

PREFACE

High-Throughput “Combichem” Crystallography

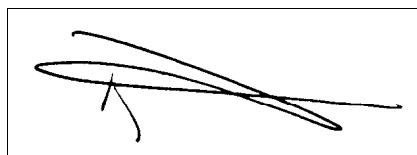
After an analysis of research in structural biology laboratories, one finds that a tremendous amount of a graduate or postdoctoral career is spent expressing, purifying, and crystallizing target proteins. The majority of structural genomics pilot projects are taking the same brute force approach and spending large sums of federal dollars to solve a number of predicted unknown fold structures. It is unfortunate that the field currently spends so much time on the above, and so little time actually analyzing what the structural data reveals. Furthermore, structure-based drug discovery using protein crystallography showed great promise in “rational design”, but the approach has not lived up to its reputation. Instead, combinatorial chemistry approaches, also known as “irrational design,” took over as a much more powerful approach in the search for novel drug molecules. The real attraction and virtue of the combichem approach is speed and real feedback in the drug discovery loop. Furthermore, genomics—the sequencing of genes and mapping of sequences to potential drug targets, has enabled researchers to identify candidates along an entire metabolic pathway. We continue to see the miniaturization of microliter plates from 96 to 384 to well beyond (3456 for Aurora Biosciences), including the advent of gene chips, for screening. Much of this development is on the heels of, or in parallel with, the advent of combinatorial chemistry and parallel synthesis technology.

Over the past decade, structural biology has become more *facile*, but not necessary *faster*. Sure, with determined effort and a little luck, we can determine a *de novo* structure in a week, but could we sustain this rate or substantially improve on it for a year? Will we see the same advances in structural biology that we have recently observed in combinatorial chemistry and genomics? The answer is almost certainly yes. The National Institute of Health and the Department of Energy have proposed that robotics workstations at synchrotrons are necessary to meet rising demands in the next decade. There is an interesting scientific race currently ongoing to reduce many of the bottlenecks in high throughput protein crystallography. As we have seen in many of the past prefaces to the *Rigaku Journal*, the focus has been on solving structures faster and faster. Bob Sweet at Brookhaven National Laboratory now publicizes the “Data by FedEx” -approach, where his group has addressed some of the issues of increased efficiencies at synchrotron beamlines with good programming protocols. Software continues to improve in automating the data analysis (e.g., HKL2000, d*trek, CrystalClear), and structure solution and rebuilding (e.g., SOLVE, SHARP, XtalView, CNS). We continue to see attempts at manual (combichem) crystallization trials using screening kits (e.g. Hampton Research), and using robotics technology in crystallization trials (e.g., CyberLab) and imaging (e.g., Diversified Scientific). However, the current robotics systems developed many years ago have not been as useful as many had hoped. Why do we believe that there will be a breakthrough in this technology? Because it is already being done in the genomics and combinatorial arena, and there is even more need today than there was yesterday.

One concern many have raised is that we might create a generation of structural biologists who do not know how to collect or interpret experimental data. However, this is analogous to the old concern that if we do not continue to teach our students how to use a slide rule, they may never learn math. As techniques advance and our data quality checking becomes more robust, we will focus our mental concerns on new areas, and tackle new problems that we cannot even imagine today. Wouldn't it be wonderful to be able to look an enzyme structure with the substrates, intermediates, ligands, co-factors, products, inhibitors, and

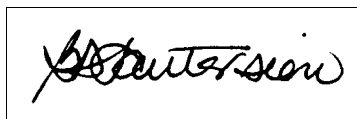
various metals bound, and to have more information in our understanding of a catalytic mechanism or conformational switches? One day this could replace the impressive guesswork many of us do in predicting how a protein works in the absence of any other protein-ligand complex data. Think of the advantages in studying protein function in almost real time, posing questions and resolving them with a derivative structure. In addition, the gauntlet is thrown down to pursue even more challenging problems, larger structures and assemblies of structures.

In reading past prefaces of the *Rigaku Journal*, we feel that the authors were overly conservative in their analysis of the pace of the field. The field is moving at an exponential rate, similar to the rate of protein structure depositions in the Protein Data Bank. Over the past decade, we've seen a parade of advances in software and hardware at the data collection level and this parade continues. Now we will see a similar assault on expression, purification, and crystallization. This will put time back into the hands of the scientist for analyzing their structures in more detail, which is what many of the pioneering crystallographers probably did in the early days with their initial view of structural information.



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