Sir Andrew Huxley (1917–2012) pioneered the physiology and biophysics of nerve conduction, skeletal muscle activation and tension generation. His ground-breaking work on nerve excitability of nerve in collaboration with Alan Hodgkin in the Cambridge Physiological Laboratory and the Plymouth Marine Biological Laboratory provided the basis for our understanding of how voltage-gated ion channels generate propagating action potentials and led to award of the 1963 Nobel Prize for Physiology and Medicine with Alan Hodgkin and Jack Eccles. Huxley then went on to perform seminal work of similar importance on muscle activation and contraction whilst at University College London. This led to the sliding filament theory and cross-bridge hypothesis of muscle contraction, completing a momentous quest within physiology, in his view, “the mechanical engineering of living things”.

Huxley was born in London within an illustrious family. His father Leonard was a writer and his grandfather Thomas an early proponent of evolutionary theory. His half-brother Julian pioneered in animal behaviour and Aldous, another half-brother, was a distinguished writer, authoring, among other books, *Brave New World*.

He was educated at University College (1925–30) and Westminster Schools (1930–5), winning a major Entrance Scholarship in 1935 to Trinity College, Cambridge. His interests turned to physiology, for which his studies pursued a medical direction including anatomy in 1937–8 and Part II Physiology in the Natural Sciences Tripos (1938–9). He also showed exceptional engineering talent, which was to be his close companion for the rest of his career, wherein he often invented equipment integral to his experiments. He thus invented a micromanipulator, an interference microscope for studying striation patterns in muscle, and a microtome for making electron microscope sections (Huxley, 1954, 1957a; Huxley & Niedergerke, 1958).
His first encounter with physiological research was in 1939 with Alan Hodgkin on the properties of the propagated impulse in giant axons of squid. It was known that this was an all-or-none event resulting in an advancing membrane potential change along the fibre cable structure thereby stimulating adjacent, initially quiescent membrane. Bernstein (1902) had attributed the resting negativity of the fibre interior to a selective permeability of the membrane to potassium relative to sodium, and the greater intracellular relative to extracellular potassium concentration. The action potential might then result from a generalized increase in membrane permeability to all ions in response to alteration of the internal potential beyond a threshold level, collapsing this potential to zero. An increased membrane permeability had indeed been demonstrated by membrane impedance measurements by a high-frequency alternating current (AC) bridge (Cole & Curtis, 1939). However, Hodgkin and Huxley's (1939, 1945) intracellular recordings of the action potential demonstrated that the membrane potential becomes substantially positive (Fig. 1). This observation was to lead eventually to the current view that this reflects an increased permeability specific for sodium ions, which would diffuse inwards carrying a positive charge. However, work in this direction was interrupted by Hitler’s invasion of Poland and the subsequent outbreak of war. It was only to resume seven years later, when Huxley returned from work first for the British Anti-Aircraft Command and later for the Admiralty, developing radar control in antiaircraft guns and naval gunnery.

Figure 1

**Intracellular recording of the squid giant axon action potential.**

A, photomicrograph of an electrode within a squid giant axon (diameter ~500 μm), showing two views of the same axon which allowed simultaneous viewing of the electrode from both front and side made visible from a system of mirrors devised by Huxley. This ensured that the electrode would not damage the nerve membrane as it was threaded down the axon (Hodgkin & Huxley, 1945). B, the first intracellular recording of an action potential and its overshoot. The sine wave time marker has a frequency of 500 Hz (Hodgkin & Huxley, 1939; by permission from Macmillan Publishers Ltd: Nature C1939).
Andrew thus resumed his collaboration with Alan Hodgkin in 1946. By 1947, voltage clamp equipment invented by Cole (Cole & Curtis, 1939; for a review see Cole, 1968) had successfully demonstrated continuous current–voltage relationships in squid nerve membrane that nevertheless included a region of negative slope compatible with the regenerative, all-or-none, property shown by the action potential. This was made possible through control of the voltage through imposed steps from a chosen, resting level to known test values ('voltage clamping') defined by the experimenter, as opposed to its variation through the complex time course of a conducted action potential. It was then also possible to explore the time courses of sodium and potassium currents traversing the membrane, and determine the underlying permeability changes, separated from the initial capacitative charging current contributions, through different, controlled, test voltages (Fig. 2; Hodgkin et al. 1952). A consecutive sequence of four experimental papers described the current–voltage relationships in squid giant axon membranes (Hodgkin et al. 1952), characterized their currents attributable to movements of sodium and potassium ions (Hodgkin & Huxley, 1952a), and the effect upon these of varying the times and durations of depolarizing and repolarizing steps (Hodgkin & Huxley, 1952b), and ended with studies on the ‘inactivation’ of the sodium permeability following its initial activation produced by depolarization (Hodgkin & Huxley, 1952c).

