# Eric Harris Davidson

1937–2015

BIOGRAPHICAL *Memoirs*

*A Biographical Memoir by*
*Marianne Bronner*

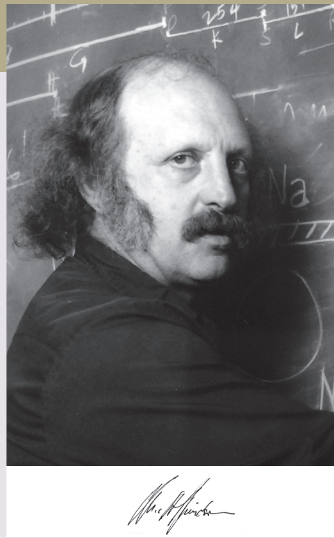


NATIONAL ACADEMY OF SCIENCES

# ERIC H. **DAVIDSON**

*April 13, 1937–September 1, 2015*

Elected to the NAS, 1985



*By Marianne Bronner*

Eric Harris Davidson, Norman Chandler Professor of Cell Biology at the California Institute of Technology and long-time member of the National Academy of Sciences, died on September 1st, 2015, at the age of 78. Eric was a pioneer in the use of modern approaches to investigate the molecular basis of animal development. His work uncovered many of the critical regulatory instructions encoded in the genome of the developing embryo that worked together to build the animal body plan. His mechanistic work on gene regulatory networks was paradigm shifting and has helped revolutionize the modern understanding of developmental biology and genomics. Eric was also deeply interested in understanding how evolution worked via changes in developmental programs. But he was a Renaissance man who, in addition to his love of science, had a keen interest in history, music, football, and motorcycles. This memoir reviews his career and achievements both in and out of the laboratory.

## Beginning of his career

Eric's interest in the way the genome controls development started early in life and was stimulated by his work at the Marine Biological Laboratory (MBL) in Woods Hole, MA. Davidson's father was a well-known painter in Provincetown, Massachusetts who introduced Eric to his acquaintance, L. V. Heilbrunn, at the MBL. At the age of 16, Eric obtained a position in the Heilbrunn laboratory, where in addition to washing dishes, he actively participated in a research project. His time at MBL spurred his interest in science not only through training in laboratory science, but also at an intellectual level. At MBL, he had the opportunity to engage in extensive discussions about the history of science, embryology, and cell physiology, and he was particularly influenced by his introduction to the embryological work of Theodor Boveri. His encounter with research at the MBL was very productive, leading to his first publication in 1953. On this basis, he entered the Westinghouse Science Talent Search (now the Intel Prize) and was chosen as a winner.

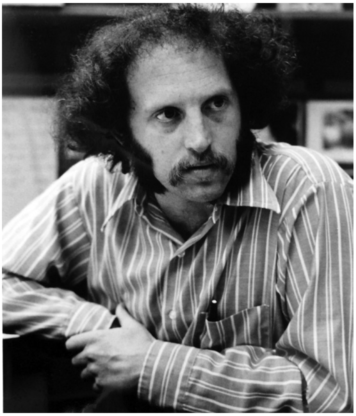
This not only launched his scientific career, but paved the way for a full scholarship at the University of Pennsylvania where he continued to work in Heilbrunn's laboratory.

After receiving his bachelor's degree, Eric's pursued his PhD at the Rockefeller University with Alfred Mirsky. There he examined production of hyaluronic acid by connective tissue as a gene marker for differentiation. By using Actinomycin D to shut down RNA synthesis, he lowered hyaluronic acid production without effects on other gene products. These findings lead to the novel concept that differential gene activity led to variation in cell phenotypes. After completing his PhD in 1963, Eric continued at Rockefeller, first as a postdoctoral fellow with Mirsky and later as an Assistant Professor. During this time, he pursued studies on RNA synthesis in embryos and was amongst the first scientists to use molecular biology to address developmental questions.

It was at Rockefeller that he met Roy Britten from the Carnegie Institution in Washington. Together, they formulated a hypothesis of gene regulation in complex multicellular animals, summarized in a theoretical paper entitled, "Gene Regulation in Higher Cells: a Theory," published in *Science* (1969). This influential paper, based on data from *Drosophila* and other organisms, proposed a mechanism of gene regulation in which transcription factors controlled expression of gene batteries. The Britten-Davidson model was based on the logic of how embryos work. They posited that gene regulatory proteins receive signals from other cells which result in the expression of other regulatory genes, now referred to as 'inductive signaling.' The visionary depiction of regulation in gene networks in the Davidson/Britten papers from 1969 to 1973 profoundly influenced many researchers both within and outside the field developmental biology. These concepts were further expanded in Eric's first book, *Gene Activity in Early Development* (1968). One of Eric's most important and lasting research themes, causality in cis-regulatory genomics, emerged from the concepts in these papers and his book. During the course of his career, growing experimental evidence for the mechanisms involved was developed and elaborated in his two subsequent editions (1976, 1986) of *Gene Activity in Early Development* as well as in his three later books.

