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SERF: A program for accessible surface area calculations

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The program SERF has been designed to facilitate the greater use of accessible surface area calculations in the analysis of protein structure, including analysis of surface area changes on binding and complexation. For comparative purposes, the program implements a number of alternative methods for calculating surface areas, including those that approximate residues by single spheres. Algorithmic details, comparative performance, and the software implementation of SERF are discussed. © 1998 by Elsevier Science Inc.

Keywords: molecular surfaces, accessible surface area, macromolecular complexation, sphere packing

INTRODUCTION

Since its introduction by Lee and Richards,[1] the concept of the accessible surface area (ASA) has proved to be a powerful, if somewhat underused, means to analyze the structures and interactions of proteins and other molecules.[2,3] For example, accessible surface areas have been used to calculate so-called hydrophobicity scales, which characterize the relative preference of particular amino acids for the solvent-exposed surface of proteins or for their inaccessible interiors,[4–6] to examine the association of oligomeric proteins,[7] and to discriminate between correct and incorrect protein models.[8,9]

Although the notion of accessible surface area has found many different, and often sophisticated, applications, its general use is not as widespread as it might be, despite the availability, in the public domain, of several programs implementing some form of surface area calculation. Table 1[10–15] lists a number of such programs.

The following describes the program SERF, which has been designed to facilitate the greater use of accessible surface areas in protein structure analysis, particularly analysis of surface area changes on binding and complexation. For comparative purposes, the program implements a number of alternative methods for calculating surface areas. Details of these different algorithms, their relative performance, and their software implementation within the program are discussed.

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Received 28 July 1997; revised 26 September 1997; accepted 30 September 1997.

A PRIMER ON SURFACE AREA CALCULATIONS

Several types of surface and surface area calculation have been proposed. Concepts and methods relevant to SERF are reviewed below. Richards[2] defines several closely related, yet distinct, types of surface:

1. The van der Waals surface is simply the exposed surface of a set of fused spheres, whose radii are the van der Waals radii of the atoms they represent.
2. The accessible surface (AS) is the surface obtained by rolling a spherical probe, such as a solvent atom, over the van der Waals surface of each atom.
3. The molecular surface (MS) is somewhat more complicated and may be viewed as being composed of surface patches of two types: the contact surface and the reentrant surface. The contact surface is that part of the van der Waals surface that is fully exposed to a probe sphere. The reentrant surface is defined by the inward facing part of the probe sphere when it is in contact with more than one atom simultaneously.

These three types of surface are defined graphically in Figure 1. Although algorithms exist for the calculation of the area of molecular surfaces,[16,17] the following deals only with the accessible surface. Many algorithms have been proposed to allow the determination of ASAs; most make use of the fact that the accessible surface can be obtained from the van der Waals surface by increasing the radius of each atom by the radius of the probe sphere: all intersections of this surface with itself are inaccessible to solvent. By summing the exposed areas and by appropriate scaling of the results, the total accessible area is obtained. All such methods make the assumption that a molecule can be adequately represented as a simple ensemble of points in three dimensions and that their surfaces and volumes can be modeled using a set of fused hard spheres centered on those points and having appropriate atomic radii. This assumption simplifies considerably the task of constructing surfaces and calculating their areas; however, it presupposes a view of

655 Avenue of the Americas, New York, NY 10010
1093-3263/97/$17.00
PII S1093-3263(97)00082-X

Table 1. Some software for accessible surface area calculations[a]

Program	Language	Availability	Ref.
ACCESS	Fortran	CCP4	1
ANAREA	Fortran	CCP4	10
AREAIMOL	Fortran	CCP4	1
MOLAREA	Fortran	QCPE	11
MOLSV	Fortran	QCPE	12
MSEED	Fortran	QCPE	13
MSMS	C	Scripps	14
MSP	C	Biohedron	15
NACCESS	C	UCL	1
SAREA	Fortran	QCPE	11
SURFACE	Fortran	CCP4	1

[a] Listing of accessible surface area calculation programs available via the Internet. Restrictions on availability vary between software. The generality of implementation also varies between different programs. URLs: UCL—http://www.biochem.ucl.ac.uk; QCPE—http://www.osc.edu/ccl/qcpe/QCPE; CCP4—http://www.dl.ac.uk/CCP/CCP4; Biohedron—http://www.biohedron.com; Scripps—http://www.scripps.edu/pub/olson-web/people/sanner/html/msms_home.html.

atoms that lacks rigor and may thus be criticized in many ways: Nyburg et al.,[18] for example, note that for many purposes atoms are modeled much better by intersecting ellipsoids than by intersecting spheres. Grant and Pickup[19] have rejected the concept of hard spheres and used a Gaussian approximation to molecular shape to derive expressions for accessible surface area.

