Molecular Modeling

Basic Principles and Applications

by Hans-Dieter Höltje and Gerd Folkers

in collaboration with Thomas Beier,
Wolfgang Sippl and Didier Rognan

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Preface

The fifth volume of the series "Methods and Principles in Medicinal Chemistry" focuses on molecular modeling. Progress in modern ligand design is intimately coupled with the access to and the continuous refinement of molecular modeling techniques. They allow the computer-aided generation of molecular structures as well as the computation of molecular properties. Predictions of the three-dimensional structures of drug and receptor molecules, visualizations of their molecular surface properties and optimizations of drug–receptor interactions by visual inspection can be realized today.

The present volume offers an introduction to the field of molecular modeling. The book is organized in two parts: the first deals with the modeling of small molecules whereas the second examines biological macromolecules, in particular proteins.

The first part describes in detail the basic know-how necessary for generating 3D coordinates of small molecules, the computational tools for geometry optimization and conformational analysis, the determination of molecular interaction potentials, approaches for the identification of pharmacophores and last but not least the use of databases. The application of this spectrum of methodical approaches is exemplified by a case study dealing with pharmacophore definition in the field of serotonin receptor (5 HT_{2A}) ligands.

The second part gives an introduction to protein modeling. After a description of terminology and the principles governing protein structures, approaches for knowledge-based protein modeling are summarized, followed by chapters on refinement and validation of protein models and on methods for the description of structural properties of proteins. The case study in the second part illustrates the application of experimental procedures to the modeling of protein–ligand complexes (design of non-natural peptides as high-affinity ligands for a MCH I protein).

The editors would like to thank the contributors for their encouragement in compiling this volume. We are sure that scientists entering the fascinating field of computer-aided ligand design will find in this volume the adequate support they need to apply molecular modeling techniques successfully.

April 1996

Düsseldorf — Raimund Mannhold
Ludwigshafen — Hugo Kubinyi
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Methods and Principles in Medicinal Chemistry

Edited by
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Volume 5
Hans-Dieter Höltje, Gerd Folkers
Molecular Modeling

A Personal Foreword

> "A Model must be wrong, in some respects, else it would be the thing itself. The trick is to see where it is right."
>
> *Henry A. Bent*

We humans receive our data through the senses of vision, touch, smell, hearing and taste. Therefore, when we have to understand things that happen on the submicrosopic scale, we have to devise a way of simulating this activity. The most immediate and accessible way to represent the world that is unobservable is to make a model that is on our scale and that uses familiar forms.

Many physical and chemical properties and behaviors of molecules can be predicted and understood only if the molecular and electronic structures of these species are conceived and manipulated in three-dimensional (3D) models. As a natural follow up nowadays the computer is used as a standard tool for generating molecular models in many research areas.

The historical process of developing concepts leading to molecular modeling started with the quantum chemical description of molecules. This approach yields excellent results on the ab initio level. But the size of the molecular systems which can be handled is still rather limited. It is therefore that the introduction of molecular modeling as a routine tool owes its beginning to the development of molecular mechanics some 25 years ago together with the appearance of new technologies in computer graphics.

The goal of this book is to show how theoretical calculations and 3D visualization and manipulation can be used not simply to look at molecules and take pretty pictures of them, but actually to be able to gain new ideas and reliable working hypotheses for molecular interactions such as drug action.

It is our intention to reach this goal by giving examples from our own research fields more than reporting literature's success stories. This is because stepwise procedures avoiding pitfalls and overinterpretation can at best be demonstrated by data from our own laboratory notebooks.

Most of the contents will therefore reflect our own ideas and personal experiences, but nevertheless represent, what we believe to be an independent view of molecular modeling.

We gratefully acknowledge the technical assistance of Matthias Worch, Frank Alber and Oliver Kuonen. Finally we wish to express our sincere gratitude to Heide Westhusen for her excellent secretarial and organizational help.

