Computational Biology

Lecture 21

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Protein folding

- The goal is to determine the three-dimensional structure of a protein based on its amino acid sequence
- Assumption: amino acid sequence completely and uniquely determines the folding
  - unfold a protein and then release it
  - it immediately folds back to the three-dimensional structure it had before, its "native" structure
- Protein secondary structures
  - α-helices
  - β-sheets
  - Neither helices nor sheets, called loops

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α-helix

- An α-helix is a simple helix having on average 10 residues (3 turns of the helix)
- Some helices can have as many as 40 residues
- Some amino acids appear more frequently on helices than other amino acids, not a strong enough fact to allow accurate prediction

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β-sheet

- A β-sheet consists of binding between several sections of the amino acid sequence
- Each participating section is called a β-strand and has generally 5 to 10 residues
- The strands become adjacent to each other forming a kind of twisted sheet
- Certain amino acids show a preference for being in a β-sheet, but again these preferences are not so positive to allow accurate prediction

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Loop

- A loop is a section of the sequence that connects the other two kinds of secondary structure
- Loops are not regular structures both in shape and size
- In general, loops are outside a folded protein, whereas the other structures form the protein **core**

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A folded protein

α-helix
β-sheet
loop

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Motifs and Domains

- A motif is a simple combination of a few secondary structure that appear in several different proteins
  - e.g. helix-loop-helix
- A motif might serve as a binding site to other molecules or may have no role at all.
- A domain is a more complex combination of secondary structures that have a very specific function; therefore, it contains a binding site (called active site)

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Protein folding

Given the amino acid sequence of a protein, determine:

- where exactly all of its α-helices, β-sheets, and loops are, and
- how they arrange themselves in motifs and domains

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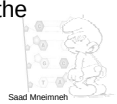
Greedy Approach

- Given enough chemical and physical information about each amino acid it should be possible to compute the free energy of a folding
- Enumerate all possible foldings, compute the free energy of each
- Choose the folding with the minimum free energy (assuming that such a folding ***is*** the protein's native structure)



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Feasibility of greedy

- Recall that proteins fold thanks in large to the angles ϕ and ψ between the carbon and the neighboring atoms
- These angles can assume only a few values independently of each other
- Therefore each residue can have a configuration given by a pair of values for ϕ and ψ
- Assume both ϕ and ψ can assume 3 values and the protein is 100 residues long, then we have to examine 9^{100} foldings!

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Other problems with greedy

- No agreement on how to compute the free energy of a folding, too many factors to consider
  - Shape
  - Size
  - Polarity of molecules
  - Strength of interactions of molecules, etc…
- Because of all these difficulties, other techniques have been developed, e.g. Protein Threading

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Similarity of protein sequences

- An early method for secondary structure prediction was based on the idea that similar sequences should have similar structures
  - folding of A known
  - B's sequence is similar to A's sequence
  - Folding of B is similar to A's

  Not generally true!
- Similar proteins at the sequence level may have different secondary structures
- On the other hand, certain proteins that are very different at the sequence level are structurally related: different loops, similar cores
- Protein threading: fit a known structure to a sequence

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Protein threading

- We are given
  - A protein sequence A with n amino acids a_i
  - A core structural model C, with m core segments, we have:
    - The length c_i of each core segment
    - Core segments i and i+1 are connected by loop for which we know the maximum l_i^{max} and minimum l_i^{min} lengths
    - Properties of each amino acid in C
  - A score function f to evaluate a threading
- We want to find a best scoring set $T = \{t_1, \ldots, t_m\}$ of integers such that each t_i indicates what amino acid from A occupies the first position from core segment i

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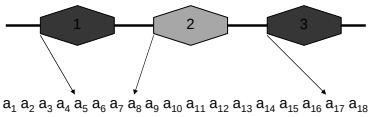
Illustration



$T = \{5, 8, 17\}$

The threading is an alignment between the sequence and the core structural model

If we ignore interactions between amino acids of different structures, while allowing variable-length loop regions, the problem can be solved by a standard dynamic programming technique

If we allow pairwise interactions, the problem becomes NP-hard

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Approach

- We will allow pairwise interactions of amino acids
- We will solve the problem exactly with a standard technique used for handling NP-hard problems
- This technique is known as branch-and-bound

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Branch-and-Bound

- Assume we want to find the maximum $f(s)$ among many solutions s in the solution space
- First, it should be possible to separate the solution space into subspaces according to some constraints [branch]
  - e.g. given a solution space X we could partition it into X_1 (all solutions that have a certain property) and X_2 (all solutions that do not)
- Second, for every partition X obtain an upper bound on the value of $f(s)$ for every solution $s \in X$ [bound]
- Assume we have $f(s)$ for a given s. Now consider a subset X of the solution space with an upper bound u. If $f(s) > u$, then we can discard X.

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Some considerations

- The upper bound should be as close to the actual function value as possible, so that we can find the maximum faster than with a weaker upper bound
- The upper bound should also be efficient to compute
- Even if we speedup the process by discarding some subsets of the solution space, the worst case running time is still exponential

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Finding the solution space

Every solution must satisfy:

$$1 + \Sigma_{j<i}(c_j + l_j^{min}) \leq t_i \leq n+1 - \Sigma_{j \geq i}(c_j + l_j^{min})$$

$$t_i + c_i + l_i^{min} \leq t_{i+1} \leq t_i + c_i + l_i^{max}$$

This implies that each $t_i \in [b_i, e_i]$ in every solution

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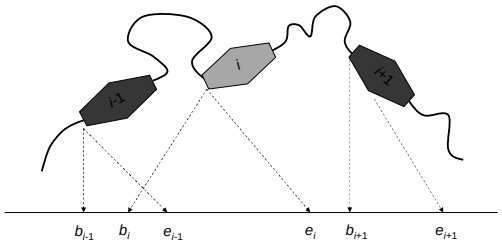
Illustration



A set of solutions is given by a collection of intervals, one for each of the m t_i's.

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Branch

Given a set of solutions:

- choose a segment, say i
- choose a position u_i inside the interval $[b_i, e_i]$
- Split the set into three sets in which the intervals for t_i will be:
  - $[b_i, u_{i-1}]$
  - $[u_{i+1}, e_i]$
  - $[u_i]$

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Bound

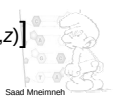
- Given a solution s, $f(s)$ can be expressed as:

$$f(s) = \underbrace{\Sigma_i g_1(i, t_i)}_{\text{score for each segment}} + \underbrace{\Sigma_i \Sigma_{j>i} g_2(i,j,t_i,t_j)}_{\text{score for interactions}}$$

- Given a set X of solutions, a simple upper bound is:

$$\max_{s \in X} f(s) = \max_{s \in X} \Sigma_i \left[g_1(i, t_i) + \Sigma_{j>i} g_2(i,j,t_i,t_j) \right]$$

$$\leq \Sigma_i \left[\max_{bi \leq x \leq ei} g_1(i, x) + \Sigma_{j>i} \max_{bi \leq y,z \leq ei} g_2(i,j,y,z) \right]$$



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Algorithm

X ← all possible threadings
ub ← upper bound for X

use a max priority queue with keys being the upper bounds
ENQUEUE(Q, (ub, X))

```
while (true)
do      (ub, X) ← DEQUEUE(Q)
        if |X| = 1                      [the only remaining threading in the set]
        then    return X
        else    split(X)
                for each new subset Xi from X
                do      ubi ← upper bound for Xi
                        ENQUEUE(Q, (ubi, Xi))
```

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