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Review

Machine Learning for Cardiovascular Biomechanics Modeling: Challenges and Beyond

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Abstract—Recent progress in machine learning (ML), together with advanced computational power, have provided new research opportunities in cardiovascular modeling. While classifying patient outcomes and medical image segmentation with ML have already shown significant promising results, ML for the prediction of biomechanics such as blood flow or tissue dynamics is in its infancy. This perspective article discusses some of the challenges in using ML for replacing well-established physics-based models in cardiovascular biomechanics. Specifically, we discuss the large landscape of input features in 3D patient-specific modeling as well as the high-dimensional output space of field variables that vary in space and time. We argue that the end purpose of such ML models needs to be clearly defined and the tradeoff between the loss in accuracy and the gained speedup carefully interpreted in the context of translational modeling. We also discuss several exciting venues where ML could be strategically used to augment traditional physics-based modeling in cardiovascular biomechanics. In these applications, ML is not replacing physics-based modeling, but providing opportunities to solve ill-defined problems, improve measurement data quality, enable a solution to computationally expensive problems, and interpret complex spatiotemporal data by extracting hidden patterns. In summary, we suggest a strategic integration of ML in cardiovascular biomechanics modeling where the ML model is not the end goal but rather a tool to facilitate enhanced modeling.

Keywords—Scientific machine learning, Data-driven modeling, Physics-based modeling, Deep learning, Hemodynamics.

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INTRODUCTION

Recent advances in data science, computational power, and open-source software have sparked an ever-increasing interest in using machine learning (ML) for physics-based modeling. ML models are generally designed to learn hidden patterns in data and use the learned representations to make predictions *via* interpolation or extrapolation in cases where a universal law is learned. In particular, deep learning is a class of ML models, which is popular in physics-based modeling due to the complexity of physics-based problems. In theory, one can design and train deep neural networks to represent any nonlinear and high-dimensional function.[1] Deep neural networks usually work well for complex function approximation problems including challenging non-convex optimizations, which is often considered magic of deep learning where over-parameterized optimization problems often converge to the global minimum.[110] This perhaps non-intuitive feature of deep learning together with the success of stochastic gradient descent applied to large data has led to successful examples of deep learning in various fields. In biomechanics, this is an attractive approach because biomechanics problems are highly nonlinear and deep learning generally is the preferred learning method when trying to learn complex processes.

In cardiovascular biomechanics modeling, a question comes to mind: Can deep learning replace traditional computational or experimental physics-based

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biomechanics models? Imagine we are interested in modeling blood flow in aneurysms or the structural stress in heart valves. The goal is to take a representation of the geometry, boundary conditions, and constitutive parameters as input and quantify physical parameters of interest such as the stress tensor fields or velocity/displacement vector fields. In an ideal setting, a deep learning model that has been trained over the landscape of all possible combinations in geometry, boundary conditions, and parameters of interest could achieve this task. The problem could also be simplified by fixing some of the features. For example, one could fix the geometry and the pressure loading applied to a heart valve leaflet and vary its constitutive parameters to learn its biomechanical response. In general, we need to realize that many of these problems are high-dimensional input-output problems. For example, the large landscape of all possible aneurysm geometries (input) and the corresponding spatiotemporally resolved velocity field (output) make directly finding such high-dimensional end-to-end ML representations a very tedious and challenging task.

