Exploring Life through Logic Programming

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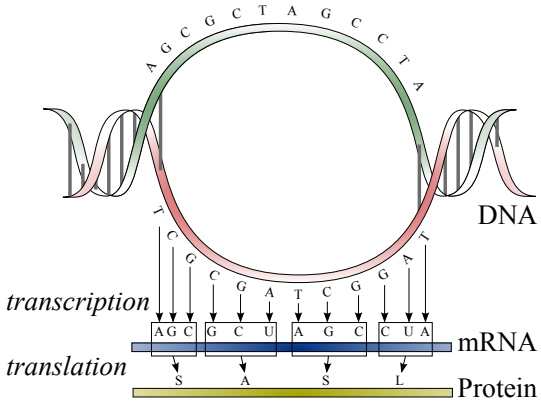
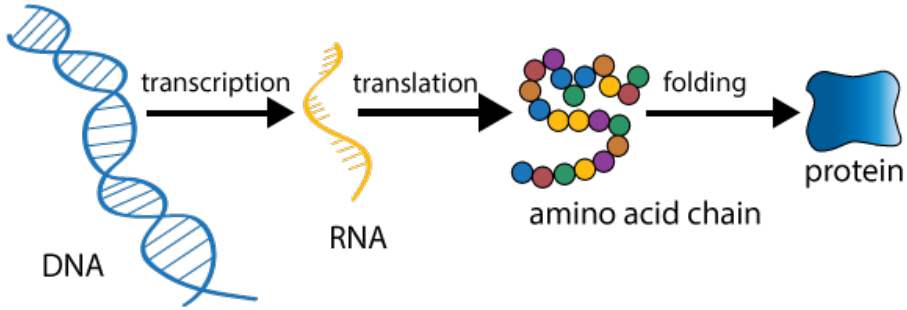
Protein Structure Prediction

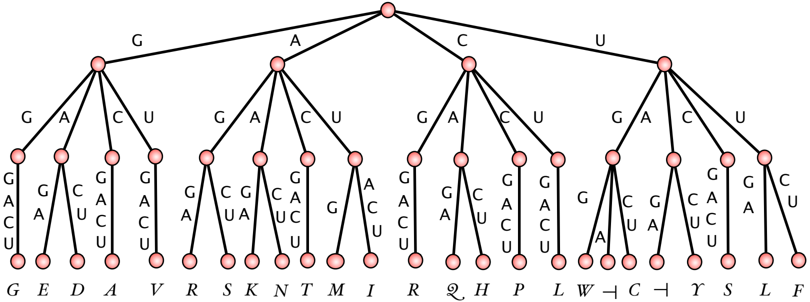
Proteins and Central Dogma





- The translation phase starts from a mRNA sequence and associates a protein sequence
- Proteins are made of amino acids (20 common different types)
- Amino acids are defined by letters $\{A, \ldots, Z\} \setminus \{B, J, O, U, X, Z\}$

Universal code

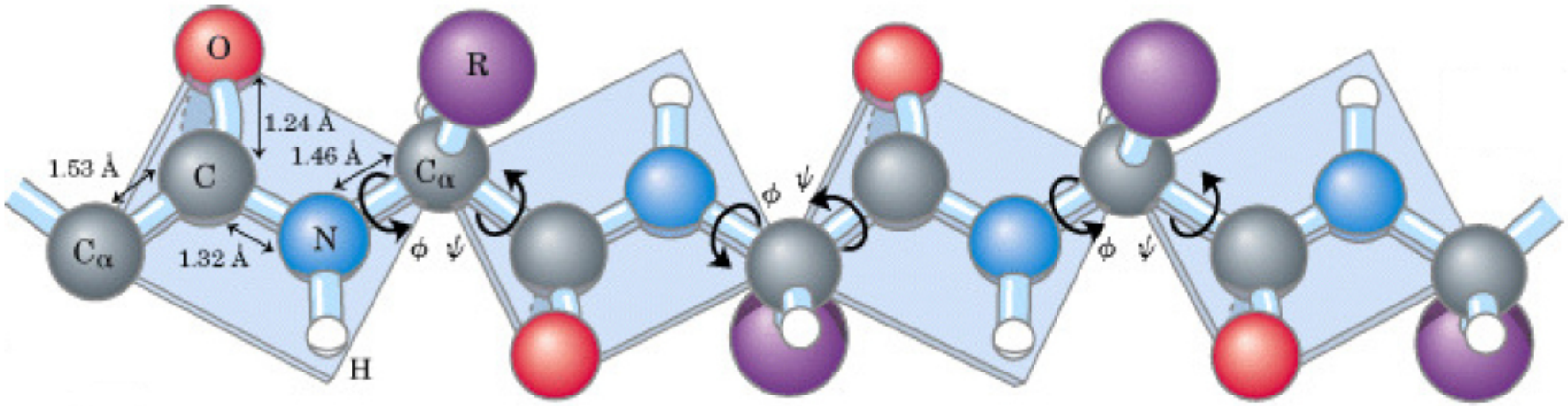


- The translation selects 3 RNA basis (codon) and associates 1 amino acid.
- The translation rules are encoded in the universal code.
- The code contains *stop* symbol and some redundant RNA triplets.

Proteins

Amino acids

- Proteins are molecules made of a linear sequence of amino acids.
- Amino acids are combined through *peptide bond*.



