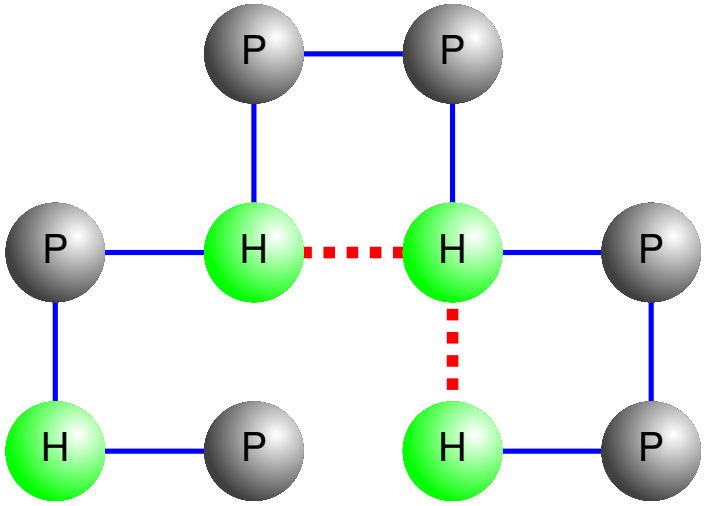
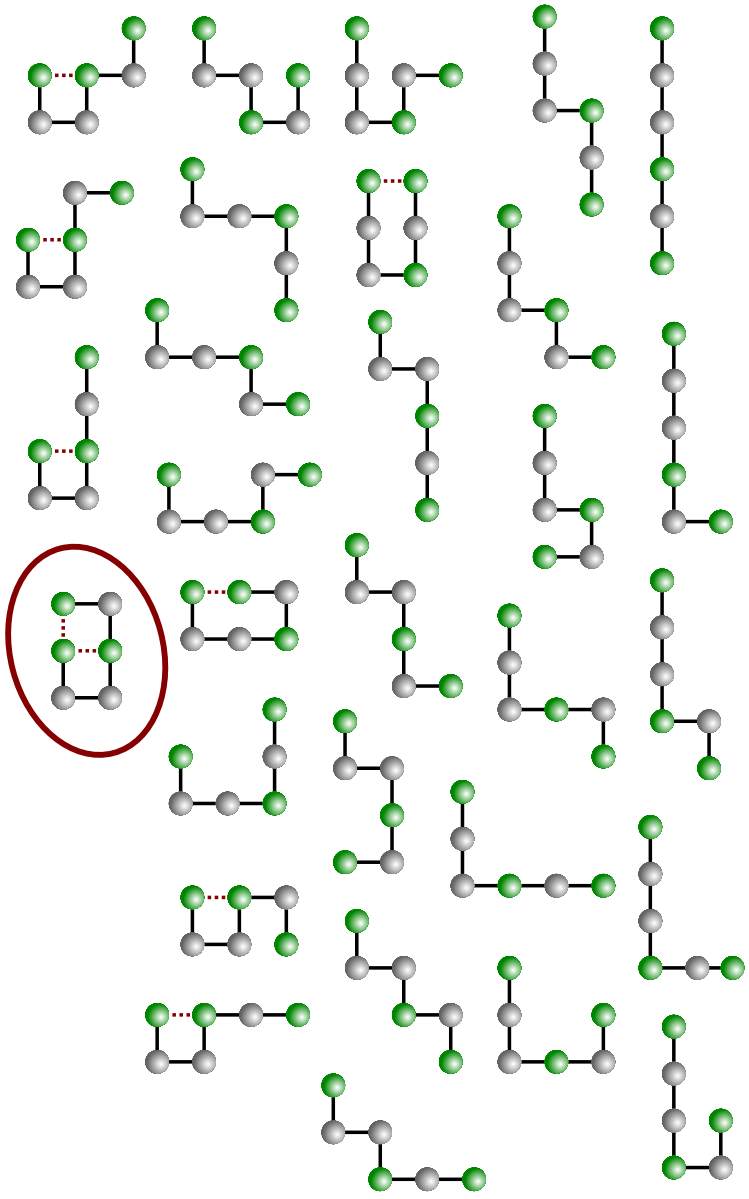
Application: Protein Structure Prediction





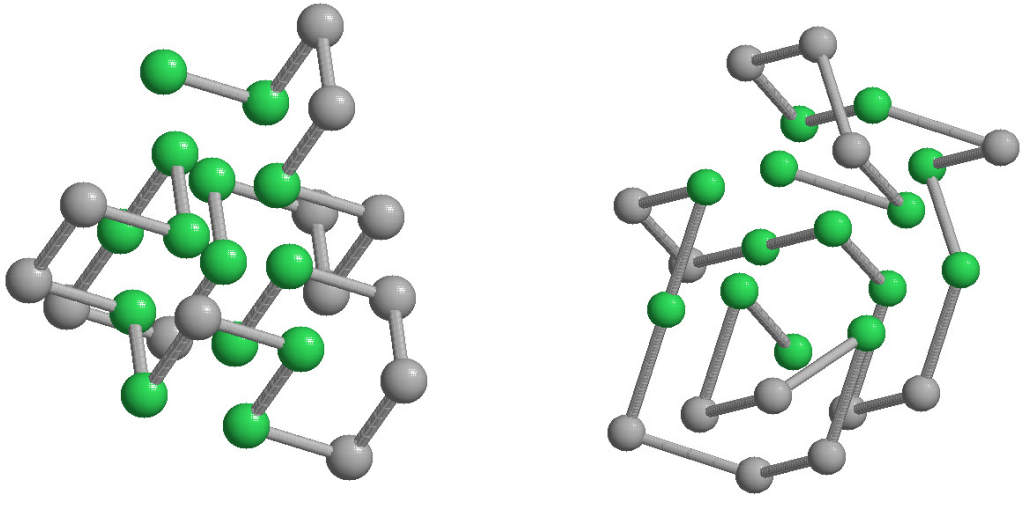
Exact Prediction in 3D cubic & FCC

The problem

IN: sequence s in $\{H, P\}^n$

HHPPPHHPHHPPHHHPPHHPPPHPPHH

OUT: self avoiding walk ω on cubic/fcc lattice with minimal HP-energy $E_{\mathrm{HP}}(s, \omega)$



