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Interactive modeling of supramolecular assemblies

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The modeling of supramolecular structure presents two major challenges: (1) managing the large amount of sequence, structural and biochemical data, and (2) presenting the data to the user in a flexible and comprehensible manner that addresses these problems. We describe a visualization environment for the creation and analysis of supramolecular models. A set of modular symmetry tools, collectively called SymGen, has been created, providing a flexible platform for the creation of complex assemblies, with interactive control of all symmetry elements and their parameters. A second tool, SymSearch, allows a range of parameters defined within SymGen to be sampled and the resulting conformations to be evaluated. The environment avoids information overload, caused by the large number of atoms in supramolecular complexes, by using a multiresolution spherical harmonic representation that allows the user to display only essential features. Spherical harmonics also enables control of the triangulation level, allowing the user to reduce the complexity of the geometric description to retain interactive speed. The visual fidelity of the surface data is retained by using texture maps that are independent of the resolution of the underlying triangulation. We describe the design and implementation of this environment, and three illustrative examples of its utility. © *1999 by Elsevier Science Inc.*

INTRODUCTION

The scale level between macromolecular structure and supramolecular ultrastructure is difficult to probe experimentally. Single, purified molecules are effectively studied at atomic resolution using X-ray crystallography and nuclear magnetic resonance (NMR) spectroscopy, as demonstrated by the wide variety of atomic structures available in the Protein Data Bank. In addition, biochemical and mutagenesis studies can provide information on sequence conservation and proximity of groups in complexes. At the other extreme, supramolecular and cellular ultrastructures, involving a large number of distinct, heterogeneous components, are studied at lower resolution by electron and light microscopy. Computational modeling can fill the gap between atomic structure and ultrastructure by combining atomic information from X-ray crystallography and NMR spectroscopy with ultrastructural information from electron and light microscopy. This approach has been used effectively, for example, in the study of virus structure,[1–3] actin–myosin interaction,[4] and ribosomal function.[5–7]

The computational analysis of supramolecular structure presents two methodological problems. The first is complexity: supramolecular assemblies, such as viruses or chromatin fibers, contain millions to hundreds of millions of atoms. All-atom representations of systems of this large size tax the capabilities of current computational approaches; interactivity may be lost, and the images may become so complex as to be incomprehensible. A multiresolution scheme for representation solves this problem. When dealing with entire assemblies, a simplified representation is used, perhaps modeling only an approximate surface for each subunit. The scheme retains atomic information, however, so that the atomic details of the interaction between each subunit may be selectively displayed and analyzed.

The second methodological problem is the need to manipulate this complex information in a flexible, but still comprehensible, manner. Different systems will often require different techniques: for viruses, an entire icosahedral capsid must be generated from a single protomer, and different placement of each protomer relative to the symmetry axes will change the final capsid structure in functionally interesting ways; for actin–myosin interaction, two separate molecules form an assembly with helical symmetry, and both the atomic details of the interaction site and the overall orientation of myosin relative to the actin filament are of interest; for the ribosome, the assembly has minimal symmetry, so a responsive method of simultaneously manipulating many different proteins and RNA is required. A flexible transformational environment is needed to provide the necessary tools to explore applications such as these. In addition, three-dimensional data from electron micrograph reconstructions or electron crystallography may also be

Color Plates for this article are on pages 162 and 163.

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available, so the representation should include the ability to display these data along with the atomic representation.

This article describes the design and implementation of a computational environment that addresses these problems (summarized in Table 1). Spherical harmonic surfaces[8] with texture mapping[9] are used to create a multiresolution representation of the subunits within an assembly, allowing facile transition from low to high resolution. The interactive creation and manipulation of supramolecular assemblies is accomplished by a set of symmetry-generating and geometric transformation tools, collectively called SymGen, which may be combined to form custom applications. A second set of tools, called SymSearch, allows a range of parameters defined within SymGen to be sampled and the resulting conformations to be evaluated. Combined with the diverse tools available for molecular visualization,[10] the spherical harmonic representation, SymGen, and SymSearch allow a wide range of useful applications to be rapidly prototyped, and then explored and analyzed in detail.

The current environment has been implemented within the Application Visualization System (AVS) dataflow environment,[11] allowing interactive construction of symmetry-generating networks, interactive control of the resolution of the spherical harmonic representation, and application of many visualization tools. The spherical harmonic representation and the SymGen and SymSearch modules, however, are not limited to the dataflow environment—they may be combined, outside of AVS, with search methods and methods for energy evaluation for quantitative analysis of supramolecular conformation and assembly.

