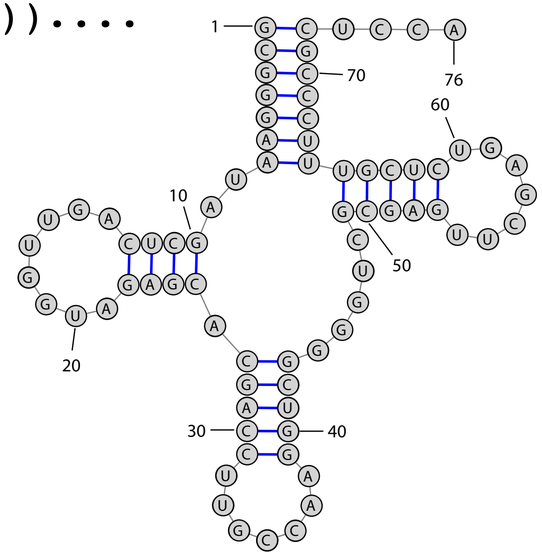
LinearFold: Linear-Time Parsing Meets RNA Folding

x GCGGGAAUAGCUCAGUUGGUAGAGCACGACCUUGCCAAGGUCGGGGUCGCGAGUUCGAGUCUCGUUUCCCGCUCCA

y ((((((((..((((........))))).((((.......)))).....(((((.......)))))))))))....



Liang Huang

Oregon State University & Baidu Research USA

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

ISMB ECCB 2019 BASEL JULY 21–25 ISCB International Society for Computational Biology

Oregon State University

Baidu Research

University of Rochester

Southern California NLP Symposium, September 2019

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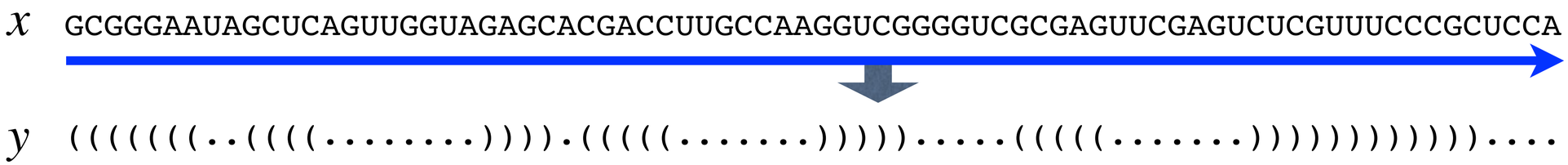

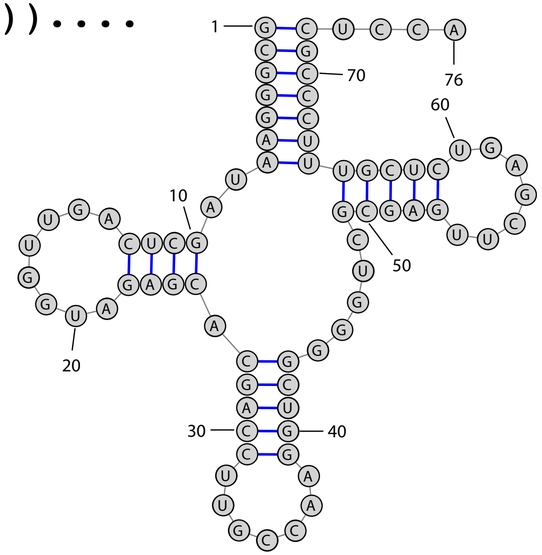

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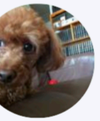
Appetizer: Simultaneous Translation

ACL 2019 Invited Talk

Simultaneous Translation: Recent Advances and Remaining Challenges

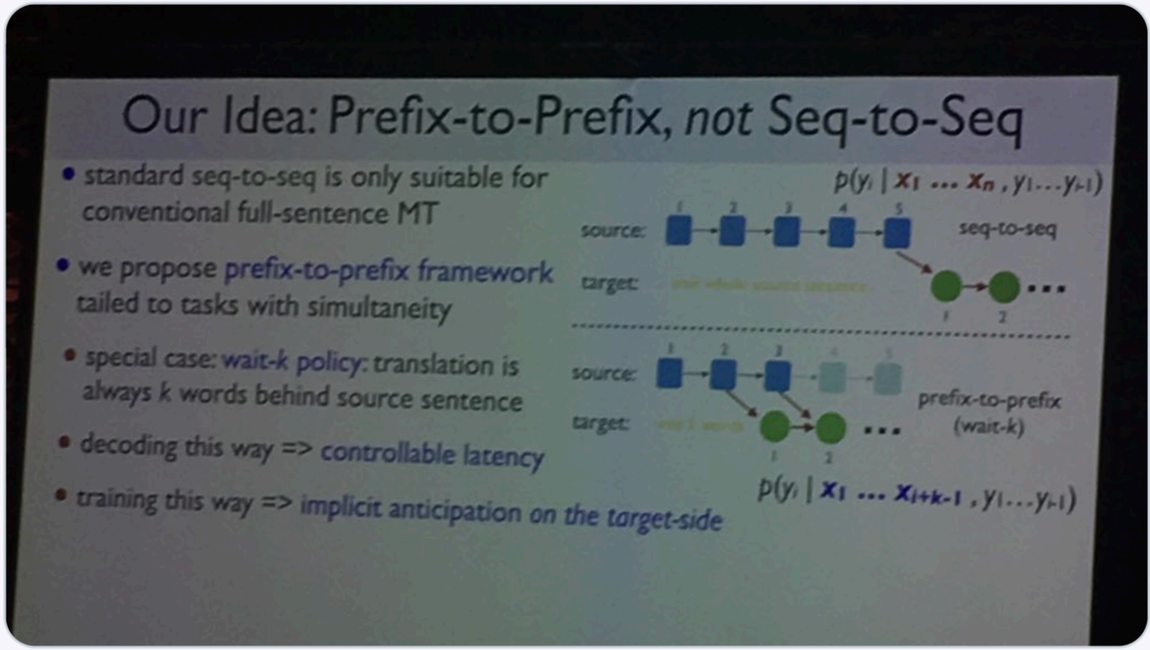


Kyunghyun Cho @kchonyc · Jul 30

very happy to see the first invited talk of the conference is on simultaneous translation. @thoma_gu I think we should've continued this direction ;)

Rada Mihalcea @radamihalcea · Jul 30

Great insight from Liang Huang's #ACL2019nlp keynote: When it comes to simultaneous tasks such as speech-to-speech MT, "forget about sequence to sequence", do instead prefix-to-prefix. Even during training when entire seqs are available, it's beneficial to only consider prefixes.



