Book Reviews

Bioinformatics. From Genomes to Drugs. Edited by Thomas Lengauer. Wiley-VCH, Weinheim, Germany. 2002. xx + 442 pp (first volume). xx + 206 pp (second volume). 17 × 24.5 cm. ISBN 3-527-29988-2. $265.00.

The word "bioinformatics", which came into use in the late 1980s, clearly and concisely conveys the meaning and scope of an important new discipline. Acceptance of the word and emergence of the field were rapid. Medicinal chemists readily appreciate the potential value of understanding the structure and function of genes and gene products through the use of computer-based techniques for handling the massive amounts of data being unwound in molecular biology and related sciences. The great demand, still unsatiated, for scientists skilled in bioinformatics has created a need for good books on the techniques of bioinformatics.

One such book is the multiauthored, two-volume set edited by Prof. Dr. Lengauer (Max-Planck-Institute for Informatics, Saarbruecken, Germany). The book constitutes Volume 14 of the book series Methods and Principles in Medicinal Chemistry. As the editor notes in his Foreword, the book looks toward opportunities that bioinformatics can open for drug discovery. The book does open doors to attractive-looking technologies but does not reveal any new pharmaceuticals that have stepped over the threshold into the drug discovery pipeline. The second half of the subtitle ("to Drugs") receives only slight treatment.

The chapters are organized into two volumes. The first volume, entitled "Part I: Basic Technologies", contains eight chapters: (1) From Genomes to Drugs with Bioinformatics, (2) Sequence Analysis, (3) Structure, Properties and Computer Identification of Eukaryotic Genes, (4) Analyzing Regulatory Regions in Genomes, (5) Homology Modeling in Biology and Medicine, (6) Protein Structure Prediction, (7) Protein−Ligand Docking in Drug Design, (8) Modelling Protein−Protein and Protein−DNA Docking. There is also an appendix: Glossary of Algorithmic Terms in Bioinformatics. The second volume, entitled "Part II: Applications", is thin and features seven chapters: (1) Integrating and Accessing Molecular Biology Resources, (2) Bioinformatics Support of Genome Sequencing Projects, (3) Analysis of Sequence Variations, (4) Proteome Analysis, (5) Target Finding in Genomes and Proteomes, (6) Screening of Drug Databases, and (7) Future Trends. Actually, each volume has a mix of chapters dealing with fundamentals and applications. Compared to other bioinformatics books, this one is application-oriented. The 15 chapters average about 40 pages in length with a range of 18−99 pages. The chapters in Part II are generally shorter than those in Part I.

Despite the title of the book, five of the chapters—those on docking, protein structure prediction, homology building, and database screening—would be equally comfortable in a book on computational chemistry or computer-aided ligand design. That leaves 10 chapters devoted to the core of bioinformatics: sequence analysis, genomics, and proteomics. Juxtaposing chapters on bioinformatics and on cheminformatics in the same book has the potential of fostering communication between the two fields.

Medicinal chemists are keenly interested in druggable targets. The book contains a short chapter on target finding, but not much is described about druggable targets that have been discovered with the aid of bioinformatics. Other topics that get only a little attention include structural bioinformatics (nee protein crystallography) and metabolomics.

The strengths of the book include the descriptions and lists of web sites of the many available databases of useful information and relevant software. There are many databases besides the obvious EMBL, GenBank, Protein Data Bank, PROSITE, SCOP, and SWISS-PROT. However, highly relevant systems such as BACIIS and TAMBIS are missed. These web tools, along with SRS, help the user by automating the process of obtaining answers to queries that require sequential retrieval of information from several databases. A variety of downloadable computer programs are listed in the two volumes. All the chapters are packed with useful information about methods. Most terms and concepts are explained.

