**Living Devices: The Physiological Point of View**

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**February 24, 2011**

The physiological tradition of biological research analyzes biological systems using reduced descriptions much as an engineer uses a ‘black box’ description of an amplifier.

An engineer is often not interested (to first order) in how the black box produces gain, or what inside the box produces gain, but studies the properties of the gain, its linearity, its frequency dependence and so on. She listens to the amplifier or uses it, almost the same way, whether it is made of tubes, bipolar transistors, or FETs (field effect transistors). A complete description of the structure of the amplifier or its internal physics is far less useful to the engineer than a reduced description of its input–output relation, when the goal is to use the amplifier or connect it to other devices to make a system.

An engineer told that an unknown black box is an amplifier is rather like a biologist confronting an ill understood biological system. Some structural knowledge is indispensible but complete structural knowledge is not. The engineer would have a terrible time if she did not know which wires were power supplies, which were inputs, and which were outputs. But the last thing the engineer would want to know is the complete circuit diagram, and she would have no idea what to do if she were given the geometrical coordinates (i.e., the locations) of all molecules or atoms in its resistors, capacitors and transistors. The engineer wants to know enough to make the device work, or perhaps to improve or even construct the device, but no more. She has other things to do more useful than knowing every coordinate of every atom in one amplifier.

Successful study of an unknown device requires some knowledge of structure; that information is indispensable. But successful study requires many more measurements of inputs and outputs, under many conditions. Those inputs and outputs are related in a reproducible way, that can be described crudely with words, or more precisely by a device equation, or even better by a physical device model from which the device equation can be derived.

An input output equation (or description in words) is not complete, to be sure, and is not enough for all engineering purposes. An input output equation (or description in words) is usually not general enough to describe how the input and output vary when parameters or components of the device are changed: investigation of these sensitivity functions (as they are called) is far more productive if the equation of the device can be related to a physical model of the system and the appropriate amount of structural information is included.

Physiologists have successfully analyzed a broad range of biological systems using a ‘device-oriented’ approach similar to the approach an engineer would use to investigate an amplifier. For more than a century, medical students have used a device oriented approach to learn that the kidney filters blood to make urine; the lungs transport oxygen from air to blood; muscles contract; sodium channels produce action potentials; and so on. Each device description in physiology — on each length scale from organ, to tissue, to cell, to organelle (e.g., membrane), to protein molecule — is associated with a device model and equation, just as a device description in engineering (such as a sketch and verbal discussion of an amplifier or a solenoid) is followed by an approximate device model and equation for its input–output relation, its gain, for example. Each device has an abstract representation in terms of its main function. Each device has a more complete description including the nonideal properties of its input and output, for example, the input and output impedances of an amplifier, and at a more detailed level yet, for the slew rate and nonlinear properties of the output of the (audio) amplifier. Each device has a still more detailed description designed to show how the outputs vary as conditions (e.g., power supply voltages) or temperature or input or output connections or components change. These more detailed descriptions involve the physics of some components inside the device and some of the connections of those components to each other. In none of these cases is a complete circuit description used, let alone a complete description of the layout (i.e., actual geometrical coordinates) of the components. No one has even thought of using a complete description of the location or movement of all the atoms of the device, as far as I know.

Until fairly recently, physiological analysis was focused on visible structures and systems and the device oriented approach was the only approach that could be used.

Then came molecular biology and now even atomic biology (i.e., molecular biology in which the biological effects of individual atoms are significant and can be measured). No one knows which of the biological systems now being investigated on the molecular scale can be viewed productively as devices. No one knows which of the unsolved complexities of biological research reflect problems of the reverse engineering of simple devices, and which reflect the inherent complexity of biological systems. No one knows how the magnificent structures of proteins so completely known on the atomic length scale determine the biological function of those proteins.

Many are attempting to calculate the properties of the proteins of biological systems, and the systems built from these proteins, one atom at a time, by simulations of the molecular dynamics of all the atoms, starting on the time scale of atomic motion roughly 10-16 sec.

The contrast with the approach of physical scientists is striking. Think of the innumerable physicists and engineers interested in semiconductor devices for the last sixty years. The atoms of a semiconductor device are in a crystal lattice, far easier to compute and analyze than the disordered atoms of a protein or ionic solution. But physical scientists have not thought it necessary, nor I suspect feasible, to calculate the properties of the ordered atoms of their crystal lattices. Almost none have tried.