In this article, while we discuss applications where ML has high potential for improving current cardiovascular biomechanics approaches, we also argue that in many cardiovascular biomechanics examples, the modeling community needs to be aware of the pitfalls of using ML for the sole purpose of replacing well-established physics-based solvers such as the finite-element or finite-volume method. We further argue that ML models should be strategically designed to provide results that cannot be readily achieved with traditional methods. A nice feature of ML models is that once trained, they can make predictions rapidly with minimal computing time. However, this seemingly amazing advantage should be critically interpreted: Is this feasible for all cardiovascular biomechanics problems? At what cost do we achieve this? When is this fast prediction needed in practical problems? Do we lose the high fidelity needed in translational patient-specific biomechanics modeling? How do we quantify the uncertainty and reliability of the ML models? We will try to answer these questions in this perspective article. Our goal is to promote the notion that ML is a tool that can help us solve ill-defined physics-based cardiovascular biomechanics problems or facilitate further downstream tasks where fast computational approaches are essential. We will only discuss ML in cardiovascular biomechanics modeling of field variables such as blood flow velocity or structural stress. There are other examples of ML in cardiovascular biomechanics modeling, which will not be discussed here. For example, ML could be used in predicting cardiovascular disease outcomes based on biomechanics simulations,[19,20,54] which at least, in theory, is an easier task because of the binary nature of the output (vs. spatiotemporally varying vectorial/tensorial variables in physics-based modeling). Additionally, automating image segmentation for creating 3D computer models is another successful application of ML in cardiovascular biomechanics modeling.[16,53,56,62,63] A summary of this perspective article is shown in Fig. 1.

CHALLENGES IN REPLACING TRADITIONAL BIOMECHANICS SOLVERS WITH MACHINE LEARNING

In this section, we will discuss some of the challenges and pitfalls of using ML to replace an established and well-defined (all parameters known) physics-based model.

Cardiovascular Biomechanics Problems have a Large Landscape of Input Variables

Suppose we want to use ML to replace a traditional continuum biomechanics model such as the finite element method (FEM). In that case, we need to realize what constitutes a well-defined FEM problem. As an input to an FEM problem, we need a discrete representation of the geometry, boundary conditions, and constitutive material properties. Recent studies have attempted to build ML models that produce blood flow data based on some of these features.[35,72] While these studies are interesting, generalization to a broad array of input features remains challenging. In patient-specific biomechanics applications, each of these inputs could possess large variability. For example, aneurysmal diseases (e.g., cerebral or aortic) lead to very complex 3D morphologies. Prior attempts in characterizing their geometry have revealed the complexity in geometric features.[73,109] Alternatively, occlusive diseases, such as, vulnerable coronary artery plaques or peripheral vascular disease can also create very complex shapes.[74,80,118] The complexity in patient-specific morphology makes it very difficult to develop ML models that can appropriately represent all morphologies. Additionally, the boundary conditions could represent significant variability. Consider a pulsatile volumetric flow rate waveform that is typically used as the inlet boundary condition in computational fluid dynamics (CFD) models of blood flow or a transvalvular pressure waveform that is used in structural mechanics modeling of heart valves. The ML model will need to learn a broad spectrum of physiological variations in the waveform. Finally, while constitutive modeling of blood is usually less variable (e.g., an established constant viscosity or non-Newtonian model), vascular tissues often possess nonlinear,

