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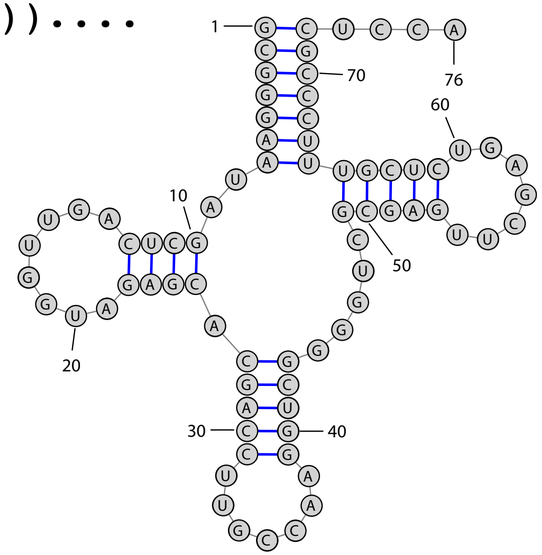
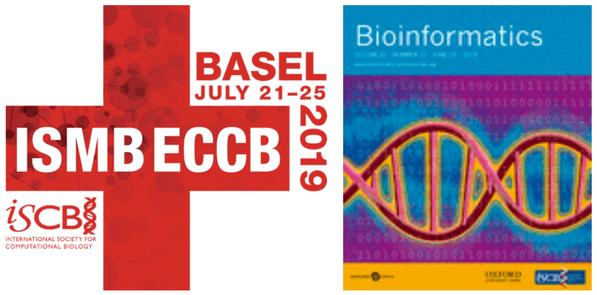


Liang Huang *

Oregon State University & Baidu Research USA

Joint work with He Zhang **, Dezhong Deng **, Kai Zhao, Kaibo Liu, David Hendrix and David Mathews



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Oregon State University

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University of Rochester

* *corresponding author* ** *equal contribution*

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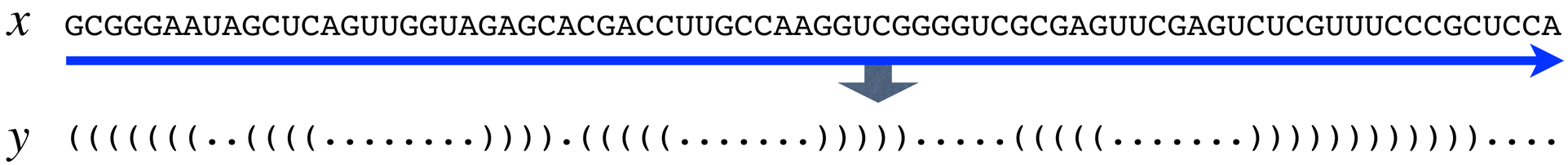

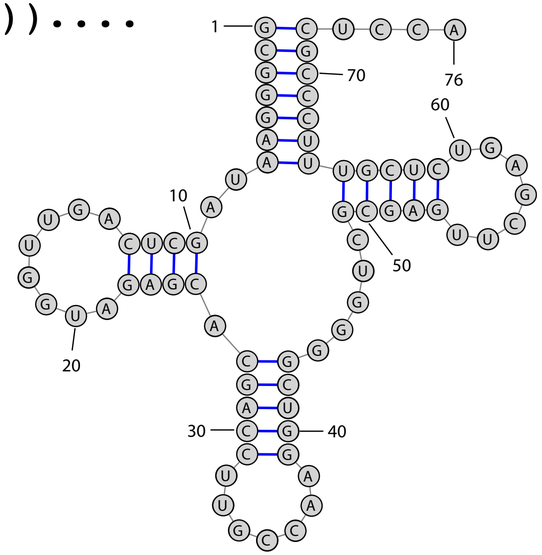

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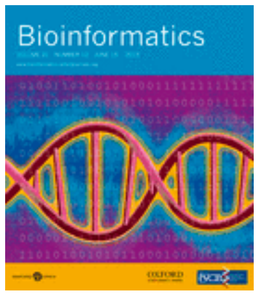

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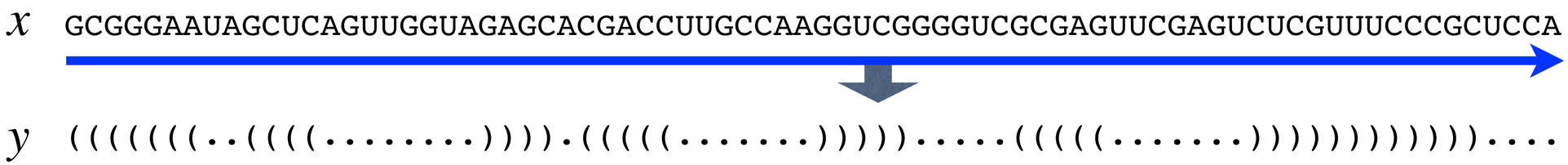

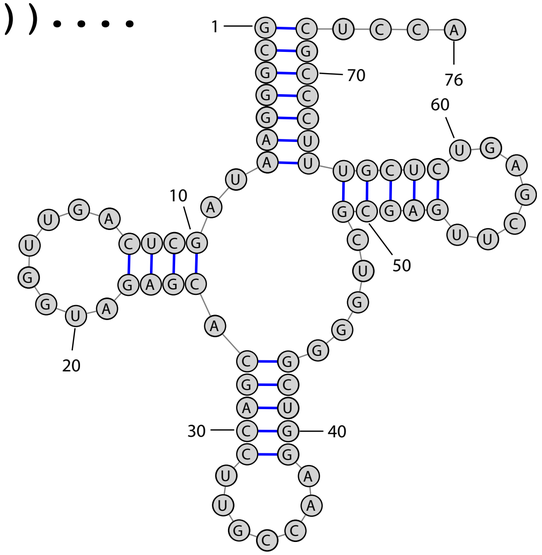

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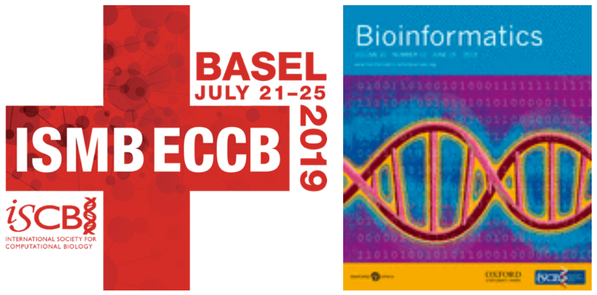
first $O(n)$ (approx.) RNA folding algorithm & server (linearfold.org) with even higher accuracy than $O(n^3)$ algorithms



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RNA Secondary Structure Prediction

allowed pairs: G-C A-U G-U

assume no crossing pairs
(no pseudoknots)

example: transfer RNA (tRNA)

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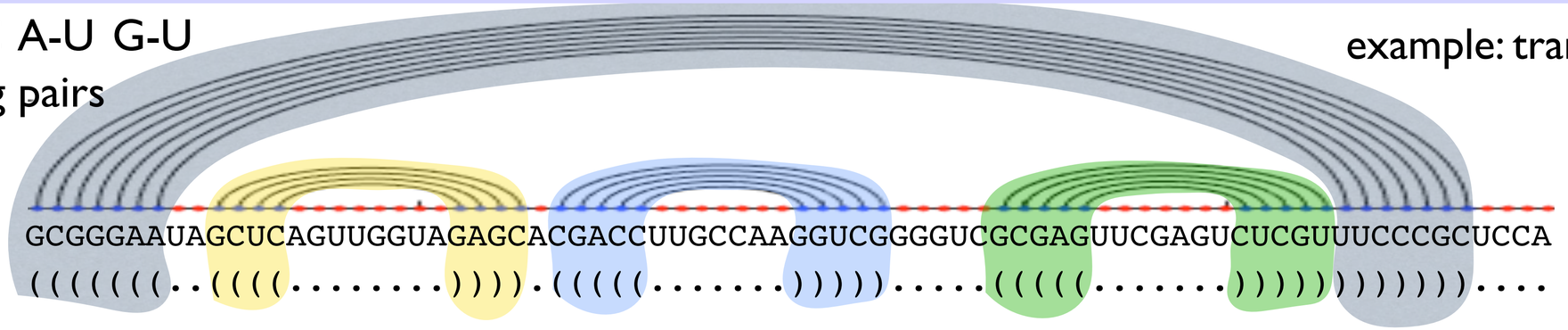

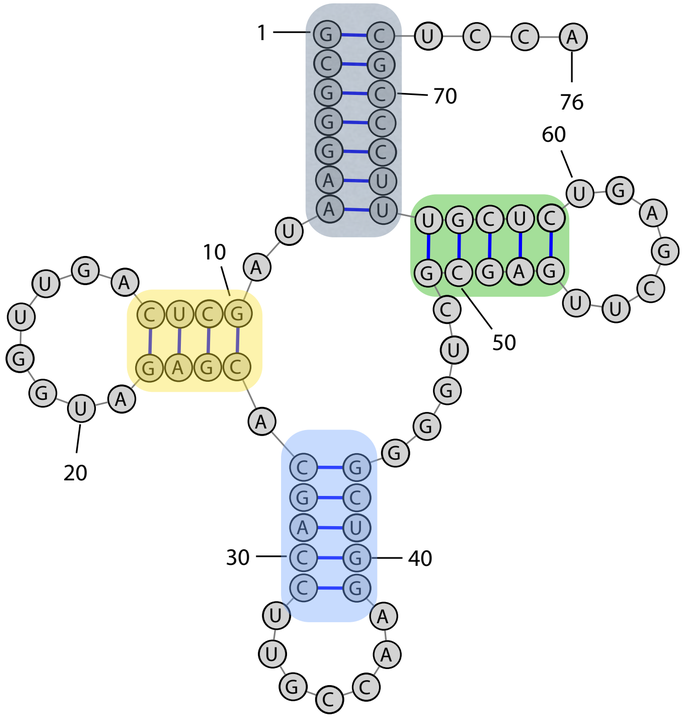

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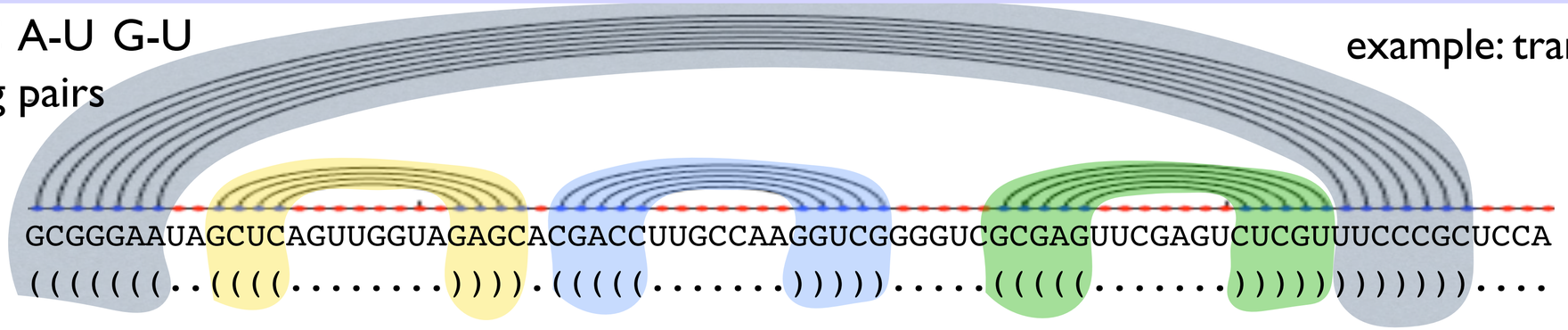

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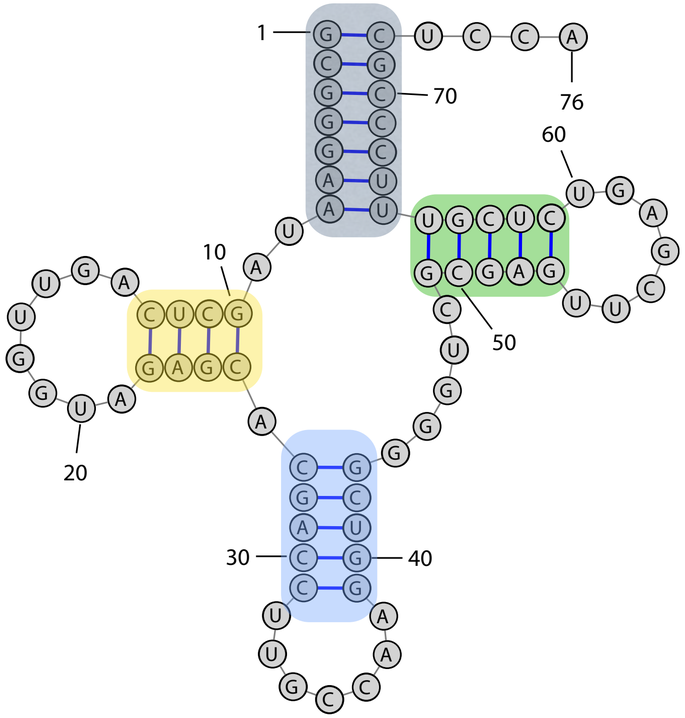

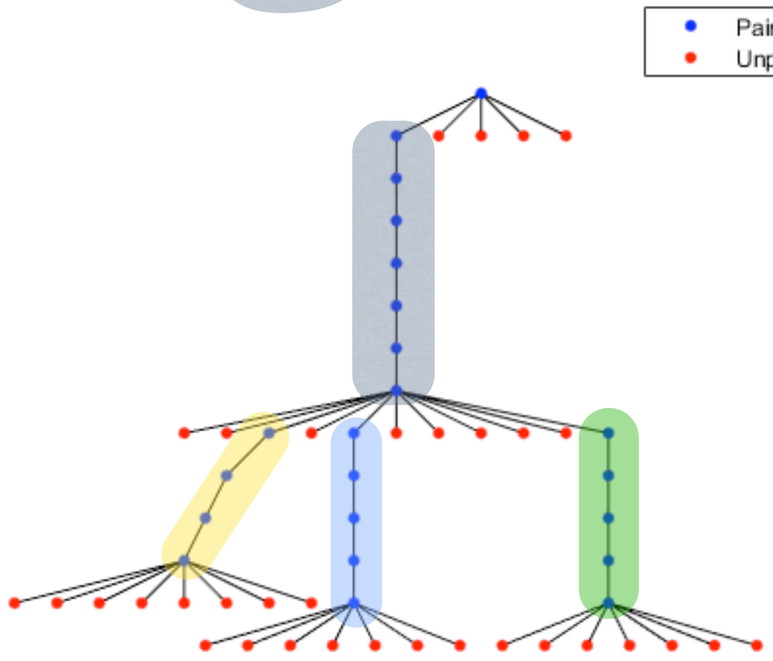

parse tree

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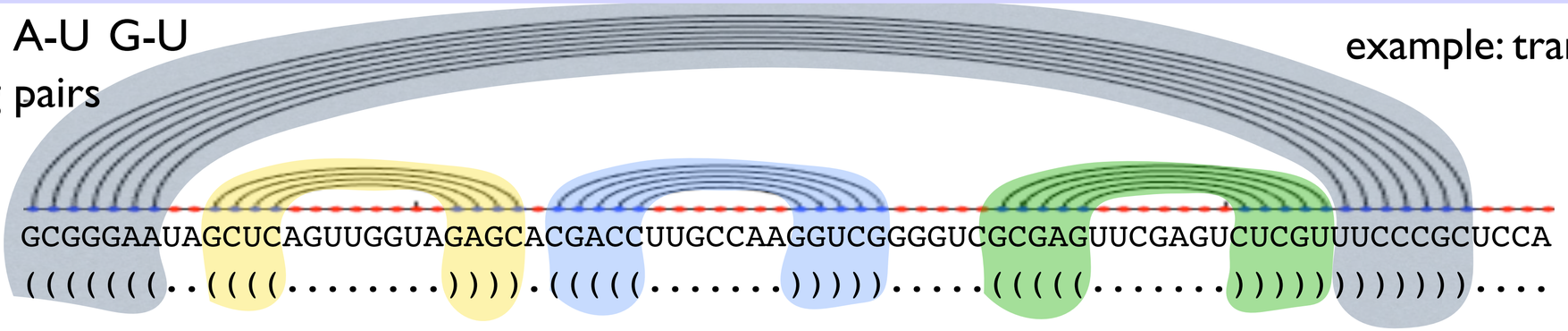

