BUILDING THE DIGITAL PATIENT: CONSIDERATIONS FOR THE NEXT DECADE

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ABSTRACT

Advancing medical practice to the level of personalized patient care is not a fanciful notion. Nor is it improbable or exaggerated. It is a credible end-state for medical M&S in the mid-term (10-15 years) future. Thus, the purpose of this paper is to provide an overview of the research and infrastructure that is needed to advance personalized patient care using the digital human and its ability to represent accurately the human physiome and diseaseome in real time for patient care, education, research and development. At the core of this endeavor to facilitating personalized healthcare is the primary beneficiary--the patient. The research agenda outlined in this paper is a call to action to ensure and compel the full development of a robust digital patient to enable personalized healthcare and, in the aggregate, more effective programs in research and in population health management.

Keywords: digital patient, physiome, personalized healthcare, research agenda, simulation

1. INTRODUCTION

The impact of new technologies during the past fifteen years has been extraordinary. It is difficult to remember that the now ubiquitous emails, web pages, text messages, I devices (pods, phones, and pads), tweets, blogs, and apps have a very brief history, widely used only in the past decade. One measure of this impact is the increasing demand for communication and information distribution: there are approximately 6 billion subscribers using some form of cellular device globally. So-called smart technologies are replete with advanced capabilities that enable the creation, imitation, and projection of virtual environments and simulated real-world experiences in most domains of everyday life.

Medical applications engaging these technologies are also experiencing exponential growth. Often the applications are developed within the confines of the discipline of modeling and simulation (M&S). In fact, medical M&S hosts the broadest spectrum of such usage, including fundamental aspects of healthcare such as human anatomy and physiology, human behavior, human systems to elaborate training and education exercises with computerized manikins and virtual operating rooms. Significantly, these advanced capabilities can even replicate aspects of a virtual human physiome to include anatomical, physiological, and behavioral attributes. Also underway is the *diseaseome* project, which maps disorders and diseases of an organism, viewed as a whole, with special reference to genetic features. The potential result of these combined capabilities can provide positive affects for the future of patient care. For example, a holistic, detailed simulation of a patient (*a digital patient*) can move diagnosis and treatment plans for that patient away from norm-driven options to patient-specific care, that is, true personalized care. Because medical M&S technology is inter-disciplinary (combining life and physical sciences, engineering, and medical expertise) and it is being executed at various levels for various purposes (at research and development institutions worldwide), there exists the substantial challenge of integrating these independent, yet complementary efforts to exploit their full potential. This is especially true with regard to the digital patient, wherein there is the necessity to assimilate the developed and developing components of the human physiome and diseaseome to advance patient care, medical practice, research and development, and education and training. In Europe, a substantial effort to develop a roadmap for the integration of data and models into a usable platform has been made through the Discipulus project and its evolving focus on the Virtual Physiological Human (VPH) and, ultimately, the Digital Patient.

Advancing medical practice to the level of personalized patient care is not a fanciful notion. Nor is it improbable or exaggerated. It is a credible end-state for medical M&S in the mid-term (10-15 years) future. Thus, the purpose of this paper is to provide an overview of the research and infrastructure that is needed to advance personalized patient care using the digital human and its ability to represent accurately the human physiome and diseaseome in real time for patient care, education, research and development. At the core of this endeavor to facilitating personalized healthcare is the primary beneficiary--the patient. The research agenda outlined in this paper is a call to action to ensure and compel the full development of a robust digital patient to enable personalized healthcare and, in the aggregate, more

effective programs in research and in population health management.

2. BACKGROUND

The dramatic growth in data about the human body and the human in social context combined with the progress in informatics, and modeling and simulation present an opportunity to realize a thirty-year old vision for a virtual human. This virtual human, however, will be far more sophisticated than the initial vision in that it will be capable of serving as a platform for research, education, patient care, drug and device testing. It will also be capable of accurately representing individuals and populations over time for purposes of screening, prevention, treatment, and analysis.

