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OVID and SUPER: Two overlap programs for drug design

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SUMMARY

Two programs, OVID and SUPER, for exploring the similarity of molecules with respect to their action at a receptor are described. OVID accepts two molecules as input and optimizes the three-dimensional overlap of specified atoms in one molecule with specified atoms in the second molecule. The result is expressed as a percent of the theoretical maximum. OVID gives a quantitative measure of the extent of a guessed correspondence between two molecules based on volume overlap of selected atoms. The Achilles' heel of OVID is that the correspondence between the two molecules has to be guessed. We realized that it would be better to systematically examine all possible correspondences of two structures to minimize the chance of overlooking a superior correspondence. We created SUPER to satisfy this need. SUPER accepts two molecules as input and finds the top twenty correspondences of their surfaces and charge distributions, giving a quantitative measure of the extent of each correspondence. An instructive example of the application of OVID and SUPER to the design of leukotriene D_4 receptor antagonists is described. SUPER appears to be a practical brainstorming tool for the medicinal chemist trying to understand how molecules whose structures may not resemble one another in an obvious way can bind to the same site.

INTRODUCTION

For the medicinal chemist, the discovery of a lead compound that binds to a specific site opens up a search for a viable drug. Customarily, one looks at the chemical structure of the lead compound, and tries to determine what structural changes might enhance desirable properties. It is recognized that for a given compound certain structural features are more important than others. Similar molecules may have similar effects, but the molecules must resemble one another in a very special, and generally hard to define, way. Comparison of one active lead structure with another or with a natural ligand can provide important clues for the design of new molecules. Systematically examining and quantitatively defining the similarity of structures with respect to their action at a receptor or other binding site is an important problem in computational medicinal chemistry [1]. Recently several investigators have published approaches to this problem [2]. In this paper

some ideas about molecular comparison are examined, especially pertaining to the comparison of molecular surfaces [3], and two new computer programs together with their particular advantages are described.

METHODS

Theoretical

The idea of comparing two molecules can be formulated in terms of an overlap integral of the two molecules, where a weighting function is introduced to make the overlap contribution in certain regions more important than it is in others. One then obtains different comparison methods depending on just what aspects of the structure are given the greatest weight. A consideration of receptor binding gives some indication of how to do this.

Previously, one measure of similarity has been through the integral over the product of the two molecular electronic density functions [4]. In this paper, however, we measure similarity by maximizing the integral:

$$S_m = \int \Big(w(xyz)\Psi_1^*(xyz)\Psi_1(xyz) \Big) A \Big(w(xyz)\Psi_2^*(xyz)\Psi_2(xyz) \Big) dxdydz \tag{1}$$

for the two systems, where $\psi_1(xyz)$ and $\psi_2(xyz)$ represent the suitably normalized wavefunctions of two molecules fixed in space relative to some coordinate system, and A represents an Euclidean transformation. This integral takes account of the receptor only through the arbitrary weighting factor w(xyz). For the maximum overlap of two similar molecules, their relative orientation in space is important. This orientation is determined by the transformation A. If the receptor were unknown and no information were available about the mode of interaction, setting the weighting factor equal to one everywhere and maximizing the overlap through the proper choice of A would then give the best quantitative measure of similarity, at least for the electronic portion of the wave-function. Two specific definitions of the weighting factor w(xyz) give rise to two algorithms, OVID and SUPER, described below.

The first program designed to approximate the overlap integral above is OVID. Several approximations are made: (1) Only selected atoms in the ligand are considered–those known from the structure–activity relationships (SARs) of the active series to be important for activity. Formally this means that the weighting factor is 1 for these important atoms and 0 for all others. (2) Their contributions toward the total molecular density are represented by a solid sphere of radius equal to the atomic van der Waals radius. (3) The overlap of two ligands is given by the sum of the overlap of the corresponding important atoms, where the atomic overlaps are given by the intersection volume of the spheres. These volumes are normalized to unity so that the maximum overlap of two spheres of the same size is 100%. The overlap of spheres at some particular distance apart is given by

$$S_T = \frac{V_{AB}}{\sqrt{V_A V_B}} \tag{2}$$

for two spheres of radii R_A and R_B and corresponding volumes V_A and V_B. V_{AB} is the absolute overlap for spheres A and B. The integral is normalized, since when $R_A = R_B$ and the centers co-

incide, then $V_{AB} = V_A = V_B$ and the integral equals (1). Thus, the best intersection of spheres of different sizes can never be 100%. This is similar to one of the measures of shape in molecular shape analysis [5].

The program first does a least-squares fit to position the molecules, then maximizes the total volume overlap as a sum of several of these integrals over selected atomic pairs and reports the results as a total percent.

In a more general program, SUPER, no assumptions are ever made as to which atoms are important in receptor binding or which atoms should correspond. In this method, the points on the molecular van der Waals surface are considered to be the only important points in the overlap integral. This is in accord with the idea that the outer region of the molecule is more important to the receptor than the inner region. The molecule is represented by its van der Waals surface by formally giving the surface a finite weight and by assigning a weight of 0 everywhere else. The exact positions of atoms that are inside or beneath the surface are thereby rendered unimportant. The ligand-receptor interaction is better represented in SUPER than in OVID; it is assumed that the receptor 'sees' essentially the van der Waals surface of the molecule.

