Complex Oscillations in Simple Neural Systems

DOUGLAS A. BAXTER AND JOHN H. BYRNE

Department of Neurobiology and Anatomy, The University of Texas Medical School at Houston, Houston, Texas 77030

One of the goals of this workshop is to explore how research on aquatic plants and animals can improve our understanding of the basic mechanisms underlying the effects of gravity on biological processes. In general, the focus of "gravitational biology" has been to investigate gravitational effects at the organismal level rather than at the cellular, subcellular, or molecular levels. Indeed, previous theoretical studies have indicated that the effects of gravity would be minuscule at the subcellular level (Albrecht-Buehler, 1991; Nace, 1983; Pollard, 1965, 1971; Todd, 1989). However, recent spaceflight and ground-based experiments have demonstrated that a broad range of basic cellular properties can be influenced by gravity, including cytoskeletal structure and cell morphology, cell-cell interactions, cellular metabolism, exocytosis and endocytosis, concentrations of electrolytes, voltage-gated channels, intracellular levels of second messengers, and enzymatic activities (Cogoli et al., 1990; Cogoli and Gmünder, 1991; Edgerton and Roy, 1994; Gruener and Hoeger, 1990, 1991; Hughes-Fulford, 1991; Hymer et al., 1994; Krasnov, 1994; Morrison, 1994; Reitstetter et al., 1991; Rijken et al., 1994; Sato et al., 1992; Schatz et al., 1994; Sibonga et al., 1989; Todd, 1989). Thus, perturbations in the gravitational environment can induce modifications in cellular activities, which in turn may contribute to gravity-dependent changes at the organismal level.

How is it possible to resolve the theoretical and empirical findings? An intriguing explanation for the influence of gravity on cells was derived, in part, from nonlinear dynamical systems theory (Kondepudi and Prigogine, 1983; Kondepudi and Strom, 1992; Mesland, 1987, 1990, 1992a, 1992b). Specifically, even if the force of gravity at the subcellular level is extremely weak by comparison with other forces, the nonlinearity of many molecular systems may provide the amplification required to allow a weak signal to influence subcellular processes. Thus, gravity may be a bifurcation parameter capable of inducing state transitions. Since nonlinear dynamical systems are the rule rather than the exception in biology, the application of these principles may help us to design new experiments that will provide insights into basic cellular physiology and the molecular basis of gravitational effects on cells.

In the present paper, we describe how some of the concepts and analytical techniques of nonlinear dynamical systems have been applied to computational and experimental analyses of single-cell and multicellular neuronal oscillators (Baxter et al., 1996; Butera et al., 1995; Byrne et al., 1994; Canavier et al., 1991, 1993, 1994; Lechner et al., 1996). Our analysis has focused on the R15 neuron, which is located in the abdominal ganglion of the marine mollusc Aplysia. R15 has intrigued neurobiologists for decades, principally because of its intrinsic ability to produce complex bursting activity. This cell also exhibits many different modes of oscillatory activity.

Previous experimental studies have demonstrated two conventional methods of shifting the activity of R15 between different modes of activity. First, the activity can be altered by intracellularly injecting a constant bias current. Sufficiently large depolarizing bias currents shift the activity of R15 from bursting to beating (i.e., tonic spiking activity), whereas sufficiently large hyperpolarizing bias currents shift R15 into a silent mode. Second, the activity of R15 can be altered by applying modulatory transmitters, such as serotonin (5-HT). By modulating biophysical parameters (e.g., membrane conductances)
various concentrations of 5-HT can shift the electrical activity of R15 between a variety of bursting modes, which vary in the intensity of spiking during the burst and the duration of the interburst interval.