Proteins

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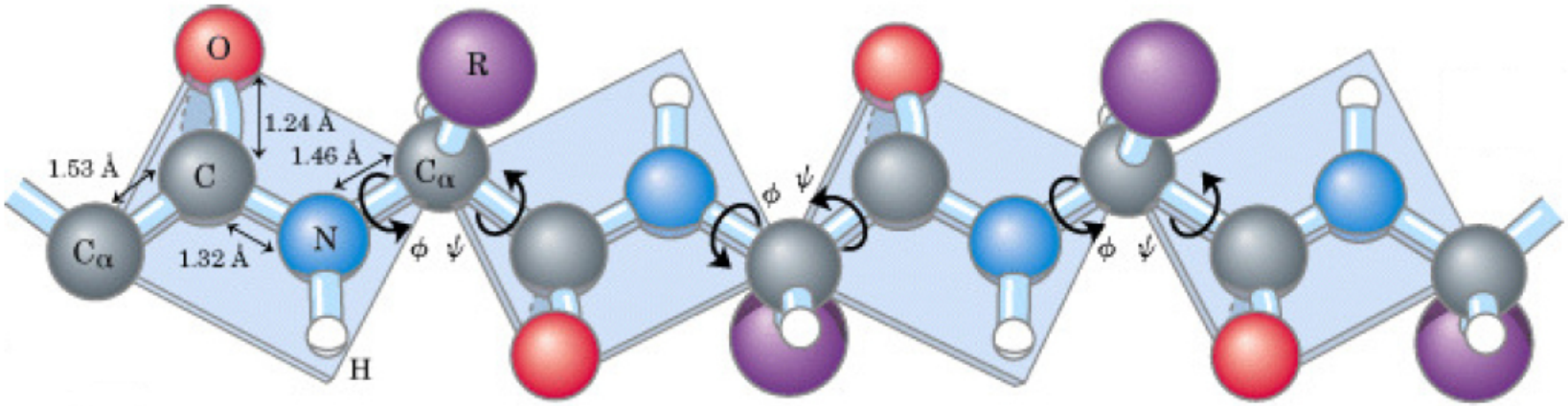
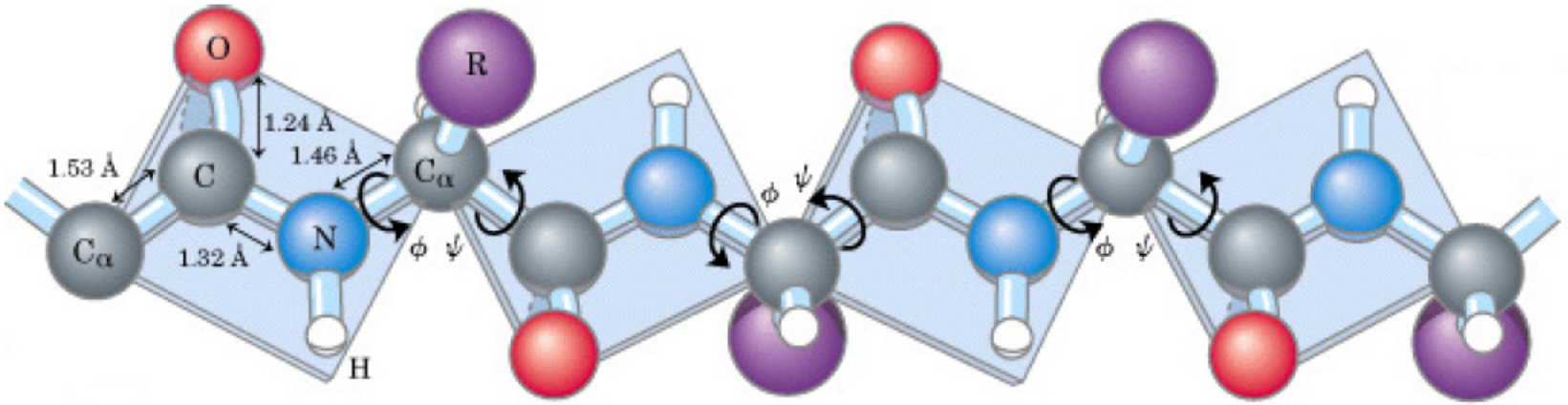


- The purple dots represent the *side chains*, that depend on the amino acid type
- Side chains have different shape, size, charge, polarity, etc.
- A side chain contains from 1 (Glycine) up to 18 (Tryptophan) atoms.

Proteins

Amino acids

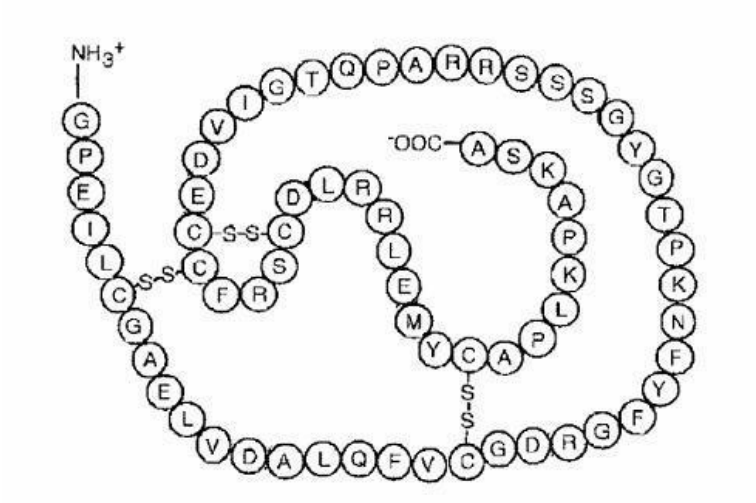


- There are 2 degrees of freedom (black arrows) for each amino acid
- A protein with n amino acids has $2n$ degrees of freedom (ignoring the side chains)
- Typical size range from 50 to 500 amino acids

