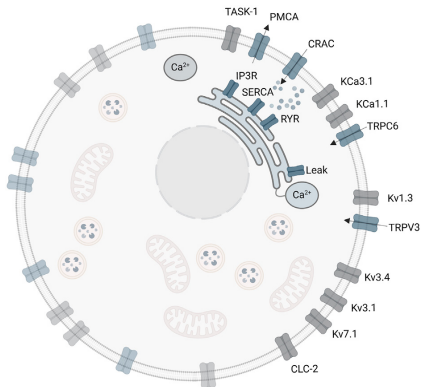


In-Silico Cancer Cell

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The Biological Setting: A Lung-Cancer Cell



- A human cell is complex. In this project, we focus on the electrophysiological behaviour!
- Specifically, on the ion channels on the membrane of an A549 cancer cell.
- We improve simulation of the world's first electrophysiological cancer cell model [2].
- And visualise!

Figure: A549 Cancer Cell Model [2]

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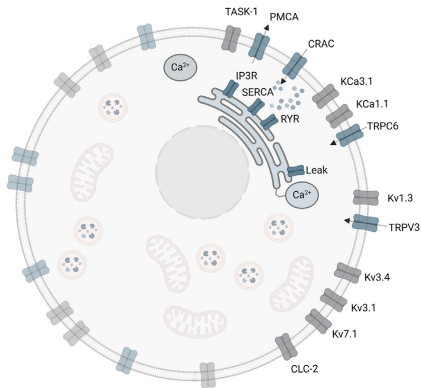


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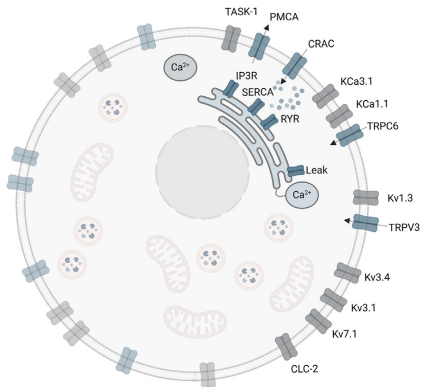


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Experiment: Patch-Clamping



Figure: Patch-Clamp System [3]

- Approach in which electrophysiological behaviour of a cell can be measured in a lab (our data from TU Graz!).
- Patch-Clamping can be differentiated into two approaches:
 - the Cell-attached recording method,
 - the *Whole-cell recording method*.

Simulation of the Experiment

- We simulate each of the ion channels individually, once per type.
- We know the ion channel types from previous research.
- Models for each of them have been identified in long-standing collaborative effort.
- We combine the models from literature into a full Rust implementation of each.

Hidden Markov 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

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

Solution of the Inverse Problem

- We want to find the best possible match between simulation and measurement current, so we take

$$\mathbf{N}_{\text{opt}} = \arg \min_{\mathbf{N} \in \mathbb{N}_0^M} \int_T \|I_{\text{sim}, \mathbf{N}}(t) - I_{\text{meas}}(t)\|^2 dt ,$$

- Where we optimise over the set \mathbb{N}_0^M (for M different channel types).
- Using some algebra, one can separate the individual models and simulate their current profiles individually.
- This makes the problem soluble much more efficiently (see later).

Runtime Optimisation

The original MatLab implementation ran the entire night, so:

- Improve what we simulate
- Improve how we simulate
- Improve the inverse solution method
- Improve the solver

Quadratic Problem Formulation I

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

$$\mathbf{N}_{\text{opt}} = \arg \min_{\mathbf{N} \in \mathbb{N}_0^M} \frac{1}{2} \|\mathbf{R}\mathbf{N} - \mathbf{d}\|^2,$$

the number of channels per type, with $\mathbf{d} \in \mathbb{R}^{N_t}$ the experimentally measured current and $\mathbf{R} \in \mathbb{R}^{N_t \times M}$ the matrix of all currents I_k per channel type. We find

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

Quadratic Problem Formulation II

We manipulate the cost function $f : \mathbb{R}^M \rightarrow \mathbb{R}^+$,

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

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 $\mathcal{O}(1)$.

