
Book Reviews

Time Warps, String Edits, and Macromolecules – The Theory and Practice of Sequence Comparison. David Sankoff and Joseph Kruskal. ISBN 1-57586-217-4. Price £13.95 (US\$22.95).

I read this book around ten years ago and it was already seven years old then. However, the decision to reprint it is a wise one. True to the title this book covers the application of sequence comparison in plenty of detail and is an easy read. It quickly gets into the nitty gritty of the various algorithms with attention to biological sequences leading into discussion of the uses of dynamic programming (the basis of the widely used Smith and Waterman sequence analysis algorithm) in other fields such as stratigraphy and the analysis of bird song.

While some parts have been updated, overall this is just a reissue but don't let that dissuade you from giving the book a chance. It is only today that computing is reaching a state where dynamic programming methods can be used on less than super-computer level hardware without having to resort to shortcuts such as those employed by FASTA and BLAST and so this book gains a new relevance. Many Universities are setting up bioinformatics courses in response to the need for skilled scientists and this book provides just the right level of instruction for those who are coming into bioinformatics either from a computing or biology background to understand the implementation and use of dynamic programming.

This book was a great introduction to me ten years ago and so it remains today, it allowed me to implement the algorithms and gain an understanding of their attributes. For students starting out on the road into sequence analysis this is as good a starting place as you could wish for.

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Transgenic mammals. John Bishop (Cell and Molecular Biology in Action series, Pearson Education Ltd, Harlow, Essex, 1999). ISBN 0 582 35730 6; pbk, 294 pages, Price £21.99.

Twenty years ago the only route to obtaining mammals with heritable genetic variations was to wait until they arose by chance. The spontaneous mutation rate could be increased in experimental animals by exposure to mutagens, but this was a random and undirected process. However, as a result of the development in the intervening years of a number of powerful techniques for introducing designed modifications into the mammalian genome, transgenic mammals have become an indispensable tool in most areas of fundamental mammalian biology and biomedicine and the impact of this technology is also being felt in livestock breeding. There has been a need for a textbook to make this subject area more accessible to non-specialists and here we have such a book, written by one of the major contributors to the field. John Bishop has had a distinguished career in this and other fields and I write these words on the day on which he retires from service to the University of Edinburgh.

The book is intended for advanced undergraduates as well as for graduate students and postdoctoral scientists and is also suitable for the motivated intelligent lay reader. It begins with a helpful introductory section which sets out the ground to be covered in the rest of the work, which is divided into two sections. Section II gives background information on mouse reproduction and development, husbandry and genetics, sex determination, uniparental gene expression, X chromosome inactivation and DNA methylation. Section III deals with making transgenic animals both by random DNA integration and by homologous recombination, expression of transgenes and transgenic livestock. It is written in a clear and accessible style that is understandable without recourse to other texts but is nevertheless well referenced to facilitate access to the primary literature for those who wish to pursue the subject more deeply. I had to work quite hard to find shortcomings but there were a few: On page 178, the description of positive-

negative selection is out of date in that more recent work has shown that the originally reported high enrichment frequencies were atypical and probably partly artifactual, and that introducing the terminal non-homology that provides the counterselectable marker does reduce the frequency of homologous recombination. In boxes 9.3 and 9.4 the positive selection medium for cells expressing the *aprt* gene should be AAT (adenine + aminopterin + thymidine) rather than the more familiar HAT, and the name of the gene should be *adenine* phosphoribosyl transferase. The discussion of ethical issues in the introductory section is also rather summary and dismissive. These are however minor criticisms and I would not hesitate to recommend this book to my students. It is a fitting finale to John's career and I wish him a long and happy retirement.

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We Can Sleep Later: Alfred D. Hershey and the Origins of Molecular Biology. Edited by F. W. Stahl. Cold Spring Harbor Laboratory Press 2000. xii + 359 pages. Hard cover. ISBN 0-87968-567-6 Price \$39.

Bacteriophage genetics was one of the two sources from which molecular biology sprang in the early 1950s, the other being the biochemical genetics of fungi and bacteria. Its relatively small group of disciples were called, by Andre Lwoff, the American Phage Church, and they were led by the Trinity of Nobel laureates, Max Delbruck, the pope, Salvador Luria, the sociable priest, and Al Hershey, the saint. Whatever his claims to sainthood, Hershey was certainly remarkable for his unwordly character and devotion to science. This book is a memorial both to his scientific achievements and to him personally. Virtually all of those prominent in the phage field in the 1950s and 1960s, and still living, have contributed to it.

Frank Stahl's collection divides into three main sections. The first eighty pages contain essays by ten prominent scientists who interacted with Hershey: Stahl, Szybalski, Weisberg, Ebert, Hotchkiss, Dove, Cairns, Tomizawa, Mosig, Skalka. They tell us much about the history of such essential aspects of phage biology as the genetic role of DNA and its relation to protein synthesis, the differences between the T-even phages and *lambda* in DNA organisation and synthesis, genetic recombination and the nature of phage "heterozygotes" – all areas to which Hershey himself contributed crucially. These essays are mostly serious pieces of scientific writing, well supplied with references, but they are also good sources of en-