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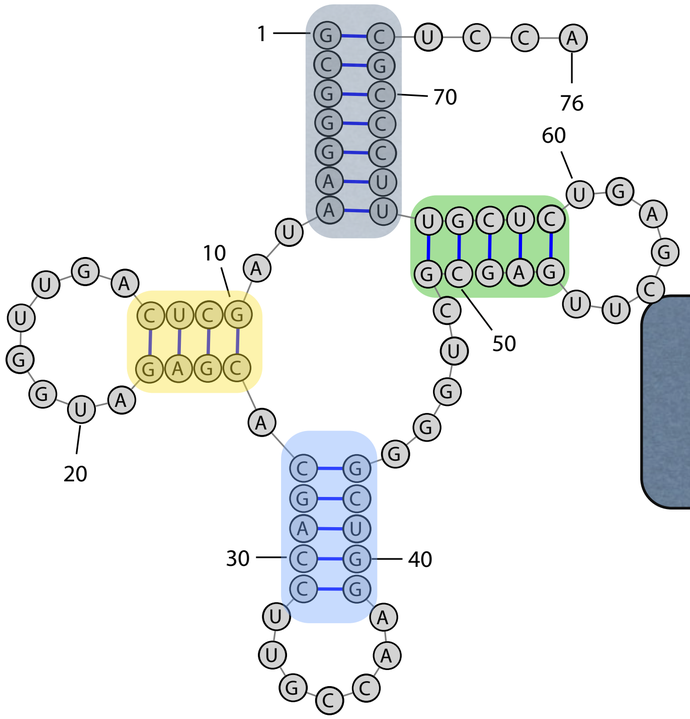
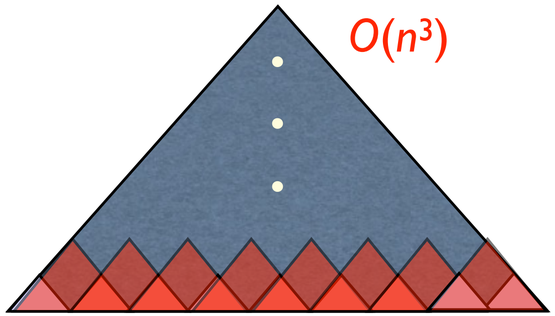
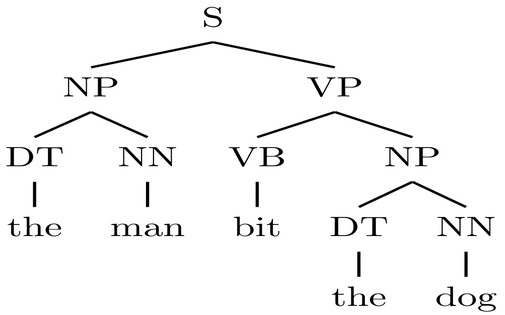
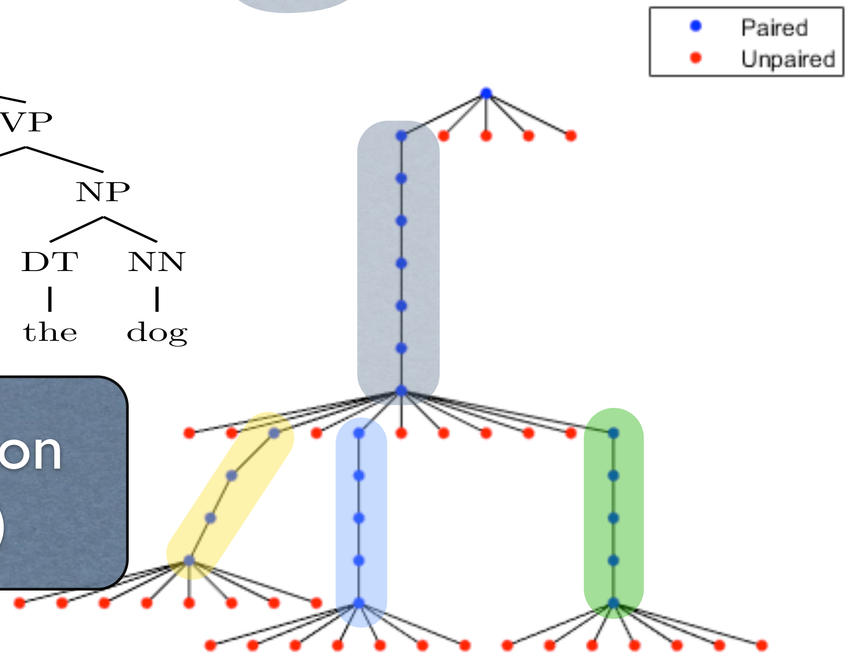




problem: standard structure prediction algorithms are way too slow: $O(n^3)$





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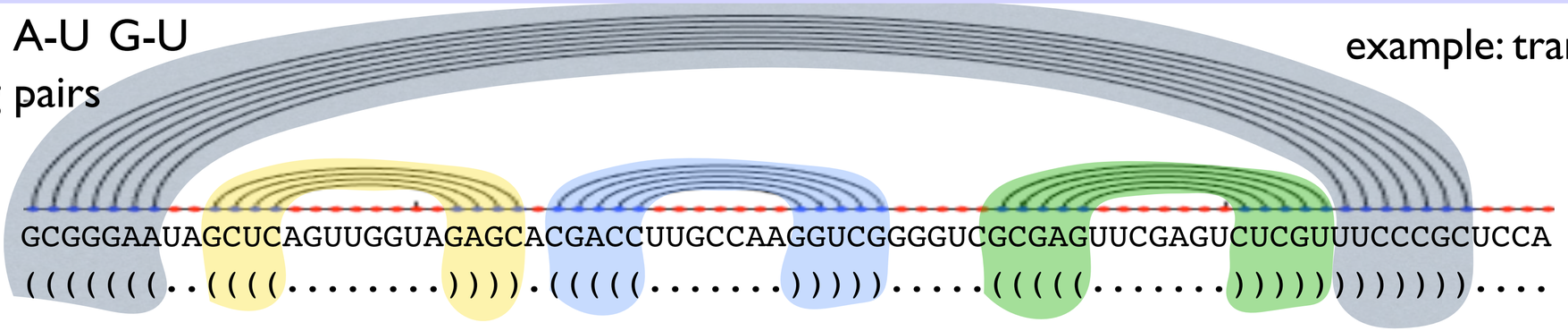

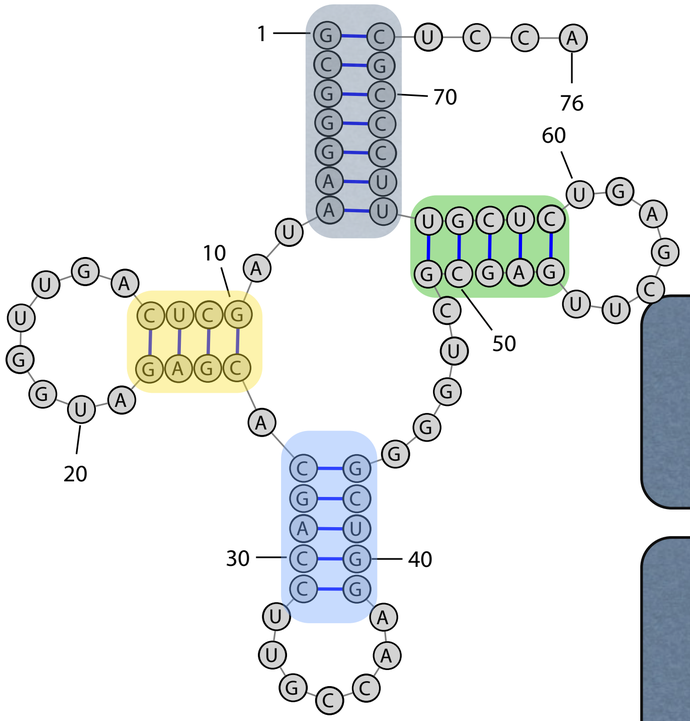

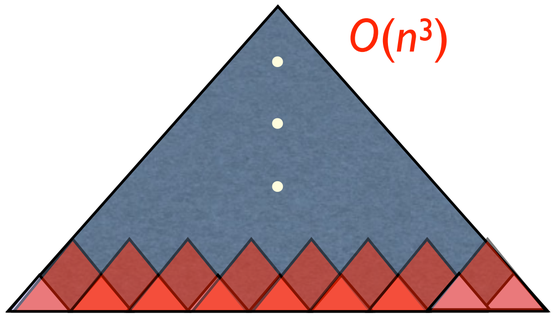

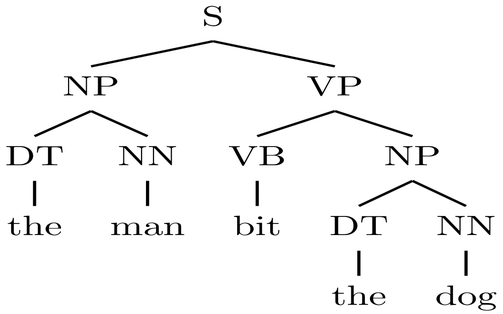

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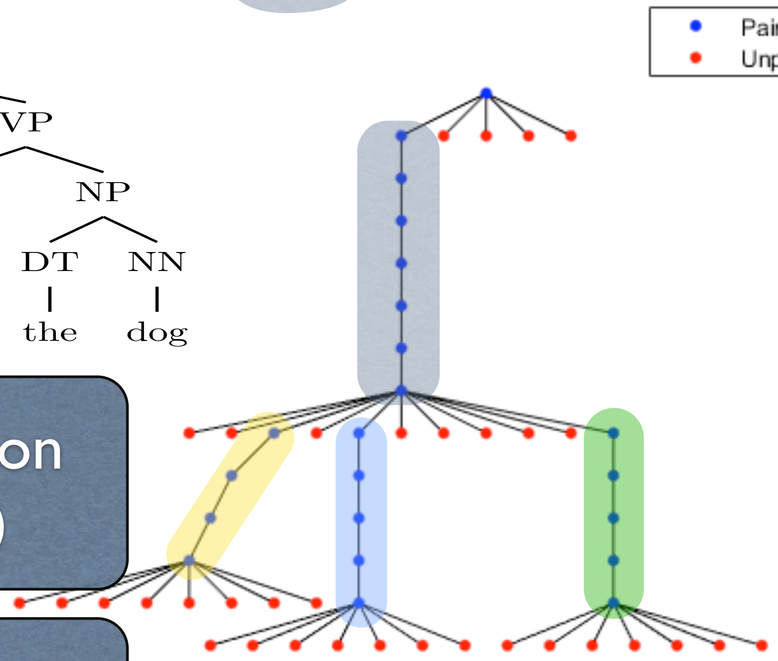
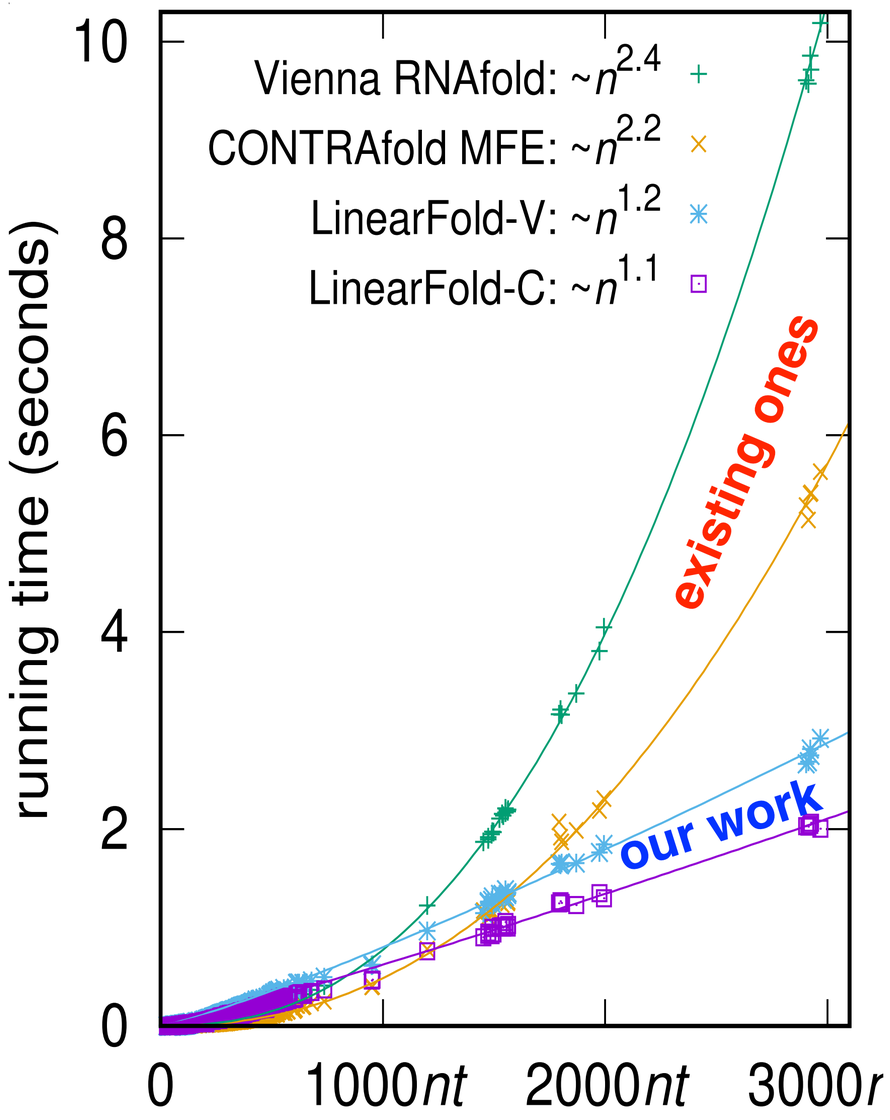
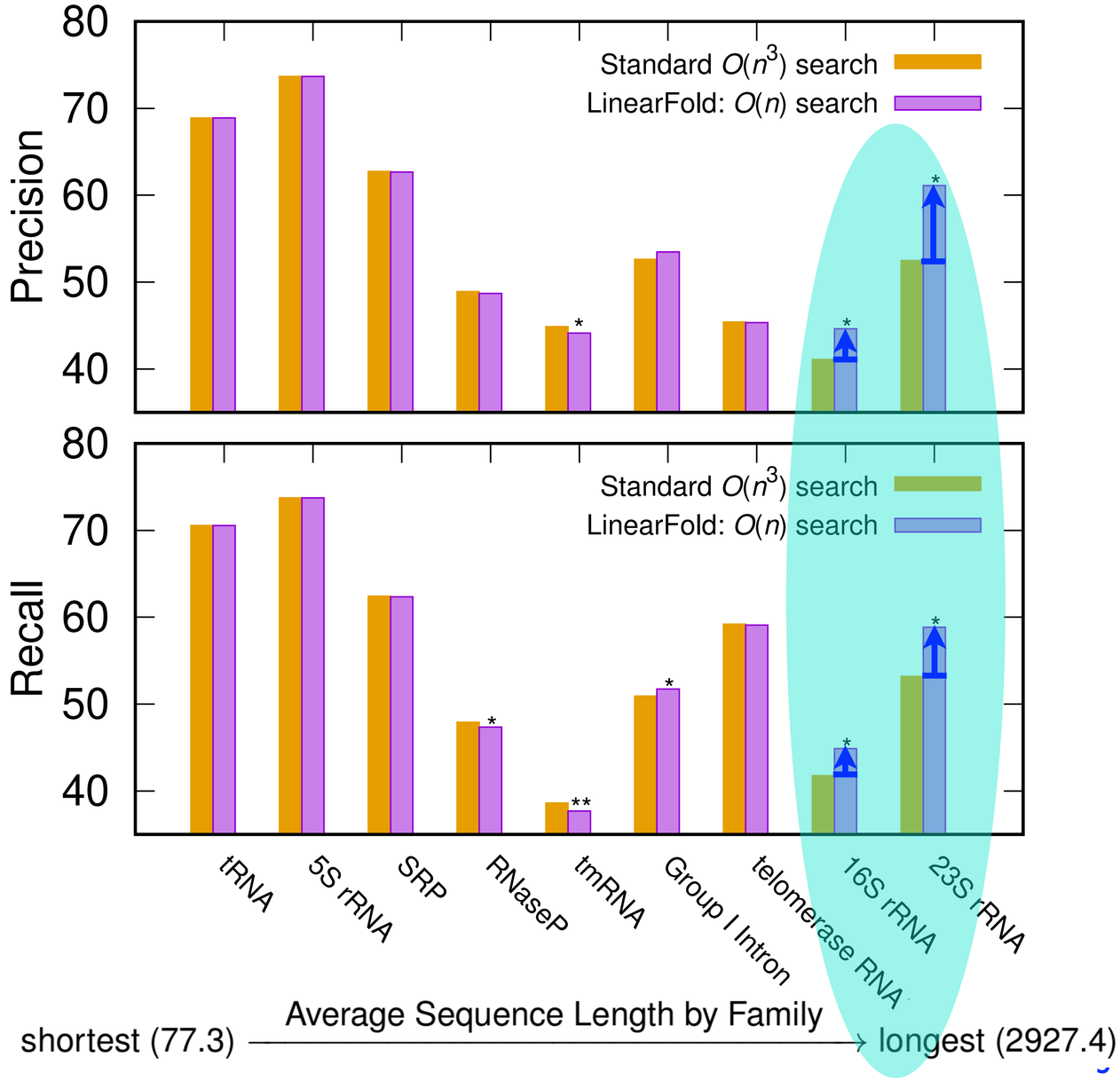
solution: adapt my linear-time dynamic programming algorithms from parsing



parse tree

Results: LinearFold is Much Faster and More Accurate





From Linguistics to Biology

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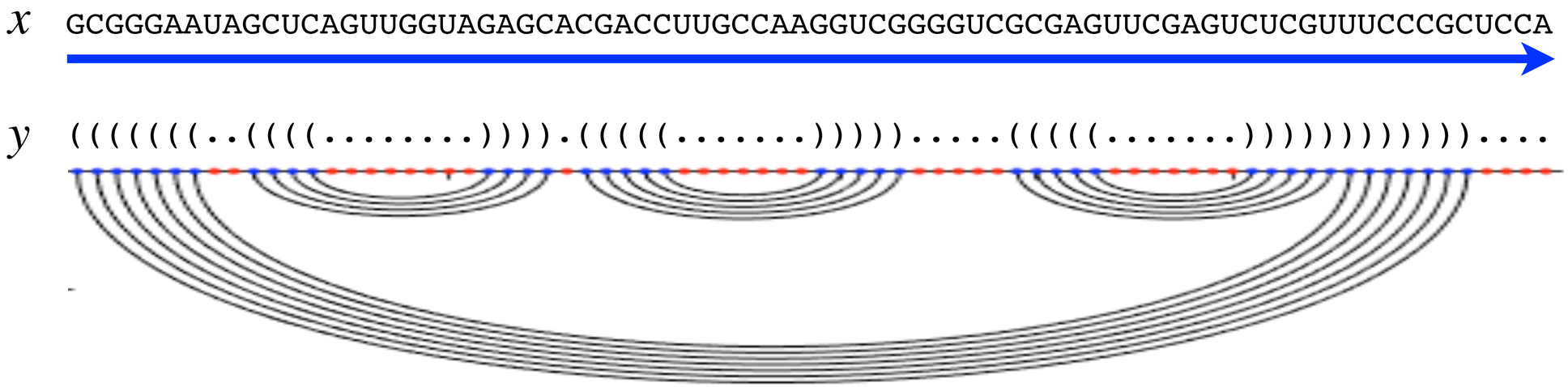

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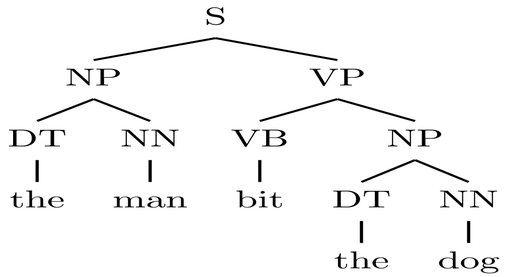
1955 Chomsky: context-free grammars (CFGs)



