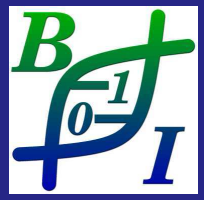
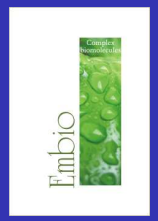




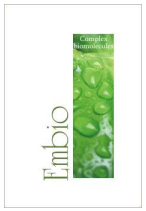
Optimal Structure Prediction and Application

Freiburg Bioinformatics Group

Martin Mann, Sebastian Will and Rolf Backofen

Albert-Ludwigs-University Freiburg
Bioinformatics at the Department of Computer Science

EMBIO Meeting Leipzig 2007



Native structure prediction

Martin Mann
Freiburg

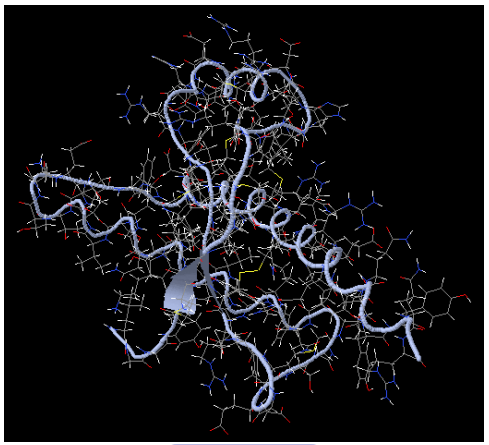
The goal

- Prediction of the native structure given an AA-sequence

LGGYMLGSA. . . RESQAYYQR

⇓

Human prion 1HJM



Zoom in

Assumptions

- Sequence determines structure
- Native structure has lowest energy

Problems

- too complex energy function
- too many degrees of freedom

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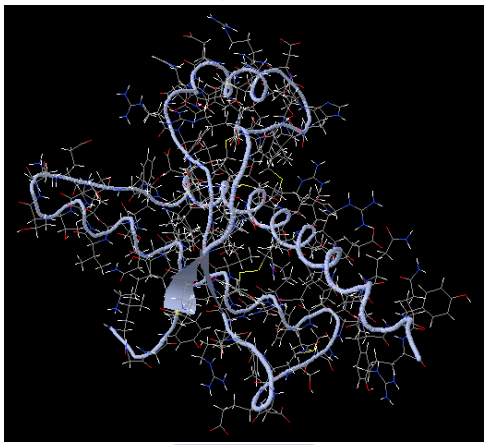


▸ Zoom in

Assumptions

- Sequence determines structure
- Native structure has lowest energy

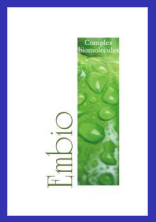
Problems

- too complex energy function
- too many degrees of freedom

Computationally not capable!

Simplified Off-Lattice Protein Models

One possible abstraction



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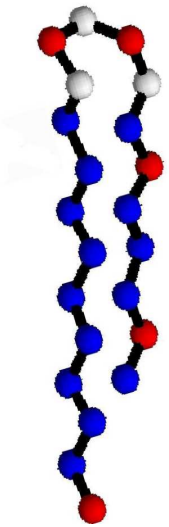
Freiburg

Backbone Structure

C_α sequence only



Full 3D Space

all angles etc. allowed

Reduced Alphabet

e.g. HP, HPNX, . . .

Contact Energy Function

e.g.

	H	P
H	-1	0.5
P	0.5	-0.5

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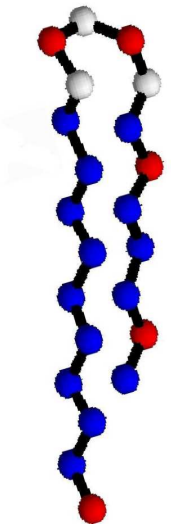

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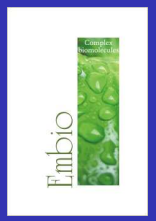
$\Rightarrow$ **Still too many degrees of freedom . . .**



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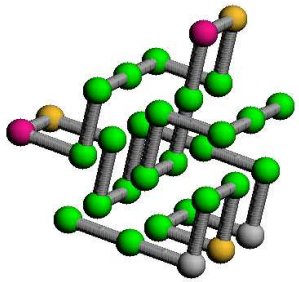


Lattice Space

e.g. cubic, fcc, . . .

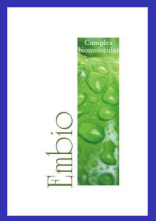
Contact Energy Function

e.g.

	H	P
H	-1	0
P	0	0

Simplified Lattice Protein Models

An other possible discrete abstraction



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Backbone Structure

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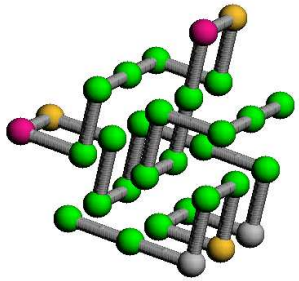
e.g. HP, HPNX, ...



