Developing a Framework for Multi-Scale Modeling of the Digital Patient: Insights from Current Status and Future Directions

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Abstract: The Digital Patient is an analytic platform that has the potential to transform personal and public healthcare, pharmaceutical research, medical device development, 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 successful and efficient integration of disparate sources of data into a validated and reliable computational model of combined biological processes, social context and treatment efficacy. That integration, successively, is largely dependent on the evolving theoretical approaches known as systems biology and physics-based modeling that lead to the successful meshing of multi-scale models.

1 WHAT IS A DIGITAL PATIENT?

The Digital Patient is a comprehensive approach to providing a computational platform for personalized medicine. It is a digital representation of a person's 'health' and 'disease' status or in another word, a whole-body system. It may include computer models of the mechanical, physical, and biochemical functions of a living human body calibrated by multi-scale and length data collected from the multiple physiological levels. This is not only the ultimate big data project, but also the ultimate technical challenge in medicine. When executed, it can be used as a powerful in silico (in silico means carried out in the computer, which is in contrast to in vitro (on the bench), ex vivo (outside the living organism), or in vivo (inside the living organism)) decision support technology that can be customized to represent each one of us, individually and/or collectively (C. D. Combs et al., 2015; Dıaz-Zuccarini et al., 2015; Parodi, 2015). It is an integrated approach for achieving a broader, more systematic understanding of the human body in a single computational platform.

One of the key aspects to the project is the need for a new analytic framework for understanding the whole-body, that is, being able to deal with the complexity of physiology by creating and integrating properly annotated, curated, validated and documented modules of individual organ systems. Ultimately, more complex models are expected to merge upon linking these modules semantically to represent the whole-body system. In the construction of a Digital Patient framework, significantly important things to consider are what level of detail is necessary, and more importantly, how to accurately predict the efficacy of a patient-specific treatment. In addition, the processes for achieving a Digital Patient framework involve generation of data and information, biomedical information management, knowledge-driven and data-driven computational modeling (i.e., in silico models based on prior knowledge on cause-and-effect relationships, and/or nature of data), clinical user interface, and end translation and adoption.

1.1 Integrative Whole-Body View

The human body is the ultimate efficient machine comprised of multiple organs, tissues, and cellular complexes that interact to maintain a homeostasis. Pathology is due to alterations in one or more tissues or systems or in a single biological process (Talbot et al., 2016). Alterations in one system often induce changes in the physiology of other systems.

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Therefore, 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 (An & Cockrell, 2022; Hester et al., 2011). However, biologists have traditionally sought to understand living entities by investigating their constituent parts in a controlled environment, i.e., in a reductionist way, popularly known as reductionism (Morchio, 1991; Schaffner, 1976; Woese, 2004). For example, first they isolated the individual genes, proteins, or signaling molecules, and then they studied them individually to learn everything they could about the structure and function of that single biological entity, without necessarily considering how they interact with one another (Bertolaso, 2022; Bricmont, 2022; Brigandt, 2013; Kuijper, 2022; Mazzocchi, 2008). In contrast, the Digital Patient concept is based on an integrated approach for achieving a broader, and more systematic understanding of the human body, and how it interacts with its environment, i.e., social and behavioral factors (e.g., age, gender, body weight, genetic make-up, lifestyle, etc. (C. D. Combs & Combs, 2014).

Future healthcare will rely more and more on data from monitoring devices and in some cases, implanted medical devices such as wearable biosensors. Interpretation of data, and their therapeutic application requires knowledge that is much more integrated and personalized than is currently available (C. D. Combs & Combs, 2014; Hatzikirou et al., 2012; D. P. Nickerson et al., 2015; D. P. Nickerson et al., 2020; Tolk et al., 2015). Most chronic diseases involve multiple organ systems. Therefore, it is crucial to understand how the body works as an integrative whole during homeostasis, and at the same time to be able to utilize our detailed knowledge of individual organs. Moreover, in order to represent a comprehensive Digital Patient, social systems and environmental factors must ultimately be integrated into this analytic framework (C. D. Combs, 2017).

1.2 Biology View

Focusing more directly on converging different levels of biological systems that are essential to the Digital Patient framework is the discipline of systems biology and its applications. Systems biology is an integrative and interdisciplinary approach in contrast to the traditional reductionist nature of biology (Bertolaso, 2022; Bricmont, 2022; Brigandt, 2013; Kuijper, 2022; Mazzocchi, 2008; Schaffner, 1976; Woese, 2004). It attempts to explain complex biological systems that include biochemical systems (e.g., enzyme activity regulation and flux in metabolic pathways), cellular processes (e.g., gene regulation, protein transport, signaling pathways, the cell cycle, and apoptosis), cell-cell interaction (e.g., cell–cell signaling), as well as cell differentiation and organismal development (Boogerd et al., 2007; Kitano, 2001; Klipp et al., 2016), using a variety of conceptual and experimental methods such as genomics, transcriptomics, proteomics, molecular biology, cell biology, and carefully developed animal models. Thus, 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 (Fitzgerald et al., 2006; Khoo et al., 2021; Kohl et al., 2010). Over the past two decades, sequencing technologies (e.g., Next-Generation Sequencing, Whole-Genome Sequencing, and etc.) have made remarkable progress (Hartman et al., 2019). As these new technologies continue to develop, the costs associated with sequencing have decreased dramatically, making these technologies more affordable and accessible. Rapid advances in high-throughput technologies coupled with the decrease in sequencing costs have led to generation of massive amounts of biological data, and in turn, the abundance of biological data has made data integration approaches increasingly popular in the field of systems biology

Systems biology not only addresses interactions in biological systems at different scales of biological organization, but also is characterized by quantitative descriptions of biological processes, using a variety of statistical and computational techniques (Baccam et al., 2006; Karr et al., 2022; Perelson et al., 1996). As was stated before, biological systems consist of a large number of functionally diverse components, which interact highly selectively and often nonlinearly to produce coherent behaviors (Klipp et al., 2005; Likić et al., 2010). These components may be individual molecules (e.g., signaling or metabolic networks), assemblies of interacting complexes, sets of physical factors that guide the development of an organism (genes, mRNA, associated proteins and protein complexes), cells in tissues or organs, and even entire organisms in ecological communities. What is common to all these examples is the sheer number of components, and their selective, non-linear interactions that render the behaviors of these systems beyond the intuitive grasp. Mathematical models of biological systems are most suitable and are

increasingly being used to represent our knowledge about these systems (Iglesias & Ingalls, 2010; Ingalls, 2013). Thus, systems biology combines the development and application of predictive mathematical and computational modeling with experimental studies. The quantitative techniques, such as high-resolution microscopy, mass spectrometry, flow cytometry, and more, that are employed to incorporate multiple spatial and temporal scales are consistent with the integrative perspective of the Digital Patient framework.

1.3 Physics-Based Multi-Scale Modeling View

Multi-scale modeling (MSM) integrates multiple physiological processes across different length and time scales to provide improved predictive and individualized healthcare. The highly complex nature of biomedical systems resulting from several distinct factors includes the non-linearity and redundancy of physiological states. They arise from multiple mechanisms simultaneously pushing and pulling on clinically relevant and/or experimentally observable response variables (Vieira & Laubenbacher, 2022). The concept of non-linearity states that many high-level and integrative behaviors of the biological system cannot be described solely through the sum of inputs from basic processes (Auslander et al., 1972; Oster & Perelson, 1973). The resulting heterogeneity along with the disparate time constraints further stimulates individual variability leading to distinct disease outcomes across the population. Despite the extensive complexities of biological and biomedical systems, researchers are using both linear and non-linear sophisticated biological and physiological models to better understand fundamental relationships within the human body (Bauer et al., 2009; Beauchemin & Handel, 2011; Hester et al., 2011).

