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Obituary

Eric Davidson (1937–2015)

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The complexity of gene regulation and its importance to evolutionary change is now a foundational principle in both development and evolution. But this was not the case in the 1960s when Eric Davidson was one of a small group of scientists who began developing a theoretical framework backed by rigorous experimental work to explore this issue. Davidson and his group made fundamental contributions to our understanding of the logical structure of gene regulatory networks, and to the importance of these networks in controlling the evolution of animal body plans. Eric Davidson, Norman Chandler Professor of Cell Biology at the California Institute of Technology, died 1 September 2015 in Pasadena, California.

From the 1970s until his death, Davidson pioneered increasingly rigorous studies of developmental patterns in sea urchins. Over the past decade he has worked out the detailed logical structure of *cis*-regulatory gene networks and explored how changes in these networks impacted evolutionary possibilities.

Davidson's career was closely tied to the Marine Biological Laboratory (MBL) in Woods Hole, Massachusetts. He found himself in the laboratory of L.V. Heilbrunn at the MBL in the summer of 1953. Heilbrunn set Davidson a research project that eventually developed into a winning project for the Westinghouse Science Talent Search. Heilbrunn was a professor at the University of Pennsylvania and Davidson worked in his lab there throughout his time as an undergraduate. Davidson moved to Rockefeller University in 1958 where he joined the lab of Alfred Mirsky and worked on gene expression and RNA synthesis in *Xenopus laevis*. Mirsky became an important mentor, and after Davidson received his PhD in 1963 he stayed at the Rockefeller as a research scientist and then assistant professor.

In 1971 Davidson moved to the California Institute of Technology, which was his academic home for the rest of his career. In 1981 he became the Norman Chandler Professor of Cell Biology at Caltech. Davidson's connection to MBL continued throughout his career, as he directed or co-directed the Embryology course in the 1970s and also from 1988 to 1996. More recently he had been leading a course on Gene Regulatory Networks each fall, which introduced two dozen or so students to the experimental and computational tools and conceptual framework needed to investigate gene regulatory networks. Sometimes known as "Network Bootcamp", this course was an immersive experience with each day ending with Davidson leading discussions long into the night.

At the core of Davidson's research was an intense drive to understand at the most mechanistic level possible the nature of developmental gene regulation. Davidson and his colleague Roy Britten published landmark papers on gene regulatory networks in the late 1960s and early 1970s. In the first of these they described the structure of developmental gene regulatory networks, discriminating between regulatory and protein-coding components of DNA and discussing the basic logic of the networks. The second paper, published in 1971, is one of the founding documents of comparative evolutionary developmental biology ('evo-devo'). Britten and Davidson had explored the extent of repetitive DNA sequences in the genome and proposed that this was the location of the regulatory information that controlled development. In this paper they described how changes in gene regulatory networks could be responsible for the evolution of animal body plans. Throughout the remainder of Davidson's career he would combine perspicacious (a favorite Davidson word) theoretical studies of the logical structure of gene regulatory networks with increasingly rigorous experimental explication of the operation of these networks in his chosen experimental subject, the purple sea urchin *Strongylocentrotus purpuratus*.

During the 1970s and into the 1980s, Davidson, Britten and their collaborators continued to investigate the role of repetitive DNA in gene regulation, not just in urchins but across a range of other animals. They measured the number of copies of messenger RNA (mRNA) in a variety of types of tissues and organisms and showed that the complexity of the mRNA populations differed considerably in different tissues and at different times of development. From these data they proposed a model in which the repetitive

transcripts formed RNA–RNA duplexes to regulate the production of mRNA. As new techniques permitted increasingly refined analysis of the mechanistic basis of gene regulation, Davidson and his group refined the levels of genomic analysis and the rigor of their conceptual framework.

In the late 1980s Davidson characterized the genomic *cis*-regulatory logic of an endoderm-specific gene known as *Endo16*, which was first expressed at the onset of sea urchin gastrulation and which appeared to encode a cell adhesion molecule. Although at the time the lab was investigating many other genes and their roles in developmental patterning, *Endo16* became the foundation of an incredibly generative project. Beginning in the mid-1990s Davidson and his group began a systematic analysis of the patterns of regulatory control in the developing sea urchin embryo (up to about 30 hours after fertilization) working outward from the connections to *Endo16*. Elucidating the nature of this regulatory control of development and generating sophisticated computational approaches was to define the work of the lab for the remainder of Davidson's career.

The work that began with *Endo16* was eventually to generate a view of the network of regulatory interactions, largely transcription factors and some signaling molecules, throughout the larval sea urchin. They systematically knocked out every regulatory gene expressed in particular domains of the embryo (mesoderm, endoderm, etc) to identify the interactions between them, gradually building up an understanding of the mechanisms of genomic control. As the experimental work proceeded, Davidson and Isabelle Peter also developed new computational approaches. Thus, the dynamic activity of the gene regulatory network was computed by a set of Boolean statements for the control logic of each gene, based on AND, OR, and NOT Boolean operators. This computational model demonstrated that the topology of the gene regulatory network determined from experimental data indeed succeeded in explaining and predicting developmental gene expression and was completed by 2012.

