D1. Molecular Graphics

1. **Introduction**
   1.1 Importance of Molecular Graphics
   1.2 Almost Science Fiction
   1.3 History of Molecular Visualizations

2. **3D Perception**
   1.4 Commercially Available Molecular Kits

3. **Visualization**
   1.5 Progress in Hardware and Algorithms

4. **Editing & Manipulation**
   1.6 Molecular Graphics Functions

5. **Surfaces & Volumes**

6. **Visualizing Interactions**
D1.1.1 Importance of Molecular Graphics

One of the most important things for the molecular modeler is to visualize molecular structures and interactions in order to calibrate his intuition and to develop a feeling of the structures concerned.
D1.1.2 Almost Science Fiction

Computer graphics enables us to visualize complex machinery underlying highly coordinated biological processes. Geometrical measurements, shape analyses, design and evaluation of candidate prototypes are all operations that are used daily by the usual locksmith but these operations are more complicated in drug discovery. Today, research teams using very unusual visual apparatus work hours and hours with 3D graphical displays and can virtually "enter" into the precise 3D structure of a protein and construct atom by atom an intelligent drug that will stop the development of a disease. One would think that that the following scene is taken from a science fiction movie but today it is possible with computer graphics!
D1.1.3 History of Molecular Visualizations

In the beginning, no graphical software programs existed for 3D drug design. Computers existed but they were mainframe computers. Physical models (plastic or metallic) were very popular and allowed "hand" manipulation of the three-dimensional structures.
D1.1.3 History of Molecular Visualizations

The second period witnessed the development of molecular modeling software in drug design. The output of these programs were generated numerically or with graphical representations produced by graphical plotters.
D1.1.3 History of Molecular Visualizations

One of the first commercially available graphical systems was "Tektronix" displays. They had poor resolution and no colors. They were so slow that it was not possible to envision that they could allow real-time rotations.
D1.1.3 History of Molecular Visualizations

"Evans & Sutherland" graphics system revolutionized molecular modeling. They provided colored pictures of excellent quality and included real time rotation and stereo. However the cost of a single display was $150,000! Towards the end of that period, "Silicon Graphics" introduced less expensive yet high performance workstations that were within the budget of most academic and industrial laboratories (approximately $30,000).
D1.1.3 History of Molecular Visualizations

A large range of graphic workstations became available to meet the need of modeling applications ranging from simple, small molecules to complex macromolecules. Basic inexpensive systems like PC or Macintosh combined with efficient graphic software were available for less than $1,000 and provided visualization means that were accessible to all.
D1.1.4 Commercially Available Molecular Kits

Hand-held commercial models have the advantage of being concrete objects that can be manipulated and provide a physical "feeling" of their actual geometrical features. It is not possible to construct on a routine basis proteins, neither is it easy to introduce a molecule in its active site or to superimpose together two or three proteins or two or three small molecules. Molecular graphic software programs offer great flexibility and include the visualization of color-coded properties that are associated to the different structural fragments.
D1.1.5 Progress in Graphical Hardware and Algorithms

The simultaneous development of advanced graphic hardware and graphic algorithms for efficient visualization revolutionized the 3D displays.

\[
\int \frac{du}{u} = \log_e u + C. \\
\frac{1}{2} \left( u \sqrt{1 - u^2} + a^2 \sin \frac{u}{a} \right) + C.
\]
D1.1.5 Progress in Graphical Hardware and Algorithms

First steps in computer graphics were very disappointing. The following represents an attempt made in 1967 to represent the surface of a molecule with relatively advanced graphic displays based on successive sections of its volume.
D1.1.5 Progress in Graphical Hardware and Algorithms

The following shows the quality of the pictures that can be generated with efficient graphical algorithms (open GL). The algorithms were developed to achieve optimal efficiency in terms of both quality and speed.
D1.1.6 Molecular Graphics Functions

A molecular graphics system should provide the following three basic functions. **Editing**: Some type of "construction kit" must be available so that molecules can be built and modified. **Visualization**: Each molecule should be visualized in three-dimensions, color-coded and labeled. **Manipulation**: It must be possible to move and rotate molecules independently in any direction and about any axis and to manipulate their torsion angles.
D1. Molecular Graphics

1. Introduction
2. 3D Perception
3. Visualization
4. Editing & Manipulation
5. Surfaces & Volumes
6. Visualizing Interactions

