

PHARMACOPHORE PERCEPTION, DEVELOPMENT, AND USE IN DRUG DESIGN

edited by

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Perface:

Perceiving a pharmacophore is the most important first step towards understanding the interaction between a receptor and a ligand. In the early 1900s, Paul Ehrlich offered the first definition for a pharmacophore: "a molecular framework that carries (phoros) the essential features responsible for a drug's (pharmacoon) biological activity" (Ehrlich P: *Dtsch Chem Ges* 1909, 42:17). That definition of a pharmacophore remained unperturbed for over 90 years. The current widely used definition was presented by Peter Gund in 1977: "a set of structural features in a molecule that is recognized at a receptor site and is responsible for that molecule's biological activity" (Gund P: *Prog Mol Subcell Biol* 1977, 5:117-143). This modern definition is remarkably loyal to the earliest definitions.

It is only appropriate, then, that this book starts with the "Evolution of the Pharmacophore Concept in Pharmaceutical Research" in Chapter 1, written by Peter Gund who also developed the first 3D searching software, Molpad, and the first ideas for computational pharmacophores.² It took 15 years for the commercial 3D searching software to become available following its original publication by Gund, Langridge, and Wipke (Gund P, Wipke WT, Langridge R: *Proc Intl Conf on Computers in Chem Res and Educa*, Ljubljana, 1973:5/33). John Van Drie, on the other hand, was involved with the development of two commercial 3D searching software applications: one of the earliest ones, Aladdin, and the latest one, Catalyst®. He has also been active and forward-looking in his work with pharmacophores as, for example, "shrink-wrap pharmacophores," (Van Drie J: *J Chem Inf Comput Sci* 1997, 37:38-42) and in his program Dante (Van Drie J: *J Comput-Aided Mol Des* 1997, 11:39-52). It is only appropriate, then, to end this book with Chapter 27 on the "Future Directions in Pharmacophores Discovery.

The information provided in between these two chapters is pretty much everything you would want to know about pharmacophores, and probably more.

The Part II of the book is dedicated to analog-based pharmacophores. Your editor, Osman Güner, presents an elementary introduction to the concept of pharmacophores in Chapter 2, entitled "Manual Pharmacophore Generation: Visual Pattern Recognition." The analog-based pharmacophore development is then introduced with the description of the Active Analog Approach by Denise Beusen and Garland Marshall in Chapter 3: "Pharmacophore Definition Using the Active Analog Approach."

This information is followed by a detailed description in Chapters 4 through 10 of various pharmacophore development and 3D-QSAR software by the pioneers in this area, their inventors, and current developers. Yvonne Martin describes and critically evaluates one of the earlier pharmacophore development software products, DISCO, in Chapter 4 entitled "DISCO: What We Did Right and What We Missed." Chapter 5 describes a common-feature based alignment software, "HipHop: Pharmacophores Based on Multiple Common-Feature Alignments," written by Omoshile Clement and Adrea Mehl. Gareth Jones, Peter Willett, and Robert Glen describe one of the recent alignment and

pharmacophore software in Chapter 6: “GASP: Genetic Algorithm Superimposition Program.” Stephen Cato then describes how to perceive pharmacophores in Chapter 7 with “Exploring Pharmacophores with Chem-X.” Moving onto the predictive model generation software, Erich Vorpapel and Valery Golander describe the importance of negative activities in Chapter 8 entitled “Apex-3D: Activity Prediction Expert System with 3D-QSAR.” Robert Clark, Joseph Leonard, and Alexander Strizhev emphasize the importance of molecular alignment in Chapter 9: “Pharmacophore Models and Comparative Molecular Field Analysis (CoMFA).” Finally, Hong Li, Jon Sutter, and Rémy Hoffmann bring the description of the methodology under Catalyst/HypoGen in Chapter 10 entitled “HypoGen: An Automated System for Generating 3D Predictive Pharmacophore Models.”

Chapters 11 through 17 involve various applications of analog-based pharmacophores and success stories. Chapter 11 introduces some scoring techniques for pharmacophores and hit lists including “Metric for Analyzing Hit Lists and Pharmacophores,” written by Osman Güner and Douglas Henry. Different database querying strategies are introduced by Osman Güner, Marvin Waldman, Rémy Hoffmann, and Jong-Hoon Kim in Chapter 12 entitled “Strategies in Database Mining and Pharmacophore Development.” Evaluation of automated methods is presented in Chapter 13, “Pharmacophore Modeling by Automated Methods: Possibilities and Limitations,” by Morten Langgård, Berith Bjørnholm, and Klaus Gundertoft. A successful example of the identification of novel structures is provided by James Kaminski, Dinanath Rane, and Marnie Rothofsky in Chapter 14 entitled “Database Mining Using Pharmacophore Models to Discover Novel Structural Prototypes.” Other successes with pharmacophores are described in Chapters 15 through 17 with “Predicting Drug-Drug Interactions in Silico using Pharmacophores: A Paradigm for the Next Millennium” by Sean Ekins, Barbara Ring, Gianpaolo Bravi, James Wikel, and Steven Wrighton. “Feature-Based Pharmacophores: Applications to Some Biological Systems” by Rémy Hoffmann, Hong Li, and Thierry Langer; and “Pharmacophore Definition of Retinoid-X-Receptor Specific Ligands” by Steven K. White.

