

Andrew Fielding Huxley (1917–2012)

Michael C. Mackey and Moisés Santillán, Coordinating Editors

In *A Mathematician's Apology*, G. H. Hardy wrote: "A mathematician, like a painter or a poet, is a maker of patterns. The mathematician's patterns, like the painter's or the poet's, must be beautiful; the ideas, like the colours or the words, must fit together in a harmonious way." In our opinion these sentiments also apply to all other areas of science. The work of Andrew F. Huxley (who passed away on May 30, 2012) is one of the finest examples not only because of its importance to applied mathematics, biomathematics, and physiology but also because of the beauty of the underlying conceptual framework. A. F. Huxley has justifiably become one of the best-known scientists of the twentieth century.

A. F. Huxley was the youngest son of the writer and editor Leonard Huxley and his second wife, Rosalind Bruce, half-brother of the writer Aldous Huxley and biologist Julian Huxley, and the grandson of biologist Thomas H. Huxley. In 1947 he married Jocelyn Richenda Gammell (Chenda) Pease (1925–2003), the daughter of the geneticist Michael Pease and his wife, Helen Bowen Wedgwood.

From 1935 to 1938 A. F. Huxley studied physics, mathematics, and physiology at Trinity College, Cambridge, where he met Alan L. Hodgkin. At the time, high table included a glittering array of scientific talent, including J. J. Thomson, Lord Rutherford, F. W. Aston, A. S. Eddington, F. G. Hopkins, G. H. Hardy, F. J. W. Roughton, W. A. H. Rushton, A. V. Hill, and E. D. Adrian.

In August 1939 Huxley joined Hodgkin at the Marine Biological Laboratory at Plymouth for his first introduction to research, and they succeeded

in recording electrically from the inside of the squid giant axon. However, this work was interrupted by the outbreak of World War II. For the first year of the war, Huxley was a clinical student, but when medical teaching in London was stopped by air attacks, he changed to work on operational research in gunnery, first for the Anti-Aircraft Command and later for the Admiralty.

In 1941 Huxley was elected to a research fellowship at Trinity College, Cambridge, and he took up this position at the beginning of 1946, together with a teaching appointment in the Department of Physiology. On his return to England after a research stay in the laboratory of Kenneth S. Cole, Hodgkin teamed up with Huxley to measure the electrophysiological phenomena associated with the generation of an action potential in the squid giant axon. This work was published in a brilliant series of five papers in the *Journal of Physiology* in 1952. The final one [Hodgkin and Huxley, 1952d] is an intellectual tour de force, combining both experimental data analysis and mathematical modeling (the Hodgkin-Huxley equations). This work earned Hodgkin and Huxley the Nobel Prize in 1963, along with J. C. Eccles, "for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane."

Huxley, the mathematician/physiologist, was not content to stop at the Hodgkin-Huxley model, however, and went on to publish in 1957 his celebrated review of muscle contraction data and its synthesis into the mathematically formulated cross-bridge theory, a theory that still stands in its essential ingredients today.

Huxley held college and university posts in Cambridge until 1960, when he became head of the Department of Physiology at University College London. In 1969 he was appointed to a Royal Society Research Professorship, which he held until 1983, when he became Master of Cambridge University's Trinity College. Named a fellow of the

Michael C. Mackey is Joseph Morley Drake Professor of Physiology at McGill University. His email address is michael.mackey@mcgill.ca.

Moisés Santillán is professor of biomedical engineering and physics at the Center for Research and Advanced Studies of The National Polytechnic Institute, Monterrey, Mexico. His email address is msantillan@cinvestav.mx.

DOI: <http://dx.doi.org/10.1090/noti998>

Royal Society in 1955, he served as its president from 1980 to 1985. In 1974 he was knighted.

We present below a brief account of the two major scientific contributions by Huxley: the Hodgkin-Huxley equations and the sliding filament theory, followed by brief personal pieces written by some of Andrew Huxley's close collaborators, friends, and students.