Appetizer: Simultaneous Translation

Baidu World Conference, Nov. 2017
full-sentence translation (latency: 10+ secs)

our work

Baidu World Conference, Nov. 2018
low-latency simultaneous translation (latency: ~3 secs)

Media coverage:

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- seq-to-seq is only suitable for conventional full-sentence MT
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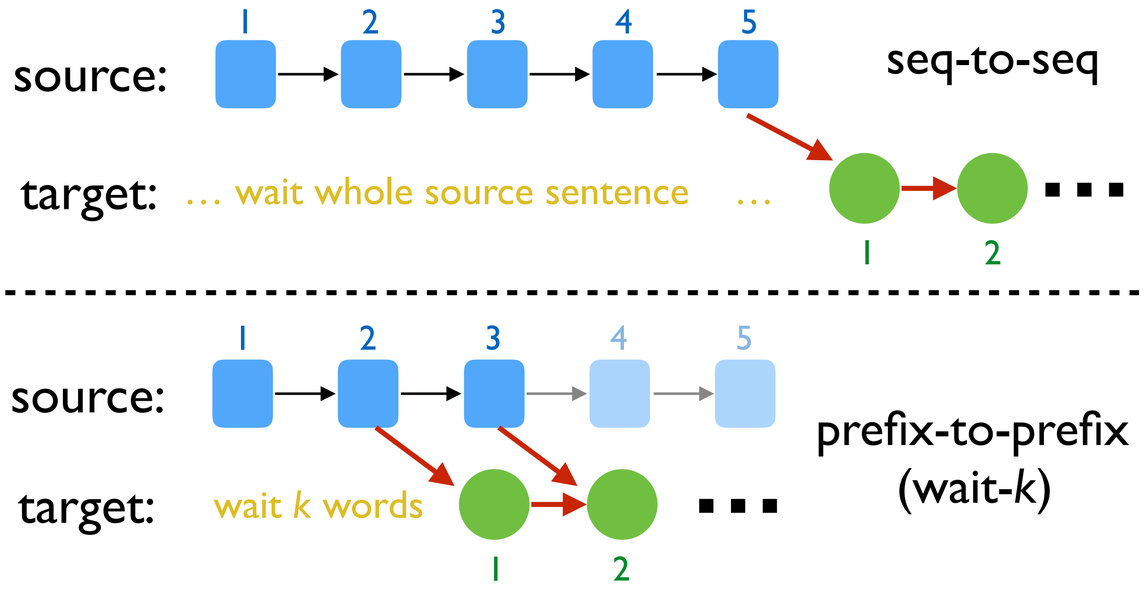
  - special case: wait-*k* policy: translation is always *k* words behind source sentence
  - training in this way enables anticipation



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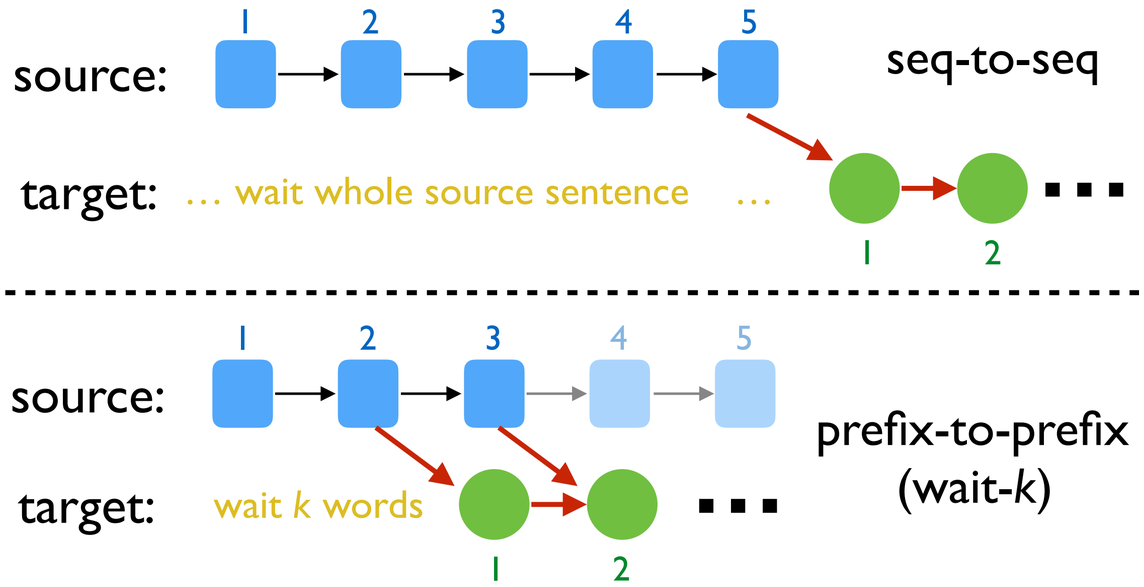

