Proc. Annual Meeting of the Austrian Society for Biomedical Engineering 2021
DOI: 10.3217/978-3-85125-826-4-04

MODELING OF ION CHANNELS – A SIDE BY SIDE COMPARISON BETWEEN HODGKIN HUXLEY AND HIDDEN MARKOV APPROACH OF KV1.1

S. Langthaler[1], T. Rienmüller[1], J. Lozanovic Sajic[1,2] and C. Baumgartner[1]

[1]Institute of Health Care Engineering with European Testing Center of Medical Devices, Graz University of Technology, Austria
[2]Innovation Center of the Faculty of Mechanical Engineering, University of Belgrade, Serbia

s.langthaler@tugraz.at

Abstract— *Mathematical models of individual ion channels form the building blocks of complex in-silico tools, enabling the investigation of biophysical mechanisms and simulation of disease processes. We here propose a first simplified hidden Markov Model (HMM) for the voltage-gated potassium channel Kv1.1, taking into account the channels' specific activation and inactivation characteristics close to physiological temperature. The modeling approach and simulation results were compared with an existing Hodgkin Huxley model based on the same experimental data. The newly developed HMM shows a higher accuracy with regard to the activation and inactivation behavior compared to the Hodgkin Huxley approach.*

Keywords— *computational electrophysiology, Hodgkin-Huxley model, hidden Markov model*

Introduction

Single channel models constitute the basis of in-silico tools for simulation of ion current kinetics and action potential alterations in excitable cells. A variety of whole-cell models of different levels of complexity and abstraction have been introduced and have become an integral part in neuroscience and cardiac electrophysiology, enabling the investigation of biophysical mechanisms, simulation of disease processes as well as prediction of therapeutic interventions.[1–4] A high degree of biophysical detail considering the specific gating properties with, at the same time, low computational burden are the fundamental requirements and challenges for a successful integration and application of ion channel models in biomedical research.

Modeling of ion channel kinetics is commonly based on Hodgkin-Huxley (HH) or hidden Markov Model (HMM) descriptions.[4–7] The HH model offers a basic paradigm in which the channel can be either open or closed depending on a set of gates, controlled by a number of gating particles. The kinetic behavior of each gating particle between a permissive and non-permissive state is described as a first order process independent from the states of the other gates. Thus, a possible dependences between activation and inactivation of the channel is not considered.[4,6,8] However, although these models lack the underlying electrophysiological processes of channel gating, HH models closely reproduce the macroscopic currents with a small number of variables and low computational burden, and hence are still widely used in computational electrophysiology.[1,7]

In comparison, Markov Models specify channel states according to the protein conformation and thus take into account the channel-specific gating behavior, which enables a highly accurate and veritable modeling of the channel kinetics.[4,7–9] In particular the investigation of channelopathies or drug-specific effects on the gating behavior through targeted changes in certain conformational states requires the use of such a probabilistic method, where ideally each state would correspond to one protein conformation.[7,10] In practice, however, even complex Markov models are only approximations to the actual channel dynamics with reduced numbers of states in order to keep the computational burden as low as possible.[7]

In this work we present a newly developed hidden Markov based approach for modeling the macroscopic current of Kv1.1 channels, considering for the first time the slow and fast inactivation close to physiological temperature.[11] Kv1.1 (KCNA1) delayed rectifier channels are strongly expressed in the central and peripheral nervous system "regulating" neuronal subthreshold excitability and spike initiation. Mutations of the KCNA1 gene are primarily associated with neurological disorders such as epilepsy and cardiac dysfunctions, but also implicated in tumor development and progression.[12–16] For model parametrization experimental data from patch clamp measurements were used and the model results quantitatively evaluated and compared with an existing HH approach, based on the same experimental data. In addition, a qualitative comparison with regard to the advantages, disadvantages and limitations of the two methods was carried out.

