Three-Dimensional Molecular Modeling and Drug Design

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Summary. A discussion of drug-receptor theory is used to show that the three-dimensional structure, or shape, of molecules is important for biological activity. The computer-assisted molecular modeling system at Merck is described, and it is shown that this system is useful for generating and storing molecular structures, determining preferred conformation, comparing molecular shapes, and computing molecular properties. Applications of the system to the study of anti-inflammatory drugs, somatostatin-like compounds, and dihydrofolate reductase inhibitors are summarized.

Until this century, drugs were "discovered" by testing extracts of natural substances for useful properties. Drug "development" properly began with Paul Ehrlich, who in 1910 developed Salvarsan as a treatment for syphilis by starting from a compound originally synthesized as a dyestuff (*1*, *2*). Since that time, the paradigm of drug development has consisted of the empirical testing of large numbers of substances for a desirable biological activity in model systems, followed by systematic chemical modification of the lead compound to optimize its properties. In the last few decades this "Edisonian" approach has become not only more expensive, but also less successful in yielding new medicinal agents (*3*)—perhaps because of increasing emphasis on finding safe (nontoxic) drugs or because there are fewer left to discover. Thus the goal of "designing" a drug to interact with a targeted enzyme or receptor has become increasingly attractive (*4*).

Such so-called rational drug design depends on an old principle, enunciated among others by Ehrlich (*2*), that a drug "fits" its biological receptor much as a key fits a lock. This concept is the basis for modern drug-receptor theory (*5*)—which in the past has been more useful in rationalizing the activity of known drugs than in designing new drugs, because of the lack of knowledge of drug-receptor interactions at the molecular level. For the purpose of this article we define a drug as any compound, natural or synthetic, which elicits a biological action.

We discuss herein some of the difficulties in using drug-receptor theory for new drug design, and describe some techniques for surmounting these difficulties. We also discuss a computer system that makes some of these techniques accessible to the practicing medicinal chemist and give some examples of applications of the system for drug design.

Implications of Drug-Receptor Theory

In its most general form, drug-receptor theory states that a drug exerts its biological action as a consequence of binding or otherwise interacting with a specific biological receptor, such as a membrane-bound protein, an enzyme, or DNA. A classic example of visualization of a drug receptor is the detailed molecular model for binding to the DNA double helix of the antibiotic actinomycin D, derived by Sobell and Jain (*6*) from the crystallographic study of model systems. Another molecular model for binding was derived from the crystal structure of bacterial dihydrofolate reductase enzyme bound to an inhibitor, the antibacterial drug methotrexate (*7*). Both of these receptor models suggest ways in which the drugs might be modified in order to increase activity or selectivity.

Usually, however, the drug-receptor structure is not known in detail; indeed it may not be possible to isolate the receptor. In these instances the well-known technique of receptor mapping may be applicable, where the three-dimensional receptor shape (topography) is taken as complementary to that of drugs that fit the receptor (*8*). In terms of Ehrlich's lock-and-key analogy, we may infer the shape of the lock by examining the shapes of the keys which fit the lock.

A problem with the complementarity approach is that it is difficult to determine the shape of drugs. Molecules are submicroscopically small and may not be observed directly; even the ultimate method of determining molecular structure, x-ray crystallography, is an indirect technique in which a model is constructed and altered to match as closely as possible the observed x-ray diffraction pattern. Fortunately, it is often possible to infer drug structure by a combination of spectroscopic and theoretical techniques and by analogy with other structures. On the basis of terminology used by Ehrlich (*2*), the geometric arrangement (topography) of key functionality, which governs a drug's interaction with its receptor, may be termed a three-dimensional pharmacophoric pattern (*8*–*10*).

Another problem is that many drug molecules are flexible and their shape may vary under different conditions. For example, the shape (conformation) of a molecule in the vapor phase may differ from its shapes in the crystal phase, in solution, and when bound to a biological receptor. In this sense of conformational permutations of a drug, a better analogy for the receptor might be a combination lock. One approach to solving this problem is to find conformationally constrained analogs of the drug which retain biological activity. Theoretical conformational analysis can also be useful in reducing the number of conformations that must be considered (*11*).

