Future of computer modeling of physiology and disease in the Virtual Physiological Human and its application to medicine.

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The theoretical debate on the definition of e-health are far from being over – meanwhile, researchers are bringing in new practical solutions to previously unmet needs. By pooling the expertise of top level medical researchers, engineers and ICT experts, Biomedical Engineering (BME) is a discipline that is constantly searching for solutions to the needs of patients and highly innovative sectors. To-day, “e-health” is often assimilated to data exchange, internet applications for self diagnosis and tele-monitoring. However, the opportunities that ICT could provide in terms of healthcare are rapidly expanding. Even though BME is little known in some European Member States, recent projects illustrate the potential of BME and its applications: one of the most promising examples of ICT-based solutions, known as the Virtual Physiological Human (VPH), will finally take e-health into daily clinical practice. This chapter provides an overview of the VPH, which is supported by the European Union’s 7th Framework Programme (FP7) in the ICT for Health activities.

The VPH is intended to be a comprehensive model of human physiology, which would integrate knowledge about the various levels of body system organization – such as the body, organs, cells or proteins. This comprehensive tool will allow a better understanding of the relationships between processes across levels of physiological organization.

The VPH could be somehow compared to popular applications such as Google Earth. The latter provides a complete view of the world, a country, a city or specific streets. These are mapped, and images are incorporated at each level. Biomedical engineers developing the VPH are performing a similar mapping of the human body and its components, but they are going even further. The level of precision of their work could be comparable to Google Earth adding each single house, identifying individuals living in it then describing their social interactions, thus showing how society is organized and functions, at each level.

The VPH is an undertaking of gigantic proportions that needs to be continuously updated, and it will take more than a decade to complete it. Biomedical Engineers behind this project notably have to bring together excellence in disciplines such as physiology, biology, mathematics and medicine.

Physiology is the science about the function of all the human body components. It implies measuring the manifestation of an organ, a cell, a protein or subsystems of the body, as well as its interaction with other subsystems – rather than just watching their on/off manifestation. Physiology is essential to understand the development of a disease, as most conditions are due to the gradual derailment of a subsystem. Furthermore, such derailment often remains unnoticed, as it is often compensated by another bodily process, a stronger stimuli or another organ. The body as a whole can still seem to perform normally, even if one of its parts is malfunctioning – but ignoring the dysfunction would be like beating a tired horse to keep him running at the same pace. One may lose the function of a kidney without noticing it before it is too late, as the other kidney can “work” harder to compensate...
the dysfunction. The VPH will therefore integrate the description of such functional interactions between all the body's subsystems.

The VPH itself is based on mathematical models that simulate a bodily process, which enables researchers to better understand a normal physiological process and the development of a disease. The VPH has multiple applications in the clinical arena: it can be used for diagnosis, for predicting the outcome of a treatment or for training clinicians on delicate procedures without endangering the patient. Many model-based simulators, treatment robots and diagnostic tools with clinical applications already exist. A perfect analogy is often drawn with flight simulators. Seen as a toy in the beginning of these developments some 30 years ago, they have developed into a training tool for pilots accounting for more time of experience than real flights. Nowadays, pilots are required to train for responses to rare events that may have detrimental outcomes such as the failure of a subsystem, an engine or even bad weather.

Similarly, biomedical engineering is developing model-based clinical tools that will form the rational basis for clinical treatment in many, if not all, areas of healthcare.

Throughout the past decades of human genome discovery and development, there has been a belief that for each disease a molecule exists; many thought that unraveling the genome would bring cures for all diseases. However, it becomes more and more apparent that the genome describes our molecular building blocks only, which only represent a small part of our system. Such blocks interact with all other systems necessitating understanding at both the cellular and organic levels. It is obvious that something would go wrong if an essential building block would be missing. However, the lack of one building block may be compensated for by others in many cases. The development of a disease is not necessarily caused by one single dysfunctional gene, but rather by on a combination of multiple dysfunctioning genes. Moreover, some genetic conditions may lead to diseases in one person but not in another depending on the interaction with other factors such as lifestyle. Examples can be found in the development of cancer and diabetes.

Let us go back to the essentials of simulators and models: the mathematical description of functions of subsystems at all levels. There are several types of models and the most important models include descriptive and predictive models. The boundary between these two models is difficult to clearly delineate, but both are useful to the VPH. In a predictive model, the mathematical relationships describing the processes of a system are based on biophysical or biochemical processes essential to the system. In a descriptive model, the subsystem is considered a “black box” and the input-output relations are based on heuristic analysis of a large dataset related to function and mal-function of the system.

A good example of how both types of models are integrally applied is the functioning of the heart, which is currently being studied in another FP7 project: euHeart®. Although the heart has the simple task of providing blood flow to all organs, it is a complicated system, which can fail in many different ways. For example, a heart valve may become leaky or lose its flexibility due to calcification. In both cases, the heart’s pump function becomes less efficient. The wall of a coronary artery may become damaged and thickened in response, thereby obstructing the blood flow through the microcirculation where oxygen is needed for the cells to function. In cases where the heart muscle or parts of it, have to function mechanically at too high a level, or on the verge of a failing oxygen supply, its structure will adapt and cope with these situations by altering the organization of muscle
fibers and cellular function. These structural changes have an effect on the electrical conduction of the pulse that the heart needs for an organized contraction. Age and function of the heart’s atria effect the organization of cells and fibers which may result in atrial fibrillation though not deadly since the heart has compensation mechanisms for atrial dysfunction. However, this type of fibrillation allows blood clots to form in the atrium - which may cause a stroke. The instances that can make these effects cause death are based on the predisposition of the molecular machinery of the heart\textsuperscript{iv}. Hence, a comprehensive understanding of all these mechanisms, and especially their interactions, are a prerequisite for an appropriate clinical response to any disease of the heart. Deviations of the body systems at every level circulate through the heart and eventually through the body.

Biomedical engineers developing the VPH models process all physiological and diagnostic information, in order to simulate the likely reaction of an individual patient to possible treatments or interventions. Such tools will not only improve the quality of treatment of ill or injured patients. They could also be used in preventive medicine, as to predict occurrence or worsening of specific diseases in people at risk e.g. through family history. The VPH clearly has the potential to enable clinicians to better understand and diagnose some of the most misunderstood body processes. Through the use of internet technologies, the VPH could likely revolutionize the healthcare sector as a whole. VPH-derived technologies will integrate, as we have seen, in all kind of healthcare-related technologies.

Translation of the VPH approach to daily medical care will provide improved health care accessible across boundaries within the European Community. The VPH project shows the benefit of promoting interdisciplinary research and Biomedical Engineering, and we can hope that the European Union will continue to support collaborations between the ICT community, physiology, biology and medicine. EAMBES works towards improving the health, wealth and well-being of the people by the application of medical and biological engineering and sciences.

\textsuperscript{1} http://eambes.org/  
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