MSM, also known as knowledge-driven modeling, mechanistic modeling, hypothesis- based modeling, or physics-based modeling, is an equation-based approach based on ordinary differential equations, partial differential equations, stochastic processes, agent-based modeling, etc. that incorporates nonlinear coupled processes that occur at different temporal and/or spatial scales, and lead to a systematic integration of knowledge at the molecular, cellular, and tissue levels (Altan-Bonnet et al., 2020; Coveney & Fowler, 2005; Perelson & Weisbuch, 1997; Pinky et al., 2021; Pinky & Dobrovolny, 2017). Since biological entities have a complex hierarchy of structure, mechanical properties, and behavior across spatial and temporal scales, MSM supports this integrative view by explicitly defining the biological hypothesis or the primary mechanisms and formalizing it into mathematical equations (Harline et al., 2021; Pruett & Hester, 2015; Radhakrishnan, 2020). This approach assumes that behavior at larger scales emerges naturally from the processes occurring at smaller scales; in other words, embedding processes at a small scale into the larger scales leads to a prediction of overall system behavior (Gold et al., 2019; Meier-Schellersheim et al., 2009). The relationship between the biological and mathematical theory determines the balance of phenomenology and quantitative prediction. This step may become iterative as the modeler balances the complexity of the biological inputs included in the system with the level of mathematical theory most suitable to form a “minimum model” Kamerlin & Warshel, 2011; Laubenbacher et al., 2021; Radhakrishnan, 2021; Sego et al., 2022).

Working through biological and mathematical theory should also reveal what data can be collected from the system to inform the model construction, i.e., what mechanisms and relationships are known to exist, and which will be inferred, and what outcomes or predictions will be tested. In addition, they can take into account the influence of behavioral and social context on the whole biological system. Thus, the model connects the association of genetics to proteins, proteins to cells, cells to organs, organs to complete whole-body systems, as well as systems to the organism itself and to the surrounding social environment. For example, social and behavioral context refers to taking into account the understanding of the impact of the behavior of family and friends on individual lifestyle choices and health (C. D. Combs et al., 2015; Tolk et al., 2015).

1.4 Artificial Intelligence View

Artificial Intelligence (AI) is ideally suited to discovering meaningful patterns in big data that may otherwise escape human attention, and can offer a more efficient means of understanding systems dynamics and hence structuring preventive care strategies more efficiently. Machine learning (ML) method, a subset of AI tools, is at its core a data-driven process, and defined as in silico models that develop a predictor automatically for the data without making any causal assumptions (Alber et al., 2019; Peng et al., 2021). Unlike ML, MSM is generally considered to be a theory-driven process and a more traditional approach. It starts with developing hypotheses, followed by collecting and analyzing data

to test these hypotheses and drawing theoretical conclusions based on the results (Pruett & Hester, 2015). It focuses on identifying abstract constructs and the relationships among them. However, due to the complexity of the environments and processes that generate data, there may not be a strong theoretical basis for the questions being studied (Teichert et al., 2019). In contrast, data-driven research involves analyzing data to extract scientifically interesting insights (i.e., robust correlations between sets of variables) by applying analytical techniques and modes of reasoning based on the data available rather than prediction based on theory. It is worth noting that some instances of ML in the literature are described as theory-guided and seek causality by integrating physics-based mechanistic models at multiple temporal and spatial scales with big data (Giansanti, 2022). In this way, ML can make up for any unknown physics by learning the dynamics of the system overall and thereby possibly classify patients into specific treatment regimens. However, this approach benefits from the knowledge and mechanistic insights achieved through MSM to develop novel learning algorithms with greater robustness, data-efficiency, and generalization of performance in data-limited situations (Peng et al., 2021). As such, perhaps this approach can be described as a meeting of ML and MSM to optimize the contributions of both techniques. There are many examples of data-driven MSM that appear to involve the use of ML to optimize the parameter estimation and functions. Perhaps these cases can also be described as precursors to the combination of MSM and ML (Alber et al., 2019; Maass et al., 2018).

In general, MSM provides insight into biological, biomedical, and behavioral systems at a high level of resolution and precision, which naturally produces massive output data sets. Because computational physiological simulations, e.g., physics-based MSM, are too slow for clinical application, AI tools can provide ways to speed up Digital Patient workflows. For example, using ML methods one can develop a simplified surrogate model (i.e., a statistical model to accurately approximate simulation output) to reduce complexity (Kennedy & O'Hagan, 2001). In the context of the Digital Patient, MSM and ML complement one another with respect to biological, biomedical, and behavioral research and are possibly even more powerful when combined (Costello & Martin, 2018; Linka et al., 2020; Muzio et al., 2021).

The most sophisticated Digital Patient models are expected to be self-improving. These models can continuously monitor divergence between predictions and observations, and use these divergences to improve their own accuracy. Their deployment would enable rapid refinement and improvement, especially if they were designed in a modular fashion to permit the parallel development and optimization of their component sub-models (Maass et al., 2018).

1.5 Personalized Medicine View

Physiology is a basic medical science as knowledge of normal functions of the body is the basis for understanding diseases and identifying targets for effective treatment (Sherwood, 2015). Just as physiology is a branch of biology, systems physiology, systems medicine and personalized medicine are subsets of systems biology. Successful responses to such a grand challenge, like the Digital Patient, require this cross-disciplinary integration (An & Cockrell, 2022; Grieves, 2019; P. Hunter et al., 2002; Niarakis et al., 2022). 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 (Sherwood, 2015). Systems medicine is a subset of systems physiology that addresses applications to clinical problems. Examples include the application of the systems physiology framework to develop quantitative understanding of disease processes, leading to drug discovery, and to the design of diagnostic tools (Tyson et al., 2001). 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.

Realizing this goal requires the ability to make accurate predictions about how a patient will react to a treatment or no treatment; however, the previous reductionist approach to science and modeling cannot satisfy that need. Instead, the systems approach to biological modeling is growing in importance as a translational tool in clinical practice (Doyle III et al., 2014). 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. Further, these data can now be analyzed at bulk or at the single-cell level, which has been particularly useful to assess the tissue-level heterogeneity in many diseases including cancer. The ability to extract useful information from these data has begun to lead to custom treatments for diseases, such as cancer (Goldenberg et al., 2019; Khoo et al., 2021), infectious diseases (Castiglioni et al., 2021; de Fátima Cobre et al., 2021), diabetes (Kavakiotis et al.,

2017) and hematological and metabolic disorders (De Bruyne et al., 2021). This will, in turn, help improve the health of individuals by converting research findings into diagnostic tools and procedures.

2 CHALLENGES IN DEVELOPING A DIGITAL PATIENT FRAMEWORK

A large-scale implementation of human health into a digital format requires the construction and execution of highly complex computer models composed of several component submodels which span multiple spatial and temporal scales (P. Hunter, 2020; Pan et al., 2021). In addition, multi-scale data is needed to build this computational representation of biological processes of the whole-body under both disease-free and diseased states. Thus, several pieces must be in place to realize this interplay in a single computational model. These pieces include reductionist modeling at a variety of spatial and temporal scales, the development of an ontology allowing models to communicate with one another, and finally, the creation of a top-level model that allows reductionist models to be plugged in, creating an integrated model framework for the testing and generation of hypotheses. Different groups have developed distinct philosophies for approaching these challenges, but none has solved the problem completely (Hussan et al., 2022). Several challenges to building a Digital Patient framework have been identified and are discussed below.

2.1 Lack of a High Throughput Approach to Modeling

A Digital Patient describing the disease state and treatment requires the development, validation, and integration of numerous component submodels in the context of a rapidly developing scientific understanding of biological behaviors and continual generation of new experimental and clinical data (Laubenbacher et al., 2021; Masison et al., 2021). Although individual laboratories around the world may construct submodels, the development of a comprehensive Digital Patient framework will require modularity to ensure validation and interoperability with one another. In this way, the submodels will handle complexity with modules that are properly annotated, curated, and documented, and then linked semantically to establish more complex models. Enabling such parallel development requires a flexible simulation architecture that uses a multi-scale map of all the relevant components of a patient's response to the disease, as well as responses to available treatments s (An & Cockrell, 2022; Grande Gutiérrez et al., 2021; Masison et al., 2021).

2.2 Lack of Model Reproducibility and Transparency

It is essential that component models utilized in the Digital Patient are reproducible and reusable. Published models relevant to this discussion demonstrate a lack of transparency in model implementation (Baker, 2016; Fitzpatrick, 2019). Not all published models are reproducible and hence not reusable. Furthermore, a significant number of published mathematical models are not experimentally validated, making model extensions more difficult (Blinov et al., 2021; Niarakis., et al., 2022).

