Computer representation of molecular surfaces

Nelson L Max
Lawrence Livermore National Laboratory

The simplest and earliest drawings of molecules had a line segment for each bond and could be modified in real time[1]. However, to understand the interaction of an enzyme with a substrate or inhibitor, or a drug or hormone with a receptor site, we must know the location of the molecular surface. Because the surfaces are so important, computer drawings have long been a useful tool in our understanding of the 3D structure of molecules.

This article reviews various algorithms for representing these surfaces, either as unions of spheres or as other smoothed surfaces.

UNIONS OF SPHERES

The most often-used molecular models today are the plastic CPK space-filling models[2], which were invented by Corey and Pauling and later improved by Koltun.

These models consist of plastic truncated-sphere parts, which can be fitted together with rotatable joints to form the union-of-spheres surfaces. Chemists are familiar with the CPK colour scheme, where each type of atom has its own colour code.

In these models each atom is represented by a sphere with a radius equal to the atom's van der Waals radius, and a molecule is represented as the union of its intersecting spheres. Since the preferred contact distance between two nonbonded atoms is the sum of their van der Waals radii, the contact between two molecules is well represented by the contact between their space-filling models.

For computer graphics line drawings, the circles where spheres intersect each other must be taken into account explicitly. These circles will project onto the picture as elliptical arcs. Smith and Gund[3] have expanded on an algorithm by Warme[4] for line drawings of space-filling models. In their work, each arc is approximated by a polygon, and the hidden-line calculation compares each polygon edge with each sphere to remove the hidden arcs. Figures 1 and 2 were produced by this system.

An earlier version of this invited review was presented at the 15th Hawaii International Conference on Systems Sciences, January 1982, and was reprinted in the *Journal of Medical Systems*, Vol 6 No 5 (1982). It is republished here with the permission of HICSS and *J. Med. Syst.* Reprinted with permission from *IEEE Computer Graphics and Applications* Vol 3 No 5 pp 21–29 (August 1983)

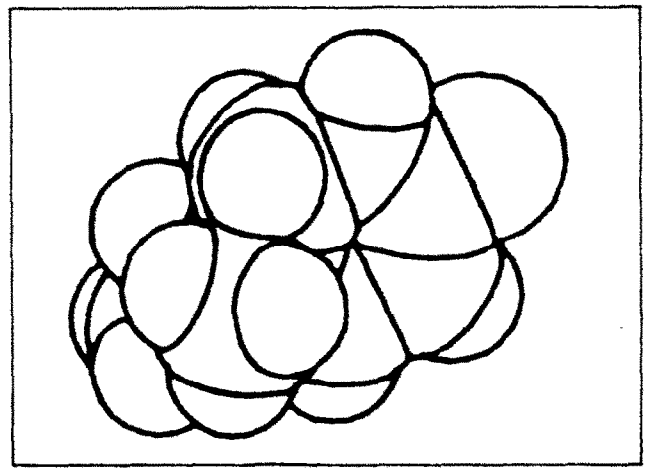

Figure 1. A space-filling outline drawing of 5-methyl-5-ethyl-5,6-dihydro-2(1H)-pyridone, produced by the Spacefil algorithm

Gary Quigley has written a similar program called PLTI, which uses concentric circles to produce shading on a pen plotter with multicoloured pens. A sample of its output is shown in Colour plate 1 (see p C2).

Motherwell[5] has written a program called Pluto, which, in addition to drawing the sphere outlines and intersection arcs, can add hatching to the parts of each sphere that face away from the light source, as shown in Figure 3. However, spheres produced in this manner do not cast shadows on other spheres.

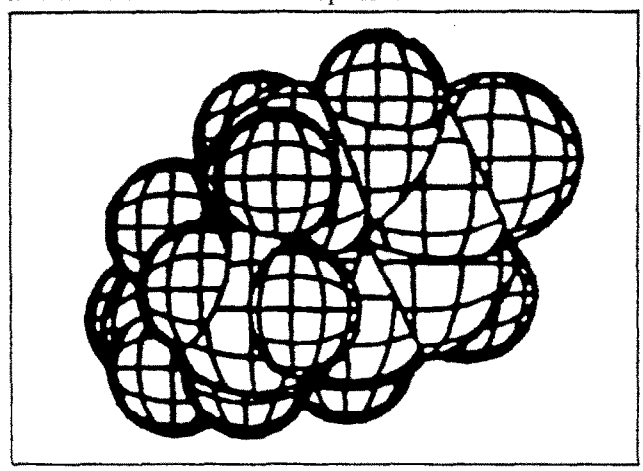

Figure 2. The same molecule as in Figure 1, with great circles rotated around the x- and y-axes to give curved cross-hatching