tertaining anecdotes. The following 26-page section, headed *Reminiscences*, consists of shorter, more personal pieces from a second set of distinguished people: Campbell, Garen, Ptashne, Stent, Symonds, Volkin, Benzer, Herskowitz, Murialdo, Wallace, Zinder. The remaining 250 pages of the book has been put together from Hershey's own writings. There are three essays: *Bacteriophage T3, Parasite or Organelle* (1956), *Idiosyncracies of DNA Structure* and *Genes (his Nobel Lecture)* and *Genes and Hereditary Characteristics* (1970), the last addressing the problem of genetic determination in general. These are followed by a reprint of Hershey's famous 1952 paper with Martha Chase, which showed, through innovative use of the Waring blender, that when *E. coli* was infected with phage T2 the phage DNA entered the cells efficiently while most (not quite all) of the phage protein remained outside. Nearly 200 pages are occupied by all of Hershey's annual research reports from his Cold Spring Harbor laboratory from 1951 to 1970, and the Introductions to these reports that he wrote during the period from 1962 when he was Director of the Genetic Research Unit, which consisted solely of his own laboratory and that of Barbara McClintock. The Introductions are particularly interesting for their philosophical reflections. The detailed research reports, copied directly from the original pages, are interesting from the point of view of History of Science, but some added page headings would have made it easier to find one's way about in them.

A recurring question in the history of molecular biology is why the Hershey-Chase experiment carried such weight as proof that DNA, not protein, was the genetic material, when the earlier demonstration by Avery *et al.* that the transforming principle of *Diplococcus* was virtually pure DNA received much less attention. The reason given by Jim Watson, in the Obituary he wrote for the N.Y. Times, reprinted at the beginning of the book, and Frank Stahl in his introductory essay, is that the pneumococcus transformation experiments affected only surface features of the bacteria, which might be subject to special rules of inheritance, whereas the infection by phage DNA gave rise to the whole organism, if a virus can be so termed. Hershey himself was not expecting his own result and was characteristically modest, and even sceptical, about it afterwards. He is quoted as saying, in a round-table discussion in 1953, that after the publication of the Watson-Crick structure of DNA both Avery's result and his own had become superfluous – the double helix just had to be genetic material!

This book can be recommended to different readerships for different reasons. For those in molecular biology, and especially the old-timers, it will be appealing for its many amusing stories about and

photographs of people they know. At a more serious but less entertaining level it will provide a good source for historians of science, though anyone just wanting an outline of the overall story could get it more quickly from a single-author book or review. But I think the book's main interest is as a portrait of Hershey and an account of his personal philosophy. He seems to have had some of the character of an ascetic monk. According to his wife, as reported by Szybalski, he steadily lost weight during the working year and had to be fed up again during his summer holiday, which he spent sailing at Georgian Bay on Lake Michigan. He was generally a man of few words both in speech and in writing. As an editor, he cut out everything he thought unnecessary and scrutinised such words as remained for correct meaning. His major editorial job was to organise the 1970 Cold Spring Harbor compendium on Bacteriophage Lambda. As an editor, he expected delivery on time; Stahl's title "We can sleep later" is taken from a letter that Hershey circulated to possibly dilatory authors. He seems to have been regarded by the post-doctoral workers in his laboratory with some awe – they always referred to him as "Dr Hershey" – but also with affection. He was not an obtrusive head of laboratory, believing that post-docs had "earned the right to make their own mistakes". But he gave close attention to any request for his opinion, sometimes replying in writing. Seemingly indifferent to personal fame, he allowed his name to appear in the authorship of papers only when he had actually done some of the experiments, and he was not inclined to rush into print to establish his priority.

Hershey seems to have loved science more as a craft and exercise in logic than as a means to progress. He was a great deviser of experimental procedures, and once wrote (as reported by William Dove) that "Ideas come and go, but a method lasts". His joy in the actual operations involved in science was most famously expressed in his much-quoted idea of heaven: "Finding an experiment that works and doing it over and over again". In his 1966 Report (quoted by Hotchkiss) he wrote: "The universe presents an infinite variety of phenomena. The faith of the scientist, if he has faith, is that these can be reduced to a finite number of categories". But, he went on, "... one cannot measure progress toward the goal of understanding". He was very much aware of

the pitfalls on the road to explanation. In his 1969 Introduction he wrote: "Phage research [he might have said research in general] is beset with the following difficulty. One notices a phenomenon that looks interesting. After suitable thought and labor one performs an experiment that ought to be instructive. What it actually does is turn up a second phenomenon not related in a simple way to the first. This sequence of events makes for lively research. It does not provide explanations." In 1967, he had considered what was needed for successful explanations and theories. He cited Darwin's hypothesis of natural selection as satisfactory as an *explanation* of evolution because its elements, heritable variation and differential survival, were independently demonstrable (a necessary condition often difficult to meet) but it failed as a *theory* because it could not have predicted everything that came about in evolution. So perhaps all the phenomena of life would have to be investigated separately. In his 1964 Introduction, he wondered whether there would be sufficient motivation for the pursuit of the myriad biological phenomena, and felt that scientists were becoming more easily bored – "the threshold of human surprise is rising". Consequently he saw novelty as an essential inducement to research, rather than progress towards any particular goal. Characteristically, he never invoked the prospect of economic benefit as a reason for scientific work. Perhaps his enthusiasm for science is best explained in an interview for the BBC in 1953 (cited by Neville Symonds): "... whatever you do is novel, so you always have this sense of novelty, even if you are only using a new gadget. That's nothing to be proud of but it's fun, And if you get some result it's doubly fun".

At the unexpectedly early age of 63, Hershey decided not to do any more experiments and retired to occupy himself with sailing, gardening, operations with his computer, and recorded music. The final piece in his book is the text of a talk with the title *Funeral Sentences* (a reference to music by Purcell), which he gave following the death of George Streisinger. It is all about poetry and music, and science is mentioned only in relation to its aesthetic content. In the last paragraph, Hershey recommended his audience to listen to Elgar's *Dream of Gerontius*.

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