Commentary: Physiology Is the Logic of Life

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Physiology has always been an integrative science concerned with quantitatively understanding how the structure and function of cells, tissues, and organs explain the complex behaviour of living systems. During the first half of the 20th century, physiologists, from Sherrington and Eccles to Hodgkin and Huxley, revealed the physical basis of human physiology all the way from cell biophysics to integrative control. In the past 50 years, however, the focus has progressively shifted to molecular biology, because of its spectacular success in explaining mechanisms at the level of genes and proteins. In recent years this success has largely been based on the development of experimental techniques such as DNA sequencing, PCR, microarrays, confocal fluorescent imaging, and above all on the realization that high-throughput measurement coupled to comprehensive databases is just as important to quantitative science as the more traditional approach of hypothesis driven research is. The inevitable consequence of this success is an explosion of data at the subcellular level that is difficult to interpret in relation to the physiological behavior of complex living organisms. One main challenge in physiology over the next few decades will therefore be interpreting the genome and ascribing physiological function to genes and proteins in the wider context of integrative systems.

The physical sciences show how this can be done because they have for the past 200 years confronted Nature’s complexity with the development of mathematical models of natural phenomena. Our ability to understand complex fluid flow, for example, in order to design aircraft or forecast weather, is a testament to the physicists and mathematicians of the 19th and 20th centuries who identified Nature’s physical conservation laws and developed the mathematical framework to describe them. The successful application of these laws to the solution of engineering problems has also advanced greatly in the past 50 years as a result of the development of computers and numerical analysis.

The use of mathematical modeling in physiology first gained prominence in the 1950s with the successful prediction by Hodgkin and Huxley of the speed of action potential propagation along a nerve fiber from cable theory coupled to models of ion channel conduction and gating kinetics. I was fortunate to be a student working on the biophysics of cardiac muscle soon after this groundbreaking work. I was able to build on it by using experiments identifying two of the key potassium channels in the heart to extend the Hodgkin-Huxley model equations to produce the first successful explanation of the long duration of the cardiac action potential, (and for the automaticity of cardiac rhythm) [1, 2].

When I published the results of that work, I had no idea where it would eventually lead. If someone had told me then that more than 40 years later, I would still be building cardiac cell models [3], I could not have believed them. I would have been even more disbelieving had I been told that these cell models will eventually include cell biochemistry, mitochondrial function, calcium signaling, contraction, and drug receptors and that they will be incorporated into large-scale modeling of detailed cardiac anatomy to form the world’s first virtual organ [4, 5].

The reconstruction of the heart and other organs of the body has thus become a major international project coordinated by the Physiome Project of the International Union of Physiological Sciences. My colleagues and I have recently described the present state of this project and how far it is hoped to develop [6].

The meeting that formed the basis of the papers in this issue of the Japanese Journal of Physiology was...
held in Kyoto, and it gathered some of the leading international scientists contributing to this project. Nic Smith and Peter Hunter describe their work on building a computational framework for integrating the electrical, mechanical, and biochemical functions of the heart. They outline the construction of efficient finite element representations of canine and porcine ventricular geometry and microstructure, including the coronary circulatory system.

A team of Korean scientists Eun Bo Shim, Jong Youb Sah, and Chan Hyun Youn present their work on modeling the cardiovascular system dynamics, with an emphasis on modeling hemodynamic characteristics, by using a lumped parameter approach. This work includes distributed models of an arterial network. They also discuss the nonlinear characteristics of the pressure-volume relationship in veins and the control pathways that participate in feedback mechanisms to explain the interaction between hemodynamics and autonomic nerve control in circulation.

I referred earlier to the incorporation of metabolic processes into cell models. In this issue, Bernard Korzeniewski describes a computer model of oxidative phosphorylation in isolated muscle mitochondria and in intact skeletal muscle. This model has been very extensively tested by the comparison of computer simulations with a broad set of experimental results concerning various kinetic properties of the oxidative phosphorylation system. The Kyoto research team has already incorporated models based on Korzeniewski’s into their impressively detailed cardiac cell models.

Another international leader, Andrew McCulloch, reviews the modeling of ventricular physiology. He shows that computational biology is integrative in several ways. Functionally, computational models are valuable for integrating the many interacting processes within biochemical networks and the many interacting physiological subsystems within the cell. Structurally detailed models provide a means of integrating across scales of biological organization from molecule to organism. Data integration across diverse laboratory and clinical measurements is another unique strength of computational biology. He describes the examples of all three categories of integration, using recent advances in modeling cardiac excitation-contraction coupling and whole-heart electromechanics.

The full significance of work of this kind in physiology has yet to be realized. It is already showing how impressive biosimulation can be when it is used in fields in which the experimental data at various levels is rich and ripe for such treatment. But there is an even more fundamental reason why the greatest achievements have yet to be realized. As its name suggests, physiology is the study of the logic of life. In Western languages this is evident in the origins of physio- (life) and -ology (logic). In East Asian languages it is evident in the meaning of the three Chinese characters used for physiology: life-logic-study (生理学).

Despite being an old and well-established discipline, physiology has not yet achieved the goal that its name proclaims. We do not yet have a fully quantitative understanding of the logic of life. There is not yet a fully fledged theory of biological functioning at higher levels, and many physiologists might wonder whether there ever will be. For them, physiology is primarily an empirical study, working piecemeal through the individual mechanisms of living systems. And indeed, it must continue to be that. But it now must also be even more. I would argue that the great successes of genomic and molecular biology cry out for higher-level functional interpretation. Some of that interpretation will be revealed by clever experimentation. But beyond a certain level of complexity, experimentation needs to be informed by quantitative theoretical work. The articles published in this volume illustrate how this will be achieved.

REFERENCES
4. Noble D: Modelling the heart: from genes to cells to the whole organ. Science 295: 1678–1682, 2002