Constraint Programming and Biology: The protein Folding Problem

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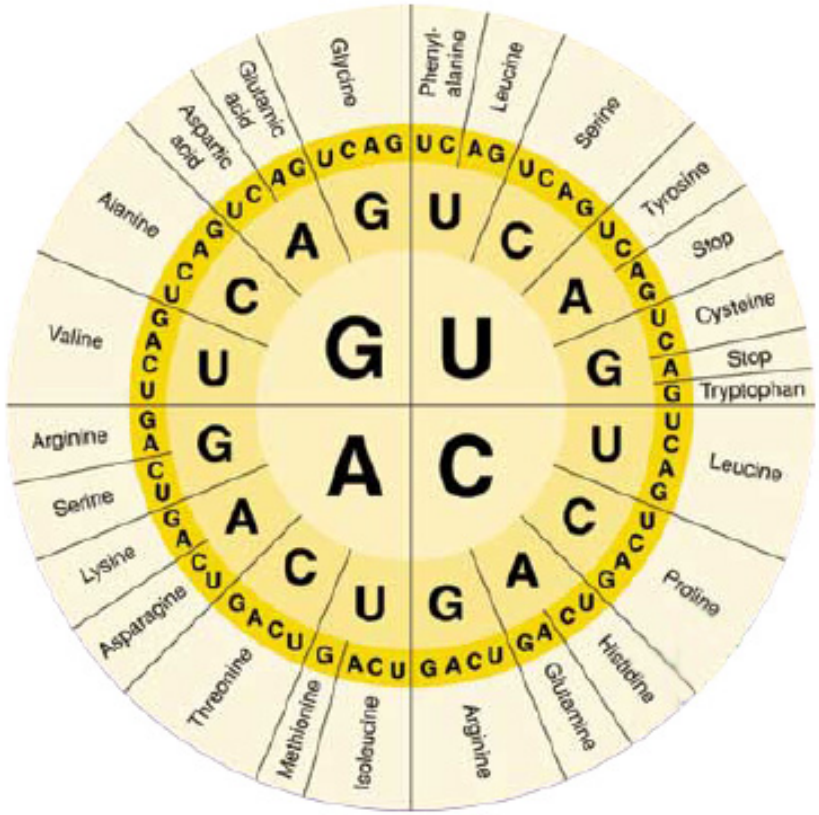
Introduction

- For the sake of completeness we spend some words on the translation stage
- The central dogma is: DNA $\mapsto$ (transcription) RNA $\mapsto$ (translation) protein.
- We have already seen some DNA problems (Haplotype inference/Phylogenetic trees) and one RNA problem (secondary structure prediction).
- Now we focus on the last stage: RNA $\mapsto$ protein, and in particular on the problem of predicting the 3D form of the protein.

Introduction

RNA $\mapsto$ protein

- RNA is a sequence of nucleotides A, C, G, U.
- Triplets of nucleotides identify a new object (monomer) called amino-acid.
- Although in principle we can have $4^3 = 64$ different amino-acids, just 20 (+ 1 rare) of them are generated.



Introduction

Proteins

- A protein is a sequence of amino acids.
- This sequence is also called *primary structure*
- Typical length is 50–500.
- Amino acids are of 20 types, identified by a letter: **Ala**nine (A), **Cys**teine (C), **Asp**artic Acid (D), **Glu**tamic Acid (E), **Phe**nylalanine (F), **Gly**cine (G), **His**tidine (H), **Isole**ucine (I), **Lys**ine (K), **Leu**cine (L), **Met**hionine (M), **As**paragi**n**e (N), **Pro**line (P), **Gl**utami**n**e (Q), **Arg**inine (R), **Ser**ine (S), **Thr**eonine (T), **Val**ine (V), **Tryp**tophan (W), **Tyr**osine (Y).

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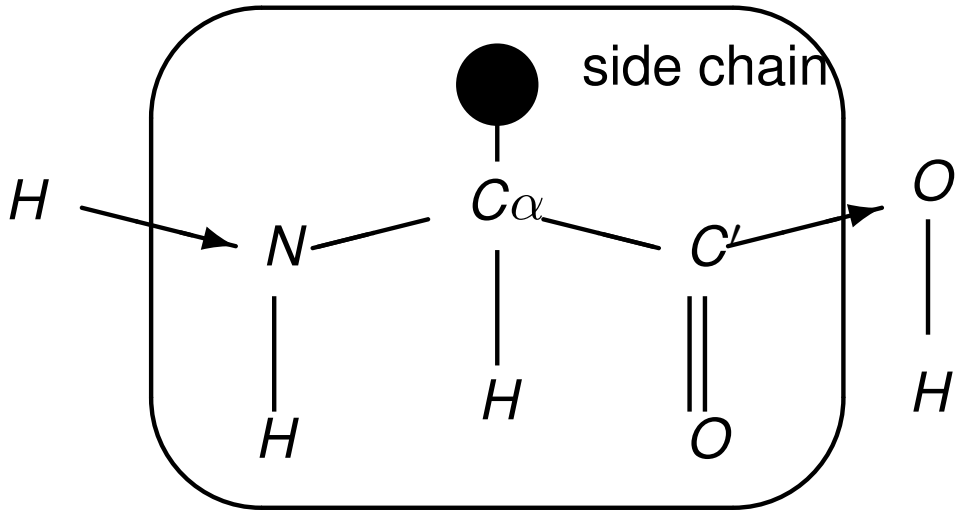
- Mathematically: The primary structure of amino acids is a string of $(\{A, \ldots, Z\} \setminus \{B, J, O, U, X, Z\})^*$.

Introduction

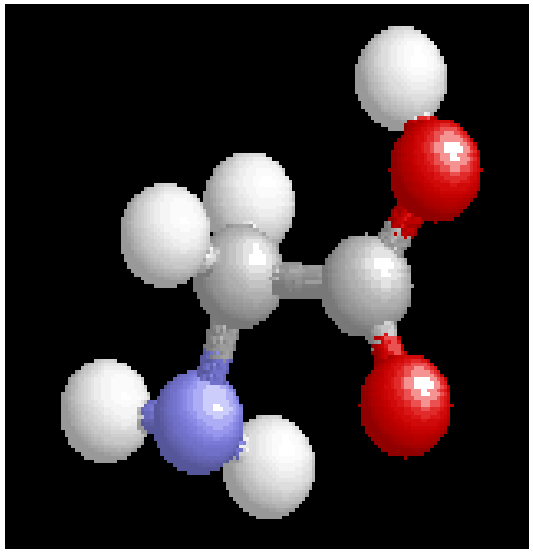
Aminoacid structure

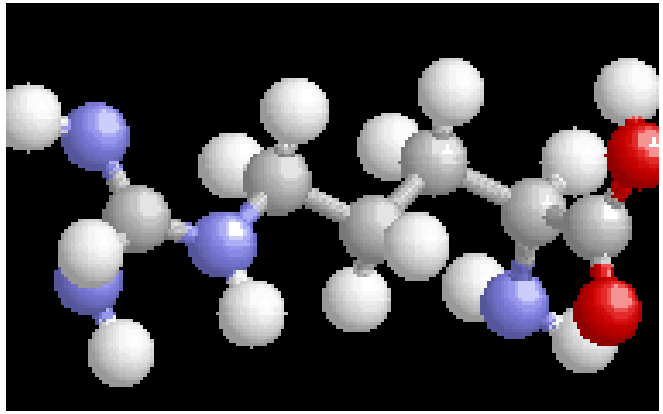


- The *backbone* is the same for all aminoacids
- The *side chain* characterizes an aminoacids.
- A side chain contains from 1 (Glycine) up to 18 (Tryptophan) atoms.

