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The International Debate on Tailoring Enzymes for Defined Industrial Applications by Integrating Accelerated Molecular Dynamics Simulation, Functional Sequence Space Clustering and Experimentally Guided Machine Learning.

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Enzymes are biological catalysts that catalyse highly specific chemical reactions in all living organisms. Enzymes have evolved over millions of years to carry out the very specific chemical reactions of life. Some of the oldest chemical reactions known to man, such as the production of vinegar, cheese, beer and wine, employ enzymes. However, up to the 1990s the availability of suitable enzymes for industrial applications was very limited. Natural enzymes were mostly unstable in industrial conditions and frequently gave low yields. Consequently, most applications were initially restricted to simple hydrolases for esterification or hydrolysis, principally in laundry detergents and leather manufacture. The exploitation of recombinant gene technologies, such as random mutagenesis, site direceted mutagenesis, rational design, DNA shuffling, directed evolution, has since enabled the commercialisation of enzymes that could previously not be implemented in industrial processes. Nowadays, enzymes play an important role in a variety of industries, including household care, food and beverages, animal health and nutrition, textiles, pulp and paper, personal care and cosmetics, agriculture, fine chemicals, diagnostics and pharmaceuticals1,2. Due to their high chemo-, enantio- and regioselectivity, resulting in higher yields of a required enantiomer, enzymes are increasingly used in the fine chemicals and pharmaceutical industries, particularly in the synthesis of chiral pharmaceutical intermediates for the production of active pharmaceutical ingredients (APIs)3. Another major advantage of enzymes is that they eliminate the requirement for protecting groups and minimise undesirable side-reactions, thereby increasing product yields and purity and reducing timelines in API manufacture. Enzymes are also able to work under mild conditions, providing a safe work environment and resulting in significant savings in production costs and resources, such as energy and water, for the benefit of both the industry in question and the environment. The importance of industrial enzymes has been further increased by the demand for the production of fuels and chemicals from alternative and renewable resources. Such a demand has been augmented by the growing need for sustainable, environmental and economic solutions due to concerns on climate change induced by greenhouse gas emissions, which have been linked to fossil fuels. Consequently, with the increased emphasis on the biorenewables industry, enzymes are also playing a fundamental role in the transformation of these raw materials into biorenewable products, such as biofuels, biopolymers, and other bio-based products, under mild and sustainable conditions4,5.

Recent advances in protein engineering and directed enzyme evolution have had a great impact on biocatalysis, providing a great diversity of customised enzymes. Engineering enzymes to fit the conditions of a desired industrial process is now standard methodology. However, even the most efficient protein engineering and directed evolution methods require multiple rounds of diversity generation, gene recombination and functional screening to identify improved variants. The iterative nature of this approach results in stepwise improvements in overall function, ultimately yielding a product with the desired properties. However, such iterative procedures are relatively time- and cost-intensive. Thus, despite the success in tailoring enzymes for defined industrial applications, there is a continuing need to make the process of improving or customising enzyme function more reliable, efficient and cost-effective6,7. One solution is to create next generation enzyme discovery and development technologies,