Ion channel diversity enables robust and flexible targeting of realistic regions in the parameter landscape of dentate granule cell models

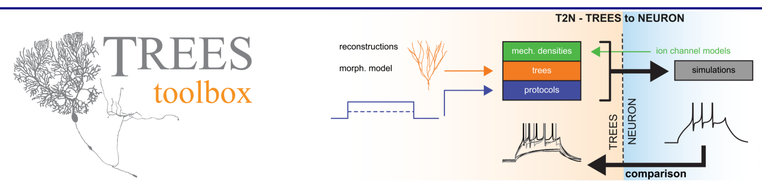
Marius Schneider[1,2,4] , Peter Jedlicka[2,3,4], Hermann Cuntz[1,2]

[1] Ernst Strüngmann Institute for Neuroscience in Cooperation with Max Planck Society, Frankfurt, Germany
[2] Frankfurt Institute for Advanced Studies, Frankfurt/Main, Germany
[3] Institute for Clinical Neuroanatomy, Goethe University Frankfurt, Frankfurt, Germany
[4] Interdisciplinary Centre for 3Rs in Animal Research (ICAR3R), Justus-Liebig-University, Giessen, Germany

Introduction

Cellular and molecular sources of intersubjective and intrasubjective (intercellular) variability in the electrical activity of nerve cells are not fully understood. An improved understanding of this variability is the key to predicting the response of nerve tissue to pathological changes. We have previously created a robust **data-driven compartmental model of the hippocampal granule cell (GC)** (Beining et al. eLife 2017) comprising 15 different ion channels and variable dendritic morphologies. Here **we addressed the question whether it is possible to reduce ion channel diversity while preserving realistic spiking behavior**. We have generated **large populations of validated granule cell models by stochastic variation of their ion channels**. Surprisingly, extremely reduced models (containing only 5 channels) were able to capture main electrophysiological characteristics of real granule cells. However, unreduced or less reduced models with a higher number of ion channels were more stable in the face of parameter perturbations. Moreover, they covered larger and more widely spread regions of the parameter landscape. This suggests that ion channel diversity allows for increased robustness and higher flexibility of finding a solution in the complex parameter space. In addition to increasing our understanding of cell-to-cell variability, our models might be of practical relevance. Instead of a one-size-fits-all approach where a computer model simulates average experimental values, the **population-based approach** reflects the **variability** of experimental data and therefore might enable pharmacological studies in silico and complement and reduce animal experiments.

1 Methods

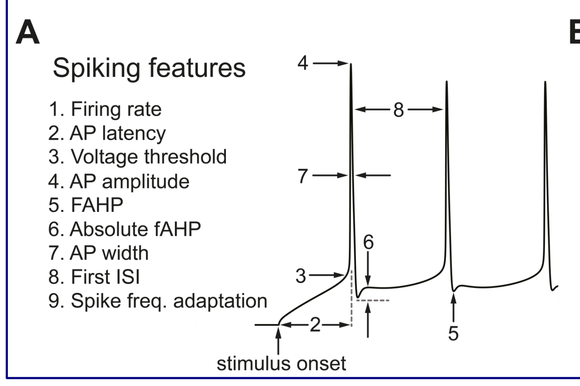


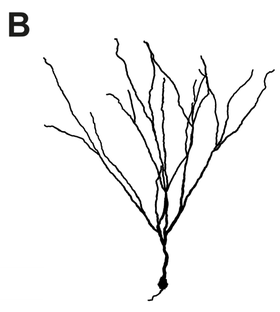
NEURON simulations:

We used **compartmental modeling** via the NEURON environment, TREES toolbox, www.treestoolbox.org) and established T2N software tool for Matlab (Beining et al. eLife 2017). Passive and active properties were obtained from published granule cell model (Beining et al. eLife 2017). In order to fit the GC model, we used traces from current clamp measurements of eight mature GCs (Mongiat et al. 2009). Parameter visualisation was carried out using the t-Distributed Stochastic Neighbor Embedding algorithm (van der Maarten et al. 2008).