Spring 1996

Berlin Hans-Dieter Höltje
Zürich Gerd Folkers

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1 Introduction

"Dear Venus that beneath the gliding stars ..." Lukrez (Titus Lucretius Carus, 55 B.C.) starts his most famous poem *De Rerum Natura* with the wish to the Goddess of love to reconcile the wargod Mars, which in this time when the Roman Empire starts to pass over its zenith, ruled the world.

Explanation is the vision of Lukrez. His aim is in odd opposition to his introductory wish to the goddess of love: the liberation of people from his fear of God, from the dark power of unbelievable nature.

The explanation of mechanism from the common is the measure with which Lukrez will take away the fear from the ancient people, the fear of the gods and their priests, the fear of the want of nature and the power of the stars.

Lightning, fire and light, wine and olive oil have been perhaps the simple things of daily experience, which people needed, which people was afraid of, whom has been dear to him:

> "... again, light passes through the horn
> of the lantern's side, while rain is dashed away.
> And why? – unless those bodies of light should be
> finer than those of water's genial showers.
> We see how quickly through a colander
> the wines will flow; how, on the other hand
> the sluggish olive oil delays: no doubt
> because 'tis wrought of elements more large,
> or else more crook'd and intertangled ..."

The atom theory of Demokrit leads Lukrez to the description of the quality of light, water and wine. For this derivation of structure–quality relationships he uses models. The fundamental building stones of Lukretian models look a little like our atoms, called *primodials* by Lukrez, elementary individuals, which were not cleavable anymore. Those elementary building stones could associate. Lukrez even presupposes recognition and interaction. He provides his building stones with mechanic tools that guarantee recognition and interaction. The most important of these conceptual tools are the complementary structure (sic!) and the barked hook. With these primordials Lukrez built his world.

How well the modeling fits is shown in his explanation of the fluidity of wine and oil. A comparison of the space-filling models of the fatty acid and water molecules amazes, because of its similarity with the 2000-years old image of Lukrez.

1.1 Modern History of Molecular Modeling

The roots from which the methods of modern molecular modeling have developed, lie at the beginning of our century, the first successful representations of molecular structures being closely linked to the rapid developments in nuclear physics.

Crystallography was the decisive line of development of molecular modeling. Knowledge of the complexity of crystal structures increased very rapidly but their solution still required huge arithmetic expense to produce only an inadequate two-dimensional (2D) paper representation. The use of molecular kits was the only possible way of obtaining a 3D impression of crystal structure.

The Dreiding Models became famous because they contained all the knowledge of structure chemistry at the time. Prefabricated modular elements, for example different nitrogen atoms with the correct number of bonds and angles corresponding to their hybridization state, or aromatic moieties, made it possible to build up very exact 3D models of the crystal structures, thus allowing molecular modeling. Dimensions were translated linearly from the Ångstrom area. Steric hindrances of substituents, hydrogen bond interactions, etc. were quite well represented by the models. A similar quality of modeling, albeit less accurate—but space filling—was provided by Stuart–Briegleb or CPK models. Watson and Crick described their fumbling with such molecular kits and self-constructed building parts, first to model base pairing and eventually, to outline the DNA helix.

Molecular modeling is not a computer science a priori, but does the computer provide an additional dimension in molecular modeling/molecular design? Indeed, development of the computer occured synergetically, as faster and faster processors repeated the necessary computational steps in shorter and shorter times so that proteins containing thousands of atoms can easily be handled today. However, the molecular graphics technology looked for a further quantum leap bound to the same fast processors. For the first time, in the 1970s the pseudo 3D description of a molecule, color-coded and rotatable, was possible on the computer screen. "Virtual Dreiding models" had been created. Without computer technology the flood of data emerging from a complex structure such as a protein would have exceeded the saturation limits of human efficiency. Proteins would not have been measurable with methods such as X-ray structure analysis and nuclear magnetic resonance without the corresponding computer technology. Indeed, it is computer technology that has made these methods what they are today.

