

## Computational Studies of the Respiratory Brainstem

(1R01NS046062-03-FY02)

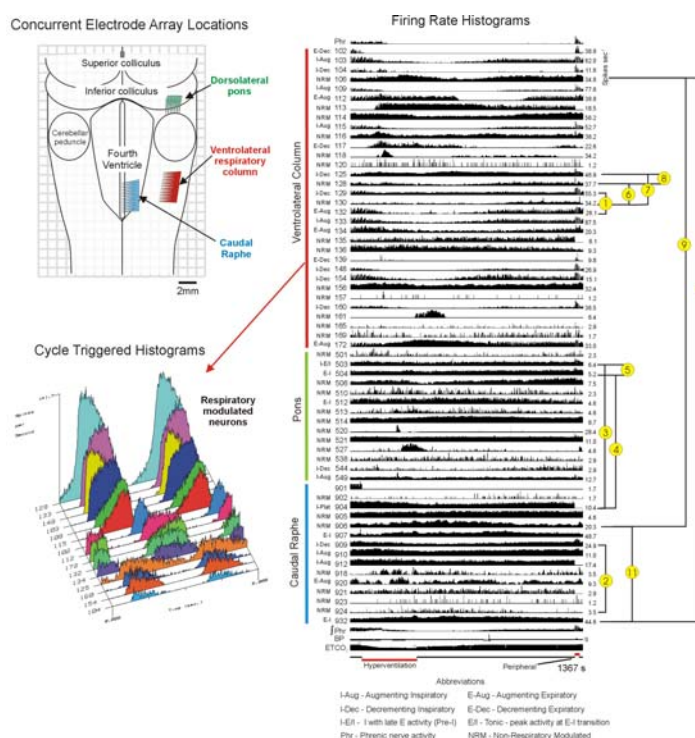
Bruce G. Lindsey

University of South Florida

The goal of this collaborative project is to develop a unified network model of the respiratory brainstem, using experiments to test and tune model-based hypotheses. We have generated respiratory-like patterns in simulated networks, reproducing several physiological phenomena and effects of pontomedullary transections. We have modeled responses to hypoxia during sleep and wakefulness, high-frequency oscillations during inspiration, the transition from eupnea to gasping, and neural pacemaker mechanisms. Simulation results, confirmed in isolated pre-Bötzing complex (pre-BötC) neurons, show that bursting in pacemaker neurons can be induced by a reduction of potassium currents or augmentation of persistent sodium currents. These conditions accompany hypoxia and support hypotheses on central hypoxia chemoreception. Multi-array recordings of respiratory neurons during transient hyperventilatory apnea have revealed distributed circuit dynamics and the dissolution and reemergence of rhythmic respiratory network activity (Figure). We have also explored in intact unanesthetized animals the effects of hypoxia on respiratory neuron discharge patterns during sleep states. Other experimental series show that pontine networks integrate cardiac and respiratory modulated inputs, suggest that pontine and medullary raphe neurons participate in hypoxia-induced gasping, and that pre-BötC neurons are involved in the generation of inspiratory high-frequency oscillations as well as phase timing and pattern generation. Results from the “working heart brainstem preparation” suggest decrementing expiratory neurons prolong expiration following hypoxia. The project is also a catalyst for the development and sharing of multi-array recording technologies and open source software, including a hybrid network simulator, an automatic spike sorting system, and enhanced tools for spike train analyses and data visualization.

**Multi-array recordings provide a window on distributed circuit dynamics during the dissolution and reemergence of rhythmic respiratory network activity.**

Parallel recordings from 61 ventral respiratory column, pontine, and raphe neurons document the first observations of concurrent “up or down” firing rate changes at multiple brainstem sites during hyperventilatory apnea. Extended correlational linkages (e.g., labeled lines, right) support the hypothesis that synaptic interactions among neurons in all three sites contribute to the observed modulation.



## **PI Website**

<http://www.hsc.usf.edu/medicine/physiology/blindsey.html>

## **Publications**

Publications supported by grant NS046062 as part of the NSF/NIH Collaborative Research in Computational Neuroscience Program.