A First Constraint Model

- Variables $X_1, \ldots, X_n, Y_1, \ldots, Y_n, Z_1, \ldots, Z_n$ and *HHContacts*

$$\begin{pmatrix} X_i \\ Y_i \\ Z_i \end{pmatrix}$$ is the position of the ith monomer $\omega(i)$

- Domains

$$D(X_i) = D(Y_i) = D(Z_i) = \{-n, \ldots, n\}$$

- Constraints
  1. positions i and $i+1$ are neighbored (chain)
  2. all positions differ (self-avoidance)
  3. relate *HHContacts* to X_i, Y_i, Z_i
  4. $$\begin{pmatrix} X_1 \\ Y_1 \\ Z_1 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}$$

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The First Model in More Detail (Cubic Lattice)

The Constraints cannot be expressed directly, i.e. we need auxiliary variables

$$Xdiff_{ij} = |X_i - X_j| \quad Ydiff_{ij} = |Y_i - Y_j| \quad Zdiff_{ij} = |Z_i - Z_j|$$

1. Positions i and $i+1$ neighbored (chain)

$$Xdiff_{i(i+1)} + Ydiff_{i(i+1)} + Zdiff_{i(i+1)} = 1$$

2. All positions differ (self-avoidance)

$$Xdiff_{ij} + Ydiff_{ij} + Zdiff_{ij} \neq 0 \quad (\text{for } i \neq j).$$

3. Relate *HHContacts* to X_i, Y_i, Z_i
   Detect HH-contact, if $Xdiff_{ij} + Ydiff_{ij} + Zdiff_{ij} = 1$ for $s_i = s_j = H$. Then add 1 to *HHContacts*.
   (Technically, use reified constraints)

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Solving the First Model

- Model is a COP (Constraint Optimization Problem)
- Branch and Bound Search for Minimizing *Energy*
- Combined with Symmetry Breaking
- How good is the propagation?
- Main problem of propagation: bounds on contacts/energy
  From a partial solution, the solver cannot estimate the maximally possible number of HH-contacts well.

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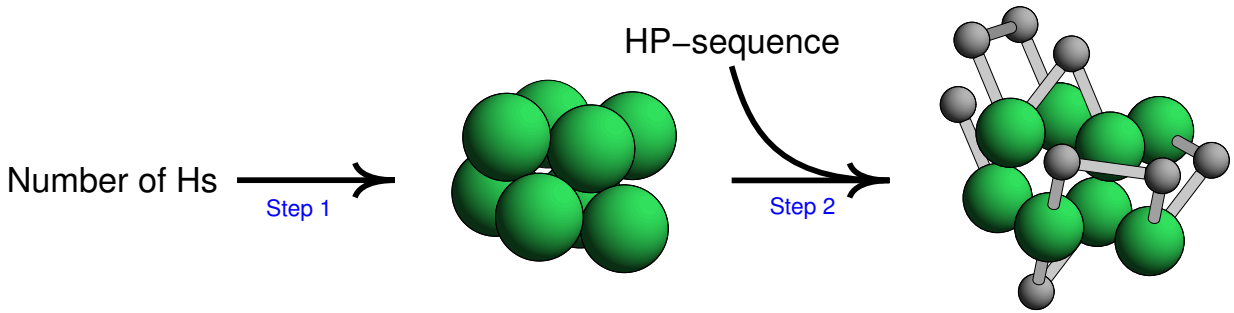
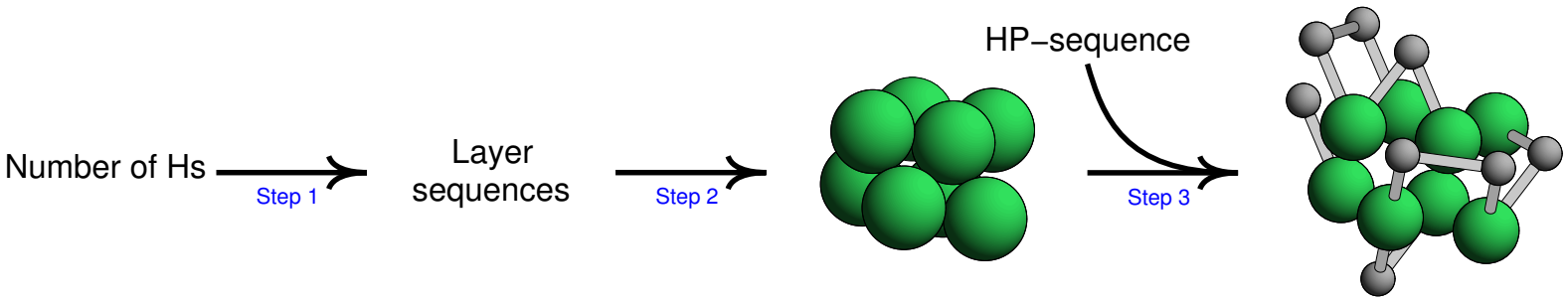
The Advanced Approach: Cubic & FCC