In the late-1980's, the U.S. National Library of Medicine established the Visible Human Project and, over the following decade, created male and female data sets designed to serve as a reference for the study of human anatomy, to serve as a set of common public domain data for testing medical imaging algorithms, and to serve as a test bed and model for the construction of network accessible image libraries. The Visible Human data sets have been applied to a wide range of educational, diagnostic, treatment planning, virtual reality, artistic, mathematical, and industrial uses by nearly 2,000 licensees in 48 countries.

In the late 1990', scientists at the U.S. Oak Ridge National Laboratory conceived the notion of a Virtual Human, a simulation of the structure and function of the human body that would integrate smaller models of individual organs, body processes, cells, and even neurons in the brain. The flesh and blood of these models would be floods of data, ranging from digitized anatomical images from the National Library of Medicine's Visible Human Project, to known electrical and mechanical properties of human tissue, to information on gene structure and function emerging from the federal.

In 2000, the International Union of Physiological Sciences Council formalized the Physiome Project. In its description, the IUPS notes that the Physiome Project is trying to put "Humpty Dumpty" back together again in a concerted effort to explain how each component in the body works as part of the integrated whole. Major diseases like cancer and neurological and cardiovascular diseases are complex in nature, involving everything from genes to environment, lifestyle and aging. Integrating knowledge of all these different components into robust, reliable computer models is expected to yield enormous medical advances in the shape of new therapies and diagnostic tools. Dozens of research institutions around the world are contributing to the building of the online computational modeling framework for integrating every level in human biology – one that links genes, proteins, cells and organs to the whole body. Ultimately, the goal of the Physiome Project is to piece together the complete virtual physiological human: a personalized, 3-D model of an individual's unique physiological make-up.

This international effort continues, but has been substantially accelerated by work lead by European Union institutions, both through the DISCIPULUS Project and its successor effort to develop the VPH. This latter effort (the description of which is drawn from the project website) aims to develop a methodological and technological framework that, once established, will enable collaborative investigation of the human body as a single complex system. The collective 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.

The Virtual Physiological Human (VPH) is a framework that aims to be descriptive, integrative and predictive:

- 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, catalogued, 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 objective is to develop a systemic approach that avoids a reductionist approach and seeks not to subdivide biological systems in any particular way by dimensional scale (body, organ, tissue, cells, molecules), by scientific discipline (biology, physiology, biophysics, biochemistry, molecular biology, bioengineering) or anatomical sub-system (cardiovascular, musculoskeletal, gastrointestinal, etc.).

The Digital Patient is a vision of what a fully developed, usable VPH (with social factors incorporated) could do in practice—in patient care, in research, in education, in drug and device development, and in population health.

3. USING A COMMON LANGUAGE

As with all interdisciplinary studies it is useful to first provide a common lexicon:

- *complicated and complex systems* – these systems diverge based on the level of understanding of the system; a physics-based model is complicated because it has numerous parts, but it is not complex in that it is predictable. On the other hand, a complex system like the human body might have fewer parts, but is complex because it is difficult to ascertain absolutes in the data. Humans are organic it is therefore not possible to predict the behavior of the human system with absolute certainty.
- *computer and computational models* – a computer model refers to the algorithms and equations used to capture the behavior of the system being modeled; while the computational model is a mathematical model that requires extensive computational resources (*e.g.*, computer memory and speed) to study the behavior of a complex system by computer simulation or, more accurately, systems/federations of simulations
- *interoperability and integration* – the technical term interoperability refers to computer systems that can exchange information; integration (of systems) seeks to embed systems into an existing environment
- *live, virtual, constructive simulation* – examples of each in the medical domain are: live – using simulated patients to mimic illness; virtual – synthetic training environments where people employ simulated equipment like the virtual operating room; and constructive – simulated people and simulated equipment augment real-world conditions
- *simulation and simulator* – simulation is a means, a technique, to replace or augment real-world experiences with case studies or guided experiences that represent or replicate substantial aspects of that real-world with an interactive capacity; the simulator is a device that can be used to accomplish this, such as a computerized manikin that can mimic fluid loss
- *digital patient* – an artificial human that includes anatomical, physiological, behavioral and, ultimately social, attributes
- *anatomical model* – models of the human anatomy ranging in complexity from single cell to organ to organ system; single or multiple components (e.g., the femur or the entire skeletal system) with a view to studying form, *what it is*
- *physiological model* – models to understand how the anatomy works in totality; how cells, muscles and organs operate together and interact from the molecular basis to whole integrated behavior of entire body with a view to studying function,
- *behavioral model* – for purposes of this study, this modeling focuses on representing changes in human behavior that result from a wide range of factors such as information, motivation, ability, physical change
- *individualized and personalized patient care* – moving from treating the individual patient based on the norms for his / her symptoms or disease patterns, then prescribing norm-set treatment options to personalized patient care with specified treatment options that are not norm driven but based on the specific effects of selected treatments on an individual human, rather than an “average” human