Bùshí *zǒngtǒng*

布什 总统

Bush *President*

President

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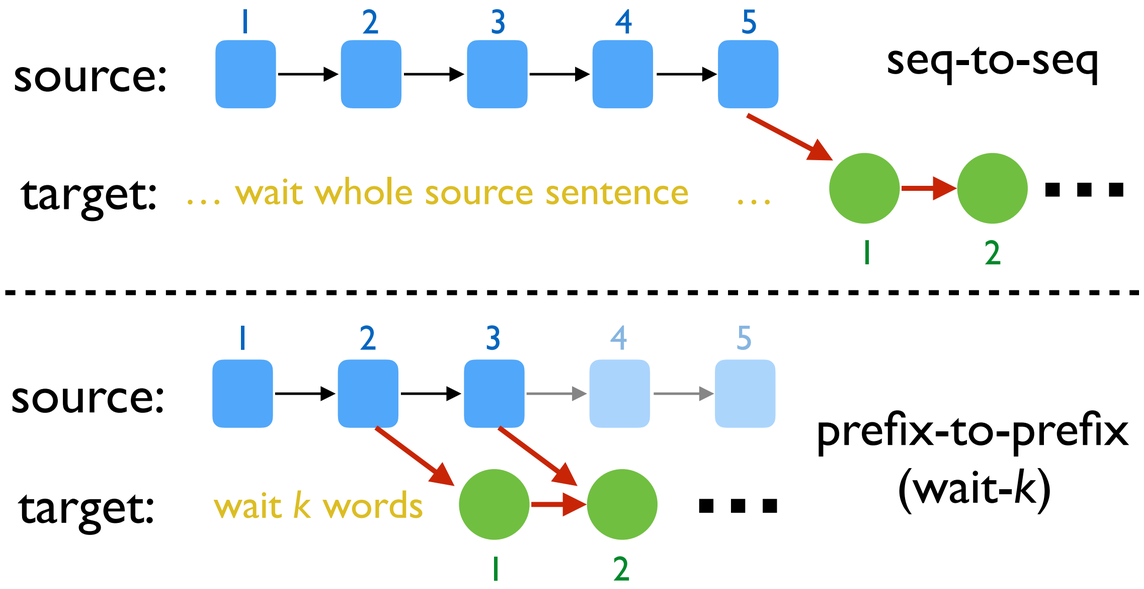

Bùshí	*zǒngtǒng*	*zài*
布什	总统	在
Bush	*President*	*in*

President Bush

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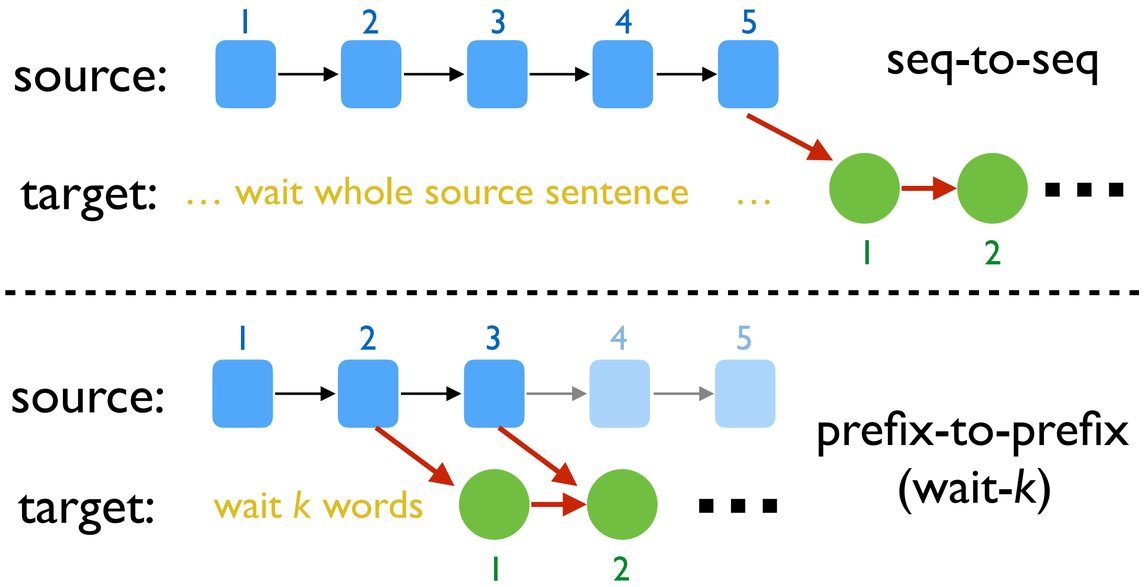

Bùshí	*zǒngtǒng*	*zài*	*Mòsīkē*
布什	总统	在	莫斯科
Bush	*President*	*in*	*Moscow*

President Bush meets

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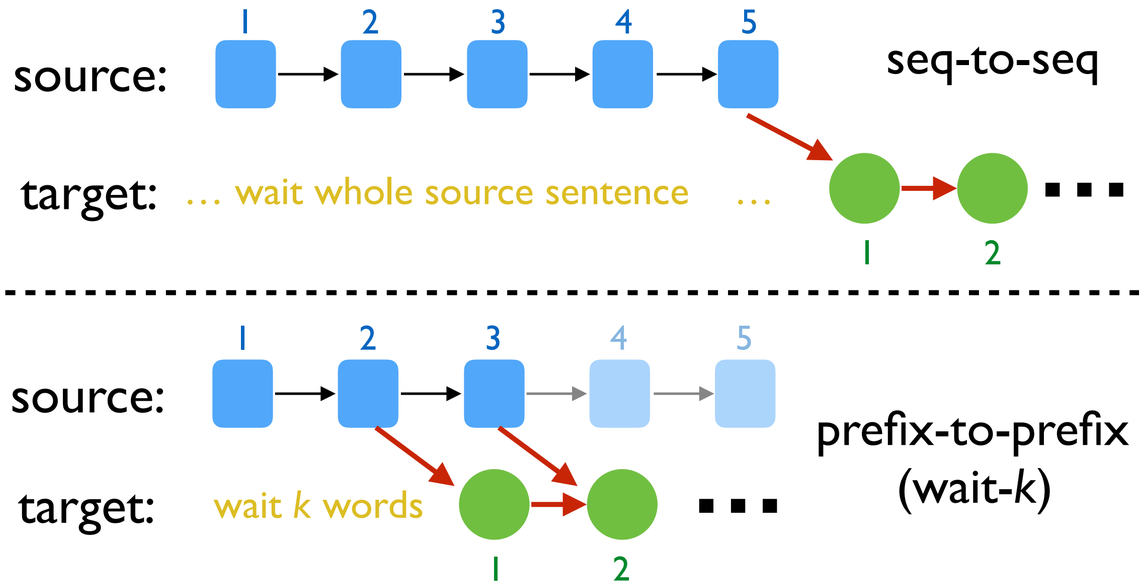

