Searching for geometric molecular shape complementarity using bidimensional surface profiles

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The study presented herein is a bidimensional approach to the complementarity of two molecular surfaces. From two chosen sections we have established a methodology of generating the optimal matching of two shapes. Our approach consists in describing two molecular surface sections by a shape vector (the angular profile), in finding their matching patterns by comparison of the two profiles, and in optimizing the relative locations of the two sections in two-dimensional space, using rotations and translations defined by geometric characteristics. The set of optimal configurations are successively displayed on a screen. Satisfying results have been obtained for the matching of the complex kallikreine A-trypsin pancreatic bovin 2. This efficient method could be used as a preprocessing for a tridimensional shape complementarity approach between two molecular surfaces.

Keywords: complex formation, molecular surface, matching pattern, section complementarity

INTRODUCTION

In molecular biology, the important notion of *complex* is defined as the interaction between two molecules. Two molecules constitute a complex if they exhibit a high affinity that is partly due to close contact of the molecules. In biological reactions, complexes are constituted between a protein and a ligand in enzymology, an antibody in immunology, or an inhibitor in drug design. The analysis of the interacting molecule surfaces shows shapes fitting spatially, like a key in a keyhole. In 1944, Pauling[1] had already noticed that the efficiency of the weak interacting forces is related to the complementarity of the shapes. Consequently, the affinity of a molecule to another is partly explained by this spatial aspect. Other phenomena, such as electric potential, energetic relationships, and chemical reactions have high impact, but may be excluded from a first approach of the complex analysis.

The problem is a part of the three-dimensional (3D) molecular analysis and recognition. Software for molecular graphics was developed to visualize and manipulate the molecules to allow the study of the surface properties and their putative complementarity.[2–4] However, visual surveys are imprecise. Quantitative approaches consist of first characterizing the surfaces features, above all their knobs and holes,[5] and then verifying the matching of two surfaces by packing complementary shapes together. For each molecule location, a fitting criterion is calculated and optimized to define the best docking.

The coordinates of the molecular surface points can be taken to find the best docking of two molecules. A procedure combining a Monte Carlo search with rapid energy evaluation using molecular affinity potentials is performed.[6] However, this method is time consuming. Hence, there is a necessity to simplify the studied surface (in general, assuming the rigidity of the molecule); this requires the definition of specific descriptors, either local or global. In the first class of descriptors, a region may, for instance, be described by its fractality, calculating by recoding each residue with its fractal indice.[7] High regional fractality, which is known to be related to high reactivity, contributes to determine matching regions. The solid angle[8] is a local geometric descriptor of a volume, varying in the range $0–4\pi$ radians, that allows the definition of concave and convex regions.[9] Two other geometric descriptors useful for concave region characterization are the radius of a sphere tangent to two surfaces points[10] (the docking is performed by minimization of a distance between the sphere centers and then optimized to reduce the overlaps), and the density of the surface neighborhood.[11]

A global descriptor may be derived from the Fourier series. Each molecular surface is defined by the vector of the Fourier coefficients. Then, the matching of the two surfaces consists of minimizing their difference vectors.[12]

To facilitate the observation of the measure, it is possible to perform a projection of the molecular surface on a particular geometric shape, such as ellipsoid[13, 14] or sphere.[15] These methods are essentially used to study globular proteins, avoiding the folding problem. The approach of a gnomonic projection[15] allows the suppression of the shape distortion

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problem, which occurs when using the projection on an ellipsoid. A possible strategy for obtaining the best docking consists of an iterative minimization process based on two steps: the two molecules are displaced in a random way; for each location, a criterion provides an evaluation of their docking. This allows one to find the optimal matching positions.[15]

In this paper, we present only a first stage for the determination of the complementary regions between two molecular surfaces and their optimal match. In fact, we study the surface sections' complementarity. The study is limited to a two-dimensional (2D) complementarity search that will be a preprocessing for a three-dimensional (3D) docking. The process consists of three steps:

(1) The choice of a shape descriptor, invariant in a reference; i.e., its geometric property is independent of the shape points coordinates (like perimeter, area, curvature).
(2) The determination of an exhaustive list of the local matching patterns.
(3) The global optimization of the relative locations of the two sections—the iterative optimization is "aided," which means that information is extracted from the shapes to improve the section complementarity at each iteration.