Several authors have sought to increase the computational efficiency of their implementations by approximating ensembles of atoms by single spheres. This has generally taken the form of representing amino acid residues as spheres of approximately correct volume. The increase in speed gained by reducing the total number of comparisons is counterbalanced by the reduced accuracy of the resulting calculation.

To make use of accessible surface area calculations in determining the area lost when a protein folds, a ligand is bound, or a macromolecular complex is formed, it is necessary to compare atomic surface areas found in context with that evaluated in a standard state. When calculating the area lost by individual residues in the folded state, as used in the calculation of hydrophobicity scales, for example, two different types of standard state have been assumed. In one the value calculated *in situ* is compared with that of an isolated residue in a standard conformation.[4] In the other, the measured area is compared with that of an isolated residue in the same conformation as that of the residue being measured.[5] Clearly, values calculated by these two methods can be different. In both cases the standard value measured is that for the central residue of a Gly-X-Gly (GXG) triplet. The area lost by packing, measured in either standard state, is usually then expressed as a normalized accessibility:

$$A_n = A_r/A_0$$

or as the fraction of surface buried:

$$f = (A_0 - A_r)/A_0$$

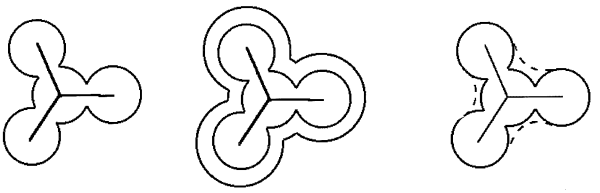

Figure 1. Diagrammatic representation of different types of molecular surface: the van der Waals surface; the accessible, or solvent-expanded, surface; and the molecular surface, composed of the contact surface (solid line) and the reentrant surface (broken line).

where A_r is the surface area measured *in situ*, and A_0 is the surface area of the residue in an isolated GXG triplet. SERF calculates these normalized values by comparing measured areas with those of an isolated residue in a GXG triplet with the same main-chain and side-chain conformations.

When analyzing complex formation, be it ligand–protein or protein–protein, accessible surface areas are again helpful.[5,20] In these calculations, a strategy similar to that described above is used: the surface areas of atoms in the complex are compared with those calculated for atoms in the separated molecules (say, an isolated protein and its isolated ligand or the two halves of a protein–protein dimer). The difference between the two quantities is the area lost on complex formation, or more formally:

$$A_{lost} = (A_1 + A_2) - A_{12}$$

where A_{lost} is the area lost on complexation, A_{12} is the surface of the complex, and A_1 and A_2 are the areas of the isolated parts of the complex. The flexible definition of groups participating in a complex and the calculation of these values, both on a group basis and on a residue-by-residue basis, are implemented in SERF, making the program a powerful potential tool for the analysis of ligand and macromolecular complexation as well as the packing of secondary structure elements.

ALGORITHMS FOR CALCULATING ACCESSIBLE SURFACE AREAS

Several different algorithms have been presented for the calculation of accessible surface areas. A number of these are reviewed briefly here.

The method proposed by Lee and Richards[1] is often called the method of *Z*-layer integration. In outline, this process takes a series of two-dimensional sections, at a number of equally spaced separations, through the molecule of interest. For each atom cutting that particular plane, the circle of intersection is sampled to determine what proportion is obscured by other atoms. By substituting each of these circles with a cylinder the same length as the separation between planes, it is possible to obtain an approximate value for the exposed area of atoms. Clearly, as the number of planes increases and their separation decreases, sampling improves and the value of derived ASAs improves. SERF implements this algorithm, together with that presented by Richmond,[10] an exact, mathematically rigorous, if complex, method for the calculation of ASAs.

