"Gene Regulation for Higher Cells: A Theory" (1969), by Roy J. Britten and Eric H. Davidson [1]

By: Wolter, Justin Keywords: gene regulatory networks [2]

In 1969, Roy J. Britten and Eric H. Davidson published "Gene Regulation for Higher Cells: A Theory," in *Science*. "A Theory" proposes a minimal model of gene regulation [3], in which various types of 'genes' interact to control the differentiation [4] of cells through differential gene expression. Britten worked at the Carnegie Institute of Washington in Washington, D.C., while Davidson worked at the California Institute of Technology [5] in Pasadena, California. Their paper was an early theoretical and mechanistic description of gene regulation [3] in higher organisms.

"A Theory' stated the hypothesis that repetitive non-coding sequences are at the core of genetic regulation [3], which was unconventional in the late 1960s and early 1970s. While working at the City of Hope Medical Center in Duarte, California, Susumi Ohno in 1972 termed repetitive non-coding DNA as junk DNA, but by the end of the 2000s many biologists abandoned that term based on multiple discoveries that indicated the functional roles of these non-coding DNA strands. "A Theory" concludes that the model proposed in it allows for both the profound developmental consistency within species, and the remarkable variation that is observed in nature. "A Theory" indicates how evolutionary novelties can arise without the requirement of chance beneficial mutations. The model predicts that, for duplications to and/or relocations of regulatory regions, if those events lead to changes in the location, level, and timing of the process of transcription, then they could allow for stable systems of genes [6] that could enable evolutionary novelties, ultimately leading to the diversity of life. While researchers later accumulated evidence for such an explanation of body plan evolution [7], many still debated the importance of regulatory expansion in evolution [7] as a whole. The descriptions and implications proposed in "A Theory" inspired thousands of papers on gene regulation [3], most of which treat "A Theory" as a cornerstone of evolutionary developmental biology [8].

Prior to "A Theory", the concept of gene regulation [3] had little theoretical support. In his 1940 book "The Material Basis of Evolution," Richard Goldschmidt [9] at the University of California in Berkeley, California had considered how mutations could lead to changes in genetic regulation [3] and impact evolution [7]. In 1940 Edgar Stedman and Ellen Stedman at the University of Edinburgh [10] in Edinburgh, UK suggested that cells may differentiate due to gene activity, and they highlighted evidence that most cells in an organism contain identical genomes, and yet protein contents of cells vary. Despite the suggestions that gene regulation [3] may be an important biological mechanism, these musings provided no causal explanations in the form of molecular mechanisms. Without such explanations, the Stedmans and other biologists couldn't infer how regulation [3] could contribute to the structure, function, and evolution [7] of higher organisms. Britten's discovery of highly repetitive DNA in higher organisms in 1968, and Davidson's work on gene expression and RNA synthesis precedded "Gene Regulation in Higher Cells: A Theory". This theory of gene regulation [3] incorporated current findings, proposed a detailed mechanistic model, and suggested broad evolutionary implications of such a regulatory mechanism.

The introduction of "A Theory" recapitulates pieces of evidence that, put together, led the authors to develop the model. It also introduces the main elements of the model. "A Theory" proposes that there must be a minimum of five interactive elements in a regulatory model to allow a genetic system to differentially respond to various stimuli.

First, there must be a producer gene, which produces a protein. This concept is analogous to a later concept of the coding region of genes [6]. Second, there must be a receptor gene, a DNA sequence that links with a producer gene that promotes DNA transcription.

Third, activator RNA binds to the receptor in a sequence specific manner and signals transcription of the producer. While the authors dubbed this element as RNA for systemic simplicity, they predicted that activator RNA may be a protein, a prediction confirmed by later research into transcription factors and RNA polymerase.

Fourth, genes [6] that code for activator RNAs Britten and Davidson named integrators, and later research showed that they code for transcription factors. The authors argued that integrator genes [6] needn't be spatially linked to the genes [6] that the activator RNA interacts with.

Finally, there must be DNA sequences that activator RNA can recognize and bind to, thus influencing the rate of transcription of the producer gene. These are termed sensor genes [6], and are analogous to the *cis*-regulatory elements described by later research.

"A Theory" argues that sensor genes [6] most likely bind to an intermediary structure that can then bind to non-genetic stimuli. For example, the intermediary structure could be a specific protein that has the ability to interact with non-genetic stimuli like

hormones [11]. This indirect binding between a non-genetic agent and a sensor gene influences the transcription of the producer or integrator genes [6] that sensors connect to.

The second section of the paper describes the integrative function of the model's elements in more detail, and it demonstrates their relationships using hypothetical wiring diagrams that Davidson would refine in later publications. Many biologists at the time held that histone proteins bind to DNA and inhibit transcription. The authors diverge from this idea, and they suggest that histones are general inhibitors and that they cannot control transcription in any meaningful way. Using the wiring diagrams as a proof of concept, "A Theory" illustrates a fine tuned response mechanism at the level of individual genes [6]. This illustration describes system that can regulate the development of complex higher organisms.