Steps

1. Core Construction
2. Mapping

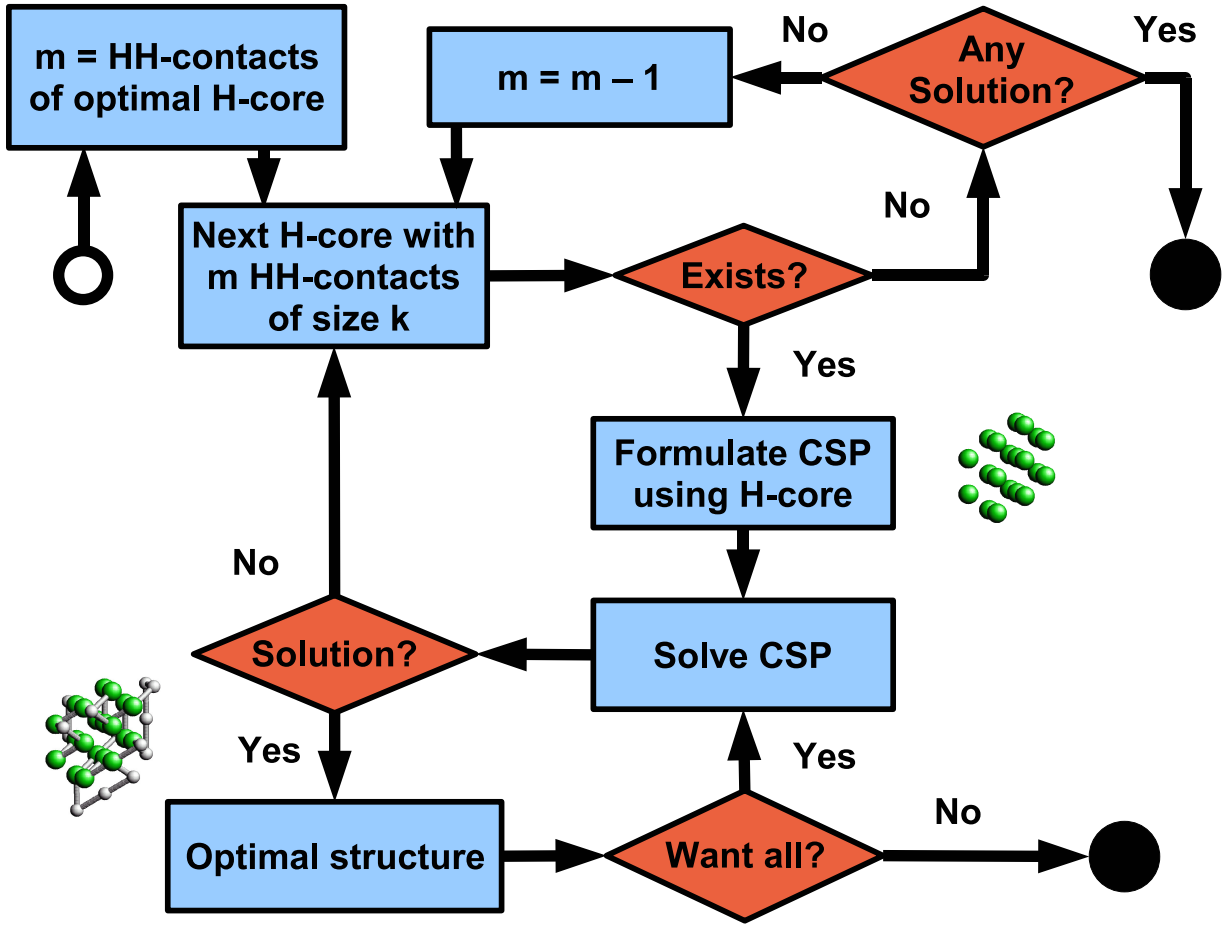
The Advanced Approach: Cubic & FCC



Steps

1. Bounds
2. Core Construction
3. Mapping

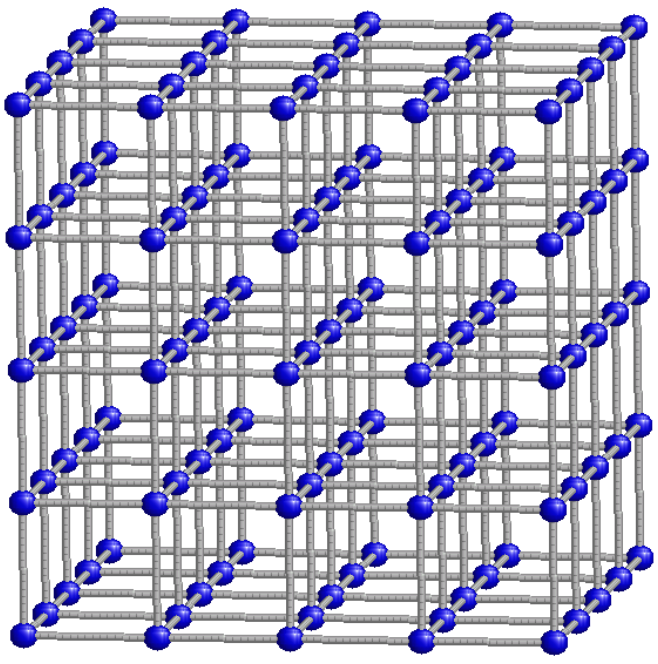
Workflow: Predict Best Structure(s) of HP-Sequence