METHODS

Generalities

The morphological complementarity between two molecules is essential for the complex formation. Only this aspect is treated here, neglecting electrostatic or energetic affinities. We will present the three stages of the method: the definition of a section descriptor from the angular deviation along a polygonal line; the extraction of complementarity patterns between sections; and the search for an optimal position of the sections.

Definition of a section descriptor A molecular surface, as implemented by Connolly's program[16] is a collection of points and vectors normal to the surface at each point. Suppose a plane is passing through the molecule, with the points at the intersection defining a 2D contour; this is the section we consider.

The contour descriptor should be independent of the coordinate system and the origin, but the points' coordinates depend on a reference system. So we have to define a contour descriptor: the angular deviation. The descriptor should have a value for any point of the molecular surface.

A polygonal line as contour The section contour defined by a set of irregularly spaced points is transformed into a regular closed polygonal line (i.e., the distance of two successive points is taken equal to a constant r to reproduce the local variations of the contour). The polygonal line of $(n + 1)$ equally spaced points P_i, with i varying from 0 to n, takes support on the observed points series M_j of the section contour. The starting point P_0 is fixed identically to an arbitrary observed point M_0. If we assume that the ith point P_i of the polygonal line belongs to the segment $[M_{j-1}, M_j]$, the position of the next point, P_{i+1}, is searched. If the distance between P_i and M_j is more than the step size r, then P_{i+1} belongs to the same segment $[M_{j-1}, M_j]$. In the opposite case, the procedure is repeated up to find a point M_{j+k} $(k \geq 1)$ such that the distance between P_i and M_{j+k} is more than r, so P_{i+1} belongs to the segment $[M_{j+k-1}, M_{j+k}]$. The last point of the polygonal line is built to constrain the distance between the last point, P_n, and the first point, P_0 (i.e., $d(P_n, P_0) = r$).

Local quantification of the contour: angular profile For each point P_i, the oriented angle Ψ_i defined by three consecutive points (P_{i-1}, P_i, P_{i+1}) of the polygonal line is calculated; $\Psi_i = (\overrightarrow{P_iP_{i+1}}, \overrightarrow{P_iP_{i-1}})$ if $i \neq 0$ and n. The resulting vector of internal angles $(\Psi_0, \Psi_1, \ldots, \Psi_n)$, varying between 0 and 2π, is called "angular profile." The signal, Ψ_i versus i, is a periodic function. In general the signal shows an additional random noise due to the approximation by a polygonal line. To eliminate this artefact, smoothing via a moving average is performed. Now we can compare the two sections descriptors to define the local shape complementarity.

Extraction of complementarity patterns between sections A pattern is defined as a set of points, locally located in the surface section. Pattern size may be variable. The interesting ones are those of high local concavity or convexity. We define precisely a pattern as a series of consecutive points of the polygonal line. It is characterized by the index of its starting point on each profile, and by its size, i.e., the total number of selected points. The size L is user-defined relative to the relevant points in the descriptor (usually, L varies between 5% and 10% of the contour length). As the two sections are characterized by their angular profiles, the determination of complementary regions or patterns may be carried out by a local comparison of the two angular profiles.

Search for the complementary patterns For a given pattern size L, all the possible relative locations of the two sections are performed, and the local similarity between two angular profiles fragments is tested. The angular profile associated with the so-called "moving section" is displaced relative to the angular profile associated with the so-called "reference section." A complementary-angles signal (i.e., for θ_i, one takes $2\pi - \theta_i$) is taken as information for the moving section, since an internal angle of the reference section should correspond to an external angle of the moving section for a complementary study (Figure 1).

Definition of a dissimilarity measure between matching patterns A local dissimilarity measure is defined to be minimal when the two patterns of same size L are of complementary shape and maximal when they can not match. It equals the square mean of the angular differences:

$$D(i,j) = \frac{1}{L}\left(\sum_{k=0}^{L-1} (\Psi_{i+k} - \theta_{j+k})^2\right) \quad (1)$$

Here Ψ_{i+k} (θ_{j+k}) is the $(i + k)$th value of the angular profile on the reference section (resp. $(j + k)$th on the moving section), and L is the size of the matching patterns.

