

# Closing in on catalysis

**Building on a century of enzymology research and new genome-wide insights into enzyme families, increased interdisciplinary communication and a broad vision will advance our understanding of biological catalysts and enhance our ability to manipulate them.**

Enzymology has made such an impression on its field that, to many scientists, the study of enzyme kinetics and the characterization of protein mutants are inseparable from the modern definition of biochemistry. However, the field in its current state would be unrecognizable to Eduard Buchner, who was awarded the Nobel Prize in Chemistry in 1907 for the astounding discovery that fermentation can occur without cells, which presaged the further identification and study of discrete enzymes. Enzymology has grown from these early challenges in simply defining what an enzyme is to encompass a huge diversity of topics. This revolution has been inspired in part by the advancement of tools and techniques, which has sped research and allowed more precise and sophisticated questions to be asked, and in part by our ongoing discoveries of unknown enzymes, new modes of regulation and unexpected behaviors. Indeed, the discoveries of catalytic DNA and RNA sequences have reshaped our view of the basic molecules involved in biological catalysis. To facilitate the next slate of astounding enzymatic discoveries, enzymologists and other chemical biologists will benefit from enhanced interdisciplinary communication, a focus on universal principles of catalysis and an increasing emphasis on research that extends beyond the test tube.

Establishing a common language between fields is critical to be sure that scientists are aware of current knowledge and understand where our current models end. As chemical biologists are often comfortable traveling between disciplines, scientists in this field can provide important new perspectives about when established ideas may need greater clarity, expansion or revision (pp. 543 and 551). Enhanced communication between fields can highlight tools or concepts from a particular discipline that could be embraced more broadly. For example, biologists may take the lead in identifying new mechanisms of controlling gene expression (p. 530), whereas chemists can apply chemical intuition to better anticipate and decipher enzyme reaction mechanisms (p. 534). Greater interdisciplinary collaboration will also better identify and overcome the limitations inherent in distinct approaches. For example, the timescales of catalysis vary drastically, and the techniques available to probe these different timescales do not cover the full spectrum of a chemical reaction. How can theoretical chemists (who primarily study picosecond dynamics) and biochemists (who typically look at reaction turnovers on the millisecond timescale and beyond) best integrate their studies to provide new insights that surpass either individual set of results? Only by combining expertise and insights across the chemical and biological spectrum will biological catalysis be fully understood from the atomic to the organismic level.

While merging ideas from researchers with different expertises will hone our awareness of what gaps remain in our atomistic picture of catalysis, there is also much to be gained from bringing together scientists who have overlapping expertise but are utilizing those skills to study disparate systems. By comparing current information and applying chemical

principles more broadly across the field of enzymology (p. 516), scientists will more quickly be able to see what behaviors are general and what fundamental information is still missing. This endeavor will be aided by the almost unlimited new data that are being provided from biochemical, structural and genomic investigations, as comparisons of a large number of proteins are likely to provide greater confidence about how behaviors interlink and should help to establish new universal principles of catalysis. In the short term, careful analysis of these rich data resources with these larger goals in mind will create greater impetus to organize and curate the data appropriately (p. 521). In the longer term, the availability of robust and more complete data sets will provide new insights that are relevant across enzyme families, species and chemical transformations, and will also provide better foundations to guide future research.

Enzymology is perhaps best known as a source of robust quantitative data regarding the function of single proteins under *in vitro* conditions. While these types of studies have been instrumental in developing our current understanding of enzyme function, enzymologists and other chemical biologists must be more committed to investigating enzyme behavior in more biologically relevant contexts. For example, biochemists are only beginning to understand how the behavior of an enzyme in the test tube mirrors its function in the cell (pp. 593 and 535). Similarly, we still have only a limited knowledge of the external forces and cellular plasticity that drive the evolution of new catalytic pathways (pp. 538 and 559).

An increased understanding of enzyme function at all levels will also advance our ability to manipulate enzyme function—a common goal in chemical biology research. Though we can describe many reactions in great detail, our capacity to create new ones is gaining traction primarily through improved randomization and screening strategies rather than more deliberate design (p. 567). As Ichiro Matsumura notes, “unfortunately, [this] proliferation of techniques has fostered confusion and a trial-and-error approach to experimental design” (p. 538). Thus, broader knowledge will complement new standards and best practices for protein engineering to ensure continued improvements in our engineering efforts (p. 526).

Enzymology is now witness to a wide array of exciting questions and challenges. As our ability to obtain vast quantities of data increases and the number of potential scientific questions escalates, we urge scientists to reflect on the field as a whole to ensure that time and resources are being directed to globally relevant and foundational questions in biological catalysis. Building a broader platform for understanding enzyme function and evolution will not only satisfy our scientific curiosity about these amazing machines, but will also significantly advance our capacity to design and manipulate them for useful applications. We hope this collection of articles catalyzes new ideas and conversations to advance enzymology. ■