IN MEMORIAM

Harold Lecar
Professor of Biophysics and Neurobiology, Emeritus
Department of Molecular and Cell Biology
UC Berkeley
1935 – 2014

Harold Lecar was born in Brooklyn, New York in 1935. He was the child of immigrants from Eastern Europe, and was educated in Brooklyn public schools before proceeding to Columbia University for his BSc and his PhD in Physics, which he completed in 1963. Under PhD supervisor Charles Townes he worked on the use of masers in microwave spectroscopy. From 1963 to 1985 he worked in the Biophysics Laboratory at the National Institute of Neurological Disorders and Stroke at NIH. In 1985 he moved to the University of California, Berkeley, where he was a Professor of Biophysics and Neurobiology.

In 1985, Dr. Lecar received the American Public Health Service Special Recognition Award for "contributions to the understanding of the role of membrane ionic channels in producing electrical excitability and for pioneering work in advancing single- channel methods." The award recognized Dr. Lecar's work with Drs. Gerald Ehrenstein, Ralph Nossal, and Ramon Latorre which observed currents turning on and off for the first time from single ion channels as they opened and closed, providing a framework for understanding the molecular mechanisms and paving the way for statistical analysis of conformational changes and functional transitions of proteins in general.

In addition, with Nossal, Lecar established the theory of how membrane noise produces action- potential threshold fluctuations. With Drs. Fred Sachs and Meyer Jackson, Dr. Lecar initiated the patch- clamping of excitable cells grown in tissue culture, which led to the study of numerous gated channels. In the late 1970s, Drs. Catherine Morris and Lecar developed the Morris- Lecar model, a set of two- dimensional "reduced" excitation equations, which describe a variety of oscillatory behaviors seen in excitable cells. With Drs. H. Peter Larsson and Michael Grabe, Dr. Lecar constructed simple mechanical models that described the mechanism by which the specialized ion channels that generate the action potential sense changes in the voltage of the membrane.

Lecar's earliest work at NIH was directed toward understanding the mechanism responsible for the conductance (or in the physics parlance of the time, the "negative resistance") underlying the ability of an axon to fire. Much of this work was done on the squid giant axon. Lecar and Ehrenstein thought that a likely mechanism for negative resistance was a voltage- dependent opening and closing of ionic channels. They were intrigued by the work of Mueller and Rudin, showing that lipid bilayers with certain impurities could exhibit negative resistance. In collaboration with Ralph Nossal, they tried to lower the concentration of the impurities, called EIM (excitability- inducing material), with the hope that they could observe single channels opening and closing in a voltage- dependent manner. The rationale was that the electrical current across a pure bilayer was so small that the change in current caused by the opening of a single ionic channel would be observable. This approach was successful, and they were able to demonstrate that the voltage- dependent opening and closing of EIM channels could account for the negative resistance that Mueller and Rudin had observed (Ehrenstein, Lecar, and Nossal, J Gen Physiol. 1970, 55: 119). There was also a bit of luck here, since the electrical currents were measured on a chart recorder with poor time resolution, and the discrete changes in current were observable only because the intervals between channel opening and closing were very long.

Soon thereafter, Lecar and Nossal undertook an analysis of threshold fluctuations in nerves. An extensive experimental literature on that subject existed, people having noted that when the giant squid axon or the frog node of Ranvier were stimulated with a current pulse, the probability of nerve firing was graded rather than "all- or- none" as predicted by Hodgkin- Huxley- like equations. Lecar and Nossal devised an analytical theory that showed how nerve firing probabilities could be expressed in terms of "reduced" (i.e., scaled) variables and thereby efficiently be related to putative sources of noise acting upon the axons (Lecar and Nossal, Biophys J. 1971, 11:1048,1068). After analyzing an extensive set of publications dealing with the way the firing probabilities depended on changes in temperature and other environmental variables, Lecar and Nossal construed that the source of the electrical noise underlying the fluctuations in axon firing was the random opening and closing of individual ion channels. This conclusion was drawn several years before the existence of individual molecular channels was established by more direct means.

Lecar then continued his investigations of the stochastic behavior of excitable cells, writing a series of pioneering papers on the subject with postdoctoral fellows and students such as Fred Sachs, Meyer Jackson, Cathy Morris, and Peter Larsson, who went on to distinguished careers of their own. Moreover, with Sachs and Jackson, Lecar initiated and analyzed patch- clamping of cells grown in tissue culture, showing the way and setting the tone for a vast number of studies of ion channels in native cells. Lecar was one of those unusual persons who, although basically a theorist, had an intuitive feeling about experiments that allowed him to produce cogent mathematical and physical analysis, which characterized all his publications. His analysis of the temporal sequences of the lifetimes of channel openings with Meyer Jackson provided the theoretical foundation for deducing the successive stages to the conformational changes underlying channel opening, and provided the underpinnings of the current effort to relate excitable membrane channel structure to physiological function.

In the latter part of the 1970s and early 1980s, Lecar joined Nossal in designing and presenting a biophysics series of lectures for students at the University of Maryland at a time when such courses were rare. Their efforts resulted in the publication of one of the first, and still highly regarded, textbooks on molecular and cell biophysics (Membrane & Cell Biophysics, Addison- Wesley, 1991).

It was clear that Lecar had a deep love of teaching and, in 1985, he moved to the Department of Biophysics and Medical Physics at the University of California, Berkeley. Once here, he expanded the University of Maryland lectures to a full course on neuronal biophysics, which was popular with quantitative biologists as well as engineering and physics students. He taught this course, usually alone and in unparalleled fashion, from 1985 until his retirement in 2013. During this time he became known for the joyous enthusiasm with which he interacted with students and shared his intellectual insights. The same energy that Lecar had shown when acting as a mentor for postdoctoral fellows at NIH became focused on guiding students. His reputation for patience and kindness towards both undergraduate and graduate students was widely known both inside and outside the Berkeley community.

At Berkeley, Lecar expanded his studies of ion channels to those found in yeast and vertebrate photoreceptors, produced a new analysis of mechanical transduction, and developed novel models of ion channel gating, of membrane proteins showing mixed ion channel and ion transport properties, and of the dynamics of neural network activity. This, with his gracious mentoring of budding biophysical professionals, including young faculty, significantly enhanced the reputation of this campus in theoretical and biophysical cellular neuroscience. Two of his students, Oliver Baker and PhD student Peter Larsson, joined the lab of Lecar's junior faculty colleague, Ehud Isacoff, as a PhD student and postdoctoral fellow, respectively, where they carried out experiments in potassium channels that tested models developed by Lecar. Lecar mentored Baker and Larsson, and extended this help to several other students and postdocs in the Isacoff lab for whom he served as co- advisor and provided his own lab facilities. This work led to breakthroughs in the understanding of voltage gating of ion channels. Lecar extended his active mentoring to the entire Biophysics Graduate Program, assuming its leadership in a critical transition between 1994 and 1996.

Like Hodgkin and Huxley before him, Dr. Lecar showed how the marriage of theory and experiment in the field of neurobiological research could furnish profound insights into the behavior of excitable cells. He was also one of the nicest people one could ever meet and one of the few science faculty at UC Berkeley who could still speak Yiddish and remember growing up in the old country of Brooklyn. He cared enough about the new country to turn his mathematical talents in recent years from theoretical neuroscience to election fraud. His work on ion channels or elections could turn into the longest conversation you had all year in the hallway. He was a unique individual, whose spirit lives on in all who knew him.

Harold Lecar is survived by his wife, Helene, two children, Matt and Josh, three grandchildren and scores of friends, colleagues and students who will treasure his memory.

Ehud Y. Isacoff