The Hodgkin-Huxley Equations

The work for which Huxley is best known is his formulation with Alan Hodgkin of the "Hodgkin-Huxley equations" in the final paper [Hodgkin and Huxley, 1952d] of a series of five papers published in 1952 [Hodgkin et al., 1952], [Hodgkin and Huxley, 1952a], [Hodgkin and Huxley, 1952b], [Hodgkin and Huxley, 1952c], [Hodgkin and Huxley, 1952d]. The first of the Hodgkin-Huxley equations, which accounts for the dynamics of the membrane potential of the axon (measured relative to extracellular fluid), V , is

$$(1) \quad C_m \frac{\partial V}{\partial t} + I_i = I_a + D \frac{\partial^2 V}{\partial x^2},$$

where x is the distance along the axon, I_i is the current carried by ions moving through the membrane, and I_a is the current applied to the axon from an external source. The brilliance of the work of Huxley with Hodgkin came in their meticulous characterization of the ionic current I_i , which from their experimental work they deduced consisted of the sum of three independent currents carried by sodium (Na^+), potassium (K^+), and a "leakage" current so $I_i = I_{Na} + I_K + I_L$. Using the voltage clamp technique, they were then able to characterize the way in which these three currents depended on both membrane potential V and time t . Introducing the notion of an equilibrium potential for these three ionic species (e.g., the equilibrium potential V_{Na} for sodium is that value of the membrane potential V for which there is no net sodium current), they then further assumed that the currents were given by an "ohmic" relation such that each current was proportional to the driving force for each ion and the proportionality factor for each was a conductance:

$$\begin{aligned} I_{Na} &= g_{Na}(V - V_{Na}), \\ I_K &= g_K(V - V_K), \\ I_L &= g_L(V - V_L). \end{aligned}$$

From these three relations they were then able to deduce the dependence of the conductances g_{Na} , g_K , g_L on both potential V and time t . The factor g_L was found to be independent of (V, t) , but g_{Na} , g_K were highly nonlinear functions of (V, t) and the problem they then faced was how to characterize this dependence.

The problem was solved for potassium by assuming $g_K = \bar{g}_K [n(V, t)]^4$, where $\bar{g}_K > 0$ is a maximal conductance and n is a so-called gating variable satisfying the simple differential equation

$$(2) \quad \frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n.$$

This was used to fit the experimental data, and from these fits they were then able to deduce the dependence of α_n, β_n on V . Since the temporal evolution of the conductance $g_K(V, t)$ at constant V had a distinctly sigmoidal nature, they concluded that n had to be raised to the fourth power to reproduce this property. In their final paper, Hodgkin and Huxley speculated that the form for the potassium conductance might represent the movement of what we now call a molecular subunit that regulated the opening and closing of the potassium gate. The fourth power would arise if it was assumed that four subunits had to be simultaneously in the correct position for potassium to move across the membrane.

The description of the behavior of the sodium conductance was conceptually the same, though more complicated in detail, since they had to assume that the equation for the sodium current was given by $I_{Na} = g_{Na}(V - V_{Na})$ with $g_{Na} = \bar{g}_{Na}[m(V, t)]^3 h(V, t)$, where m was an activation variable and h was an inactivation variable. Thus three m subunits had to be open to allow Na^+ to cross the membrane, but one h subunit could stop that movement. The kinetics of m and h were described by

$$(3) \quad \frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m$$

and

$$(4) \quad \frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h.$$

From the behavior of g_{Na} as a function of t at constant V , the functional dependence of the activation (α_m, β_m) and inactivation (α_h, β_h) rate constants on V was deduced.

Equations (1)–(4), along with the expressions for the α 's and β 's, are now known as the Hodgkin-Huxley equations and were the first proposed to explain the nature of the action potential in an excitable cell based firmly on experimental evidence. The explanation that they offered was impressive in its breadth, because the solutions conformed to the "form, duration and amplitude of (the action potential), both 'membrane' and propagated; the conduction velocity, the impedance changes during the (action potential); the refractory period; ionic exchanges; subthreshold responses; and oscillations." Though mention was not made in [Hodgkin and Huxley, 1952d] about difficulties in the solution of the equations, Hodgkin in his autobiography [Hodgkin, 1992, p. 291] notes that it

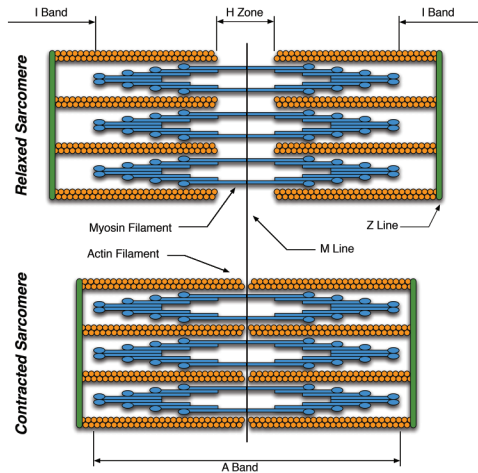


Figure 1.

took Huxley three weeks of work using a Brunsviga mechanical calculator to compute one solution to equations (1)–(4).

