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Macromolecular crystallography / Small molecule crystallography / Structural genomics / Bioinformatics / Structure-based drug design / Crystallographic methods / Crystallography education

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High throughput crystallography / Structural genomics / Structure-based drug design / Automated structure determination methods / Structure validation / Crystallographic education

Crystallography Quo Vadis?

Practically all information about the molecular structure of matter at atomic resolution is the result of crystallographic analysis. Diffraction methods have contributed at an unprecedented level to our understanding and design of material properties, impacting the development of novel nanomaterials and micromachinery, pharmaceutical drug target structures and engineered enzymes. More than in any other basic science, results of advanced crystallographic studies directly and tangibly affect all our lives, through advances in biosciences up to space-age high tech materials development.

Substantial advancements in crystallographic techniques made over the past 25 years allow individuals with quite diverse background and preparation interested in a specific structural problem to use crystallography as a tool in their problem-oriented, hypothesis-driven research. The practitioner in crystallography today and perhaps even more in the future is the structural biologist, structural chemist or material scientist. Ironically, as a result of exactly the great methodological advances that now enable users with little training to produce quality results, crystallography as a science has had to struggle in recent years with the attitudes of some members of the research community, who consider our science either too easy, irrelevant beyond the solid state, or who deem it service rather than scholarly. As a result of this mistaken opinion, the biggest challenge

that modern crystallography faces is the declining number of “card-carrying” crystallographers.

Teaching crystallography in a way that attracts the most talented young people is therefore a must, if we want to keep our science alive and vibrant. Given the high caliber and rapid pace of methods development in crystallography, (and unfortunately, the many cautionary tales where unguided users have gone badly astray, particularly in biological crystallography), there should be ample opportunity to advertise the importance of studying crystallography to the brightest students. Trained crystallographers develop more and more sophisticated methods, algorithms and automation, they solve the most challenging structures, and frequently they are consulted on difficult problems, which do require depth of knowledge and expertise.

Twenty-five years ago, we knew very little if anything about recombinant DNA, maximum likelihood methods, direct methods applied in protein crystallography, multi-wavelength anomalous diffraction (MAD) phasing, or now routinely employed cryo-techniques. Modern crystallography therefore encompasses not only core crystallographic techniques and methods, but also, particularly in biomolecular crystallography, the front end aspects of protein production, purification and crystallization. The strong feedback taking place nowadays between the actual crystallography and protein engineering has long been standard practice in the pharmaceutical industry, and it has increasingly become the norm in most biomolecular structure determination projects. Equally important now also are the bio- and chemi-informatic details of annotating structural coordinates with functional and genomic information, and genomic sequences with structural information. Developments in structural genomics and high throughput crystallization also have found their way into modern structure determination. High throughput crystallography was the topic of the transactions symposium at the American Crystallographic Association meeting in Los Angeles, 2001.

With advancements in crystallographic methods and availability of increasingly powerful analysis tools, crystallographers may need to part from some beloved traditions: PhDs are no longer awarded for solving a Patterson map; a few small molecule structures or a single protein structure solved by molecular replacement may not suffice for a publication; nor does mere data collection deserve co-authorship. Such demands only serve to cheapen our science and perpetuate the view that the role of the crystallographer in structural chemistry and biology is limited to service work not considered scholarly. Skillful analysis of a structure in its chemical or biological context, intense feedback with material preparation and knowledge of the synthetic methods, as well as a solid repertoire of techniques tailored towards the demands of more and more challenging structure determinations, these will be the trademarks of the successful crystallographer of the 21st century.

Paul Ewald described our science in *Acta Crystallographica* **1** (1948) pp. 2: “Crystallography borders, naturally, on pure physics, chemistry, biology, mineralogy, technology and also on mathematics, but is distinguished by

being concerned with the methods and results of investigating the arrangement of atoms in matter, particularly when that arrangement has regular features.” This statement is as true today as it was more than 50 years ago. Modern crystallography provides enabling technology, methodology and information, and the bounty of knowledge gained from analysis of its structures is a key underpinning of modern science and technology.