## The Caltech Years

In 1971, Eric moved from The Rockefeller University to Caltech where he became an associate professor and began his work with sea urchin embryos. He chose this organism because it proved optimal for nucleic acid molecular biology. The ability to obtain large numbers of synchronous oocytes and embryos enabled him to purify mRNA, DNA, polysomes and ribosomes to explore repetitive sequences, genome organization, and general questions regarding gene regulation during animal development. By using Cot curves to analyze reassociation kinetics, he explored the complexity of RNA in sea urchin eggs and embryos.



His next phase of work was on transcriptional kinetics. With Roy Britten, he wrote a series of papers on genomic organization and expression, analyzed in terms of sequence complexity and RNA/DNA transcription rates, turnovers, synthesis, and decay rates. These insights and the approaches needed to generate them were highlighted in the 1976 edition of *Gene Activity in Early Development*. In parallel, he also began to explore the function of transcription factors in early development using new cloning approaches and introducing DNA and RNA constructs into the egg. This research led to his interest in studying the role of gene regulation in cell lineage and embryonic territory specification. He initiated work on in-depth cis-regulatory analysis which remained an important component of his laboratory's work throughout his life. By this time, his work had become well-recognized, leading to his election to the National Academy of Sciences in 1985.

Eric's assembly of the sea urchin gene regulatory network (GRN) was greatly aided by the sequencing of the genome of the purple sea urchin, a project that he spearheaded. By taking advantage of whole genome sequencing of multiple sea urchin species, he was able to uncover regulatory regions controlling expression of near genes and establish gene interactions leading to cell fate decisions. This led to formulation of a near-complete gene regulatory network of the early sea urchin embryo that determines the animal's body plan. His analysis of the sea urchin GRN, a complex feed-forward network encoded in genomic DNA, remains the most detailed understanding of gene regulation in any developmental system. For this pioneering work, he was awarded the International Prize in Biology in 2011.

Eric always incorporated the newest techniques in molecular biology into his toolkit and applied these techniques to classical embryology questions. In recent years, he began working with computational modeling, becoming interested in theoretical modeling of gene regulatory networks. With Isabelle Peter, he formulated a dynamic Boolean computational model based on the cis-regulatory logic requirements of ~50 individual genes, on the known positions of embryonic cleavage planes, and on an absolute developmental time clock, which predicted embryo-wide outcomes in silico. These could be tested experimentally and validated the predicted inputs and outputs of the network.

## Evolution

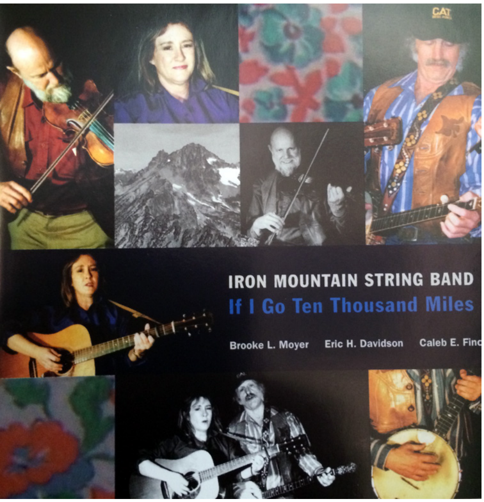
Eric had a deep interest in understanding evolution and how it works. This got him interested in the fossil record and how it might inform the understanding of how GRN changes explain the evolutionary process. He was particularly interested in a fossil find in China that dated to the Precambrian (~600 million years old) and contained microfossils that appear to be embryos of early animals. These Doushantuo fossils are unusual in that they preserve the remains of soft-bodied marine organisms, some of which resemble modern sea urchin embryos and predate the Cambrian explosion by ~50-70 million years. The fossil data can inform upon when important characters may have evolved. He recognized that these data combined with knowledge of the genes important for production of these characters in modern organisms can help to clarify when these specific genes first evolved. He also wrote a number of seminal papers on gene regulatory networks and evolution and this remained a passion of his throughout his life. Unsurprisingly, his office was filled with beautiful fossils.

Eric's interest in evo-devo helped to foster the research of others in the field. Remarkably, he persuaded NASA to fund a group of investigators in a program to help understand the "Origin of Life on Earth." This was extremely important for launching the evo-devo field since garnering funding for this area of science was and remains notoriously difficult. On a personal note, this is what helped launch my own evo-devo research on the origin of the neural crest at the base of vertebrates, using both a basal vertebrate (lamprey) and basal chordate (amphioxus). Other young investigators were similarly enabled by this program. This is just another example of Eric's over-arching influence on the field as well as his selflessness in promoting the field in general. Eric was always interested in getting the answers but had no time for politics or self-promotion.