Proteins

Primary sequence

Amino acid sequence:
GPEILCGAELVDALQFVCGDRGFYFNKPTGYGSSS
RRAPQTGIVDECCFRSCDLRRLEMYCAPLKPAKSA

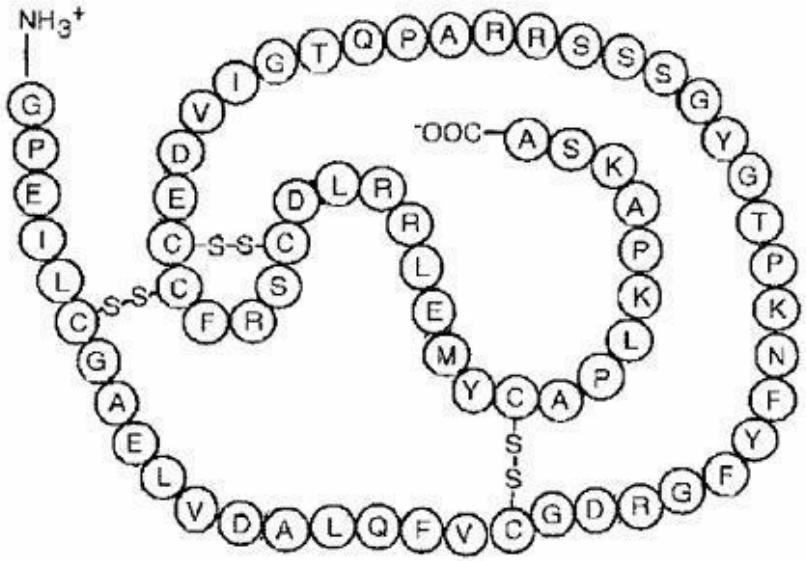


Primary sequence...

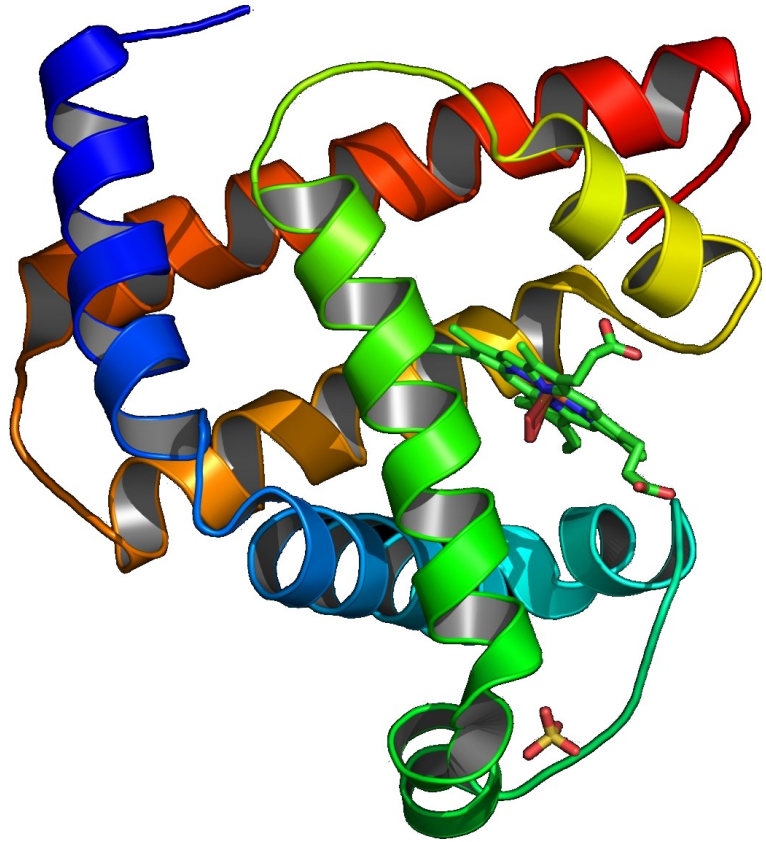
...embedded in the 3D space

Proteins

Tertiary structure



Primary sequence...



... tertiary structure

- Proteins FOLD spontaneously (when in their natural environment)