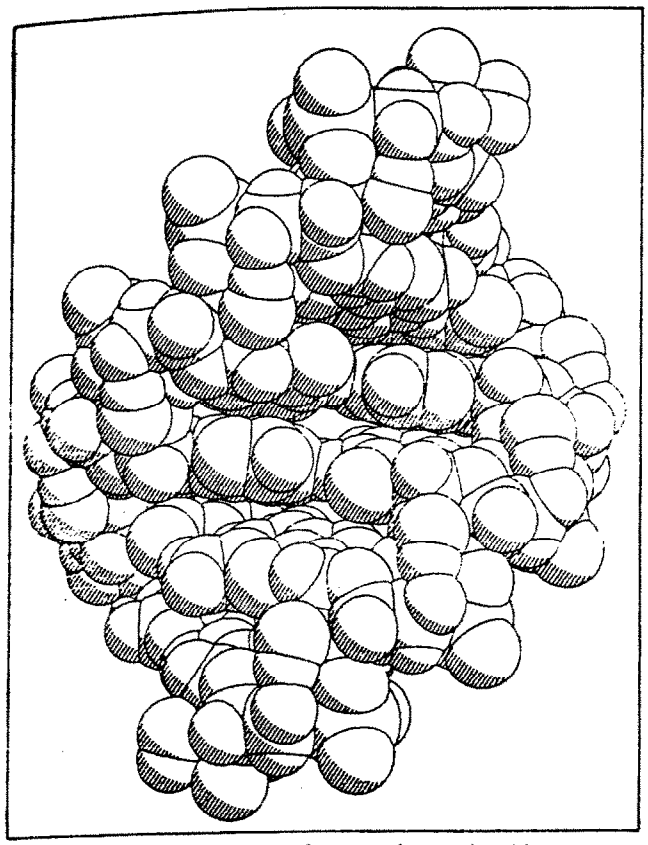

Figure 3. Six base pairs of DNA drawn by Pluto. Note the hatching on portions of the spheres facing away from the imaginary light source

Ortep-II, by Johnson[6], is widely used for publication-quality drawings of molecular structures. It can produce hidden line renderings of ball-and-stick models similar to those in Figure 4; it uses thermal ellipsoids instead of spheres but does not allow the atom surfaces to intersect for a surface model.

Franklin[7] has a very efficient 'linear-time' algorithm for suppressing the hidden arcs, but at present it is also limited to nonintersecting spheres. Herbison-Evans[8,9] has algorithms that work for ellipsoids and can produce both vector drawings (Figures 4 and 5) and raster drawings (see Colour plate 2). The shading for Herbison-Evans' drawings is found for a pixel by computing the normal vector at the appropriate point on the ellipsoid and relating it to the light source direction.

The strategy for shaded pictures of unions of spheres depends on the available raster hardware. Most raster terminals contain a frame buffer that has a memory location for the colour at each pixel. A colour video screen is refreshed continually from this buffer, while a computer can simultaneously add to the picture on the screen or create the next picture in a disjoint area of memory. Many such terminals also contain a local microprocessor that can write polygons into the memory and fill them with colour.

One simple way to draw a molecule on such a system is to sort the spheres in order of the depth of their centres and then paint them back-to-front into the frame buffer as filled circles. Of course, the spheres will look as if they never intersect, but the image will give a good idea of the overall shape of the molecule, and it can be generated very rapidly.