Figure 2

A family of currents acquired using large depolarizing steps under voltage clamp control

Early records of this kind plotted both current traces with inward currents represented as positive and voltages with depolarizations given relative to the holding potential and the outside voltage plotted relative to the inside. The −91 mV step represents a depolarization of the inside of the nerve fibre to +15 mV (Hodgkin et al. 1952).
The final, theoretical paper then synthesized these results into a ‘Quantitative description of membrane current and its application to conduction and excitation in nerve’ (Hodgkin & Huxley, 1952d), describing amongst the most elegant applications of computational methods in the biological sciences. The sodium and potassium conductances were described in terms of first order transitions with steeply voltage-dependent forward and backward rate constants, with variables raised to their third ($m^3$) and fourth ($n^4$) powers, respectively, with the sodium conductance additionally incorporating an inactivation ($h$) variable. The resulting reconstruction of the in vivo conducted action potential closely agreed with the observed time courses and conduction velocities (Fig. 3a-d) (Hodgkin & Huxley, 1952d). It was also possible to reconstruct the detailed Na⁺ and K⁺ movements through the action potential time course (Fig. 4). Thus was established the ionic hypothesis implicating movements of sodium ions in the production and overshoot property of the in vivo action potential. An initial stimulation or pre-existing activation of adjacent membrane would produce a rapid, steeply voltage-dependent activation of the sodium conductance. This would result in a further depolarization, in turn further increasing sodium permeability, initiating a positive feedback process terminated only as the membrane voltage approaches the sodium Nernst potential, and with a slower potassium permeability activation driving a repolarizing outward current. The latter would also contribute to membrane potential restoration to its resting level into a period of refractoriness over which the sodium permeability and therefore the membrane regains its capacity for activation (Historical accounts: Hodgkin, 1976; Huxley, 2002; Waxman & Vandenberg, 2012; Schwiening, 2012).

Figure 3

Computed (a and b) and experimentally recorded (c and d) action potentials propagated in squid giant axon at 18.5°C, plotted on fast and slow time scales.
Calculated conduction velocity was 18.8 m s⁻¹; that actually observed was 21.2 m s⁻¹ (Hodgkin & Huxley, 1952d).
Figure 4

Time courses of propagated action potential and underlying ionic conductance changes computed from voltage clamp data.

The constants used corresponded to a 18.5°C temperature. Conduction velocity, 18.8 m s\(^{-1}\) (Hodgkin & Huxley, 1952a).

Over this time, Huxley also collaborated with Robert Stämpfli on the function of the myelin sheath in vertebrate nerve fibres in restricting inward and outward local current passage to the nodes of Ranvier, resulting in an enhanced, salutatory, conduction of their nerve impulses between nodes (Lillie, 1925). This reflected the reduced stimulation thresholds and greater sensitivity to anodal polarization and to local anaesthetics at nodal than along internodal regions (Tasaki, 1953). Huxley and Stämpfli (1949) refined those earlier techniques, pulling an isolated frog myelinated fibre through a short glass capillary traversing a partition separating two Ringer-solution-filled compartments (Fig. 5A). The capillary diameter was small enough to impart the fluid-filled space around the nerve an appreciable, 0.5 MΩ, resistance. Longitudinal current flow between neighbouring nodes would then generate a measurable voltage across the two sides of the partition. The resulting records of longitudinal current showed (Fig. 5B) that currents were similar in magnitude and timing at all points outside any one internode but their peaks were displaced stepwise in time by ~0.1 ms as successive nodes were traversed. The current flowing radially into or out of the fibre could be determined by subtracting successive pairs of records from one another (Fig. 5C). This demonstrated only slight current leaks over the internodes but a brief pulse of outward current followed by a much larger pulse of inward current restricted to each node.
Method used by Huxley and Stämpfli (1949) to investigate saltatory conduction.

