Review

A BRIEF REVIEW ON "COMPUTER AIDED DRUG DESIGN"

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ABSTRACT

Drug design through computer, is very effective technique in modern arena. Now a day Computer Aided Drug Design (CADD) technologies are used in many fields like nanotechnology, molecular biology, biochemistry etc. The main advantage of the CADD is cost effective in research and development of drugs. There are wide ranges of software are used in CADD, Grid computing, window based general PBPK/PD modeling software, PKUDDS for structure based drug design, APIS, JAVA, Perl and Python, CADD as well as software including software libraries. There are various techniques used in CADD visualization, homology, molecular dynamic, energy minimization molecular docking, QSAR etc. Computer aided drug design is applicable in Cancer disease, transportation of drug to specific site in body, data collections and storages of organics and biological. Conformational properties and energetic of small molecules and DNA cleavage, molecular diagnostics based on fluorescence are focusing using this technique.

KEY WORDS: CADD, Energy functions, Molecular dynamics, Bond angles, Electronic Properties.

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1. INTRODUCTION

Design, development and commercialization of a drug is a tedious, time-consuming and cost-intensive process. The cost of this process has increased significantly during the past thirty-four years. Industry averages reported to the Pharmaceutical Manufacturer's Association, have shown that the cost of drug development has increased from $4 million in 1962 to over $350 million in 1996 . Between 1960 and 1980, the development time of a substance from the first synthesis to its introduction on the market, has almost quadrupled and has remained relatively unchanged since 1980 with a present time period of 9- 13 years . Moreover, during this process, only a small amount of candidates will be examined in the clinic and few will be marketed. In 1950, it was estimated that 7,000 compounds had to be isolated or synthesized and then tested for therapeutic activity for each one that became a pharmaceutical product. The challenge is becoming more difficult: 10,000compounds had to be evaluated in 1979, and this number could be as high as 20,000 today. The reasons for this are several-fold. The market for so- called high value-added compounds is very competitive. The new compound must offer improved characteristics in order to be worthwhile for commercialization. Also there are serious hurdles regarding ease and cost of synthesis, patentability, safety, and social need for the new compound.

Computer aided drug design as the name suggest that the new drug discovery is totally depends on the computational scientist who are able to manipulate molecules on their computer screen; drug-design is very complex process. Group of Scientists work together to provide various types of information. Considering both the potential benefits to human health and the enormous costs in time and money of drug discovery, any tool or technique that increases the efficiency of any stage of the drug discovery enterprise will be highly prized. Computer-aided drug design (CADD) is one of these tools which can be used to increase the efficiency of the drug discovery process. CADD cannot, however, maximize its utility in isolation and will not do so. Rather, it can form a valuable partnership with experiment by providing estimates when experiments are difficult, expensive, or impossible, and by coordinating the experimental data available. A close coupling between computational chemists and experimentalists allows information to flow immediately and directly between the two. This helps CADD chemists to better understand the details of the problem and to refine their approach. It also provides valuable information for the experimentalist; it helps to guide further experimental planning and potentially makes this process more efficient. CADD is, however, not a direct route to new drugs, but it provides a somewhat more detailed map to the goal. The hope is that by providing bit and pieces of information and by helping to coordinate the information, CADD will help to save days and money for drug discovery projects.

The mechanistic approach to drug discovery begins with knowledge of the disease process itself. It also requires that one know about the chemical structure of the interacting molecules. Since substrates, legends, or drugs that mimic them and their enzymes or receptors interact via a lock-and-key mechanism, knowledge of their

three-dimensional structures is of critical importance. Once these are known, scientists can begin to begin new chemical entities to influence the targets which are involved in the disease process.

CADD is critically dependent on the physical techniques of crystallization and spectroscopy to provide the practical parameters for its calculations, and on the wisdom of the medicinal scientists to interpret and utilize its output data.

