

## Perspective

## Perspectives of physiome research



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## ABSTRACT

Physiome is an area of physiology to generate a whole system by analyzing and integrating scattered and discrete information. The term “physiome” was first introduced by James B. Bassingthwaight in 1993, and officially announced by the International Union of Physiological Societies as the new field to be accomplished in the 21st century. In this review, I introduce the concepts of physiome, why physiome should be pursued, what kind of strategy is necessary to form physiome, and how physiome can be used.

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## 1. History and concepts of physiome

The study of paradigms of life has been moved from the macroscopic view, such as the organism or organ/tissue, to the microscopic view, such as cell/protein/genome. This shift was caused by the reductionism in scientific fields; if we know the elements, we can understand the systems. The vast amount of data in life science related to the elements has accumulated in recent decades; however, the efforts to integrate such results and understand the life of the organism has not been properly performed. Life sciences failed to show the tree and the forest together, especially in functional aspects. From this reflection, new scientific approaches became acquainted for integrating the information to understand the life system.

Physiological scientists have been interested in functional aspects of life and put substantial efforts toward finding the mechanisms associated with life systems. The focus of the research has moved from the organism to the subcellular level

in order to understand life in an integrative way. When the total amount of knowledge was smaller, such reductionism-based approaches were inevitable. In parallel, after the structure of the genome was identified, molecular biology techniques were developed extensively over recent decades, and vast amounts of knowledge related to the genome and proteome have accumulated. However, the linkage between structural components, such as the genome and proteome, and functional knowledge were not formed properly. Physiological scientists have great interest in how to link both sets of knowledge to understand life. Additionally, physiological experimental techniques were developed, and the speed of information accumulation increased, with scientists unable to catch up with such speed to integrate the data into life systems. The information became scattered and discreet, and microscopic categorical research prevailed. To overcome such obstacles in physiological science, physiome was introduced.

Physiome is a combinatory word from “physio” and “ome” for “life” and “as a whole”, respectively. The first introduction

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of physiome appeared in a report from the Commission on Bioengineering in Physiology to the International Union of Physiological Sciences (IUPS) Council at the 32nd World Congress in Glasgow, UK, in 1993. The aim of the project was to provide a comprehensive framework for modeling the human body using computational methods, which can incorporate the biochemistry, biophysics, and anatomy of cells, tissues, and organs. The project was officially launched at the 33rd World Congress of IUPS (St Petersburg, Russia, 1997) and was, at the 34th World Congress (Christchurch, New Zealand, 2001), designated as a major focus for the next millennium.<sup>1</sup>

The physiome is the quantitative and integrated description of the functional behavior of the physiological state of an individual or species. The physiome describes the physiological dynamics of the normal intact organism and is built upon information and structure (genome, proteome, and morphome). In its broadest sense, the physiome should define relationships from genome to organism and from functional behavior to gene regulation. In context of the Physiome Project, it includes integrated models of components of organisms, such as particular organs or cell systems, biochemical, or endocrine systems ([www.physiome.org](http://www.physiome.org)).

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## 2. Model simulation is a central tool for physiome

The development of computer-based quantitative models in physiome is inevitable to integrate the information in a quantitative way. Quantitative models in physiome differ most significantly from other database-driven research areas, such as bioinformatics, network biology, or big-data analysis. The physiomic model is a repository of the previous data and also a tool to test or predict the results by varying factors. Other data-driven research can show the linkage between components, however, they only see the strength of the linkage of the data itself, and the interpretation tends to be subjective. The data repository role of the model is very important for the researchers, and it greatly reduces the burden to search the appropriate results from the sea of references.

To perform data repository roles, models need two kinds of data: structure and function. Model structure is very important, because it is a backbone of the model. Therefore, the appropriate identification of the structure is essential to compose the model. If the structure is set, the functions of the structural element need to be known. Structure is the static component of the system and function is the mechanistic description of the dynamic change. The model domain determines the necessary structure and function. For example, if a heart model is created to generate the electrical activity of the heart, first, the anatomical structure component of the heart, such as a shape, location, and direction of different cells, interstitial space, etc., need to be known. Second, functional components of the heart, such as the electrical activities of the cardiac myocytes in different locations (sinoatrial node, atrium, atrio-ventricular node, Purkinje fiber, and ventricle) and cell-to-cell electrical connectivity through gap-junction channels, need to be known. Finally, both structure and function need to be combined using mathematical methods, which are usually used in mechanical and electrical engineering.

