Counting Protein Structures by DFS with Dynamic Decomposition

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Constraint Based Methods for Bioinformatics 2006

Overview

Lattice Proteins

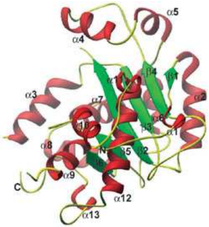
'Counting Protein Structures
by DFS with Dynamic Decomposition'

What we need to know:

- Protein Structures ? ✘
- Prediction as CSP ?
- Counting by Decomposition ?

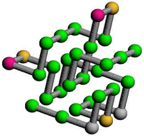
Protein structures

Real protein structure



⇒

Simple lattice proteins

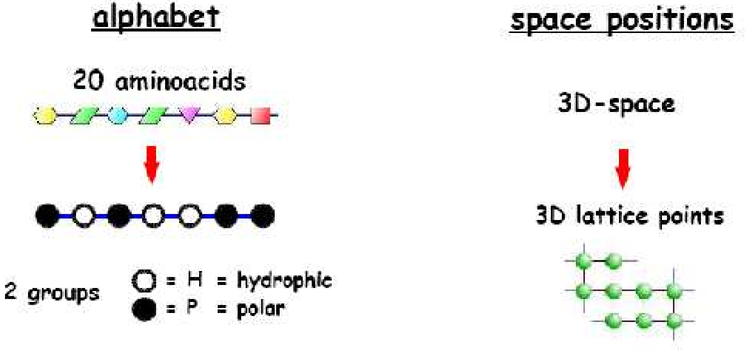


Lattice Proteins

- protein simplified to chain of monomers
- structure depends on underlying lattice
- energy depends on contact energy function

HP-Model

Abstractions



alphabet

20 aminoacids

2 groups

○ = H = hydrophic

● = P = polar

space positions

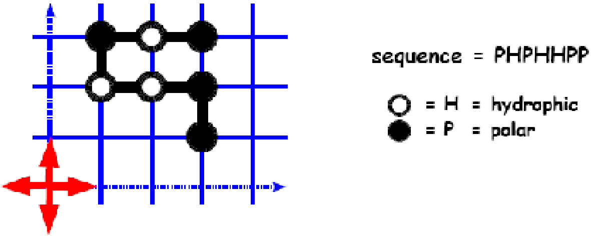
3D-space

3D lattice points

HP-Model
Structure Model

Structure

- sequence monomers are placed on lattice positions
- structure = selfavoiding walk on the lattice

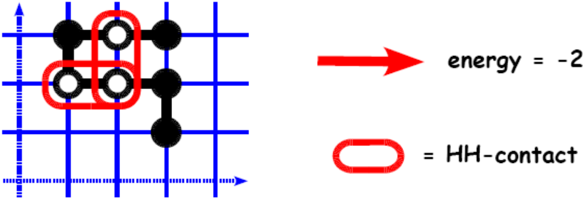


HP-Model
Energy function

Energy function

- focus on hydrophobic forces
- contact based → HH-contacts

$$\text{energy}(x,y) = \begin{cases} -1 & \text{if } (x,y == H) \text{ and } (x,y \text{ neighbors}) \\ 0 & \text{else} \end{cases}$$



Simple and nice... But what for?

Applications

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)

Ok, what next?
CSP formulation

'Counting Protein Structures
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What we need to know:

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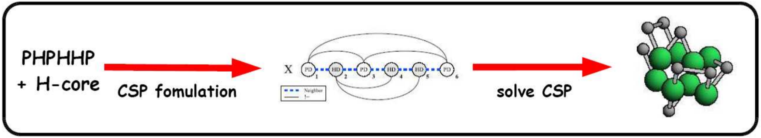
The Constraint Satisfaction Problem

A CSP for optimal structure prediction in the HP-lattice-model


PHPHHP
+ H-core

CSP fomulation

solve CSP

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

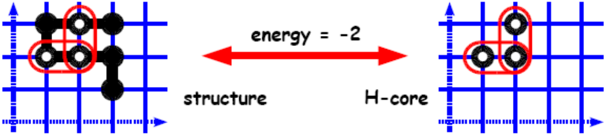
in three-dimensional protein models' 2006

Preliminary

H-Cores

H-Core of a given structure

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



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

⇒ for now used as black box and given … !

The Idea

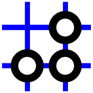
given

an HP-sequence

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

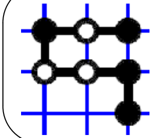
and

an optimal H-core



there is the question:

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



YES!