Intersection methods

Gibson and Scheraga[21,22] have proposed an algorithm for calculating the accessible surface areas and volumes of atomic

coordinates. Their approach is formulated in terms of the surface area lost when spheres intersect: Kratky[23] had shown previously, from consideration of symmetry, that one need only account for the intersection of two, three, and four spheres to account for the surface area lost by an arbitrary collection of intersecting spheres.

Thus the surface area of sphere *i* is equal to the surface area of the free sphere S_A minus the area of each intersection with spheres *B, C,* and *D*:

$$S_i = S_A - S_A \cap S_B + S_A \cap S_B \cap S_C - S_A \cap S_B \cap S_C \cap S_D$$

Lustig[24,25] has given expressions for the intersection of two, three, and four spheres of equal radii. Gibson and Scheraga extend and simplify these results to give expressions for the areas of intersection of spheres of unequal radii solely in terms of their intercenter distances. Dodd and Theodorou[26] have, in turn, noted shortcomings in this formulation and have suggested a more general approach. Algorithmically, the principal problem with this method is the difficulty involved in initially, and correctly, identifying the number and type of two-, three-, or fourfold intersection. Although there has been progress in this direction, existing methods remain complex.

In a similar vein, Wodak and Janin[27] present a fast and approximate method for the calculation of accessible surface areas. An encoding of their algorithm, within SERF, was undertaken. This indicated that it was not a suitable method for the calculation of individual atomic areas but could be useful when approximating whole residues as large single spheres. Hasel and co-workers[28] have further modified this approach to better deal with atomistic accessibility. They parameterize the equations of Wodak and Janin for different atom types and apply empirically derived correction factors derived by calibrating their method against independently calculated surface areas.

The Shrake and Rupley algorithm and generation of spherical point distributions

Perhaps the simplest method proposed to calculate the accessible surface area of a molecule is that owing to Shrake and Rupley.[12] In their original implementation, the spherical surface of each atom is covered with 92 approximately equally spaced points, and the points that lie within other expanded atoms are determined. The number of exposed atoms determines the proportion of the total surface area that is accessible. In addition to being straightforward, this approach is also general and robust. Moreover, whatever the shape of atoms used, an appropriate surface net of points can, in principle, be created and used to determine the accessible part of that surface.

Although Shrake and Rupley originally used 92 surface points,[12] there is no reason why some other arbitrary number cannot be used. However, there is a trade-off between the accuracy to be gained by fine sampling of the surface with an increasing number of points and the decrease in efficiency that the extra number of required calculations will cause.

At first glance the problem of positioning a given number of points, *n*, evenly on the surface of a sphere seems facile, but exact solutions of this problem exist only for $n \leq 12$ and $n = 24$. Consequently, many studies have sought to derive approximate methods or to solve the problem individually for particular numbers of points. The case of 12 points or less is discussed by Williams.[29] For other numbers of points many solutions have been conjectured, some of which are reviewed by Kottwitz,[30] who presents a list of solutions for points numbering 13 to 90. A commonly used approach—the Monte Carlo method, in which a pseudo-energy is minimized to generate even point distributions—will give approximate solutions. Weinrach et al.[31] discuss distributions of 2 to 50 points using this method. Many of the solutions offered by Kottwitz make use of a similar approach. An alternative route to approximately even distributions of points comes from symmetry. For small numbers of points the vertices of simple polyhedra, such as the five platonic solids, provide even distributions. For larger numbers, the geodesic arrangements of points characteristic of the surface symmetry of virus particles and the domes of Buckminster Fuller provide many approximately equal distributions.[32] Another approach to the general problem of covering the surface of a sphere evenly is the use of random distributions. Such approaches are reviewed by Watson.[33] For

