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COMPUTER REPRESENTATION OF MOLECULAR SURFACES

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Abstract

This review article surveys recent work on computer representation of molecular surfaces. Several different algorithms are discussed for producing vector or raster drawings of space-filling models formed as the union of spheres. Other smoother surfaces are also considered.

1. INTRODUCTION

Computer drawings have long been a useful tool in the understanding of the three dimensional structure of molecules. The simplest and earliest were line drawings (see Levinthal [1]), with a line segment representing each bond. To understand the interaction of an enzyme with a substrate or inhibitor, or a drug or hormone with a receptor site, the location of the molecular surface is more important than the location of the bonds. This paper will review various algorithms for representing these surfaces, either as unions of spheres or as other smoothed surfaces.

2. UNIONS OF SPHERES

The most familiar molecular models are the CPK space-filling models [2], invented by Pauling and Corey and improved by Koltun. Here each atom is represented by a sphere of 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 non-bonded 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. The models consist of plastic truncated-sphere parts, which can be fitted together with rotatable joints to form the union-of-spheres surfaces. Chemists are familar with the CPK color scheme, where each type of atom has its own color code.

In a computer picture, the spheres can be rendered as line drawings, or as shaded raster drawings. For line drawings, the circles where spheres intersect each other must be explicitly taken into account. These circles will project into the picture as elliptical arcs. Smith and Gund [3] have expanded on an algorithm of Warme [15] for line drawings of space-filling models.

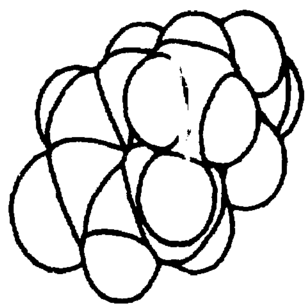

Figure 1. A space filling outline drawing of 5-methyl-5-ethyl-5,6-dihydro-2(1H)-pyridone, produced by SPACEFIL algorithm of Smith and Gund. Reprinted with permission from [3], Journal of Chemical Information and Computer Science, Copyright (1978) American Chemical Society.

Each circle is approximated by a polygon, and the hidden surface calculation compares each polygon edge with each sphere. Figures 1 and 2 were produced by this system.

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Figure 15. Six transparent base pairs of DNA, with an opaque ethidium ion slipped between the center two.

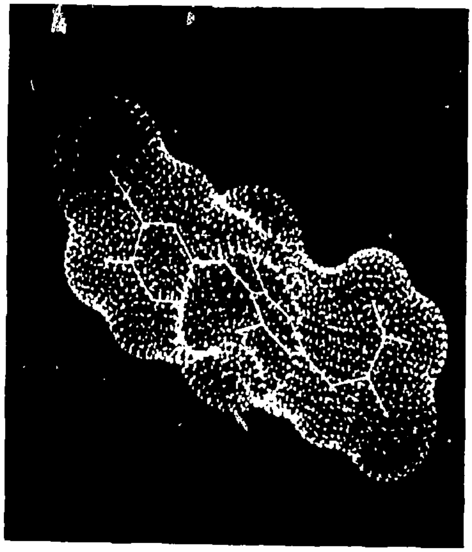

Figure 16. The surface of a thyroxin molecule.

Figure 17. Section of the surfaces and stick figures for trypsin inhibitor inserted into trypsin, clipped between two planes parallel to the viewing screen.

Staudhammer [13] has proposed building hardware which could rapidly generate shading for raster segments precomputed and stored on a digital disc, so that a movie sequence could be viewed in real time video.

5. OTHER SMOOTH SURFACES

Spheres are only one way to visualize the shape of a molecular surface. The volume near the corner at the circle where two atoms intersect is not accessible to another atom or molecule, whose surface has a curvature of its own, and cannot fit into the corner. Langridge, Ferrin, Kuntz, and Connolly [14] study interactions between molecules by displaying the surface of the volume around or inside each molecule which could be occupied by a disjoint probe such as a water molecule. As described in Connolly [17], this surface is bounded by pieces of the spheres for each atom, pieces of toroidal fillets tangent to two spheres near their intersection, and pieces of the probe sphere where it is tangent to three atom spheres. Dots are scattered across this surface, with approximately constant density per unit area. Once the dots are precomputed, such a surface can be rotated, translated, and clipped in real time, while being refreshed on a color, vector CRT with perspective and depth cueing. Figures 16 and 17 were taken from this display.