Keith Davis developed a package called Chemgraf,

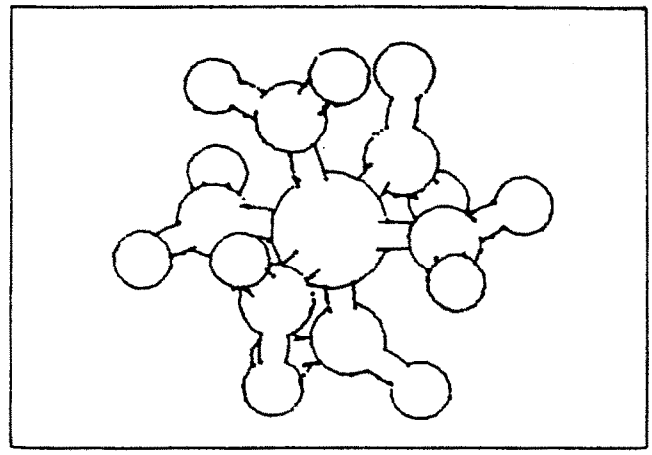

Figure 4. The ion $Co(NO_2)_6$ – – – drawn by the algorithm of Herbison-Evans[8]

which uses three overlapping filled circles of different intensities for each sphere; this gives a rough version of highlights and shadows, as illustrated in Colour plate 3. To give a more accurate representation of the union-of-spheres surface like the one in Colour plate 4, this package can also use a hidden-line algorithm to generate polygonal outlines for the visible parts of each sphere. These can then be rapidly filled with colour by frame buffer firmware.

Another clever use of firmware for shading was developed by Pete Harris to demonstrate the Advanced Electronic Design AED 512, a frame buffer terminal having a routine in its microprocessor that can draw a circle, when given its centre, radius, and colour.

If r is the radius in pixels of the projected sphere, concentric circles are drawn of radius r, r-1, r-2, . . . , 1, 0, with the outer one darkest and the inner one lightest. The spheres appear shaded, as if illuminated by a light source behind the viewer. In addition, if z is the depth in pixels of the sphere, these circles can be thought to lie in the depth planes z, z-1, z-2 . . . z-r, respectively, forming a cone in space. The circles for all

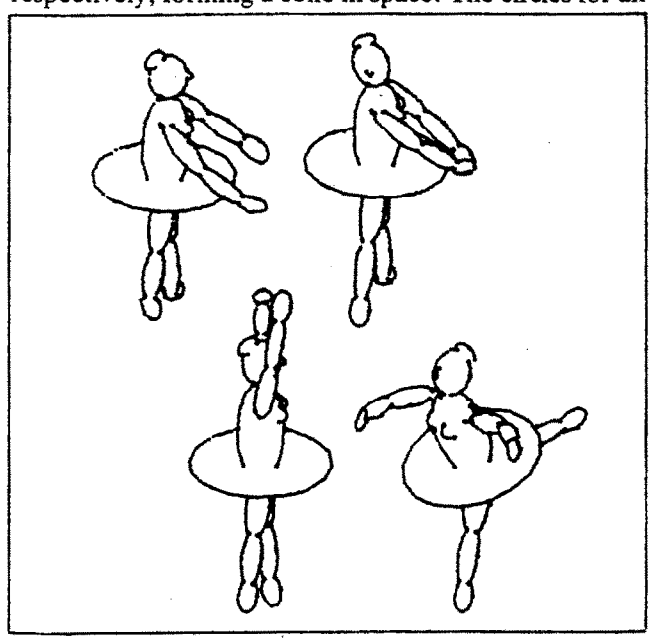

Figure 5. Four positions of a dancer. The body is composed of intersecting ellipsoids with the hidden arcs removed and was drawn by the algorithm of Herbison-Evans[9]

spheres are entered into the frame buffer one plane at a time, from back to front. Then if two spheres intersect, their arc of intersection will appear in the picture. However, since cones are used instead of spheres, this arc will lie on a hyperbola instead of an ellipse, and if the centres of the spheres lie in different z planes, the hyperbola may terminate abruptly at the profile circle of the closer sphere.

Colour plate 5 was created by this algorithm. The method could be improved by using spheres instead of cones, but then the resulting concentric circles would not be evenly spaced in radius, and special attention would be needed to make sure there were no pixels missed between them.

Parr[10] made the earliest colour union-of-spheres movies, drawing the concentric circles on a drum plotter (Colour plate 6) and computing beforehand the visible arcs of each circle. A different colour pen was used for each atom. After all the atoms for a sequence were drawn in all colours, they were repositioned by the drum under a movie camera. A negative was used for the movie, resulting in spheres in complementary colours against a black background (see Colour plate 7). Parr has since added sidelighted shading to this concentric circle algorithm (Colour plate 8), which now runs with a frame buffer.