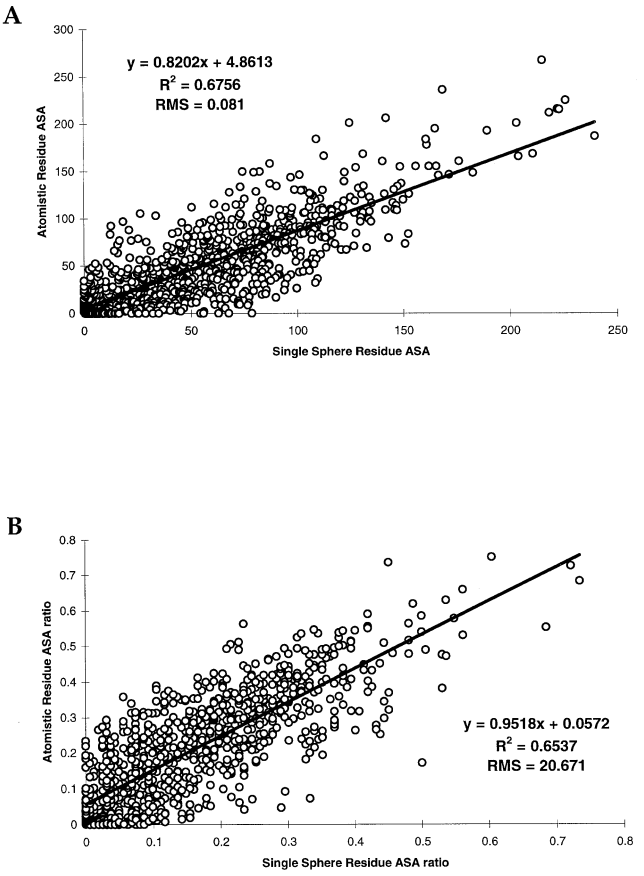

Figure 2. Plots of accessible surface area in angstroms squared (A) and accessible surface area ratio (B) using an atomistic and single-sphere representation of protein amino acid residues. One thousand points correspond to residues taken from 10 high-resolution protein structures (PDB codes: 1AMM, 1ARB, 1CBN, 1CTJ, 1IFC, 1IGD, 1LKK, 2ERL, 5PTI, and 8RXN). Data points are shown as open circles. Regression line and equation, R^2, and RMS for the data set are also shown.

Table 2. Comparison of algorithms implemented in SERF[a,b]

	1	2	3	4	5	6	7	Relative timings
1		0.9998	0.9982	0.9997	0.9835	0.9921	0.9965	5.85
2	0.206		0.9981	0.9995	0.9834	0.9924	0.9964	4.11
3	0.793	0.821		0.9978	0.9812	0.9933	0.9950	2.11
4	0.327	0.388	0.883		0.9834	0.9928	0.9962	6.41
5	2.493	2.491	2.649	2.509		0.9691	0.9791	1.00
6	1.651	1.680	1.512	1.655	3.357		0.9894	1.31
7	1.135	1.149	1.365	1.169	2.762	1.967		1.55

[a] Values in the upper triangle are correlation coefficients and values in the lower triangle are mean differences (in Å^2).
[b] References: (1) Richmond [10]; (2) Lee and Richards [1]; (3) Shrake and Rupley [12] with 162 points; (4) Shrake and Rupley [12] with 642 points; (5) Shrake and Rupley [12] with 32 points; (6) Shrake and Rupley [12] with 60 points; (7) Shrake and Rupley [12] with 92 points.

the more mathematically minded reader, Conway and Sloane[34] provide a thorough exploration of many recondite aspects of the subject.

During the development of a Shrake and Rupley algorithm within SERF, a number of different point distributions were implemented. Distributions derived from the study of icosahedral viruses[32] were implemented, giving a choice of 12, 20, 32, 42, 60, 72, and 92 points with an approximately even spread over the surface of a sphere. To provide greater samplings new distributions were sought. Starting with the vertices of an icosahedron, an iterative interpolation algorithm was used to produce successively finer samplings. The coordinates of the vertices of an icosahedron are given by

$$(\pm 1,0, \pm g)\ (0, \pm g, \pm 1)\ (\pm g, \pm 1,0)$$

where g is the golden ratio:

$$g = (1 + \sqrt{5})/2$$

At each cycle of this process the midpoint of each edge is added, as a new vertex, to the polyhedron generated by that cycle. Beginning with the icosahedron, each cycle takes the polyhedron resulting from the previous cycle and applies the same division. After 2 cycles this has produced 162 approximately evenly distributed points, and after 3 cycles 642 points; these 2 distributions were incorporated into the program SERF.