2.1 The Perception of the Third Dimension
2.2 From 3D Coordinates to Screen
2.3 Real Time Manipulation
2.4 Depth Cueing
2.5 Perspective
2.6 Stereo
2.7 Hardware Stereo
D1.2.1 The Perception of the Third Dimension

Although defined in 3D, the molecular representations are visualized on a 2D computer screen. In drug design, good perception of the three-dimensional nature of the molecule is essential and many techniques of graphic software provide a three-dimensional illusion.
D1.2.2 From 3D Coordinates to Screen Coordinates

The representation of a molecule (3D object) on a graphic display actually consists of calculating a series of projections of the 3D object onto the 2D plane of the screen.
D1.2.2 From 3D Coordinates to Screen Coordinates

The 2D projection is not sufficient. You have to rotate the object to perceive its 3D features. The following represents the crystal unit of Zirconium. Notice the difference when you rotate it!
Real-time manipulation of a representation of molecular structure can provide a convincing three-dimensional illusion of the molecules.
D1.2.4 Depth Cueing

Depth cueing is a technique in which distant objects are drawn progressively darker. This creates the perception of depth in the representation.
Perspective is a technique in which distant objects are drawn progressively smaller.
Whereas real-time manipulations provide a 3D feeling, stereo is critical to maintain that three-dimensional perception. Stereo perception involves presenting a left and right eye view of the molecule to the appropriate eye of the user. In this case, dividing the screen into two halves provides stereo and the left and right views are represented and are ready to be mentally superimposed by the user.
Hardware stereo is a trick incorporated in graphics systems. The monitor runs at double the frequency so that the screen presents alternate eye views one after another. The user wears a pair of goggles containing liquid crystal shutters and an infrared emitter on the workstation synchronizes the visibility of the screen to each eye. These capabilities are sometimes incorporated in the hardware and software equipment of a workstation and are available to support effective hardware stereo.
D1. Molecular Graphics

1. Introduction
2. 3D Perception
3. Visualization
4. Editing & Manipulation
5. Surfaces & Volumes
6. Visualizing Interactions

3.1 3D Representation of Small Molecules
3.2 Quality of Rendering
3.3 Atomic Color-Code Convention
3.4 Coloring Molecules or Sets of Atoms
3.5 Labeling Functionalities
3.6 Alpha Carbon Trace
3.7 Ribbon Representation
3.8 Ribbon Types
3.9 Visualization of Protein Properties
D1.3.1 3D Representation of Small Molecules

This is the simplest and most common way to visualize molecules where the bonding arrangement is represented in 3D. This type of representation is also called "wireframe".
D1.3.1  3D Representation of Small Molecules

In this type of representation the bonds are represented as tubes. It is also called "polytube".
D1.3.1 3D Representation of Small Molecules

Here the molecule is displayed as the assembly of atoms and bonds. Atoms are represented as small spheres and bonds as tubes.
D1.3.1  3D Representation of Small Molecules

In this type of representation the molecule is defined as a set of spheres of Van der Walls radii of the individual atoms.
D1.3.2 Quality of Rendering

Although considered as a sphere, in molecular graphics visualizations, an atom is treated as a polyhedron. A view calculated with a small number of faces is of poor quality; however, by increasing the number of faces the quality increases. With high performance processors, excellent real-time rendering can be obtained with small molecules. With proteins, visualization is possible but not in real-time.
D1.3.2 Quality of Rendering

Although considered as a sphere, in molecular graphics visualizations, an atom is treated as a polyhedron. A view calculated with a small number of faces is of poor quality; however by increasing the number of faces the quality increases. With high performance processors, excellent real-time rendering can be obtained with small molecules. With proteins, visualization is possible but not in real-time.
D1.3.2 Quality of Rendering

Although considered as a sphere, in molecular graphics visualizations, an atom is treated as a polyhedron. A view calculated with a small number of faces is of poor quality; however, by increasing the number of faces, the quality increases. With high performance processors, excellent real-time rendering can be obtained with small molecules. With proteins, visualization is possible but not in real-time.
D1.3.3 Atomic Color-Code Convention

A color is associated with each type of atom. The following color-code convention is generally accepted and implemented in most popular molecular graphic systems.
D1.3.4  Coloring Molecules or Sets of Atoms

In this representation the atoms are colored according to the atomic color-code convention and a color is also given to half of the bonds of this atom.
D1.3.4 Coloring Molecules or Sets of Atoms

A different color is given to each of the molecules visualized in the screen. It is useful when several molecules are superimposed to distinguish and recognize the individual molecules in the view.
D1.3.4 Coloring Molecules or Sets of Atoms

