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COMMENTARY

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How can AI accelerate advances in physiology?

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A popular refrain in the post-genomic era is that biologists are "drowning in data," but that is not a complaint that you will often hear from a physiologist. While our ability to collect more data on DNA and protein sequences, transcriptional activity, protein abundances, and cell and molecular structure have grown rapidly, relating genotype and structure to tissue and organ function remain the rate-limiting steps to advancing physiological understanding. Recently, advances in deep learning and artificial intelligence (AI) have held up the prospect of finding short-cuts for predicting pathophysiological clinical phenotypes from molecular data. But not only do these approaches require large amounts of training data and are only as reliable as the data used for training, machine learning algorithms themselves are black boxes. They do not explain relationships in terms of biological mechanisms. At best, they suggest new avenues for mechanistic investigation.

One promising new strategy for taking advantage of supervised and unsupervised machine learning in physiology is to use well-validated, predictive, mechanistic computational models based on known molecular interactions to discover new genotype–phenotype relationships and generate new structure–function hypotheses. In cardiac myocytes, among the most fundamental phenotypic readouts are the cardiac action potential and the isometric twitch tension. Both are critical and specific determinants of tissue and organ scale electrical and mechanical function, and both are the emergent outcome of hundreds of tightly regulated molecular interactions distributed throughout the cell. Molecular perturbations cause subtle variations in the morphologies of these signals that in turn can lead to pathologies such as arrhythmia or chamber remodeling.

The wide variety of gain- or loss-of-function mutations in sarcomeric proteins that are associated with hypertrophic and dilated cardiomyopathies have been studied in depth and added new insight not only into the molecular mechanisms of inherited cardiomyopathies but those of acquired heart diseases too. For example, in a landmark paper, Davis et al. (2016) found that the time integral of the isometric twitch tension curve (tension-time index) was a strong predictor of the cardiomyopathy phenotype associated with a particular sarcomeric gene mutation. Larger, longer twitches were associated with hypertrophic phenotypes, whereas smaller, shorter twitches predict dilated morphologies.

In this issue of *JGP*, Asencio et al. (2023) use a stochastic, spatially explicit, multi-filament model of a half-sarcomere to simulate isometric twitch dynamics in response to an experimentally derived driving calcium transient. By varying kinetic rate parameters in the model representing calcium binding to troponin-C or crossbridge formation, they generated a training set of cardiac myocyte twitches corresponding to six combinations of sarcomeric gene mutations and dosage associated with different cardiomyopathic phenotypes. Using unsupervised and supervised machine-learning algorithms, the authors identified specific, novel features of twitch morphology that classified disease mutations with nearly 80% accuracy. Interestingly, the tension-time index and just two principal modes of twitch variation were a slightly better classifier than the entire twitch time-course. This latter observation may become very helpful in applying this approach to measured twitches, which are confounded by experimental variability.

This article shows one new way that machine learning can help to accelerate the discovery of novel and physiologically important genotype–phenotype relationships while at the same time reminding us of the wealth of biological information in classically studied physiological signals like isometric twitch tension. There is still much left to do. In addition to training classifiers with many more mutations, the real test comes when these tools are applied to measured twitches in muscles from humans with unknown mutations.

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