film writer (Max, 1983) and Olson had used an early colour vector display from Evans and Sutherland to produce an eight-minute animation depicting the structure of tomato bushy stunt virus (Olson, 1981). By the early 1980s, animation projects became more ambitious. Olson produced large-screen OmniMax DNA and virus animation segments for Disney's EPCOT center in 1983. Max produced a red–blue stereo OmniMax film for Fujitsu entitled *We Are Born of Stars*, which included a continuous scene depicting the hierarchical packaging of DNA from atoms to chromosomes, based on the best current model of the time.

Computer-graphics animation has presented both great potential and significant challenges to the molecular scientist wishing to communicate the results of structural research. Animation can not only enhance the depiction of three-dimensional structure through motion stereopsis, it can show relationships through time, and demonstrate mechanism and change. The use of pans, zooms, cuts and other film techniques can effectively lead the viewer through a complex scene and focus attention on specific structures or processes. The vocabulary of film, video and animation is familiar to all, but can be a difficult language to master. While short animations showing simple rotations or transitions between molecular states, or dynamics trajectories, are now routinely made for video or web viewing, extended animations showing molecular structure and function in depth are still relatively rare. The time, tools and expertise that are required are not generally available to structural researchers.

17.2.4.3. *The return of physical models*

While the use of physical models of molecules has largely been replaced by computer graphics, new computer-driven rapid-prototyping technologies which originated in the manufacturing sector have begun to be utilized in the display of molecular structure. A number of 'three-dimensional printing' methods have been developed to build up a physical model directly from a computational surface representation of an object (Burns, 1954). One of the earliest methods, stereolithography, uses a resin which is polymerized when exposed to laser light of a given wavelength. The laser is passed through a vat of the liquid resin and is lowered, layer-by-layer as it plots out the shape of the object (Fig. 17.2.4.2). Other approaches build up layers of paper or plastic through lamination or deposition. These methods have been used by a number of scientists to produce various representations of molecular structure (Bailey *et al.*, 1998). The ability to hold an accurate representation of a molecular surface in one's hand and feel its shape can give great insight, not only to people with visual impairments, but to anyone. Moreover, when one is dealing with processes such as docking and assembly, these physical models can add a haptic and manipulative appreciation of the nature of the problem. While at this point colour has not been implemented in these technologies, there remains the promise that such automated production of molecular models will enhance the communication and appreciation of molecular structure.

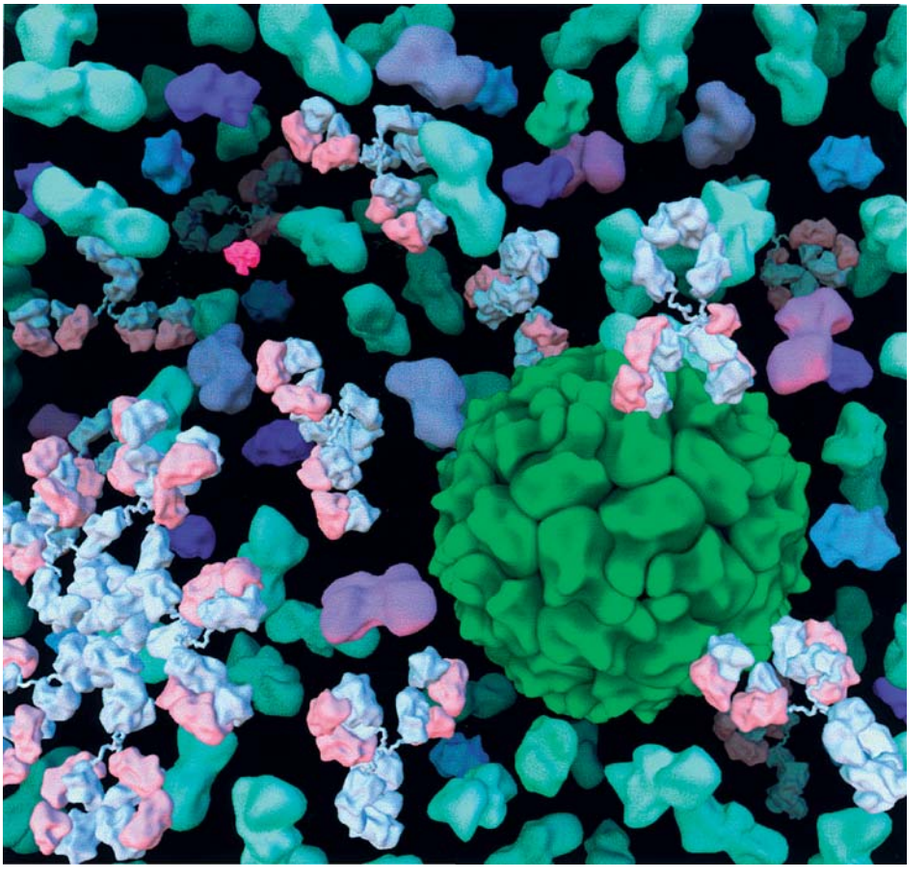

Fig. 17.2.5.1. This image represents a volume of blood plasma 750 Å on a side. Within the three-dimensional model, antibodies (Y- and T-shaped molecules in light blue and pink) are binding to a virus (the large green spherical assembly on the right), labelling it for destruction. It shows all macromolecules present in the blood plasma at a magnification of about 10 000 000 times. This model is composed of over 450 individual protein domains, ranging in size from the 60 protomers making up the poliovirus to a single tiny insulin molecule (in magenta). The model was constructed using atomic level descriptions for each molecule, for a total of roughly 1.5 million atoms. Detailed surfaces were computed for each type of protein using *MSMS* by Michel Sanner and then smoothed to a lower resolution using the *HARMONY* spherical-harmonic surfaces developed by Bruce Duncan. The model geometry contains over 1.5 million triangles.

