Low-resolution conformational exploration for Rosetta Ab initio by bi-level optimisation of structural features

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Low-resolution conformational exploration remains a problem area in fragment assembly approaches for protein structure prediction, and is a key factor limiting the usefulness of these methods for larger target structures. This effect is typically more pronounced for loop regions, which determine the spatial arrangement of secondary structure elements. We are currently exploring the use of a new low-resolution conformational sampling algorithm that systematically explores conformations for the target by prioritisation of loop segments. The algorithm makes use of a bi-level optimisation scheme, in which regions identified as loops (using a secondary structure predictor such as PSIPRED) are sampled first, followed by exploration in other regions by hill-climbing. The decision on whether to accept a proposed loop insertion is governed by the result of the subsequent hill-climbing step.
We will compare the performance of our protocol against standard Rosetta for different types of targets, and evaluate the results both in terms of predictive accuracy as well as in terms of the diversity of the structures explored during the runs.