THE DIGITAL PATIENT
Wiley Series in

Modeling and Simulation

A complete list of the titles in this series appears at the end of this volume.
THE DIGITAL PATIENT

Advancing Healthcare, Research, and Education

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WILEY
To Pam, Cole, and Ford
— C. Donald Combs

Marsha, Amy, and Whitney
— John A. Sokolowski

The two boys in my life
— Catherine M. Banks
CONTENTS

List of Contributors xiii
Preface xvii

PART 1 The Vision: The Digital Patient—Improving Research, Development, Education, and Healthcare Practice 1

1 The Digital Patient 3
C. Donald Combs

Health, The Goal, 4
Personalized Medicine, 4
The Best Outcomes, 5
The Emergence of the Digital Patient, 5
The Human Physiome, 6
Enabling the Digital Patient, 8
P4 Medicine, 11
Conclusion, 11
References, 12

2 Reflecting on Discipulus and Remaining Challenges 15
Vanessa Díaz-Zuccarini, Mona Alimohammadi, and César Pichardo-Almarza

Introduction, 15
A Brief Contextual Background and a Call for Integration:
  Personalized Medicine is Holistic, 16
The Many Versions of the Digital Patient:
  On the Road to Medical Avatars, 18
Discipulus: The Digital Patient Technological Challenges and Main Conclusions, 19
CONTENTS

The Remaining Challenges and Big Data, 24
Conclusion, 25
References, 26

3 Advancing the Digital Patient
Catherine M. Banks

Introduction, 27
The Digital Patient: Its Early Start, 28
Engaging the Digital Patient, 30
Conclusion, 31

4 The Significance of Modeling and Visualization
John A. Sokolowski and Hector M. Garcia

Introduction, 33
Modeling a Complex System: Human Physiology, 34
Medical Modeling, Simulation, and Visualization, 35
Modes and Types of Visualization, 40
Visualization for Patient-Specific Usefulness, 43
Conclusion, 43
References, 45

PART 2 State of the Art: Systems Biology, the Physiome, and Personalized Health

5 The Visible Human: A Graphical Interface for Holistic Modeling and Simulation
Victor M. Spitzer

Introduction, 51
Education, 53
Modeling, 55
Virtual Reality Trainers and Simulators, 56
Conclusion, 58
References, 59

6 The Quantifiable Self: Petabyte by Petabyte
C. Donald Combs and Scarlett R. Barham

Introduction, 63
Smarr’s Quantified Self, 64
Extending Smarr’s Research, 67
The Quantified Self-Vision, Simplified, 69
Criticism, 69
Conclusion, 71
References, 72
Future Challenges, 142
Conclusion, 142
Acknowledgments, 143
References, 143

11 Modeling and Understanding the Human Body with SwarmScript
Sebastian von Mammen, Stefan Schellmoser,
Christian Jacob, and Jörg Hähner

Introduction, 149
Related Work, 150
Multiagent Organization, 152
Designing Interactive Agents, 152
Speaking SwarmScript, 153
Answering Demand: The Design of SwarmScript, 153
Graph-Based Rule Representation, 153
The Source–Action–Target, 154
SwarmScript INTO3D, 154
A SwarmScript Dialogue, 155
Discussion, 164
Summary, 166
References, 166

12 Using Avatars and Agents to Promote Real-World Health Behavior Changes
Sun Joo (Grace) Ahn

Introduction, 171
Avatars and Agents, 172
Using Agents and Avatars to Promote Health Behavior Changes, 173
Conclusion, 178
References, 178

13 Virtual Reality and Eating, Diabetes, and Obesity
Jessica E. Cornick and Jim Blascovich

Introduction, 181
Virtual Reality, 181
Obesity and Weight Stigma, 186
Virtual Reality as a Tool for Combatting Health Issues, 187
Conclusion, 191
References, 191

14 Immersive Virtual Reality to Model Physical: Social Interaction and Self-Representation
Eric B. Bauman

Introduction, 199
Theory for Immersive Virtual Learning Spaces, 199
PART 3 Challenges: Assimilating the Comprehensive Digital Patient

15 A Roadmap for Building a Digital Patient System

Saikou Y. Diallo and Christopher J. Lynch

Introduction, 209
Approach, 212
Building the Digital Patient Through Interoperability, 213
Conclusion, 222
Acknowledgments, 223
References, 223

16 Multidisciplinary, Interdisciplinary, and Transdisciplinary Research: Contextualization and Reliability of the Composite

Andreas Tolk

Introduction, 225
Interdisciplinarity and Interdisciplinary Research, 226
Data Engineering to Support Interdisciplinarity and Interoperability, 228
Base Object Models to Support Transdisciplinarity and Composability, 233
Open Challenges on Reliability, 235
Summary and Conclusion, 237
References, 239

17 Bayes Net Modeling: The Means to Craft the Digital Patient

Joseph A. Tatman and Barry C. Ezell

Introduction, 241
Other Interesting Applications, 246
Conclusion, 251
References, 253

PART 4 Potential Impact: Engaging The Digital Patient

18 Virtual Reality Standardized Patients for Clinical Training

Albert Rizzo and Thomas Talbot

Introduction, 257
The Rationale for Virtual Standardized Patients, 258
Conversational Virtual Human Agents, 259
UsC Efforts to Create Virtual Standardized Patients, 260
Conclusion, 269
References, 270

19 The Digital Patient: Changing the Paradigm of Healthcare and Impacting Medical Research and Education 273
V. Andrea Parodi