4. WHY THE DIGITAL PATIENT IS IMPORTANT

Simply stated, human biology is a science of complexity. The typical approach to studying the complex entity that is the human body has been reductionist biology, wherein a scientist looks at specific segments of the body, in essence taking the pieces apart. This has its place in the examination of individual anatomical components, but it falls short when attempting a holistic analysis of the body. Thus, an ideal approach is one that accommodates an integrated, interoperable and necessarily complex and dynamic, examination of human biology coupled with physiological and behavioral components of the individual’s experience. And that is what simulation can deliver in the form of the digital patient. Moreover, employing a digital human simulation in patient care can provide the best personal healthcare because it encourages, even requires, that the patient be more aware of consequences and take an active role in his/her own health as opposed to depending solely on guidance gained from hospitals, clinics, and specialists that may, or may not, be implemented appropriately.

Personalized Healthcare – this is the primary goal for the digital patient – personalized healthcare with the patient actively participating. Among the groups spearheading this discussion is *Intel's Health Strategy & Solutions Group*, which advocates for proactive healthcare models using technology for broadband infrastructure, interoperability, and care in the home. Intel's three-pillar approach, *Care Anywhere, Care Networking, Care Customization*, requires fully exploiting the capability of smart technology. The ideal situation is to make *care-at-home* the default location for the patient in contrast to clinics and hospitals with their associated challenges and costs. All-too-often these disparate teams address the patient as distinct parts of the body, individual pathologies, and isolated aspects of physiology. The data prove that healthcare is more effective when it is a coordinated effort: 80% of medical errors are the result of communication errors as multi-disciplinary units fail to communicate effectively as a team. The digital patient facilitates a self-care approach coupled with a networking capability that can (because the same information is available to everyone who is involved) avert communication gaps while fostering care customization.

A 2012 study by the National Institute for Medicine found that approximately 75 million Americans have more than one chronic condition. Effective treatments therefore require substantial coordination among multiple specialists and therapies, which increases the potential for miscommunication, misdiagnosis, potentially conflicting interventions, and dangerous drug interactions. The study noted the importance of mobile technologies and electronic health records that offer significant potential to capture and share health data more efficiently. To accomplish this, clinicians and care organizations need to fully adopt these technologies, while encouraging patients to use these tools as personal health information portals that allow them to actively engage in their own care.

To facilitate an active, engaged patient community, other segments of the medical community must subscribe. Three additional areas where the digital patient can significantly affect the future of healthcare are: Practice, Research, and Education.

***Practice* –** the future of health care, in the US and globally, is proving to be fraught with overwhelming challenges. Changing practice to provide holistic, personalized care in an expanding (longer-lived and growing population) and demanding (multiple pathologies and needs per individual patient) environment requires optimizing research, technology, and training. Clinicians must exploit new generation capabilities in diagnostic and therapeutic patient care for the burden of patient need to be met. Medical technology can be leveraged to provide safe and effective personalized patient care through the use of digital patient technology. Gone will be the "normed set of symptoms, normed set of treatments" approach.

***Research* –** for purposes of this discussion, research encompasses using the digital patient platform to conduct medical studies and to develop new devices, tools and medications.