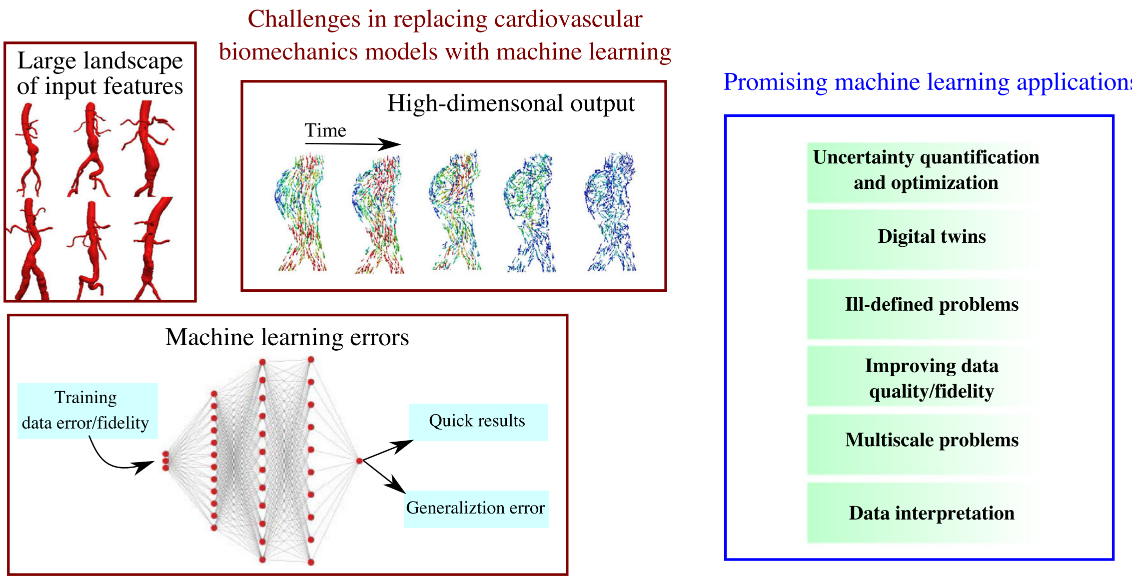

FIGURE 1. Replacing a well-established cardiovascular biomechanics model of field variables with machine learning is challenging and tedious in most cases. On the other hand, machine learning could be used to augment traditional modeling and enable solution to difficult problems.

anisotropic properties that could vary from patient to patient, within one patient based on the location,[94] as a result of mechanical forces such as pressure,[106] and finally during the course of disease progression. What makes all of these challenges worse is that the combined effect of these features on the biomechanical output is nonlinear. Therefore, a broadly applicable ML model may need to learn vast physiologically-possible combinations of these features (at least in the range of interest) to enable reliable interpolations or mild extrapolations in the extremely high-dimensional input space. Finding a reduced-order representation of these input features is one approach to mitigate some of these challenges. For example, statistical shape modeling based on the principal component analysis (PCA) discovers a mapping to a hidden reduced-order space that can explain the geometric features more efficiently.[22,29,52]

Cardiovascular Biomechanics Problems Result in High-Dimensional Output Fields

In physics-based biomechanics modeling, we are interested in tensor fields (e.g., structural stress tensor) and vector fields (e.g., blood flow velocity or wall shear stress vector field). In 3D patient-specific applications, these outputs are high-dimensional fields that vary in space and time. That is, we need to have a good ML model that can learn vectors/tensors that not only have more than one variable but also could have complex spatial and temporal variations. Although successful ML model development has been witnessed in certain applications such as predicting pressure drop across an aortic valve or a stenosed vessel (e.g., fractional flow reserve), where the output is a single scalar,[28,52] developing a ML model to replace full-fidelity numerical solvers by directly learning a mapping between the aforementioned high-dimensional input feature space and output solution space remains very challenging. ML models have been proposed for predicting structural stress tensor[69] or blood flow velocity vector fields[72] with quasi-static and steady assumptions. Admittedly, the rapid development of advanced learning architectures based on graphs has enabled end-to-end spatiotemporal learning on mesh-based high-dimensional data to certain extent. For instance, MeshGraphNet by DeepMind has demonstrated scalable predictions of spatiotemporal dynamics of a wide range of physical systems in an end-to-end manner,[92] and a recently proposed discretization-aware graph net has been successfully tested on complex turbulent combustion-reaction applications over multiple scales of mesh resolution.[124] However, the end-to-end learning of high-dimensional input/output relation is still a very challenging task and has a long way to go, particularly when it comes to 3D patient-specific cardiovascular simulations as mentioned above. Table 1 summarizes some of the studies that have used ML to predict hemodynamics. It could be seen that most studies have either used simplifying assumptions and/or have focused on simplified output variables.

TABLE 1. Representative studies performing machine learning modeling of hemodynamics in different cardiovascular biomechanics problems.

