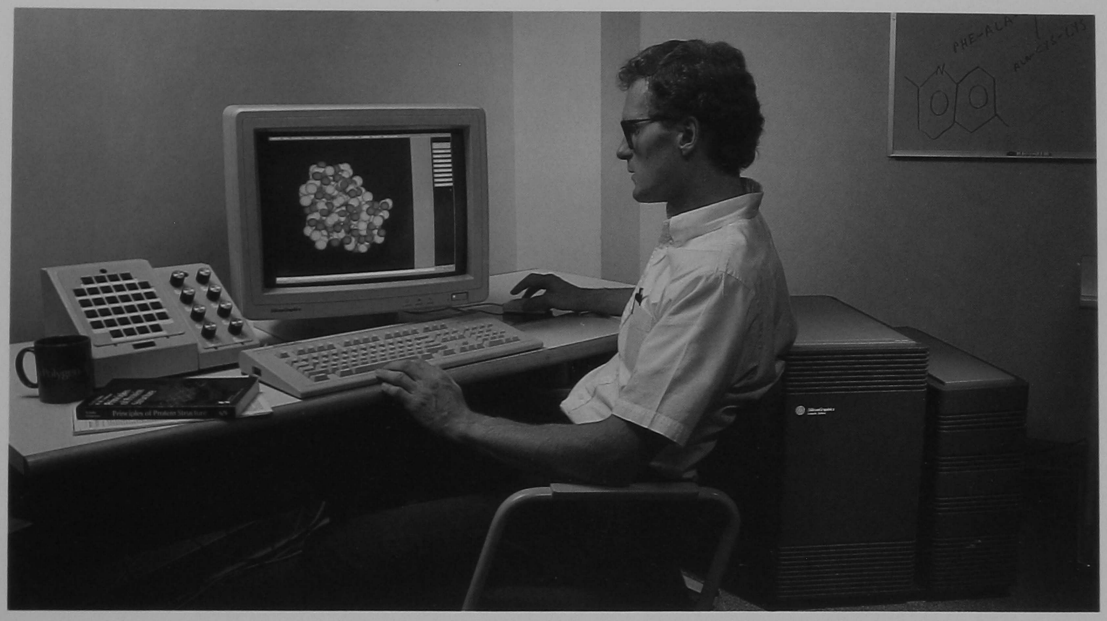
Polygen

QUANTA



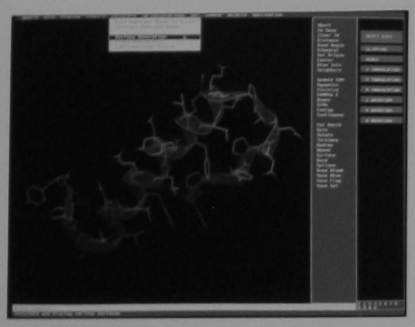
An Integrated, Multi-tasking Graphics System for Molecular Modelling, Simulation and Analysis

FEATURES

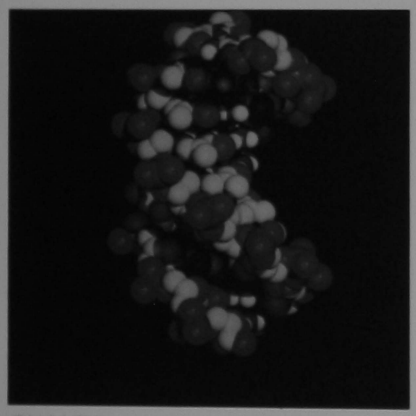
- ***Comprehensive, integrated molecular modelling system***
- ***Flexible molecule construction, data entry, display, and analysis facilities***
- ***Multi-tasking, transparent access to local and remote computing resources***
- ***Supports small molecule, polymer, and protein design with intermolecular, solvent and crystal effects***
- ***Open Interface permits development of complementary applications***

QUANTA™ is a comprehensive software system for the construction, graphical modelling and analysis of molecular structures. QUANTA is designed to accommodate all classes of molecular and macromolecular systems, including the particular requirements of small organic structures, proteins and peptides, crystal and polymeric systems, with complete support for drug design applications. Available on a range of high-performance color graphics systems and workstations, QUANTA provides menu-driven, interactive, local and remote access to Polygen's **CHARMm**™ system and its extensive set of energy minimization and molecular dynamics simulation functions. Committed to helping protect the user's hardware investment, Polygen offers a planned upgrade path, allowing the user to take full advantage of new advances in graphics workstation hardware and network computing software.