The selection rule of a pair of matching patterns between the two sections is as follows: the pattern of size L beginning at the index i on the reference section is complementary to the pattern of size L beginning at the index j on the moving section if the dissimilarity measure $D(i,j)$ is less than a user-defined threshold D_0. A matching pattern is defined as a set of consecutive point pairs taken on the reference and moving

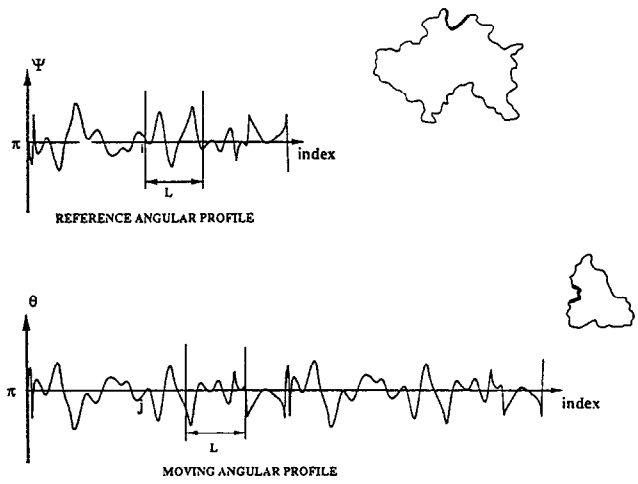

Figure 1. Determination of the complementary zone of size L *between two sections from the angular profiles. For each index* i *and for each size* L *of the pattern, by varying the index* j *between 1 and* 2n-*1 in the moving angular profile, the value* D(i, j) *of the mean of the squared angular deviation is calculated. This simulates a displacement of the moving section relative to the reference section.*

sections that satisfy this rule. The patterns are successively stored with their sizes and their starting indexes. Also, those included in a larger file are deleted to eliminate the information redundancy in the complementarity pattern file.

Search for an optimal position When fitting the matching patterns of the two surfaces defined in the preceding search, overlap domains can appear. A molecular contact is defined as unacceptable if the overlap domains are too large. The procedure necessary to obtain the best fit between sections consists of moving a section (the smallest one) relative to the other, maintaining the docking and reducing the overlapping. The process consists in two stages: an initial matching of the section, which requires the determination of the location parameters for the translatory motion and rotation, and the adjusting stages.

Initial matching of the sections A rotation and a translatory moving applied to the moving section are necessary to obtain the initial optimal fit of a given matching pattern formerly obtained. These geometric transformations are defined by the value of $\Delta\phi$, rotation angle around the mean point Ω of the moving section pattern, and the coordinates of the translatory vector $\vec{\mathbf{T}}$ (Figure 2). The new positions of the moving section points after displacement are defined by the vectorial equation:

$$\overrightarrow{OQ'_{j+k}} = \vec{T} + R(\Omega, \Delta\phi)\,\overrightarrow{\Omega Q_{j+k}} \tag{2}$$

where O is the origin; $R(\Omega, \Delta\phi)$ is the matrix operator indicating the rotation of center Ω and of angle $\Delta\phi$; and Q_{j+k} (Q'_{j+k}) is the $(j + k)$th point of the moving section before (after) displacement.

The chosen criterion S for the parameters determination is the minimization of the pattern interpoint distances. The pattern begins at the points P_i and Q'_j on the reference and moving section, respectively, and has the size L:

$$\epsilon(i,j) = \sum_{k=0}^{L-1} (\overrightarrow{Q'_{j+k}P_{i+k}})^2 \tag{3}$$

where (P_{i+j}, Q'_{j+k}) is the kth pair of complementary points (k varies from 0 to $L - 1$), respectively, taken on the reference and on the moving sections; i and j are the starting indexes of the pattern; and L is the size of the pattern.

The optimal values of the translatory vector $\vec{\mathbf{T}}$ and the rotation angle $\Delta\phi$ must correspond to the minimum of the criterion. By derivating $\epsilon(i, j)$ relative to the parameters, we obtained the expressions of the translatory vector $\vec{\mathbf{T}}$ and of tan $\Delta\phi$.

$$\vec{\mathbf{T}} = \frac{1}{L}\left(\sum_{k=1}^{L} \overrightarrow{Q_{j+k}P_{i+k}}\right) \tag{4a}$$

and

$$\tan\Delta\phi = -\frac{\left|\sum_{k=1}^{L} \overrightarrow{Q'_{j+k}P_{i+k}} \times \overrightarrow{Q_{j+k}\Omega}\right|}{\sum_{k=1}^{L} \overrightarrow{Q'_{j+k}P_{i+k}} \cdot \overrightarrow{Q_{j+k}\Omega}} \tag{4b}$$

where P_{i+k} (Q_{j+k}) is the point of the pattern on the reference section (moving section), L is the pattern size, $|\vec{\mathbf{u}}|$ denotes the modulus of the vector $\mathbf{u}$ and $\vec{\mathbf{u}} \times \vec{\mathbf{v}}$ ($\vec{\mathbf{u}} \cdot \vec{\mathbf{v}}$) denotes the vectorial (scalar) product of the vectors $\vec{\mathbf{u}}$ and $\vec{\mathbf{v}}$.