Study	Application	Sample size	Predicted measures	Spatiotemporal?	Scalar/vector	Accuracy	Assumptions
Feiger *et al.*[35]	Aortic coarctation	One patient (varied stenosis degree, viscosity, and flow rate)	ΔP and circumferentially averaged WSS	No (single value)	Scalar	Mean error: 1.18 mmHG for ΔP and 0.99 Pa for WSS	–
Fossan *et al.*[39]	Coronary artery	64 patients	FFR	No (single value)	Scalar	Error: 0.005 ± 0.021	Steady flow. Combined deep learning model with ROM
Rengarajan *et al.*[100]	Abdominal aortic aneurysm	148 patients	Spatially averaged wall stress	No (single value)	Scalar	17% mean relative error	Simple and fixed constitutive equation
Yevtushenko *et al.*[125]	Aortic coarctation	228 patients and 3000 synthetic patients	Velocity and pressure	Locally averaged along centerline	Scalar	1.8 ± 5.6 mmHG for pressure excluding outliers	Steady flow.
Liang *et al.*[70]	Thoracic aorta	25 patients and 729 synthetic patients	Velocity and pressure	Spatial field	Vector and scalar	1.96% error for velocity and 1.42% error for pressure	Steady flow and low resolution mesh (150–350 K elements)
Su *et al.*[113]	Coronary artery	2000 idealized geometries	WSS magnitude	Spatial field	Scalar	2.5% error	Steady flow and idealized models
Li *et al.*[72]	CABG and aorta	110 patients and 1100 synthetic patients	Velocity and pressure	Spatial field	Vector and scalar	10% error	Steady flow

ΔP Pressure drop, *WSS* wall shear stress, *FFR* fractional flow reserve, *ROM* reduced-order model, *CABG* Coronary artery bypass graft.

Learning the Output with Respect to One Input Feature or Specific Input Variations

One possible way to mitigate the above challenges is to focus on just varying specific input parameters. For example, if we focus on one specific patient, the geometry could be fixed, and the ML model could learn how the biomechanics fields such as stress and velocity vary as a function of the boundary conditions. Further, one could also simplify the output fields. For instance, in predicting aneurysm rupture or aortic dissection, one might be interested in finding the peak stress instead of its spatiotemporal distribution. Collectively, these will significantly reduce the complexity of the ML model and provide a more feasible setting for developing ML representations of the biological system. However, some critical issues need to be considered. When do we need a model to make a rapid prediction when specific parameters are varied? In addition to justifying the need for rapid prediction, we need to understand the sources of error in our ML model. After all, the ML model is generally built based on data produced from physics-based simulations so at best it could have accuracy as good as the training data. Additionally, we need to make sure that the speedup gained by the ML model is actually needed in practice. These issues will be discussed next.

Sources of Error in Developing a Machine Learning Representation in Cardiovascular Biomechanics

A purely data-driven ML model relies on training data to learn a mapping between the input parameters and the output. Therefore, at best the ML model can hope to achieve an accuracy as good as the training data. The challenge here is that high-fidelity 3D computational models are expensive. For examples, high-fidelity CFD models of blood flow often involve O(1–10) millions elements and O(10^3–10^4) time-steps per cardiac cycle.[4,60] Based on the authors' experience, performing high-resolution computational cardiovascular biomechanics modeling on a high-performance computing cluster (e.g., with 40–60 CPUs) typically takes 2–3 days on average. As a result, doing hundreds of simulations to create a large training dataset is computationally prohibitive unless a compromise is made in the fidelity of the computational model to reduce the computational cost. For example, steady simulations are performed or a low-resolution (therefore less accurate) CFD strategy is adapted to reduce the cost. Pretraining on low-fidelity data and subsequently using the gained knowledge to train with high-fidelity simulations using transfer learning is a promising approach to mitigate the high computational cost issue,[68] however, the success of transfer learning in complex 3D patient-specific problems remains to be investigated.

Generalization error is a common issue in ML models. A ML model that has been trained appropriately should have a small generalization error. However, this is only true if the new input data falls within the landscape of the training data. ML models are better at interpolation but are generally not reliable for extrapolating outside of the landscape of the training data. Therefore, it is important to ensure that the training dataset covers an appropriate combination of the input parameters that ultimately represent the input parameters of interest.

Tradeoff Between Accuracy and Speed: Which One is Preferred in Translating Biomechanics Models?

Based on the above discussion, we need to first answer an important question before considering ML as an alternative to an established physics-based biomechanics model: Is the speedup gained by the ML model (once trained) worth the loss in accuracy? From a translational biomechanics modeling perspective, the clinical application of the developed biomechanics model needs to be considered. For example, in planning aneurysm surgery or coronary artery disease treatment, do clinicians need results immediately, or can they afford to get the results in 2 days? What level of accuracy do they need? Ultimately, there is a tradeoff between accuracy and speed. An established continuum biomechanics model can produce more accurate results but will be more time-consuming compared to a previously trained ML model that can produce results quickly.