Optimization:
The accuracy of a model was calculated with a spike-feature-based error function, comparing 9 spiking properties during a 50 and 90pA current-clamp. Each feature can be compared between model and experimental mean, in units of experimental standard deviation, thereby incorporating into the fitting this variability. GC model was accepted as behaving accurate if deviation from experimental data was lower than 2 standard deviations.

Population sampling:
We generated populations of GC models by sampling the maximum conductances of all ion channels in a two-fold range of accurate optimized models.

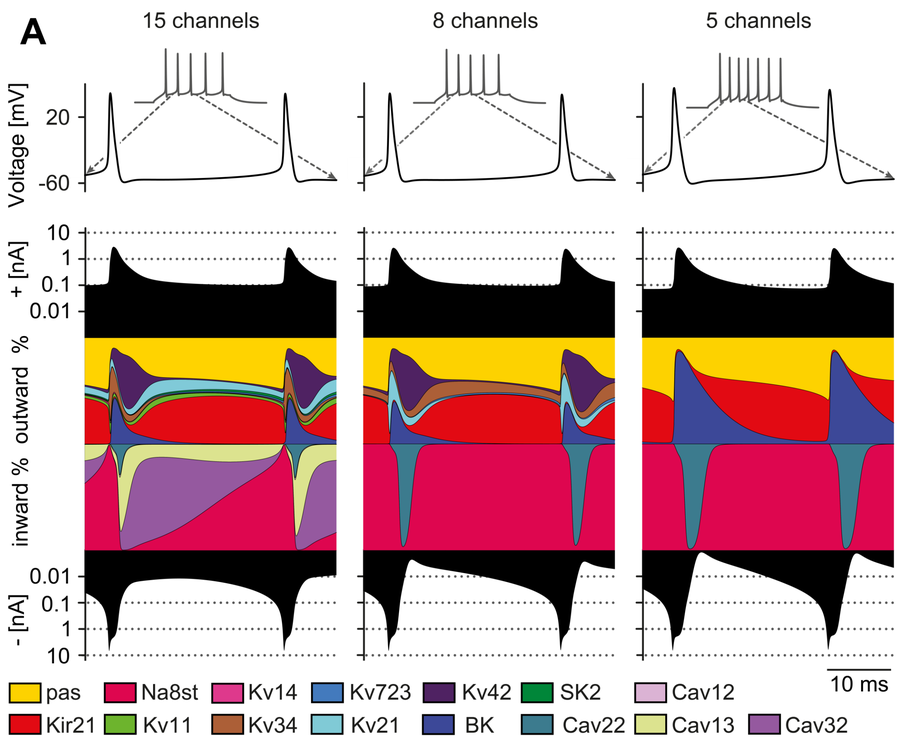




A: Spike features extracted for optimization (Mongiat et al. 2009).

B: Representative example for 3-D reconstruction of granule cells (Schmidt-Hieber et al. 2007).

2 Reduced models captured electrophysiology of real granule cells (GCs)

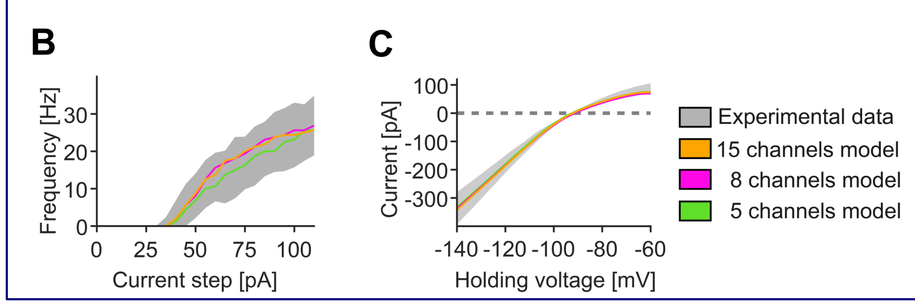


A: Membrane potential during second and third spike (top). The colored curves show the relative contribution of all implemented ion channels to the total inward and outward current at each time step as a percentage of the total current. The black filled curves illustrate the total inward and outward currents on a logarithmic scale (inspired by Alonso and Marder, 2018).

