Multiscale modeling of the neural control of breathing: complex and simplified models

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Over the past two decades, models of varying complexity have been formulated for neural networks in the mammalian brainstem that are allowing mechanistic study of how neural activity patterns controlling breathing are generated and regulated. These models range from small networks of neurons with detailed, quasi-realistic biophysical properties, to large-scale network models of many interacting heterogeneous populations of neurons. Heuristic mathematical models with various levels of abstraction have also been developed to represent the dynamics of small and large networks. Furthermore, recent modeling efforts have attempted to couple neural models to simplified models of lung gas exchange and gas transport with feedback control, which represents an important new avenue for understanding the integrated neurophysiological control system that we are pursuing.

Our project supported by the NIH Multiscale Modeling Program involves a collaboration between six research groups in three countries (USA: Dick, Rogers, Rybak, and Smith; United Kingdom: Paton; and New Zealand: Ben-Tal). As a central part of this project, we are developing a comprehensive, multiscale model of the brainstem respiratory neural network responsible for generating the respiratory rhythm and pattern. One specific problem in this direction is finding and adjusting values of critical parameters that define the behavior of the large-scale, biophysically detailed network model under different physiological and pathological conditions. We are applying various mathematical descriptions of the dynamical behaviors of neural populations that represent subsystems within the larger network. Versions of the subsystem models with reduced complexity have the same basic network architecture as their more complicated prototypes, but are developed using simplified, activity-based models of neural populations instead of interacting populations of neurons simulated in the Hodgkin-Huxley style and incorporating specific biophysical details. This allows us to use dynamic systems theory methods to investigate the models' operating regimes and identify critical values of parameters such as the average weights of connections between populations and the values of input drives that define each regime and transitions between them.

The "kernel" subsystem of the full model comprises interacting populations located in the pre-Bötzinger and Bötzinger complexes of the medulla. The initial organization of interactions between these populations in the model was based on existing experimental data and previously published models. The network structure of the kernel along with cellular properties incorporated in single neuron models allows the complex model of the kernel to express multiple breathing patterns, similar to those observed in different physiological states and metabolic conditions. By employing the reduced models, we have been able to surmise that the expression of each pattern depends on the balance of excitatory drives from several key brainstem populations. We have analyzed various features of the dynamics of pattern generation such as control of oscillation frequency and the conditions causing transitions between the different respiratory patterns.

The ultimate goal of this project is the development and implementation of a new, fully operational, multiscale model of the integrated neurophysiological control system for breathing based on the current state of physiological knowledge. The model developed in this project can then be used as a computational framework for formulating predictions about possible neural mechanisms underlying respiratory disorders and to suggest possible treatments.