QUANTA's Open Interface and extensive data handling facilities permit Polygen as well as QUANTA users to integrate proprietary, third-party and QCPE applications, such as CNDO and AMPAC, with complete access to QUANTA's graphics functions and advanced user interface. Full documentation and linkable object libraries are available to support the development process. QUANTA accepts input and can generate structural data in all standard molecular file formats, including Brookhaven, Cambridge, MOPAC and Polygen **ChemNote**® format. Low-cost, distributed access to QUANTA is available through Polygen's **CENTRUM**™ research information system. CENTRUM is supported on a variety of desktop workstations as well as PCs attached to network-based servers.



QUANTA's user interface includes pulldown menus, dialog boxes, a rapid access table of commands, and a message window.



QUANTA can generate high quality ray-traced renderings of the molecular system being displayed. These realistic images, which include specular highlights and shadow casting, are suitable for publication. In the picture above, a section of DNA is displayed and colored by atom type.

QUANTA was developed by an interdisciplinary team of Polygen scientists, graphics and systems engineers working in collaboration with industry, academia and Polygen's molecular graphics group at the University of York, England. QUANTA is based upon and data file compatible with its predecessor, the **HYDRA**™ program. QUANTA and HYDRA are now installed at over 200 academic, government and industrial research sites worldwide.

QUANTA FUNCTIONALITY

QUANTA is designed to provide both the first-time user and advanced theoretician with a convenient and powerful way of interactively constructing, visualizing, and analyzing the behavior of molecular and macromolecular systems in the chemical, pharmaceutical and materials sciences.

QUANTA's mouse-driven user interface, using Macintosh-like pulldown menus, graphical icons and dialog boxes, provides unparalleled ease-of-use. Completely integrated interactive structure sketching facilities, 2-dimensional to 3-dimensional geometry conversion, and polymeric sequence generation facilitate data entry. Automatic input of machine-readable structural data in standard file formats is also provided.

Menu-driven, interactive access to CHARMm for energy minimization and molecular dynamics enables a QUANTA user to quickly generate energy minimized structures using either local or remote CHARMm host computing resources. QUANTA's uniquely flexible coloring facility allows an unlimited number of small or large molecular systems to be colored on a wide range of structural attributes, and graphically manipulated in any logical combination. QUANTA provides full interactive support for advanced 3-dimensional stereo viewing systems.

Multi-structure interactive docking and structure comparison features, coupled with QUANTA's real-time geometry and energy analysis, provide powerful automated support for the drug design process. QUANTA's automatic, template-driven, structural feature generation and manipulation capability has broad application in the fields of polymer and materials science as well as protein engineering.

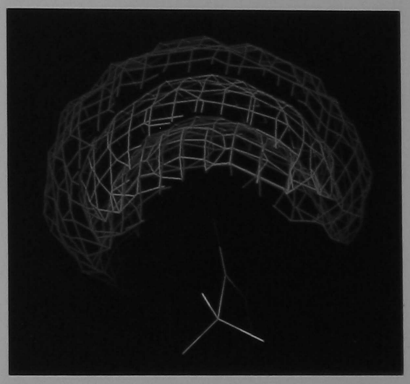
Support for laser and color printers and plotter output, helps QUANTA users easily document and communicate valuable research results through CENTRUM. QUANTA's fully-supported "C" and FORTRAN development environment enables advanced users and internal modelling support groups to integrate existing software and develop new applications, taking full advantage of QUANTA's advanced user interface environment and graphics functionality.

QUANTA APPLICATIONS

Drug Design

QUANTA's interactive molecular construction facilities allow development of molecules by sketching new structures, dynamically connecting 3-dimensional fragments and by modifying structures from outside sources, such as the Cambridge Crystallographic Database. These new molecules can then be studied through real-time molecular mechanics or quantum mechanics tools, offering powerful support for drug design.