Methods

Electrophysiological data: Comprehensive experimental data on Kv1.1 channels is provided via the ion channel knowledge base Channelpedia (https://channelpedia.epfl.ch).[11] Data used for model evaluation is based on the CHO_FT Rat KV1.1 35°C activation dataset (n = 66 individual cell measurements). Patch-clamp measurements were performed with the automated patch clamp system Nanion NPC-16 Patchliner Quattro (Nanion Technologies, Munich Germany) in whole-cell configuration.[11] Macroscopic currents

Published by Verlag der TU Graz
Graz University of Technology

DOI: 10.3217/978-3-85125-826-4-04

were recorded with activation protocols consisting of a 100 ms long initial- and re-pulse at -80 mV and test pulses starting at -90 mV to 80 mV (increment 10 mV) of 500 ms duration. The applied deactivation protocol consisted of an initial- and re-pulse of -80 mV for 100 ms, a depolarization pulse at 70 mV over 300 ms for activation, followed by 300 ms long deactivation pulses from -80 mV to +30 mV in 10 mV steps.

Hodgkin Huxley model: The Kv1.1 HH model by Ranjan et al. [11] for direct comparison comprises a single activation gate m and inactivation gate h. The macroscopic current is given by:

$$I_{Kv1.1} = \overline{g_{Kv1.1}} m^p h^q (V - E_K) \quad p = q = 1 \qquad (1)$$

with

$$\frac{dm}{dt} = \frac{m_\infty - m}{\tau_m} \quad \text{and} \quad \frac{dh}{dt} = \frac{h_\infty - h}{\tau_h} \qquad (2,3)$$

The model was implemented in the simulation environment MATLAB and differential equations for activation and inactivation gates solved numerically by the Forward Euler method. All model parameters and equations of gating variables can be found in Ranjan et al. [11].

Hidden Markov Model: Considering the specific knowledge on the protein structure and gating of Kv1.1 ion channels, demonstrating a fast activation in response to membrane depolarization and inactivation by both, a slow C and fast N-type inactivation [11,17], a 12-state HMM was defined and parametrized based on the activation curves. Fig. 1 illustrates the final HMM kinetic scheme consisting of 4 closed (C), 1 open (O), 4 inactivated states (I_C), representing the slow inactivation, which can only occur from a closed state, and 3 states depicting the fast inactivation path (I_N).

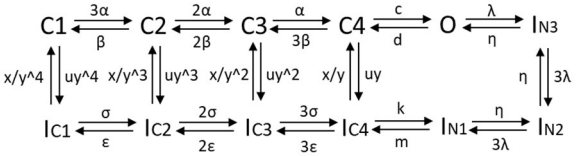

Figure 1: Kv1.1 hidden Markov Model, C: closed, O: open, IC: slow inactivation, IN: fast inactivation

Forward transition rates α, λ, σ and backward transitions β, η, ε are voltage-dependent and described by first order differential equations:

$$\alpha(V) = \alpha_1 . exp\left(\frac{V}{\alpha_2}\right) \qquad (4)$$

$$\beta(V) = \beta_1 . exp\left(\frac{-V}{\beta_2}\right) \qquad (5)$$

where α_i and β_i represent specific gating parameters and V the applied voltage. c, d, m, k and x, y and u denote constants without voltage-dependence. As P_o defines the probability of a channel being in the open state, the time evolution of the open probability is given by equation 6:

$$\frac{dP_O}{dt} = P_{C_4}(t).c + P_{I_{N3}}(t).\eta - P_O(t).(d + \lambda) \qquad (6)$$

where the first two terms represent all transitions entering the open state and the rightmost term all transitions leaving the open state.
The open probability P_o, the ion channel number N_c, the single channel conductance $g_{Kv1.1}$ and reversal potential E_K allow the calculation of the channels' macroscopic current:

$$I_{Kv\ .1} = g_{Kv1.1} N_c P_O (V - E_K) \qquad (7)$$

Parameterization of the rate constants is based on the averaged activation data (n = 66 single cell measurements) using a particle swarm optimization approach (MATLAB, Global Optimization Toolbox). Since the HMM approach models the current through a single ion channel, the number of ion channels has to be estimated for simulation of the macroscopic current. For the given dataset the channel number was determined to be N_c = 8987. The final model parameters are listed in Tab. 1.

