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IN MEMORIAM

Andrew Fielding Huxley (1917–2012)

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> *If I have seen further, it is by standing on the shoulders of giants.* (Isaac Newton, in a letter to Robert Hooke (1676). From *The correspondence of Isaac Newton*, vol. 1, *1661–1675*, ed. Turnbull, HW, 1959, p. 416.)

Andrew Fielding Huxley, OM 1983; Kt 1974; FRS 1955; PRS 1980–1985, MA, Hon. ScD Cantab. Physiologist and Biophysicist. Born Hampstead, London, 22 November 1917. Demonstrator, 1946–50, Assistant Director of Research, 1951–59, and Reader in Experimental Biophysics, 1959–60, Physiological Laboratory, Cambridge; Director of Studies, Trinity College, Cambridge, 1952–60; Jodrell Professor 1960–69, Royal Society Research Professor, 1969–83, University College London. Master, 1984–90, Fellow, 1941–60 and since 1990, Trinity College, Cambridge (Hon. Fellow, 1967–90). Died 30 May 2012, aged 94.

Sir Andrew Huxley, shown in his laboratory in Fig. 1, was a giant among modern physiologists, pioneering the fields of nerve conduction, and skeletal muscle activation and tension generation. He worked with exceptional and elegant originality and had a characteristically quantitative approach to physiological analysis within a physically rigorous framework, an approach now beginning to permeate from physiology and biophysics into their cognate biological and biomedical sciences.

He was born in Hampstead, London, to the writer Leonard Huxley and Rosalind Bruce in 1917, within an illustrious family. His grandfather Thomas Huxley was a distinguished 19th-century biologist and early proponent of evolutionary theory. Julian Huxley, a pioneer in animal behaviour, and Aldous Huxley, the author of *Brave New World* among other works, were half-brothers from his father's first marriage. He was educated at University College (1925–30) and Westminster Schools (1930–5), where he was inspired by J. F. Rudwick's teaching to turn from Classics to physical sciences. He chose to apply to Trinity College, Cambridge, through his family's friendship with George Trevelyan, where he won a major Entrance Scholarship (1935). His interests eventually turned to Physiology through his contact with Delisle Burns, and then with E. D. Adrian, Jack Roughton, William Rushton, Alan Hodgkin and Glenn Millikan amongst others. To this end his studies proceeded along a medical direction pursuing Anatomy in 1937–8 and Physiology in Part II of the Natural Sciences Tripos in Cambridge in 1938–39.

His first introduction to physiological experimental work began when he joined Alan Hodgkin, who had previously tutored him in Trinity, at the Plymouth Marine Biological Laboratory in 1939. They succeeded in making electrophysiological recordings from the inside of the squid giant axon, whose structure was first demonstrated by Young (1936), of the time course of its action potential, demonstrating its overshoot for the first time (Hodgkin & Huxley, 1939, 1945). For the first year of the Second World War, Huxley was a clinical student in London. However, when medical teaching was stopped by air attacks, he turned to operational research in gunnery, first for the British Anti-Aircraft Command and later for the Admiralty for the rest of the war, developing radar control of antiaircraft guns and naval gunnery. This was after a brief interlude working as an experimental subject for Robert McCance and Elsie Widdowson, who had been making physiological analyses of calorific values of food before the war, and were then conducting studies on food rationing. The wartime research sharpened his already considerable mathematical and engineering skills: this interest and aptitude in engineering dated from his receiving, as a gift from his parents as a young boy, a lathe which he continued to use in the course of his subsequent scientific work and which remains in his garage in his home in Grantchester, where he continued to live following retirement. This had led him to design and build microscopes and other scientific instruments. These skills proved invaluable in his subsequent scientific work, enabling him to design much of his experimental equipment. In the course of his career, he developed an interference microscope for studying striation patterns in isolated muscle fibres, a microtome for making electron microscope sections, and a micromanipulator, testimony to the importance of technical skills and to the good mechanical workshop facilities then available to physiologists (Huxley, 1954, 1957*a*; Huxley & Niedergerke, 1958).