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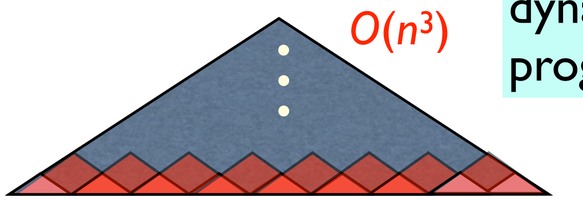
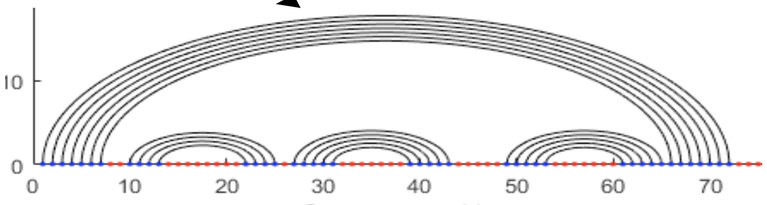


dynamic programming



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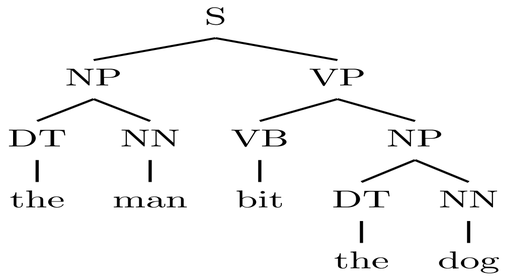

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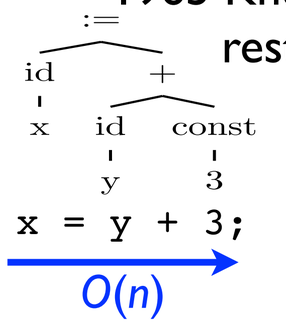

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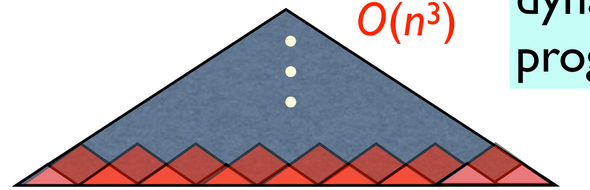

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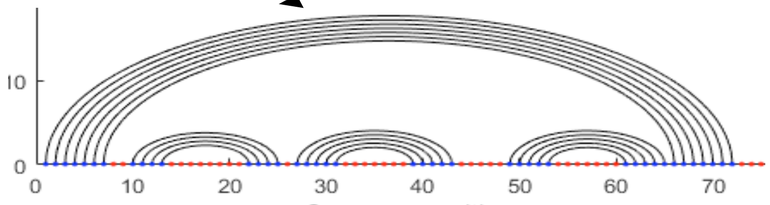

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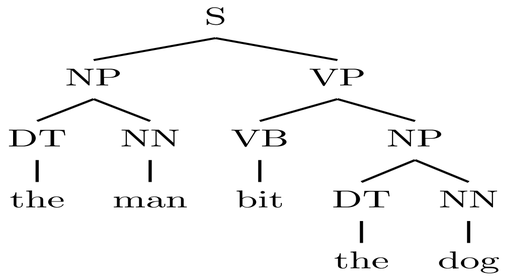

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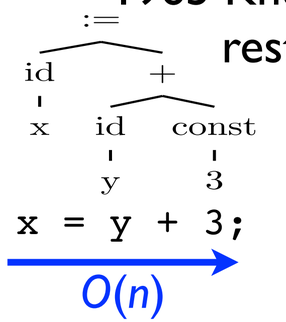

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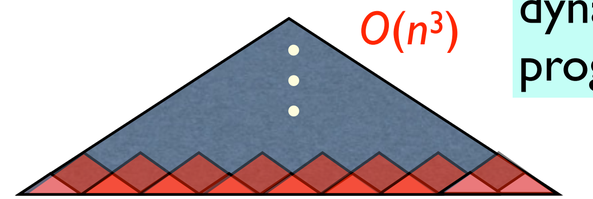

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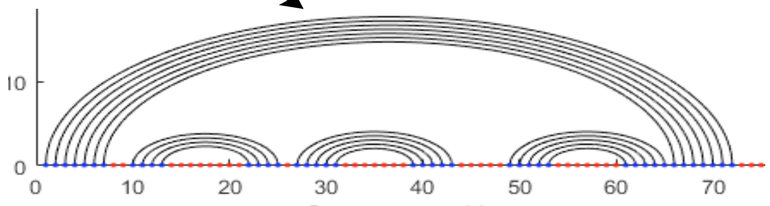

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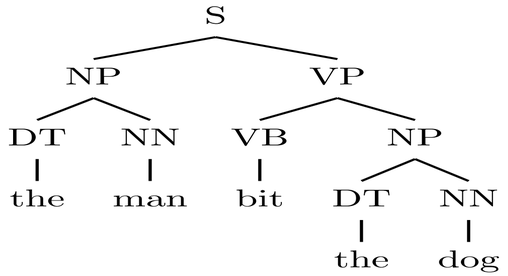

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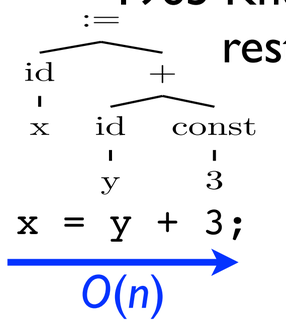

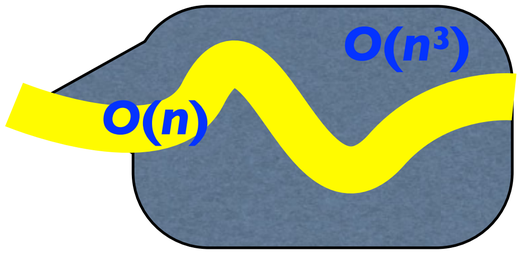

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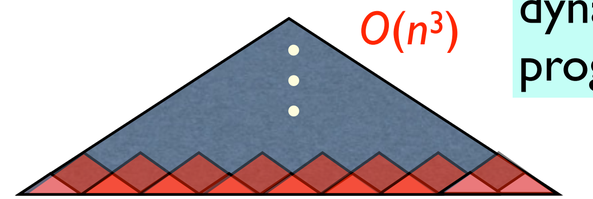
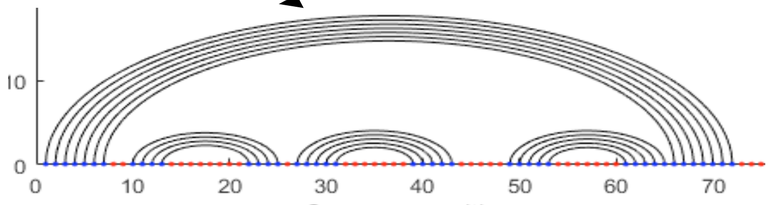


dynamic programming



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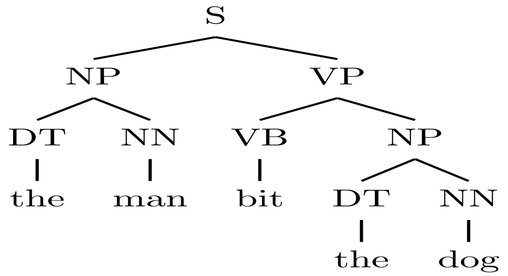

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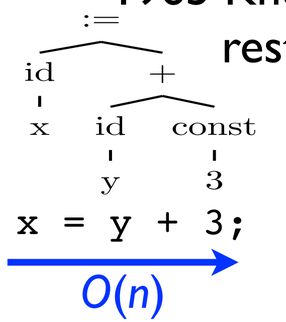

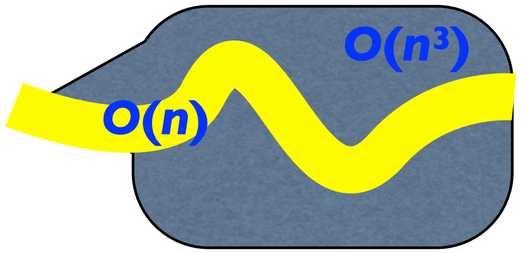

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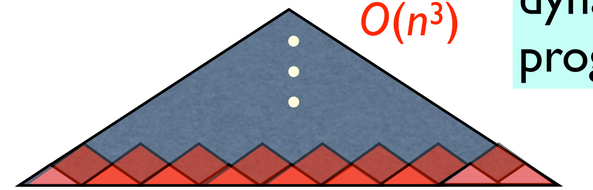
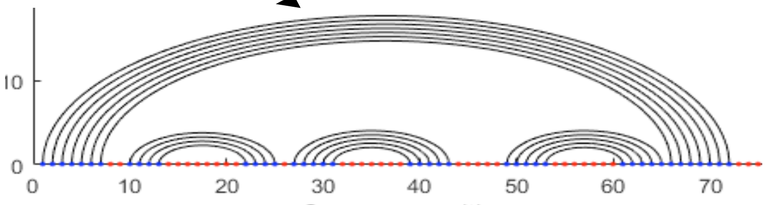
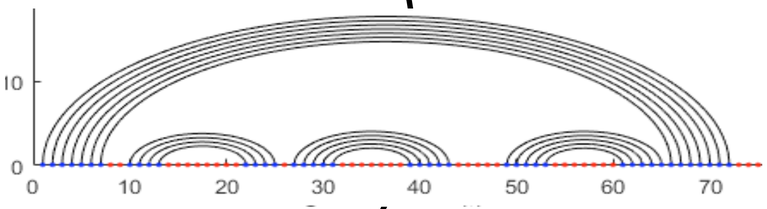


dynamic programming



1978: Nussinov ***O(n³)*** RNA folding
1981: Zuker & Siegler

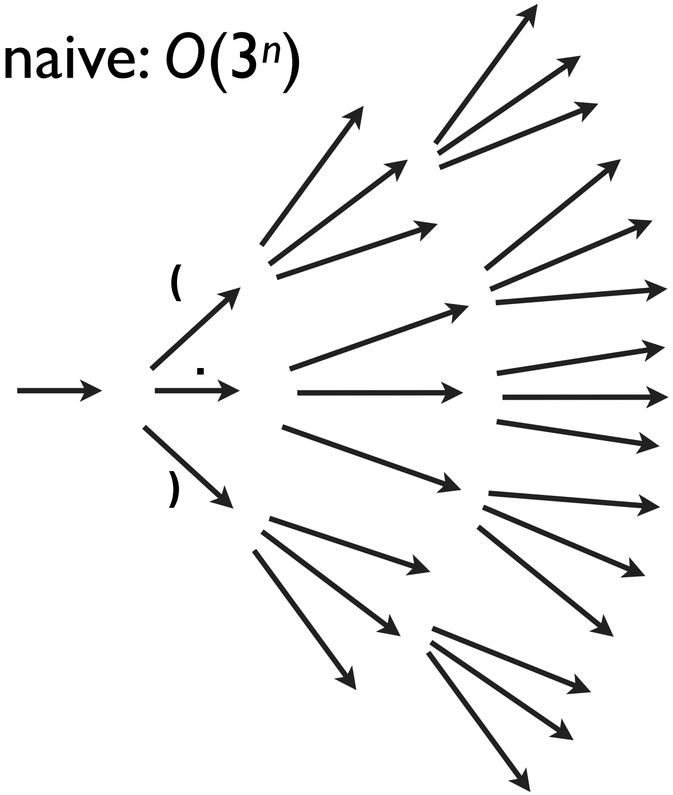


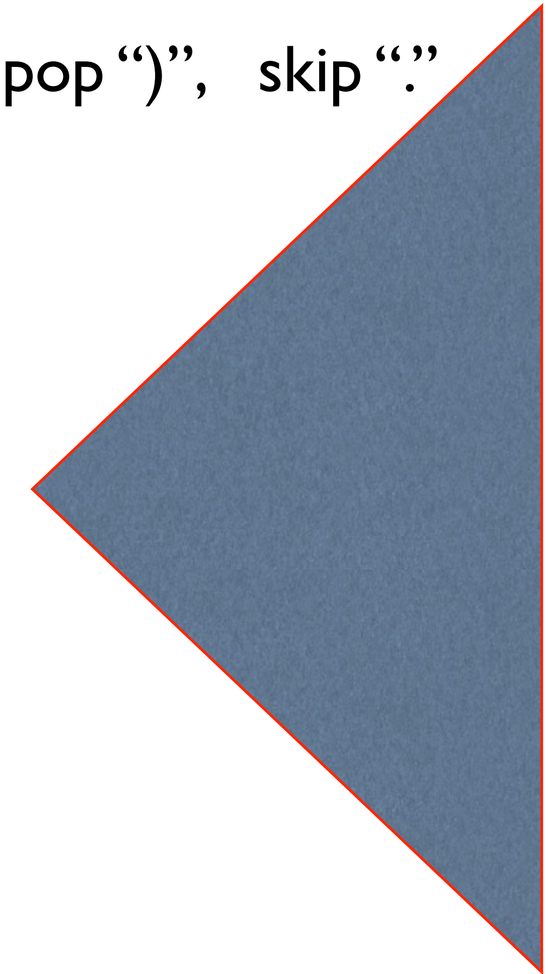
2019: LinearFold O(n)
(approx.) RNA folding

How to Fold RNAs in Linear-Time?

GCGGGAAUAGCUCAGUUGGUAGAGCACGACCUUGCCAAGGUCGGGGUCGCGAGUUCGAGUCUCGUUUCCCGCUCCA

- idea 0: tag each nucleotide from left to right
  - maintain a stack: push "(", pop ")", skip "."
  - naive: $O(3^n)$





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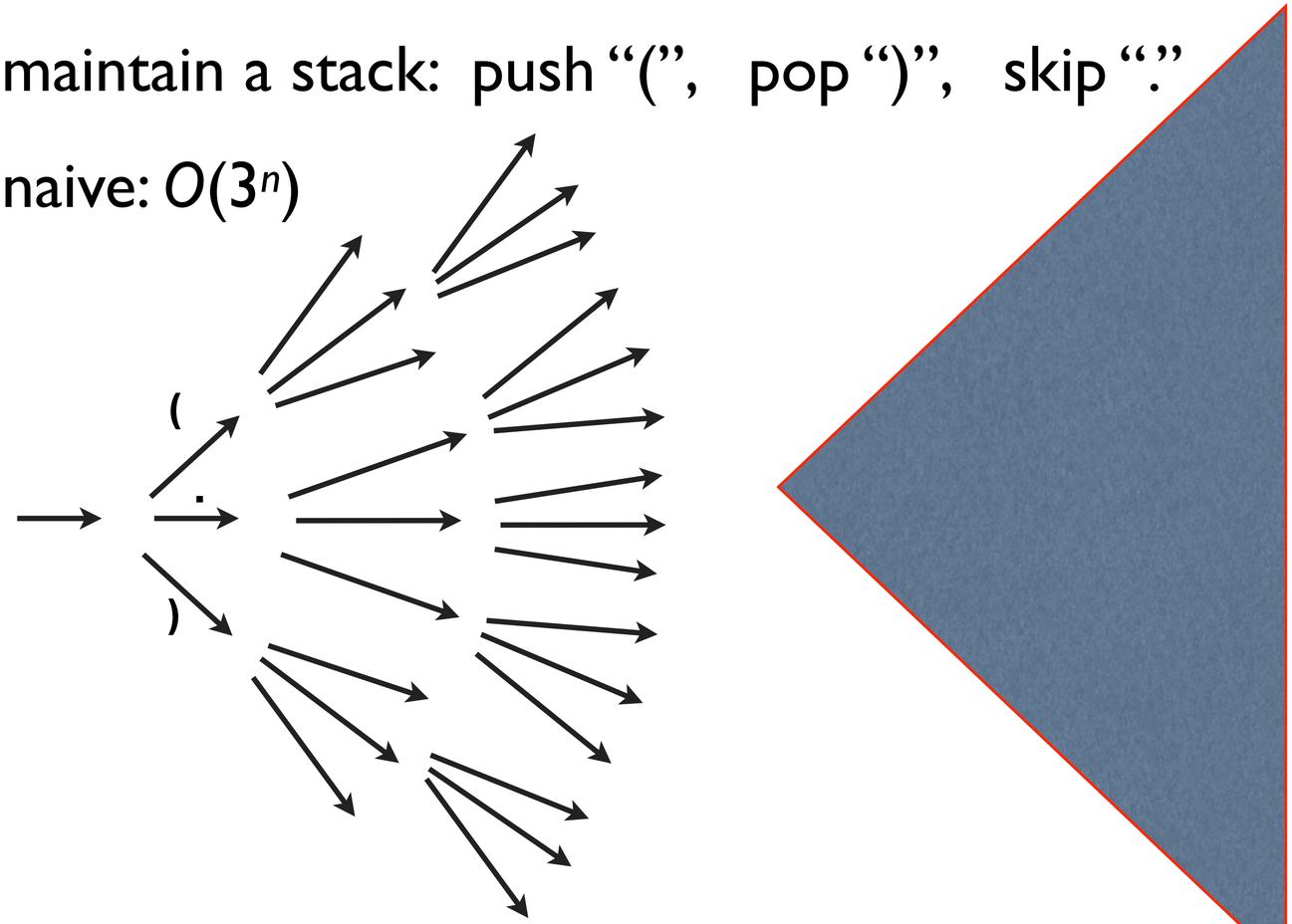