Baekey, D. M., Jaber, M. A., Morris, K. F., and Dick, T. E. Differential activation of expiratory activity during and after brief episodes of hypoxia in the WHBP from rats. Soc. Neuroscience Abstract. Program No. 187.10, 2004.

Baekey, D. M., Morris, K. F., Dick, T. E. Disinhibition of expiratory activity during and immediately after hypoxia in the rat in situ preparation. FASEB J. Abstract, In press, 2005

Dunin-Barkowski, W. L., J. M. Orem, A.T. Lovering, E. H. Vidruk, M. G. Sirota, I. N. Beloozerova. Precise Rhythmicity in Activity of Neocortical, Thalamic and Brain Stem Neurons in Unanesthetized Cats. Soc. Neurosci. Abst. Program No. 661.5, 2003.

Dunin-Barkowski, W.L., Escobar A.L., Lovering A.T., Orem J.M. Respiratory Pattern Generator Model Using Ca<sup>++</sup>-induced Ca<sup>++</sup> Release in Neurons Shows both Pacemaker and Reciprocal Network Properties – Biol. Cybernetics, 89: 274-288, 2003.

Jaber, M. A., David M. Baekey, D. M., Chris G. Wilson C. G., and Dick, T. E. Control of expiration: Predictions from a current model. Soc. Neurosci. Abst. Program No. 187.11, 2004.

Lindsey, B.G., Morris, K.F., Segers, L.S., O'Connor, R. E., and Shannon, R Simulations of modulatory circuits in the respiratory brainstem. FASEB J. 18: Abstract No. 223.2, 2004.

Lovering A.T. The Effects of Hypoxia on Sleep, Breathing, and Medullary Respiratory Neurons in the Cat. Ph. D. Thesis, Texas Tech University Health Sciences Center, June 2003 (mentor: J.M. Orem).

Lovering, A. T., W. L. Dunin-Barkowski, E. H. Vidruk, J. M. Orem. Medullary Respiratory Neural Activity during Hypoxia in Sleep and Wakefulness in the Cat. FASEB J. 18: Program No. 689.1. 2004.

Lovering, A. T., W. L. Dunin-Barkowski, E. H. Vidruk, J. M. Orem. Behavior of Medullary Respiratory Neurons during Hypoxia-Induced Periodic Breathing. FASEB J. 18: Program No. 468.17. 2004.

Lovering, A.T., Dunin-Barkowski W.L., Vidruk E.H., Orem J.M. Ventilatory Response of the Cat to Hypoxia in Sleep and Wakefulness. J. Appl. Physiol., 95:545-554, 2003.

Lovering, AT, J. J. Fraigne, WL Dunin-Barkowski, EH Vidruk, JM Orem. Hypocapnia reduces the amount of REM sleep in Cats. Sleep 26 Abstract Supplement, A62, 2003.

Morris, K. F. Nuding, S. C. Dick T. E., Baekey D. M., Segers L. S., Shannon R. and Lindsey B. G. Pontine cardiorespiratory network interactions. Soc. Neurosci. Abst. 29: program No. 503.8, 2003.

**NSF/NIH Collaborative Research In  
Computational Neuroscience Workshop  
Spring 2005 Principal Investigators' Meeting**

