DOI: 10.1002/pul2.12392

REVIEW ARTICLE

Pulmonary Circulation Open Access | PVRI Pulmonary Vascular Research Institute | WILEY

A perfectly imperfect engine: Utilizing the digital twin paradigm in pulmonary hypertension

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Funding information
US Army ACC-APG-RTP, Grant/Award Numbers: W911NF, NIH 1 R01 HL169974-01; US DoD DARPA, Grant/Award Numbers: HR00112220038, NIH 1 R011AI135128-01, NIH 1 R01 HL169974-01

Abstract

Pulmonary hypertension (PH) is a severe medical condition with a number of treatment options, the majority of which are introduced without consideration of the underlying mechanisms driving it within an individual and thus a lack of tailored approach to treatment. The one exception is a patient presenting with apparent pulmonary arterial hypertension and shown to have vaso-responsive disease, whose clinical course and prognosis is significantly improved by high dose calcium channel blockers. PH is however characterized by a relative abundance of available data from patient cohorts, ranging from molecular data characterizing gene and protein expression in different tissues to physiological data at the organ level and clinical information. Integrating available data with mechanistic information at the different scales into computational models suggests an approach to a more personalized treatment of the disease using model-based optimization of interventions for individual patients. That is, constructing digital twins of the disease, customized to a patient, promises to be a key technology for personalized medicine, with the aim of optimizing use of existing treatments and developing novel interventions, such as new drugs. This article presents a perspective on this approach in the context of a review of existing computational models for different aspects of the disease, and it lays out a roadmap for a path to realizing it.

KEYWORDS

computational modeling, pulmonary hypertension, treatment

INTRODUCTION

Computer simulation of engineered devices and processes is a central tool in today's technology world. In particular, the use of so-called "digital twins" of individual pieces of equipment for the purpose of preventive maintenance and troubleshooting is an increasingly common approach. It combines mechanistic mathematical specifications of devices with artificial intelligence (AI) and machine learning analysis of

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operational data to "evolve" the digital and physical twins in tandem when additional data are available to update the physical twin. One of the industrial pioneers of the concept put digital twin development at the center of the vision of "No more unplanned downtime!"

Medicine has not yet benefited from the ubiquitous use of computer simulation in a similar way, and the analogous vision of "No more unplanned doctor visits" is unrealized. Human patients are more complex than plane engines, of course, so mathematical specifications of medically important human biology are still under development for the most part. Complicating the matter is the fact that many human systems require biologically based specifications, rather than descriptions based on physics. Biological systems, such as the immune system, for instance, are less-well understood than many physical systems and may require larger amounts and types of data other than what is currently available. Additionally, the technological and mathematical tools for the construction and efficient use of complex multi-scale computational models underlying medical digital twins need further improvement. And model-based control theory for models in this context is still in its infancy.

The heterogeneous nature of pulmonary hypertension (PH) is a prime disease example of the complexity of the "human machine." PH is defined clinically as mean pulmonary artery pressure (mPAP) > 20 mmHg with a pulmonary vascular resistance ≥ 3 Wood units (WU)[1] and embodies the shortcoming of a uniform application of existing therapies to each patient with this disease without considering patient-centered variations in disease response. However, this heterogeneity across the patient population also represents an opportunity in harnessing deep phenotyping data to the application of personalized medicine for patients with disease. PH is thus uniquely well-suited to the digital twin paradigm, given the large amount of existing data on a wide range of variables contributing to disease: from cellular-molecular signaling to hemodynamic flow patterns, clinical imaging, as well as functional clinical outcomes. For example, integration of "omics" data (such as that generated through the PVDOmics consortium[2]) has great potential to serve as the hypothesis-generating base for understanding the variety of mechanisms contributing to disease.[3] An illustrative case of this application in "scaling up" our understanding of disease translated to pharmacotherapeutic targets, lies in monogenic disease due to bone-morphogenetic protein receptor 2 (BMPR2) dysfunction in familial-cases of pulmonary arterial hypertension (PAH). Resulting from decades of research on this TGF-β super family-related receptor's role in pulmonary arterial remodeling,[4] the PH community has a first-in-class disease modifying agent for imminent use in the clinic, sotatercept.[5,6] With eventual development of the digital twin system, one could imagine rapid development of individualized treatment based upon these granular databases, in combination with characteristics of known cellular signaling networks,[7] organ-level fibrotic and angiogenesis-based physiologic assessment,[8] and even development of in silico clinical trials to speed up drug development for patients, given the relatively rare yet complex and deadly nature of the disease.[9]

Despite challenges in modeling, there are already successful examples of medical digital twins in use today. For example, the company HeartFlow provides sophisticated personalized three-dimensional images of cardiac patient blood vessels, which are used for surgical planning.[10] In data-rich settings, such as cancer genetics, AI-based digital twins match patients with "nearest neighbors" from a reference population to design optimal treatment approaches.[11,12] Following the industrial paradigm, for a given disease, the first step is to create a mathematical specification of the relevant biology. For patients with PH, this would include at a minimum the lungs, the immune system, the heart, and the pulmonary circulation. The resulting mathematical model could consist of a mixture of mechanistic and phenomenological parts, using data-driven models where mechanisms are not known or not measurable to a sufficient level of accuracy. Such a model will need to be parameterized and validated extensively, using data from animal models or in vitro experiments. Digital twins of devices can also be updated with data from monitoring the real-world object. This approach relies on streaming or at least frequently-collected operational data from the specific piece of equipment being modeled, together with an appropriate data analysis pipeline that transforms the streaming data into a periodically-updated "personalized" parametrization of the digital twin. In this way, the software instantiation (the digital twin) of the equipment evolves in real time together with the physical object that it represents. Once this is accomplished, the digital twin can be used for a variety of purposes, such as forecasting the effect of treatments or the development of novel treatments through virtual clinical trials.

This perspectives article aims to apply—or at least propose a methodology by which to apply—this version of the digital twin paradigm to the study of PH, its management, prognosis, and mechanistic hypothesis generation for the development of disease-modifying therapies. Explicitly, it is not intended as an exhaustive review of the literature in the field of cardiovascular mathematical modeling. Simply put, the goal of this commentary is to provide a series of carefully discerned references that highlight—in our opinion—a map of

where the field may look to move forward over the next several decades. Like all maps, however, there will be details that are lost depending upon scale and, in some cases, perspective. Thus, we propose to explore existing mathematical models related to PH at three different scales: intracellular, intercellular, and organismal. Then we consider models that deal with treatment decisions such as expected toxicity and efficacy. We also consider how digital twins can be used for in silico trial development. Finally, we describe what work needs to be done to realize a digital twin for PH.

THE PH PATIENT ENGINE

Determinants of PH and its treatment span several scales, from the molecular to the physiological. To effectively integrate data characterizing the different scales and to use them for the personalized optimal treatment of PH patients, multiscale computational models are indispensable. Mechanistic models are best suited for this purpose since they allow the simulation of the effect of different treatments over time. In the following sections we will describe some available computational models at each of the scales and those that cut across scales. The purpose is not an exhaustive review of the literature, but to make an inventory of what part of the human biology relative to PH has been encoded in selected computational models, and what is still needed for a PH digital twin, that is, a PH model that can be personalized to an individual patient and used over time to optimize treatment (refer to conceptual model illustrated in Figure 1).

A. intracellular modeling

Case: A 30-year-old woman presents to her primary care physician with fatigue, light-headedness, and shortness of breath with exertion. An echocardiogram is concerning

