

A New Mathematics-Inspired Understanding of Breathing and the Brain

By Jeffrey C. Smith

The brain produces movement and also controls homeostasis of the internal physiological state of the brain and body. These two facets of brain function converge in the neural system that controls breathing. Breathing is a primal homeostatic neural process, regulating brain and body oxygen and carbon dioxide levels; rhythmic movements, generated continuously throughout life by the nervous system, are responsible for the process. The automatic and seemingly simple nature of the act of inspiration and expiration belies the complexity of the neural machinery involved. Indeed, neurophysiologists have been conducting intensive investigations of the underlying mechanisms for more than a century. Mathematicians and other brain modelers have gotten into the act and are making profound contributions.

For experimentalists, a major focus has been to discover, at the level of nerve cells and circuits, how the breathing rhythm in mammals is generated. For modelers, the problem, like problems elsewhere in the brain, entails analyses of how oscillations and patterns of neural activity evolve in nonlinear dynamical systems. The experimental breakthrough occurred in the early 1990s, when, after decades of searching, the rhythm generator was found. Experiments on rodent nervous systems showed that the oscillator—at least the excitatory components that activate inspiration—resides in a brainstem structure, named the pre-Bötzinger complex. Astonishingly, researchers were able to isolate a slice of tissue containing the pre-Bötzinger complex from the rodent brainstem and keep it alive in a dish *in vitro*!—an experimentalist's dream come true with immediate prospects for discovery. Indeed, it was soon established that the *in vitro* pre-Bötzinger complex had autorhythmic properties: Some type of neural pacemaker was generating inspiration [1,4]. Establishing the biophysical mechanisms, however, proved to be a much more technically formidable challenge. Fortunately, the problem immediately captured the attention of dynamical systems modelers fascinated by neural oscillators.

In a classic example of a multidisciplinary team, Robert Butera (an engineer), John Rinzel (a mathematician), and I (an experimental neuroscientist) joined forces to formulate hypothetical biophysical models for the pre-Bötzinger complex pacemaker cells [1,2]—at the time with limited biophysical data. The models were to explain the phenomenological observation that individual cells, and the pre-Bötzinger complex network as a whole, autonomously generate periodic bursts of activity alternating with silent periods, on a time scale of seconds. The models—simplified electrodynamic representations of neurons incorporating ionic mechanisms to produce the flow of electrical current across the neuronal membrane, with kinetic mechanisms gating the currents—were typical of the approach championed by biophysicists to capture realistic mechanisms.

Our group's work is a case study in the application of approaches from nonlinear dynamics to deal with systems of differential equations describing a complex biological process. The state variables were dimensionally reduced by a fast-slow variable decomposition analysis—a framework developed earlier by Rinzel and colleagues—that dissects the dynamics into a fast subsystem coupled to a slowly varying subsystem. The fast system, operating on a millisecond time scale, models the membrane voltage and neuronal firing during the bursts of activity. The slow system, on a time scale of seconds, provides slowly varying ionic current underlying the rhythm.

One of the models mimicked the bursting behavior of pre-Bötzinger complex cells, leading to a startling new hypothesis: Rhythm generation might hinge biophysically on a remarkable type of ionic current mechanism—a persistent sodium current—that initiates cellular bursting, is slowly inactivated during the activity, and then slowly recovers from the inactivation. This oscillatory process was captured by the model's slow subsystem. The model also predicted continuous leakage of potassium ions by another membrane current, dynamically opposing the slowly inactivating sodium current. A mechanism for control of the oscillation frequency was predicted. Testable biophysical mechanisms were proposed.

Mathematical analysis and modeling then provided insight into how collections of pacemaker cells dynamically synchronize in an excitatory network [2,6]. The pre-Bötzinger complex network is distributed on both sides of the brainstem (inspiratory movements are symmetrical on the two sides of the body). Synchronization is key to the network's operation. Other mathematicians—David Terman, Jon Rubin, and colleagues—joined the modeling effort [3,6], and several remarkable network properties were deduced. The same cellular burst-generating mechanism involving persistent sodium current was found to promote network-wide synchronization. Moreover, new oscillatory dynamics were found for networks. The network oscillations were more robust, in the sense that they could occur over a wider dynamic range than those produced by single cells. This robustness arose from the heterogeneity of cellular properties, which was incorporated within model networks to account for known variability of bursting behavior among real cells. And, remarkably, heterogeneous networks were shown to have several dynamically different rhythm-generating states (see discussions in [3]).

These surprising insights could not have been derived from experiments alone. The work provided neurophysiologists with tantalizing and satisfying results: An oscillator as vital as the inspiratory rhythm generator must be robust; the existence of multiple dynamical mechanisms for generating rhythms implied that the pre-Bötzinger complex is a functionally flexible neural machine.

Stunning experimental confirmation of some of the model predictions has followed. The persistent sodium current was searched for, found, and confirmed to underlie pre-Bötzinger complex pacemaking. A remarkable finding is that oxygen levels may directly regulate this mechanism, which becomes critical when the brain is severely deprived of oxygen (see [5]). The molecular identity of the postulated potassium leak channel was revealed recently, and this channel was shown to have precisely the biophysical properties predicted. Multiple mechanisms for rhythm generation, reflecting different dynamical states of the pre-Bötzinger complex, have also been identified. This is a triumphant example of a story

that began with models, motivated by rudimentary phenomenological observations, and went on to detailed experimental confirmation.

Many opportunities for modeling remain. The pre-Bötzinger complex is an oscillatory “kernel,” embedded in a much more spatially distributed system that generates both inspiratory and expiratory activity. Populations of cells active during expiration inhibit the pre-Bötzinger complex and introduce novel dynamics. There is actually a hierarchy of interacting network components that can transform the rhythm-generation process between pacemaker-driven and inhibitory network-based mechanisms. Again, these observations indicate remarkable functional flexibility, beyond the rhythmogenic capabilities of the pre-Bötzinger complex.

Ultimately, multipopulation network models of different levels of biophysical complexity and scale will be required. For an understanding of homeostatic regulation of oxygen and carbon dioxide levels, neural models will need to be coupled to realistic models of the respiratory pump, with gas exchange and transport, including feedback to the brain for closed-loop control. These are only a few open problems on which modeling efforts are in progress. Moving forward, mathematicians can continue to provide much more than inspiration.

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Jeffrey Smith is a researcher in the Cellular and Systems Neurobiology Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, in Bethesda, Maryland.