Part III deals with more recent ideas on receptor-based pharmacophores. It starts with “Receptor-Based Pharmacophore Perception and Modeling” in Chapter 18 by Venkatachalam, Paul Kirchhoff, and Marvin Waldman, followed by Chapter 19 where Bert Thomas IV, Diane Joseph-McCarthy, and Juan Alvarez describe “Pharmacophore-Based Molecular Docking.” Successful applications of receptor-based pharmacophores are presented in the next two Chapters 20 and 21: “Pharmacophores Including Multiple Excluded Volumes Derived from X-Ray Crystallographic Structures of Nuclear Receptors: Their Application in 3D Database Searching and 3D-QSAR” by Mikael Gillner and Paulette Greenidge, and “Docking-Derived Pharmacophores from Models of Receptor-Ligand Complexes” by Renate Griffith, John Bremner, and Burak Coban. The complications arising from the flexibility of the receptor structure is covered by Kevin Masukawa, Heather Carlson, and Andrew McCammon in Chapter 22 entitled “Technique for Developing a Pharmacophore Model That Accommodates Inherent Protein Flexibility: An Application to HIV-1 Integrase.”

Part IV provides new ideas and algorithms in pharmacophore development. It starts with a contribution from Sandra Handschuh and Johann Gasteiger in Chapter 23 entitled “Pharmacophores Derived from the 3D Substructure Perception.” Isaac Bersuker,

Süleyman Bahçeci, and James Boggs present “The Electron-Conformational Method of Identification of Pharmacophore and Anti-Pharmacophore Shielding” a novel perspective towards pharmacophore identification. Ali Özkabak, Mitchell Miller, Douglas Henry, and Osman Güner discuss the concept of pharmacophore optimization in Chapter 25, “Development and Optimization of Property-Based Pharmacophores.” An enhancement to predictive pharmacophore model generation, “Effect of Variable Weights and Tolerances on Predictive Model Generation,” is introduced in Chapter 26 by Jon Sutter, Osman Güner, Rémy Hoffmann, Hong Li, and Marvin Waldman

Finally, Chapter 27 provides a closing with John Van Drie's perception of the future directions in this area.

If you are new to this area, you should start with Chapters 1, 2, 3, and 27 for an introduction; then move on to the desired software discussions, DISCO at 4, HipHop at 5, GASP at 6, Chem-X at 7, Apex-3D at 8, CoMFA at 9, and HypoGen at 10. If you feel you still need to be persuaded that these approaches are effective, you will want to read Chapters 14, 15, 16, and 17 for some real-world success stories.

Seasoned database searchers who want to improve their skills should first understand the limitations outlined in Chapter 26, and then enrich their portfolio of different querying techniques with Chapter 25. Finally, they can learn how to analyze their hit lists by reading Chapter 11.

If the receptor structure is available and you want to use it to improve your pharmacophore models, different techniques in this area are described in Chapters 18 and 19 and successful applications of receptor-based pharmacophores are presented at sections 20 and 21. You should also read chapter 22 to appreciate the conformational flexibility of the receptor structure and its impact on pharmacophore models.

If you are involved in development of software tools in this area, several new ideas and algorithms are detailed in Chapters 23, 24, and 26. If you are interested in automating the pharmacophore optimization process, Chapter 25 provides good ideas and Chapter 11 provides some scoring functions that can be used for this purpose.

To get the full picture of pharmacophores, it is always good to go back and read Chapters 1 and 27 for a historical perspective and future directions.

In closing, consider the history of aviation with the very first flight taking place in the early 1900s and, the moon landing a mere 50 years later. Contrast this to the first use of the term “pharmacophore.” It was first used in early 1900s as Peter Gund explains in Chapter 1; however, the meaning of the definition remained remarkably unperturbed during its close to 90 years of existence. Today, pharmacophores are considered one of the most important types of “information” that can be obtained from receptor-ligand interactions. Yet, quite surprisingly, this book is the first book that has the word “pharmacophore” in its title. We therefore wanted to be very comprehensive in this first volume, covering all aspects of pharmacophore perception, development, and use in drug design. We hope that you will find this book useful to bring your computer-aided drug design endeavor to a higher level.