---

- Morris, K.F., Nuding, S.C., Dick, T. E., Baekey, D.M., Segers, L.S., Shannon, R., and Lindsey B.G. Brainstem cardiorespiratory network interactions. *FASEB J.* 18: Abstract No. 844.3, 2004.
- Nuding, S. C., Morris, K. F., Baekey, D. M., Segers, L. S., Shannon, R., and Lindsey B.G. Functional connectivity between pontine and medullary raphe neurons responsive to chemoreceptor stimulation. *FASEB J.* 18: Abstract No. 690.2, 2004.
- Nuding S. C., Lindsey, B. G., Segers, L. S., Baekey, D. M., Dick T. E., Shannon, R. and Morris, K. M. Pontomedullary respiratory correlational assembly dynamics during transient hyperventilatory apnea. *FASEB J.* Abstract, in press, 2005
- Orem, J. Neural control of breathing in sleep. In: *The Physiological Nature of Sleep*, edited by P.L. Parmeggiani and R.A. Velluti. Imperial College Press, London, In press.
- Orem, J. and Kubin, L.: Neural control of breathing in sleep and wakefulness. In *Principles and Practices of Sleep Medicine*, 4th edition, edited by M. Kryger, T. Roth, and W.C. Dement. Elsevier, Philadelphia, Pennsylvania, In press.
- Orem, J., Dunin-Barkowski, W., Vidruk, E.H., Lovering, A.T. Tonic Excitatory Drive to Central Respiratory Neurons in REM Sleep in Cat APSS (Associated Professional Sleep Societies) Abstract.18th Annual Meeting. June 5-10, 2004.
- Pierrefiche, O., N. A. Shevtsova, W. M. St.-John, J. F. R. Paton, and I.A. Rybak. Ionic currents and endogenous rhythm generation in the pre-Bötzinger Complex: Modeling and in vitro studies. *Adv. Exp. Med. Biol.* In press.
- Pierrefiche, O., Shevtsova, N. A., St.-John, W. M, Paton, J. F. R., and Rybak, I. A. Ionic currents and Endogenous rhythm generation in the pre-Bötzinger Complex: Modeling and in vitro studies. IX Oxford conference "Modeling and Control of Breathing", Abstract, Paris, France, 2003.
- Potts, J. T., Rybak, I. A., and Paton, J. F. R. Respiratory rhythm entrainment by somatic afferent stimulation. *J. Neurosci.* 2005 (in press).
- Rogers, R. F., Marchenko, V., and Rybak, I. A. Graphical representation of eupnea and gasping states in mammalian breathing. *Soc. for Neurosci Abs.*, 2004.
- Rybak, I. A., K. Ptak, N. A. Shevtsova, and D. R. McCrimmon. Sodium currents in neurons from the rostroventrolateral medulla of the rat. *J. Neurophysiol.*90: 1635-1642, 2003.
- Rybak, I. A., N. A. Shevtsova, J. F. R. Paton, O. Pierrefiche, W. M. St.-John, and A. Haji Modeling respiratory rhythmogenesis: Focus on phase switching mechanisms. *Adv. Exp. Med. Biol.* In press.
- Rybak, I. A., N. A. Shevtsova, J. F. R. Paton, T. E. Dick, W. M. St-John, M. Mörschel, and M. Dutschmann. Modeling the ponto-medullary respiratory network. *Respir. Physiol. Neurobiol.* 143: 307-319, 2004.
- Rybak, I. A., N. A. Shevtsova, K. Ptak, and D. R. McCrimmon. Intrinsic bursting activity in the pre-Bötzinger Complex: Role of persistent sodium and potassium currents. *Biol. Cybern.* 90: 59-74, 2004.

**NSF/NIH Collaborative Research In  
Computational Neuroscience Workshop  
Spring 2005 Principal Investigators' Meeting**

---

Rybak, I. A., N. A. Shevtsova, W. M. St.-John, J. F.R. Paton and O. Pierrefiche. Endogenous rhythm generation in the pre-Bötzinger complex and ionic currents: Modeling and in vitro studies. *Eur. J. Neurosci.*18: 239-257, 2003.

Rybak, I. A., Shevtsova, N. A., Paton, J. F. R., Pierrefiche, O., St.-John, W. M., and Haji, A. Modeling respiratory rhythmogenesis: Focus on the respiratory phase-switching mechanisms. IX Oxford conference "Modeling and Control of Breathing", 2003, Paris, France. Abstract, In press.

Solomon, I. C., Morris, K. F., Dick, T. E., Baekey, D. M., Nuding, S. C. Shannon, R. and Lindsey, B. G. Dorsolateral pontine neurons discharge synchronously with hypoxia-induced gasps and augmented bursts. *Soc. Neurosci. Abst.* 29: Program No. 503.15, 2003.

Solomon, I.C. Excitation of phasic inspiratory activity produced by chemical stimulation of the pre-Bötzinger complex modifies spectral activity in vivo. *Soc. Neurosci. Abst.* Program No. 424.14, 2004.

Solomon, I. C., Morris, K. F., Nuding, S. C., Segers, L. S., and Lindsey, B. G. Raphe neuron responses during hypoxia-induced gasps and augmented bursts. *FASEB J. Abstract*, in press, 2005