1.1 DISCOVERY OF DRUGS

Sometimes new drugs are found by accident. New drugs are developed by various methods and effects are taken to discover new ways to treat disease. From many years, new pharmaceutical agents has gone through an evolution and new technologies are also been added to this increasingly complex process. (1)

1.1.1 SCREENING FOR NEW DRUGS

In new drug discovery it is require screening a large number of synthetic chemical compound or natural products for desirable effects. In current because of the drawback of requirement of appropriate screening produce it is not ideal one. Apart from this the advantage of screening is large amount of info is not required to carry out the process. There is generally two types of screening is performed. Primary screening in case of large number of chemicals to choose the desire one and secondary screening which is carried out by using animal model system. But there is problem in using secondary screening

and that are 1. No accurate reflection of human disease. 2. Conversion and metabolized in to different compound before reaching to target site. 3. Absorption or distribution of chemical in humans. (2)

1.2.2 MODIFICATIONS AND IMPROVEMENT

Once a lead compound has been recognized and its chemical structure is known, it is possible to improve on this activity to decreases adverse effect by making modification to the basic structure.

A primary example of this approach is modification in the basic structure of cephalosporin have led to second and now third generation offspring with substantially improve characteristic.(3)

1.1.3 MECHANISM –BASED DRUG DESIGN

As more and more info is available regarding the biological basis of a disease, then it is possible that by means of mechanical approach new drug design can begin when the disease process is understood at the molecular level and the target molecule are defined drugs can be designed specifically to interact with target molecule in such a way as to disrupt the disease. (1- 6)

1.1.4 COMBINING TECHNIQUES

Drug discovery is both accumulative and a reiterative process. Potential drugs developed by modifying a lead structure and developed mechanistically.

1.2 THE BASIC OF MECHANISTIC DRUG DESIGN

Numbers of diseases are recognized by the clinical manifestations which are affecting man. Now a day the main focus of the researchers is to study diseases at the molecular level and to recognize the factor responsible for producing the chemical effects. Steps are 1.defining the disease process. 2. Defining the target. 3. Defining the effector.4. Designing new drug to effect targets. 5. Overcoming obstacles in mechanistic drug design. (7-11)

1.3 IMPORTANT TECHNIQUUES FOR DRUG DESIGN

The different technique which provide the information of drug molecule interactions they are chemical, physical and theoretical techniques.

1.3.1 X-RAY CRYSTALLOGRAPHY

X-ray Crystallography is the starting point for collecting the info for mechanistic drug design. It is very helpful to determine total structural info about a molecule. To carry out x-ray crystallography material of very high quality and purity is needed.

1.3.2 NMR SPECTROSCOPY

NMR is the technique of determine the structural information of molecule in solution. The advantage of it is that even small as well as macromolecule can be examined. The disadvantage of NMR is that the data obtained are not as precise as compare to the data obtained from X-ray crystallography.

1.3.3 COMPUTERIZED MOLECULAR MODELING

The important advances in drug design have been the recent development of computerized molecular modeling. it provides 5 major types of info to scientists that are1. The 3D structure of molecule. 2. The chemical and physical characteristics of a molecule. 3. Comparison of the structure of one molecule with other different molecule.4. Visualization of complexes formed between different molecules.5. Predictions about how related new molecule might look.

2. METHODS

2.1 USES OF COMPUTER GRAPHICS IN COMPUTER –ASSISTED DRUG DESIGN

Molecular stick figures give idea about the number of types of atoms that make up a molecule. it gives the information that how the atoms are bonded to one another

In this we explain how molecular models are constructed which can define the 3D and electronics properties of the molecule. The general use of molecule (35-38) and use of these molecules in drug design. (39-46)

2.2 X-RAY CRYSTALLOGRAPHY

This technique is concern with the determination of structure of the drug and structure of drug target and the interaction of the two. Nowadays this is only one technique which provides the broad and accurate information regarding complete 3Dstructure in detail at high resolution

including bond distance, angles, stereochemistry and absolute configuration.(12)

2.2.1 METHODOLOGY

a) THEORY

Crystals are made up of repeating unit of molecular structure. This order gives rise to a periodicity that can be analyzed at the atomic level with the X-ray radiation is ideal, since the obtainable are of the order of 0.75A which is about one-half distance of an aliphatic c-c bond.

