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THE DIGITAL PATIENT

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Whatever we do together is pure invention,
The maps they gave us were out of date by years.

—Adrienne Rich, *21 Love Poems*

"Men's courses will foreshadow certain ends, to which, if persevered in, they must lead," said Scrooge."But if the courses be departed from, the ends will change."

—Charles Dickens, *A Christmas Carol*

It is, perhaps, odd to begin a book about a highly technical subject, the Digital Patient, with quotations from a poem and a book that, in very different ways, confront the vagaries of relationships. Then again, perhaps it is not so odd after all. Rich identifies the reality that relationships change and head in unexpected directions and that, often, what we thought was settled turns out to be in flux. Dickens describes the inevitable intertwining of past, present, and future in a hopeful homily. Imagine if we could all, without the ghosts, have the opportunity to revisit our past, understand clearly how it affects the present, and realize that the future can be changed into a more rounded, healthier human experience. In its essence, that is what the Digital Patient entails—the development of an evolving foundation for a better future in terms of personal and population health, in the validity of biological and social research, and in the development of more effective drugs and devices.

Dickens' story is a useful metaphor because it invokes the passage of time and describes that passage within a social context. Incorporating those two factors, time and social context, into the discussion of the Digital Patient foreshadows the emergence of an infinite array of applications that will advance our understanding of health and the factors affecting its realization. This introductory chapter provides some historical context for the concept

The Digital Patient: Advancing Healthcare, Research, and Education, First Edition.
Edited by C. Donald Combs, John A. Sokolowski, and Catherine M. Banks.

of a Digital Patient, refines the definition to reflect explicitly the impact of the emerging fields of systems biology and computational physiology, and provides a rationale for the chapters that follow. The chapter draws heavily from the writings of Vanessa Díaz-Zuccarini, Peter Hunter, Robert Hester, Leroy Hood, Richard Satava, Peter M. A. Sloot, and other chapter authors. It draws as well from the research conducted by hundreds of international researchers who address topics important to the Digital Patient as diverse as Big Data, the human physiome, systems biology, human behavior, multiscale modeling and simulation, ontologies in healthcare, and Bayesian analysis.

HEALTH, THE GOAL

The most widely accepted definition of health is the one developed by the World Health Organization: *Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity* [1]. The definition applies to individuals and to populations. From a societal perspective, achieving the goal of health, both individually and as a whole, is why we fund (through both public and private sources) research and development efforts in the domains related to the Digital Patient.

PERSONALIZED MEDICINE

Historically, understanding in detail and with certainty what is going on within the human body has been an elusive quest. Partial glimpses and general understanding are the best we have been able to do with the data we have at our disposal and within the limitations of population-normed theories of what the data mean for the diagnosis and treatment of individuals. In the not-too-distant future, however, that will change as the Digital Patient is developed. 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 realize the vision of personalized medicine. The capacity to aggregate and integrate data from millions of individuals will provide a means to improve health across populations with differing cultures and behaviors.

President Barack Obama stated in the 2015 State of the Union speech that his administration wants to increase the use of personalized genetic information to help treat diseases such as cancer and diabetes. He urged Congress to boost research funding to support new investments in precision medicine. Obama wants "the country that eliminated polio and mapped the human genome to lead a new era of medicine—one that delivers the right treatment at the right time" [2, 3].

He will seek hundreds of millions of dollars for a new initiative to develop medical treatments tailored to genetic and other characteristics of individual patients. "Most medical treatments have been designed for the average patient," said Jo Handelsman, associate director of the White House Office of Science and Technology Policy. "In too many cases, this one-size-fits-all approach is not effective." Dr. Ralph Snyderman, a former chancellor for health affairs at Duke University, often described as the father of personalized medicine, said he was excited by the president's initiative. "Personalized medicine has the potential to transform our healthcare system, which consumes almost $3 trillion a year, 80% of it for preventable diseases," said Dr. Snyderman [3].

THE BEST OUTCOMES

A patient is a person who is receiving healthcare. Healthcare involves surveillance, diagnosis, treatment, monitoring, and quality assessment. The goal of healthcare is, of course, a healthy outcome. Several analytic frameworks for assessing quality have guided initiatives in the public and private sectors to develop measures of the outcomes of healthcare. One of the most influential is the framework put forth by the Institute of Medicine (IOM), which includes the following goals for the healthcare system [4]:

Safety, avoiding harm to patients from the care that is intended to help them.