As the authors explore the idea of the sensitivity of a genetic regulatory system, they proposes their first genetic regulatory motif: the feed forward loop. The model predicts that a fine tuned network response to a specific initiating event requires that sensor genes [6] be sensitive to the gene product that they activate. The authors state that self-regulation [3] of a gene could be the reason for sequential patterns of gene activation that result in the stabilization and subsequent differentiation [4] of cell types. This type of interaction, in which a transcription factor maintains transcription of its own gene via a sensor gene, Davidson later dubbed the feed-forward loop. Researchers have found feed-forward loops in nearly all genetic networks. Consistent with "A Theory's" predictions, this motif helps lock in a cell's differentiated state.

The third section of "A Theory" discusses the model's implications for evolution [7]. First, the authors discuss genome [12] size as it relates to phenotypic complexity. Citing previous studies on genome [12] sizes in extant taxa, the paper suggests that an increase in producer gene sequences cannot account for the nearly thirty-fold increase in genome [12] size between simple organisms such as sponges, and higher organisms such as mammals. "A Theory" suggests that the principle difference between organisms of different complexity must be due to an expansion in regulatory genes [6], resulting in an expanding range of cellular activities and complexity. Researchers confirmed that proposal in the 1980s when they discovered Hox genes [13] in many different taxa and correlated expansions and duplications of Hox genes [13] with with established explosions in physiological diversity. The model suggests that the most efficient way to facilitate evolutionary change is not to evolve novel gene function, but to make use of existing network components in novel ways. The model contains all the elements that enable such a regulatory expansion to happen.

The fourth section of "A Theory" addresses the experimental justification of the elements of the model. The authors admit that while the definitions of the elements of their model may not be strictly accurate, the functions described must be present in the true mechanism of gene regulation [3]. The evidence that supports the existence of each element is then discussed using specific examples, such as the two subunits of hemoglobin, whose producer genes [6] were known to be genetically unlinked but mutually exclusive to proper biological function of red blood cells (erythrocytes). The model indicates that separate genes [6] can be co-opted into a single network by the presence of the same sensor genes [6], and that these sensor genes [6] would be repeated throughout the genome [12]. Roy Britten and David Kohn's 1968 publication "Repeated Sequences in DNA. Hundreds of Thousands of Copies of DNA Sequences Have Been Incorporated into the Genomes of Higher Organisms" described highly repetitive sequences in the genomes of higher organisms. Building off of that description, "A Theory" indicates that sensor genes [6] may be utilized repeatedly throughout the genome [12], and suggests the widespread expansion of regulatory genes [6] throughout the genome [12] correlates with the complexity of higher organisms.

The authors state that activator RNA is the heart of the regulatory model, though its existence posed a problem for their model, as the existence of nuclear confined RNA was unclear in 1969. While there was evidence for the ability of RNA to bind to DNA, there was no evidence that this happened *in situ* in the nucleus [14]. However, the authors' proposal that activator RNA may not be RNA at all, but a protein that can bind to DNA, was confirmed with the discovery of transcription factors in the early 1970's. As predicted in "A Theory", transcription factors are at the heart of gene regulation [3].

In the next section "A Theory" suggests that if the products of integrator genes [6] impact a multitude of different genes [6], then a mutation to an integrator gene should have many effects in various tissues throughout an organism. Throughout the 1920's Thomas Hunt Morgan [15], working at Columbia University [16] in New York, New York, cataloged the extensive range of phenotypic abnormalities caused by mutations in the *Notch* locus in the fruitfly *Drosophila* [17]. The wide range of abnormal morphologies caused by *Notch* mutants seemed to provide evidence for the existence of integrator genes [6]. While it has since been discovered that the *Notch* gene is not an integrator by the original definition, the Notch signaling pathway does influence development by indirectly regulating transcription.

In the final section, "A Theory" contemplates the evolutionary and genetic consequences of the model. First, because DNA sequences are inactive in transcription unless something turns them on, the genome [12] of an organism can withstand potentially deleterious or neutral mutations in inactive regions of the genome [12]. Only through direct incorporation into a regulatory system would the biological repercussions of a divergent DNA sequence be tested. Second, the authors argue that the model balances both extreme consistency with flexibility. Conservation of developmental patterns is maintained through complex and often redundant regulatory interactions, while flexibility is allowed through integration of gene products in different tissues without changing the genes [6] themselves. After decades of theoretical and methodological contributions, Eric Davidson [18] published the first experimentally validated, systematic description of a complete gene regulatory network in 2002. "A Genomic Regulatory Network for Development" describes the gene regulatory network controlling specification of the endomesoderm of the purple

sea urchin [19], *Strongylocentrotus purpuratus* [20]. This publication describes the complex interactions of over forty genes [6], and the network architecture reveals many features of the early development of an organism. Inspired by the regulatory circuit first described in “A Theory”, this publication maps this gene regulatory network. “A Theory” predicts that development unfolds through activation and interaction of multiple gene networks, such as the endomesoderm specification network in *S. purpuratus*, and that the architectural flexibility of those networks results in countless combinations of genetic interactions.

“Gene Regulation for Higher Cells: A Theory” influenced the fields of genetics and development. Thousands of publications have been produced on gene regulation [3] since “A Theory’s” publication, including greater than 350 by Davidson. By incorporating molecular descriptions of development into evolutionary accounts of variation, this publication was a forerunner for evolutionary developmental biology [8], that, according to many evolutionary and developmental biologists such as Sean Carroll and Günter Wagner, both in the US, holds some of the most promising perspectives on evolutionary biology.

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Subject

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