Computational modeling of the lamprey CPG

from subcellular to network level

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Abstract

Due to the staggering complexity of the nervous system, computer modelling is becoming one of the standard tools in the neuroscientist’s toolkit. In this thesis, I use computer models on different levels of abstraction to compare hypotheses and seek understanding about pattern-generating circuits (central pattern generators, or CPGs) in the lamprey spinal cord. The lamprey, an ancient and primitive animal, has long been used as a model system for understanding vertebrate locomotion. By examining the lamprey spinal locomotor network, which is a comparatively simple prototype of pattern-generating networks used in higher animals, it is possible to obtain insights about the design principles behind the spinal generation of locomotion.

A detailed computational model of a generic spinal neuron within the lamprey locomotor CPG network is presented. This model is based, as far as possible, on published experimental data, and is used as a building block for simulations of the whole CPG network as well as subnetworks. The model construction process itself revealed a number of interesting questions and predictions which point toward new laboratory experiments. For example, a novel potential role for KNaF channels was proposed, and estimates of relative soma/dendritic conductance densities for KCaN and KNaS channels were given. Apparent inconsistencies in predicted spike widths for intact vs. dissociated neurons were also found. In this way, the new model can be of benefit by providing an easy way to check the current conceptual understanding of lamprey spinal neurons.

Network simulations using this new neuron model were then used to address aspects of the overall coordination of pattern generation in the whole lamprey spinal cord CPG as well as rhythm-generation in smaller hemisegmental networks. The large-scale simulations of the whole spinal CPG yielded several insights: (1) that the direction of swimming can be determined from only the very rostral part of the cord, (2) that reciprocal inhibition, in addition to its well-known role of producing alternating left-right activity, facilitates and stabilizes the dynamical control of the swimming pattern, and (3) that variability in single-neuron properties may be crucial for accurate motor coordination in local circuits.

We used results from simulations of smaller excitatory networks to propose plausible mechanisms for obtaining self-sustaining bursting activity as observed in lamprey hemicord preparations. A more abstract hemisegmental network model, based on Izhikevich neurons, was used to study the sufficient conditions for obtaining bistability between a slower, graded activity state and a faster, non-graded activity state in a recurrent excitatory network. We concluded that the inclusion of synaptic dynamics was a sufficient condition for the appearance of such bistability.
Questions about rhythmic activity intrinsic to single spinal neurons – NMDA-TTX oscillations – were addressed in a combined experimental and computational study. We showed that these oscillations have a frequency which grows with the concentration of bath-applied NMDA, and constructed a new simplified computational model that was able to reproduce this as well as other experimental results.

A combined biochemical and electrophysiological model was constructed to examine the generation of IP3-mediated calcium oscillations in the cytosol of lamprey spinal neurons. Important aspects of these oscillations were captured by the combined model, which also makes it possible to probe the interplay between intracellular biochemical pathways and the electrical activity of neurons.

To summarize, this thesis shows that computational modelling of neural circuits on different levels of abstraction can be used to identify fruitful areas for further experimental research, generate experimentally testable predictions, or to give insights into possible design principles of systems that are currently hard to perform experiments on.