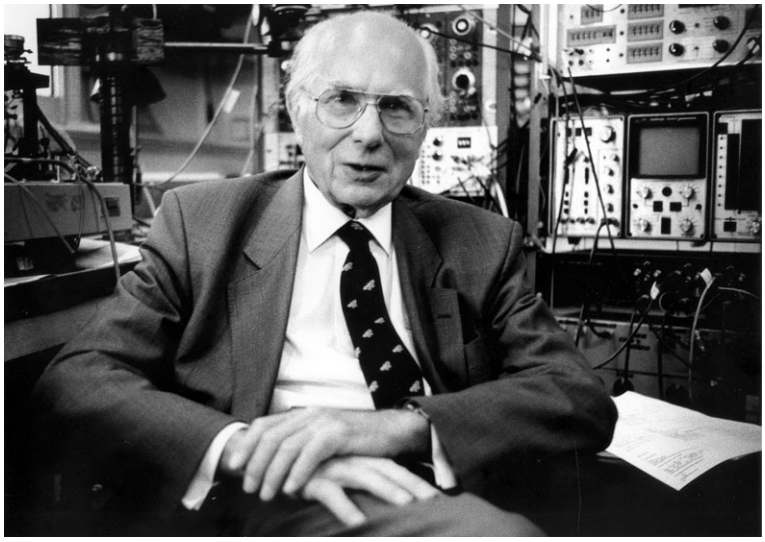

Figure 1. Sir Andrew Huxley photographed in his laboratory
Taken in 1997 by Martin Rosenberg (Physiological Society Archive, Contemporary Medical Archive Centre, Wellcome Institute for the History of Medicine, London).

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Andrew resumed his collaboration with Alan Hodgkin between 1946 and 1951, pursuing their study on squid nerve axons, with the able assistance of Hodgkin's technician, Ron Cook, in the handling, transport and maintenance of the squid. They used the voltage-clamp technique first invented by K. S. Cole (review: Cole, 1968). This permitted detailed study of permeability changes through the separation and measurements of ionic currents crossing the membrane when the potential across it was stepped from a chosen resting level to a known test value ('voltage clamping') defined by the experimenter, rather than permitting this voltage to vary through the complex time course of a conducted action potential. It was thus possible to explore the voltage-sensitive properties of sodium and potassium currents and their time courses, separated from the initial capacitative charging current contributions, through different, controlled test voltages (Hodgkin *et al.* 1952). The behaviour of the underlying sodium and potassium conductances could then be computed with the aid of their known intracellular and extracellular concentrations that furnished the driving forces for such currents (Hodgkin & Huxley, 1952*a*,*b*). These resembled first order transitions incorporating steeply voltage-dependent forward and backward rate constants, whose variables were raised to their third (m^3) and fourth (n^4) powers, respectively. The Na^+ conductance showed an additional, first order inactivation (h) variable that was to prove of fundamental importance in understanding post-excitation refractoriness (Hodgkin & Huxley, 1952*c*).

The final step in the analysis of the data obtained under voltage clamp conditions owed much to Huxley's mathematical ability, scientific imagination and endurance in then computing how the *in vivo* conducted action potential might behave (Hodgkin & Huxley, 1952*d*). This gave excellent agreement between the predicted and observed time courses as well as solutions for conduction velocities of the propagated action potential at 18.5°C (Fig. 2*a*–*d*). Lastly, this computation also quantitatively predicted the exchange of Na^+ and K^+ through the action potential time course (Fig. 2*e*). These results thus established and quantified the *ionic hypothesis* implicating movements of Na^+ in the production and overshoot property of the *in vivo* action potential. An initial membrane depolarization produced either by applied stimulation or pre-existing activation of adjacent membrane would produce a rapid, steeply voltage-dependent activation of the Na^+ conductance. The resulting depolarization produced by the resulting net inward Na^+ movement down its concentration gradient then further increases Na^+ permeability, initiating an accelerating positive feedback process. This terminates only as the membrane potential approaches the Nernst potential E_{Na}, set by the higher extracellular compared to intracellular Na^+ concentrations, when the net inward driving force on Na^+ becomes zero, and with the slower development of a similarly voltage-dependent inactivation. A similar, but more gradual activation of K^+ permeability permitting outward movement of K^+ along an opposite concentration gradient also contributes to membrane potential restoration to its original level. This ends the action potential, but a further time interval, the refractory period, is required for the Na^+ permeability to recover its capacity for further excitation (for historical accounts see Hodgkin, 1976; Huxley, 2002; Waxman & Vandenberg, 2012; Schwiening, 2012).

