

Book Reviews

Enzyme Kinetics: Principles and Methods (1st English Ed.; translation of 3rd German Ed.)

Bisswanger, H. (Bubenheim, L., translator); Wiley-VCH, Weinheim, 2002, 255 pp. + CD-ROM, ISBN 3-527-30343-X, \$95.00.

This book on enzyme kinetics takes what is, to my knowledge, a unique approach to the discipline. The first part is a thorough discussion of substrate binding, independent of the enzymatic reaction, and deals with the phenomena of multiple binding sites, both independent and interacting. There is detailed graphical representation of the various equations showing what would be expected for weak and strong interactions and cooperativity, both positive and negative.

The second part is the most traditional with detailed derivation of kinetic equations for single and multisubstrate enzymes and the various methods for graphical representation. Most useful is the discussion of the strengths and weakness of each of the graphical methods including analysis of error propagation induced by the various transformations.

The third part describes various methods for measurement of kinetics and binding. Each is presented with the appropriate theory. Strengths and weakness of each are discussed, although not in great detail.

The mathematical treatment assumes a strong background in physical chemistry and in calculus, making the book unsuitable as a primer for most beginning biochemistry students. The book is primarily theoretical, and the reader will search mostly in vain for specific enzymes that illustrate the various kinds of kinetics or mechanisms presented.

There is an accompanying CD-ROM that which presumably provides practical means of kinetic analysis. As the disc is compatible only with PC-format computers, not Macintosh, I was unable to evaluate it.

On the whole, the book is recommended for the most detailed theory and kinetic derivations that I have ever seen in one place. However, it is not a “how to” book to actually do kinetics.

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Meselson, Stahl, and the Replication of DNA: A History of “The Most Beautiful Experiment in Biology”

Holmes, Frederic Lawrence; Yale University Press, 2001, 503 pp., ISBN 0-300-08540-0, \$40.

The author interviewed Matthew Meselson and Franklin Stahl separately and together over a period of a decade in

an effort to reconstruct the history of “The Most Beautiful Experiment in Biology” (this quote is attributed to John Cairns as reported in Horace Judson’s *Eighth Day of Creation*). The trio examined extant records, notes from Meselson’s workbook, centrifuge logs, and photographs containing the results of centrifugation experiments (many of which are reproduced in the book). Holmes also examined periodic reports written for the California Institute of Technology (Caltech) and the National Association for Infantile Paralysis; these were generally the work of Stahl. Other sources include discussions with Gunther Stent, John Cairns, James D. Watson, and Howard Schachman. As an historian of science, Holmes sought the help of these experts to learn the scientific principles involved. His explanations are thorough, and his sources are cited in notes that accompany each chapter.

Matthew Meselson and Franklin Stahl first met at Woods Hole in the summer of 1954 when both were graduate students. Meselson was at Caltech with the legendary Linus Pauling, and Stahl was at the University of Rochester with A. H. (Gus) Doermann. Meselson and Stahl discussed ways to test the prediction of semiconservative duplication of DNA as proposed by Watson and Crick (the terms conservative, semiconservative, and dispersive modes of replication had not yet been invented by Gunther Stent and Max Delbrück). The initial idea was to infect bacteria growing in ordinary medium with deuterium-labeled phage particles and allow one cycle of phage growth. The phage would then be centrifuged in a density-adjusted solution that would allow the resolution of original phage from newly synthesized phage. Holmes emphasizes the boldness and originality of the idea of using heavy and light isotopes to resolve the newly synthesized molecules from existing molecules as proposed by the young principals. This strategy was used later by Sidney Brenner, Francois Jacob, and Meselson to demonstrate the existence of messenger RNA.

In 1956, Stahl (now a postdoctoral scholar with Giuseppe Bertani) joined Meselson at Caltech; they lived together in a house on San Pasqual Avenue in Pasadena with Jan Drake, who was a graduate student with Renato Delbecco. Holmes describes the various social activities at this house where the inhabitants were able to live well despite their modest means. We learn that Howard Temin and John Cairns lived in the house later.

Meselson and Stahl started with 5-bromouracil (5BU) to produce heavy DNA. The 5BU substitutes for thymine, and the bromine atom produces a more dense nucleotide and DNA molecule. With Jerome Vinograd’s assistance, Meselson examined the sedimentation patterns of T4 phage, grown in medium with and without 5BU, in a Spinco Model E ultracentrifuge (The Big Machine). The first series of ultracentrifugation experiments, initiated in December 1956, did not go well for a whole host of reasons including the uncertainty of how much 5BU was

incorporated into progeny DNA. Stahl's role in the project involved the preparation of the phage samples, and he performed comprehensive analyses of the sedimentation data. A long detour transpired because of the inability to detect phage or DNA molecules with intermediate amounts of parental 5BU.