17.2.5. Looking ahead

Moore's law has already delivered on the promise of three-dimensional graphics capability for the desktop and laptop. The internet and World Wide Web have made molecular structure data and display software available to the masses. Have molecular graphics reached a stage of maturity beyond which only small incremental changes will be made?

The Human Genome Initiative and high-throughput structure determination are beginning to change the scope of the questions asked of molecular modelling. Prediction of function, interactions, and large-scale assembly and mechanism will become the dominant domain of molecular graphics and modelling. These tasks will challenge the capabilities of the hardware, software and, particularly, the user interface. New modes of interacting with data and models are coming from the computer-graphics community. Molecular docking and protein manipulation using force-feedback devices have been demonstrated at the University of North Carolina (Brooks *et al.*, 1990). The same team has developed a 'nanomanipulator' which couples a scanning atomic force microscope with stereoscopic display and force-feedback manipulation to control and sense the positioning and interactions of the probe

within the molecular landscape (Taylor *et al.*, 1993). The challenge of bridging across the scales of size and complexity of the molecular world may lead us into the realm of virtual reality. Data from X-ray crystallography are being combined with data from large molecular complexes, characterized by electron microscopy. These data, in turn, can be integrated with those from optical confocal microscopy and other imaging techniques. With structures of molecules, assemblies and distributions, as well as data on molecular inventories, we can start to piece together integrated pictures of cellular environments, but with full atomic modelling at the base (Fig. 17.2.5.1). Thus, while climbing around inside a protein molecule might not add much in the way of perceptual advantage, navigating through the molecular environment of a cell may prove to be instructive as well as inspirational.

References

17.1

Allen, F. H. & Johnson, O. (1991). *Automated conformational analysis from crystallographic data. 4. Statistical descriptors for a distribution of torsion angles. Acta Cryst.* B**47**, 62–67.

Bairoch, A. & Apweiler, R. (1997). *The SWISS-PROT protein sequence data bank and its supplement TrEMBL. Nucleic Acids Res.* **25**, 31–36.

Bairoch, A. & Bucher, P. (1994). *PROSITE: recent developments. Nucleic Acids Res.* **22**, 3583–3589.

Bernstein, F. C., Koetzle, T. F., Williams, G. J. B., Meyer, E. F. Jr, Brice, M. D., Rodgers, J. R., Kennard, O., Shimanouchi, T. & Tasumi, M. (1977). *The Protein Data Bank: a computer-based archival file for macromolecular structures. J. Mol. Biol.* **112**, 535–542.

Brünger, A. T. (1992*a*). *Free R value: a novel statistical quantity for assessing the accuracy of crystal structures. Nature (London)*, **355**, 472–475.

Brünger, A. T. (1992*b*). *X-PLOR: a system for crystallography and NMR.* Yale University, New Haven, CT, USA.

Brünger, A. T., Adams, P. D., Clore, G. M., DeLano, W. L., Gros, P., Grosse-Kunstleve, R. W., Jiang, J.-S., Kuszewski, J., Nilges, M., Pannu, N. S., Read, R. J., Rice, L. M., Simonson, T. & Warren, G. L. (1998). *Crystallography & NMR System: a new software suite for macromolecular structure determination. Acta Cryst.* D**54**, 905–921.

Collaborative Computational Project, Number 4 (1994). *The CCP4 suite: programs for protein crystallography. Acta Cryst.* D**50**, 760–763.

Fan, C., Moews, P. C., Shi, Y., Walsh, C. T. & Knox, J. R. (1995). *A common fold for peptide synthetases cleaving ATP to ADP: glutathione synthetase and* D*-alanine:*D*-alanine ligase of Escherichia coli. Proc. Natl Acad. Sci. USA*, **92**, 1172–1176.

Fan, C., Moews, P. C., Walsh, C. T. & Knox, J. R. (1994). *Vancomycin resistance: structure of* D*-alanine:*D*-alanine ligase at 2.3 Å resolution. Science*, **266**, 439–443.

Gribskov, M., McLachlan, A. D. & Eisenberg, D. (1987). *Profile analysis: detection of distantly related proteins. Proc. Natl Acad. Sci. USA*, **84**, 4355–4358.

Gribskov, M. & Veretnik, S. (1996). *Identification of sequence patterns with profile analysis. Methods Enzymol.* **266**, 198–212.

