positive and negative CG pairs, $y = \mathrm{V}(1)$. (Right): The circuit split into the "positive" and "negative" subcircuits, $y = \mathrm{V}(1+) - \mathrm{V}(1-)$ extracted as the voltage of a null current source that connects the two subcircuits.

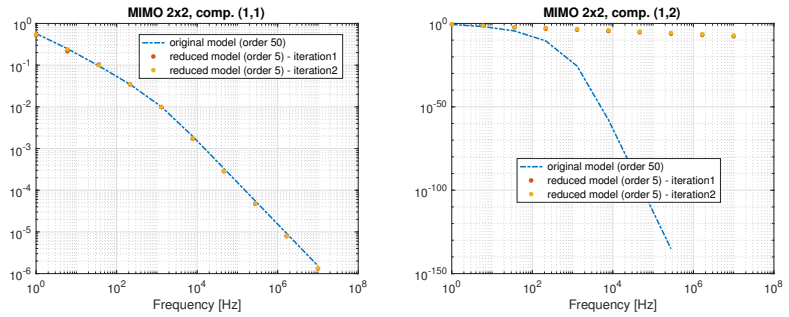

Fig. 5 The frequency responses of the original (50 cells) and reduced (order 5) systems.

of the system matrix. Hence $\mathbf{G}$ has only positive values on the diagonal. This means that for every cell, C_k and G_k are either both positive or both negative.

Consider the synthesized circuit of $\mathbf{Z}_{\mathrm{xx}}$ as in Fig. 4 (left), where the first two cells have positive values and the third has negative values. In Fig. 4 (right) the circuit is split into the "positive" and the "negative" contributions [17]. For the negative subcircuit the signs for both C_k and G_k are reversed and the same excitation is used for both subcircuits. The initial circuit has the same output $y = \mathrm{V}(1)$ as the circuit after splitting, computed as the difference of two voltages $y = \mathrm{V}(1+) - \mathrm{V}(1-)$.

5 Results and Conclusions

Figure 5 shows the frequency responses of the two components of the original (50 cells) and reduced (order 5) systems. The response of the transfer component (1,2) is very far from the original system's, but the values are so small that this graph is in fact not relevant accuracy-wise, because the reduction procedure has an implicit minimization of the H_2 norm. This is proved by almost identical step responses.

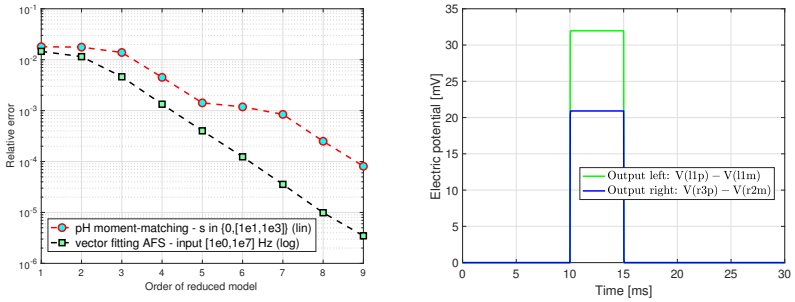

Fig. 6 (Left): The relative error vs. the order of the reduced model for pH and VF methods; $\mathrm{err}_{\mathrm{rel}} = \int_{f_m}^{f_M} w(f) \left\| \mathrm{Z}_{\mathrm{orig}}(f) - \mathrm{Z}_{\mathrm{red}}(f) \right\|_2 \mathrm{d}f / \mathrm{Z}_0$, frequency $f \in [f_m, f_M] = [10^0, 10^7]$ Hz, logarithmically spaced, $w(f)$ is the weight function, Z_0 is the d.c. impedance of the line [11]. (Right): The reproduced output of the reduced circuit (order 3) built in NEURON.

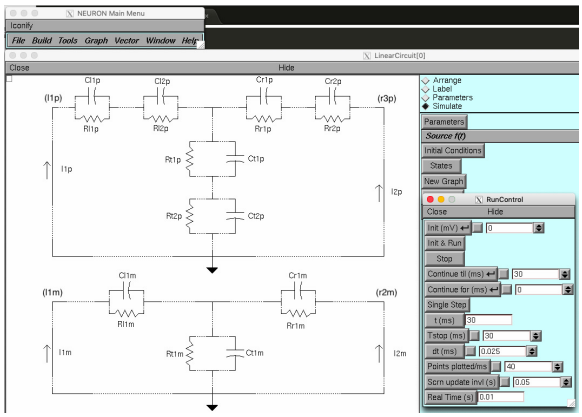

Fig. 7 The **ECi+** circuit extracted from the reduced system of order 3 and reproduced in NEURON. The output is $[\mathrm{V(l1p)} - \mathrm{V(l1m)}; \mathrm{V(r3p)} - \mathrm{V(r2m)}]$.

The relative error is under 2% even for order 1 and is comparable with the one obtained with vector fitting (Fig. 6 left) with the adaptive frequency sampling (AFS) procedure described in [8].