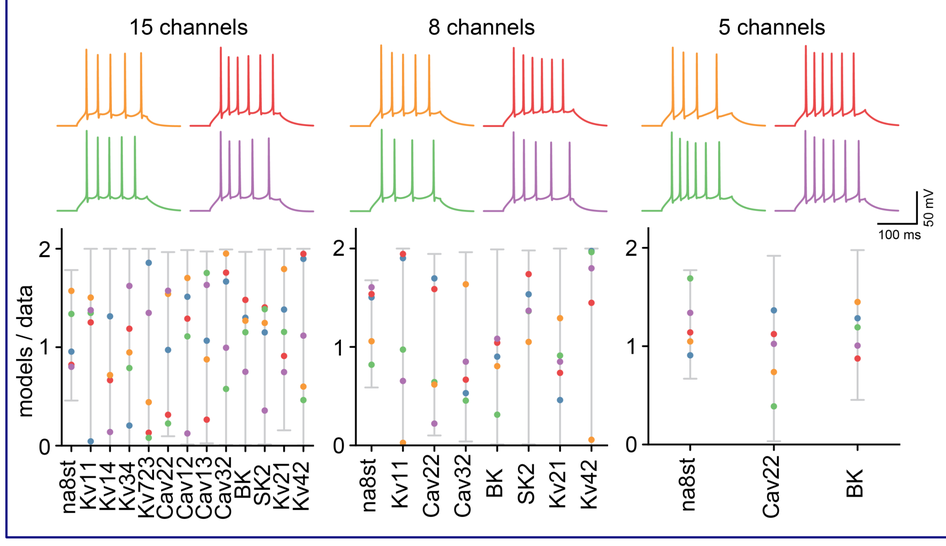
B: Spike-frequency elicited by different 200 ms lasting current steps (F-I relationship).

C: Current–voltage relationship (IV-Curve).

Experimental standard deviation shown as gray patches (Mongiat et al., 2009).



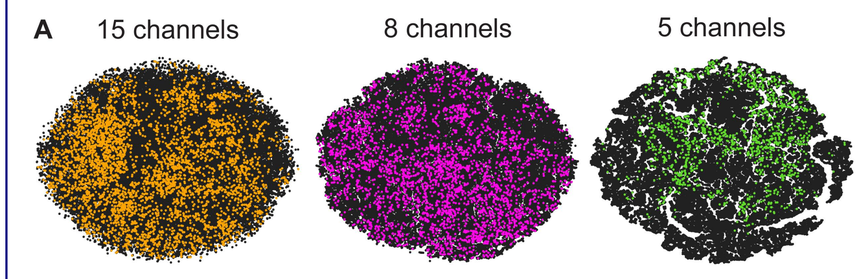
3 Populations of realistic GC models created by stochastic variation of their ion channels

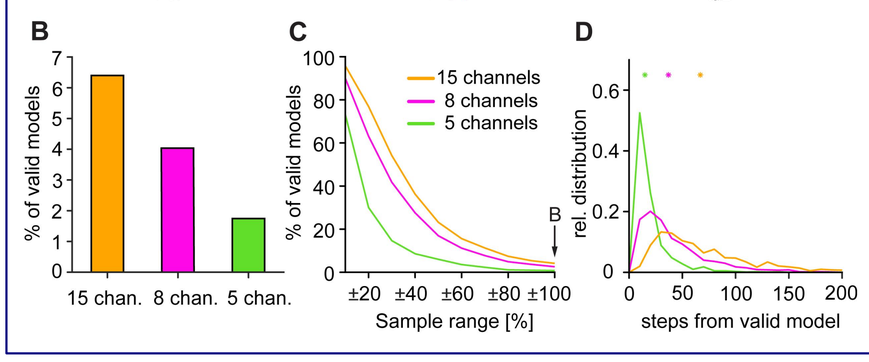


Top:
Spiking traces while 200ms lasting 90pA current-clamp into the soma.

