Where The Actin Is

Between biochemistry and physiology a physical model of muscle fiber behavior

BY DIETRICK E. THOMSEN

Physics has been defined as an attempt to put numbers on natural phenomena. No physicist is satisfied until a problem has been written down in mathematical terms and solved for the relevant numbers with the proper units attached. Give physicists — or biophysicists, if you prefer — a sample of contracting muscle fibers, and one of the first things they do is make a mathematical statement. Early in his talk at the meeting of the American Physical Society in San Francisco, Roger Cooke of the University of California at San Francisco said, "[We want to find] a function for force as a function of ATP [adenosinetriphosphate] concentration." And in case anyone hadn't taken the point, he wrote it down in the kind of shorthand physicists are accustomed to using: f (conc ATP).

ATP is one of the biochemical molecules involved. It interacts with two proteins, actin and myosin, to cause contraction. The actin and myosin form a system of interdigitated fibers in a sample of muscle. The myosin molecule has two "heads" or protrusions that bridge the gap between fibers. The question concentrates on the behavior of these crossbridges. Their ability to attach to the actin and move the fibers past one another appears to be the heart of the contractile motion.

Biochemistry has extracted the molecules involved from the muscle tissue and studied their reactions with each other. In the process it has come up with proposed models of muscle action. Physiology has studied the ability of muscles to exert force. The task of biophysics is to mediate between the two. Cooke and his colleague, William Bialek write, "The recent work of our lab has been aimed at correlating these two fields by constructing a model which explains the physiological properties of the muscle in terms of the biochemistry of the contractile molecules."

To use the words of David D. Thomas of Stanford University, who spoke at the same session of the APS meeting as Cooke, biophysicists must "explain the macroscopic motion of the fibers by the action of the proteins." They "must make direct observations of crossbridges in contracting muscle fibers." Because, as Cooke puts it, "the rate constants for reactions that occur with crossbridges intact are different in muscle than in solution."

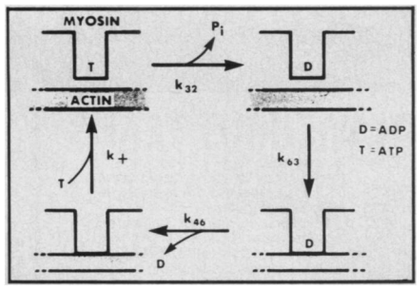
The model of the action is quite a mechanical one. One draws alternating fibers of actin and myosin (leaving out their molecular complexity), and the myosin has little round heads that attach to the actin, making the crossbridges. The crossbridges then rotate, pulling the fibers past one another. This constitutes what Cooke calls a "power stroke." Then the crossbridges detach themselves from the actin. Cooke and Bialek say that this model is more comprehensive than others because "it incorporates the interactions of ATP explicitly." It is ATP that supplies the energy for the action, and the key to any physical process is where the energy comes from and where it goes.

The tension in a muscle can be related to the number of crossbridges that happen to be connected, and that, in turn, can be related to the concentration of ATP in the tissue. When the crossbridges are detached, the muscle is not stiff. When crossbridges are attached, the number of attachments can be measured by the stiffness. This is the isometric state, in which the muscle is stiff, but not contracted.

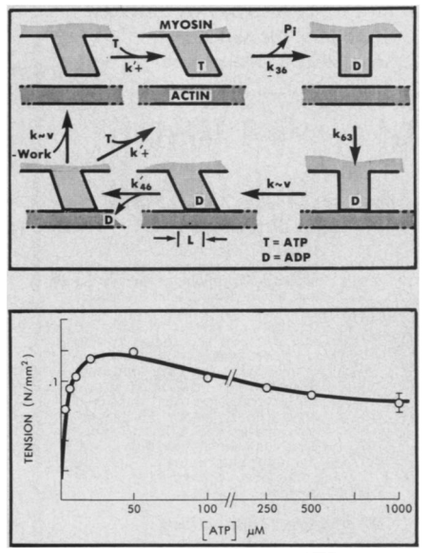
Then follows the isotonic contraction or power stroke, in which the stiffened muscle shortens its length. It is at this point that the muscle does work and expends energy. Cooke says that although this model needs some adjustment in dealing with the isotonic part of the action, it predicts the mechanical properties of muscle quite well. As an example he discussed the Young's modulus of muscle. Young's modulus is a number that expresses the relative stiffness of a material; physicists are accustomed to using it in talking of springs or wires. Shades of R2-D2!

Thomas and his co-workers at Stanford did a detailed study of the motions of the myosin heads that form the crossbridges. They use a technique called saturation transfer spectroscopy, in which they attach a labeled tracer to the myosin heads and follow its motion by means of electron paramagnetic resonance.

First they had to satisfy themselves that the tracers, nitroxide molecules with a labeled electron spin, were rigidly attached to the myosin heads so that the tracers took part in the motion of the heads and contributed no twists of their own. When that had been done, the experimenters went on to study particularly the characteristics of crossbridge motion in relaxed and contractile muscle and to compare them. Thomas says they achieved "the first detection of crossbridge motion in contractile muscle." They also found that ATP itself does not make the difference between relaxed and contractile states. ATP alone does "nothing" to the motion, a finding that is somewhat in contradiction to the model. It is the presence of calcium ions that seems to make the difference. If one adds ATP plus calcium to the myosin and actin, the result is contraction. Addition of ATP minus calcium produces relaxation. The difference between the two states is not in the motion of crossbridges, but in the presence of calcium, which allows the motion to generate power.



In isometric contraction crossbridges connect myosin and actin fibers to stiffen muscle; in isotonic phase crossbridges rotate to shorten muscle.



Relation of muscle tension to ATP concentration is one datum leading to model.

Another question is whether the two heads of the myosin work together or independently. Cooke and Bialek were able to investigate this problem by using digestive enzymes to prepare myosin that had only one head. They elaborated a technique to produce threads of purified muscle proteins and to measure the force generated by such threads when they contract. In such threads one-headed myosin generates half as much force as two-headed myosin, indicating that the two heads operate independently and each makes its own contribution.

The gradual elaboration of models for the action of muscle tissue that permit the calculation of its physical properties could lead to the development of methods of treatment for muscle that is failing in its job. Cooke and Bialek are now extending their work to some control mechanisms that may determine the strength of the contractions of cardiac muscle. "Knowledge of these control mechanisms will be of great value in the treatment of heart disease," they conclude. □