Steric fit is not the only effect governing drug-receptor interaction; most drugs possess partial or full electrostatic charges that match complementary charges on the receptor. (Compare a key with hidden magnets that engages a magnetized tumbler when inserted in the lock.) Recently, the technique of electrostatic contour mapping has been developed for visualizing the electrostatic potential field around a drug molecule (*12*). As the drug approaches the receptor, electrostatic fields are perturbed and the reactivity of the drug becomes im-

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portant. Theoretically derived reactivity indices may provide insights into this process (*13*).

Other problems abound: the keys must be transported to the lock by various mechanisms before they are inserted in the wrong lock (nonspecific binding), altered (metabolism), or lost (excretion); some locks require more than one key (cofactors); and other locks may change shape to fit the key (induced fit). In some cases dynamic reshaping of both lock and key may be required for effecting the biological activity (*14*). Thus, while a key normally opens a lock or does not (binary response), different drugs may cause a variety of responses when binding to a receptor.

A receptor model is nevertheless a useful starting point for designing new drugs, and the more detailed a model of the receptor is available, the more useful this approach can be. Computer-assisted molecular modeling can help scientists understand the complex three-dimensional relationships between drugs and real or hypothetical receptors.

Molecular modeling graphics systems originated with Project MAC at Massachusetts Institute of Technology in 1965 (*15*), and developed independently at a number of universities and institutes; a 1974 review listed 19 such systems (*16*), and many more have been developed since then. Several are becoming commerically available. Table 1 lists some current modeling systems and their major uses. We have implemented a molecular modeling system, described below, which appears to be unusual in the degree to which it has become accepted as a research tool by the Merck chemists.

The Merck Molecular Modeling System

The development of a computer-based molecular modeling system at Merck was stimulated by a theoretical study (*17*) of the geometries and reactivities of penicillins and cephalosporins that provided insight into the antibacterial properties of these antibiotics. A prototype system, developed at minimal cost in order to demonstrate the feasibility of the system, consisted of a Tektronix storage tube display connected to our IBM 370/155 computer under time-shared option (TSO) by telephone line (communicating at 30 characters per second). After 2 years the prototype system (Mermod), which had been expanded to run on three terminals in two different laboratories (*18*), was upgraded to the current Merck molecular modeling system (MMMS). With four more powerful DEC GT42 and GT43 display terminals, the system is in use at Merck research laboratories in Rahway, New Jersey, in West Point, Pennsylvania, and in Montreal, Canada (Merck Frosst Labs). The terminals are connected by fourfold faster telephone lines to an upgraded central computer (IBM 370/168). The MMMS was used in 1979 for an average of 2 hours per working day by 35 different scientists (out of 60 checked out on the system). The same terminals are used to run computer-assisted synthetic analyses (*19*).

Some of the uses to which the MMMS has been put are shown in Table 2; this list by no means exhausts the applications of MMMS, which has been successfully used to design novel drug candidates. Before describing the system, we wish to illustrate the utility of MMMS for drug design by considering some of these applications in more detail.

Prostaglandin cyclooxygenase active site. By starting from the crystal structure of indomethacin (*20*) (**1** in Fig. 1) and performing conformational calculations on this compound and its α-methyl derivative, it was possible to suggest a conformation for this and other arylacetic acids when they bound to a hypothetical anti-inflammatory receptor (*21*). Since prostaglandin synthesis is inhibited by nonsteroidal anti-inflammatory drugs,