After representing the molecules by surfaces, SUPER then matches the surface of ligand A with the surface of ligand B. Two such van der Waals surfaces, represented numerically by a grid of dots about 0.4 Å apart, are compared by devising a closeness criterion for the dots. For simplicity, we chose to use a method whereby two dots correspond if the distance between them is less than one half the distance between two dots on the same molecule.

The molecular charge distribution was also taken into account in the following way. The electrostatic potential is computed at each surface point from the sum of potentials due to the atomic point charges at the atomic centers. However, instead of introducing the potential by way of the weighting factors $w_i(xyz)$ in the integral (1), the importance of the potential in the matching process is introduced through a difference criterion. The matched pair of surface points is simply discarded if the absolute value of the difference between the two potentials is greater than a given number. Furthermore, a united atom treatment is used to define the surface of both carbon and heteroatoms, so it is a united atom charge that is used to calculate the potentials.

In implementing the above algorithm, an orientational search must be made. The molecules are moved according to the following procedure. In the current version of SUPER, for each input molecule, the atom closest to the geometric center (the center of gravity when all atomic masses are set equal to 1) is found and placed at the origin. Then molecule A is held fixed and molecule B is rotated incrementally about its atom at the origin. The molecule is rotated such that all increments are about the same size. If a vector is attached to the atom at the origin, and defined by the polar coordinate angles θ and φ then the molecule is rotated 0–360° around the vector as well as carried with the vector as the vector goes through θ (0–180°) and φ (0–360°).

The translations in the search are carried out as a succession of superpositions of each pair of atoms in the molecule pair. Each atom B_j of the second molecule is eventually paired with each atom A_i of the first, beginning with the atoms closest to the centers of gravity and proceeding outward. The second molecule is then translated so that successive pairs overlap. The complete set of rotations described above is carried out on the second molecule for each translational position. This rather arbitrary method of translation, while not as flexible as a grid search, has the advantage of more rapidly and significantly covering translation space, at least for small molecules.

In an early version of SUPER, called SUPER1*, the approximation of representing the mole-

cule by atomic centers was used. This makes SUPER1 a 'fitting' algorithm rather than an overlap routine.

Computational

For the construction of the surfaces, each united atom surface is represented by a sphere of radius 2 Å with 177 dots/sphere. While the surfaces are not exactly at the van der Waals radii, a uniform density of dots is maintained over the surface. The dots fitting inside other atomic spheres are eliminated. Using the united atom charge density, the electrostatic potential is calculated at each surface dot. Dots calculated to correspond on the basis of a distance criterion alone (≈ 0.5 Å) are then checked to see how close the potentials of the pair are, and an appropriate cutoff is used whereby a difference in potential larger than the cutoff causes the pair not to be counted as a correspondence. In the SUPER runs described here, the input parameters used are 4 translations of each molecule, 24 rotations (15° increments), and a scalar potential difference criterion (SPDC) of 0.5 using Gasteiger charges as implemented in SYBYL. These values have to be chosen by trial and error for each SUPER pair. The number of translations is the smallest number that allows the surface of each molecule of the pair to adequately explore the surface of the other molecule. In the present case 4 translations were chosen because inspection of the starting structures indicated that 4 translations would allow the length of the planar acetophenone ether moiety of LY171883 to slide the length of the planar triene moiety of LTD_4. An identical calculation using 12 translations for each molecule was carried out and produced the same 801 dot best correspondence as 4 translations for each molecule. To allow the surface of each molecule to completely explore the surface of the other, each molecule would have to be translated a number of times equal to the number of atoms in the other molecule. An SPDC value of 0.1 requires the difference in electrostatic potential between two dots to be < 0.1 for a match. The importance of electrostatic potential in choosing matches can be increased by choosing a smaller value for this parameter or decreased by choosing a larger value. An SPDC value should be chosen to give charge a significant role in making the matches without overwhelming the steric factor. Our initial choices of 4 translations, an SPDC value of 0.5, and 15° increments for rotation are not necessarily the optimum values.

OVID and SUPER are written in FORTRAN and run under the current version of the VAX VMS operating system (OVID and SUPER code will be provided to investigators who request it).