A crystal placed in an X-ray beam will different according to Bragg's law:

$$n\lambda = 2d \sin\theta \cdot \cdots \cdots \cdots (1)$$

Where, n= order of the diffraction, λ= wavelength of the radiation, d= the distance between a given family of plane& θ= angle of diffraction.

b) CRYSTALLIZATION

Linus Pauling once entitled "The Importance of Being Crystalline" (13). Crystallization plays a very important role in advance structural molecular biology which is foundation for rational

drug design based on the behavior of receptor (14-16). Other methodologies are Data collection, The Phase Problem, Computing, Resolution, Refinement, and Data Bases. (17-31)

The role of x-ray crystallography is divided into five categories which are as follows:

1. Aimed at structure elucidation of the complex biological molecules that have interesting pharmacological properties
2. Compare the conformation aspects of X-ray structure with solution of protein –bound states
3. Map out the structure of the receptor or binding site
4. Attempt to define the molecular mechanism of action of drugs and
5. Are focused primarily on the design of new agents by discovering general characteristics and rules related to drug binding

   A various examples mentioned to explain their categories like-

   a. Use of small molecule crystallography to determine the structure of biological active molecule. (12)
   b. Conformational analysis of drug molecule. (31)
   c. Mappins the receptor site from agonist and antagonists. (32)
   d. Elucidating the molecular mechanism and action of drugs. (33)
   e. Drug design. (34)

2.3 COMPUTER GRAPHIC DISPLAYS

There are different ways to constructs molecular models. One of them is CPK and deriding models. [CPK] models are physical models and it represents the atoms by color-coded, snap together spherically shaped, plastics pieces. It provides a good representation of the shape of the molecule.

Deriding models are physical models which use thin metals or plastic rods to represents bonds. But deriding models give poor idea about molecular volume and also about electronic properties.

Computer graphics is used to draw a virtually limiters variety of molecular representation from stick figures

to molecular surface. It also represents the electronic properties of molecules.

Thus one other computer graphics system such as the [PS 350] and the silicon graphics [IRIS] work station allow one to combine the technique of real-time graphics stereographic and intensity depth cuing to produce 3D image.

a) VECTOR VERUS RASTER SYSTEM

There are two types of computer graphics display one is vector and another is raster.

On vector displays, the lines making up the images are traced on the face of the CR7.

On raster displays, the CR7 is repeatedly horizontally scanned, as on a television screen. The image is made of discrete pixels.

Because of the pixel method used in raster system, filled areas are more readily drawn on their systems than on vector system.

b) WORK-STATIONS

Work-station is raster system in which a computer full operating system and man's storage facility is integrated with the graphical display.

Example: silicon graphics, [IRIS], sun graphics work-station, Apollo workstation.

2.4 COMPUTED MOLECULAR MODELS

The intension of molecular modeling is to represent some aspect of molecular structure using a computer graphical model. There are two aspects of molecular structure that have been found to be useful in drug design. The first is the atomic connectivity and atom types, and other is the volume and shape of the molecule. (47-49)

a) MOLECULAR STICK FIGURES

The most familiar computer molecular model is the molecular stick figures. It is possible to do a systematic search (50). But this technique requires a large amount of computer time which increases exponentially as the number of rotatable bonds increase.

b) MOLECULAR SURFACE

The general concept of molecular surfaces was proposed in a paper by Lee and Richards (51). The distinction was made between molecular surface and solvent accessible surface. Connolly published an algorithm (47) and program (52) for computing either molecule or solvent-accessible surfaces (53-54).

c) COLOR CODED SURFACES TO REPRESENT MOLECULAR PROPERTY

One could color the dots to show which type of atom they are belong to and another useful property that is frequently used to color- code surface is electrostatic potential energy.

d) OTHER MOLECULE PROPERTIES

Apart from properties at surfaces, other molecular properties can be represented using computer graphics. One form is a quantum mechanical calculation on a molecule is the electron density. The quantity has a particular value at each in space surrounding the molecule.

e) OTHER MOLECULER REPRESENTATION

For representing a large molecule like protein, drawing a complete stick method which is used is an alpha carbon plot. It helps to avoid clutter during drawing a complete stick figure (55).

2.5 MOLECULAR MODELING STRUCTURE FOR DRUG DESIGN

There are many molecular modeling systems available.

