Computational Enzyme Design for Metabolic Engineering

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Metabolic engineers strive for optimal enzymes to assemble into highly efficient metabolic pathways. Improvements in the catalytic activity, substrate specificity, or enantioselectivity of enzymes are traditionally achieved by modification of the active sites of enzymes. We have proposed that enzyme engineering endeavours should target both active sites and access tunnels/channels [1,2]. Using haloalkane dehalogenases as model enzymes, we have demonstrated that engineering the access tunnels can significantly improve their catalytic properties [3] and stability [4]. User-friendly software tools such as Caver [5], Caver Analyst [6], CaverDock [7] and Caver Web [8] have been developed for the computational design of protein tunnels/channels; or as FireProt [9] and HotSpot Wizard [10] for the automated design of stabilizing mutations and smart libraries. Using these tools, we were able to introduce a new tunnel to a protein structure and modify its conformational dynamics [11]. We envisage that the next generation of computational enzyme design tools will rely on big data analysis using machine learning [12]. See: https://loschmidt.chemi.muni.cz/peg/software/.

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