THE FOUNDATION FOR MULTI-SCALE MODELING

OF THE DIGITAL PATIENT

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ABSTRACT
The Digital Patient is a technological platform that has the potential to transform personal and public health care, as well as pharmaceutical and device development and testing, research, and patient and professional education. It is the ultimate Big Data project in healthcare; however, its power will derive not from the volume of data, but from the integration of disparate sources of data into valid and reliable information—about biological processes, social context and treatment efficacy. That integration, in turn, is largely dependent on the evolving theoretical approach known as systems biology and the successful meshing of multi-scale models. This paper provides an overview of the digital patient, the domains of systems biology and multi-scale modeling and the implications for personalized medicine.

Keywords: systems biology, multi-scale modeling, digital patient, convergence

1. INTRODUCTION

What is a Digital Patient? It is a digital representation of 'health' and 'disease' and a sophisticated decision support system that can be customized to represent each one of us, individually or collectively. Imagine a "virtual twin" of sorts, living in digital form, inside a computer. *That virtual twin is shaped by your medical history. It keeps inside a digital record of your insulin levels, which are constantly tracked by that micro-sensor the doctors installed when they did your angioplasty and stented one of your carotids. Your virtual twin is a bit sleep-deprived, just like you, since you are not sleeping so well due to that back injury. It is allergic to some antibiotics and has 'let itself go,' after overeating for the past few years.*

This description represents a vision of truly personalized medicine, which was at the heart of the project DISCIPULUS. That project was given the task of engaging the European Union (EU) research community in order to develop a Roadmap towards the *Digital Patient*, a key component and conceptual child of the Virtual Physiological Human (VPH) initiative (www.vph-institute.org). Within the scope of DISCIPULUS, the Digital Patient was defined as "*a technological framework that, once fully developed, will make it possible to create a computer representation of the health status of each citizen that is descriptive and interpretive, integrative and predictive*".

2. CONVERGENCE, SYSTEMS BIOLOGY AND MULTI-SCALE MODELING

In January 2011 the Massachusetts Institute of Technology submitted a report to the health science research community introducing a new research model that is essential to the continued development of the Digital Patient. The research paradigm they developed is called *convergence*, the merging of distinct technologies, processing disciplines, or devices into a unified whole to create a host of new pathways and opportunities. Convergence implies the technical tools, as well as the disciplined analytic approaches, from design, engineering and physics and their adaptation to the life sciences. The strength in this research methodology is that it does not rest on a particular scientific advance, but on an integrated approach for achieving advances.

Focusing more directly on the type of convergence essential to the Digital Patient is systems biology. Systems biology addresses interactions in biological systems at different scales of biological organization, from the molecular to the cellular, organ, organism, societal and ecosystem levels. It is characterized by its integrative nature as compared to the reductionist nature of molecular biology. It is also characterized by quantitative descriptions of biological processes, using a variety of mathematical and computational techniques. Thus, systems biology combines the development and application of predictive mathematical and computational modeling with experimental studies. The modeling techniques that are employed incorporate multiple spatial and temporal scales that are consistent with the integrative perspective of systems biology. Just as physiology is a branch of biology, systems physiology, systems medicine and personalized medicine are subsets of systems biology. These levels of systems and their supporting informatics are shown in *Figure 1*. The Digital Patient will eventually integrate data and models across scales and time and thereby enable the realization of truly personalized medicine.

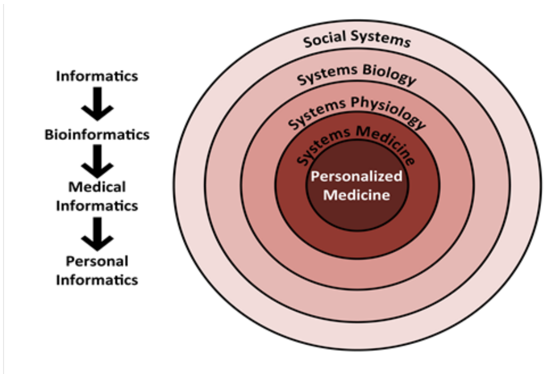

Figure 1: System of Systems and Levels of Informatics

Systems physiology focuses on the function of interacting parts of the system at the cell, tissue, organ and organ system scales, and is tightly coupled with structural anatomical information. Systems medicine is a subset of systems biology that addresses applications to clinical problems. Examples include the application of the systems biology framework to develop quantitative understandings of disease processes, to drug discovery, and to the design of diagnostic tools. A subset of systems medicine that relies on individual patient data or the data from a specific group of similar patients is the emerging domain of personalized medicine.