His award of the 1963 Nobel Prize, with Sir Alan Hodgkin in recognition of their ionic hypothesis, and Sir John Eccles for his work on synaptic signalling, recognized these contributions as providing the conceptual foundation for the study of excitable cell signalling. They also prompted a cascade of important discoveries with implications ranging from the fundamentals of channel function to their translation into the basic mechanisms of disease. The 1991 Nobel Prize was to be subsequently awarded to Erwin Neher and Bert Sakmann for the

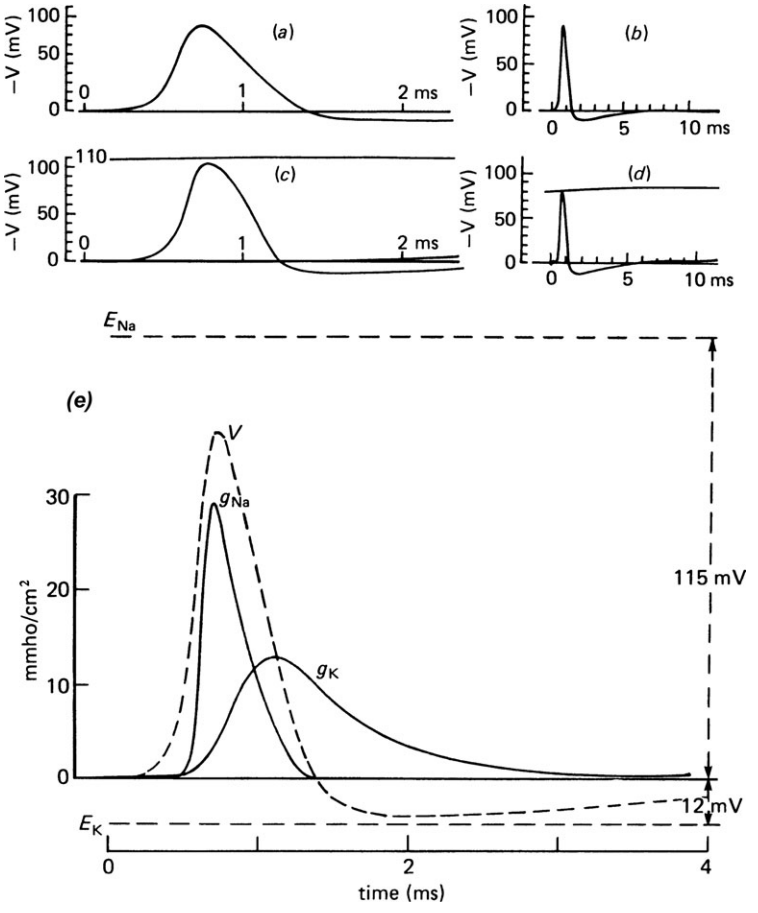

Figure 2. Computed (*a* and *b*) and experimentally recorded (*c* and *d*) propagated action potentials in squid giant axon at 18.5°C, plotted on fast and slow time scales, and underlying conductance changes
Calculated conduction velocity was 18.8 m s^{-1}; that actually observed was 21.2 m s^{-1}. *e*, time courses of propagated action potential and underlying ionic conductance changes computed from voltage-clamp data. The constants used corresponded to an 18.5°C temperature. Conduction velocity = 18.8 m s^{-1} (Hodgkin & Huxley, 1952*d*).

novel, direct patch-clamp demonstration of small electric Na^+ currents directly demonstrating events involving single ionic channels underlying the observed conductances (Sakmann & Neher, 1983, 1984; Hamill *et al.* 1981; Raju, 2000; Nilius, 2003). A loose-patch adaptation of this technique went on to characterize channel distributions over the membrane area (Almers *et al.* 1983). The voltage dependence of the sodium conductance implies a gating mechanism involving charge movements down the trans-membrane electric field. These were subsequently demonstrated directly in the form of the gating currents that proved invaluable for studying the mechanisms of the molecular configurational changes underlying channel activation (Armstrong & Bezanilla, 1973; Keynes & Rojas, 1974). This line of work has recently culminated in the full structural characterization of the Na^+ channel and its gating transitions (Payandeh *et al.* 2012; Yarov-Yarovoy *et al.* 2011).

