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BENEFITS OF DETAILED MODELS OF MUSCLE ACTIVATION AND MECHANICS

By Steven L. Lehman and Lawrence Stark

University of California, Berkeley

SUMMARY

Recent biophysical and physiological studies have identified some of the detailed mechanisms involved in excitation-contraction coupling, muscle contraction, and deactivation. Mathematical models incorporating these mechanisms allow independent estimates of key parameters, direct interplay between basic muscle research and the study of motor control, and realistic model behaviors, some of which are not accessible to previous, simpler, models. The existence of previously unmodeled behaviors has important implications for strategies of motor control and identification of neural signals. New developments in the analysis of differential equations make the more detailed models feasible for simulation in realistic experimental situations.

INTRODUCTION

Mathematical models and computer simulations are often used in manual control studies in an attempt to deduce the properties and strategies of the controller from the dynamical behavior of the whole system. In such inverse problems, the properties of the plant (muscles and load) must be carefully identified in order for the deduced model input to reflect the actual system control signal.

This identification problem for neuromuscular systems has attracted the attention of two groups of investigators, with two divergent points of view (reference 1). Biomedical engineers have tended to construct and identify models on the basis of macroscopic mechanical behavior, while muscle physiologists and biophysicists have concentrated on detailed microscopic mechanisms.

While not all microscopic mechanisms have macroscopically significant influences, i.e., unobservable states, some profoundly affect observable behaviors. We present two examples, one in muscle mechanics and one in activation/deactivation, for which detailed biophysical models have distinct advantages over the more widely used phenomenological ones.

MUSCLE MECHANICS

The dichotomy between macroscopic phenomenological description and microscopic mechanism is clear in the two prevalent classes of models of muscle mechanics. Engineers tend to use the classic three-element model (figure 1), while muscle physiologists consider ever more detailed cross-bridge models (figure 2). It is instructive to compare the two types with respect to the three main mechanical characteristics of muscle: the static length-tension relationship, the force-velocity curve, and the transient behavior evident in quick length change experiments.

Length-Tension Curve

The length-tension characteristic for passive muscle is of course independent of the contractile mechanism per se, so is modeled the same way for both types (element labelled PE in figure 1). The characteristic added for active muscle, on the other hand, was not explained until Gordon et al (reference 2) invoked a cross-bridge model, and showed that the active characteristic was simply the result of varying cross-bridge overlap. Cross-bridge models thus have the advantage of a natural implementation of the length-tension curve, and comparability with an actual measurement (the filament lengths as measured from electron micrographs).

Although the classical phenomenological model neither explains the full length-tension curve nor implements it elegantly, it may be made to exhibit the known characteristic. In fact, the length-tension curve is generally included in this model ad hoc as an additional, length-dependent element.

Force-Velocity Relationship

By the force-velocity relationship we mean both the relationship between force and (constant velocity) shortening velocity first characterized by Fenn and by A.V. Hill (reference 3) and its extension to steady-state force exerted by a muscle lengthening at constant velocity (figure 3). Hill fit the shortening curve with his well-known hyperbola, the two parameters of which he related to the maximum shortening velocity and the shortening heat.

The force-velocity relationship has been included in the phenomenological models in various ways, both directly (as part of the box labelled CE in figure 1) and as a velocity-dependent viscosity. The Hill formalism makes it possible to construct the entire shortening characteristic from two constants---a compression of experimental data valuable in computation.

The force-velocity relationship (both shortening and lengthening) is produced by the cross-bridge models, as a consequence of the choice of kinetic rate constants between cross-bridge states. Here again the cross-bridge models are more elegant than the phenomenological type, because they explain the observed macroscopic effect from a lower level. The production of the force-velocity curve is not, however, surprising. Indeed, the rate constants are chosen to fit the curve. A.F. Huxley explained the relationship between his rate constants and the Hill constants in his report of the first cross-bridge model. (reference 4)

The most significant difference between the two types of model is not shown in Figure 3. It is now well-known that the curve for lengthening muscles (velocity less than zero in the figure) is only valid in the steady state. Actual muscle, when lengthened at constant velocity, produces first more force than that indicated by the curve, then yields to tensions lower than those indicated (references 5,6). This transient behavior of lengthening muscle is not produced by the phenomenological models, because their imposed force-velocity relationships are single-valued. This behavior is produced by almost any cross-bridge model, including the simplest (two-state) models.