Lattice Space

e.g. cubic, fcc, ...

Contact Energy Function

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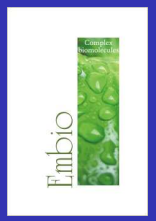
Discrete, Enumerable, Computationally Capable



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Applications e.g.

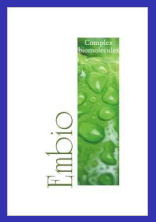
- Neutral nets and protein evolution
- Exploring energy landscapes and protein kinetic
- Base for more complex protein models
- . . .

Therefore you need:

Prediction of optimal structures

- NP-complete in 3D-lattice (Berger & Leighton, 1998) (even in 2D)
- can be solved by Constraint Programming !
  (Backofen & Will, 2006)

. . .



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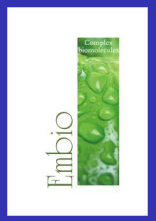

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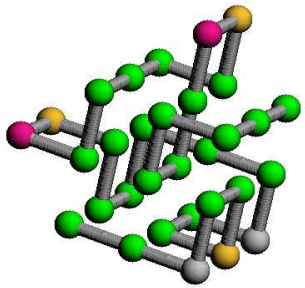
Freiburg

Constraint-based Protein Structure Prediction[1]

- **Short introduction**
  - **Optimal structure prediction (CPSP)**
- **Applications in**
  - **Protein stability**
  - **Inverse folding problem**



[1] R. Backofen and S. Will

The CPSP Approach

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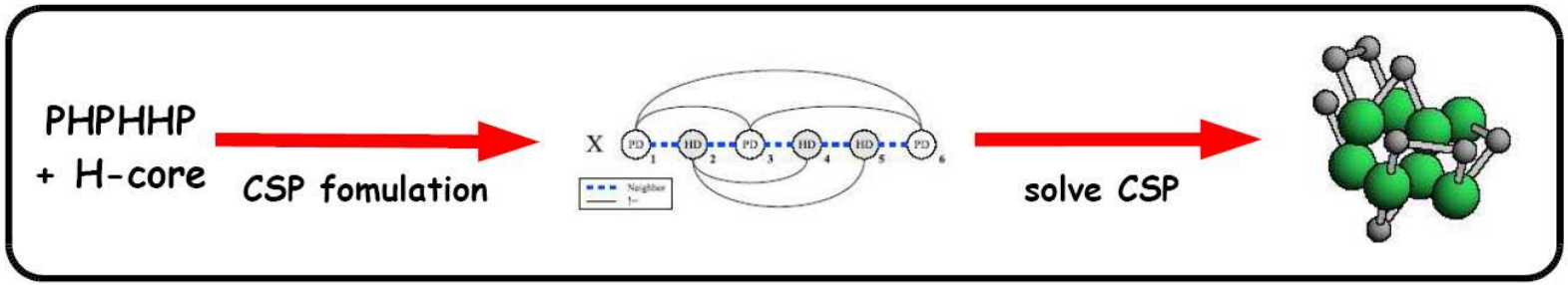
Freiburg

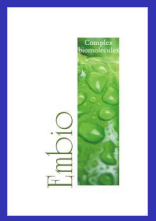
Constraint-based Protein Structure Prediction (CPSP)

An Approach for optimal structure prediction
in the HP-lattice-model



Rolf Backofen and Sebastian Will
'A constraint-based approach to fast and exact structure prediction

in three-dimensional protein models' 2006



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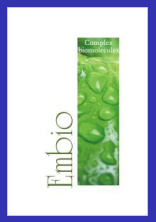
The HP-Model

- simplest energy function available
- focus on hydrophobicity (hydrophobic cores)
- maximizing HH-contacts $\leftrightarrow$ minimizing surface

CPSP - The central idea

- optimal H-monomer distribution is *sequence independent*
- precalculate such optimal and suboptimal so called *H-cores*
- try to find a mapping of a given sequence to H-cores
  $\Rightarrow$ *Sequence-Threading*



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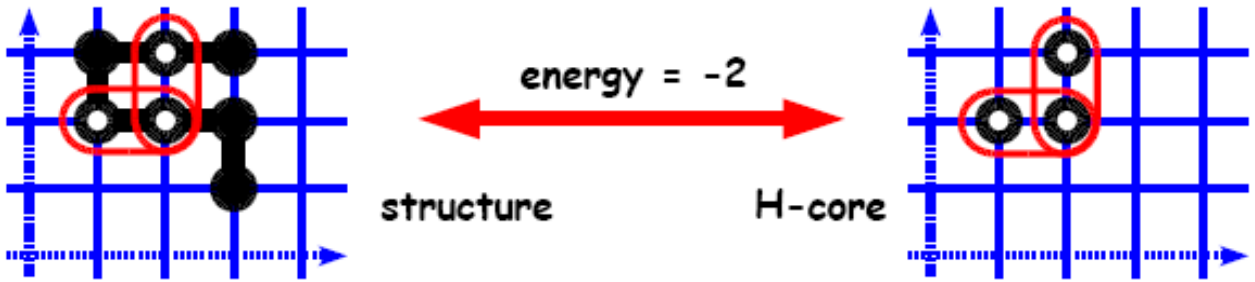
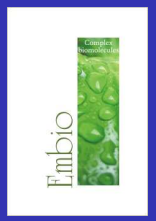
H-Core of a given structure