Bùshí	*zǒngtǒng*	*zài*	*Mòsīkē*	*yǔ*
布什	总统	在	莫斯科	与
Bush	*President*	*in*	*Moscow*	*with*

President Bush meets with

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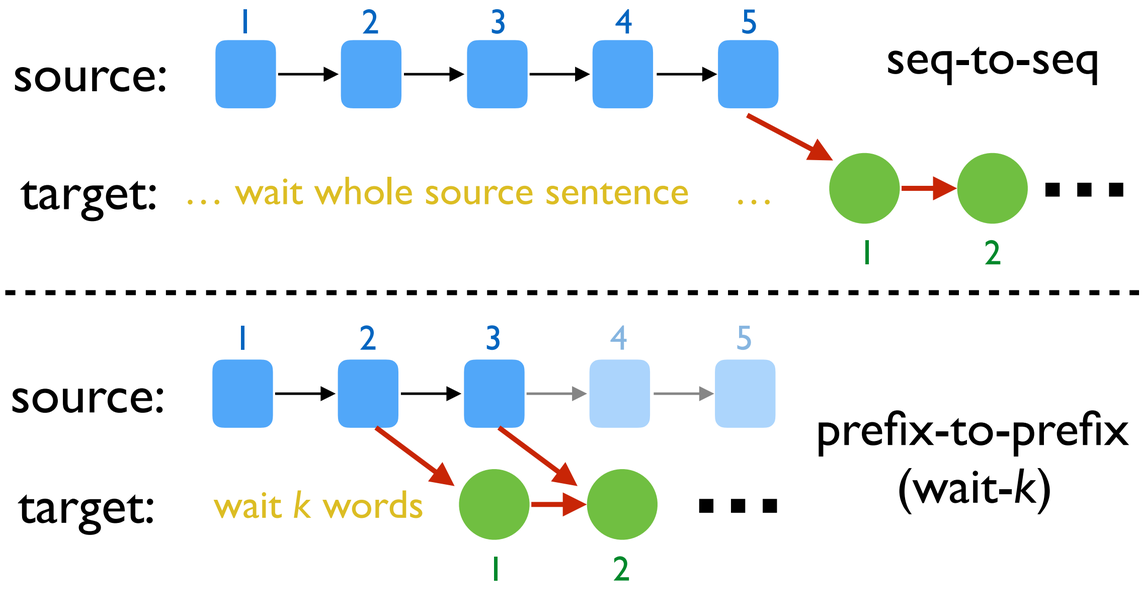

Bùshí	*zǒngtǒng*	*zài*	*Mòsīkē*	*yǔ*	*Éluósī*
布什	总统	在	莫斯科	与	俄罗斯
Bush	*President*	*in*	*Moscow*	*with*	*Russian*

President Bush meets with Russian

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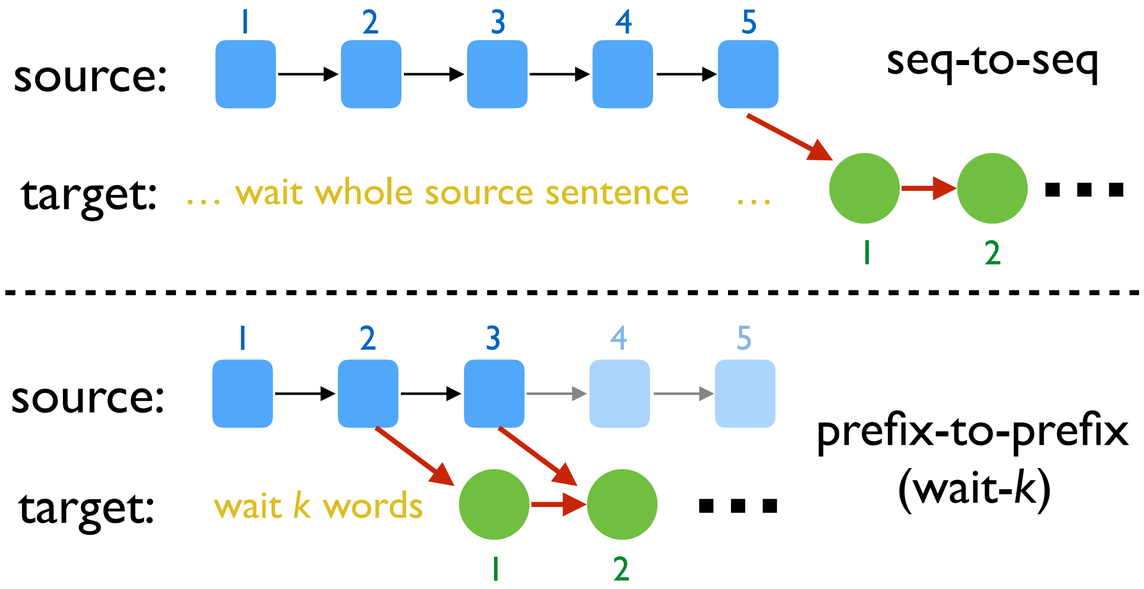