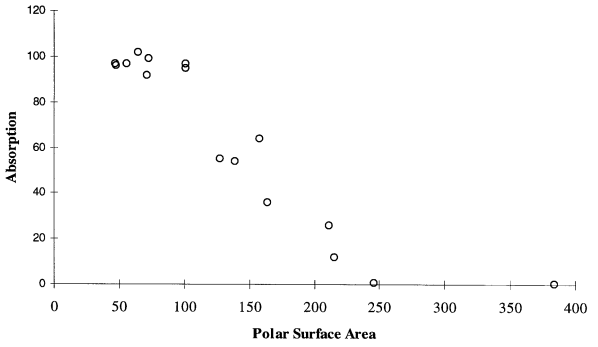

Figure 3. Relationship between oral absorption (%) and polar surface area (Å^2) calculated using SERF for 16 pharmaceutical compounds. Absorption data from Palm et al.[39] Note the sigmoidal relationship between polar ASA and absorption.

The algorithm used is as follows. For a given distribution, the coordinates of each point on the surface of a sphere, of unit radius centered on the origin, are stored. The corresponding point distribution on the surface of an atom to be measured is given, in terms of vectors, by

$$V_i = R_j D_i + P_j$$

where V_i is the position on the surface of the atom j of the *i*th point from the distribution D, R is the radius of that atom, and P_j are the coordinates of the atom center. Each point is tested to see if it lies within the solvent-expanded surface of another atom. Only other atoms that cut the surface of the tested atom are considered. A city-block algorithm is used to determine the distance of each surface point to other atoms. Once a point is found to be inaccessible it is not considered again. This strategy permits the algorithm to execute efficiently despite the large number of comparisons made.

COMPARISON OF ALGORITHMS

Because SERF contains implementations of several algorithms for the calculation of accessible surface areas, it affords the opportunity to assess the characteristics of these various methods. Table 2 presents pertinent statistics comparing the performance of different algorithms.

It is clear from these results that the methods of Richmond,[10] Lee and Richards,[1] and Shrake and Rupley[12] with 642 points compare well in terms of accuracy and execute in similar times. The method of Shrake and Rupley with 92 or fewer points does not give equivalent results but is much faster. The best compromise between accuracy and speed is the Shrake and Rupley method with 162 points: it is faster than the methods of Richmond, Lee and Richards, and Shrake and Rupley with 642 points yet agrees with them well. It is the algorithm of choice for optimal program performance although all the algorithms described above are available as options.

The opportunity also arises to assess the usefulness, or otherwise, of approximating whole amino acid residues by single spheres. This option is implemented in SERF, using standard values for whole residue radii. The accessible surface areas and normalized accessibility residues from 10 high-

Table 3. Default atomic radii used by SERF[a]

