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Oral presentation

Computational design of proteins with new functions

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Introduction

In Synthetic Biology we are often confronted by the task of designing new parts and devices composed of proteins with specified functionalities that are not found in nature. We will discuss the applications of our computational protein design methodology to design proteins with new functionalities. We have developed an automated computational method that uses high-resolution protein structures together with molecular modelling techniques to simulate the result of combinatorial mutagenesis and dynamics of protein structures. We use a physical model of the protein's unfolded and folded states to rank the proteins according to their folding free energy. For that we use an all-atom force field, a high-resolution protein structure and a rotamer library. Our methodology combines the sequence and rotamer searches with the docking problem into a single combinatorial optimisation procedure to generate protein sequences and their structures, able to bind a specified molecular target. Our computational procedure can also be applied to reduce the library size in directed evolution experiments. We will discuss the applications of our methodology to design new synthetic proteins and enzymes. In particular, we have added an esterase activity into a Thioredoxin protein while maintaining its wild-type activity. We verify our predictions with experimental results.

Background

We use a computational approach that allows the insertion of optimal amino acids into a protein scaffold with the aim of designing new proteins with enhanced functions. The computational algorithm scores candidate proteins according to both their folding free energy, which is computed by modeling both an unfolded and folded state at the atomic level using a molecular mechanics force field, and the binding free energy of the complex of the protein with the high-energy transition state. This methodology had been successfully tested by de novo redesigning 45 proteins that were successfully compared with their corresponding natural sequences [1,2] and by the experimental validation of peptides designed to bind to MHC-I proteins. Similarly to recent work where a TNT biosensor was designed using a computational design procedure [3], we have redesigned a ribose-binding protein that stabilises the closed conformation when bound to a vanillin molecule.

Conclusion

We have developed a methodology that allows designing new proteins with a given function. We have applied it to the design of a ribose-binding protein with altered specificity towards a vanillin molecule. We have also designed a Thioredoxin protein with esterase activity. We propose the use of automated protein design methodologies to engineer new parts and devices for synthetic biology projects.

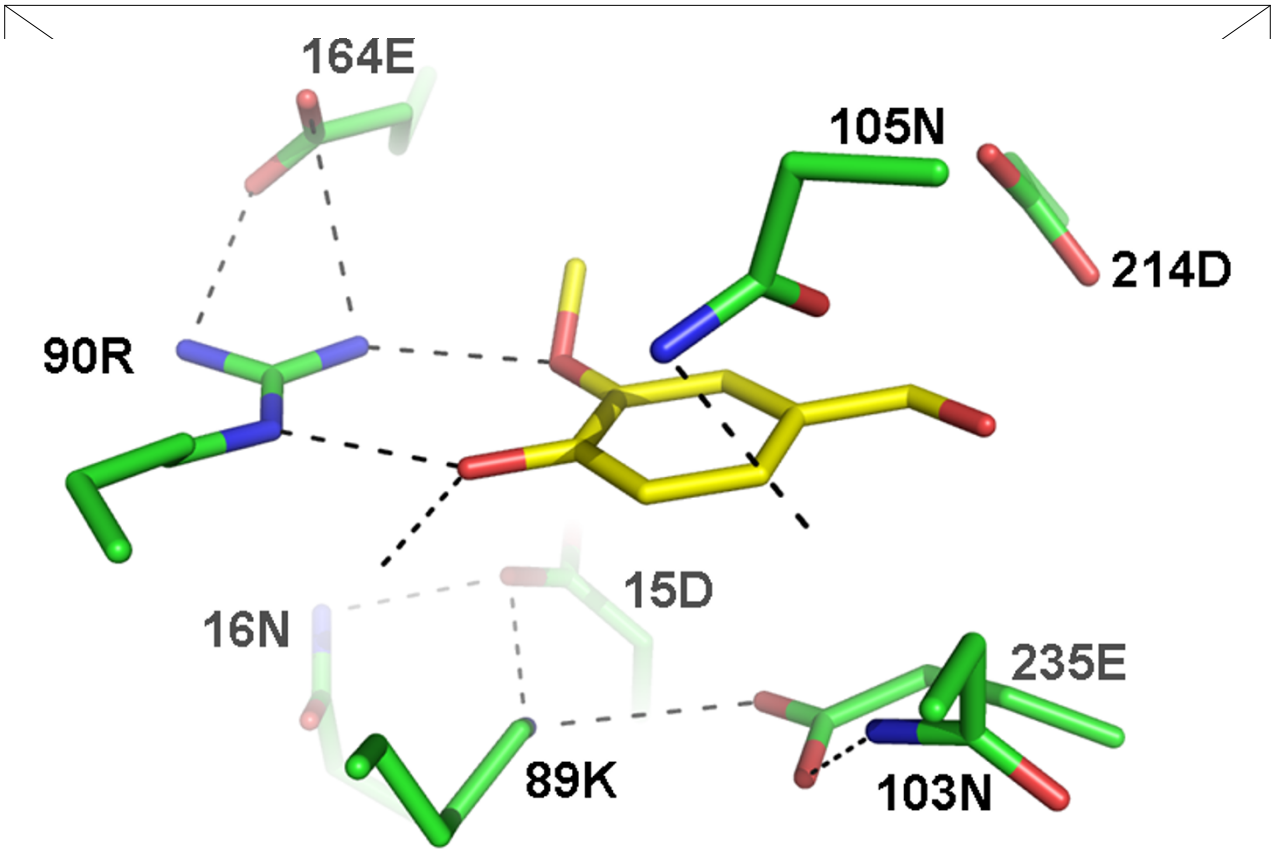

Figure 1
Model of computationally designed binding site for vanillin. Dashed lines denote h-bonds. Only the residues making h-bonds with the vanillin molecule are shown on top. This designed protein was used by the iGEM 2006 Valencia team to design a cellular biosensor.

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