Effectiveness, providing services based on scientific knowledge to all who could benefit and refraining from providing services to those not likely to benefit (avoiding underuse and misuse, respectively).

Patient-centered, providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions.

Timeliness, reducing waits and sometimes harmful delays for both those who receive and those who give care.

Efficiency, avoiding waste, including waste of equipment, supplies, ideas, and energy.

Equity, providing care that does not vary in quality because of personal characteristics such as gender, ethnicity, geographic location, and socioeconomic status.

Having the goal of improved healthcare outcomes in mind helps to frame the importance of the Digital Patient: *it is among the most powerful technological tools that we can develop and deploy to improve health outcomes*. The Digital Patient is not a panacea; it will become, however, an essential component of the twenty-first-century healthcare toolkit.

THE EMERGENCE OF THE DIGITAL PATIENT

The Digital Patient's origins are recent, tied as they are to computer and imaging technologies developed during past 40 years. Although some of the modeling related to the human physiome dates back to the early 1980s and the emergence of computers as a significant factor in biomedical research, the clearest point of origin for the Digital Patient is the US Library of Medicine's Visible Human Project (VHP).

The Visible Human

The VHP has now celebrated the twentieth anniversary of the completion of the male (1993) and female (1994) image collections [5]. The data has been used broadly and remains a primary resource for research in the areas of human modeling and simulation of structures. The need for the VHP was predicted by the National Library of Medicine's (NLM) 1986 Long-Range Plan to include applications in education, training, modeling, simulation, morphometrics, information interfaces, reference standards, and entertainment [6].

The VHP (described more fully in Chapter 5) has contributed significantly to the education and training of both healthcare professionals and the general public. The data have been used extensively in atlases of both cross-sections and three-dimensional images of the human anatomy. The segmented image data has been the foundation for models used for 3D printing and virtual and augmented reality surgical simulators. Yet, further dynamic tissue modeling enhancements are needed to bring the Visible Human's cadaveric anatomical images to life.

Dead humans, such as the cadavers used in the VHP, are obviously not the same as living humans. They are, however, very useful models of human anatomy, both diseased and healthy. The data derived from analysis of human anatomic structures is an important component of the Digital Patient. That said, the pressing challenge is to build accurate human simulations, comprising many interacting models, capable of representing living humans moving through time.

THE HUMAN PHYSIOME

There are several international collaborative efforts directed toward the analysis of the human physiome. Two of those most inclusive efforts are described here. The International Union of Physiological Scientists (IUPS) began the Physiome Project in the 1990s. Joining the IUPS Physiome effort in 2006, the European Union funded the Europhysiome initiative. The effort ultimately evolved into the DISCIPULUS Project, which had the goals of further developing both the VPH and a Roadmap toward the Digital Patient. The VPH is a methodological and technological framework that will be capable of enabling the collaborative investigation of the human body as a complex system [7, 8]. The framework will make it possible to share resources and observations formed by institutions and organizations creating disparate, but integrated, computer models of the mechanical, physical, and biochemical functions of a living human body. It is thus central to refining the Digital Patient.

The VPH is a framework that aims to be descriptive, integrative, and predictive [9–11]:

Descriptive. The framework should allow observations made in laboratories, hospitals, and the field, at a variety of locations situated anywhere in the world, to be collected, cataloged, organized, shared, and combined in any possible way.

Integrative. The framework should enable experts to analyze these observations collaboratively and develop systemic hypotheses that involve the knowledge of multiple scientific disciplines.

Predictive. The framework should make it possible to interconnect predictive models defined at different scales, with multiple methods and varying levels of detail, into systemic networks that solidify those systemic hypotheses; it should also make it possible to verify their validity by comparison with other clinical or laboratory observations.