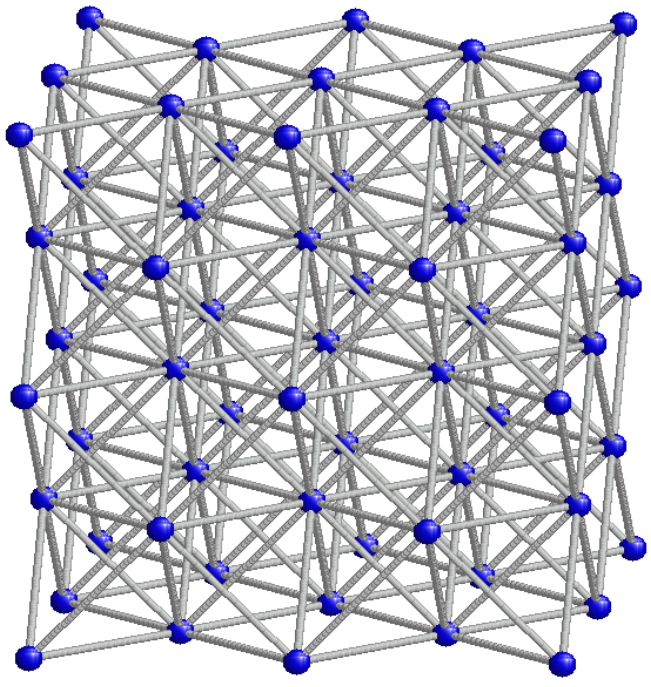


Computing Bounds

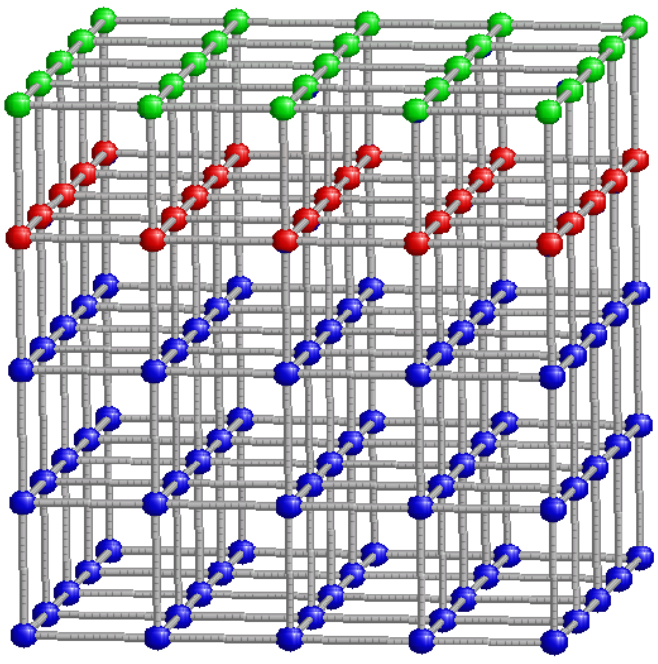
- Prepares the construction of cores
- How many contacts are possible for n monomers, if freely distributed to lattice points
- Answering the question will give information for core construction
- Main idea: split lattice into layers
  consider contacts
  - within layers
  - between layers