Jones, T. A. (1978). *A graphics model building and refinement system for macromolecules. J. Appl. Cryst.* **11**, 268–272.

Jones, T. A. (1982). *FRODO: a graphics fitting program for macromolecules.* In *Computational crystallography*, edited by D. Sayre, pp. 303–317. Oxford: Clarendon Press.

Jones, T. A. (1992). *A, yaap, asap, @#*? A set of averaging programs.* In *Molecular replacement*, edited by E. J. Dodson, S. Glover & W. Wolf, pp. 91–105. Warrington: Daresbury Laboratory.

Jones, T. A. & Kjeldgaard, M. (1997). *Electron density map interpretation. Methods Enzymol.* **277**, 173–208.

Jones, T. A. & Kleywegt, G. J. (2001). *New tools for the interpretation of macromolecular electron-density maps.* In preparation.

Jones, T. A. & Liljas, L. (1984). *Crystallographic refinement of macromolecules having noncrystallographic symmetry. Acta Cryst.* A**40**, 50–57.

Jones, T. A. & Thirup, S. (1986). *Using known substructures in protein model building and crystallography. EMBO J.* **5**, 819–822.

Jones, T. A., Zou, J.-Y., Cowan, S. W. & Kjeldgaard, M. (1991). *Improved methods for building protein models in electron density maps and the location of errors in these models. Acta Cryst.* A**47**, 110–119.

Kleywegt, G. J. (1996). *Use of non-crystallographic symmetry in protein structure refinement. Acta Cryst.* D**52**, 842–857.

Kleywegt, G. J. (1997). *Validation of protein models from Cα coordinates alone. J. Mol. Biol.* **273**, 371–376.

Kleywegt, G. J. (1999*a*). *Recognition of spatial motifs in protein structures. J. Mol. Biol.* **285**, 1887–1897.

Kleywegt, G. J. (1999*b*). *Experimental assessment of differences between related protein crystal structures. Acta Cryst.* D**55**, 1878–1884.

Kleywegt, G. J. & Brünger, A. T. (1996). *Checking your imagination: applications of the free R value. Structure*, **4**, 897–904.

Kleywegt, G. J. & Jones, T. A. (1994*a*). *Detection, delineation, measurement and display of cavities in macromolecular structures. Acta Cryst.* D**50**, 178–185.

Kleywegt, G. J. & Jones, T. A. (1994*b*). *Halloween . . . masks and bones.* In *From first map to final model*, edited by S. Bailey, R. Hubbard & D. A. Waller, pp. 59–66. Warrington: Daresbury Laboratory.

Kleywegt, G. J. & Jones, T. A. (1996*a*). *xdlMAPMAN and xdlDATAMAN – programs for reformatting, analysis and manipulation of biomacromolecular electron-density maps and reflection data sets. Acta Cryst.* D**52**, 826–828.

Kleywegt, G. J. & Jones, T. A. (1996*b*). *Efficient rebuilding of protein structures. Acta Cryst.* D**52**, 829–832.

Kleywegt, G. J. & Jones, T. A. (1996*c*). *Phi/Psi-chology: Ramachandran revisited. Structure*, **4**, 1395–1400.

Kleywegt, G. J. & Jones, T. A. (1997*a*). *Template convolution to enhance or detect structural features in macromolecular electron-density maps. Acta Cryst.* D**53**, 179–185.

Kleywegt, G. J. & Jones, T. A. (1997*b*). *Detecting folding motifs and similarities in protein structures. Methods Enzymol.* **277**, 525–545.

Kleywegt, G. J. & Jones, T. A. (1998). *Databases in protein crystallography. Acta Cryst.* D**54**, 1119–1131.

Kleywegt, G. J. & Jones, T. A. (1999). *Software for handling macromolecular envelopes. Acta Cryst.* D**55**, 941–944.

Kleywegt, G. J. & Read, R. J. (1997). *Not your average density. Structure*, **5**, 1557–1569.

Korn, A. P. & Rose, D. R. (1994). *Torsion angle differences as a means of pinpointing local polypeptide chain trajectory changes for identical proteins in different conformational states. Protein Eng.* **7**, 961–967.

Matte, A., Goldie, H., Sweet, R. M. & Delbaere, L. T. J. (1996). *Crystal structure of Escherichia coli phosphoenolpyruvate carboxykinase: a new structural family with the P-loop nucleoside triphosphate hydrolase fold. J. Mol. Biol.* **256**, 126–143.

Mowbray, S. L., Helgstrand, C., Sigrell, J. A., Cameron, A. D. & Jones, T. A. (1999). *Errors and reproducibility in electron-density map interpretation. Acta Cryst.* D**55**, 1309–1319.

Pflugrath, J. W., Saper, M. A. & Quiocho, F. A. (1984). *New generation graphics system for molecular modeling.* In *Methods and applications in crystallographic computing*, edited by S. R. Hall & T. Ashida, pp. 404–407. Oxford: Clarendon Press.

Qiu, X., Verlinde, C. L. M. J., Zhang, S., Schmitt, M. P., Holmes, R. K. & Hol, W. G. J. (1995). *Three-dimensional structure of the*