We have used a Hodgkin-Huxley type model of the R15 neuron and computer simulations to investigate a novel method for shifting the electrical activity of R15 among different modes of oscillatory activity. This novel method does not rely on alterations in model parameters, but rather exploits the intrinsic nonlinear properties of the cell. The simulations indicated that, for a single set of parameter values, the model cell can generate up to eight distinct modes of oscillatory activity. These modes of electrical activity corresponded to multiple stable attractors, whose coexistence in phase space was an emergent property of the nonlinear dynamics of the cell. Brief perturbations, which were simulated postsynaptic potentials (PSPs), could switch the activity of R15 between different modes. These mode transitions did not require any changes in the biochemical or biophysical parameters of the neuron and provided an enduring response to a transient input. Moreover, the nature of the mode shift, as well as whether the mode shift occurred at all, was dependent upon the timing of the PSP (i.e., perturbation) relative to the ongoing activity, thus providing a mechanism for phasic sensitivity (i.e., temporal specificity). Finally, the multistability of this neuronal oscillator was regulated by modulatory transmitters. The actions of modulatory transmitters were simulated by systematically altering the conductances of specific membrane currents within physiological ranges (e.g., +20% of control values). Changing these parameters regulated the number of coexisting modes of electrical activity, such that at control values eight modes coexisted, at intermediate values two or three modes coexisted, and at the maximum and minimum values only a single mode existed. Thus, by modulating membrane conductances, transmitters could position the neuronal oscillator in different regions of its parameter space; some regions supported multistability, whereas others did not.

Recently, we have begun to extend our analyses of the dynamics of neuronal oscillators to include multicellular oscillators (Baxter et al., 1996, 1997; Canavier et al., 1995). These analyses have focused on a ring network composed of identical cellular and synaptic elements. The individual cells consist of modeled R15 neurons. The parameter values that were used in these simulations positioned the cells in a region of their parameter space that supported only a single attractor, which was a bursting limit cycle. Thus, the individual circuit elements by themselves did not support multistability. We found, however, that the ring network exhibited multistability. Simulations also illustrated that, as the number of cells in the ring network was increased, the number of coexisting patterns also increased. Similarly, if the parameter values for the individual cells were modified such that the cells themselves became multistable, then the number and diversity of coexisting multistable oscillatory patterns increased dramatically.

Electrophysiological experiments have tested several key predictions of the computational studies. First, we examined whether the oscillatory electrical activity of individual R15 neurons exhibited multistability. Second, we examined whether modulatory transmitters regulated the multistability. Finally, we examined whether networks of R15 neurons that were artificially connected into a ring network could support multistability. The results of these electrophysiological experiments were consistent with the predictions of the computational studies and indicated that nonlinear processes may endow individual cells with a richer repertoire of cellular state transitions than has been previously appreciated.

In summary, the data described above indicate that there are two fundamentally different methods of producing an enduring change in the mode of oscillatory activity in R15. One method is parameter dependent (e.g., application of a bias current or a modulatory transmitter), whereas the second method is parameter independent. Parameter-independent changes in the mode of activity emerge from the proliferation of attractors in the phase space of this nonlinear system. Each of these attractors correspond to a different pattern of oscillatory activity, and brief perturbations (e.g., synaptic inputs) can switch the electrical activity from one stable pattern of oscillation to another. These mode transitions do not require any changes in the parameters of the model, and such parameter-independent transitions can provide an enduring response to a transient input. These studies have provided novel insights into the ways in which nonlinear dynamics at the cellular level might be exploited in the generation and control of oscillatory patterns of electrical activity and to process and store information.

Note, finally, that electrical activity is only one of the nonlinear dynamical activities in cells. The interactions among most, if not all, biochemical reactions and second messenger systems are highly nonlinear. Thus, nonlinear state transitions (i.e., bifurcations) at the molecular level might function to amplify relatively weak signals (e.g., gravity) above the level of random thermal noise, and the weak signals could thus be manifest at the cellular level. R15 may provide a useful model system with which to investigate these possibilities. For example, R15 can be maintained in vitro for many days while its electrical activity is being monitored by means of a number of noninvasive techniques (e.g., Parsons et al., 1991). Moreover, the parameter-independent mode transitions that we have characterized could serve as a very sensitive measure of the effects of gravity on cellular processes.