$\vec{\mathbf{T}}$ is the mean displacement between the complementary points pairs. Applying the translatory moving and the rotation, the moving section is docked to the reference section. However, the result is not, in general, acceptable since overlap zones appear.

Adjusting stages of the moving section relative to the reference section The last step consists of displacing the moving section to reduce the overlap zones, avoiding the destruction of the matching. The process is iterative and consists of repeating successively two procedures: the rede-

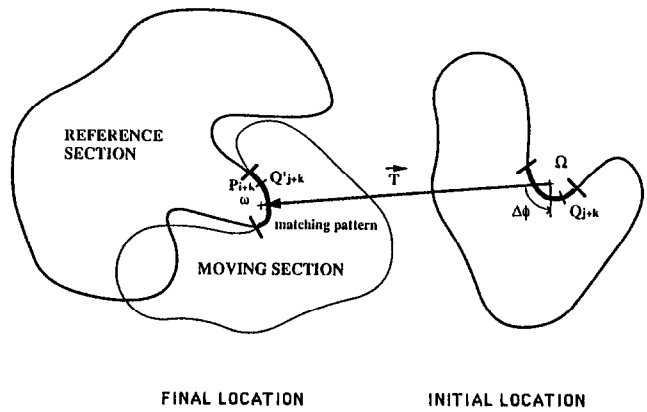

Figure 2. Initial matching of the two sections: Ω, *mean point of the pattern on the moving section;* ω, *mean point of the pattern on the reference section;* $\vec{\mathbf{T}}$, *translation vector* ($=\vec{\Omega}\omega$); *and* $\Delta\phi$, *rotation angle.*

finition of the matching patterns, and the adjustment of sections by displacement of the moving section. The displacement of the moving section is carried out by a rotation around the pattern mean point Ω and by a translatory motion $\vec{t}$.

A matching pattern is now defined as a region where the two sections are closer than a user-defined value Δr. It may be composed of several motifs (Figure 3).

To define a criterion allowing an "aided optimization," it is necessary to characterize different parameters: the matching area A_m is the surface included between the two sections on the matching pattern, the overlap area A_o is the surface of overlapping of the two sections, the hole area A_h is the surface between the two sections which is not A_m or A_o. Figure 4 shows all the characteristics of the overlap and contact areas between the two sections.

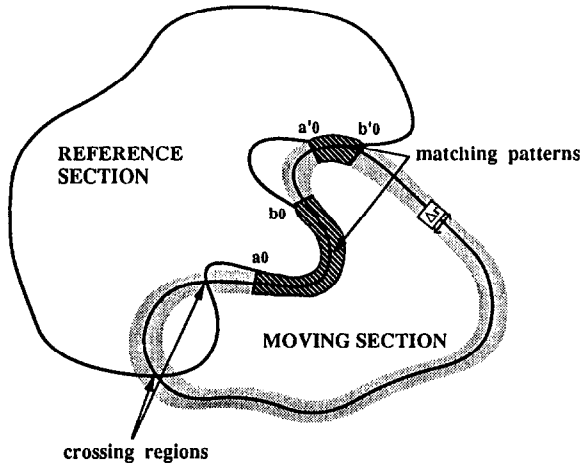

Figure 3. Redefinition of the matching pattern. The two sections have matching patterns when they are closer than Δr.

