Multiple routes to similar network output

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Neuronal networks are built from neurons with different properties and from synapses of different strengths. Modeling suggests that networks can tune these parameters to many different combinations that nonetheless produce very similar network outputs.

What would happen if we measured the ability of humans to write with their left and right hands and averaged the results without accounting for the population's bimodality? Rather than identifying the true case that 10% of people write exclusively with their left hand and 90% exclusively with their right, we would report that people write 90% of the time with their right hand and 10% with their left.

Characterizing every conductance and synaptic strength within a neuronal network in a single experiment is generally impossible. Instead, experimentalists often make a few measurements in the 'same' neuron or synapse from multiple animals, then repeat the process for another set of measurements in a different group of animals and eventually obtain multiple measurements of all the network's conductances and synaptic strengths. These measurements are then typically reported as an average ± standard deviation or error. This procedure is perfectly acceptable if the neurons and networks that are said to be the 'same' have similar conductances and synaptic strengths in different individuals, and if variations in one parameter are uncorrelated with variations in other parameters. However, it does not account for the possibility that neurons or networks with different conductances or synaptic composition might be able to produce the same activity if changes in one conductance or synapse were compensated by changes in other conductances or synapses. Eve Marder and her co-workers have investigated this hypothesis extensively in single neurons, both experimentally and computationally.

In this issue, Prinz et al. now show that model neural networks with different combinations of intrinsic neuronal properties and synaptic strengths can produce extremely similar outputs (Fig. 1). The neurons or networks that are compared over different individuals might therefore be the same only with respect to their output, not their underlying makeup.

Prinz et al. simulated 20,250,000 model neural networks consisting of three neurons, each of which existed in five or six different intrinsic-property versions and could be interconnected with five or six different synaptic strengths. They then identified which of these models produced outputs resembling the triphasic bursting activity of the well-known decapod crustacean pyloric network. Remarkably, even with fairly stringent selection criteria based on 15 measures of experimental spiking activity, over 2% (452,516) of the models produced correct ('pyloric') outputs. Even more remarkably, models producing pyloric output could be built with all six model-neuron types and with synapses spanning the entire range of conductance values (with the exception of one synapse that needed to be weak). This suggests that compensatory, function-maintaining changes in cellular and synaptic properties can occur in a graded fashion.

Such graded correlations would be much less obvious experimentally than simple cases of bimodality—where, for example, a low value of current X is associated with a strong synapse Y and a high value of Y with a weak synapse X. The Prinz et al. work thus indicates that experimentalists must re-examine their data to test whether their standard deviations actually represent graded, correlated changes of neuronal and network properties. Wide current-density variations (up to threefold) and synaptic-strength variations (with standard deviations as large as ±100% of the mean) have been experimentally observed in the pyloric network. Cross-correlations among the measured parameters were not calculated, and it is therefore not

Figure 1. Example illustrating how different combinations of synaptic strength and intrinsic neuron properties could produce outputs that have the same cycle period, spike number and phase relationships (albeit with fine differences in action potential timing and slow-wave trajectories). The system modeled by Prinz et al. had nine dimensions (three neurons whose intrinsic properties could vary, and six synapses).
Back to the future: carbon dioxide chemoreceptors in the mammalian brain

Gordon S Mitchell

Neurons that increase breathing in response to increased CO₂ have long been sought along the ventral medullary surface, but not found, until now. Exquisitely CO₂-sensitive neurons identified near this site may be the long-lost central chemoreceptors.

The brain defends itself from large and damaging changes in carbon dioxide and pH by controlling breathing, which regulates carbon dioxide levels to within an acceptable range by classical negative feedback. More than 40 years ago, R.A. Mitchell and colleagues proposed that CO₂- or pH-sensitive neurons initiating this reflex are located on the ventral surface of the medulla oblongata. This hypothesis rapidly became textbook knowledge, learned by medical and physiology students alike. However, despite intensive investigation over many years, the specific chemosensitive neurons implicated could not be found. Eventually, investigators focused their attention elsewhere, and CO₂-/pH-sensitive neurons have now been identified at a number of other sites in the central nervous system, including the nucleus of the solitary tract, the cerebellum, the locus coeruleus and the raphe nucleus near the brainstem midline. We still, however, do not know the relative contribution of each of these sites to the breathing response when carbon dioxide levels change. Now Mulkey et al. have identified a population of exquisitely sensitive chemoreceptors near the ventral brainstem (in anesthetized rats and in slices from near the medullary surface), a site closely approximating that originally proposed in 1963.

The region investigated by Mulkey et al. is known as the retrotrapezoid nucleus (RTN; Fig. 1), a population of cells located ventral to the facial nucleus, which was first reported in cats. The cell bodies of the RTN chemosensitive neurons are located just below, and extend dendrites to, the ventral medullary surface, where the dendrites are exposed to cerebrospinal fluid. Cells in the RTN project to important groups of respiratory...