2.3 Generation of Heterogeneous High-Dimensional Data

Development of a multi-scale model of an organ requires the collection of synchronous measurements at multiple physiological scales. This includes omics data from tissues and single cells, from diverse experimental systems, including two-dimensional (2D) and 3D cell cultures, in vivo and ex vivo animal models, patients, and biophysical and structural data from tissues and organs, combined with data characterizing transport throughout the body. Technologically this is very challenging if not impossible (Vieira & Laubenbacher, 2022).

2.4 Lack of Standardization in Data Collection and Model Specification

Ever growing uncoordinated and heterogeneous formats of data that capture the various determinants of our health from genomic sequences to behavioral influence lack (Vieira & Laubenbacher, 2022).

Thus, the use of incompatible data structures along with almost no standard model specification and different software environments, make distributed collaboration difficult (Lubbock & Lopez, 2021; Malik-Sheriff et al., 2020).

2.5 Lack of Effective Communication and Collaboration Among Biomedical Researchers

Building a useful Digital Patient requires improved communication between clinicians, experimentalists,

and modelers in order to create sufficiently credible interchangeable computational models and/or tools that have value in the clinic, such as mobile apps, dedicated web pages and medical devices. Inevitably, this has led to the inability to efficiently translate basic science knowledge obtained from pre-clinical studies into effective therapies (An & Cockrell, 2022; Grieves, 2019. To date, relatively few clinical and biological insights are currently translated into computational models that could serve as building blocks for the Digital Patient framework.

2.6 Health Information Management

Having clinical information in electronic form that is computable has been a grand challenge for biomedical informatics (Acosta et al., 2022). Unfortunately, most health information still sits in silos today and health information exchange for the purpose of supporting care between organizations and levels of care (e.g., hospital to primary care), has, until very recently, been the exception rather than the norm. It is fair to say that, to a large extent, management of health information has encountered the most variability when we consider other related domains like bioinformatics, pharmaceutical research and development and medical device technology in the quest for integrated biomedicine. Post-hoc data collection has been shown to be very expensive and error-prone because data sources can be very diverse and range from operational electronic health record systems to well-structured longitudinal disease registries and bio-banks. Therefore, capturing structured and computable clinical data as part of routine clinical practice is ideal as it may otherwise impossible to capture the clinical context in which the data were collected initially. In addition, effectively managing the enormous amount of personalized data requires the development of broadly accepted policies addressing security, quality control, data mining, and privacy protection. This represents another fundamental challenge to completing the Digital Patient.

2.7 Patient Data Management

Further complicating the construction of the Digital Patient framework is the current lack of agreement on how we categorize patient information. An individual patient's ideal data set includes molecular data, clinical data, and social context data, and these data sets are not often integrated in a manner that is understandable or easily usable by patients or healthcare providers or even by research domain experts (Kondylakis et al., 2015). Developing a consistent terminology and aggregation methodology for this disparate data is therefore an additional fundamental challenge to building the Digital Patient framework. Privacy, synchronicity (the timeliness with which models produce actionable information), and clarity of data organization and analysis are also fundamental challenges that must be addressed in completing the Digital Patient platform. Recent

3 DEVELOPMENT IN BUILDING THE DIGITAL PATIENT FRAMEWORK

There are many collaborative and individual efforts underway that address some of the issues important to building out the Digital Patient framework. Following is a summary of several past and current efforts, and tools developed. This list is a selection and not exhaustive.

Projects that contributed most significant progress are the Physiome and the 12 Labours projects; briefly described below, the Physiome Project is an umbrella term that refers to human modelling with methods accommodating cross-disciplinary science (chemistry, biology, physics) and a breadth of dimensional and temporal scale (sub-cellular to organs, sub-microsecond to tens-of-years) (P. Hunter et al., 2002). The International Union of Physiological Sciences (IUPS) Physiome Project, established in 1993, focused on providing a "computational framework for understanding human and other eukaryotic physiology". This effort resulted in databases, markup languages, software for computational models of cell functions, as well as software for interacting with organ models, as was described in P. J. Hunter & Borg, 2003; P. Hunter, 2004. The primary limitation with the Physiome Project has been the lack of integration of the multiple narrow-focused models that could, if successfully integrated, lead to a comprehensive and integrative model of human physiology (D. P. Nickerson et al., 2015; Viceconti et al., 2008). Today this project has been extended into the 12 Labours research effort currently underway within the Auckland Bioengineering Institute at the University of Auckland in New Zealand.

3.1 12 Labours Project

Initiated by the Auckland Bioengineering Institute (ABI), University of Auckland in New Zealand, the

intent of 12 Labours project is to extend the Physiome Project to clinic and home-based healthcare applications (P. Hunter, 2020). The focus and goal of 12 Labours is to create the infrastructure to integrate multi-scale models into a whole-body computational physiology system. This will include a platform for precision medicine and sensor-based health monitoring. Migrating the efforts from a research focus to a clinical focus will necessarily require changes in design and execution, e.g., model reduction strategies must be utilized in order to increase the speed at which models can be analyzed and output a useful result. Additional foci include coupling the physiome to body sensors for real-time data exchange, an energy based mathematical framework for understanding physiology, and a new semantic approach to physics based multi-scale modeling. In addition, with the goal of integrating medical data with predictive physics modeling, this project includes the development of workflow management systems, the identification of technologies for clinical translation of those workflows, and the infrastructure for deploying those workflows in a clinical environment. Some of the suitable tools for workflow and data management initially include Snake Make, NextFlow, iRods, Pennsieve (Rajagopal et al., 2022).

Through the NIH Stimulation Peripheral Activity to Relieve Conditions (SPARC) program, ABI has been developing scaffolds of high-level descriptions of organ anatomy on a 3D coordinate system framework to relate multi-species organ models (Osanlouy et al., 2021). These frameworks provide a single common reference frame, upon which one can register (or align) data across species, i.e., human, mouse, pig. In other words, the framework is consistent across multiple species, and the scaffolding method facilitates cross-species comparisons as well as the analysis of variation within a population. Likewise, sub-scaffolds are used to define individual characteristics within these scaffolds. The concept of the whole-body scaffold reflects the use of this logic for personalized models for virtual clinical trials via a workflow in which organs and systems could be assembled into whole body reference coordinates.

3.2 Computational Frameworks

Modularity is a particularly important consideration when model dependencies are involved as the introduction and absence of models can throw off the entirety of a simulation. Similarly, multiple scales require a framework with internal compensation to account for varying definitions of, e.g., time. Following are two examples of recent frameworks that have been developed specifically to address these concerns and that may serve to better light the way forward for a Digital Patient framework. The first is focused on medical digital twins and is a multi-institutional effort of the Universities of Connecticut, Michigan, and Florida. The second supports global resource management and is out of Johns Hopkins APL. Despite unrelated disciplines, the designs are strikingly similar. If this review proves useful, there may be others that can be reviewed in a similar fashion. Following are two example computational platforms for the integration of multiple, disparate models.

- **A Modular Computational Framework for Medical Digital Twins** With a focus on digital twins in a medical context, researchers from University of Florida Health sought to optimize modularity by eliminating the potential pitfalls of model dependencies with an open source, “digital twin” architecture (Masison et al., 2021). Characterized as “hub and spoke” and hereafter referred to as MCF for Modular Computational Framework, it includes four components: a runtime configuration file, a global model state, modules, and a simulation framework that controls simulation runtime and provides data structures and algorithms useful for the development of modules. Modules are individual models, which can be added and taken away at will; each module must provide a subclass that defines the data relevant to that module to be stored in the model state, i.e., a pure data API. As such, the model state houses all potential model inputs and outputs, providing an indirect connection between modules. One model’s output is stored in the model state and can only from there be accessed as input by another model. This also ensures that all model processes stay contained within a particular module, thereby providing a clear separation between the model and the data. In one paper (Masison et al., 2021), MCF was applied to an existing dynamic computational model of the immune response to a respiratory fungal pathogen to illustrate the potential of extending it to a full digital twin use case. The MCF simulator is open-source and available at (Masison, Joseph and Beezley, Jonathan and Mei, Yu and Ribeiro, Henrique Assis Lopes and Knapp, Adam C and Sordo Vieira, L and Adhikari, Bandita and Scindia, Yogesh and Grauer,

Michael and Helba, Brian and others, 2021). Additional platform access information is available in the reference.

