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T. Gerrits and C. Gillmann (Poster Chairs)

Poster

Optimization of a Parametrized, Time-Dependent Hidden Markov Model by Example of an Electrophysiological Cancer Cell

P. Waldert[1†], S. Langthaler[2], T. Rienmüller [3] B. Kantz[1] and T. Schreck[1]

[1] Institute of Visual Computing, Graz University of Technology
[2] Diagnostics and Research Institute for Pathology, Medical University of Graz
[3] Institute of Biomechanics, Graz University of Technology

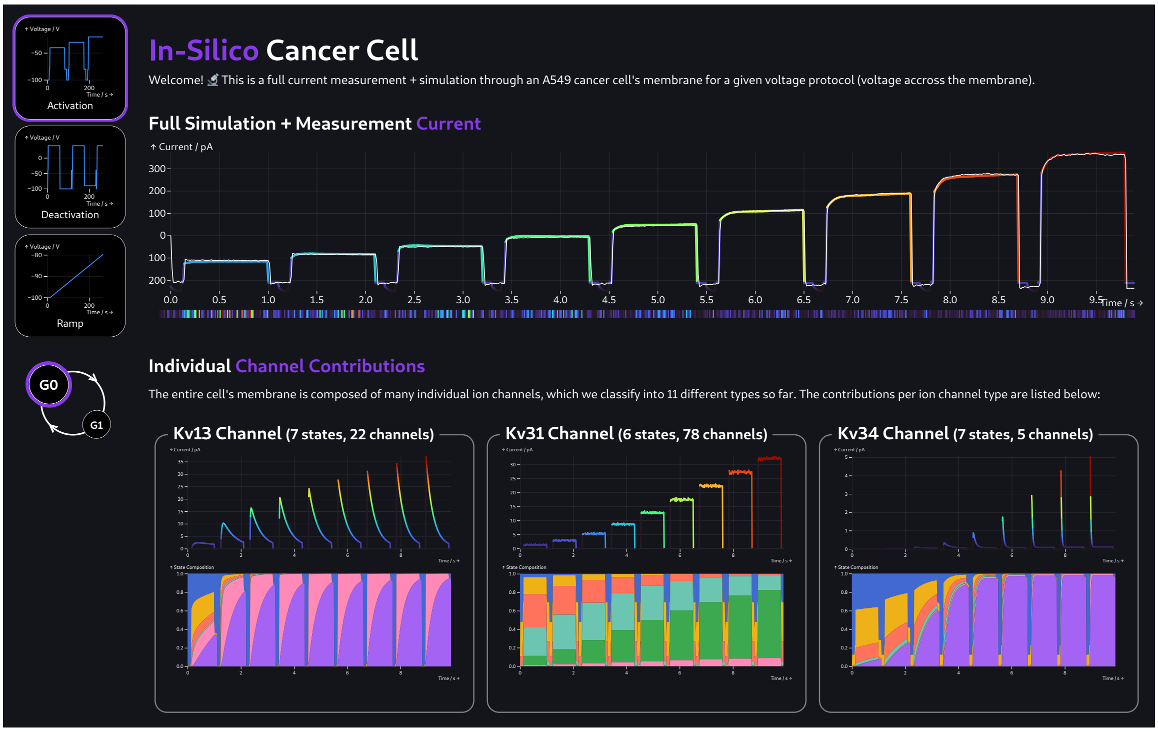

Figure 1: Live, In-Browser Cell Simulation Interface including Per-Cell State Progression and Current Contributions.

Abstract

*Lung cancer is one of the most widespread pathologies worldwide and its mechanisms, specifically at the level of individual cells, are not well understood. We improve on the A549 electrophysiological cancer cell model introduced in [LRS*21; LZR*24], combining numerical methods with an efficient implementation to reduce simulation time to a level where it is feasible for live interaction. More specifically, we were able to accelerate the simulation with adaptive timestepping and a highly efficient implementation in the Rust programming language, while we also managed to approach the corresponding inverse problem using a quadratic program, solving it within milliseconds. We introduce a visualisation approach of the entire model in the form of a live simulation dashboard available at `https://in-silico.hce.tugraz.at/`, running directly in the browser.*

CCS Concepts

• ***Computing Methodologies*** → ***Modeling and Simulation;*** • ***Human-Centered Computing*** → *Visual Analytics;*

1. Introduction

The mechanisms behind lung adenocarcinoma, specifically those of individual A549 cells (cf. Figure 2), are not well understood. Computational techniques can help to gain more insight on the behaviour of these cancer cells. A single cell's membrane consists of multiple ion channels, categorized into $M \in \mathbb{N}$ different types. In electrophysiology, ion channels are usually represented by a Hodgkin-Huxley model [SGG*23; ACD*19]. In our model however, each ion channel is represented in one of $N_{s,k} \in \mathbb{N}$ states,

† Corresponding Author. Email: peter.waldert@tugraz.at.