2.5.1 THE CAMD SYSTEM

The molecular modeling tasks were accomplished by using computer assisted molecular design. The CAMD was desired and written at Abbott laboratories for the use of molecular modeling researches. CAMD is made up of several pieces which are connected in different ways. It uses [GRAMPS] (56) to do its graphics, in order to provide us much graphical flexibility as possible in doing molecular modeling.

These are GRAMPS, a general purpose graphics program for display of arbitrary graphical objects; [PDS] a protein modeling system; [CMD]a small molecule modeling systems; and Interact, a program to co-ordinate information transfer among GRAMPS/ CMD/ PDS and provide a convenient users inter face.

There are many programs used in CAMD system which include molecular mechanics (57-59), molecular dynamics, quantum mechanics (60-61), distance geometry. (62)

2.5.2 USES OF COMPUTER ASSISTED DRUG DESIGN

A. Crystallography (63)
B. Receptor mapping (64)
C. Molecular docking, graphics and dynamics
D. NMR and computer graphics (65)
E. Molecular docking, surface, and hydrogen bonds (66)
F. Quantum mechanics (67)

3. THEORETICAL ASPECTS OF DRUG DESIGN

It's identified that peptides and proteins play a very important role in biological function and regulation. Molecules mechanics and molecular dynamics the functions of conformational calculations on biomolecules and information available from these calculations depend on how the potential functions used actually represent the energy of the biomolecule as a function of its atomic displacement. There is many application of empirical energy calculation for determines the peptide conformations, but new experiment technique often more hope that these methods can be useful in drug design. These have recent been numerous review on the application of empirical potential functions. (68-71)

3.1 POTENTIAL ENERGY FUNCTION

Potential energy function or molecular mechanics are analytical expressions which express the potential energy in term of valance interactions. The most common forms of these potential employed today are known as valance force field. The valance force fields are made up of three main energy terms:

Non-bonded energy, Electrostatic energy, intramolecular energy. (72-79)

The expression is given by:

$$V = \tfrac{1}{2}\Sigma K_b(b-b_0)^2 + \tfrac{1}{2}\Sigma K_\theta(\theta-\theta_0)^2 + \tfrac{1}{2}\Sigma K_\phi(1 + s\ \cos n\phi)$$

$$+ \tfrac{1}{2}\Sigma\, K_x x^2 + \Sigma\Sigma F_{bb'}(b-b_0)(b'-b'_0)$$

$$+ \Sigma\Sigma F_{\theta\theta'}(\theta-\theta_0)(\theta'-\theta'_0) + \Sigma\Sigma F_{b\theta}(b-b_0)(\theta-\theta_0)$$

$$+ \Sigma F_{\phi\theta\theta'\cos\phi}(\theta-\theta_0)(\theta'-\theta'_0) + \Sigma\Sigma F_{xx'}xx'$$

$$+\Sigma\left(\frac{B_{ij}}{r^1ij^2} - \frac{A_{ij}}{r^6ij} - \frac{e_ie_j}{r^2ij}\right) \quad (2)$$

This equation reflects the energy necessary to stretch bonds (b), to distort bond angles (θ) from their reference values, and to generate strain in the torsion angles bytwisting about bonds. Here $K_b, K_\theta, K_\phi, K_x, F_{bb'}, F_{\theta\theta'}, F_{b\theta'}, and\ F_{\phi\theta\theta'}$ are force constants for the corresponding deformations, such as bond stretching, angle bending, torsional barriers, out-of-plane deformations, and the coupling between various movements such as bond stretch and angle bending. The last summation in eq. (2) contains terms for the non bonded energy and the electrostatic energy. There are many variations on the above expression, but with the exception of the cross term$\left(F_{bb'}, F_{\theta\theta'}; \cdots\cdots\right)$, most potential functions employed today such as Amber (72), Charmm (73), and Discover (74) are variations on this type of empirical equation.

