Real-time interaction with an electrophysiological cancer cell model

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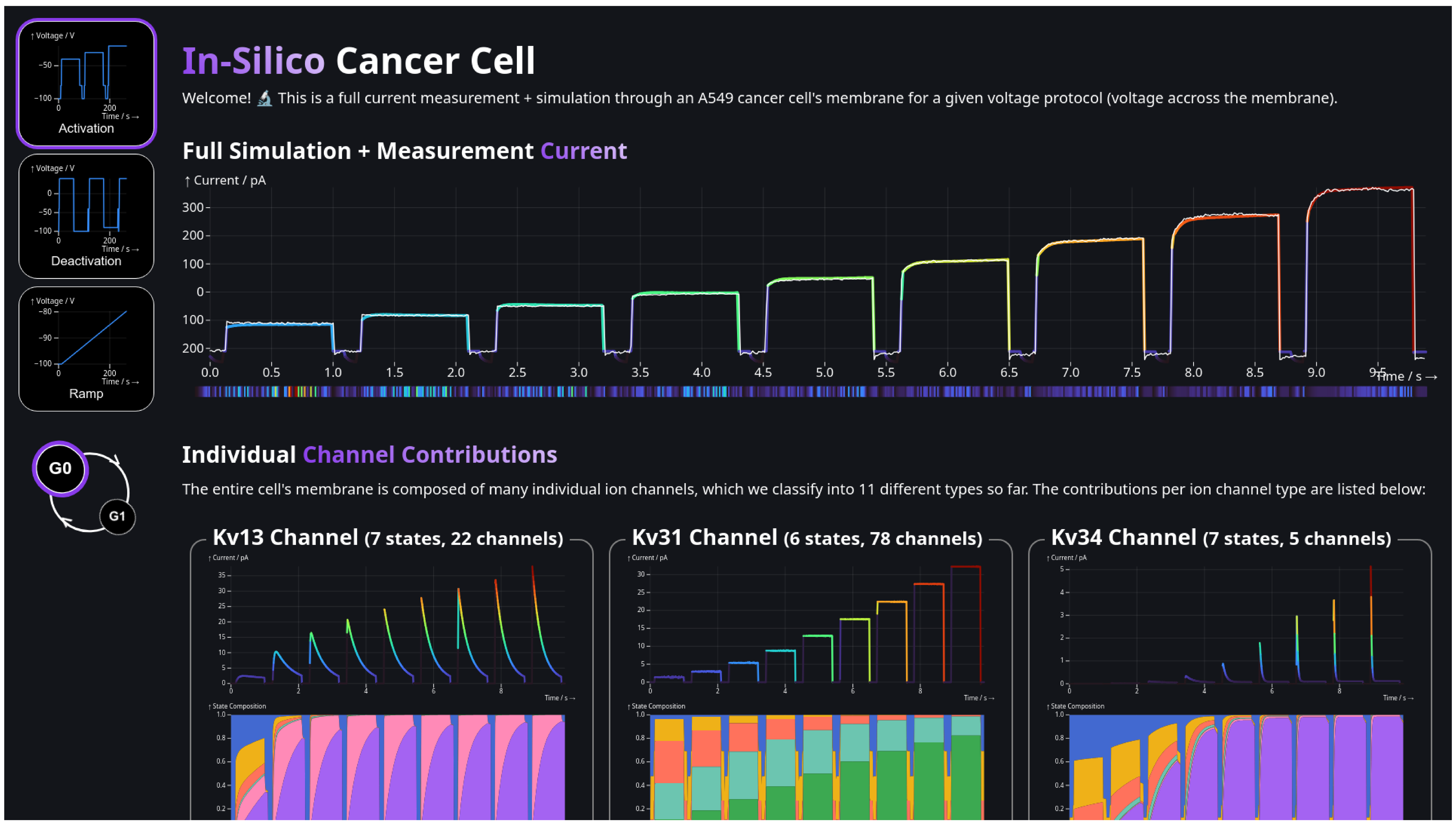
Introduction

We extend the previous work [1] by a faster, in-browser implementation in Rust [2] using compilation to WebAssembly.

Number of Channels

Channel Type	N_k [1]	Our N_k
Kv13	22	13
Kv31	78	247
Kv34	5	10
Kv71	1350	1176
KCa11	40	38
KCa31	77	7
Task1	19	24
CRAC1	200	188
TRPC6	17	15
TRPV3	12	10
CLC2	13	234

Live, In-Browser Cell Simulation Interface



Available live on in-silico.hce.tugraz.at.

