Real-time interaction with an electrophysiological cancer cell model

Peter Waldert, Theresa Rienmüller, Christian Baumgartner, Sonja Langthaler

Institute of Health Care Engineering with European Testing Center of Medical Devices

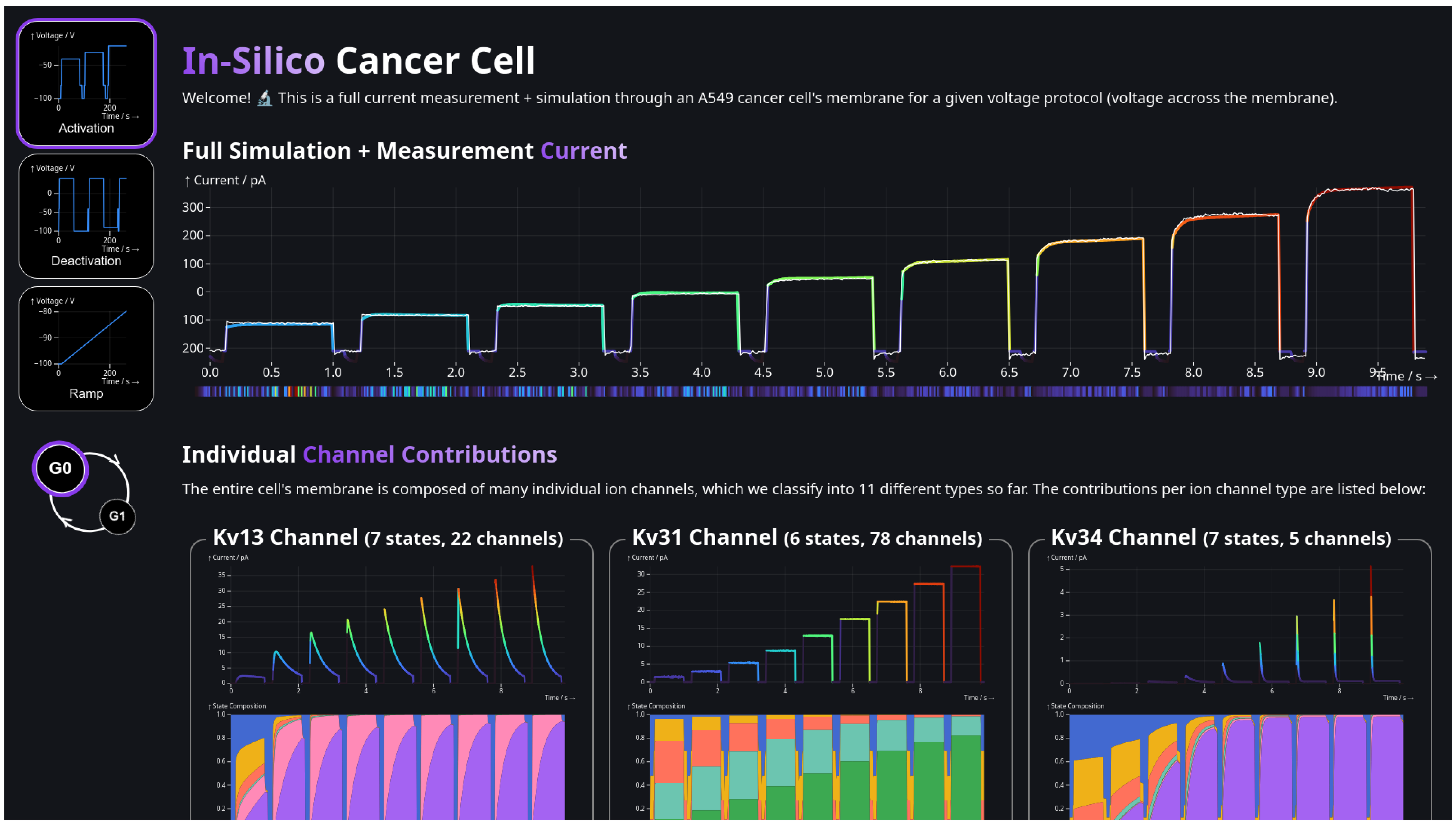
Introduction

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

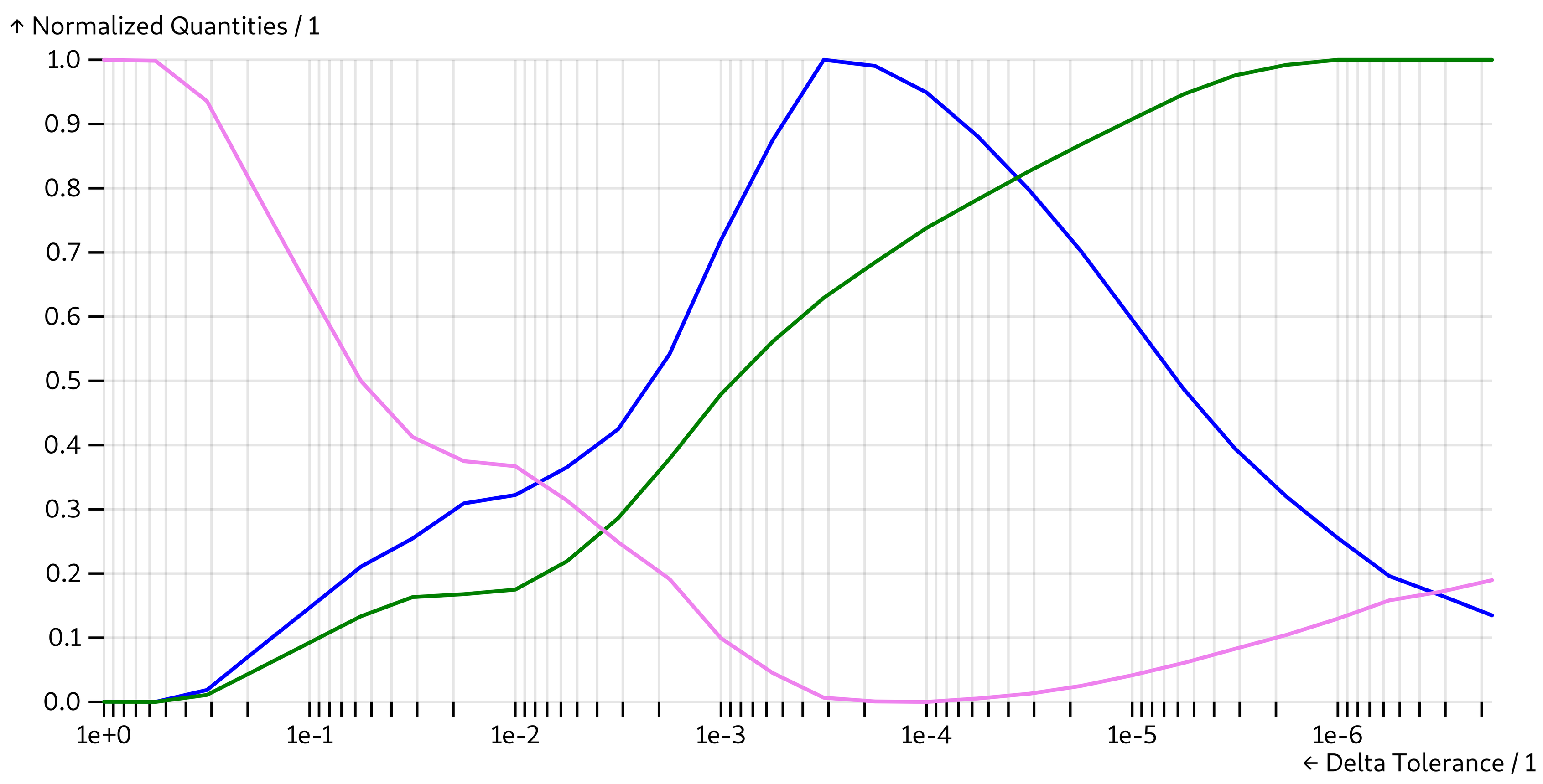
$$I(t) := \sum_{k=1}^{M} N_k I_k(t) = \sum_{k=1}^{M} N_k g_k p_{o,k} \left(V(t) - E_k\right) , \tag{1}$$