Table 1. Modeling of supramolecular assemblies

Problem	Solution
Information overload	Multiresolution Models
	Only essential features displayed
Interactivity	Triangulation Control and Texture Mapping
	Model resolution commensurate with data
	Texture resolution independent of triangulation level for visual fidelity
Transformation control	SymGen
	Modular for reconfigurability
	Objects transformed at end of symmetry-specification pipeline
	Basic geometry duplicated for identical components
Configuration evaluation	SymSearch
	Search space automatically sampled
	Incorporated into existing energy evaluation tools

METHODS

SymGen: symmetry-generating modules

The goal of SymGen is the rapid, interactive creation and manipulation of supramolecular assemblies composed of many subunits. SymGen is partitioned into two steps: the first step creates a stream of transformation matrices, and the second step applies them to the objects. Separation of these two steps improves both the speed and the flexibility of coordinate generation. The representation of each subunit may be complex, composed of a ribbon diagram, full bond diagrams, or a surface representation, so the actual transformation of geometry is performed only at the end of the symmetry pipeline. This allows fast, interactive control of individual symmetry and transformation elements in a complex symmetry network, requiring only a single coordinate transformation per object, and reduces memory requirements, as only one copy of each geometric object is stored. The flexibility of SymGen is also improved: the stream of matrices may be applied to a series of nonidentical objects, allowing the modeling of quasisymmetry or even multicomponent objects with no symmetry.

SymGen consists of six modules that read, write, generate, merge, multiply (concatenate), and apply transformation matrices. A seventh module, separate from the symmetry-generating stream, is necessary to create the names of each of the objects in the composite object. The matrix generator module is available in many forms, each performing a different symmetry or transformation operation, allowing for creation of simple, interpretable networks. An example, described in more detail below, is included in Color Plate 1. Matrix generator modules have been implemented for the operations shown in Table 2. These fall into two classes: transformations, which generate a transformed matrix for each matrix input, and symmetries, which generate an entire symmetry group, including the identity matrix, for each matrix input. Transformations include: translation along an arbitrary axis, and two methods for rotation, one about an arbitrary axis and the other about an arbitrary center using Euler angles. Symmetries include: cyclic, dihedral, tetrahedral, octahedral, icosahedral, and helical. He-

Table 2. SymGen operations

Operation	Description
Transformations: Return a single matrix	
Translate	Translate along an arbitrary axis
Rotate	Rotate about an arbitrary axis
Orient	Rotate using Euler angles
Random	Random orientation and translation vector
Symmetries: Return matrices defining the symmetry including (optional) identity matrix	
Cyclic	Cyclic N-fold point group
Dihedral	Dihedral N-fold point group
Tetrahedral	Tetrahedral point group
Octahedral	Octahedral point group
Icosahedral	Icosahedral point group
Helical	Helix with user-defined parameters and bounds

lical symmetries require a description of the bounds (currently, the number of subunits is specified). Mirror and inversion transformations, their corresponding symmetries, and homogeneous scaling have not been implemented, as the current applications are limited to biological molecules with fixed stereochemistry and scale; however, other transformations, such as these, may be easily implemented within the environment for general applications.

The matrix generator modules are the heart of SymGen: custom combinations may be devised to fit each specific application. A single matrix generator module may operate by itself, producing one matrix, as in the case of rotations and translations, or a stream of matrices may be generated, as in the case of the point group and helical symmetries. Alternatively, each matrix generator can act as a filter, applying the symmetry to an input stream of matrices from another matrix generator. In this way, nested symmetries may be generated: for instance, a "dimer of trimers" may be created by feeding the output of a cyclic threefold generator, which creates three matrices, into a cyclic twofold generator, yielding a total of six matrices. In many cases, it is also useful to connect several matrix generators in parallel: for instance, if one needed two separate helices side by side. For this, a module has been written to merge two separate matrix streams into a single stream. Color Plate 1 shows examples of sequential and parallel combinations for building a viral capsid.

The symmetry-generating modules use two data types: matrices and object names. In the AVS[11] implementation, both are treated as text strings and are passed through the network as fields. The object names are read from an external text file or are generated within the network. By using a field for object names, the binding of names is controlled by individual modules, providing considerable flexibility in configuration of the network. The matrix string includes a typical 4×4 transformation matrix, and character data that describe how the matrix was generated. This additional information represents the conformational space that a network of matrix-generating modules defines and is used by the search generator, described below, to explore systematically the space defined by the network.

