

## MOLECULAR BIOLOGY

# New Insights from a Classic System

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It has been nearly 20 years since Mark Ptashne's *A Genetic Switch (1)* was first published. That short book, an instant classic, nourished a generation of molecular biologists and helped establish phage  $\lambda$ 's genetic switch as a paradigm of gene regulation. A lot has happened in biology since then. In particular, the development of various high-throughput technologies has propelled molecular biology into the -omics era distinguished by vast amounts of data. We are shifting from a component-centric focus (characterizing the parts) to a system-level quest to understand how a limited number of parts work together to perform complex functions. The third edition of *A Genetic Switch* arrives at a critical juncture when the new field of systems biology is seeking direction. The book takes on a special significance because  $\lambda$ 's genetic switch represents perhaps the best characterized of any biological system, from its molecular components to their effects on the organism's modes of living.

The third edition's first four chapters are reprinted from the original text with only minor modifications. They present the classic exposition of how proteins bind DNA to turn genes on and off as phage  $\lambda$  grows in bacteria. With his unique style, Ptashne first describes this story in simple molecular terms aided by cartoon illustrations. Then, in the fourth chapter, he discusses supporting evidence and briefly explains the methodology of key experiments. Ptashne's clear and concise articulation of the essential scientific and experimental issues makes the book an ideal introductory text for the increasing number of interdisciplinary scientists moving into systems biology. More importantly, the detailed studies (summarized in these chapters) that relate properties of the molecular components to the function of the switch establish a high standard for the systems biology of more complex organisms.

The new chapter in the third edition describes a number of recent advances that

refine our understanding of the  $\lambda$  switch. I prefer this way of updating the story to a complete rewrite. The presentation should be particularly educational to students and newcomers from other fields, because it exposes the potential pitfalls of deductions drawn from various experimental approaches (even the old-fashioned, low-throughput ones) and illustrates realistically how progress is made in molecular biology.

None of the recent findings that Ptashne describes seem to challenge the big picture of how the switch works. Rather, they help to understand how it works so efficiently. For instance, a long-range interaction between the regulatory proteins (mediated by DNA looping) provides the cooperativity needed for the very tight negative autoregulation observed. To those already familiar with the basic  $\lambda$  story, these new materials may initially appear as fine details. But it is clear that the author's intention was hardly to settle the unresolved points. As with the first edition, the real value of the work on the  $\lambda$  switch that Ptashne describes lies not so much in the knowledge of the switch operation itself as in the insight the work offers into gene regulation in general. Through his discussions of the new findings, Ptashne presents a number of themes that may prove to be major directions for systems biology.

One such theme concerns the meta-rules for transcriptional regulation. Ptashne summarizes numerous experiments on the molecular mechanism of transcriptional activation in the  $\lambda$  switch. He suggests that their results point collectively toward a common molecular basis of gene regulation:

the recruitment of transcriptional machinery to the appropriate genomic location. [In another thought-provoking book (2), Ptashne and Alexander Gann generalized and developed this theme into a coherent principle of "regulated recruitment" that seems to apply to many biological regulatory processes.] If generally true, the idea that complex control processes such as gene regulation may be implemented in the cell by simple recruitment will be very significant for systems biology. It is an example of the kind of rules one seeks to relate component properties to system functions. Recent studies of combinatorial gene regulation (3) and signal transduction (4)

illustrate how such simple rules can generate complex functions.

Another important theme touched on in the new chapter is evolvability, always a difficult issue to address for complex, multi-part systems. By definition, a system is not a system before its parts come together.

Given that evolution prefers small steps, how do such systems evolve? The  $\lambda$  switch may well be simple enough to allow this important issue to be dissected and understood. The author reviews experiments conducted by Little *et al.* (5), whose original goal was to probe the robustness of the switch

to alterations in various molecular properties deemed important for the switch. These experiments showed the switch to be surprisingly robust, suffering only incremental deterioration in function. Ptashne argues that these results provide clues to how the  $\lambda$  switch could have evolved incrementally. There appear to be many issues waiting to be elucidated in this fruitful direction.

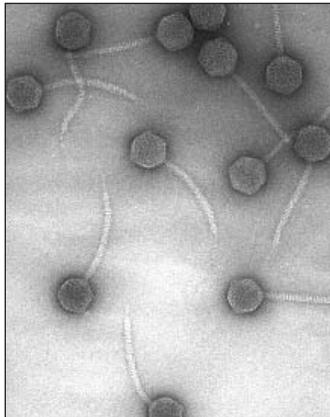
Efforts during the last decade to quantitatively model the  $\lambda$  switch are, regrettably, not discussed. Although modeling of biological systems is difficult and suffers from a number of shortcomings, these efforts have yielded important insights and initiated new research into broader issues such as the sources of stochasticity in gene regulation (6, 7) and the factors affecting the stability of genetic circuits (8). Also, recent efforts in synthetic biology—the construction of artificial genetic toggle switches *in vivo* (9), for example—can be regarded as the logical outgrowth of the studies on artificial transcription activators Ptashne describes. Artificial activators have taught us a great deal about the mechanism of transcriptional initiation. In similar ways, I believe we can learn much about genetic circuits from artificial switches. Perhaps we will find these topics in a future edition of this classic.

## References

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## A Genetic Switch Third Edition, Phage Lambda Revisited by Mark Ptashne

Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 2004. 168 pp. Paper, \$39, £24.99. ISBN 0-87969-716-4.



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