Transitions in cartwheel cell electrical activity: bifurcations of super-slow equilibria explain effects of ion current blockers | Matteo Martin

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Cartwheel cells (CWCs) are inhibitory interneurons of the dorsal cochlear nucleus (DCN), a brainstem region where parallel fibers and primary auditory afferents are integrated. CWCs exhibit different types of activity, which can be classified as bursting, spiking and complex spiking. Electro-pharmacological experiments [1] have shown that the L-type Ca^{2+} blocker, nifedipine, impairs complex spiking dynamics by promoting continuous spiking behaviour; on the other hand, iberiotoxin, a BK channel blocker, has the opposite effect on CWC dynamics.

In this work, we aim to explain these transitions by investigating a reduction of a novel conductance-based CWC model. The reduced model comprises a six-dimensional (6D) system of ODEs, and its dynamical variables evolve at different rates. For this reason, we exploit timescale separation along with bifurcation and averaging theories to understand how changes in the L-type Ca^{2+} and BK channel conductances affect the model dynamics.

The timescale hierarchy of the 6D model is complicated due to unclear distinctions between some of the time constants involved. Nevertheless, we find that the use of a three-timescale decomposition provides insights into the mechanisms mediating the transitions observed in the experiments.

Within this hierarchy, the slow-fast subsystem of the full model is studied through the calculation of one- and two-parameter bifurcation diagrams by using the super-slow variables as bifurcation parameters. To analyze the dynamics of these super-slow variables, we apply averaging theory where the slow-fast subsystem exhibits stable periodic orbits. For this computation, we customize numerical continuation techniques to track the super-slow averaged nullclines efficiently. We find that due to the intricate timescale structure of the 6D system, averaging theory predicts the behaviour of the full model only for certain ranges of CWC excitability, comprising the regimes of continuous and complex spiking. In these regimes, we exploit changes in the stability of the unique super-slow averaged equilibrium point to explain the changes in dynamics that occur as the parameters associated with L-type Ca^{2+} and BK channel conductances are varied.

In conclusion, through the development of a novel conductance-based model, analysis of the model dynamics based on a three-timescale hierarchy, and the study of super-slow dynamics based on averaging over slow-fast oscillations, this work proposes a possible mathematical interpretation for the transitions in CWC dynamics observed experimentally with calcium and potassium channel inactivation.

[1] Kim Y. and Trussell L.O., Ion Channels Generating Complex Spikes in Cartwheel Cells of the Dorsal Cochlear Nucleus, Journal of Neurophysiology, (2007), 97:2, 1705-1725.