nature structural & molecular biology

In praise of biochemistry

When asked to write a guest editorial on the importance of biochemistry Arthur Kornberg, one of the most revered biochemists of the 20th century, was concerned that what he wanted to say "would be as welcome as a skunk at a picnic. Structural, molecular and cell biology have been so successful and attractive that as a result the old-fashioned biochemistry has been neglected."

The value of biochemistry is also in danger of being overshadowed by an increased emphasis on high-throughput methods. As genome sequencing projects are completed, attention is shifting to the proteome. Most recently, large-scale approaches have spawned the linguistically ungainly fields of transcriptomics, metabolomics and phenomics. In a scientific climate where bigger seems sexier (and better funded), what is the role of biochemistry?

Classical biochemistry seeks to understand how molecules interact and function at an atomic level. The questions asked are specific and, initially at least, common to almost any molecule being studied. What is the ligand or substrate? What cofactors are required? How do reaction conditions affect activity? And, if the molecule is an enzyme, what is the mechanism of catalysis? Although most biochemistry begins by defining a particular molecule's activity, eventually more complex systems are constructed from these well-characterized single component reactions to determine how interactions with other molecules under differing conditions could change their properties or confer new functionalities.

But such a reductionist approach does not just provide details—it can lead to new insights into the function of a molecule that could not be derived by other means. Here are a few particularly striking examples. The source of a biochemically-identified histone acetyltransferase activity turned out to be the previously well-characterized transcriptional activator GCN5. This surprising finding directly linked histone acetylation and chromatin modification to gene activation. *In vitro* experiments demonstrated the requirement for cytochrome *c* in apoptosis thus establishing an unexpected role for mitochondria. Finally, the discovery of catalytic RNAs was only possible by *in vitro* studies. This remarkable finding propelled the search for other ribozymes and revitalized the idea of RNA's central role in the origin of life. Without biochemical characterization the functions of these molecules would have remained elusive.

If the ultimate goal of biology is to understand cellular processes in sufficient detail to enable accurate predictions about cellular behavior (for example, signaling, differentiation, death, motility), then a systems biology approach will undoubtedly move us closer to that goal. High-throughput measurements of DNA, RNA, and protein have made possible an integrative approach to studying the complexity of networks and pathways that constitute the cell. So why emphasize the particular value of a reductionist approach such as biochemistry? Although large-scale studies generate data sets that can be mined for overall trends, a detailed understanding of how a particular process works will depend on the biochemical characterization of individual components and the way in which they interact. In fact, the quantitative data generated from such experiments (on and off rates, rates of reaction, affinities, etc.) are required by systems biologists to refine their computational models.

It is also worth remembering that one cannot always judge a molecule's function by its sequence or even its structure. Many ORFs in the annotated genomes encode putative proteins sufficiently diverged from all current database entries that they appear unique. How will we determine their functions? Some hints may come from their placement into networks or pathways by cluster analysis of microarray data or protein-protein interaction studies, but we may only truly understand how they work by measuring their activities. The methods used may be different (for example, single molecule studies now allow us to appreciate the variability in activity and behavior among individual molecules that isn't possible in bulk solution measurements), but the requirement for biochemists will remain strong.

In this spirit, *Nature Structural & Molecular Biology* would like to become the home for exceptional biochemistry that provides new mechanistic insights into any biological process. We are also committed to making these studies accessible to our broad readership. In time we hope that terms such as K_m, K_d and k_{cat} will become as familiar to our readers with non-biochemistry backgrounds as R-factors and co-IPs. Of course, biochemistry cannot stand in isolation, and the more we can integrate different approaches the deeper our understanding of cellular processes will be.