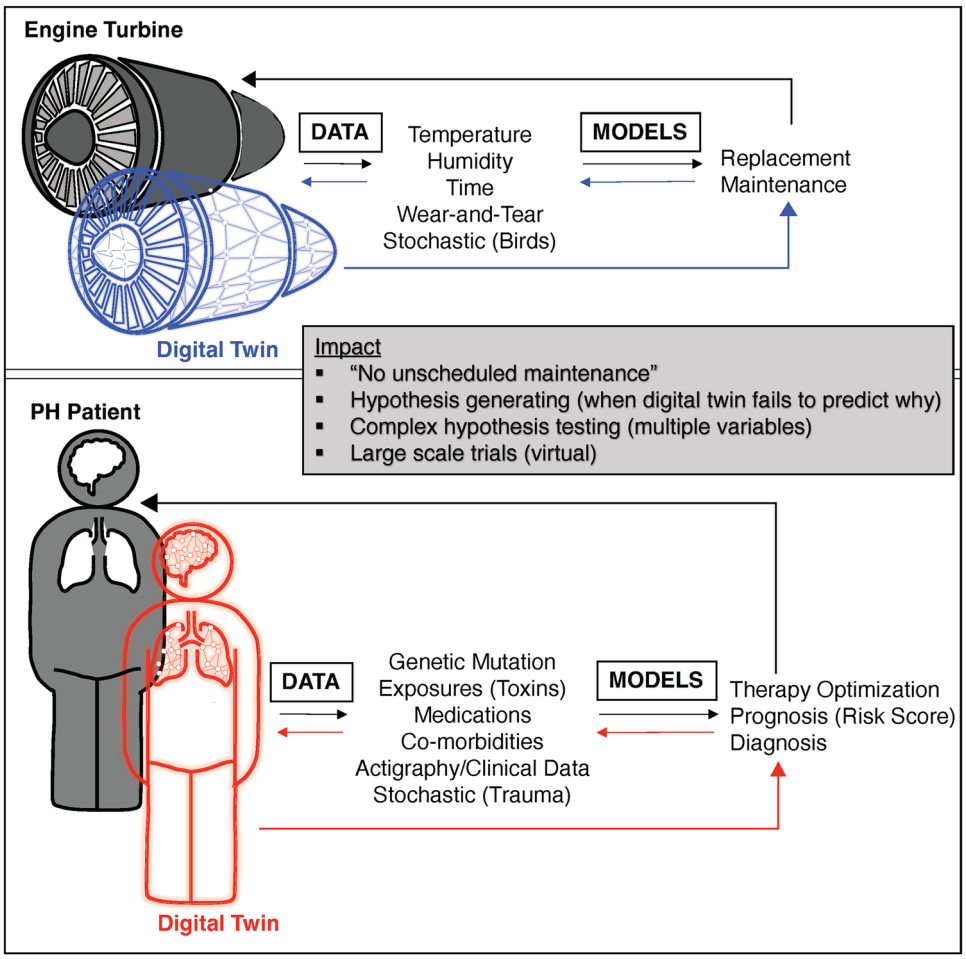

FIGURE 1 Conceptual personalized pulmonary hypertension model. A computational PH model that can be personalized to an individual patient, similar to the concept of engine turbine digital twin. Patient data over time serves as input for personalized and optimized treatment. PH, pulmonary hypertension.

for elevated right ventricular systolic pressure (RVSP), and the patient is referred to a PH center where a diagnosis of precapillary PH with high-risk features is made by right heart catheterization (RHC). She is initiated on triple therapy for severe decompensated right heart failure, including a phosphodiesterase type 5 (PDE5) inhibitor, an endothelin receptor antagonist, and a parenteral prostacyclin analogue. After genetic testing she is found to have a nonsense mutation of BMPR2, the most commonly described heritable cause of PH.[13] She is negative for other genetic mutations indicated as possible causes of PAH, including BMP9, SOX17, and TBX4.[14,15] In addition to questions regarding screening of family members for BMPR2 mutation, the patient requests input into how the mutation itself could potentially inform individualized treatment?

The use of genomic data has great potential in predicting outcomes of individual patients, such as the patient in the clinical vignette, and currently there are already multiple examples of work in this area that could be applied to creation of a PH digital twin. As mentioned above, specifically the use of omics will be helpful in the case of PH due to monogenic mutations. Already, novel analyses of transcriptomic data have allowed the discovery of many dysfunctional genes in the progression of PH.[16] With the continued improvements in high-throughput technology, there is a massive influx of data with the potential hope of finding pathways to target for treating PH.[2] Commensurate with interest in the field, there are many published reviews focusing on use of -omics data to find mechanisms that will help understand the progression of PH, diagnosing the phenotype, and eventually personalized treatment.[17–22] Much of the current research includes analysis to explicitly determine upregulated or downregulated genes or pathways, through single interactions between variables. Therefore, the logical next step in the application of these data is to study dynamic changes in the homeostatic regulation of cellular health due to perturbations of gene-level*networking* within the cell. A common method of using intracellular data is to build dynamic mathematical models of regulatory networks, using either systems of ordinary differential equations or Boolean networks. The former is based on a view of the regulatory network as a biochemical reaction network, while the latter views it as a decision process based on logical rules. Boolean networks are typically easier to construct since they do not require rate constants for parametrization. For Boolean networks, a data-driven top-down approach can be applied through binarization of high-throughput data (e.g., gene expression patterns in PH), allowing for reconstruction algorithms to predict regulatory rules within the cell.[23] In the creation of a digital twin paradigm for patients with PH, such networks for different cell types could serve as the basis for the intracellular scale of a PH digital twin.

An instance of this approach is based upon phosphoproteomics data.[24] Relevant to PH biology, endothelin signaling has been extensively studied and is known to signal through two receptors, A and B. Schafer and colleagues thus considered the study of endothelin biology in a single melanoma cell line that only expresses endothelin B receptor (EDNRB), making it ideal to study the effects without the interaction of both receptors. The group then used experimentally described, as well as predicted, kinase-substrate relationships and protein-protein interactions to construct binary relationships between these molecules. Using an algorithmic approach (PHONEMeS),[25] they then optimized the pathways from EDNRB to target sites. From known interactions they finally constructed a Boolean network model that showed pathways of interest from EDNRB and was consistent with their data. (Note that in Boolean models the status of each gene or molecule is either "on" or "off" (binary) along with the elements they interact with, forming something akin to a logical decision model characterizing the dynamics of the network.) In this example, the group found five main pathways related to relevant signaling: arrestin-MAPK cascade, AMPK-CAMKII-CaMKK2, PI3K-PDK1-AKT, PKC, and PKA in EDNRB signaling. From these initial experiments, they then validated the phosphorylation of 11 out of 12 central nodes from the model with stimulation via endothelin. This study, and studies like it, thus provide a roadmap for crafting a comprehensive model of the signaling pathway influencing endothelin-induced cell-specific migration.[24] The same techniques could then be applied to other well-defined PH-relevant signaling pathways of interest to develop a comprehensive model, taking into account even novel molecular signals, for testable hypothesis generation.

Similar to this broad exploration of endothelin manipulation, cell-specific metabolic pathways are known to play an important role in PH.[26] To this end, many mathematical modeling studies have investigated various aspects of intracellular metabolism.[27] One such study considered arginine catabolism,[28] an important source of nitric oxide in vaso-reactive diseases such as PH.[29] With their model they were able to replicate experimentally determined values, ascertaining how much each element (enzyme or transporter) affects the

flux of arginine, labeled flux control coefficients. They found that while ornithine decarboxylase and nitric oxide synthase are key enzymes, this did not strongly control the flux through the arginine catabolic pathway. Instead, they discovered that low affinity arginine transporter and arginase had the most control over the flux.[28] Similar insight into amino acid utilization in PH could reveal novel chokepoints for NO-production, the foundation of traditional vasodilator-based therapies.

Finally, related to vasodilatory biological pathway regulation, the role for hypoxic signaling in PH is well described across tissue types and cells,[30] although mathematical modeling of intracellular signaling models related to hypoxia has yet to be incorporated into models of PH. This represents an unfortunate knowledge gap, as hypoxia-inducible factor (HIF) signaling is intimately linked to pulmonary vascular remodeling with ongoing preclinical and clinical studies examining outcomes related to pathway inhibition on disease outcomes.[31] To this end, the relationship between duration of hypoxic exposure and cell growth and stabilization of HIF through a variety of synergistic pathways is of potential interest to the field at large. Exploration of these pathway interactions lends itself to a network modeling approach.[32] For example, such modeling techniques can help our understanding of hypoxic effects seen within PH-relevant vascular endothelial cells. One potential application is the utilization of computational models to predict microRNA-mediated control of HIF-regulated VEGF.[33] Likewise, in another intracellular computational model focusing on the role of endothelial cells in angiogenesis, a total of 143 molecules were examined in the full model, including signaling related to shear stress and oxygen effects and ANG/TIE, Notch, TGF, AKT/SRC, VEGF, fibroblast growth factor (FGF), CyclinD1, RAS/PLCg, WNT, and NO pathways.[34] This report stratified molecules by relevance and impact to endothelial cell sprouting, narrowing down candidates for empiric testing to 64 molecules relevant to the microenvironment for different stages of novel vessel growth. A similar method of hierarchy could be utilized to narrow unwieldy lists of candidates for testing in high and medium throughput assay analysis, or even prioritizing clinical trial development, directed at treatment of PH. To illustrate this final point, an intracellular network model based specifically on pulmonary arterial adventitial fibroblasts with signals particular to the development of PAH was subjected to hypoxia and mechanical overload. Using results from 20 publications to validate their model, the group found it to accurately predict experimental outcomes with 80% accuracy. Model analysis revealed the most influential molecules in mechanical overloading, which included targets such as αSMA, cGMP, ET1, syndecan4, and the Hippo pathway,[15] as well as novel targets for analysis. Broader application of this type of computational modeling could thus yield novel insights into the pathogenesis of disease progression. Once calibrated to an individual patient, this intracellular component will contribute to model forecasting of a patient trajectory in a digital twin paradigm, including the young female patient in the case presentation.

