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,

developed by the PIR at NBRF), which allow us to search, with or without mismatches, the residues of an unknown protein fragment within our sequence database. Successful matches are used to generate command procedure files. These command procedures, interfaced with the molecular modeling program MIDAS (Molecular Interactive Display and Simulation, IRIS version, University of California, San Francisco), in turn automatically display the 3D structures of the matched residues and extract their internal parameters. The advantages of this new methodology, as an effective tool, will be illustrated in the modeling of a putative calcium-binding site of (Ca^{2+} + Mg^{2+})-dependent ATPase (Ca^{2+} −ATPase) of rabbit muscle sarcoplasmic reticulum.[1]

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Molecular Graphics of Lipid Structures

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Molecular graphics display of lipids and lipid aggregates has received only minor attention due to the difficulty of obtaining crystal structures. Reasonable depictions of lipids are crucial, however, for understanding the molecules' physical chemistry. Three-dimensional models are necessary because membrane formation by lipids is dominated by subtle intramolecular forces. Furthermore, the iconographic or schematic representations of the past cannot provide a suitable starting point for subsequent higher-level molecular modeling of lipid/lipid, lipid/small molecule and lipid/protein interactions. Physical CPK models suffice for individual molecules but are too cumbersome for larger structures consisting of lipid arrays (i.e. monolayers and bilayers). In this abstract we describe our strategy for the depiction of lipids in general, some of the problems unique to these systems, and several applications of our methodology.

A database composed of the 14 lipid crystal structures available in the literature has been established. The database is maintained in the PDB format and can be used with a variety of existing tools (MIDAS, FRODO, MOGLI, etc). Modifications were made to the acyl chains when needed to conform to standard hydrocarbon geometry. Novel lipids are constructed by adding or deleting library fragments. Monolayers and bilayers were constructed by propagating the lipid structures in an x-y plane using symmetry operations based on the crystallographic data.

Visualization of lipid superstructures (monolayers and bilayers) is often more difficult than viewing protein models because of the greater packing density and repetitive features of lipid structures. Selective use of color, van der Waal's, and Connolly surfaces was required to differentiate one lipid molecule from another and to examine their interactions. Stereo viewing was not always useful with lipid aggregates because of the planar nature and low depth of field of a monolayer.

A common problem with both protein and lipid depiction is the requirement for hard-copy output for archival and publishing purposes. Color print technology is expensive at best and is often not available. Strictly black-and-white pictures, on the other hand, cannot convey enough information to be useful. Gray scaling is required for meaningful results. One can photograph a black-and-white picture from a color screen, but it is difficult to predict how color intensities will translate into gray scales. Therefore, it is better to photograph a gray-scale monitor. When a photograph is not required, or is not convenient, it is often possible to "print" a plain black-and-white picture from the display program to a PostScript file. PostScript is a page-description language for printers, and PostScript files can be directly modified by a programmer to include gray scaling or to selectively highlight lines by increasing their width. We have found the ability to post-process our images in PostScript extremely valuable in compensating for the lack of color (see Figure 1).

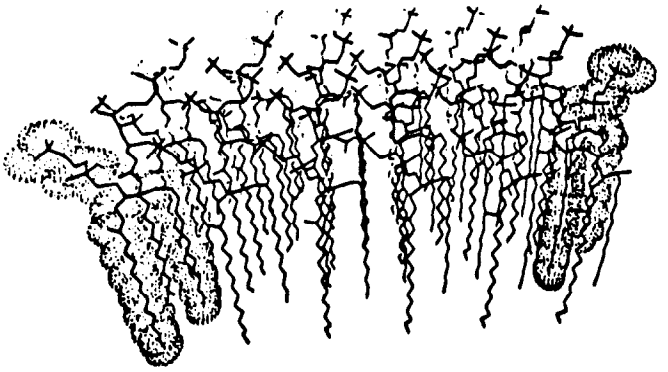

Figure 1. Perspective view of a DMPC monolayer

We have also examined the mechanics of computer graphics display. Our early efforts resulted in the development of SPOCK on a VAX 8650 using a Ram Tek display. SPOCK does not have all of the features of a program such as MIDAS, but it does display our lipid molecules in a timely and attractive manner and is easily altered for either color or gray-scale viewing. With this success, a new program is being implemented on more readily available personal computers. We chose the Apple Macintosh family as our hardware platform because of the high graphics standards, the unique interface, and the availability of a wide range in price/