Knowlton [11] has used a frame buffer to show large numbers of spheres (see Colour plate 9). Each sphere is represented by two discs — a shaded disc in one plane and a slightly larger black disc in another plane, which is somewhat to the rear. All discs for all spheres are sorted in depth and are then rendered back to front. If a sphere is far in front of another group of spheres, its black disc will outline it against the spheres to its rear. However, if two spheres intersect in space, their shaded discs will occlude each other's outline discs, and their interiors will merge.

Assume, as in the previous method, that the discs have concentric circles of increasing brightness and that the painting rule will not paint a darker shade over a lighter one (a slight simplification of Knowlton's method). This rule again gives a picture equivalent to one formed from cones instead of spheres. The images are particularly effective for shapes formed by the union of large numbers of small spheres, as can be seen in Colour plate 10.

Another standard tool for raster images is the depth buffer algorithm. A depth buffer contains a memory cell for the depth at each raster point, in addition to one for the colour. The spheres need not be sorted in depth, but are rendered one by one into the depth buffer. At each raster point, the depth of the new sphere is compared to the current depth value in the buffer, and if the new sphere is closer, the depth and colour values are both updated.

A variant that requires less memory is the line buffer algorithm. Here, the depth and colour information are only accumulated for one scan line. Spheres intersecting the current scan line have a horizontal row of shaded pixels rendered into the line buffer (the depth comparison stays as before). When all of the relevant spheres have been considered, the colour information for the scan line can be sent to a simple frame buffer or recorded on film. For efficiency, the spheres should be preprocessed to determine which scan lines they intersect, and they should also be organized for efficient retrieval when they become relevant.

Porter[12] has created such a line buffer system, and it is currently in use at the National Institutes of Health, USA. He used incremental methods across a horizontal row of pixels to compute the depth of a sphere, thus avoiding the time-consuming computations of square roots. Colour plate 11 was produced by this algorithm.

Knowlton and Cherry[13] have developed a hidden surface algorithm for chemical models that is based on subdivision. With their algorithm, each sphere's image is divided into a list of regions bounded by arcs of circles and by vertical line segments. To keep all arcs circular, the elliptical intersection arcs are approximated by circular arcs passing through three points on the ellipse. When a sphere intersects or is hidden by another sphere, the regions in its list are removed, modified, or subdivided to take this interaction into account. When all possible interactions have been processed, the regions remaining in the list of a sphere can be coloured in.

In my own work[14], I have added shading and highlights to these images as the regions are rendered offline on a colour film recorder. The regions have vertical sides, so they are constructed using vertical raster segments. The shading intensity function is defined as a paraboloid of revolution, taking its maximum value at the centre of the sphere and its minimum value on the sphere's profile circle. The intensity along vertical raster segments is then a quadratic polynomial and can be evaluated efficiently using forward differences, with two additions/pixel. A colour look-up table can be used to modify the values generated by this polynomial, thus allowing the creation of any shading function that is constant on concentric circles.

The dream of many chemists is an inexpensive device that can compute images like the one in Colour plate 11 so rapidly that they can be rotated and deformed in realtime. Michael Pique has come close to realizing this dream with a depth buffer algorithm compiled into microcode on an Ikonas frame buffer, a device with a powerful internal processor. Pique used my forward difference scheme[14] along with a table of square roots to determine the spheres' depth from the paraboloid of revolution. A 256 × 256 pixel image of 50 atoms, as illustrated in Colour plate 12, can be updated eight times/s and rotated with a joystick.

Recently, I have modified the quadratic shading algorithm to produce side lighting[15]. Elliptical highlights are rendered at the appropriate position for specular reflection. As in the Pluto program mentioned above, the surface regions facing away from the light source are darkened. In addition, the hidden surface algorithm can be repeated from the point of view of the light source. The visible fraction of the highlight and sphere areas can be incorporated into the algorithm to multiply the shading, thus casting diffuse shadows, as shown in Colour plate 13. Transparency has also been implemented (Colour plate 14) by using multiple exposures through masks representing the opaque and semitransparent surfaces. The masking procedure for the special effects optical printer is described elsewhere[15].