Table 1: Parameters of the Kv1.1 HMM

Rate constants and parameters					
α_1	900 s^{-1}	λ_1	49.83 s^{-1}	σ_1	1049.7 s^{-1}
α_2	0.02 V	λ_2	2.94 V	σ_2	522.68 V
β_1	77.35 s^{-1}	η_1	51.18 s^{-1}	ε_1	1 s^{-1}
β_2	0.0441 V	η_2	1.1024 V	ε_2	944.2 V
c	108840 s^{-1}	k	3685 s^{-1}	x	78.04 s^{-1}
d	37851 s^{-1}	m	42310 s^{-1}	$g_{Kv1.1}$	10 pS
u	1*10^{-8} s^{-1}	y	181.39	E_K	0.065 V

Model evaluation: Accuracy of fitting results was quantified using the averaged root mean square error values (RMSE) over all voltage steps for both approaches, see Eq. 8.

$$RMSE = \sqrt{\sum (I_{\mathrm{Kv1.1\_model}}(t) - I_{\mathrm{measured}}(t))^2 / N} \qquad (8)$$

Results

Model simulation of activation protocols: Fig. 2a and 2b illustrate the simulated activation curves with the HMM and HH approach over all voltage-levels. Note that the figures represent the normalized currents, since the original HH model was derived from the normalized activation curves only. The newly developed HMM simulates the measured whole-cell currents with high accuracy. In particular, the fast inactivation can be modeled with high precision compared to the HH approach which demonstrates a too strong and prolonged inactivation ($RMSE_{HMM\_act}$ = 0.017 vs $RMSE_{HH\_act}$ = 0.0355). A comparison of both models is shown in Fig. 2c, revealing the normalized current at 50 mV with different fitting results ($RMSE_{HMM\_act}$ = 0.0145 vs $RMSE_{HH\_act}$ = 0.0287).

Published by Verlag der TU Graz
Graz University of Technology

DOI: 10.3217/978-3-85125-826-4-04

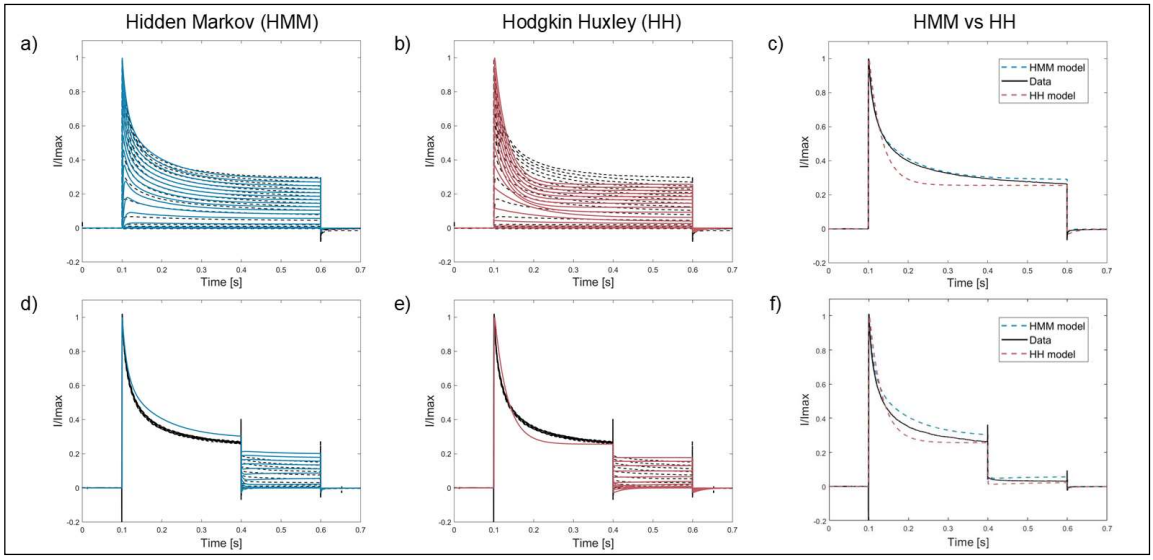

Figure 2: Normalized currents of the HHM and HH model over all voltage levels for a,b) activation $RMSE_{HMM\_act}$ = 0.017, $RMSE_{HH\_act}$ = 0.0355) and d,e) deactivation $RMSE_{HMM\_deact}$ = 0.0423, $RMSE_{HH\_deact}$ = 0.0425) measurements. Comparison of the normalized macroscopic current between HH and HMM for activation at +50 mV c) and for deactivation measurements at -30 mV f).