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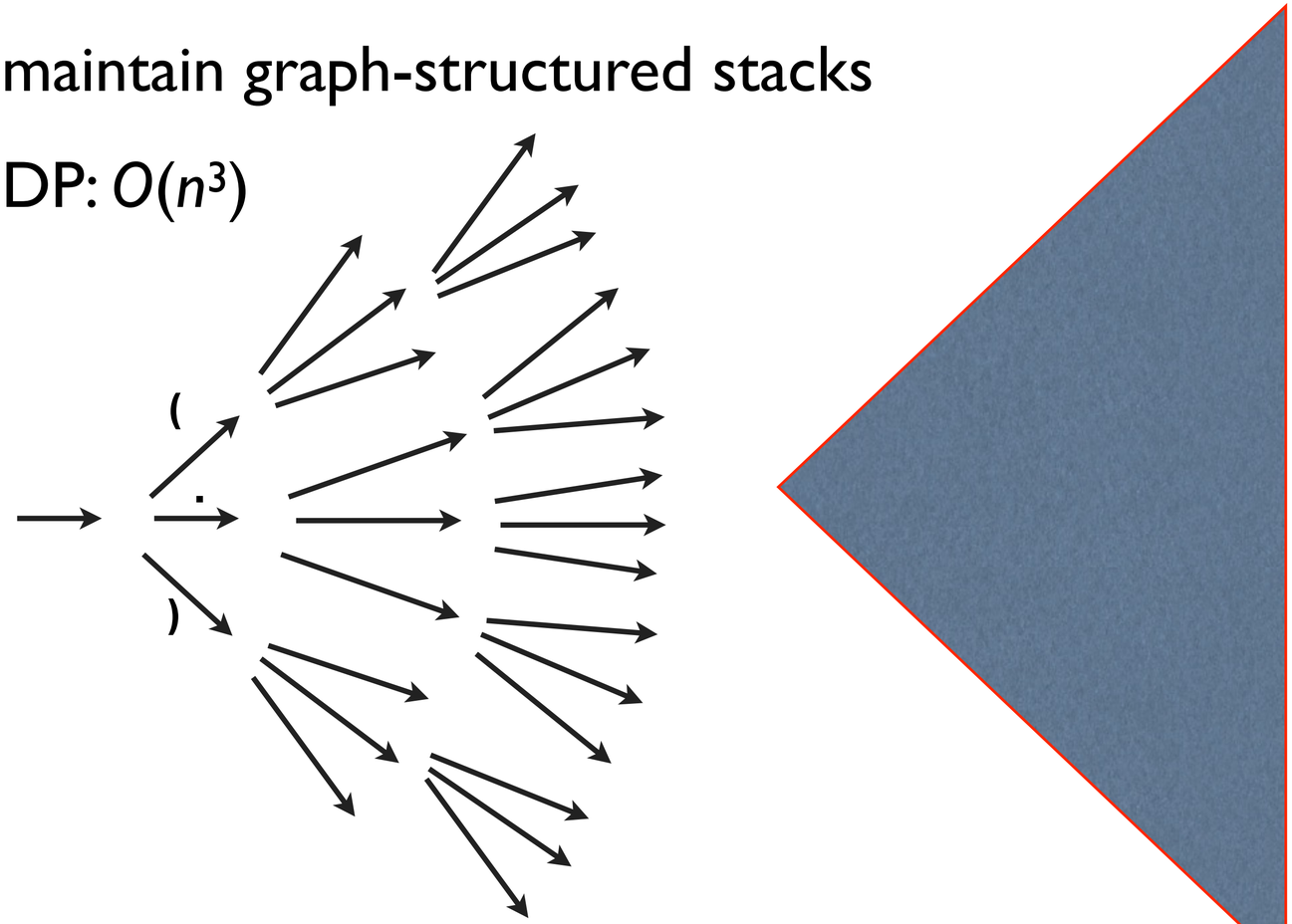
  - maintain graph-structured stacks
  - DP: $O(n^3)$



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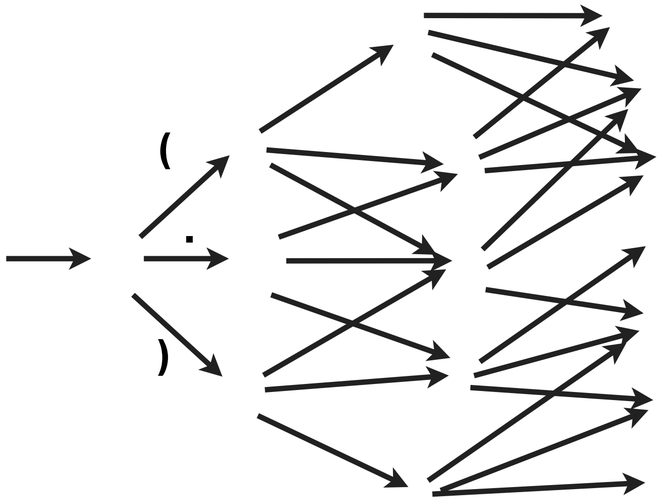

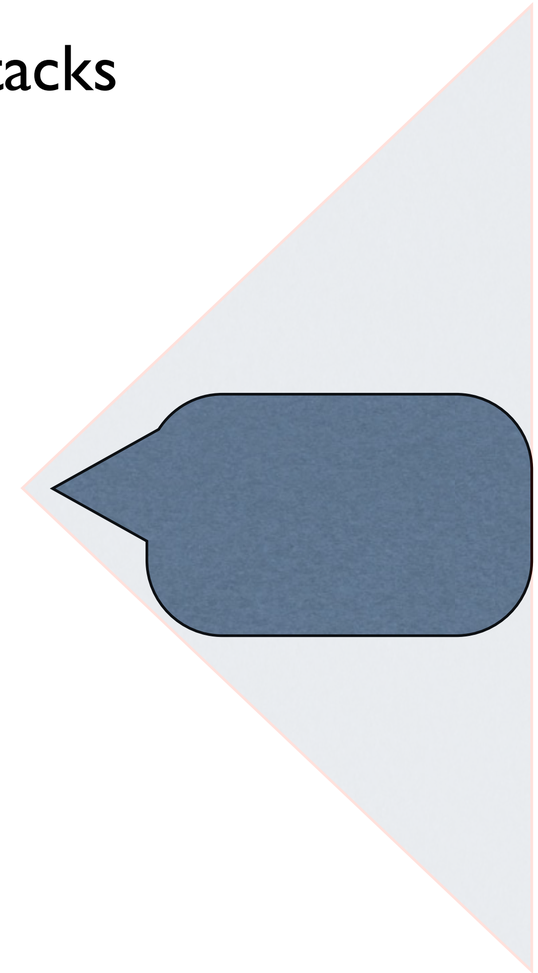

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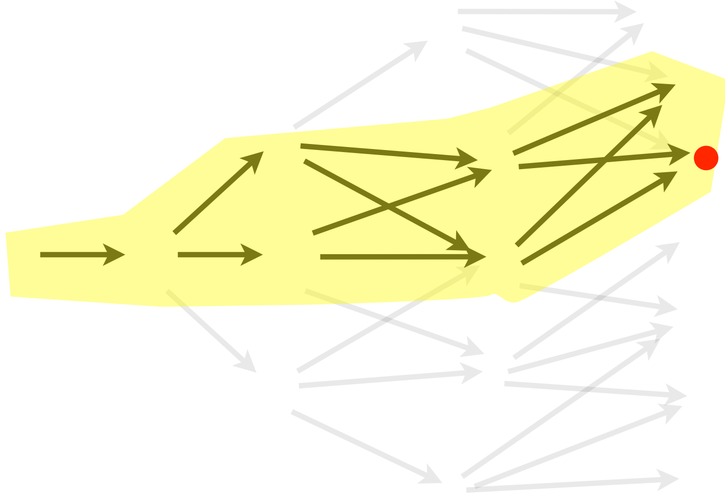
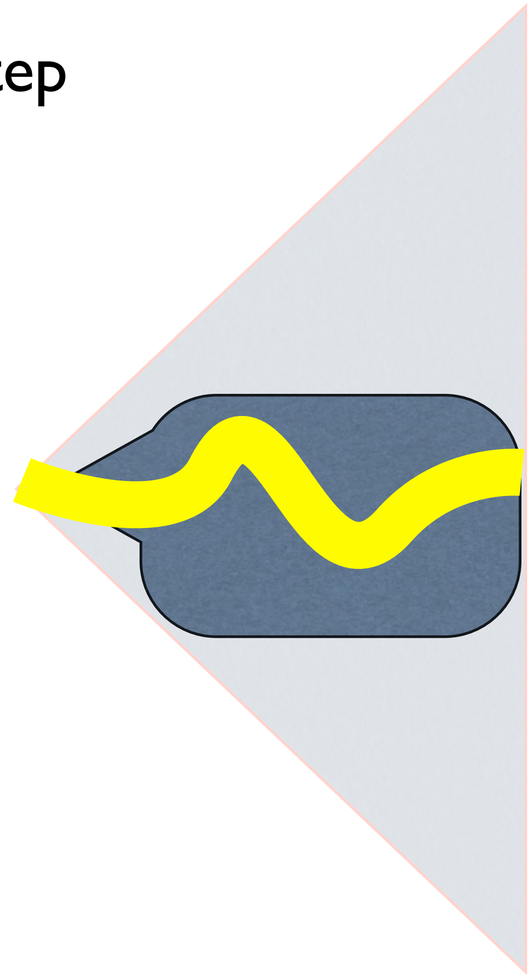
  - keep only top *b* states per step
  - DP+beam: *O*(*n*)





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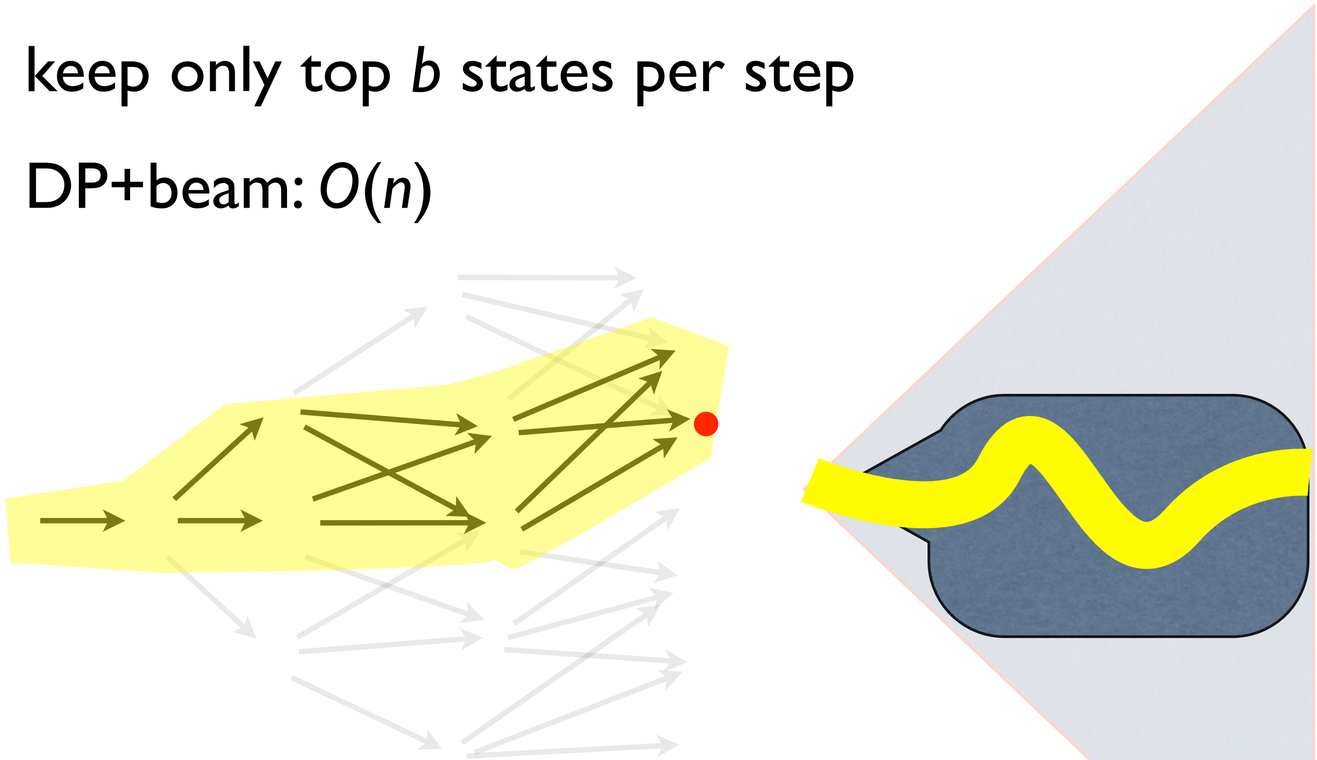

each DP state corresponds to exponentially many non-DP states

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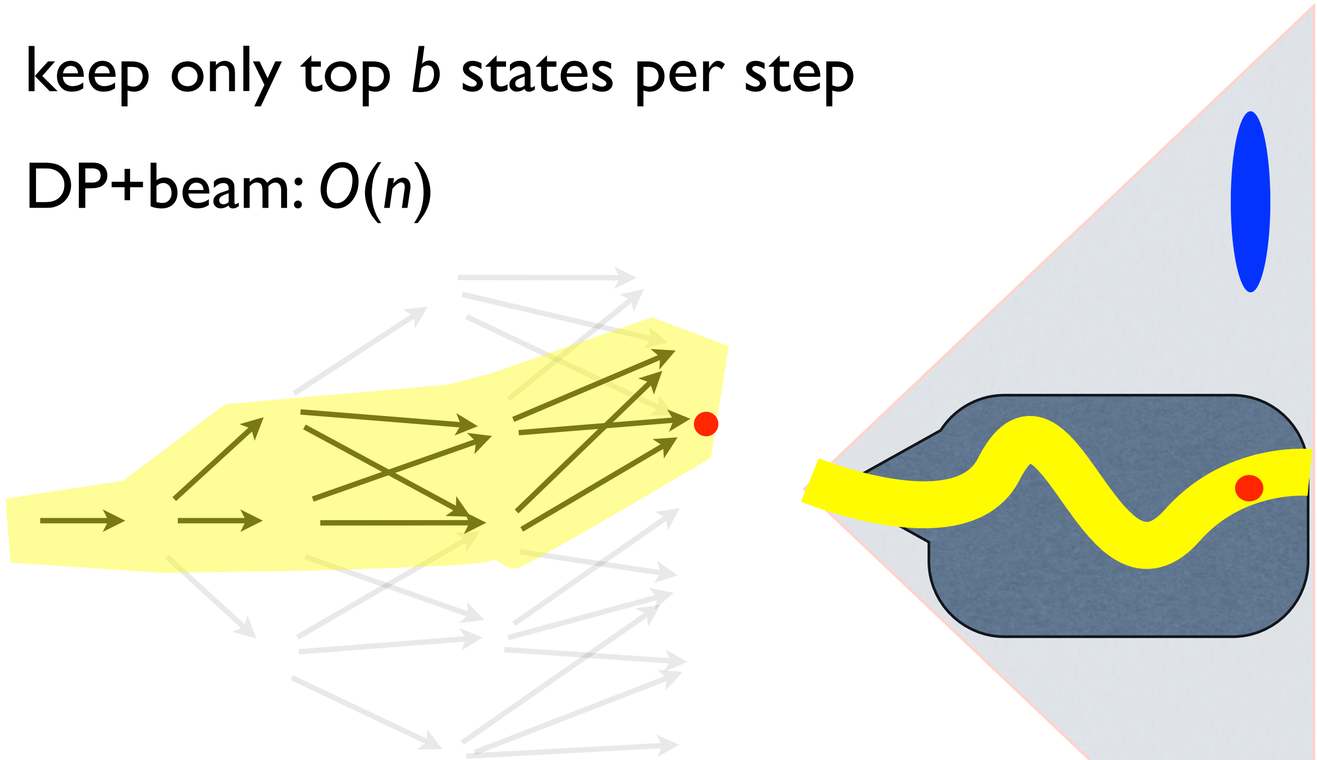

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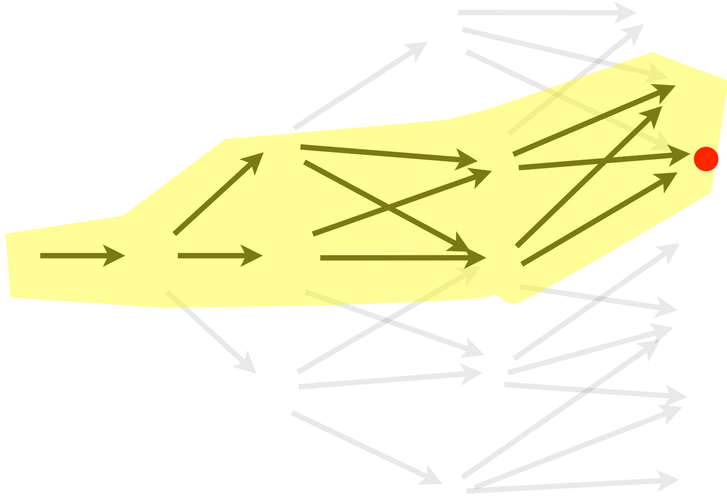

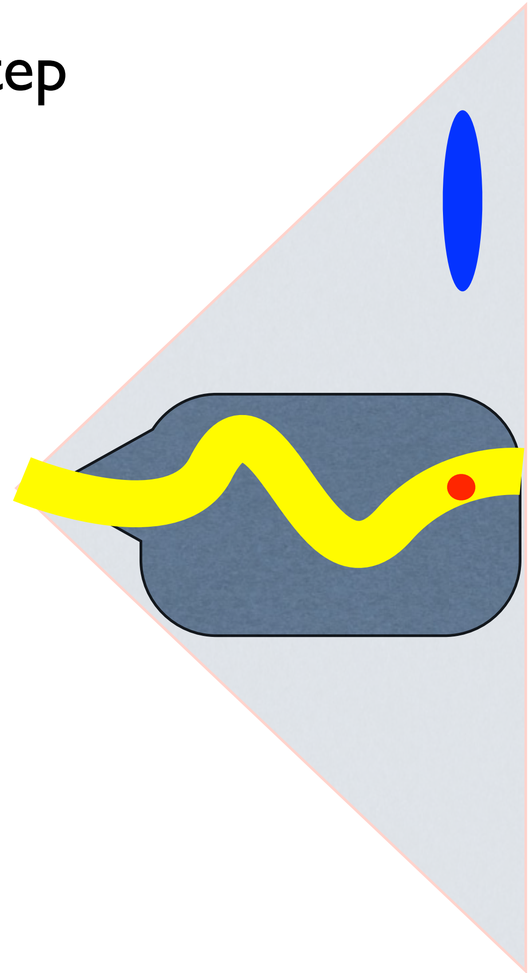

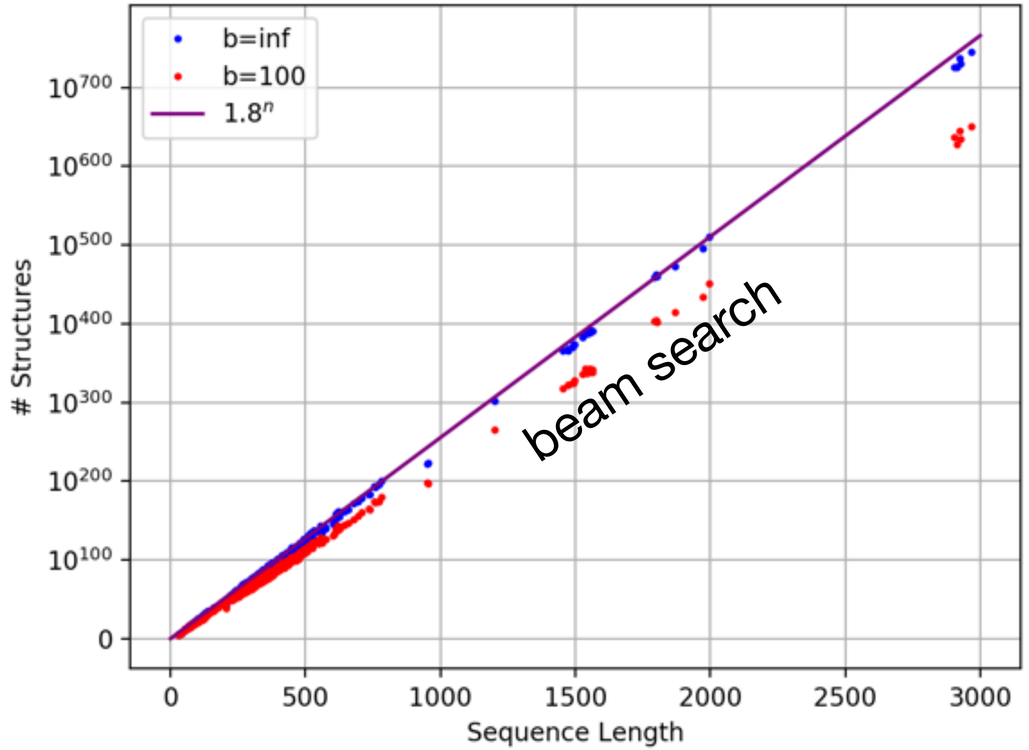

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Details: Packing "Temporarily Equivalent" States

