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Closing the Therapeutic Loop

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One of our clinical colleagues once told us, “There are PhD problems, and there are important problems. You should work on important problems.” We reject our colleague’s blunt criticism of basic science but we recognize that, as fields advance, researchers can do more to increase the tangible impact of their work. It seems to us that the field of myocardial contraction has reached this point. Decades of work by thousands of scientists has provided us with detailed information about the molecular, cellular, and tissue-level mechanisms that drive and regulate ventricular function. In our opinion, it is time for researchers to put more emphasis on leveraging that knowledge to improve patient care. This article outlines one potential approach based on multiscale computer modeling of cardiac function. Our vision is a transdisciplinary team that optimizes treatment plans for patients who have cardiac disease by predicting how the heart will respond to each of the potential therapeutic options using personalized computer models that integrate genomic, proteomic, imaging, and functional data. Over the next few years, we want to work towards that moonshot goal by planning a clinical trial that tests whether implementing model-predicted therapies helps patients more than the current standard of care.

Reductionist techniques have dominated myofilament research for the last 70 years. Our field now understands that contractile force is generated by interactions between myosin heads and binding sites on actin [1]. The energy that drives cross-bridge cycling comes from the hydrolysis of ATP molecules and we have detailed knowledge about many aspects of myosin’s mechano-chemistry [2]. We have also learned that the intracellular Ca^{2+} concentration controls contractile activity through complex mechanisms involving troponin and tropomyosin [3]. These processes are cooperative so the status of one binding site depends on the status of its neighbors [4]. Thick filaments are also dynamic with myosin heads transitioning between OFF and ON states at rates that are likely to depend on force [5–7].

Many, perhaps most, of these mechanisms are regulated by signaling pathways that modulate the posttranslational status (for example, phosphorylation, acetylation, glycosylation) of sarcomeric proteins [8]. Some of these pathways can be manipulated using drugs, which gives clinicians the ability to implement therapies that adjust cellular-level cardiac contractility [9].

Of course, what really matters to a patient, and thus the clinician that is treating them, is organ-level function – how much blood did the heart eject, at what pressure, and how much energy did that require? Mathematical techniques have been developed to predict hemodynamics from the behavior of a single cell [10] but these are too simplistic for clinical use because they omit patient-specific factors such as the shape of the heart.

A better approach for translational work is to use finite element modeling. This mathematical technique simulates the behavior of a large structure by first deconstructing it into smaller interconnecting blocks (the elements). The physical properties of each block (for example, force per unit area) are then defined. Finally, sophisticated algorithms integrate the block-level data to determine the global function of the whole structure. For beating hearts, outputs of the calculations include factors that have clinical utility such as ejection fraction and cardiac torsion.

Cardiac finite element systems have been available for more than 40 years [11] but most are still based on phenomenological models of contraction (for example, steady-state force-calcium relationships). As a result, it can be challenging to simulate transient data, such as load-dependent relaxation [12]. The phenomenological basis of most models also makes it difficult to scale from molecular mechanisms to organ-level function. Our groups have been working to overcome this limitation and recently published a finite element system [13] that is built on a molecular-level model of contraction called MyoSim [14]. Note that our “molecular-level model” simulates transitions between states (for example, attachment of cross-bridges) rather than fluctuations within proteins, as would be the case for calculations based on molecular dynamics. Accordingly, MyoSim simulates myosin heads interacting with Ca^{2+}-dependent binding sites and predicts contractile force using cross-bridge distribution techniques [15]. MyoSim thus mimics velocity-dependent contractile forces better than calculations based on steady-state assumptions. Intriguingly, this allows our finite element system to reproduce regional cardiac mechanics (specifically, heterogeneous re-lengthening during diastole) better than conventional modeling techniques [13].

While the ability to simulate a cardiac cycle might be interesting to scientists, it is not, by itself, important to clinicians. If a physician wanted to know how much blood their patient’s heart was ejecting, they could just measure stroke volume using one of several standard techniques (for example, echocardiography). It would be more useful to have a model that could predict how the heart’s performance will change over time.

We are working on this too and are currently integrating growth and remodeling algorithms into our finite element simulations [16, 17]. Specifically, we are creating a modeling framework that couples element-level mechanics (cyclical patterns of stress and strain) to

long-term changes in tissue-level structure and function. In simple words, our models will evolve.

Most of the prior implementations of cardiac growth and remodeling algorithms have focused on geometrical effects that correspond to the addition [18] and deletion [19] of sarcomeres. This allows the models to change shape. For example, a finite element model of the heart might dilate following a simulated infarct. We plan to augment these structural changes with algorithms that modulate tissue-level function. For example, the passive stiffness of the elements could increase to mimic an elevated N2B:N2BA titin isoform ratio [20], or the contractile system could be sensitized to Ca^{2+} by reduced phosphorylation of troponin I [21]. It will even be possible to impose regional variation in our models. For example, we will be able to increase the passive stiffness of the middle transmural portion of the left ventricular free wall above that of the sub-endocardial and sub-epicardial portions. This will allow us to reproduce the transmural patterns of fibrosis that we've previously measured in failing human hearts [22].

