Paths to depolarization block: modeling neuron dynamics during spreading depolarization events | Marisa Saggio

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Spreading Depolarization (SD) is a pathological state of the brain involved in several brain diseases, including epilepsy and migraine. SD consists of a slowly propagating wave of nearly complete depolarization of neurons, classically associated with a depression of cortical activity. This homology between SD and spreading depression has been recently challenged [1]: during SD events, which only partially propagate from the cortical surface to depth, neuronal activity may be suppressed, unchanged or elevated depending on the distance to the SD stop depth. These patterns can be explained by analysing the activity of single neurons. In layers invaded by SD, neurons lose their ability to fire entering Depolarization Block (DB) and far from the SD neurons maintain their membrane potential. However, neurons in between unexpectedly displayed patterns of prolonged sustained firing.

In the present work [2], we build a phenomenological model, incorporating some key features observed during DB in this dataset (current-clamp patch-clamp recordings from 10 L5 pyramidal neurons in the rat somatosensory cortex during SDs evoked by distant application of 1M KCl), that is able to predict the new patterns observed. We model the L5 neuron as an excitable system close to a SNIC bifurcation [3], using the normal form of the unfolding of the degenerate Takens-Bogdanov singularity for the fast dynamics [4], under the modulatory effect of two slow variables. The model's bifurcation diagram provides a map for neural activity that includes DB together with the patterns observed for intermediate values of depolarization. We identify five qualitatively different scenarios for the transition from healthy activity to DB. A SNIC bifurcation accounts for the transition from the healthy state to sustained oscillations, and

either a supercritical Hopf or Fold Limit Cycle bifurcation for the transition to DB for strong levels of depolarization. Both can occur with or without bistability between the healthy and pathological state, giving four possible scenarios. These scenarios encompass the mechanisms for DB present in the modeling literature and allow us to understand them from a unified perspective. We add another mechanism based instead on movement in state space. Time series in our dataset are consistent with the scenarios, however the presence of bistability cannot be inferred by our analysis.

Understanding how brain circuits enter and exit SD is important to design strategies aimed at preventing or stopping it. In this work we use modeling to gain mechanistic insights on the ways a neuron can transition to DB or to different patterns of sustained oscillatory activity during SD events, as observed in our dataset. While our work provides a unified perspective to understanding modeling of DB, ambiguities remain in the data analysis. These ambiguities could be solved by scenario-dependent theoretical predictions, for example for the effect of stimulation, for further experimental testing.