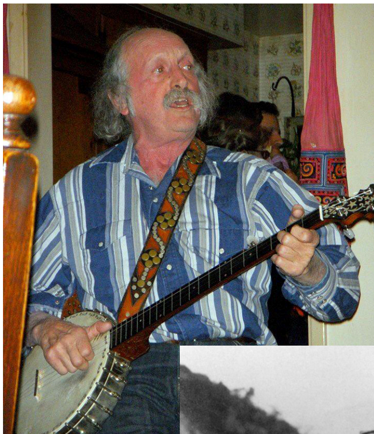
## Music, history and football

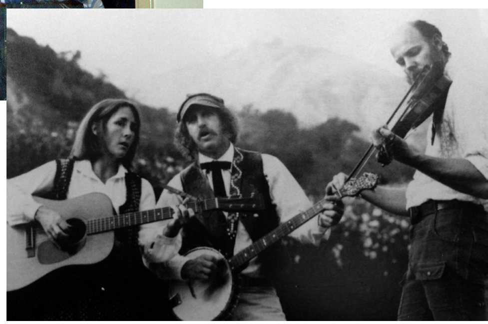
During his years at Rockefeller, Eric began to play the banjo and became interested in Appalachian music. Together with his friend and colleague Caleb (Tuck) Finch, he started the Iron Mountain String Band, which performed old-time music in traditional styles. He traveled throughout Carroll and Grayson counties in southwestern Virginia, learning from and making recordings of traditional folk musicians. These recordings are now held by Smithsonian Folkways, and have made important contributions to preservation of this musical genre.

But Eric was equally interested in other intellectual pursuits, and he read as intently about history as about science. Eric also was passionate about football. He played club football for a Caltech intramural team until well into his 50's and organized and played on a highly competitive team called the Tiger Toads in a local city league for over 35 years. He had seasons' tickets to Los Angeles NFL teams and was a consummate fan to the end of his life. Into his 60's, he actively participated in dives off the California coast to collect sea urchins for his lab's research. He also loved gardening, cats, riding motorcycles, and Knob Creek bourbon. Eric was his own man and uncompromisingly so.



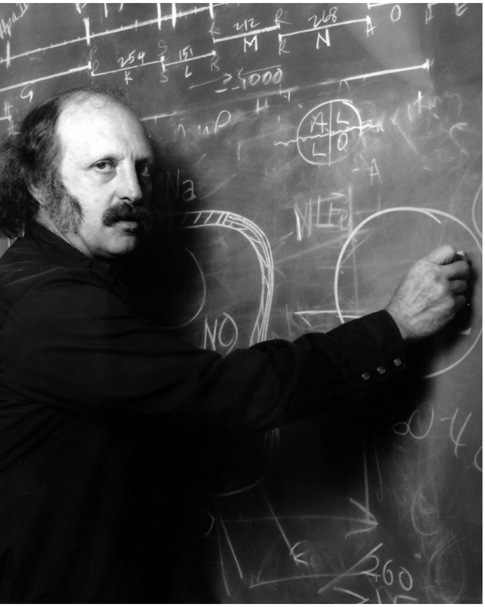

Cover of 1998 CD, "Songs of Old Time America," on the Peachbottom Records label.





## Contributions to teaching—the Marine Biological Laboratory

Eric trained many influential scientists who have made major contributions to molecular, developmental, and cell biology. Amongst this illustrious group are Andy McMahon, Richard Scheller, Frank Constantini, Henry Sucov, Barbara Wold, and Bob Goldberg.