Bottom:
Corresponding channel-expression in models of different complexity.

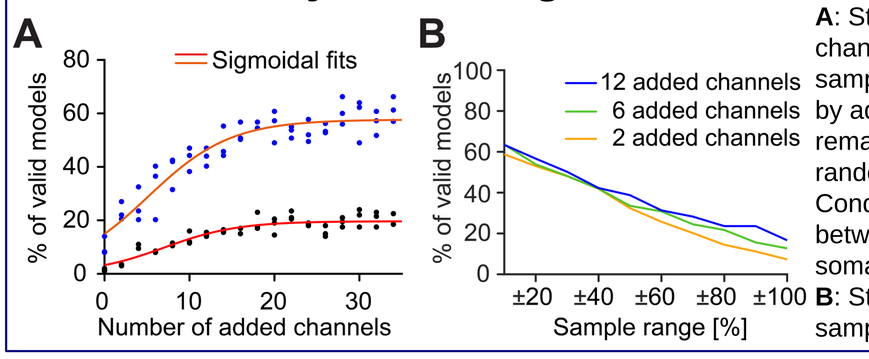
4 Models with a larger ion channel diversity covered larger regions of the parameter landscape





A: 2-dimensional illustration of the parameter space in a two-fold sample (dimensions reduced with the t-SNE algorithm). Colored dots represent functional models.
B: Statistics of valid models in two-fold sample.
C: Statistics of valid models in sample with different ranges.
D: Random walk through parameter space, starting from valid models of different complexity. Distribution of the number of random iterations models underwent without losing characteristic activity.

5 Addition of ion channel isoforms helps increase the efficiency of finding valid models



A: Statistics of extended 5-channel models in two-fold sample. Diversity was expanded by adding altered copies of remaining channels with randomized time constants. Condition of anticorrelation between sodum conductance in soma & axon (blue dots).
B: Statistics of valid models in sample with different ranges.

6 Summary

- **Full GC model with 15 ion channels can be successfully reduced to 5 channels**
- **Random variation of channel densities leads to a larger solution region in the parameter landscape (6.3% solutions) in the full model as compared to reduced models**
- **Solutions are well spread the parameter landscape in full but patchy in reduced models**
- **High dimensional model is able to compensate for pathological conditions such as ion channel deletion (knock-out)**

Conclusion

Ion channel diversity may allow for increased robustness and higher flexibility of finding a solution in the complex parameter space.

References:
Alonso L.M., Marder E. (2018) Visualization of the relative contributions of conductances in neuronal models with similar behavior and different conductance densities. *bioRxiv* 427260.
Beining M., Mongiat L. A., Schwarzacher S. W., Cuntz H., Jedlicka P. (2017) T2N as a new tool for robust electrophysiological modeling demonstrated for mature and adult-born dentate granule cells. *eLife* 6:e26517.
Cuntz H. , Forstner F., Borst A., Häusser M. (2010) One Rule to Grow Them All: A General Theory of Neuronal Branching and Its Practical Application. *PLoS Computational Biology* 6(8):e1000877.
Mongiat L. A., Espósito M.S., Lombardi G., Schinder A. F. (2009) Reliable Activation of Immature Neurons in the Adult Hippocampus. *PLoS ONE* 4(4): e5320.
Schmidt-Hieber C, Jonas P, Bischofberger J (2007) Subthreshold dendritic signal processing and coincidence detection in dentate gyrus granule cells. *J Neurosci* 27:8430-8441 .
van der Maaten L.J.P., Hinton G.E. (2008) Visualizing High-Dimensional Data Using t-SNE. *Journal of Machine Learning Research* 9:2579-2605.

Acknowledgements
This work was funded by a DFG grant (CU 217/2-1), by a BMBF grant (No. 01GQ1406 – Bernstein Award 2013) and by University Medical Center Giessen and Marburg (UKGM).