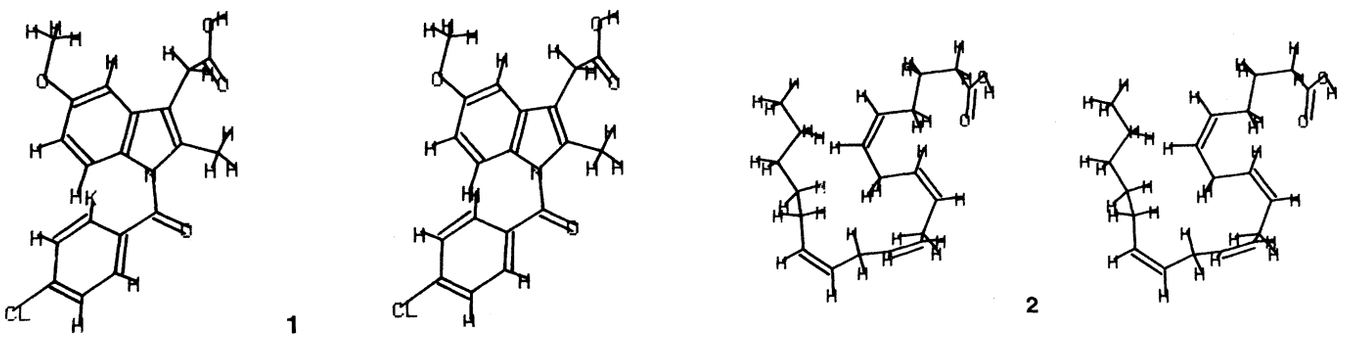


Fig. 1. Stereoscopic views of indomethacin (**1**) and arachidonic acid (**2**) in conformations that could fit the same receptor site on prostaglandin cyclooxygenase (*21*). A stereoscopic viewer is helpful for seeing the structures three dimensionally. Alternatively, try holding an index card vertically between the matching images and staring at them until they "fuse." Crossing your eyes to fuse the images gives the molecular enantiomer (mirror image). [From Gund and Shen (*21*), courtesy of American Chemical Society]

Table 1. Some current molecular modeling systems for drug design.

System and source	Typical function	Reference
Chemical Information System: National Institutes of Health/Environmental Protection Agency	Small molecule crystal structure search and display; network access; conformational analysis (Camseq)	(*34, 35, 45*)
Crystnet: Brookhaven Laboratories	Network access to protein data base; large molecule display; drug-enzyme "docking" studies	(*62*)
Prophet: National Institutes of Health/Bolt Beranek and Newman	Pharmacologists' notebook; drug design; conformational analysis; molecule superposition; network access	(*52*)
MMS-X: Washington University, St. Louis, Missouri	Conformational analysis; drug design; receptor mapping; protein crystal structure fitting	(*63*)
Moloch-2: Searle Co., Chicago, Illinois	Drug design; conformational analysis; small molecule display	(*64*)
Tribble: Du Pont, Wilmington, Delaware	Drug design; small molecule theoretical studies	(*65*)
Moly: Rohm & Haas, Philadelphia, Pennsylvania	Drug design; small molecule conformational analysis, display and superposition	(*53*)

we considered the possibility that the prostaglandin precursor, arachidonic acid (**2**), could fit the same receptor site. Since a conservative estimate placed the number of possible conformations of **2** above 10 million (*21*), no attempt was made to calculate the energetically preferred conformation. Rather, a Corey-Pauling-Koltun (CPK) model of **2** was manipulated in an attempt to find a conformation that would fit the same receptor as **1**, while being consistent with the known stereospecificity of the transformation of **2** into the cyclic endoperoxide prostaglandin G_2 (PGG_2). Such a conformation was found (**2** in Fig. 1), and led to a model of the prostaglandin cyclooxygenase active site shown in Fig. 2. This model provides a mechanism for the stereospecific conversion of arachidonic acid to PGG_2, and is consistent with the structure-activity relationships (SAR's) of fatty acid substrates of the enzyme; it accommodates **1** and other arylacetic acid inhibitors, and is consistent with their SAR's; and it is consistent with biochemical information about the enzyme (*21*). Clearly this model could serve as a template for the design of novel anti-inflammatory drugs. A different template, based on a model of the peroxy radical intermediate, was said to have been successfully employed for the design and synthesis of potent new anti-inflammatory compounds (*22*).

Somatostatin analogs. Although MMMS was designed for studying the structure of small molecules, it is possible—although tedious—to use the system for modeling larger molecules such as polypeptides. Somatostatin, which is a very large and flexible polypeptide hormone containing 14 amino acid residues, inhibits the release of glucagon, insulin, and growth hormone, and inhibits gastric secretion. Various clinical applications of somatostatin or its analogs have been proposed (*23*). Again, no attempt was made to calculate the energies of the large number of possible conformations; Momany *et al.* (*24*) have published the results of such calculations on 10^6 randomly chosen somatostatin conformations.

An analog synthesis program made it possible to narrow the conformational possibilities through selective conformational constraint (*25*). Ultimately a bridged analog (**3** in Fig. 3) was prepared that had only four of the original 14 amino acid residues, yet had three times the insulin secretion inhibiting activity but only 1/20th of the gastric secretion inhibition (greater biological selectivity). It also exhibited increased duration of action, decreased metabolic degradation, and some activity when given orally (*26, 27*). Detailed nuclear magnetic resonance analysis of **3** and other rigid analogs led to a proposed bioactive conformation (*26, 28*), and classical mechanical calculations on part of the backbone led to a refined proposed bioactive conformation for **3** as shown (Fig. 3).