3.2 NON-BONDED ENERGY TERMS

Quantum mechanics provide a major source of information about molecular interaction, but accurate results are limited to system with only a few electrons. Info about non-bonded interactions can also obtained from crystal packing data. (80)

In the long-range region, even electroneutral molecules exert attractive forces on each other. These forces are functions of the intermolecular distances as well as of the electronic structures. The theory of attractive interactions is due to London (81,82), and the forces acting on the system of particles are called dispersion forces. Although the mathematical derivation of the theory of these forces is complex, the qualitative origin of the force is straightforward. At any given moment, instantaneous dipoles are created because of nuclear and electronic fluctuations. These fluctuating dipoles induce dipoles in other atoms, and the interaction of these two dipoles creates a net attraction.

From London's theory the dispersion term can be represented by an r^{-6} dependence, where r is the distance between two atoms, I and j. The dispersion energy can be related to polarizabilities and various other macroscopic properties such as ionization potentials. Slater and Kirkwood (83) derived a relationship for the dispersion energy.

$$V_{disp} = \frac{-1}{r^6}\frac{3eh}{2Me^{1/2}}\frac{\alpha_a\alpha_b}{(\alpha_a/N_a)1/2 + (\alpha_b/N_b)1/2} \ldots\ldots\ldots\ldots (3)$$

Where α_a, is the polarizability of atom a, N_a, is the number of electrons in the outer shell of atom a, and similarly for atom b. This expression is frequently used by various groups in determining the dispersion terms (84,85).

3.3 ELECTROSTATISTIC ENERGY (V_{es}) – THEORTICAL CONSIDERATIONS

These are used for conformational calculations:

3.3.1 Coulombs laws (87)

The forms of electrostatic potential is given by coulomb's law

$$V_{es} = q_a q_b / Dr \ldots\ldots\ldots\ldots (4)$$

Where q_a and q_b are the charges on the particles a and b, r is the distance between the particles, and D is the dielectric constant. The electrostatic potential for the interaction of polar molecules is sometimes expanded in series of multipole interactions. For example, the next two higher- order terms are

$$V_{q\mu} = -\overrightarrow{q\mu} \times \left(\frac{\vec{r}}{r}\right) / Dr^2 \ldots\ldots\ldots\ldots\ldots\ldots (5)$$

$$V_{\mu a \mu b} = (1/Dr^3) \times [\overrightarrow{\mu_a} \times \overrightarrow{\mu_b} - 3(\overrightarrow{\mu_a} \times \vec{r})(\overrightarrow{\mu_a} \times \vec{r}) / r^2] \ldots\ldots\ldots\ldots\ldots (6)$$

3.3.2 Second – order Effects-induction forces. (87)

When a charged particle, a, interacts with a neutral, nonpolar atom or molecule, b, the charged particle induces a dipole moment in the nonpolar atom. This induced dipole moment is due to the relative displacement of the nuclei and electrons by the field of the charged particle. The moment induced is directly proportional to the field, E_a, due to the charge q_a acting on atom b, where the constant of proportionality is the polarizability of atom b, α_b i.e.

$$\mu_b = \propto_b E_a \ldots\ldots\ldots\ldots (7)$$

The interaction of this charge with the induced dipole then leads to a net attractive force. The energy of charged-induced dipole interaction $V_{q\text{-}\mu\alpha}$ given by (87)

$$V_{q-\mu\propto} = -\frac{q_a^2 \propto_b}{2Dr^4} \ldots\ldots\ldots (8)$$

A permanent dipole also induces a dipole moment in nonpolar atoms and likewise with higher moments. The potential energy $V_{\mu\text{-}\mu\alpha}$ of the interaction between a permanent dipole and the dipole it induces is (87)

$$V_{\mu-\mu\propto} = (\mu_a^2 \propto_b / 2De^6)(3cos^2\theta + 1) \ldots\ldots (9)$$

Where μ_a is the permanent dipole moment of molecule a and θ is the angle between μ_a and the line connecting it to the induced dipole. Thus this interaction goes as the inverse sixth power of the intermolecular distance. Interactions involving dipole induced quadrupole go as inverse eighth power and so on for still higher-order interaction.