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* Description of SUPER1: In fitting one molecule to another with no stipulation as to which atom corresponds to which, SUPER1 proceeds by maximizing the correspondences between atoms. One molecule is held fixed and the other is rotated and translated so that a maximum number of matching pairs of atoms can be identified Given two pairs of molecules, the pair that is most similar is the one which has the largest number of corresponding atom pairs, according to this procedure. The criteria for matching an atom of one molecule with an atom in a second molecule can be defined in a number of ways One might, as for the surface points in SUPER, define a distance criterion, e.g. two atoms within 0.5 Å would be a corresponding pair. In SUPER1, however, a parameter-independent and more symmetrical method was chosen, called 'the method of mutual closeness'. Here atom r in molecule A corresponds to atom s in molecule B if and only if the distance from atom r in A to any other atom in B is greater than the distance from r to s and, simultaneously, the distance from atom s in B to any atom in A is greater than the distance s to r. In essence, two atoms must 'agree' that they are closest in order to become a corresponding pair

OVID jobs on the VAX 8800 typically take only minutes of cpu time. Super jobs on the VAX 8800 take days of cpu time to finish. The SUPER code was therefore optimized to run on the Cray 2 supercomputer, as a SUPER run on the Cray 2 takes about two hours of cpu time. Input structures for OVID and SUPER are in SYBYL molefile format and were generated using the programs of the SYBYL molecular modeling system (Tripos Associates, St. Louis). SUPER output requires an Evans and Sutherland PS300 series workstation.

Chemical

The synthesis and pharmacology of LY137617 are described by Herron et al. [6].

RESULTS

During our early work on the design of LTD_4 receptor antagonists, we proposed [7] that the apparently dissimilar LTD_4 receptor antagonists LY140801 [8] and LY171883 might resemble one another in that the dichlorophenyl group of LY140801 and the hydroxyacetophenone group of LY171883, might bind to the same part of an LTD_4 receptor as the peptide moiety of LTD_4. The propyl group of LY171883 and the naphthyl group of LY140801 might bind to the same part of a receptor as part of the lipid chain of LTD_4, and the carboxyalkyl chains of both antagonists might bind to the same parts of an LTD_4 receptor as the C(1) to C(5) carboxyalkyl chain of LTD_4. This correspondence was also proposed by Musser et al. based on SAR considerations [9].

We tested this idea by (1) fitting each antagonist to the same LTD_4 conformer (the lowest-ener-

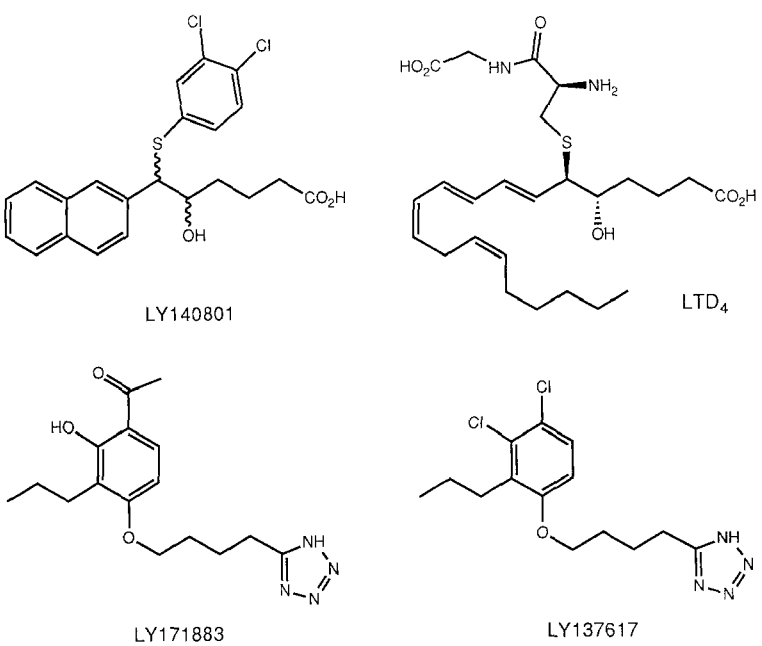

Fig. 1. Three-dimensional structures of the leukotriene antagonists LY140801, LY171883, and LY137617 and the leukotriene agonist leukotriene D_4 (LTD_4) were compared using OVID and SUPER.

TABLE 1
OVID CALCULATIONS: PERCENT OVERLAP OF ANTAGONIST CONFORMATIONS WITH LTD_4

Structure	Percent overlap[a]
LY171883 Search minimum	51.7
LY171883 Flexible fit[a]	97.7
LY140801 Search minimum	49 5
LY140801 Flexible fit[a]	87.3
LY137617 Search minimum	62.8
LY137617 Flexible fit[a]	88.3

[a] The atoms which were specified in the flexible fits and in the OVID runs are as follows: LTD_4: cysteine carbonyl oxygen, triene carbon atom C(9), C(1) carboxyl oxygen; LY171883: carbonyl oxygen, propyl γ-carbon, tetrazole N(1); LY137617. *p*-Cl, propyl γ-carbon, tetrazole N(1); LY140801: *p*-Cl, naphthalene α-carbon, carboxyl oxygen

gy conformer found in a SYBYL search) using the flexible fit program in SYBYL and then using OVID to calculate the percent of three-dimensional overlap of the critical atoms of each antagonist with the critical atoms of LTD_4 and (2) finding low-energy conformers of both antagonists using the search program of SYBYL and using OVID to calculate the percent of three-dimensional overlap with the critical atoms of LTD_4. The results, shown in Table 1, indicated to us that the antagonist structures might resemble one another in the way suggested. To test the proposed homology between parts of the two antagonists, we synthesized LY137617, in which the hydroxyacetophenone group of LY171883 is replaced by the dichlorophenyl group of LY140801, and we found [3] that LY137617 is indeed a competitive antagonist of LTD_4 in vitro.

