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Historical Note

MACROMOLECULAR CRYSTALLOGRAPHY IN INDIA IN THE HISTORICAL CONTEXT

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Diffraction of X-rays by crystals was discovered by Max von Laue and others at Munich in 1912. This discovery was followed up soon after in England by William Bragg and Lawrence Bragg. The structure of sodium chloride was determined by Lawrence Bragg in 1913, thus marking the beginning of X-ray crystal structure analysis. Sodium chloride is made up of just two atoms. The largest structure to be determined using X-ray crystallography during the first decade of this century was that of ribosome which contains more than a hundred thousand atoms. That is a rough measure of the progress of the field in a century.

The early efforts in X-ray crystallography were mainly concerned with inorganic compounds, particularly minerals. By the third and fourth decades of the last century, organic compounds began to receive increased attention. There have been many important structure determinations, the most important of which has been that of vitamin B_{12} by Dorothy Hodgkin and her colleagues. It is often said that she relieved organic chemists of the drudgery of structure determination. Inorganic and organic chemical crystallography continues to thrive. Crystallography is an important tool in current materials science research as well.

The most spectacular applications of X-ray crystallography have indeed been in biology, particularly in relation to biological macromolecules. The beginning of biological macromolecular crystallography can be traced to the recording of the diffraction pattern from the crystals of pepsin by J.D. Bernal and his student Dorothy Hodgkin (then Crowfoot) at Cambridge in 1934. The latter returned to Oxford and recorded the X-ray pattern from insulin crystals in 1935. Max Perutz, a student of Bernal at Cambridge, crystallized hemoglobin and carried out preliminary X-ray diffraction studies on them in 1937. A few other preliminary studies of this type were also carried out during this period. The early pioneers were, however, well ahead of their time as even the precise nature of proteins was not known at that time. The crystallographic methodology was also then not adequate to cope with large protein structures.

The first protein structures to be determined were those of myoglobin and hemoglobin by the groups of John Kendrew and Max Perutz, respectively, during the late fifties and the early sixties. The structures of lysozyme, ribonuclease A, several proteolytic enzymes and insulin were determined in the sixties. By the seventies, macromolecular crystallography began to spread to different centers in many parts of the world. Structural biology resulting from X-ray studies and methodological and technological innovations progressed hand in hand. Macromolecular crystallography is now central to modern biology.

India has a long tradition in crystallography starting with the efforts of K. Banerjee at Kolkata (then Culcutta) in the mid-thirties. G.N.

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Ramachandran and his colleagues gave a head start to India in computational structural biology. They also made outstanding contributions to the methodology of crystallography. A few Indians have been involved in crystallographic projects abroad. I was the first trained Macromolecular crystallographer to return to India, to the Indian Institute of Science, Bangalore, in 1971, after participating in the structure solution of insulin in Dorothy Hodgkin's group at Oxford. The time was not then propitious for starting macromolecular crystallography in India, primarily on account of financial constraints. I established myself as an independent researcher working mainly on the supramolecular association involving amino acids and peptides, with its implications to chemical evolution and origin of life. However, I remained focused on initiating macromolecular crystallography in India. In the meantime, K.K. Kannan, who had worked on carbonic anhydrase at Upsala, joined the Bhabha Atomic Research Centre, Mumbai (then Bombay) in 1978.

Macromolecular crystallography in India took off the ground after the Department of Science and Technology (DST) supported generously our group at the Indian Institute of Science under their Thrust Area Programme in 1983. The Bangalore centre was also recognized as a national nucleus for the development of the area in India. Since then, over the years, the work has spread out to different parts of India. A majority of the research groups in the area in the country are manned by scientists trained at Bangalore or their academic descendents. Many groups are headed by those trained in other centers in India and abroad as well. All of them put together, although large in number, form a reasonably coherent community. In addition to the continued support from DST, the effort is now generously supported by other agencies such as the Department of Biotechnology (DBT) and the Council of Scientific and Industrial Research (CSIR) as well.

Much of the early efforts at Bangalore were concerned with lectins, viruses and protein hydration while those at Mumbai centered on carbonic anhydrase. Work on lectins is now being pursued at other centers as well. Problems now being studies in different laboratories of India encompass a side spectrum and include proteins in body fluids, phospholipases, molecular mimicry, antibody maturation, proteases and their inhibitors, xylanases, penicillin acylase, editing during protein synthesis, lipases, crystallines, integral membrane proteins, ureases and transcription factors.

Macromolecular crystallography came of age in India by the turn of the century and it was then time to give added emphasis to problems of national relevance. Infectious diseases have been the bane of India for millennia. Therefore, an overall programme of structural biology of microbial pathogens was orchestrated at the beginning of the century. This effort now encompasses proteins from *Mycobacterium tuberculosis*, *Salmonella typhimurium*, malarial parasite, *Leishmania donovani*, *Entamoeba histolytica* and HIV. The most concerted effort in this context is that on *M. tuberculosis* (TB) proteins. Now ten different institutions in the country are involved in this structural effort. It turns out that more than ten percent of the total number TB proteins structures analyzed todate is from India.

From humble beginnings in the early eighties of the last century, macromolecular crystallography has grown into an important component of biological research in the country. The area is being pursued in more than 30 institutions in India. The results produced so far have been impressive and encompass different aspects of modern biology. Macromolecular crystallography in India is now poised to reach greater heights.