Amino acids

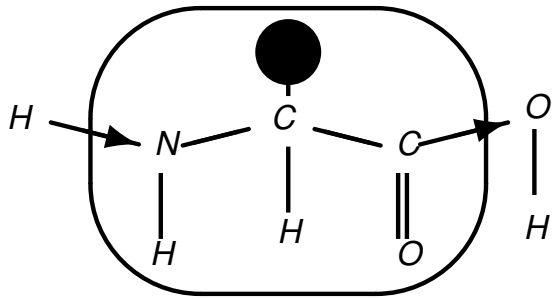
Glycine e Arginine





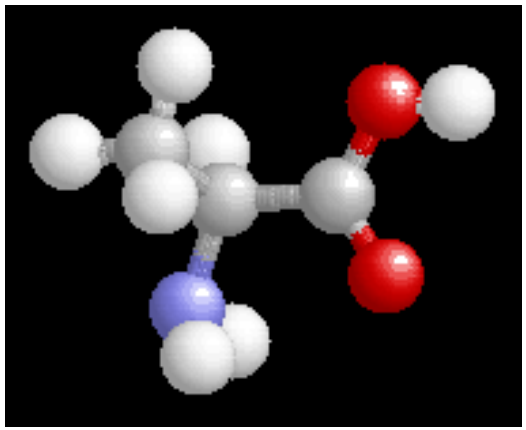
$C_2H_5NO_2 \rightarrow 10$ atoms $\quad C_6H_{14}N_4O_2 \rightarrow 26$ atoms

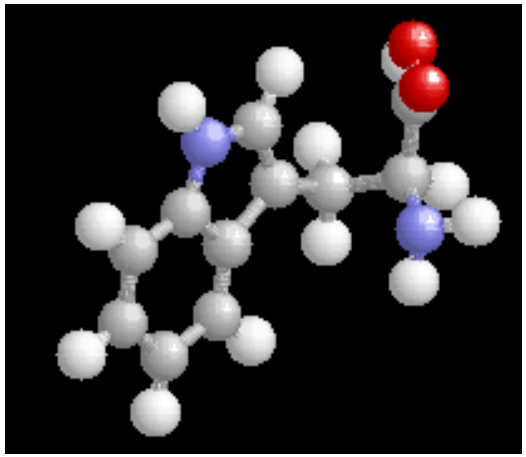
White $=$ H
Blue $=$ N
Red $=$ O
Grey $=$ C



Amino acids

Alanine e Tryptophan





$C_3H_7NO_2 \rightarrow$ 13 atoms $\quad C_{11}H_{12}N_2O_2 \rightarrow$ 27 atoms

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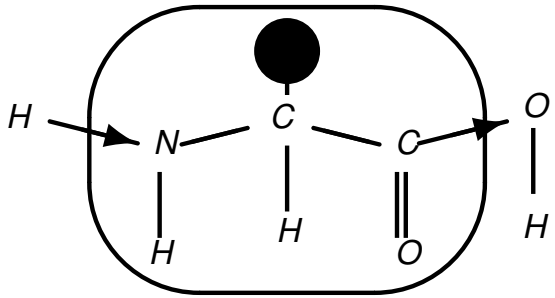


Amino acids

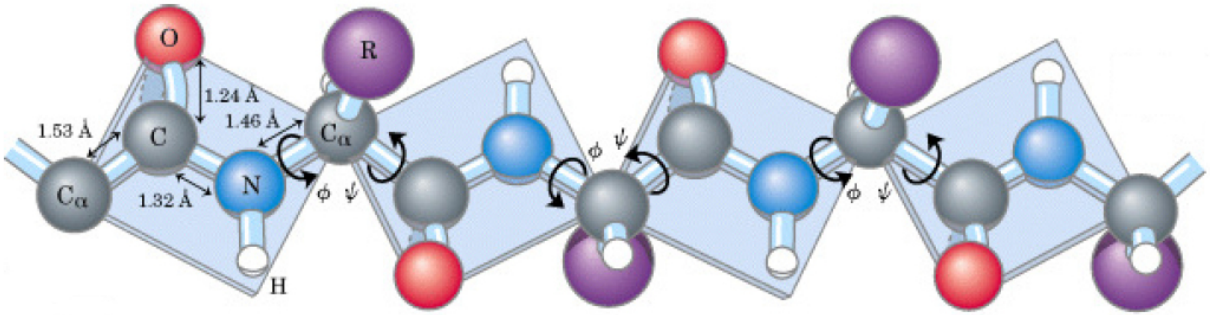
Chemical composition (for completeness)

Name	Chemical	Side Chain
A	$C_3H_7NO_2$	4
C	$C_3H_7NO_2S$	4
D	$C_4H_7NO_4$	16
E	$C_5H_9NO_4$	10
F	$C_9H_{11}NO_2$	14
G	$C_2H_5NO_2$	1
H	$C_6H_9N_3O_2$	11
I	$C_6H_{13}NO_2$	13
K	$C_6H_{14}N_2O_2$	15
L	$C_6H_{13}NO_2$	13

Name	Chemical	Side Chain
M	$C_5H_{11}NO_2S$	11
N	$C_4H_8N_2O_3$	8
P	$C_5H_9NO_2$	$8(*)$
Q	$C_5H_{10}N_2O_3$	11
R	$C_6H_{14}N_4O_2$	17
S	$C_3H_7NO_3$	5
T	$C_4H_9NO_3$	9
Y	$C_9H_{11}NO_3$	15
V	$C_5H_{11}NO_2$	10
W	$C_{11}H_{12}N_2O_2$	18

