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17.2. Molecular graphics and animation

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17.2.1. Introduction

Visualizing the unseeable world of molecules is the fundamental goal of crystallographic structure determination. Thus there is a natural synergy between the science of unravelling molecular structure and the technology of representing it. Graphics have always had a significant role in the analysis of diffraction data, the synthesis of molecular models and the communication of the information and knowledge gained in these scientific pursuits. At least since the time of René Häuy in the 18th century, crystallographers have attempted to use graphics and physical models to understand and explain the underlying nature of the solid state (Fig. 17.2.1.1). Over the years, crystallography has pushed the development of new technologies to aid in structure solution, and crystallographers have been early adaptors of new technologies. No technology has had more impact on crystallography than electronic computing. Nowhere is that impact more apparent than in what we have been able to study and how we have been able to visualize our structural results. With the pervasiveness of three-dimensional computer graphics in many aspects of everyday life, it is easy to forget the role that X-ray crystallography has played in its genesis and the role that graphics technology continues to play in the advancement of molecular structure analysis.

The human genome project and other efforts in biology and medicine have produced heightened emphasis on molecular depictions of increasing complexity. Visualization of such systems through computer-graphics technology is a key component in our understanding of these data and the models that we use to explain them. In fact, modelling and visualization techniques provide a bridge between experimental data at different scales, enabling placement of detailed atomic models of molecules from crystallography into lower-resolution data on large assemblies from electron microscopy or scanning probe imaging.

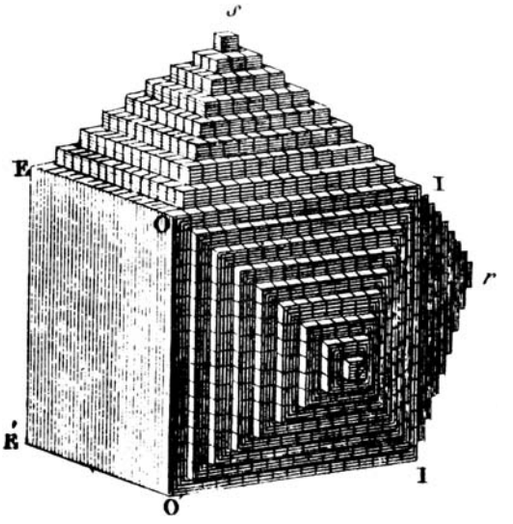

Fig. 17.2.1.1. Model of a crystal structure proposed by René Häuy in *Traite elementaire de Physique*, Vol. 1 [Paris: De L'Imprimerie de Delance et Lesueur, 1803]. This model, proposed in 1784, was the first to connect the external facets of a crystal with an underlying regular arrangement of building blocks.

17.2.2. Background – the evolution of molecular graphics hardware and software

The complexity of molecular structure and the fact that these submicroscopic objects of study are not directly visible have necessitated the use of physical or pictorial representations to aid in interpretation, manipulation and understanding. Illustrations and models made of wood, plastic or metal served these purposes from the development of the original theories of molecular structure through to the first nucleic acid and protein structures solved in the 1950s. Over the following years, computer graphics has evolved into a significant and ubiquitous technology, helping to sustain the explosive growth of macromolecular structure research. Today, computer graphics pervade the activities of much molecule-based research, from quantum chemistry to molecular biology.

Computer-based molecular graphics can be traced back to 1948 and the X-RAC project of R. Pepinsky at Pennsylvania State University (Pepinsky, 1952). Pepinsky developed an analogue computer to carry out the Fourier transformation of X-ray structure factors to produce electron-density maps. Integrated within X-RAC was an oscilloscope that could display the contours of the electron density (Fig. 17.2.2.1). These displays were, to my knowledge, the first computer-generated images of molecular structure. Crystallographers from around the world came to Pennsylvania State University to use X-RAC and to marvel at the speed and automation possible in the solution of molecular structures. While the digital revolution quickly overtook the analogue approach, X-RAC clearly set the precedent for molecular scientists as early implementors and adaptors of computational and graphics technology.