Bùshí	*zǒngtǒng*	*zài*	*Mòsīkē*	*yǔ*	*Éluósī*	*zǒngtǒng*
布什	总统	在	莫斯科	与	俄罗斯	总统
Bush	*President*	*in*	*Moscow*	*with*	*Russian*	*President*

President Bush meets with Russian President

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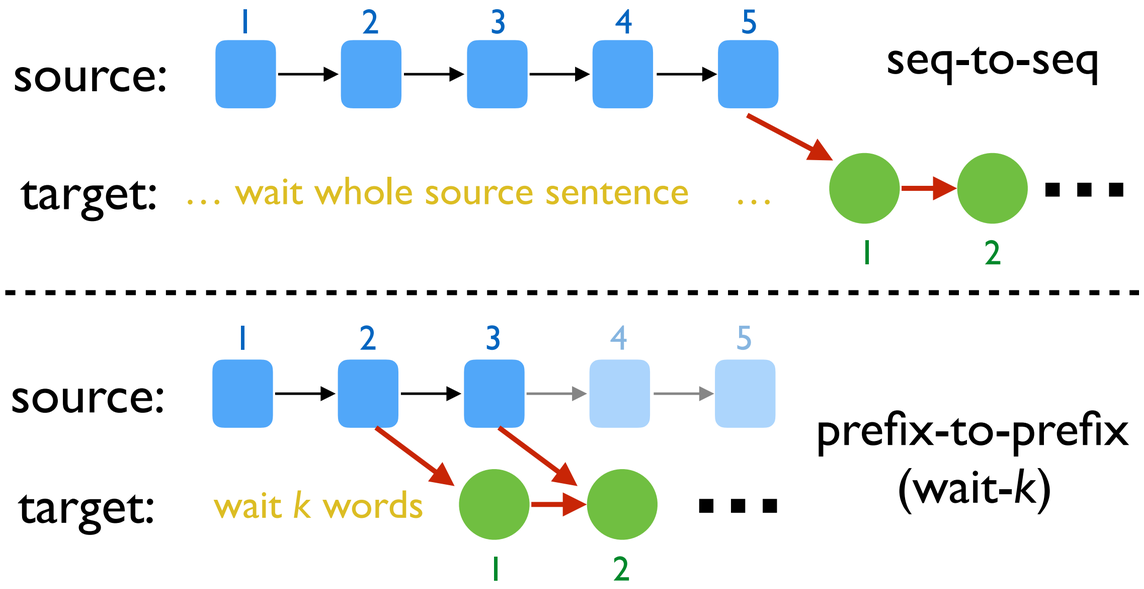

Bùshí	*zǒngtǒng*	*zài*	*Mòsīkē*	*yǔ*	*Éluósī*	*zǒngtǒng*	*Pǔjīng*
布什	总统	在	莫斯科	与	俄罗斯	总统	普京
Bush	*President*	*in*	*Moscow*	*with*	*Russian*	*President*	*Putin*

President Bush meets with Russian President Putin

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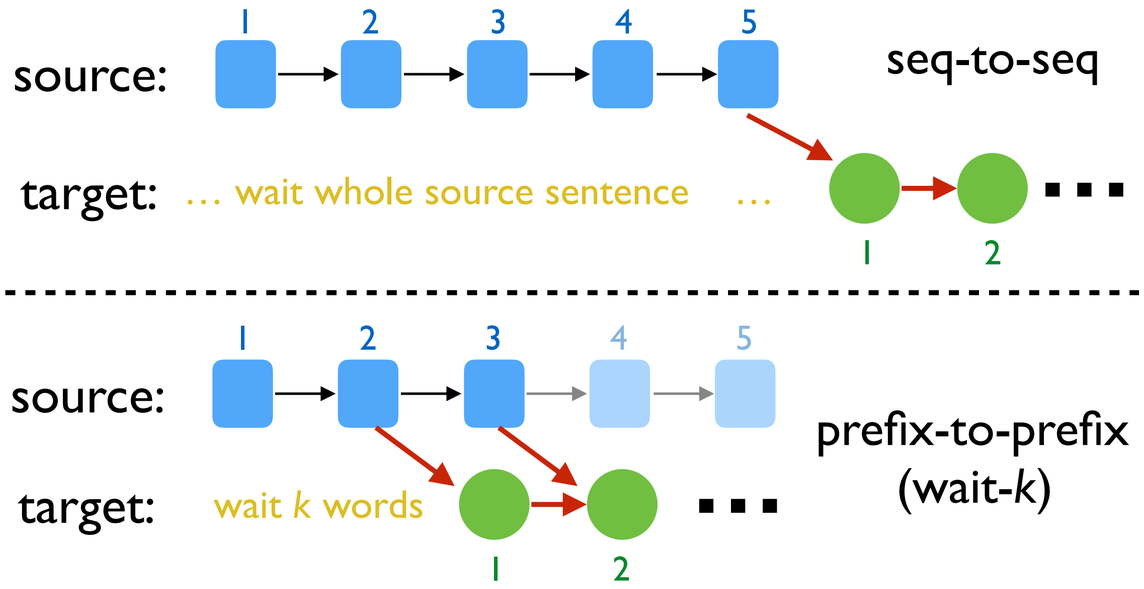

Bùshí	*zǒngtǒng*	*zài*	*Mòsīkē*	*yǔ*	*Éluósī*	*zǒngtǒng*	*Pǔjīng*	*huìwù*
布什	总统	在	莫斯科	与	俄罗斯	总统	普京	会晤
Bush	*President*	*in*	*Moscow*	*with*	*Russian*	*President*	*Putin*	*meet*

President Bush meets with Russian President Putin in Moscow

Entreé: Linear-Time RNA Folding

x GCGGGAAUAGCUCAGUUGGUAGAGCACGACCUUGCCAAGGUCGGGGUCGCGAGUUCGAGUCUCGUUUCCCGCUCCA

y ((((((..((((........))))).((((.......)))).....((((.......))))))))))....

