

## A DIGITAL TWIN FRAMEWORK FOR VISUALISING CELLULAR RESPONSES TO ELECTRICAL STIMULATION

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Electrical stimulation is a promising approach to promote tissue regeneration. However, its clinical application is limited by an incomplete understanding of the underlying mechanisms and the stimulation parameters necessary to activate them. In this study, we developed a digital twin framework to rationally select stimulation parameters and evaluate whether induced transmembrane potential (iTMP) is a key indicator of the efficacy of electrical stimulation. The stimulation chamber was modelled as an equivalent circuit, parameterised with electrochemical impedance spectroscopy data and voltage–current measurements. Once the circuit predictions agree with the measurements, the voltage drop across only the medium can be computed reliably. These macroscopic predictions served as boundary conditions for fine-grained simulations of cells reconstructed from 3D fluorescence images. The coupled model solved the electro-quasistatic field equations [1] to derive electric fields and iTMP.

Because electrical stimulation has been reported to elevate intracellular calcium via voltage-gated calcium channels [2], we combined kilohertz frequency and direct current stimulation with live cell calcium imaging. Kilohertz stimulation adjusted to about 10 mV iTMP did not change the intracellular calcium levels, whereas direct current stimulation increased them. However, chemical controls revealed that this effect arose from electrochemical by-products rather than purely electrical activation.

Finally, we present an automated, user-friendly pipeline that generates realistic numerical models directly from imaging data and can be readily deployed on high-performance computing clusters. Although we demonstrated this workflow with bone cells, it can be generalised and applied to any cell type subjected to electrical stimulation. This approach provides mechanistic insights into the cellular effects of electrical stimulation and its relevance for therapeutic innovation.

### REFERENCES

- [1] U. van Rienen, et al., “Electroquasistatic simulations in bio-systems engineering and medical engineering,” *Adv. Radio Sci.*, vol. 3, 2005.
- [2] S. Staehlke, et al., “Pulsed electrical stimulation affects osteoblast adhesion and calcium ion signaling,” *Cells*, vol. 11, 2022.