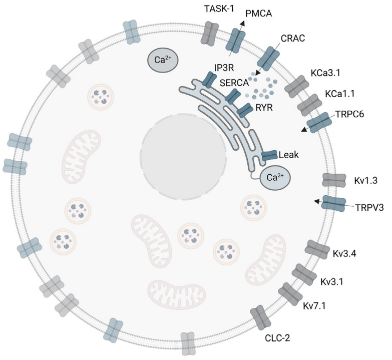

Figure 2: Schematic depiction of the cancer cell and its channels, source: [LZR*24].

which, in physical terms, is related to a positional configuration of a protein within the ion channel. Only some states can be observed directly, and its development only depends on the one previous state. Hence, we are working with a Hidden Markov Model (HMM). For many ion channel categories, their corresponding transition probabilities are voltage or ion-concentration dependent, significantly impacting the simulation performance (runtime).

The whole cell current $I : T \to \mathbb{R}$ over time $t \in T \subset \mathbb{R}^+$ is then obtained as the sum of all individual channel contributions $I_k, k \in \{1,\dots,M\}$ over $M \in \mathbb{N}$ channel types

$$I(t) := \sum_{k=1}^{M} N_k I_k(t) = \sum_{k=1}^{M} N_k g_k p_{o,k} \left(V(t) - E_k\right), \tag{1}$$

where N_k is the number of channels of type $k \in \{1,\dots,M\}$, g_k is the respective ion channel's conductivity, $p_{o,k} \in [0,1]$ is the probability of observing the channel in a state where an ion current can flow ("open states"), $V : T \to \mathbb{R}$ is the voltage across the membrane and $E_k \in \mathbb{R}$ the reversal potential.

When regarding the cell model as a whole, the number of ion channels N_k per type k may be put into a configuration vector $\boldsymbol{N} \in \mathbb{N}_0^M$ and the total simulated current I sampled at (dynamically adjusted) measurement points can be expressed as a product $\boldsymbol{I} = \sum_{k=1}^{M} N_k \boldsymbol{I_k} = R\boldsymbol{N}$ where $R \in \mathbb{R}^{N_t \times M}$ is the matrix of all current measurements per channel type. Given the individual ion channel type models' parameters, which we know from literature [e.g. HZL*14], the question that remains is how many channels there are of each type to fit the measurements. We solve this problem using a number of optimization approaches, comparing them quantitatively to propose a best fit for our conditions. The best performance for our use case is obtained using the *Clarabel* solver [GC24] upon formulation of the inverse problem as a quadratic program.

2. Methods

We simulate the coupled, time-dependent Hidden Markov Model (HMM) using a straightforward numerical Forward Euler scheme and visualise the results in a dashboard (cf. Figure 1) to make the process more understandable. In this case, the full model encapsulates $M = 11$ sub-model routines for each channel type, where each channel's time- and voltage-dependent transition matrix is collected from the literature [LRS*21]. The coupled model and all channels are implemented in Rust, whereas the interface components are written in TypeScript. The entire source code is freely available on GitHub and reusable through three different channels: the simulation interface (powered by compilation to WebAssembly), the Rust linkable library and a Python package (simply run: `pip install in-silico-cancer-cell`). Our aim behind a distribution in this way is to make the topic and simulation as accessible as possible.

3. Conclusion

Efforts to further enhance and complete the first electrophysiological cancer cell model simulation were fruitful, resulting in a new library implementation, an improved inverse problem solution technique and a live in-browser simulation dashboard. Numerically, the stability of the simulation varies greatly with the time step state change tolerance Δ^{tol}, this could be improved using a higher-order integration scheme. There are also many ideas for further customizations that would improve the live simulation dashboard, opening up future usage perspectives.

Acknowledgements

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