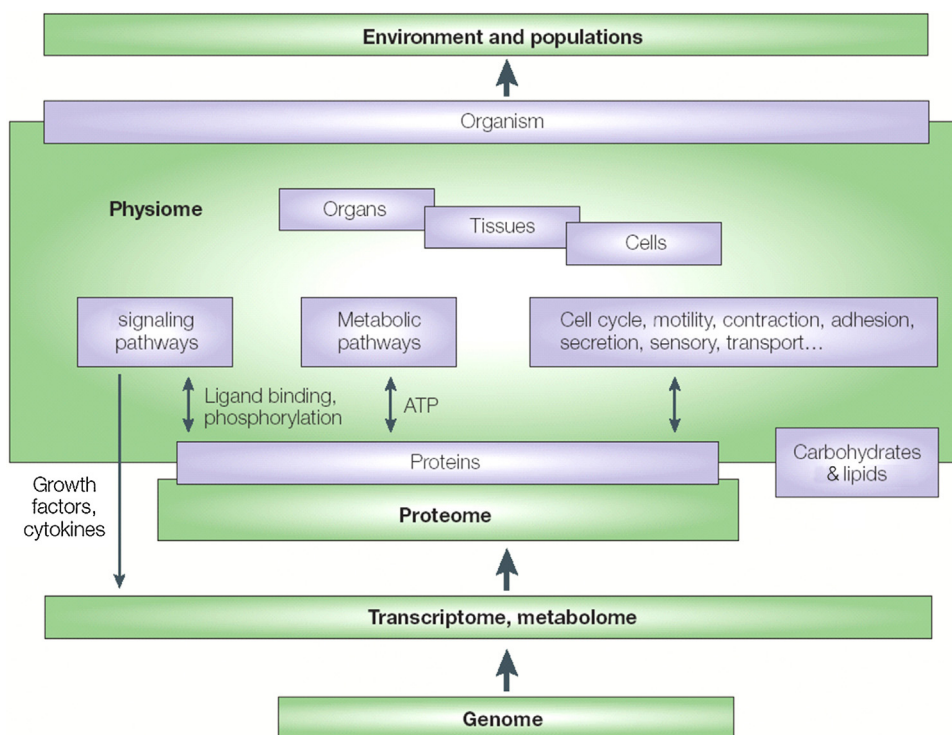
This model will show the electrical activity of the whole heart; however, it cannot directly reflect neuronal or hormonal effects. For linking those effects, a cellular model needs to be created. Each cell has common or different elements that respond to neuronal or hormonal effects. The cell model needs the same unit, structure, and function. Structure can be composed of cell dimension, ion channels, ligand receptors, intracellular organelles, each ion concentration inside and outside of cells, and temperature. Part of the function can include ion-channel kinetics reflecting environmental changes, such as voltage, phosphorylation, and ion concentrations. Additionally, the functions of intracellular organelles that control intracellular ion concentration or mechanistic descriptions of the signal transduction pathways on receptor activation need to be composed. If a model is to incorporate the genetic transcription or molecular mechanisms of proteins, such a model can also be made. Therefore, the model domain can be extended from the molecular level to whole planet population. The domain of physiome was introduced as shown in Fig. 1. If there are unknown mechanisms, they can be treated as a black box and can be incorporated into models in a descriptive way.

The predictability of the model is the important reason why the model needs to be developed; however, creating biological models like physiome capable of making predictions is a very difficult task due to its complex structure and functions. Additionally, obtaining good data is another obstacle. Since most scientists have not done their research to create a good model, the majority of experimental results were not comparable and were difficult to use in model construction. There was also a strong tendency for the experimentalist to regard the model as a decoration for their research. For the repository role of the model, the developed model should be tested by the experimentalists. If there are discrepancies, the reasons must be discovered and the model improved. If a model can explain and reproduce the previous data more and more, the predictability of the model can be continually improved. The cooperation between the experimentalist and model developers is essential to succeed in physiome. As a model is developed in this way, eventually it can perform better than most experiments. To see the tree and the forest together clearly in the future, it is essential to pursue physiome.

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## 3. How physiome can be used

The most important application of physiome is to develop a new drug. The failure rate of new drug development is > 99.9%. The investment for new drugs is huge, with major pharmaceutical companies merging to cover the expense of new drug development. Target identification for curing disease is the most important aspect of new drug development. If a physiome model can reproduce human biology in an appropriate way, it can be used to simulate disease states and for discovery of the most effective targets curing disease. Furthermore, since physiome models already regenerate human responses, the burden of clinical testing and development time for the new drug can be reduced substantially.<sup>2,3</sup> Another benefit includes reduction of ethical issues involved with using animal or human subjects through the use of simulations.



**Fig. 1 – Illustration of the relationship between the physiome and other areas of biological organization.**

**Note.** From Hunter PJ, Borg TK. Integration from proteins to organs: the Physiome Project. *Nat Rev Mol Cell Biol* 2003;4:237-43. Copyright 2003, Nature Publishing Group. Reprinted with permission.

Another place is academic research. As mentioned, an important role of physiome is as a data repository and a kind of preliminary test bed for research ideas. If model results and experimental results contradict each other, it is worth pursuing the reason. If the model is the center for the research, the speed of understanding life processes accelerates. Examples of this have been shown in physics. Currently, virtually all physics research is based on models. Model prediction, e.g., the Higgs boson, is to be proven by using cyclotron. Biological complexity retards development of physiome; however, physiome will eventually be accomplished and used. In the field of heart research, physiome is created and ready to be used in clinical fields. Numerous trials using cardiac-related physiome from the molecular to the organ level have been accomplished and displayed significant improvements in new drug development, academic research, and education.

#### 4. Physiome and oriental medicine

Oriental medicine is basically holistic medicine; however, even though oriental medicine is intended toward holism, there have been many trials to obtain mechanistic explanations, including five-chi or Sasang constitution. Because of these conceptual approaches, the knowledge associated with oriental medicine is difficult to grasp in a systematic way. These kinds of difficulties were described by Noble.<sup>4</sup> To obtain a model system like physiome, it should contain the structure and the clear function. Oriental medicine has vast amounts of functional knowledge, but very vague and conceptual structures to assemble. As Noble<sup>4</sup> mentioned, since the physiome

in the form of systems biology is at an early stage of development as a fully quantitative and computational discipline, it remains unclear what kind of higher level concepts might map well to traditional oriental medical concepts. From the Western point of view for physiome, the knowledge structure of oriental medicine is too weak and fragile. Since physiome and oriental medicine like Sasang constitutional medicine direct similar goals, e.g., a holistic approach, the development of the proper higher level of physiome in the future may open the way to understanding oriental medicine mechanistically. Meanwhile, both approaches can contribute clinical data supporting holistic models for physiome.<sup>4,5</sup>

#### Conflicts of interest

The author declares no conflicts of interest.

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