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Editorial

EDITORIAL

Harmony in Chaos: Protein Crystallography

"All the work of the crystallographers serves only to demonstrate that there is only variety everywhere where they suppose uniformity ... that in nature there is nothing absolute, nothing perfectly regular."

-**Georges-Louis Leclerc, Comte De Buffon, 18th Century**

Crystals have always fascinated the human beings by their beauty and mystery, be it in the form of gemstones, falling snowflakes during winters or simply adding salt grains into the food, one comes across crystals in different shapes in the nature. The year of 2014 is not just being celebrated as the International year of Crystallography as decided by UNESCO but also the work done by William Henry, William Lawrence Bragg father-son duo and Max Von Laue. The field of X-ray crystallography is celebrating 100 years of incredible discoveries - from helping to make medicine, to enhancing the efficiency of batteries, to improve the taste and texture of chocolate. The International Year of Crystallography 2014 commemorates not only the centennial of X-ray diffraction, which allowed the detailed study of crystalline material, but also the 400th anniversary of Kepler's observation in the year 1611 of the symmetrical form of ice crystals, which began the wider study of the role of symmetry in matter.

Today, surprises seemingly lie in wait around every corner, with fields such as genomics, proteomics, and pharmacology benefiting from lightning fast and significant speed of various analytical procedures their high and accurate levels of throughput and the most importantly easy accessibility. These processes though continually undergoing evolution provide a plethora of data and an endless supply of tiny molecular players to be determined in 3D to help answer the most fundamental questions and identify their role in biology, health and tricky diseases. The development of next generation i.e. 2nd generation synchrotrons and electron lasers that are free from any X-rays add to this sense of anticipation. Today they present a huge opportunity to overcome, which otherwise would have been nearly impossible due to many of our current limitations, particularly in the study of larger and more complex biological systems. Crystallography, also called the "Science of Fortune" however, till date remains a very difficult science - and the quantities, size differences and unique nature of crystals demanded by modern research projects increasingly require us to quickly think on our feet.

From its beginnings up to this day, structural biology as a whole and protein crystallography owes a lot to many fortunate events. Going way back, the first such fortuitous circumstance was the non-existence of tenure system for the scientists at the University of Cambridge, UK. This limitation actually gave Max Perutz to spend years and years to study the structure of hemoglobin, which almost went for more than 20 years before he could come up with the first set of structural analysis and those significant structural results could be published. His work that also led him to be awarded the Nobel Prize in chemistry in the year 1962 resulted in a new dawn towards developing a completely new methodology. This was later used

by all other groups investigating many other protein structures. Today if you look back at that excellent piece of invention, you realize that in addition to being innovative about the method, the choice of hemoglobin as a target protein for that effort was also in a way lucky one, as a larger part of its secondary structure only consisted of a α-helix. This resulted in making Hemoglobin stable, very rigid, diffracting excellently and ultimately comparatively easy to model. Later, the development of synchrotrons by high-energy physicists catalyzed the explosion of protein structures solved by x-radiation.

While doing structural biology analysis of complex pathways, proteins or any other system, the most often needed things are significant amount of work and much luck to decipher the path from gene to publication. And in many of such complicated cases, the period between the first instance of getting the initial crystallization conditions stabilized and publishing a wholesome structure with its deduced physiological significance may extend over a decade. The bottlenecks and the critical steps of the whole process, though called as the "low hanging fruit" by some people turns this frequently-used term into a "high-hanging fruit", are being constantly redefined. The major difficulty is the same as in any other cutting-edge experimental science—differentiation, identification and then isolation of a low signal data from high background noise. Nowadays, the whole process of determining macromolecular structures is faster than ever. The scientists are still of the belief that with proliferation of the best experimental protocols and techniques and new methodologies being continually developed, there would be a decreased dependence for the crystallographers on the so called fortunate circumstances, there would still be a significant luck factor playing a role in the foreseeable future.

The rapid technical progress and a fast growing number of spectacular scientific achievements in the last five years demonstrate that micro-crystallography is indeed the "new normal" in macromolecular crystallography. Nevertheless several challenges still are standing face-to-face to the Scientists. Building the micro-focus beamlines with requisite stability for 5-µm diameter or smaller X-ray beams is extremely difficult to develop and especially very challenging for retrofitting on older beamline built to a different standard. With advent of micro beams and microcrystal samples, one has to be very swift and efficient with a greater support in terms of powerful, rapid, automated methods to locate and center crystals in the beam. The key to a successful study come from automation to monitoring and maintaining beamline robustness and stability, and to minimize the chaos created by human hands at the x-ray diffraction end-station hardware. One perpetual challenge, irrespective of crystal cryo-protection is the damage caused by radiation. Efficient and fast-readout detectors may effectively extend the lifetime of room-temperature crystals by outrunning damage caused by diffusing free radicals. Through improved signal-to-noise, fast detectors also push the envelope toward even smaller and more weakly diffracting crystals. Smaller samples, hotter beams and more in situ experiments return us to an era of multi-crystal data sets, but in this era multi-crystal, ultra-high-redundancy data can be taken very quickly.

There is a great need for sophisticated software to sift through many partial data sets from many crystals and to assemble complete merged data sets of the highest redundancy, taken from the most isomorphous subset of crystals, in their least damaged state. The need is especially acute for data taken at room temperature in in-situ experiments. The challenges are substantial but not insurmountable and the future is bright – we will see more biology on more difficult systems with hotter, smaller beams that are delivered with great precision and controlled by sophisticated tools.

Summarizing, the major challenges that we as scientists facing today are: routine growth of diffraction-quality crystals – particularly difficult in studies involving complex membrane proteins or biological assemblies and efficient measurement of diffraction data from these crystals. With ingenious approaches to automation, robotics, computation, software and more, we will enhance our efforts to interpret the wealth of information produced by modern science.

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