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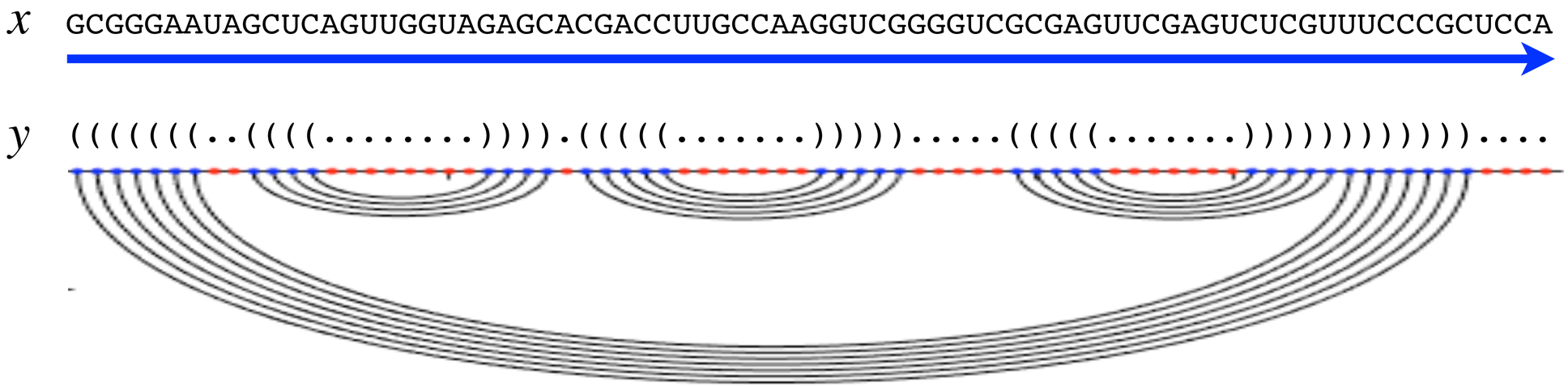

Background: RNAs and RNA folding

RNA has dual roles:
informational (DNA=>RNA=>protein)
functional (non-coding RNAs)
knowing structures can infer function

RNA sequence

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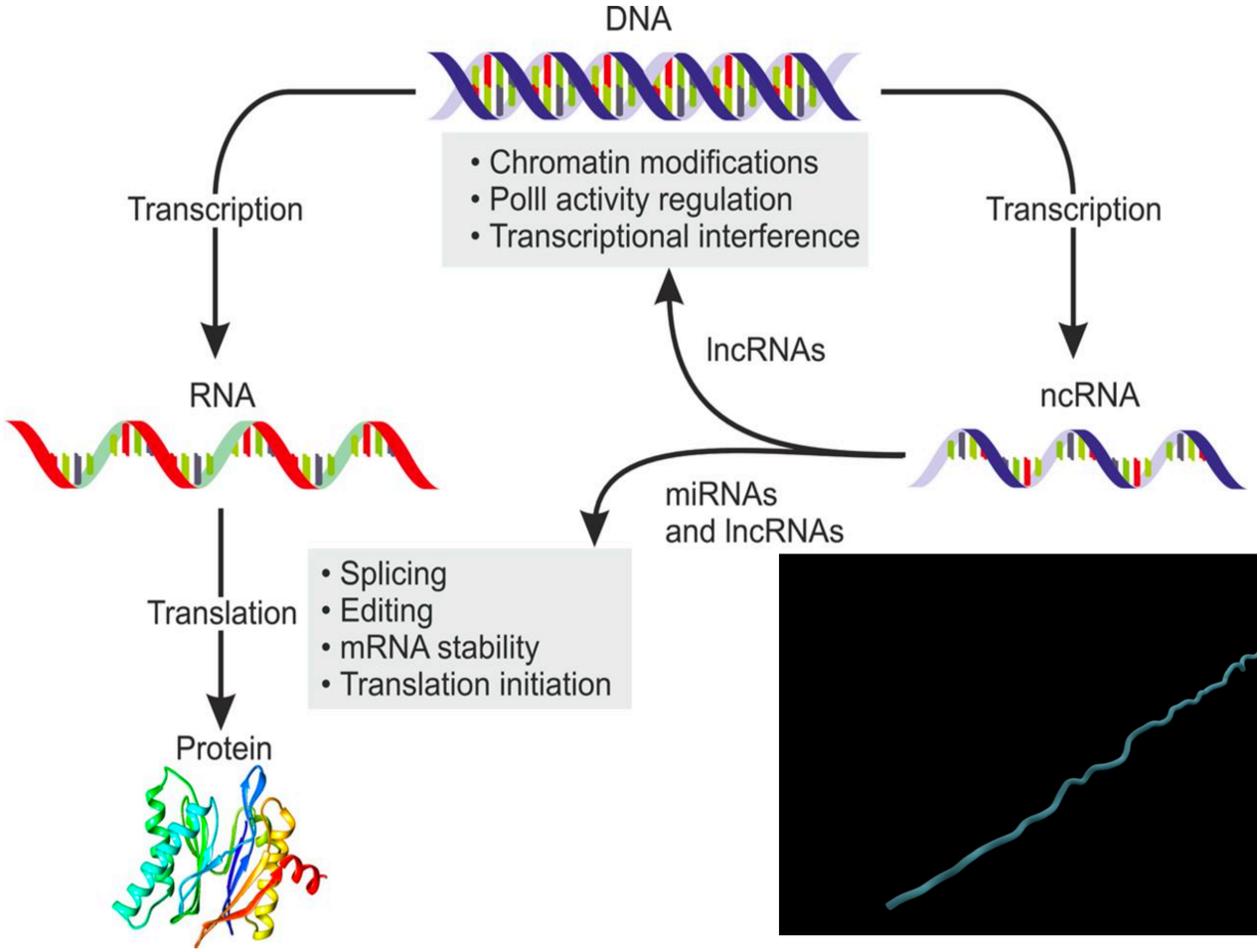