The CSP

A very very simple Formulation

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

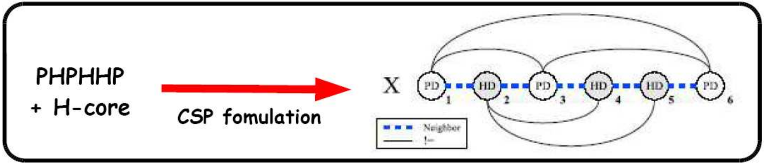
Constraints

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

$\Rightarrow$ encodes the selfavoiding walk

Structure prediction as CSP

The CSP as Constraint Graph:



From Solution to structure

- a CSP solution assigns a lattice position to each monomer
- solution = structure, and optimal due to H-core !
- normal CSP-solving approaches can be applied
  e.g. DFS-branching combined with constraint propagation

Ok, what next?

Decomposition strategy

'Counting Protein Structures
by DFS with Dynamic Decomposition'

What we need to know:

- Protein Structures ? ✓
- Prediction as CSP ? ✓
- Counting by Decomposition ? ✗

Counting CSP solutions

via Depth-first Search (DFS)

Counting all solutions

- is in complexity class #P-complete for counting problems
- = an important field of CP

- can be done by Constraint Propagation and DFS branching
- iterative process
- can be formulated as a recursion . . .

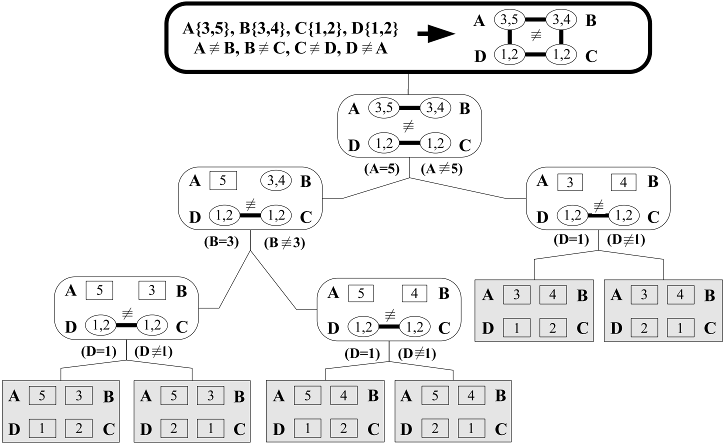
Counting DFS recursion

The 3 steps . . .

```
function CDFS($\mathcal{X}, \mathcal{D}, \mathcal{C}$)
                                                        ▷ reduce domains
    $(\mathcal{D}', \mathcal{C}') \leftarrow$ Propagate($\mathcal{X}, \mathcal{D}, \mathcal{C}$)
                                                        ▷ check for recursion stop
    if IsFailed($\mathcal{X}, \mathcal{D}', \mathcal{C}'$) then return 0
    else if IsSolved($\mathcal{X}, \mathcal{D}'$) then return 1
    else
                                                        ▷ branch search
        $c \leftarrow$ Select($\mathcal{X}, \mathcal{D}'$)
        return CDFS($\mathcal{X}, \mathcal{D}', \mathcal{C}' \cup \{c\}$) + CDFS($\mathcal{X}, \mathcal{D}', \mathcal{C}' \cup \{\neg c\}$)
    end if
end function
```

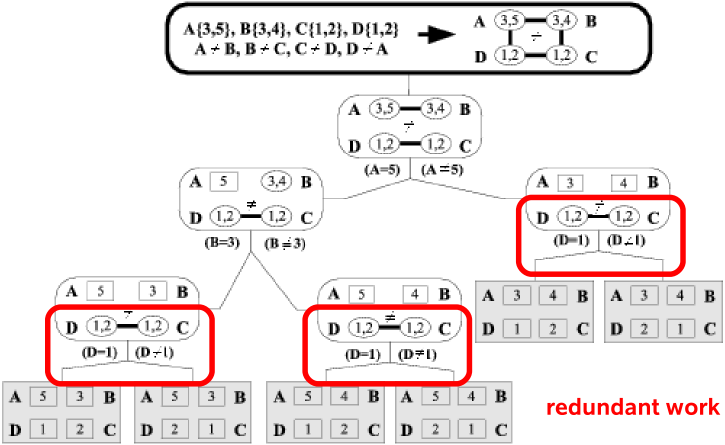
Counting DFS recursion

An example



Counting DFS recursion

The problem: redundancy!



redundant work

Counting DFS recursion

The problem: redundancy!

The problem

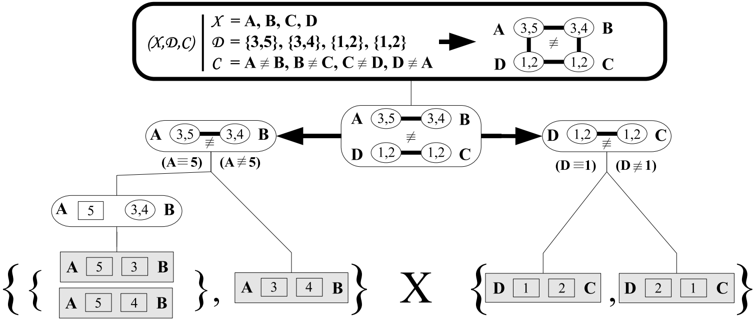
✘ Redundant work due to independent partial problems!