OTHER SMOOTH SURFACES

Unions of spheres are only one way to visualize the surface of a large molecule. Lee and Richards[17] defined the solvent-accessible surface of a molecule as the boundary of the volume that could be occupied by the solvent *without* penetrating the molecule. For simplicity, the solvent is represented by a probe sphere, and the accessible surface bounds the union of the possible positions of the probe sphere's interior. It thus excludes crevices into which the sphere will not fit. The volume accessible to the probe sphere is bounded in three ways:

- by the pieces of the atom spheres that can actually be contacted by the probe sphere (shaded blue in Colour plate 15)
- by toroidal fillets (shaded green in Colour plate 15) generated by the surface of the probe sphere as it rolls in contact with two atom surfaces
- by pieces of the probe sphere in contact with three atom spheres (shaded yellow)

(See Richards[18] or Connolly [19] for further details.)

Greer and Bush[20] have approximated this accessible surface by a single-valued function of two variables. Such a function is useful in studying simple contacts between near-planar faces of two proteins, but it is inadequate for more convoluted surfaces. Connolly[19] has written a program to scatter dots across the entire accessible surface at an approximately constant density per unit area. Langridge, Ferrin, Kuntz, and Connolly[21] have used this dot representation, in combination with line drawings of the covalent bonds, on an interactive colour vector display with clipping, perspective, and depth cueing. Colour plates 16 and 17 were taken from this display. This system is currently being used heavily by chemists, crystallographers, molecular biologists, and pharmacologists studying molecular interactions. Connolly[19] has also recently generated shaded raster images of the accessible surface, using a depth buffer algorithm (see Colour plate 15).

Connolly's surfaces are continuously differentiable but have abrupt changes between positive and negative curvature. Blinn[22] has written a program to render infinitely differentiable analytic surfaces that represent various contours of electron density. In Blinn's algorithm, a spherically symmetric Gaussian electron density is centred at each atom, and the surface is the contour where the sum of these densities takes on a specific value. Since the Gaussian is effectively zero outside a certain radius, sorting can be used to select efficiently those atoms that can affect a scan line, pixel, or depth region behind a pixel. For each pixel, the nearest point on the surface is found by Newtonian iteration; then the surface normal is computed by taking the gradient of the analytic density function. The normal vector is used to compute the shading intensity, and colour is assigned according to the nearest atom. Colour plate 18 was made in this way.

Vector drawings of contour surfaces are routinely produced by X-ray crystallographers and are used to fit computer models of large macromolecules to their electron densities. These densities are reconstructed from X-ray diffraction data and are contoured in three perpendicular planes; this gives a cage-like wire mesh surface where the interpolated density takes on a specific value, as described in Miller *et al*[23].

These contouring algorithms can also be applied to a simulated density, which can be represented as the sum of the Gaussian density functions centred at the atomic nuclei, as discussed here. The resulting vector mesh then represents the same surface that we see in Blinn's raster images. Barry[24] has applied such surfaces to molecular interactions (see Colour plate 19). If the density and contour values are chosen to approximate the van der Waals contact surfaces, two such surfaces can be manipulated to nestle together. If instead, the contours are chosen at twice the van der Waals radius, the resulting voids in one molecule represent spaces that could be occupied by atomic centres of another molecule. The second molecule is represented in zero-radius stick form. Barry has found the latter format easier to understand and manipulate, since two surfaces, as shown in Colour plate 19, can be confusing.

Another advantage in making the second molecule out of vector sticks is that it can then be manipulated in realtime by changing torsion angles about various bonds. The vector mesh for the first molecule can also be rotated or translated as a rigid body in real time, but the molecule cannot be deformed, because recomputing the mesh is too lengthy a process. On the other hand, if both molecules are rigid bodies, two molecular surfaces of normal thickness can be moved in realtime with respect to each other. Also, the image as a whole can be rotated or wobbled back and forth to give the added 3D cue of motion parallex. Finally, two stereo images can be presented through a stereo viewer.

Similar realtime interaction is available on the system of Langridge *et al*[21]; here, the dots on the accessible surfaces must be precomputed, but two surfaces can then be moved or rotated independently, or a vector backbone can be deformed. Both of these operations can be performed by using dials or joysticks. Realtime motion is accomplished by pipelined processors that perform the matrix multiplication, clipping, and perspective division involved in 3D transformations of vector images. From the same laboratory, Bash *et al*[25] have recently put the dots on the union-of-spheres surface instead of the solvent-accessible surface so that if the molecule is deformed in real time, it can carry its surface along.