- **System Integration with Multiscale Networks (SIMoN) SIMoN** was built to realize the complex inter-relationships that exist between the different facets of global resource management (Hughes et al., 2020). Each of these facets is a domain unto itself, and models use their own geospatial, temporal, and other scales. SIMoN is an open-source framework built to allow these disparate models to be coupled. In the referenced paper, they include climate, population, and food-energy-water systems. Specifically, SIMoN is used to "integrate models and data from disparate domains by predicting water availability in 2050, as it depends on population growth, climate change, and corresponding increases in demand for thermoelectric cooling". While SIMoN is not a biomedical use-case, the challenges of integrating multiple distinct models with different processes and scales remain the same, requiring a framework that is modular and extendable. Interestingly, SIMoN employs a similar approach to the previous example, with a "broker" construct taking the place of the model state. Each model exists inside of wrapper to standardize its interface with the broker. The broker performs the transformations necessary to reconcile the varying geo-spatial scales of each model so that those models can be integrated seamlessly. In addition, it handles all data inputs and outputs between models; like MCF, this broker prevents direct dependencies of one model on another. The only requirement is that the models agree on the "scope" of a given scale, e.g., the entirety of the contiguous United States is the geo-spatial scope. The scope can be subdivided by an individual model as needed with the assumption that the sum of all subdivisions exactly equals the scope, with no overlap. It is not hard to imagine how the same principle might be applied to temporal and possibly other scales. SIMoN is available at (Hughes, Marisa and Kelbaugh, Michael and Campbell, Victoria and Reilly, Elizabeth and Agarwala, Susama and Wilt, Miller and Badger, Andrew and Fuller, Evan and Ponzo, Dillon and Arevalo, Ximena Calderon and others, 2020).

3.3 Collaborative Organizational Efforts

The challenges of maximizing value from big data are being addressed by the U.S. National Institutes of Health's (NIH) BD2K program, through the European Union's Horizon 2020 initiative, through the European Big Data Value Association and through various Chinese Ministry of Science and Technology initiatives. In addition, the challenge of encouraging consistency in terminology, ontology, and registries is being addressed through the International Health Terminology Standards Development Organization, the Simulation Industry Standards Organization and the NIH Data Discovery Index Consortium. Moreover, model construction and interoperability are the foci of the Physiome and 12 Labours Project, and of the researchers that are involved in several organizations, including the Virtual Physiological Human Institute (VPHi), the U.S. Interagency Modeling and Analysis Group, and its companion group, the Multi-Scale Modeling Consortium. More such organizational efforts are listed below.

- **Insigneo**, based on the Institute for In Silico Medicine, is a collaboration between the University of Sheffield, UK and the Sheffield Teaching Hospitals with a focus on clinical translation of in silico medicine. The project implements the ambition behind the European VPHi program. This is the largest organization in Europe dedicated to the development, validation, and use of in silico medical technology.
- **InSilco**, dedicated to coronary artery disease, is an international multidisciplinary consortium focused on in silico trials for drug eluting bioresorbable vascular scaffold design, development, and evaluation.
- **Physiome Journal** is dedicated to the reproducibility and reusability of models. Each article is linked to a primary publication in a peer-reviewed journal and includes access to the presented model itself. This effort is supported by the IUPS, VPHi, the University of Auckland, Digital Science, and more.
- **IMAG** stands for Interagency Modeling and Analysis Group (IMAG) based on NIH, USA, holds multi-scale Modeling (MSM) Consortium. Their goal includes supporting research funding for modeling and analysis of biomedical, biological, and behavioral systems.
- **InSilicoWorld** is a worldwide community of

practice working towards wider adoption of in silico trials in the biomedical industry that is currently led by Marco Viceconti (Viceconti et al., 2008).

- **SimBios**, lead by NIH and Stanford University, is a center for physics-based simulation of biological structures. It provides SimTK, developed OpenSim, and publishes Biomedical Computation Review. It has also established an inventory of bio-sim tools called SimBiome in 2017.

Tools that were developed by the organizational efforts are listed below.

- **Markup Language Standards** have been developed to adequately describe physical and physiological properties and processes including CellML (Lloyd et al., 2004, FieldML (Chang et al., 2007), TissueML (J.Q. et al., 2004), AnatML (J.Q. et al., 2004), PhysioML (J.Q. et al., 2004), SBML (Hucka et al., 2003).
- **DICOM:** Digital Imaging and Communications in Medicine (DICOM) is the international standard for medical images and related information (Lim & Zein, 2006). It defines formats for medical images that can be exchanged with the data and quality necessary for clinical use.
- **OpenSim** is an open-source simulation software that was developed by the Stanford National Center for Simulation in Rehabilitation Research (Delp et al., 2007).
- **BioModels** is a repository of mathematical models representing biological systems and is written in SBML (Li et al., 2010). Models include signaling, protein-drug interactions, metabolic pathways, epidemic, and more. BioModels was developed by the Molecular Networks team EMBL-EBI based in UK and the SBML Team from Caltech, USA.
- **SimTK** is a free biomedical project hosting platform for the biomedical computation community (Project-hosting platform for the biomedical computation community, n.d.). It provides an easy data sharing, shared resource tracking and an infrastructure for community connection and growth.
- **OpenEHR** is an open standard specification in health informatics that allows semantic mapping annotations into EHR data storage formats (openEHR, 2017). From 2010-2020, OpenEHR has been deployed in Australia, Brazil, Switzerland, Germany, Finland, UK, Italy, Malta, Netherlands, Norway, Philippines, Russia, Sweden, and Slovenia.
- **BioUML** is web-based integrated environment for systems biology and collaborative analysis of biomedical data (Russian Science Foundation, 2002). It was funded and initiated by the Russian Science Foundation in 2002. The initial goal of BioUML was common purpose visual language for formal descriptions of the structure and function of biological systems. The long-range plan is to be a computational platform for the VPH and digital patient. BioUML spans a comprehensive range of capabilities, including access to biological databases, powerful tools for systems biology (visual modelling, simulation, parameters fitting and analyses), a genome browser, scripting (R, JavaScript), and a workflow engine. The architecture is plugin-based. Users create a visual representation of a model and BioUML automatically generates the code to simulate the model behavior. The current version generates code in Java and uses its own simulation engines. To support collaborative work, there is a central authentication and authorization system. BioUML is open-source, in continued development, and is actively used.
- MLBox was developed by the collaboration with the University of Miami's Miller School of Medicine, the Media and Information Lab (MIL), Amazon Web Services, and the OpeHealth Network to create MLBox. MLBox is an automated machine learning Python library to support the development of digital twins that can take the place of patients to better test treatments options (Das & Cakmak, 2018). Inputs include data from wearable sensors and other smart devices, including biological, clinical, behavioral, and environmental. These are collected over a period of seven days and combined into a "biological health algorithm", which in turn acts as a digital twin in treatment tests. The MLBox platform is in Python and is device agnostic, i.e., modular, which will allow input types to adjusted based on individual needs and constraints, as well as expanded in the future as technology evolves. The initial focus area is sleep apnea and its link to dementia and heart disease and inputs include sleep patterns, weight, environmental pressures, and stress levels.
- **promor** was developed by researchers at the Eastern Virginia Medical School. Promor is an

open-source R package that streamlines biomarker discovery from proteomics data and builds predictive models of disease diagnosis and/or prognosis with top protein biomarker candidates (Ranathunge et al., 2023).