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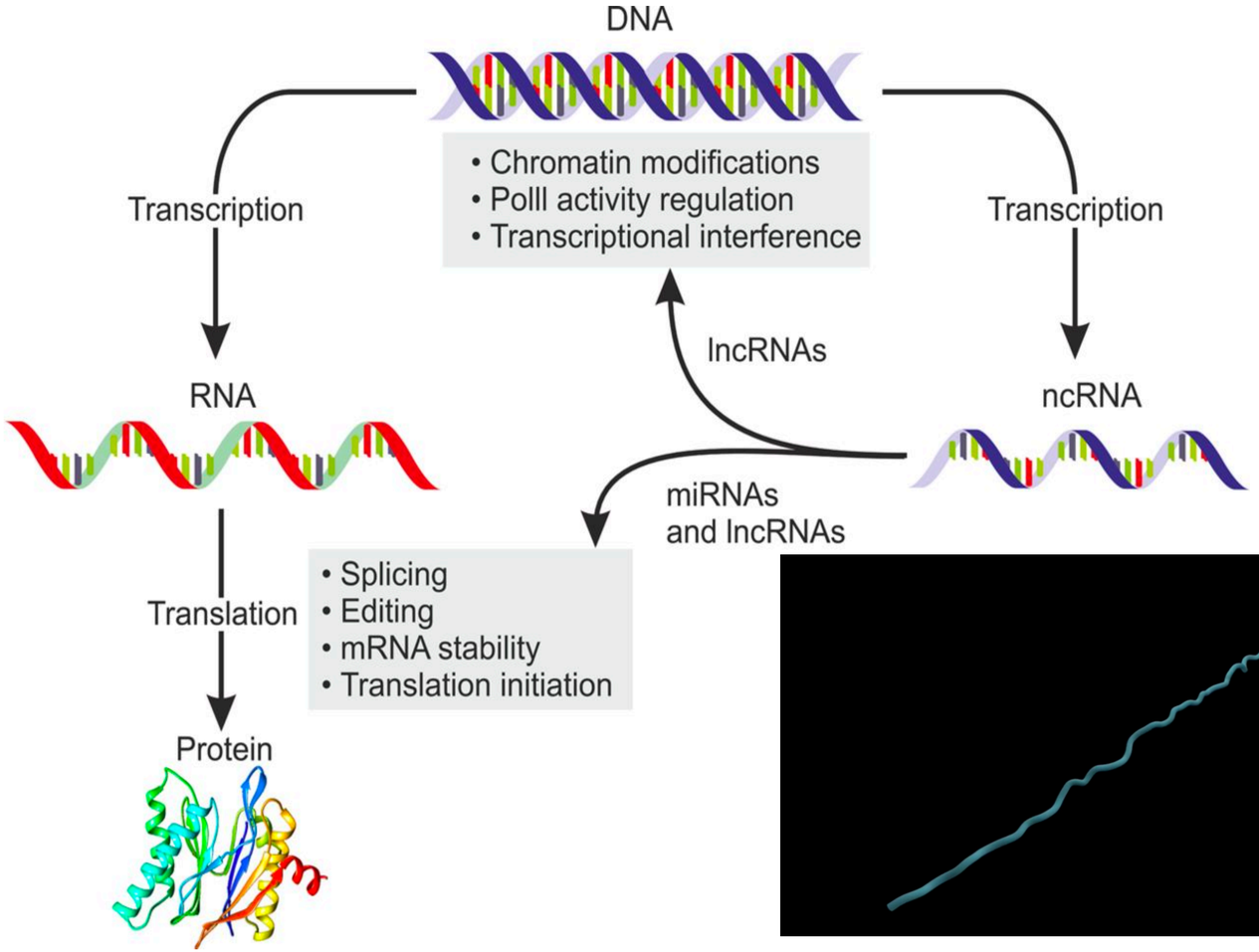

RNA sequence

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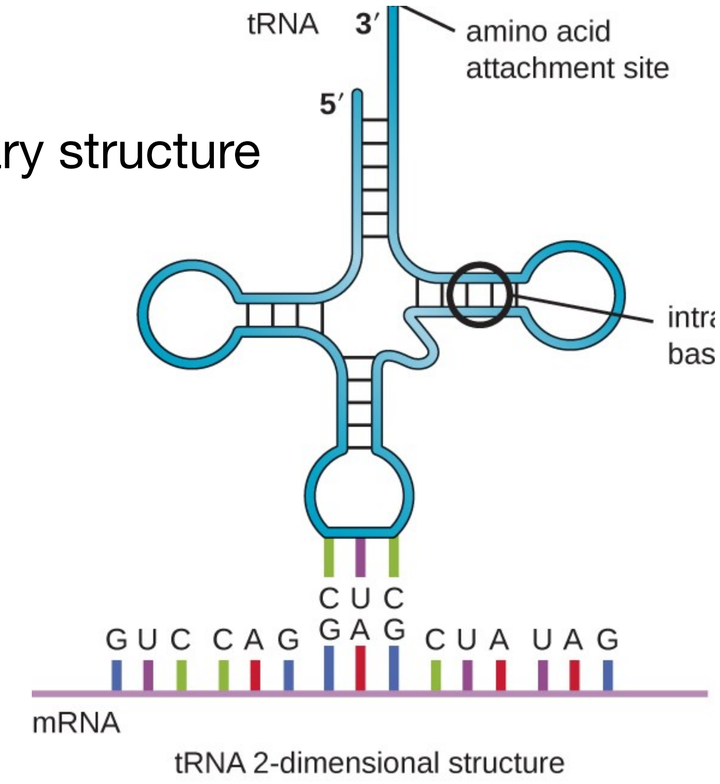
structure prediction
("RNA folding")

