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.