Model simulation of deactivation protocols: In addition, the measured deactivation curves were simulated and compared for model evaluation (see Fig. 2d-e). In contrast to the activation data, the deactivation currents cannot be simulated as precisely, showing greater deviations and an overestimation of the current especially at higher voltage levels (0 to 30 mV). However, fitting results of the HMM are comparable to the HH model with $RMSE_{HMM\_deact}$ = 0.0423 vs $RMSE_{HH\_deact}$ = 0.0425. Fig. 2f shows a comparison at -30 mV of both approaches ($RMSE_{HMM\_deact}$ = 0.0416 vs $RMSE_{HH\_deact}$ = 0.0423).

Qualitative comparison between the HH and HMM approach: The models represent completely different approaches in terms of model derivation, optimization and simulation. Tab. 2 outlines important modeling parameters and features that were taken into account and rated qualitatively, such as computational burden, model complexity or experimental data required for model parametrization.

Table 2: Comparison of the HH and HMM approach

	HH	HMM
model accuracy	(<<) +	+ (>>)
explainability of channel gating	+	+++
flexibility and adaptability	+	+++
model complexity	+	+++
comp. burden optimization	++	+++
comp. burden simulation	+	++
experimental data for model parametrization	+++	+++ (>>)

Assessment of methods: low (+) to high (+++) scores

Discussion

Single channel modeling constitutes a central part in computational electrophysiology. Extensive experimental investigations and the growing body of knowledge on ion channels enable the development of detailed models, simulating the specific gating behavior and bioelectric properties of ion channels.
We here proposed a new, simplified hidden Markov model of the voltage-gated potassium channel Kv1.1 close to physiological temperature (35°C) and compared the simulation results with a previously developed HH model. The developed HMM exceeds the accuracy of the HH model for the activation, inactivation and deactivation kinetics in terms of fitting the experimental data. However, the model showed less accuracy with regard to the deactivation characteristics. Thus, in a next step more focus should be taken on the deactivation path e.g. by consideration of deactivation protocols in model parametrization in order to further improve the validity of this initial model.
In general, by considering the protein structure and underlying gating mechanisms, HMMs provide a more accurate and reliable approach compared to HH. The kinetic schemes, depicting the transitions between different conformational states offer a better explainability and enable the investigation of specific modifications in the opening and closing behavior of the channel. Moreover, since HMM model the single channel dynamics they also offer a high degree of flexibility, allowing the application to different datasets with varying current amplitudes by adapting the number of ion channels. In contrast, HH models represent the macroscopic current and are only valid for a specific dataset. Hence, the adoption to other experimental data, sample populations or cells with varying ion channel composition, in particular without appropriate reparameterization is almost not possible.

Published by Verlag der TU Graz
Graz University of Technology

DOI: 10.3217/978-3-85125-826-4-04

Nevertheless, the high level of detail and complexity of HMM results in a huge number of parameters and a set of differential equations which increases the computational cost for both parametrization and simulation, and thus represents the major limitation of HMMs. Hence, various simplifications by reducing the number of states are proposed in order to keep the computational burden as low as possible, while maintaining the complex protein structure and accurately estimating the measured ion current. Such simplified models, as the one proposed, are rather phenomenological than representing the actual conformational states and are used, similar to HH models, to deterministically simulate the measured macroscopic currents from whole-cell measurements.[1,7]
In case of phenomenological modeling the experimental data required for model parametrization is comparable to that of HH models. However, in order to fully characterize the kinetic properties and improve the validity of HMMs, extensive experimental investigations are necessary including, for example, single channel patch clamp measurements, determination of fast and slow inactivation as well as possible cross links, or structural studies to gain a deeper knowledge on the actual protein conformation. All this together increases the experimental effort for HMM validation enormously compared to HH approaches.

We can summarize that both modeling approaches have strong advantages as well as disadvantages, and should always be selected with regard to the respective application. While HH models still represent the golden standard in neuroscience, offering a simple to use method with low computational burden and high integrability into complex cell models, HMMs are mainly considered in biomolecular and pharmacological research, better addressing the random nature of channel gating as the transitions of a channel between the different conformational states is represented by a stochastic process. Thus, HMMs implemented in whole cell applications with sufficient complexity and lower computational load have the potential to further improve the reliability and validity of such cell models and provide a valuable tool in the field of next generation in-silico electrophysiology.