3.3.3 Total electrostatic energy

The total electrostatic energy for the interaction of two polarizable atoms, a and b, separated by a distance r bearing partial charges q and qb of opposite signs is then given by

$$V_{es} = -\frac{q_a q_b}{r} - \frac{q_a \mu_b}{r^2} - \frac{q_b \mu_a}{r^2} + \frac{\mu_a^2}{2 \propto_a} + \frac{\mu_b^2}{2 \propto_b} - \frac{2\mu_a \mu_b}{r^3} + \cdots\cdots \quad \cdots\cdots (10)$$

where the terms in Eq. (10) correspond in order to: the Coulomb interaction; the attraction between the charge on a and the dipole it induces in b; similarly for charge on b and induced dipole in a; the energy of inducing the dipole in a; similarly for b; and finally the interaction between the two induced dipoles on a and b*. Solving for the induced dipoles by requiring that the energy be a minimum (88) one obtains

$$V_{es} = -\frac{q_a q_b}{r} - (½r)\left[\left(q_b^2 \propto_a + q_a^2 \propto \frac{b}{r^3}\right) + 4 q_a q_b \propto_a \propto \frac{b}{r^6}\right] \times (1 - 4 \propto_a \propto b/r^6)^{-1} \ldots\ldots (11)$$

where again the first term is the Coulomb term, the second is the charge induced dipole interaction, and the last is the induced dipole-induced dipole interactions. Higher-order terms have been omitted, and we have assumed unlike charges. For like charges the first and third terms have opposite sign To give an idea of the relative order of magnitude of the terms in Eq. (11)

To give an idea of the relative order of magnitude of the terms in Eq. (11), we consider an interaction between two typical atoms in a protein (i.e, H, C, N, O, etc). To get an upper estimate for the importance of the induction ternis, which go as F4 and r 7, respectively, a relatively small, although not unreasonable value of 3 A is chosen for the inter atomic interaction distance. The polarizabilities of the atoms are of the order of 1 53, while the partial charges are taken as ~:0.33 electrons for the purpose of this rough estimate. It should be noted that the value of the partial charges does not affect the relative values of the terms. For this case the three terms have the values q_A, q_b/r~10 kcal/mole, α_b, q_a^2/r_4~0.5 kcal/mol, and $4q_a$, q_b, α_a, α_b/r^7~0.05 kcal/mole.

From this rough estimate it is seen that typically the last term is not significant (< 1%), while the value of the charge-induced dipole interaction is on the order of 5%, of the Coulomb energy. The relation given in Eq. (11) represents the interaction between an isolated pair of polarizable charges. The situation is much more complicated in a protein or in other biological macromolecules, where the dipole induced in a given atom is due to a field of the charges on all the other atoms in the molecule as well as the induced moments in these atoms. Thus in general the induced dipole in an atom due to the field of all the other atoms would have to be calculated by minimizing the total energy given by an expression analogous to Eq. (11) except that the energy is now a sum over all possible interactions in the protein. Arridge and Cannon (89) have considered this polarization (induction) energy in a treatment of the lattice energy of amides, polyamides, and peptides. They were only able to solve for the exact polarization energy in the one dimensional case of a collinear array of polarizable dipoles. For the general three-dimensional lattice, the problem became intractable, and numerical methods are required.

3.3.4 Relative magnitude of electrostatic and non-bonded interactions

London (82) and Hirschfelder et a1.(87) have considered the relative magnitude of the various

contributions to the intermolecular potential, for representative polar molecules, ranging from carbon monoxide with a dipole moment 0f 0.12 D to water with a dipole moment of 1.84 D. In the majority of cases, the dispersion forces are most important. However, in highly polar molecules the Coulomb or dipole dipole forces are more important. In water these forces account for approximately 8070 of the total interaction energy, but even here the. dispersion forces are not negligible, accounting for another _ 16%. The induction effect is never very important for polar molecules, accounting for at most approximately 5% of the energy (in the case of NH_3)." However, the case of interactions between ions and nonpolar (although polarizable) molecules is different. For these systems, the induction force-s become a dominant contribution to the energy (87),, although here again the '_ dispersion forces are not negligible, being also related to polarizability. There are often highly polarizable moieties in proteins such as tryptophan, histidine, and tyrosine and ionizable ~NH2 and COOH groups as well as other ions in the media. In cases where these groups interact, the effects of induction energy could be significant.

