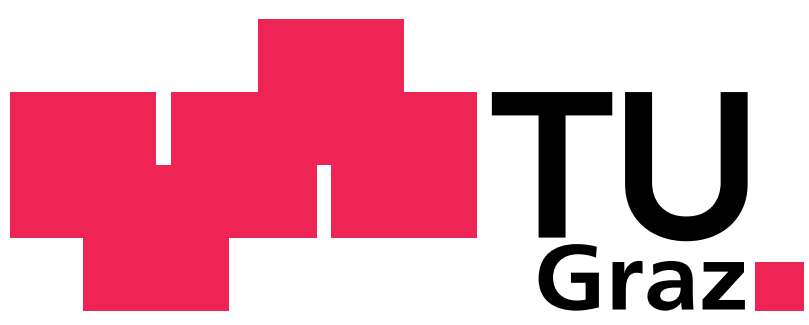


# REAL-TIME INTERACTION WITH AN ELECTROPHYSIOLOGICAL CANCER CELL MODEL

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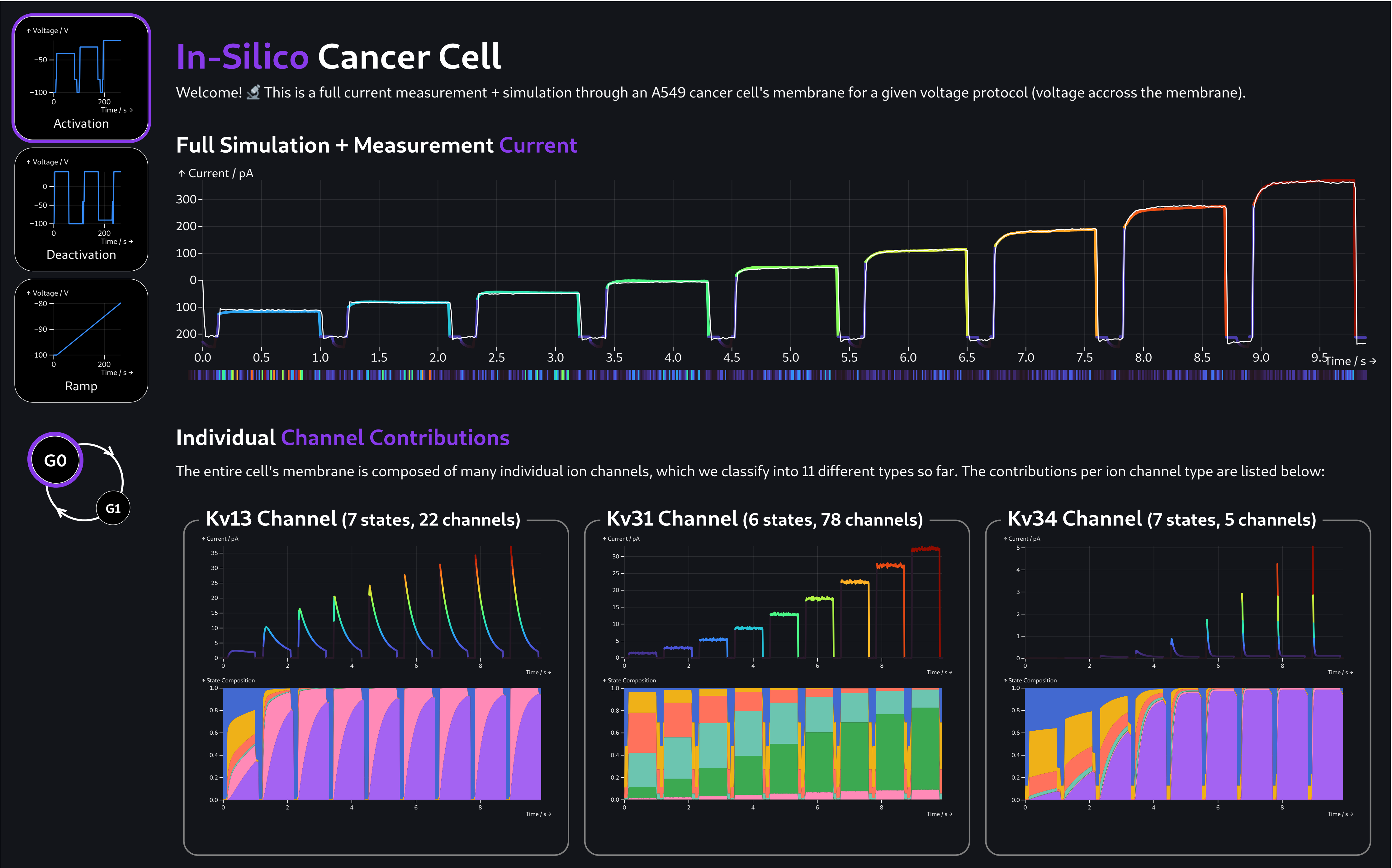
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## Introduction

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. 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 online, running directly in the browser. 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 implementation and a Python package.

## Live, In-Browser Cell Simulation Interface



This interface is available online via [in-silico.hce.tugraz.at](https://in-silico.hce.tugraz.at), try it out!