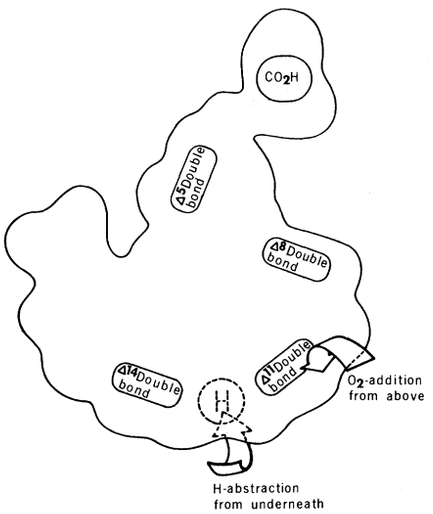
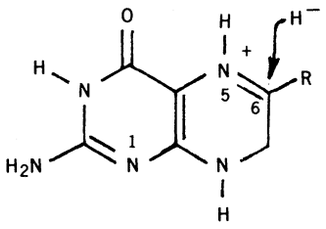


Fig. 2. A model for the fatty acid binding site of prostaglandin cyclooxygenase. [From Gund and Shen (*21*), courtesy of the American Chemical Society]

Dihydrofolate reductase inhibitors. Complete neglect of differential overlap (CNDO/2) orbital molecular calculated protonation energies suggested that dihydrofolic acid (**4**) is preferentially protonated at N-5 rather than at N-1 (*29*), and this was confirmed by a spectroscopic study (*30*). Furthermore, the lowest unoccupied molecular orbital of **4** has a very large amplitude at C-6 (coefficient, 0.71), so that N-5 protonation may activate the molecule to hydridelike reduction at that position (*29*). Although a calorimetric study indicates that dihydrofolate is not protonated before binding to the enzyme (*31*), it must undergo N-5 protonation during reduction.



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Recently, the crystal structure of methotrexate bound to *Escherichia coli* dihydrofolate reductase (DHFR) has become available (*7*), as well as the structure of methotrexate and cofactor (reduced nicotinamide adenine dinucleotide phosphate) bound to DHFR from *Lactobacillus casei* (*32*). These crystal structures have been entered into the MMMS; they lead to a detailed model for the mechanism of reduction of the dihydrofolic acid natural substrate, and they have suggested useful approaches for developing stronger DHFR inhibitors.

MMMS Features

The MMMS has thus proved useful in understanding mechanisms of drug action and in designing new and improved drugs. As summarized in Fig. 4, the system may be divided into four functional categories. Various input programs create a standard molecular structure representation, which may be stored on the computer; the resulting structure may be subjected to geometry refinement, to structure display and comparison, and to the calculation of various structural properties.

Structure representation. The MMMS

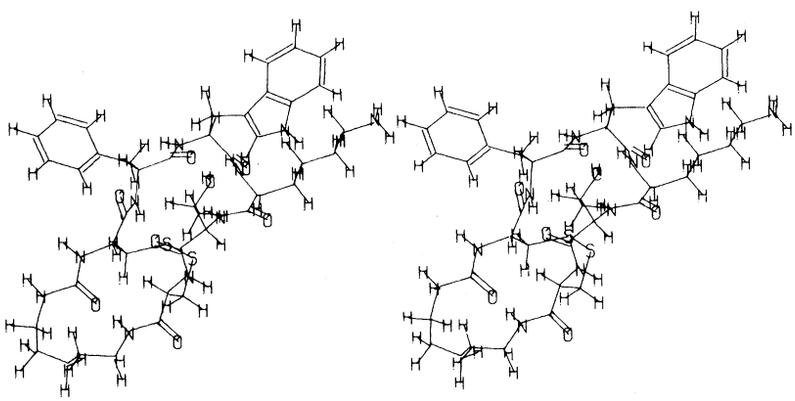

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Fig. 3. Stereoscopic view of a bicyclic analog of somatostatin possessing enhanced selective biological activity (*26, 27*). [From Veber (*26*), courtesy of Pierce Chemical Co.]