B. Intercellular modeling

> *Case: A 76-year-old man with untreated obstructive sleep apnea (OSA) and idiopathic pulmonary fibrosis (IPF) diagnosed 6 months ago, currently stable on nintedanib, presents with worsening dyspnea on exertion over 8 weeks, bilateral lower extremity edema, and increasing oxygen requirement from 3 to 6 liters nasal cannula. A surface echocardiogram demonstrates concern for right-ventricular strain with an estimated RVSP of 70–80 mmHg and grade II diastolic dysfunction with preserved left-ventricular ejection fraction. RHC concerning for the following consistent with diagnosis of PH: mPAP 48 mmHg, a pulmonary artery occlusion pressure (PAOP) of 12 mmHg, with a PVR of 6 WU. A combination of loop diuretic, PDE5 inihibitor, and inhaled prostacyclin analogue are initiated, along with encouragement of continuous positive airway pressure (CPAP) adherence for underlying OSA. A referral is placed to the Lung Transplant Clinic. The patient, overwhelmed, messages the healthcare team regarding interactions of the currently prescribed medications with each other, and how he can best approach the two diseases: lung scarring in combination with blood vessel narrowing?*

Many patients—such as the one described above—have questions about how drug classes act on different aspects of the lung, amounting to how presumably cell-specific targets interact within the complex environment of the pulmonary vasculature. Often drugs target signaling changes at the intracellular level, but the way an individual cell behaves does not completely explain the impact of changes complicated by interactions of many cell types. Logically, the next scale of mathematical modeling relevant to the formation of a digital twin is at this intercellular level. Fortunately, there are many

mathematical models at this scale, including—for example—interactive endothelial cells during angiogenesis, influencing one another in a predictive model that mimics the process of forming new blood vessels.[35–37] To predict this process, computational models must account for how endothelial cells behave differently depending on their location on the new blood vessel and their response to cytokine levels secreted by neighboring cells, as an example. Exemplary of this approach, one study considered how the extracellular environment of VEGF affects migration capacity of cells through the extracellular matrix (ECM). Noting that VEGF is taken up into the endothelial cell, the model incorporates intracellular signaling with extracellular signaling. The linking of these scales is to signal to the cell to proliferate, migrate, or undergo apoptosis, endothelial cells in the model formed correct vessel structures similar to experimental observations.[35] Acknowledging that VEGF is not the sole signal in angiogenesis, another modeling study compared how the growth of new vessels changed with FGF compared to VEGF signaling.[36] This study validated the model against length of endothelial cells induced by FGF and VEGF, showing that FGF induces greater sprouting response.

One can extrapolate from application of a similar model of homeostatic aortic tissue, including endothelial cells and smooth muscle cells in preserved systemic vasculature with an intact medial and adventitial layer. The combined cell populations were then individually represented to behave autonomously as "agents," the basis of so-called agent-based modeling.[37] The agents or individual cells are given rules to govern their behavior. This model was then used to study transient pressure changes within the system, modeling sequelae of systemic hypertension. The report went on to present a method of scoring each rule in the model based on the type of experiment (e.g., in vivo vs. in vitro) used to validate each component of the model. An important focus was on how well the model with increased pressure replicated in vivo behavior of the aorta in the setting of systemic hypertension. Such a modeling system could easily be applied to the lower flow states and unique cellular make-up of the pulmonary circulation.

Finally, such modeling could ultimately be utilized to address the patient's question above regarding interactions of cell populations in the setting of adventitial lung disease coupled with PH, especially given how lung fibrosis is considered to be a large part of PH progression in this setting. Interestingly, at least one model has shown the capability to replicate lung fibrosis caused by damage to the epithelium, though without consideration of the endothelial compartment. In the model, in the absence of "damage," the homeostatic lung environment remained preserved, but by causing a damage response within the epithelial cells, the model showed how the ECM is thickened. This stochastic pattern of damage to the epithelium was due to various concentrations of the chemokine MCP-1 leading to heterogeneity in monocyte recruitment and retention across simulations and leading to different ECM patterns of late fibrosis stage.[38] Coupling a similar model to study vascular deformation, or rarefaction, in a curated fashion could be used to speed discovery and translation of therapeutics introduced into the in-silico system, cutting down the investment of physical resources and time. Importantly, one must consider how representative these models are within the PH-field, as there are many other important cellular features that are not currently addressed by the highlighted models.

C. Organismal modeling: Physics/flow dynamics

> *Case: A 59-year-old man with history of unprovoked pulmonary embolisms presents with chronic thromboembolic PH (CTEPH) after symptoms of worsening dyspnea on exertion prompted a ventilation-perfusion scan read to have a high probability of thromboembolic burden. An echocardiogram was found to have an estimated RVSP of 50–60 mmHg. He had earlier been evaluated for thrombophilia and found to have a heterozygous mutation for prothrombin G20210A. RHC is notable for a mPAP of 28 mmHg, a PAOP of 12 mmHg, with a PVR of 4 WU. His current treatment regimen includes apixaban and riociguat. He is functionally limited in activities of daily living, and a 6-min walk distance is recorded at 450 m. He is referred for pulmonary endarterectomy given proximal nature of clot burden as evidenced by computed tomography angiography scan. The patient notes anxiety regarding planned support of cardiopulmonary hemodynamics immediately post-surgery, and asks what his expected prognosis is regarding recovery of heart and lung function over time?*

In PH, and especially CTEPH, the right ventricle of the heart experiences either acute, chronic, or acute-on-chronic alterations in pulmonary pressures that uniquely stress the cardiovascular circuit, the underlying sentiment for the patient's concerns in the vignette.

Computational modeling represents a unique opportunity for assessing and predicting response of individual right ventricles to rapid off-loading, such as in the case above. In response to this potential, one group—Velez Rendon et al.—empirically measured RV pressure and volume, heart contractility, and end-diastolic elastance in an animal model creating a mathematical model to separate morphological and intrinsic contribution to RV overload. In the acute model, the data demonstrated that RV pressure increased by the second week as well as hypertrophy, with the stroke volume and cardiac output remaining unchanged. Using the mathematical model, they showed that wall thickening and remodeling by themselves were unable to account for the increase in the elastance and contractility of the right ventricle ("intrinsic inotropy of RV myocardium").[39] The group then performed an elegant series of experiments to test the strain of tissue from PH patients compared to controls, in a chronic translational manner. The model was able to replicate the experimental data, later demonstrating that circumferential stress was higher in the RV of PH patients, and that the ratio of collagen-to-myocardial physical stress did not change significantly over time once established.[40] The group then expanded upon this work to show that wall thickening alone is sufficient to maintain cardiac function for the first 4 weeks, but by week five there was a significant increase in wall stiffness. The stiffness was secondary to thickening that countered any gain in function, similar to canonical left-sided diastolic dysfunction or heart failure with preserved ejection fraction. The model showed that this phenomenon could be explained by static myocardial material stiffness, even without significant fibrosis, suggesting an independent predictive biomarker for determining which subjects may respond well to RV unloading.[41]

In a similar model focused on RV remodeling in PAH, a group created a spatial representation of the RV over time resulting in heart failure. In alignment with prior data, this model indicated that intrinsic contractility of myofibers and passive stiffness is the initial ventricular response to maintain cardiac output. While individual fibers were found to have increased contractility upon development of PAH, reorientation of these myofibers caused the contractions to be less effective, and thus prone to organ failure.[42]

To fully integrate such modeling systems into a digital twin paradigm, it is first necessary to demonstrate integration of some of the previous cellular modeling techniques within this larger organ-based construct. As an example of this integrated approach, one study recorded cardiac magnetic resonance imaging to create an individual 3D geometric model of the right ventricle for PH patients. The researchers then calculated the estimated average wall thickness and radius in a spatial manner using these data to calculate wall stress in a spatial segment of the RV. The goal was to then integrate metabolic signals of RV adaptation in the individual PH models, so they measured 10 known metabolites relevant to disease and found a strong correlation to wall stress. The group could then delineate negative and positive associations between metabolites, with the ultimate goal of utilizing these data to define functional metabolic biomarkers for patient risk-stratification, and hypothesis generation.[43]

Relevant to the case described above, to comprehend fully the response to alleviating clot burden it is necessary to understand the RV response to perfusion as well as anticipated changes in the pulmonary vascular bed to ventilation mismatch. Relevant to the study of this concept is the design of a mathematical model to account for a two-dimensional pulmonary vascular network, including fluid and wall mechanics, that are related functionally to alveolar pressure and oxygen transport to the blood. In the physiologic response to hypoxia, the body teleologically tries to redirect blood flow by constricting pulmonary arteries, a unique response confined to the lung, termed hypoxic pulmonary vasoconstriction. A group of investigators was able to model this response, replicating native matching of perfusion to ventilation resulting in a homeostatic—expected—response to acute hypoxia exposure.[44] Such a model could be applied to postoperative predictive algorithms of CTEPH patients, as well as a number of acute lung injury scenarios or even high-altitude simulated testing.[45] Finally, in addition to a number of primary articles and reviews on the topic of modeling gas exchange in the lung,[46–49] there is also a physiology "engine" in nascent stages of production, called Pulse Engine. This includes a lumped parameter model of respiration, and has several simulation models that can be run to simulate a variety of disease states (i.e., bronchial constriction, pneumothorax, and mechanical ventilation). These open-source engines are based on previously published work using differential equations[50,51] and can be applied to a variety of pulmonary vascular diseases, and treatment responses.

