HPdesign: Inverse Folding of Proteins

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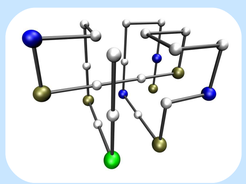
Introduction

Sequence design is a neccessary tool for the investigation of sequence-structure relations. Insights into such fundamental properties will aid to understand protein folding, their evolution, and drug design.

The HP-model by Lau and Dill [1] mimics globular water-soluble proteins. It is lattice based and focuses on hydrophobic forces. Even in this coarse-grained model, structure prediction and sequence design is NP-complete [2]. Nevertheless, Backofen and Will introduced a Constraint-based Protein Structure Prediction (CPSP) approach [3] that allows the enumeration of all optimal structures.



3D Lattice protein

HPdesign uses the CPSP approach to solve the inverse folding problem for three-dimensional lattices. Here, a sequence X is searched that adopts a given structure S as its single optimal one.

Preliminaries

Energy and Optimality of a Structure: The contact *energy* in the HP-Model is the negated sum over all non-successive H-monomer contacts. A structure with minimal energy (i.e. maximal H-H contacts) is called *optimal* and has usually a globular shape as in nature [4].

H-cores: The placing of the H-monomers in a structure is called *H-core* [3]. For a fixed sequence, the energy is completely determined by the H-core internal contacts. This is visualized in Fig. 1 by two structures with energy -3 and -1 (left/right) and the corresponding H-core with 4 contacts. The optimal H-cores are independent of a concrete sequence and can be precalculated in advance [3].

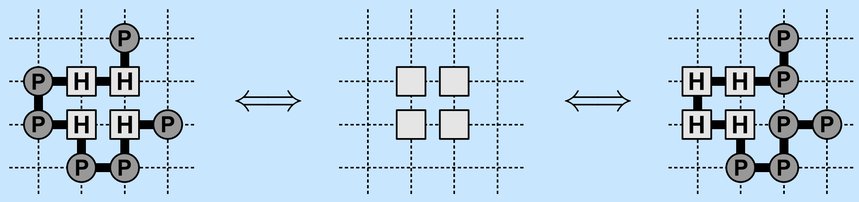


Figure 1: Lattice protein structures and the corresponding H-core.

Protein-like Sequences: In contrast to random sequences proteins adopt only one stable optimal structure. Therefore for simplicity, HP-sequences are regarded *protein-like* only if they have exactly one (or only a few) optimal structure [5].

Method

The algorithm is a Generate-and-Test method that allows, in contrast to existing methods [6, 7], a systematic and complete enumeration of target sequences within user defined limits. First, a good set of candidate sequences is generated that have a high chance to form the given structure as an optimal one. Afterwards, these sequences are checked if this is true and if they are protein-like.

Step 1 : Candidate Set Generation

In the HP-model, the number of possible sequences $S \in \mathcal{S}$ for a given structure $\mathcal{L}$ is 2^N. To enable a Generate-and-Test approach we have to keep the number of sequences to test as small as possible.

In HPdesign, this is done using a database of (sub-)optimal H-cores. As visible in Fig. 1, the placing of an H-core into a given structure determines a sequence. Following the constraint, that the sequences have to form $\mathcal{L}$ as optimal structure, we use optimal H-cores for sequence generation.

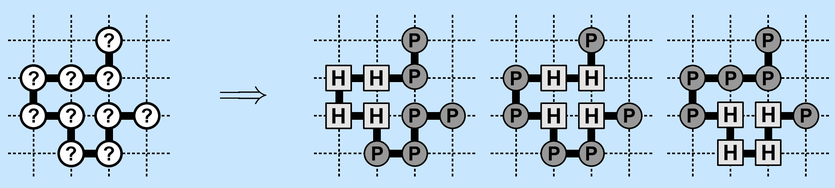


Figure 2: Different matches and derived sequences for a structure and the H-core in Fig. 1.

For each arbitrary optimal H-core $\mathcal{H}$ we shift the core through $\mathcal{L}$. If all positions of $\mathcal{H}$ can be mapped to positions of $\mathcal{L}$ a match is found and we store the resulting candidate sequence S in $\mathcal{S}$. This procedure yields a set of sequences $\mathcal{S}$ that can adopt $\mathcal{L}$ with a low energy and have high chance to form $\mathcal{L}$ as an optimal structure. The number of optimal H-cores is still exponential in the core size but increases much slower than the number of possible sequences (see Fig. 3).

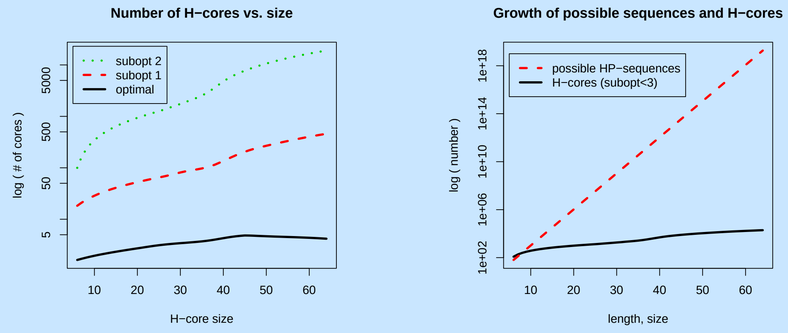


Figure 3: Number of (sub-)optimal H-cores v.s size and the growth vs. # of possible sequences.

An example illustrating the first step is given in Fig. 2. Here, the H-core of Fig. 1 can be mapped in three ways on the given structure and yields three different candidate sequences.

Step 2 : Sequence Filtering

CPSP: The *Constraint-based Protein Structure Prediction* (CPSP) approach [3] allows the optimal structure enumeration of 3D lattice proteins using Constraint Programming methods.

Given a sequence S with k H's: For each H-core $\mathcal{H}$ of size k a CSP is formulated that constrains the monomer sequence S to form a selfavoiding-walk in the lattice, placing all H-monomers on positions in $\mathcal{H}$. Starting with the optimal H-cores, this iterative process ensures optimality and allows further the complete enumeration of all optimal structures.

Filtering: To check each candidate sequences $S \in \mathcal{S}$ of step 1 to be proteinlike and to form the given structure stable we enumerate up to 2 optimal structures of S (CPSP). If there is only one, S forms only one stable structure $\mathcal{L}'$ and we check if $\mathcal{L}' \equiv \mathcal{L}$. If S fullfills both criteria it is reported otherwise rejected.

Conclusion

FCC structure

The presented method HPdesign is the first exact method that solves the Inverse Folding Problem for 3D lattice proteins in the HP-model. Using HPdesign one can generate HP-sequences that adopt a given structure as their optimal one. Further the number of optimal structures they can adopt, an important measure for protein-like sequences, can be constrained.

The Generate-and-Test approach is based on a precalculated database of optimal and suboptimal H-cores and the fast and exact CPSP-method by Backofen and Will [3]. It is currently implemented using the cubic and more complex face-centered-cubic (FCC) lattice (see figure).

The free CPSP-tools package including HPdesign and other tools is accessible at

http://www.bioinf.uni-freiburg.de/sw/cpsp/

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