Perturbing the energy landscape for improved packing during computational protein design

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Abstract

The FastDesign protocol in the molecular modeling program Rosetta iterates between sequence optimization and structure refinement to stabilize de novo designed protein structures and complexes. FastDesign has been used previously to design novel protein folds and assemblies with important applications in research and medicine. To promote sampling of alternative conformations and sequences, FastDesign includes stages where the energy landscape is smoothened by reducing repulsive forces. Here, we discover that this process disfavors larger amino acids in the protein core because the protein compresses in the early stages of refinement. By testing alternative ramping strategies for the repulsive weight, we arrive at a scheme that produces lower energy designs with more native-like sequence composition in the protein core. We further validate the protocol by designing and experimentally characterizing over 4000 proteins and show that the new protocol produces higher stability proteins.

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