Prognosis and defining outcomes

Case: A man in his 80 s with PH associated with myelodysplastic syndrome (MDS; myelofibrosis diagnosed 1 year prior), status-post treatment with ruxolitinib, is initiated on

tadalafil and ambrisentan. The latter is discontinued due to lower extremity swelling and chest pain. He has a past surgical history notable for traumatic splenectomy. He has OSA on CPAP and nocturnal oxygen, in addition to continuous ambulatory 2–3 L oxygen. Additionally, he is undergoing evaluation for extramedullary hematopoiesis within the lung, gives concern for progressive parenchymal changes in setting of his MDS. Before leaving the office to pick up his latest prescription, he asks, "with all of my problems, how on earth do you all figure out how to treat me, which of the drugs are working, and how much longer I've got?"

To answer our patient's question, as clinicians we must first figure out which combinations of drugs to treat with, an exponentially complex task, requiring us to take into account the expected toxicity and efficacy of individual agents. To determine whether a treatment is not harming excessively (e.g., having too much *toxicity*) and is actually helping (e.g., having *efficacy*), we need metrics for toxicity and efficacy. Experimental and clinical data have traditionally been used to screen drugs for toxicity.[52] However, mechanistic mathematical models, such as those in DILIsym,[53] have been used in recent decades to predict liver toxicity for a variety of compounds in advance, just using in vitro data. Mechanistic models have been developed for other potentially toxic effects relevant for mechanisms of toxicity of PH drugs. For example, models of platelet activation signaling are relevant for the PH treatment iloprost.[54,55] Models also exist for absorption processes and a general intracellular signaling response of sildenafil,[56,57] and for hepatic uptake and metabolism of bosentan.[58]

Efficacy has been more challenging to model, due to the issue of determining a suitable metric for efficacy. For example, the 6-min walk test (6MWT), as a measure of exercise capacity, has been used as a primary endpoint metric for multiple therapies for PAH patients. It is considered an easy-to-measure, quantitative surrogate marker for longer-term outcomes: a therapy that increases the 6MWT distance (6MWD) by 70 yards not only achieves that specific benefit, but is also expected to result in longer-term improved outcomes. Although increased survival is the metric that is really preferred, surrogate markers such as the 6MWD have been used to shorten clinical trials. However, increase in baseline 6MWD does not always correlate with long-term outcomes in PAH,[59–61] raising questions about its suitability as a surrogate metric of efficacy. There are confounding factors that can cause a patient's 6MWD to not increase after starting a new therapy, such as frailty, hospital stays, or comorbidities, and a ceiling effect for those who perform well at baseline.[60] Increasing complexity in the treatment of PAH and the use of vasodilators have also decreased the predictive capacity of increased 6MWD.[61] In place of change in 6MWD, morbidity and mortality events are being used by some as primary clinical endpoints for PAH therapies. Increase in 6MWD can still be useful in clinical trials that cannot be run long enough to analyze events, and it can be useful in short-term management of PAH patients. However, a decrease in 6MWD, declining functional class, or worsening cardiac function as determined by metrics such as brain natriuretic peptide (BNP) and N-terminal pro-BNP, were predictive of longer-term complications or death in PAH patients.[59,62,63] Further, risk calculators such as the registry to evaluate early and long-term PAH disease management (REVEAL) 2.0 are prognostic for long-term morbidity and mortality outcomes.[64] If a mechanistic model was created that included the confounding factors for an individual, it might be able to differentiate the cases when a change in 6MWD is impactful. A digital twin would theoretically be able to be updated to incorporate new treatment.

As an alternative to such empirical predictive scores and correlation methods, mechanistic models are well-suited for determining drug combinations to use and for making prognostic predictions of outcomes. Although there is little work directly linking treatment with PH progression in a mechanistic model, there are multiple models for related conditions such as right ventricular failure and fibrosis. One model of right ventricular failure due to pressure overload incorporated A61603 (A6), a selective α_{1A}-adrenergic receptor agonist. This model predicted that A6 preserves ejection fraction of the RV and cardiac output. It inhibits RV failure by restoring myocyte maximum force generation but did not change the pressure overload.[65] A model that can be individualized by CT images for CTEPH patients was created that predicts the best targets for balloon pulmonary angioplasty therapy.[66] There is also a model which considers how to non-invasively diagnose PH by using a model with pressure flow and volume of the body's vasculature system.[67] There is more work related to symptoms of PH, such as pulmonary fibrosis. Warsinske et al. looked at combination strategies to treat the effects of fibrosis. Their model predicted that targeting both fibroblast regulation and epithelial cell survival at the same time were needed to successfully treat fibrosis.[68] A mathematical model of IPF tested several drugs and found that pirfenidone was the drug that could stop the progression

of fibrosis.[69] There is also work studying the impact of using a left ventricular assistance device for support after the right ventricular failure has also been explored.[70] While most of these models are not directly related to PH, they represent the beginning work that could be assimilated into a digital twin.

In silico clinical trials

> *Case: A 73-year-old obese woman with long-standing systolic heart failure presents in referral from a cardiology clinic for evaluation of PH. She had previously been initiated on sildenafil, with resultant worsening shortness of breath for which the drug was discontinued. She is wheelchair bound due to dyspnea and fatigue. Her current treatment regimen includes a beta-blocker, angiotensin-receptor blocker, and combination of loop and thiazide diuretics. She has diabetes mellitus and was recently started on an SGLT2 inhibitor. A serum BNP is obtained in clinic (1380 pg/mL; normal less than 100 pg/mL). Echocardiogram is significant for a left atrium size of 4.9 cm, a left-ventricular ejection fraction of 30%, and an estimated RVSP of 50–60 mmHg. RHC is significant for elevated pulmonary pressures, with a PAOP of 23 mmHg, with a significantly depressed cardiac output and mixed venous gas oxygen saturation. Her son accompanies her today in clinic and inquires as to the utility of a new PH drug he read about, sotatercept, in patients like his mother.*

For many decades, there has been strong interest in conducting clinical trials virtually (in silico) to make the process of drug development more efficient, including in cardiovascular research and PH. Early clinical trial simulations were based on empirical models of drug concentrations and drug effects.[71,72] These models used nonlinear mixed-effects modeling and fit lognormal distributions to clinical data, incorporating covariates such as age, weight, and renal function. Such in silico clinical trial simulations were first used to design subsequent clinical trials, after early trial data became available.[73] They were later run based on distribution data available from preclinical in vivo studies, with allometric scaling used to adapt the models to simulate human subjects.

The use of mechanistic mathematical models was a major step forward to ensure better simulations of interpolated populations and to finally allow for simulation of extrapolated populations. Such models are called quantitative systems pharmacology (QSP) models by the biotechnology/pharmaceutical (biopharma) industry. QSP models have been used extensively in drug discovery programs to suggest potential drug targets. More recently they have been used to make internal decisions in clinical drug development programs. A mathematical model of an anti-PCSK9 therapy was used for in silico clinical trial simulation to test whether there would be patient benefit if it was added to a statin.[74] The model predicted the therapy would not significantly benefit a certain subpopulation of patients. This prediction was later validated clinically when another company tested their own anti-PCSK9 therapy and found that adding it to statins did not significantly help this same subpopulation. In silico clinical trial simulation with a QSP model for COVID-19 viral dynamics was also used to test different starting days for the antiviral therapy Paxlovid. The simulations predicted that the risk of hospitalization or death was reduced the most when Paxlovid was initiated no later than 5 days after the onset of COVID-19 symptoms.[75,76] This result was used to design the clinical trials of Paxlovid, and the data from the clinical trials validated the simulation predictions. Additionally, simulation of a population of 300 patients with diabetes, based on a mechanistic mathematical model of glucose-insulin dynamics, was accepted by the US Food and Drug Administration (FDA) in lieu of preclinical animal testing.[77]

In a recent breakthrough, trial simulations from a QSP model of drug mechanism of action and efficacy were used for the 2022 clinical approvals by the FDA [78] and the European Medicines Agency (EMA) of olipudase alfa for pediatric patients.[79] This is the first citation by regulatory agencies of mechanistic systems modeling and simulation of patients as central to a drug approval rather than just supportive evidence, and serves as proof-of-concept for future studies streamlining the "trial" of PH novel drugs.

These mechanistic models and many others are used to generate thousands of virtual patients (VPs) by sampling from specified parameter distributions. Cohorts of virtual populations (VPops) are selected from these VPs by ensuring they match prior clinical patient data. For example, if patient data include blood pressure and cell counts at various times, then distributions can be estimated from the data and simulations that do not lie in the distributions are discarded. Two major challenges arise from the greater complexity of the mechanistic models: (1) the time it takes to simulate each patient is longer for a more complex model; and (2) the model parameter space for a more complex model has a higher

dimension and thus requires more samples to explore it. Multiple methods have been employed to try to ensure VPops are as representative of the clinical data as computationally possible.[80–83] Of course, if digital twins for everyone existed, all could run in silico trials using the digital twins. This would be the goal for all registered PH patients, a true precision medicine approach to drug discovery and testing, one that would both address the case patient's concerns and provide data before the fact on suitability of a novel drug for their unique disease process.

