Development and Use in Drug Design

Pharmacophore Perception

Osman F. Güner

$ 109.95

International University Line, 2000, pp

Hardback ISBN 0-9636817-6-1

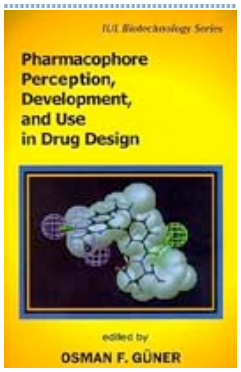
This book is a comprehensive look at pharmacophore history and use in drug design. The term 'pharmacophore' was first used in the early 1900s, and since that time has become the underlying tenet of drug design. In principle, it is a simple idea, but in practice the large number of different methods, as well as the wide variety of problems to which these methodologies are applied, make this a very hard field to get started in — much of the information is not published anywhere, and there is no single complete source that includes information on all the different methods.

That is, until now.

If I had to describe this book in one word, it would be 'comprehensive'. The 27 chapters in this volume describe not only the history of pharmacophore development, but the techniques and methods for developing pharmacophores from either a series of active compounds, or from a known receptor site. Included are quantitative and qualitative analysis methods, those that broke ground in the past, those considered state of the art today, and those recently developed methods that have not yet made it into commercial software.

This book is interesting on many levels. There is the historical perspective that describes how pharmacophores were described in the past, what types of approaches have been tried, and which ones worked best under what circumstances. For those just getting started in the field, this would be excellent preliminary background reading, to be followed by a reading of the chapters that describe the particular applications/methods that will be used.

For those currently applying these methods to real world problems, this book contains a great review of currently available methods, and could be used to learn about unfamiliar pharmacophore mapping methodologies, to perhaps add some of these techniques into their own work. Many seemingly obvious but easily overlooked techniques, such as using protonated groups if appropriate for the pH you are modelling, and how to select a good training set (what size, what molecular characteristics), are explicitly listed.



For those developing new methods and applications, the descriptions of new techniques will prove most interesting. For all working in this field, the predictions of future directions and identification of current problems will prove useful, and hopefully inspirational in their own work. The level of detail given in most chapters is appropriate for those who are going to actually use the methods described. Many details normally omitted from journal articles are included here, such as typical ranges for various parameters, when should a number different from the default be used, for what types of structures and problems does this method work, and just as importantly, for what types of problems is it inappropriate.

The parts I found particularly fascinating were the reasons behind the decisions, and the limits of the various applications. Why was a particular method chosen? Why was a particular default setting used? What ranges of values are appropriate to try? What other ideas were tried, and found lacking? This information is rarely published, but is invaluable to those using the methods, or continuing their development.

Most chapters are written by those who developed or commercialized the methods described. The author list includes most of the major players in the field, with just a few notable exceptions. As is to be expected, some authors are less critical of their own work, but overall the tone is excellent.

In addition to the comprehensive content, other aspects of this volume also add to its value. While the reference lists are not exhaustive, the combination of references and contact information for all chapter authors (including email addresses) provides ample starting points for those wanting more information on any topic. Similarly, the index is useful, but a more comprehensive one would improve the value as a reference volume. Since color is necessary to clearly illustrate the ideas presented, there is an insert of 20 pages of color plates, and one color table inserted elsewhere.

Much of the information in this volume can be directly applied to high throughput screening problems and combinatorial chemistry applications, areas of significant interest currently. These areas generate huge amounts of data, and are driving the need for more robust, more automated analysis methods. This comprehensive book reviewing current state of the art will be a valuable resource for those continuing the work in this area — new students and experienced researchers alike.

The book is divided into 5 major sections, containing a total of 27 chapters. Each chapter begins with an abstract, that summarizes the ideas and methods presented in that chapter, followed by an introductory section, to bring the uninitiated up to speed. Most chapters begin by describing the general strategy and methodology of the technique being discussed, then give explicit details, and finally end with examples of successful applications of the methods they describe. This is exceptionally useful in answering that often asked question "But do these methods really *work*?"

Part I is entitled "The Origins of Pharmacophore Research", and consists of a single chapter. This chapter is a historical overview of the "Evolution of the Pharmacophore Concept in Pharmaceutical Research", from man's earliest beginnings to the present time. This is an excellent orientation for those not familiar with the field, and a history lesson for those who are.