The interest in systems biology has been growing steadily during the past decade. As Noble noted: "Systems biology … is about putting together rather than taking apart, integration rather than reduction. It requires that we develop ways of thinking about integration that are as rigorous as our reductionist programs, but different. … It means changing our philosophy, in the full sense of the term."

Although the framework is being developed, many currently available systems biology studies are not multilevel; they do not integrate physiological responses from the molecular to the cellular, organ and whole organism levels. The development of an integrated model of human physiology is essential for the understanding of how molecular, cellular, organ and system levels interact for a total physiological response. Then, of course, the higher levels of biological systems and social systems must ultimately be integrated into the analytic framework.

3. MULTI-SCALE MODELING

Biological and physiological systems are highly complex. This complexity results in large measure from the following factors:

> *Non-linearities*: Many responses have upper and lower boundaries with different levels of sensitivity in between.
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> *Redundancy*: Many physiological states are the result of multiple mechanisms pushing and pulling on the observable response. Redundancy makes it difficult to identify important causal mechanisms.
>
> *Disparate time constants*: The importance of an observation often depends on the timing of the protocol. For instance, the control of arterial blood pressure is a mix of fast-acting neural mechanisms, slow-acting hormonal mechanisms, and long-term effects of body fluid volume and composition.
>
> *Individual variation*: Physiological responses are a qualitative and quantitative function of sex, age, body composition and other individual characteristics.
>
> *Emergence*: Many high-level, integrative behaviors of the biological system cannot be described solely by aggregating the respective inputs from basic processes.

Biomedical researchers are increasingly using integrative physiological and biological models to better understand fundamental relationships that have been hidden in the complexity.

4. SYSTEMS BIOLOGY, MULTI-SCALE MODELING AND PERSONALIZED MEDICINE

Translational biomedical research has made the integrative analysis of human physiology more relevant to clinical practice. The explosion of data over the past twenty years is providing novel opportunities to develop new clinical treatments. New technologies such as DNA sequencing, imaging, and proteomics provide massive amounts of new information about the human body. The ability to extract useful information from these data is beginning to lead to custom treatments for diseases, such as cancer, infectious diseases, and hematological and metabolic disorders. The existence of these newly available data sources has created a necessity for new methods of analysis. Genetic analysis suggests which genes may be important for clinical outcomes; however, the physiological relevance of changes in genetic makeup is not yet clear. This ambiguity necessitates a systematic approach to the integrative analysis.

Systems biology has the potential to provide valuable insights into the physiological workings of the human body. The current goal of systems biology research is to utilize scientific advancements from the past two decades, such as genomics and proteomics, in an effort to develop targeted therapeutic strategies. The effective creation of these strategies, however, can only be realized with an in-depth understanding of the multi-faceted etiologies of complex diseases.

The highly complex nature of biomedical systems results from several distinct factors previously mentioned. These factors include non-linearities, redundancy of physiological states as a result of "multiple mechanisms pushing and pulling on the observable response", disparate time constraints, individual variation, as well as the concept that many high-level and integrative behaviors of the biological system cannot be described solely through the sum of inputs from basic processes. Despite the extensive complexities of biomedical systems, researchers are using sophisticated biological and physiological models to better understand fundamental relationships within the biological system.

Some scientists predict that understanding the data resulting from the systems biology approach will ultimately lead to the widespread availability of personalized medicine. In order to accomplish this feat, scientists must analyze data in a manner that recognizes the data as "a highly complex system comprising multiple inputs and feedback mechanisms." Translational medicine, a growing domain within biomedical and population oriented health research that aims to improve the health of individuals by converting research findings into diagnostic tools and procedures, requires complex functional and conceptual linkages. These linkages include the association of genetics to proteins, proteins to cells, cells to organs, organs to complete systems, as well as systems to the organism itself and to the surrounding social environment.

The creation of a comprehensive mathematical model is essential to understand the integration of these systems and to successfully apply a systems biology approach. Such a mathematical model would accurately link the functioning of all organs and systems, providing a useful framework for the development and testing of new hypotheses likely to contribute to improved clinical outcomes.

There are currently several intensive efforts underway to develop a human model.

A number of centers around the world are in the process of developing specific environments to facilitate the creation of integrative models of human physiology, or 'physiomes'. The Physiome Project is an effort to develop databases and models with the intent to understand human physiological responses. The International Union of Physiological Sciences (IUPS) Physiome Project focuses on providing a "computational framework for understanding human and other eukaryotic physiology," and comprises databases, markup languages, software for computational models of cell function, as well as software for interacting with organ models. Currently, the primary limitation with the Physiome Project is the lack of integration of the multiple narrow-focus models that could, if successfully integrated, lead to a comprehensive and integrative model of human physiology.