3.3.5 Dielectric constant and partial atomic charges

The macroscopic dielectric constant, which attenuates charge interactions arises from permanent or inducible multipole moments between interacting, charges and is related to the dielectric permittivity of the medium. In conformational calculations the dielectric is used to account for the effect of solvent in attenuating the electrostatic interactions of charged groups in an aqueous environment. Rather than attribute any physical significance to the dielectric constant, in molecular mechanics it is often considered an empirical parameter. More recently a distance-dependent dielectric has been employed in empirical potential functions (72,73). The relationships have ranged from a r linear dependence on r to an inverse second-power dependence. The rationale is that by using a distance dependence the polarization effects fer closer interactions are weighed more heavily and longer-range interactions are dampened more than shorter-range interactions. Macroscopic dielectric functions have recently been replaced by modeling the electric field numerically through a finite element approach (90,91). This model accounts for different parts of a macromolecule having completely different dielectric properties. Of course, if explicit solvent molecules are included in the simulation, an empirical dielectric may be unnecessary. For example, in a full- scale simulation including many explicit water, the dielectric shielding is accounted for by the physics of the interacting waters as they reorient their dipoles to counteract the local electrostatic field.

First suggested by Tomasi (92,93), some of the recent work in this area is due to Cox and Williams (94) and Kollman s group (95). Momany (96) found that partial atomic charges fitted to the electrostatic potential are a better representation of the SCF unperturbed electrostatic potential than those obtained from a Mulliken population analysis

3.4 HYDROGEN BONDS

The description of hydrogen bonding in empirical potential energy function 15 problematic. The original theories of the hydrogen bond were mainly electrostatic (87,97,98), while some have argued that the effect is primarily due to charge transfer (99). Most efforts to include hydrogen bonding in empirical energy functions are to use properly choosen partial atomic charges and Lennard-Jones

parameters to reflect the strength of hydrogen bonding. Poland and Scheraga (100) developed an empirical hydrogen bond function which is of the form shown below

$$V_{hb} = \frac{d}{r^2} - \frac{c}{r^6} \text{..... (12)}$$

for the interaction of the O & H atoms participating in the hydrogen bond. The values of d and c were obtained by requiring that the total interaction energy for a pair of hydrogen-bonded molecules at a specified minimum distance be equal to an estimated experimental dimerization energy, McGuire et al. (101) proposed a hydrogen bond potential which describes the O . . . H interaction by

$$V_{HB} = \frac{A}{r_{OH}^{12}} - \frac{b}{r_{OH}^{10}} \text{.....(13)}$$

This potential was obtained by subtracting from the CNDO/2 energy of two hydrogen-bonding molecules, calculated as a function of r, the empirical nonbonding and electrostatic interaction for all atoms except the O . . . H atoms. The differences between the two energy curves for many molecules were fit by a least-squares procedure with a potential of the form

3.5 ENERGY MINIMIZATION

The Newton Raphson procedure (86) is a powerful, convergent minimization procedure. In the Newton-Raphson algorithm, one needs to have the second derivative matrix available. Then the new coordinates in each interaction can be found by the following equation

$$V_{HB} = \frac{A}{r_{OH}^{12}} - \frac{b}{r_{OH}^{m}} \text{.....(14)}$$

where F is the matrix of the second derivative with respect to the coordinates and $(\partial V)/(\partial_{xi})$ are the first derivatives. The Newton-Raphson method is based on the assumption that the energy is quadratically dependent, i.e., behaves like a classical spring. If the energy function were quadratic, the increments it would lead directly to the minimum in one step. This is, of course, almost never the case for the potential surface of complex biomolecules. Newton- Raphson methods do not need to do linear interpolations like conjugate gradient, so energy evaluations can be speeded up by a factor of about 2 -3. The major drawback of the Newton Raphson method is that one must spend the time to calculate the second derivatives, which is computationally expensive, and, to save time, one would have to be able to express the second derivatives in an analytical form, which is not necessarily easy for complex potential functions. (102-104)

$$\Delta X = F_S^{-1} \frac{\partial V}{\partial x_1} \text{....(15)}$$

APPLICATIONS OF THEORETICAL TECHNIQUES TO DRUG DESIGN

1. Monte Carlo (105)
2. Molecular Dynamics (106)

3. Use of Theoretical Simulations in Drug Design (107)
4. Use of NOE Data from NMR (108)
5. Use of Simulated Annealing (109)