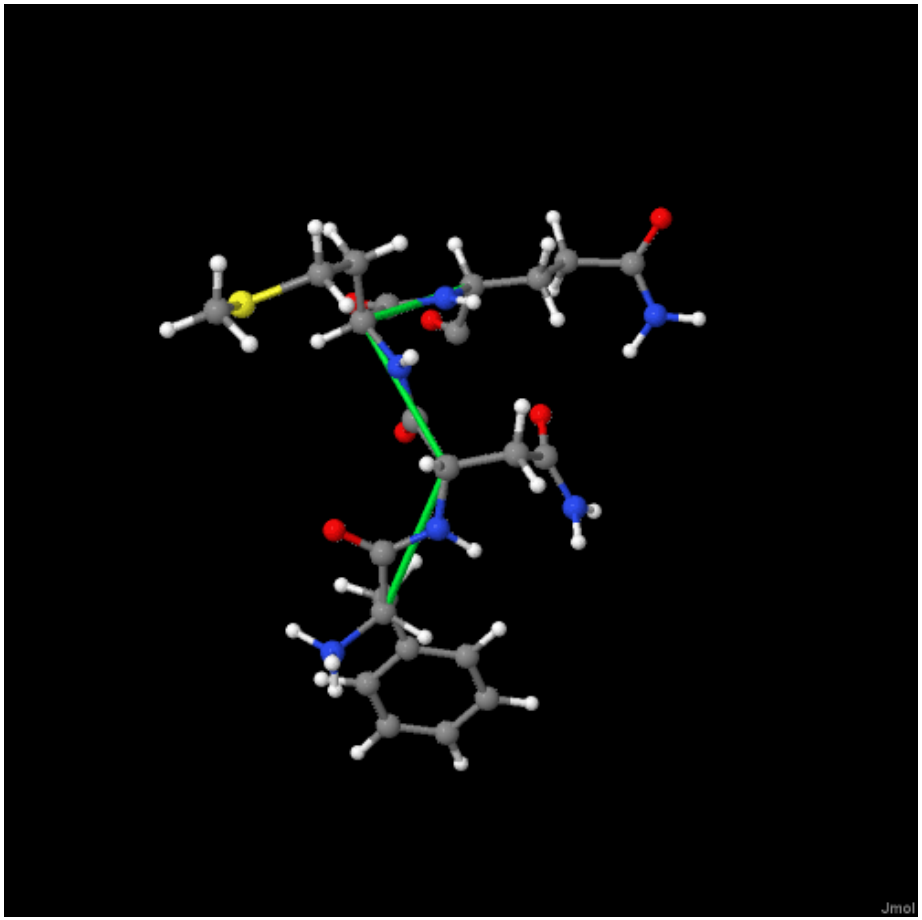
Proteins

Facts

- Folding is consistent $\Rightarrow$ same protein folds in the same way [Anfinsen74]
- Folding is fast $\Rightarrow$ 1μS – 1mS
- Driven by non covalent forces: electrostatic interactions, volume constraints, Hydrogen Bonding, van der Waals, Salt/disulfide Bridges
- Backbone is rigid

Proteins

Simplified structure

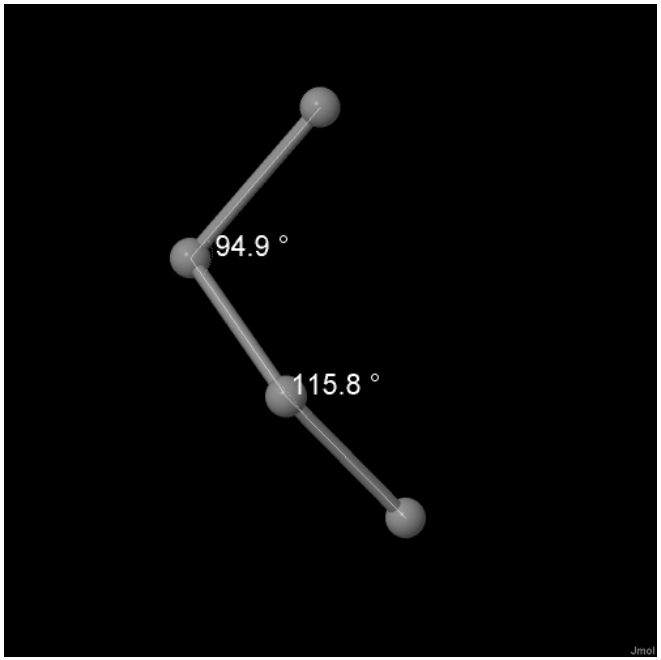


- The *backbone* (green) links consecutive amino acids
- Each amino acid can be identified by its carbon alpha (C_α)
- The distance between consecutive $C\alpha$ points is constant (3.81Å).