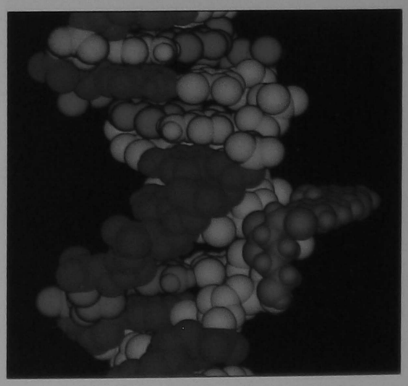
QUANTA provides a full range of molecular surface generation facilities, including Connolly, electrostatic potential, solvent accessible and van der Waals surfaces; 3-dimensional "wire" grids, and electron density maps with complete user control over color selection. These visualization features help define and improve understanding of molecular shape and similarity.



A probe map of N-methyl acetamide using a proton probe. Two contour levels are depicted.

As another aid in drug design, QUANTA provides the ability to calculate and display probe maps. Multiple energy levels can be contoured, with user-selectable iso-energy levels, and drawn around the molecule as a series of 3D "wire" grids. From these probe maps, the user can determine lines of possible approach to a molecule, areas of relatively lower energy which might serve as binding sites for the probe, and internal spaces where the probe could fit inside the molecule.

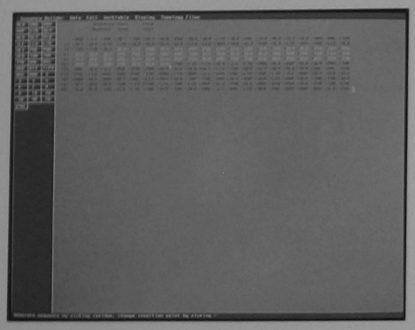
QUANTA also offers a powerful method of graphically comparing multiple structures or particular conformational features in order to identify similarities and explain conformational changes. Flexible selection facilities permit the user to identify particular features to be compared or fitted, and an extensive set of analysis tools allow results to be rigorously evaluated and graphically displayed. Multiple structures can be interactively moved and rotated relative to each other with real-time display of resultant distance and energy characteristics, particularly important for studies involving enzyme-substrate binding. Integration of third-party and proprietary surface generation and structural comparison software is fully supported by QUANTA's unique open-architecture environment.



Binding of methotrexate, colored in pink, to the DNA double helix.

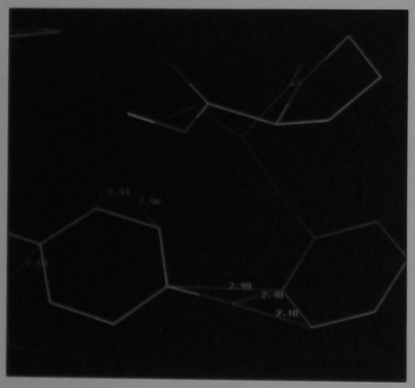
Further integration has been provided for interactive setup and submission of CNDO/INDO and AMPAC calculations. QUANTA can take data from the resulting CNDO calculation and apply the computed partial atomic charges to the molecule. Data from an AMPAC calculation can be used to generate and display molecular orbitals. Another useful tool in drug design is conformational search. QUANTA allows the user to search and analyze conformational space with a variety of search techniques.

Protein Engineering



The QUANTA Sequence Generator is used to easily construct or modify a sequence of monomers.

QUANTA's mouse-driven Sequence Generator allows users to rapidly construct and display polypeptides utilizing predefined standard or abnormal amino acid residue libraries or structure fragments sketched by the user. QUANTA's menu-driven interface to local or remote CHARMm systems permits fast energy minimization of protein structures for realistic graphics visualization and manipulation. Both structure and sequence homology can be used to determine the conformation of protein structures. In graphics mode, QUANTA also allows protein structures to be altered interactively – including commands for mutation, insertion, and deletion of any number of residues – again, with full access to CHARMm energy minimization and molecular dynamics functions to assure the conformational integrity of the modified structure. A versatile conformational search facility may be applied to any section of the protein to generate alternate conformations for further study. Structures can be rotated around chemical bonds with completely interactive on-line distance and energy monitoring. Bonds can be broken, permitting independent movement, rotation or joining of individual or groups of atoms and user-defined structural fragments. QUANTA's fully supported Open Interface environment permits integration of proprietary protein engineering functions to enhance user productivity.