Transients

The series elastic element (SE in figure 1) was introduced into the phenomenological models to account for the changes in muscle tension observed during quick stretches and releases. It was observed that the response consisted of at least two phases, the first of which implied the existence of an elasticity in series with the active contractile machinery.

Clearly, the addition of a series elasticity makes an allowance for this important compliance, but does not fully solve the problem of the transient. The simulation of the quick-stretch and quick-release data in detail is possible using cross-bridge models.

ACTIVATION AND DEACTIVATION

The complex of processes comprising muscle activation, from the arrival of a nerve action potential to the binding of myosin heads to actin, and the process of deactivation by active pumping of calcium into the sarcoplasmic reticulum have been intensively studied in recent years. Corresponding to the increase in understanding of these fundamental mechanisms, an immensely rich, complex, and frustratingly fragmented literature has grown up. The synthesis of this literature and building of models will certainly provide better estimates of the time scales and relative influences of the many processes involved, and may also reveal new dynamical possibilities.

Already, there are specific, well-identified models for many of the individual processes. For example;

1. Active invasion of the T-system by action potentials has been modeled. (Adrian and Peachey, reference 7)
2. A gating mechanism for calcium release from the sarcoplasmic reticulum has been shown, and its voltage dependence found. (Schneider et al, reference 8)
3. The detailed biochemical kinetics of the protein that pumps calcium into the sarcoplasmic reticulum, thus relaxing muscle, have been investigated, to the level of finding twelve distinct biochemical states of the enzyme and rate constants between those states. (Inesi, reference 9)

The extreme reductionism of the muscle activation and deactivation studies has both good and bad effects. The unfortunate fragmentation and specificity of the large literature inhibits synthesis of results and evaluation of the relative importance of different effects. On the other hand, the reductionistic trend means that the mechanisms found are characteristic of specific proteins, for example, and not of specific muscles or organisms. Because these proteins are likely to be used in all sorts of muscles, the models may be more generally useful. For example, the calcium-pumping protein mentioned above seems to have the same kinetic properties in many types of vertebrate striated muscle. Furthermore, its concentration in sarcoplasmic reticulum membrane is very nearly constant. Therefore, from estimates of the surface area of the sarcoplasmic reticulum easily obtained from electron micrographs, one can reduce the general time course of deactivation or the muscle. Such a conclusion is exceedingly difficult to draw from other (e.g. dynamical) data. (reference 10)

CONCLUSIONS

There are several clear advantages to using detailed biophysical models for muscle activation, deactivation and mechanics. Among them:

1. Such models allow direct comparison with basic muscle research.
2. Some of the detailed models have <u>behaviors</u> that are not in the repertoire of simpler, phenomenological models:

2a. Yielding in strongly stretched lengthening muscle.

2b. Dependence of time constants of deactivation on history that allows for a fused tetanus at lower tonic firing rates.

3. Biophysical models allow independent estimation of mechanically influential parameters from simple measurements (e.g., time constant of deactivation from measurements of electron micrographs.)
4. Detailed mechanistic models permit the natural inclusion of known characteristics (e.g., the length-tension curve for active muscle.)

The <u>disadvantages</u> of such detailed models are, of course, clear to bio-engineers. Conceptual and computational difficulty are the main ones;

these are, of course, diminishing with increasing specialization of humans and power of computers. While some detailed mechanisms have important influences on macroscopic observables, others do not justify their computational cost for manual control studies. The advantages listed above are, however, compelling reasons for the consideration of more detailed and biophysical models.