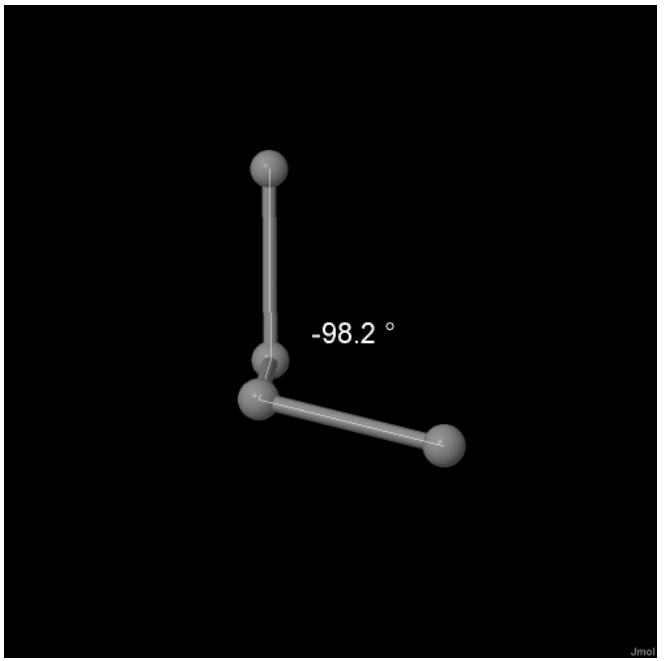
Proteins

Backbone

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



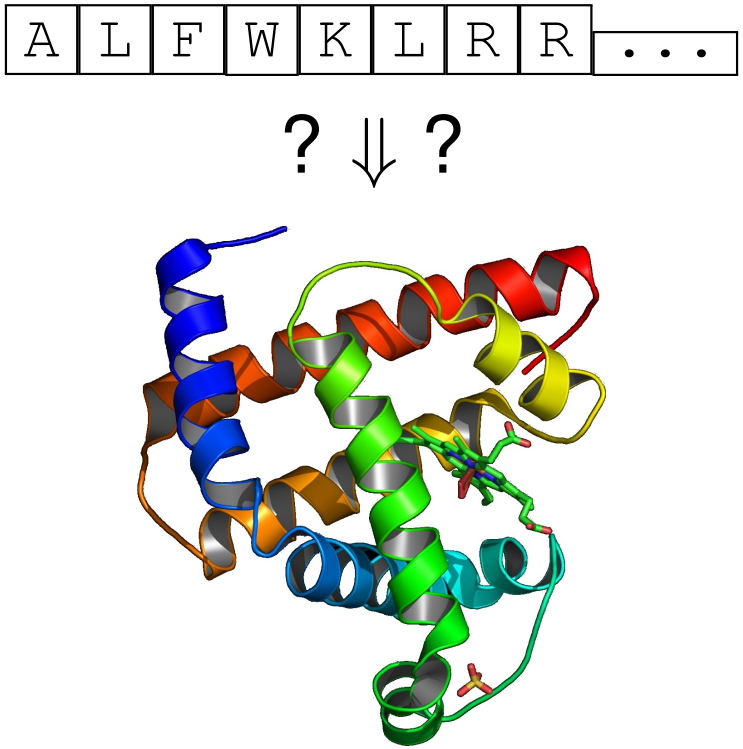
There are two bend angles



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)



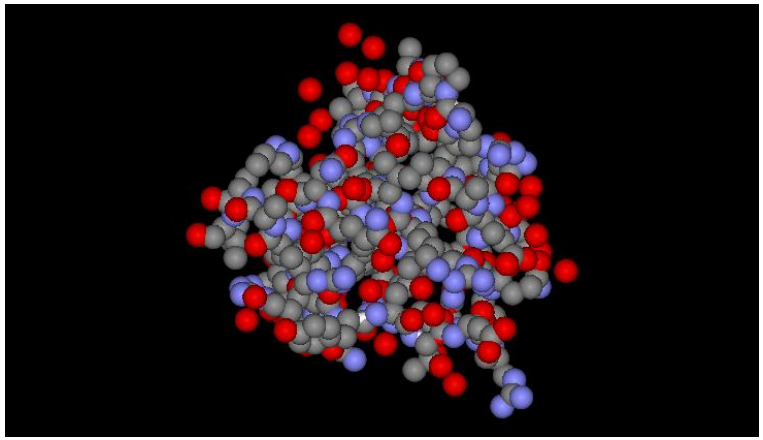
The structure prediction problem

... 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)

The protein structure prediction problem

- In this presentation we have two simplifications:
- Protein model: only one atom per amino acid, and only 2 classes of amino acids (Hydrophobic and Polar)



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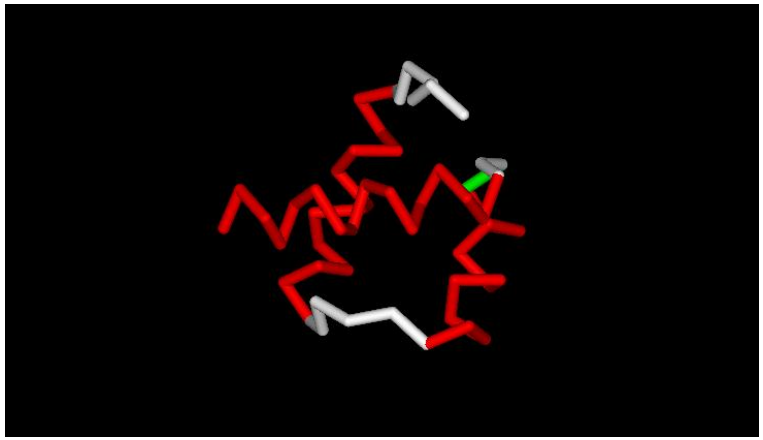
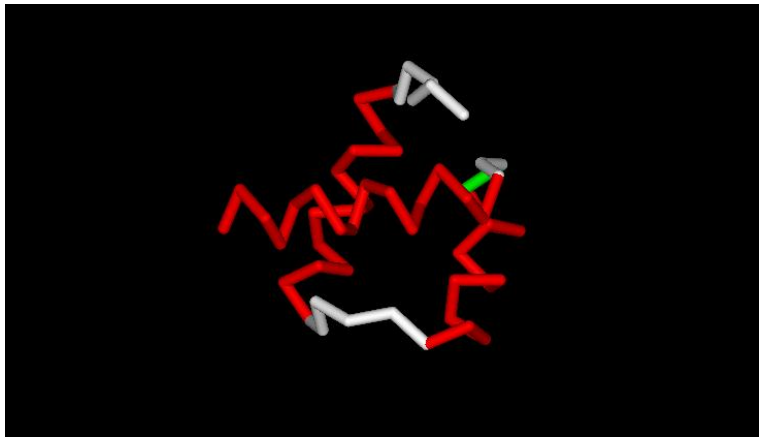
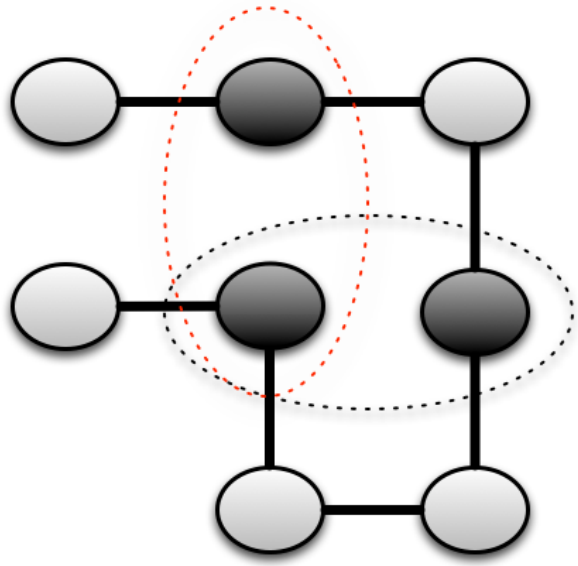