In spite of this initial success, we realized that we had proposed one particular correspondence of the LTD_4 and antagonist structures based on little more than a hunch, and that we had not systematically examined other possibilities. This lack of a systematic, unbiased approach for identifying similarities between structures is a well-known gap in the methodology of drug design, and we created SUPER to fill this gap.

A preliminary application of SUPER1 to the LTD_4 and LY171883 structures gave best overlaps that suggested the molecules might resemble one another in that the hydroxyacetophenone group of LY171883 might bind to the same part of an LTD_4 receptor as the triene moiety of LTD_4, the propyl group of LY171883 might bind to the same part of a receptor as the C(1) to C(5) carboxyalkyl chain of LTD_4, and the alkyltetrazole chain of LY171883 might bind to the same part of an LTD_4 receptor as the cysteine residue of LTD_4. SAR evidence supporting this correspondence has been reported by Marshall et al. [10] and by our group [11]. Our earlier suggested correspondence also appeared in the SUPER1 output but with a lower ranking. The observed biological activity of LY137617 is as consistent with the new correspondence as with the old one. The dichlorophenyl moiety of LY137617 corresponds to the triene of LTD_4, the propyl group corresponds to C(1)–C(5), and the tetrazole corresponds to the cysteine carbonyl.

We then used SUPER to compare structures of LTD_4 and LY171883. When the input structures were a low-energy conformer of LTD_4 from a SYBYL search and a conformer of LY171883 flexible fitted to the LTD_4 conformer so that the tetrazole carbon of LY171883 fit the cysteine

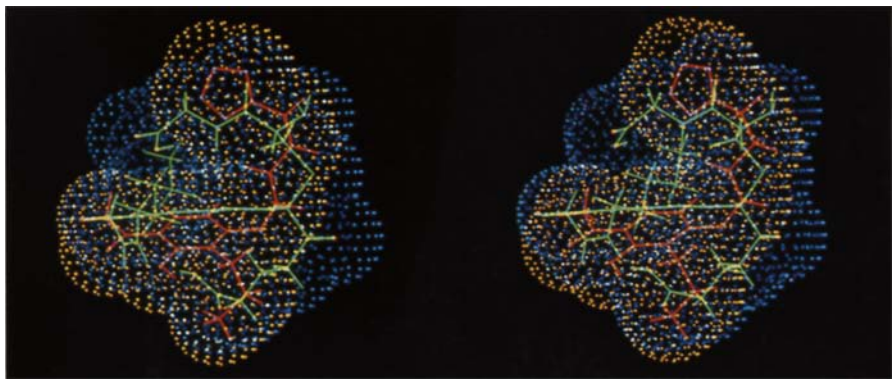

Fig. 2. LTD_4 (green molecule with blue surface) and LY171883 (red molecule with orange surface) in their starting orientations before the SUPER run (view down the z-axis).

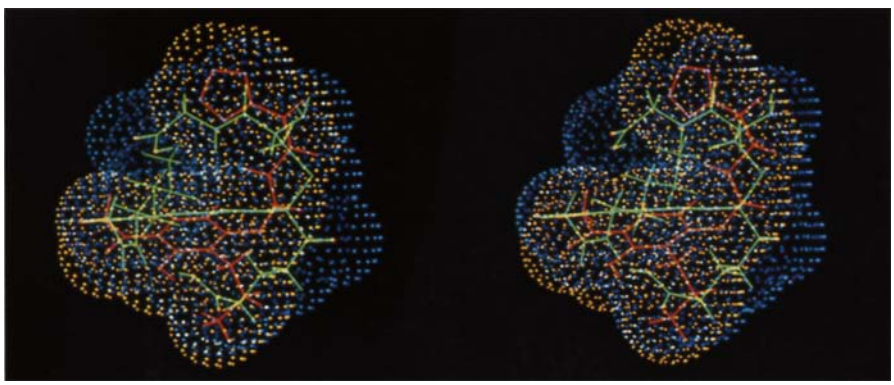

Fig. 3. LTD_4 and LY171883 in their starting orientations (view down the x-axis).