The VPH framework is formed by large collections of anatomical, physiological, and pathological data stored in digital format, by predictive models and simulations developed from these collections, and by services intended to support researchers in the creation and maintenance of these models, as well as in the creation of end-user technologies for clinical practice. VPH models aim to integrate physiological processes across different spatial and time scales (multiscale modeling). These models make possible the combination of patient-specific data with population-based representations. The objective is to develop a systemic framework that replaces the reductionist approach to biology and supports the integration of biological systems by dimensional scale (body, organ, tissue, cells, molecules), by scientific discipline (biology, physiology, biophysics, biochemistry, molecular biology, bioengineering), and by anatomical subsystem (cardiovascular, musculoskeletal, gastrointestinal, etc.) [12–14]. The VPH thus represents the human physiological operating system that is a central component of the Digital Patient.

The Digital Patient

Vanessa Díaz-Zuccarini, one of the leading researchers in the DISCIPULUS project, defines the Digital Patient 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, interpretive, integrative and predictive* [15].

Peter Hunter, one of the early leaders of the IUPS and VPH efforts, identified three major challenges to the development of the Digital Patient in his 2013 article:

Providing medical professionals and biomedical researchers with advanced user interfaces based on the Digital Patient metaphor that makes it easier to cope with large amounts of information related to different organ systems, different space/time scales, and different diagnostics;

Providing healthcare practitioners with an information and communications technology (ICT) layer capable of recovering and integrating all available health information for each patient into a coherent whole;

Providing biomedical and clinical researchers technology to capture existing knowledge and the digital artifacts in the form of predictive models and to compose digital quanta of knowledge into integrative models of complex system mechanisms [14].

This perspective views the VPH as a comprehensive collection of models and the Digital Patient as the broader infrastructure, providing the technological and logistical platform required to convert those models to an integrated, patient-specific clinical tool as well as to an improved analytic tool addressing health and health outcomes across populations of different sizes and patient characteristics.

Díaz-Zuccarini also provides one example of *a* Digital Patient in Chapter 2:

> a digital representation of a person's "health" and/or "disease" and a sophisticated decision support system, tailored to each one individual. Imagine, she says, a "virtual twin" of sorts, living in digital form, inside a computer. The virtual twin is shaped by the patient's medical history. It keeps a digital record of insulin levels, which are constantly tracked anyway, by a micro-sensor the doctors installed when they did that angioplasty and stented one of the patient's carotids. The virtual twin is a bit sleep-deprived, just like the patient, since he is not sleeping so well due to that back injury when he fell backwards skiing two years ago. It is allergic to that type of antibiotics and just like the patient, has "let itself go" a little bit, after binging on far too many chocolates.

Implicit in this example, and important for future research, are those characteristics of the "twin" that are related to time, behavior, and social context. Also important to note is the distinction between the realization of *a* Digital Patient and *the* Digital Patient platform.

One manifestation of the Digital Patient discussed in the DISCIPULUS project is the Patient Avatar. It is tempting to conflate the Patient Avatar and the Digital Patient. Although the Patient Avatar is *one* possible realization of the Digital Patient, it is only one such representation. The Digital Patient can be represented in an almost infinite variety of configurations—for example, avatars, mathematical models, curated data repositories, and animated graphs [16].

The DISCIPULUS Roadmap defined different "versions" (or levels of maturity) for the Digital Patient. These different "versions" correspond to what could be a short-/mid-/long-term vision for the Digital Patient. It was too difficult for the experts involved in the DISCIPULUS discussions to come up with definite categorizations and timescales, but nevertheless, the recommendations they provided will be relatively easy to position along a time continuum that goes from "I could come up with a small prototype if I work on this for a little while" to "this is achievable in a sensible time period with a lot of work" to "we don't know how to get there yet" [15].

Díaz-Zuccarini also notes that, in addition to patient data, Big Data in healthcare includes data from a myriad of other sources. For example, it includes data on claims and the cost of products and services, pharmaceutical data related to therapeutic mechanisms, side effects and toxicity, and patient behavior and patient activity data (such as from recordings of activity on smartphones or a Nintendo Wii, just to cite two examples). Important privacy issues are also obviously involved in aggregating and integrating the data required for the Digital Patient. One of the formidable challenges of having this diversity in data sources will be the determination of the ownership of the data: Does it belong to patients or to service providers or both, and who can use the data and under what conditions? These questions raise issues that must also be addressed during the continuing evolution of the Digital Patient.