Introduction, 273
Overview Digital Medicine Projects, 275
Personalized Patient Care Clinical Use, 279
Recommended Education and Training for VPH Project Participation, 281
From Flexner to the 2010 Carnegie Report, 284
Summary Statements, 286
References, 287

20 The Digital Patient: A Vision for Revolutionizing the Electronic Medical Record and Future Healthcare 289
Richard M. Satava

Introduction, 289
Applications of the Digital Patient as the EMR, 291
Discussion, 296
Conclusion, 297
References, 297

21 Realizing the Digital Patient 299
C. Donald Combs and John A. Sokolowski

Index 305
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Understanding in detail and with certainty what is going on within one’s own 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 with the limitations of population-normed theories of what the data mean for diagnosis and treatment of individuals. In the not-too-distant future, however, that will change as the Digital Patient platform 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. Incorporating all of this rich data in simulations will have significant impacts on medical research, education, and healthcare systems around the world, as more interventions are simulated and assessed in silico prior to their use in therapy.

So, what exactly is the Digital Patient? The most commonly referenced definition of the Digital Patient is that provided through the European Union’s DISCIPULUS project: 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. Not explicitly stated, but implied, is that this framework will include behavioral, social, temporal, and spatial dimensions.

Major technological advancements in recent years have paved the way for more systematic approaches to modeling, simulation, and visualization of biological and social processes that make the realization of the Digital Patient possible. Modeling now encompasses high degrees of complexity and holistic methods of data representation. Various levels of simulation capability allow for improved outputs and analysis of discrete and continuous events. Simulation complements both natural language and mathematical and statistical analysis by introducing new ways of thinking. Simulation also provides tools to build understanding and generate insight into complex biological systems and processes, thus allowing much more comprehensive human models.

In the past, biologists sought to understand living things largely by examining their constituent parts. They studied individual genes, proteins, or signaling molecules to learn
everything they could about the structure and function of a single and largely isolated biological entity. The emerging scientific strategy adds a new dimension to this traditional approach. Researchers now seek to understand both each constituent of a biological network and how all of a network’s constituents function together. They use cutting-edge technologies to gather as much information as they can about a biological system. They then use this information to build mathematical and graphical models that account for the behavior of the system. They test these models by gathering additional data, often by perturbing a system through genetic or environmental changes. In this way, they build an understanding of biological systems that can be used, for example, to explore what goes wrong when a biological system becomes diseased and how to treat or prevent that disease.

The Digital Patient will not be constructed based solely on new information from all the “omics” fields, 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.

People will ultimately be able to have personalized genetic codes and medical imaging stored in a cloud database, along with charts of vital signs and detailed nutritional analysis of everything they consume. They can then compare this data with data on millions of other similarly monitored bodies across the world, resulting in a colossal database (now widely referred to as Big Data) mined by software that can utilize the data to provide specific, personalized guidance regarding diet, vitamins, supplements, sleep, exercise, medication, treatments, social interactions, and overall health. That, simply stated, is the overarching goal of the Digital Patient.

The text is divided into four parts. To begin the discussion, Part 1—The Vision—makes the case for engaging the Digital Patient in all facets of healthcare: research and development, education, and practice (Chapter 1). A brief review of some of the most significant efforts in the development of the Digital Patient is presented (Chapters 2 and 3) as well as a discussion of the challenges of modeling a complex system such as the human body (Chapter 4).

Part 2—State of the Art—presents the corpus of research cataloging and analyzing the progress that has been made in developing a Digital Patient during the past decade. Since the Visual Human Project of the 1990s that focused on developing models of male and female anatomy based on dissection, substantial progress has been made in the development of physiological, anatomical, and social models and simulations. Chapters 5 through 14 present the various projects underway across the world; these contributions address anatomical modeling, facial and expressive modeling, and social and cultural modeling of humans.

Part 3—Challenges—attends to the substantial challenges of assimilating the various “parts” of the Digital Patient to make it whole. Chapters 15 through 17 address issues with the integration of all (modeled) components, interoperability of all models, and reliability and contextualization of the composite Digital Patient. Also included is Chapter 17 as the means to calibrating or refining the Digital Patient specific to an individual patient.
Part 4—Potential Impact—looks to the future of medicine and the usefulness of enabling the Digital Patient. Chapters 18 and 19 present the potential impact of the Digital Patient in research and experimentation in medical devices and technology, biologic development and testing, medical education and training, and, of course, patient care. Chapter 20 provides a closing word on the potential impact of the Digital Patient in medicine and healthcare vis-à-vis an increasing global population, lengthening life spans, and a mounting demand for medical care. Chapter 21 proposes a research and policy agenda aimed at fully constructing the Digital Patient: that is, why and how this needs to take place at an all-encompassing level.

EDITORS’ NOTE

The editors stress that this text has set the topic of discussion within the reasonable bounds of the research and development currently underway. Thus, we make no claims that this is an exhaustive study of model development, simulation design, and applications of modeling and simulation in the structuring of the Digital Patient; rather, the text provides sufficient examples to present the breadth and depth of research in the field, speaks to the need for an overarching process to assimilate these projects, and suggests the means to do this in the form of a research and policy agenda. The intent of the agenda is twofold: (i) bring together these resources in a holistic approach for completing the Digital Patient and (ii) fully utilize the Digital Patient in the medical community for research, education, and practice.
PART 1

THE VISION: THE DIGITAL PATIENT—IMPROVING RESEARCH, DEVELOPMENT, EDUCATION, AND HEALTHCARE PRACTICE
1

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
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