In the 1960s, two seminal projects laid the foundation for modern molecular graphics. Early in the decade, Johnson's *ORTEP* (Johnson, 1970) program became widely available, allowing crystallographers to produce illustrations of three-dimensional (3-D) molecular structures on a pen plotter. These black-and-white line drawings of ball-and-stick models were used both for working drawings during structure analysis and for creating illustrations for publication. A few years later, experiments lead by Levinthal under Project MAC (Levinthal, 1966) at MIT pioneered the interactive display and transformation of 3-D molecular structures on a computer screen. By the end of the

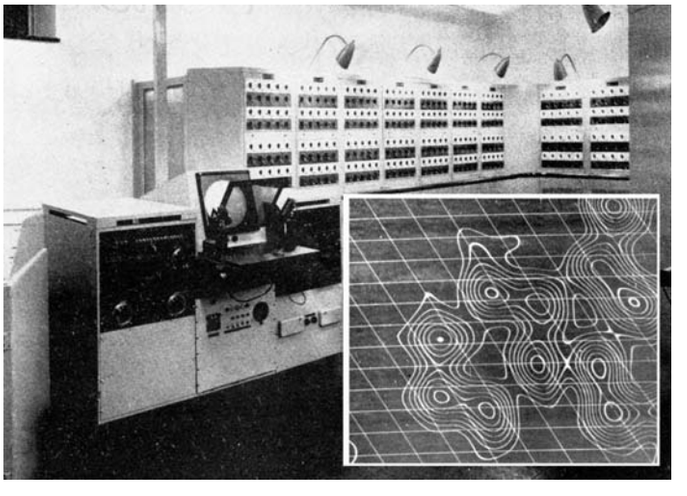

Fig. 17.2.2.1. One bay of X-RAC showing coefficient panels and the display oscilloscope. Inset: photo from the oscilloscope, showing a region of the phthalocyanine Fourier map. Reproduced from Pepinsky (1952).

decade, the groundwork for molecular graphics was set: *ORTEP* convincingly demonstrated to a large number of scientists that the computer could be used as an alternative to the human hand to produce accurate drawings and stereoscopic pairs for the analysis and communication of the results of structural research. Project MAC showed that the computer could be used as an interactive environment in which to model and simulate on the molecular scale. These two projects helped define the two broad functions of molecular graphics: publication graphics, for which clarity of presentation is the essential goal, and working graphics, for which rapid feedback and high interactivity are the key elements.

In the 1970s, 3-D interactive computer-graphics systems became commercially available. Hardware offerings from companies such as Evans and Sutherland, Vector General, and Adage prompted a number of laboratories to develop interactive molecular-modelling software. Several of these early systems were devoted to the task of building an atomic model of a protein into the crystallographically derived electron-density map. Programs such as *BILDER* (Diamond, 1982), *MMSX* (Barry & McAlister, 1982), *FRODO* (Jones, 1978) and *GRIP* (Wright, 1982) began to replace metal Kendrew models and the cumbersome 'Richards Box' optical comparitors. This application, more than any other, sold these expensive (>$100 000) monochrome line-drawing graphics devices to the molecular-research community. Moreover, during that time, biomolecular structure determination was a major civilian consumer of 3-D interactive graphics devices.

Technical, commercial and scientific advances in the 1980s prompted enormous growth in the use of molecular graphics. As late as 1983, a worldwide list of laboratories using high performance graphics computers for molecular work could be maintained – the number was below 100 (Olson, 1983). By the end of the decade, that number grew into the thousands, and utilization spread beyond any ability to track it. At the beginning of the decade the expensive vector-graphics terminals were the only way to achieve interactive 3-D display. Ten years later, the colour raster display had taken over the interactive computer-graphics market, driving prices down and broadening display capabilities from lines and dots to include shaded surface representation. Early in the 1980s, several academic software packages, such as *GRAMPS/GRANNY* (O'Donnell & Olson, 1981; Connolly & Olson, 1985), *MIDAS* (Ferrin *et al.*, 1988) and *HYDRA* (Hubbard, 1986), went beyond electron-density fitting to provide general graphics functionality for examining molecular structure and properties. Over the decade, the remarkable evolution of computer hardware – the advent of microprocessors, very large scale integration (VLSI) devices, personal computers and scientific workstations – increased the accessibility of molecular graphics. By the mid-1980s, the demand was such that several commercial companies had been established to market molecular graphics and modelling software. By the end of the decade, structural scientists in academic and industrial research settings had a wide variety of use-tested hardware and software platforms with which to perform molecular modelling.