About half the chapters are by German authors, with the rest by American, British, and Swiss contributors. The editor contributed three of the chapters and a useful appendix giving short explanations of some of the algorithms that are alluded to in the chapters. The editor's introductory and concluding chapters are filled with many stimulating ideas and knowledgeable strategic visions. The chapter on homology modeling by Roland J. Dunbrack, Jr. was particularly well written. The two chapters on docking and screening by Matthias Rarey, Martin Stahl, and Gerhard Klebe will appeal to computational chemists in pharmaceutical research.

A comparison of the text and subject index suggests that the latter is 85−90% complete. No author index is given unfortunately, but an index of people mentioned in the text is included. Most of the references cited in the chapters date from 1998 to 2000. In chapter 1 of Part II, 30 references are cited in the text, but over half of these are missing from the list of references at the end of the chapter. The affiliation of the authors of this chapter is misspelled. In contrast, most of the chapters do not include the affiliation of the authors at the beginning of each chapter. Several other minor inconsistencies in production style are noticeable from chapter to chapter. For the book as a whole, usually only one author from each chapter manages to appear in the List of Contributors with an address and affiliation. Coauthors are thus not identified except by name. The table of contents does not show the authors of each chapter, which makes it difficult to find the work of a particular investigator. (A second printing reportedly addresses some of these problems.)

One cannot help but notice that the contents of this book have been stretched and duplicated to consume two volumes. The front matter and the indexes are the same in Parts I and II. Thus, the book has 630 nonreplicated pages. These pages are not filled. A typical scientific

book fills 60−65% of the area of each page for printing (margins consume an amazing amount of each page). As an example, the book "Structural Bioinformatics" (edited by P. E. Bourne and H. Weissig, Wiley-Liss, Hoboken, NJ, 2003, xix + 649 pp) fills about 63% of each page with prose, tables, figures, header, etc. In contrast, "Bioinformatics. From Genomes to Drugs" uses about 52% of available page space in the text sections and even less (ca. 38%) in the reference sections. If the publisher had made usual use of the available space, the entire book could have been printed as one volume of about 500 pages. One wonders what motivated the inflation of the book to two volumes, if other than the price. The price of the two-volume set was cut from $320 to $265 in the past year but remains high on any per page basis.

A general problem with scientific books published in recent years is that the standards in writing and punctuation are being allowed to slowly deteriorate. Our comments here are not directed at any one book or any one publisher. The American Chemical Society newspaper, *Chemistry* (Winter 2003), quoted Nobel Laureate John B. Fenn, father of soft ionization mass spectrometry, as observing that "Decent writing is the missing ingredient in too many scientific papers." It is not uncommon for some authors to leave it up to copy editors to clean up their manuscripts. Too frequently copy editors and production editors of scientific books are not given adequate time and incentive by the publishers to produce a stellar book. Hence, someone else must take responsibility. Unfortunately, commas are becoming an increasingly neglected punctuation mark. Ignoring punctuation rules is like ignoring a traffic light as it changes from yellow or green to red. Ignoring the change may save the authors a little time when typing their sentences, but the other drivers (readers) must slow down and compensate. It is not hard to learn simple punctuation rules; many college-level dictionaries have a section on punctuation rules. Awkward English such as "allowing to examine" is better expressed as "allowing the examination of". Again, copy editors cannot always be trusted to clean up such things. Publishers perform a useful service by disseminating writings to a worldwide audience. Publishers can add value to these writings by making sure they are presented according to the highest standards of punctuation and grammar.

At the end of the book, one is left wondering whether bioinformatics will be a wellspring for filling the pipeline of new marketable pharmaceutical products. One recalls that in the 1980s pharmaceutical researchers and investors were excited about computer-aided ligand design and structure-based ligand design. Both approaches proved to be of irreplaceable value but were not panaceas to filling the pipeline. In the 1990s, researchers and investors became excited thinking that combinatorial chemistry and high-throughput screening would be the salvation for finding new drugs. Yet, for all the enthusiasm, the results so far from these expensive, widespread technologies have been modest. Will bioinformatics be a panacea or just one more approach to the extraordinarily difficult task of finding those extremely rare molecules that exhibit all the attributes required for becoming a modern marketable product?