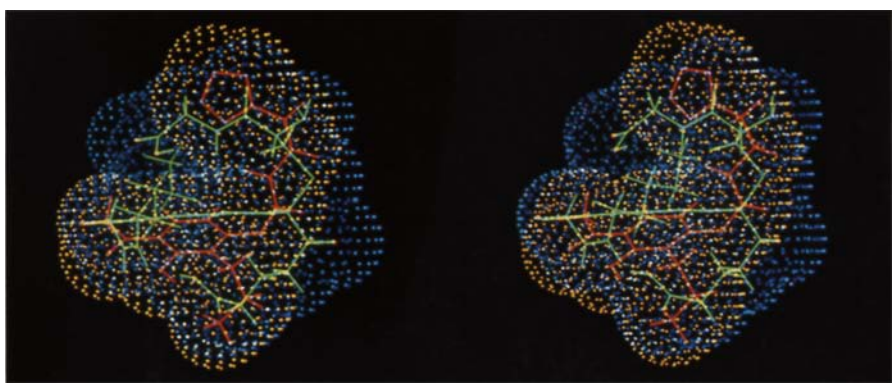

Fig. 4. LTD_4 and LY171883 in their starting orientations (view down the y-axis).

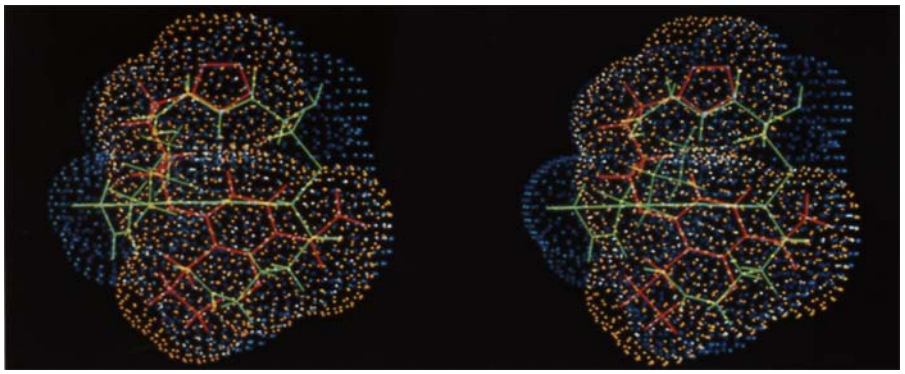

Fig. 5. Best surface correspondence (801 dots) for LTD_4 and LY171883 from SUPER (view down the z-axis)

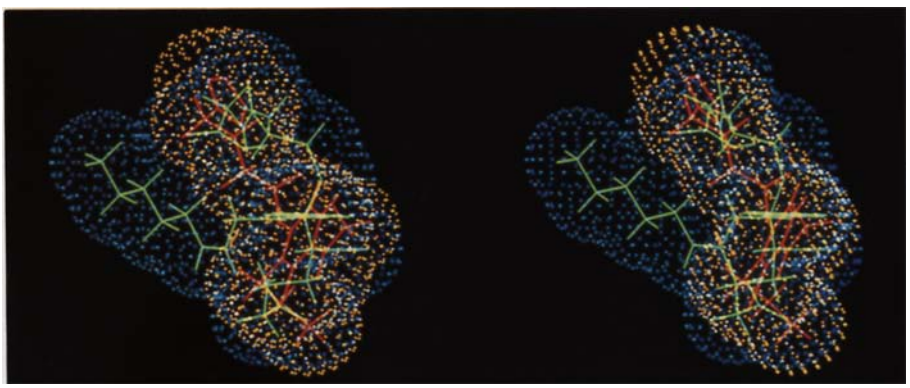

Fig. 6. Best surface correspondence for LTD_4 and LY171883 from SUPER (view down the x-axis).

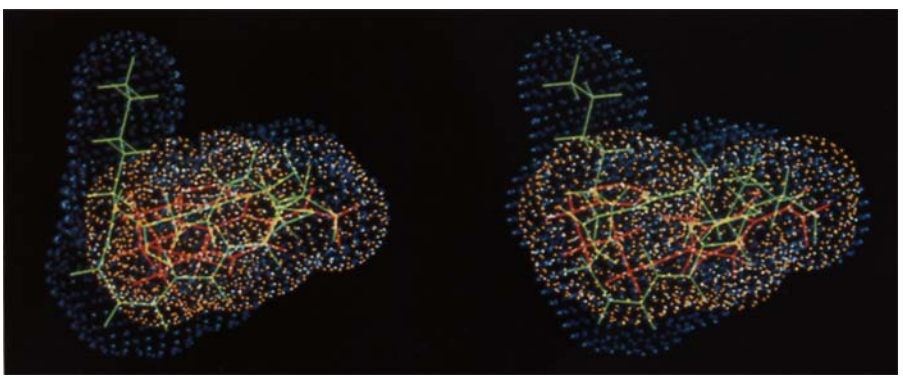

Fig. 7. Best surface correspondence for LTD_4 and LY171883 from SUPER (view down the y-axis).