The 1990s witnessed remarkable advances in the technology and sociology of computing as well as in the science of molecular structure and design. Moore's law of the microcosm, which estimates that 'the effectiveness of microprocessors doubles every 18 months', continued to track growth accurately. Thus the performance-to-cost ratio of late 1990s computers was a millionfold higher than those of the mid-1960s. A 1997 $200 Nintendo-64 game machine was faster and had more memory and far superior graphics than the Control Data 6600 supercomputer and peripherals of the 1960s, and, with its optional ($70) disk, bettered almost every technical specification of a 1980 VAX 11/780. Gelder's law of the telecosm posited in 1993 that 'bandwidth will treble every year for at least the next 25 years'. This, coupled with Metcalf's law, that 'the total value of a network to its users grows as the square of the total number of users' implies that the 'teleputer', or non-localized computing, is becoming the computational environment of the future.

While software development continues to lag behind hardware growth, the emergence of the World Wide Web and the concepts of network-based computing have catalysed a rethinking of the nature of software, its development, distribution and inter-operability. The concepts of cyberspace and 'virtual reality' have been implanted into the minds and expectations of the general public, promoting a renaissance in user-interface exploration and development. It is transforming the computer from a window through which to look into a portal through which to step. Suddenly, the other senses – sound, touch, taste and smell – can become part of the computational experience.

17.2.3. Representation and visualization of molecular data and models

In the early days of molecular computer graphics, the major goal was to represent the spatial structures of molecules, principally the locations of the atom centres and the covalent connectivity between them. Using X-ray diffraction analysis, one would first plot the electron density as line contours projected onto a plane and locate the atom centres from multiple projections. The molecule would then be represented by a simple bond diagram. As experimental and computational methods advanced, other representations were used to convey additional information about the structure. Johnson's *ORTEP* program plotted the thermal ellipsoids of each of the atoms, visualizing the magnitude and direction of their thermal vibrations as derived from the anisotropic temperature factors (Fig. 17.2.3.1). As colour raster displays became available, space-filling CPK representations were used to visualize molecular shape and volume while using an atom-based colour scheme to show atomic composition and distribution (Porter, 1979) (see Fig. 17.2.3.4). The complexity of protein molecules prompted the introduction of simplified representations that replaced the all-atom visualization with tubes or ribbons (Branden *et al.*, 1975; Carson, 1991) (Fig. 17.2.3.2) that represented the fold of the protein chain. This simplification allowed the comparison of protein folds, and led to the beautiful classification of protein motifs by Richardson (1981).

As more structural information has become available, and as computational hardware technology has advanced, the ability to visualize a variety of molecular properties has become possible. Meanwhile, issues of interactivity, intelligibility and interpretability have become increasingly important as the systems under study have become more complex. There are three general approaches to visualizing the structures, properties and relationships of molecular systems: geometric construction, direct volumetric rendering and

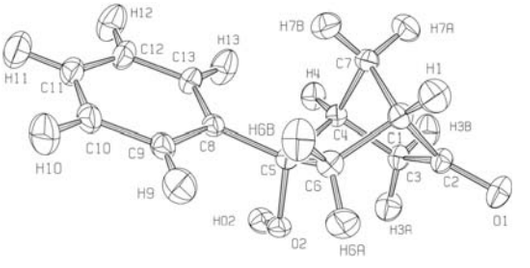

Fig. 17.2.3.1. *ORTEP* plot of phenylhydroxynorbornanone showing atomic thermal ellipsoids (from *Thermal ellipsoid analysis: the fossil footprints of restless atoms*, by Carroll K. Johnson and Michael N. Burnett, Buerger Award Lecture at the ACA meeting in St. Louis, July 20–26, 1997).

references