- H-Core = set of H-monomer positions
- core energy $\leftrightarrow$ structure energy (only HH-contacts important)



- optimality implies optimal structure energy
- candidates can be precomputed based on H-number
- hard problem too $\rightarrow$ (solved via CP)

$\Rightarrow$ for now used as black box and given in a DB ... !



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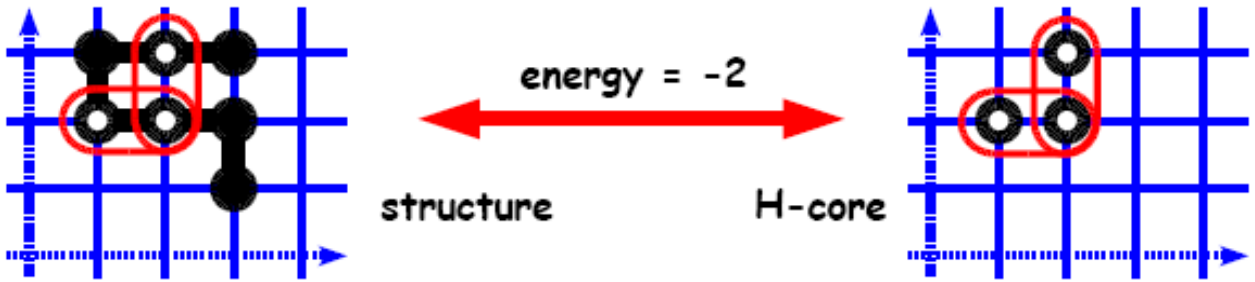

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The CPSP Approach

Sequence Threading : The Question to solve . . .

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Freiburg

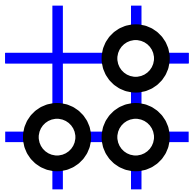
Given

an HP-sequence

P-H-P-H-H-P-P

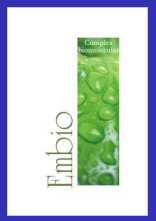
and

an optimal H-core



there is the question:

Exists a structure, so that all H-monomers are placed on H-core positions?



Martin Mann
Freiburg

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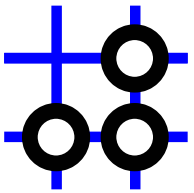

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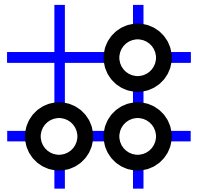

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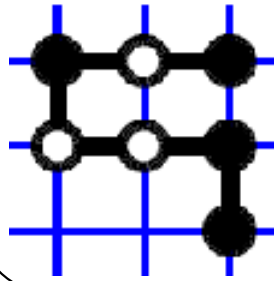

YES!

The CPSP Approach

Solving a Constraint Satisfaction Problem (CSP)

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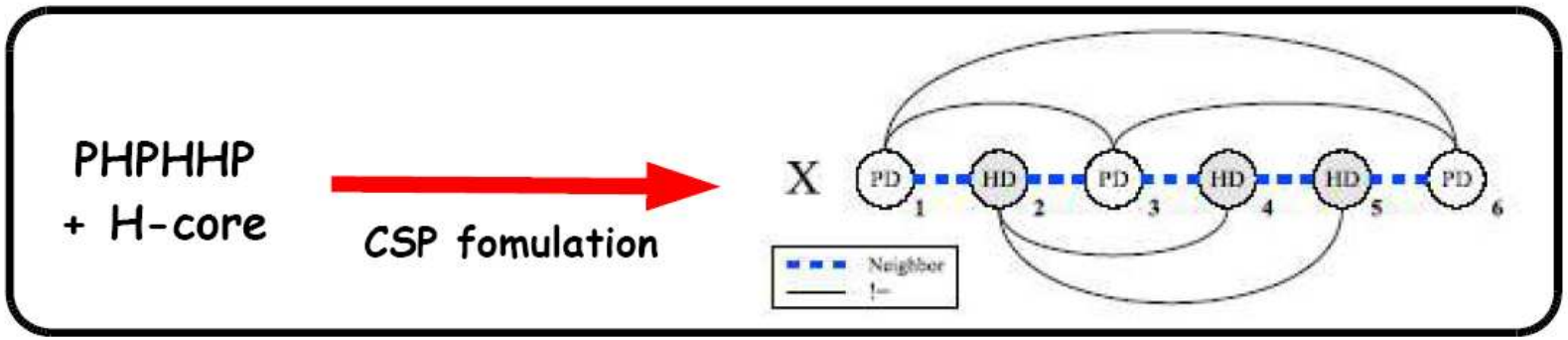
Freiburg