ENABLING THE DIGITAL PATIENT

As the preceding narrative demonstrates, discussion about the subjects of a virtual human, the human physiome, and the Digital Patient highlights the need for integrating a broad spectrum of related topics. The chapters that follow showcase some of that diversity: various academic disciplines, methodologies, hypotheses, purposes, technologies, and practices that collectively contribute to advancing the Digital Patient. The narrative in this chapter simply foreshadows some of those topics: convergence, systems biology, multiscale modeling, standards, and the progress toward personalized medicine.

In January 2011, the Massachusetts Institute of Technology submitted a report to the health sciences 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 advancement, but on an integrated approach for achieving advancements [17].

Focusing more directly on the type of convergence essential to the Digital Patient are systems biology and its subdiscipline systems physiology. 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 mostly 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 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 1.1.

Systems physiology focuses on the function of interacting parts of the system at the cell, tissue, organ, and organ system scales, and it 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” [18].

An important question arises from a systems perspective about the construction of the Digital Patient: *What level of detail is necessary to simulate and, more importantly, accurately predict the efficacy of a patient-specific treatment?*

The understanding of human health, disability, and disease, and the rational design of preventive, diagnostic, or therapeutic strategies, depends on the quantitative knowledge of human anatomy and physiology and biological and social systems captured in reliable, validated mathematical models. Every other scientific discipline (from weather forecasting to the manufacture of everything from cell phones to aircraft) uses *a priori* knowledge of the

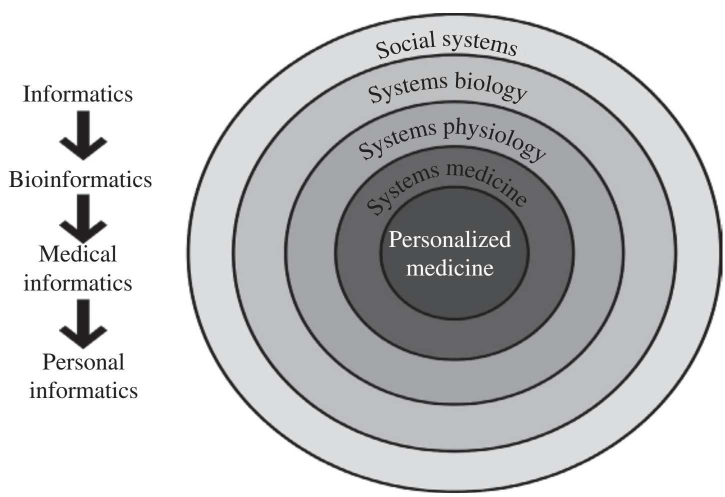

FIGURE 1.1 System of systems and levels of informatics.

physical laws of nature with model-based analysis and design. There is no reason to think that, ultimately, it will not be the same for biology. Indeed, the continued development of the Digital Patient will not be possible without the broad adoption of a system-of-systems analytic approach.

Computational physiology, for example, draws on techniques from numerous disciplines to address anatomical and physiological complexity by solving the mathematical equations that arise when the laws of physics and chemistry are coupled with the measurements of biological material properties. Disease is often a manifestation of the dysfunction of molecular-level processes, but the consequences are seen at scales ranging from the tissue to the organism. Computational physiology must therefore also address the challenges of multiscale physiological processes that operate over a 10^9 range of spatial scale (molecules to organ systems) and 10^{15} range of temporal scale (microseconds of biochemical reactions to the decades of aging processes). As we gain a quantitative understanding of human physiology through multiscale mathematical modeling and begin to adapt these generic models to an individual patient, there is an increasing need to describe disability and disease in terms of model parameters and to incorporate these parameters into electronic health records [19, 20]. The linking of computational models with health information from electronic health records, for example, has the potential to open up new vistas for biomedicine. The vast amount of clinical and wellness data could help validate models and allow for the customization of such models to individual patients and subpopulations [21].