Both the voltage clamp techniques and their associated mathematical formulations have also been applied, corrected for their cellular geometry by cable theory, to other excitable tissues, notably myelinated nerve (Huxley & Stampfli, 1949; Frankenhaeuser & Huxley, 1964), and skeletal (Adrian *et al.* 1970) and cardiac muscle (Noble, 1962, 1984). The fundamental ideas have had wide and fundamental translational implications for clinical medicine including understanding of local anaesthesia and pain, the neurological condition myotonia congenita in skeletal muscle (Adrian & Bryant, 1974), and arrhythmia in cardiac muscle (Lei *et al.* 2008). Even when he had ceased active laboratory work, Huxley himself encouraged the recent studies of genetically modified murine cardiac models for Na^+ channelopathies in Cambridge (Papadatos *et al.* 2002; Sabir et al 2008; Killeen *et al.* 2008). These demonstrated the importance of their consequently altered Na^+ channel activation and recovery properties in producing sino-atrial pacemaker (Lei *et al.* 2005) and atrial and ventricular arrhythmic disorders, findings applicable to the human arrhythmogenic Brugada and long QT3 syndromes (Martin *et al.* 2012; Matthews *et al.* 2012), with implications for management of patients with sinus node dysfunction, atrial fibrillation and at risk of sudden cardiac death (Martin *et al.* 2011). Finally, the electrical circuit theory formulations describing the ionic hypothesis prompted subsequent realistic mathematical simulations of the effects upon cellular homeostasis of not only electrogenic but also electroneutral and osmotic fluxes (Fraser & Huang, 2004).

In 1952 Andrew turned to muscle physiology. Prompted by previous electron-microscope observations (Huxley, 1982), he demonstrated that surface electrical activation initiated mechanical activity visible under interference microscopy following localized micropipette stimulation only in specific areas along the muscle fibre sarcomere (Fig. 3; Huxley & Taylor, 1958). These corresponded to the Z line in frog sartorius but the boundary between A and I bands in crab muscles, thereby implicating their invaginating, transverse tubular membrane systems in contractile activation. The latter structures, including their fragility to osmotically induced volume change (Gage & Eisenberg, 1969; Fraser *et al.* 1998), were to be subsequently studied in detail by, among others, Clara Franzini-Armstrong, Robert Eisenberg, and Lee Peachey, all of whom had begun their scientific work in Huxley's laboratory. This led to application of electrical cable representations of their tubular geometry using some of Hodgkin & Huxley's original mathematical formulations to determine their role in active conduction of excitation into the fibre interior (Adrian & Peachey, 1973; Huang & Peachey, 1992). This further led to the recent view of a rapid surface action potential propagation along the muscle fibre length with only its lower frequency components filtered into, thereby activating, the extensive tubular capacitance without compromising surface conduction (Sheikh *et al.* 2001; Pedersen *et al.* 2011). Finally, clarifications of the resulting initiation of excitation–contraction coupling through dihydropyridine receptor-mediated voltage sensing and allosterically coupled, ryanodine receptor mediated calcium release processes similarly used voltage