3.4 Other Collaborative Efforts

Biomedical research groups worldwide are employing "digital twin" technologies to realize the promise of personalized medicine. For example, digital twins of the human heart can improve diagnosis, prognosis, and therapies (Martinez-Velazquez et al., 2019). Developers expect that automated workflows for generating cardiac digital twins could serve as a blueprint for the generation of other types of medical digital twins (Corral-Acero et al., 2020). Although medical digital twins are much more difficult to develop than those for engineered devices, they have begun to find applications in improving human health. Examples include the "artificial pancreas" for type 1 diabetes patients (Breton et al., 2020; Brown et al., 2019; Kovatchev, 2019). In the artificial pancreas model, a template mathematical model of human glucose metabolism and a closed-loop control algorithm modeling insulin delivery and data from an implanted glucose sensor are customized into a patient-specific digital twin that continuously calculates insulin needs and drives an implanted pump that adjusts blood insulin concentrations. Additionally, pediatric cardiac digital twins combine template models of the heart with patient-derived clinical measurements to optimize some heart surgeries (Shang et al., 2019) and assess the risk of thrombosis (Grande Gutiérrez et al., 2021; Kondratova et al., 2019). The ARCHIMEDES diabetes model expands these technologies by including models not only of the progression of diabetes within individual patients but also of medical diagnosis, treatments, and the functioning of the health care system that is providing the treatment (Du et al., 2013; Eddy & Schlessinger, 2003a, 2003b).

More recently, the NIH Maximizing Investigators Research Award (MIRA) was awarded to Dr. Tomas Helikar, Professor of Biochemistry, University of Nebraska, Lincoln, for the further development of a virtual immune system. The virtual immune system is meant to increase the understanding of immune related diseases as well as to speed up drug development and the time-to-market timeline. The first MIRA award resulted in the successful modeling of CD4+ T cells, which stimulate other cells to fight pathogens. This model encompasses four mathematical approaches, three spatial scales, and multiple tissues involved in immune response. The project established a method for computationally connecting multiple scales of the immune system (Wertheim et al., 2021. The goal of this second MIRA award is to expand the model to include more types of cells, molecules, genes, and organs.

A large part of the focus will be on computational cost-effectiveness, improving the speed and efficiency of the model's algorithms.

In Europe, Neurotwin was initiated and funded by the EU Horizon 2020 on January 1, 2021. It is currently led by Neuroelectrics in Spain. It seeks to predict the effects of non-invasive stimulation for treatment of neurological disorders, e.g., Alzheimer's disease and epilepsy. Two proof-of-concept clinical trials are planned for 2022 and 2023 in order to refine the application of this stimulation technology for the conditions of Alzheimer's disease and epilepsy. If successful, the condition use cases will be extended to multiple sclerosis stroke rehabilitation, depression, and the effects of psychedelics in the future. Neurotwin combines 30 minutes of MRI and 10 minutes of EEG to create a personalized digital twin that captures a brain's electrical activity and simulations the brain's main parts, including the scalp, skull, cerebrospinal fluid, and gray and white matter. The digital twin also includes neural mass models, or computational models of the average behavior neurons using a map of neural connections (connectome). This digital twin will be used to optimize the stimulation position or locations and strength of current via a headcap.

These examples illustrate how current digital twins can operate in real time to maintain health continuously, or they can be used off-line to design personalized medical interventions.

3.5 Community Efforts

Community efforts such as the Systems Medicine Disease Map Project, COVID-19 Disease Map Project (Mazein et al., 2018; Ostaszewski et al., 2019; Ostaszewski et al., 2020) and Computational Modeling in Biology Network (COMBINE) are working to build such infrastructure, although much work needs to be done to adapt those for use in Digital Patient framework. To this end, these groups have built a large-scale data repository (Kondylakis et al., 2017; Kondylakis et al., 2018; Kondylakis et al., 2015; Kouroubali et al., 2019).

4 CONCLUSIONS AND FUTURE DIRECTIONS

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. We also recognize that our privacy may be 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 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 and provide optimal therapy based on the characteristics of each individual and reduce adverse responses to therapy. Similarly, pharmaceutical companies will improve the process of drug discovery and clinical trials. In this way, 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 in clinical practice. Underlying this focus is, of course, the development and integration of multi-scale models based on the understandings emerging from systems biology.

While the application of physics-based models to the Digital Patient are exciting and varied, several substantial challenges face the community. The two most critical needs are connecting the top-down and bottom-up model approaches. Modeling languages have been established separately, and so the community must spend valuable time and effort replicating work already done by other groups. This represents a gross inefficiency in the development process, and hampers cooperation between groups. It is our belief that organizations such as, the industry-academia-regulatory agency consortia Avicenna (European Commission, University of Sheffield and the consortium, 2013) and the Medical Device Innovation Consortium (Research collaborations in regulatory science, 2011) will provide the force to consolidate these efforts into a unified whole. The more troubling challenge is that of rigorous model validation. The assumptions that underlie the model induce a standard for evaluating the model. In the case of a larger target such as tissue, organ, or an individual, validation becomes a more difficult concept to define. Intense inter-subject variations exist in humans. A person even demonstrates different physiological characteristics at different ages, so the existence of a data set that represents a target for validation is often in question. Population modeling may be the key; by generating many individuals, a class of subjects similar to a given patient might be selected over a collection of observable variables. Consideration of differences in that population may suggest other observations to make in the patient, establishing an iterative process for matching an individual to a reasonable model. This challenge is not unique to biological models; it exists across all nonlinear dynamic models, and no systematic solution has been accepted (Barlas, 1996; Coveney & Fowler, 2005). That said, the potential for improving the modeling of individual patients and the strata of patients that is represented by the Digital Patient is clearly worth pursuing.

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REFERENCES

Acosta, J. N., Falcone, G. J., Rajpurkar, P., & Topol, E. J. (2022). Multimodal biomedical ai. Nature Medicine, 28 (9), 1773–1784.

Alber, M., Buganza Tepole, A., Cannon, W. R., De, S., Dura-Bernal, S., Garikipati, K., Karniadakis, G., Lytton, W. W., Perdikaris, P., Petzold, L., et al. (2019). Integrating machine learning and multiscale modeling—perspectives, challenges, and opportunities in the biological, biomedical, and behavioral sciences. NPJ Digital Medicine, 2 (1), 1–11.

Altan-Bonnet, G., Mora, T., & Walczak, A. M. (2020). Quantitative immunology for physicists. Physics Reports, 849, 1–83.

An, G., & Cockrell, C. (2022). Drug development digital twins for drug discovery, testing and repurposing: A schema for requirements and development. Frontiers in Systems Biology, 2.

Auslander, D., Perelson, A., Clifford, G., & Oster, G. (1972). On systems with coupled chemical reaction and diffusion. The American Society of Mechanical Engineers.

Baccam, P., Beauchemin, C., Macken, C. A., Hayden, F. G., & Perelson, A. S. (2006). Kinetics of influenza a virus infection in humans. Journal of virology, 80 (15), 7590–7599.

Baker, M. (2016). Reproducibility crisis. Nature, 533 (26), 353–66.

Barlas, Y. (1996). Formal aspects of model validity and validation in system dynamics. System Dynamics Review: The Journal of the System Dynamics Society, 12 (3), 183–210.

Bauer, A. L., Beauchemin, C. A., & Perelson, A. S. (2009). Agent-based modeling of host–pathogen systems: The successes and challenges. Information Sciences, 179 (10), 1379–1389.

Beauchemin, C. A., & Handel, A. (2011). A review of mathematical models of influenza a infections within a host or cell culture: Lessons learned and challenges ahead. BMC Public Health,11 (1), 1–15.

Bertolaso, M. (2022). Understanding complexity in life sciences. In Environmental alteration leads to human disease (pp. 1–13). Springer.

Blinov, M. L., Gennari, J. H., Karr, J. R., Moraru, I. I., Nickerson, D. P., & Sauro, H. M. (2021). Practical resources for enhancing the reproducibility of mechanistic modeling in systems biology. Current Opinion in Systems Biology, 27, 100350.

Boogerd, F. C., Bruggeman, F. J., Hofmeyr, J.-H. S., & Westerhoff, H. V. (2007). Towards philosophical foundations of systems biology: Introduction. In Systems biology (pp. 3–19). Elsevier.

Breton, M. D., Kanapka, L. G., Beck, R. W., Ekhlaspour, L., Forlenza, G. P., Cengiz, E., Schoelwer, M., Ruedy, K. J., Jost, E., Carria, L., et al. (2020). A randomized trial of closed-loop control in children with type 1 diabetes. New England Journal of Medicine, 383 (9), 836–845.

Bricmont, J. (2022). Conclusion: Statistical mechanics and reductionism. In Making sense of statistical mechanics (pp. 311–314). Springer.