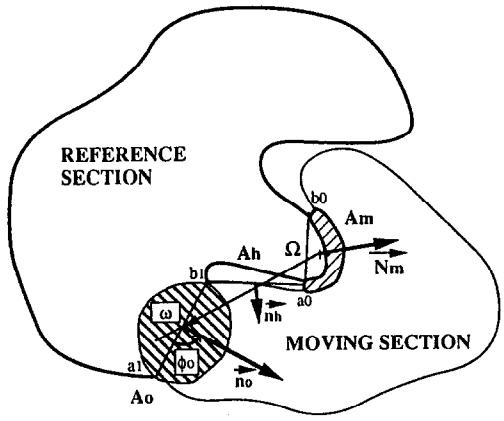

Figure 4. Characterization of the contacts between the two sections: Ω, *mean point of the pattern on the reference section;* A_m, *matching area (defined by the couple of points of the pattern);* $\vec{N}_m$, *unitary vector normal to the matching area, perpendicular to the line* (a_0, b_0); ω, *middle of the segment* $[a_1, b_1]$; A_o; *overlap area;* $\vec{n}_o$, *unitary vector normal to the line* (a_1, b_1); ϕ_o, *angle between the vector* $\vec{\Omega\omega}$ *and the normal vector* $\vec{n}_o$; A_h, *hole area; and* $\vec{n}_h$, *unitary vector normal to the line* (b_1, a_0).

To displace the moving section, some rules are used: maintain the contacts (i.e., reduce the matching area A_m) and reduce the overlap area A_o. Another type of parameter is introduced, the hole areas A_h, which are to be filled in. The holes are surrounded with overlap or matching zones. Also between two overlap regions, the sections show either a hole or a matching region. The displacements to be defined must reduce the whole set of areas. The chosen criterion, called *lack of fit* (LOF), is the weighted sum of the different areas:

$$LOF = p \sum_{o=1}^{O} A_o + q \sum_{h=1}^{H} A_h + \sum_{m=1}^{M} A_m$$

where p is the overlap weight, q is the holes weight, and O, H, and M are the zone numbers of overlapping, hole, and matching, respectively.

The solution is optimal when after a given number of successive steps, the criterion has no longer decreased. So, an equilibrium state is considered found. To reduce the criterion, at each step a translation $\vec{t}$ and a rotation of angle α around Ω are carried out on the moving section. The translation vector $\vec{t}$ and the rotation angle α are defined by the following expressions:

$$\vec{t} = k \frac{p \sum_{o=1}^{O} A_o \vec{n}_o - q \sum_{h=1}^{H} A_h \vec{n}_h - \sum_{m=1}^{M} A_m \vec{N}_m}{p \sum_{o=1}^{O} A_o + q \sum_{h=1}^{H} A_h + \sum_{m=1}^{M} A_m} \quad (6a)$$

$$\alpha = \Delta\alpha \frac{p \sum_{o=1}^{O} A_o \sin \phi_o - q \sum_{h=1}^{H} A_h \sin \phi_h}{p \sum_{o=1}^{O} A_o + q \sum_{h=1}^{H} A_h} \quad (6b)$$

where k is the scale parameter of the translatory vector and $\Delta\alpha$ is the scale parameter of the rotation angle.

To maximally reduce the overlapping areas, a translation must be performed in the direction of the normal vector $\vec{n}_o$ and its modulus must be proportional to the area A_o (considered as a geometric area, so positive). Furthermore, to reduce the hole areas, the translation must be performed in an opposite direction of the normal vector $\vec{n}_h$ of each region and be proportional to the area A_h (considered positive). In return, the translation must be opposed to the extension of the matching area A_m, so it must act in the contrary direction of $\vec{N}_m$, the local normal vector. The sign of A_m is positive if the contact points on the moving section are exterior to the reference section, and negative otherwise. So the translatory vector $\vec{t}$ is proportional to a weighted sum of these vectors (see the numerator of the Expression 6a). Normalizing this quantity by the lack of fit *LOF* (similar to an area), the parameter k of the Formula 6a is independent of the areas. Practically it is chosen sufficiently small that the translation is of little variation at each optimization iteration.

The rotation efficiency for the overlapping area A_o is maximal when the vector $\vec{n}_o$ is orthogonal to $\vec{\Omega\omega}$; i.e., the sine of the angle ϕ_o (angle between $\vec{\Omega\omega}$ and $\vec{n}_o$) is close to +1—likewise, when the surface A_o is large. The same rule is taken

to calculate the influence of the hole area, inducing a rotation in the inverse direction, hence the expression of the Formula 6b. The parameter $\Delta\alpha$ is an angular variation, it is chosen to be small to avoid a large modification of the relative locations of the two sections.

RESULTS: APPLICATION TO THE STUDY OF THE COMPLEX PROTEINASE INHIBITOR

The method is applied to the section complementarity study of the complex proteinase inhibitor: kallikréine A-bovine pancreatic trypsine 2. The complex is visualized in three dimensions with help of the graphic software MANOSK.[2] The active site of the complex is known and can be displayed. The general purpose is to determine other complementarity zones between the two proteins.