- two states are "temporarily equivalent" if they share the same stack top index
  - because they are looking for the same nucleotide(s) to match this stack-top nucleotide
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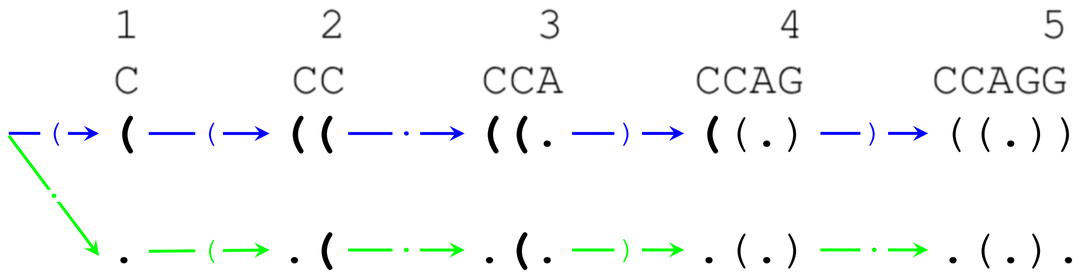
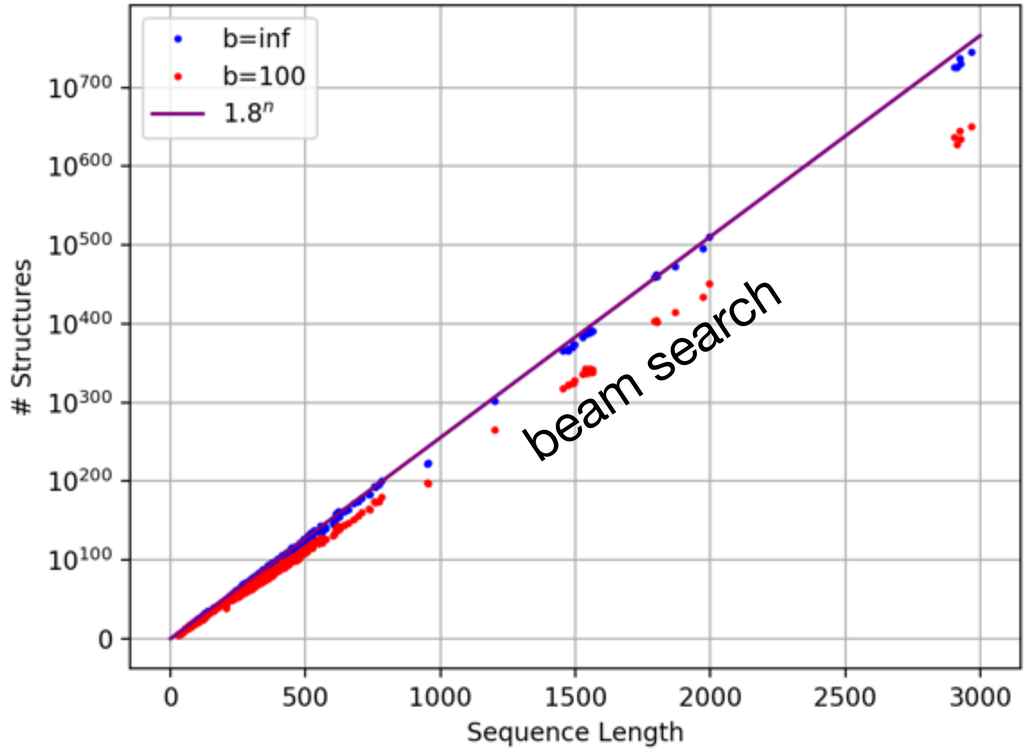
  - this is how we can explore exponentially many structures in linear time





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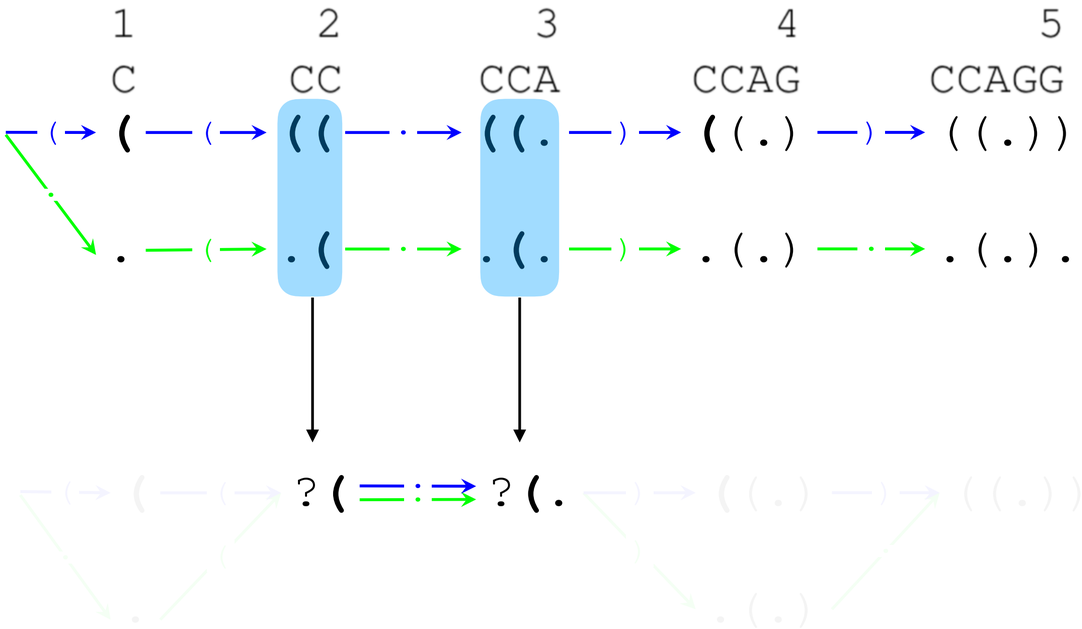

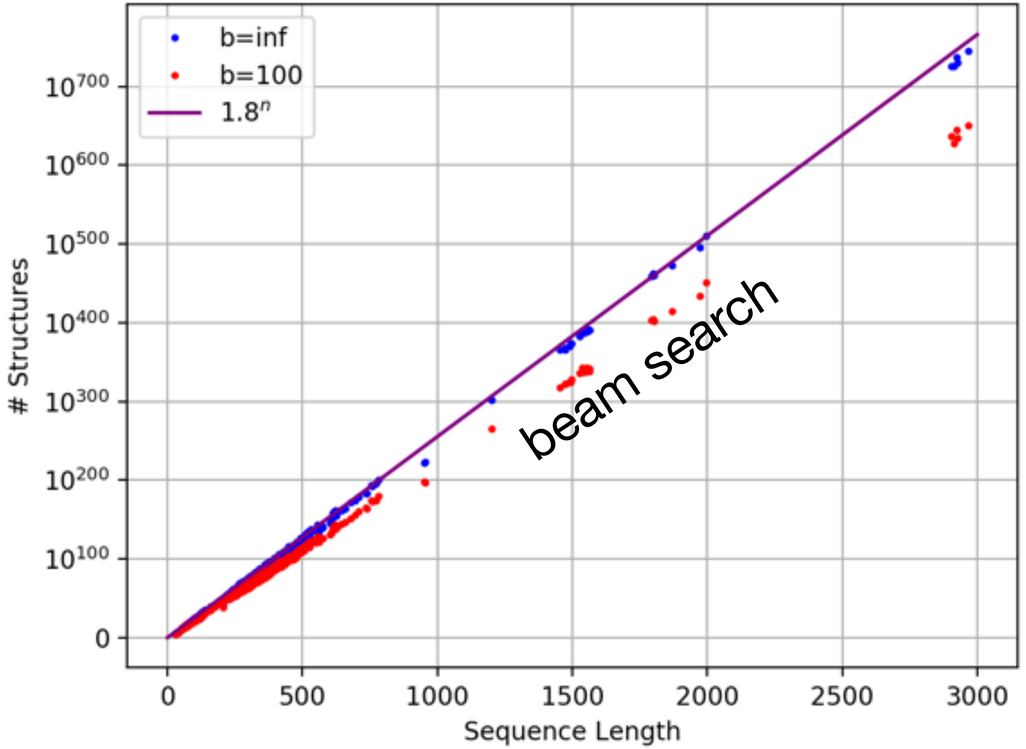

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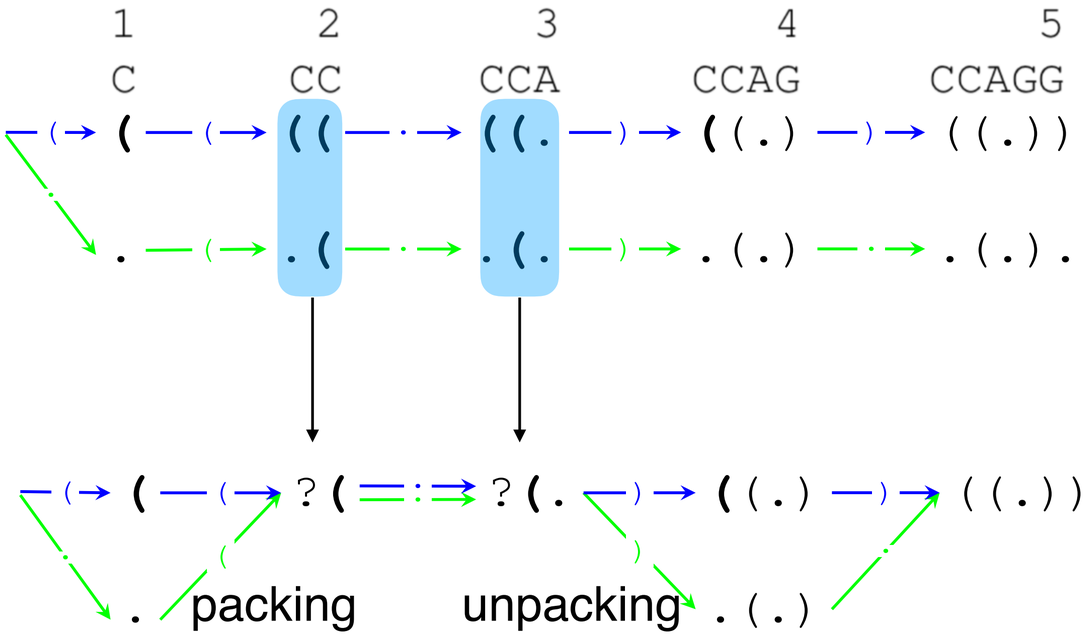
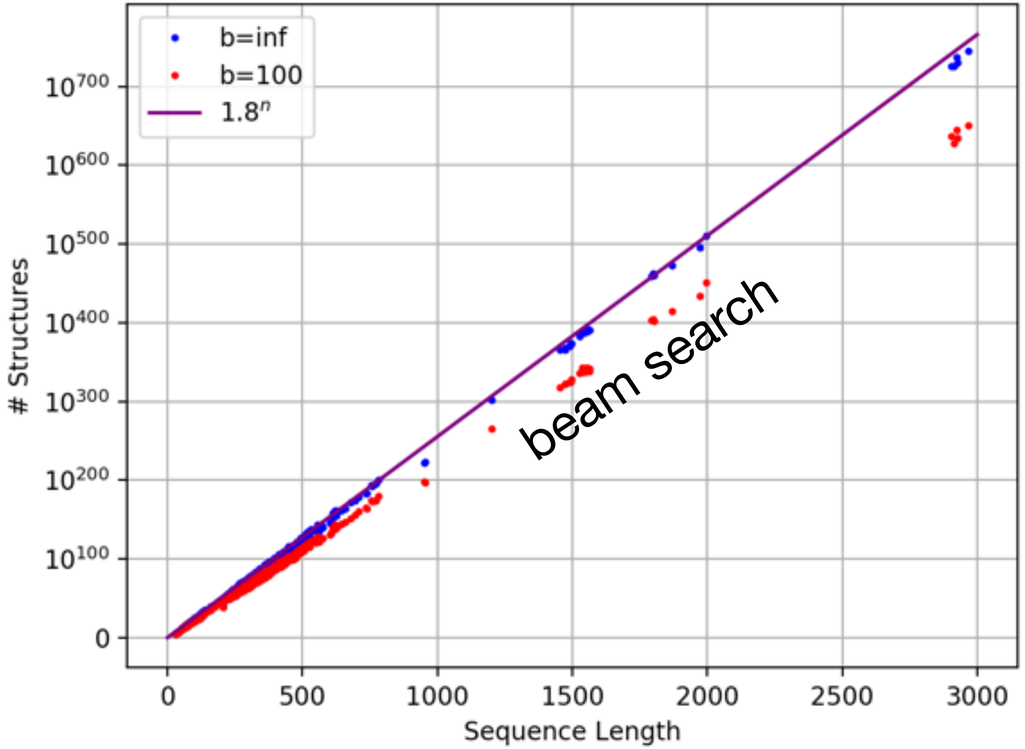
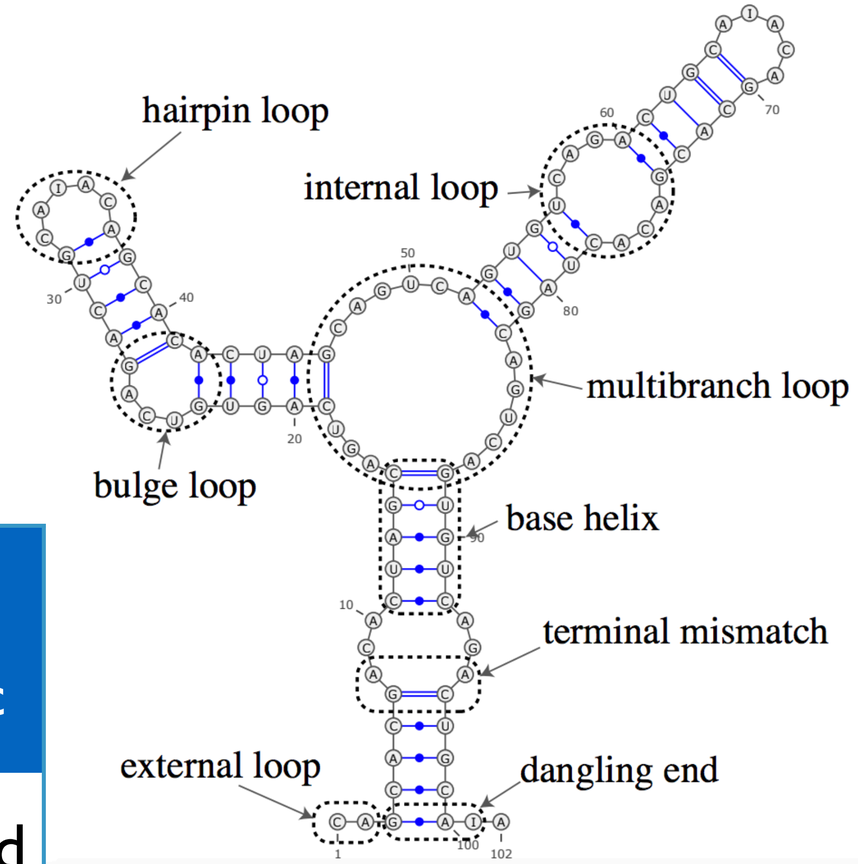




Results

LinearFold with SOTA Prediction Models

- models from two widely-used folding engines
  - CONTRAfold MFE (machine-learned)
  - Vienna RNAfold (thermodynamic)
- we linearized both systems from $O(n^3)$ to $O(n)$



	efficiency		*systems*	
	time	space	machine-learned	thermo-dynamic
baselines	$O(n^3)$	$O(n^2)$	**C**ONTRAfold	**V**ienna RNAfold
our work	$O(n)$	$O(n)$	LinearFold-**C**	LinearFold-**V**

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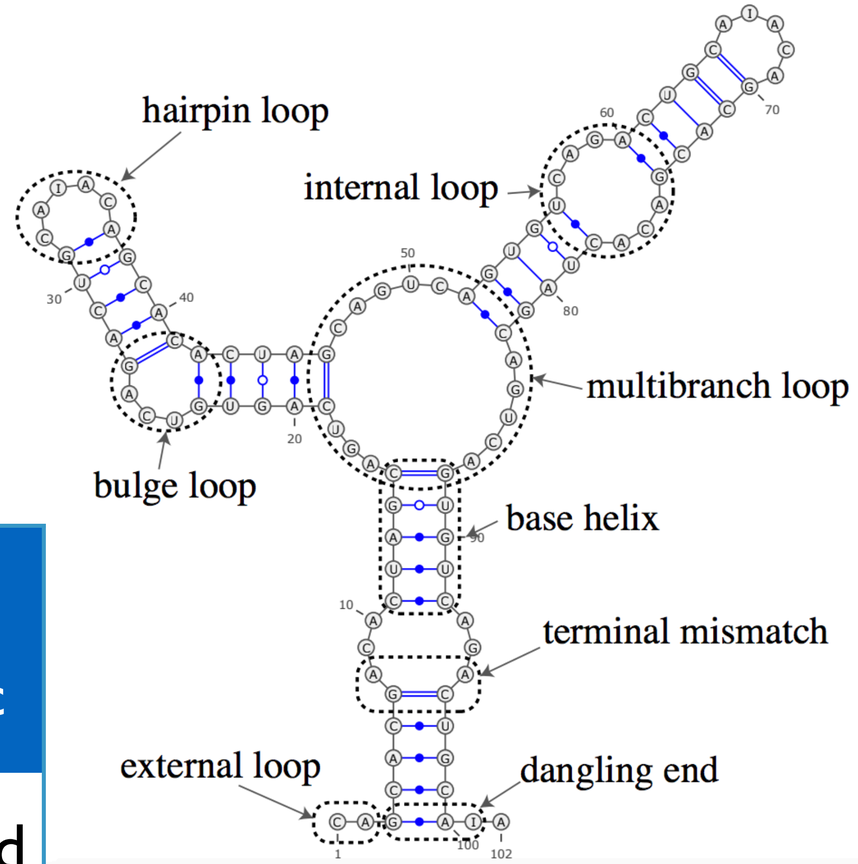