Pearl and Honegger[26] have a simpler way of generating either kind of dot surface. They start with a uniform 3D lattice of dots, test for adjacency with the desired surface, and then move the dots which pass the test radially along a line to an atom or probe sphere centre, so that they lie on the surface.

Molecular surfaces may be colour coded to indicate varying physical properties. In Colour plate 11, produced by Richard Feldmann, atoms or groups of atoms are coloured according to their charge. Weiner *et al*[27] have coloured the individual dots on the surface according to their electrostatic potential. This gives useful cues for 'docking' one molecule with another. Quarendon *et al*[28] calculate raster union-of-spheres surfaces using spatial subdivision, and then colour the pixels according to physical properties (see Colour plate 20).

The hard-sphere model and the Gaussian model are

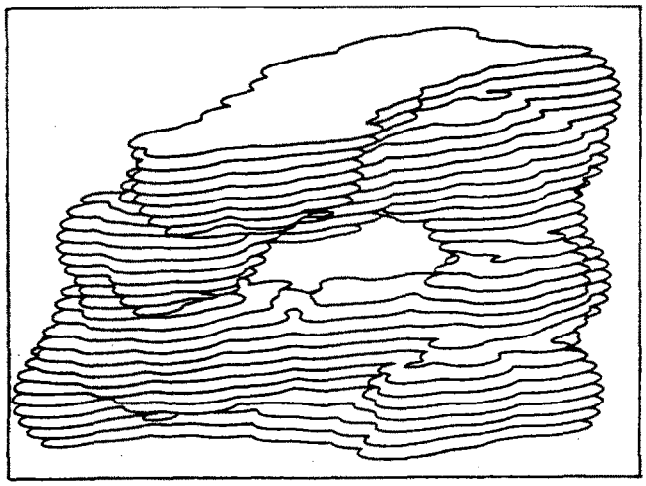

Figure 6. The soft potential surface of four base pairs of DNA, opened to create an intercalation site, as drawn by Miller's algorithm[29]

only approximations of the surface felt by a probe atom. For any semiempirical force law with long-range attraction and short-range repulsion, one may consider the surface along which the probe atom centre can move in equilibrium, keeping the attractive and repulsive forces in balance. Miller *et al*[29] compute the contours of this zero-force surface (Figure 6) potential and then apply a hidden line algorithm especially designed for contours in parallel planes. Using a variant of Newtonian iteration, it takes a substantial amount of time to compute these contours. However, if the contours are known, different views of the surface can be rapidly generated, together with a stick drawing of a second molecule just touching it. As with the other methods discussed above, this rapid interaction is very useful when studying the 'docking' of a flexible molecule with a rigid one[29].

CONCLUSIONS

Many research laboratories in universities and the drug and chemical industries now have facilities for interactive computer graphics. The rapidly increasing use of molecular surface representations is reflected in the diversity of techniques described here.

ACKNOWLEDGMENTS

This work was performed by the Lawrence Livermore National Laboratory (contact No W-7405-ENG-48) under the auspices of the US Department of Energy. Neither the US Government, nor the University of California, nor any of their employees, make any warranty, express or implied, or assume any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represent that its use would not infringe upon privately owned rights. Reference herein to any specific commercial products, process, or service by trade name, trademark, manufacturer, or otherwise, does not necessarily constitute or imply its endorsement, recommendation, or favouring by the US Government or the University of California. The views and opinions of authors expressed herein do not necessarily state or reflect those of the US Government thereof and shall not be used for advertising or product endorsement.