CONCLUSION

The human biology relevant to PH extends across scales, from the molecular to the organismal. For effective treatment and the development of novel treatment modalities, it is essential to leverage our knowledge about each of these scales through their integration and a data assimilation process that allows us to capture a multiscale representation of a given patient. The most efficient way of accomplishing this is through computational modeling that provides a principled way to integrate data at the different scales. In this review, we have shown that there is considerable computational modeling work that has been done at each of the relevant scales (Figure 2). We have also highlighted work that shows how computational models can be used to develop novel therapeutic approaches. The first challenge now is to complete the construction of comprehensive computational models at each relevant scale. The second challenge is to integrate the models at the different scales into a multiscale model of human biology that controls the processes involved in the development, progression, and treatment of PH. Multiscale modeling of biological systems has progressed substantially in the last two decades, and the computational and theoretical tools are in place to complete this task. Beyond the technical aspects, an integration of scales requires that researchers and clinicians working at the different scales, as well as in the clinic, collaborate in this effort.

The third, and possibly biggest, challenge is to personalize the model to an individual patient, alluded to in the case studies we presented along the way, to complete the construction of the digital twin of this patient. One of the characteristics of a digital twin, as opposed to simply a model, is that this personalized model can be recalibrated periodically, as the patient's condition changes, and is up to date in its predictions. The problem is twofold. One is to transform periodic measurements of the state variables of the model (gene expression, concentrations of relative molecules, vital signs, etc.) and transform them into new values of the parameters. The other problem is to develop appropriate forecasting methods. While forecasting is being done in

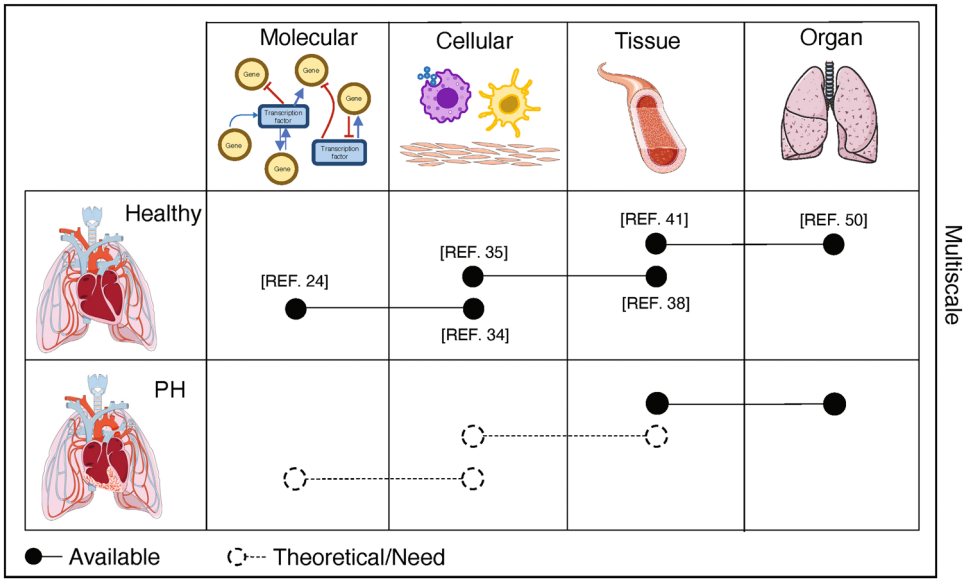

FIGURE 2 Multiscale computational modeling framework. Existing computational model work done at relevant scales (i.e., molecular to cellular, cellular to tissue, and tissue to organ) in healthy individuals or PH patients. References above dots represent papers built at the indicated scale that have been extended to a difference scale. For example, both hemodynamics and vascular remodeling are considered in CTEPH.[66,67] To create a digital twin of PH, multiple scales need to be connected. Future work might connect published models, such as intracellular hypoxia signaling[32] with angiogenesis[36] and specify them to PH. CTEPH, chronic thromboembolic PH; PH, pulmonary hypertension.

several different settings, such as numerical weather prediction, the challenges for medical applications tend to be different.

This review/perspective is intended to frame the overall challenge and promise of a PH digital twin, and serve as a blueprint for further development. Here, we have focused primarily on the use of mechanistic models as the digital twin engine, as is the case for almost all digital twins used in industry. Our choice was informed by the advantage of mechanistic dynamic models of allowing the simulation of novel therapies or novel combinations of therapies and their effects over time. Data-driven AI or machine learning models do not generally allow this type of extrapolation beyond existing data. Furthermore, in many cases, the limited quantity of data makes it challenging to obtain robust results and predictions without mechanistic models. We envision increased use of mechanistic medical digital twins as essential tools for simulation, hypothesis testing, and prediction in medicine.

In summary, we believe the digital twin paradigm to be a viable model for future PH-directed research, prognostication, and translational application of novel drugs or behavioral interventions. The Digital Twin offers unique insight into not only patient monitoring for the aspirational "no more unplanned doctor visits," but also offers a glimpse into unveiling new innovative hypotheses for when the system fails to live up to this explanation. Ostensibly, there are greater opportunities in figuring out why a theory didn't work, than simply expecting a perfectly planned outcome. In other words, the human condition is often unexpectedly messy, and figuring out why is what drives the research enterprise.

Finally, the approach to complex multivariable hypothesis testing through use of a digital twin, much less patient treatment, remains largely a conceptual model (refer to Table 1 and Figure 2). Therefore, to facilitate the development of this unique and powerful tool, we propose the following research and development priorities:

- The jet engine prototype necessitates longitudinal, and frequently continuous, analysis of variables relevant to flight: temperature, humidity, and time-of-flight. Similarly, for a digital twin model to be used to reduce unplanned doctor visits, regular patient monitoring must be available. While development of novel invasive monitoring techniques are underway,[111] these devices carry the contingent risk of any invasive monitoring device—infection, bleeding, or embolization. Fortunately, wrist-actigraphy is a safe alternative for monitoring activity as well as heart-rate variability in this patient population,[112] and likely the workhorse for a successful digital twin model that includes updates.
- Development of learning and validating cohort databases for refinement of initial cross-sectional patient endophenotyping; a starting point for the digital twin preferably based upon actual patient data.

TABLE 1 Summary of references available for scale of modeling in application to pulmonary vascular disease and related manuscripts to specific mathematical models.

Scale	Related modeling reviews
Intracellular	Omics and image data,[84] HIF,[85] general intracellular,[86] NO,[87] metabolism[27]
Intercellular	Angiogenesis,[88,89] extracellular matrix remodeling[90]
Physics/flow dynamics	Pulmonary circulation (pulmonary hypertension [PH]),[91] cardiac hypertrophy,[92] neonatal PH,[93] ventricular mechanics[94]
Prognosis	Pulmonary system,[95] drug combinations cancer,[96] nanoparticle drug delivery cancer[97]
Clinical trials	In silico trials,[98] drug design[99]
Mathematical model	**Related manuscripts**
Multiscale	PH vascular resistance,[100] fibrosis,[101] precision medicine[102]
Boolean models	System medicine,[103] gene regulatory,[104] tutorial[105]
Agent based models	Multiscale vascular,[106] system biology,[107] tutorial[108]
Differential equations	Metabolic,[109] air flow in lungs[110]

Abbreviation: HIF, hypoxia-inducible factor.

- Lastly, we require inference into the model for stochastic, or unexpected, occurrences such ranging from unanticipated trauma to more predictable dietary indiscretion.

AUTHOR CONTRIBUTIONS

Melody Walker, Helen Moore, Reinhard Laubenbacher, and Andrew J. Bryant wrote and edited the manuscript. Ann Pham provided illustrations and edited the manuscript. Ali Ataya and Paul A. Corris edited the manuscript, and Paul A. Corris, Reinhard Laubenbacher and Andrew J. Bryant conceived of manuscript.

ACKNOWLEDGMENTS

The authors would like to acknowledge the contribution of Martin Wilkins in initiation of this manuscript. US Army ACC- APG-RTP W911NF, NIH 1 R01 HL169974-01, US DoD DARPA HR00112220038, NIH 1 R011AI135128-01, NIH 1 R01 HL169974-01 (R. L.).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

N/A.

