biophysica

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Editorial

Protein Engineering: The Present and the Future

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Yes, we are made of proteins, and yes, we can profit from them [1]. From a synthetic point of view, proteins are uncomplicated polymers with extraordinary properties of biological and economic value. They are widely used as biological catalysts in industry, as key components of analytical methods, or as highly specific drugs for personalized medicine. No wonder we want to learn how to fabricate proteins to specifications. After all, that is more or less how airplanes are built today [2], is it not? In our hearts and minds, we look forward to a future where we will have mastered protein design and where making proteins will become a highly skilled but fairly straightforward activity rather than a fascinating but rather difficult challenge.

With an estimated 10 million species on the planet, the Earth's proteome is very large, but it only represents a small fraction of the theoretical protein chemical space that encompasses all synthesizable polypeptides of reasonable size. Protein engineering is, in the words of pioneers of the field, "the design and construction of novel proteins, usually by manipulation of their genes" [3]. At the dawn of protein engineering, practitioners focused on modifying the active sites of enzymes through site-directed mutagenesis, which quickly led to many biotechnological and biomedical advances. Only 10 years after the first protein variants were engineered in 1982, the extraordinary possibilities that opened up for the analysis of protein structure and function and for the synthesis of new therapeutic agents had already materialised. At the same time, difficulties in designing function were also perceived, associated with the inadequacy of existing computational methods for predicting structure from sequence and activity from structure [3]. Since then, there has been substantial progress. Nowadays, protein engineering techniques are available worldwide and have become routine in both basic research and biotechnology. Most of the time, new protein functions are obtained by combining existing ones into single polypeptides [4], redesigning or evolving natural proteins [5], or from scratch [6]. Occasionally, new functions are discovered for a known protein [7].

In order to fully harness the potential of protein engineering, some practical limitations remain that need to be addressed. While limitations in the use of protein directed-evolution techniques to improve or generate protein functions may relate to the need to devise efficient selection or identification methods on a case-by-case basis, limitations in exercising biophysics-based design are related to more general issues such as insufficient knowledge or computing power. To overcome these barriers, the gap between sequence and structure is being filled by novel modelling approaches [8], accurate Molecular Dynamics simulation techniques are used to analysing and designing protein stability, binding and catalysis [9], and machine learning approaches [10] are providing new tools to help us solve general problems associated with protein production. In some cases, the challenge facing the protein engineer may be relatively easy to solve. The stabilization of natural proteins for their cheaper production, easier transport and storage, and longer shelf life may represent affordable, yet decisive achievements that can make a big difference. In other cases, completely new properties will be sought, and being able to engineer them in polypeptide

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Citation: Sancho, J. Protein Engineering: The Present and the Future. *Biophysica* **2022**, *2*, 111–112. https://doi.org/10.3390/biophysica2020011

Received: 25 March 2022
Accepted: 26 March 2022
Published: 29 April 2022

format will require a much greater amount of design and testing. An impressive illustration of the power of protein engineering has recently unfolded before us in the form of new RNA-based vaccines [11]. Somewhat reflecting on early achievement in the protein engineering field, carefully designed synthetic nucleic acids have been used to orchestrate the fabrication of a most convenient protein variant inside more than a billion human beings, providing effective vaccines for covid-19 pandemic.

Amid clear and continued progress, the protein engineering community stands to lose opportunities if the idea dominates that the field is so well established that the remaining problems (essentially insufficient predictive power for the more demanding protein design goals) will be swiftly solved in due time. Sure they will, but some concerted work to increase the visibility of the field may contribute to accelerating this progress. Initiatives aimed at strengthening the protein engineering community, for example by clearly defining its grand challenges or organizing protein design competitions, can help, while supporting protein engineering curricula focused on quantitative tools that meet the needs of industry can attract talent.

Protein Engineering began as an empirical field much based on trial and error and is becoming a quantitative discipline where success is guaranteed by good design. In this Special Issue, we aim to show, with examples of their application to specific proteins, advanced methods that anticipate the transformation of Protein Engineering from an art for practitioners to a reliable technology.

Conflicts of Interest: The author declares no conflict of interest.

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