Proteins

- Amino acids combine sequentially to form a flexible chain



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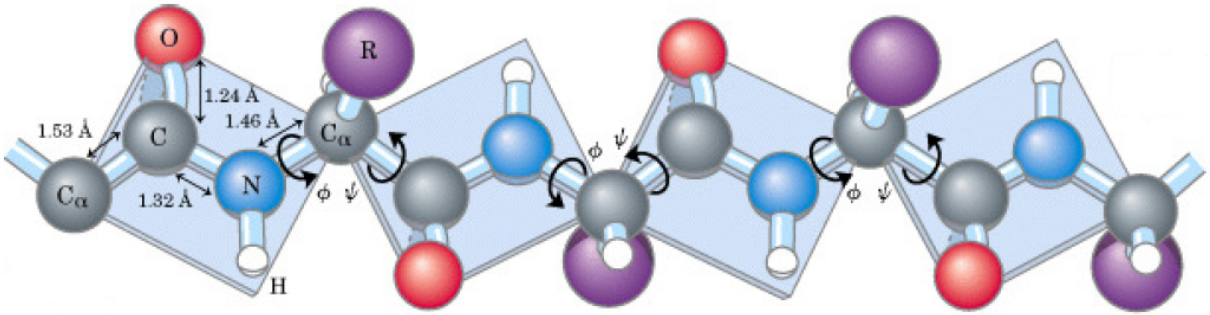
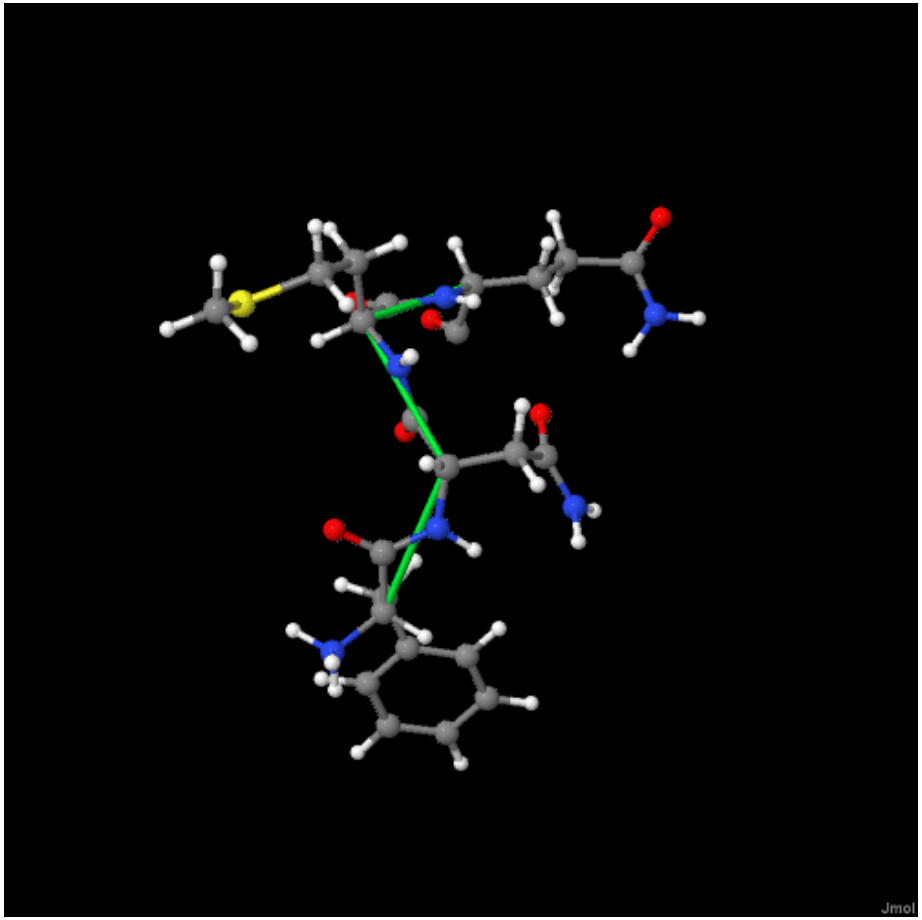


- There are several degrees of freedom (black arrows)
- The purple dots represent the *side chains*, that is a sub molecule that depends on the amino acid type

Proteins

Simplified structure

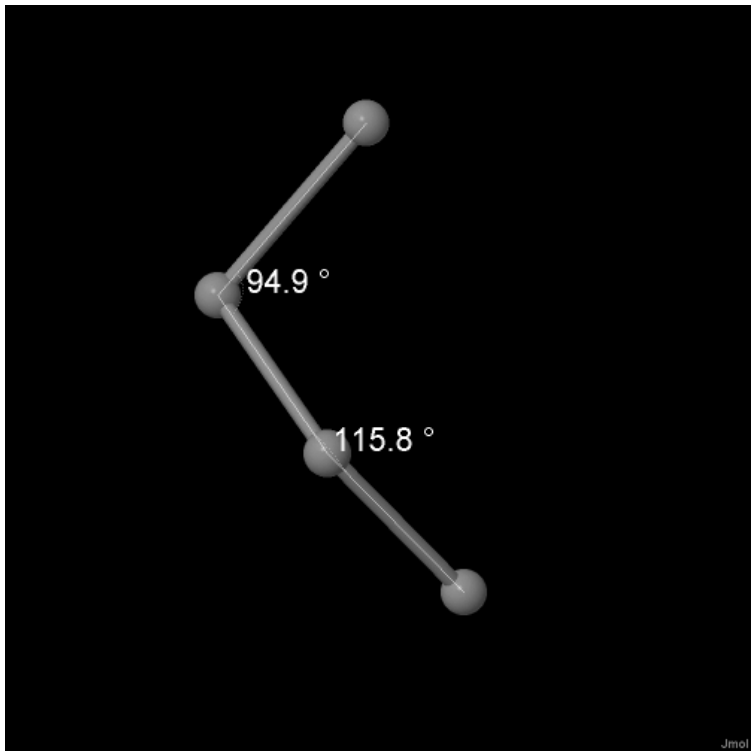


- The *backbone* (green) links consecutive amino acids
- Each amino acid can be identified by its carbon alpha (C_α)
- The distance between consecutive $C\alpha$ points is constant (3.81Å).

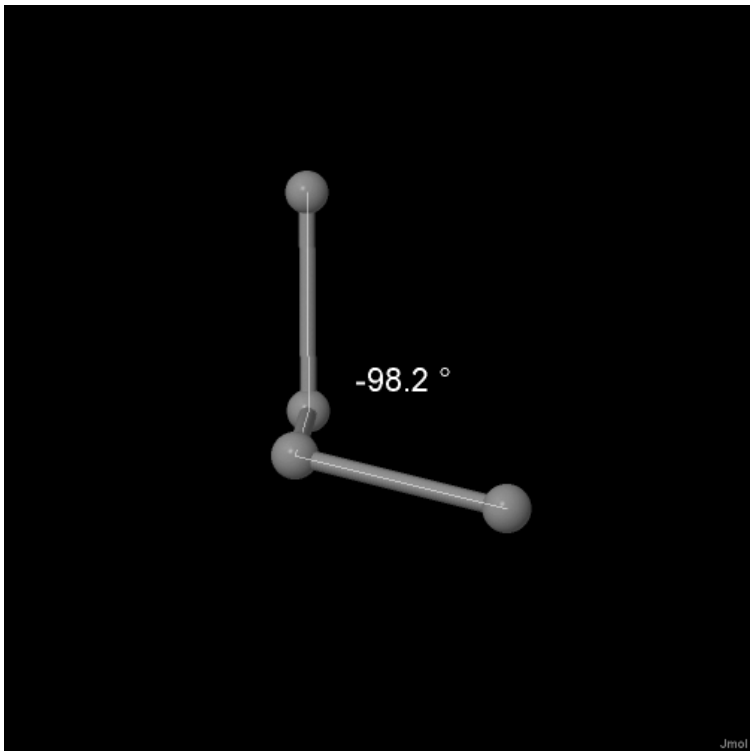
Proteins

Backbone

- The distance between $C\alpha$ points is constant (3.81Å).
- Let us consider a backbone made of 4 amino acids.