Setting aside the difficulties that Hodgkin and Huxley had in solving their proposed equations, there is something buried in their structure that is even more astonishing. The kinetic equation for the temporal evolution of $g_K(V, t)$, as pointed out, could be interpreted as requiring the simultaneous opening of four n subunits. We now know that potassium channels are tetrameric structures with four subunits that must all be in the correct position before ion movement is allowed.

The Hodgkin-Huxley equations were not only extremely influential in the further development of physiology, but they also had a great impact on mathematics. With respect to the full equations, the study of waves in nonlinear parabolic partial differential equations (reaction diffusion equations with excitable dynamics) was initiated by Hodgkin and Huxley when they calculated a traveling wave solution to their equations. Since this initial work, the study of these types of systems has become a flourishing area of research, with applications in biology as well as many other applied areas. Furthermore, various reductions of the Hodgkin-Huxley equations (e.g., the Fitzhugh-Nagumo equations) have provided an extremely active and fertile area of development in dynamical systems theory over the past sixty years.

The Sliding Filament Theory

Huxley was also instrumental in clarifying the mechanisms underlying muscle contraction. He built the first working interference microscope to follow changes in the striation patterns in muscle when it changes length, and this led him (with Rolf Niedergerke) to lay the foundation of what

has become known as the sliding filament theory [Huxley and Niedergerke, 1954].

Myofibrils are one of the most abundant constituents of a muscle fiber. They are long proteinic filaments aligned along the cell longitudinal axis. Under the microscope it becomes apparent that they are composed of a repeated series of so-called sarcomeres, with sarcomeres appearing as dark and light bands and lines (see Figure 1).

Among other structural elements, sarcomeres consist of thin and thick filaments that overlap, as depicted in Figure 1, thus explaining the sarcomere arrangement of bands and lines. Thin filaments are mainly made of the protein actin, while the major component of thick filaments is the protein myosin. The I-band is the zone of thin filaments that is not overlapped by thick filaments, the A-band contains the full length of thick filaments, and the H-zone is the zone of thick filaments that is not overlapped by thin filaments.

According to the sliding filament theory, sarcomeres are the muscle's basic contracting unit. Contraction occurs because the two ends of the thick filaments slide along the thin filaments in opposite directions toward the Z-lines. As this happens, the A-bands do not change their length, whereas the I-bands and the H-zone shorten. All this causes the Z-lines to come closer, therefore causing sarcomere contraction.

The sliding filament theory has been fully corroborated since it was proposed, but it was necessary to develop experimental techniques that were not available at the time this theory was introduced. Since a direct experimental verification was impossible when the theory was proposed, [Huxley, 1957] developed a mathematical model to examine testable consequences of his theory.

A central assumption in the model was that myosin heads, which can attach to (by forming cross-bridges) and detach from specific sites on the actin protein, are responsible for moving the myosin along actin filaments. This assumption predates the notion of rotation of the myosin head. As a matter of fact, it was debatable at that time whether the cross-bridges played an important role in generating the relative sliding of the two filament types. Huxley considered a half-sarcomere (as depicted in Figure 2) and pictured

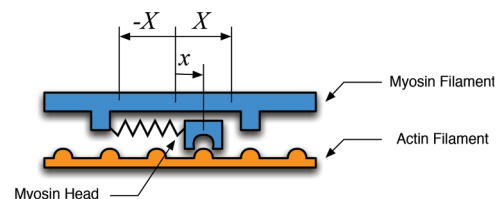


Figure 2.

the myosin heads as attached to the parent myosin filament by elastic tails. He further assumed that when the muscle is stimulated, those heads in the neighborhood of a binding site in the actin filament can be expected to attach to it. Force would then be applied to the actin filament by the stretched elastic tail of the cross-bridge, a contracting force if the elastic tail is in a state of extension. Since a contraction velocity would tend to shorten the elastic tail, in order for such a force to be created, one must assume that the tail is already extended when the cross-bridge is formed. Huxley proposed that this extension could originate from thermal agitation. However, this agitation would likely make the tail extend or contract with the same probability. Hence, Huxley suggested that attachment would, by means of an unspecified chemical-mechanical mechanism, be facilitated for cross-bridges that are displaced positively and be more difficult for those whose tails are in a resting position or contracted.