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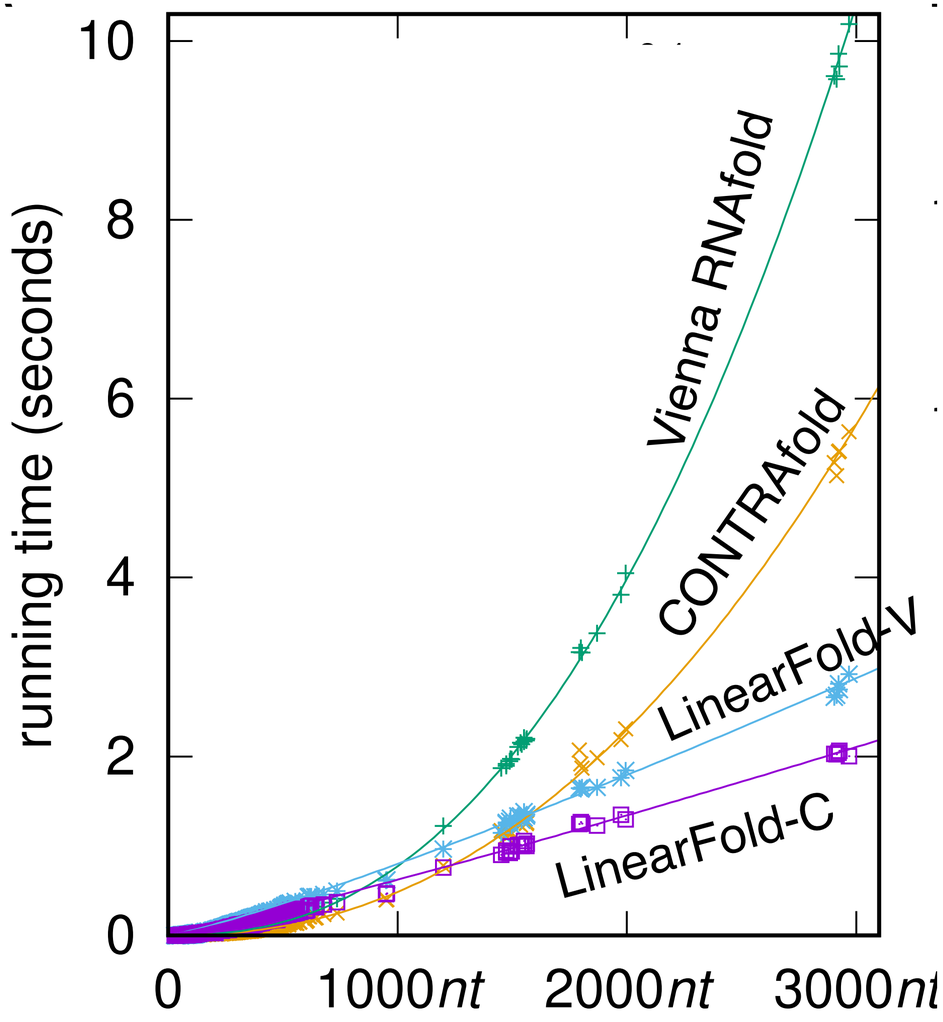
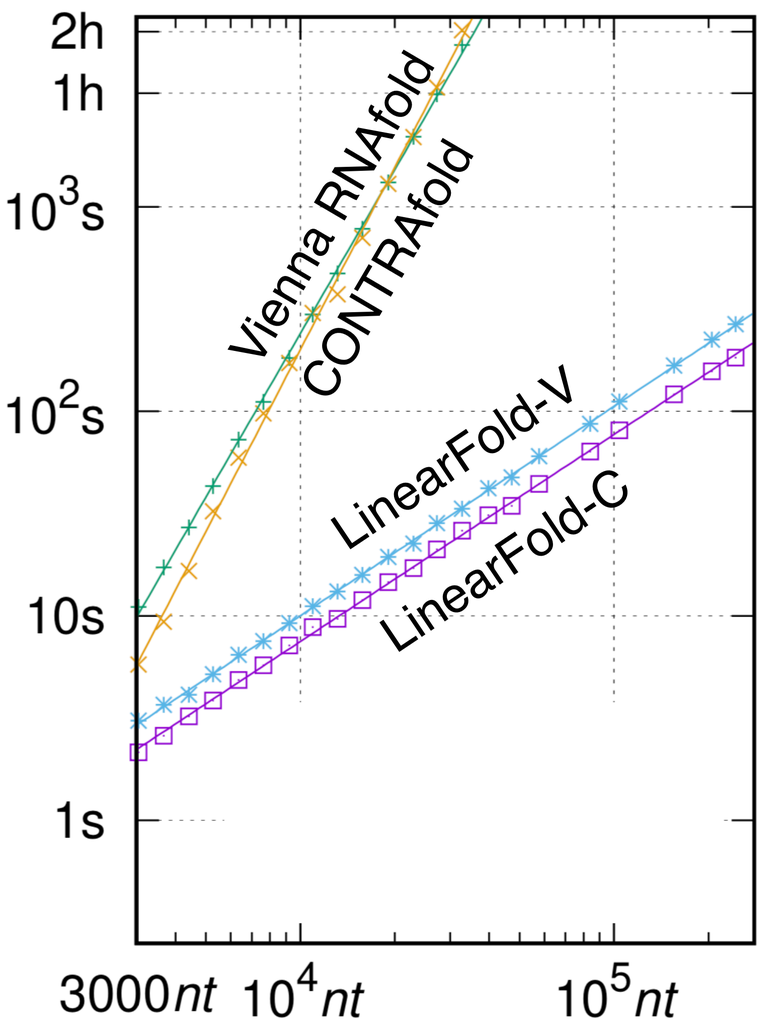
Efficiency & Scalability: *O*(*n*) time, *O*(*n*) memory



Archive II data set
(~3,000 seqs, max len: ~3,000 *nt*)



RNAcentral data set
(sampled, max len: ~250,000 *nt*)

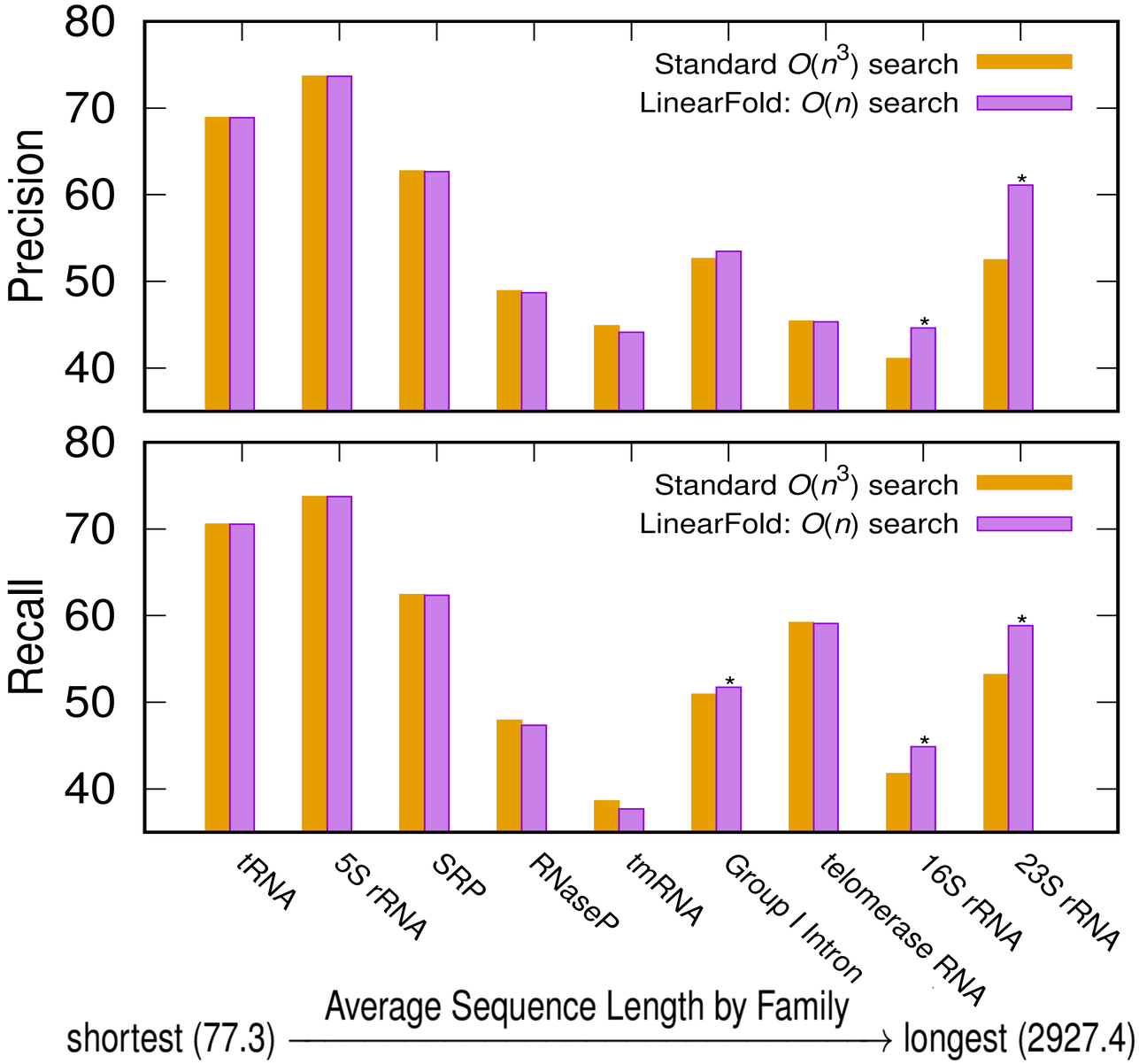
10,000*nt* (~HIV)
4min → 7s

244,296*nt*
(longest in RNAcentral)
~200hrs → 120s

Accuracy

- Tested on Archive II dataset (on a family-by-family basis)
  - significantly better on 3 long families
  - biggest boost on the longest families: 16S/23S rRNAs
- LinearFold-V vs. Vienna is similar

Overall	(precision) PPV		(recall) Sensitivity	
CONTRAfold MFE	54.51		55.36	
LinearFold-C	55.84	(+1.3)	56.24	(+0.9)
Vienna RNAfold	50.22		58.74	
LinearFold-V	50.51	(+0.3)	58.97	(+0.2)



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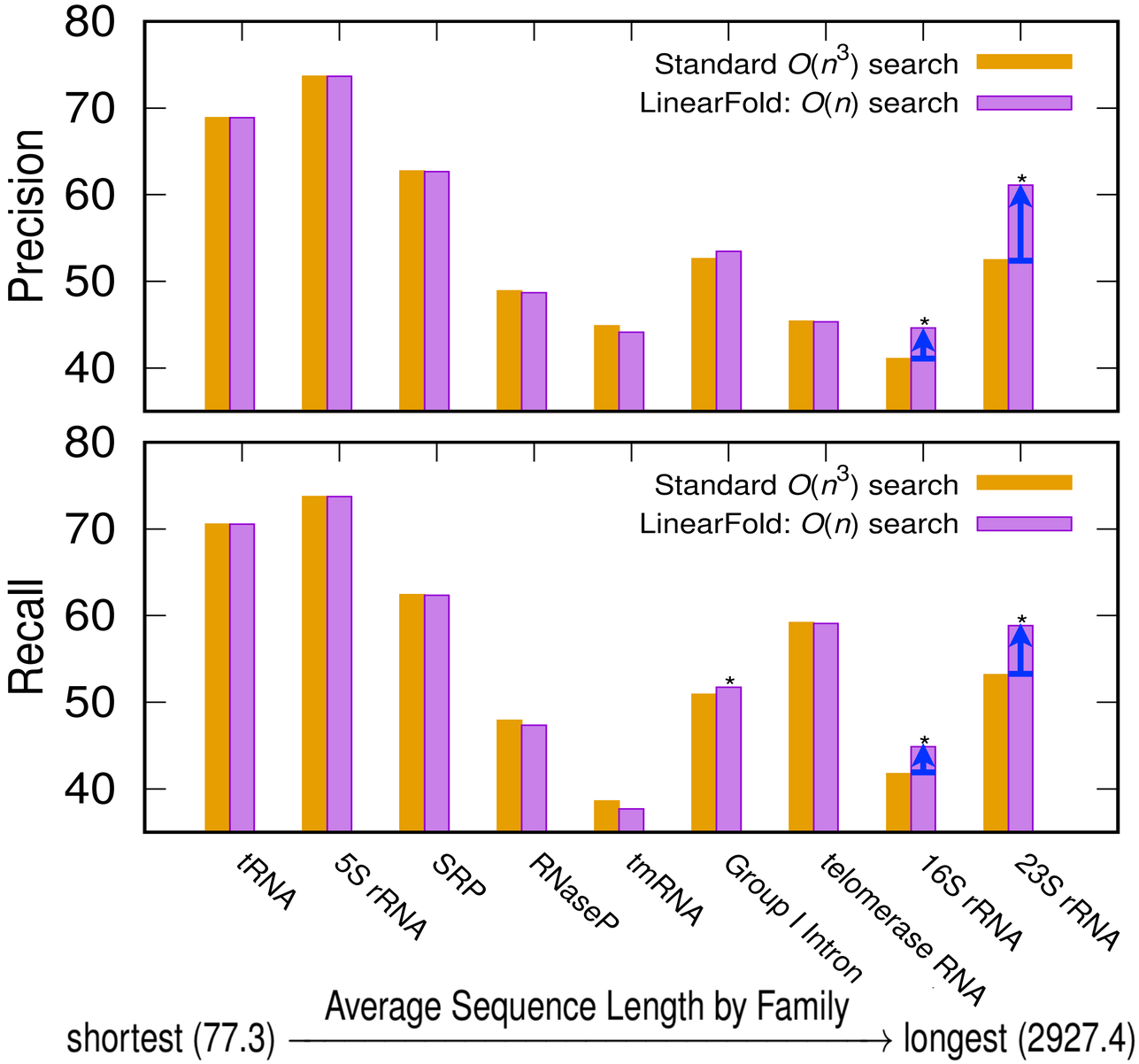
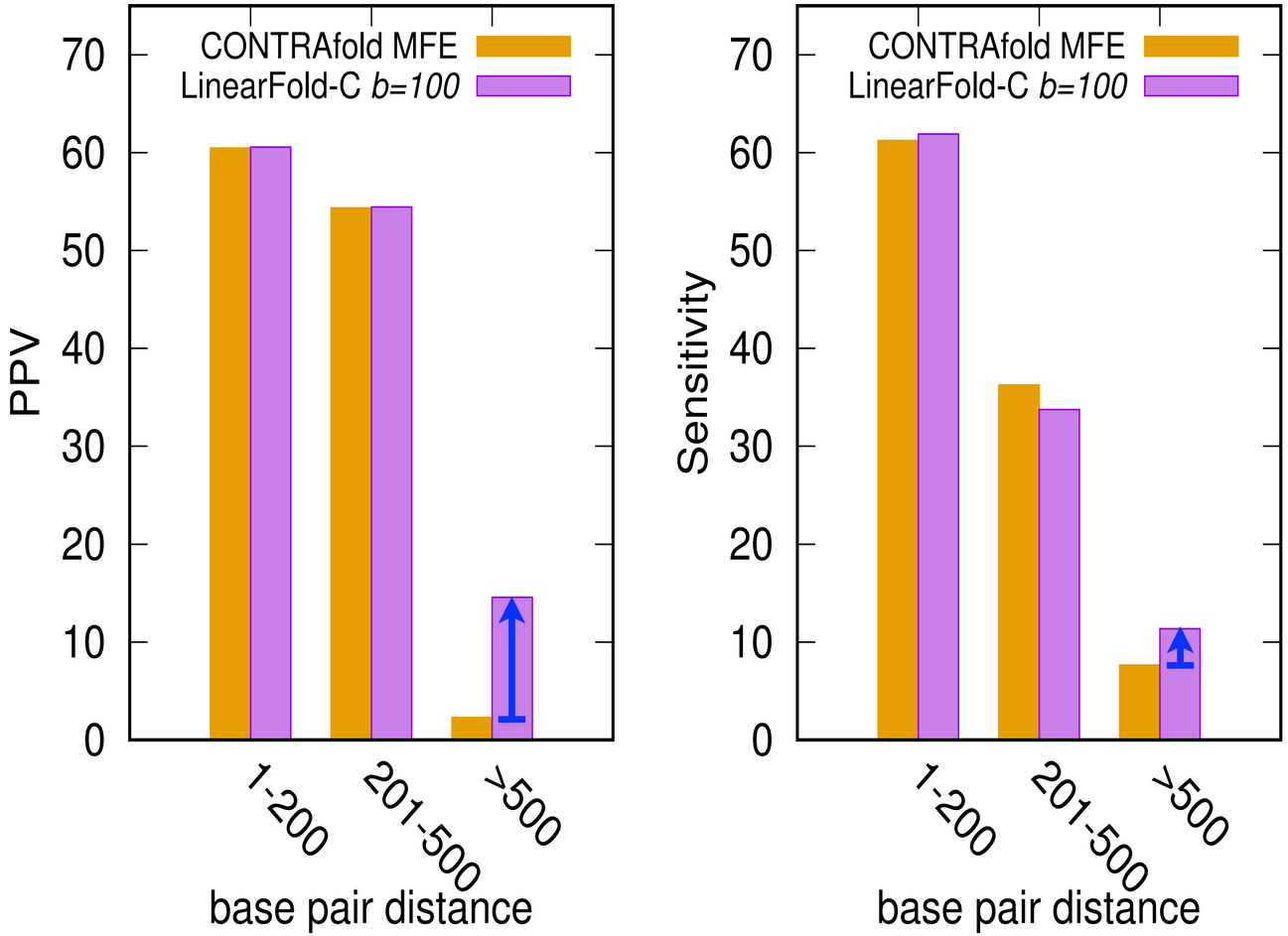