The protein structure prediction problem

- In this presentation we have two simplifications:
- Protein model: only one atom per amino acid, and only 2 classes of amino acids (Hydrophobic and Polar)
- Spatial model: 2D square lattice to represent amino acid positions

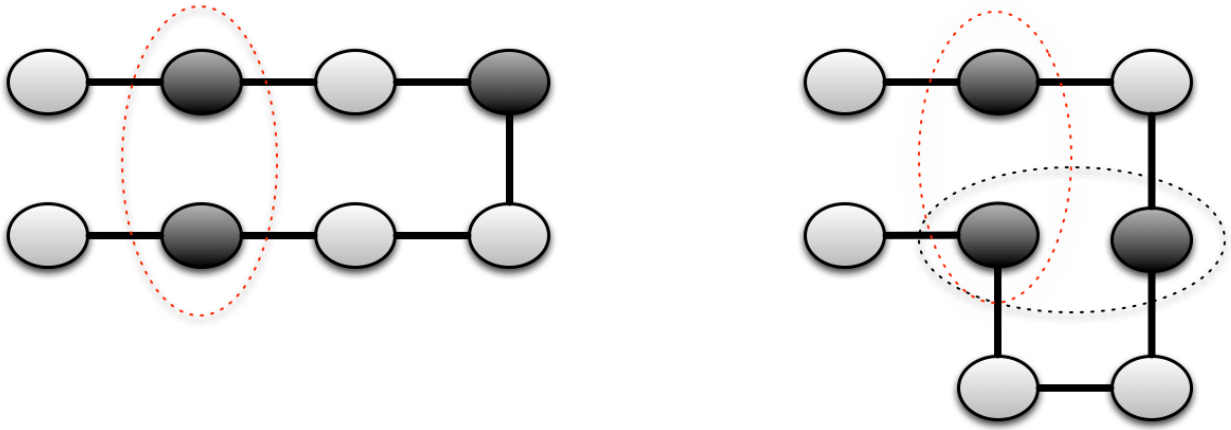




The protein structure prediction problem

Model

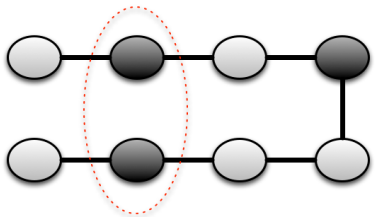
- The input is a list S of amino acids $S = s_1, \ldots, s_n$, where $s_i \in \{h, p\}$
- Each s_i is placed on a 2D grid with integer coordinates
- Any pair of two amino acids cannot occupy the same position
- If two amino acids are at distance 1, they are in contact

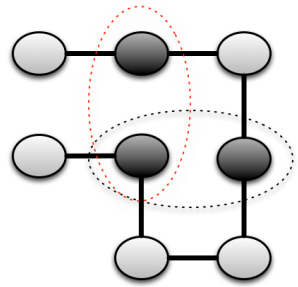


The protein structure prediction problem

Model

- Let: $\text{next}(\langle X_1, Y_1\rangle, \langle X_2, Y_2\rangle) \iff |X_1 - X_2| + |Y_1 - Y_2| = 1$.
- A folding is a function $\omega : \{1, \ldots, n\} \longrightarrow \mathbb{N}^2$ where:
  - For each $1 \leq i < n$: $\text{next}(\omega(i), \omega(i+1))$
  - For each $1 \leq i, j \leq n$: $(i \neq j \rightarrow \omega(i) \neq \omega(j))$





The protein structure prediction problem

Model

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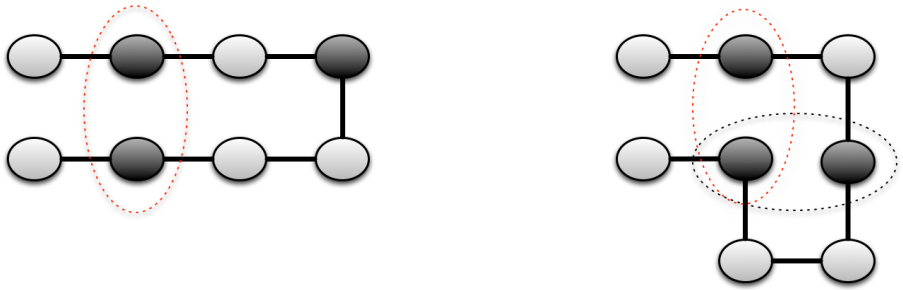
- A folding is a function $\omega : \{1, \ldots, n\} \longrightarrow \mathbb{N}^2$ where:
  - For each $1 \leq i < n$: $\text{next}(\omega(i), \omega(i+1))$
  - For each $1 \leq i, j \leq n$: $(i \neq j \rightarrow \omega(i) \neq \omega(j))$
- Find a folding that minimizes the (simplified) energy function:

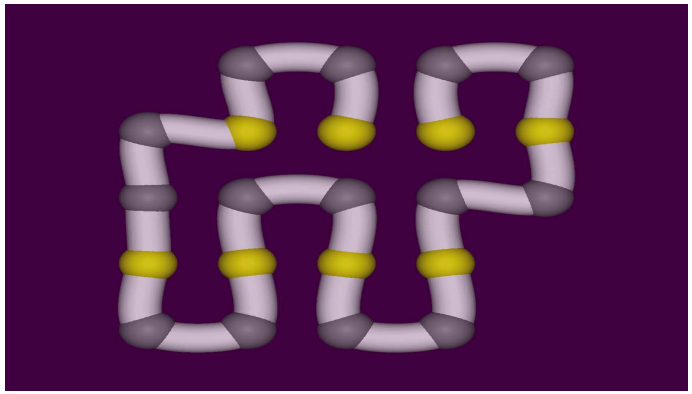
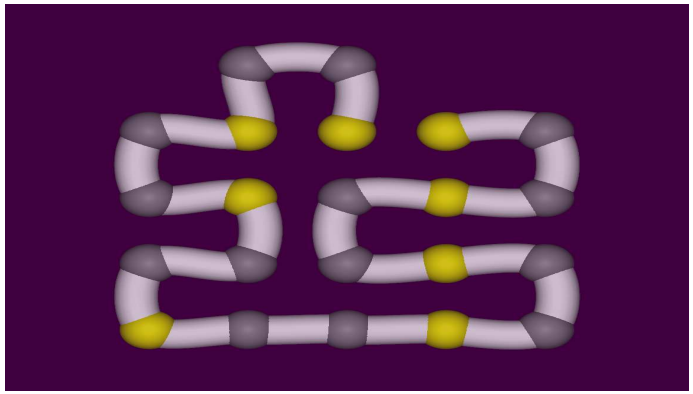
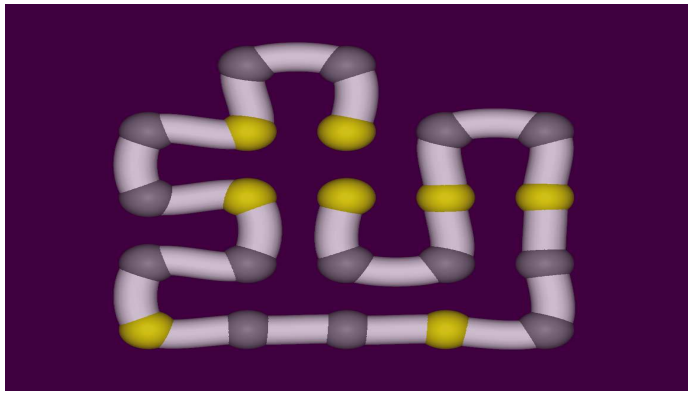
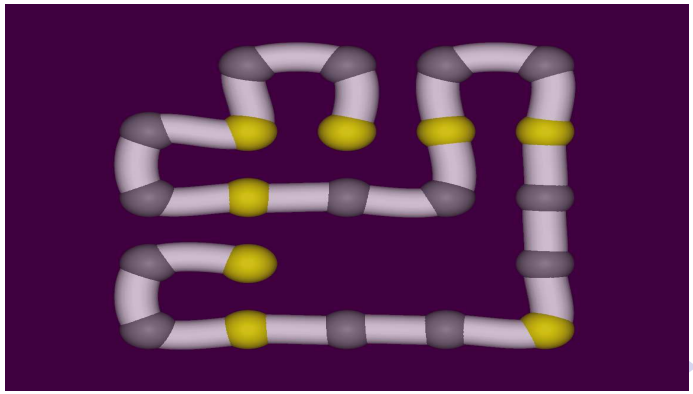
$$E(S, \omega) = \sum_{\substack{1 \leq i \leq n-2 \\ i+2 \leq j \leq n}} \text{Pot}(s_i, s_j) \cdot \text{next}(\omega(i), \omega(j))$$

where $\text{Pot}(p, p) = \text{Pot}(h, p) = \text{Pot}(p, h) = 0$ and $\text{Pot}(h, h) = -1$.



Model

- H: Yellow; P: Grey
- All foldings have energy -6

The protein structure prediction problem

Complexity

- Establishing whether there is a folding with energy $< k$ in the HP model and $\mathbb{N}^2$ space is NP-complete

  (Crescenzi, Goldman, Papadimitriou, Piccolboni, Yannakakis. On the Complexity of Protein Folding. Journal of Computational Biology 5(3): 423-466 (1998))

The protein structure prediction problem

ASP Model

- The positions can be restricted to $[1 \ldots 2n] \times [1 \ldots 2n]$
- The first two amino acids are set to $\omega(1) = \langle n, n \rangle$ and $\omega(2) = \langle n, n+1 \rangle$
- Sequence is represented by n facts:

```
prot(1,p).  prot(2,h).  prot(3,p).
prot(4,h).  prot(5,p).  prot(6,p).
prot(7,h).  prot(8,p).
```

- Each placement is stored as `sol(i,X,Y).`

ASP Encoding

```
(1)   size(N)          :- N = #count{ I:prot(I,J) }.
(2)   board(1..2*N)    :- size(N).
(3)   range(X,Y)       :- size(N), board(X), board(Y),
                          |X-N|+|Y-N| < N.
```

- Count the protein length and defines the board size
- `range` is loaded with all combinations from 1 to 2N