The matching patterns are determined by a bidimensional analysis of the two sections. To determine the sections, a plane intersecting the protein surface is chosen. The plane is chosen to display a large part of the proteins, so that the active site is well defined. Figure 5 shows the two sections to be matched; in the chosen plane, the active site appears like an association concave and convex zones.

The sections are transformed into polygonal lines, and the step size is chosen sufficiently small to approximate correctly the contours; the latter depends on the density of points on the Connolly's surface.

Pattern adjustment

The complementary patterns are then determined for a threshold value (2%) of the criterion equivalent to a mean angular deviation of 0.14 rad (18°). Patterns whose size varies from 5% to 20% of the smaller section size (i.e., that of the moving shape) are searched. The larger pattern found corresponds to a value of 15%.

The two sections are initially matched according to their complementary patterns. Then, the last stage is carried out. The twelve best optimal locations of the sections are shown in Figure 6. Some remarks can be deduced:

(1) Some patterns have initial positions quasi identical to the final one. The matching is either perfect without overlapping, or with overlap zones, which do not allow a displacement without disturbing the matching. This is when the initial length pattern is large. A special case corresponds to a matching that is not realistic; the two sections are nearly superimposed—no movement for the fit is acceptable.

(2) For some patterns, the fit procedure is necessary to reduce the different zones of overlapping, keeping intact the matching.

(3) Some patterns are of no interest, since the interactions between two sections are not sufficient.

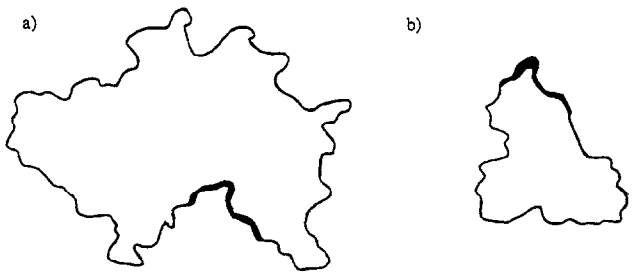

Figure 5. The molecular surface sections of the kallikreine A (a) and its inhibitor, the bovine pancreatic trypsine inhibitor 2 (b). The experimentally determined contact zone is indicated with a thick line.

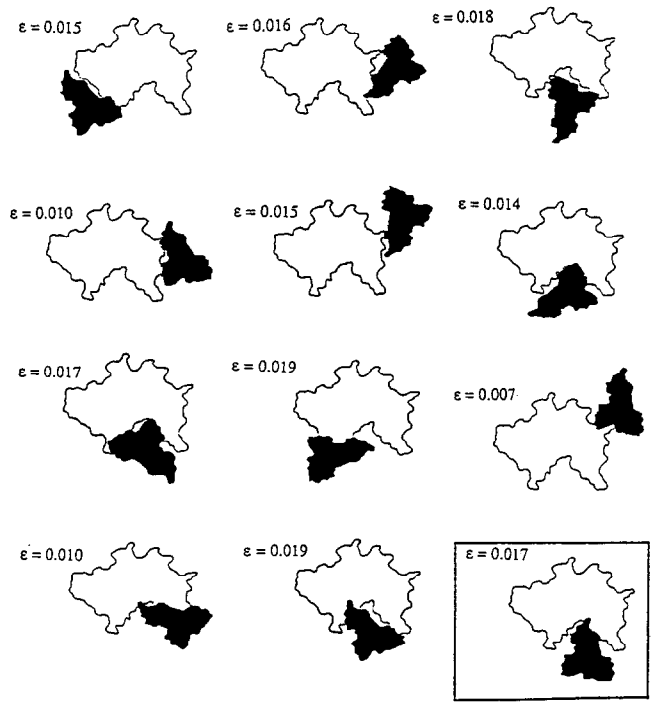

Figure 6. Set of optimal fits between the two sections: ϵ is the dissimilarity measure between the matching patterns.

The algorithm finds the real solution with an initial criterion value of 0.017. This does not correspond to the best matching according to our criterion.

Influence of the weights p and q

The parameters p and q are introduced in the criterion controlling the section fit to balance, respectively, the effects of the overlaps and the holes on the displacements.

