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Computational protein design: a tool for protein engineering and synthetic biology

Computational protein design is a strategic area for biotechnology and synthetic biology. We have developed and experimentally validated a complete toolbox, including a unique distributed computing ressource, Proteins@Home. The method and toolbox have been used to engineer computationally around 100 proteins, several of which are being produced and tested experimentally.

The thesis project will go in two directions. First, further improvements of the method will be implemented and tested. These will include more sophisticated treatments of the aqueous solvent surrounding the protein, as well as improved models of the unfolded state of the protein (which has to be modelled if one wants to select proteins based on their stability or folding free energy). Given the current state of our technology, the improvements that can be made over one PhD cycle should leave us with a method that is truly state-of-the-art, and performs as well as the best competing methods.

The second direction will be two carry out a set of applications, which involve the creation of one or more "mini-proteins". These will correspond to the catalytic domain of an existing enzyme, which is naturally made up of four domains: the tyrosyl-tRNA synthetase enzyme, which contains two copies each of two distinct domains. The design should lead to a monomeric, mono-domain protein. In a later stage, the domain will be created using a reduced library of amino acids, instead of the full, natural repertoire of 20 amino acid types. In particular, a variant of the protein will be created which only so-called "class II" amino acids (which refers to the well-known subdivision of the 20 amino acid types into two subclasses of ten types each). The designed miniproteins will be tested experimentally.

The project will thus lead to an improved toolbox for protein engineering and synthetic biology, a highly strategic area, and will demonstrate its power by re-engineering an important component of the cellular machinery for protein biosynthesis.

Thomas Simonson

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