Real-time interaction with an electrophysiological cancer cell model

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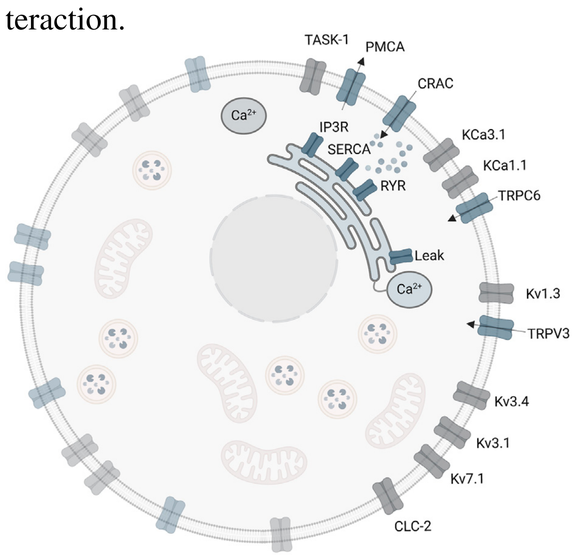
Introduction

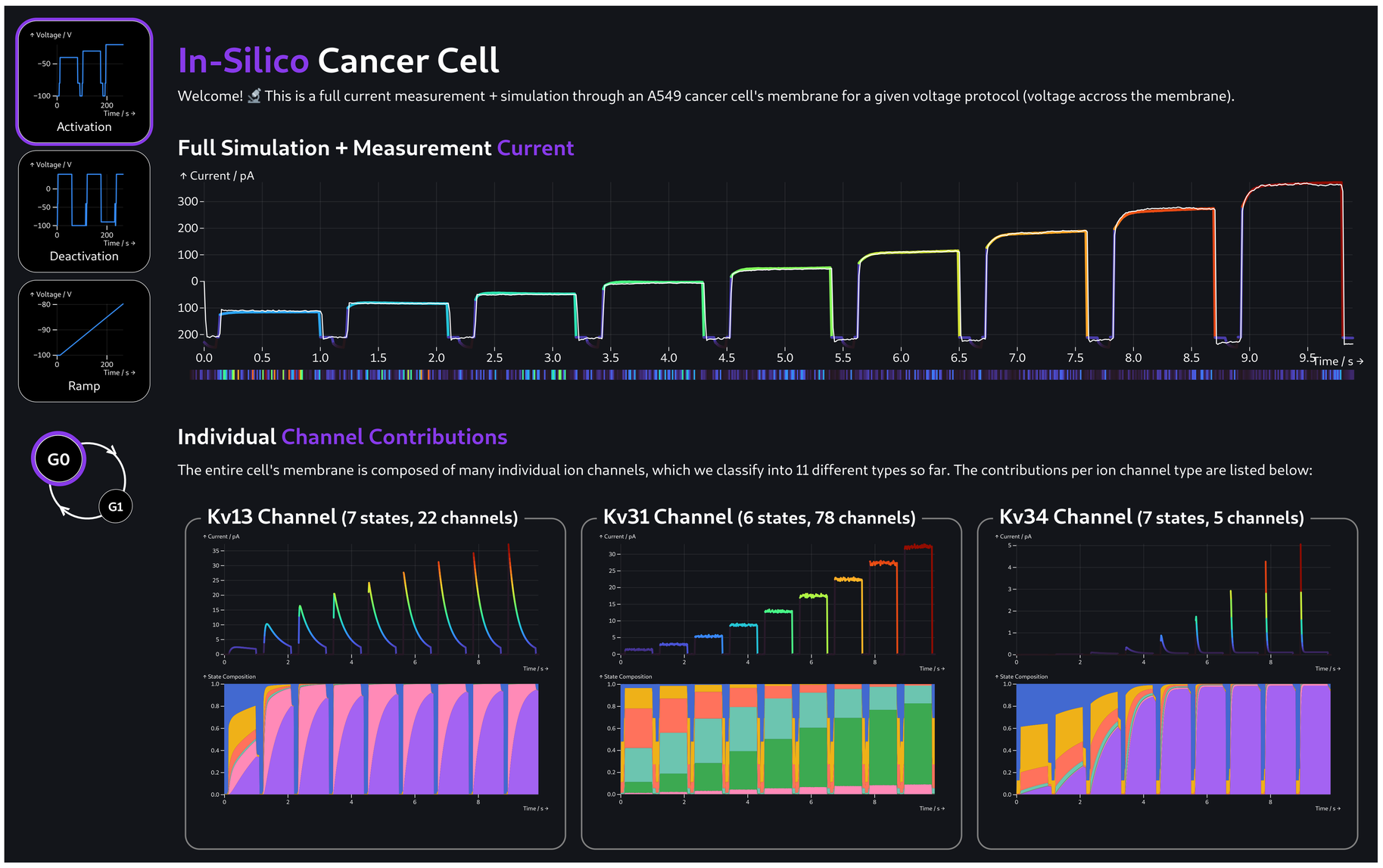
We improve on the A549 electrophysiological cancer cell model introduced in [1, 2], combining numerical methods with an efficient implementation to reduce simulation time to a level where it is feasible for live interaction.