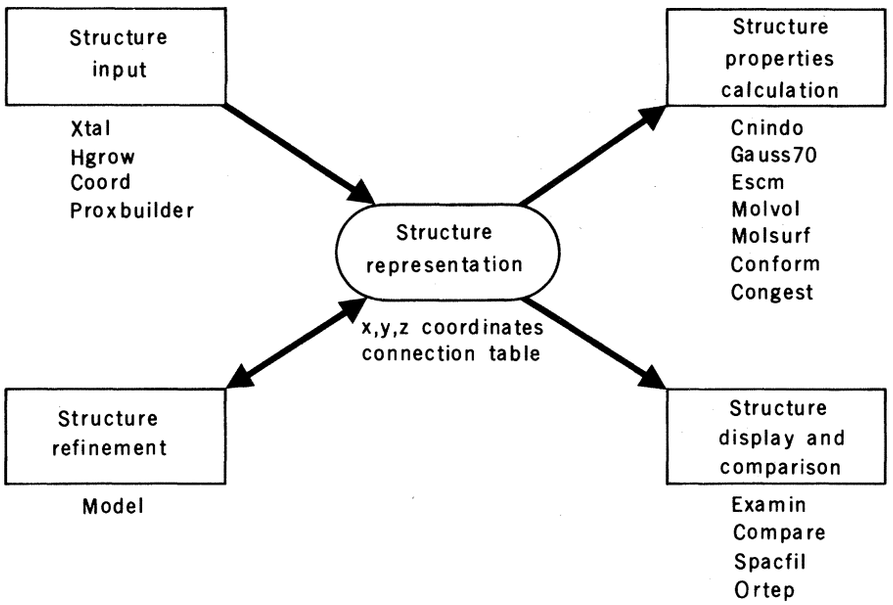

Fig. 4. Functional organization of the MMMS.

standard molecule format contains a title, atomic coordinate positions in angstroms, atomic number and charge code, a list of bonded pairs of atoms, and bond types. All other structural information is generated from the above data as needed. Molecules are typically represented as valence structures with localized multiple bonds, since this aids in locating unfilled valences for placing hydrogens (program Hgrow). Procedures are being developed for collecting modeled structures in a common file for general use.

Molecule input. One of the most difficult problems is obtaining a satisfactory geometry for a molecule of interest. Over 24,000 crystal structures of molecules are available from the Cambridge Crystallographic Data File (*33*) available through the NIH-EPA Chemical Information System (*34*); other interesting crystal structures are routinely determined at Merck. When a crystal structure is available, program Xtal is used to convert fractional cell coordinates to molecular Cartesian coordinates, and to locate bonded atoms. Wilson and Huffman (*35*) recently reviewed uses of published crystal structures for modeling various organic chemical phenomena.

Usually a crystal structure is not available for a hypothesized new drug. For this normal case, program Coord is used to generate a structure in the form of "internal coordinates" (bond lengths, bond angles, and dihedral angles). These are obtained from suitable fragments of available crystal structures or from standard lists (*36*). Coord allows one to determine interatomic distances and angles in a created structure, to view the structure stereoscopically, and to change internal coordinates as necessary to improve the structure. The internal coordinates may be saved and later input to Coord for generating a series of conformational isomers of a molecule, or, by adding or deleting atoms or bonds, for creating a series of related structures. This procedure has been used for building structures as large as somatostatin.

A convenient method of generating three-dimensional structures, originally developed at Princeton University (*37*), involves sketching a two-dimensional structural diagram on the terminal screen by means of a light pen, and using a rough strain energy minimization procedure to create a stereochemically correct model. A version of the SECS (*19*) model builder (*38*), which we call Proxbuilder, is under development.

Structure refinement. For many drug molecules that are sterically strained or that contain one or more rings, a structure built from standard fragments is inaccurate. For such structures one can generate a strain-minimized geometry by giving the Model command. This initiates a program (*18*) which enumerates the various classical mechanical interactions present in the molecule, looks up parameters for these interactions in a computer file, calculates approximate parameters if none are available, and produces a data file suitable for use by Boyd's Molbld2 molecular mechanics energy minimization program (*39*).

The other major method for determining preferred conformation is by "rigid rotation" about various bonds. We have in the past frequently generated a series of conformers, and subjected each to CNDO/2 quantum mechanical calculation (*40*). An experimental program, Conform, now allows the automatic searching of conformational space for any two specified rotatable bonds, with calculation of an empirical strain energy. For small model molecules, conformational studies by molecular orbital calculations at the ab initio level (*41*) are now also possible.