A, the isolated frog nerve fibre was pulled through a 40 µm diameter aperture in an insulating partition. Current flowing along the axis cylinder out of one node and into the other indicated by the arrows causes a voltage drop outside the myelin sheath. The 0.5 MΩ resistance of the fluid in the gap between the two pools permits measurement of the potential difference between them. The internodal distance in a frog’s myelinated nerve fibre is about 2 mm. B, longitudinal currents flowing at different positions along the fibre with the right hand diagram showing the position where each record was taken. Distance between nodes ~2 mm. C, transverse currents at different positions along the fibre with each trace showing the difference between successive longitudinal currents. Vertical mark above each trace shows the time at which membrane potential change reached its peak at that position along the fibre. Outward current plotted upwards (Huxley & Stämpfli, 1949).

The 1963 Nobel Prize to Hodgkin and Huxley for their ionic hypothesis and Sir John Eccles for his work on synaptic signalling thus recognized key contributions that provided the conceptual foundation for studies of excitable cell signalling. They had a similar significance for neurophysiology and biophysics as the structure of DNA reported by Watson and Crick had for biochemistry. The findings in nerve prompted a cascade of important discoveries whose implications range from the fundamentals of channel function, through their application to excitable tissues generally, to their translation to understanding the basic mechanisms of disease. Firstly, of
those concerning sodium channel properties and function itself, the voltage dependence of the sodium conductance and its rate constants led Hodgkin and Huxley to predict that channel opening and closing would involve net transfers of intramembrane charge in response to alterations in the transmembrane electric field. Such gating currents were to be demonstrated twenty years later, providing a direct biophysical handle for studying the mechanisms of the molecular configurational changes underlying channel activation (Armstrong & Bezanilla, 1973; Keynes & Rojas, 1974). The 1991 Nobel Prize was then to be awarded to Erwin Neher and Bert Sakmann for their introduction of the patch clamp technique. This made direct measurements of currents traversing single sodium channels, thereby directly demonstrating the unit channel events through single ionic channels underlying the observed conductances (Sakmann & Neher, 1983, 1984; Hamill et al. 1981; Raju, 2000; Nilius, 2003). Finally, in more recent years, the field of biochemistry was to describe the structure of the sodium channel and characterize its gating transitions (Yarov-Yarovy et al. 2011; Payandeh et al. 2012).

Secondly, both the voltage clamp techniques and their associated mathematical formulations were applicable to analysis of function in other excitable tissues, including mammalian nerve (Huxley & Stampfli, 1949; Frankenhaeuser & Huxley, 1964), skeletal (Adrian et al. 1970) and cardiac muscle (Noble, 1962, 1984), and in neuronal encoding processes exemplified by repetitively firing gastropod nerve (Connor & Stevens, 1971 a-c). Thirdly, the electrical circuit theory formulations used in the ionic hypothesis prompted subsequent more realistic mathematical simulations that could reconstruct not only electrophysiological, but also volume regulatory effects, of not only electrogenic, but also electroneutral and osmotic fluxes and metabolic change (Fraser & Huang, 2004; Fraser et al. 2005; Usher-Smith et al. 2006).

