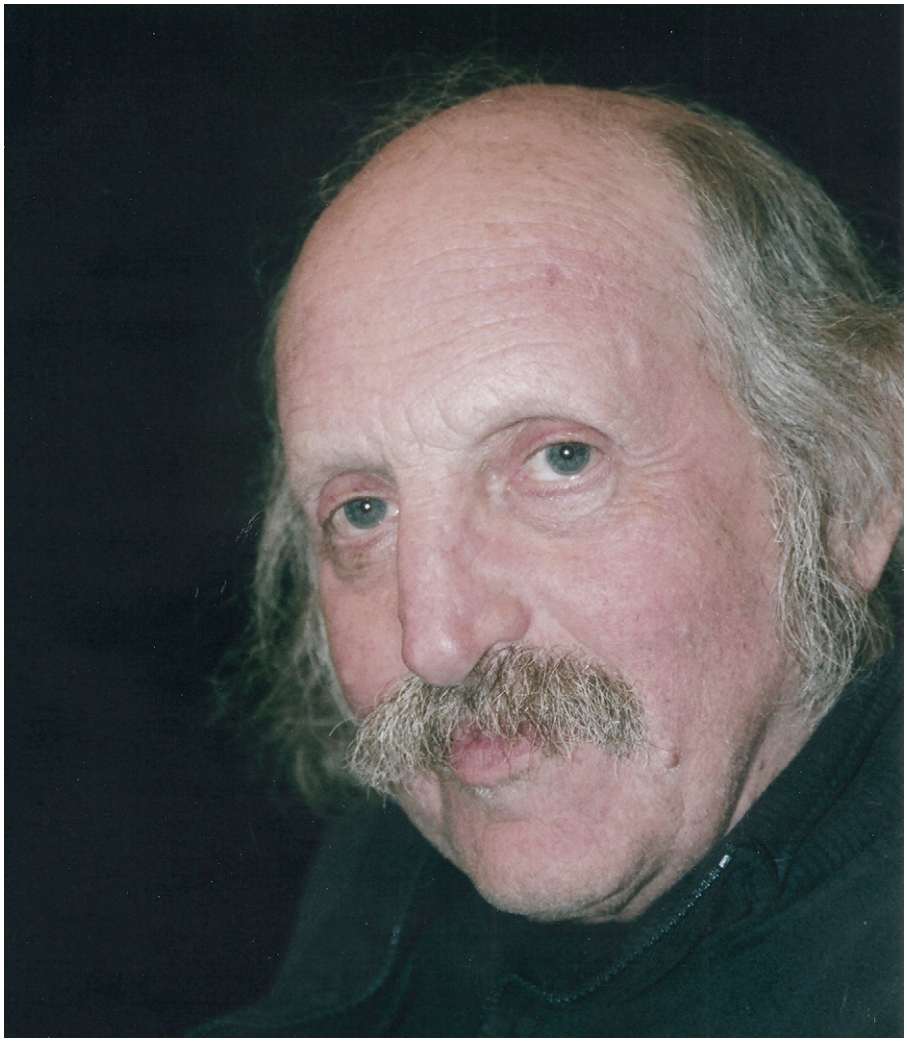
Developmental biologist Eric H. Davidson, 1937–2015

Leroy Hood[a,1] and Ellen V. Rothenberg[b,1]

[a]*Institute for Systems Biology, Seattle, WA 98109; and* [b]*Division of Biology and Biological Engineering, California Institute of Technology, Pasadena, CA 91125*

Eric H. Davidson, a world leader in developmental biology, demonstrated that most of development is, indeed, regulated by the genome. He was a pioneer researcher and theorist of the gene regulatory networks that execute the most complex biological processes, such as the cascade of molecular mechanisms that transform a single-celled egg into a complex creature. He insisted that the seemingly infinite details of classical developmental biology had to be explained in terms of the function of DNA sequences inherited in the genome, and showed how genomic information is used to initiate and drive forward development. His work emphasized a quantitative understanding of the biological mechanisms and the logic functions encoded in genetic networks, and focused on the question of how the genomic DNA could encode not only protein sequences but also the complex "software" needed for differentiating a myriad of cell types in the right places and proportions to make complex animals. He authored six books, ranging from his classic 1968 monograph, *Gene Activity in Early Development*, to his final book, *Genomic Control Process: Development and Evolution* (coauthored with Isabelle Peter), published this year.



