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Computer Modeling of Physiological Phenomena at the Cellular Level

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Physiology is the study of function in living organisms. Since life itself is usually defined by these functions or processes, it is not surprising that research physiologists use approaches ranging from biochemical and molecular techniques in the laboratory to behavior observation in field studies. It is often in their first physiology course that undergraduate biology students begin to appreciate the relevance of courses they took in chemistry, physics, and mathematics. In the current research environment, students may also find that a background in computer science provides additional assistance in the study of physiology.

For many years, neurophysiologists have depended on the tools commonly found in a physics or engineering laboratory to gather information about functioning nerve cells, neurons. Since information is passed from one part of a neuron to another (and occasionally directly to a separate neuron) through minute electrical signals brought about by the movement of ions, the major tools of the neurophysiologist are an electrode inserted into or near a neuron, an amplifier to increase the magnitude of the neuronal response to a detectable level, and an oscilloscope and/or audio monitor to measure the response. The advent of affordable, high speed computers has allowed neurophysiologists to gather, store, and analyze increasingly large amounts of information about neuronal function, often in experiments involving the simultaneous recording of multiple neurons.

Recently, the use of computing power has expanded to include the use of programs that simulate the activity of functional cells. Computer modeling, like the study of physiology, can be done at a variety of levels. Some computer models attempt to simulate the activity of organelles within a cell or of small patches of the plasma membrane. Other models simulate a full, functional cell or even a small network of interconnected cells. Less detailed models may try to simulate a complete process in a living organism such as moving a limb or identifying a sensory stimulus.

The advantage of working with computer models of physiological

processes is that information from anatomical, physiological, pharmacological, and behavioral studies can be integrated into a model in ways that may be impossible in a single controlled study with a living organism. If that information is simulated well, the model may be used for "experiments" that were too difficult or too expensive to carry out in living organisms. Computer models can also reduce the number of animals needed for complex neurophysiological research. If one has seven possible explanations for an observed response, one can use the model to evaluate each of the seven, possibly reducing the field of possible explanations to two or three that actually require testing in animals.

Computer models of physiological properties have several disadvantages, however. Any model is only as good as the assumptions upon which it is based. When insufficient information is available from animal research, assumptions must be made that may or may not accurately reflect the living system. Second, computer models of life processes can become quite cumbersome if all aspects of the anatomy, biochemistry, etc. are accurately reflected in the model. A slow, cumbersome model is not useful, so most computer models ignore many details that one decides are not essential. The decisions about which details to include or exclude are difficult and if made incorrectly may limit the predictive capability of the model. For this reason, any prediction made by a computer model of a physiologic process must ultimately be validated by animal studies. Third, computer modeling requires that the physiological or anatomical components of the living system be describable by mathematical relationships. As students of physiology know, many relationships in living organisms can be described by equations, but the equations rarely fit exactly with the observations or account for the variability observed in animals. As long as the researcher has a good grasp on these limitations however, computer models can be a valuable tool in research.

A set of auditory models

In my laboratory, undergraduate students are currently working with a set of models related to auditory physiology. This series of models was developed and published for public use by Dr. Ray Meddis and his colleagues, currently at Essex University in the United Kingdom (Meddis 1986; Meddis and Hewitt 1991a and b; Hewitt et al. 1992). The models, referred to as the Development System for Auditory Modeling (DSAM), are written in the programming language C, have a rudimentary graphics interface, and are useable (with minor manipulation) on UNIX, PC and Apple systems (Dr. Meddis's laboratory maintains a website, including extensive information about the auditory system and access to the DSAM, at

www.essex.ac.uk/psychology/hearinglab). This set of models simulates function at the cellular level. Dr. Meddis's group recently created a hardware chip that is capable of simulating multiple neuronal cells simultaneously (van Schaik and Meddis 1999).

The DSAM is organized as a series of modules, all of which are called as needed by a main program. At the first stage, one can create a variety of digital stimuli including a pure tone of a certain frequency, intensity and duration, white noise, a short multi-frequency stimulus called a click, or amplitude or frequency modulated tones. One of my undergraduate students working on the project has expanded the capabilities to include the use of a WAV file as a stimulus. He is also expanding the graphics capabilities of the DSAM to allow easy visualization of the output at each stage of processing.