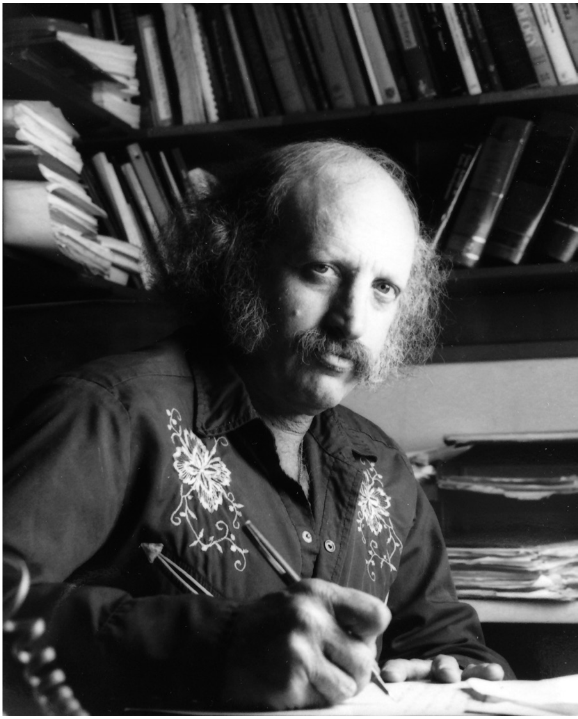


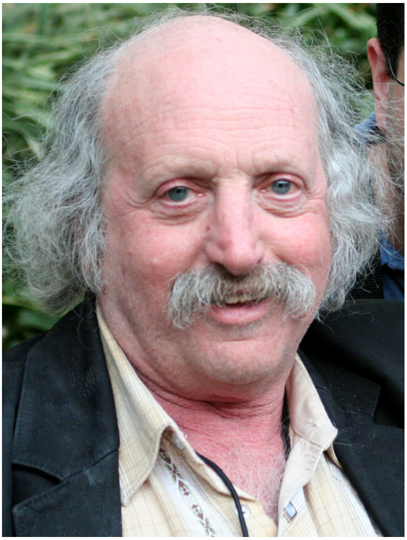
In addition, his six books have greatly influenced generations of graduate students interested in gene regulatory networks. But his largest influence in mentoring came from his revitalization of the embryology course at the MBL, where his own scientific career started.

Eric became director of the embryology course in 1987 and he completely transformed the course from a classical embryology course to one focused on understanding the modern molecular basis of animal development. The course became intensively rigorous with lectures by the best developmental biologists in the field followed by experiment-based laboratories and intense intellectual discussions. Each year, 24-25 graduate and post-doctoral students took the course. Their most common description of the course is that it was 'life-changing.' Eric directed the course for 10 years and gave lectures until relatively recently. As a testament to his influence, the format he devised is still in use to this day.

Eric also started a gene regulatory network course taught at the MBL that is still ongoing: "Gene Regulatory Networks in Development." The enduring role he played in helping to sculpt the careers of young developmental biologists will have as long-lasting an effect on science as his important discoveries.

In conclusion, Eric Davidson is one of the greatest developmental biologists of the 20th/21st centuries. Eric advanced our current understanding of how the genome encodes the complex body plan. He pioneered the idea of gene regulatory networks comprised of interacting genes organized into subcircuits with feedback loops, working in coordination to lead to the formation of distinct cell types. His formulation and testing of how complex gene regulatory networks control developmental processes and his quantitative approaches to understanding developmental questions have been paradigm shifting for the field. His experimental work for over fifty years stressed the importance of examining animal development from an all-encompassing "systems biology" point of view rather than examining a single gene at a time. His pioneering achievements in studies of gene regulatory networks together with his textbooks, teaching and mentoring will continue to influence future generations for decades to come.





## ACKNOWLEDGEMENTS

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## SELECTED BIBLIOGRAPHY

1953 Clotting of the perivisceral fluid of the sand dollar *Echinarachnius parma*. *Biol. Bull.* 105:372.

1964 With V. G. Allfrey and A. E. Mirsky. On the RNA synthesized during the lampbrush phase of amphibian oogenesis. *Proc. Nat. Acad. Sci.* 52:501-508.

1968 *Gene Activity in Early Development.* New York: Academic Press.

1969 With R. J. Britten. Gene regulation for higher cells: a theory. *Science* 165:349-357.

1971 With B. R. Hough. Genetic information in oocyte RNA. *J. Mol. Biol.* 56:491-506.

1973 With R. J. Britten. Organization, transcription, and regulation in the animal genome. *Quart. Rev. Biol.* 48:565-613.

1976 With G. A. Galau, W. H. Klein, M. M. Davis, B. J. Wold, and R. J. Britten. Structural gene sets active in embryos and adult tissues of the sea urchin. *Cell* 7:487-505.

1978 With R. H. Scheller, F. D. Costantini, M. R. Kozlowski, and R. J. Britten. Tissue-specific representation of cloned interspersed repetitive sequences in sea urchin RNAs. *Cell* 15:189-203.

1980 With F. D. Costantini and R. J. Britten. Message sequences and short repetitive sequences are interspersed in sea urchin egg poly(A) RNAs. *Nature* 287:111-117.

1982 With B. R. Hough-Evans and R. J. Britten. Molecular biology of the sea urchin embryo. *Science* 217:17-26.

1984 With R. J. Shott, J. J. Lee, and R. J. Britten. Differential expression of the actin gene family of *Strongylocentrotus purpuratus*. *Devel. Biol.* 101:295-306.

With R. C. Angerer. Molecular indices of cell lineage specification in the sea urchin embryo. *Science* 226:1153-1160.

2015 With L. S. Peter. *Genomic Control Processes: Development and Evolution*. New York: Academic Press.