This conceptual model can be translated into equations by letting $n(x, t)$ denote the density of heads attached to the actin filament at position x and time t and $v(t)$ represent the actin-filament contraction velocity. A balance equation can then be written as

$$\frac{\partial n(x, t)}{\partial t} - v(t) \frac{\partial n(x, t)}{\partial x} = F(x, t) - G(x, t),$$

where $F(x, t)$ and $G(x, t)$ respectively represent the myosin head binding and detachment rates. Huxley further assumed that these functions are given by $F(x, t) = (U - n(x, t))f(x)$, $G(x, t) = n(x, t)g(x)$. In these equations U represents the total density of possible cross-bridges, which is assumed to be independent of both x and t . Furthermore, in agreement with the nonuniformity of the attachment rate, the functions $f(x)$ and $g(x)$ are assumed to be

$$f(x) = \begin{cases} ax & \text{if } 0 \leq x \leq h, \\ 0 & \text{otherwise,} \end{cases}$$

$$g(x) = \begin{cases} b & \text{if } 0 \leq x \leq h, \\ cx & \text{otherwise,} \end{cases}$$

where a, b, c, h are all constant. In particular $b \gg 1$, while h is chosen to be smaller than the maximum myosin-tail extension length, X . Finally, the total force exerted by the attached filament tails can be computed as

$$F(t) = \int_{-X}^X \mathcal{E}(x)n(x, t)dx,$$

in which $\mathcal{E}(x)$ represents the elastic force due to a myosin tail elongated a length x . In his paper, Huxley assumed this function to be given by $\mathcal{E}(x) = \mathcal{E}_m x$, with \mathcal{E}_m the tail elastic modulus. Solving these equations by employing the method of characteristics, Huxley was able to reproduce the

celebrated force-velocity curves (experimentally obtained by A. V. Hill) with a proper choice of parameter values. Another important success of this model was that it correctly predicted the dependence of longitudinal stiffness on the speed of shortening, which had not previously been measured. Huxley himself was aware of his model's incompleteness; however, despite all criticisms, its influence in the evolution of cross-bridge theories has been paramount: practically all current theories qualitatively share the central features of Huxley's model.

Lincoln E. Ford

Personal Remembrances

I was a somewhat disinterested student until my first course in physiology in medical school. What I learned was that physiologists were positing theories of how things worked and conducting experiments to test their theories. I became especially fascinated with the nerve work of Hodgkin and Huxley. In my day it was almost a certainty that all medical graduates would be drafted, so, to indulge my interest in research, I applied to go to the NIH as a commissioned officer to fulfill my National Service obligation. While there I worked with Richard Podolsky, and from the NIH I went to the Peter Bent Brigham Hospital, where I learned that there was a great deal of useless research being done. Wanting to be a better researcher, I asked Podolsky if he would recommend me to Andrew Huxley, which he very kindly did. It was a terrific experience. Andrew had peculiar work habits that meshed very well with my own. He lived in Cambridge and came up to London for the middle three days of every week. We usually ate supper together two nights per week and then worked until 11 o'clock or sometimes later.

At a personal level, Andrew Huxley was kind and sympathetic, particularly to younger scientists, but he had a reputation for being ferocious. This arose, in large part, from his overcommitment. He only rarely turned down a request for help or to be on a committee, with the result of being chronically short of time. There is a class of person who joins committees for the pleasure of dominating the discussion, frequently with specious arguments. He almost always spoiled their fun with irrefutable logic that decimated their arguments and greatly shortened the discussion.

Of all the very intelligent things he did in his life, by far the smartest was his asking Richenda to marry him. She once told me that what she

Lincoln E. Ford is professor emeritus of medicine and of cellular and integrative physiology at Indiana University School of Medicine. His email address is l1eford@iupui.edu.

regarded as her primary role was to provide a secure home life for Andrew and their six children so that he could get on with his work without other worries, and she did this admirably.

Clara Franzini-Armstrong

Clay M. Armstrong and I were postdocs with Sir Andrew at University College London in the sixties. The imposing atmosphere of University College's physiology and biophysics departments, with their tradition of muscle/nerve research (A. V. Hill, B. Katz), the gloomy, old-fashioned laboratories, and the ceremony of afternoon tea in the library were a part of the experience. Most important was the interaction with Sir Andrew. Despite his encouraging gentleness, I was awed. His accomplishments had established him as an innovative and rigorous scientist, and it was quite clear that his mind was always immersed in meaningful thoughts. We claimed that we could hear the gears moving in his mind while he was performing mental computations.

Clay and I have been deeply influenced by A. F. Huxley's work. Two cherished lessons from Sir Andrew were honesty in publication and the fact that motherhood and science are not inconsistent. Even though he had suggested my postdoc project and guided me through it, Sir Andrew did not coauthor the final paper, because he had not directly contributed to the actual performance of the work. I have tried to follow that precept throughout my life. The arrival of my first child in the middle of my postdoc period did not disturb him; he just gave me a generous period for recovery and kept my position open. I went on to have three more children and to enjoy a life in science. I owe that to his encouragement.