Part II deals with "Analog-Based Pharmacophores". An introductory chapter is included for those unfamilar with the area, followed by detailed chapters describing some of the main techniques in this area, written by the developers of those methods. It includes sections on "Automated Pharmacophore Development Systems", "Predictive Model Development — 3D QSAR" and "Applications in Drug Design". Some of

these approaches are still being actively used and extended, others have fallen out of favor.

The chapters in this section are:

2. Manual Pharmacophore Generation: Visual Pattern Recognition O. F. Güner
3. Pharmacophore Definition Using the Active Analog Approach D. D. Beusen, G. R. Marshall
4. DISCO: What We Did Right and What We Missed Y. C. Martin
5. HipHop: Pharmacophores Based on Multiple Common-Feature Alignments O. A. Clement, A. T. Mehl
6. GASP: Genetic Algorithm Superposition Program G. Jones, P. Willett, R. CGlen
7. Exploring Phamracophores with Chem-X S. J Cato
8. Apex-3D: Activity Prediction Expert System with 3D QSAR E. R. Vorpagel, V. E. Golander
9. Pharmacophore Models and Comparative Molecular Field Analysis (CoMFA) R. D. Clark, J. M. Leonard, A. Strizhev
10. HypoGen: An Automated System for Generating Predictive 3D Pharmacophore Models H. Li, J M. Sutter, R. Hoffman
11. Metric for Analyzing Hit Lists and Pharmacophores O. F. Güner, D. R. Henry
12. Strategies in Database Mining and Pharmacophore Development O. F. Güner, M. Waldman, R. Hoffman, J-H. Kim
13. Pharmacophore Modeling by Automated Methods: Possibilities and Limitations M. Langgård, B. Bjornholm, KGundertofte
14. Database Mining Using Pharmacophore Models to Discover Novel Structural Prototypes JJ Kaminski, D. F. Rane, M. L. Rothofsky
15. Predicting Drug-Drug Interactions in Silico using Pharmacophores: A Paradigm for the Next Millenium S. Ekins, B. J. Ring, G. BRliavi, J. H. Wikel, S. A. Wrighton
16. Feature-Based Pharmacophores: Applications to Some Biological Systems R. Hoffmann, H. Li, T. Langer
17. The Design and Pharmacophore Definition of Retinoid-X-Receptor Specific Ligands S. K White

Part III is entitled "Receptor-Based Pharmacophores". These are more recently developed techniques, which have become possible as computer power and speed has increased. Chapters included are:

18. Receptor-based Pharmacophore Perception and Modeling C. M. Venkatachalam, P. Kirchhoff, M. Waldman
19. Pharmacophore-Based Molecular Docking B. E. Thomas IV, D. Joseph-McCarthy, JCAlvarez
20. The Use of Multiple Excluded Volumes Derived from X-Ray Crystallographic
    Structures in 3D Database Searching and 3D-QSAR M. Gillner, P. Greenidge
21. Docking-Derived Pharmacophores from Models of Receptor-Ligand Complexes R. Griffith, J. B. BRliemner, B. Coban
22. Technique for Developing a Pharmacophore Model That Accommodates Inherent Protein Flexibility: An Application to HIV-I Integrase K M. Masukawa, H. A. Carlson, J. A. McCammon

Part IV deals with "New Algorithms in Pharmacophore Development". These chapters describe new ideas and algorithms, as well as improvements to existing algorithms. The chapters in this section are listed below.

23. Pharmacophores Derived from the 3D Substructure Perception S. Handshuh,J. Gasteiger
24. The Electron-Conformational Method of Identification of Pharmacophore and Anti-Pharmacophore Shielding I. B. Bersuker, S. Bahceci, J. E. Boggs

25. Development and Optimization of Property-Based Pharmacophores A. G. Ozkabak, M. A. Miller, D. R. Henry, O. F. Güner
26. Effect of Variable Weights and Tolerances on Predictive Model Generation JM. Sutter, O. F. Güner, R. Hoffman, M. Waldman

Part V is entitled "The Future of Pharmacophore Research", and consists of a single chapter. This chapter discusses where the field stands now, how far it has come, and where we should go from here. The author makes the point that even thought there are plethora of methods and software packages, the phamacophore problem is far from being solved.

Lisa M. Balbes
28 July 2000