Distorting the sarcomere

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One of the goals of cardiovascular science is to create a mathematical model of the heart that can predict ventricular function in healthy and diseased states, and that can be used to help improve treatment options for patients with heart disease. To be clinically useful, the model will have to include structural information about the shapes of the chambers and the action of the valves, and about how the electrical activity spreads from the sino-atrial node to the ventricular cells. It will also have to incorporate information about the contractile properties of the myocardial cells in different regions of the heart. In this issue, Ford et al. present a mathematical model that could provide a simpler and better way of predicting how force varies within real ventricular cells during the cardiac cycle.

Mathematical modeling of striated muscle was dominated in the latter half of the 20th century by a technique developed by A.F. Huxley (1957). In this approach, the mechanical properties of the muscle are attributed to a single population of myosin heads, each of which independently undergoes cyclic interactions with binding sites on actin filaments. If a myosin head is attached, it is assumed to behave as a Hookean spring so that the force produced by the muscle at any instant can be calculated simply by summing the forces due to the individual bound cross-bridges (the product of a spring constant and the cross-bridge extension in each case). Predicting the mechanical behavior of the muscle during a perturbation thus reduces to calculating how the cross-bridge population distributions (the proportion of cross-bridges attached with each range of spring lengths) evolve after the imposed movement. In Huxley's original formulation, this can be done simply by integrating a single partial differential equation.

This general approach has been tremendously successful, and many authors have used the technique to simulate the behavior of different types of skeletal and cardiac muscle. It has become common to incorporate multiple bound states into the actin–myosin cycle, and models of this type can explain many features of experimental data including, for example, the double hyperbolic nature of the force–velocity curve (Månsson, 2010) and the effect of phosphate on isometric tension (Pate and Cooke, 1989). The main drawback of these more recent models is that they are quite complex. Månsson's recent publication, for instance, describes simulations performed with 17 free parameters and an attachment rate function that depends on the velocity of interfilamentary movement. Although simulations of this type can potentially reproduce the behavior of real muscle cells extremely accurately, it is not always clear that the parameters defining the model responses are uniquely defined. Calculations with other parameter values might reproduce the experimental data almost as well. The mathematical complexity of these "bottom up" models means that they will also be difficult, although certainly not impossible, to integrate into larger multi-scaled simulation systems.

If mathematical models based on cross-bridge distributions lie at the "complex" end of the modeling continuum, the system described in this issue by Ford et al. lies toward the "simpler" end. Instead of calculating muscle force as the sum of the forces produced by each of the bound cross-bridges, their model predicts force from the product of the number of bound cross-bridges and the mean length of the cross-bridge springs. Although this approach sounds quite similar to the original Huxley scheme, the mathematics underlying this "distortion" approach (originally developed by Thorson and White, 1983) is much simpler, and Ford et al.'s model has only five free parameters. Two of these parameters, the recruitment rate constant and the distortion rate constant, describe, respectively, how quickly the number of attached cross-bridges and the mean length of the cross-bridge springs return to their steady-state values after a perturbation. The next two parameters describe how the steady-state number of attached cross-bridges varies as a function of muscle length, and the mean length of the cross-bridge springs at steady-state. The final parameter, which is unique to this work, defines the magnitude of a nonlinear effect through which changing the mean length of the cross-bridge springs alters the number of cross-bridges that will attach subsequent to the perturbation.

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Ford et al. show that their simple model can reproduce the family of force transients that are measured when samples of chemically permeabilized rat cardiac muscle are subjected to sudden lengthening or shortening movements. (This type of experiment is often used to measure stretch activation and has attracted considerable attention in the last few years; for example, Stelzer et al., 2006.) The simulations fit the experimental data impressively well, and the authors use an interesting, cogently presented argument to show that a nonlinear interaction between cross-bridge strain and cross-bridge cycling is required to explain the asymmetry of the tension responses to lengthening and shortening movements. Another important observation is that changing only two of the five parameters from their "control" values allows the model to reproduce the mechanical properties of rat cardiac muscle in which the wild-type troponin T molecules have been replaced by a protein kinase C phosphorylation mimetic containing S199E and T204E mutations. Specifically, the research suggests that phosphorylating cardiac troponin T increases the rate of cross-bridge detachment and augments the nonlinear interaction between strain and cross-bridge cycling. This is a convincing example of how it may be possible to use this distortion model in future work to produce new insights into interactions between biochemical modifications and contractile function, such as helping to understand how changes in the isoform content and posttranslational status of sarcomeric proteins influence force development.

Ford et al. make it clear that their primary goal was not to produce the closest possible fit between the experimental data and the simulations, but rather to minimize the qualitative ratio between the quality of the fit and the number of assumptions that their model made. In essence, this approach is analogous to using F-tests to determine whether a conventional curve fit is over-parameterized (Motulsky and Ransnas, 1987). To attain this goal, Ford et al. appear to have eliminated all parameters that might distract from the main object of the work. For example, the model does not contain any passive structural components (such as titin or collagen filaments) and thus would not predict any measurable force in the absence of cycling cross-bridges. Passive forces probably augment active forces in real muscles, and they could have been added into the model framework quite easily. Presumably, they were omitted because the authors did not believe that they would make a statistically useful contribution to the simulated records. Similarly, the model is designed to fit force records that have been normalized to the steady-state value of isometric force. This again reduces the number of parameters necessary for the simulations but, once more, at the expense of a potential loss of flexibility. For example, it

might not be easy to use the model to distinguish between two types of cardiac muscle that developed different maximal isometric forces but that exhibited similar stretch activation behaviors. The model also omits any features describing how contractile force varies with the activating Ca^{2+} concentration. This type of mechanism would probably have to be added into the model before it could be integrated into simulations of working hearts.

Some may therefore argue that Ford et al. have, on this occasion, applied Occam's razor a little too ruthlessly. The small number of parameters means that the model may only be able to fit a small subset of the experimental data that can be measured in mechanical experiments. On the other hand, there is no reason to think that the distortion approach will not be able to reproduce data such as force–velocity curves and tension recovery measurements when the simulations are inevitably tried. It is also true that the current model does a tremendous job of reproducing an intriguing set of mechanical data based on a very small number of plausible and easily understood assumptions. This is an obvious strength.

Another potential weakness is that most of the parameters in the model are phenomenological and not readily associated with specific biochemical and/or structural transitions. This could make it difficult to integrate computational results obtained by simulating different types of muscle with experimental data obtained using other techniques (for example, measurements of single molecules performed using laser tweezers). Again, however, the strengths of Ford et al.'s model heavily outweigh the weaknesses of their approach. To most muscle biologists, for instance, the prediction that a specific mutation of troponin I increases the average rate of cross-bridge detachment is probably just as useful as the hypothesis that the mutation increases the strain dependence of a specific transition from an identified strongly bound biochemical state.

There is much to admire about Ford et al.'s work, not least the authors' use of information theory to compare models. Their careful description of many of the nonlinear interactions that they investigated and that did not improve the fit to the data are also worthy of credit. (This information will surely prevent much wasted effort by other parties in the future.) In their conclusion, Ford et al. recommend their model as an "easily applicable tool for routine use in studies of cardiac muscle." Only time will tell whether the field follows this suggestion, but it is, at the very least, worthy of very serious consideration. In the meantime, Ford et al.'s simple, nonlinear distortion model may, with a simple modification to include Ca^{2+} dependence, be the best contractile system yet to integrate into multi-scale models of working hearts.

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