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Editorial

Eric Davidson: Steps to a gene regulatory network for development

A B S T R A C T

Eric Harris Davidson was a unique and creative intellectual force who grappled with the diversity of developmental processes used by animal embryos and wrestled them into an intelligible set of principles, then spent his life translating these process elements into molecularly definable terms through the architecture of gene regulatory networks. He took speculative risks in his theoretical writing but ran a highly organized, rigorous experimental program that yielded an unprecedentedly full characterization of a developing organism. His writings created logical order and a framework for mechanism from the complex phenomena at the heart of advanced multicellular organism development. This is a reminiscence of intellectual currents in his work as observed by the author through the last 30–35 years of Davidson's life.

1. Introduction

Eric H. Davidson's career had an uncommonly unified trajectory over a half-century span and more. His late works from 2009–2015 emphasized a general theory of gene regulatory networks that drive developmental processes (Davidson, 2009, 2010; Erwin and Davidson, 2009; Peter and Davidson, 2009b, 2011a, 2015; Peter et al., 2012), but harked straight back to two potent theoretical papers that he wrote with Roy J. Britten about gene control in networks in between 1969 and 1971 (Britten and Davidson, 1969, 1971). His experimental work for 50 years stressed using the ensemble of all the transcribed and regulatory components of a system to explain development, not just a "minimal" set of "important" components, and in this sense he was a father of Systems Biology[1]. This emphasis held from his breakout book Gene Activity in Early Development (1st edition) (Davidson, 1968) to the comprehensive catalogues of sea urchin regulatory genes that his group published in the 2000's (Howard-Ashby et al., 2006a, 2006b; Materna et al., 2006) and the exceptional comprehensiveness of the Boolean model that he developed with Isabelle Peter and Emmanuel Faure in 2012 (Peter et al., 2012). In his final written commentary he emphasized repeatedly the need for models to be complete in terms of the components they included, and also completely validated by experimental evidence for linkages between the components, in order to provide causality. He contrasted the explanatory value of models fully rooted in genomic sequence, which show how the genome controls development, against models based on more limited analysis of regulatory pathways mediating parts of a process, e.g. controlling signaling "off the DNA" (Davidson, 2015). By 2015, the completion of the trajectory of his work could be deeply inspiring but also somewhat intimidating).

By the last years, one could be forgiven for imagining that his career leaped directly from the late 1960's, as a systems biology theorist and pioneer, to the magisterial repleteness of the 2010's with nothing in between. However, this retrospective view would misstate the record of how Davidson, his group, and his intellectual collaborators progressively developed these causal networks. It would telescope into nothing the risk-taking exploration, the swift responses to the findings of others, the key role of teaching in shaping emergent hypotheses, and the exciting experimental progress partly based on a series of technological advances, which filled at least three decades and kept revealing new features of developmental biology along the way. In reality, Eric Davidson led a highly effective experimental group that discovered major properties of his own system, and the group's research both repeatedly corrected and provided increasingly firm foundations for his theoretical extrapolations to generality. The path from his theory of the late 1960's to his theory of the 2010's involved a sequence of strategic research moves in different directions as well as dynamically changing system-level insights based on the new discoveries by colleagues inside and outside his group. As a colleague and friend since the early 1980's I was in a position to observe many of these moves and to see them eventually lead to the mature, well-validated models that emerged.

Here I offer one person's vantage on a key segment of Eric Davidson's complex and multifaceted career, anchored primarily by my own memories. A fuller, documented story of Eric's career at Caltech awaits telling by Jane Rigg, who helped to build the lab from Eric's first arrival there, ran it with him for decades afterwards, and shared in a vast range of Eric's enterprises in science, institution building, and writing till the last year of his life.

[1] That is, the ensemble of expressed protein-coding genes, their promoters, intronic regions, and extended cis-regulatory sequences across the genome were interesting to him from the earliest years. In the 1960's he speculated that the main specific regulators in gene networks would be noncoding RNAs, possibly similar to lncRNAs that are now being defined. Curiously, though, by the time that actual miRNAs and lncRNAs were discovered and characterized by others in the second half of his career, he argued that they played little role in the developmental systems of his greatest interest.

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2. Some comments on background

Eric had already focused on the central importance of tissue-specific differential gene expression from his days as a student with Alfred Mirsky, but this was systematized into a theory when he met Roy J. Britten. Eric's deep engagement with Roy Britten was extremely important to his career, as described by a number of the other contributors in this issue, and Roy brought a great influence on him in several ways. One was the intellectual glamor of physics, which Roy embodied. The lure of doing biology that could meet the lofty standards of physicists was further reinforced by Eric's interactions with his immediate neighbor at Caltech, Max Delbrück. (It was always a point of pride with Eric that he accepted Delbrück's challenge to take an intensive tutorial in advanced math with Delbrück's research fellow. Eric enjoyed formulating and troubleshooting differential equations himself ever afterwards.) The emphases on logic, quantitative precision and big-picture conceptual orientation, all intrinsic to physics, were values Eric prized to the end of his life, and he also savored the honored physics tradition of bare-knuckle, direct intellectual argument. Another thing that the collaboration with Roy provided was a distinctive experimental path unlike others in developmental biology. It was a heady thing to be able to measure the behavior of whole ensembles of nucleic acids and the structural features of whole genomes simply by using biophysical measurements of hybridization kinetics. Many (including multiple members of my own graduate school class at MIT) were impressed by this, and articles by Roy and Eric's joint groups were a regular feature in issues of the journal *Cell* when it was launched in the 1970's (Davidson et al., 1975; Galau et al., 1976, 1977; Hough et al., 1975). The excitement of this approach for Roy and Eric themselves must have been heightened by their prediction that repeat sequences, the elements that were most prominently distinguished by this experimental method, included the regulatory sequences that control differential gene expression. They hoped that they were driving to the heart of gene regulation as well as characterizing genomic and transcript structures. But by the early 1980's when I first encountered Eric, characterizing repeat sequence expression and repeat sequence distribution in different genomes had come to be regarded by many people as his main interest. This structural genomics focus had drifted some way from the larger theory about gene regulation.