Final Thoughts

We recommend approaching ML modeling with a clear ultimate goal in mind. The speedup gained in these models needs to be interpreted in the context of the potential loss in accuracy based on how the input variables can vary. We suggest that ML models be used in these scenarios: 1. The speedup gained by the ML model compared to the physics-based model is necessary for clinical decision making. 2. The ML model enables a solution to problems where a traditional biomechanics model cannot readily achieve. 3. The ML model facilitates further downstream tasks that cannot be efficiently performed by a physics-based model. We will discuss items two and three in the next section.

WHEN ARE MACHINE LEARNING MODELS MORE USEFUL FOR PHYSICS-BASED BIOMECHANICS MODELING?

In this section, we will discuss some promising applications of ML where traditional physics-based cardiovascular biomechanics models have difficulty. Finally, we argue that finding a ML representation in cardiovascular biomechanics modeling should not be the ultimate goal but rather a step towards solving problems where traditional models have struggled.

Need for Multiple Evaluations: Uncertainty Quantification and Optimization

Fast predictions are an attractive feature of a trained ML model. In certain modeling applications, we need to run expensive computer models repetitively. Uncertainty quantification (UQ) and optimization are typical examples that are commonly performed in cardiovascular biomechanics modeling.[76,102] For example, extensive work has been done in quantifying the influence of variations in inflow/outflow boundary conditions,[57,77,82,95,116] segmented vessel geometry,[21,26,86,87,103,104] mechanical properties,[17,33,67,91,111] which are often uncertain/unknown in practice. Rigorous UQ frameworks can be formulated by modeling the uncertain inputs as random variables/fields, which are propagated to the outputs of interests *via*, e.g., stochastic collocation methods[10,11,105] or Monte Carlo methods.[71,89,101] If additional indirect observations of the state are available, the uncertainty can be reduced within a Bayesian framework, and unknown variables can be inferred *via* variational optimization. However, these processes usually need large ensembles of forward simulations, especially when the input dimension is high. In most practical scenarios, traditional full-fidelity solvers are computationally infeasible, even with many remedies, e.g., sparse grid,[78,85] multi-resolution expansion,[65,108] or sparsity-promoting techniques.[31,90] To address the challenges in multi-query applications, researchers usually resorted to developing reduced-order models (e.g., lumped parameter model,[41,81] 1D model,[32] Galerkin-projection-based reduced-order model[13,14,75]) or surrogate models (e.g., Gaussian process,[8,59] radial basis[99] *etc*.) with lower accuracy but fast evaluation speed, enabling UQ for complex cardiovascular systems. Nonetheless, most of these traditional model-reduction approaches only focus on global information (e.g., scalar/integral quantities) instead of local information (e.g., spatiotemporal fields of velocity or wall shear stresses), and the latter is critical in many areas of cardiovascular research/healthcare. Deep learning has become a popular surrogate modeling approach and shown great potential to deal with high-dimensional nonlinear UQ problems.[15,43,132,133] These models extend the linear fitting in most data-driven reduced-order models, easily incorporate 3D variability compared to geometric reduced-order models (e.g., 1D and lumped parameter models), and are faster (in the evaluation phase) than reduced-order modeling. Moreover, multi-fidelity strategy (leveraging the efficiency of low-fidelity models and accuracy of high-fidelity models to balance the trade-off of speed and accuracy) has been developed for years and demonstrated effectiveness in UQ and optimization tasks.[18,38] For example, Gao et al. developed a bi-fidelity approach to solve both forward and inverse high-dimensional UQ problems in 3-D patient-specific modeling applications.[44,45] In the multi-fidelity modeling framework, the development of ML models of different fidelities using multi-resolution data, together with a high-fidelity traditional solver, is very promising for maintaining a balance of accuracy and efficiency in high-dimensional many-query UQ and optimization applications.

