Free energy calculations to predict the effect of single point mutations on protein stability

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Predicting the effect of amino acid point mutations on protein stability via structure based computational modelling is a difficult but potentially very valuable task for protein engineering. Over the last few years, substantial experience has been accumulated in the related field of predicting ligand binding strengths from MD-based free energy (FEP+) calculations and we have found the overall approach to be highly transferable to questions of protein energetics. The general idea of mutating protein side chains via free energy simulation tool is not new, but has never been rigorously tested in practice. We have undertaken a large scale study of applying FEP+ to over 200 protein side chain mutations and have found very encouraging results on established public test data sets. The method matches or outperforms the predictive power of several alternative computational tools and is capable of correctly categorizing mutations as stabilizing or destabilizing in >85% of cases. We now aim at applying FEP+ for protein stability on real-world protein engineering questions.