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

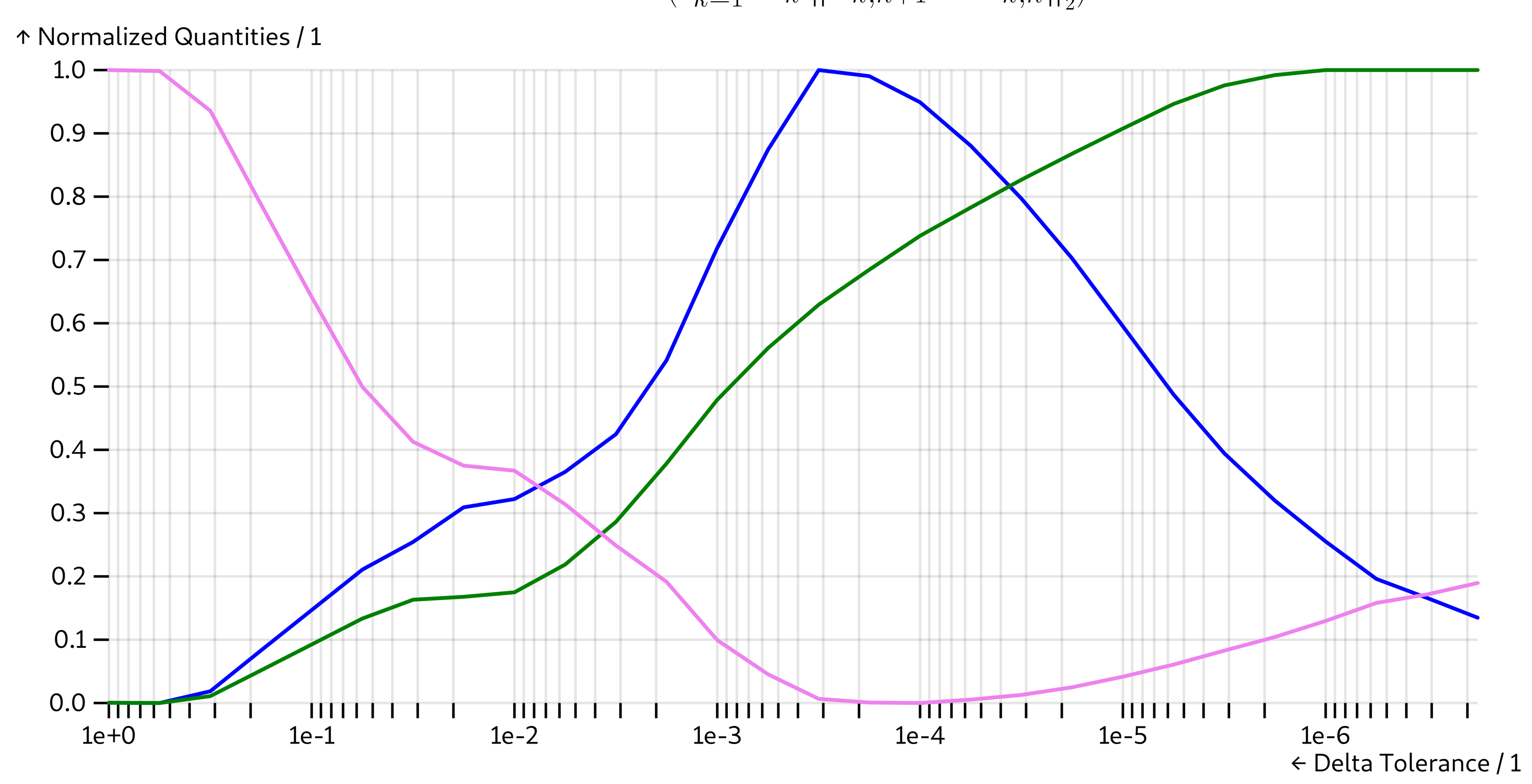
$$I(t) := \sum_{k=1}^{M} N_k I_k(t) = \sum_{k=1}^{M} N_k g_k p_{o,k} \left(V(t) - E_k\right) , \tag{1}$$