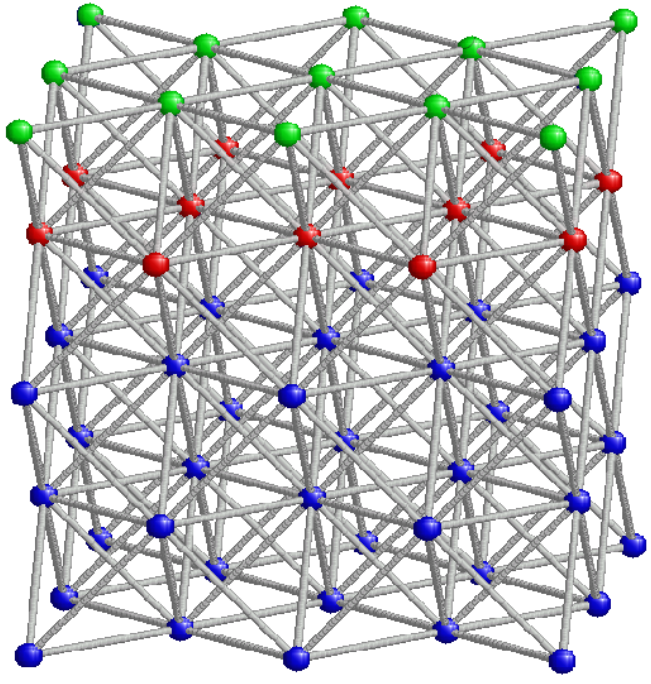
Layers: Cubic & FCC Lattice





Layers: Cubic & FCC Lattice



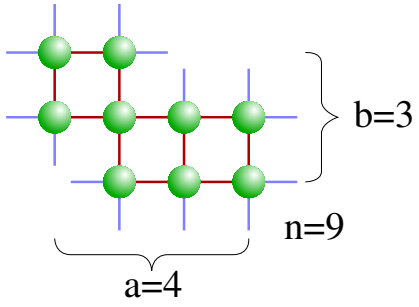


Contacts

Contacts =

Layer contacts + Contacts between layers

- Bound Layer contacts: Contacts $\leq 2 \cdot n - a - b$

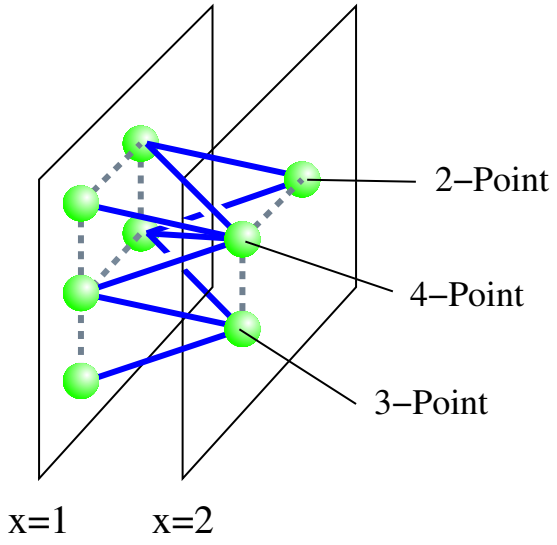


- Bound Contacts between layers
  - cubic: one neighbor in next layer

    $$Contacts \leq \min(n_1, n_2)$$

  - FCC: **four** neighbors in next layer

    $$i - \text{points}$$

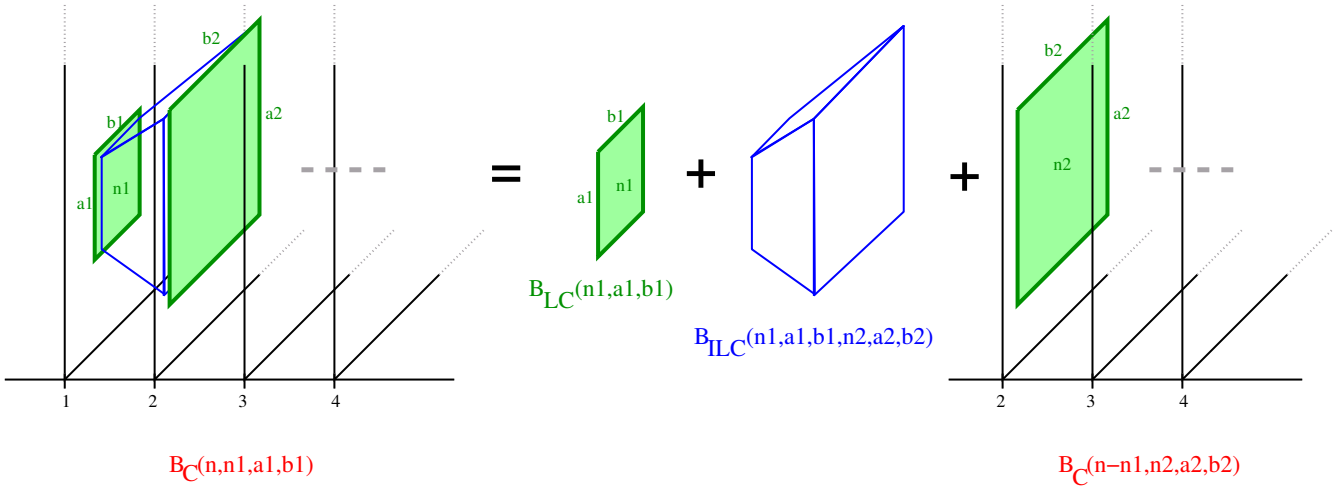


Bounding Interlayer Contacts in the FCC

- **Needed:**
  - upper bound for number of contacts between two successive layers in FCC
  - NOTE: Layers only described by parameters $(n_1, a_1, b_1); (n_2, a_2, b_2)$
- **Method:**
  - compute bounds for number of 1/2/3/4-points of first layer
  - distribute n_2 points greedily
  - technical difficulty: tight bounds of 1/2/3/4-points depend on further parameters
- **Result:** $\mathrm{B}_{\mathrm{ILC}}^{\mathrm{FCC}}(n_1, a_1, b_1, n_2, a_2, b_2)$

Recall: $\mathrm{B}_{\mathrm{ILC}}^{\mathrm{cubic}}(n_1, a_1, b_1, n_2, a_2, b_2) = \min(n_1, n_2)$

Recursion Equation for Bounds

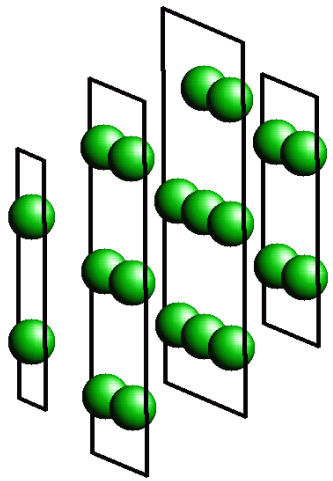


- $\mathrm{B_C}(n, n_1, a_1, b_1)$: Contacts of core with n elements and first layer L_1 : n_1, a_1, b_1
- $\mathrm{B_{LC}}(n_1, a_1, b_1)$: Contacts in L_1
- $\mathrm{B_{ILC}}(n_1, a_1, b_1, n_2, a_2, b_2)$: Contacts between E_1 and E_2 : n_2, a_2, b_2
- $\mathrm{B_C}(n - n_1, n_2, a_2, b_2)$: Contacts in core with $n - n_1$ elements and first layer E_2

Layer sequences

From Recursion:

- by Dynamic Programming: Upper bound on number of contacts
- by Traceback: Set of layer sequences



layer sequence $= (n_1, a_1, b_1), \ldots, (n_4, a_4, b_4)$
Set of layer sequences gives distribution of points to layers in all point sets that possibly have maximal number of contacts

Core Construction

Problem

IN: number n, contacts c

OUT: all point sets of size n with c contacts

- Optimization problem
- Core construction is a hard combinatorial problem

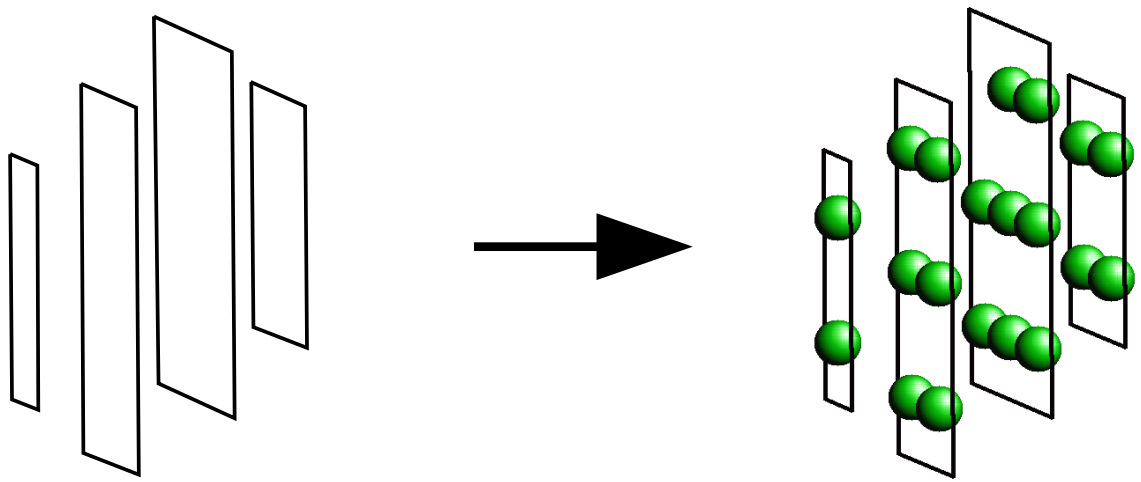
Core construction: Modified Problem

Poblem

IN: number n, contacts c, set of layer sequences S_{ls}

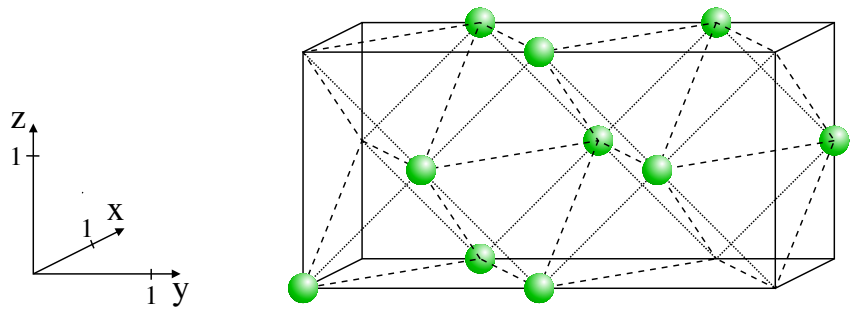
OUT: all point sets of size n with c contacts and layer sequences in S_{ls}