Saul Winegrad

I first met Sir Andrew Huxley when I was a postdoctoral fellow working at NIH. I became rather enthusiastic during my presentation to him, when he listened attentively for several minutes and then said, "You needn't take credit because nature is so clever." I thought, "Boy, did I blow this one." At the end of the discussion Professor Huxley said that it was important to "treasure your exceptions," and he then invited me to pursue my research in London where I also met and married my wife, Dilys.

Clara Franzini-Armstrong is emeritus professor of cell and developmental biology at the Perelman School of Medicine, University of Pennsylvania. Her email address is armstroc@mail.med.upenn.edu.

Saul Winegrad is emeritus professor of physiology at the Perelman School of Medicine, University of Pennsylvania. His email address is bsg@mail.med.upenn.edu.



Picture of Andrew Huxley taken by Saul Winegrad on the occasion of Huxley's 90th birthday celebration. Courtesy of Saul Winegrad.

The years that followed were filled with deepening friendship and memorable experiences, some of which stand out. During one of our early visits to the Huxleys at Cambridge, Andrew was particularly interested in showing Dilys and me the Fellows Room at Trinity College, Cambridge University. Restrictions would not allow Dilys to enter, but Andrew wanted both of us to see it. He went ahead to reconnoiter, looking around corners and along corridors. He then signaled for us to come, and so we did. Andrew was more chuffed than we at having successfully broken tradition. We then followed tradition and dined with him at high table at Trinity, followed by Stilton cheese, claret, and superb port at the Masters Lodge.

Andrew once said to me, as he was reviewing a thesis in which the author had praised the multidisciplinary approach, that multidiscipline is fine, especially when all of the disciplines are present in the same person. I shall miss him for his warm friendship, his ability and willingness to bring his powerful intellect to problems outside his own major interest, and his intellectual honesty and integrity. I shall miss him and all of these admirable characteristics present in one person.

J. Walter Woodbury

In late July 1961 I spent an afternoon at University College London with Andrew Huxley. Knowing Huxley's penchant for mathematics, I summarized some research from my lab showing that current injected into a single cell in a planar sheet of rat atrium spreads to adjacent cells and that the steady state current spread was accurately described by the 2-D equivalent of the 1-D cable equation. The solution is a Bessel function of the

J. Walter Woodbury is a retired professor of physiology from the University of Utah. His email address is walt.woodbury@utah.edu.



Picture of Andrew Huxley taken by Walter Woodbury in July 1961. Courtesy of J. Walter Woodbury.

second kind with imaginary argument. I mentioned in passing that I hadn't worked out the solution of the 3-D cable equation. He was obviously intrigued, because when I saw him a day or two later at the Physiological Society meetings at Oxford, he had worked out the 3-D solution!

As I prepared to leave, I asked Professor Huxley for permission to take a photograph of him. He readily agreed and carefully composed himself in his office chair. As you can see, the photo turned out very well. He was quiet, unflinching, polite and cordial, the embodiment of the reserved British gentleman. I knew from his papers that he was an enormously talented, insightful, and creative scientist. My overall impression was that behind the reserve there was a highly capable and genuinely caring human being. There is a pleasant glow attached to my memory of the afternoon I spent with Andrew Huxley.

Albert M. Gordon

I was privileged to work with and study under Andrew Huxley as a postdoctoral fellow in his laboratory at University College London (UCL) from December 1960 until June 1962. I had just completed my Ph.D. in solid state physics from Cornell University and was making the transition to physiology and biophysics. The Prof (as we called him) had just moved to UCL as the Jodrell Professor in Physiology and department head. He was now working on muscle, having developed the sliding filament theory of contraction, along with others.

Albert M. Gordon is professor emeritus of physiology and biophysics at the University of Washington School of Medicine. His email address is amg@u.washington.edu.

The Prof provided the complete model of what it meant to be a scientist, combining excellence in experimentation, in instrumentation, and in mathematical theory. His experiments were carefully controlled and designed to clearly test important hypotheses. The hypotheses came out of his theoretical studies. The experiments were possible because of his dexterity in dissection combined with his excellence in instrumentation. He showed that it was not sufficient to just have a hypothesis to explain qualitatively the experimental data, but that one needed mathematical models that could explain the experimental observations.

Andrew Huxley was an outstanding scientist, mentor, and friend. I will miss him and the annual Christmas card with his photographs of scenes from his favorite vacations in Scotland and the Lake District.

Reinhardt Rüdel

To begin with, I must say that I am suffering from a progressive paralysis of the legs, which was not yet evident in the years 1968 to 1970, when I was working as a postdoc in the lab of A. F. Huxley. Prof, as we used to call him confidentially yet respectfully, had a general predilection for competitions. This was well known to us from the annual departmental outings when he was eager to win all games, in particular the tennis tournament, the "yard-of-ale" (his record: 23 s!), and even the harmless musical chairs!