REFERENCES

1 **Levinthal, C** 'Molecular model building by computer' *Sci. Am.* Vol 214 No 6 (June 1966) p 42
2 *Catalogue of CPK precision molecular models* Ealing Corp, S Natick, MA, USA (1981) p 1
3 **Smith, G M and Gund, P** 'Computer-generated space filling molecular models' *J. Chem. Inf. Comput. Sci.* Vol 18 (1978) p 207
4 **Warme, P K** 'Space-filling molecular models constructed by a computer' *Comput. Biomed. Res.* Vol 10 (1977)
5 **Motherwell, S** 'PLUTO — a program for plotting molecular and crystal structures' University Chemical Laboratory, Cambridge, UK
6 **Johnson, C K** 'ORTEP-II, a Fortran thermal-ellipsoid plot program for crystal structure illustrations' *ORNL-5138* third revision, Oak Ridge National Laboratory, TN, USA (1976)
7 **Franklin, W R** 'An exact hidden sphere algorithm that operates in linear time *Comput. Graphics Image Proc.* Vol 15 No 4 (1981) p 364
8 **Herbison-Evans, D** 'Nudes 2: a numeric utility displaying ellipsoid solids version 2' *Comput. Graphics* Vol 12 No 3 (1978) p 356
9 **Herbison-Evans, D** 'Rapid raster ellipsoid shading' *Comput. Graphics* Vol 13 No 4 (1980) p 355
10 **Parr, C** *Reaction Dynamics* 16mm movie available from Parr at University of Texas at Dallas, TX 75080, USA
11 **Knowlton, K** 'Computer-aided definition, manipulation, and depiction of objects composed of spheres' *Comput. Graphics* Vol 15 No 1 (1981) p 48
12 **Porter, T** 'Spherical Shading' *Comput. Graphics* Vol 12 No 3 (1978) p 282
13 **Knowlton, K and Cherry, L** 'ATOMS — a three-D opaque molecule system for color pictures of space-filling or ball-and-stick models' *Comput. Chem.* Vol 1 (1977) p 161
14 **Max, N** 'ATOMLLL — ATOMS with shading and highlights' *Comput. Graphics* Vol 12 No 3 (1978) p 348
15 **Max, N** 'ATOMLLL with transparency and shadows' *Proc. 16th Annual Hawaii Int. Conf. Syst. Sci.* (1983) p 407
16 **Max, N and Blunden, J** 'Optical printing in computer animation' *Comput. Graphics* Vol 14 No 3 (1980) p 171
17 **Lee, B and Richards, F M** 'The interpretation of protein structures: estimation of static accessibility' *J. Mol. Biol.* Vol 55 (1971) p 379
18 **Richards, F M** 'Areas, volumes, packing, and protein structure' *Ann. Rev. Biophys. Bioeng.* Vol 6 (1977) p 151
19 **Connolly, M** 'Solvent-accessible surfaces of proteins and nucleic acids' *Science* Vol 221 No 4612 (19 August 1983) p 709
20 **Greer, J and Bush, B L** 'Macromolecular shape and surface maps by solvent exclusion' *PNAS* Vol 75 (1978) p 303
21 **Langridge, R, Ferrin, T, Kuntz, I and Connolly, M** 'Real-time color graphics in studies of molecular

interactions' *Science* Vol 211 No 4483 (1981) p 661

22 **Blinn, J** 'A generalization of algebraic surface drawing' *ACM Trans. Graphics* Vol 1 No 3 (1982) p 235

23 **Miller, S, Abdel-Meguid, S, Rossman, M and Anderson, D** 'A computer graphics system for the building of macromolecular models into electron density maps' *J. Applied Crystallogr.* Vol 14 No 2 (1981) p 94

24 **Barry, C D, Bosshard, H E, Ellis, R A and Marshal, G R** 'Evolving macromolecular modelling system' in **Siler and Lindberg (eds)** *Computers in life science research* Plenum Publishing, NY, USA (1975)

25 **Bash, P, Huang, C, Pattabiraman, N, Ferrin, T and Langridge, R** 'Van der Waals surfaces in molecular modeling and implementations using real-time computer graphics' *Science* (1983)

26 **Pearl, L H and Honegger, A** 'Generation of molecular surfaces for graphic display' *J. Mol. Graphics* Vol 1 No 1 (1983) pp 9–12

27 **Weiner, P K, Langridge, R, Blaney, J, Shaefer, R and Kollman, P** 'Electrostatic potential molecular surfaces' *Proc. Natl. Acad. Sci. USA* Vol 79 (1981) p 3754

28 **Quarendon, P, Naylor, C and Richards, W G** 'Display of quantum mechanical properties on Van der Waals surfaces' *J. Mol. Graphics* (see p 4)

29 **Miller, K J, Kowalczyk, P, Segmuller, W and Walker, G** 'Interaction of molecules with nucleic acids VIII. Evaluation and presentation of steric contours and molecules in binding sites' submitted to *J. Computational Chem.*