Schematic depiction of the cell, source: [2]

We accelerated the simulation with adaptive timestepping and a highly efficient implementation in the Rust programming language. The corresponding inverse problem is expressed as a quadratic program, solving it within milliseconds. We introduce a visualisation approach of the entire model: a live simulation dashboard available online, running directly in the browser.

Live, In-Browser Cell Simulation Interface



This interface is available online via in-silico.hce.tugraz.at, try it out!

Model

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

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

At each time step, the next state $\boldsymbol{s}_{k,n+1} \in [0,1]^{N_{s,k}}$ of the k-th channel type is obtained by

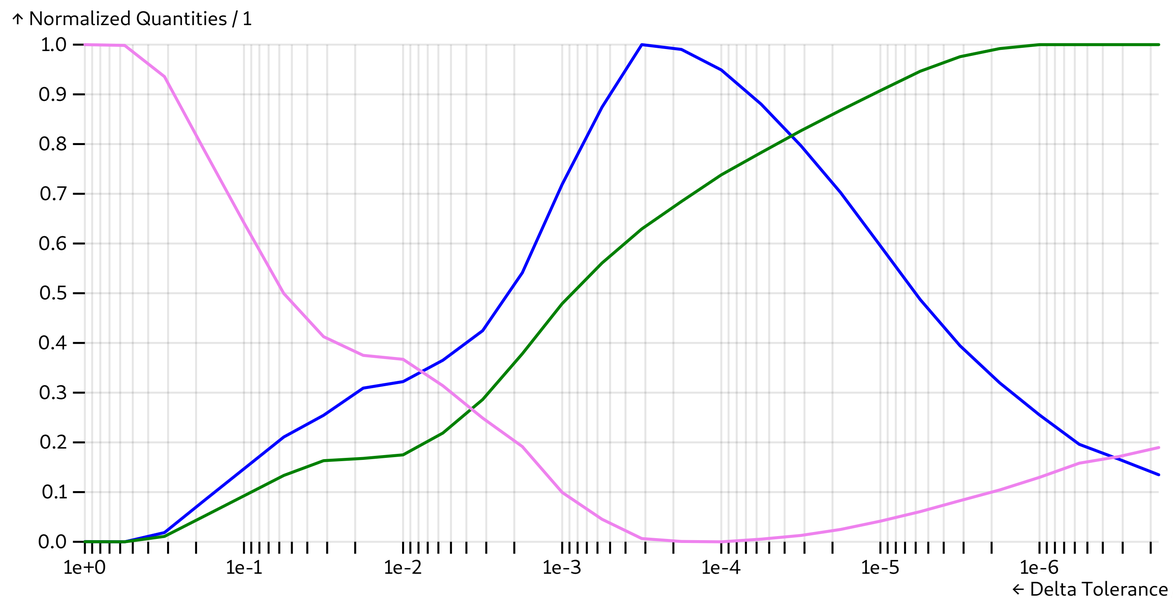
$$\boldsymbol{s}_{k,n+1} = H_k\left(V(t_n), \boldsymbol{C}(t_n), t_n\right) \boldsymbol{s}_{k,n} , \quad \text{with} \quad t_n := \sum_{i=0}^{n} (\Delta t)_i .$$

Adaptive Timestepping

In order to accelerate the simulation in areas where there is little change to the dynamics, we choose an adaptive step size $(\Delta t)_n$ based on

$$(\Delta t)_{n+1} = (\Delta t)_n \left(\frac{\Delta^{\text{tol}}}{\sum_{k=1}^{M} N_k \left\| \boldsymbol{s}_{k,n+1} - \boldsymbol{s}_{k,n} \right\|_2} \right)^{1/2} .$$

In order to find the optimal $\Delta^{\text{tol}} \in \mathbb{R}^+$ (the allowed state change in between steps):



Relative change of the average timestep Δt (in blue), simulation runtime (in violet) and step acceptance rate (in green) when varying the delta tolerance Δ^{tol} on a log-scale. All three quantities were normalized from their individual extent to $[0, 1]$. The most effective Δ^{tol} is arguably on the order of 10^{-4}.

Formulation as a Quadratic Program

After simulation of the individual channel currents, we want to find

$$\boldsymbol{N}_{\text{opt}} = \underset{\boldsymbol{N} \in \mathbb{N}_0^M}{\arg\min} \frac{1}{2} \left\| R\boldsymbol{N} - \boldsymbol{I}_{\text{meas}} \right\|_2^2 .$$

the number of channels per type, with $\boldsymbol{I}_{\text{meas}} \in \mathbb{R}^{N_t}$ the experimentally measured current and $R \in \mathbb{R}^{N_t \times M}$ the matrix of all currents I_k per channel type. Letting $\boldsymbol{d} := \boldsymbol{I}_{\text{meas}}$ for brevity,