Element number	Element	van der Waals radius (Å)	Element number	Element	van der Waals radius (Å)	Element number	Element	van der Waals radius (Å)
1	H	1.10	41	Nb	1.50	81	Tl	1.94
2	He	1.38	42	Mo	1.42	82	Pb	2.05
3	Li	1.78	43	Tc	1.34	83	Bi	1.80
4	Be	1.10	44	Ru	1.33	84	Po	1.65
5	B	1.72	45	Rh	1.35	85	At	1.55
6	C	1.70	46	Pd	1.65	86	Rn	2.42
7	N	1.65	47	Ag	1.70	87	Fr	2.92
8	O	1.42	48	Cd	1.61	88	Ra	2.45
9	F	1.45	49	In	1.97	89	Ac	1.85
10	Ne	1.55	50	Sn	2.15	90	Th	1.80
11	Na	2.25	51	Sb	1.59	91	Pa	1.60
12	Mg	1.75	52	Te	2.10	92	U	1.84
13	Al	1.45	53	I	2.00	93	Np	1.56
14	Si	2.12	54	Xe	2.16	94	Pu	1.60
15	P	1.92	55	Cs	2.76	95	Am	1.75
16	S	1.85	56	Ba	2.25	96	Cm	1.75
17	Cl	1.78	57	La	1.86	97	Bk	1.75
18	Ar	1.90	58	Ce	1.84	98	Cf	1.87
19	K	2.72	59	Pr	1.83	99	Es	1.87
20	Ca	2.00	60	Nd	1.80	100	Fm	1.86
21	Sc	1.65	61	Pm	1.82	101	Md	1.86
22	Ti	1.46	62	Sm	1.78	102	No	1.85
23	V	1.34	63	Eu	2.10	103	Lr	1.85
24	Cr	1.30	64	Gd	1.81	104	Rf	1.61
25	Mn	1.38	65	Tb	1.76	105	Ha	1.50
26	Fe	1.24	66	Dy	1.80	106	Sg	1.45
27	Co	1.28	67	Ho	1.75	107	Ns	1.42
28	Ni	1.62	68	Er	1.80	108	Hs	1.40
29	Cu	1.41	69	Tm	1.76	109	Mt	1.38
30	Zn	1.40	70	Yb	1.91			
31	Ga	1.90	71	Lu	1.80			
32	Ge	1.40	72	Hf	1.60			
33	As	1.83	73	Ta	1.50			
34	Se	1.91	74	W	1.40			
35	Br	1.84	75	Re	1.40			
36	Kr	2.05	76	Os	1.35			
37	Rb	2.52	77	Ir	1.36			
38	Sr	2.17	78	Pt	1.74			
39	Y	1.70	79	Au	1.70			
40	Zr	1.62	80	Hg	1.54			

[a] Default van der Waals radii (in Å), used by SERF for each element.

resolution protein structures were calculated using the same method: Shrake and Rupley's method with 642 points. Plots of these 2 quantities for the first 1 000 data points are shown in Figure 2. Visual examination of the trend, taken with the value of RMS and R^2, for the data in these plots indicates a good general agreement between an atomistic and single-sphere approach to determination of whole residue accessibility, although a small subset of values displays significant deviation. Regression equations allow useful correction of the magnitudes of calculated values, but improvements in the underlying methodology are required to reduce inherent scatter.

APPLICATIONS

SERF has been fashioned to help facilitate the use of accessible surface areas in molecular structure analysis. The program was initially developed to facilitate the analysis of protein structures, and its presentation here has been in this context. A particular feature of the program is the analysis of surface area changes on binding and complexation.[35] We have been exploring the use of the program in the analysis of small molecule structures. For example, solvent-accessible areas have been used to improve atomistic approaches to the calculation of

octanol–water partition coefficients.[36] ASAs, in combination with atomic partial charges, have also been used to derive various molecular descriptors for use in generating quantitative structure–activity relationships.[37] SERF also calculates other useful, but simpler, partitions of the accessible surface, including the polar and hydrophobic surface.[38] The polar surface has been shown to correlate well with *in vitro* measures of absorption[39] (see Figure 3).

SOFTWARE

SERF is written in standard Fortran 77 and was developed initially on a VAX running under VMS. The program was subsequently ported to run under Unix on a series of Silicon Graphics workstations.

SERF is controlled via a simple command line interface through a set of keywords. The parameters used by the program are fully configurable. The program operates with a set of default atomic radii, which it uses in surface calculations. These radii are listed in Table 3. The user of SERF can override these values by specifying different radii using atom names as identifiers: this allows the use of more carefully selected radii depending on the chemical environment of the atom. For flexibility, this option, and the values used, are left to the discretion of the individual user.

SERF is flexible in the type and quantity of output generated and can read structure coordinate data in a number of different formats. The program can operate in either of two modes, either reading and subsequently analyzing structures on an individual basis or automatically batch processing sets of structures for the large-scale analysis of multiple molecular structures. SERF is flexible in the type and quantity of textual output it generates. Data associated with each type of surface area analysis, as well as different types of partial or overall summary, are written to separate, self-naming files.

SERF can be obtained from the author, or by anonymous FTP, from the following: guitar.rockeller.edu/pub/jpo/serf.tar.gz (login: FTP).

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