

Eric H. Davidson

(1937–2015)

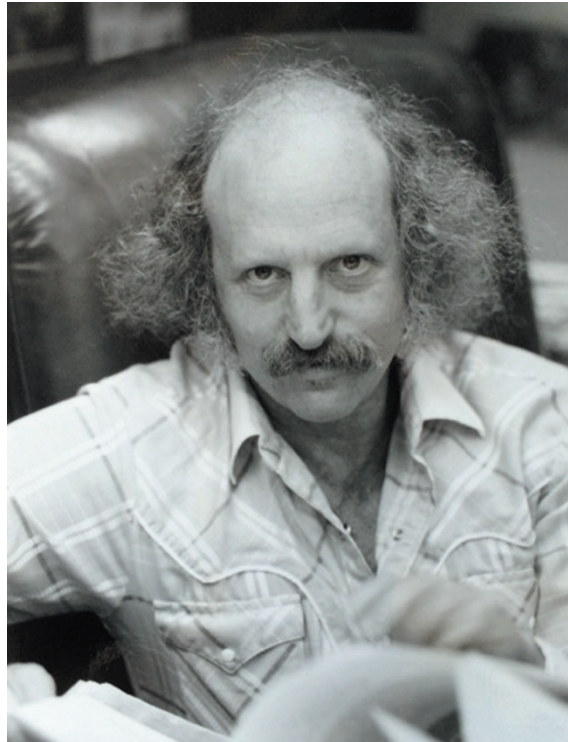
Systems biologist who described gene regulatory networks.

Eric Harris Davidson spearheaded many of the advances that led to our current understanding of how organisms are made from genomes. He helped to show how the coordinated expression of a whole suite of genes determines what progenitor cells specialize into during development. He also helped to pioneer the idea of gene regulatory networks — systems of interacting genes made up of multiple feedback loops, or subcircuits, each performing a specific job in the regulation of gene activity in the cell.

Davidson, who died on 1 September, was born in New York City in 1937. He found his way into research during his teenage years, working with cell physiologist L. V. Heilbrunn at the Marine Biological Laboratory (MBL) in Woods Hole, Massachusetts. During the academic year, Heilbrunn worked on calcium signalling at the University of Pennsylvania in Philadelphia, but he spent the summer at the MBL where he could study cellular processes in marine organisms such as starfish and sea urchins.

It was Davidson's father, Morris, a renowned abstract painter, who had brought Eric and Heilbrunn together. Morris, who ran a summer art school in Provincetown at the tip of Cape Cod in Massachusetts, knew Heilbrunn's wife, Ellen, a painter and teacher. The story goes that Davidson initially joined the MBL to wash dishes but Heilbrunn gruffly told him that anyone working there had to have a research project. Aged just 16, Davidson published an abstract in the *Biological Bulletin* on clotting in sand dollars (*Echinarachnius parma*) — a calcium-dependent cellular process that protects the organisms from infection following injury (E. H. Davidson *Biol. Bull.* **105**, 372; 1953).

In 1954, Davidson began a degree in biology at the University of Pennsylvania, where he worked in Heilbrunn's laboratory. On graduating, he wanted to stay in the lab, but Heilbrunn recommended that he switch to studying gene expression, and Davidson went to work with molecular biologist Alfred Mirsky at Rockefeller University in New York City. He received his PhD in 1963 and remained at Rockefeller until 1971 when he moved to the California Institute of Technology in Pasadena.



By the early 1960s, the 'central dogma' of molecular biology — DNA makes RNA makes protein — had been postulated. The idea that the RNA made from DNA contains specific instructions needed to make proteins had also just been confirmed experimentally. The question that Davidson was interested in was how the coordinated expression of multiple genes brings about cellular differentiation.

To investigate, Davidson applied 'solution hybridization' methods, first to frog oocytes and then to other animal models. Here, fragments of DNA in solution are heated to the point at which the two complementary strands of the double helix separate. Each single strand is then allowed to re-anneal with a partner strand floating in the solution; the more copies there are of any particular sequence fragment, the quicker the strands re-anneal. The approach provided a way to analyse genomic sequences as well as RNA transcripts.

A long-term collaboration with physicist-turned-molecular biologist Roy Britten — who had been working on ways to model hybridization kinetics — led to the publication in 1969 of a paper entitled 'Gene regulation for higher cells: a theory' (R. J. Britten and

E. H. Davidson *Science* **165**, 349–357; 1969). Here, the pair presented the first diagram showing how groups of genes could be expressed in coordination during cellular differentiation.

With the development of recombinant DNA technology in the early 1980s, in which fragments of DNA from multiple sources are spliced together, it became possible to dissect the molecular machinery needed to turn a gene on and off. Through a series of experiments in sea-urchin embryos, Davidson and his colleagues showed that protein-coding genes are controlled by what are usually nearby regulatory modules — DNA sequences that serve as binding sites for transcription factors, the proteins that form complexes to control the transcription of DNA into RNA.

In the mid- to late-1990s, Davidson and his collaborators took advantage of advances in DNA-sequencing technology to examine the genomic sequences near genes. Coupled with data on when genes were being turned on, and in what cells, during the early development of sea urchins, they showed how

the sequences near many genes have a regulatory role. This approach rapidly led to the description of gene regulatory networks. Davidson's work was key in establishing that it is through gene interactions playing out in different ways that cells are assigned their fates and organisms are created. He also helped to show that changes in these networks can result in altered morphologies and traits, the raw material for evolution.

The best scientists, in my view, are the ones who can stand fast in the face of bewildering complexity until they see the patterns emerge. Eric was a good example of such a person. He deeply enjoyed embracing the complexity and trying to develop a cogent view. In the third edition of his book *Gene Activity in Early Development* (Academic, 1986), he credits his father with teaching him about 'the ordering of complex perceptions'. As his father taught him, he taught us. ■

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