Brigandt, I. (2013). Systems biology and the integration of mechanistic explanation and mathematical explanation. Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences, 44 (4), 477–492.

Brown, S. A., Kovatchev, B. P., Raghinaru, D., Lum, J. W., Buckingham, B. A., Kudva, Y. C., Laffel, L. M., Levy, C. J., Pinsker, J. E., Wadwa, R. P., et al. (2019). Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. New England Journal of Medicine, 381 (18), 1707–1717.

Castiglioni, I., Ippolito, D., Interlenghi, M., Monti, C. B., Salvatore, C., Schiaffino, S., Polidori, A., Gandola, D., Messa, C., & Sardanelli, F. (2021). Machine learning applied on chest x-ray can aid in the diagnosis of covid-19: A first experience from lombardy, italy. European Radiology Experimental, 5 (1), 1–10.

Chang, D., Lovell, N. H., & Dokos, S. (2007). Field markup language: Biological field representation in xml. 2007 29th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 402–405.

Combs, C. D., Sokolowski, J. A., & Banks, C. M. (2015). The digital patient: Advancing healthcare, research, and education. John Wiley & Sons.

Combs, C. D. (2017). Developing a framework for multi-scale modeling of the digital patient. International Journal of Privacy and Health Information Management (IJPHIM), 5 (2), 21–33.

Combs, C. D., & Combs, W. C. (2014). The digital patient: An emerging platform for health analytics. Wiley StatsRef: Statistics Reference Online, 1–9.

Corral-Acero, J., Margara, F., Marciniak, M., Rodero, C., Loncaric, F., Feng, Y., Gilbert, A., Fernandes, J. F., Bukhari, H. A., Wajdan, A., et al. (2020). The 'digital twin' to enable the vision of precision cardiology. European Heart Journal, 41 (48), 4556–4564.

Costello, Z., & Martin, H. G. (2018). A machine learning approach to predict metabolic pathway dynamics from time-series multiomics data. NPJ Systems Biology and Applications, 4 (1), 1–14.

Coveney, P. V., & Fowler, P. W. (2005). Modelling biological complexity: A physical scientist's perspective. Journal of the Royal Society Interface, 2 (4), 267–280.

Das, S., & Cakmak, U. M. (2018). Hands-on automated machine learning: A beginner's guide to building automated machine learning systems using automl and python. Packt Publishing Ltd.

De Bruyne, S., Speeckaert, M. M., Van Biesen, W., & Delanghe, J. R. (2021). Recent evolutions of machine learning applications in clinical laboratory medicine. Critical Reviews in Clinical Laboratory Sciences, 58 (2), 131–152.

de Fátima Cobre, A., Stremel, D. P., Noleto, G. R., Fachi, M. M., Surek, M., Wiens, A., Tonin, F. S., & Pontarolo, R. (2021). Diagnosis and prediction of covid-19 severity: Can biochemical tests and machine learning be used as prognostic indicators? Computers in Biology and Medicine, 134, 104531.

Delp, S. L., Anderson, F. C., Arnold, A. S., Loan, P., Habib, A., John, C. T., Guendelman, E., & Thelen, D. G. (2007). Opensim: Open-source software to create and analyze dynamic simulations of movement. IEEE Transactions on Biomedical Engineering, 54 (11), 1940–1950.

Dıaz-Zuccarini, V., Alimohammadi, M., & Pichardo-Almarza, C. (2015). Reflecting on discipulus and remaining challenges. The Digital Patient: Advancing Healthcare, Research, and Education, 15.

Doyle III, F. J., Huyett, L. M., Lee, J. B., Zisser, H. C., & Dassau, E. (2014). Closed-loop artificial pancreas

systems: Engineering the algorithms. Diabetes Care, 37 (5), 1191–1197.

Du, P., O'Grady, G., Gao, J., Sathar, S., & Cheng, L. K. (2013). Toward the virtual stomach: Progress in multiscale modeling of gastric electrophysiology and motility. Wiley Interdisciplinary Reviews: Systems Biology and Medicine, 5 (4), 481–493.

Eddy, D. M., & Schlessinger, L. (2003a). Archimedes: A trial-validated model of diabetes. Diabetes Care, 26 (11), 3093–3101.

Eddy, D. M., & Schlessinger, L. (2003b). Validation of the archimedes diabetes model. Diabetes Care, 26 (11), 3102–3110.

European Commission, University of Sheffield and the consortium. (2013). Avicenna: A strategy for in silico clinical trials [http://avicenna-isct.org/].

Fitzgerald, J. B., Schoeberl, B., Nielsen, U. B., & Sorger, P. K. (2006). Systems biology and combination therapy in the quest for clinical efficacy. Nature Chemical Biology, 2 (9), 458–466.

Fitzpatrick, B. G. (2019). Issues in reproducible simulation research. Bulletin of Mathematical Biology, 81 (1), 1–6.

Giansanti, D. (2022). Artificial intelligence in public health: Current trends and future possibilities. Gold, K., Gaharwar, A. K., & Jain, A. (2019). Emerging trends in multiscale modeling of vascular pathophysiology: Organ-on-a-chip and 3d printing. Biomaterials, 196, 2–17.

Goldenberg, S. L., Nir, G., & Salcudean, S. E. (2019). A new era: Artificial intelligence and machine learning in prostate cancer. Nature Reviews Urology, 16 (7), 391–403.

Grande Gutiérrez, N., Alber, M., Kahn, A. M., Burns, J. C., Mathew, M., McCrindle, B. W., & Marsden, A. L. (2021). Computational modeling of blood component transport related to coronary artery thrombosis in kawasaki disease. PLoS Computational Biology, 17 (9), e1009331.

Grieves, M. W. (2019). Virtually intelligent product systems: Digital and physical twins.

Harline, K., Martınez-G´omez, J., Specht, C. D., & Roeder, A. H. (2021). A life cycle for modeling biology at different scales. Frontiers in Plant Science, 1724.

Hartman, P., Beckman, K., Silverstein, K., Yohe, S., Schomaker, M., Henzler, C., Onsongo, G., Lam, H. C., Munro, S., Daniel, J., et al. (2019). Next generation sequencing for clinical diagnostics: Five year experience of an academic laboratory. Molecular Genetics and Metabolism Reports, 19, 100464.

Hatzikirou, H., Chauviere, A., Bauer, A. L., Leier, A., Lewis, M. T., Macklin, P., Marquez-Lago, T. T., Bearer, E. L., & Cristini, V. (2012). Integrative physical oncology. Wiley Interdisciplinary Reviews: Systems Biology and Medicine, 4 (1), 1–14.

Hester, R. L., Iliescu, R., Summers, R., & Coleman, T. G. (2011). Systems biology and integrative physiological modelling. The Journal of Physiology, 589 (5), 1053–1060.

Hucka, M., Finney, A., Sauro, H. M., Bolouri, H., Doyle, J. C., Kitano, H., Arkin, A. P., Bornstein, B. J., Bray, D., Cornish-Bowden, A., et al. (2003). The systems biology markup language (sbml): A medium for representation and exchange of biochemical network models. Bioinformatics, 19 (4), 524–531.

Hughes, M., Kelbaugh, M., Campbell, V., Reilly, E., Agarwala, S., Wilt, M., Badger, A., Fuller, E., Ponzo, D., Arevalo, X. C., et al. (2020). System integration with multiscale networks (simon): A modular framework for resource management models. 2020 Winter Simulation Conference (WSC), 656–667.

Hughes, Marisa and Kelbaugh, Michael and Campbell, Victoria and Reilly, Elizabeth and Agarwala, Susama and Wilt, Miller and Badger, Andrew and Fuller, Evan and Ponzo, Dillon and Arevalo, Ximena Calderon and others. (2020). System integration with multiscale networks [https://github.com/JHUAPL/SIMoN].

Hunter, P. (2020). Modeling framework for computational physiology. Encyclopedia of Continuum Mechanics, 1691–1702.

Hunter, P., Robbins, P., & Noble, D. (2002). The iups human physiome project. Pfl¨ugers Archiv,445 (1), 1–9.

Hunter, P. J., & Borg, T. K. (2003). Integration from proteins to organs: The physiome project. Nature Reviews Molecular Cell Biology, 4 (3), 237–243.