At each time step,

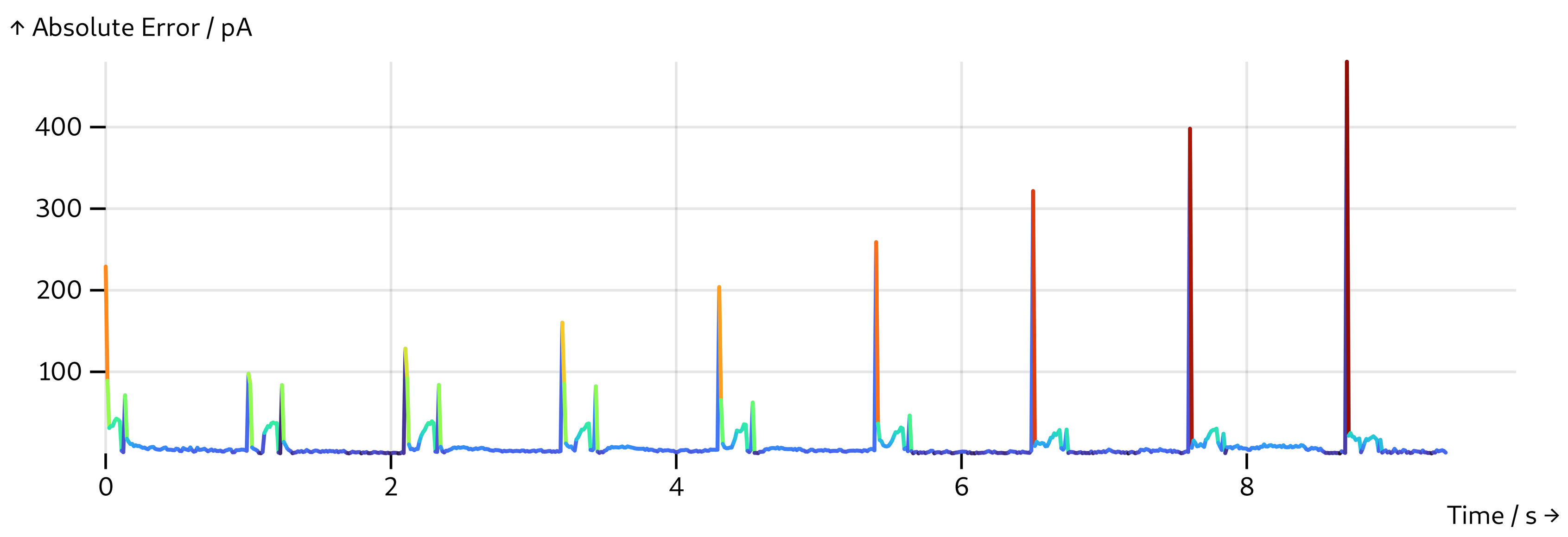
$$\boldsymbol{s}_{k,n+1} = H_k \left(V(t_n), \boldsymbol{C}(t_n), t_n\right) \boldsymbol{s}_{k,n} \tag{2}$$

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.

Matsakis, Nicholas D. and Felix S. Klock (Oct. 2014). 'The rust language'. In: *Ada. Lett.* 34.3, pp. 103–104. ISSN: 1094-3641. DOI: 10.1145/2692956.2663188.

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