Interactive rotation about the C^{α}-C^{β} and C^{β}-C^{γ} bonds of a residue in immunoglobulin. Dashed lines represent nearest-neighbor interactions which are continuously updated during the rotation.

QUANTA can read Brookhaven Protein Data Bank (PDB) format files directly and communicate the relevant information to CHARMm for energy-based calculations. QUANTA offers a complete and flexible method for generating hydrogen atom positions. Furthermore, structures can be automatically solvated, including a solvation method using periodic boundary conditions. PDB-format files can be written for exchange of new or modified structures with other software systems.

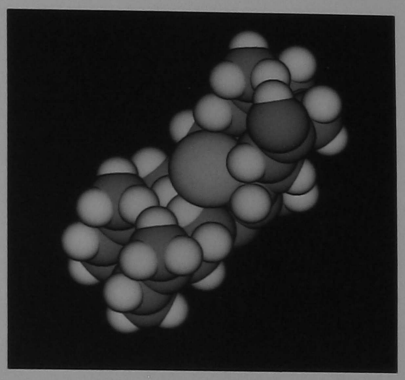
QUANTA is able to display symmetry-generated molecules and electron density maps. This facility together with the use of geometry regularization or energy refinement in CHARMm and the extensive interactive modelling facilities, provides the basis for electron density map fitting. Display and handling of crystallographic data from the Protein Data Bank is facilitated by QUANTA's comprehensive data structure, which allows atoms to be assigned chain identifiers, insertion codes and alternate position indicators.

Molecular Biology

QUANTA can also be used to study a wide range of biological systems. Various biopolymers including nucleic acids, polysaccharides and lipids can be constructed using the Sequence Generator and pre-defined monomers. Full simulations are possible on interacting systems of biological molecules to aid research in such areas as DNA-drug binding, protein-nucleotide interactions and lipid bilayer dynamics.

Polymer Chemistry

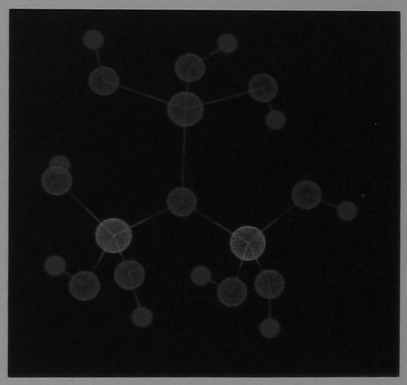
Generic polymer structures can be built using the mouse-driven sequence generator. Standard monomers are included in a fragment library which users can augment using QUANTA's interactive chemical structure sketching facility. Users have flexible control over tacticity, positional isomerism and initial conformation. These polymer chains can be interactively studied using CHARMm's molecular mechanics tools directly from the QUANTA workstation. Simulations can be made on isolated chains, packed chains, simulated polymer melts or crystals in the presence of any solvent environment. These techniques can be used to study chain flexibility, hydrodynamic properties, interchain energetics and small molecule mobility (plasticizers, cross-linkers, etc).



Polyisoprene incorporating a sulfur bridge between polymer strands.

Materials Science

QUANTA can also be used to model crystalline or amorphous solids composed of both inorganic and organic materials. Unit cells of crystals can be interactively designed and then used to construct more extended structures. These can then be modelled using CHARMm to examine their structural energetics, vibrational modes and defect structures.



Molecular clusters such as $Mg(OH)_3$-$SiSiO(OH)_6^{-1}$ can be used in examining the binding forces of complex crystal structures for studying problems in silicate crystal chemistry.

QUANTA FEATURES

Sketching, Construction and Data Entry

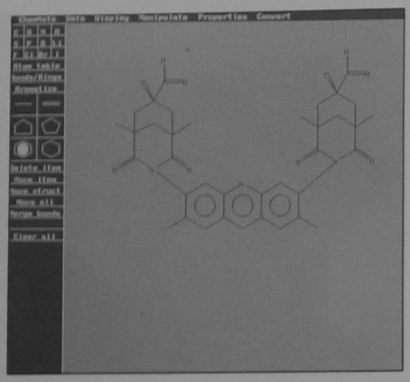
QUANTA provides a fully-featured, interactive, mouse-driven, free-hand structure sketching and 2-dimensional to 3-dimensional conversion facility, permitting rapid and flexible construction of proprietary and non-standard fragments or entire molecular systems. Comprehensive routines for the input, output, and management of structural data in machine-readable form, following standard file formats, are also provided.