Interestingly, in many of these problems, the accuracy of the ML model is less crucial compared to its use for deterministic hemodynamics analysis. For example, in forward and inverse UQ applications, Markov chain Monte Carlo (MCMC) is the gold standard Bayesian sampling approach, where ML-based surrogate (e.g., Gaussian process) is widely used to assist the convergence. If ML-surrogate is directly used in likelihood evaluations, the prediction error of ML models could distort the sampled posterior to a certain extent, but the overall probability distribution can be captured reasonably well if the surrogate prediction is not completely wrong.[130] Additionally, in optimization problems, the purpose of model evolution is to obtain the gradient information, guiding the optimization direction (e.g., for gradient descent). Even if the ML-based surrogate model is not as accurate as the full-order model, it can still provide roughly correct gradient direction, enabling efficient optimization. Finally, it should be noted that there is always a trade-off between surrogate predictive accuracy and costs of data generation and training, which can significantly benefit the UQ and optimization tasks that require numerous model queries. For example, MCMC usually requires hundreds of thousands of model evaluations to reach convergence, which justifies the data generation at the cost of hundreds of model evaluations during training.

Solving Ill-Defined Problems

As mentioned above, a common difficulty in patient-specific biomechanics modeling is the lack of information about certain parameters and/or boundary conditions. For example, patient-specific constitutive material properties of the vascular wall or heart are usually not known in structural mechanics finite element analysis, and the inlet flow rate waveform measurement is not available in many patient-specific CFD models. Lack of such data makes these problems ill-defined and not possible to solve using a purely physics-based model. A common approach in the literature is to use population-averaged or idealized data in assigning these parameters, which introduces error.[97,126] It is possible to solve these problems within an "inverse modeling framework" by estimating the unknown parameters with data measured from the patient. In general, data assimilation Bayesian inference methods have been used to combine imperfect experimental measurements with uncertain computational models to obtain more accurate blood flow data (e.g., References 5, 25, 42, and 49). ML models can be very useful in inverse modeling.[79] In addition to being used as a fast surrogate model to enable scalable Bayesian inference and data assimilation, the ML models can also be directly used as inverse models themselves where unknown physical parameters are discovered along with trainable parameters during the training process based on measurement data. For example, one can estimate constitutive material properties based on experimental data.[51] Interestingly, not only the material constants but also the form of the constitutive equation could be learned.[37] It should be noted that in inverse modeling, typically parameters (e.g., material constants) or boundary/initial conditions need to be learned, which exhibit simpler variability compared to the aforementioned spatiotemporal variations in vector/tensor field variables that need to be estimated when ML is replacing a comprehensive forward model.

A more recent ML paradigm that has shown promise in solving hybrid physics-based and data-driven problems is physics-informed neural network (PINN).[58,96] In PINN, the governing partial differential equations are integrated into the deep learning framework where the physical variables of interest such as velocity are represented as a function of space and time. PINN provides an intuitive framework for estimating physical field variables as functions of space and time similar to traditional numerical methods. The nice feature in PINN is that these functions could be approximated to satisfy the governing equations, boundary conditions, and measurement data. That is, PINN provides a hybrid physics-based and data-driven ML model. PINN could use measurement data, even sparse, to solve ill-defined problems and simultaneously identify unknown parameters. For instance, PINN has been used to identify wall shear stress in blood flow problems where the inlet and outlet boundary conditions are not known but instead sparse measurement data are available.[7] PINN can be used to find the best velocity and pressure fields such that the governing equations (Navier-Stokes), the partially imposed boundary conditions (e.g., the no-slip condition), and available measurement data are satisfied.[7] PINN has shown success in solving fluid[24] and solid[50] mechanics problem and is gaining attention in cardiovascular biomechanics modeling.[7,23,61,112] We should point out that PINN could also be used to solve well-defined PDE models without any data.[55] Unfortunately, currently, PINN's computational cost for solving well-defined forward problems is much higher than traditional numerical methods such as FEM. Additionally, unlike traditional numerical methods, no theoretical guarantee exists for achieving machine precision accuracy. Therefore, using PINN for a well-defined cardiovascular biomechanics problem currently is not as attractive as an ill-defined problem augmented with data.