There is however a second factor, without which today's computer-assisted molecular design would be unthinkable. Since the 1930s, nuclear physics has required not only analytical but also systematic thought, a component that was vital in construction of the atomic bomb. Consequently, mathematical modeling techniques were employed for the computation of physical states, and even their prediction.

In the 1940s the computers in Los Alamos were, in the true sense of the word, made of soldiers. Gathered in large groups, everyone had to solve a certain calculation step, but always the same step for the same man. It was here that computer development sought a revolution. The Monte Carlo Simulation, which originated at that time, was applied to the prediction of physical states of gas particles. From that time also the first applications of mechanical analogies on molecular systems were developed. The force fields were born and optimized and, in the course of time have achieved the unbelievable efficiency of modern times.

Mathematical approximation techniques have now made possible the quantum chemical calculation of systems even larger than the hydrogen atom, permitting "quantum dynamic" simulations of ligand binding at the active site of enzymes.

1.2 Do Today's Molecular Modeling Methods Illustrate only the Lukretian World?

This is in fact a question of quality of use. The methods could be used naively or intelligently, though the results are clearly distinguishable. However, naive uses should not be condemned, as it is vital for the quality of the use that a sufficiently critical position is taken when examining the results. In other words, the user realizes his or her naive use of the methods. Now, the researcher is conscious of the restrictions of the method and knows how to judge the results. Here, even with a very simple approach, this critical position results in further knowledge of the correlation between structure and properties.

Often however, such a critical attitude is not present—perhaps the result of modern commercial modeling systems. Those programs always provide a result, the evaluation of which is at liberty of the user. The programs tend stubbornly to calculate every absurd application and present a result—not only a number, but also a graph—and represent a further instrument of seduction for the uncritical use of algorithms. In contrast, the merits of molecular graphics is undisputed because of their essential contribution to the development of other analytical methods such as nuclear magnetic resonance spectroscopy and the X-ray analysis of proteins.

The tendency to perfect data presentation is the reverse situation. For example, visualization of isoelectrical potentials is one of the most valuable means of comparing molecular attributes. Very often a positive and a negative potential of a certain energy is used to describe structures. The presentation of potentials is based upon a charge calculation and may be used to find a suitable alignment of a training set of biologically active molecules. The latter can be realized on quite different quality levels. There are, for example, algorithms that perform well in calculations for simple carbohydrates, but are incapable of handling aromatic structures. Unfortunately these algorithms do not always signal their incapability if an aromatic system is to be calculated. A result is obtained, an isopotential surface is calculated, and a graph created. With that, an attempt is made to derive structure–activity relationships—the second trap comes next.

The training set that is selected, represents of course a drastic reduction of the parameter space. You may hope to receive a most possible representative distribution of the attributes by careful selection, but you are never sure. Thus, the correlations originate from the coincidential reciprocal completion of two errors, which relate back to the uncritical selection of methods and data sets.

1.3 What are Models Used for?

Models in science have different natures. They serve first of all to *simplify*; that means limiting of analysis to the phenomena that are believed to be the most important. Secondly, models serve as *didactical illustration* of very complicated circumstances, which are not easily accessible. Here, it must be taken into account in any explanation that the model does not show complete reality. A third model is that of *mechanical analogies*. These benefit from the fact that the laws of classical mechanics are completely defined, for example Hooke's law.

Model building of this kind plays a decisive role in the development of uniform theories. It is their special feature that it is not presupposed that the models reflect reality, but that first of all a structural similarity of two different fields is supposed. This is, for example, the presumption that the behavior of bonds in a molecule corresponds partly to springs, as described by Hooke's law. These mechanical analogy models have very successfully expanded theories, because the validity of a theory can in many cases be scrutinized experimentally, but the most important point is that predictions of new phenomena can be made.