• User Interface

QUANTA has a simple, consistent user interface. Applications are selected from a menu bar which incorporates pull-down menus at the top of the screen as well as a rapid access table of frequently used commands on the side. Additional selections are available through pop-up dialog boxes and graphical icons, as well as a command line input. On-screen dial bars can be used to rotate, translate and scale structures. A message window at the bottom of the screen displays information on the program status or the type of input required.

• Construction and Sketching

QUANTA provides the means to sketch a new molecule or fragment from scratch, or to retrieve an existing structure from any file directory,



QUANTA provides interactive two-dimensional structure sketching and 2 to 3-dimensional conversion facilities.

Electrostatic potential surface of glutamic acid with each dot colored by energy value.

display it on the screen and edit as required. The mouse and keyboard are used to create the two-dimensional diagrams. QUANTA's extensive construction and editing features enable drawing of single, double, triple, and resonant bonds, as well as a variety of ring structures. Atoms may be selected from a periodic table and placed in the diagram. Graphical icons display the available options, and the mouse is used to select an item and position it on the screen. In addition to the extensive sketching capabilities, properties such as partial atomic charges, coordination, chirality, isotopes, lone pairs, free radical and cis/trans bonds can be assigned. Partial atomic charges can be optionally assigned using a modified Gasteiger method.

QUANTA converts a 2-dimensional diagram of a molecule into a "first order" 3-dimensional model. The 2 to 3-dimensional conversion facility sets accurate bond lengths and angles, using approximations for initial dihedral angle values. The user can then improve the conformation by changing the dihedral angles. Thus, 3-dimensional models can be displayed in a variety of forms which the user can manipulate and analyze before submitting them to the CHARMm molecular mechanics program for detailed analysis.

Besides allowing for 2-dimensional construction, QUANTA also supports 3-dimensional construction. Molecules can be constructed by merging bonds within molecular fragments with automatic geometry regularization assisting the user in determining an appropriate conformation. While constructing the molecule, users can query and change atom types and chiral centers. In addition, conformations can be modified by rotating about any dihedral angle.

Graphical Display Functions

QUANTA's device-independent graphics architecture and data structures allow the user practically unlimited flexibility in color assignment and labelling, by structural component, calculated attribute or structural feature. Real-time generation of complex surfaces and full interactive control over movement in 3-dimensional space, coupled with support for the latest active stereo viewing systems offer unparalleled graphics functionality.

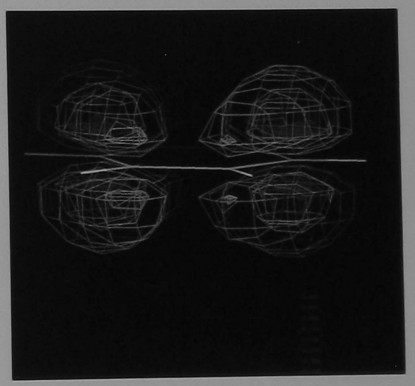
Taking advantage of some of the most recent developments in graphics hardware and graphics software algorithms, QUANTA provides several advanced rendering techniques. QUANTA can generate high quality ray-traced renderings of the molecular system being displayed. These realistic images, which include specular highlighting and shadow casting, are suitable for publication. To further assist the understanding of a molecule's structure, QUANTA can manipulate molecular surfaces generated using sphere primitives or triangular meshes. These surfaces can be smoothly rotated on several powerful high-end graphics workstations.

• Display and Coloring Options

Various types of information can be associated with a molecule and used as criteria for selecting and coloring atoms. This facility enables easy and effective representation of such important atomic and molecular properties as surface accessibility, electrostatic potential, and crystallographic thermal parameters.

QUANTA has the ability to calculate and display "dot" representations of a simple van der Waals (VDW) or Connolly surface with the same flexible coloring and selection facilities described above. This capability to represent the molecular surface is very useful when studying how multiple structures interact with each other. The shape, depth and chemical characteristics of receptor sites on the surface are critical in understanding how substrates bind.

