A window on signaling

Genes & Signals

By Mark Ptashne and Alex Gann

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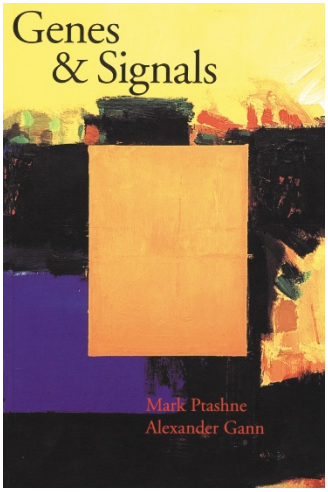
Reviewed by Mike Carey
UCLA School of Medicine, Los Angeles, California, USA

Genes and Signals, authored by Mark Ptashne and Alex Gann, is a compelling and deeply conceptual work about how biological reactions are regulated. I write this review, however, with the following disclaimer: I worked with Ptashne during my postdoctoral training and shared a lab bay and too many evenings at the local pub with Gann. Thus, I found the style and substance of the book to be engaging, reminiscent of the polemical arguments and never-ending group meetings that characterized the Ptashne lab. Each chapter begins with an interesting quote, and so I begin my review with a quote from Tennyson: "Knowledge comes, but wisdom lingers." Although the book presents a litany of facts, its main strength is the synthesis of concepts, making it a terrific text for both advanced undergraduates and the cognoscenti.

The underlying theme of the book is that determinative events in biology are regulated by recruitment of components, through simple protein–protein contacts, to a specific location within the cell. The focus is on mechanisms of gene activation but with numerous insights on repression. An activator attaches to a specific address in the genome and turns on a gene by recruiting RNA polymerase and its helpers. Transcription ensues. Cooperativity and context play key roles in the specificity of a response. Chapters 1 through 3 describe the author's version of the gene regulation field moving from bacteria to yeast to flies and mammals. Chapter 4 extrapolates the principle of recruitment to general aspects of enzyme specificity.

Chapter 1 is a delightful read and extends issues and ideas introduced in Ptashne's first book, *A Genetic Switch*. The chapter contrasts the roles of simple recruitment and allostery, while highlighting the detailed mechanistic work performed on prokaryotic transcription over the past two decades or so. It includes the newest insights on autoregulation by λ-repressor; that is, looping between the two distal operators O_R and O_L, and recent work on the mechanism of catabolite activator protein. Whereas the chapter focuses on events that establish recruitment of polymerase as the predominant mechanism, it also notes the exceptions, where allosteric events are important (MerR and NTRC). The special roles of cooperativity are emphasized and expanded upon in the appendix. To appreciate Chapter 1 is to appreciate the book.



As we move onto Chapter 2, the facts become fuzzier and subject to various interpretations, yet the authors inform the reader of this handicap and articulate the caveats. This chapter summarizes the state of knowledge of yeast transcription using GAL4 as an example—how an activator is designed, how it recruits RNA polymerase to the proper genes and so on. The chapter is bulging with examples of truly unique experiments that established fundamental aspects of eukaryotic gene activation. However, the reader should be aware that the focus on GAL4, an understandable necessity, limits the authors to a tangential exploration of many elegant and definitive transcription experiments that have been performed in yeast. Further, whereas *A Genetic Switch* succeeded by melding experimental methodology, outcome and interpretation, Chapter 2 of *Genes and Signals* succeeds brilliantly on interpretation but at the expense of methodology. The chapter might have provided greater coverage of genetics, microarray analysis and chromatin immunoprecipitation, and how important new information has been gleaned from them.

Given the complexity of mammalian and fruit fly gene regulation, I was curious about how the authors would approach Chapter 3. However, numerous examples of regulatory circuits, from simple gene activation to imprinting, were clearly presented and cogently linked to the concepts established in the first two chapters. The prevalent use of combinatorial control in advanced eukaryotes was emphasized with a superb albeit perfunctory description of Eve-regulated stripes in flies and the β-interferon enhanceosome in mammalian cells. My one concern was that the quantitative nuances of eukaryotic gene regulation were not fully explored. The comparison of a multimerized NF-κB site to the action of the β-interferon enhanceosome might be misconstrued by a student. The point to be made is that many activators can be placed in many contexts to elicit fundamental responses. That says something about how activators can interact with the transcriptional machinery. Regulation, however, is about responses of the proper magnitude and specificity. This says something about how activators interact with the transcriptional machinery. I think the distinction is important but under-emphasized.

Chapter 4 extends the general concepts of recruitment and cooperativity to enzymatic events controlling aspects of cellular metabolism, from tyrosine kinases to the proteosome. I am confident that those who study such systems appreciate the concept of recruitment; however, the comparison of these systems to gene regulation highlights the point for students, making it easier to conceptualize and appreciate.

I sat in a seminar last week that delved deeply into intermediary metabolism and its importance in drug design. I was amazed at how the over-50 crowd hung on every word and asked detailed questions in discussion. The under-50 crowd fidgeted throughout and slithered out of the room prior to the discussion. I vaguely recall memorizing intermediary metabolism for a graduate school entrance exam (although it didn't do me much good, as I forgot it all afterwards). What this book provides is a guide to the concepts that form the framework for the gene expression field. The concepts allow students to understand the context of the facts and apply this information to their own studies. Students who are lucky enough to read *Genes and Signals* won't be slithering out of transcription seminars in 30 years, when our field has been condensed to an *in silico* version of an intermediary metabolism wall chart. □