without the intermediate calculation of surface primitives. Two algorithms for the rasterization process have been implemented. In the integrative approach, partial opacities are assigned to a range of scalar data values, which are summed along rays cast from each pixel away from the viewer through the data space. Opacities are summed until the pixel is totally opaque, or until an atomic surface is reached. Shading is performed using local gradient vectors as shading normals, and antialiasing of silhouettes is performed easily during the assignment of partial opacities. These images appear as colored clouds surrounding a solid van der Waals molecular surface. The second approach yields a series of transparent isovalue surfaces, shaded by the method of Phong,[2] with an option for fully self-consistent cast shadows. Antialiasing of the surfaces is performed as a post-process. These images are much more interpretable, due to the presence of well-defined edges and highlights. The programs have shown utility in the visualization of molecular electrostatic potentials, molecular mobility and crystallographic electron density.

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Approximating Molecular Surfaces by Spherical Harmonics

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Smoothed molecular surfaces can be used to analyze the general shapes of proteins and as reference surfaces for locating clefts and projections. The radius of the surface in a given direction is defined by a polynomial or spherical harmonic function on the unit sphere. Starting with equally spaced points on a solvent-accessible molecular surface, generated by an algorithm of Connolly, we can either evaluate the spherical harmonic coefficients by a summation over the surface points, or by the "QR" least-squares algorithm. The resulting surface can be drawn with randomly spaced dots, or by ray tracing after conversion to an implicit polynomial equation.

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A Real-Time Malleable Surface for Molecular Modeling

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The use of surfaces in molecular modeling and drug design is well documented.[1–3] The two most common surfaces for these applications are the solvent-accessible[1,4,5] and the van der Waals[6,7] representations. In drug design studies, we require a surface that is both dynamic and interactive in real-time, with multiple visual cues, such as color and density, and efficient global and local manipulations to provide the user with additional feedback. We have recently described a method for generating a molecular surface using a parametric patch representation based on three-dimensional (3D) molecular structures.[8] Unlike previous methods for representing molecular surfaces, this algorithm produces a parametric patch surface that is *smooth* and *continuous* and can be manipulated in real-time. Crucial to our approach is the creation of a net of approximately equilateral triangles from which we generate the control points used as the basis for describing the surface.

A molecular surface model can be described as a continuous surface that envelopes a set of intersecting spheres. The algorithm that generates the surface must be able to generate a surface about a simple volume. Required properties include smoothness of the surface (i.e., continuity of position and tangent to the surface). Our algorithm provides for a dynamically manipulable surface based on a set of control points. For example, a user can interactively select a control point on one of the surface patches with a pointing device and move the control point outward along the surface normal. After the control point data has been modified, the graphics interface recalculates and redraws the patches of the surface model based on the new data.

Our algorithm provides for the generation of control points in such a fashion that we are able to generate a net of approximately equilateral triangles about a given surface. These equilateral triangles then become the basis for triangular parametric patches. Triangular patches, which are better at describing free-form shapes, can be described using nonpolynomial Gregory patches.[9] Gregory patches are interpolated between cubic boundaries.[10]

Our method for smooth and continuous surface generation uses cubic Bézier curves for the boundaries between patches. Quartic Gregory patches are joined with tangent-plane continuity to provide a smooth interpolated surface. Gregory patches are used as opposed to Bézier patches because Gregory patches provide twice as many interior control points and guarantee tangent-plane continuity between patches. To determine which points define which patches, a triangular net is calculated from atomic coordinates and radii. The triangular net is then converted to a parametric representation in three steps, as described by Shirman. The first step calculates the vertex normals based on the vertices of the triangles and the angles associated with these vertices. The second step involves the determination of Bézier control points

for the curved edges. Lastly, the internal control points used for the Gregory patches are determined.

The resultant molecular surface is easily malleable and hence useful in describing receptor sites for scientists performing molecular modeling studies. Key properties of our new molecular surface generation technique are as follows: (1) the surface is closed and generated about a volume, (2) the surface is smooth and continuous, and (3) the surface can be manipulated in real time. Generation of an equilateral triangular net and accompanying control points about the surface have allowed for the creation of a smooth and continuous parametric patch surface based on Gregory patches. Gregory patch surfaces successfully and efficiently meet the above criteria and provide the basis for an implementation of a real-time malleable surface for molecular modeling applications.

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As the Helix Turns, or, Rational Design of Sequence Specific DNA Minor Groove Binding Drugs

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In seeking DNA binding drugs that can be targeted to specific sequences, minor groove binders are preferable to intercalators because they are more strongly sequence-specific. X-ray structural analysis of DNA/drug complexes — for example, CGCGAATTCGCG with the antibiotic netropsin — reveals the basis for the preference of most minor groove binders for regions of the DNA containing A.T. base pairs. The presence of the N2 amino of guanine in the minor groove sterically prevents a drug from settling down against the floor of the groove. Since reversals of base pairs are not distinguishable in the minor groove, the floor of the groove reads essentially as binary code: A hydrogen bond donating group is either absent or present for an A.T. or a G.C. base pair, respectively. The substitution of an imidazole for one of the pyrrole rings of netropsin (creating a "lexitropsin") is a possible way to read a G.C. in the minor groove: The hydrogen bond donating amino can be accommodated by a cleft in the drug, which also provides a hydrogen bond acceptor. However, such a change in drug structure may not result in a G.C. requirement but simply permit it.

In an animated film, the details of the crystal structures of the dodecamer CGCGAATTCGCG, and of netropsin complexed with it, are presented as bond skeletons and van der Waals dotted surfaces using vector graphics. Cartoon representations of the DNA and drugs are used to illustrate the rational, for the design of hypothetical sequence-specific minor groove binders.

Automated Protein Structure Data Bank Similarity Searches and Their Use in Molecular Modeling with MIDAS

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Active site modeling of proteins and molecular structure prediction are important approaches in molecular biology. An automated approach for structure predictions of novel sequences is a search for complete or partial match of the new protein sequence against the sequences of known three-dimensional (3D) structures. Data analysis is further aided by fast and accurate pictorial representation of the 3D structures.

The most widely used protein database for sequence searches, PIR (Protein Identification Resource, developed at NBRF, National Biomedical Research Foundation, Washington, DC), does not contain any 3D structure information. The Brookhaven Protein Data Bank does contain 3D coordinates, but it is not formatted for extensive similarity searches. We have generated a protein sequence database with the format and structural advantages of PIR and the Brookhaven Protein Data Bank. Modifications were made to PSQ (Protein Sequence Query program, VMS version,