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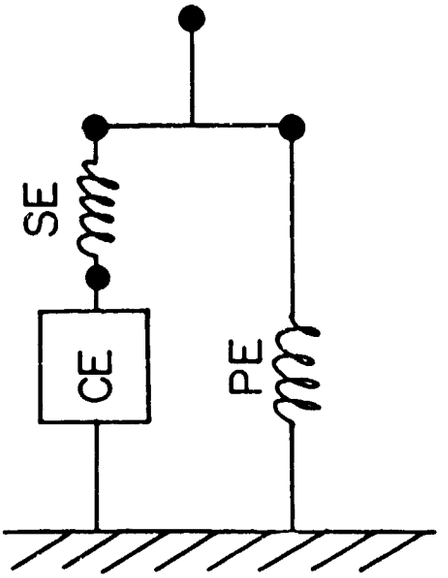

Figure 1: Classical 3-element muscle model
CE : contractile element
PE : parallel elasticity
SE : series elasticity

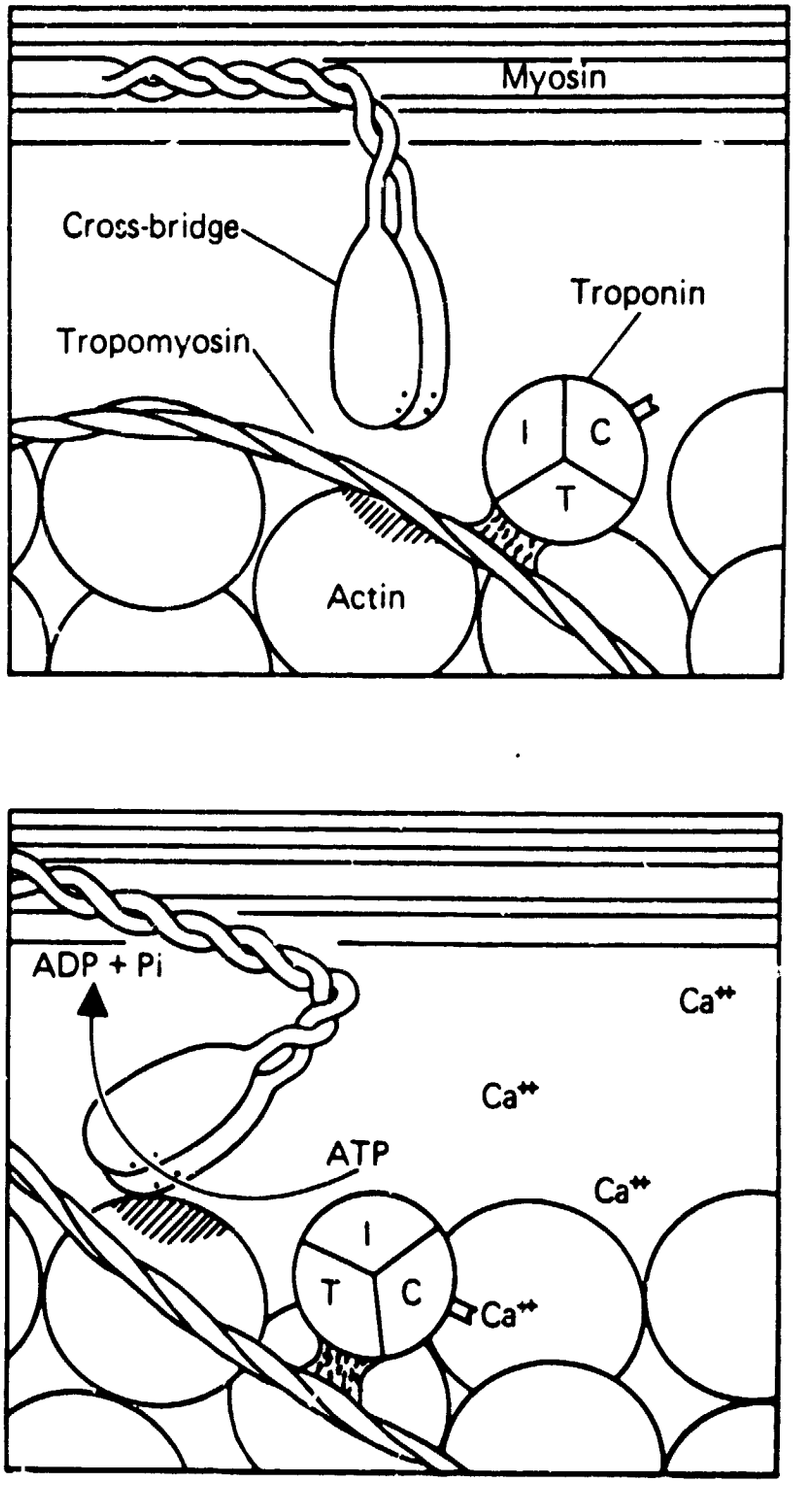

Figure 2: Cross-bridge mechanism of muscle contraction, including possible role of regulatory