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REFERENCES

1. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1):1801913.
2. Hemnes AR, Beck GJ, Newman JH, Abidov A, Aldred MA, Barnard J, Berman Rosenzweig E, Borlaug BA, Chung WK, Comhair SAA, Erzurum SC, Frantz RP, Gray MP, Grunig G, Hassoun PM, Hill NS, Horn EM, Hu B, Lempel JK, Maron BA, Mathai SC, Olman MA, Rischard FP, Systrom DM, Tang WHW, Waxman AB, Xiao L, Yuan JXJ, Leopold JA. PVDOMICS: a multi-center study to improve understanding of pulmonary vascular disease through phenomics. Circ Res. 2017;121(10):1136–9.
3. Johnson S, Sommer N, Cox-Flaherty K, Weissmann N, Ventetuolo CE, Maron BA. Pulmonary hypertension: A contemporary review. Am J Respir Crit Care Med. 2023;208(5):528–48.
4. Morrell NW, Yang X, Upton PD, Jourdan KB, Morgan N, Sheares KK, Trembath RC. Altered growth responses of pulmonary artery smooth muscle cells from patients with primary pulmonary hypertension to transforming growth factor-β1and bone morphogenetic proteins. Circulation. 2001;104(7):790–5.
5. Humbert M, McLaughlin V, Gibbs JSR, Gomberg-Maitland M, Hoeper MM, Preston IR, Souza R, Waxman AB, Ghofrani HA, Escribano Subias P, Feldman J, Meyer G, Montani D, Olsson KM, Manimaran S, de Oliveira Pena J, Badesch DB. Sotatercept for the treatment of pulmonary arterial hypertension: PULSAR open-label extension. Eur Respir J. 2023;61(1):2201347.
6. Hoeper MM, Badesch DB, Ghofrani HA, Gibbs JSR, Gomberg-Maitland M, McLaughlin VV, Preston IR, Souza R, Waxman AB, Grünig E, Kopeć G, Meyer G, Olsson KM, Rosenkranz S, Xu Y, Miller B, Fowler M, Butler J, Koglin J, de Oliveira Pena J, Humbert M. Phase 3 trial of sotatercept for treatment of pulmonary arterial hypertension. N Engl J Med. 2023;388(16):1478–90.
7. Gallardo-Vara E, Ntokou A, Dave JM, Jovin DG, Saddouk FZ, Greif DM. Vascular pathobiology of pulmonary hypertension. J Heart Lung Transplant. 2023;42(5):544–52.
8. Condon DF, Agarwal S, Chakraborty A, Auer N, Vazquez R, Patel H, Zamanian RT, de Jesus Perez VA. Novel mechanisms targeted by drug trials in pulmonary arterial hypertension. Chest. 2022;161(4):1060–72.
9. Divers C, Platt D, Wang E, Lin J, Lingohr-Smith M, Mathai SC. A review of clinical trial endpoints of patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension and how they relate to patient outcomes in the United States. J Manag Care Spec Pharm. 2017;23(1):92–104.
10. Driessen RS, Danad I, Stuijfzand WJ, Raijmakers PG, Schumacher SP, van Diemen PA, Leipsic JA, Knuuti J, Underwood SR, van de Ven PM, van Rossum AC, Taylor CA, Knaapen P. Comparison of coronary computed tomography angiography, fractional flow reserve, and perfusion imaging for ischemia diagnosis. J Am Coll Cardiol. 2019;73(2):161–73.
11. Hasan ME, Mostafa F, Hossain MS, Loftin J. Machine-learning classification models to predict liver cancer with explainable AI to discover associated genes. AppliedMath. 2023;3(2):417–45.
12. Manogaran G, Vijayakumar V, Varatharajan R, Malarvizhi Kumar P, Sundarasekar R, Hsu CH. Machine learning based big data processing framework for cancer diagnosis using hidden Markov model and GM clustering. Wireless Pers Commun. 2018;102:2099–116.
13. Ye F, Jiang W, Lin W, Wang Y, Chen H, Zou H, Huang S, Zhu N, Han S. A novel BMPR2 mutation in a patient with heritable pulmonary arterial hypertension and suspected hereditary hemorrhagic telangiectasia: a case report. Medicine. 2020;99(31):e21342.
14. Taha F, Southgate L. Molecular genetics of pulmonary hypertension in children. Curr Opin Genet Dev. 2022;75:101936.
15. Wang A, Cao S, Aboelkassem Y, Valdez-Jasso D. Quantification of uncertainty in a new network model of pulmonary arterial adventitial fibroblast pro-fibrotic signalling. Philos Trans R Soc, A. 2020;378(2173):20190338.
16. Tang S, Liu Y, Liu B. Integrated bioinformatics analysis reveals marker genes and immune infiltration for pulmonary arterial hypertension. Sci Rep. 2022;12(1):10154.
17. Adua E. Decoding the mechanism of hypertension through multiomics profiling. J Hum Hypertens. 2023;37(4):253–64.

18. Rhodes CJ, Sweatt AJ, Maron BA. Harnessing big data to advance treatment and understanding of pulmonary hypertension. Circ Res. 2022;130(9):1423–44.
19. Lopez-Crisosto C, Arias-Carrasco R, Sepulveda P, Garrido-Olivares L, Maracaja-Coutinho V, Verdejo HE, Castro PF, Lavandero S. Novel molecular insights and public omics data in pulmonary hypertension. Bioch et Biophy Acta. 2021;1867(10):166200.
20. Oldham WM, Hemnes AR, Aldred MA, Barnard J, Brittain EL, Chan SY, Cheng F, Cho MH, Desai AA, Garcia JGN, Geraci MW, Ghiassian SD, Hall KT, Horn EM, Jain M, Kelly RS, Leopold JA, Lindstrom S, Modena BD, Nichols WC, Rhodes CJ, Sun W, Sweatt AJ, Vanderpool RR, Wilkins MR, Wilmot B, Zamanian RT, Fessel JP, Aggarwal NR, Loscalzo J, Xiao L. NHLBI-CMREF workshop report on pulmonary vascular disease classification. J Am Coll Cardiol. 2021;77(16):2040–52.
21. Kedzierski P. Precision medicine: the future of diagnostic approach to pulmonary hypertension? Anato J Cardiol. 2019;22(4):168.
22. Hemnes AR. Using omics to understand and treat pulmonary vascular disease. Front Med. 2018;5:157A.
23. Schwab JD, Kühlwein SD, Ikonomi N, Kühl M, Kestler HA. Concepts in Boolean network modeling: what do they all mean? Comput Struct Biotechnol J. 2020;18:571–82.
24. Schäfer A, Gjerga E, Welford RW, Renz I, Lehembre F, Groenen PM, Saez-Rodriguez J, Aebersold R, Gstaiger M. Elucidating essential kinases of endothelin signalling by logic modelling of phosphoproteomics data. Mol Syst Biol. 2019;15(8):e8828.
25. Terfve CDA, Wilkes EH, Casado P, Cutillas PR, Saez-Rodriguez J. Large-scale models of signal propagation in human cells derived from discovery phosphoproteomic data. Nat Commun. 2015;6(1):8033.
26. Xu W, Janocha AJ, Erzurum SC. Metabolism in pulmonary hypertension. Annu Rev Physiol. 2021;83:551–76.
27. Watson E, Yilmaz LS, Walhout AJM. Understanding metabolic regulation at a systems level: metabolite sensing, mathematical predictions, and model organisms. Annu Rev Genet. 2015;49(1):553–75.
28. Montañez R, Rodríguez-Caso C, Sánchez-Jiménez F, Medina MÁ. In silico analysis of arginine catabolism as a source of nitric oxide or polyamines in endothelial cells. Amino Acids. 2008;34:223–9.
29. Bueno M, Wang J, Mora AL, Gladwin MT. Nitrite signaling in pulmonary hypertension: mechanisms of bioactivation, signaling, and therapeutics. Anti Redox Signa. 2013;18(14):1797–809.
30. Pullamsetti SS, Mamazhakypov A, Weissmann N, Seeger W, Savai R. Hypoxia-inducible factor signaling in pulmonary hypertension. J Clin Invest. 2020;130(11):5638–51.
31. Dai Z, Zhu MM, Peng Y, Machireddy N, Evans CE, Machado R, Zhang X, Zhao YY. Therapeutic targeting of vascular remodeling and right heart failure in pulmonary arterial hypertension with a HIF-2α inhibitor. Am J Respir Crit Care Med. 2018;198(11):1423–34.
32. Qutub AA, Popel AS. Reactive oxygen species regulate hypoxia-inducible factor 1α differentially in cancer and ischemia. Mol Cell Biol. 2008;28(16):5106–19.
33. Zhao C, Popel AS. Computational model of microRNA control of HIF-VEGF pathway: insights into the pathophysiology of ischemic vascular disease and cancer. PLoS Comput Biol. 2015;11(11):e1004612.
34. Weinstein N, Mendoza L, Gitler I, Klapp J. A network model to explore the effect of the micro-environment on endothelial cell behavior during angiogenesis. Front Physiol. 2017;8:960.
35. Salavati H, Soltani M. The impact of endothelial cells proliferation in a multiscale realistic reproduction of angiogenesis. Biochem Eng J. 2019;142:74–83.
36. Song M, Finley SD. Mechanistic characterization of endothelial sprouting mediated by pro-angiogenic signaling. Microcirculation. 2022;29(2):e12744.
37. Thorne BC, Hayenga HN, Humphrey JD, Peirce SM. Toward a multi-scale computational model of arterial adaptation in hypertension: verification of a multi-cell agent based model. Front Physiol. 2011;2:20.
38. Cogno N, Bauer R, Durante M. A 3D Agent-Based model of lung fibrosis. Symmetry. 2022;14(1):90.
39. Vélez-Rendón D, Zhang X, Gerringer J. Compensated right ventricular function of the onset of pulmonary hypertension in a rat model depends on chamber remodeling and contractile augmentation. Pulm Circ. 2018;8(4):2045894018800439.
40. Vélez-Rendón D, Pursell ER, Shieh J, Valdez-Jasso D. Relative contributions of matrix and myocytes to biaxial mechanics of the right ventricle in pulmonary arterial hypertension. J Biomech Eng. 2019;141(9):091011.
41. Kwan ED, Vélez-Rendón D, Zhang X, Mu H, Patel M, Pursell E, Stowe J, Valdez-Jasso D. Distinct time courses and mechanics of right ventricular hypertrophy and diastolic stiffening in a male rat model of pulmonary arterial hypertension. American J Physiol Heart Circ Physiol. 2021;321(4):H702–15.
42. Avazmohammadi R, Mendiola EA, Li DS, Vanderslice P, Dixon RAF, Sacks MS. Interactions between structural remodeling and hypertrophy in the right ventricle in response to pulmonary arterial hypertension. J Biomech Eng. 2019;141(9):091016.
43. Attard MI, Dawes TJW, de Marvao A, Biffi C, Shi W, Wharton J, Rhodes CJ, Ghataorhe P, Gibbs JSR, Howard LSGE, Rueckert D, Wilkins MR, O'Regan DP. Metabolic pathways associated with right ventricular adaptation to pulmonary hypertension: 3D analysis of cardiac magnetic resonance imaging. Euro Heart J Cardiovas Imag. 2019;20(6):668–76.
44. Marquis AD, Jezek F, Pinsky DJ, Beard DA. Hypoxic pulmonary vasoconstriction as a regulator of alveolar-capillary oxygen flux: a computational model of ventilation-perfusion matching. PLoS Comput Biol. 2021;17(5):e1008861.
45. Georges T, Menu P, Le Blanc C. Contribution of hypoxic exercise testing to predict high-altitude pathology: a systematic review. Life Basel Switz. 2022;12(3):377.
46. Ben-Tal A. Simplified models for gas exchange in the human lungs. J Theor Biol. 2006;238(2):474–95.
47. Jiang S, Fu Z, Li P, Shen Y, Su Q, Cai G, Ning G. A model of the pulmonary acinar circulatory system with gas exchange function to explore the influence of alveolar diameter. Respir Physiol Neurobiol. 2022;300:103883.