References

[1] Andreozzi E, Carannante I, et al. Phenomenological models of Na V 1.5. A side by side, procedural, hands-on comparison between Hodgkin-Huxley and kinetic formalisms. Sci Rep. 2019;9: 17493. doi:10.1038/s41598-019-53662-9

[2] Yarov-Yarovoy V, Allen TW, et al. Computational Models for Predictive Cardiac Ion Channel Pharmacology. Drug Discov Today Dis Models. 2014;14: 3–10. doi:10.1016/j.ddmod.2014.04.001

[3] Beheshti M, Umapathy K, et al. Electrophysiological Cardiac Modeling: A Review. Crit Rev Biomed Eng. 2016;44: 99–122. doi:10.1615/CritRevBiomedEng.2016016454

[4] Nelson ME. Electrophysiological models of neural processing. Wiley Interdiscip Rev Syst Biol Med. 2011;3: 74–92. doi:10.1002/wsbm.95

[5] Maffeo C, Bhattacharya S, et al. Modeling and simulation of ion channels. Chem Rev. 2012;112: 6250–6284. doi:10.1021/cr3002609

[6] Sigg D. Modeling ion channels: Past, present, and future. J Gen Physiol. 2014;144: 7–26. doi:10.1085/jgp.201311130

[7] Sterratt D, Graham B, et al. Principles of Computational Modelling in Neuroscience. Cambridge University Press, New York. Jun 2011. ISBN 978-0-521-87795-4

[8] Carbonell-Pascual B, Godoy E, et al. Comparison between Hodgkin-Huxley and Markov formulations of cardiac ion channels. J Theor Biol. 2016;399: 92–102. doi:10.1016/j.jtbi.2016.03.039

[9] Fink M, Noble D. Markov Models for Ion Channels: Versatility versus Identifiability and Speed. Philosophical Transactions: Mathematical, Physical and Engineering Sciences. 2009;367: 2161–2179.

[10] Lampert A, Korngreen A. Markov modeling of ion channels: implications for understanding disease. Prog Mol Biol Transl Sci. 2014;123: 1–21. doi:10.1016/B978-0-12-397897-4.00009-7

[11] Ranjan R, Logette E, et al. A Kinetic Map of the Homomeric Voltage-Gated Potassium Channel (Kv) Family. Front Cell Neurosci. 2019;13. doi:10.3389/fncel.2019.00358

[12] D'Adamo MC, Liantonio A, et al. Kv1.1 Channelopathies: Pathophysiological Mechanisms and Therapeutic Approaches. Int J Mol Sci. 2020;21. doi:10.3390/ijms21082935

[13] Ovsepian SV, LeBerre M, et al. Distinctive role of KV1.1 subunit in the biology and functions of low threshold K(+) channels with implications for neurological disease. Pharmacol Ther. 2016;159: 93–101. doi:10.1016/j.pharmthera.2016.01.005

[14] Glasscock E. Kv1.1 channel subunits in the control of neurocardiac function. Channels. 2019;13: 299–307. doi:10.1080/19336950.2019.1635864

[15] Ouadid-Ahidouch H, Chaussade F, et al. KV1.1 K(+) channels identification in human breast carcinoma cells: involvement in cell proliferation. Biochem Biophys Res Commun. 2000;278: 272–277. doi:10.1006/bbrc.2000.3790

[16] Jang SH, Ryu PD, et al. Dendrotoxin-κ suppresses tumor growth induced by human lung adenocarcinoma A549 cells in nude mice. J Vet Sci. 2011;12: 35–40. doi:10.4142/jvs.2011.12.1.35

[17] Hasan S, Megaro A, et al. Electromechanical coupling of the Kv1.1 voltage-gated K+ channel is fine-tuned by the simplest amino acid residue in the S4-S5 linker. Pflugers Arch. 2020;472: 899–909. doi:10.1007/s00424-020-02414-0

Published by Verlag der TU Graz
Graz University of Technology