Half way through the book (p. 270) we find the first illusion to the Meselson-Stahl experiment as we know it today. Meselson wrote in his workbook about the need to abandon phage DNA and use bacterial DNA grown in the presence of ^{15}N , the heavy isotope of nitrogen with a transfer to ^{14}N , the ordinary isotope (October, 1957). All of a sudden, voilá, the DNA prior to transfer was all heavy, the first generation after transfer showed all intermediate density DNA, and the DNA after two generations showed equal amounts of intermediate and light DNA.

Caltech was the home of Max Delbrück, a father of phage research, and Delbrück served as a mentor of the two principals. The results of these experiments were freely communicated by letter to members of the "phage group" including Watson. However, the principals procrastinated in writing up a definitive paper. Impatient, Delbrück transported Meselson and Stahl to the Kerkhoff Marine Station at Corona del Mar and confined them to an upstairs room with a typewriter for several days (it wasn't as bad as it sounds, and the manuscript was not completed at this time). Apparently the principals and others under Delbrück's tutelage preferred to perform experiments rather than write.

Holmes provides an analysis of organization of the paper and the authors' strategy and thoughts regarding the manuscript. Like most experimental reports, the Meselson-Stahl paper is presented in a logical fashion and fails to reflect the numerous side paths and dead ends of the study. Moreover, the introduction does not mention the Watson-Crick structure. Paradoxically, the paper can be interpreted as though the authors were trying to distance themselves from Watson and Crick.

Stahl interviewed for a faculty position at the University of Missouri in October 1957 (while the definitive experiments were initiated). Stahl would accept a position there the next spring, even though Delbrück would try to retain him at Caltech. Stahl left Caltech about 20 minutes after their paper was completed (May, 1958). Meselson spent part of December and January in the East and Midwest on a holiday vacation. He met in Chicago with a group of fellow students from his undergraduate days at the University of Chicago. One classmate was Horace Judson, the noted chronicler of molecular biology. Meselson also had a job interview at Washington University in St. Louis in Arthur Kornberg's Microbiology Department. He rapidly consumed several martinis at dinner and became so sick that he had to lie down. He did not receive a job offer.

Meselson took his Ph.D. defense examination, chaired by Linus Pauling, in May (1958). Richard Feynman, a committee member who had not read the dissertation prior to the defense, told the participants that there was a much easier way to calculate the time course of the distribution of macromolecules in a density gradient. Feynman stepped to the blackboard and derived his new equations. Independent of Feynman's impressive impromptu derivation,

Meselson passed and received complements from Pauling afterward.

The penultimate chapter, "Images of an Experiment," describes how this classical finding is described in textbooks of biochemistry and molecular biology. The conclusions are so ingrained in the lore of science that the experiment - but not the conclusion - is omitted from many contemporary books, surely a loss for students. The last chapter, "Afterward" describes the academic careers of Meselson (at Harvard) and Stahl (at the University of Oregon), along with some personal and family highlights. In a few places in the text, Holmes relates the impressions of Meselson and Stahl about their work together. Meselson thought the work was fully shared and involved the two nearly equally. Stahl felt that Meselson was the primary mover and he (Stahl) was secondary. Holmes believes this difference reflects the styles, attitudes, and personalities of the two former MacArthur fellows.

For those who learned their science after the Meselson-Stahl experiment (the vast majority of scientists), it will be surprising to learn of the grave doubts about the semiconservative replication mechanism received from stalwarts such as Max Delbrück. A main concern is the unwinding of one strand from the other (Delbrück called this the untwiddling problem). The result of the Meselson-Stahl experiment more or less resolved the doubts of such people, and it also provided evidence and gained support from other scientists for the Watson-Crick structure and the semiconservative replication mechanism.

The author succeeds in the central aim of the book, which is, "to contrast the core simplicity of this beautiful experiment with the many dimensions of complexity that made it possible." The book describes accurately how science, even extraordinary science, is accomplished. Holmes describes the personalities and idiosyncrasies of many of the participants in an even-handed fashion. This book is informative, joyful, and can be read profitably by undergraduate students and scientists of all persuasions. It can easily be made part of the readings in a course of molecular biology where DNA replication is covered, and it promises to provide critical insight and to win the accolades of students, many of whom are unenthusiastic about scientific history. It is up to the high standards of Holmes's two volumes on the discoveries of Hans Krebs, and this book is highly recommended.

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Discovery: Windows On The Life Sciences

Lewis, R. A.; Blackwell Science, Inc., 2001, 235 pp., ISBN 0-632-04452-7, £24.99.

Science is a systematic and rational way of acquiring knowledge about, and making sense of, the world in which we live. It is often a slow and largely incremental activity