We advocate the application of both classical and quantum mechanical methods to the same conformational problem where appropriate. Thus "rigid rotation" determined minima may be subjected to further strain minimization with full geometry relaxation (Model), and "Model'ed" structures are subjected to CNDO/2, INDO, or ab initio energy calculations. According to the Born-Oppenheimer approximation, the total wave function of a molecule may be separated into electronic, vibrational, and rotational parts. On the basis of this approximation, the forcefield or "molecular mechanics" approach represents an inductive method for finding a common analytical representation of the motion of atomic nuclei in a field of fast-moving electrons (*42*). The quantum mechanical approach, while also based on the Born-Oppenheimer approximation, is a deductive method for describing the average arrangement of electrons about a constellation of fixed nuclei according to the Schrodinger equation. (Note that the lower level, semiempirical quantum calculations contain empirical parameters and therefore are also inductive methods.) The molecular mechanics and quantum mechanical approaches thus present two different, complementary models of physical reality; and where the two methods agree, as they often do, there is increased confidence that the results are meaningful.

Molecule display and comparison. Although humans are quite accomplished in recognizing patterns in two dimensions, their ability to recognize three-dimensional relationships is usually not well developed. Consequently, the greatest use of MMMS has been simply for studying three-dimensional molecular structure. Several representations are available to aid the chemist in this perception. For example, the Examin program gives a stick figure stereoscopic representation, such as illustrated in Figs. 1 and 3 (which were photographed from the terminal screen), in any orientation desired. A ball-and-stick view may be plotted via the familiar Ortep program (*43*), and a space-filling representation is created by Spacfil (*44*). A homemade viewer may be used for looking at stereo

images on the display screen; alternatively, one may take a Polaroid photograph of the screen and view the resulting reduced stereo image with a stereoscopic viewer.

As the molecules get larger in size, stereoscopic presentation of the structure becomes increasingly less satisfactory. Some other modeling systems can display consecutive rotated two-dimensional images so quickly that the molecule appears to rotate in real time; the resulting illusion of three dimensionality is called "dynamic stereo" (*45*). The MMMS does not now support this technique because of hardware and software limitations.

Other techniques that we use for viewing molecules three dimensionally include converting Polaroid photographs of the display to red-green stereoscopic slides that are viewed through red-green 3-D glasses; and displaying consecutive rotated views of a molecule and photographing each view as one frame of a motion picture which, when projected, gives the dynamic stereo illusion. Printing such a movie film holographically (*44*, *46*) gives an integral hologram (*47*) of the molecule. Such a hologram was made of a modeled structure of cefoxitin (*48*), a new antibiotic of the cephamycin family (*49*), and animation was added to illustrate the hypothesis that the molecule's 7-methoxy group confers stability against β-lactamase by interfering with approach of the enzyme to the 4-membered ring (*50*).

Medicinal chemists often need to compare different structures possessing similar biological activities, in order to detect non-obvious similarities. Space-filling (CPK) and even stick (Dreiding) models are difficult or impossible to overlay in a way which illustrates their similarities,