While passive mechanics could be adjusted in most prior cardiac finite element models, few of the other approaches allowed fine control of the contractile mechanisms. This will not be a problem with our approach because the MyoSim framework allocates parameters to each step in the contractile process. For example, in a recent study that used MyoSim to investigate length-dependent activation [23], k_1 and k_2 defined the rates of the OFF to ON and ON to OFF myosin states respectively, while k_3 and k_4 set the rates at which myosin heads attached and detached from force-generating states. Other parameters defined additional sarcomere level effects including the affinity of binding sites on actin for Ca^{2+}, the strength of cooperative activation, and the power stroke of a force-generating cross-bridge.

Including this type of molecular level data in our finite element model provides two main advantages. First, we can perform sensitivity analyses to predict which parameters have the biggest influence on ventricular function. In essence, this is as simple as defining a metric (for example, stroke work divided by ATP consumed by cross-bridge cycling) and then calculating how that metric changes when each parameter is systematically adjusted. Some parameters will produce large changes in function while others will have more modest effects. For example, prior analysis of cell-level simulations has shown that varying thin filament Ca^{2+} binding properties has a bigger impact on unloaded shortening profiles than adjusting the strain-dependence of cross-bridge detachment rates [14]. When implemented in our finite element simulations, this type of analysis could form a useful screening tool in drug development pipelines because manipulations that don't have a big impact on function are unlikely to be useful therapies. The sensitivity data might also be useful to experimentalists who could use it to guide and refine their measurements – for example, by identifying variables (perhaps heart rate and/or afterload) that have a particularly large effect on the measured outcome. It is our view that experimental and computational data can be used synergistically to accelerate the rate of scientific progress.

The second main advantage of including molecular level data is that we can use our model to predict the effects of potential therapies. For example, mavacamten is a drug that reduces

cellular level contractile force and is currently being tested in patients who have hypertrophic cardiomyopathy [24]. Biophysical studies show that it directly inhibits the myosin ATPase cycle and stabilizes the myosin OFF state [25]. We could reproduce this effect in our finite element models by decreasing the k_1 parameter described above, and calculate how suppressing cellular level force will impact ejection during a cardiac cycle. More importantly, we can then run the model forward in time and watch how the simulations evolve. Since the drug changes cellular level force, it will change the cyclical patterns of stress and strain in each model element, and thus the growth and remodeling of our virtual organ. In other words, we can use our finite element calculations to predict how the drug will change the structure and function of the heart over time.

The devil, of course, will be in the detail. One obvious limitation is that our calculations can only mimic mechanisms that are included in the modeling framework. As an example, we do not currently simulate mitochondrial function so our current models are not sensitive to perturbations that impair electron transport chain activity or shift metabolic substrate utilization [26]. We could fix this specific problem quite easily (by integrating MitoCore [27] into the simulations, for instance) but the general problem remains. How will we know which aspects of a patient's physiology need to be simulated to predict their individualized response to a potential therapy? This problem is not new, and was summarized by Rosenblueth & Wiener in 1945 as "The best material model of a cat is another, or preferably the same, cat." [28].

Another limitation is the difficulty of running models forward in time. Our predictions will depend on the initial conditions that we set at the beginning of the calculations. Given the complexity of cardiac physiology, it is possible that the simulations will exhibit chaotic behavior; subtle changes in the initial conditions amplify over time and lead to radically different outcomes. Similar issues plague scientists' ability to predict the weather and the vagaries of the stock market!

We are optimistic that this general strategy will eventually contribute to improved patient care. We envisage a scenario in which clinicians collaborate with scientists to create personalized models for their patients. Each model would include all of the clinical data that were available and might potentially be of use. For example, if a patient's heart had been imaged, a personalized finite element mesh would be created from the MRI, CT, or echocardiographic data. This would produce a model that matched the patient's current cardiac dimensions. The mesh could also incorporate information about the shape and location of a fibrotic scar if the patient had suffered an infarction. Similarly, if a biopsy had been performed, data related to the current posttranslational and/or isoform status of sarcomeric proteins could be incorporated. Genomic mutations could also be integrated, perhaps using complementary functional results obtained from in vitro assays performed by basic scientists. In short, the team would work to create the most personalized model possible.

A battery of simulations would then be run, each predicting how the patient's heart would evolve over weeks and months in response to a different potential therapy. Presumably, cardiac function would deteriorate markedly in many of the simulations, but perhaps a few

of the calculations would predict improvements. Combinations of pharmaceutical therapies could also be tested to see if they produced additive effects. Similarly, the virtual hearts could be unloaded to mimic the effect of treatment with a ventricular assist device [29]. The end result of these calculations would be a dataset consisting of potential therapeutic interventions and patient-specific predictions for their result.

The final step, which we term “closing the therapeutic loop”, will be to work as a transdisciplinary research team to implement the therapies that are predicted to be most efficacious for each patient. Obviously, this will need to be done in a carefully regulated clinical trial with appropriate supervision from a data safety monitoring board. However, the goal is simple – test the hypothesis that implementing model-predicted therapies helps patients more than the current standard of care.

We already know that our plan has tens of challenges, and recognize that this means we probably need to overcome hundreds more. Clinical logistics, ethical issues relating to return of results, and training of physicians all present significant barriers that would need to be overcome. However, in our opinion, the end goal is worth it. If a team can demonstrate that model-predicted therapies help patients who have cardiac disease, they will have succeeded in leveraging our field’s knowledge to advance patient care. And that will be a wonderful and important thing!

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