These models are also often called *empirical.* Force fields belong to this class. The benefit of empiric models is that their parameters are optimized on reality. The "mechanization" does not provide explicit information from the non-mechanical contributions, but by empirical correction the non-mechanical contributions are convoluted in some way. That is why empirical models often are very close to reality.

Finally, the fourth type of model is *mathematical modeling.* These models serve for the simulation of processes, as for instance the kinetic simulation of a chemical reaction step in an enzyme. By suitable choice of parameters, kinetic simulations of real processes can be performed.

1.4 Molecular Modeling Uses All Four Types for Model Building

Didactical models are used for the combined representation of structure and molecular properties. In the case of *small molecules* the graphical representation of results from quantum chemical calculations or from the representation of the mobility of flexible ligands such as peptides. In the case of *proteins,* the structure itself is already a complex problem. Interactions of ligand and protein can also be studied with didactical models. It is already clear, that the different types of models are overlapping. Mechanical analogies, as well as reductions, aim at simplifying essential parts of the objects under study and are typical applications of molecular modeling.

1.5 The Final Step is *Design*

Design is perhaps the most essential element of all. Molecular modeling creates its own world, which is connected with reality by one of the four model types. Within this world—which exists in the computer—extrapolations can be made because, in contrast to the "real" world, a completely deterministical universe is created. Based on the analytical description of the system, the possibility is available to design inhibitors in advance of the synthesis and for them to be tested in a virtual computer experiment.

With that final design step, the circular course of a scientific study is completed. The study does not simply remain an analytical description of a system, which has been devised in "clockwork" fashion, but goes further by reassembling the system's parts. Molecular design creates a realization for our understanding—that a system could be more than simply the sum of its parts. This is especially effective for biological systems within which drug design is confronted by preference.

The design step itself actually is not as straightforward, even in the virtual world, as would be desirable. As *Gulliver* learns on his visit to the academy of Lagado, there is a machine, which at some time will have written every important scientific book of the world by a systematic combination of letters and words. *Jonathan Swift's* wonderful science fiction of the 18th century gives us at once the main problem: the time span of human beings is not large enough to test all possibilities. There has to be an intelligent algorithm to obtain the correct solutions. In the case of *Gullivers Travels,* Swift is somebody who introduces an additional criterion of quality. This is based on knowledge, experience, and is able to reject combinations of words and sentences: the human–machine network. Actually, Swift introduces such a criterion in the person of the professor who gives orders to his students, who serve the machines and decides after every experiment upon the result, e.g. lets the combination of words enter the book. Unfortunately, the experimenter himself is not defined qualitatively in Swift's novel; that is Swift's irony in *Gullivers Travels*. Hence, the result depends not only on an error-free function of the machine, but on the quality of its user! (Fig. 1)