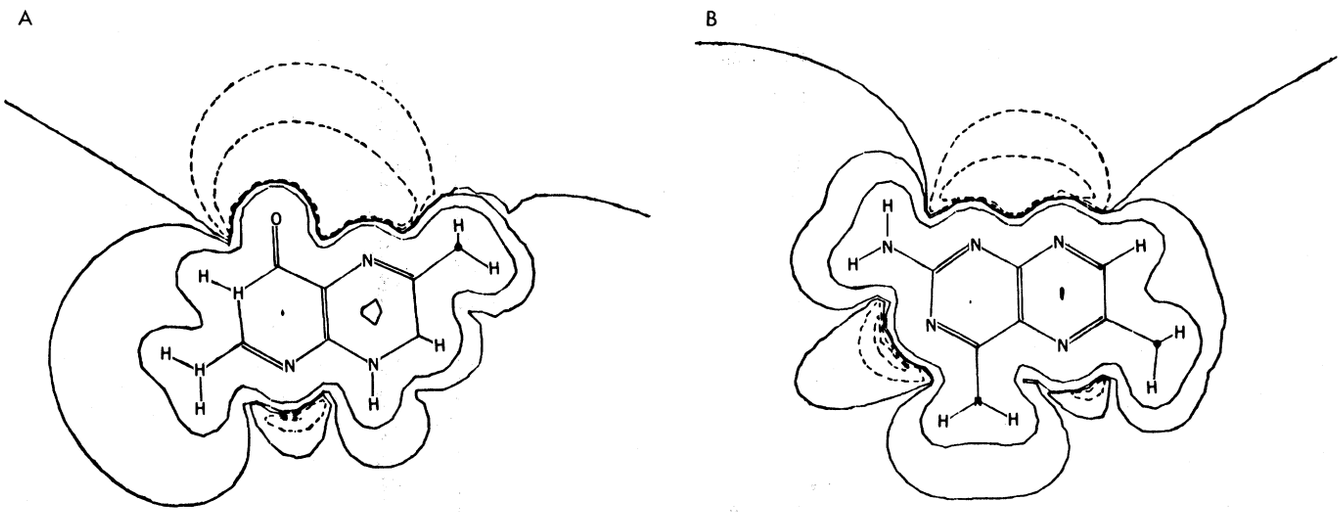

Fig. 5. Electrostatic contour maps for the heterocyclic portions of dihydrofolic acid (A) and methotrexate (B). The electronegative in-plane regions (dashed contours) align best by flipping one pteridine ring with respect to the other, as shown. (The dot represents the point of attachment of the *p*-aminobenzoylglutamate side chain.) There is evidence that methotrexate does indeed bind to DHFR with its pteridine ring "flipped" compared to dihydrofolic acid (*71*).

Table 2. Some recent molecular modeling studies.

Molecular system	Technique	Conclusion	Reference
Anticoccidial 4(1H)-pyridinone hydrazones	Conformation generation; molecule superposition; preferred geometry calculation	Rationalized cross-resistance of this class of anticoccidial compounds with Robenidine	(*66*)
Anti-inflammatory arylacetic acids	Conformation generation; preferred geometry calculation	Model of prostaglandin cyclooxygenase active site	(*21*)
Dihydrofolic acid	CNDO/2 calculated proton affinity	Predicted protonation site; mechanism of reduction	(*29*)
Amiloride	Conformation generation; preferred geometry and rotational barrier calculations	Guided interpretation of spectroscopic results; predicted ground state geometry and dynamic conformation	(*60*, *61*)
N-methylated polypeptides and diketopiperazines	CNDO/2 deprotonation energy calculations	Rationalized ease of base-catalyzed epimerization	(*67*)
Piperazinylpyrazines	Conformation generation; CNDO/2 calculated preferred geometry and charge density	Rationalized serotonin-like central nervous system activity of these compounds	(*68*)
Pyrazino[2,3-e][1,2,4]-triazepines	Conformation generation; energy calculation	Sorted out ring flip and nitrogen inversion motions to explain the dynamic nuclear magnetic resonance spectrum in terms of two equilibrating conformations	(*69*)
Somatostatin analogs	Conformation generation; energy calculation	Refined the model for the bioactive conformation	(*26*)
Cyclic polypeptides	Conformation generation; molecule superposition	Rationalized different biological activity of the retro-enantiomers	(*55*)
Carcinogenic arylamines	INDO, ab initio calculated geometry and energy of derived nitrenes	Found empirical correlation between carcinogenicity and singlet-triplet energy separation	(*70*)

but the computer performs this task quite well. Since Nyburg (*51*) published an algorithm for this purpose, molecule superposition programs have been implemented in several modeling systems (*35, 52, 53*). A locally developed interactive graphical program, Compare (*54*), which is used frequently in our laboratories, allows specified atoms of one molecule to be superimposed on specified atoms of a second molecule by a least-squares fitting routine, with or without side-chain rotations in the moving molecule. Atom selection for the superposition is by one of three commands: "all" matches consecutive atoms of two molecules, for example, for an approximate structure and strain energy minimized structure; "match" allows specifying atoms by number; and "select" permits the choice of superimposable atoms by pointing with a light pen. The resulting superimposed structures may be viewed stereoscopically, and distances determined between atoms which were not used for the superposition. Superposition allows fine distinctions not obvious from examining physical models; for example, L-polypeptides and their D-retro-enantiomers become obviously different (*55*).

Structure properties calculation. A range of molecular properties may be calculated. Quantum mechanical calculations afford charge densities (overlap populations), protonation and deprotonation energies, and frontier orbital coefficients, which may be related to various types of chemical reactivity. The charge densities may be used to generate electrostatic contour maps (program ESCM) (*56*), which may also often be related to chemical reactivity. Other calculable molecular properties include molecular volume (Molvol) and surface area (Molsurf) at the van der Waals radius, and steric congestion at a reaction center [Congest (*57*)]. Table 2 indicates how several of these calculated properties may be related to physical, chemical, or biological properties. As an additional example, electrostatic contour maps of parts of dihydrofolate and methotrexate, shown in Fig. 5, suggest their relative orientations at the active site of DHFR.

