Neuronal rhythmic activity induced by the electrogenic Na+/K+-ATPase

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Brain rhythms observed during slow-wave sleep or seizures exhibit frequencies significantly lower than typical neuronal firing rates. Their underlying mechanisms of slow brain waves are still subject of research. These rhythms are thought to arise from synaptic interactions, network delays, intrinsic neuronal properties, or a combination of all. This study aims to investigate a generic mechanism through which any individual neurons can generate slow rhythms - the interplay with ionic concentration dynamics without expressing dedicated ion channels with slow kinetics.

Previous theoretical studies have linked neuron-intrinsic slow bursting to slow ion channels. Here, we demonstrate that the electrogenic nature of the Na+/K+-ATPase, through its influence on extracellular potassium dynamics, could play a role in generating rhythmic activity in all neuron models with class I excitability. While this concept was first suggested by Ayrapetyan (1971) based on experimental observations, it lacked precision and received limited attention.

Specifically, we demonstrate that such pump-mediated slow rhythmic activity appears as square-wave bursting, a rhythmic activity pattern found in class I excitable neurons (Fig 1A), organised around a hysteresis loop in a bistable region resulting from a saddle-node

loop codim-2 bifurcation. Using slow-fast analysis, we demonstrate that the hysteresis loop formation relies on shear in the bifurcation diagram induced by the electrogenicity of the pump (Fig 1B and C).

Accordingly, we find that, depending on the density of the sodium-potassium pump, the system can exhibit four distinct regimes: rest, tonic spiking, bursting, and depolarization block. Through a comprehensive bifurcation analysis of the entire system, we identify that the transition from tonic spiking to bursting occurs via a cascade of period doubling, ultimately leading to chaotic behaviour at the border of changing dynamics (Fig 1D).

Finally, we propose an approach to reduce our conductance-based model to a quadratic integrate-and-fire framework, a simple class I excitable system, capturing the interaction between extracellular potassium and voltage dynamics. To preserve the heterogeneity and rich dynamics of the original system, we fit the bifurcation structure rather than voltage traces. This simplification allows for the study of network behaviour during fluctuations in extracellular potassium.

Our analysis clarifies how the Na+/K+-ATPase electrogenicity not only drives slow bursting but also plays a fundamental role in shaping diverse neuronal dynamics in simple class I excitable neuron models. The dynamics which have been linked to various healthy and pathological conditions. Moreover, to facilitate the analysis of the dynamics we identified within a network framework, we propose a method for simplifying class I excitable systems through fitting the bifurcation structure.