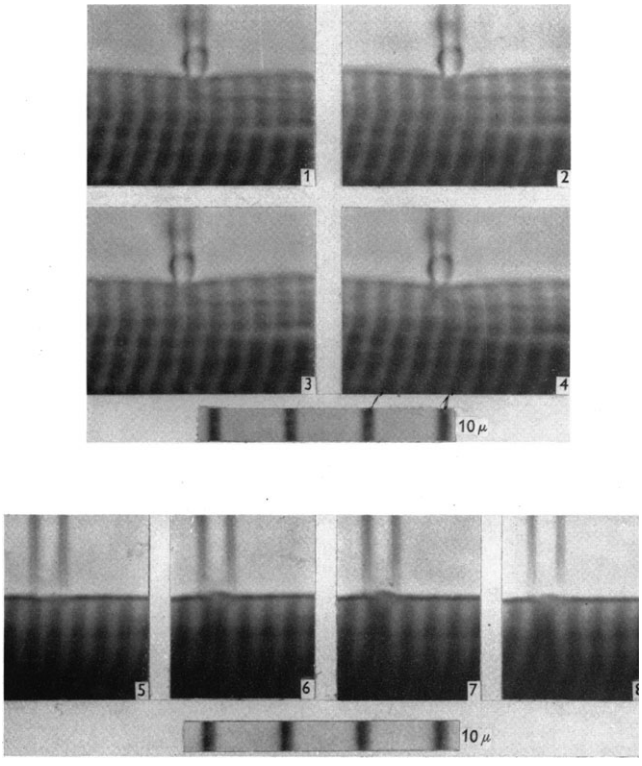

Figure 3. Local activation experiments in amphibian skeletal muscle
Panels 1–4, edge of isolated frog muscle fibre with contacting pipette photographed under polarized light with A bands appearing dark. Photographic results of applying the pipette to an A (panels 1 and 2) and to an I band (panels 3 and 4) before (panels 1 and 3) and during (panels 2 and 4) stimulation demonstrate that contraction results only if the pipette is opposite an I band (panel 4). Panels 5–8, successive cine frames (at 16 frames s^{-1}) following the shortening following local depolarization applied between panels 5 and 6 (Huxley & Taylor, 1958).

clamp techniques (Huang, 1993, Huang *et al.* 2011). Some of these experiments were performed in collaboration with Lee Peachey, who returned to Cambridge in the late 1980s as Huxley's house guest in Trinity College's Master's Lodge (Huang & Peachey, 1989, 1992).

The remainder of Huxley's working life turned to muscle contraction itself. In 1954, Andrew Huxley and Rolf Niedergerke, and Hugh Huxley and Jean Hanson independently suggested a *sliding filament theory* (Huxley & Niedergerke, 1954; Huxley & Hanson, 1954), replacing existing suggestions that muscle contraction involved coiling and contraction of long protein molecules akin to shortening of a helical spring. Their independent methods showed that sarcomeric A band lengths did not change in either stretched or actively or passively shortening muscle. Contraction thus resulted from relative movements of thin filaments between thick filaments through cross bridge interactions between them. Perhaps the most elegant test of this hypothesis examined the resulting prediction that isometric tension in a single muscle fibre would then be proportional to the filament overlap (Gordon *et al.* 1966). This was varied experimentally in amphibian muscle fibres using optical servomechanisms to maintain sarcomere lengths in the middle of a fibre constant at a chosen value during contraction. Figure 4*A* annotates the resulting length–tension diagram, which consists of a series of straight lines connected by short curved regions. This shows a plateau between 2.05 and 2.2 μm, above which tension falls linearly with increasing length through a line extrapolating to zero at 3.65 μm, and below which tension falls first gradually with decreasing length to ~1.65 μm, then much more steeply to reach zero at ~1.3 μm. Its correlation with predictions from electron microscopic determinations of 2.05 μm long actin, including a 0.05 μm Z-line, and 1.6 μm long myosin filaments with 0.15 to 0.2 μm middle regions bare of cross-bridges (Fig. 4*B*) elegantly confirm such a crossbridge hypothesis. Thus (1) sarcomere lengths >3.65 μm would not permit crossbridge formation thereby excluding tension development (Fig. 4*C*). In contrast, between 3.65 μm and (2) 2.2–2.25 μm, crossbridge number and therefore isometric tension would linearly increase with decreasing sarcomere length. However, further shortening between (2) and (3) would leave constant cross-bridge numbers, predicting the tension plateau. However, further shortening beyond (3) could increase the internal resistance to shortening due to actin filament overlap. Beyond (4) actin filaments from one half of the sarcomere might interfere with the cross-bridge formation in the other half of the sarcomere, predicting a fall in tension below ~2.0 μm. At (5) 1.65 μm myosin filaments hitting the Z line should considerably increase the resistance to further shortening predicting a distinct kink in the curve beyond which tension falls much more sharply to zero tension at ~1.3 μm before (6). The need for electron-microscopic determination of sarcomeric dimensions that formed the basis of this comparison prompted his invention and manufacture of his novel microtome which was subsequently marketed by Cambridge Scientific Instruments and whose design is still in current use.

