Letter to the Editor

Mechanochemical Coupling in Muscle

In a recent paper published in the *Biophysical Journal* (Baker et al., 1999), we showed that the biochemical and orientational distribution of myosin heads in fully activated, isometric muscle is independent of muscle force. In the discussion section of that paper, we argued that this observation challenges the fundamental assumptions of the Hill formalism. Regarding this statement and the arguments that followed, we would like to make the following clarifications.

First, we want to distinguish between A. F. Huxley's muscle model (1957) and T. L. Hill's formalism for that model (1974, 1977, 1989). In 1957, Huxley proposed a molecular model of muscle contraction in which myosin heads participate *independently* in individual, force-generating ATPase cycles. In 1974, Hill developed a rigorous, physical formalism for Huxley's model, generalizing it to arbitrary kinetic diagrams for individual myosin heads. Only through Hill's self-consistent theoretical formalism are the physical requirements of the independent force generator model realized, and it is for this reason that in Baker et al. (1999) we relied on Hill's formalism to formulate our arguments against the independent force generator model. We want to emphasize that while our data challenge the independent force generator model, they do not challenge the correctness of Hill's theoretical formulation of that model.

Based on the assumption that myosin heads in a half-sarcomere form a "solid solution" of independent macromolecules (i.e., the Huxley model), Hill (1974, 1977, 1989) introduced free energies of individual states in the kinetic diagram of a single myosin head, as legitimized by the thermodynamics of small systems (Hill, 1994). Although this procedure is "unconventional," it is an appropriate and correct alternative to ordinary biochemical thermodynamics if independent macromolecules are assumed. Again, it is this assumption that we argue is inconsistent with our data (Baker et al. 1999). Our data imply that molecular forces equilibrate among, not within, individual myosin heads, and that muscle, not individual myosin heads, is the near-equilibrium thermodynamic system (this thermodynamic muscle model is developed in Baker, 1999). If this is correct, the detailed molecular description of muscle provided by Huxley and Hill would have to be modified to include cooperative interactions among myosin heads, a possibility discussed by Hill (1975).

Finally, we note that muscle contraction is a very special case of free energy transduction that was not included in the discussion between Tanford (1984), Hill and Eisenberg (1981), and Hill (1983) on the possible localization of the point of free energy transfer in free-energy-transducing biochemical cycles.

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