A prototype neuromechanical model of airway defensive reflexes

R.O'Connor[1], L.S. Segers[1], K.F. Morris[1], S.C. Nuding[1], T.E. Pitts[2], D.C. Bolser[2], P.W. Davenport[2], B.G. Lindsey[1]

1. Physiological Sciences, University of Florida, Gainesville, FL
2. Molecular Pharmacology and Physiology, University of South Florida, Tampa, FL

The operational features, identity, and specific neural mechanisms which regulate and coordinate the occurrence of cough, swallow, and breathing to optimize airway protection are poorly understood. The lack of such knowledge hampers understanding of pathophysiological deficits in airway protection and impairs progress in the development of novel therapeutic approaches in dysphagia and dystussia that occur because of neurologic disease. The long-term goal of this project is to determine the brainstem mechanisms that control and coordinate cough, swallow, and breathing. We have developed a predictive computational distributed neural network model, based on elements and connectivity inferred from simultaneous extracellular recordings of many (100+) brainstem neurons. Computer simulations reproduce some of the known regulatory mechanisms in the neurogenesis of cough and we are beginning to simulate the pharyngeal phase of swallow. Computational models add significant value to *in vivo* approaches by allowing refinement of a limited set of testable hypotheses for further *in vivo* testing. The stochastic neural network simulator is implemented in the *C* language for the Linux environment (Rybak et al., J. Neurophysiol, 2008).

The networks consist of discrete "integrate and fire" populations. The program allows neuron excitability to be modulated by injected current and added noise "fiber populations" external to the network are used to represent transiently active afferent inputs to the network. A network editor program is used as a graphical interface to build and edit networks, specify parameters, and invoke the simulator. This program allows populations and their synaptic connections to be added, edited, and deleted. Retrograde and anterograde "trace" functions selectively mark all direct sources of inputs and targets of a particular population, respectively. Other C language programs display two types of outputs from the simulator: (*i*) formatted text file that list the spike times of selected neurons and the integrated activity of a population, usually the simulated phrenic motoneurons, and (*ii)* text files that represent membrane potentials of selected neurons, or average firing rates of selected populations on neurons.

The current hybrid prototype converts respiratory neural outputs in the form of spike trains representing lumbar, phrenic, expiratory laryngeal and inspiratory laryngeal motor neuron activity generated by a stochastic model of the brainstem respiratory network deterministically into mechanical outputs such as lung volume, tracheal flow and alveolar pressure. Lung volume is fed back to the network model to simulate pulmonary stretch receptors. The mechanical model components include (*i*) three-element Hill muscle models of the diaphragm and abdominal muscles (A.V. Hill, Proc R Soc Lond. B, 1938), (*ii*) a model of the larynx based on the results of Tully et al. (J Appl Physiol. 1990) and Rohrer's equation (Arch Ges Physiol, 1915), and (*iii*) lung/diaphram/ribcage/abdomen volume relationships modeled on the data of Grassino et al (J. Appl. Physiol, 1978) and the analysis of Mead & Loring (J Appl Physiol. 1982).

This prototype provides a framework for integrating respiratory network model development with respiratory mechanics and will guide and facilitate scaling and timing of motor neuron activity patterns and functionally antecedent connectivity for generating breathing, coughing and swallow.

Preliminary simulations of cough and breathing suggest that an important area of focus for modeling efforts will be reconciliation of known differential effects of pulmonary volume-related feedback on these two behaviors. Specific components of the model that are proposed to have the greatest effect on its potential for prediction are the gain of pulmonary volume-related feedback and the interaction this feedback with cough-related sensory information. Supported by NIH HL 89104; HL 89071; HL 103415.