Connolly's surfaces are continuously differentiable, but have abrupt changes between positive and negative curvature. Blinn has written a program to render infinitely differentiable analytic surfaces which represent contours of electron density. A spherically symmetric

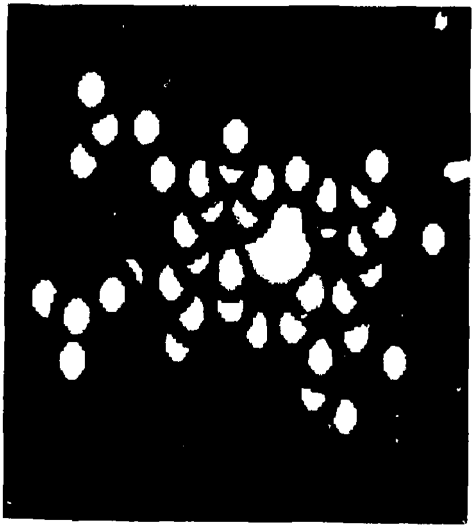

Figure 7. A picture of the heme group in hemoglobin, taken from the color monitor of the AED512.

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

One simple way to draw a molecule on such a system is to sort the spheres in order of the depth of their centers, 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.

There are several ways to improve such an image. One improvement was written by Pete Harris to demonstrate the AED 512, a frame buffer terminal having a routine in its microprocessor which can draw a circle given its center, radius, and color. If r is the radius in pixels of the projected sphere, concentric cirlces 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 spheres are sorted in z, and entered into the frame buffer a 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 centers of the spheres lie in different z planes, the hyperbola may terminate abruptly at the profile circle of the closer sphere. Figure 7 was made 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 made some of the earliest color union-of-spheres movies [16], drawing the concentric circles on a drum plotter (figure 8), and computing beforehand the visible arcs of each circle. A different color pen was used for each atom. After all atoms for a sequence were drawn in all colors, they were repositioned by the drum under a movie camera. A negative was used for the movie, giving complementarily colored spheres against a black background (figure 9). Parr has since added side lit shading to this concentric circle algorithm (figure 10) which now runs with a frame buffer.

Knowlton [7] has a second improvement to the frame buffer algorithm. Each sphere is represented by two discs; a shaded disc in one plane

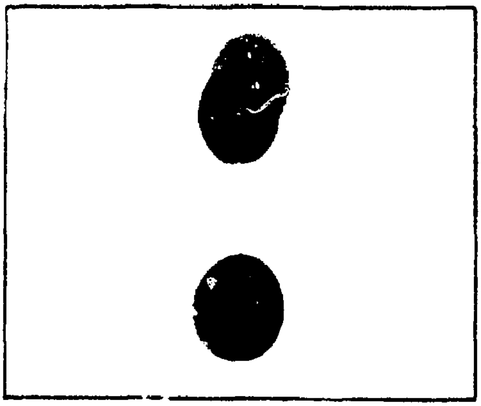

Figure 8. Four atoms in a bimolecular reaction, as drawn on a pen plotter.

Figure 9. The negative of figure 7, as in the movie [16].

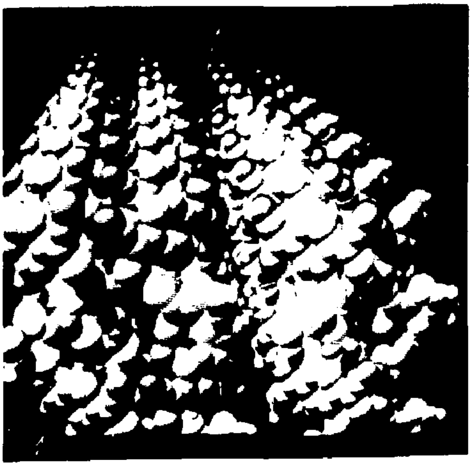

Figure 10. The structure of TTF-TCNQ, an organic metal at room temperature.

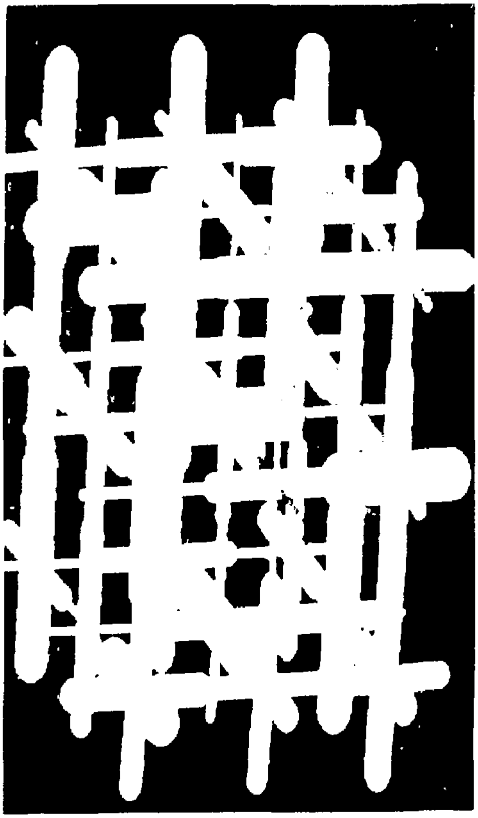

Figure 11. A structure formed as the union of many small spheres, as drawn by the algorithm of Knowlton [7].

and a slightly larger black disc in another plane somewhat to the rear. All discs for all spheres are sorted in depth, and 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 the painting rule refrains from painting a darker shade over a lighter (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 in Figure 11.