Many scientists are currently working on various systems biology-driven studies ranging from gene analysis to cellular metabolism and localized blood flow responses. Technological developments during the past few decades have also provided unique opportunities in the development of new clinical treatments. These technologies, such as DNA sequencing, imaging and proteomics, provide a vast array of new and untapped information about the human body. As scientists are able to extract usable information from the massive amounts of raw data, the research will infiltrate clinical practice in the form of customized treatments for disease in specific individuals. One notable example of this research effort to improve healthcare at the individual patient level follows.

Systems biology seeks an understanding of how and why complex systems behave as they do, and thus will have far-reaching implications for agriculture, energy production, environmental protection, and many other human activities. As Dr. Leroy Hood has noted, biology will be the dominant science of the 21st century, just as chemistry was in the 19th century and physics was in the 20th century.

Dr. Hood and his colleagues envision personalized medicine in a construct they call P4 medicine: predictive, preventive, personalized and participatory. Key benefits of P4 medicine to the patient and to the healthcare system will potentially include being able to:

- Detect disease at an earlier stage, when it is easier and less expensive to treat effectively;
- Stratify patients into groups that enable the selection of optimal therapy;
- Reduce adverse drug reactions by more effective early assessment of individual drug responses;
- Improve the selection of new biochemical targets for drug discovery;

- Reduce the time, cost, and failure rate of clinical trials for new therapies; and
- Shift the emphasis in medicine from reaction to prevention and from disease to wellness.

A coordinated and integrated program is envisioned by the Institute for Systems Biology (ISB) to accelerate the solving of technical challenges of P4 medicine. The program includes:

- Developing methods for determining individualized genomes and for integrating the findings with diagnostic measurement data;
- Developing methods for determining the levels of organ-specific proteins, microRNAs and other possible biomarkers, including cells, in the blood to assess the health or disease in all major human organ systems and thus enabling the monitoring of the earliest onset of disease;
- Digitizing medical records and creating effective, secure databases for individual patient records (new, data intense records with gigabytes of data);
- Developing new mathematical and computational methods for extracting maximum information from molecular information on individuals (including their genomes), and from other clinical data and personal history;
- Developing new computational techniques for building dynamic and disease-predictive networks from massive amounts of integrated genomic, proteomic, metabolic and higher level phenotypic data (This is the heart of the emerging field of personalized medicine: new methods for interrogating data and understanding the interaction between the environment and the genome of the individual.);
- Predicting drug perturbations of biological networks and developing therapeutic perturbations of biological networks (that is, re-engineering of networks in higher organisms with drugs, moving from a diseased state back to normal);
- Creating pluripotent cells (stem cells) from normal, differentiated cells, and then differentiating them to specific body cell types. The ability to create stem cells with a given individual's genome will be remarkable, understanding it will be revolutionary;
- Developing new *in vivo* molecular imaging methods and analysis methods to follow disease, drug response, drug effectiveness, and drug dosage determinations;
- Effectively managing the enormous personalized data sets that will result, which requires the development of broadly accepted policies addressing security, quality control, data mining, privacy protection, and reporting;

5. CONCLUDING DISCUSSION

Data is everywhere now, being aggregated, analyzed, and repackaged. We are in an era of Big Data, living with the recognition that almost everything we do is being captured as one or another type of data, with the hope that all that data can be used to help us become smarter, healthier, safer and richer and with the fear that our privacy is being invaded and that our risk for harm is increasing. It is in this broader context that this article addresses one of the more hopeful Big Data undertakings—that is, the construction and deployment of the Digital Patient.

The capacity to measure one's personal physiological and social metrics, compare those metrics with the metrics of millions of other humans, personalize needed therapeutic interventions and measure the resulting changes will ultimately realize the vision of personalized medicine—wherein patients and their providers will be able to detect disease at an earlier age; provide optimal therapy based on the characteristics of each individual and reduce adverse responses to therapy; where pharmaceutical companies can improve the process of drug discovery and clinical trials; and where the healthcare industry's emphasis truly shifts from reaction to disease to prevention of disease and promotion of wellness. Implicit in this vision is the integration of a sustained focus on improving the outcome measures of healthcare—safety, effectiveness, patient-centeredness, timeliness, efficiency, and equity—into clinical practice. Underlying this focus is, of course, the development and integration of multi-scale models based on the understandings emerging from systems biology.

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