Finally, the fundamental ideas indicated paths through which work seeking translational implications for clinical medicine would follow. Within nerve function these concerned our fundamental understanding of local anaesthesia and pain, as well as of the importance of the Schwann cell sheath on conduction velocity in demyelinating conditions. Skeletal muscle proved a fertile ground for the application of both the Hodgkin-Huxley analysis and cable theory in an analysis of the repetitive firing in the neurological condition of myotonia congenita (Adrian & Bryant, 1974). Arrhythmic and abnormal excitation conditions in cardiac muscle have proven an important area for the application of basic biophysical ideas (Lei et al. 2008). These included recent studies of genetically modified murine cardiac models for sodium channelopathies (Papadatos et al. 2002; Sabir et al. 2008; Killeen et al. 2008). These demonstrated how altered sodium channel activation and recovery properties would result in sino-atrial pacemaker (Lei et al. 2005), atrial and ventricular arrhythmic disorders, in murine models for the human arrhythmogenic conditions including the Brugada and Long QT3 syndromes (Martin et al. 2011, 2012; Matthews et al. 2012).
Huxley moved from Cambridge to University College London in 1960, turning his interests to skeletal muscle, starting with the recognition that the excitation beginning in its surface membrane need to be transduced into a contractile activation of myofilaments in the fibre interior. AV Hill (1948; for a full historical account see Hill, 1965) had demonstrated that the timescale of such excitation was difficult to explain in terms of diffusion into the interior of an activating substance liberated at the surface membrane. However, preliminary light microscope evidence suggested a “Krause’s membrane” that might form a continuous structure across the fibre at the Z-line. Huxley and Taylor (1958) depolarized very small patches of the surface membrane of isolated muscle fibres by placing the end of a ~1 μm diameter micropipette in contact with the surface and applying a negative electric potential to the fluid contained within the pipette. They demonstrated a highly localised contraction, visible under interference microscopy, only when the pipette apposed an I band, and never when the pipette was opposite an A band (Fig. 6). A loose-patch adaptation of this localized micropipette technique was to prove useful to characterize channel distributions over the membrane area (Almers et al. 1983). Electron microscopic studies correlated this with an occurrence of a transverse tubular membrane system continuous with the surface membrane and open to the extracellular space (Huxley & Taylor, 1958; Huxley, 1982). The latter structure, including its fragility following osmotically induced volume change (Gage & Eisenberg, 1969; Fraser et al. 1998), was to be the subject of subsequent study by, among others, Clara Franzini-Armstrong, Robert Eisenberg and Lee Peachey, who had begun scientific work with Huxley. These prompted the application of electrical cable representations of that tubular geometry to Hodgkin & Huxley’s original analysis, in a reconstruction of its role in active conduction of excitation into the fibre interior and the activation of contraction (Adrian & Peachey, 1973; Huang & Peachey, 1992). This, in turn, led to the current view suggesting a rapid propagation of the action potential along the membrane surface to the ends of the fibre. The lower frequency components of this action potential then activate the tubules by initiating a further centripetal wave of excitable activity (Sheikh et al. 2001; Pedersen et al. 2011). Finally, clarifications of the subsequent excitation–contraction coupling mechanisms at the molecular level, involving dihydropyridine receptor-mediated voltage sensing allosterically coupled to ryanodine receptor-mediated release of intracellularly stored calcium, similarly involved voltage clamp techniques (Huang, 1988, 1993; Huang et al. 2011; Huang & Peachey, 1989, 1992).
Local activation experiments in amphibian skeletal muscle.

Panels 1–4 show the edge of an isolated frog muscle fibre with apposed pipette. This is photographed under polarized light with A bands appearing dark. Comparison of the results of stimulation at an A (panels 1 and 2) and an I band (panels 3 and 4) before (panel 1 and 3) and during (panels 2 and 4) stimulation demonstrates contraction only with the pipette opposite an I band (panel 4). Successive cine frames (at 16 frames s⁻¹; panels 5–8) show the shortening where the local depolarization is applied between panels 5 and 6 (Huxley & Taylor, 1958).
Huxley's interest then turned to muscle contraction itself. It had previously been assumed that muscle contraction involved coiling and contraction of long protein molecules akin to the shortening of a helical spring. Andrew Huxley & Rolf Niedergerke, and Hugh Huxley & Jean Hanson, independently suggested the *sliding filament theory* (Huxley & Niedergerke, 1954; Huxley & Hanson, 1954), prompted by findings that sarcomeric A band lengths remained constant in both stretched and actively or passively shortening muscle. Huxley then produced elegant evidence that contraction thus resulted from a relative sliding of thin filaments between thick filaments probably driven by cross bridge interactions between them (Gordon et al. 1966). This compared isometric tension and filament overlap itself held at a range of fixed lengths by optical servomechanisms in single amphibian muscle fibres. The resulting length–tension diagram (Fig. 7A) closely correlated with predictions from electronmicroscopy determinations (Fig. 7B) of 2.05 µm long actin, including a 0.05 µm Z-line, and 1.6 µm long myosin, filaments whose 0.15 to 0.2 µm middle regions were bare of cross bridges. Thus, (1) sarcomere lengths >3.65 µm would not permit cross bridge formation directly explaining the accompanying loss of tension development (Fig. 7C). In contrast, between 3.65 µm and (2) 2.2 to 2.25 µm, cross bridge number would linearly increase with decreasing sarcomere length. This correlated with the corresponding linear increase in isometric tension. However, further shortening between (2) and (3) would leave constant cross bridge numbers, predicting the tension plateau between 2.05 and 2.2 µm. Tension fell with further shortening beyond (3) attributable to actin filament overlap. (4) Below ~2.0 µm a clash between actin filaments between halves of the sarcomere would predict the fall in tension. (5) At 1.65 µm, myosin filaments would hit the Z line, predicting a distinct kink in the curve beyond which tension falls much more sharply to zero tension at ~1.3 µm before (6).
Figure 7