- Use constraints from layer sequences
- Model as constraint satisfaction problem (CSP)



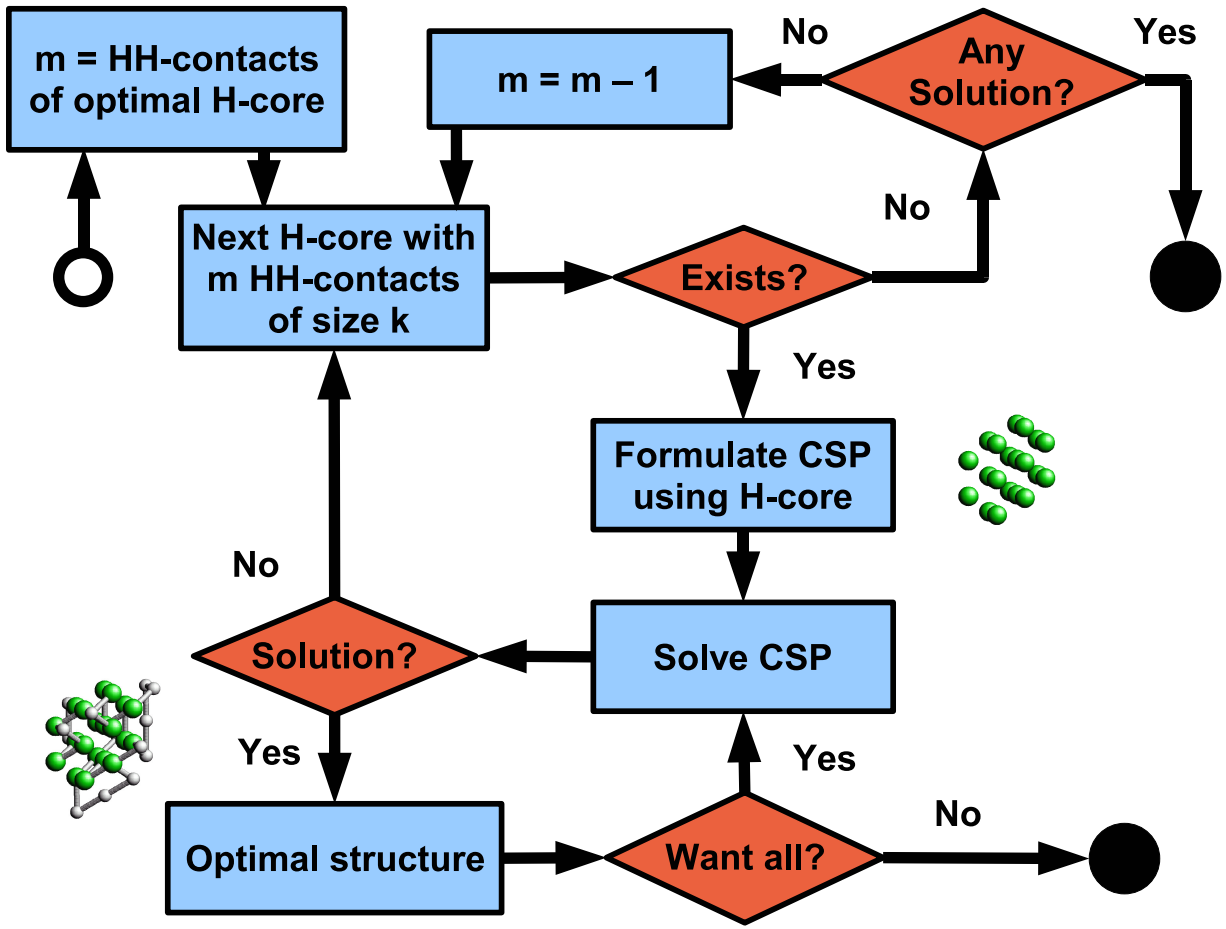
$(n_1, a_1, b_1), \ldots, (n_4, a_4, b_4)$ Core = Set of lattice points

Core Construction — Details



- Number of layers = length of layer sequence
- Number of layers in x, y, and z: Surrounding Cube
- enumerate numbers of layers $\Rightarrow$ fix cube $\Rightarrow$ enumerate points

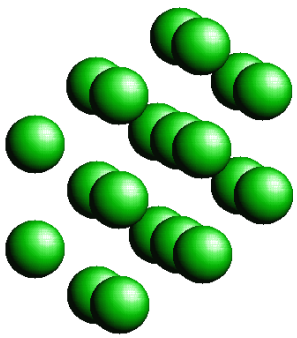
Workflow


m = HH-contacts of optimal H-core
m = m – 1
No
Any Solution?
Yes
Next H-core with m HH-contacts of size k
Exists?
No
Yes
Formulate CSP using H-core
No
Solution?
Solve CSP
Yes
Yes
Optimal structure
Want all?
No

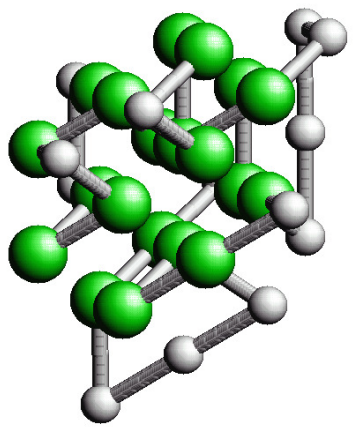
Mapping Sequences to Cores

find structure such that

- H-Monomers on core positions $\rightarrow$ hydrophobic core
- all positions differ $\rightarrow$ self-avoiding
- chain connected $\rightarrow$ walk



compact core



optimal structure

Mapping Sequence to Cores — CSP

Given: sequence s of size n and n_H Hs
core *Core* of size n_H

CSP Model

- Variables $X_1, \ldots, X_n$
  X_i is position of monomer i

  Encode positions as integers

$$\mathrm{I}\begin{pmatrix} x \\ y \\ z \end{pmatrix} \equiv x + M * y + M^2 * z$$

