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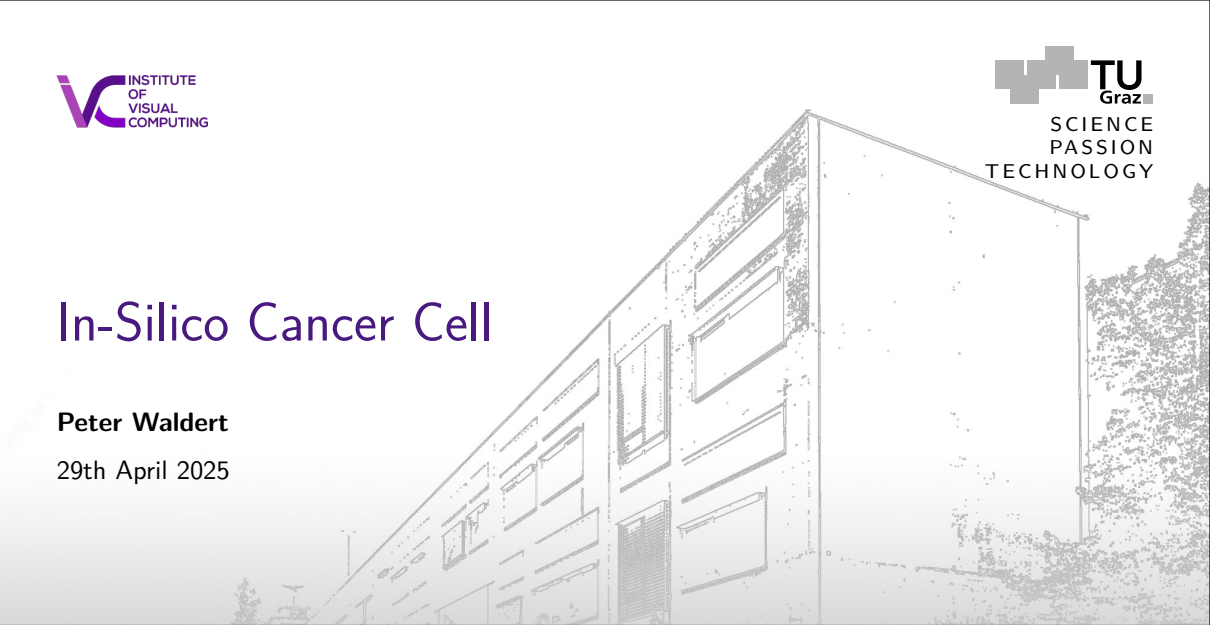

In-Silico Cancer Cell

Peter Waldert

29th April 2025

The Biological Setting: A Lung-Cancer Cell

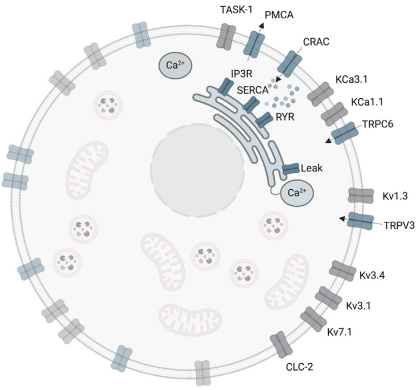

Figure: A549 Cancer Cell Model [1]

- 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 [1].
- And visualise!

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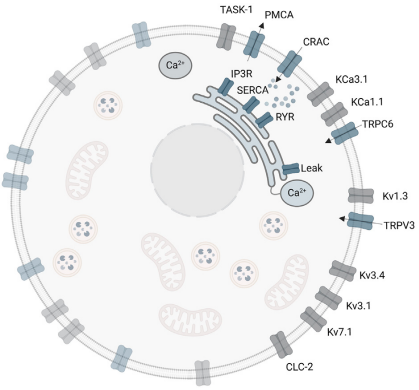

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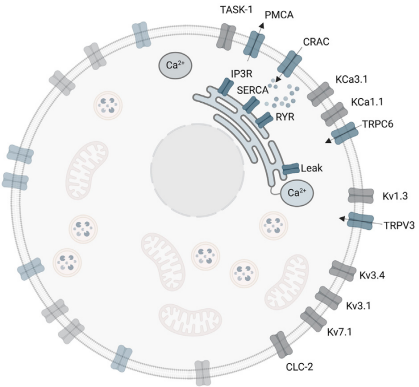

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Experiment: Patch-Clamping

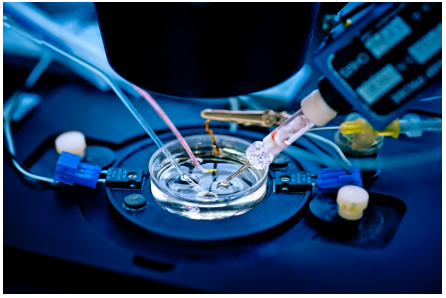

Figure: Patch-Clamp System [2]

Approach in which electrophysiological behaviour of a cell can be measured in a lab. Patch-Clamping can be differentiated into two approaches:

- the Cell-attached recording method and
- the *Whole-cell recording method*.

Simulation of the Experiment

Hidden Markov 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

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

Solution of the Inverse Problem

- We want to find

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

$$\boldsymbol{N}_{\text{opt}} = \underset{\boldsymbol{N}\in\mathbb{N}_0^M}{\arg\min}\, \frac{1}{2}\|R\boldsymbol{N} - \boldsymbol{d}\|^2 .$$

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

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

Quadratic Problem Formulation II

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

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

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 $\mathcal{O}(1)$.

Quadratic Problem Formulation III

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

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

This leaves us with a constrained *quadratic program*,

$$\begin{aligned} &\min_{\boldsymbol{x} \in \mathbb{R}^M} \ {}^1\!/_2\, \boldsymbol{x}^T P \boldsymbol{x} + \boldsymbol{q}^T \boldsymbol{x}, \\ &\quad s.t.\ A\boldsymbol{x} + \boldsymbol{s} = \boldsymbol{b}\,,\ \boldsymbol{s} \in \mathbb{R}^M_+ . \end{aligned}$$

Quadratic Problem Formulation IV

The integer solution can then be obtained from rounding,

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

One obtains:

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

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

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

Runtime Optimisation

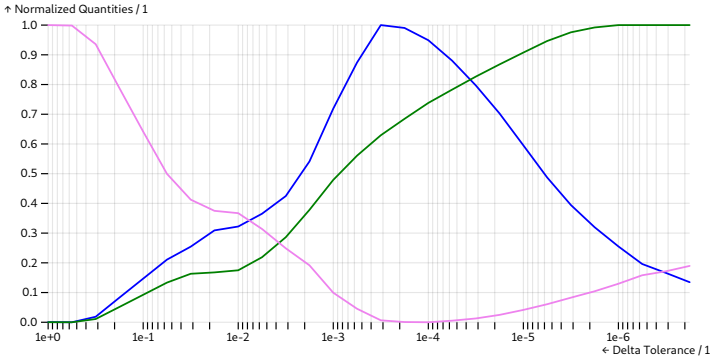

Figure: Relative change of the average timestep Δt (in blue), simulation runtime (in violet) and step acceptance rate (in green) when varying the delta tolerance Δ^{tol}.

Visualisation Dashboard

WebAssembly

Cancer Cell Simulation

- Let's go!

References I

[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.** *PLoS Comput. Biol.* 17.6 (June 2021), e1009091. DOI: 10.1371/journal.pcbi.1009091.

[2] **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).