Improving Data Quality

While in computational biomechanics modeling, we are usually faced with unknown parameters, experimental measurements are accompanied by noise, have low resolution, and are sometimes incomplete (limited field of view). ML could be used to improve the quality of the data collected by these measurements. Superresolution is a classical ML application commonly used in image processing.[120] ML models such as deep learning can learn a mapping from a low-resolution image to a high-resolution image. Similar ideas have been used for superresolution of turbulent flow data.[40,47] In cardiovascular fluid mechanics, similar methods have been applied to 4D flow magnetic resonance imaging (MRI) data.[36] Alternatively, PINN has shown promise in superresolution by incorporating physical equations[43] and has been successfully applied to 4D flow MRI hemodynamics data.[34] Deep learning models can also be trained for denoising purposes.[123] For instance, autoencoders, which are a class of deep learning models that learn a nonlinear low-dimensional representation of data, have been trained for denoising data.[46] Finally, ML algorithms have been developed for treating corrupt and outlier data, which typically arise in experimental measurements. Variants of principal component analysis (PCA), which is a key tool at the heart of many unsupervised learning algorithms, could be used to learn models that can discover corrupt or outlier data.[119]

Solving Multiscale Problems

ML models could be developed within multiscale biomechanics models to accelerate spatially and temporally multiscale problems. Vascular tissues have spatially multiscale material properties. For example, smooth muscle cells and fibroblasts regulate their surrounding extracellular matrix, and the collagen fibers, elastin, and other constituents determine vascular tissue's mechanical properties. Multiscale models have been developed to couple micro-scale models representing these vascular wall constituents to organ-scale models representing the vascular tissue.[12,122,128] These models are computationally expensive as the micro-scale model needs to be computed multiple times. ML has the potential to facilitate the execution of these multiscale models. Namely, representative volume elements (RVE) could be defined to represent the micro-scale model. The RVEs are typically defined as structured cubes and therefore have simple geometries, which mitigates the issue raised above regarding learning ML models of complex morphologies. Namely, due to their simple geometry, they are computationally easier to simulate and could exhibit less complicated variability in their output. The RVE could be trained over the landscape of different constituent distributions and/or loading conditions and the learned model could be used in the multiscale model. Additionally, turbulence models specifically tailored for the unique physics of turbulence in blood flow[3,107] could be learned based on direct numerical simulation (DNS). In these problems, ML is not replacing physics-based modeling but it is enabling physics-based modeling by providing a closure model that could be used within the physics-based model. ML could also be used to facilitate temporally multiscale models. For example, coupling cell-scale particle dynamics models such as molecular dynamics with organ-scale models is restricted by the limited time-step of the molecular dynamics model. Machine learning models have shown promise in learning the temporal behavior of the molecular dynamics model and advancing the model forward in time in a computationally efficient manner. Such models have been developed in modeling platelet activation coupled with blood flow.[131] The readers are referred to an excellent review in Ref. 2 for integrating ML in multiscale biomechanics models.

Need for Real-Time Data Integration and Evaluation: Digital Twins

A digital twin is a predictive computer model representation of a complex system.[84] The digital twin should be designed to interact with data as they become available to update its structure and remain predictive.[84] Ideally, a digital twin should interact with available data in real-time. In cardiovascular biomechanics applications, hybrid physics-based and ML models are essential to combine first-principle continuum governing equations with data to build a predictive digital twin model. For example, a digital twin could be designed to model hemodynamics-driven cardiovascular disease growth. The hybrid physics-based and data-driven nature of the digital twin will allow the integration of sparse measurement data from the actual system (the patient) as such measurements become available. The continuous interaction with new data through ML techniques will improve model prediction.

The fidelity of any digital twin depends on a detailed understanding of the system as a whole and its subunits. Multiscale approaches will thus be a critical modeling component for organ and system-level function, which occur at the molecular, cell, tissue, and organ scales. However, there remain both theoretical and practical challenges in applying traditional multiscale techniques to digital twin systems in biomechanics. For example, defining something as basic as the RVE can be problematic in any biological structure due to the presence of a large number of relevant length scales, whose magnitudes are not sufficiently differentiated. For example, within the apparently simple heart valve leaflet lies a complex micro-environment of interstitial cells and collagen/elastin fibers.[9] Even when identifiable, it can be quite difficult to obtain representative material properties. Moreover, digital twins require knowledge of *real-time* material properties, which in living systems typically evolve over time and are generally inaccessible *in vivo*. Therefore, there are several exciting future research opportunities for developing digital twins in biomechanics problems.