  (unique encoding for 'large enough' M)

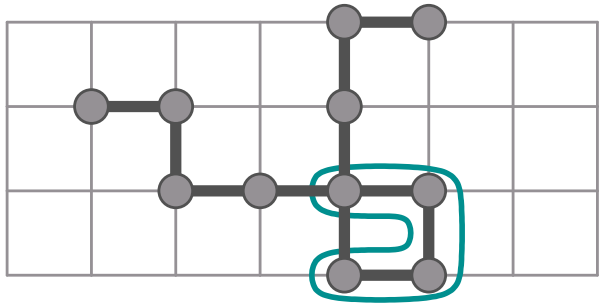
- Constraints
  1. $X_i \in \mathit{Core}$ for all $s_i = H$
  2. X_i and X_{i+1} are neighbors
  3. $X_1, \ldots, X_n$ are all different

Constraints for Self-avoiding Walks

- Single Constraints "self-avoiding" and "walk" weaker than their combination
- no efficient algorithm for consistency of combined constraint "self-avoiding walk"
- relaxed combination: stronger and more efficient propagation

k-avoiding walk constraint

Example: 4-avoiding, but not 5-avoiding



Putting it together

Predict optimal structures by combining the three steps

1. Bounds
2. Core Construction
3. Mapping

Some Remarks

- Pre-compute optimal cores for relevant core sizes
  Given a sequence, only perform Mapping step
- Mapping to cores may fail!
  We use suboptimal cores and iterate mapping.
- Approach extensible to HPNX
  HPNX-optimal structures at least nearly optimal for HP.
- Approach extensible to side chains
  H side chains form core.

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Time efficiency

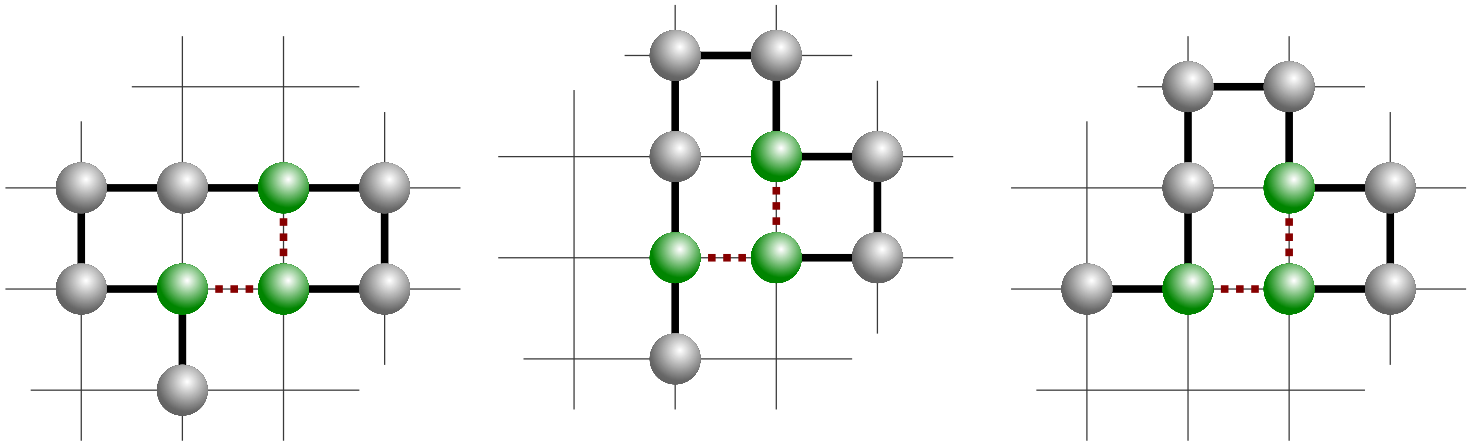
Prediction of one optimal structure
("Harvard Sequences", length 48 [Yue *et al.*, 1995])

CPSP	PERM
0,1 s	6,9 min
0,1 s	40,5 min
4,5 s	100,2 min
7,3 s	284,0 min
1,8 s	74,7 min
1,7 s	59,2 min
12,1 s	144,7 min
1,5 s	26,6 min
0,3 s	1420,0 min
0,1 s	18,3 min

- CPSP: "our approach", constraint-based
- PERM [Bastolla *et al.*, 1998]: stochastic optimization

Many Optimal Structures

Sequence HPPHPPPHP



. . . ?

- There can be many ...
- HP-model is degenerated
- Number of optimal structures = degeneracy

Completeness

Predicted number of all optimal structures
("Harvard Sequences")

CPSP	CHCC
10.677.113	1500×10^3
28.180	14×10^3
5.090	5×10^3
1.954.172	54×10^3
1.868.150	52×10^3
106.582	59×10^3
15.926.554	306×10^3
2.614	1×10^3
580.751	188×10^3

- CPSP: "our approach"
- CHCC [Yue *et al.*, 1995]: complete search with hydrophobic cores

Unique Folder

- HP-model degenerated
- Low degeneracy $\approx$ stable $\approx$ protein-like
- Are there protein-like, unique folder in 3D HP models?
- How to find out?