Improvements on Long-Range Base Pairs

- long-distance pairs are well-known to be hard to predict
  - LinearFold outputs less long-range base pairs, but more correct ones



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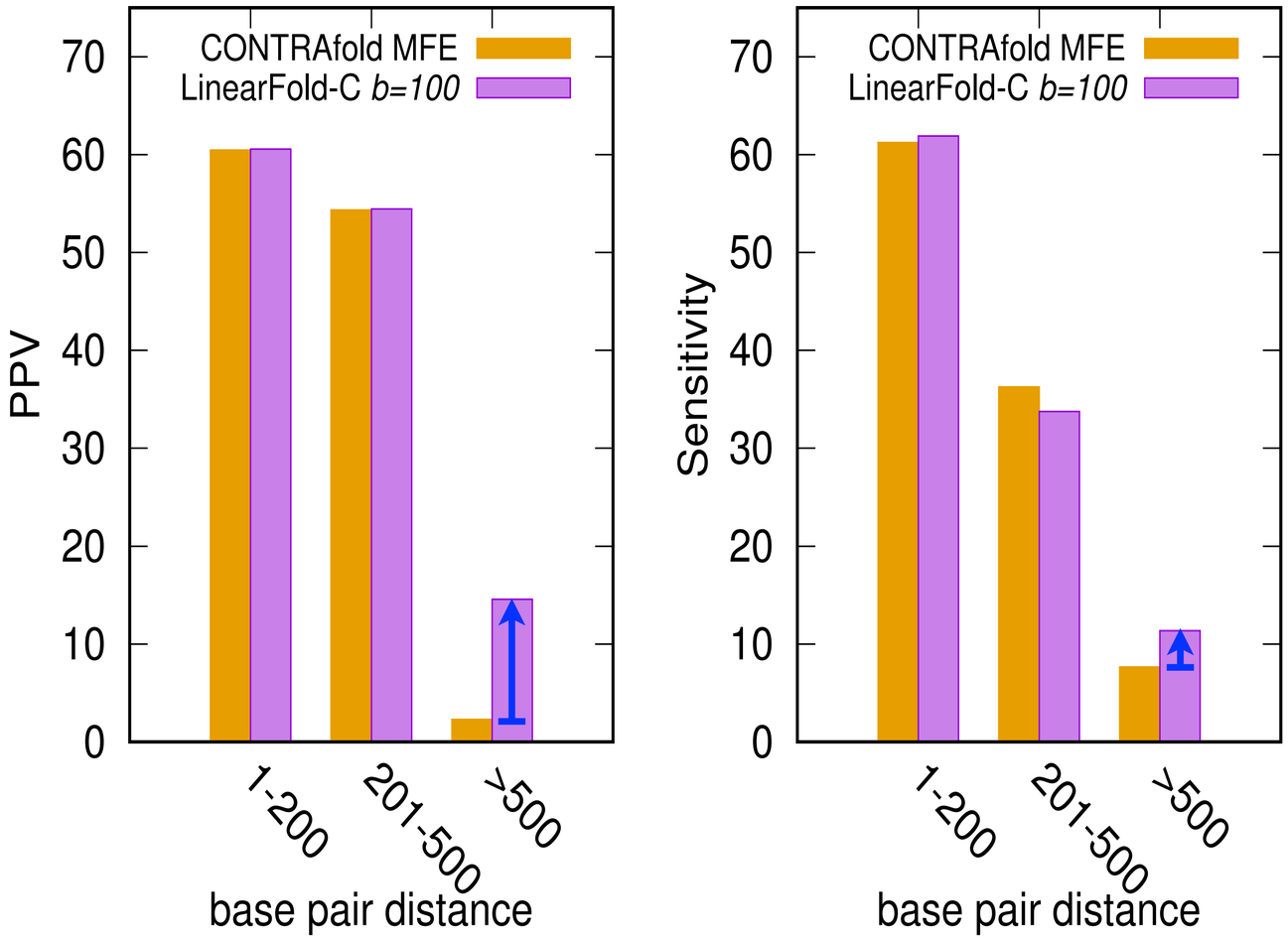
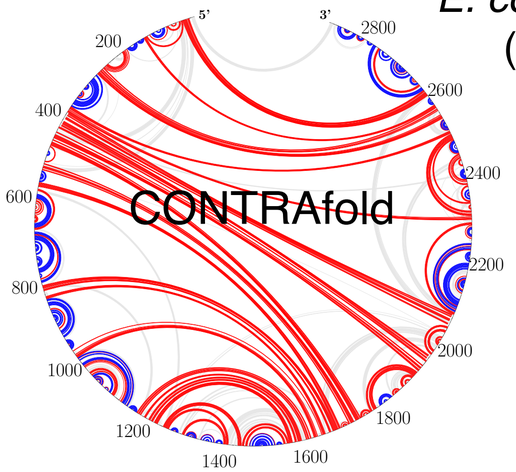
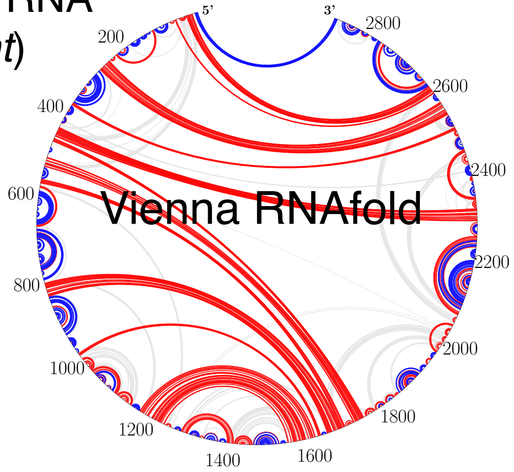


E. coli 23S rRNA
(2,904 *nt*)





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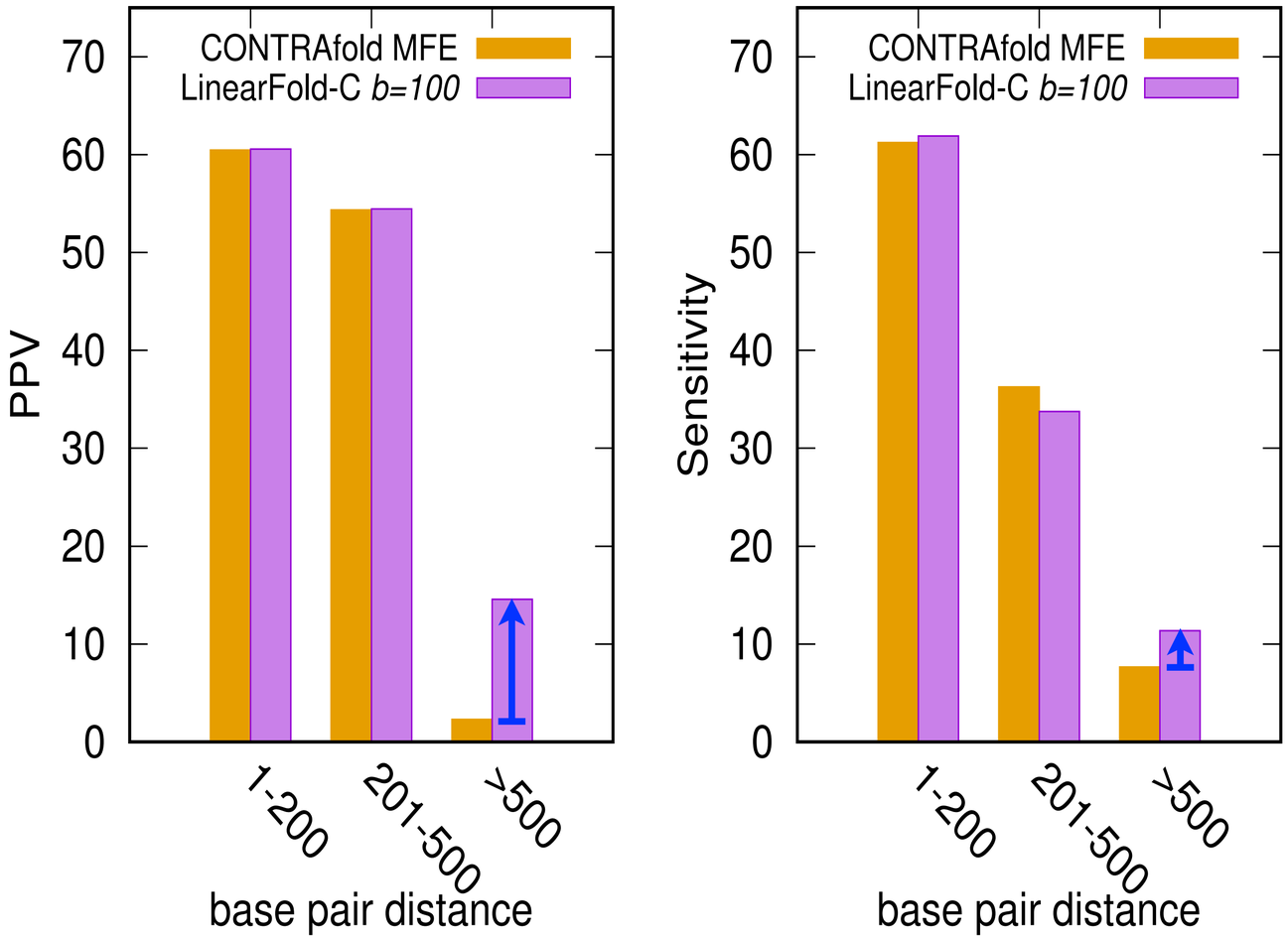

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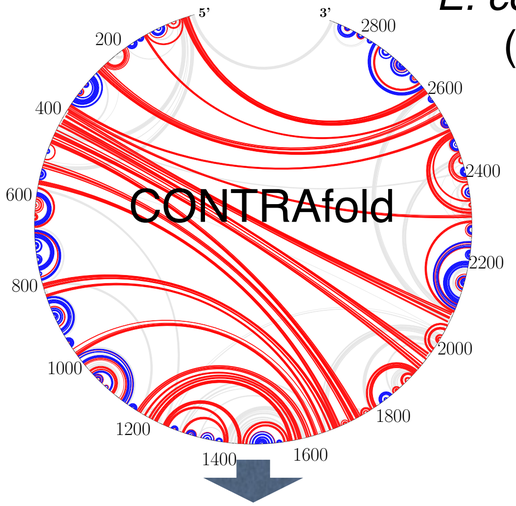
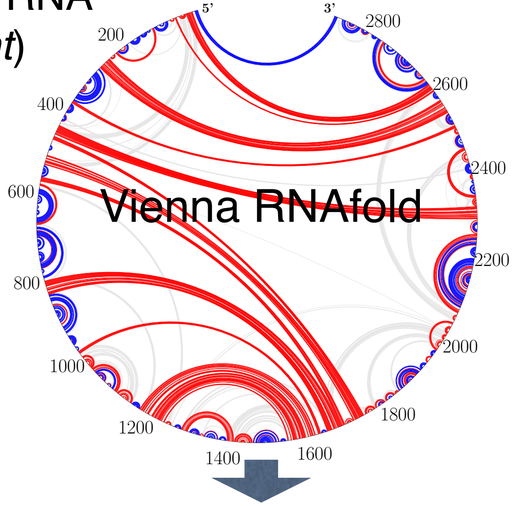
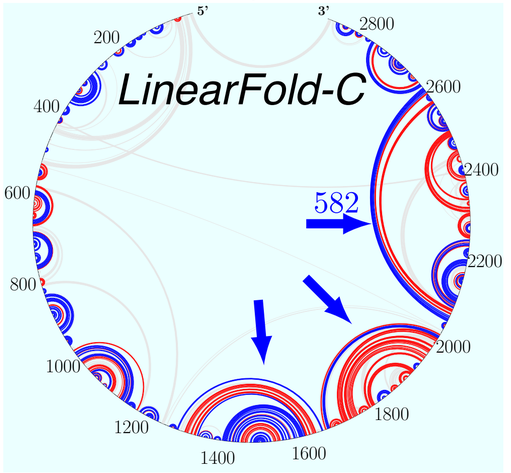
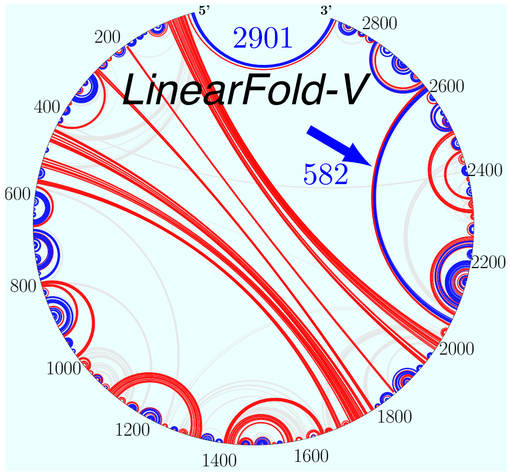


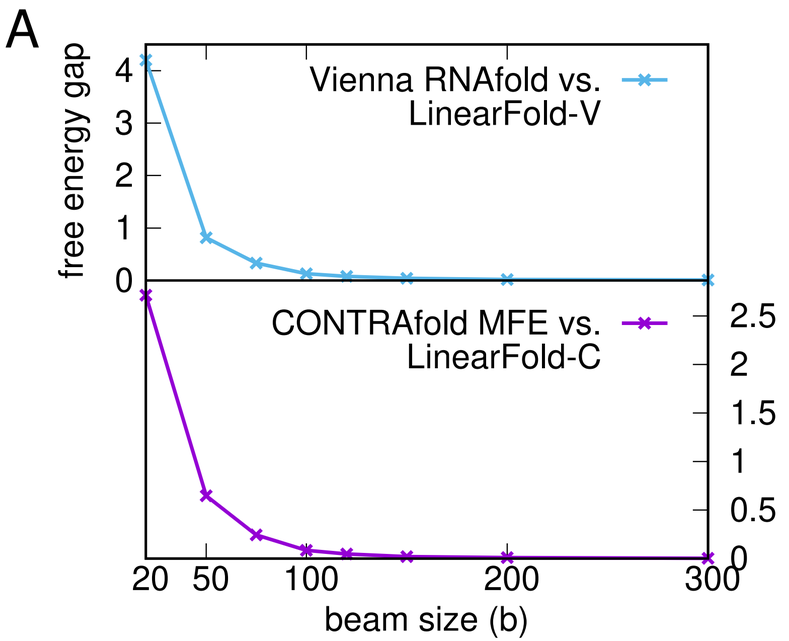


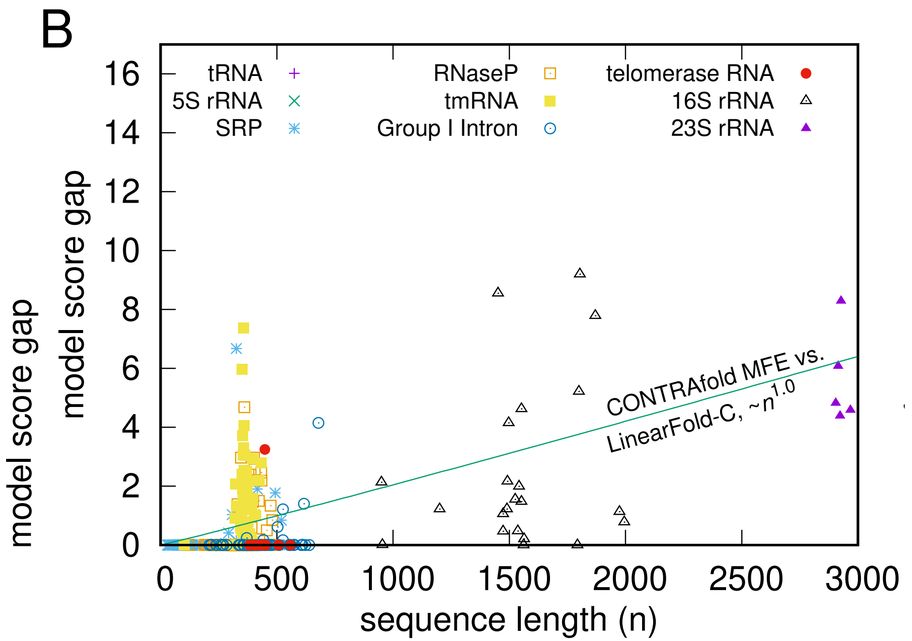


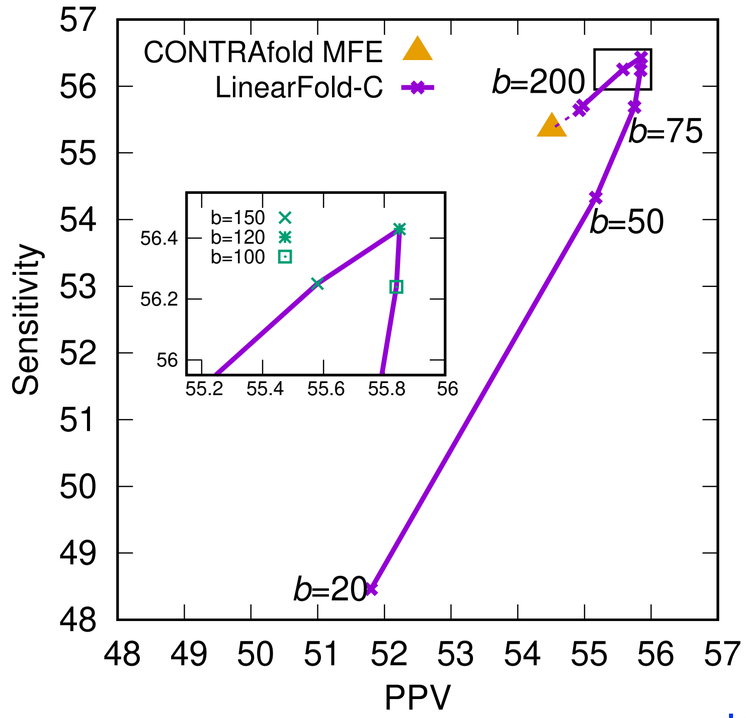


Search (Approximation) Quality

- search error = energy (or model score) gap between exact search and our search
  - search error quickly shrinks to 0 as beam size increases
  - search error grows linearly with sequence length (constant search error per nucleotide)
  - both PPV & Sensitivity peaks around beam=120, but we choose beam=100 for simplicity

