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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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Commentary

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DESCRIPTION

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 directed mutagenesis, rational design, DNA shuffling, directed evolution, has since enabled the commercialization 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 pharmaceuticals[1,2]. 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 minimize 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

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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 conditions[4,5].

Recent advances in protein engineering and directed enzyme evolution have had a great impact on biocatalysis, providing a great diversity of customized 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 customizing enzyme function more reliable, efficient and cost-effective [6,7]. One solution is to create next generation enzyme discovery and development technologies, such as accelerated molecular dynamics simulation and experimentally guided machine learning.

Machine learning, combined with artificial intelligence, which has made a significant impact in several fields, such as image recognition, self-driving cars, takes advantage of the availability large and diverse sequence and structural data on a plethora of enzymes to identify sequence to function correlations, predict beneficial mutations, and explore novel protein sequences. Such methods, which are already being offered by a number of Biotech companies, accelerate directed evolution by learning from the properties of characterized variants, to simultaneously optimise multiple protein properties and explore sequence space more efficiently[8].

One of the recently developed technologies making an important contribution to the discovery of novel proteins and the engineering of tailor-made enzymes for defined industrial applications integrates accelerated molecular dynamics simulation and functional sequence space clustering with experimentally guided machine learning[9]. This powerful technique, developed by the company candidum GmbH, involves the application of a proprietary enzyme design platform that overcomes key efficiency bottlenecks in statistical structure-dynamics analysis to enable the streamlined functional clustering of the protein sequence space. This technology allows the fast, reliable and cost-effective identification and subsequent engineering of hotspots in a protein. Consequently, enzyme properties, such as chirality, catalytic activity, pH stability, thermostability, substrate specificity, or stereoselectivity, can be rapidly and inexpensively improved. In addition, integrating hotspot profiles to sequence database analysis enables the discovery of enzymes based on their functionality as opposed to sequence homology. This procedure thereby results in the identification of protein homologues with potentially better properties than the target enzyme. Combination of the two approaches with short experimental validation cycles yields powerful focused combinatorial libraries and provides outstanding opportunities for the selection and subsequent design of industrial enzymes with the desired properties.

Recent developments in modern biotechnology have already made a major impact on the implementation of enzymes in a wide range of industrial applications. Further advances in computational and experimental techniques combined with the increased understanding and ability to tailor enzymes with hereto unknown novel functions will increase further the scope of chemical reactions catalysed and the industrial applications of such enzymes.

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