Eric H. Davidson, Caltech's Norman Chandler Professor of Cell Biology, passed away on Tuesday, September 1, 2015. He was 78 years old.

Davidson entered the field of developmental biology in the 1960s, when there was an enormous richness of descriptive embryology for a staggering range of organisms but little understanding of genetic mechanisms. He emphasized that the solutions to developmental problems had to lie in the genome and was always a pioneer in developing and exploiting quantitative genomic techniques. However, throughout his career, his mastery of the earlier literature of embryology also gave him an unusually broad scope of knowledge and interest in evolutionarily diverse organisms. Davidson found an organism that would be ideal both for experimental embryology and for deep molecular analysis: the purple sea urchin, *Strongylocentrotus purpuratus*. His work focused on this organism for the last 40 years, and it was in the purple sea urchin that his group made its landmark achievements on the delineation of the specifics of their gene regulatory networks in the context of the first 30 hours of sea urchin development.

Davidson's search for an abstract logic that could make sense of cascades of molecular developmental mechanisms had deep roots. In 1969, Davidson and his longtime colleague, molecular biophysicist Roy Britten, published the first model of a gene regulatory network, a web of interacting regulatory genes. This network included both regulatory DNA sequences, i.e., segments of DNA at each gene that specified the conditions for when and where that gene will be turned on or off, and also genes that code

Author contributions: L.H. and E.V.R. wrote the paper.

The authors declare no conflict of interest.

[1]To whom correspondence may be addressed. Email: lhood@systemsbiology.org or evroth@its.caltech.edu.

for molecules that bind to the regulatory DNA of other genes to turn them on or off (1). Many of Davidson's 1970s DNA regulatory predictions have been verified over the last 20 years. Now, more than 40 years later, biologists in the Davidson laboratory and in many others inspired by his work have shown experimentally how these gene regulatory networks—which have many of the properties first predicted in 1969—function to control the process of development. In 1971, Britten and Davidson published another landmark paper concluding that the evolution of an animal's body plan also depends on changes in how genes are regulated during development (2). This concept was the foundation for the field of evolutionary developmental biology.

Inherent in the idea of gene regulatory networks was the concept that genome sequences that provided information about how genes should be expressed would be as important as the genome sequences that coded for the proteins themselves. Although many considered non-protein-coding DNA to be "junk" at that time, Davidson recognized that this was where the key regulatory code resided and therefore that it must be fully understood. Davidson realized that to validate this concept, one must determine the complete genome sequence of the sea urchin, and he campaigned for a full-fledged sea urchin genome project. In 2006, Davidson co-led a group of 240 researchers from more than 70 institutions that sequenced the purple sea urchin's genome (3). This consortium of institutions led by Davidson's laboratory characterized the 23,000 genes of that genome and provided the genome framework for years of detailed gene regulation analysis (4).