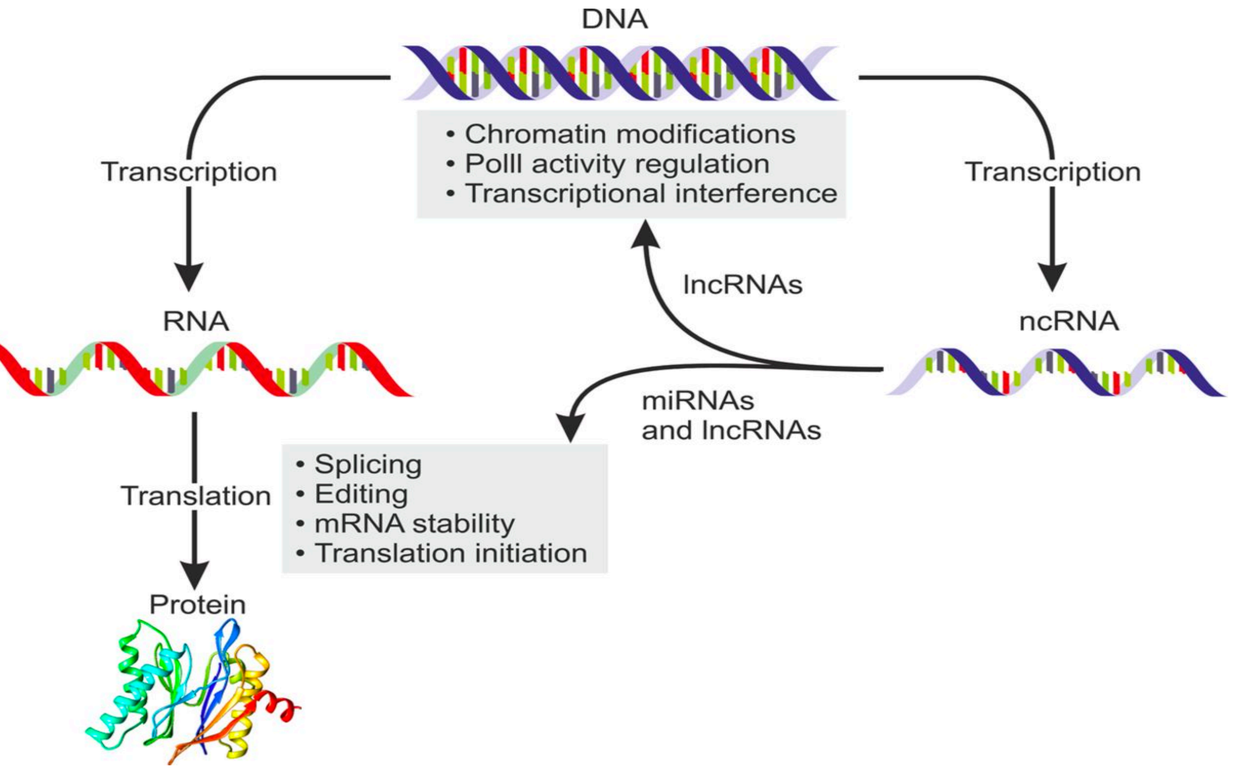


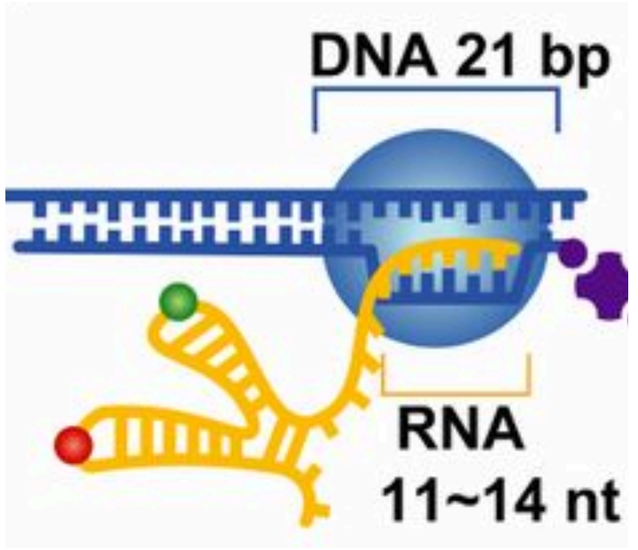


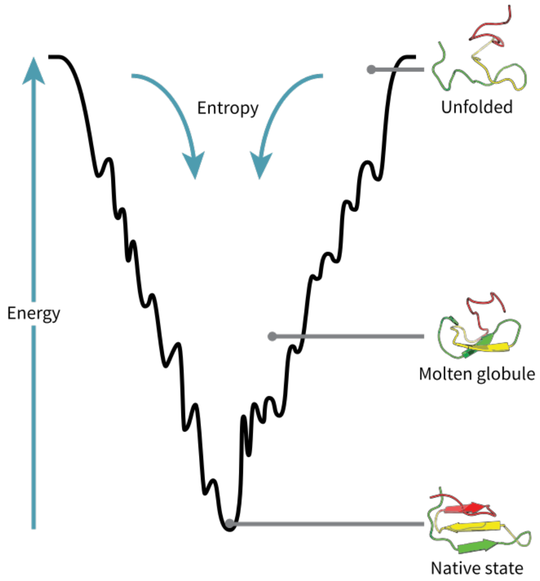


Connections to Cotranscriptional Folding

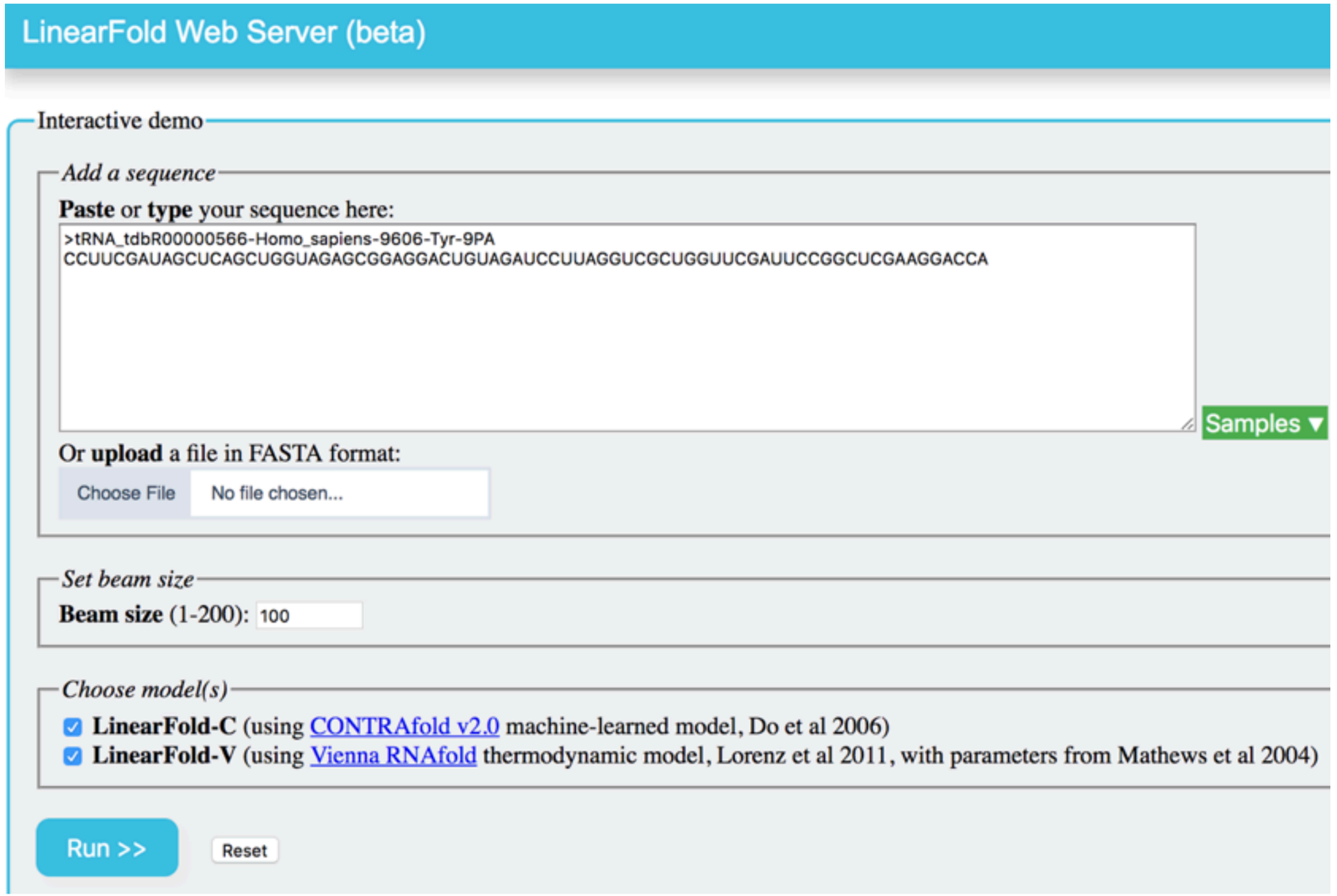
- RNAs & proteins fold while being assembled
- RNA & protein sequences evolve to be incrementally foldable
- these might explain why LinearFold performs better than exact search







LinearFold Server & GitHub

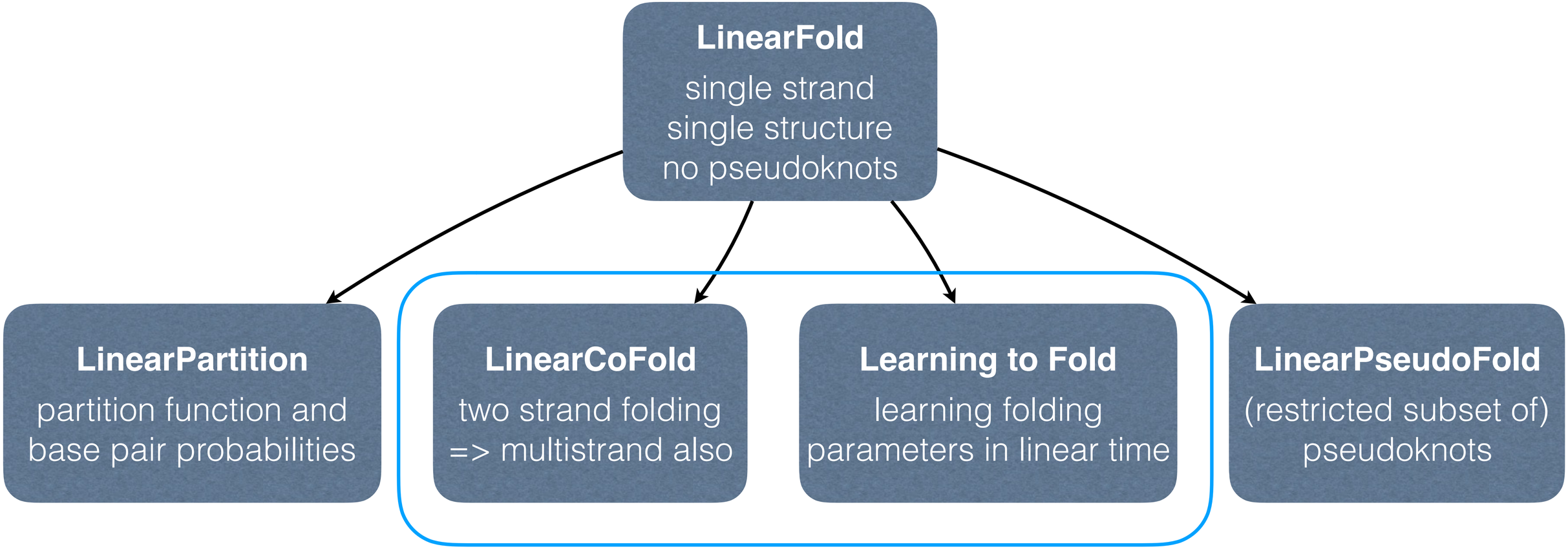


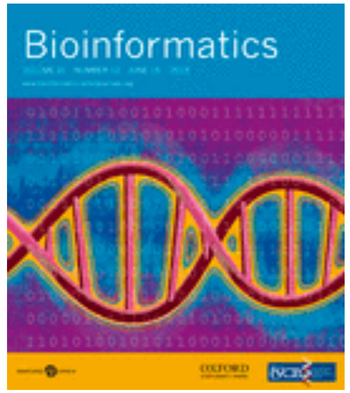
- fastest RNA folding server (by a very large margin)
  - thanks to O(n) time
- longest sequence limit
  - 100,000 nt (10x Vienna)
  - thanks to O(n) space
- source code on GitHub
  - unified implementation of LinearFold-C & LinearFold-V

http://linearfold.org

https://github.com/LinearFold/LinearFold

Extensions of LinearFold



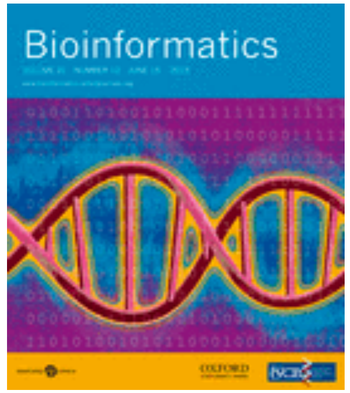


first linear-time (approximate) RNA folding algorithm

better in accuracy (esp. long seqs and long-range pairs)

http://linearfold.org

Thank you very much !



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http://linearfold.org

Oregon State University

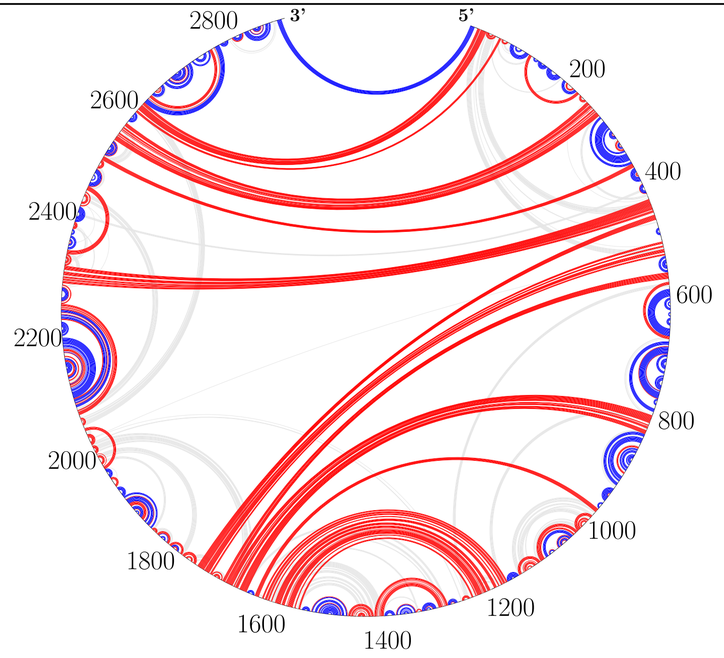
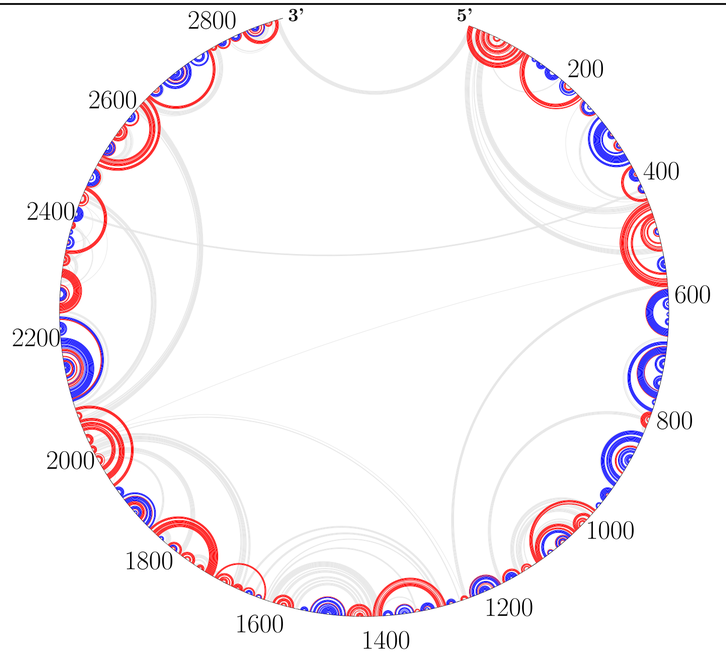
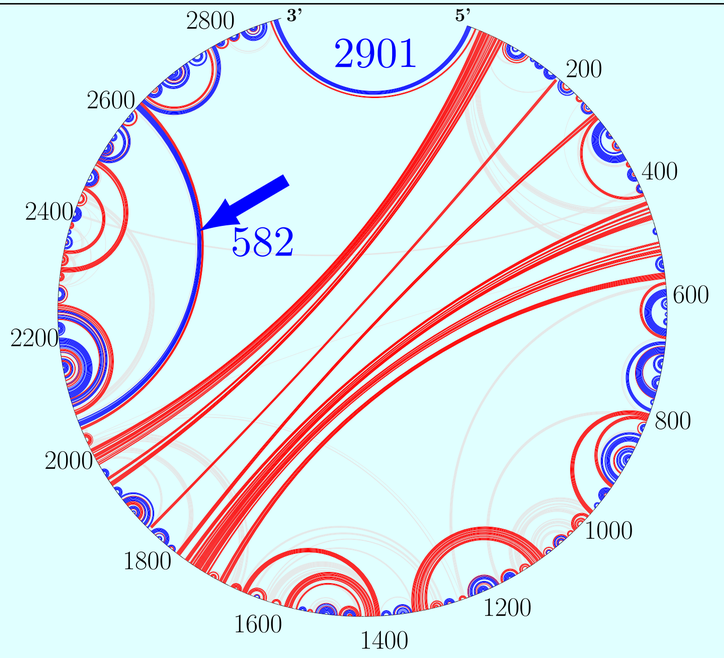
Baidu Research

UNIVERSITY of ROCHESTER

Backup Slide: Local Folding

type	*pair distance*	*time*	*space*	*systems/examples*
global	unbounded	$O(n^3)$	$O(n^2)$	RNAstructure, RNAfold, ...
local	$\leq L$	$O(nL^2)$	$O(nL)$	Rfold, RNAplfold, LocalFold, ...
global	unbounded	$O(nb \log b)$	$O(nb)$	LinearFold (**this work**)

23S rRNA *E. coli* (2904 *nt*, 830 pairs)

Vienna RNAfold	Vienna RNAfold Local (L=150)	LinearFold-V b = 100
		
PPV: 52.02, Sens.: 57.47, pairs: 917, time: 7.6s.	PPV: 51.63, Sens.: 55.18, pairs: 887, time: 6.3s.	PPV: 55.60, Sens.: 62.17, pairs: 928, time: 2.2s.