SymSearch: sampling conformations within a SymGen network

A SymGen network, with a set of fixed symmetry elements oriented in space, defines a family of supramolecular structures. For instance, imagine a single 10-fold helical axis. By placing an individual subunit at different positions and orientations relative to the helix axis, many different, but related, composite structures may be obtained. In most biological complexes, only one of these positions and orientations will yield a stable helical complex. Often, the task facing a researcher is to find that single stable position and orientation, given a known structure for the subunit and the approximate symmetry relations.

By interactive manipulation in SymGen, users are given the freedom to place any given symmetry elements in the desired positions, then to explore reasonable values of the variable parameters defining these elements, such as helical rotations and translations or arbitrary cyclic rotations, and finally to explore the placement and orientation of subunits relative to the elements. In many cases, however, a more quantitative analysis is desired. For instance, one might wish to set up a helical symmetry, and then modify the helical parameters and the placement of subunits to best fit an experimental electron density map. The ability to sample values of each parameter and to perform an energetic analysis of each resulting conformation would allow systematic and quantitative generation and evaluation of complexes that cover the entire space defined by the symmetry. We have implemented SymSearch, a general conformation sampling tool, that facilitates this type of analysis.

Rather than implementing energy evaluation and data comparison methods within SymGen, SymGen automatically generates a set of C functions that can be incorporated into existing programs to allow them to perform searches on the transformation space defined by a given SymGen network. This approach was motivated by the desire to make SymSearch as general as possible. The calling program provides a description of the space to be searched (the ranges of rotations and translations, helical pitches and angles, etc.) and SymSearch functions incorporated into the program return a stream of matrices or coordinates for each configuration in this space. An example of a search through conformations of the cardiac gap junction is presented below. For systems with prohibitively large search spaces, Monte Carlo or other nonexhaustive approaches may be taken, again using the symmetry modules to generate matrices or coordinates for each conformation.

SymSearch requires two types of information: (1) a description of the symmetry elements to be used, and (2) a description of the ranges of each parameter to be searched. The former is incorporated into the matrix data type used in SymGen modules: it is a typical 4×4 transformation matrix, but also contains information that describes how the matrices were generated from the fundamental geometric operations. The ranges to be searched are read from a text file that contains the upper bound, lower bound, and increment for each symmetry parameter to be searched.

Exhaustive searches are often implemented with nested loops, with one loop for each dimension in the search space. This direct algorithm suffers from a drawback: a high-dimensional space requires a deep nesting of loops, whereas the dimensionality of the problem, or at least its upper limit, is fixed when the program is compiled. At a small additional bookkeeping cost, this loop nest can be collapsed into a single loop with an index that ranges from 1 to $(C_1 \times C_2 \times ... \times C_N)$, where C_i are the counts of the $i = 1$ to N individual loops. This index increments a mixed radix counter where each digit of the counter represents a search variable and ranges from the lower to the upper bound of the variable. Each time a variable exceeds its upper bound, it is reset to its lower bound and the value of the next variable is advanced by its increment. A carry-out of the last variable indicates that the search has been exhausted.

Spherical harmonic representation of molecular surfaces

The spherical harmonic representation (described in full in Refs. 8 and 9) is a parametric approximation of the molecular surface, with natural multiresolution properties. Generation of the surface begins with a triangulated molecular surface, calculated from atomic coordinates using a program such as MSMS.[12] To model the complex overhangs and invaginations of typical protein surfaces, a topological mapping of the sur-

face to a unit sphere is performed by smoothly deforming the surface into a sphere while retaining the topology and triangulation of the original molecular surface. After this mapping, each point on the sphere is associated with a particular Cartesian coordinate on the original surface, and may also be associated with any physicochemical properties of the atom at that location. The spherical harmonic functions are then used to approximate these Cartesian coordinates, and the atomic properties, in a parametric manner.

Spherical harmonics provide a natural method for multiresolution representation. By choosing an appropriate level of expansion, the level of detail may be chosen, as shown in Color Plate 2. Using coefficients to order 5 yields a very smooth, low-resolution representation, requiring a small number of triangles for display. Using an order 30 expansion yields a high-resolution representation, which shows most of the atomic features of the surface. Texture mapping of surface properties may also be modified in this multiresolution fashion: using a low-order expansion, the overall features of the surface are seen, and with high-order expansions, the local detail may be displayed. The triangulation level of the surface is also under separate interactive control, allowing a coarse triangulation (for rapid manipulation) to be combined with a finer level of texture-mapped detail.

