Investigation of ensemble dwell-time histograms for the inference of ion channel kinetics using neural networks

As the famous electrophysiologist Clay Armstrong said: „Ion channels are involved in every thought, every perception, every movement, every heartbeat“. The single-channel patch-clamp technique allows us to investigate the activity of these molecular machines with a temporal resolution of the 100 kHz order, by recording the current that is *channeled* through them in form *ion* flow. The obtained time series are very long and can amount to ten million or even more samples, rendering it problematic for deep learning approaches to process the data directly. Thankfully, the two-dimensional dwell-time histograms (2D-histograms) (Magleby & Weiss, 1990; Oikonomou et al., 2023) have been devised , that transform the long time series with varying length to a relatively small, fix-sized, data structure (image).

Given that the signal arises from a *single* ion channel, the generated electrical current is very small and has to be amplified and filtered to become recordable with an acceptable signal-to-noise ratio. This process inadvertedly distorts the signal, such that purely analytical approaches fail to resolve “fast gating” kinetics i.e. high frequent activity of the ion channel. Nevertheless, it was previously shown that neural networks trained on simulated 2D-histograms are capable of extracting the underlying kinetic model of the ion channel under such conditions (Oikonomou et al., 2024), which is usually described via the Markov model formalism.

The goal of the proposed thesis is to improve the deep learning algorithm (Oikonomou et al., 2024), by expanding the 2D-histogram modality such that instead of one, multiple 2D-histograms are computed per recorded time series (image). This entails programming and evaluation of a custom layer, in a sense a trainable filter, that optimizes this transformation given the observed signal distortions in the training data.

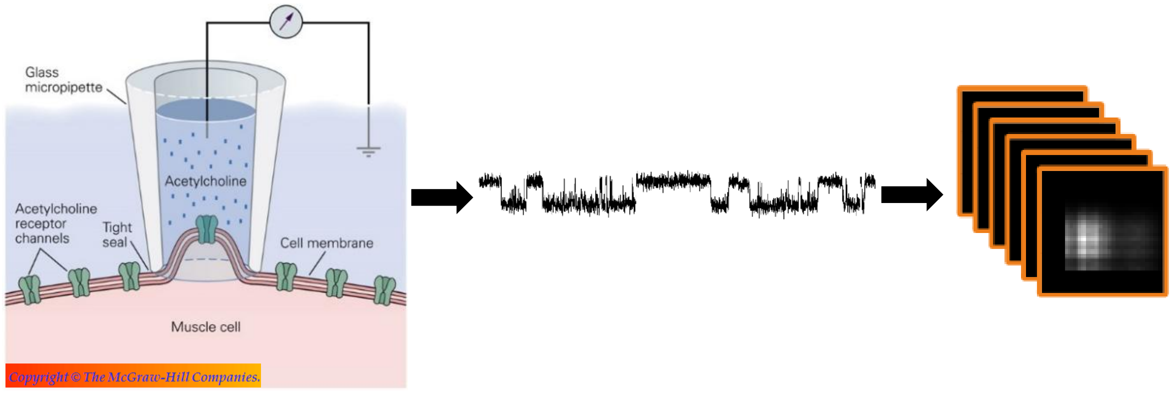

Image. **An Example of a single-channel patch-clamp recording and the transformation to a stack of 2D-histograms**

Citations

Magleby, K. L., & Weiss, D. S. (1990). Identifying kinetic gating mechanisms for ion channels by using two-dimensional distributions of simulated dwell times. *Proceedings. Biological Sciences*, *241*(1302), 220–228. https://doi.org/10.1098/rspb.1990.0089

Oikonomou, E., Gruber, T., Chandra, A. R., Höller, S., Alzheimer, C., Wellein, G., & Huth, T. (2023). 2D-dwell-time analysis with simulations of ion-channel gating using high-performance computing. *Biophysical Journal*, *122*(7), 1287–1300. https://doi.org/10.1016/j.bpj.2023.02.023

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Contact

Medical faculty supervisors:

PD Dr. Dr. Tobias Huth
Institute of Physiology and Pathophysiology
Friedrich-Alexander-Universität Erlangen-Nürnberg
Universitätsstraße 17
91054 Erlangen
tobias.huth@fau.de

Efthymios Oikonomou
Institute of Physiology and Pathophysiology
Friedrich-Alexander-Universität Erlangen-Nürnberg
Universitätsstraße 17
91054 Erlangen
timi.oikonomou@fau.de

Technical faculty supervisor:

TBD