Medical University of Graz

Computer-aided (re)design of enzymes for therapeutics

Summary

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Supervisor:	Dr. Pedro Alejandro Sanchez Murcia
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between March 24, 2021 00:00 and May 05, 2021 23:59 (Europe/Zurich)

Description

Background: The design of novel enzymes as drugs has opened up new avenues in therapy. The versatility and substrate affinity of these biocatalysts make them ideal scaffolds for the design of new drugs with high potency. Even so, enzymes can suffer from problems of low availability and poor enzymatic activity in plasma. Protein engineering techniques can help overcome these drawbacks. The sequence and structure of the enzyme can be modified by changing the amino acid composition and thus its properties. However, this process still requires a large number of trial-and-error experiments as the coverage of the entire mutation landscape is not manageable, which makes this process an extremely resource and time consuming process. With this in mind, there is great hope in computational enzymology to perform such multiscale tasks on computers to reduce the cost of protein engineering campaigns and provide some rationale for future designs. Some successful examples in this direction have been reported in recent years (e.g. FuncLib).[1]

Hypothesis and Objectives: The main goal of this project is the implementation of a novel modular computing framework for the (re)design of enzymatic variants with improved properties such as substrate specificity, enzyme activity and/or protein stability. The successful candidate will identify and suggest virtual enzymatic variants that will later be expressed and experimentally cross-validated by our team at the Laboratory for Computational Molecular Design at the Medical University of Graz (CAMDgraz.com). In this doctoral project, we will be particularly concerned with the design of new protease variants (e.g. the zinc metalloprotease ADAMTS13[2]) that could be used against some pathologies such as coagulopathies.

Methodology: Computer techniques such as molecular dynamics (MD) and quantum mechanics/molecular mechanics (QM/MM) simulations, free energy calculations, and machine learning methods will be integrated into a common computing framework and used to investigate all-atom catalyzed reaction mechanisms.[3] As a result, a novel computing platform for the delivery of predictive-decision models in protein engineering campaigns will be provided.

References:

[1] Sarel J. Fleishman *et al. Automated Design of Efficient and Functionally Diverse Enzyme Repertoires Mol. Cell* **2018**, *72*, 178–186

[2] Jonas Emsley, James T. B. Crawley *et al. Crystal structure and substrate-induced activation of ADAMTS13 Nat. Commun.* **2019**, *10*, 3781-3781

[3] Pedro A. Sánchez-Murcia *et al. Reaction mechanism of nucleoside 2'-deoxyribosyltransferases: free-energy landscape supports an oxocarbenium ion as the reaction intermediate Org. Biomol. Chem.* **2019**, *17*, 7891-7899

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