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EDITORIAL FOCUS

Toward bedside computation of myocardial infarction risk using noninvasive analysis of patients living with coronary artery disease

Peter Michael Kekenes-Huskey

Department of Cell and Molecular Physiology, Stritch School of Medicine, Loyola University Chicago, Chicago, Illinois

A myocardial infarction (MI) is a common occurrence in coronary artery disease. Inflammatory arterial plaques that form stenotic lesions are implicated in the disease progression. If stenosis is caught early, lifestyle changes including improved diet, exercise, weight management, and smoking cessation can reduce cardiac events. Surgical interventions, including coronary artery bypass surgery, stents, and angioplasty, may however be necessary. It is critical to identify potentially obstructive, stenotic arteries before an MI occurs. Inspection of pathological artery anatomy and conventional coronary angiography (1) are invasive techniques for this purpose. The pressure change before and after an arterial lesion can also be measured using a pressure-sensitive guidewire; this yields low fractional flow reserve (FFR; 2), an indicator of coronary stenosis (3). Percutaneous coronary interventions can improve patient outcomes and reduce subsequent events but have limited therapeutic utility in severe lesions and distal arterial vasculature (1). Furthermore, these invasive approaches only provide coarse metrics such as vessel narrowing, with little detail about the degree of atherosclerosis, and can be susceptible to motion artifacts (1).

In a recent issue of the *American Journal of Physiology-Heart and Circulatory Physiology*, Sun et al. (4) developed a noninvasive protocol to predict FFR and stenotic risk from computational classifiers applied to patient-specific coronary artery data. This entailed *1*) developing a large set of three-dimensional (3-D) idealized geometries informed from patient-derived coronary artery data, *2*) simulations to estimate FFR for idealized geometries, and *3*) training classifiers based on simulated FFR data to index patient-derived coronary artery data (see Fig. 1).

The Sun et al. (4) study leverages published patient vascular data to predict stenosis in arterial geometries from a noninvasive technique: computerized tomography angiography. This technique creates 3-D reconstructions of patient vasculature from X-rays that can identify stenoses, which strongly associate with cardiovascular disease (2). Computerized tomography angiography provides ample data including vessel length and width that can be used with analytic mathematical models to reliably predict FFR. One such model, the Bernoulli equation, quantifies energy losses within a lesion because of "pressure drops" from convection and constriction at the stenotic region, diffusion, and expansion from the lesioned vessel to nonstenotic regions (3).

More detailed and potentially more accurate modeling of blood flow in stenotic vessels relative to analytic models has been afforded through computational fluid dynamics (CFD) simulations (2). These numerical approaches solve fluid dynamics models of blood pressure and velocities subject to the aforementioned energy losses (3) but using 3-D models of patient vasculature. The FFRs from the predicted pressures offer improved diagnoses relative to using the computerized tomography angiography data alone (2). A main reason for the improved performance of CFD models over analytic methods is that the energy losses are more accurate when realistic arterial geometries are used. Despite their accuracy, CFD is not appropriate for clinical use, as the simulations are time intensive and require specialized expertise and computing resources. Sun et al. (4) address this short coming by precomputing CFD-derived FFR data for idealized patient vessel geometries. The simulated FFR data were then indexed by easy-to-measure geometric data using a machine-learning technique. They approached this by creating novel CFD input geometries with randomized features including stenotic percentage and vessel length. The result was a classifier for predicting stenotic resistance in novel arterial geometries imaged via computerized tomography angiography, but without performing CFD simulations at a significant computational expense. The classifier was based on a machine learning tool called a neural network that can determine complicated relationships between FFRs and features derived from computerized tomography angiography. With this framework, they demonstrated that 3-D CFD simulations improve FFR estimates relative to results from less detailed analytic mathematical models. In addition, they confirmed that stenotic percentage and minimum area were among the strongest predictors of FFR.