Ironically, Eric had been drawn into this field from a much earlier immersion in classical embryology. This had started at least as far back as his undergraduate work with Heilbrunn at the University of Pennsylvania and was almost certainly primed by his high-school work during summers at the Marine Biological Laboratory in Woods Hole. By the late 1970's and early 1980's, Eric's group may have been doing experiments in the lab like biophysicists, but his mind was also filled with something else, which was already becoming increasingly rare for the field: namely, a vast furnishing of encyclopedic knowledge of classical observational embryology from the late 1800's and the early 1900's. The oddness of this combination was very evident when I first critiqued chapters of what became his 1986 edition of Gene Activity in Early Development (3rd edition) (Davidson, 1986). The meticulously reproduced glossy plates of hand-drawn interpretations of microscopy from the early 20th century by Conklin and Wilson were presented and discussed in Eric's book in intimate detail, interspersed with brand new gene expression reporter assay data, hybridization kinetic measurements, and theoretical primers on macromolecular synthesis and turnover kinetics and nucleic acid reassociation kinetics. Especially in the chapter on cytoplasmic localization and the origins of embryonic axes (Chapter VI), even the names of the organisms described were unfamiliar – very few of them have continued to be studied as “model systems” – and their modes of development seemed dizzyingly individualized. Use of body plan patterning features such as reversible extrusion of polar lobes in snails and budding segmentation in leeches made it obvious that these organisms had diverged in their developmental processes very far from patterns familiar from work in models such as mammals or flies.

Most striking was what was missing in this synthesis. François Jacob and Jacques Monod, and virtually all precedents for gene regulation from microbial molecular biology and genetics, were barely noted; Jacob and Monod were not even listed in the bibliography. Now, by the 1970's, most regulatory biologists in my own molecular biology orbit (at Harvard, MIT, University of California San Francisco, and the Salk Institute) had been massively influenced by Jacob and Monod's work, by models of bacterial operon regulation, and by the precedents for elegant λ phage regulation of lytic vs. lysogenic growth by a mini network of mutually antagonistic activator/repressor proteins (Jacob and Monod, 1961; Jacob et al., 2005; Maniatis et al., 1974; Monod et al., 1963; Ptashne, 1967; Ptashne et al., 1980). How could these be skimmed over so lightly in a book about differential gene regulation as the foundation for development? It was not just this particular work of Eric's that failed to draw upon Jacob and Monod. Interestingly, one of the most controversial predictions in the 1969 Britten and Davidson paper was that regulatory RNAs rather than regulatory proteins might be responsible for complex gene regulation (Britten and Davidson, 1969). Yet this was presented without regard for the clear evidence already in hand at the time that gene regulatory molecules were proteins in these bacterial systems. Why? Asked about this many years later, Eric often explained that for him in the 1960's, the evident differences between bacterial gene regulation and complex eukaryotic gene regulation in development completely dwarfed the similarities. Hybridization kinetic analyses of bacterial and multicellular eukaryotic genomes had already showed these to have vastly different kinds of sequence organization, with a severe paucity of repeat sequences in the bacterial genomes compared to the multicellular eukaryotes. If these repeats were regulatory sites, then bacteria were missing this kind of regulation. Also, Eric's view of development was that this irreversible, hierarchical process of increasing complexity that he was interested in was so different from the reversible, physiological nutrient responses of bacteria that there was no reason to posit the same kinds of molecular mechanisms. In this way, Eric and Roy were indeed charting their own course. But were they actually solving developmental mechanisms?.

3. A reorientation: cell type specificity and the significance of fate mapping

By the early 1980's when I reached Caltech, change was in the air. This was not yet evident in the publications that came out at the time, but various members of the lab were creating enabling technologies that would bring the lab back to developmental process. The advent of nucleic acid cloning in the mid 1970's had made a difference to the terms in which one could study embryo development. With a way to study genes individually within a developmental context, there was finally a choice about whether to study specific sequences or not. Now that one could get hold of different, unique mRNAs in cDNA form, one could monitor differential gene expression directly. Much of the research in the lab was still focused on characterizing complex sequence ensembles in genomes and bulk populations of RNA, but some projects began taking a different path. By using genes newly cloned in the lab or by collaborators, Eric's lab began to look systematically at how cell type specific gene expression patterns appeared.

In view of what followed, note that at this key juncture the