Although texture mapping has several variations, for example, one-, two-, three-dimensional, and procedural textures, our methods rely primarily on two-dimensional texture mapping. A two-dimensional image is applied to a surface in 3-space, analogous to applying a "decal" to the surface. In general, however, a two-dimensional image cannot be applied to an arbitrary surface without distortion, and therefore we compute a predistorted texture image so that these distortions are removed when applied to the molecular surface.[9] This procedure is analogous to computing a planar map of the world so that the resulting image, when stretched at the equator or compressed at the poles, forms a correct globe when applied to a sphere. This procedure improves rendering efficiency because different surface properties can be displayed by changing only the texture image; the underlying geometry is constant.

Availability

Information regarding availability of the spherical harmonic surface software and the symmetry tools may be obtained by contacting the authors via olson@scripps.edu. The interactive tools have been designed for use within the AVS dataflow environment (available from AVS Inc., Waltham, MA, www.avs.com), which runs on Unix and NT platforms.

RESULTS

The results presented here have been produced in the AVS dataflow environment,[11] using graphics workstations from Silicon Graphics, Digital Equipment, and Sun Microsystems. The software can be implemented on a large number of Unix- and Linux-based workstations. AVS allows independent modules to be connected graphically and interactively to create a network to produce a custom application. AVS has many of the features necessary for effective modeling and visualization of biomolecules: its rendering capabilities are of high quality, allowing the creation of detailed representations; it has extensive tools for the handling of three-dimensional data; and the modular nature of the environment allows rapid prototyping of new visualization techniques with a minimum of new coding effort. A number of auxiliary modules have been created for biomolecular visualization in AVS, providing a rich set of tools for analysis of biomolecular assemblies. These include efficient programs for creating solvent-accessible surfaces, space-filling representations, bond diagrams, ribbon diagrams, and bent-tube diagrams, and an extensive facility for handling biomolecular coordinates.[10]

Poliovirus capsid

Poliovirus has icosahedral symmetry, with a protomer composed of four separate protein chains occupying each symmetry position. Assembly is thought to proceed through formation of pentamers, 12 of which then assemble to form the capsid. Color Plate 1 shows a SymGen network within AVS that allows individual orientation of protomers within a pentamer, and pentamers along the six fivefold axes of the icosahedron. The uppermost two modules orient and place an individual protomer in space. A fivefold cyclic point group then creates the pentamer. Subsequent rotation and translation modules allow this pentamer to be translated along the fivefold axis and rotated about it. The threefold, and then the three twofold, modules generate the entire icosahedron. Separate control panels (not shown) allow the parameters of each module to be set. For instance, the three twofold axes, apart from having different orientations in space, must be flagged such that only one passes through the identity matrix.

The snapshots in Color Plates 1 and 2 incorporate a multiresolution representation for the surface of the protomer using spherical harmonics. The effective resolution of the surface may be modified interactively by incorporation of terms to higher or lower order, creating a surface that closely matches the solvent-accessible surface or a surface that displays only the major morphological features of the protomer. AVS also supports texture mapping of geometry, so chemical and physical properties of the viral proteins may be used to color the surface. Color Plate 2 incorporates a texture map that colors the surface based on the chain identifier, revealing the location of the four protein chains.

Gap junction

Cardiac gap junctions electrically couple neighboring cells, organizing the pattern of current flow to allow coordinated muscle contraction. Yeager[13] has reconstructed a three-dimensional map of the cardiac gap junction CX43 from electron diffraction of two-dimensional crystals. The gap junction is composed of six subunits arranged in C_6 symmetry. Each subunit is composed of four α-helical segments that extend through the membrane. SymGen allows evaluation of atomic models based on this low-resolution map.

The map was interpreted interactively to define the central axis vector of each α helix in one subunit. A SymGen network was then developed to allow hierarchical control of each of the four helices separately. Ideal α helices were constructed from the sequence,[14] and then superimposed on the vectors defining the electron density of the helices. Translations along this vector and rotations about it are under interactive control, and a SymGen network then creates the entire sixfold complex.

