The Threading Problem

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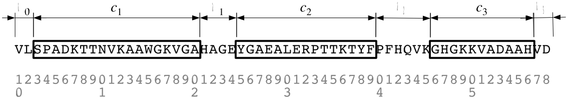
May 30, 2011

Predicting Protein Tertiary Structures

- approx. 650–10000 different tertiary structures
- $\rightsquigarrow$ even sequences no obvious sequence similarity can fold into similar tertiary structures
- Idea of threading: utilize a known tertiary structure and “thread” the unknown structure into it
- Branch-and-Bound-Algorithm by Lathrop and Smith (1996).

Threading-Models

- Idea: Essential for tertiary structures are often structurally highly conserved, e.g. those parts that fold into α-helices or β-strands
- Transitions between these conserved parts are less relevant.
- Secondary structure of a sequnece s with m componenets (α-Helices, β-Strands) as abstract model:



Threading-Models

- Length of transitions between sequence parts (λ_i) underly certain conditions:

$$\ell_i \leq \lambda_i \leq L_i.$$

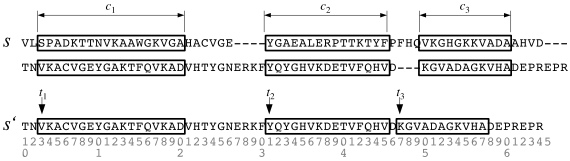
Definition

A Core Model M is a 5-tupel $M = (m, c, \lambda, \ell, L)$, where

- $m \equiv$ number of sec. struct. elements
- $c = (c_1, \ldots, c_m) \equiv$ length of the segments
- $\lambda = (\lambda_0, \ldots, \lambda_m) \equiv$ length of the transitions
- $\ell = (\ell_0, \ldots, \ell_m) \equiv$ lower
- $L = (L_0, \ldots, L_m) \equiv$ upper bounds for transition lengths

Threading a sequence into a model

- structure s with model M; thread sequence s' into M.
- Goal of threading: sec. struct. elements are mapped onto subsequences of same length in s' length of transitions may vary (within bounds)
- threading representable as a sequence $t_1, \ldots, t_m$



Formal Definition of a Threading

Definition

Let s' be sequence of length n' and M a core-Model. A sequence $t = (t_1, \dots, t_m)$ is called a threading of s' through M, if

(T1) $1 + \ell_0 \leq t_1 \leq 1 + L_0$

(T2) $t_i + c_i + \ell_i \leq t_{i+1} \leq t_i + c_i + L_i$ for $1 < i < m$ and

(T3) $t_m + c_m + \ell_m \leq n' + 1 \leq t_m + c_m + L_m$

- In general, given model M and sequence s, there are many threadings satisfying (T1)–(T3).
- Which of those is best? $\rightsquigarrow$ scoring-function

Scoring-Functions: Structure

- Scoring function f has two indgredients:
  - How well "matches" a segment of s' into a segment C_i?
    $\rightsquigarrow g_1(i, t_i)$
  - Extendable to higher-order interactions e.g. of triplets of elements
    $g_3(i, j, k, t_i, t_j, t_k)$ ...
- g_1, g_2 are based on knowledge-based approaches
- g_2 e.g. through pairwise potentials $\rightsquigarrow$ Sippl (1990/1995)

Scoring-functions: interaction graphs

- Segments C_i and C_j from model M do not interact $\rightsquigarrow g_2(i, j, k, k') = 0$ for all k, k'
- interaction graph: Graph G_I with vertices $V_I = \{1, \ldots, m\}$ and nodes
$$E_I = \{(i,j) \mid \exists k, k' \colon g_2(i, j, k, k') \neq 0\}.$$
- Scoring-function for $t = (t_1, \ldots, t_m)$ formally:
$$f(t) = \sum_{i \in [1:m]} g_1(i, t_i) + \sum_{(i,j) \in E_I} g_2(i, j, t_i, t_j)$$

Threading as Optimization problem

- Given Core-Model M for sequence s and sequence s' with unknown tertiary structure
- Wanted: $\min_t f(t)$
- Computing $\min_t f(t)$ is (MAX-S)NP-hard: Akutsu/Miyano (1999)
  $\rightsquigarrow$ Backtracking-algorithm ("brute-force")
  $\rightsquigarrow$ Branch-and-Bound-algorithm by Lathrop and Smith (1996)
- Without g_2 solvable in polynomial time (dynamic programming)

