k-Local Folding

A Local Alignment Approach to RNA folding

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RNA Folding

RNA consists of the four base pairs Adenine (A), Guanine (G) , Cytosine (C) and Uracil (U). These base pairs of RNA pair in a complementary fashion: Adenine to Uracil (A – U) and Cytosine to Guanine (C – G).

Unlike DNA for which we are concerned with optimally aligning two strands, for RNA we are concerned with how the strand folds with itself.

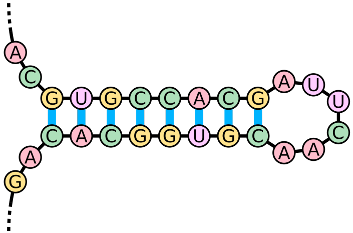


Figure: Source: http://rosalind.info/problems/pmch/

RNA Folding

There are several frameworks with which we can model RNA folding. We will use the Energy Minimization Model.

In this model, matches are scored as +1 and non-matches as 0. This lends itself to a dynamic programming algorithm: Nussinov's algorithm which we will call Nussinov.

RNA Folding

Let $r = r_1, \ldots, r_n$ be a strand of RNA, where $r_i \in \{\mathtt{A}, \mathtt{C}, \mathtt{G}, \mathtt{U}\}$ and let $S(i,j)$ denote the optimal score of folding the subsequence $s_i, s_{i+1} \ldots s_j \subset s$. Then,

$$S(i,j) = \max \begin{cases} S(i+1, j-1) + 1, & \text{if } i,j \text{ base pair} \\ S(i+1, j), & \\ S(i, j-1), & \\ \max\limits_{i<k<j} \{S(i,k) + S(k+1, j)\}, & \text{bifurcation.} \end{cases}$$

It's clear that the runtime is $O(n^3)$.

k-Local Folding

Nussinov returns the mathematically optimal alignment under the energy minimization model. Therefore, any new approach cannot hope to beat the scores, but only improve the running time.

Idea: Subsequences of an RNA strand which are (near) palindromes of each other are likely to be a good match. Pair these regions and pass the leftover segments to Nussinov.

k-Local Folding

Formal Goal: We propose a heuristic based approach to speed up Nussinov with a fast preprocessing step.

Formally, we define an algorithm k-Local Folding which takes as input an RNA strand r and a parameter k, runs a local alignment algorithm on the strand to find k high scoring — and disjoint — palindromic regions of r. It then passes the remaining unpaired regions to Nussinov to be folded as usual.

k-Local Folding

```
procedure k-Local Folding($(r, k)$)
    Initialize stack $S \leftarrow r$
    while The number of local alignments found is $\leq k$ and $S$ not empty do
        $s \leftarrow \mathrm{pop}(S)$
        Let $\overline{s}$ be the reverse of $s$
        Call Local Alignment on $s$ and $\overline{s}$.
        if Local alignment found then
            Remove the aligned regions from $s$
            Push all unmatched regions of $s$ back onto stack
        end if
    end while
    Call Nussinov on all unmatched regions of $r$.
end procedure
```

k-Local Folding

example

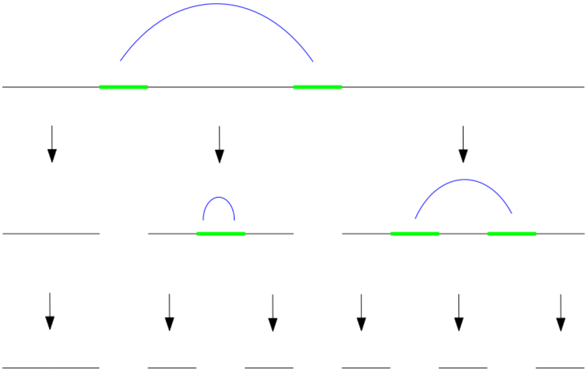


Figure: A strand of RNA undergoing multiple local alignments on successive subsequences. The unmatched regions at the bottom will be passed into Nussinov

k-Local Folding: Runtime Analysis

Fix an RNA strand r with length n.

Lemma (1)

Let $\mathscr{A}$ be the set of local alignments found. Finding k disjoint local alignments of r takes time $O(n^2k)$.

Lemma (2)

k-Local Folding *runs in time*

$$O\left(\left(n - \sum_{A \in \mathscr{A}} \ell_A\right)^3 + n^2k\right),$$

where ℓ_A is the length of an alignment $A \in \mathscr{A}$.

Proof of Lemma 1.

We can view the progress of the algorithm as a ternary tree: amortized across each level we perform local alignment on a sequence of size $n - \sum_{A \in \mathscr{A}} \ell_A$. Local alignment takes time squared in the size of the input. Since the tree in the worst case has depth k, the result follows. ◀

Proof of Lemma 2.