All or part of a given molecule is visualized in one color. Interactive "picking" of the molecule or a set of atoms allows one to associate a color with a specified set.
D1.3.4 Coloring Molecules or Sets of Atoms

Various molecular properties can be visualized. The quantitative or qualitative variations can be color-coded defined and visualized for every element considered: atom, bond or the molecular surface.
D1.3.5 Labeling Functionalities

Various labels can be added: those who are associated with the molecules and those associated with the screen. The first ones move with the molecules (green) and the other ones are fixed (white).
D1.3.5 Labeling Functionalities

If an entire molecule is represented in one color, it is not possible to recognize the different types of atoms. It is useful to label specific atoms in order to facilitate further analyses (e.g. hydrogen bonding capabilities or atomic mimicry).
D1.3.5 Labeling Functionalities

This type of representation is useful when associated with computerized numerical treatments or to follow the 3D view associated with a publication in which some details are given and atoms are described by their number (Nitrogen 24, or hydroxyl of Ser-76).
Macromolecules are complex entities. They can be displayed as small molecules using various techniques (ball and stick, space-filling, etc.). Other representations are specific to macromolecules and give an overview of the overall molecular architecture of the protein.
D1.3.6 Alpha Carbon Trace

This representation is also called “carbon-alpha trace”. It is useful for editing and aligning different proteins.
D1.3.7 Ribbon Representation

Ribbon representations are specific to protein and provide an overview of the overall molecular architecture (secondary structure) of the protein. Alfa-helixes, beta-sheets and beta-turns are easily recognized.
D1.3.8 Ribbon Types

Here are different types of ribbon displays.
D1.3.8  Ribbon Types

Here are different types of ribbon displays.
D1.3.8  Ribbon Types

Here are different types of ribbon displays.

- Line
- Flat
- Solid
- Tube
- Schematic
D1.3.8  Ribbon Types

Here are different types of ribbon displays.
D1.3.8 Ribbon Types

Here are different types of ribbon displays.

Line  Flat  Solid  Tube  Schematic
D1.3.9  Visualization of Protein Properties

The macromolecular structure can be color-coded according to various physico-chemical properties such as residue types, electrostatic or hydrophobicity. The representation of color-coded surfaces of molecular systems has revolutionized molecular design analyses.
D1.3.9  Visualization of Protein Properties

The macromolecular structure can be color-coded according to various physico-chemical properties such as residue types, electrostatic or hydrophobicity. The representation of color-coded surfaces of molecular systems has revolutionized molecular design analyses.
D1.3.9 Visualization of Protein Properties

The macromolecular structure can be color-coded according to various physico-chemical properties such as residue types, electrostatic or hydrophobicity. The representation of color-coded surfaces of molecular systems has revolutionized molecular design analyses.
D1.3.9 Visualization of Protein Properties

The macromolecular structure can be color-coded according to various physico-chemical properties such as residue types, electrostatic or hydrophobicity. The representation of color-coded surfaces of molecular systems has revolutionized molecular design analyses.
D1.3.9 Visualization of Protein Properties

The macromolecular structure can be color-coded according to various physico-chemical properties such as residue types, electrostatic or hydrophobicity. The representation of color-coded surfaces of molecular systems has revolutionized molecular design analyses.
D1. Molecular Graphics

1. Introduction
2. 3D Perception
3. Visualization
4. Editing & Manipulation
   4.1 Structure Manipulation & Editing
   4.2 3D Molecular Editing Functions
   4.3 3D Molecular Constructions
   4.4 Real-Time Rotations and Translations
   4.5 Zoom Function
   4.6 Control of Torsion Angles
   4.7 Slab or Clip
5. Surfaces & Volumes
6. Visualizing Interactions
D1.4.1 Structure Manipulation & Editing

In molecular modeling, the computer software provides tools that interact with the molecules visualized onto the screen. The most basic structure manipulations are: translation of all molecules, translation of one molecule relative to another, rotation of all molecules, rotation of one molecule relative to another, rotation of flexible bonds in a molecule, and molecular editing. These operations also are useful for the superimposition of molecules or for the insertion of a small molecule into the cavity of a macromolecule.
D1.4.2 3D Molecular Editing Functions

Add  Delete  Fuse  Connect
D1.4.3 3D Molecular Constructions

A simple method for adding new atoms in a molecule is to add hydrogen atoms on a given atom and then exchange the hydrogen with another atom (e.g. C, N, O)
D1.4.4  Real-Time Rotations and Translations