48. Reynolds A, Bard Ermentrout G, Clermont G. A mathematical model of pulmonary gas exchange under inflammatory stress. J Theor Biol. 2010;264(2):161–73.
49. Neelakantan S, Xin Y, Gaver DP, Cereda M, Rizi R, Smith BJ, Avazmohammadi R. Computational lung modelling in respiratory medicine. J R Soc Interface. 2022;19(191): 20220062.
50. Fukui Y, Smith NT. Interactions among ventilation, the circulation and the uptake and distribution of Halothane—use of a hybrid computer multiple model. Anesthesiology. 1981;54(2):107–18.
51. Clipp R, Scott G. Humansim: a physiology engine for the simulation of anesthesia/anaphylaxis. Military Health Research Symposium. 2012.
52. S. P. Toxicological screening. J Pharmacol Pharmacothera. 2011;2(2):74–9.
53. DILIsym®. DILIsym [Internet]. [cited 2023 Nov 16]. Available from: https://www.simulations-plus.com/software/dilisym/
54. Mischnik M, Hubertus K, Geiger J, Dandekar T, Timmer J. Dynamical modelling of prostaglandin signalling in platelets reveals individual receptor contributions and feedback properties. Mol BioSyst. 2013;9(10):2520–9
55. Wangorsch G, Butt E, Mark R, Hubertus K, Geiger J, Dandekar T, Dittrich M. Time-resolved in silico modeling of fine-tuned cAMP signaling in platelets: feedback loops, titrated phosphorylations and pharmacological modulation. BMC Syst Biol. 2011;5:178.
56. Garmaroudi FS, Handy DE, Liu YY, Loscalzo J. Systems pharmacology and rational polypharmacy: nitric oxide–cyclic GMP signaling pathway as an illustrative example and derivation of the general case. PLoS Comput Biol. 2016;12(3):e1004822.
57. Kim TH, Shin S, Jeong SW, Lee JB, Shin BS. Physiologically relevant in vitro-in vivo correlation (ivivc) approach for sildenafil with site-dependent dissolution. Pharmaceutics. 2019;11(6):251.
58. Sato M, Toshimoto K, Tomaru A, Yoshikado T, Tanaka Y, Hisaka A, Lee W, Sugiyama Y. Physiologically based pharmacokinetic modeling of bosentan identifies the saturable hepatic uptake as a major contributor to its nonlinear pharmacokinetics. Drug Metab Dispos. 2018;46(5):740–8
59. Farber HW, Miller DP, McGoon MD, Frost AE, Benton WW, Benza RL. Predicting outcomes in pulmonary arterial hypertension based on the 6-minute walk distance. J Heart Lung Transplant. 2015;34(3):362–8.
60. Gaine S, Simonneau G. The need to move from 6-minute walk distance to outcome trials in pulmonary arterial hypertension. Eur Respir Rev. 2013;22(130):487–94.
61. Waxman AB, Farber HW. Using clinical trial end points to risk stratify patients with pulmonary arterial hypertension. Circulation. 2015;132(22):2152–61.
62. Chin KM, Rubin LJ, Channick R, Di Scala L, Gaine S, Galiè N, Ghofrani HA, Hoeper MM, Lang IM, McLaughlin VV, Preiss R, Simonneau G, Sitbon O, Tapson VF. Association of N-Terminal pro brain natriuretic peptide and Long-Term outcome in patients with pulmonary arterial hypertension. Circulation. 2019;139(21):2440–50
63. Wronski SL, Mordin M, Kelley K, Anguiano RH, Classi P, Shen E, Manaker S. The role of noninvasive endpoints in predicting long-term outcomes in pulmonary arterial hypertension. Lung. 2020;198(1):65–86.
64. Sitbon O, Chin KM, Channick RN, Benza RL, Di Scala L, Gaine S, Ghofrani HA, Lang IM, McLaughlin VV, Preiss R, Rubin LJ, Simonneau G, Tapson VF, Galiè N, Hoeper MM. Risk assessment in pulmonary arterial hypertension: insights from the GRIPHON study. J Heart Lung Transplant. 2020;39(4):300–9.
65. Philip JL, Pewowaruk RJ, Chen CS, Tabima DM, Beard DA, Baker AJ, Chesler NC. Impaired myofilament contraction drives right ventricular failure secondary to pressure overload: model simulations, experimental validation, and treatment predictions. Front Physiol. 2018;9:731.
66. Colebank MJ, Qureshi MU, Rajagopal S, Krasuski RA, Olufsen MS. A multiscale model of vascular function in chronic thromboembolic pulmonary hypertension. American J Physiol Heart Circ Physiol. 2021;321(2):H318–38.
67. Colunga AL, Colebank MJ, Olufsen MS. Parameter inference in a computational model of haemodynamics in pulmonary hypertension. J R Soc Interface. 2023;20(200):20220735.
68. Warsinske HC, Wheaton AK, Kim KK, Linderman JJ, Moore BB, Kirschner DE. Computational modeling predicts simultaneous targeting of fibroblasts and epithelial cells is necessary for treatment of pulmonary fibrosis. Front Pharmacol. 2016;7:183
69. Hao W, Marsh C, Friedman A. A mathematical model of idiopathic pulmonary fibrosis. PLoS One. 2015;10(9):e0135097.
70. Sack KL, Dabiri Y, Franz T, Solomon SD, Burkhoff D, Guccione JM. Investigating the role of interventricular interdependence in development of right heart dysfunction during LVAD support: a patient-specific methods-based approach. Front Physiol. 2018;9:520
71. Holford N, Ma SC, Ploeger BA. Clinical trial simulation: a review. Clin Pharm Ther. 2010;88(2):166–82.
72. Pappalardo F, Russo G, Tshinanu FM, Viceconti M. In silico clinical trials: concepts and early adoptions. Brief. Bioinform. 2019;20(5):1699–708.
73. Aarons L, Karlsson MO, Mentré F, Rombout F, Steimer JL, van Peer A. Role of modelling and simulation in Phase I drug development. Eur J Pharm Sci. 2001;13(2):115–22.
74. Gadkar K, Budha N, Baruch A, Davis JD, Fielder P, Ramanujan S. A mechanistic systems pharmacology model for prediction of LDL cholesterol lowering by PCSK9 antagonism in human dyslipidemic Populations. CPT. 2014;3(11):e149
75. Dai W, Rao R, Sher A, Tania N, Musante CJ, Allen R. A prototype QSP model of the immune response to SARS-CoV-2 for community development. CPT. 2021;10(1):18–29.
76. Rao R, Musante CJ, Allen R. A quantitative systems pharmacology model of the pathophysiology and treatment of COVID-19 predicts optimal timing of pharmacological interventions. NPJ Syst Biol Appl. 2023;9(1):13
77. Kovatchev BP, Breton M, Dalla Man C. In silico preclinical trials: a proof of concept in closed-loop control of type 1 diabetes. Los Angeles, CA: SAGE Publications Sage CA; 2009.
78. Hon C, Patel M, Doan J. Integrated review: Xenpozyme [Internet]. Silver Spring. 2022. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761261Orig1s000IntegratedR.pdf