proteins. (From Ganong,W.F., Review of Medical Physiology)

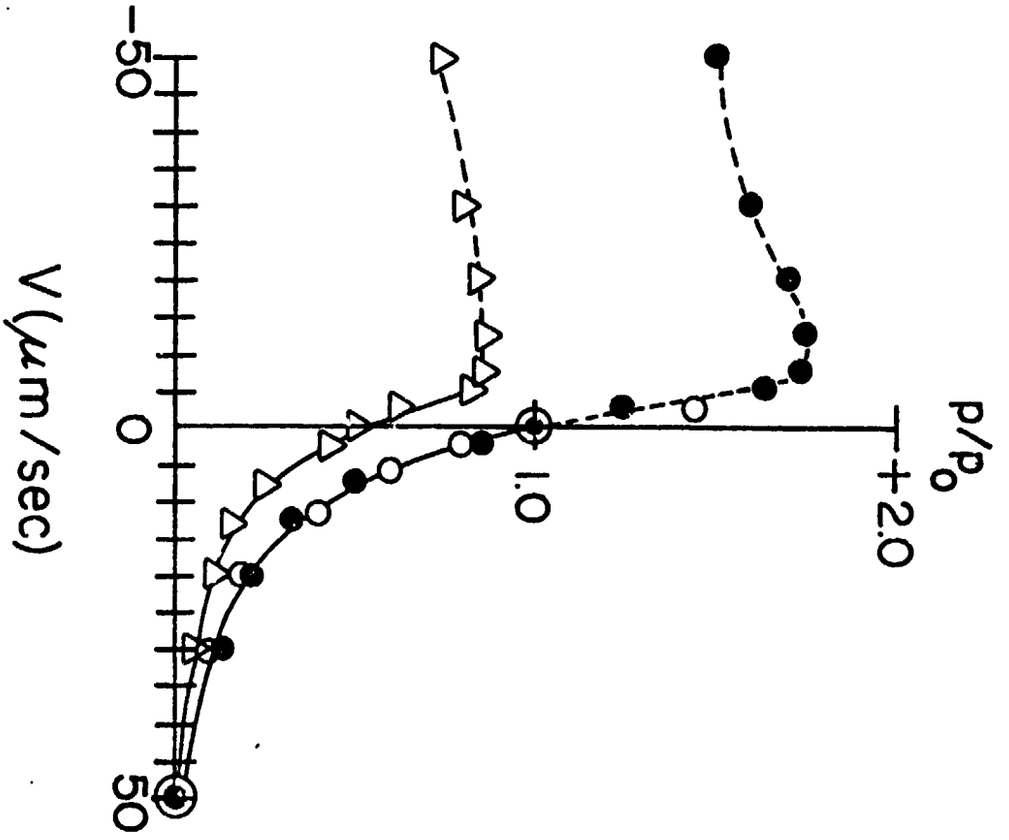

Figure 3: Force-velocity relationship for a fast-twitch muscle (rat EDL).
Open circles: experimental data
Closed circles: model simulation with full activation.
Triangles: model simulation with half activation.
Model is two-state cross-bridge.