Current graphic displays offer real-time rotation and translation capabilities. Dials, joysticks and a mouse allow one to interactively manipulate items on the screen with a great deal of rotational and translational freedom.
D1.4.5 Zoom Function

Zoom functionalities are important for the visualization. They allow global and local analyses to be made in a flexible fashion.
D1.4.6 Control of Torsion Angles

Molecules have rotatable bonds defining many conformations. Dials, joysticks and a mouse allow to interactively rotate bonds with a single hand.
D1.4.7 Slab and Clip

Some molecular softwares incorporate "slab" functionalities. The aim of this operation is to visualize sections of the molecular volume. A projection plane can be moved and everything which is either above (top slab) or below (bottom slab) are removed. This allows one to better analyze for example the detailed volume of a macromolecular cavity or a free protein or with a bound ligand.
D1. Molecular Graphics

1. Introduction
2. 3D Perception
3. Visualization
4. Editing & Manipulation
5. Surfaces & Volumes
6. Visualizing Interactions

5.1 Molecular Surfaces
5.2 Surface Representation
5.3 Surface Types
5.4 Properties on Molecular Surfaces
5.5 The Visualization of Volumes
5.6 Boolean Operations with Volumes
D1.5.1 Concept and Definition of Molecular Surfaces

Currently there are three types of surfaces in molecular representations. The Van der Waals surface: it corresponds to the molecular envelope containing atomic spheres of Van der Waals radii.

<table>
<thead>
<tr>
<th>Atom</th>
<th>Van der Waals Radius</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>1</td>
</tr>
<tr>
<td>O</td>
<td>1.4</td>
</tr>
<tr>
<td>F</td>
<td>1.4</td>
</tr>
<tr>
<td>N</td>
<td>1.5</td>
</tr>
<tr>
<td>C</td>
<td>1.7</td>
</tr>
<tr>
<td>S</td>
<td>1.8</td>
</tr>
<tr>
<td>Cl</td>
<td>1.8</td>
</tr>
<tr>
<td>Br</td>
<td>2.0</td>
</tr>
<tr>
<td>I</td>
<td>2.2</td>
</tr>
</tbody>
</table>
D1.5.1 Concept and Definition of Molecular Surfaces

The solvent accessible surface: it corresponds to the molecular envelope of the surface of each atom which is accessible to the center of a probe sphere of a given radius, generally 1.4 Å (sphere including a water molecule).
D1.5.1 Concept and Definition of Molecular Surfaces

The Connolly surface is somewhat similar to the Van der Waals, however it is mathematically defined in order to make it smoother. The Connolly surface is defined as the contact surface and the inward facing part of a probe sphere when it is simultaneously in contact with more than one atom.
D1.5.2 Surface Representations

This visualizes the molecular envelope of the structure considered. This displays the molecular envelope of the structure.
D1.5.3 Surface Types

This is the same previous surface but with full transparency, which is essential for analyzing the detailed structural elements.
D1.5.4 Visualization of Properties on Molecular Surfaces

Molecules are not inert entities. They have subtle physico-chemical properties (atomic charges, electrostatic potentials, hydrophobicity, polarizability) that strongly influence the way in which molecules interact with one another. The display of molecular surfaces that incorporates the added dimension of molecular properties will allow one to understand and predict how molecules interact with one another and dock with one another as well. It also aids in designing new molecules that will optimally bind to a target receptor. The corresponding surfaces can be displayed using color codes and contour lines.
In color-coding procedures, each point of the molecular surface is color coded by the value of a given property. The following view displays the distribution of the electrostatic potential on the molecular surface.
D1.5.4 Visualization of Properties on Molecular Surfaces

Contour lines are usually drawn in a plane like in geography. In the case of molecules, the contour lines are drawn on the 3D envelope of the molecule. The line connects points with the same value of the property (e.g. electrostatic potential) and a number is associated to the curve indicating the actual value of this property (e.g. energy). Contours with positive values are drawn in red while contours with negative values are drawn in blue.
D1.5.5 The Visualization of Volumes

The volume occupied by a molecule is an important molecular determinant: it can be visualized, manipulated and also calculated.
D1.5.6 Mathematical Boolean Operations with Volumes