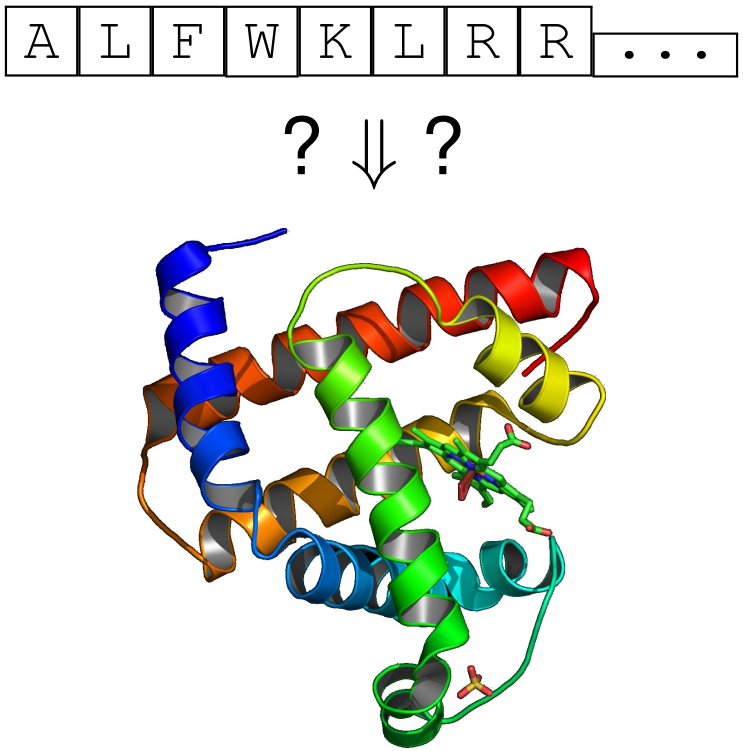
There are two bend angles



And one torsional angle

The structure prediction problem

- Given the primary structure of a protein (its amino acid sequence)
- For each amino acid, output its position in the space (tertiary structure of a protein)



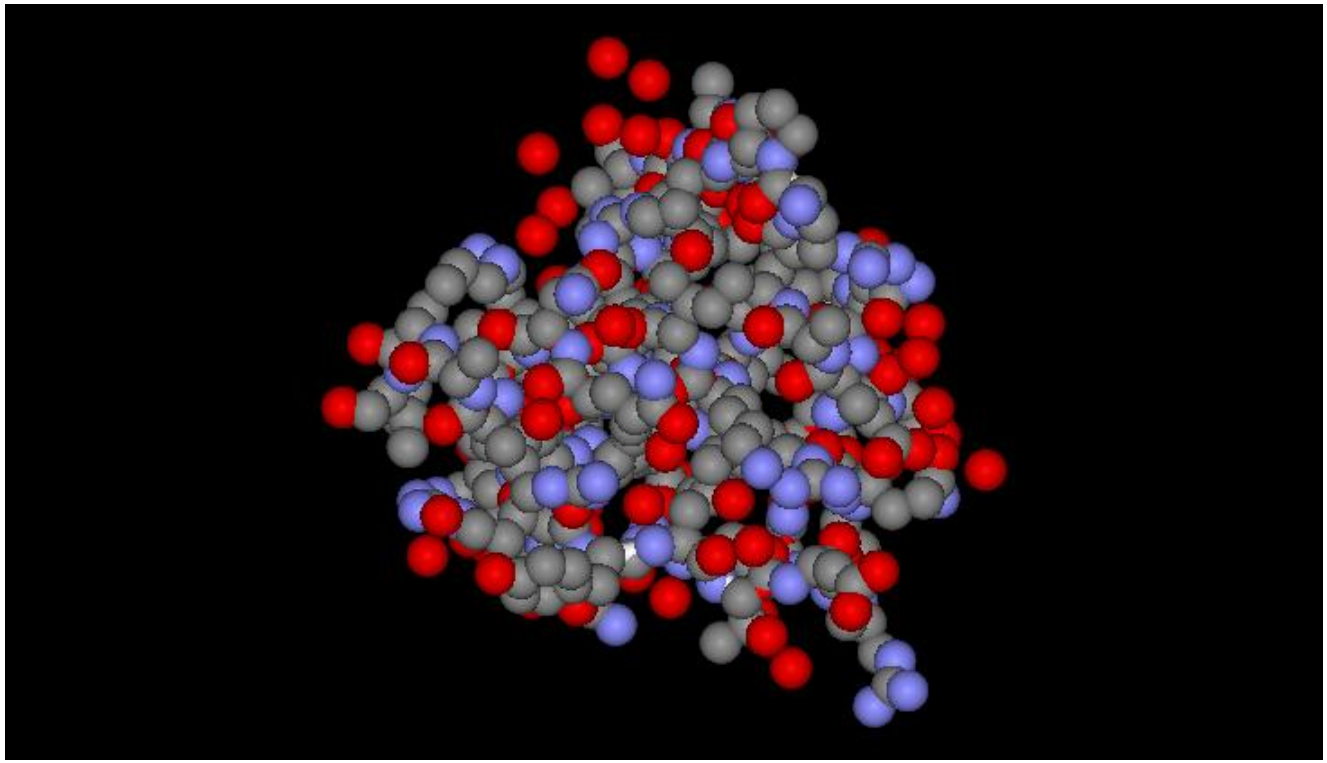
The structure prediction problem

... and this is the hard part:

- In nature a protein has a unique/stable 3D conformation
- A cost function (that mimics physics laws) can be used to score each conformation
- Searching for the optimal score produces the best candidate is difficult (NP-complete even in extremely simplified modelings)
- Abstractions are either spatial or energetic.

The structure prediction problem

Primary: rprtafsseqlarlkrefnenrylterrrqqlsselglneaqikiwfqnkraki



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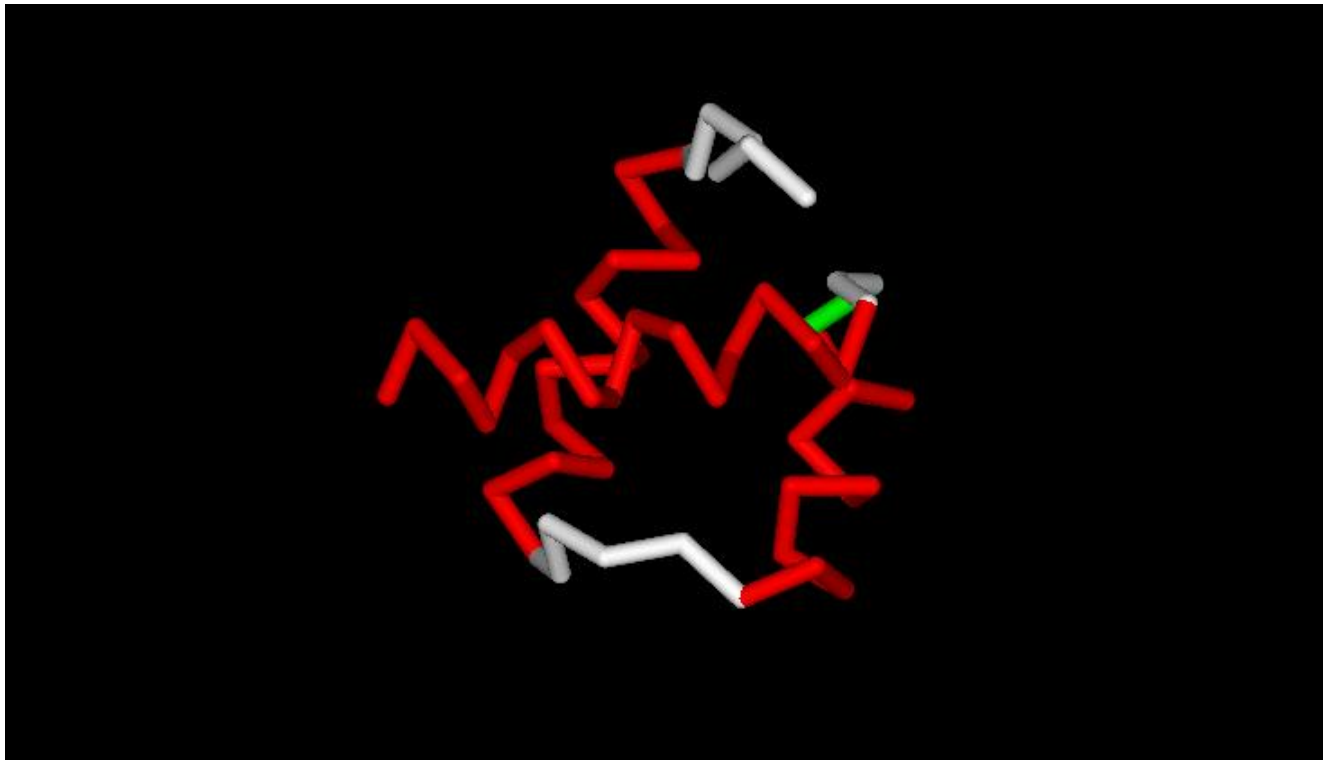