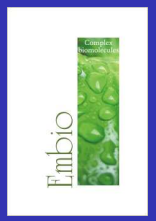
Modelling of the question as CSP



From Solution to structure

- fast standard CP-solvers can be applied for solving
- a CSP solution assigns a lattice position to each monomer
- solution = structure, and optimal due to H-core !
- usually a huge number of solutions / optimal structures

CSP Formulation



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The CPSP-Approach

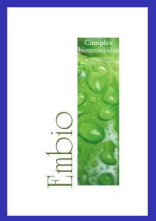
- proven optimal structures via precalculated H-cores
- fast (first hit within seconds)
- deterministic (no stochastic structure space exploration)
- CP yields a very flexible, extensibel modelling

Extensibility

- lattices (cubic, face centered cubic, . . .)
- energy functions (HP, HPNX, . . .)
- exclusion of symmetric solutions during enumeration
- solution space sampling via distance constraints (D-10)
- advanced CP-techniques for solution counting (D-9)
- . . . future: side chain models, structure shapes, . . .

The CPSP Approach

Fast and very flexible . . .



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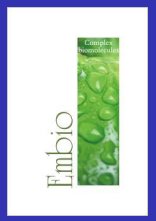

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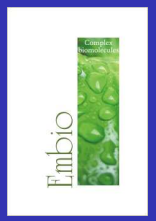
The CPSP-Approach

- Prediction of optimal structures without folding simulation
- Exhaustive enumeration possible

Use

- Verifying folding simulation results
- Creation of interesting test sets for analysis
- Clustering of sequences into proteinlike or not
- Enumeration of the low energy part of the landscape
  $\longrightarrow$ base for kinetic studies
- Base to solve other problems e.g. sequence evolution, inverse folding / designability



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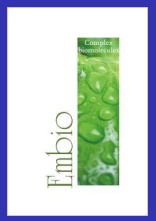

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Constraint-based Protein Structure Prediction

- Short introduction
  - Optimal structure prediction (CPSP)
- Applications in
  - Protein stability
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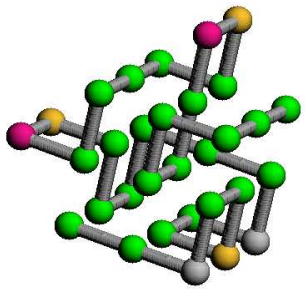


What needs an AA-sequence to be a protein?

Martin Mann
Freiburg

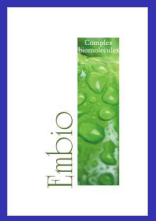
Observations

- Not all possible AA-sequences used
- Fast folding process
  (folding funnel hypthesis)
- Usually ***one*** stable, native structure
- ...

Human prion 1HJM

Degeneracy

A measure of protein stability



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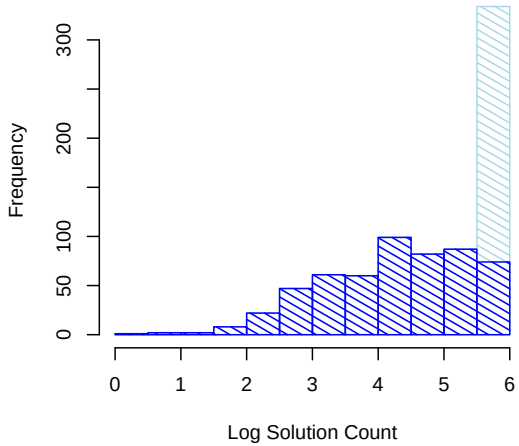
Degeneracy

- = the number of optimal structures
- important for protein stability
- deg. 1 = indicator for being stable

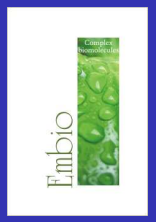
Degeneracy in Lattice-Models

- is high for most sequences
- due to simple energy function
- assumption: deg. 1 = stable



log_{10}(degeneracy) histogram
of 809 HP-sequences (H:P=1:1)
(32% with deg. > 10^6)

$\Rightarrow$ **exact determinable via CPSP approach**



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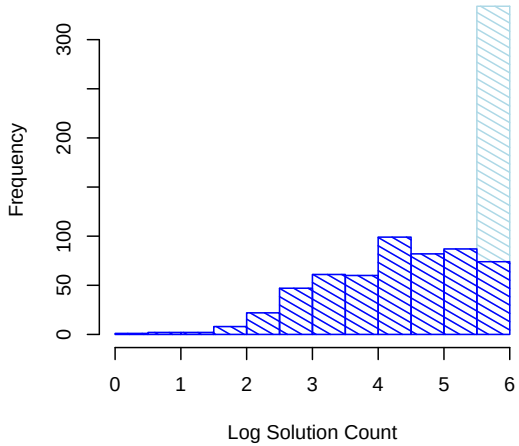
Degeneracy