Relative Threading

- Goal: "Address" all possible threadings $T_M(s')$ for sequence s' into a model M for traversing $T_M(s')$ systematically
- Let $t = (t_1, \ldots, t_m)$ a threading of s' through M.
- Relative threading $t' = (t'_1, \ldots, t'_m)$ to t is defined as

$$t'_i := t_i - \sum_{j<i} (c_i + \ell_i).$$

Scaffold for B-&-B-Algorithms

```
branch-and-bound(X)
    S.push(X);
    x_opt := ∞;
    while (!S.empty())
       Y = S.pop();
       if (B(Y) < x_opt) then
          if (Y == {t'}) then
             if (f(t') < x_opt) then x_opt := f(t');
          else
             split Y into Y_L and Y_R
             S.push(Y_L);
             S.push(Y_R);
end.
```

Threading using Branch-and-Bound

- Branch-and-Bound-algorithm traverses a spanning tree of sets of solutions
- Cutting-bounds allow to drop parts of the solution tree
- We need:
  - Sets of threadings that can be decomposed into parts
  - Lower bounds for sets of threadings that can be easily computed

Threading-Sets

- Define intervals $[b_i : d_i]$ (for $1 \leq i \leq m$)
- $\leadsto$ vectors $b = (b_1, \ldots, b_m)$ and $d = (d_1, \ldots, d_m)$.
- Yields set

  $$T_M(b, d) = \{t' = (t'_1, \ldots, t'_m) \mid b_i \leq t'_i \leq d_i, \quad t' \text{ is rel. threading}\}$$

  of (relative) threadings.
- $T_M(\mathbf{1}, \mathbf{n}') = T_M(s')$

Splitting Threading sets ("Branch")

- Choose i such that $b_i < d_i$.
- Divide Intervals $[b_i : d_i]$ into $[b_i : v]$ and $[v + 1 : d_i]$
- Define analogous vectors b', d' and b'', d''
- $T_L := T_M(b', d')$ and $T_R := T_M(b'', d'')$ yield split of $T_M(b, d)$.

Lower Bounds for Threading-Sets

- Wanted: Lower bound $B_M(b, d)$ with properties
  - $B_M(b, d) \leq \min_{t' \in T_M(b,d)} f(t')$
  - $B_M(b, d)$ should be computable fast
- Choose

$$\begin{aligned} B(b, d) \quad := \quad & \sum\nolimits_i \big((\min_{x \in [b_i : d_i]} g_1'(i, x) \\ & + \sum\nolimits_{j<i} \min_{x,y} g_2(i, j, x, y)) \end{aligned}$$

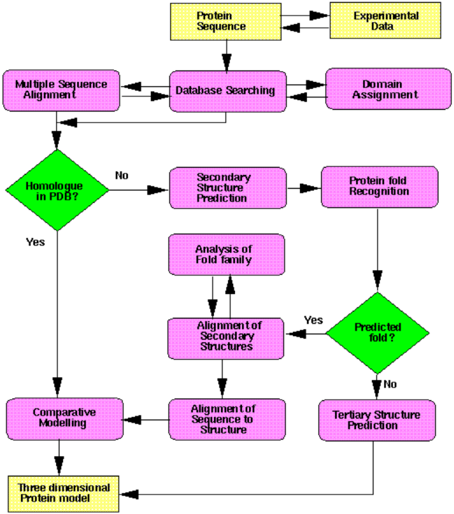
B-&-B-Threading-algorithm

```
thread(s, M)
    S.push(1, n);
    x_opt := ∞;
    while (!S.empty())
        (b, d) = S.pop();
        if (B(b, d) < x_opt) then
            if (T_M(b, d) == {t'}) then
                if (f(t') < x_opt) then x_opt := f(t');
            else
                split (b, d) into (b', d') and (b'', d'')
                if (T_M(b', d') ≠ ∅) then
                    S.push((b', d'));
                if (T_M(b'', d'') ≠ ∅) then
                    S.push((b'', d''));
end
```

How complex is Protein-Threading?

- B-&-B-algorithm is faster than naive Bachtracking, but still exponentiel worst-case running time
- threading-Problem is MAX-SNP-complete
- Means: we won't even get good approximate solutions in polynomial time unless P$\neq$NP!
- How "complex" is the interaction graph?
- Diverse successful structure predictions (CASP)

Structure Prediction in Practice



Literature

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