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Does reliable neuromodulation require that neuronal network parameters are tightly regulated?

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Previous experimental results and simulation studies show that similar spontaneous electrical activity can arise from different cellular and synaptic properties, both at the level of single neurons and at the level of neuronal circuits [1,2]. Neuronal circuits thus appear to have large "solution spaces" at their disposal, rather than having to fine-tune their cellular and synaptic parameters to specific values in order to function properly. On the other hand, neuromodulators often have reliable and reproducible effects on the same circuit in different animals [3]. If different animals generate the same circuit output on the basis of different circuit properties, how can they react in the same way to application of a neuromodulator?

To address this question we separately simulated the cellular and synaptic effects of the I_A channel blocker 4-aminopyridine (4-AP) and of dopamine in 452,516 models of the pyloric pattern-generating network of crustaceans. These three-cell circuit models differed substantially in their cellular membrane conductance composition and in the strengths of the seven synapses in the circuit, but all 452,516 circuit models had previously been shown to generate spontaneous network activity that closely mimics the biologically observed pyloric rhythm [2]. We then identified those pyloric network models among the 452,516 original models that responded to application of 4-AP or dopamine in the same way that the biological circuit responds [3,4] with respect to rhythm criteria such as period, burst frequencies, and duty cycles.

For both 4-AP application and dopamine application, we found that only a subset of the original 452,516 network models showed a response similar to that of the biological circuit. This implies that although similar spontaneous circuit activity can arise from different circuit properties, the requirement that a circuit respond correctly to neuromodulation can impose additional constraints on circuit parameters and thus decrease the size of the solution space available to a neuronal circuit. However, the subset of network models that performed correctly during simulated application of 4-AP or dopamine contained models that differed widely in some of their cellular and synaptic parameters. This suggests that even neuronal networks that need to be able to generate a variety of biologically functional behaviors in the presence of different neuromodulators can do so without having to narrowly tune their circuit parameters.

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