Running Nussinov takes cubic time in the size of the input. k-Local Folding first finds k disjoint alignments, then runs Nussinov on the remaining unmatched regions, which have total length $n - \sum_{A \in \mathscr{A}} \ell_A$. The result follows by applying lemma 1. ◀

How big is the tree?

remark

It's a very unlikely case that the depth of the tree is k: it will more likely be $\log(k)$. Therefore, an average case analysis will yield that k-Local Folding runs in time

$$O\left(\left(n-\sum_{A\in\mathscr{A}}\ell_A\right)^3+n^2\log(k)\right).$$

k-Local Folding: Runtime Analysis

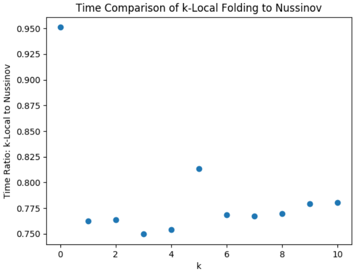
We remark that since $\sum_{A\in\ell_A}\ell_A^3 \in O(n^3)$, $O((n-\sum_{A\in\mathscr{A}}\ell_A)^3) = O(n^3)$ so there is no asymptotic difference between k-Local Folding and Nussinov. However, our hypothesis was that there may a difference in the run times in practice.

example

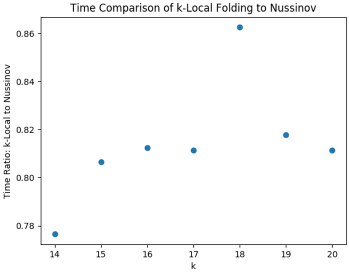
In the extreme case, suppose r is a perfect palindrome. Then we do $O(n^2)$ work instead of $O(n^3)$, so we gain a factor of n.

Results: Runtimes

Each trial was run with 20 random sequences, and the results were taken as the average of those trials. The following data is for 16S Ribosomal Subunit RNA.



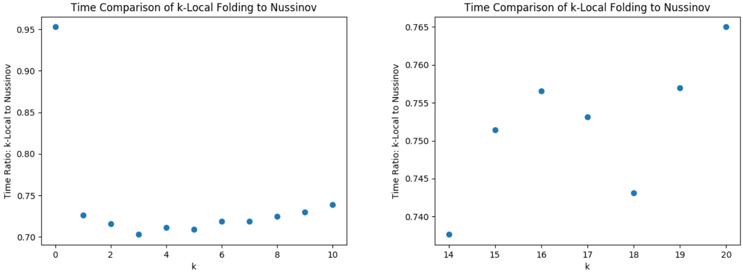
(a) $k \in \{0, 1, \ldots, 10\}$



(b) $k \in \{14, \ldots, 20\}$

Results: Runtimes

Ciliate Telomerase RNA data.

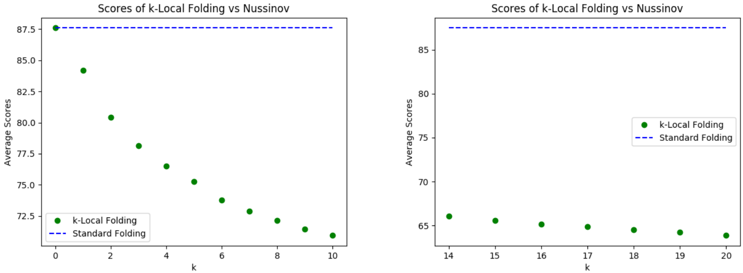


(c) $k \in \{0, \ldots, 10\}$

(d) $k \in \{14, \ldots, 20\}$

Results: Scores

16s Ribosomal Subunit RNA

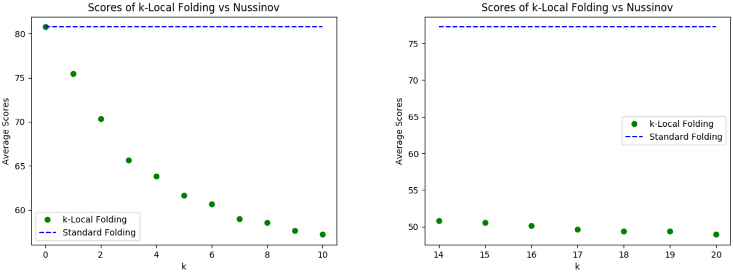


(e) $k \in \{0, \ldots, 10\}$

(f) $k \in \{14, \ldots, 20\}$

Results: Runtimes

Ciliate Telomerase RNA data.



(g) $k \in \{0, \ldots, 10\}$ (h) $k \in \{14, \ldots, 20\}$

Concluding Remarks

1. Results look fairly invariant under different data.
2. k-Local Folding may be best used as a preprocessing step for traditonal RNA folding algorithms for regions which are likely hairpinned.

Extensions and Further Research

1. Can we speed up k-Local Folding by being smarter with our data structures? Tempting to only do local alignment once ...
2. Modify k-Local Folding to report possible pseudoknots
3. Implement k-Local Folding to use the Four Russians speedup of Nussinov.
4. Probabilistic (Viterbi-like) Approach
5. Providing better bounds on the runtime based on the expected number of palindromic like regions found on an alignment.

The code and slides can be found at `https://github.com/bchugg/bwt`.