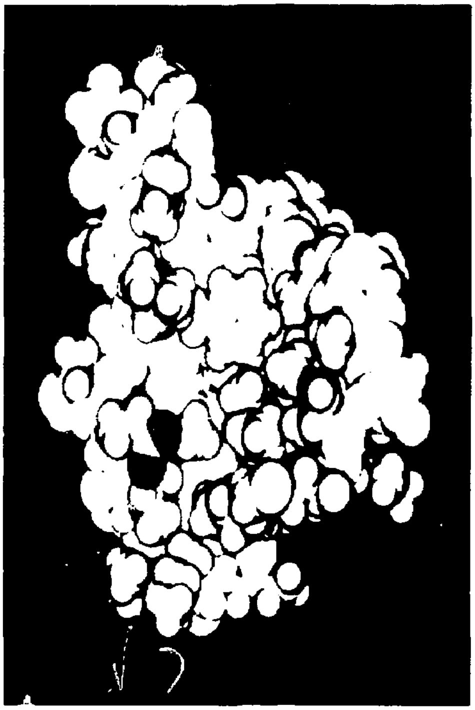

Figure 12. Bacterial Flavodoxin, from Teaching Atlas for Molecular Structure, produced at the National Institutes of Health using the program of Porter [6].

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 color. 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 color values are both updated.

A variant which requires less memory is the line buffer algorithm. Here, the depth and color information are only accumulated for a scan line at a time. Spheres which intersect the current scan line have a horizontal row of shaded pixels rendered into the line buffer, using the depth comparison as before. When all the spheres have been considered, the color information for the scan line can be sent to a simple frame buffer, or recorded onto film. For efficiency, the spheres should be preprocessed to determine which scan lines they intersect, and organized for efficient retrieval when they become relevant. Porter [8] has written such a line buffer system which is currently being used at the National Institute of Health. He uses incremental methods across a horizontal row of pixels to compute the depth of a sphere, avoiding time consuming computations of square roots. Figure 12 was produced by this algorithm.

Knowlton and Cherry [9] have developed a hidden surface algorithm for chemical models, based on subdivision. 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 which pass 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, as in figure 13. When all possible interactions have processed, the regions remaining in the list of a sphere can be colored in. Max [10] has added shading and highlights to the images as the regions are rendered offline on a color film recorder. The regions have vertical sides, so they are rendered using vertical raster segments. The shading intensity function is defined as a paraboloid of revolution, taking its maximum value at the center 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 per pixel. Using a color look-up table to modify the values generated by this polynomial, any shading function which is constant on concentric circles can be achieved.

Recently, Max [2] has modified the quadratic shading algorithm to produce side lighting.

Figure 14. Half of the 180 subunits in the protein coat of the tomato bushy stunt virus. The large spheres are whole proteins, and the smaller spheres represent individual amino acids. Shadows are cast by a light source above the virus.

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 may be repeated from the point of view of the light source, and the visible fraction the highlight and sphere areas used to multiply the shading, giving diffuse cast shadows, as in figure 14. Transparency has also been implemented as in figure 15, by using multiple exposures through masks representing the opaque and semi-transparent surfaces. The procedure for the special effects optical printer is described in Blunden and Max [11].

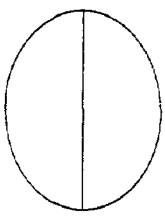

Figure 13a. Initial subdivision of an atom.

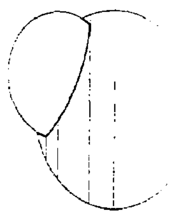

Figure 13b. Subdivision caused by intersecting atom.

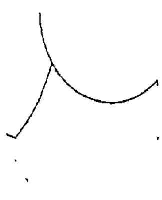

Figure 13c. Further subdivision caused by occluding atom.