- = # of optimal structures
  $\longrightarrow$ measure for protein stability
- exactly determinable using CPSP
- usually very high in HP-Model
- e.g. to distinguish proteinlike or random sequences
- counting can be improved (’06)



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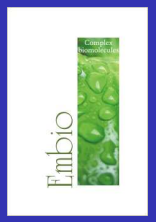

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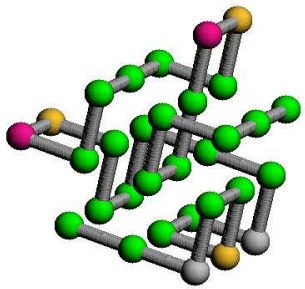


The Inverse Folding Problem

Design of proteinlike Sequences

Martin Mann
Freiburg

The goal

- design of sequences for a given structure

Sequence constraints

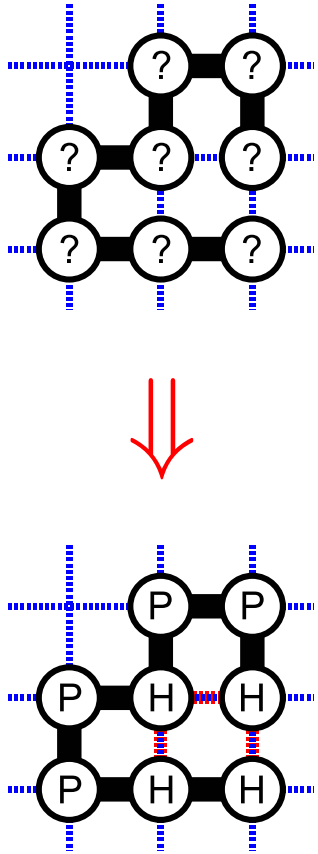
- proteinlike (low degeneracy)
- forms structure as optimal one

Problem

- # of sequences is expontentially in length

Addressed Questions (Designability)

- Is a structure X codeable?
- How many sequences code X?



The Inverse Folding Problem

Design of proteinlike Sequences

Martin Mann
Freiburg

The goal

- design of sequences for a given structure

Sequence constraints

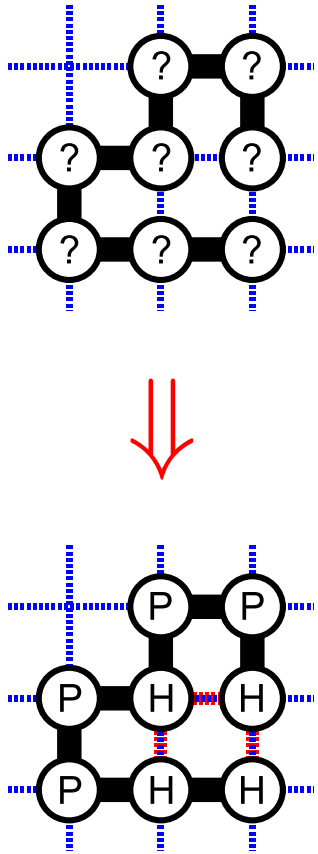
- proteinlike (low degeneracy)
- forms structure as optimal one

Problem

- # of sequences is expontentially in length

Addressed Questions (Designability)

- Is a structure X codeable?
- How many sequences code X?



$\Rightarrow$ **Solved using H-cores and CPSP . . .**

HPdesign

A 'Generate and Test' Workflow

Martin Mann
Freiburg

Input

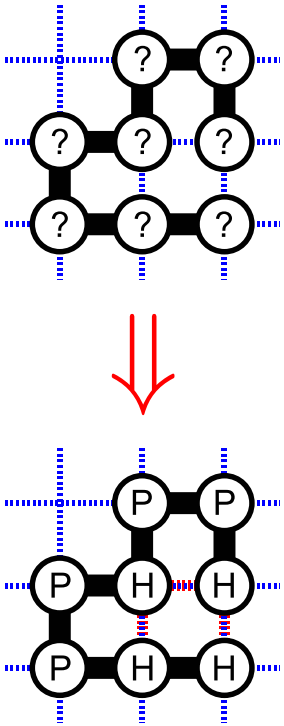
- a structure X

HPdesign workflow

1. Generate good candidates
2. Validate the sequences

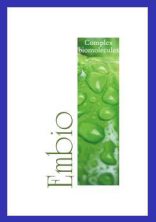
Output

- a set of sequences that:
  - form X as their optimum
  - are stable (degeneracy 1)



?

HPPHPPHH
HPHHPHHH
...