Figure 7a shows an initial location of the moving section, where the overlap is very important. So to reduce it, p is taken greater than $n(p > q)$ (it is more important to reduce the overlap than the hole). The moving section is mainly rotated around the pattern, a hole appears, but the overlap area is reduced (Figure 7b). Thus the hole must be reduced, so q is taken greater than p $(q > p)$. This allows an important translation of the moving section (Figure 7c). To finish the fit, p and q are taken equal, so the hole and the overlap areas are maintained at the same level. The final section location is quite interesting (Figure 7d). Note that after each displacement of the moving section, the matching pattern is redefined; it may be constituted of several patterns.

With other values of the parameters, the result will be quite

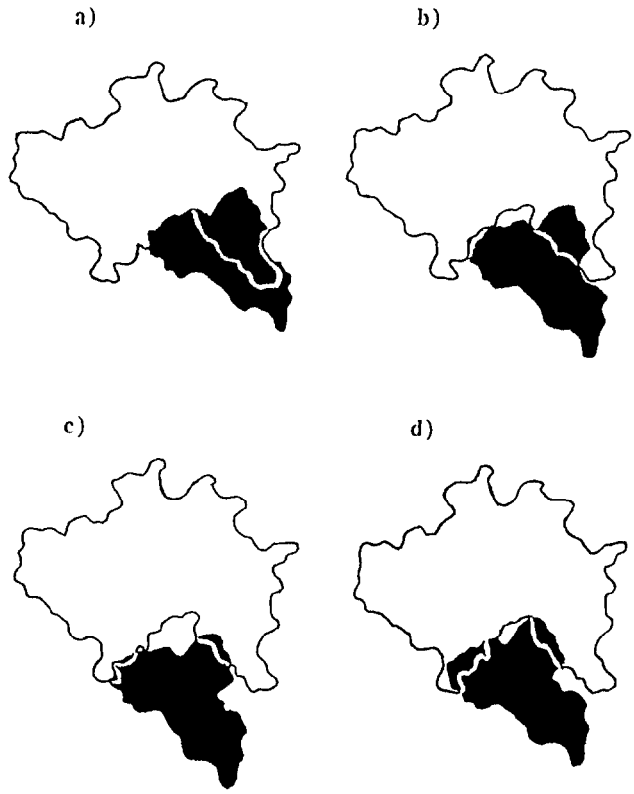

Figure 7. Example of a series of movements depending on the choice of the weight p *and* q *of the LOF criterion (see text).*

different, and will depend on the fixed target: reduction of overlap or hole area, or increase of the matching area. It is possible to define different strategies of fit by modifying the weights p and q during the procedure. We have shown one among several others.

The method is implemented on a PC-AT. For these two sections, it takes about 20 minutes to obtain the whole set of the matching solutions.

CONCLUSION AND PERSPECTIVES

The problem of the fit of two bidimensional molecular surface sections has been completely studied:

(1) The surface sections are represented by polygonal line contours, then transformed into "angular profiles."
(2) The local comparison between these descriptor vectors, (i.e., angular profiles) internal angle series for the reference section and external angle series for the moving section allows one to define a complementary patterns file between two shapes.
(3) A third stage consists of matching the sections in the complementary pattern region by minimizing the interpoint distance of the patterns.
(4) A global fit is performed by successive rotations and translations, automatically defined on the basis of the matching, hole, and overlap areas. This last step allows one to verify if the local complementarity defined in Step 3 is compatible or not with a global fit.

The method applied to the 2D complementarity analysis gives correct results. The obtained patterns are effectively complementary zones. A preview study on two manually constructed complementary sections allows one to test the exhaustiveness of the search. However, this demonstrated that the morphological complementarity should be completed with a notion of energy optimality. The movements, translatory motion, and rotation are simple and give an efficient adjustment of the sections.

It is easy to transpose the method to the shape similarity studies: the pattern search consists of taking the original signal (internal angles) for the two sections, and not the complementary one (external angles), at the comparison step. The fit in this case lies in the maximization of the overlapping areas.

With a criterion improvement by introducing electrostatic or energetic properties or geometric characteristics (holes and knobs), a more realistic selection of matching patterns will probably be found.

The method provides improvement in the final adjustment of two molecules for a complex formation. Choosing different sections on the two molecules, it could compare each couple of sections and determine the 3D complementary zones. The problem is to define the selection strategy of the sections on each molecule. For example, a first analysis of the molecules' local convexity allows the determination of the planes where the holes and the knobs are significantly important. In conclusion, this method could be used as preprocessing for a tridimensional study of the shape complementarity between two molecular surfaces.

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