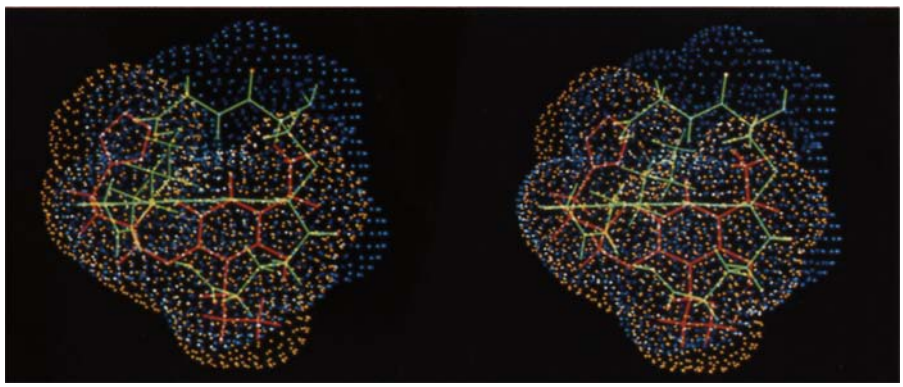

Fig. 8 Sixth-best (692 dots) surface correspondence for LTD_4 and LY171883 from SUPER (view down the z-axis).

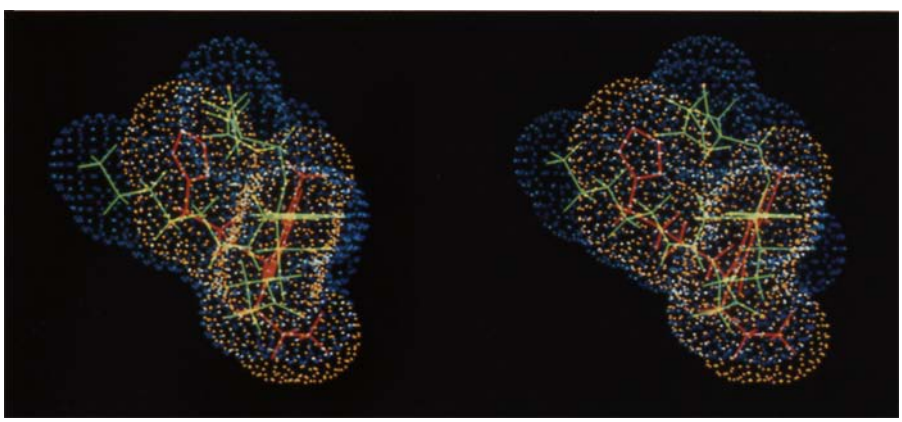

Fig. 9. Sixth-best surface correspondence for LTD_4 and LY171883 from SUPER (view down the x-axis).

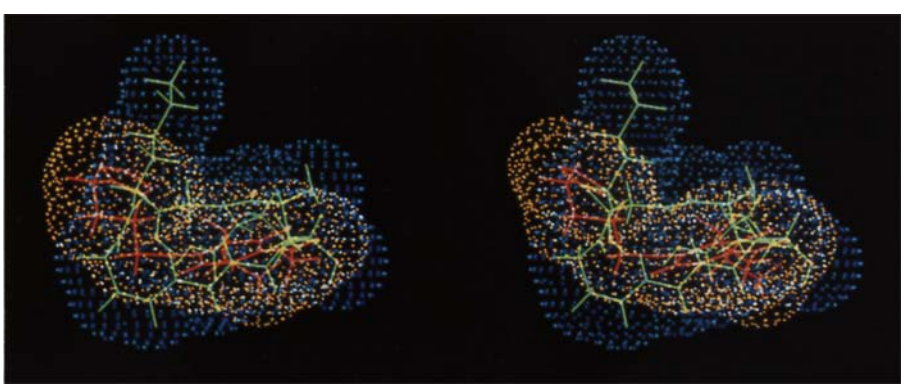

Fig. 10. Sixth-best surface correspondence for LTD_4 and LY171883 from SUPER (view down the y-axis).

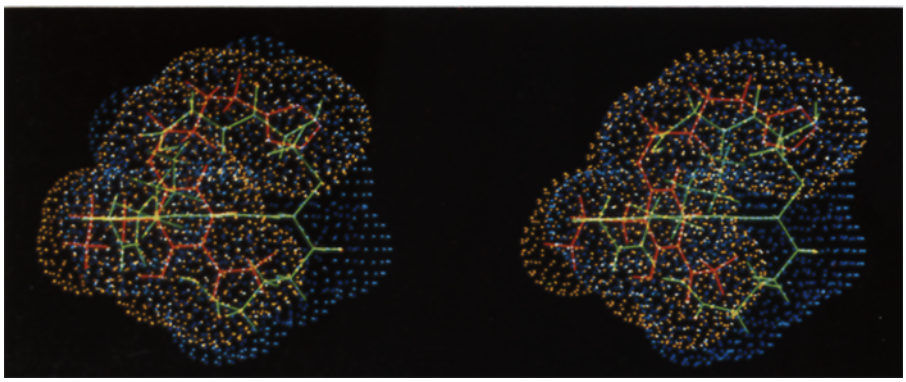

Fig. 11. Eleventh-best surface correspondence (666 dots) for LTD_4 and LY171883 from SUPER (view down the z-axis)