Hunter, P. (2004). The iups physiome project: A framework for computational physiology. Progress in Biophysics and Molecular Biology, 85 (2-3), 551–569.

Hussan, J. R., Trew, M. L., & Hunter, P. J. (2022). Simplifying the process of going from cells to tissues using statistical mechanics. Frontiers in physiology, 279.

Iglesias, P. A., & Ingalls, B. P. (2010). Control theory and systems biology. MIT press.

Ingalls, B. P. (2013). Mathematical modeling in systems biology: An introduction. MIT press.

J.Q., D., Q., L., & Q.M., L. (2004). Java and xml based graphic software package for modeling biochemical and gene regulatory networks. Computational Engineering Application, 40 (6), 202–204.

Kamerlin, S. C. L., & Warshel, A. (2011). Multiscale modeling of biological functions. Physical Chemistry Chemical Physics, 13 (22), 10401–10411.

Karr, J., Malik-Sheriff, R. S., Osborne, J., Gonzalez-Parra, G., Forgoston, E., Bowness, R., Liu, Y., Thompson, R., Garira, W., Barhak, J., et al. (2022). Model integration in computational biology: The role of reproducibility, credibility and utility. Frontiers in Systems Biology, 2.

Kavakiotis, I., Tsave, O., Salifoglou, A., Maglaveras, N., Vlahavas, I., & Chouvarda, I. (2017). Machine learning and data mining methods in diabetes research. Computational and Structural Biotechnology Journal, 15, 104–116.

Kennedy, M. C., & O'Hagan, A. (2001). Bayesian calibration of computer models. Journal of the Royal Statistical Society: Series B (Statistical Methodology), 63 (3), 425–464.

Khoo, A., Liu, L. Y., Nyalwidhe, J. O., Semmes, O. J., Vesprini, D., Downes, M. R., Boutros, P. C., Liu, S. K., & Kislinger, T. (2021). Proteomic discovery of non-invasive biomarkers of localized prostate cancer using mass spectrometry. Nature Reviews Urology, 18 (12), 707–724.

Kitano, H. (2001). Foundations of systems biology. The MIT Press Cambridge, Massachusetts London, England.

Klipp, E., Herwig, R., Kowald, A., Wierling, C., & Lehrach, H. (2005). Systems biology in practice: Concepts, implementation and application. John Wiley & Sons.

Klipp, E., Liebermeister, W., Wierling, C., & Kowald, A. (2016). Systems biology: A textbook. John Wiley & Sons.

Kohl, P., Crampin, E. J., Quinn, T., & Noble, D. (2010). Systems biology: An approach. Clinical Pharmacology & Therapeutics, 88 (1), 25–33.

Kondratova, M., Czerwinska, U., Sompairac, N., Amigorena, S. D., Soumelis, V., Barillot, E., Zinovyev, A., & Kuperstein, I. (2019). A multiscale signalling network map of innate immune response in cancer reveals cell heterogeneity signatures. Nature Communications, 10 (1), 1–13.

Kondylakis, H., Bucur, A., Dong, F., Renzi, C., Manfrinati, A., Graf, N., Hoffman, S., Koumakis, L., Pravettoni, G., Marias, K., et al. (2017). Imanagecancer: Developing a platform for empowering patients and strengthening self-management in cancer diseases. 2017 IEEE 30th International Symposium on Computer-Based Medical Systems (CBMS), 755–760.

Kondylakis, H., Koumakis, L., Tsiknakis, M., & Marias, K. (2018). Implementing a data management infrastructure for big healthcare data. 2018 IEEE EMBS International Conference on Biomedical & Health Informatics (BHI), 361–364.

Kondylakis, H., Spanakis, E. G., Sfakianakis, S., Sakkalis, V., Tsiknakis, M., Marias, K., Zhao, X., Yu, H. Q., & Dong, F. (2015). Digital patient: Personalized and translational data management through the MyHealthAvatar EU project. 2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 1397–1400.

Kouroubali, A., Koumakis, L., Kondylakis, H., & Katehakis, D. G. (2019). An integrated approach towards developing quality mobile health apps for cancer. In Mobile health applications for quality healthcare delivery (pp. 46–71). IGI Global.

Kovatchev, B. (2019). A century of diabetes technology: Signals, models, and artificial pancreas control. Trends in Endocrinology & Metabolism, 30 (7), 432–444.

Kuijper, H. (2022). Reductionism or holism? In Comprehending the complexity of countries (pp. 247–273). Springer.

Laubenbacher, R., Sluka, J. P., & Glazier, J. A. (2021). Using digital twins in viral infection.Science, 371 (6534), 1105–1106.

Li, C., Donizelli, M., Rodriguez, N., Dharuri, H., Endler, L., Chelliah, V., Li, L., He, E., Henry, A., Stefan, M. I., et al. (2010). Biomodels database: An enhanced, curated and annotated resource for published quantitative kinetic models. BMC Systems Biology, 4 (1), 1–14.

Likić, V. A., McConville, M. J., Lithgow, T., & Bacic, A. (2010). Systems biology: The next frontier for bioinformatics. Advances in Bioinformatics, 2010.

Lim, J., & Zein, R. (2006). The digital imaging and communications in medicine (dicom): Description, structure and applications. In Rapid prototyping (pp. 63–86). Springer.

Linka, K., Peirlinck, M., & Kuhl, E. (2020). The reproduction number of covid-19 and its correlation with public health interventions. Computational Mechanics, 66 (4), 1035–1050.

Lloyd, C. M., Halstead, M. D., & Nielsen, P. F. (2004). Cellml: Its future, present and past. Progress in Biophysics and Molecular Biology, 85 (2-3), 433–450.

Lubbock, A. L., & Lopez, C. F. (2021). Programmatic modeling for biological systems. Current Opinion in Systems Biology, 27, 100343.

Maass, W., Parsons, J., Purao, S., Storey, V. C., & Woo, C. (2018). Data-driven meets theory-driven research in the era of big data: Opportunities and challenges for information systems research. Journal of the Association for Information Systems, 19 (12), 1.

Malik-Sheriff, R. S., Glont, M., Nguyen, T. V., Tiwari, K., Roberts, M. G., Xavier, A., Vu, M. T., Men, J., Maire, M., Kananathan, S., et al. (2020). Biomodels—15 years of sharing computational models in life science. Nucleic Acids Research, 48 (D1), D407–D415.

Martinez-Velazquez, R., Gamez, R., & El Saddik, A. (2019). Cardio twin: A digital twin of the human heart running on the edge. 2019 IEEE International Symposium on Medical Measurements and Applications (MeMeA), 1–6.

Masison, J., Beezley, J., Mei, Y., Ribeiro, H. A. L., Knapp, A. C., Sordo Vieira, L., Adhikari, B., Scindia, Y., Grauer, M., Helba, B., et al. (2021). A modular computational framework for medical digital twins. Proceedings of the National Academy of Sciences, 118 (20), e2024287118.

Masison, Joseph and Beezley, Jonathan and Mei, Yu and Ribeiro, Henrique Assis Lopes and Knapp, Adam C and Sordo Vieira, L and Adhikari, Bandita and Scindia, Yogesh and Grauer, Michael and Helba, Brian and others. (2021). A modular computational framework for medical digital twins [https://github.com/NutritionalLungImmunity/nlisim].

Mazein, A., Ostaszewski, M., Kuperstein, I., Watterson, S., Le Nov`ere, N., Lefaudeux, D., De Meulder, B., Pellet, J., Balaur, I., Saqi, M., et al. (2018). Systems medicine disease maps: Community-driven comprehensive representation of disease mechanisms. NPJ Systems Biology and Applications, 4 (1), 1–10.

Mazzocchi, F. (2008). Complexity in biology: Exceeding the limits of reductionism and determinism using complexity theory. EMBO Reports, 9 (1), 10–14.

Meier-Schellersheim, M., Fraser, I. D., & Klauschen, F. (2009). Multiscale modeling for biologists. Wiley

Interdisciplinary Reviews: Systems Biology and Medicine, 1 (1), 4–14.

Morchio, R. (1991). Reductionism in biology. In The problem of reductionism in science (pp. 149–160). Springer.