Analysis of the length–tension relationship of skeletal muscle in terms of a cross bridge hypothesis.

A, the isometric tension of isolated frog muscle fibre at different sarcomere lengths. The numbers 1 to 6 refer to the myofilament positions shown in C. B, electronmicroscopic measurements of myofilament dimensions in frog muscle. C, myofilament arrangements at different lengths. Letters a, b, c and z refer to dimensions given in panel A (Gordon et al. 1966).

Huxley’s final interest concerned the cross bridge interactions mediating the cross bridge sliding itself accompanied by ATP breakdown (Huxley, 1957b). Cytosolic Ca$^{2+}$ elevation then initiates cyclic reactions between projections on the myosin filaments and active sites on the actin filaments in the form of cross bridge formation and configurational change that drives a filament sliding and ATP breakdown. Huxley’s 1974 model (Huxley & Simmons, 1971; Huxley, 1974) explained the resulting tension transients in terms of elastic and step-wise shortening elements driven by an actin–myosin binding through a sequence of attachment sites each reflecting increasing strengths of interaction (1 to 3 in Fig. 8). Myosin detachment, permitting re-initiation of a further
cross bridge cycle with a fresh actin binding site, would then take place in position 3 accompanied by ATP hydrolysis. This final direction of work involved amongst others, Lincoln Ford, Yale Goldman, Hugo Gonzalez-Serratos, Lucy Brown, Vincenzo Lombardi and Gabriella Piazzesi.

Figure 8

The Huxley-Simmons (1971) model for cross bridge interaction.
This incorporates elastic and step-wise shortening elements and three possible myosin head positions 1, 2 and 3 of successively greater strengths of binding to actin. The myosin head can dissociate in position 1 without, but in position 3 only with ATP utilization (Huxley, 1974).
Sir Andrew was elected to the Royal Society in 1955 and was its President between 1980 and 1985. He became Jodrell Professor of Physiology in 1960, then Royal Society Research Professor in University College London in 1969. He was Master of Trinity College, Cambridge between 1984 and 1990, knighted in 1974 and appointed Order of Merit in 1983. He was elected Ordinary and Honorary Member of the Physiological Society in 1942 and 1979, served in its Committee (1957–61; 1970–4) and served on the Editorial Board of *The Journal of Physiology* (1950–57). He was joint president of the International Union of Physiological Societies in 1986 to 1993. 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), who predeceased him in 2003. They had five daughters and a son.

**Acknowledgements**

I would like to record my deep gratitude to Andrew Huxley for his encouragement of work I pursued on surface and tubular action potential conduction in skeletal muscle, channelopathic models for arrhythmogenesis in cardiac muscle, and with Lee Peachey and the late Richard Adrian on excitation-contraction coupling, during which Lee Peachey stayed with Huxley in the Trinity College Master’s Lodge. I thank Carol Huxley for important biographical details, Jeremy Skepper and Alan Catell for archival information, particularly concerning instrumentation invented by Huxley. I apologize in advance to those whose contributions and roles in Sir Andrew’s life I may have inadvertently omitted or slighted.

**Christopher L-H Huang**

Professor of Cell Physiology, University of Cambridge
References