How to avoid?

- detect decomposition into independent partial problems
- do it dynamically during search (CSP changes)
- solve each partial problem independently
- generate the overall solution number (via product)

Counting using Decomposing DFS

First try with an example



$(\mathcal{X},\mathcal{D},\mathcal{C})$ | $\mathcal{X}$ = **A, B, C, D**

$\mathcal{D}$ = **{3,5}, {3,4}, {1,2}, {1,2}**

$\mathcal{C}$ = **A ≠ B, B ≠ C, C ≠ D, D ≠ A**

$$\{\,\{\ \boxed{A\ 5\ 3\ B},\ \boxed{A\ 5\ 4\ B}\ \},\ \boxed{A\ 3\ 4\ B}\,\}\ \times\ \{\,\boxed{D\ 1\ 2\ C},\ \boxed{D\ 2\ 1\ C}\,\}$$

Counting using Decomposing DFS

Counting using dynamic decomposing DFS

```
function DDFS($\mathcal{X}, \mathcal{D}, \mathcal{C}$)
                                                        ▷ reduce domains
    $(\mathcal{D}', \mathcal{C}') \leftarrow$ Propagate($\mathcal{X}, \mathcal{D}, \mathcal{C}$)
                                                        ▷ check for recursion stop
    if IsFailed($\mathcal{X}, \mathcal{D}', \mathcal{C}'$) then return 0
    else if IsSolved($\mathcal{X}, \mathcal{D}'$) then return 1
                                                        ▷ decomposing branching
    else  $s \leftarrow 1$                                        ▷ initialize counter
        $\mathfrak{D} \leftarrow$ Decompose($\mathcal{X}, \mathcal{D}', \mathcal{C}'$)
        for all $(\hat{\mathcal{X}}, \hat{\mathcal{D}}, \hat{\mathcal{C}}) \in \mathfrak{D}$ do
            $c \leftarrow$ Select($\hat{\mathcal{X}}, \hat{\mathcal{D}}$)
            $s = s \cdot ($ DDFS($\hat{\mathcal{X}}, \hat{\mathcal{D}}, \hat{\mathcal{C}} \cup \{c\}$) + DDFS($\hat{\mathcal{X}}, \hat{\mathcal{D}}, \hat{\mathcal{C}} \cup \{\neg c\}$))
        end for
        return $s$
    end if
end function
```

Decomposing DFS

What was it?

DDFS

- DFS → redundant solving of independent partial problems
- can be avoided by DDFS via dynamic decomposition
- overall solutions are generated during backtracking
- = general approach for exhaustive solution enumeration

But . . .

- early and strong decompositions neccessary
- ⇒ new requirements to variable and value selection
- ⇒ problem specific heuristics important
- applicable for global constraints too! (using binarisation)
- first recursion draft can be improved (see paper) ☺

Ok, what next?

Results

'Counting Protein Structures
by DFS with Dynamic Decomposition'

What we need to know:

- Protein Structures ? ✓
- Prediction as CSP ? ✓
- Counting by Decomposition ? ✓

OK, but does it help? Results . . .

Results

for structure prediction

Using DDFS for structure counting in HP-model

Decomposing versus 'normal' DFS

- in a first implementation:
  - 10x less branchings
  - 2x faster
- possible speedup higher !!!
  - further algorithmic improvements
  - optimize implementation (e.g. constraint graph handling)
  - better problem specific branching heuristics

Summary

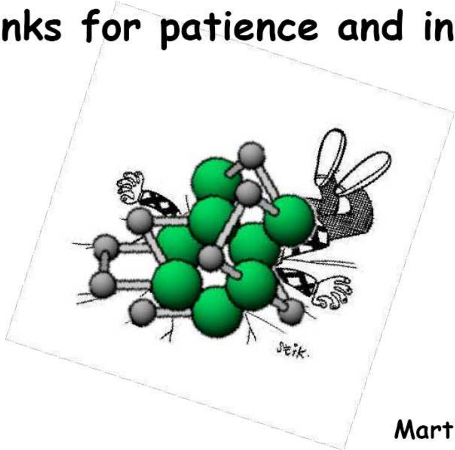
'Counting Protein Structures
by DFS with Dynamic Decomposition'

Lets summarise:

1. optimal structure prediction for lattice proteins can be formulated as CSP
2. counting all solutions via DFS yields redundancy
3. can be avoided by dynamic decompositions ⇒ DDFS
4. leads to big speedups and less branchings
5. DDFS is a general approach ⇒ other CSPs

That's all folks!

Thanks for patience and interest



Martin Mann