QUANTA also calculates and displays ribbons and grids. By displaying a simplified representation of a protein backbone, ribbons help visualize the topology of chain folding. QUANTA provides the capability to interactively contour and display data from a 3-dimensional grid along with the molecular structure. The grid can be calculated within QUANTA to provide a computationally efficient and visually effective method to display molecular surfaces. Grids can also represent the electrostatic potential calculated from a QCPE package, the energy potential calculated by QUANTA, molecular orbitals calculated by AMPAC, or an electron density map resulting from a crystallographic analysis.

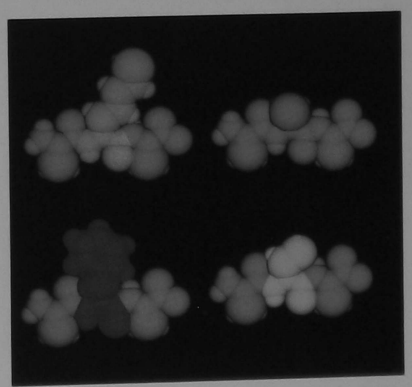


The highest occupied molecular orbital on benzene is displayed using QUANTA's 3D contouring facility.

QUANTA also contains a number of facilities for displaying molecules generated by crystal symmetry. For crystallographic studies, the user can view a region of a molecule together with all symmetry contacts, or generate crystal packing diagrams.

• Multiple Structures

QUANTA can display and manipulate an unlimited number of independent molecules or molecular fragments. These can be interactively added to or removed from the display, joined or split to construct new 3-dimensional molecules or fragments. Each molecule or user-specified group of molecules can be moved or rotated dynamically. In addition, interaction energies can be calculated in real time between any two molecules or group of molecules.



A series of tripeptides displayed simultaneously on the screen. The second residue in each peptide is colored according to amino acid type.

• Stereo Viewing

QUANTA supports the latest stereo viewing technology. This includes StereoGraphics 3Display and ZScreen and Tektronix SGS-610 viewing devices, which provide flicker-free stereo viewing. QUANTA's use of stereo allows the chemist to better perceive 3-dimensional structures and assist in those application areas, such as docking and comparing multiple molecules, where 3-dimensional visualization is essential.

• Data Plotting

QUANTA also provides 2-dimensional data plotting facilities. This capability allows for the plotting of any set of x,y data. Automatic display of plots from CHARMm molecular dynamics simulations, such as energy and temperature vs. time, are provided. These data plots can be displayed on the screen or written out to an external file in HP-GL or PostScript format. In turn, these plots can be incorporated into a CENTRUM document.

QUANTA's interface, which includes menus and dialogue boxes, is integrated with CHARMm's energy minimization and molecular dynamics calculations.

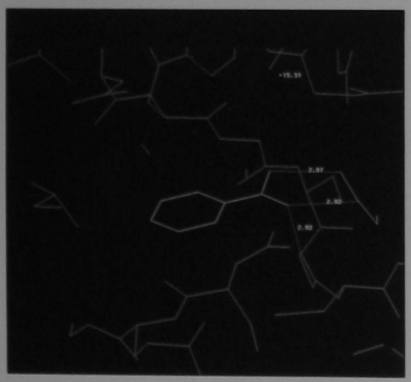
Structural Analysis

QUANTA's completely integrated menu-driven interface to Polygen's CHARMm energy minimization and molecular dynamics system provides the first-time or expert user with direct access to a broad range of structural analysis and simulation capabilities. From simple minimization of newly sketched structures to complex real-time docking and molecular dynamics studies, QUANTA permits easy access to local **or remote** CHARMm host computing systems, including remote supercomputing resources. QUANTA's close coupling of an energy calculation with a graphic display helps assure the scientific integrity of the modelling and simulation process. QUANTA's Open Interface eases development and integration of proprietary analysis applications.

• Energy Minimization

Accessed directly from a QUANTA menu, CHARMm can determine global minimum-energy configurations for small systems or local minimum-energy configurations for larger systems. Atomic, internal coordinate, dihedral, NOE and target constraints can be interactively applied to the molecular structure prior to minimization.

Minimization methods may be combined with internal or generalized coordinate constraints to study barrier crossing or internal rearrangement in systems where dynamic analysis may not be feasible.