Another significant body of work is in the area of the human diseaseome. One of the most advanced diseaseome projects is a collaborative effort, the Human Disease Network – HDN – housed at the Center for Complex Network Research at the University of Notre Dame, Indiana. This research is in the form of a web-based disease/disorder relationships explorer via an innovative map-oriented network. The team of researchers and engineers use a HDN dataset to facilitate intuitive knowledge discovery by mapping the complexity of disease. The premise of the research is that a network of disorders and disease genes are linked by known-disorder gene associations. The network that has been developed offers a platform to explore in a "single graph-theoretic framework all known phenotype and disease gene associations." Their findings support the notion that there is a common genetic origin of many diseases. This is done via a bi-partite graph of two disjoint sets of nodes, one to correspond to known genetic disorders and one to correspond to known disease genes. A disorder and a gene are connected by a link if a mutation in the gene is implicated by the disorder (data for which was found in OMIM – Online Mendelian Inheritance of Man, reference 18, which includes 1,284 disorders and 1,777 disease genes as of 2005.) The significance of this research is the representation of a genome-wide roadmap for future studies of disease associations via the disease map which details all diseases and the genes associated with different disorders.

Another important research domain wherein the digital patient can be a significant asset is in pharmacology and biologic medicine. There are numerous agencies and institutions, for various reasons, that contribute to the growing body of literature condemning animal research in disease studies, pharmaceutical development, and biologic medicine. The literature details some of the failures of animal research and testing specific to toxicity safety and vaccine development by declaring this research as unreliable and not especially predictive when applied to humans. In short, the literature contends that animals have proven to be inadequate models for human disease research because they are genetically different from humans; therefore, studying diseases in animals can give us inadequate or erroneous information.

Research also entails the development of devices and tools: devices to support the body, such as stents, heart valves, dental implants, spine and joint implants as well as tools to interrogate the body from the surgical scalpel to ultrasound technology. In 2006 the U.S. registered 46 million such devices and tools engaged in patient care.

The U.S. Food and Drug Administration is responsible for the oversight of the development of these apparati under its Center for Device and Radiological Health. The Center regulates via four evaluation models: animal, bench, computational, and human. Simulation supports this evaluation as it is premised on mathematical modeling. The FDA will soon to publish a guidance document, "Reporting Computational Modeling Studies in Medical Device Regulatory Submissions," as a means of encouraging simulation in medical research. The FDA is also developing the Virtual Physiological Patient (VPP), a library of computer models of the human body at various levels of disease states. Additionally, there is the partnership among device developers, software providers, and medical professionals, the Medical Device Innovation Consortium (MDIC) that serves as a center for disease-specific information gathering. Significantly, the goal of the VPP is to serve as a shared point of reference that will improve both understanding the value and limitations of models. For the FDA and its associate partners in this endeavor, these applications are distinct parts of what could grow into a whole representation.

The FDA commitment is one example of an excellent component of this study – an integrated, inter-operable fully developed digital patient that can serve all aspects of medical development to a more complete, perhaps spanning the whole-body, device assessment and evaluation.

***Education* –** there are two essential skill-sets that must be mastered by students: 1) cognitive, to identify human anatomy / pathology; and 2) motor (or psychomotor) to distinguish and diagnose physiology via physical manipulation of the body (with one's hands or with devices). Medical training can be both patient-centric and education-centric with each perspective requiring varying levels of model and/or simulation fidelity. A digital patient can support both: for cognition training very high levels of modeling can facilitate a detailed teaching curriculum can be developed; the training of motor skills can take place with physical models that can support robotics or ultrasound training intent on manipulation skills of the probe. Of course, better education and training leads to better medical practice. The education prospects of the digital human support the means to train and assess learner performance more effectively.

5. CONCLUDING DISCUSSION

This paper shows the potential of the digital patient across all healthcare domains—education, research, product and drug development, and patient care. Integral to realizing this potential is understanding how the digital patient is being pieced together. For purposes of this paper, the state-of-the-art in the development of the virtual human physiome (the necessary precursor to the digital patient) includes three general areas: 1) anatomical, 2) physiological, and 3) behavioral.

This paper has outlined a general research agenda aimed at assimilating these various resources toward completing the digital patient, and then extending that integrated, interoperable capability to further research and development, augment education and training, and advance patient care.

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