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Freiburg

Observation

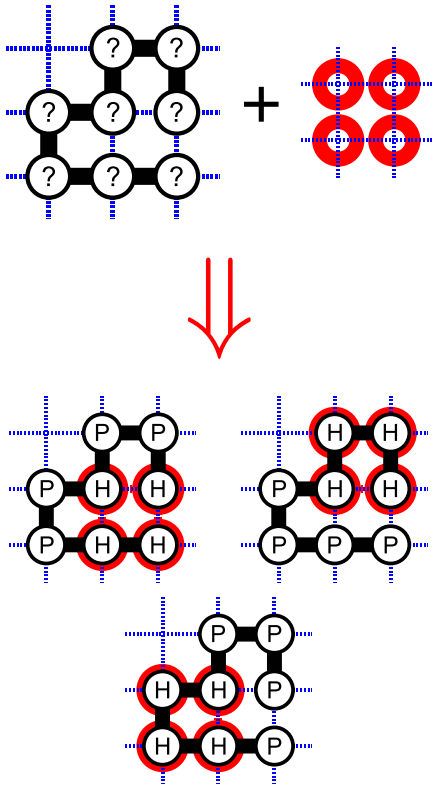
- optimal structure $\Leftrightarrow$ optimal H-core

Generation

- take an arbitrary optimal H-core *C*
- shift *C* through structure *X*
- store resulting sequence for each hit

Result

- sequences with high chance to form *X* as their optimal structure



HPdesign

Step 2 : Sequence Validation via CPSP Approach

Martin Mann
Freiburg

Task

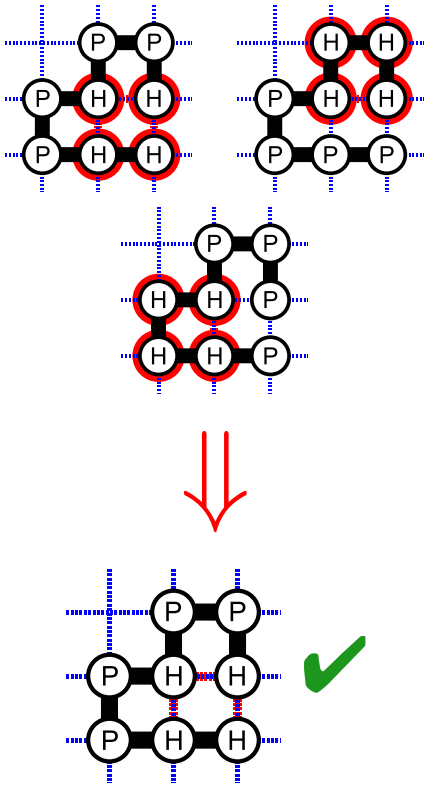
- Check for each sequences if it
  - is stable (degeneracy 1)
  - forms X as optimal structure

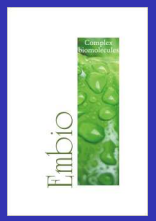
Workflow using CPSP

1: **for all** sequences S **do**
2: $\quad \mathscr{X} \leftarrow \text{CPSP}(S, max = 2)$
3: $\quad$ **if** $(|\mathscr{X}| = 1 \wedge X \in \mathscr{X})$ **then**
4: $\quad\quad$ STORE(S)
5: $\quad$ **end if**
6: **end for**

Result of Filtering

- stable S that form X as optimum





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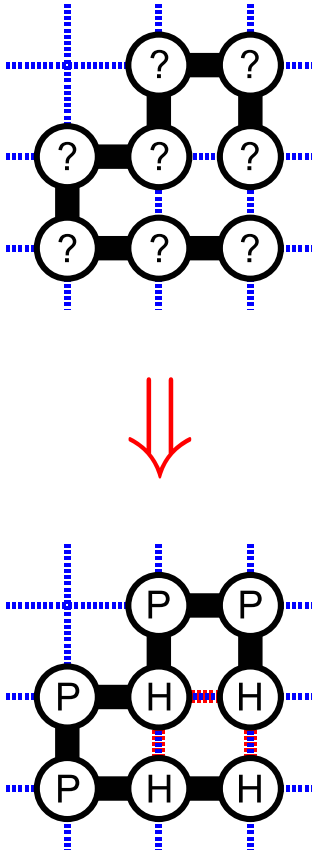
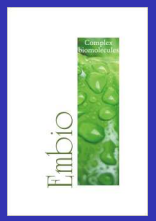
The Inverse Folding Problem

- Design of stable sequences that form a given structure as optimum is a hard task
- Can be solved using 'Generate and Test'
- Candidate set can be shrinked (H-cores)
- Validation via CPSP approach possible





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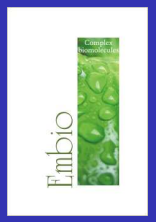
Open . . .

- What distinguishes proteinlike and random sequences?
- Relations to real protein sequence properties?
- Are there common patterns in stable structures?
- How big are the bassins of attraction of stable optima?
- Leads one optimal structure to a folding funnel?
- What makes a structure designable?
- . . .