Future Developments

The MMMS is now being used to study molecules much larger than the system was designed to handle. For example, when the DHFR crystal structure (*7*) became available, there was an immediate need to study this large structure by computer. The Examin program was modified to read a data file containing all 1300 atoms of the drug-enzyme complex, but display terminal limitations required that no more than 250 atoms at a time be visible—either sequential atoms, or all those within a given number of angstroms of a given atom. This method proved inadequate for designing inhibitors of the enzyme, and it was found necessary to build a large Kendrew model of the structure. Future plans call for upgrading of the display equipment to handle enzymes and other polypeptides in a more satisfactory manner. Such advanced hardware has been shown to be useful for revealing structural details of very large molecules (*58, 59*).

Although semiempirical molecular orbital calculations have proved to be useful, they have limitations. For example, CNDO/2 calculations on Amiloride led to a proposed nitrogen equilibration mechanism that did not hold up to experimental test (*60, 61*). Also, CNDO/2-derived charge densities appear to be somewhat unreliable, in our experience. Consequently, the Gaussian 76 program (*41*) has been added to the system, and a quantum theoretician has joined the support staff.

Conclusion

Drug-receptor theory at the molecular level can be a useful guide for new drug design. Study of molecular shape (conformation) and reactivity can aid in formulating models of drug receptors and mechanisms of drug action. Computer-assisted molecular modeling makes such studies convenient to perform. The MMMS enables medicinal chemists to run computer experiments to test and refine ideas before going to the laboratory.

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Resources, Population, Environment: An Oversupply of False Bad News

Julian L. Simon

Summary. False bad news about population growth, natural resources, and the environment is published widely in the face of contradictory evidence. For example, the world supply of arable land has actually been increasing, the scarcity of natural resources including food and energy has been decreasing, and basic measures of U.S. environmental quality show positive trends. The aggregate data show no long-run negative effect of population growth upon the standard of living. Models that embody forces omitted in the past, especially the influence of population size upon productivity increase, suggest a long-run positive effect of additional people.

In September 1977 *Newsweek* reported that "more than 100,000 West Africans perished of hunger" in the Sahel between 1968 and 1973 because of drought (*1*). Upon inquiry, the writer of the account, Peter Gwynne, informed me that the estimate came from Kurt Waldheim's message to the United Nations' Desertification Conference. I therefore wrote to Waldheim asking for the source of the estimate.

Three mutually contradictory documents came back from the United Nations' Public Inquiries Unit: (i) Waldheim's message to the conference, saying, "Who can forget the horror of millions of men, women and children starving, with more than 100,000 dying, because of an ecological calamity that turned grazing land and farms into bleak desert?" (ii) A two-page excerpt from a memo by the U.N. Sahelian Office, dated 8 November 1974, saying, "It is not possible to calculate the present and future impact of this tragedy, on the populations. . . . Although precise figures are not available, indeed unobtainable . . . certainly there has been an extensive and tragic loss of life. . . ." (iii) A one-page memo written for the United Nations by Helen Ware, an Australian expert on African demography, who was a visiting fellow at the University of Ibadan in March 1975 when she wrote it. From calculations of the normal death rate for the area, together with "the highest death rate in any group of nomads" during the drought, she estimated "an absolute, and most improbable, upper limit [of] a hundred thousand. . . . Even as a maximum [this estimate] represents an unreal limit."

Ware's statement, which makes nonsense of Waldheim's well-publicized assessment, was on page one of a document written for the United Nations well before the Desertification Conference. Apparently it was the only calculation the United Nations had, and it was grossly misinterpreted.

More recently, the U.N. press releases have retreated to the more modest assertion that "tens of thousands" died in the Sahelian drought (*2*). But even this assertion is undocumented. "The problem with deaths in the Sahel," Ware says, "is precisely that there was so little evidence of them—rather like the photograph of the dead cow which kept turning up in illustration to every newspaper story" (*3*). A recent summary of the scientific evidence on the drought's effects by John Caldwell, a demographer who was familiar with the area prior to the drought and spent 1973 there, says, "One cannot certainly identify the existence of the drought in the vital statistics . . . nutritional levels, although poor, were similar to those found before

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