The reduced circuit of order 3 is built in NEURON (Fig. 7) and the output is reproduced in Fig. 6 (right). The input is a rectangular pulse in the left ($i_1 = \mathrm{I1p} = \mathrm{I1m}$) and open-circuit in the right ($i_2 = \mathrm{I2p} = \mathrm{I2m} = 0$). The corresponding outputs copy the shape of the input and the relative difference between the corresponding peaks of the original circuit (50 cells) and the reduced one is between 2% and 3%.

This paper uses a structure-preserving reduction method for pH systems to reduce a myelinated compartment in the model of a neuron. The automatic procedure starts from the netlist of the original model and generates its port-Hamiltonian form. The pH system is reduced using an interpolatory method through moment-matching,

resulting in a reduced system that is still port-Hamiltonian, therefore preserving the passivity and the stability of the original model. The relative error is acceptable even for order 1 (less than 2%). This procedure allows for a trade-off between a good approximation error and the desired structure preservation. The choice of interpolation points is a degree of freedom to be used for potentially improved accuracy in the moment matching reduction. The state-space representation of the reduced system is subsequently synthesized into an equivalent circuit with no controlled sources and only positive RLCs (a **ECi+** circuit). This circuit can be used in neuronal simulators such as NEURON and further integrated into larger models. The current method will further prove beneficial for the reduction of the entire myelinated axon, with the nonlinear HH model of a Ranvier node included.

Acknowledgements This work was partially supported by Portuguese national funds through FCT, Fundação para a Ciência e a Tecnologia, under project UIDB/50021/2020 as well as project PTDC/EEI-EEE/31140/2017.

References

1. Babak Maboudi Afkham and Jan S Hesthaven. Structure-preserving model-reduction of dissipative hamiltonian systems. *Journal of Scientific Computing*, pages 1–19, 2018.
2. Athanasios C. Antoulas. Approximation of large-scale dynamical systems. *SIAM*, 6, 2005.
3. R. Appali, K.K Sriperumbudur, and U. van Rienen. 3d axonal network coupled to microelectrode arrays: A simulation model to study neuronal dynamics. In *2015 37th Annual Int. Conf. of the IEEE Eng. in Medicine and Biology Society (EMBC)*, pages 4700–4704. IEEE, 2015.
4. Ruxandra Barbulescu, Daniel Ioan, and Gabriela Ciuprina. Coupled macromodels for the simulation of the saltatory conduction. *UPB Scientific Bulletin Series C*, 2019.
5. C. Beattie and S. Gugercin. Chapter 7: Model reduction by rational interpolation. In *Model Reduction and Approximation: Theory and Algorithms*, pages 297–334. SIAM, 2017.
6. N. T Carnevale and M.L Hines. *The NEURON book*. Cambridge University Press, 2006.
7. S. Chaturantabut, C. Beattie, and S. Gugercin. Structure-preserving model reduction for nonlinear port-hamiltonian systems. *SIAM J. on Scientific Computing*, 38(5):B837–B865, 2016.
8. Gabriela Ciuprina et al. Vector fitting based adaptive frequency sampling for compact model extraction on HPC systems. *IEEE Transactions on Magnetics*, 48(2):431–434, 2012.
9. I. M Elfadel, D. D Ling, et al. A block rational Arnoldi algorithm for multipoint passive model-order reduction of multiport RLC networks. In *ICCAD*, volume 97, pages 66–71, 1997.
10. A. L Hodgkin and A. F Huxley. A quantitative description of membrane current and its application to conduction and excitation in nerve. *The J. of physiology*, 117(4):500–544, 1952.
11. D. Ioan, R. Bărbulescu, L. M. Silveira, and G. Ciuprina. Reduced order models of myelinated axonal compartments. *Journal of computational neuroscience*, 47(2-3):141–166, 2019.
12. T. C. Ionescu and A. Astolfi. Moment matching for linear port hamiltonian systems. In *50th IEEE Conf. on Decision and Control and Europ. Control Conf.*, pages 7164–7169, 2011.
13. T. C. Ionescu and A. Astolfi. Families of moment matching based, structure preserving approximations for linear port hamiltonian systems. *Automatica*, 49(8):2424–2434, 2013.
14. KA Lindsay et al. An introduction to the principles of neuronal modelling. In *Modern techniques in neuroscience research*, pages 213–306. Springer, 1999.
15. AJ Van Der Schaft. *L2-gain and passivity techniques in nonlinear control*. Springer, 2000.
16. Arjan Van Der Schaft. Port-hamiltonian systems: an introductory survey. In *Proceedings of the international congress of mathematicians*, volume 3, pages 1339–1365. Citeseer, 2006.
17. J.F. Villena and L.M. Silveira. Circuit synthesis for guaranteed positive sparse realization of passive state-space models. *IEEE Trans. on Circuits and Systems I*, 64(6):1576–1587, 2017.