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A model for muscle based on a molecular mechanical system

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ABSTRACT

To understand human and animal movement, the biological motor that powers this movement, skeletal muscle, must be understood. Ideally, one would like a constitutive law for muscle, an equation that describes muscle work output and chemical energy input as a function of state variables of the system (such as the generalized coordinates of the system and their rates of change). Over the past twenty years, the picture of how exactly muscle works at the molecular level has become considerably clearer. Properties that, fifty years ago, could only be guessed (such as the stiffness of the molecules involved in contraction, or the rate at which they undergo certain chemical reactions) have been painstakingly measured. One might suspect that it could be possible to incorporate this molecular knowledge into a macroscopic constitutive law for muscle. The typical assumption that the molecules in muscle are "independent force generators" [1], i.e. that each one acts independently of its neighbor, implies that this approach should be viable. This assumption is equivalent to the assumptions in an ideal gas, where derivation of macroscopic properties, such as heat capacity, pressure and/or entropy follows directly from molecular properties.

Unlike the molecules in an ideal gas, the proteins in muscle are organized into a specific, ordered array. During muscle contraction, a scaffolding of "thin filaments," made of actin, slides by another ordered array of "thick filaments," made of myosin. Projections from the thick filaments, called cross-bridges, can convert chemical energy from ATP into mechanical work as they form transient interactions with the thin filaments and displace them against an external load. Thus, the chemical interaction between the myosin cross-bridges and the actin filaments usually occurs under some external load. This external load affects the rate of the chemical reaction. Understanding precisely how this load affects chemical transitions is fundamental to any molecularly-based muscle model.

To understand the connection between molecular mechanics and the governing equations of muscle, and as a proof of concept for the following multi-scale method, we present a simple 1D example. We finish with a discussion of how the steps outlined here can be paralleled in a more realistic and more complicated model.

In our simple 1D molecular mechanical model, a point mass connected to a linear spring moves frictionlessly in one dimension. At some distance, there is a binding site, represented by a steep potential well with a minumum at the binding site. We divide phase space into a "bound" region, the set of states

where the system's equilibrium behavior is to oscillate about the binding site and an "unbound" region, the remaining states.

This simple mechanical system is constantly bombarded with solvent molecules. We may simulate these systems directly, using Monte-Carlo simulations of the Langevin equation (Newton's equations including a stochastic force term to model solvent collision). We may also simulate these systems in a more elegant probabilistic fashion, using the generalized Fokker-Planck equation (a generalization of the Liouville theorem in phase space to include solvent collisions, [2]), or assuming small forces and a viscous fluid, the Smoluchowski equation (a generalization of the diffusion equation to include external forces, [2]) or assuming that the time scale of moving between states is relatively slow when compared to solvent collisions, Kramers theory [3] modified slightly to fit this specific case. We find excellent agreement between these various equations when reasonable parameter values are used.

By applying a uniform load to the system (a linear curve in potential energy-strain space) we examine how load affects the rate of moving between the "bound" to the "unbound" states. Even the simplest of these equations, Kramers theory, depends on integration of the potential energy-strain function over its whole range. However, we may write an expansion around several critical points (assuming relatively small forces) and we find that these rates depend primarily on several properties of the potential energy function. Interestingly, the lowest order of these expansions is the standard expression for the load-dependence of rate constants in biochemical reactions, often attributed to G. Bell [4], though Bell postulated a curve fit from Zhurkov's work on metal fracture [5] to apply to biological reactions. We therefore predict that there should be biological applications where higher-order terms are important. We find evidence for these deviations in published literature [6], adding support to our conclusions.

This simple model could perhaps apply to the molecular understanding of friction or the general understanding of load on reaction rate, but is of limited application to muscle as it does not include an energy source. Further, it does not include much of the current biochemical understanding of molecular events that occur in muscle contraction. However, the simple model shows the series of steps that we must go through with a more realistic model. A simple 2 degree of freedom (DOF) mechanical model can replicate much more of the experimental data and can lead to force-generation and motion. The simplicity of this 2 DOF model will allow us to go from a molecular model to a kinetic model (as we did in the 1D case). The successful completion of this analysis will allow a clear understanding of how molecular-mechanical parameters affect kinetic-biochemical parameters and should result in a reliable constitutive law for muscle force and energetics.

REFERENCES

[1] A. F. Huxley. "Muscular contraction". *J. Physiol.*, Vol. **243**, 1–43, 1974.

[2] S. Chandrasekhar. "Stochastic problems in physics and astronomy". *Rev. Mod. Phys.*, Vol. **15**, 1–88, 1943.

[3] H. A. Kramers. "Brownian motion in a field of force and the diffusion model of chemical reactions". *Physica*, Vol. **7**, 284–304, 1940.

[4] G. I. Bell. "Models for the specific adhesion of cells to cells". *Science*, Vol. **200**, 618–627, 1978.

[5] Zhurkov, S. N. "Kinetic concept of the strength of solids". *Int. J. Fracture Mech.*, Vol. **1**, 311–323, 1965.

[6] Marshall et al. "Direct observation of catch bonds involving cell-adhesion molecules". *Nature*, Vol. **423**, 190–193, 2003.