In parallel, the Davidson group began a systematic mapping project of another kind: a comprehensive functional testing program to detect all of the control connections between the genes involved in the key events in the earliest stages of sea urchin embryo development. They devised a strategy to determine how the activity of each gene affected the ability of every other gene in that part of the embryo to be expressed. The first demonstrated parts of the gene regulatory network they derived from the results were reported in 2002 in *Science* (5), and this network model was filled out and extended many times in the subsequent 13 years. In so doing, Davidson and his collaborators recognized that the regulatory networks governing high-level processes—the formation of a specific type of cell, for example—are built from gene circuits that can have striking similarities even when the identities of the genes in the circuits themselves are different. These logic circuits can be viewed as a few dozen types of modules that perform specific functions, such as creating a positive feedback loop that stabilizes expression of a pair of genes in a future tissue type, or an exclusion circuit that creates irrevocable boundaries between different tissue types in parts of the future organism. Davidson's laboratory has now defined nearly all of the gene networks that specify development in the five tissue types of the 30-hour-old sea urchin—from fertilization of the egg to the development of an organism—a tour de force unmatched in developmental biology. Davidson paved the way to the demonstrations that similar modular systems appear to exist in flies, frogs, chicks, mice, and zebrafish, suggesting that such logic modules may be a universal feature of higher organisms (6, 7).

The work, Davidson noted at the time, would allow scientists to tinker with and reengineer genetic networks, a process that would simulate the genetic changes that accompany the evolution of organisms in real life (8). "The evolution of animals is due to changes in the structure of these gene regulatory networks, so this work provides us with an opportunity to study evolution in a new and decisive way," he said.

The question raised by these network models was whether they embodied sufficient understanding to account for all of the gene expression changes that occur in real development. In 2012, Davidson, Peter, and Emmanuel Faure devised the first complete computational model of the early sea urchin embryo network, consisting of about 50 key regulatory genes, published in PNAS (9). Each gene was modeled as an ON/OFF switch, and the outputs of regulatory genes were connected to the target genes that they control. Whether or not the target gene would respond to a given combination of regulators was modeled based on the Boolean logic functions that had been determined for each gene individually from earlier experimental studies. The model also incorporated information about the spatial pattern of cell division in the embryo and thus, at each time point, which cells would be adjacent to others that might begin to affect their gene expression. The initial state of each switch was set, and the model was allowed to run. The team found that the entire unfolding progression of gene expression changes in each spatial territory of the embryo, as predicted by this network model, matched results in normal and genetically manipulated sea urchins, validating a powerful tool for understanding gene regulatory networks in a way not previously possible.

Eric Davidson was born on April 13, 1937, in New York, NY. His father was Morris Davidson, and his mother was Anne (Schlesinger) Davidson, who were both raised in Baltimore from families with roots in Lithuania. He was brought up in Piermont, NY, in the Hudson River Valley, and in Provincetown, MA, where he spent summers and his father operated an art school. Eric attended Nyack High School. His first experimental science job was at Woods Hole, MA, when he was 15. He worked there in the summer laboratory of L. V. Heilbrunn as a high school student, a connection initially made through Heilbrunn's wife, who was an art student of Eric's father. Eric's summer work with Heilbrunn at Woods Hole was published in *Biological Bulletin* (10) and won him a Westinghouse Science Talent Search scholarship. He then went to the University of Pennsylvania as an undergraduate and continued to work with Heilbrunn there. Davidson earned his Bachelor of Arts degree from the University of Pennsylvania in 1958 and his doctorate from Rockefeller University in 1963, working with Alfred Mirsky. After an initial stint as an assistant professor at Rockefeller, he moved to California Institute of Technology (Caltech) in 1971 and rose through the ranks to become Chandler Professor of Cell Biology in 1982.

Davidson was a member of the National Academy of Sciences and a fellow of the American Association for the Advancement of Science. In 2011, he was awarded the International Prize for Biology by the Japan Society for the Promotion of Science. He was also the recipient of the Lifetime Achievement Award from the Society for Developmental Biology, and the Alexander Kovalevsky Medal from the St. Petersburg Society of Naturalists.