Frank Lehmann-Horn and I organized the 7th International Conference on Neuromuscular Diseases in Munich, 1990. One of our novel ideas was to add the theoretical subjects of physiology, pharmacology, and genetics to the canon of clinical subjects treated at the conference. To convince the skeptical clinicians, we asked Professor Huxley to participate in the conference as a kind of figurehead. Of course we organized a press conference for our star guest. The journalists asked him all kinds of questions about squid neurons and his Nobel Prize, but he could not be diverted from expressing his happiness about his theoretical work having so quickly assumed such importance for the understanding of human diseases. He stressed that this was another example of pure research being a useful forerunner to applied research.

Prof also came to our social event, a Bavarian get-together in one of Munich's most famous beer halls, the *Löwenbräukeller*. Beer is served there only in steins of one liter. Participants in the evening told me afterwards that they were impressed by Professor Huxley's purposeful

Reinhardt Rüdel is a professor at the Division of Neurophysiology of Ulm University. His email address is reinhardt.ruedel@uni-ulm.de.

method of mustering the jar before he put it to his mouth with one hand without spilling a drop. On the other hand, they reported that the muscle expert seemed a bit stranded when he had to dissect the enormous grilled *haxen* (calf's leg) that followed. After dinner we engaged in a wheelchair ballet. The dancers wearing reflecting jackets under stroboscopic illumination operated in perfect synchrony, obtaining almost unnoticeably supportive momentum from their partners.

When I drove him to the airport two days later I asked him about his favorite impressions of the conference. Huxley pondered for a moment, and then he replied with the little stutter that was characteristic for him when disclosing an opinion: "Well, I was most impressed by the wheelchair ballet." I considered this as highest appreciation.

Vincenzo Lombardi

My collaboration with Andrew Huxley was fundamental in my scientific education and the most important driving force for my research achievements. My first visit to his laboratory at the University College London took place from October 1979 to July 1980, when he developed the striation follower, the optoelectronic apparatus for investigating the function of molecular motors inside a muscle cell, with still presently unequalled resolution. At that time Andrew was busy most of the day with his duties as president of the Royal Society and often came to the lab only after dinner. He usually spent quite a large part of the night testing and assembling the optical components, checking the performance of the electronic circuits I had built during the day, and planning my work and tests for the following day. Back in Florence I was able to set up my lab thanks to the enthusiasm and generous perseverance of Andrew in involving his coworkers in every single step during the realization of his ideas.

Andrew is rightfully recognized as one of the most prominent scientists of the twentieth century. He was an extraordinarily gifted man of science, but he also possessed other not-so-popular qualities, such as his natural curiosity for any aspect of life, his widespread knowledge of the natural sciences, and his dedication to the education of youngsters.

Andrew was an exceptionally interesting and pleasant person. For instance, during his visit to my country house in Fietri, Chianti, in the summer of 1989, Andrew enjoyed in a special way discovering the variety of butterflies in the yard and astonished everybody by following them and telling the proper scientific name of each species. From my first visit

Vincenzo Lombardi is professor of physiology at the University of Florence. His email address is vincenzo.lombardi@unifi.it.

to his lab at University College London in 1980 and until April 2011, we exchanged hundreds of letters that accompanied and supported my life in any sort of event. These letters are my personal legacy and remind me of his role as *Magister vitae*.

Gabriella Piazzesi

In 1990 I started to collaborate with Professor Huxley after he and Vincenzo Lombardi had moved the laboratory from University College London to the Department of Physiology of the University of Cambridge. As a researcher at the University of Florence, I had the opportunity to spend one month a year in his lab.

During my collaborative visits, several times I had the honor to be invited to join him for dinner at Trinity College or to have supper in his house in Grantchester, where I could enjoy the familiar and warm atmosphere he and his wife, Richenda, extended to me. On the occasions that the data analysis and discussion required us to meet but I was unable to go to Cambridge, he and Richenda came to Florence. Beyond the scientific work, this was a perfect opportunity to reciprocate their hospitality, exploiting the unique Florence environment. A most remarkable quality of Andrew was his ability to freely share with his younger coworkers any aspect of life.

Makoto Endo

I worked under Professor Andrew Huxley from September 1962 to April 1964 at the Department of Physiology, University College London. The results of our work were reported in my name only. Huxley declined to add his name to the report as being the person to suggest this work to me and giving his valuable advice throughout the experiments because, he pointed out, he himself had not carried out the experiments. I adopted this attitude in my later work with postdocs.

