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This Week's Citation Classic

Huxley H E. Electron microscope studies on the structure of natural and synthetic protein filaments from striated muscle. *J. Mol. Biol.* **7**:281-308, 1963.
[Medical Research Council Laboratory of Molecular Biology, Cambridge, England]

The author describes a technique for fragmenting striated muscle into its component thick and thin filaments by homogenization in a 'relaxing medium,' and discusses the functional implications of the polarity of the filaments thus revealed. [The *SCI*® indicates that this paper has been cited over 790 times since 1963.]

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"I am flattered to learn that one of my papers is a 'most cited article,' and I have been wondering why this should be. I suspect the reason is that, although the paper is primarily concerned with the structure of muscle, and therefore (at the time it was published anyway) of interest to a somewhat restricted audience, it does contain descriptions of a number of techniques which have had more widespread applications since then.

"One of these is a method for examining the filament-forming properties of the protein myosin. If the ionic strength of a solution of myosin in potassium chloride is lowered by dilution or dialysis from 0.6 to 0 1 M, or less, a precipitate or an opalescence forms, as was well-known at the time. If the precipitate is examined (at high dilution) in the electron-microscope by the negative staining technique, it can be seen very clearly and easily to consist of tilaments somewhat similar to those in muscle and often showing a very characteristic bipolar appearance in the arrangement of the projections on them. This appearance arises because the myosin molecules have a 'head and tail' structure and because they associate so that the tails form the backbone of the filament and the heads project sideways; the molecules are inserted with opposite polarity in either end of the filament. Thus there are projections on the lateral regions and a bare zone in the centre.

"The method is very simple and the appearance very characteristic, so that in fact it constitutes a good simple test for myosin or myosin-like molecules. With the great expansion of interest in contractile proteins from a wide variety of cells other than muscle, the method has been used quite often to confirm that a particular component was indeed myosin-like in its structural behaviour. The negative staining technique was itself relatively new at that time, being one that I had first used on tobacco mosaic virus in 1956,[1] and which was subsequently greatly improved by Brenner and Horne.[2] The description of the technique probably added to the popularity of the paper.

Another technique first described in the paper, which has become very popular as a diagnostic tool, was the observation, again by the negative staining technique in the electron-miscroscope, of actin filaments which had been 'decorated' with myosin, heavy meromyosin, or HMM-subfragment 1, and which show a very characteristic 'arrowhead' structure. This arises in a very specific way from the precise angle of attachment of the myosin heads to actin, and it also shows up on the pitch and subunit repeat of the actin helix. Thus it can be used as a good simple test for either actin or myosin. and it also enables the polarity of the actin filaments to be established. More recently the technique has been used very extensively to identify actin in non-muscle systems.

"There were some other things in the paper of which I am quite fond, including, i believe, the first specific suggestion that cytoplasmic streaming might be due to a relative sliding or shearing interaction between polarized actin and myosin filaments in solution But, I think, it must be the two methods to which I have referreed which account for its popularity."

1. **Huxley, H E.** Some observations on the structure of Tobacco Mosaic Virus. *Proc. 1st European Regional Conf. Electron Microscopy.* Stockholm: Almqvist & Wiksell, 1956. p. 260.
2. **Brenner S & Home R W.** A negative staining method for high resolution electron microscopy of viruses. *Biochem. Biophys. Acta* **34**:103-10, 1959.