79. European Medicines Agency (NL). Assessment report: Xenpozyme [Internet]. Amsterdam (NL): European Medicines Agency. 2022. [cited 2023 Nov 15]. Available from https://www.ema.europa.eu/en/documents/assessment-report/xenpozyme-epar-public-assessment-report_en.pdf
80. Allen R, Rieger T, Musante C. Efficient generation and selection of virtual populations in quantitative systems pharmacology models. CPT. 2016;5(3):140–6.
81. Cheng Y, Thalhauser CJ, Smithline S, Pagidala J, Miladinov M, Vezina HE, Gupta M, Leil TA, Schmidt BJ. QSP toolbox: computational implementation of integrated workflow components for deploying multi-scale mechanistic models. AAPS J. 2017;19:1002–16.
82. Rieger TR, Allen RJ, Bystricky L, Chen Y, Colopy GW, Cui Y, Gonzalez A, Liu Y, White RD, Everett RA, Banks HT, Musante CJ. Improving the generation and selection of virtual populations in quantitative systems pharmacology models. Prog Biophys Mol Biol. 2018;139:15–22.
83. Sinisi S, Alimguzhin V, Mancini T. Complete populations of virtual patients for in silico clinical trials. Bioinformatics. 2020;36(22–23):5465–72.
84. Tang Y, Hoffmann A. Quantifying information of intracellular signaling: progress with machine learning. Rep Prog Phys. 2022;85(8):086602. https://doi.org/10.1088/1361-6633/ac7a4a
85. Cavadas MA, Nguyen LK, Cheong A. Hypoxia-inducible factor (HIF) network: insights from mathematical models. Cell Commun Signaling. 2013;11(1):42.
86. Kardynska M, Kogut D, Pacholczyk M, Smieja J. Mathematical modeling of regulatory networks of intracellular processes—aims and selected methods. Comput Struct Biotechnol J. 2023;21:1523–32.
87. Buerk DG. Can we model nitric oxide biotransport? A survey of mathematical models for a simple diatomic molecule with surprisingly complex biological activities. Annu Rev Biomed Eng. 2001;3(1):109–43.
88. Crawshaw JR, Flegg JA, Bernabeu MO, Osborne JM. Mathematical models of developmental vascular remodelling: a review. PLoS Comput Biol. 2023;19(8):e1011130.
89. Stepanova D, Byrne HM, Maini PK, Alarcón T. Computational modeling of angiogenesis: the importance of cell rearrangements during vascular growth. WIREs Mech Dis. 2024;16(2):e1634.
90. Hastings JF, Skhinas JN, Fey D, Croucher DR, Cox TR. The extracellular matrix as a key regulator of intracellular signalling networks. Br J Pharmacol. 2019;176(1):82–92.
91. Kheyfets VO, O'Dell W, Smith T. Considerations for numerical modeling of the pulmonary circulation—a review with a focus on pulmonary hypertension. J Biomech Eng. 2013;135(6):061011. https://doi.org/10.1115/1.4024141
92. Yoshida K, Holmes JW. Computational models of cardiac hypertrophy. Prog Biophys Mol Biol. 2021;159:75–85.
93. Jones CB, Crossland DS. The interplay between pressure, flow, and resistance in neonatal pulmonary hypertension. Sem Fetal and Neo Med. 2022;27(4):101371.
94. Odeigah OO, Valdez-Jasso D, Wall ST. Computational models of ventricular mechanics and adaptation in response to right-ventricular pressure overload. Front Physiol. 2022;13:948936. https://www.frontiersin.org/journals/physiology/articles/10.3389/fphys.2022.948936
95. Beni HM, Mortazavi H, Islam MS. Biomedical and biophysical limits to mathematical modeling of pulmonary system mechanics: a scoping review on aerosol and drug delivery. Biomech Model Mechanobiol. 2022;21(1):79–87.
96. Duarte D, Vale N. Evaluation of synergism in drug combinations and reference models for future orientations in oncology. Curr Res Pharmacol Drug Dis. 2022;3:100110.
97. Sahai N, Gogoi M, Ahmad N. Mathematical modeling and simulations for developing nanoparticle-based cancer drug delivery systems: a review. Curr Pathobiol Rep. 2021;9(1):1–8.
98. Jose J, S. S, Mathew B, Parambi DGT. In silico trial approach for biomedical products: a regulatory perspective. Comb Chem High Through Screen. 2022;25(12):1991–2000.
99. Hasan MR, Alsaiari AA, Fakhurji BZ, Molla MHR, Asseri AH, Sumon MAA, Park MN, Ahammad F, Kim B. Application of mathematical modeling and computational tools in the modern drug design and development process. Molecules. 2022;27(13):4169.
100. Vélez-Rendón D, Valdez-Jasso D. Multiscale modeling of ventricular–vascular dysfunction in pulmonary arterial hypertension. Curr Opin Biomed Engine. 2019;11:68–75.
101. Leonard-Duke J, Evans S, Hannan RT, Barker TH, Bates JHT, Bonham CA, Moore BB, Kirschner DE, Peirce SM. Multi-scale models of lung fibrosis. Matrix Biol. 2020;91–92:35–50.
102. Stalidzans E, Zanin M, Tieri P, Castiglione F, Polster A, Scheiner S, Pahle J, Stres B, List M, Baumbach J, Lautizi M, Van Steen K, Schmidt HHHW. Mechanistic modeling and multiscale applications for precision Medicine: theory and practice. Net Syst Med. 2020;3(1):36–56.
103. Hemedan AA, Niarakis A, Schneider R, Ostaszewski M. Boolean modelling as a logic-based dynamic approach in systems medicine. Comput Struct Biotechnol J. 2022;20:3161–72.
104. Barbuti R, Gori R, Milazzo P, Nasti L. A survey of gene regulatory networks modelling methods: from differential equations, to Boolean and qualitative bioinspired models. J Memb Comput. 2020;2(3):207–26.
105. Saadatpour A, Albert R. Boolean modeling of biological regulatory networks: a methodology tutorial. Methods. 2013;62(1):3–12.
106. Corti A, Colombo M, Migliavacca F. Multiscale computational modeling of vascular adaptation: a systems biology approach using agent-based models. Front Bioeng Biotechnol. 2021;9:744560. https://www.frontiersin.org/articles/10.3389/fbioe.2021.744560
107. Soheilypour M, Mofrad MRK. Agent-based modeling in molecular systems biology. BioEssays. 2018;40(7):1800020.
108. Macal C, North M. Introductory tutorial: agent-based modeling and simulation. *Proceedings of the Winter Simulation Conference 2014*, Savannah, GA, USA. 2014:6–20. https://ieeexplore.ieee.org/abstract/document/7019874
109. Smallbone K, Mendes P. Large-scale metabolic models: from reconstruction to differential equations. Ind Biotechnol. 2013;9(4):179–84.

110. Faizal WM, Ghazali NNN, Khor CY, Badruddin IA, Zainon MZ, Yazid AA, Ibrahim NB, Razi RM. Computational fluid dynamics modelling of human upper airway: a review. Comput Meth Prog Biom. 2020;196:105627.
111. Kanelidis AJ, Raikhelkar J, Kim G, Sayer G, Bishop MR, Polonsky TS, Uriel N. CardioMEMS-Guided CAR T cell therapy for lymphoma in a patient with Anthracycline-Induced cardiomyopathy. JACC: CardioOncology. 2020;2(3):515–8.
112. Howard LS, Rosenkranz S, Frantz RP, Hemnes AR, Pfister T, Hsu Schmitz SF, Skåra H, Humbert M, Preston IR. Assessing daily life physical activity by actigraphy in pulmonary arterial hypertension: insights from the randomized controlled study with selexipag (TRACE). Chest. 2023;163(2):407–18.

How to cite this article: Walker M, Moore H, Ataya A, Pham A, Corris PA, Laubenbacher R, Bryant AJ. A perfectly imperfect engine: utilizing the digital twin paradigm in pulmonary hypertension. Pulm Circ. 2024;14:e12392. https://doi.org/10.1002/pul2.12392