Huxley visited Japan several times, the first time being in summer 1965 to attend the Physiological Congress held in Tokyo. He stayed in Tokyo about a month, and toward the end he gave a lecture on his famous work on nerve excitation at Waseda University. While in Japan he became interested in Japanese, about which he knew nothing before coming. After only three weeks he could read both types of Japanese alphabets and even some Chinese characters. He then proposed to give his lecture in Japanese! He was confident enough,

Gabriella Piazzesi is professor of physiology at the University of Florence. Her email address is gabriella.piazzesi@unifi.it.

Makoto Endo is professor emeritus at the University of Tokyo and Tohoku University. His email address is qqf38h69@topaz.ocn.ne.jp.

because he had successfully done a similar thing in Russia despite having no previous knowledge of Russian. People at Waseda University were quite apprehensive but were steamrolled by Huxley's self-confidence.

Huxley gave me the English manuscript of his lecture two days before his lecture, and I translated it into Japanese. With the aid of a Japanese-English dictionary, Huxley checked the Japanese version, commenting that unless he knew what he was talking about, the lecture would be unsuccessful. Having rushed through the translation, I made a mistake: I wrote "Osmotic pressure is low," whereas it should have been "Osmotic pressure is high." Huxley came to me and politely said that this sounded odd but was probably how it should be said in Japanese, allowing me to find my mistake! His lecture at Waseda University was extremely successful. He was even able to insert a joke and make everybody laugh. We were even more amazed, because after returning to England, his Japanese vocabulary further increased!

Jan Lännergren

It is now thirty-nine years since I pushed open the heavy oak door marked "Anatomy" in Gower Street, entering University College London. High ceiling, a smell of wax polish, stairs leading upwards. At the second floor there was the entrance to Andrew Huxley's lab (previously occupied by the legendary muscle physiologist A. V. Hill). Inside there were three people: Bob Simmons, Lincoln Ford, and Andrew Huxley ("Prof"—I soon learned that all called him Prof). He was very kind and very welcoming and presented the other two.

Setting up for the experiments at King's was probably the most exciting and instructive time of my whole stay in London. Prof was present during the whole process, and it was absolutely marvelous to realize how deep his knowledge of optics and other things was. During that time I learned a massive amount of basic optics. Prof was very patient and took ample time to explain things to his humble pupil. He also suggested a course in optics at King's, which I took.

In summary, my one and a half years with Prof, later Sir Andrew F. Huxley, was the most enjoyable and educating period of my scientific life. I am extremely grateful for having had the opportunity to work together with a true scientific giant.

Jan Lännergren is professor of physiology at Karolinska Institutet, Stockholm, Sweden. His email address is jan.lannergren@ki.se.



Top: Picture of the mechanical calculator Andrew Huxley used to do the calculations of the propagated action potential. Bottom: Andrew Huxley and Lee D. Peachey. Pictures taken in 2009. Courtesy of Lee Peachey.

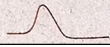
Lee D. Peachey

I have many fond memories of Andrew Huxley, going back more than fifty years. I first met him in 1956 while I was a graduate student at the Rockefeller Institute for Medical Research (now Rockefeller University) when he visited for a week to lecture and meet with the students. In June of 1958, I joined Huxley in Cambridge. That first collaboration was the beginning of a long friendship with Andrew and led to several more collaborations. It seemed as if nothing was too big for Andrew to master or too small to be worthy of his full attention. Our relationship also had a personal side. Andrew and Richenda were very good friends to my wife, Helen, and me and opened many doors for us.

During my last visit with Andrew in 2009, I asked about the mechanical calculator that he had used to do the calculations of the propagated action potential. He found it, sat down with it, and

Lee D. Peachey is professor of biology at the University of Pennsylvania. His email address is lpeachey@sas.upenn.edu.

In this building E.D. Adrian first recorded impulses from single nerve fibres, and A.L. Hodgkin & A.F. Huxley determined their mechanism and principles of conduction, transforming our understanding of how the nervous system processes information.



Plaque mounted in July 2012 outside the Department of Physiology, Development and Neuroscience, Cambridge University, to commemorate the sixty-year anniversary of the famous Hodgkin and Huxley 1952 publications. Photograph courtesy of Professor Idan Segev.

became totally engrossed, reminding himself when to turn the crank, when to flip the lever to move the carriage left or right, and so on.

Andrew Huxley's intellectual brilliance and skill as an experimenter, his infectious enthusiasm in all things, and his generosity in sharing his knowledge rubbed off on me and on many others who worked with him, and through us to more generations of physiological scientists. It was very special to have known him for so long and to have gained so much from our friendship and collaborations. He was a very important part of my life.