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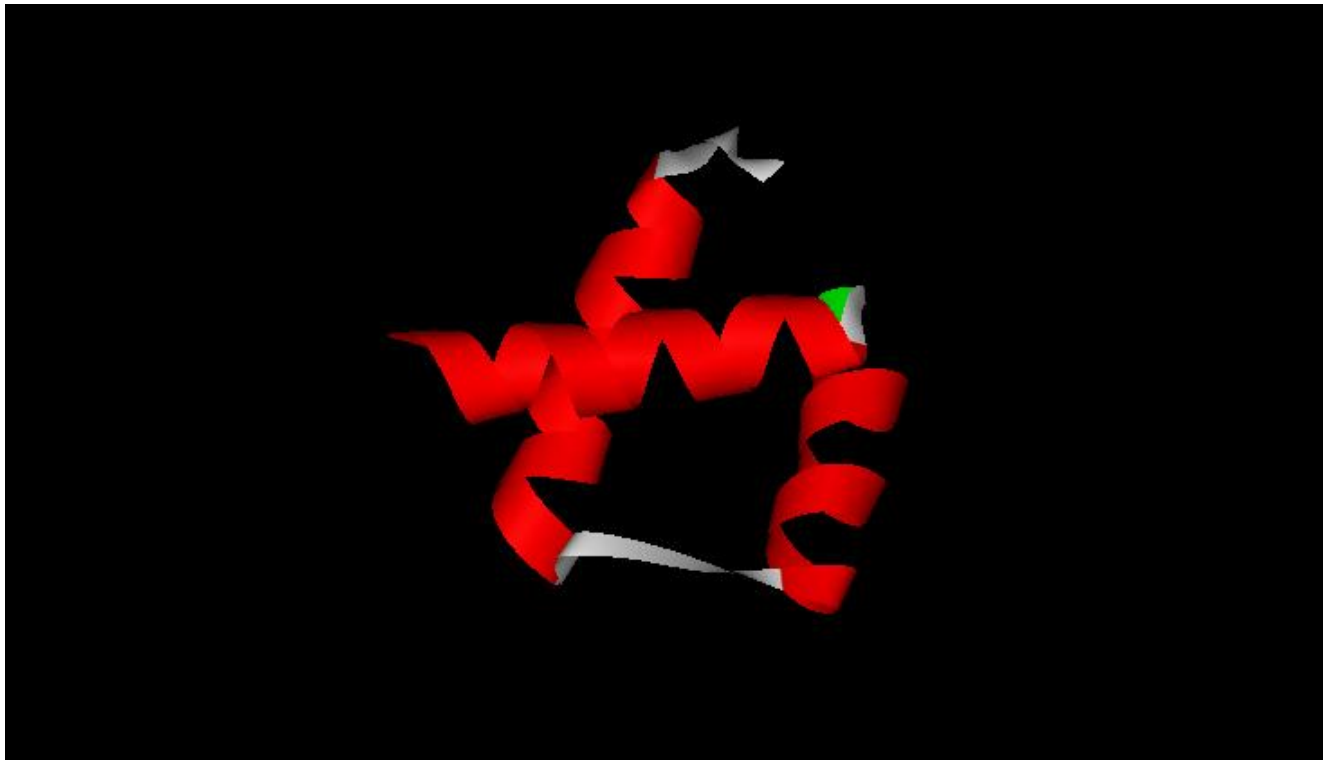

The protein folding problem

- Let $\mathcal{D}$ be a set of admissible points for the amino acids (for which part of the aminoacid? E.g., the $C\alpha$ atom—First simplification)
- Let c, d two fixed distances. For two points $p, q \in \mathcal{D}$, we say that next(p, q) if and only if $|p - q| = d$ ($d = 3.8$Å)
- A function $\omega : \{1, \ldots, n\} \longrightarrow \mathcal{D}$ is said a *folding* if
  - for $i, j \in \{1, \ldots, n\}$ if $i \neq j$ then $|\omega(i) - \omega(j)| \geq d$ (or simply $\omega(i) \neq \omega(j)$ in lattice)
  - for $i \in \{1, \ldots, n-1\}$ it holds that next$(\omega(i), \omega(i+1))$

The protein folding problem

- For two points $p, q \in \mathcal{D}$, we define the Boolean function contact as follows: contact$(p, q) = 1$ if and only if $|p - q| \leq c$ (Second simplification: contact energy)
- Let Pot be a function from pairs of amino acids to integer numbers. The free energy of a folding $E(\omega, \vec{s})$ is computed as follows:

$$E(\omega, \vec{s}) = \sum_{\substack{1 \leq i < n \\ i+2 \leq j \leq n}} \text{contact}(\omega(i), \omega(j))\text{Pot}(s_i, s_j)$$

- The protein structure prediction problem (PSP) is the problem of determining the folding(s) ω with minimal energy.

Lattice models

- The fixed distance between $C\alpha$s (and some statistics on the most frequent angles) prompts for using discrete lattice models.

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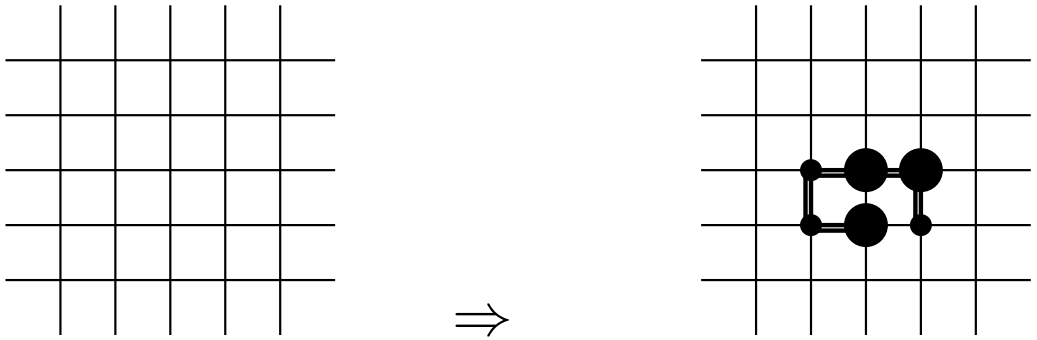
- The fixed distance between $C\alpha$s (and some statistics on the most frequent angles) prompts for using discrete lattice models.
- Just to play with, let us start with $\mathbb{N}^2$



- A folding is just the writing (e.g. by pencil) of a line of length $n-1$ on the paper following the N^2 grid. Different circle size for different aminoacids. Difficult for 20 kind of amino acids, but ...