Docking of the benzamidine inhibitor to the active site of beta trypsin. Interaction energy and distances are dis-played in real time.

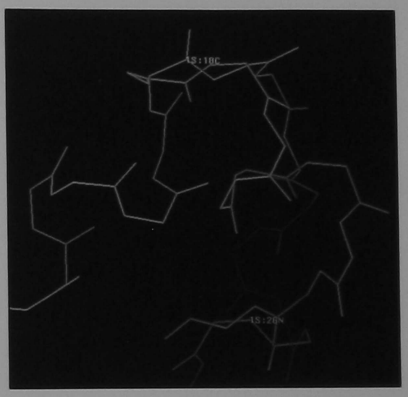
• Molecular Dynamics

Through QUANTA, CHARMm's molecular dynamics capability simulates the evolution of a molecule over time and produces a trajectory or series of coordinates and velocities which describe atomic motion within the system. This information enables the analysis of local atomic fluctuations and certain types of internal rearrangements. CHARMm performs molecular dynamics simulations of molecules in vacuum and crystalline environments. Additional capabilities are provided for systems in a solvated environment. Target molecules are inserted in a bounded region of solvent and properly adjusted. CHARMm carries out dynamics simulations on a full or limited molecular system over a range of temperatures, automatically eliminating unnecessary degrees of freedom, reducing computing requirements. In addition, restrained and

quenched molecular dynamics simulations can be performed on the molecular system.

• Docking

QUANTA's docking capability allows the user to move and rotate one molecule relative to another while displaying the results of real-time distance and energy calculations. This function is useful for studying the interactions between molecules as in enzyme substrate and protein-nucleic acid complexes. Multi-substrate binding can also be studied.



QUANTA provides a versatile protein modelling environment. A fragment chosen from a protein database is displayed as a beta turn of crambin.

• Structural Comparisons

Comparison of structures is important for rationalizing changes in conformation between closely related molecules and for identifying similarities between less closely related structures. Comparison is also useful in identifying structural patterns among the increasingly large number of crystal structures available. QUANTA provides powerful tools for graphically comparing similar structures, using a least squares algorithm to optimize the overlap between two structures. Flexible routines allow the user to easily designate which parts of the structures are to be fitted to each other. Extensive facilities are provided to analyze the resulting fit between the two structures.

• Protein Modelling

To assist the protein chemist, QUANTA allows rapid construction and modelling of protein structures based on sequence and structural homology. Interfaces are provided to structural fragment libraries as well as a full sequence database facility. Commands to mutate, insert and delete residues are available. It is also possible to either copy the conformation of a known structure onto a sequence or map a sequence onto a 3-dimensional structure. In addition, an automatic facility to generate a protein from a known homologous structure is provided. Also included is a regularization method for rationally inserted or deleted residues.

Energy trace of a conformational search using the Boltzman Thermal Jump procedure.

• Conformational Searching

QUANTA includes several facilities for performing conformational searches. Using torsion angles as variables, systematic search, Monte Carlo sampling and simulated annealing methods of conformational search are made available to the user. The conformations produced by the search methods can be automatically sent to CHARMm for energy calculations, energy minimization and other conditional tasks. Analysis facilities are included to inspect the various conformations that are produced during the search procedure, allowing the user to view various conformations, compare conformations, and determine conformational clusters. Several types of 2-dimensional data plots can be produced and viewed. Examples of these plots include: CHARMm energy trace, energy histogram of a set of conformations, energy contour maps, and scatter plots that show the torsional space covered. The search proce-

dures can handle both linear and cyclic molecules. Cyclization algorithms using the method of Go and Scheraga have been built into the search procedures. These algorithms work transparently, ensuring that a cyclic condition is preserved during torsional manipulations.

• *Structure Refinement*

QUANTA provides an interface to Polygen's X-PLOR crystallographic NMR refinement software. X-PLOR uses experimental information coupled with high temperature molecular dynamics to automatically improve the structural models. An interface to NMR-2, from New Methods Research, Inc., will supply direct NOE distance data to be used in the refinement process.

Multitasking Architecture

QUANTA has been designed to serve as the hub of a multitasking environment. Molecular mechanics and quantum mechanics calculations are carried out as separate independent tasks. For example, CHARMm can run either on the local workstation or on a remote host. As molecules are built in QUANTA, the requisite structural information is transmitted to CHARMm transparently, and energy calculations or dynamics simulations can be initiated at the user's request, on either local or remote host computers.