David R. Trentham

Perhaps of greatest interest to this readership is the impact on mathematics of the Hodgkin-Huxley equations in that they describe an excitable nonlinear system that has a solution in the form of a nonlinear solitary wave. As these waves are different from solitons in conservative nonlinear systems, their discovery made a huge impact in the emerging field of nonlinear dynamics and their applications in biology and engineering [Scott, 1975]. Apart from providing the mathematical basis for the entire fields of neural [Scott, 1975] and cardiac [Noble et al., 2012] modelling, the Hodgkin-Huxley equations became one of the cornerstones in the theory of nonlinear waves (autowaves) in physical, chemical, and biological excitable systems [Krinskiĭ, 1984], [Guckenheimer and Holmes, 1997], [Keener and Sneyd, 2009]. Interestingly, after decades of research, soliton-like behavior was also discovered in the Hodgkin-Huxley equations [Aslanidi and Mornev, 1999].

In July 2012 the Huxley family celebrated the life of Andrew on the grounds of his lovely home in Grantchester, near Cambridge. It was a beautiful

David R. Trentham is honorary professor in the Randall Division of Cell and Molecular Biophysics at King's College London. His email address is drtrentham@aol.com.

summer's day and memorable for the gathering of Huxley, Darwin, Pease, and Wedgwood family members. One could imagine a similar reunion of such names in the same idyllic surroundings a century earlier. The dynastic nature of these families is well embedded in English culture, as is reflected in the ditty below, which appeared in *Punch* [Anon., 1964] following the engagement of Angela Darwin (née Huxley), one of the guests present.

A DARWIN is marrying a HUXLEY
A fate which no Darwin escapes;
For the Huxleys speak only to Darwins,
And the Darwins speak only to apes.

How Andrew would have enjoyed being at such a gathering!

References

- Anonymous, —. *Punch*, 247(3):83, 1964.
- O. V. ASLANIDI and O. A. MORNEV, Soliton-like regimes and excitation pulse reflection (echo) in homogeneous cardiac Purkinje fibers: Results of numerical simulations, *J. Biol. Phys.*, 25(2-3):149–164, 1999.
- J. GUCKENHEIMER and P. HOLMES, *Nonlinear Oscillations, Dynamical Systems, and Bifurcations of Vector Fields*, volume 42 of Applied Mathematical Sciences, Springer, New York, corr. 5th print edition, 1997. ISBN 0387908196.
- A. L. HODGKIN, *Chance and Design: Reminiscences of Science in Peace and War*, Cambridge University Press, 1992.
- A. L. HODGKIN and A. F. HUXLEY, Currents carried by sodium and potassium ions through the membrane of the giant axon of *Loligo*, *J. Physiol.*, 116(4):449–472, 1952a.
- , The components of membrane conductance in the giant axon of *Loligo*, *J. Physiol.*, 116(4):473–496, 1952b.
- , The dual effect of membrane potential on sodium conductance in the giant axon of *Loligo*, *J. Physiol.*, 116(4):497–506, 1952c.
- , A quantitative description of membrane current and its application to conduction and excitation in nerve, *J. Physiol.*, 117(4):500–544, 1952d.
- A. L. HODGKIN, A. F. HUXLEY, and B. KATZ, Measurement of current-voltage relations in the membrane of the giant axon of *Loligo*, *J. Physiol.*, 116(4):424–448, 1952.
- A. F. HUXLEY, Muscle structure and theories of contraction, *Prog. Biophys. Biophys. Chem.*, 7:255–318, 1957.
- A. F. HUXLEY and R. NIEDERGERKE, Structural changes in muscle during contraction: Interference microscopy of living muscle fibers, *Nature*, 173:971–973, 1954.
- J. P. KEENER and J. SNEYD, *Mathematical Physiology*, volume 8 of Interdisciplinary Applied Mathematics, Springer, New York, 2nd edition, 2009. ISBN 9780387094199 (set).
- V. I. KRINSKIĬ, *Self-organization: Autowaves and Structures Far from Equilibrium: Proceedings of an International Symposium, Pushchino, USSR, July 18–23, 1983*, volume 28 of Springer Series in Synergetics, Springer-Verlag, Berlin, 1984. ISBN 0387150803 (U.S.).
- D. NOBLE, A. GARNY, and P. J. NOBLE, How the Hodgkin-Huxley equations inspired the Cardiac Physiome Project, *J. Physiol.*, 590(Pt. 11):2613–28, June 2012. doi10.1113/jphysiol.2011.224238.
- A. C. SCOTT, Electrophysics of a nerve-fiber, *Rev. Mod. Phys.*, 47(2):487–533, 1975.