Mathematical operations (e.g. logical Boolean treatments such as AND, NOT, OR) are useful. These kind of operations are essential for some drug design techniques, such as the Active Analog Approach. Operations such as addition or subtraction of volumes are also useful in measuring for example the quality of a superimposition or the amount of space that is occupied by a ligand in a receptor site. The following example displays the volume common to two molecules.
Mathematical Boolean Operations with Volumes

Mathematical operations (e.g. logical Boolean treatments such as AND, NOT, OR) are useful. These kind of operations are essential for some drug design techniques, such as the Active Analog Approach. Operations such as addition or subtraction of volumes are also useful in measuring for example the quality of a superimposition or the amount of space that is occupied by a ligand in a receptor site. The following example displays the volume common to two molecules.
D1.5.6 Mathematical Boolean Operations with Volumes

Mathematical operations (e.g. logical Boolean treatments such as AND, NOT, OR) are useful. These kind of operations are essential for some drug design techniques, such as the Active Analog Approach. Operations such as addition or subtraction of volumes are also useful in measuring for example the quality of a superimposition or the amount of space that is occupied by a ligand in a receptor site. The following example displays the volume common to two molecules.
D1. Molecular Graphics

1. Introduction
2. 3D Perception
3. Visualization
4. Editing & Manipulation
5. Surfaces & Volumes
6. Visualizing Interactions

6.1 Visualization of Hydrogen Bonds
6.2 Visualization of Molecular Bumps
6.3 Surface Representations for Bump Analyses
6.4 Complementary Surface Properties
6.5 Visualization of Intramolecular Interactions
6.6 Schematic Complex Interactions
6.7 Visualization of a Complex Cavity
6.8 Results of Quantum Mechanical Calculations
Molecules have rotatable bonds defining many conformations. Dials, joysticks and the mouse allow one to interactively rotate bonds with a single hand in order to maximize inter and intra molecular hydrogen bond interactions.
D1.6.1 Visualization of Hydrogen Bonds

Molecules have rotatable bonds defining many conformations. Dials, joysticks and the mouse allow one to interactively rotate bonds with a single hand in order to maximize inter and intra molecular hydrogen bond interactions.
D1.6.2 Visualization of Molecular Bumps

Unfavorable steric interactions (bumps) occurring between two molecules or between different structural entities of the same molecule can be displayed with molecular graphics in a simple way.
D1.6.3 Surface Representations for Bump Analyses

Surface representations are very useful for identifying bumps in the modeling of a ligand interacting with its target protein.
D1.6.4 Complementary Surface Properties

It is possible to visualize the complementary features of a given property (e.g. lipophiliticy, electrostatic potential etc.) of a ligand when it binds to its receptor. This can be done by displaying the property concerned onto the surface of the molecule when it is outside and inside the active site of the receptor.
D1.6.4 Complementary Surface Properties

Electrostatic potentials: a surface can be color-coded by electrostatic potentials and for example displayed in two colors (red & blue) when the surface is either positive or negative. A good affinity between the ligand and the receptor occurs when positive regions (red) interact with negative ones (blue).

Electrostatic potential created by the protein on the surface of the ligand

Electrostatic potential created by the ligand on its own surface
D1.6.4 Complementary Surface Properties

Lipophilicity potentials: favorable complementary features of lipophilicity potentials are achieved in interactions of the same type, namely hydrophobic-hydrophobic and lipophilic-lipophilic interactions.
D1.6.5 Visualization of Intramolecular Interaction

Current workstations with their fast processors can do "bump-checking" (checking for steric contacts closer than Van der Waals) to visualize hydrophobic interactions and hydrogen bonds.
D1.6.6 Schematic Complex Interaction

Schematic illustrations are useful in representing the interactions observed (or calculated) in a molecular complex. The following view represents a drawing generated automatically by the graphical program Ligplot and shows the detailed interactions of a small molecule and a protein.
D1.6.7  Visualization of a Complex Cavity

The following two views show the volume occupied by a ligand when it interacts with its target macromolecule. The view below focuses on the situation around the ligand...
D1.6.7 Visualization of a Complex Cavity

... while this view provides an overview of what the entire complex looks like.
D1.6.8 Results of Quantum Mechanical Calculations

Quantum mechanical calculations provide a way to measure many properties of the molecule including electronic densities, localized orbitals, molecular orbitals (in particular the LUMO and HOMO orbitals). They provide detailed insight into the electronic nature of the molecular structures. Instead of treating them numerically, it is recommended to use computer graphics to visualize this information and take advantage of the graphical capabilities to facilitate their analysis.