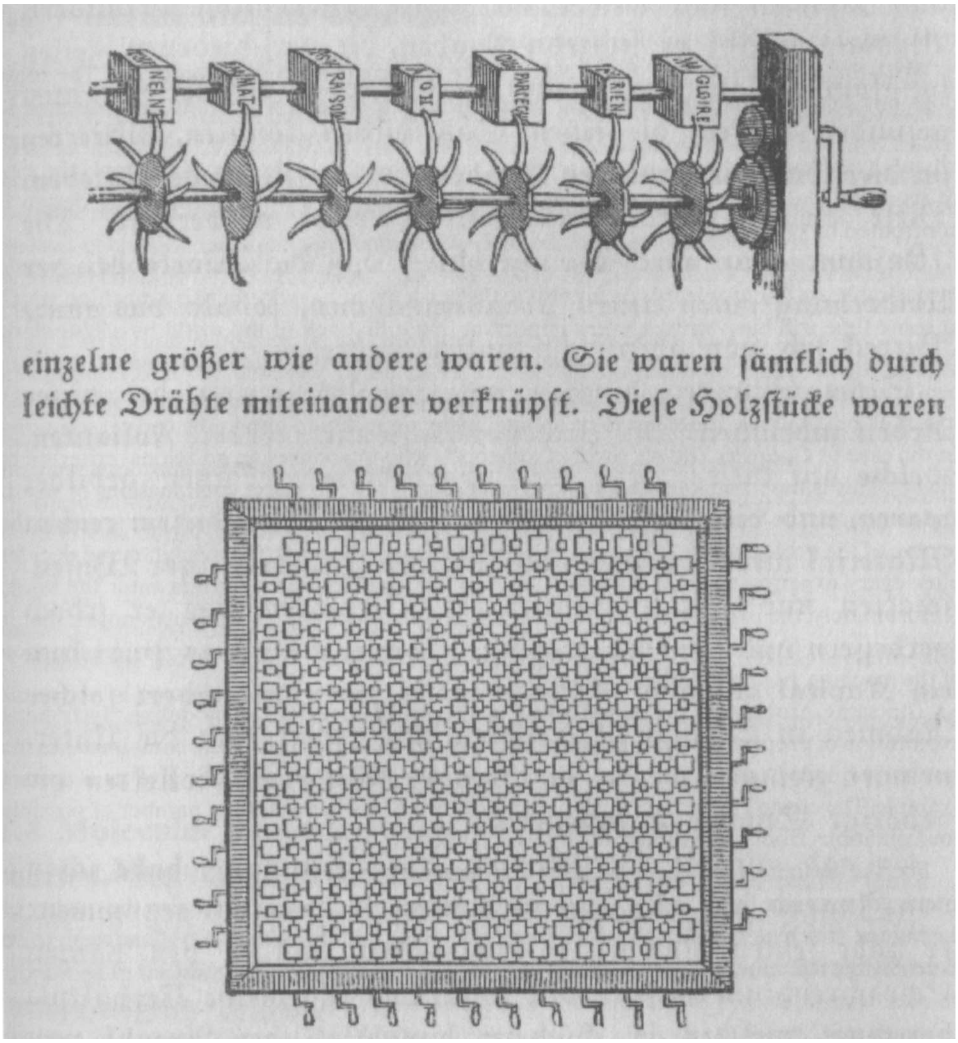
The same problem is presented to us in the artificial world of modeling. Systematic exploration of properties is only possible for small numbers. Because of the combinatorics the system "explodes" after only a few steps. Flexibility studies on peptides give us a correct example. The change from four torsion angles to five or six increases the number of possible conformations from some thousands to several billions.

For the design of a ligand the situation becomes more complex. It demands a most intelligent restraint by suitable experiments, intuition or knowledge. Here also the quality of the human–machine network plays a decisive role. Fully automatic design systems seem to be like a Swift prediction machine in Gulliver's visit to the academy of Lagoda.

1.6 The Scope of the Book

The scope of this book is to provide support for the beginner. The recognition of principal concepts and their limitations is important to us—more important even than a complete presentation of all available algorithms, programs and data banks. As with all areas associated with computer techniques the technical development in this area has been more than exponential. Almost every day, new algorithms are offered on the network, suitable for comparison of protein sequences or for searching of new data banks, etc. The user has no other possibility to judge their quality than to use the programs and to explore their limitations.

He or she must know, therefore, that energy-minimizing in vacuo does not make sense in any case for the analysis of the interaction geometry of a ligand. He or she also has to know



einzelne größer wie andere waren. Sie waren ſämtlich durch leichte Drähte miteinander verknüpft. Dieſe Holzſtücke waren

Figure 1. J. J. Grandville's imaginary concept of the "book-writing machine" in Gulliver's visit to Lagoda.

that a protein can not be simply folded up from a linear polypeptide chain. It must be realized that there is alternative or multiple binding mode: inhibitors binding to an enzyme show alternative binding geometries in the active site, even within a set of analogs. Very small changes in the molecular structure could provoke another orientation of the ligand in the active site. It is not necessarily true that a structure-orientated superposition would be better than an intuitive one or even one, which is oriented by steric or electrostatic surface properties.