## Model

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

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

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

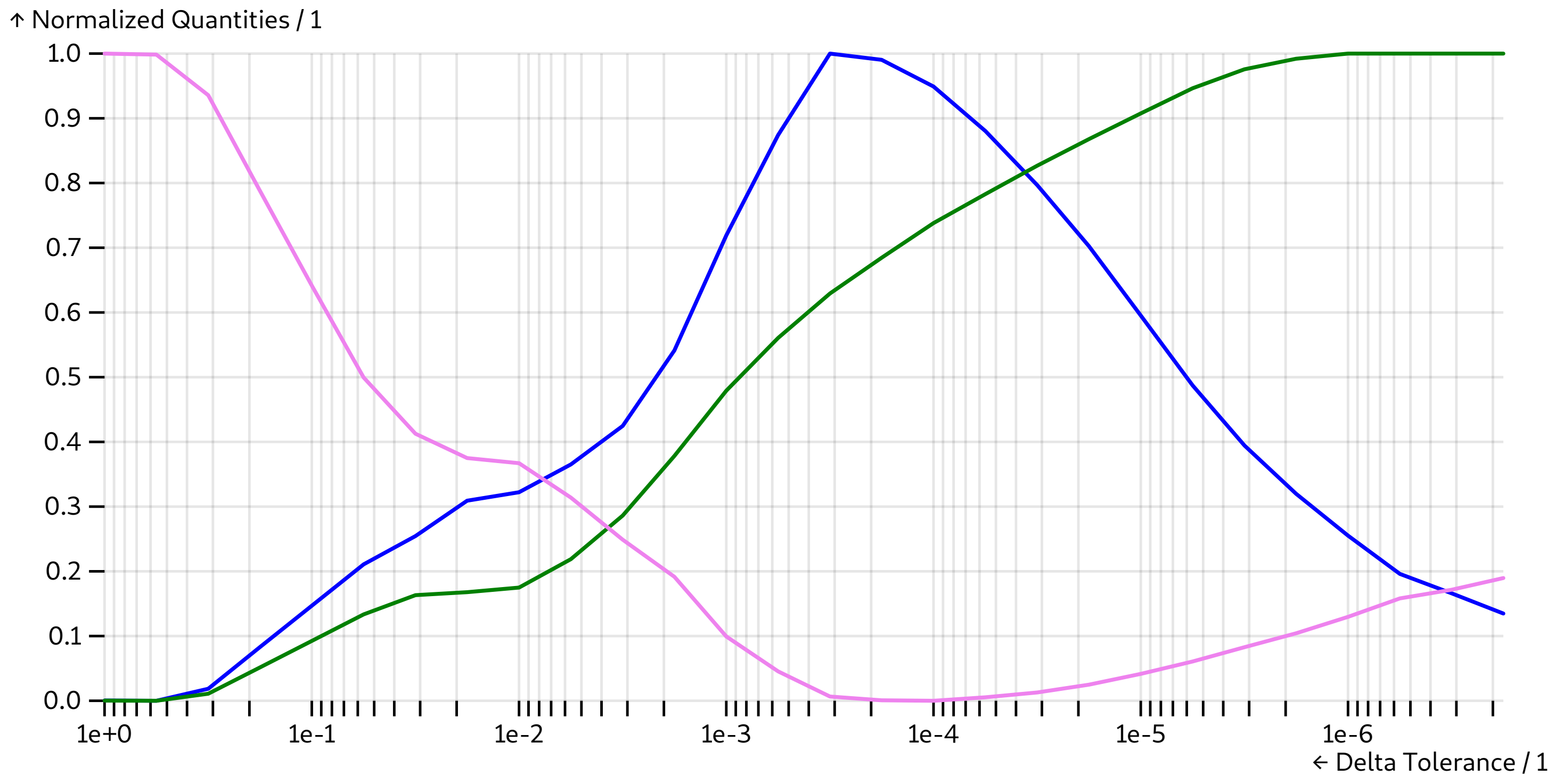
$$\mathbf{s}_{k,n+1} = H_k(V(t_n), \mathbf{C}(t_n), t_n) \mathbf{s}_{k,n}, \quad t_n := \sum_{i=0}^n (\Delta t)_i.$$

## 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

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

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

## 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.

## 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](https://doi.org/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](https://doi.org/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](https://doi.org/10.1002/(SICI)1099-128X(199709/10)11:5<393::AID-CEM483>3.0.CO;2-L).

## Formulation as a Quadratic Program

We want to find

$$\mathbf{N}_{\text{opt}} = \arg \min_{\mathbf{N} \in \mathbb{N}_0^M} \frac{1}{2} \|\mathbf{R}\mathbf{N} - \mathbf{I}_{\text{meas}}\|_2^2.$$

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

$$\mathbf{N}_{\text{opt}} \approx \arg \min_{\mathbf{x} \in \mathbb{R}_+^M} f(\mathbf{x}) = \arg \min_{\mathbf{x} \in \mathbb{R}_+^M} \frac{1}{2} \|\mathbf{R}\mathbf{x} - \mathbf{d}\|_2^2,$$

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

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

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

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

This leaves us with a constrained *quadratic program*,

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

The integer solution can then be obtained from rounding,

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

## 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