Simplified (contact) energy

The HP Energy model (Dill)

- Aminoacids are split into two families: Hydrophobics (H) and Polar (P)
- Two aminoacids of kind “H” in contact at distance *d* (lattice unit) contribute with an energy of -1, otherwise the contribution is 0.

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- This formulation of the problem has a nice property: you can teach it to a children without speaking of proteins and so on: *Write a folding using paper and pencil that maximizes the contacts between “H” aminoacids (large circles)*

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- With $\mathbb{N}^2$ and HP, establishing whether there is a folding with energy $< k$ is NP-complete (Crescenzi, Goldman, Papadimitriou, Piccolboni, Yannakakis. On the Complexity of Protein Folding. Journal of Computational Biology 5(3): 423-466 (1998))

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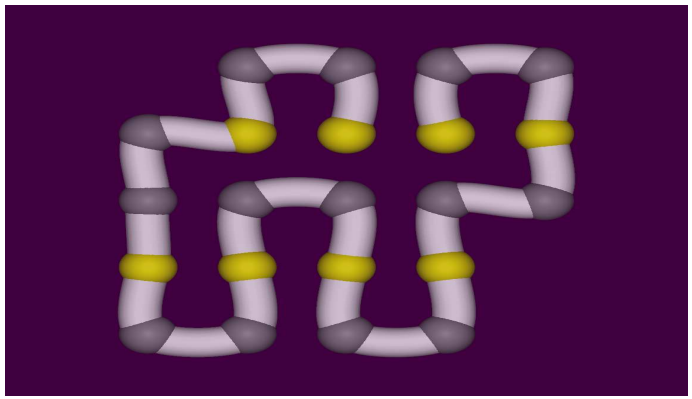
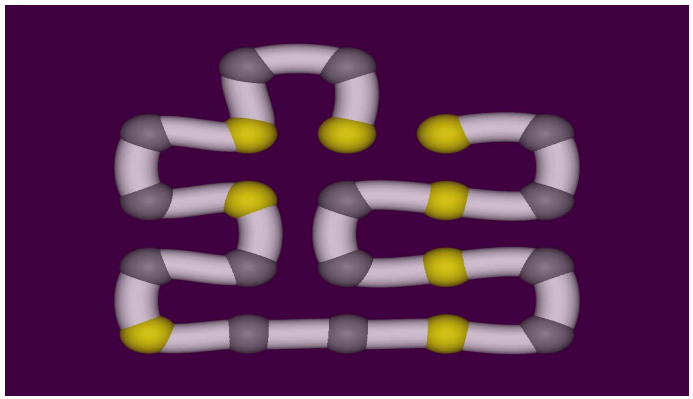
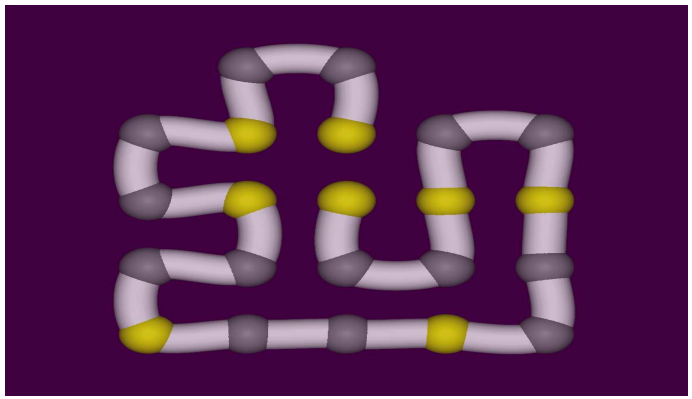
- Combinatorial exercise. Assume to fix the first point: what is the size of the search space?
  (hint: it is the number of self-avoiding-walks)

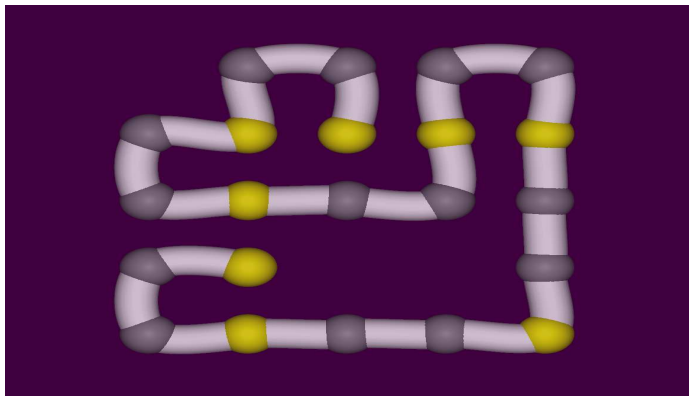
Example of PF HP N^2

Yellow: H, Grey: P. All foldings have energy -6









HP on $\mathbb{N}^2$: FD encoding

- Primary $= [a_1, \ldots, a_n] = [h/p, p/p, h/p, ...]$
- Tertiary$_x = [X_1, \ldots, X_n]$, Tertiary$_y = [Y_1, \ldots, Y_n]$

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- W.l.o.g., let $X_1 = X_2 = Y_1 = n$, $Y_2 = n + 1$.

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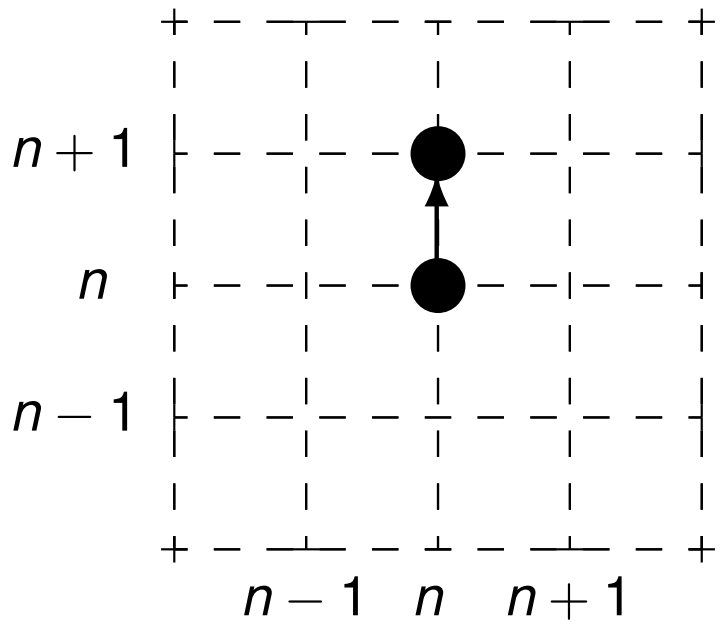
- Namely, we start with