Despite ever larger investments in pharmaceutical discovery and development, the number of new chemical entities coming onto the market has obstinately refused to increase. The number of compounds being screened for biological activity has leaped by two three orders of magnitude over the last 10 years. Yet, who would have predicted in the early 1990s that there would not now be a flood of new chemical entities being launched as pharmaceutical products? Why so few useful candidates are found from current methods deserves reflection. The divergence between rapidly escalating R&D spending and flat R&D output was pointed out in *Modern Drug Discovery*, the American Chemical Society magazine, as far back as 1998. While free enterprise investments and competition have been essential for driving the development of most new therapeutic agents over the past 50 years, R&D expenditures for bioinformatics and other technologies can grow if and only if the pharmaceutical and biotechnology companies have the potential to recoup their investments.

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Free Energy Calculations in Rational Drug Design. Edited by M. Rami Reddy and Mark D. Erion. Kluwer Academic/Plenum Publishers, New York. 2001. xxiii + 384 pp. 17 × 25.5 cm. ISBN 0-306-46667-7. $110.00

This is a very timely volume on a subject of interest to medicinal chemists. This book is important because it contains chapters on the theory and utility of computer simulations in drug design in a single source. The publication consists of an introduction followed by five sections in which 18 chapters are devoted to various aspects of free energy calculations. All of the 38 contributors are recognized as the leaders in this field. One of the contributors is the late Peter Kollman, to whom the volume is dedicated.

The first section deals with theory and includes a chapter on the estimation of ligand binding energies from molecular dynamics and Monto Carlo methods. The second chapter deals with the development of molecular mechanics force field. Both of these chapters are reviews and are recommended for researchers seeking a method for a particular application. The molecular mechanics chapter is particularly recommended to those who would like to know what goes on in the "black box" that gives a low-energy conformation(s).

The second section focuses on molecular properties and consists of three chapters. The first chapter is a discussion of the estimation of solution properties. Here, the thermodynamics for a quantitative description of the free energy of solutes in solution are presented. The discussion begins with the thermodynamic treatment of ideal gases and progresses through a description of solutions. In the end, however, the inexactness of our

understanding of solution phenomena creeps into the discussion with the presentation of some semiempirical treatments. The next two chapters are a bit more practical discussions. The first reviews are summaries of the performances of various force fields and software in the simulation of aqueous solutions of low molecular weight model compounds and amino acids. The latter is a discussion of tautomerism and ionization with a special emphasis on DNA.

The third section consists of two chapters. The subject of the first is computation of free energies of enzyme−inhibitor complexes, and the second describes free energy calculations of ligand−DNA interactions. The fourth section is by far the most extensive in its range of topics. It consists of five chapters that present in detail the results of free energy calculations. The last chapter discusses the mechanism of dihydrofolate reductase and presents the catalytic mechanism at the molecular level. Enzyme inhibition is also discussed.

The fifth section, case studies, could have easily been combined with the former section, but this is no distraction from the volume. The first case study is the design of adenosine monophosphate mimetics. A discussion of Monte Carlo simulations of COX-2, SRC SH2 domain, HIV reverse transcriptase, and thrombin follows, and this is followed by a presentation of a structure-based drug design study of HIV-1 protease inhibitors. Thymidylate synthase inhibitors are discussed, and following this, inhibition of dihydrofolate reductase is revisited.

Free Energy Calculations in Rational Drug Design is an impressive volume, especially considering the editorial effort required to bring it to press. The style and depth of discussion of the topics is not highly rigorous, but this is not a particular fault. The volume will be a good source of material to include in an advanced graduate course on computational chemistry. It should be a good reference for those interested in applications. Its only fault would be the latest work cited is from year 2000. The book should be included in any academic or industrial library. Its cost is easily justified.

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