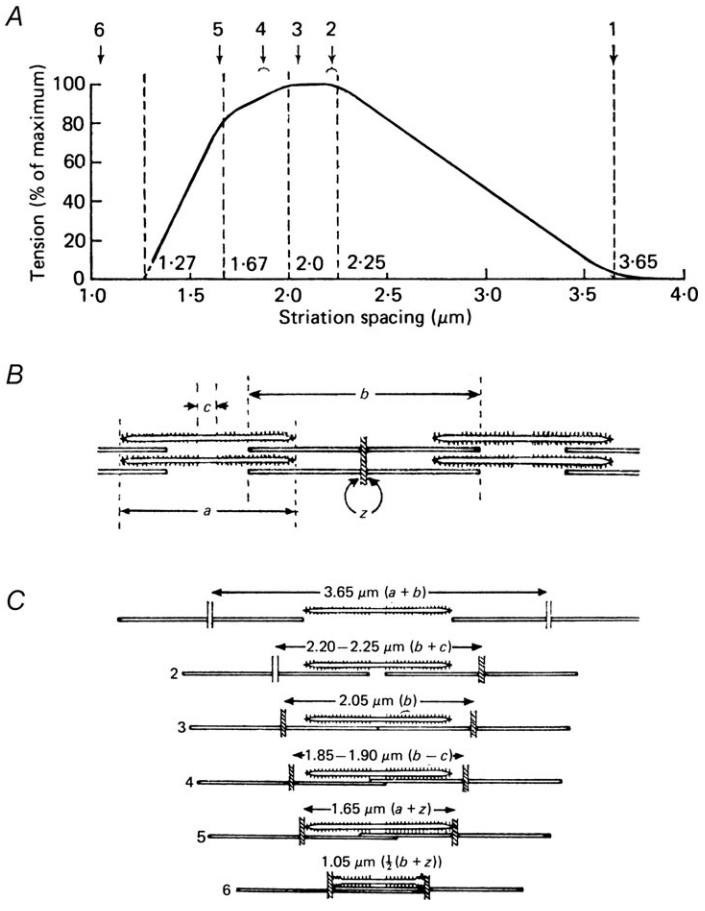

Figure 4. The length-tension relationship in amphibian muscle and myofilament overlap
A, the isometric tension (active increment) of a frog muscle fibre at different sarcomere lengths. The numbers 1 to 6 refer to the myofilament positions shown in *C*. *B*, myofilament dimensions in frog muscle. *C*, myofilament arrangements at different lengths. The letters *a*, *b*, *c* and *z* refer to the dimensions given in panel *A* (Gordon *et al.* 1966).

Huxley's subsequent experiments went on to clarify the crossbridge interactions producing the relative sliding between these actin and myosin filaments (Huxley, 1957*b*). The cytosol of resting muscle contains adequate ATP and very low Ca^{2+} concentrations, conditions under which there is no actin–myosin interaction. Increases in Ca^{2+} initiate a crossbridge formation with a filament sliding and ATP breakdown brought about by cyclic reactions between projections on the myosin filaments and active sites on the actin filaments. Huxley's studies on the resulting tension transients were ultimately synthesized into his 1974 model (Huxley & Simmons, 1971;