Quadratic Problem Formulation III

We can express the nonnegativity constraint $\mathbf{x} \geq \mathbf{0}$ as an equality constraint using a slack variable $\mathbf{s} \in \mathbb{R}_+^M$,

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

This leaves us with a constrained *quadratic program*,

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

Quadratic Problem Formulation IV

The integer solution can then be obtained from rounding,

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

One obtains:

$$\mathbf{N}_{\text{opt}} = [13, 247, 10, 1176, 38, 7, 24, 188, 15, 10, 234] ,$$

for the G0 cell cycle phase.

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

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

where the heuristic we choose to stay fast while preventing instability of the simulation, is based on the difference in state change (and also dependent on the channel counts $\mathbf{N} \in \mathbb{N}_0^M$).

Runtime Optimisation

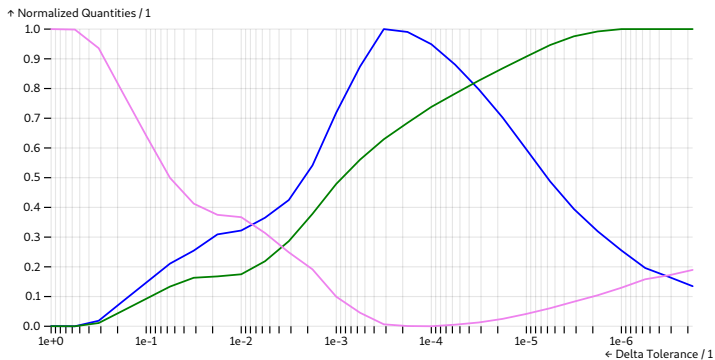


Figure: Relative change of the average timestep Δt (in blue), simulation runtime (in violet) and step acceptance rate (in green) when varying the delta tolerance Δ^{tol} .

Optimisation Approaches

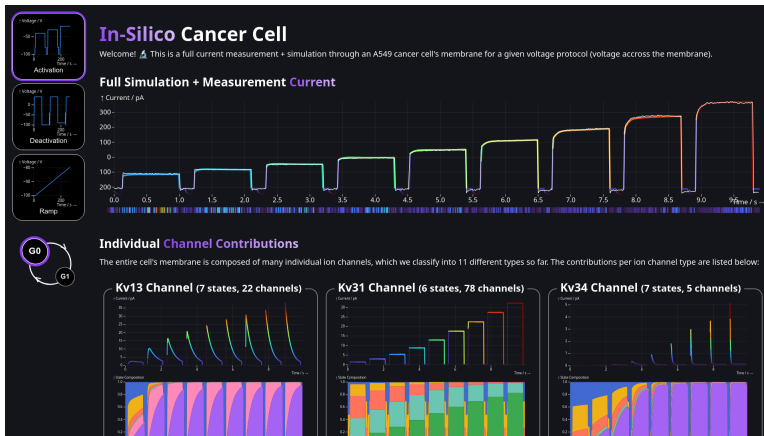
Algorithm	Abbreviation	Runtime / ms	RMSE / pA
Particle Swarm Optimization	PSO	22571	27.69
Gradient Descent + More Thuente	GD	18924	32.34
Limited-Memory BFGS + Hager Zhang	LBFGS	4845	32.20
Non-Negative Least Squares [1]	NNLS	318	28.00
Quadratic Program	QP	18	28.13

Table: Comparison of different algorithms for the solution of the inverse problem.

Visualisation Idea and Accessibility

- A complicated setup, hard to understand for non-experts
- Make the simulation accessible by providing it in multiple formats
- Rust linked library, Python (pip) package and visualisation dashboard!
`pip install in-silico-cancer-cell`

Visualisation Dashboard



Compilation to WebAssembly

- Rust's compiler can target **wasm** architectures.
- Not all functionality is supported in a **wasm** environment, such as timing.
- But of course, numerical code does run and we leverage the compile-time optimisations.
- Communicate the results in-memory and visualise them using frontend libraries.

References I

- [1] Rasmus Bro and Sijmen De Jong. **A fast non-negativity-constrained least squares algorithm.** *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).
- [2] 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.** *PLoS Comput. Biol.* 17.6 (June 2021), e1009091. DOI: [10.1371/journal.pcbi.1009091](https://doi.org/10.1371/journal.pcbi.1009091).
- [3] **Patch-Clamp Electrophysiology.** Apr. 2025. URL: <https://www.criver.com/products-services/discovery-services/pharmacology-studies/neuroscience-models-assays/neuroscience-methods-endpoints/electrophysiology/patch-clamp?region=3696> (visited on 29/04/2025).