• *On-Line Simulation Control*

Once minimization or dynamics calculations are started, the user has the option of watching the calculations progress graphically or disconnecting and allowing them to run in batch mode. Any batch calculation can be reconnected for interactive monitoring or adjustments and detached again. Completed batch computations can also be reviewed interactively. This sophisticated environment offers the user highly interactive, real-time energy minimization and molecular dynamics capabilities.

Communications Options

Polygen has designed a communications protocol which allows commands and molecular data to be exchanged between tasks. These tasks can be physically located on the same machine or on local or remote networked host computers using Ethernet. This multiprocessing environment allows users to take full advantage of available computer resources.

Development Tools

QUANTA is designed to anticipate the advanced user's or corporate modelling group's need for a cost-effective and supportable molecular

graphics development environment. QUANTA's object oriented, pull-down menu system can be used to integrate a wide variety of complementary applications, as well as providing access to QUANTA's display and structure manipulation capabilities. Graphics and windowing functionality are supported within QUANTA using standards such as PHIGS+ and the X Window System version 11. By supporting these graphics standards, QUANTA allows users to implement proprietary graphics functionality in a device independent manner to protect their software investment. Communications features permit easy access to local or remotely hosted applications, facilitating systems integration and use of corporate network resources. Full Polygen documentation and support assure productive use of the QUANTA development environment.

• *Open Architecture/Extensibility*

QUANTA provides an open architecture for users to add their own applications to the system. By following straightforward, well -documented procedures, users can integrate existing and future modelling application programs. To assist in this activity, Polygen makes available linkable object libraries which customers can combine with their own applications to enable input/output functions to be performed in a QUANTA-compatible manner.

Hardcopy Output

QUANTA comes equipped with an HP-GL plotter interface, allowing use of a range of popular Hewlett-Packard and compatible color plotting devices. PostScript is also supported, allowing the user to produce hardcopy on devices such as the Apple LaserWriter. Support is also provided for direct screen copying, including the Seiko D-Scan CH-5300 Series color thermal printer, for purposes of archival storage or presentation to wider audiences.

Hardware Configurations

QUANTA's structured design and modular architecture is engineered for device independence and portability. At the same time, performance critical code is isolated and optimized for the highest possible throughput on supported graphics displays and workstations. Communications support assures access to distributed high performance host computing resources and remotely located supercomputers and array processors. Integration with Polygen's CENTRUM facilitates distributed access to QUANTA workstation resources. QUANTA is supported on a wide range of graphics workstations. Please refer to the Hardware Configuration Data Sheets which describe the family of currently supported hardware configurations.

POLYGEN APPLICATIONS SUPPORT, TRAINING, DOCUMENTATION AND USERS GROUP

Polygen provides complete user documentation, training and applications support for QUANTA throughout the United States, Western Europe and Japan. Polygen's maintenance support includes regular updates, hot-line telephone service and access to Polygen's scientific resources for potential and parameter development. Applications contributed by users to Polygen's User Application Library are available for integration using QUANTA's Open Interface.

The scientific and technical staffs at Polygen can provide customized training, scientific consulting and contract research. User meetings are held regularly in the United States, Europe and Japan providing a valuable exchange of information to Polygen's customers.

POLYGEN MAINTENANCE AND ENHANCEMENTS

QUANTA is backed by the largest professional systems engineering, applications development and scientific groups ever dedicated to the field of molecular graphics and computational chemistry. Polygen's internal development resources, located both in the United States and Europe, are augmented by funded long-term research collaborations with leading industrial and academic research institutions worldwide. This partnership between industry and academia assures continued, state-of-the-art performance and support for the latest scientific and technological developments. Polygen's consistent development methodology, adherence to industry standards, and an unqualified commitment to engineering excellence offers the security of a planned, upwardly compatible migration path to new generations of technology, while protecting valuable investments in existing data bases and computing resources.

Polygen Corporation, operating in the USA, Europe, and Japan, is a leading supplier of molecular modelling, simulation, and technical information management systems for the pharmaceutical and chemical industries.

Polygen

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