The neural network approach adopted by Sun et al. (4) predicted FFR given stenosis length, width, and vessel length, at a negligible computational cost compared with CFD modeling. This is another example of machine learning approaches that have exploded in popularity in recent years to solve multidimensional and nonparametric problems given complex data sets. Machine learning methods are numerous and diverse in both the algorithms used and the computational costs in training and validation. The most robust and commonly used machine learning approaches include support vector machines and neural networks, including the backpropagation neural network implemented by Sun et al. (see Fig. 1). These approaches are more accurate

Correspondence: P. M. Kekenes-Huskey (pkekeneshuskey@luc.edu).
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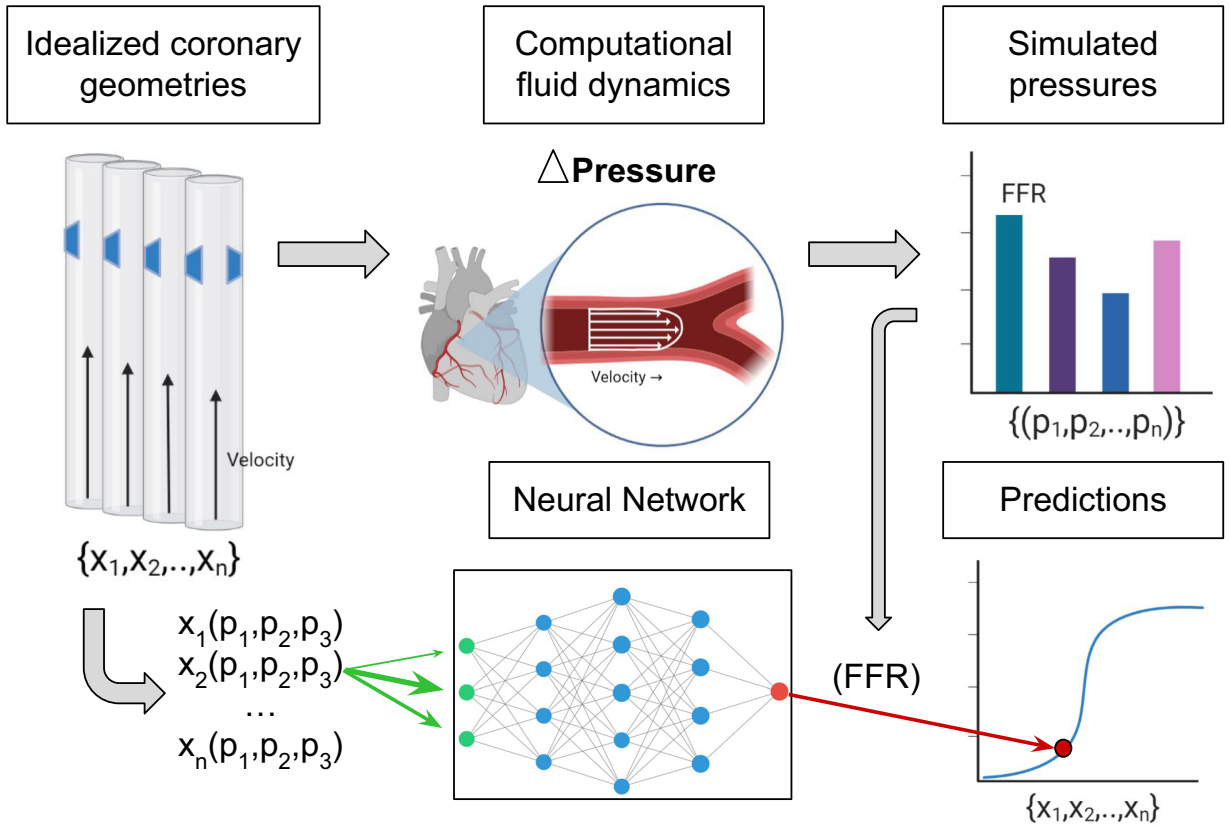

Figure 1. The framework of Sun et al. (4) for estimating fractional flow reserve (FFR). Idealized coronary artery geometries were created based on parameters evaluated in patients, such as the percent stenosis. Computational fluid dynamics modeling estimates FFR for these geometries. In parallel, neural networks were trained to predict FFR values based on coronary artery parameters. Created with BioRender.com and published with permission.

compared with simpler approaches, such as decision trees or statistical classifiers, but require large data sets for model training.

Sun et al. (4) trained a backpropagation neural network to reproduce FFRs computed from either CFD or an analytic mathematical model. A backpropagation neural network consists of hierarchical sets of nodes that are linked via directional edges as shown in Fig. 1. This resembles the organization of neurons in the brain that distill massive sources of data into a physiological response. Neural networks are based on a set of input, "hidden" and output layers that convert an input data set into a predicted output. In short, a vector of data, e.g., features representing a coronary artery geometry, is assigned to the nodes in the input layer (Fig. 1, green circles). The values from a set of input nodes (orange) are individually multiplied by a weight and added to the node (blue), to which they are connected in the next layer. This sum is evaluated by an activation function that sets the output of the node. This procedure continues for all connected nodes, for each subsequent layer, until the output layer (red) representing the final result is reached. These networks can have variable numbers of nodes and layers, as well as activation functions on each node; the weights in a given network topology are optimized (trained) to minimize the error between network predictions from inputs and truth data (FFR). Performance assessments like the F1 score are typically used to gauge the precision and recall of the trained classifiers.