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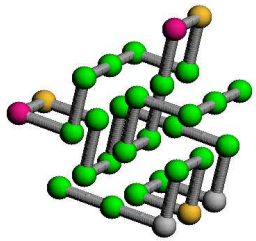
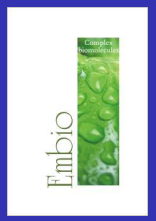
Constraint-based Protein Structure Prediction

- **CPSP Approach**
  - **Enumeration of optimal structures**
  - **Fast and extensible**
- **Degeneracy**
  - **Important measure of protein stability**
- **Inverse folding problem**
  - **Find stable sequences that form a structure X as optimum**





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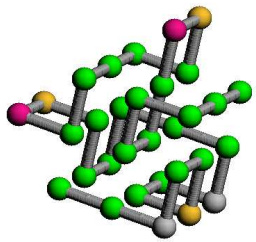
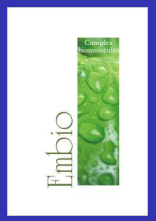
Constraint-based Protein Structure Prediction

CPSP-tools

- **HPstruct:** CPSP Approach
  - Enumeration of optimal structures
  - Fast and extensible
- **HPdeg:** Degeneracy
  - Important measure of protein stability
- **HPdesign:** Inverse folding problem
  - Find stable sequences that form a structure X as optimum
- ...





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CPSP-tools

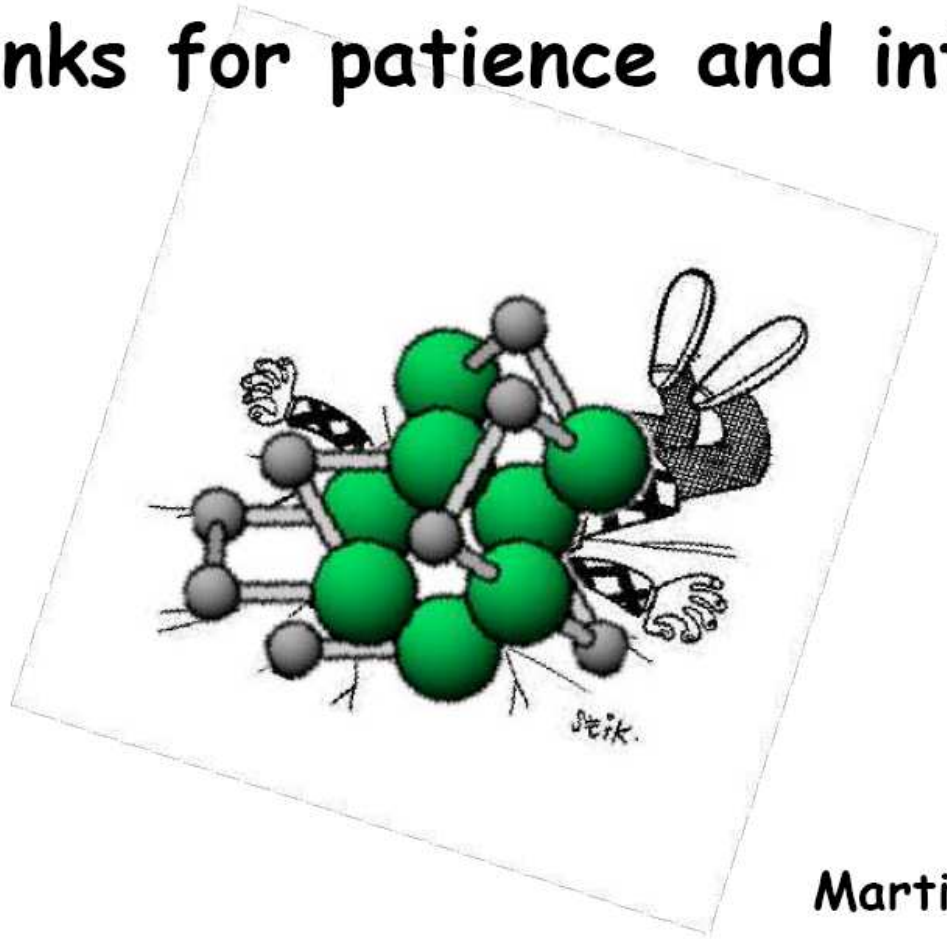
- Implements the CPSP approach etc.
- Object oriented C++
- Library of core classes and functionality
- Completely documented / API
- Freely available

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

That's all folks!