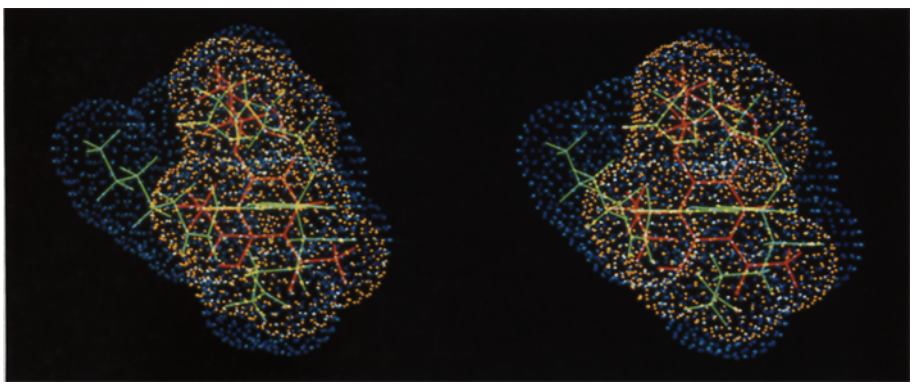

Fig. 12. Eleventh-best surface correspondence for LTD_4 and LY171883 from SUPER (view down the x-axis).

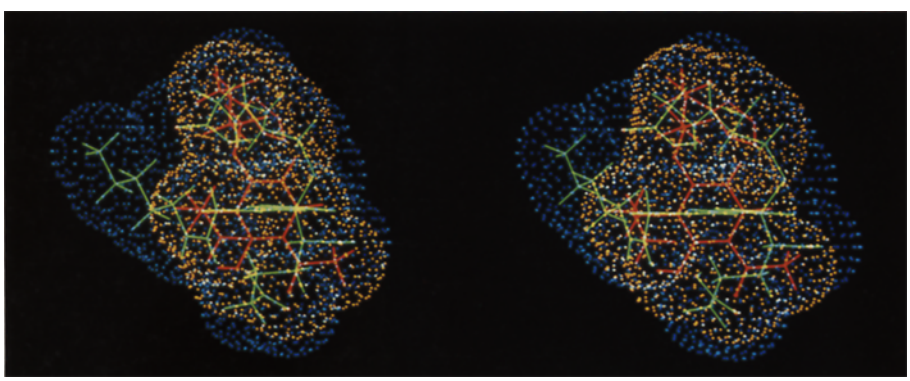

Fig. 13. Eleventh-best surface correspondence for LTD_4 and LY171883 from SUPER (view down the y-axis).

carbonyl of LTD_4, the terminal atom of the propyl group fit C(2) of LTD_4, and the 1- and 4-positions of the phenyl group of LY171883 fit C(8) and C(10) of the triene of LTD_4, the maximum number of surface dot correspondences found was 801. The flexible fitted structures are shown superimposed in Figs. 2–4. The superposition of these two conformers that gave the best surface match is shown in Figs. 5–7. It is obvious from these results that the orientations of the two molecules that give the best match of the molecular surfaces are not the orientations that give the best match of atomic centers, thus demonstrating that SUPER is capable of suggesting possibilities which methods based on matching atomic centers are unlikely to find. Correspondences of two molecules unlikely to occur to a chemist thinking in terms of matching atomic centers may be important in understanding how the molecules interact with the same binding site. The next four matches all resemble the best one. The sixth best correspondence (692 dots) appears in Figs. 8–10, and also bears little resemblance to the flexible fit. The next four matches resemble the sixth best, while another unexpected one appears as the eleventh best correspondence (666 dots), shown in Figs. 11–13.

DISCUSSION

In the often encountered situation where structures of a number of ligands for a receptor are known, but the structure of the receptor itself is unknown, features of receptor binding may be inferred by perceiving critical similarities and differences among the ligand structures. Almost always, however, certain assumptions about the receptor or the mode of binding to the receptor are made. For example, if the receptor and ligand are thought of as binding via atom–atom interactions (rather than lone pairs, etc.), then atom positions and types become important. Assumptions about the importance of some of the atoms may be made. Certain atoms may be thought of as being at a binding site, for example. In these cases, when comparing two molecules, atom centers are often matched via a least-squares fit. It is often useful to consider 'projected binding sites' (i.e., to include with the ligand a receptor atom in the correct relative bound position) as part of the system to be overlapped [12].

In a least-squares fitting method, as opposed to a true overlap algorithm, the molecule is usually represented only by atomic centers. A least-squares fit routine may measure molecular similari-

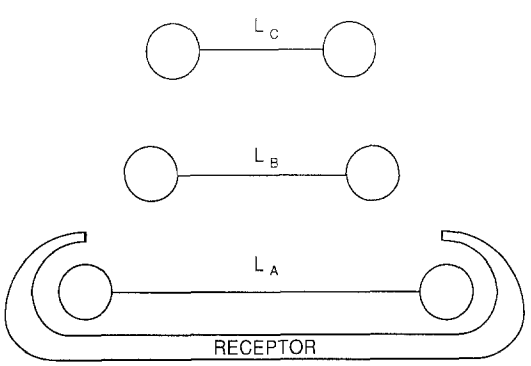

Fig. 14. Comparison of receptor binding using least squares.