One of the major limitations in developing digital twins is that computational tasks can be enormous and preclude real-time direct simulations. For example, in-silico implementation of complex 3D continuum soft tissue constitutive models to obtain the responses of varying boundary conditions and fibrous structures requires the solution of the associated hyperelasticity problem. Novel ML methods are being developed for the simulation of hyperelastic soft tissues such as those of the heart using real-time deep learning.[127,129] Such approaches for solving the governing PDEs can potentially allow for greater simulation realism across scales in practical time frames.[115] In addition to the real-time evaluation, digital twin models should ideally be able to incorporate sparse longitudinal clinical data to update their structure and remain predictive for a longer duration. These features (real-time model evaluation and integration of new data) are key aspects of digital twins that distinguish them from standard predictive patient-specific models.

For example, a neural network-based method that can simulate the 3D mechanical behavior of soft tissues has been developed using a physics-informed approach to train the neural network surrogate model to give a physically correct solution for a range of loading conditions by minimizing the potential energy without any training dataset generated by finite element solver.[127] The finite element discretization of the solution field is applicable to problems defined with complex geometry and boundary conditions such as ventricular simulations and it enables strong enforcement of the Dirichlet boundary conditions in a natural manner. Although a specific type of hyperelastic material model was developed, the approach does not restrict the applicability for other types of hyperelastic materials. By shifting the computation expense from finite element solutions to neural network training in a physics-informed manner, these surrogate models can be used to give significantly fast predictions of complex 3D deformations in full kinematic space with given fiber structures by forward propagation in the neural network. Similar methods may pave the way for building an efficient template model of hearts with add-on heart-specific attributes, with neural network-based surrogates for fast predictions to evaluate the need to conduct high-fidelity real-time simulations.

Using Unsupervised Learning to Learn Physics and Interpret Data

Physics-based cardiovascular biomechanics models typically generate large spatiotemporal datasets of field variables. While we discussed how ML could facilitate such modeling, often in well-defined problems obtaining these datasets is not the main issue. In many problems, these datasets have complex and chaotic spatiotemporal variations, which make their physical interpretation difficult. For example, blood flow in diseased vasculature is often chaotic,[6] transitional,[117] or turbulent,[83] and therefore difficult to interpret. Unsupervised learning could reduce the dimensionality of the data by clustering the data into different modes. Specifically, proper orthogonal decomposition (POD) and dynamic mode decomposition (DMD) are common modal analysis approaches[114] that have also been used in cardiovascular fluid mechanics[27,30,48,66] and structural biomechanics modeling[64,93,98] to facilitate physical interpretation of large spatiotemporal datasets. At the heart of these algorithms, singular value decomposition (SVD) is used to detect redundancy and high correlation within the data and provide an optimal basis for reconstructing the data (POD) or provide a dynamically interpretable basis for the temporal evolution of the dataset (DMD). The low dimensionality discovered by these models could also facilitate the solution to ill-defined problems and denoising of blood flow data (and possibly vascular mechanics data) as reviewed in Ref. 5. These methods have also been successfully applied to inverse modeling in cardiovascular solid mechanics problems[93,121] and medical image segmentation.[88]

CONCLUSION

We have summarized some of the key challenges in using ML for the purpose of replacing a well defined physics model and suggested applications where ML could augment physics-based modeling. We suggest that ML models without a ''clearly justified end goal'' are not attractive for cardiovascular biomechanics modeling of field variables. If the ML model is developed to replace a well-defined continuum biomechanics model, it should justify the application of the model and justify the need for the gained speedup vs. the loss in accuracy. Finally, we suggest many exciting applications of ML in biomechanics modeling where the ML model is not the purpose but a tool to enable further modeling and solve difficult problems.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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