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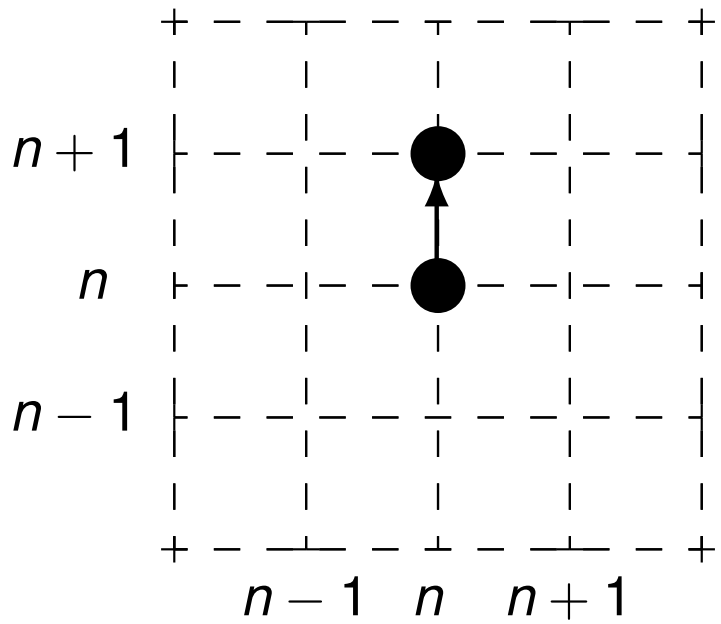

- $\mathrm{dom}(X_1) = \cdots = \mathrm{dom}(X_n) = \mathrm{dom}(Y_1) = \cdots = \mathrm{dom}(Y_n) = 1..2n$

HP on $\mathbb{N}^2$: FD encoding

- $\text{Tertiary}_x = [X_1, \ldots, X_n], \text{Tertiary}_y = [Y_1, \ldots, Y_n]$
- next: for $i = 1, \ldots, n-1$: $|X_i - X_{i+1}| + |Y_i - Y_{i+1}| = 1$
- saw: for $i = 1, \ldots, n-1$, for $j = i+1, \ldots, n$: $|X_i - X_i| + |Y_i - Y_j| \geq 1$

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- Let $[P_1, \ldots, P_n]$ be a list and M a "big" integer (100 is ok for us).
- for $i = 1, \ldots, n-1$: $P_i = X_i + MY_i$.

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- We can now post: alldifferent($[P_1, \ldots, P_n]$).

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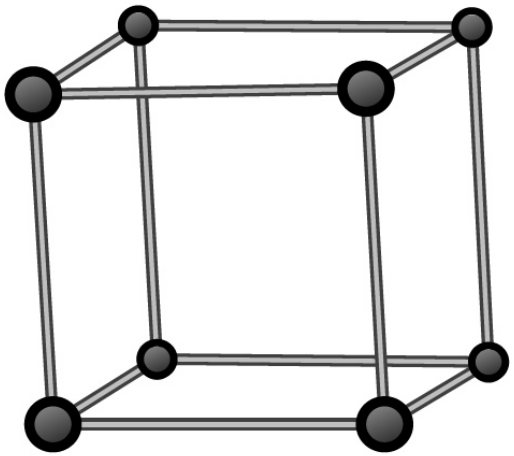
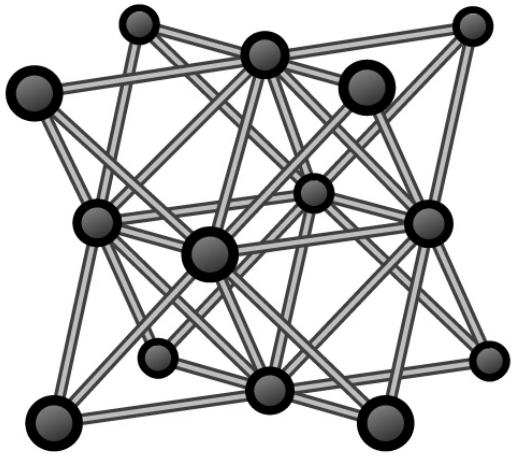
- Tertiary$_x = [X_1, \ldots, X_n]$, Tertiary$_y = [Y_1, \ldots, Y_n]$
- energy: for $i = 1, \ldots, n-2$, for $j = i+2, \ldots, n$: $c_{i,j} \in \{0, -1\}$

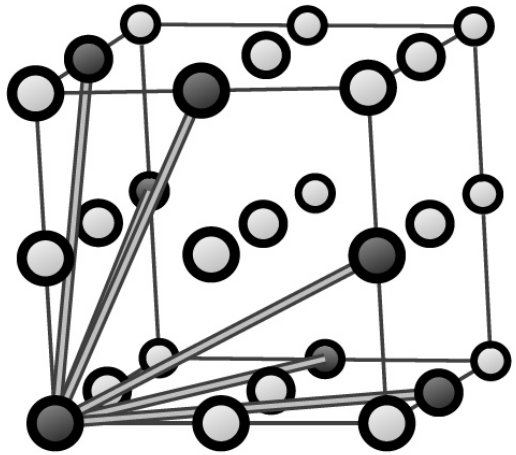
$$c_{i,j} = -1 \leftrightarrow (|X_i - X_i| + |Y_i - Y_j)| = 1) \wedge (a_i = a_j = h)$$

- Energy $= \sum_{i=1}^{n-2} \sum_{j=i+2}^{n} c_{i,j}$
- See the code `pfhp.pl`

Lattice models: Cube, FCC, Chess Knight



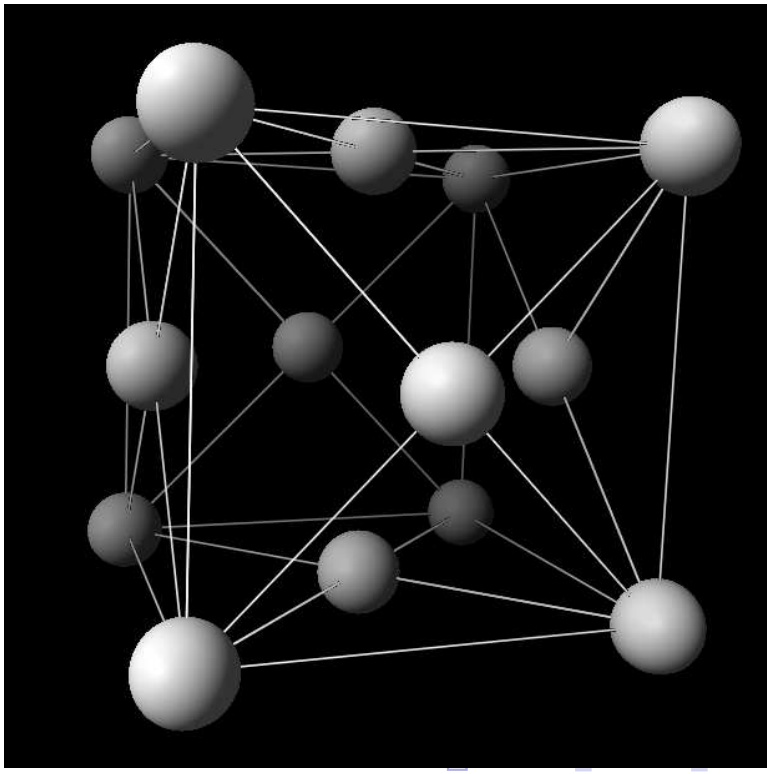




The FCC lattice

- The Face Centered Cube lattice models the discrete space in which the protein can fold.
- It is proved to allow realistic conformations.
- The cube has size 2.

- Two points are *connected* (next) iff $|x_i - x_j|^2 + |y_i - y_j|^2 + |z_i - z_j|^2 = 2$,
- Each point has 12 neighbors (but 60° and 180° can be removed).



The protein folding problem

HP on FCC

- Backofen and Will fold HP-proteins up to length 200 on FCC using constraint programming
- Clever propagation, an idea of stratification and some geometrical results on the lattice.
- Drawbacks: It is only an abstraction. The solutions obtained are far from reality. For instance, helices and sheets are never obtained.
- Problems:
  - Energy function too simple.
  - Contact too strict.