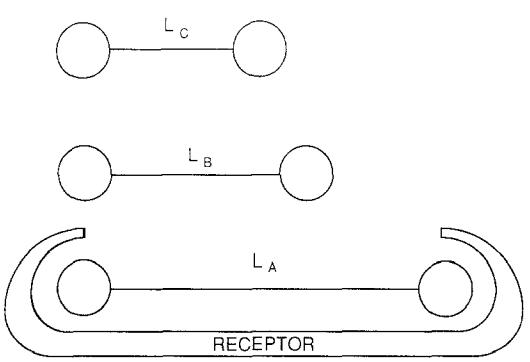

Fig. 15. Comparison of receptor binding using OVID.

ty (as simplified with the use of atomic centers), but it does not result in a comparison which reflects similarity of their binding modes. One would not expect two different ligands to bind in the relative positions predicted by their least-squares fit to each other. This is illustrated in Fig. 14. Least-squares fit would say L_B is better than L_C in looking like L_A because average deviation is less. A least-squares fit takes no account of the receptor. It is of course true that in OVID one must specify which atoms are thought to interact most strongly with the receptor. In Figs. 14 and 15 the spheres are meant to represent the volumes of pharmacophore atoms on the ligands L_A, L_B and L_C. The point being made is that least-squares fitting of the atomic centers of the pharmacophore atoms will split the difference between the centers (Fig. 14), while maximizing the total volume overlap for the pharmacophore atoms can give a different kind of result (for instance, the one shown in Fig. 15. Figure 15 could also have been drawn with L_B right and L_C left, or with L_B left and L_C right, or with both L_B and L_C right).

The program OVID first does a least-squares fit to position the molecules, then maximizes the total volume overlap. This yields a comparison which is more representative of the mode of binding, as illustrated in Fig. 15.

We frequently propose correspondences between parts of apparently dissimilar molecules, usually based on pharmacological or enzymological evidence that the molecules must be able to resemble one another because they bind to the same receptor or enzyme active site. The first reasonable looking correspondence that the investigator discovers may not be the correct one, however, and so we felt that we should be able to examine all of the possible correspondences between two molecules to be certain that we consider the correct one.

The chief feature of SUPER which we find to be most useful and unique among existing overlap programs is its ability to blindly and systematically search for and find similarities that are likely to be relevant but which may not be obvious. Even when no specific information is available, in general it is still true that due to the nature of molecular interactions, the boundary region of the ligand is the most important part. Thus, an arbitrary search based only on this feature often turns up new and surprising modes of correspondence.

In its current version, SUPER only works on a single conformation of each of the molecules whose surfaces are being compared. To thoroughly explore the possible correspondences between the molecules, it is necessary to compare a number of conformers of each molecule. The maximum number of surface dot correspondences found for each pair of conformers can be used to compare the degree of surface correspondence for different pairs. In the ongoing leukotriene study the 801 dot correspondence reported here is the best result that has been found thus far. SYBYL flexible fit structures, low-energy structures from SYBYL searches or other conformation searching procedures, X-ray structures, and commonly occurring conformations from molecular dynamics runs are likely sources of input structures for SUPER. It is also necessary to keep in mind that since SUPER works with static structures (i.e., dihedral angles which do not change during a SUPER run) identical mirror image conformers of molecules that are not optically active are not equivalent in SUPER and produce different results. The inability of SUPER to explore conformational flexibility while doing an overlap is a shortcoming that will be addressed in a future version, but for the time being SUPER should be applied to several different conformers of each molecule when a reasonably comprehensive list of possible correspondences is desired.

The number of times that the molecules are translated in the course of a SUPER run is dependent on the shapes of the molecules. For example, to include overlap of a small molecule with both

ends of a long molecule requires a larger number of translations compared with two molecules of similar size. While this approach is somewhat time consuming, it preserves the systematic and unbiased spirit of SUPER as a brainstorming tool.

SUPER does not use any measure of the ability of a portion of a molecular surface to participate in hydrogen bonding. The partial charges coded onto the surfaces used by SUPER serve to achieve gross alignment of the molecules necessary for binding to the same site, but a more refined match might be obtained if each surface dot were also assigned a new variable which would measure the ability to donate or receive a hydrogen bond. Hydrogen bonding will be incorporated into our next version of SUPER. This consideration of surface shape, charge, and hydrogen bonding ability would then take into account the main factors that operate in molecular recognition.

CONCLUSION

The need to be able to perceive relevant similarities between structures that bind to the same site has led to the evolution of a new computer program, SUPER, which has proven to be a practical brainstorming tool. SUPER will examine the possible correspondences between dot surfaces of two molecules in an unbiased and systematic way, and produce pictures of the best correspondences for that pair of structures ranked according to the number of surface dot correspondences. This process reduces the likelihood that a relatively poor correspondence will be accepted as a working hypothesis because alternatives which may be superior were not considered.

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