Research and development of applications in the physiome, systems biology, the VPH, and personal health systems share one important challenge: *the need for integration*. That integration is the Digital Patient. To implement the outputs of biomedical research in clinical practice and within the healthcare industry, we need to integrate different data, information, knowledge, and wisdom. There is a need to integrate different types of data for the same patient stored across different systems, across different hospitals, across different countries, and in clinical research databases; patient-specific knowledge; information related to various parts and processes of the human body into a systemic understanding of pathophysiology; knowledge digitally captured via metadata, ontologies and models; and wisdom produced in research laboratories and in clinical practice, which can be formalized in guidelines, standards, and protocols and then used to promote translation of basic science and integrative models into improved healthcare outcomes [14].

One effort to address this required integration is the work of the US Interagency Modeling and Analysis Group (IMAG) and its companion group, the Multiscale Modeling Consortium (MSM). These two groups have several goals:

- to grow the field of multiscale modeling and biomedical biological and behavioral systems;
- to promote multidisciplinary scientific collaboration among multiscale modelers;
- to encourage future generations of multiscale modelers;
- to move the field of biological computational modeling forward in the following disciplines: predictive models of biology, health, disease, bioenergy, and bioremediation;
- to develop accurate methods that cross the interface between multiple spatial temporal scales;
- to promote model sharing in the development of reusable multiscale models; and
- to disseminate the models and insights derived from the models to the larger biomedical biological and behavioral research communities.

The IMAG/MSM efforts focus on the very important point that to realize the Digital Patient, data has to be valid, reliable, and capable of being accessed in many interacting models operating at different scales of time and space [13, 22, 23].

P4 MEDICINE

The convergence of systems approaches to disease, new measurement and visualization technologies, and new computational and mathematical tools can be expected to replace the current, largely reactive mode of medicine, where we wait until the patient is sick before responding with personalized, predictive, preventive, and participatory (P4) medicine that will be cost effective and increasingly focused on wellness.

One of the leaders in this P4 translational effort is Leroy Hood and his colleagues at the Institute for Systems Biology. According to Hood, the benefits of P4 medicine, to the patient and to the system, include new abilities 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 [24, 25].

P4 medicine promises to sharply reverse the ever-escalating costs of healthcare by introducing personalized diagnosis, less-expensive approaches to drug discovery, a renewed emphasis on preventive medicine and wellness, and numerous cost-decreasing measurement technologies. P4 medicine also promises to improve patient outcomes and to empower both the patient and the physician [26]. Having much more, and more accurate, information to be used by the patient and the physician to make decisions about prevention and treatment is at the heart of aspirations for twenty-first-century medicine.

CONCLUSION

The expansion of the Digital Patient platform and its many possible representations and applications will be possible through careful attention over time to six focus areas: requirements, modeling and simulation, standards, tools and technology, infrastructure, and systems engineering. The focus on requirements highlights the importance of data, system, user, and interoperability requirements in building the Digital Patient out of a collection of simulations. The focus on modeling and simulation highlights the importance of obtaining information about the validity and usability of the many individual simulations that are being merged into the Digital Patient. The focus on standards provides a platform for success by establishing a standard format, language, tool set, and practice for aggregating simulations and forming the Digital Patient. The focus on tools and technology allows for emerging technologies to be integrated into the Digital Patient in the future.

The focus on infrastructure provides an environment through which the users can express their needs and requirements over time. The focus on systems engineering highlights that the Digital Patient needs to have guidelines for how it can be improved upon or updated over time in order to remain useful to the community.

The Digital Patient will not be constructed based solely on new information from all the “omics” studies, from the various efforts to model the human physiome and represent it virtually, from systems analysis, or from Big Data. It will only be realized through the purposeful collaboration of researchers (whether they are patients or scientific, clinical, or policy researchers) on both their research and the framework into which their research will fit. The Digital Patient will continue to depend on the efforts of a wide variety of individual researchers and modelers across many disciplines worldwide. It is inevitably an emergent phenomenon, governable only by sustained cooperation among those with an interest in its development and with guiding principles of openness, flexibility, rigorous validation and reliability processes, and respect for personal privacy.

That takes us back to Rich’s observation that “the maps they gave us were out of date by years” and Dickens’ statement that “if the courses be departed from, the ends will change.” The chapters in this book raise issues and offer suggestions important to the continued realization of the Digital Patient, promising both a more current map and the prospect of a toolkit capable of helping us change the course toward better health.

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