International Tables for Crystallography (2012). Vol. F, Section 1.4.1, pp. 39–40.

Chapter 1.4. Perspectives for the future

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1.4.1. Gazing into the crystal ball (E. Arnold)

We live in an era when there are many wonderful opportunities for reaching new vistas of human experience. Some of the dreams that we hold may be achieved through scientific progress. Among the things we have learned in scientific research is to expect the unexpected – the crystal ball holds many surprises for us in the future. Alchemists of ancient times laboured to turn ordinary materials into precious metals. These days, scientists can create substances far more precious than gold by discovering new medicines and materials for high-technology industries. Crystallography has played an important role in helping to advance science and the human endeavour in the twentieth century. I expect to see great contributions from crystallography also in the twenty-first century.

Science of the twentieth century has yielded a great deal of insight into the workings of the natural world. Systematic advances are permitting dissection of the molecular anatomy of living systems. This has propelled us into a world where these insights can be brought to bear on problems of design. The impact in such fields as health and medicine, materials science, and microelectronics will be continually greater.

1.4.1.1. What can we expect to see in the future of science and technology in general?

Just as few were successful in predicting the ubiquitous impact of the Internet, it is difficult to predict which specific technologies will accomplish the transition into the culture of the future. It is possible to envision instantaneous telecommunication and videoconferencing with colleagues and friends throughout the world – anytime, anywhere – using small, portable devices. Access to computer-based information *via* media such as the Internet will become continually more facile and powerful. This will permit access to the storehouse of human knowledge in unprecedented ways, catalysing more rapid development of new ideas.

Experimental tests of new ideas will continue to play a crucial role in the guidance of scientific knowledge and reasoning. However, more powerful computing resources may change paradigms in which ever more powerful simulation techniques can bootstrap from primitive ideas to full-blown theories. I still expect that experiment will be necessary for the foreseeable future, since nearly every well designed experiment yields unexpected results, often at a number of levels.

In the realm of biology, greater understanding of the structure and mechanism of living processes will permit unprecedented advances in health and medicine. Even those scientists most sceptical of molecular-design possibilities would be likely to admit that revolutionary advances have been achieved. In the area of drug design, for example, structure-based approaches have yielded some of the most important new molecules currently being introduced worldwide for the treatment of human diseases ranging from AIDS and influenza to cancer and heart disease. This is a relatively young and very rapidly changing area, and it is reasonable to expect that we have witnessed only the tip of the iceberg. Dream drugs to control growth and form, ageing, intelligence, and other physiologically linked aspects of health and well-being may be developed in our lifetime. As greater understanding of the structural basis of immunogenicity emerges, we should also expect to benefit from structure-based approaches to vaccine design.

Other areas where molecular design will play revolutionary roles include the broad field of material sciences. Traditionally, 'materials science' referred to the development of materials with desired physical properties – strength, flexibility, and resistance to damage by physical and chemical agents. Now, materials science includes key foci in development of new biomaterials and in the burgeoning field of nanotechnology. The acrobatics of new smart materials could include computation at speeds that may be much faster than can be accomplished with silicon-based materials.

1.4.1.2. How will crystallography change in the future?

Potential future advances in the fields of crystallography, structural chemistry and biology are tantalizing. Owing to the limitations of current physical theories and experimental possibilities, large numbers of molecules have generally been required for detailed investigations of molecular phenomena. Given the complexity of large biological molecules, only techniques such as X-ray crystallography and nuclear magnetic resonance (NMR) have been suitable for describing the detailed atomic structures of these systems. New technologies, unforseen and currently under development, will make the successful imaging of single specimens and single molecules at high resolution far more commonplace than is now achievable. Even now, we are beginning to see X-ray and electron microscopy (EM) methods harnessed to visualize single particles at high resolution. Methods such as coherent X-ray diffraction microscopy (CXDM), discussed in Chapter 9.3 of this volume, and the X-ray (free-electron) laser (XFEL) are challenging the limits of our ability to image single particles directly at high resolution (see Section 1.4.4, below). Merging of information from multiple specimens, as is currently done in electron microscopy, may be very powerful in X-ray microscopy as well.

X-ray sources will continue to evolve. High-intensity synchrotron sources have allowed the development of dramatically faster and higher-quality diffraction data measurements. Complete multiwavelength X-ray diffraction data sets have been measured from frozen protein crystals containing selenomethionine (SeMet) in less than one hour, leading to nearly automatic structure solution by the multiwavelength anomalous diffraction (MAD) technique. At present, such synchrotron facilities are enormous national or multinational facilities that sap the electric power of an entire region. Perhaps portable 'table-top' X-ray sources will be developed that can be used to create synchrotron-like intensity in the laboratory. If such sources could have a tunable energy or wavelength, then experiments such as MAD would be routinely accessible within the laboratory. Better time resolution of molecular motion and of chemical reactions will be achieved with higher-intensity sources.