SymSearch was used to sample conformations defined by

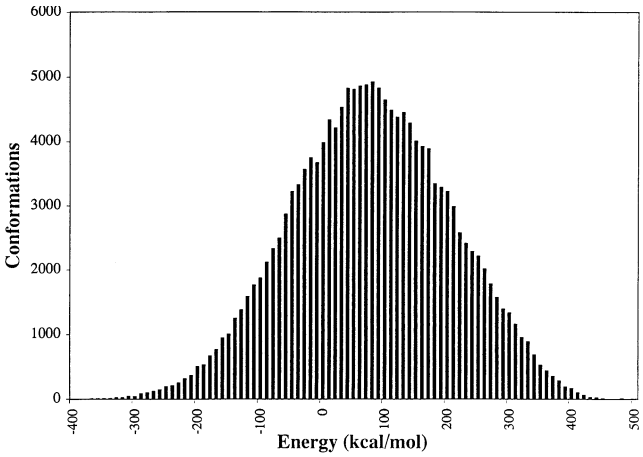

Figure 1. Energy spectrum of a simulation of the cardiac gap junction. An exhaustive search of conformations was performed using SymSearch, rotating each of the four helices by 60° increments, and translating three of the helices from –3.0 to 3.0 Å in 1.5-Å increments. Energies were calculated by a residue-based scoring function.[15] *The number of conformations found to be in various ranges of energies are shown in the graph. Points are included only for those regions with nonzero counts. SymSearch allows custom conformational searches of this type to be easily designed and performed.*

this network. Rotations about each of the four axes and translations along three of the axes were sampled, and the conformations analyzed by a residue-based scoring function.[15] The energy spectrum of this search is included in Figure 1. Conformations at the low end of this bell-shaped curve provide starting models for further refinement.

Molecules *in vivo*

Models of the molecular structure of living cells.[16,17] quickly run into the problem of complexity and management of large molecular ensembles. A typical 100-nm cube of red blood cell stroma contains more than 3,000 hemoglobin molecules. As spheres this is not a computational challenge, but at higher levels of detail the data become unmanageable, so multiresolution structure descriptions are essential.

Color Plate 3 shows a model of a volume of blood plasma, including 240 plasma molecules and a virus. SymGen, combined with spherical harmonic models, allows this complex environment to be modeled with a minimum of computational expense. For the virus, the surface is calculated for a single protomer, and the surface is replicated 60 times to form the capsid. The antibodies are generated similarly: one heavy and one light chain are modeled at atomic detail and the surface calculated, and copies of the surface used to generate all of the dimeric IgG molecules as well as the decameric IgM at lower left. SymGen was configured to place all molecules randomly in the space, and overlaps were resolved interactively to form the image.

The spherical harmonic representation facilitates display that is commensurate with the resolution of the data. For instance, serum albumin has not been solved at the atomic level, so the model was generated to represent the observed molecular weight and proposed domain structure of the molecule.[18] Only low-order expansions are used, giving an approximate, low-resolution image. The symmetry-generating modules simplified the merging of high-resolution data (i.e., the antibodies and the virus) and low-resolution data (i.e., serum albumin) within the same system.

DISCUSSION

A proliferation of exciting applications appeared when the Evans and Sutherland MultiPicture system was first made available to the molecular community in the late 1970s. GRAMPS captured the utility of this graphics engine in a unique manner, allowing new applications to be configured with a minimum of programming time.[19] In particular, GRAMPS made the creation of complex transformation schemes unusually simple. Unfortunately, this facile reconfigurability of transformation, so simple in GRAMPS, has been lost in many current packages. So perhaps it comes as no surprise that one of the most popular applications of SymGen has been one of the most mundane. Several collaborators have created a network that simply displays two copies of a molecule side by side, each colored by a different property, such as hydrophobicity on one and amino acid conservation on the other. Then, as one molecule is interactively manipulated for observation, the other performs the same motions, presenting an identical view of both molecules for easy comparison. SymGen, because of its modular formulation, easily accommodates unforeseen applications such as this.

Rapid, multiresolution computation and visualization techniques are essential as we take the next step in structural molecular biology, from macromolecular structure to supramolecular and cellular structure. The dataflow environment, exemplified by AVS, is an ideal testbed for these applications, allowing interactive construction of visualization techniques and interactive control of parameters. By partitioning tasks such as geometry creation from structural data, generation of assemblies and ensembles, and rendition of options into separate modules, the user is allowed unprecedented flexibility in structural exploration. The resultant images are also very beautiful.

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