Machine learning approaches generally perform best when they are trained with comprehensive and diverse data sets. The study, however, was limited to 30 sets of patient-derived coronary data. The authors confronted this challenge by building randomly generated, idealized artery geometries based on ranges of stenotic percentages, lengths, and entrance diameters presented in the literature. This allowed the researchers to broaden the parameter space of artery topologies that is likely spanned by a diverse patient population beyond their test data. These idealized topologies were used for analytic and CFD models to predict FFR truth data. Geometric parameters from the training sets were then used as inputs for the backpropagation neural network; the nodal weights were iteratively refined to best reproduce the simulated FFR truth data. The optimized backpropagation neural networks were then tested against data obtained from patient-specific computerized tomography angiographies, which yielded FFR accuracies of 3% compared with direct evaluation of the analytic mathematical model. More importantly, the optimized backpropagation neural network enabled FFR predictions at a negligible cost compared with CFD calculations. The approach's high level of accuracy and small computational cost make a compelling argument for its later use in the clinic.

The Sun et al. (4) study provided a strong foundation for machine learning-based assessments of coronary artery stenosis severity that could be further developed. A very actionable next step would be to assess FFR prediction accuracies

according to patient subpopulations, such as women, African Americans, and smokers, as well as with respect to common comorbidities. More translational developments could include curating data from longitudinal studies of patients who underwent surgical or nonsurgical interventions following computerized tomography angiography procedures. This may enable machine learning-based predictions of the best treatment modality for a given patient and their potential responsiveness to intervention. Other technical developments might consider alternative formulations of CFD models (reviewed in Ref. 5) to improve upon the approach's 3% accuracy for FFR predictions, especially given difficulties in predicting or measuring FFR in distal artery segments or complex vascular geometries (2). There are likely additional types of data that could be noninvasively collected to improve upon FFR calculations, if not patient outcomes, from blood draws, nonstandard computerized tomography angiography measurements (6), and electronic health records. These data could take the form of information on the cellular composition of a lesion, inflammatory and metabolic markers, arterial compliance (7), patient age, and sex. These additional features would require expanding the training set significantly to adequately train the appropriate machine learning classifiers.

Machine learning algorithms, their implementations and special-purpose hardware, such as graphics processing units, applied to biomedical data have developed to the stage that they can be broadly deployed for diverse applications in cardiac care. From a simulation perspective, we have likely reached the stage where we no longer ask "could ML be used to help solve this problem?" to "how should ML be used to most effectively solve this problem?" Nonetheless, building, training, and deployment of these models for medical applications still remains a nontrivial challenge. Technological limitations include the variable quality of CTA-derived meshes and motion artifacts (8) as well as overfitted or underdetermined machine learning models. For one, machine learning approaches including the backpropagation neural network are inherently limited by the availability and accuracy of data from which they are trained. Curating larger data sets introduces its own challenges, not the least of which involves human intervention and biases. Intriguingly, ML can also suffer from an abundance of data that can obscure trends that would otherwise be apparent in data sets with fewer parameters. As a recent and expensive example, IBM spent several billion dollars creating and acquiring data procurement firms for their AI framework Watson. The primary goal was to develop machine-learning tools to facilitate health care assessments using training data from millions of patient records (9). Although their approach was promising and potentially revolutionary, within just a few years, Watson was sold off at a loss, based on insufficient data or overly complex patient records that hindered reliable predictions.

Despite these challenges and cautionary tales, we will continue to see machine learning and computer simulations serve increasingly important roles in medical diagnostics and treatments. Studies such as Sun et al. (4) are taking the foundational steps to advance this direction, through enriching existing patient data sets, using detailed computer modeling to analyze data, and distilling results into computationally inexpensive classifiers.

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AUTHOR CONTRIBUTIONS

P.M.K.-H. prepared figures; drafted, edited, and revised manuscript; and approved final version of manuscript.

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