Sample preparation for macromolecular structural studies has undergone a complete revolution thanks to the advent of

recombinant DNA methods. Early macromolecular studies were limited to materials present in large abundance. By the late 1970s and early 1980s, molecular biology made it possible to obtain desired gene products in large amounts, and new methods of chemical synthesis permitted production of large quantities of defined oligonucleotides. Initial drafts of the entire human genome have been mapped and sequenced, allowing even broader access to genes for study. The combination of structural genomics and already ongoing studies will lead to knowing the structure of the entire human proteome in a finite amount of time. Many materials are still challenging to produce in quantities sufficient for structural studies. Engineering methods (site-directed mutagenesis, combinatorial mutagenesis and directed evolution techniques) have permitted additional sampling of molecular diversity, and we can expect that even more powerful methods will be developed. Engineering of solubility and crystallizability will help make more problems tractable for study. Perhaps, as suggested before, techniques for visualization of single molecules may become adequate for *in situ* visualization of molecular interactions in living cells and organisms. However, traditional considerations of amount, purity, specific activity *etc.* will remain important, as will hard work and good luck.

The phase problem has continued to be a stumbling block for structure determination. Experimental methods, including isomorphous replacement and anomalous-scattering measurements, are currently a mainstay, and will be for the foreseeable future. New isomorphous heavy-atom reagents and preparation methods will emerge; witness the valuable engineering of derivatives *via* mutagenesis to add such heavy-atom-binding sites as cysteine residues in proteins. Anomalous-scattering measurements from macromolecular crystals containing heavy metals or SeMet replacements of methionine residues in proteins have led to tremendous acceleration of the phase-problem solution for many structures – especially in the last two decades with the availability of 'tunable' synchrotron radiation. It should become possible to take better advantage of anomalous-scattering effects from lighter atoms already present in biological molecules: sulfur, phosphorus, oxygen, nitrogen and carbon. The increasingly higher intensity of synchrotron-radiation sources may permit structure solution from microcrystals of macromolecules. Incorporation of non-standard amino acids into proteins will become more common, leading to a vast array of new substitution possibilities. Molecular-replacement phasing from similar structures or from noncrystallographically redundant data is now commonplace and is continuing to become easier. Systematic molecular replacement using all known structures from databases may prove surprisingly powerful, if we can learn how to position small molecular fragments reliably. Systematic molecular-replacement approaches should help identify what folds may be present in a crystalline protein of unknown structure. Direct computational assaults on the phase problem are also becoming more aggressive and successful, although direct-methods approaches still work best for small macromolecular structures with very high resolution data.

Crystallography and structural biology have been helping to drive advances in three-dimensional visualization technology. Versatile molecular-graphics packages have been among the most important software applications for the best three-dimensional graphics workstations. Now that personal computers are being mass-produced with similar graphics capabilities, we are beginning to see a molecular-graphics workstation at every computer, whether desktop or portable (terms that soon may become antiquated since everything will become more compact). Modes of input will include direct access to thought processes, and computer output devices will extend beyond light and sound. Universal Internet access will provide immediate access to the rapidly increasing store of molecular information. As a result, we will achieve a more thorough understanding of patterns present in macromolecular structures: common folds of proteins and nucleic acids, three-dimensional motifs, and evolutionary relationships among molecules. Simulations of complex molecular motions and interactions will be easier to display, making movies of molecules in motion commonplace. Facile 'virtual reality' representation of molecules will be a powerful research and teaching aid. Chemical reaction mechanisms will become better understood over time through interplay among theory, experiment and simulation. The ability to simulate all coupled chemical reactions in living cells and organisms will be achieved over time.

Advances in computational productivity depend on the intricate co-evolution of hardware and software. For silicon-based transistor chips, raw computational speed doubles approximately every 18 months (Moore's law). Tools and software for writing software will continue to advance rapidly. With greater modularity of software tools, it will become easier to coordinate existing programs and program suites. Enhanced automation, parallelization and development of new algorithms will also increase speed and throughput. More powerful software heuristics involving artificial intelligence, expert systems, neural nets and the like may permit unexpected advances in our understanding of the natural world.

In summary, we eagerly await what the future of science and of studies of molecular structure will bring. There is every reason to expect the unexpected. If the past is a guide, many new flowers will bloom to colour our world in bright new ways.

1.4.2. Brief comments on *Gazing into the crystal ball* (M. G. Rossmann)

Eddy Arnold and I had planned to write a joint commentary about our vision of the future of macromolecular crystallography. However, when Eddy produced the first draft of '*Perspectives for the future*', I was fascinated by his wide vision. I felt it more appropriate and far more interesting to make my own brief comments, stimulated by Eddy's observations.

When I was a graduate student in Scotland in the 1950s, physics departments were called departments of 'Natural Philosophy'. Clearly, the original hope had been that some aspects of science were all encompassing and gave insight to every aspect of observations of natural phenomena. However, in the twentieth century, with rapidly increasing technological advances, it appeared to be more and more difficult for any one person to study all of science. Disciplines were progressively subdivided. Learning became increasingly specialized. *International Tables* were created, and updated, for the use of a highly specialized and small community of crystallographic experts.

As I read Eddy's draft article, I became fascinated by the wide impact he envisioned for crystallography in the next few decades. Indeed, the lay person, reading his article, would barely be aware that this was an article anticipating the future impact of crystallography. The average reader would think that the topic was the total impact of science on our civilization. Thus, to my delight, I saw that crystallography might now be a catalyst for the reunification of fragmented science into a coherent whole. I therefore hope that these new *Tables* commissioned by the International Union of Crystallography may turn out to be a significant help to further the trend implied in Eddy's article.