At each time step,

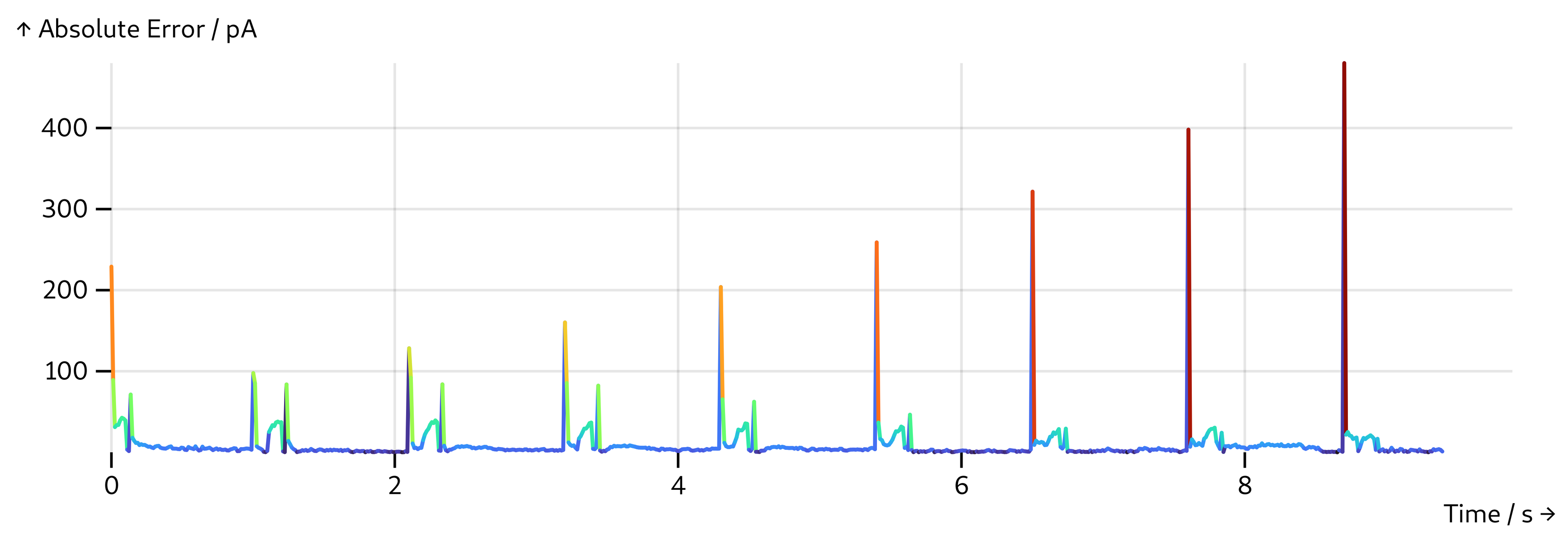
$$\boldsymbol{s}_{k,n+1} = H_k\left(V(t_n), \boldsymbol{C}(t_n), t_n\right) \boldsymbol{s}_{k,n} \tag{2}$$

Adaptive Timestepping

$$(\Delta t)_{n+1} = (\Delta t)_n \left(\frac{\Delta^{\text{tol}}}{\sum_{k=1}^{M} N_k \left\| \boldsymbol{s}_{k,n+1} - \boldsymbol{s}_{k,n} \right\|_2} \right)^{1/2} , \tag{3}$$



Pointwise Error between Simulation and Measurements



Formulation as a Quadratic Program

We want to find

$$\boldsymbol{N}_{\text{opt}} = \underset{\boldsymbol{N} \in \mathbb{N}_0^M}{\arg\min} \frac{1}{2} \left\| R\boldsymbol{N} - \boldsymbol{I}_{\text{meas}} \right\|_2^2 , \tag{4}$$

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,

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

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

$$\begin{aligned} f(\boldsymbol{x}) &= {}^1\!/_2 (R\boldsymbol{x} - \boldsymbol{d})^T (R\boldsymbol{x} - \boldsymbol{d}) \\ &= {}^1\!/_2 \left(\boldsymbol{x}^T R^T R \boldsymbol{x} - \boldsymbol{x}^T R^T \boldsymbol{d} - \boldsymbol{d}^T R \boldsymbol{x} + \boldsymbol{d}^T \boldsymbol{d} \right) \\ &= {}^1\!/_2 \left(\boldsymbol{x}^T P \boldsymbol{x} + \boldsymbol{x}^T \boldsymbol{q} + \boldsymbol{q}^T \boldsymbol{x} \right) + \mathcal{O}(1) \\ &= {}^1\!/_2 \boldsymbol{x}^T P \boldsymbol{x} + \boldsymbol{q}^T \boldsymbol{x} + \mathcal{O}(1) \end{aligned}$$

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 $\mathcal{O}(1)$. We can express the nonnegativity constraint $\boldsymbol{x} \geq \boldsymbol{0}$ as an equality constraint using a slack variable $\boldsymbol{s} \in \mathbb{R}_+^M$,

$$-\boldsymbol{x} + \boldsymbol{s} = \boldsymbol{0} \quad \Leftrightarrow \quad A\boldsymbol{x} + \boldsymbol{s} = \boldsymbol{b} ,$$

where we set $A := -\mathbb{1} \in \mathbb{R}^{M \times M}$ and $\boldsymbol{b} := \boldsymbol{0} \in \mathbb{R}^M$. This leaves us with a constrained *quadratic program*,

$$\min_{\boldsymbol{x} \in \mathbb{R}^M} \frac{1}{2} \boldsymbol{x}^T P \boldsymbol{x} + \boldsymbol{q}^T \boldsymbol{x} , \tag{5}$$

$$\text{s.t. } A\boldsymbol{x} + \boldsymbol{s} = \boldsymbol{b} , \ \boldsymbol{s} \in \mathbb{R}_+^M . \tag{6}$$

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

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

References

Langthaler, Sonja, Theresa Rienmüller, Susanne Scheruebel, Brigitte Pelzmann, Niroj Shrestha, Klaus Zorn-Pauly, Wolfgang Schreibmayer, Andrew Koff and Christian Baumgartner (June 2021). '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, e1009091. DOI: 10.1371/journal.pcbi.1009091.
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