



## INTRODUCTION

# Proteins at Work

IMPORTANT INSIGHTS INTO BIOLOGICAL PROCESSES HAVE COME FROM TRADITIONAL *in vitro* biochemistry experiments and from static structures determined by x-ray crystallography and nuclear magnetic resonance (NMR) spectroscopy. Now scientists seek to gain a quantitative understanding of how dynamic macromolecules function inside of cells. This special issue highlights technological advances that are facilitating progress in this field.

Knowing the players is fundamental to a quantitative understanding of cellular processes. To this end, the field of proteomics is aimed at the systematic analysis of all proteins in a cell or tissue. Mass spectrometry is central to most proteomic strategies, and Domon and Aebersold (p. 212) describe how recent advances in mass spectrometry instrumentation are allowing not only descriptive studies that identify proteins and characterize posttranslational modifications, but also quantitative studies looking at changes in protein concentration between samples. But a cast list, even with exits and entrances marked, cannot tell the whole story. Ultimately, we would like to view the action as it happens. Giepmans *et al.* (p. 217) discuss developments in fluorescent probes and techniques to determine protein expression, activity, and function in fixed and live cells; and Xie *et al.* (p. 228) provide examples where single-molecule imaging techniques are used to follow gene expression, active transport, and metabolism in live cells.

Exciting as this global view is, it does not show us how each protein works. It has become clear that protein motions are important for function, with much of the experimental data coming from NMR spectroscopy. Mittermaier and Kay (p. 224) give an overview of NMR methods that allow internal motions to be probed with very high time and spatial resolution. Some of these methods were used by Koglin *et al.* (p. 273) to show that a protein that acts in nonribosomal peptide synthesis displays a double two-state conformational equilibrium that is important to its function. Computational methods provide additional tools to study dynamics. Masgrau *et al.* (p. 237) used a combination of kinetic and crystallographic experiments and computer simulation to show that in one enzyme, short-range thermal motions are sufficient to explain hydrogen tunneling. An associated Perspective by Benkovic and Hammes-Schiffer (p. 208) suggests that looking outward from the active site may reveal a more complex picture.

In related online resources, *Science's* Signal Transduction Knowledge Environment (STKE) (<http://stke.sciencemag.org/>) features a Protocol by England on monitoring AMPA receptor trafficking and a Review by Vogel *et al.* discussing how to overcome potential pitfalls of fluorescence resonance energy transfer (FRET) analysis.

We look to a future where the tools described here, and those yet to come, will allow us to watch biochemical reactions in live cells and understand how each molecule plays its role.

— VALDA J. VINSON

## Tools for Biochemistry

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