It is a wonderful testament to the enthusiasm and optimism of biologists that they are trying so hard to compute the motions of all the atoms of their proteins and the surrounding and interacting ionic solutions. One can only wish them luck, and remind them that when they enter realms where others fear to tread, comparisons with experimental measurements (on the experimental time and distance scales, in realistic biological conditions) are necessary to validate and calibrate their computations. Without validation and calibration, it is difficult to know what to make of the work.

It is necessary to show that the methods of molecular dynamics produce realistic descriptions of the properties of ions in water in the mixed solutions of Na+ , K+, Ca2+ and Cl¯ ions found inside and outside cells. It is hard to believe that methods that cannot deal with divalents — or mixtures of salts like those found inside and outside cells — can actually compute the properties of a protein in those salts. Many of those proteins, including those of greatest medical and biological interest, are controlled by a trace concentration trace concentrations of small organic molecules (or ions), called hormones, vitamins, cofactors, coenzymes, and such. These trace concentrations control function much as much as the loudness of an amplifier is controlled by its volume control and on-off switch. Specificially, Ca2+ is often a controller of biological function at a concentration of 10-7 or 10-8 M). Small organic molecules work at even lower concentrations some as low as 10-11 M. All the controlling molecules work are components of a complex salt solution. The salt solution is ~2 × 10-1 M inside and outside cells. But the salt solution is much more concentrated inside proteins. It is ~2×101 M in ion channels and near active sites of proteins.

Simulation of such systems in atomic detail poses formidable challenges that are likely to require substantial improvements in computation to fulfill.[[1](#_ENREF_1)] Simulation in detail is needed to understand molecular devices because some of the details actually control the devices. Some of the details are the gain control, for example, or the on-off switch.

Devices can be difficult to investigate for many reasons. They can be complex and have interacting components and many internal nonlinear connections like the integrated circuit modules of digital computers or the central nervous system of animals. Systems can have overall function that only emerges when the entire system is connected. Such overall functions are not visible in the components, because they do not exist there. The overall functions depend on connections of components and particular properties of the components in a way that may become apparent only after all connections are made. Complex systems like this are hard to investigate because they are complex!

Complex systems may not be easily analyzed as devices, no matter how much experimental information is available, because they are complex, as described above. But one can also imagine simple systems—even as simple as an amplifier—that are hard to investigate only because of the paucity of experimental knowledge. If an engineer is given a black box, is told it is an amplifier, but is not told which wires are the power supply, input, or output; or if she is not told what are the specifications of the power supply (and not told which voltages damage the inputs), the investigation becomes more or less impossible. Reverse engineering of even simple systems is often ‘ill posed’—mathspeak for “practically impossible”—simply because crucial information is missing. An entire branch of mathematics (called theory of inverse problems) has been developed to help squeeze useful information from ill-posed problems typical of reverse engineering. The math provides useful approximations to more of these ill posed problems than one would imagine. It is in fact possible to actually solve specific molecular problems, like the selectivity of models of ion channels, using the theory of inverse problems.[[2](#_ENREF_2)]

In any case, it seems clear, at least to one physiologist, that productive research is catalyzed by assuming that most biological systems are devices.

Thinking today about your biological preparation as a device tells you what experiments to do tomorrow. Thinking about preparations as devices leads to the design of useful experiments, in most cases. Thinking about biological systems as devices will eventually lead to the device description, equation, and model, if they exist.

If no device description emerges after extensive investigation of a biological system, one can look for other, more subtle descriptions of nature’s machines. After all, many machines do not have well defined inputs and outputs, or even device descriptions. What is the input of a video game? Or the computer itself? What are the outputs? Useful abstract descriptions of machines like video games or computers are hard to construct, particularly if little is known about the machine and its use in the first place.

Physiologists have been thinking this way—specifically about their next experiments, or generally about life—for a long time, perhaps since Aristotle, and certainly before the development of engineering, molecular biology, or even biochemistry. It would be a setback if this device approach were lost to modern scientists who have such extraordinary tools available that were unimaginable to their ancestors. But science needs questions as well as the tools to answer them. When the wrong outputs are sought, inverse problems are ill posed. When the wrong questions are asked, or no questions are asked at all, science proceeds slowly if at all. Answers to unasked questions are slow to emerge.

An important task for many of us is to transmit the physiological tradition to the next generation of biophysicists to help them adapt traditional questions to the new length scales and techniques of molecular and atomic biology.

**References**

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2. Burger, M., R.S. Eisenberg, and H. Engl, Inverse Problems Related to Ion Channel Selectivity*.* SIAM J Applied Math, 2007. **67**(4): p. 960-989