Muzio, G., O'Bray, L., & Borgwardt, K. (2021). Biological network analysis with deep learning. Briefings in Bioinformatics, 22 (2), 1515–1530.

Narkhede, S. M., Luther, L., Raugh, I. M., Knippenberg, A. R., Esfahlani, F. Z., Sayama, H., Cohen, A. S., Kirkpatrick, B., & Strauss, G. P. (2022). Machine learning identifies digital phenotyping measures most relevant to negative symptoms in psychotic disorders: Implications for clinical trials. Schizophrenia Bulletin, 48 (2), 425–436.

Niarakis, A., Waltemath, D., Glazier, J., Schreiber, F., Keating, S. M., Nickerson, D., Chaouiya, C., Siegel, A., No¨el, V., Hermjakob, H., et al. (2022). Addressing barriers in comprehensiveness, accessibility, reusability, interoperability and reproducibility of computational models in systems biology. Briefings in Bioinformatics.

Nickerson, D. P., Atalag, K., de Bono, B., & Hunter, P. J. (2015). The physiome project, openehr, archetypes, and the digital patient. The Digital Patient: Advancing Healthcare, Research, and Education, John Wiley & Sons, 101–124.

Nickerson, D. P., Lundeng˚ard, K., Watts, J., Porter, S., Yu, T., Nielsen, P., & Hunter, P. (2020). Physiome: Encouraging reproducible and fair computational modelling. The FASEB Journal, 34 (S1), 1–1.

openEHR. (2017). An open domain-driven platform for developing flexible e-health systems.

Osanlouy, M., Bandrowski, A., De Bono, B., Brooks, D., Cassar`a, A. M., Christie, R., Ebrahimi, N., Gillespie, T., Grethe, J. S., Guercio, L. A., et al. (2021). The sparc drc: Building a resource for the autonomic nervous system community. Frontiers in Physiology, 12.

Ostaszewski, M., Gebel, S., Kuperstein, I., Mazein, A., Zinovyev, A., Dogrusoz, U., Hasenauer, J., Fleming, R. M., Le Novere, N., Gawron, P., et al. (2019). Community-driven roadmap for integrated disease maps. Briefings in Bioinformatics, 20 (2), 659–670.

Ostaszewski, M., Mazein, A., Gillespie, M. E., Kuperstein, I., Niarakis, A., Hermjakob, H., Pico, A. R., Willighagen, E. L., Evelo, C. T., Hasenauer, J., et al. (2020). COVID-19 disease map, building a computational repository of SARS-CoV-2 virus-host interaction mechanisms. Scientific Data, 7 (1), 1–4.

Oster, G. F., & Perelson, A. S. (1973). Systems, circuits and thermodynamics. Israel Journal of Chemistry, 11 (2-3), 445–478.

Pan, M., Gawthrop, P. J., Cursons, J., & Crampin, E. J. (2021). Modular assembly of dynamic models in systems biology. PLoS Computational Biology, 17 (10), e1009513.

Parodi, V. A. (2015). The digital patient: Changing the paradigm of healthcare and impacting medical research and education. The Digital Patient: Advancing Healthcare, Research, and Education, 273–88.

Peng, G. C., Alber, M., Buganza Tepole, A., Cannon, W. R., De, S., Dura-Bernal, S., Garikipati, K., Karniadakis, G., Lytton, W. W., Perdikaris, P., et al. (2021). Multiscale modeling meets machine learning: What can we learn? Archives of Computational Methods in Engineering, 28 (3), 1017–1037.

Perelson, A. S., Neumann, A. U., Markowitz, M., Leonard, J. M., & Ho, D. D. (1996). Hiv-1 dynamics in vivo: Virion clearance rate, infected cell life-span, and viral generation time. Science, 271 (5255), 1582–1586.

Perelson, A. S., & Weisbuch, G. (1997). Immunology for physicists. Reviews of Modern Physics, 69 (4), 1219.

Pinky, L., Burke, C. W., Russell, C. J., & Smith, A. M. (2021). Quantifying dose-, strain-, and tissue-specific kinetics of parainfluenza virus infection. PLoS Computational Biology, 17 (8), e1009299.

Pinky, L., & Dobrovolny, H. M. (2017). The impact of cell regeneration on the dynamics of viral coinfection. Chaos: An Interdisciplinary Journal of Nonlinear Science, 27 (6), 063109.

Project-hosting platform for the biomedical computation community. (n.d.). Web-based integrated environment for systems biology [https://simtk.org/whatIsSimtk.php].

Pruett, W. A., & Hester, R. L. (2015). Physics-based modeling for the physiome. The Digital Patient: Advancing Healthcare, Research, and Education, 127.

Radhakrishnan, R. (2020). Multiscale modeling: Foundations, historical milestones, current status, and future prospects. Authorea Preprints.

Radhakrishnan, R. (2021). A survey of multiscale modeling: Foundations, historical milestones, current status, and future prospects. AIChE Journal, 67 (3), e17026.

Rajagopal, V., Arumugam, S., Hunter, P., Khadangi, A., Chung, J., & Pan, M. (2022). The cell physiome: What do we need in a computational physiology framework for predicting single cell biology? arXiv preprint arXiv:2202.13282.

Ranathunge, C., Patel, S. S., Pinky, L., Correll, V. L., Chen, S., Semmes, O. J., Armstrong, R. K., Combs, C. D., & Nyalwidhe, J. O. (2023). promor: a comprehensive R package for label-free proteomics data analysis and predictive modeling [vbad025]. Bioinformatics Advances,3 (1). https://doi.org/10.1093/bioadv/vbad025

Research collaborations in regulatory science. (2011). Medical device innovation consortium [http://mdic.org/].

Russian Science Foundation. (2002). Web-based integrated environment for systems biology [https://bio-store.org].

Schaffner, K. F. (1976). Reductionism in biology: Prospects and problems. PSA 1974, 613–632.

Sego, T., Mochan, E. D., Ermentrout, G. B., & Glazier, J. A. (2022). A multiscale multicellular spatiotemporal model of local influenza infection and immune response. Journal of Theoretical Biology, 532, 110918.

Shang, J. K., Esmaily, M., Verma, A., Reinhartz, O., Figliola, R. S., Hsia, T.-Y., Feinstein, J. A., & Marsden, A. L. (2019). Patient-specific multiscale modeling of

the assisted bidirectional glenn. The Annals of Thoracic Surgery, 107 (4), 1232–1239.

Sherwood, L. (2015). Human physiology: From cells to systems. Cengage learning. Smith, A. M. (2018). Validated models of immune response to virus infection. Current Opinion in Systems Biology, 12, 46–52.

Talbot, S., Foster, S. L., & Woolf, C. J. (2016). Neuroimmunity: Physiology and pathology. Annual Review of Immunology, 34, 421–447.

Teichert, G. H., Natarajan, A. R., Van der Ven, A., & Garikipati, K. (2019). Machine learning materials physics: Integrable deep neural networks enable scale bridging by learning free energy functions. Computer Methods in Applied Mechanics and Engineering, 353, 201–216.

Tolk, A., Balci, O., Combs, C. D., Fujimoto, R., Macal, C. M., Nelson, B. L., & Zimmerman, P. (2015). Do we need a national research agenda for modeling and simulation? 2015 Winter Simulation Conference (WSC), 2571–2585.

Tyson, J. J., Chen, K., & Novak, B. (2001). Network dynamics and cell physiology. Nature Reviews Molecular Cell Biology, 2 (12), 908–916.

Viceconti, M., Clapworthy, G., & Jan, S. V. S. (2008). The virtual physiological human—a european initiative for in silico human modelling—. The Journal of Physiological Sciences, 0810200082–0810200082.

Vieira, L. S., & Laubenbacher, R. C. (2022). Computational models in systems biology: Standards, dissemination, and best practices. Current Opinion in Biotechnology, 75, 102702.

Wertheim, K. Y., Puniya, B. L., La Fleur, A., Shah, A. R., Barberis, M., & Helikar, T. (2021). A multi-approach and multi-scale platform to model cd4+ t cells responding to infections. PLoS Computational Biology, 17 (8), e1009209.

Woese, C. R. (2004). A new biology for a new century. Microbiology and Molecular Biology Reviews, 68 (2), 173–186.