ASP Encoding

```
(1)  size(N)          :- N = #count{ I:prot(I,J) }.
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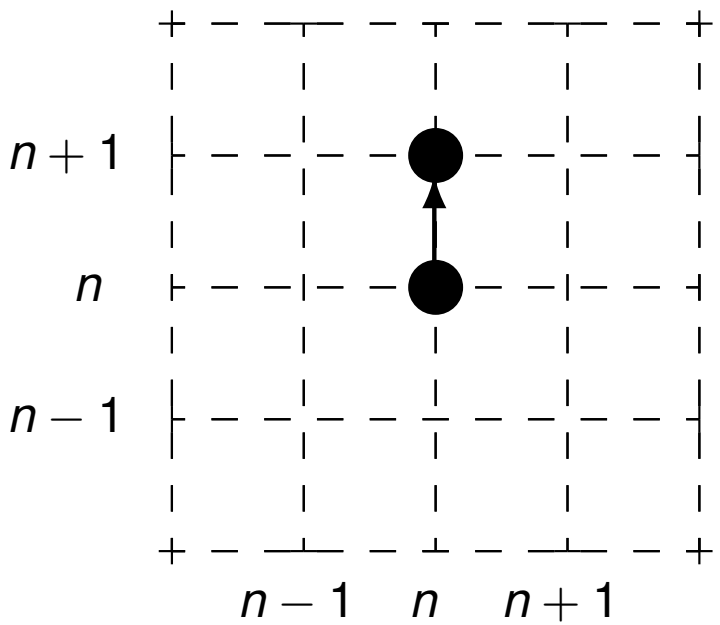
(3)  range(X,Y)       :- size(N), board(X), board(Y),
                         |X-N|+|Y-N| < N.

(4)  sol(1,N,N)       :- size(N).
(5)  sol(2,N,N+1)     :- size(N).
```

- Set the first two amino acids positions



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(5)   sol(2,N,N+1)    :- size(N).

(6)   1 { sol(I,X,Y) : range(X,Y) } 1 :- prot(I,Amino).
```

- Each amino acid *I* is associated to a unique position

ASP Encoding

```
(1)  size(N)          :- N = #count{ I:prot(I,J) }.
(2)  board(1..2*N)    :- size(N).
(3)  range(X,Y)       :- size(N), board(X), board(Y),
                         |X-N|+|Y-N| < N.

(4)   sol(1,N,N)      :- size(N).
(5)   sol(2,N,N+1)    :- size(N).

(6)   1 { sol(I,X,Y) : range(X,Y) } 1 :- prot(I,Amino).

(7)   :- prot(I1,A1), prot(I2,A2), I1<I2,
         sol(I1,X,Y), sol(I2,X,Y),  range(X,Y).
```

- Constraint: two distinct amino acids cannot overlap

ASP Encoding

```
(8)   :- prot(I1,A1), prot(I2,A2),  I2>1,
                I1==I2-1, not next(I1,I2).
(9)    next(I1,I2) :- prot(I1,A1), prot(I2,A2), I1<I2,
                sol(I1,X1,Y1), sol(I2,X2,Y2),
                range(X1,Y1), range(X2,Y2),
                1 == |X2-X1| + |Y2-Y1|.
```

- Constraint: two consecutive amino acids in sequence are `next` in space

ASP Encoding

```
(8)   :- prot(I1,A1), prot(I2,A2),  I2>1,
                I1==I2-1, not next(I1,I2).
(9)    next(I1,I2) :- prot(I1,A1), prot(I2,A2), I1<I2,
                sol(I1,X1,Y1), sol(I2,X2,Y2),
                range(X1,Y1), range(X2,Y2),
                1 == |X2-X1| + |Y2-Y1|.

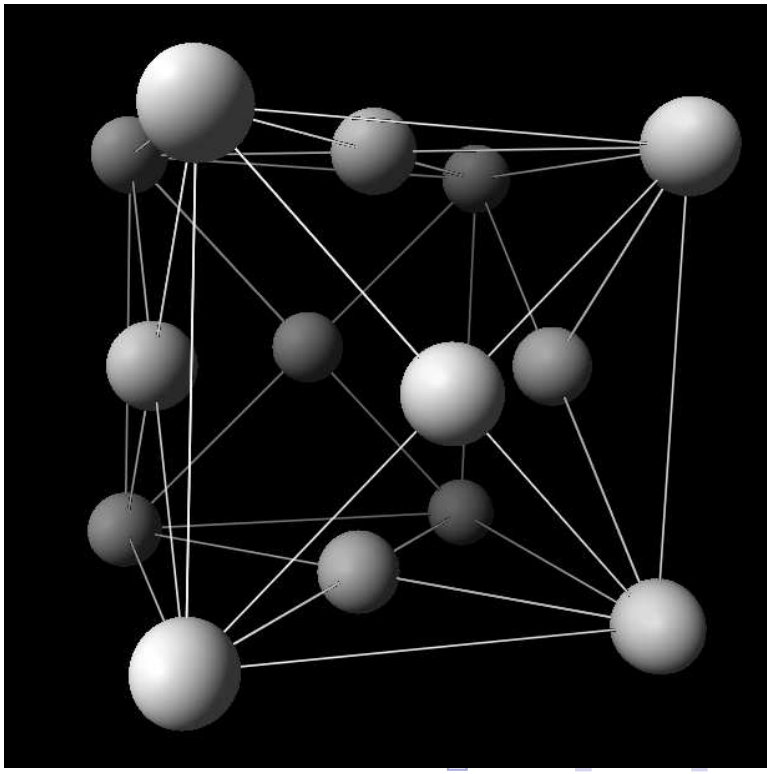
(10)  energy_pair(I1,I2) :- prot(I1,h), prot(I2,h),
                 next(I1,I2), |I1-I2|>2,
                 1==(I2-I1)  \ 2. %%% "\" is "mod"
(11)  energy(N) :- N = #count{(I1,I2):energy_pair(I1,I2)}.
(12)  #maximize { N:energy(N)}.
```

- If two amino acids of type *h* are `next`, count one contact (energy_pair)
- Optimization: at least one amino acid in sequence between the pair
- Optimization: only odd distances in space can contribute to a contact

Extensions

- Generalization to 3d cubic space is trivial.
- organization of the space have been explored
- The Face Centered Cube lattice models the discrete space in which the protein can fold.

- 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



Some References

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