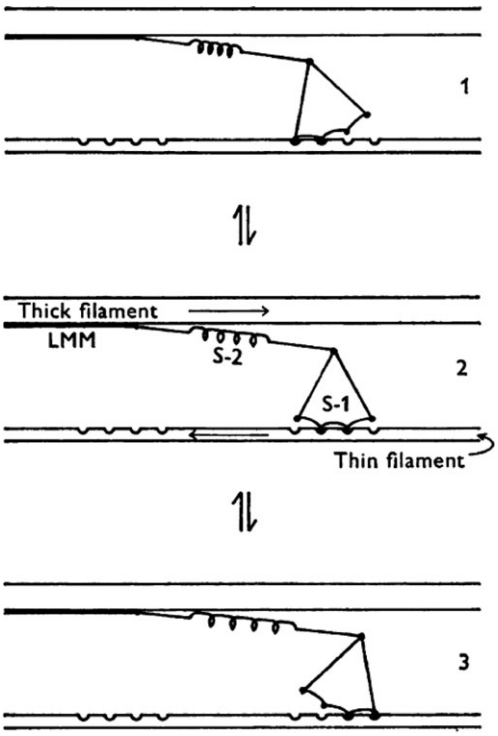

Figure 5. The Huxley–Simmons (1971) model for crossbridge interaction
The model incorporates elastic and stepwise shortening elements in the generation of crossbridge tension, exemplified by three possible myosin head positions 1, 2 and 3 of successively greater strengths of binding to actin in which the myosin head can dissociate in position 1 without, but in position 3 only with ATP utilization (Huxley, 1974).

Huxley, 1974) incorporating elastic and stepwise-shortening elements deduced from the nature of the observed tension transients. The sequence in Fig. 5 represents actin–myosin binding at possible attachment sites as the system moves from position 1 to position 3, doing so with successively increasing strengths of interaction. Finally, myosin detachment can take place in position 3 with utilization of a molecule of ATP, thereby permitting the myosin head to attach to another site further along the actin filament in position 1, repeating the process of successive myofilament shortening. In this final direction of his work, he was joined by, amongst others, Lincoln Ford, Yale Goldman, Hugo Gonzalez-Serratos, Lucy Brown, Vincenzo Lombardi and Gabriella Piazzesi in this investigation into what was to him, the heart of Physiology as 'the mechanical engineering of living things'.

To add to these momentous scientific contributions, Andrew was generous with his time in activities of The Physiological Society, to which he was elected as an Ordinary Member in 1942 and an Honorary Member in 1979. He served on the Editorial Board of *The Journal of Physiology* (1950–57) and its Committee (1957–61; 1970–74). He was joint president of the International Union of Physiological Sciences from 1986 to 1993. Huxley was also an Editor of the *Journal of Molecular Biology*. He became a Fellow of the Royal Society in 1955, and served on its Council (1960–1962). He worked at Woods Hole, Massachusetts, in 1953 as a Lalor Scholar, and gave the Herter Lectures at Johns Hopkins Medical School (1959); and the Jesup Lectures at Columbia University (1964).

In 1947 Andrew Huxley married Jocelyn Richenda Gammell Pease, daughter of the geneticist M. S. Pease, and the Hon. H. B. Pease (née Wedgwood). She was a Justice of the Peace, and was active in a variety of public work in Cambridgeshire, but predeceased him in 2003. At the end of what must have been busy days for both of them, they delighted in reading to each other in the evening, greatly enjoying Jane Austen's works and leaving the television to the grandchildren on rainy days. They have five daughters and a son.

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Acknowledgements

I first met Sir Andrew as a graduate student when he was demonstrating signal filtering instrumentation to a Physiological Society meeting at University College London around 1980. I would like to take this last opportunity to record my deep gratitude to him for his subsequent encouragement of work I have pursued on surface and tubular action potential conduction in skeletal muscle, arrhythmogenesis in channelopathic models for cardiac muscle, and with Lee Peachey and the late Richard Adrian on excitation–contraction coupling. I am also grateful to Professor W. A. Harris and Dr Ann Silver for encouragement and help in writing this tribute, Carol Huxley for important biographical details and reading through and checking drafts of this account, Jeremy Skepper and Alan Catell for archival information, particularly concerning instrumentation invented by Huxley, and David Trentham for information about some of Andrew's colleagues in the cross-bridge field. I apologize in advance to those whose contributions and roles in Sir Andrew's life I may have inadvertently omitted or slighted.