4. Application of computer in drug design

4.1 Anticancer agent

The sequencing of the human genome represents one of the major scientific endeavors of this century. A major aspect of the utilization of this information will be the provision of small molecules which will recognize selected sequences, perhaps with the goal of switching off particular genes as in cancer chemotherapy. For some time antibiotics such as netropsin have been known to bind preferentially to sequences richin A-T pairs. A variant based on this research has been to try to design a bioreductive ligand based upon netropsin. The idea of bioreductive anti-cancer agents starts with the fact that tumors receive less blood and hence less oxygen than normal tissue. Thus it becomes possible, at least in principle, to contemplate having a ligand which can exist in two forms, oxidized and reduced, and if the redox potential is appropriate to be in the oxidized form in normal tissue but reduced in tumours. If only the reduced form will bind to the macromolecular target and cause cell death, then differentiation in action between cells which it is desirable to destroy and normal cells is achievable, with concomitant reduction in side-effects. A second starting point for sequence selective ligands is an organometallic molecule with chiral properties. The propeller-likeruthenium tris-phenanthroline complexes do show differential binding between A-T and G-C sequences and moreover may exhibit a preference for purine 3', 5' pyrimidine sites in DNA. (110)

4.2 Target Enzyme

If an enzyme structure is known then designing inhibitors which will block activity in the test-tube should be a relatively straightforward problem. More spice to such a challenge is added if we at the same time attempt to make the ligand bioreductive as outlined above. (111) The published work has taken dihydrofolate reductase as the target enzyme, but current activity is being focussed on thymidylate synthetase. The binding free energy of the inhibitor to the enzyme is a crucial quantity: strong binding is essential.

4.3 Drug Transport

Sceptics quite rightly point out that designing an enzyme inhibitor which will work in the test-tube is one thing; getting a compound which will work in a cell is another. Transport across the biological membrane is essential. Compounds must be soluble enough in the lipid to get into the membrane, but not so soluble that they remain there. Within the pharmaceutical industry the partition coefficient between water and n-octanol is used as a guide to membrane transport. The free energy perturbation technique just described can also be adapted to compute partition coefficients. (112).More excitingly, however, it is becoming possible to model biological membranes. Starting with crystal structures of membranes involving DMPC (1,2-dimyristoyl-sn-glycero-3-phosphoryclh oline) a highly realistic simulation is possible, involving ahydrated lipid bilayer. After very long molecular dynamics simulations the result in membrane model is in agreement with all the available experimental data; lead p u p separation; order parameters and diffusion coefficients 'Ibis model can be used as the 'solvent' in calculations of partition coefficients which should

be considerably more realistic than experimental values in n-octanol. Furthermore it will be able to introduce cholesterol and protein into the model membrane to produce a truer simulation of how a given drug is transported into a cell.(111)

4.4 Biochemical Transformation

Where no knowledge about the macromolecular target in atomic detail exists, then it isstill possible to utilize computer-aided design techniques. A popular idealized approach would be to compute the energy profile of a biochemical transformation which it would be desirable to inhibit; locate the transition state or intermediate and then create as table mimic of these unstable transients recognized by the enzyme responsible for catalyzing the reaction and would hence act as an inhibitor. Such a mimic should be only two logical steps are necessary: find the transient structure and secondly design astable mimic. The former task is probably best achieved by using a combination of quantum and molecular mechanics. A recent review suggests that the combined potential method used by Bash et a1 for the triosephosphateisomerase reaction is probably the technique likely to be followed in the future. The second stage of the process invokes the introduction of the idea of molecular similarity, a quantitative measure of just how similar one molecule is to another. Perhaps the most important Aspect of similarity is similarity of shape and secondly similarity of molecular Electrostatic potential, both of which can be represented by Gaussian functions which Introduce major computational gabiS in the calculation of similarity indices, of which several different types may be defined. (112)

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