The simulated sound is then processed by a series of modules that recreate the anatomical and physical properties of the peripheral auditory system (for an introduction to auditory processing, see Geisler 1998). The sound is filtered by a bandpass filter that enhances particular frequencies just as the external auditory canal, tympanic membrane, middle ear ossicles, and oval membrane do in a living animal. A second student in my laboratory is currently working on verifying the assumptions upon which the filter is based, and modifying it to create versions that will allow us to simulate auditory responses of non-human vertebrates (rats, gerbils, and mice) as well as the current human version.

The filtered signal obtained can then be processed by a module that simulates the action of the basilar membrane in the cochlea. The basilar membrane has complex physical properties related to the fluid movement in the cochlea and the varying thickness and breadth of the membrane as one moves from the basal to the apical end of the cochlea. There are several versions of the basilar membrane filter included in the DSAM, each of which reflects experimental findings and hypotheses concerning the importance of different details of basilar membrane function in the filtering of sound signals. However, most of the models work as a series of filters, separating a sound signal by frequency components. A third student is currently studying these different basilar membrane filters and assessing the accuracy of each as compared with the animal literature. He is also establishing a series of basilar membrane models to reflect the variability among various species, as is being done with the outer and middle ear filter.

The DSAM continues with a probabilistic model of hair cell function reflecting neurotransmitter release from the inner hair cells to the auditory nerve synapses. The auditory nerve model then simulates the movement of that signal into the brainstem, where a series of nerve cell models can be used, as needed, to reflect the processing of signals in the cochlear nucleus and higher brainstem structures.

The nerve cell models are based on the classic view of neuronal membrane properties developed by Hodgkin and Huxley (1952). The parameters can be adjusted to reflect the neurophysiological properties of the many types of neurons found in the auditory brainstem.

Our goal in working with these models is to create a satisfactory reflection of auditory processing as it occurs in young, healthy adult animals. We want to have not only a human model, but also models of several rodent species commonly used in auditory research so that both differences and similarities among these organisms will be clearly reflected. Once the young adult models are in place, our goal is to alter the models to reflect changes that occur in the auditory system during the process of aging (for a review of aging in the auditory system, see Willott 1991). During aging, anatomical changes occur in the peripheral auditory system including collapsed ear canals, a stiffening of the tympanic membrane, calcification of the ossicles, changes in the ion concentrations in the endolymph and perilymph, and death of hair cells. In the central auditory system, there is also some cell death, although it appears to be limited. However, neurotransmitter concentrations, receptor configurations, and some cellular response properties appear to change with age (Caspary et al. 1995, Palombi and Caspary 1996).

If we are successful in modeling some known aspects of age-related hearing loss, the computer models will then be able to serve as predictors of experimental outcome. For example, how big an impact does embedding a signal in a noisy background have on the neuronal processing of that auditory signal? If partial hair cell regeneration could be induced, what would be the impact on cochlear nucleus processing? If a drug could increase the concentration of a depleted neurotransmitter, what would be the impact on neuronal processing? The ability to simulate experiments such as these should allow fine-tuning of them before undertaking animal experiments, which are particularly difficult and expensive in studies of aging.

Advice for students interested in computer modeling

Students interested in studying the dynamic processes of life, physiology, need to have a broad educational background. In addition to biology courses ranging from the molecular to the behavioral level, it is important for the student to have a strong background in chemistry and physics. With the increasing use of computer models in physiology research, students would also do well to have some computer programming experience and an appreciation of mathematics including a course in differential equations. However, the most important skills an undergraduate can gain are good oral and written communication skills, and the willingness and confidence to plunge into a new area.

The three students working with the computer models all come from different undergraduate majors. The student who first downloaded and implemented the models is a computer science major who worked with the assistance of one of the computer science professors to trouble-shoot the compilation of the DSAM and its graphics links. That student is now expanding the graphics capability of the programs. Of the two students working with the auditory periphery modules, one is a psychology major and the other a biology major. All three of these students have learned to find, read, and critically evaluate the primary literature upon which these models are based. This includes biology, physics, mathematics and engineering publications.

Computer modeling of biological processes is a truly interdisciplinary field. It is not uncommon for a research team to include biologists, physicists, mathematicians, and computer scientists. The greatest challenge faced by these teams is establishing and maintaining clear communication. Breadth in education at the undergraduate level and experiences working closely with faculty and students from different disciplines will prepare future biologists to become valuable members of cross-disciplinary research teams.

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