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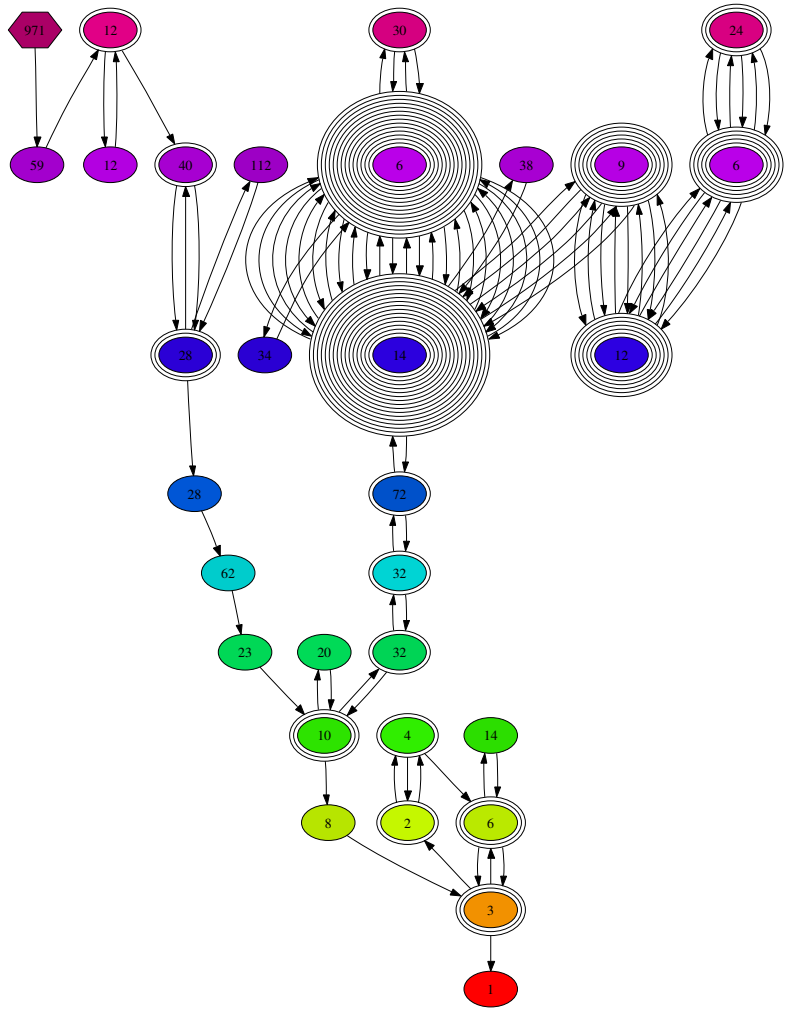
MC-search through sequence space



Unique Folder

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- Low degeneracy $\approx$ stable $\approx$ protein-like
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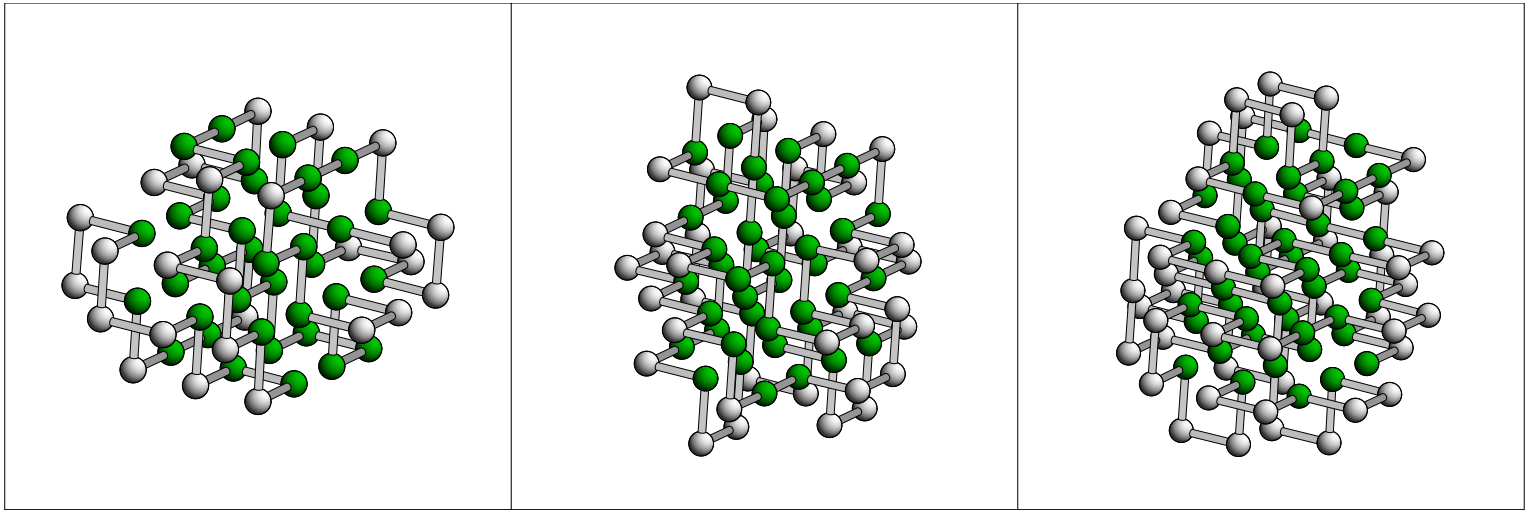
Yes: many, e.g. about 10,000 for n=27



Software: CPSP Tools

http://cpsp.informatik.uni-freiburg.de

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CPSP Tools

Constraint-based Protein Structure Prediction

Bioinformatics Group
Albert-Ludwigs-University Freiburg

web-tools version 1.1.1 (06.04.2011)

The CPSP-tools package provides programs to solve exactly and completely the problems typical of studies using 3D lattice protein models. Among the tasks addressed are the prediction of globally optimal and/or suboptimal structures as well as sequence design and neutral network exploration.

Choose a tool from the left for ad hoc usage
(CPSP-tools version 2.4.2) (LatPack version 1.7.2)

or

Download the full CPSP-tools or LatPack package for local usage!

If you use the CPSP-tools please cite the following publications:

- Martin Mann, Sebastian Will, and Rolf Backofen.
CPSP-tools - Exact and Complete Algorithms for High-throughput 3D Lattice Protein Studies.
In *BMC Bioinformatics*, 9, 230, 2008