Martin Mann
Freiburg

Thanks for patience and interest



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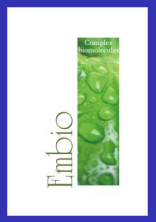

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Appendix section

Protein folding and native structure prediction

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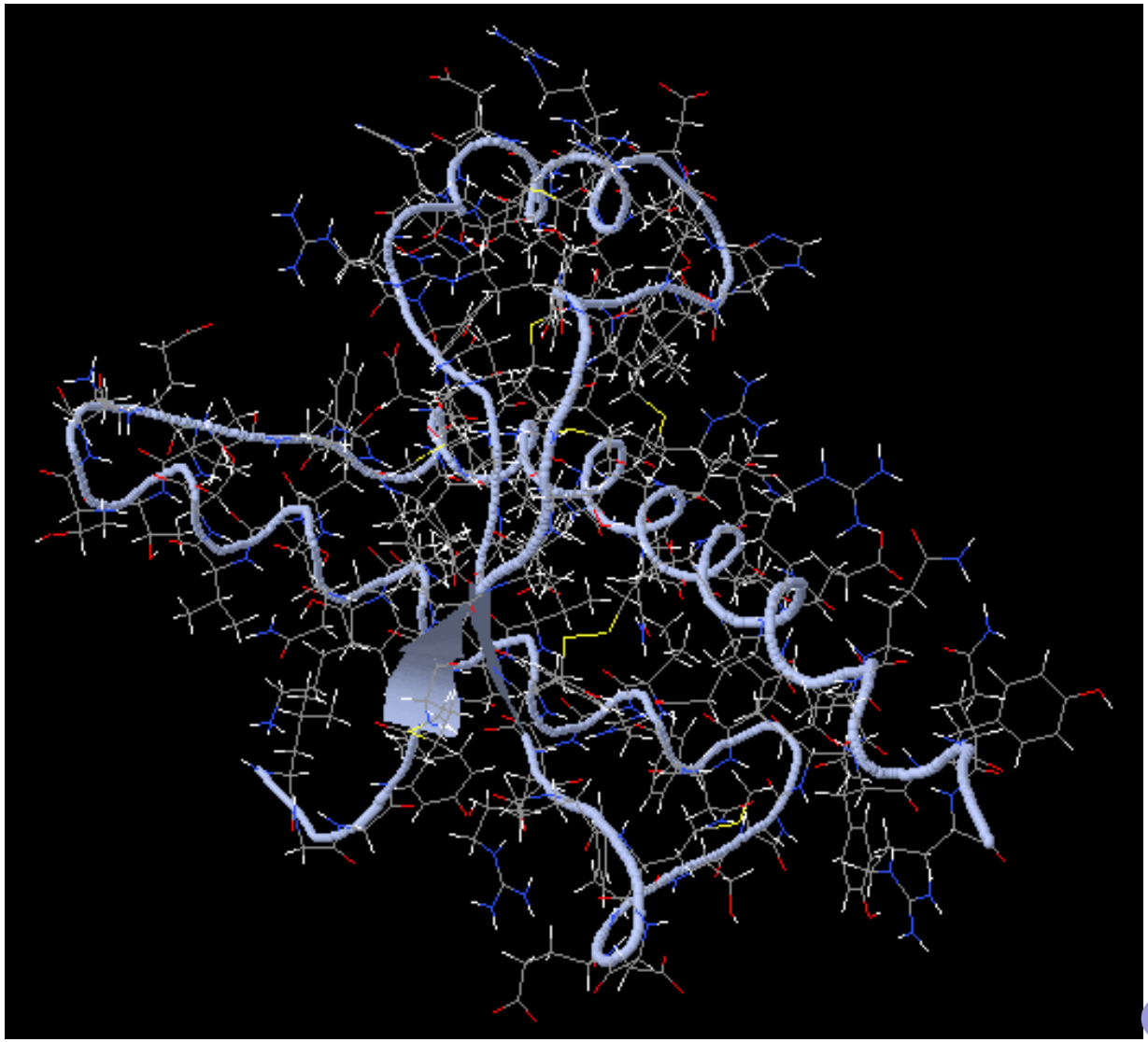
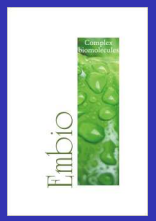


Zoom out



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Advantages

- discrete $\longrightarrow$ full enumeration for result validation
- computationally capable
- folding dynamics similar to real proteins (time scale)
- unique folders

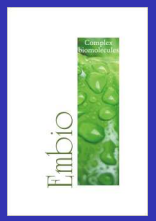
Possible Critics

- Energy function (HP) $\Rightarrow$ HPNX, ...
- Lattice type (3D-cubic) $\Rightarrow$ FCC, ...
- Lattice vs. angles $\Rightarrow$ discrete angle model, ...

Return

The CSP

A very very simple Formulation



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For a given HP-sequence and an optimal H-core:

Variables

- one for each sequence monomer

Domains = sets of lattice positions

- H-Monomers: H-core positions (ensures optimality)
- P-Monomers: remaining lattice

Constraints

- binary Neighboring constraints along the chain (backbone)
- one global Alldifferent constraint (selfavoiding structure)

$\Rightarrow$ encodes the selfavoiding walk

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The CSP

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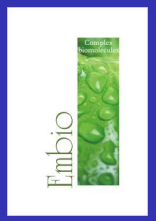

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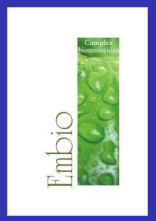

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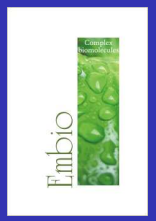

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