The protein folding problem

A more realistic Energy function

- A 20×20 *potential matrix* Pot storing the contribution for each pair of aminoacids is used.
- Values are either positive or negative.
- The notion of *contact* (easy) on lattice models is slightly extended:
- if distance $(a_i, a_j) < k$ then $\text{Pot}(a_i, a_j)$ else $\frac{\text{Pot}(a_i, a_j)}{\text{distance}^2}$

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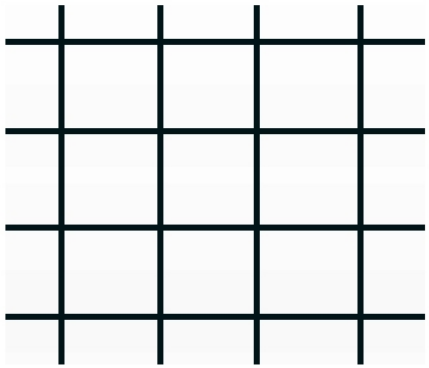
- COLA (COnstraint solving on LAttices) can predict on FCC proteins of length 100–120 in reasonable time

Global constraints

contiguous



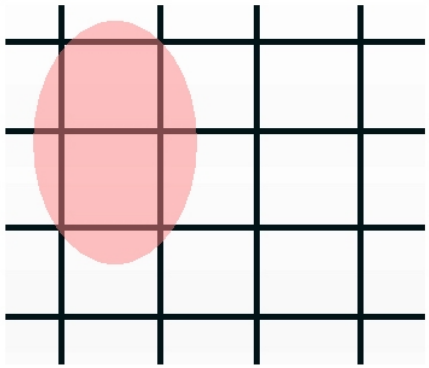
- Let $X_1, \ldots, X_n$ be variables with domains $D_1, \ldots, D_n$:

$$\begin{aligned}\texttt{contiguous}(X_1, \ldots, X_n) = (D_1 \times \cdots \times D_n) \setminus \\ \{(a_1, \ldots, a_n) \in (D_1 \times \cdots \times D_n) : \\ \exists i.\ (1 \leq i < n \wedge (a_i, a_{i+1}) \notin E)\}\end{aligned}$$

  where E is the set of lattice edges.
- CON (consistency chcking) and GAC (generalized arc consistency filtering) are polynomial

Global constraints

contiguous



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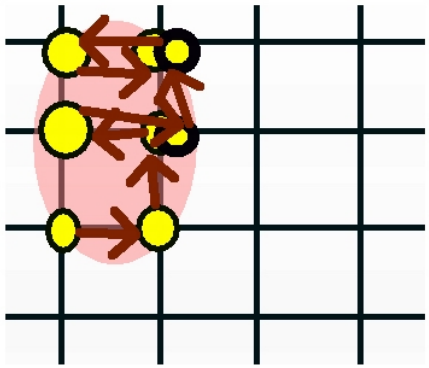

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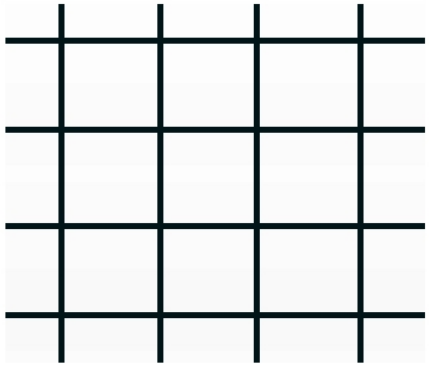

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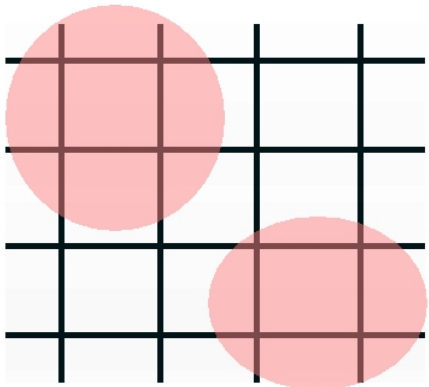
Global constraints

alldifferent



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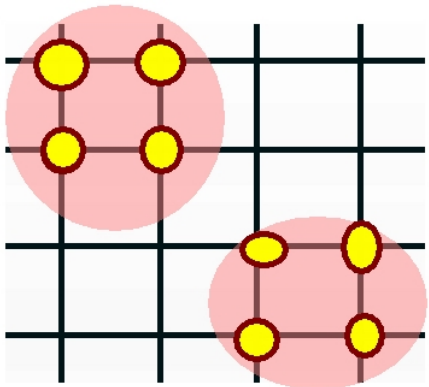

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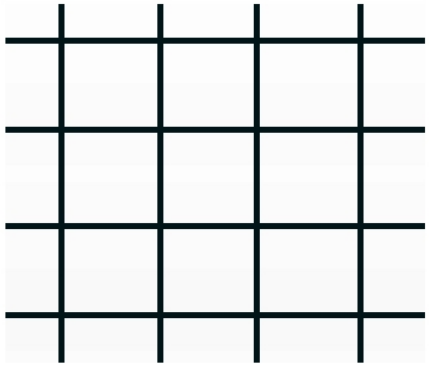
Global constraints

self avoiding walk



- Given n variables $X_1, \ldots, X_n$, with domains $D_1, \ldots, D_n$, the global constraint `saw` is the following:

$$\texttt{saw}(X_1, \ldots, X_n) = \texttt{alldifferent}(X_1, \ldots, X_n) \cap \texttt{contiguous}(X_1, \ldots, X_n)$$

- CON (and GAC) are NP-complete (Dal Palù, Dovier, Pontelli. IJDMB 4(1), 2010)

Global constraints

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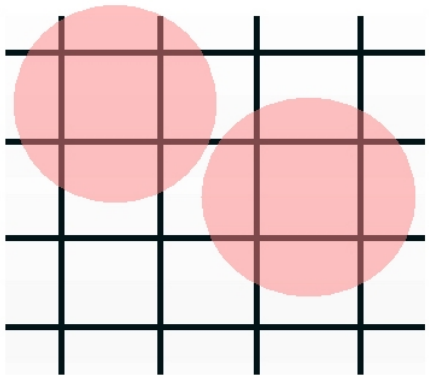

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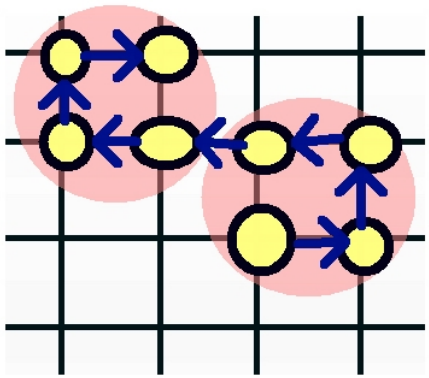

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Global constraints

Other constraints

- all distant (NP)
- chain (NP)
- rigid block (P)
- Density maps (NP)
- These constraints are built-in in the tool COLA, in order to predict proteins in the FCC lattice with a 20×20 contact energy function.

Conclusions (of this part)

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- The $C\alpha$-$C\alpha$ model has limits. The same holds for contact energy potentials.
- We'll see how exiting from lattices while using a discrete reasoner.

Some References

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- Approximated results with local search and/or LNS by Hoos et al. and by Van Hentenryck et al.