Viewing the gene regulatory network as a logical structure rather than only as a physical pattern of interactions opened up new conceptual perspectives on the operation and evolution of these networks. One insight that came out of this work was that similar motifs or circuits recur in the networks in different species and with different genes. In 2006 Davidson identified highly recursive subcircuits of genes as the core of the control of regional patterning, which he described as kernels, as well as other types of circuits. From 2008 onward, Davidson published a series of influential papers describing the design patterns of developmental gene regulatory networks that fed back into additional experimental work. The growing elucidation of these networks was aided by the parallel determination and annotation of the sea urchin genome, a project where Davidson also played a leading role.

Davidson understood that the fossil record contained the best record of the origin and early diversification of animal body plans, and he collaborated with several paleontologists over the past several decades. Changes in the skeletal system between Paleozoic echinoids (sea urchins), cidaroids and the more recent euechinoids were a compelling problem that could be addressed through both paleontological and developmental studies. The Ediacaran (635–542 million years ago) and Cambrian (542–485 million years ago) explosion of animal life was an even more attractive target. As the result of a meeting in China, Davidson developed a strong collaboration with paleontologists at the Nanjing Institute of Geology and Palaeontology that led to studies of early fossil embryos. Visits to China also appealed to Davidson's long-standing interest in the food and culture of China. I discovered the Britten and Davidson models of *cis*-regulatory evolution as an undergraduate and they transformed my thinking about evolution. I was already headed toward paleobiology (the chemistry faculty had *strongly* suggested that a career in laboratory science was not in anyone's best interests), but I never gave up my interests in integrating evolution, development and the fossil record. Thus, I was thrilled one day in 2001 when I received an email from Davidson who wanted to see the museum's collections of Cambrian Burgess Shale fossils. That visit led to a collaboration that continued until Eric's death. We shared a common interest in integrating data from the fossil record and development to understand the mechanisms that generated animal body plans. Davidson's capacity to absorb and integrate vast amounts of detail was always remarkable and was quite evident in our last conversation only a few days before his death, when he questioned me about the details in some recent papers on Ediacaran fossils.

Davidson was the author of a number of books on gene regulation, volumes that trace the progressive development of the field and the author's own approach to how genetic information is used in embryogenesis across an array of animals, and how developmental mechanisms have evolved over time. *Gene Activity in Early Development* (Academic Press, 1968, 1974, 1986) is an exhaustively detailed discussion of developmental mechanisms in the usual model systems of nematodes, fly, sea urchin and various vertebrates, but also includes a discussion of annelids, molluscs and other groups for which there was relevant information. The approach continued with *Genomic Regulatory Systems* (Academic Press, 2001), *The Regulatory Genome: Gene Regulatory Networks in Development and Evolution* (Academic Press, 2006) and most recently, with his colleague Isabelle Peter, *Genomic Control Process, Development and Evolution* (Academic Press, 2015). These volumes are marked by increasingly sophisticated treatment of developmental gene regulatory networks in many different animal systems. Each volume includes detailed wiring diagrams of gene regulatory networks, produced by Davidson's lab, which themselves trace the growth in knowledge of *cis*-regulatory interactions. One common thread that runs through the last three books in particular is the tight conceptual focus with experimental results used to illustrate the mechanistic basis of genome control processes. The latest volume with Peter provides a concise discussion of the logical networks that these two have generated over the past few years.

Among the honors and awards that Davidson received were election to the National Academy of Sciences, the A.O. Kowalevsky Medal from the St. Petersburg Society of Naturalists, and the International Prize for Biology, awarded for outstanding fundamental achievements in biology.

Davidson's interests and talents extended far beyond biology. In his office at Caltech he proudly displayed a photograph of himself on the Caltech football team and collaborators quickly learned that Sunday afternoons in the fall were reserved for football. Davidson also had a deep knowledge of traditional Appalachian folk music and many students and colleagues remember his banjo playing in bars in Woods Hole. From the 1950s into the 1980s Davidson traveled through Appalachia, particularly in Grayson and Carroll counties, Virginia, recording traditional musicians. The tapes of these recordings were deposited with the Smithsonian Institution and thirteen discs of music he recorded, produced or played can be found on the Smithsonian Folkways website. Davidson wrote the liner notes for many of these recordings. The notes for *Traditional Music from Grayson and Carroll Counties* are particularly worth reading. He played banjo in the Iron Mountain String Band that recorded some of the music he had collected on these trips.

There are journals full of papers on how various gene regulatory networks *should* work in principle. However, it was Eric Davidson's often single-minded drive and persistence in working out the empirical structure of the sea urchin network and deriving a logical model from those data that has provided the deepest insights into the mechanistic basis of animal development, and how it has evolved over time.

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