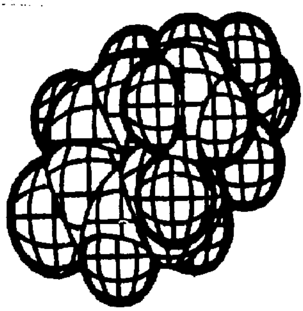

Figure 2. The same molecule as in figure 1, with great circles rotated around the x and y axes to give curved cross hatching. Reprinted with permission from [3], Jorunal of Chemical Information and Computer Science, Copyright (1978) American Chemical Society.

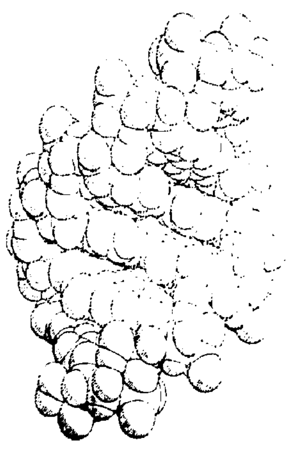

Figure 3. Six base pairs of DNA, with hatching on portions of spheres facing away from light, as drawn by PLUTO.

Motherwell has written a program called PLUTO [18], which, in addition to drawing the sphere outlines and intersection arcs, can add hatching to the parts of each sphere which face away from the light source, as in figure 3. However, spheres do not cast shadows on other spheres.

Franklin [4] has a more efficient linear time algorithm for suppressing the hidden arcs, but at present it is limited to non-intersecting spheres. Herbison-Evans [5,6] has algorithms which work for ellipsoids, and can produce drawings (figure 6) as well as vector drawings (figures 4 and 5). The shading is found for each raster element, or pixel, by computing the normal vector at the appropriate point on the sphere, and relating it to the light source direction.

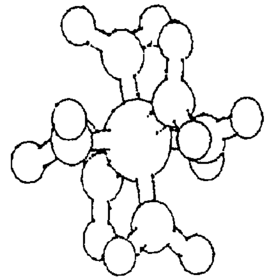

Figure 4. The ion $Co(NO_2)_6^{---}$, produced by the algorithm of Herbison-Evans [5].

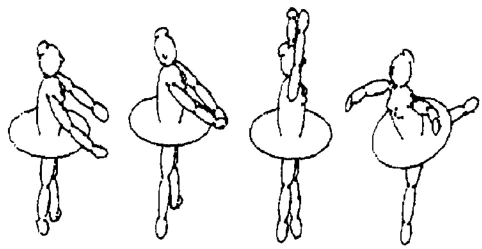

Figure 5. Four positions of a dancer, composed of intersecting ellipsoids with the hidden arcs removed by the algorithm of Herbison-Evans [5].

Figure 6. A raster drawing of the dancer, shaded by the algorithm of Herbison-Evans [6].

Gaussian electron density is centered at each sphere, and the surface is the contour where the sum of these densities takes on a specific value. For each pixel, the nearest point on the surface is found by Newton iteration, and 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 the color is assigned according to the nearest atom. Figure 18 was made in this way.

Figure 18. A base pair of DNA, represented as a shaded contour surfaces for the electron density.

Vector drawings of contour surfaces are routinely produced by x-ray crystallographers, and used to fit computer models of large macromolecules to their electron densities, as reconstructed from x-ray diffraction data. The calculated electron density is contoured in three perpendicular planes, to give a wire mesh cage-like surface where the interpolated density takes on a specific value. Once computed, the vectors in the cage can be rotated in real time or presented in stereo, as described in [20].

These contouring algorithms can also be applied to a simulated density, represented as a sum of Gaussian density functions centered at the atomic centers, as discussed above. The resulting vector mesh then represents the same surface as in Blinn's raster images. Barry [19] has applied such surfaces to molecular interactions as in Figure 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 which could be occupied by another, as represented in zero radius stick form. Barry has found the latter format easier to understand and manipulate.

All of these surface renderings can now be performed rapidly enough to produce movies, either in real time, or by frame by frame recording. Several representative movies will be shown at the meeting.

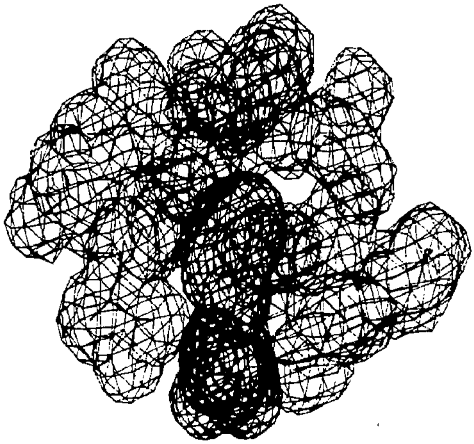

Figure 19. Leucine 32 and phenylalanine 33 in whale myoglobin, together with the atoms in the immediate neighborhood of the phenyl ring.

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