$$\boldsymbol{N}_{\text{opt}} \approx \underset{\boldsymbol{x} \in \mathbb{R}_+^M}{\arg\min} f(\boldsymbol{x}) = \underset{\boldsymbol{x} \in \mathbb{R}_+^M}{\arg\min} \tfrac{1}{2} \left\| R\boldsymbol{x} - \boldsymbol{d} \right\|_2^2 ,$$

with cost function $f : \mathbb{R}^M \to \mathbb{R}^+$, which we manipulate to

$$\begin{aligned} f(\boldsymbol{x}) &= \tfrac{1}{2}(R\boldsymbol{x} - \boldsymbol{d})^T (R\boldsymbol{x} - \boldsymbol{d}) \\ &= \tfrac{1}{2}\left(\boldsymbol{x}^T R^T R\boldsymbol{x} - \boldsymbol{x}^T R^T \boldsymbol{d} - \boldsymbol{d}^T R\boldsymbol{x} + \boldsymbol{d}^T \boldsymbol{d}\right) \\ &= \tfrac{1}{2}\left(\boldsymbol{x}^T P\boldsymbol{x} + \boldsymbol{x}^T \boldsymbol{q} + \boldsymbol{q}^T \boldsymbol{x}\right) + \mathcal{O}(1) \\ &= \tfrac{1}{2}\boldsymbol{x}^T P\boldsymbol{x} + \boldsymbol{q}^T \boldsymbol{x} + \mathcal{O}(1) \end{aligned}$$

where we let $P := R^T R \in \mathbb{R}^{M \times M}$ and $\boldsymbol{q} := -R^T \boldsymbol{d} \in \mathbb{R}^M$ and leave out the constant $\boldsymbol{d}^T \boldsymbol{d}$ as $\mathcal{O}(1)$. We can express the nonnegativity constraint $\boldsymbol{x} \geq \boldsymbol{0}$ as an equality constraint using a slack variable $\boldsymbol{s} \in \mathbb{R}_+^M$,

$$-\boldsymbol{x} + \boldsymbol{s} = \boldsymbol{0} \quad \Leftrightarrow \quad A\boldsymbol{x} + \boldsymbol{s} = \boldsymbol{b} \quad \text{with} \quad A = -\mathbb{1} \in \mathbb{R}^{M \times M} \quad \text{and} \quad \boldsymbol{b} = \boldsymbol{0} \in \mathbb{R}^M .$$

This leaves us with a constrained *quadratic program*,

$$\begin{aligned} &\min_{\boldsymbol{x} \in \mathbb{R}^M} \tfrac{1}{2}\boldsymbol{x}^T P\boldsymbol{x} + \boldsymbol{q}^T \boldsymbol{x}, \\ &\quad s.t.\ A\boldsymbol{x} + \boldsymbol{s} = \boldsymbol{b},\ \boldsymbol{s} \in \mathbb{R}_+^M . \end{aligned}$$

The integer solution can then be obtained from rounding,

$$\boldsymbol{N}_{\text{opt}} = \lfloor \boldsymbol{x} \rceil \in \mathbb{N}_0^M .$$

Comparison of Optimization Methods

The different approaches were evaluated on the G0 cell cycle phase with the activation voltage protocol. Runtime estimates were obtained on an Intel™i7-5600U CPU.

Algorithm	**Abbreviation**	**Runtime** / ms	**RMSE** / pA
Particle Swarm Optimization	PSO	22571	27.69
Gradient Descent + More Thuente	GD	18924	32.34
Limited-Memory BFGS + Hager Zhang	LBFGS	4845	32.20
Non-Negative Least Squares [3]	NNLS	318	28.00
Quadratic Program	QP	18	28.13

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.

References

[1] Sonja Langthaler, Theresa Rienmüller, Susanne Scheruebel, Brigitte Pelzmann, Niroj Shrestha, Klaus Zorn-Pauly, Wolfgang Schreibmayer, Andrew Koff and Christian Baumgartner. 'A549 in-silico 1.0: A first computational model to simulate cell cycle dependent ion current modulation in the human lung adenocarcinoma'. In: *PLoS Comput. Biol.* 17.6 (June 2021), e1009091. DOI: 10.1371/journal.pcbi.1009091.

[2] Sonja Langthaler, Christian Zumpf, Theresa Rienmüller, Niroj Shrestha, Julia Fuchs, Rui Zhou, Brigitte Pelzmann, Klaus Zorn-Pauly, Eleonore Fröhlich, Seth H. Weinberg and Christian Baumgartner. 'The bioelectric mechanisms of local calcium dynamics in cancer cell proliferation: an extension of the A549 in silico cell model'. In: *Front. Mol. Biosci.* 11 (May 2024), p. 1394398. DOI: 10.3389/fmolb.2024.1394398.

[3] Rasmus Bro and Sijmen De Jong. 'A fast non-negativity-constrained least squares algorithm'. In: *J. Chemom.* 11.5 (Sept. 1997), pp. 393–401. ISSN: 0886-9383. DOI: 10.1002/(SICI)1099-128X(199709/10)11:5<393::AID-CEM483>3.0.CO;2-L.