Living Devices: The Physiological Point of View

The physiological tradition of biological research analyzes biological systems using reduced descriptions much as an engineer uses a reduced description of an amplifier. An engineer is often not interested (to first order) in what inside the box produces gain, but studies the properties of the gain, its linearity, its frequency dependence and so on. She uses the amplifier or listens to it, almost the same way, whether it is made of tubes, bipolar transistors, or FETS. A complete description of the structure of the amplifier is far less useful 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 unknown biological system. Some structural knowledge is indispensable. 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 given 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 construct the device, but no more. She has other things to do more useful than knowing everything about just one amplifier.

Successful study of an unknown device requires some (indispensable) knowledge of structure; but it 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 words) are usually not general enough to describe how the input and output vary when parameters or components of the device are changed: investigation is far more productive if the equation of the device can be related to physical model of the system.

Physiologists have successfully analyzed a broad range of biological systems using this ‘device-oriented’ approach. For more than a century, medical students have used it 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 function, for example, its input–output relation.

Until fairly recently, physiological analysis was focused on visible structures and systems. 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 molecular scale biological systems now being discovered 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 how many reflect the inherent complexity of biological systems.

One can certainly 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.

Complex systems—for example, with many internal nonlinear connections like the integrated circuit modules of digital computers or the central nervous system of animals—may not be easily analyzed as devices, no matter how much experimental information is available. But it seems clear, at least to a 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 know 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. An important role of our department 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.***