Davidson had varied interests that he pursued with passion and deep commitment. He was a knowledgeable and voracious reader of history, not only of America but also of Europe and the Mediterranean from classical antiquity to the present. He loved American football, and participated as a player from high school into the 1990s (in his 50s), on the Caltech tackle football team and as player–manager on the Pasadena flag football team, the Tiger Toads. Beginning in the late 1950s, he was deeply engaged with the old-time traditional music of the Appalachian Mountains at the Virginia/North Carolina border, and he collected voluminous field recordings dating back to the 1960s for Folkways Records that are now available from the Smithsonian Institution. As a performer of old-time music, he played clawhammer banjo with the Iron Mountain String Band, which performed and recorded until 2010. He was a superb experimental gardener. Finally, we would be remiss if we did not mention Eric's deep commitment to quality for

PNAS—even when sick in his last years, he attended most of the editorial meetings and never compromised his demand for quality.

He is survived by his former wife Lyn Davidson and her daughter, Elsa Davidson Bahrampour. He is also survived by his first wife, Mary Rose Zipser, by his long-term laboratory associate Jane Rigg, and by his long-term scientific and intellectual companion, Ellen Rothenberg.

Finally, Davidson acknowledged a strong influence on his own career from the work of his father, Morris Davidson, who was a successful Modernist painter. Davidson dedicated his third book to his father, and chose a painting by Morris Davidson for the cover of his final book with Isabelle Peter. He explained that the emphasis on abstract architecture of space and color in his father's work had set a precedent for thinking about complexity in terms of elements related by a finite set of transformations, and for seeing the way an element in one part of the composition could alter the impact of a related element in another part of the composition. This laid a foundation for his own abstract visualization of the logic that could explain the way gene expression control can generate systems as complex as embryos from a single fertilized egg. Davidson was fascinated by the generation of complexity from simplicity, specifically, how a finite set of generative rules could operate to produce great biological complexity in a highly ordered and reproducible way. He emphasized that it was the role of the genome to ensure that all embryos of a particular type of creature generate the same pattern of complexity during their development, and the role of the scientist to understand the mechanistic and logical rule sets through which this is achieved.

Eric's memorial service was profoundly moving. It consisted entirely of about 15 testimonies to his character, accomplishments, and interactions with friends. These people came from all walks of life—science, sports, entertainment, business, and a diverse array of friends. Eric was clearly the most outstanding developmental biologist of his time, and he forever changed our understanding of developmental biology. We knew Eric very well, yet we came away overwhelmed with his intellect, his honesty, his commitment to excellence, his determined optimism, his passion for accomplishment, his powerful scholarship, and his unique ability to touch deeply and in many different ways so many people. His life is an incredible inspiration. We celebrated a most wonderful human being—the likes of whom we will not see again.

1 Britten RJ, Davidson EH (1969) Gene regulation for higher cells: A theory. *Science* 165(3891):349–358.

2 Britten RJ, Davidson EH (1971) Repetitive and non-repetitive DNA sequences and a speculation on the origins of evolutionary novelty. *Quart Rev Biol* 46(2):111–138.

3 Sea Urchin Genome Sequencing Consortium (2006) The genome of the sea urchin Strongylocentrotus purpuratus. *Science* 314(5801): 941–952.

4 Davidson EH (2006) Special issue: The sea urchin genome. *Dev Biol* 300(1):1.

5 Davidson EH, et al. (2002) A genomic regulatory network for development. *Science* 295(5560):1669–1678.

6 Davidson EH, Levine M (2008) Properties of developmental gene regulatory networks. *Proc Natl Acad Sci USA* 105(51):20063–20066.

7 Davidson EH (2010) Emerging properties of animal gene regulatory networks. *Nature* 468(7326):911–920.

8 Erwin DH, Davidson EH (2009) The evolution of hierarchical gene regulatory networks. *Nature Rev Genet* 10(2):141–148.

9 Peter IS, Faure E, Davidson EH (2012) Predictive computation of genomic logic processing functions in embryonic development. *Proc Natl Acad Sci USA* 109(41):16434–16442.

10 Davidson EH (1953) Clotting of the perivisceral fluid of the sand dollar *Echinarachnius parma*. *Biol Bull* 105:372.