Phase plane modelling from voltage clamp experiments

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Phase plane analysis is a common and useful tool to study the behaviour of nonlinear systems. In mathematical neuroscience it is often used to study single neuron models that can be reduced to two variables. These neuron models often have the property of timescale separation, e.g. the activation of the sodium current is much faster than the other (in)activations, which behave on approximately the same timescale. This property greatly simplifies the phase plane reduction and analysis, since the system will jump between stable branches of the fast nullcline.

A standard method to construct phase portraits of neuronal models is via a two-dimensional reduction of a conductance-based model. But the conductance-based model itself is the result of tedious electrophysiological experiments, pharmacological manipulations and manual curve fits. Here we address the question of identifying a phase portrait directly from the classical voltage clamp experiment. Previous efforts to do so relied on assumptions that only hold for currents without inactivation [2].

We propose a simple procedure to obtain a phase portrait from a series of voltage clamp experiments. The method works for every neuron with dynamics in two distinct timescales. The only prior information necessary is the approximate time constant of the fast dynamics. The fast current response of the voltage clamp is extracted for different combinations of holding potential and step amplitude. The locus where the fast current vanishes defines the fast nullcline of the phase portrait. Assuming the dynamics can be described as a function of a fast and slow voltage, which are equal at equilibrium, the slow nullcline is the linear bisectrix in the phase plane of fast and slow voltages. When a conductance-based model is available, an equivalent analytical method exists, avoiding the need for voltage clamp simulations.

We use this method to study the phase portrait of neurons with slow regenerativity. Slow regenerative channels as defined in [1] are ion channels which induce a positive feedback on the membrane potential in a timescale slower than that of the spike upstroke. The simplest neuron with slow regenerativity is the squid giant axon with a modified extracellular potassium concentration, as observed by Moore [3]. This was subsequently modelled by Rinzel [4] by changing the Nernst potential V_K. A phase portrait of this model obtained with the voltage clamp method clearly shows that the slow regenerativity adds a lower branch to the fast nullcline, explaining the bistability and spike latency [1, 5]. This appearance of a lower branch on the fast nullcline is also observed when reducing the conductance-based model using classical methods [1].

The method also allows to study the effect of modulation of the slow regenerativity on the neural dynamics. Experiments with the Connor-Stevens model for different values of the maximum conductance g_A, show that the phase portrait provides a good prediction of the region of bistability and hysteresis.

References

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