secondary structure



tRNA 2-dimensional structure

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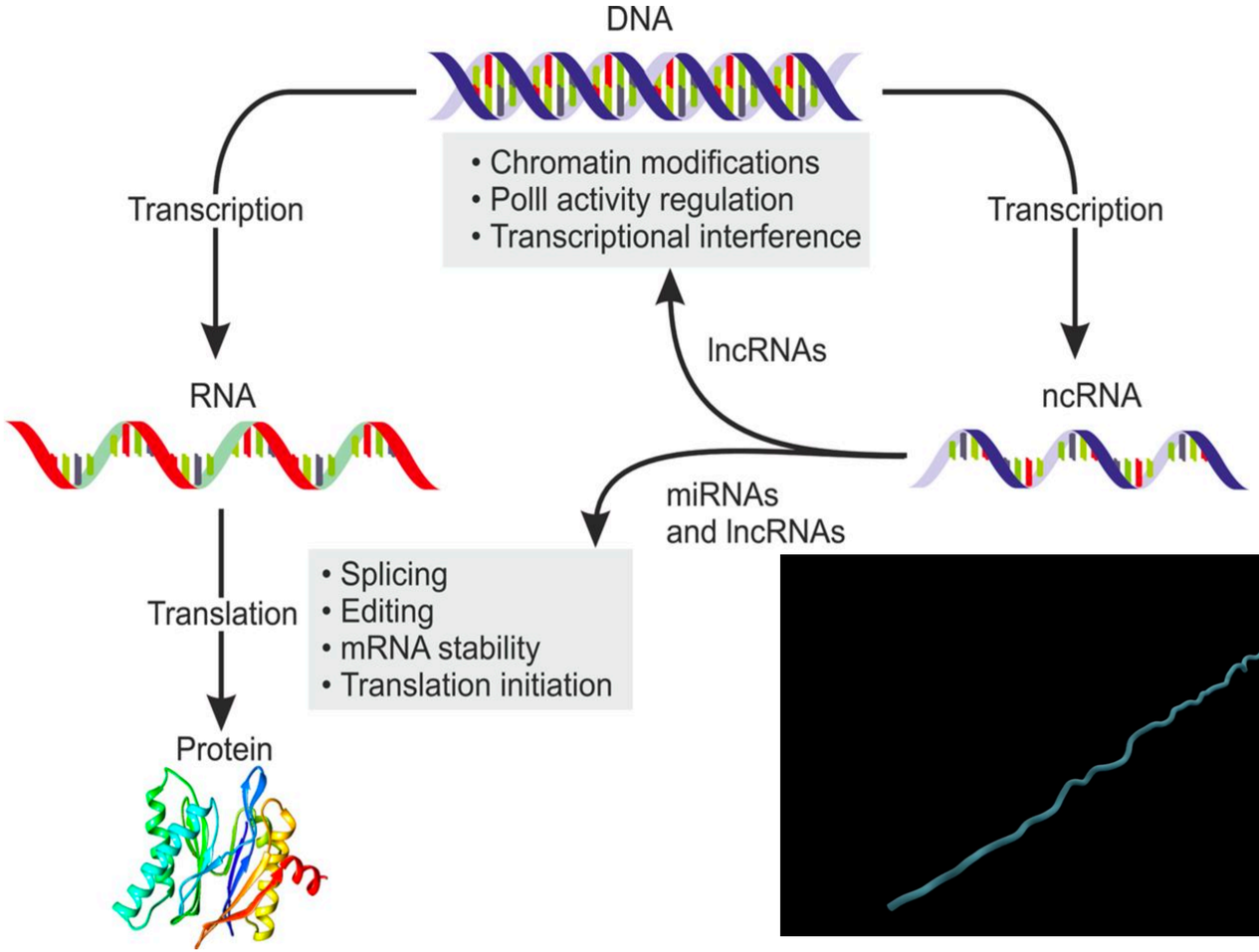

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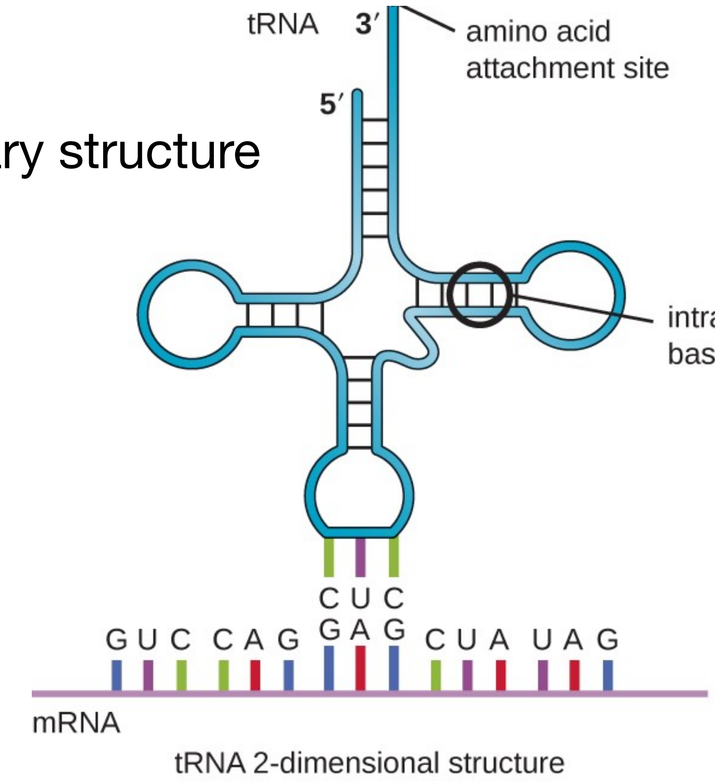

tRNA 2-dimensional structure

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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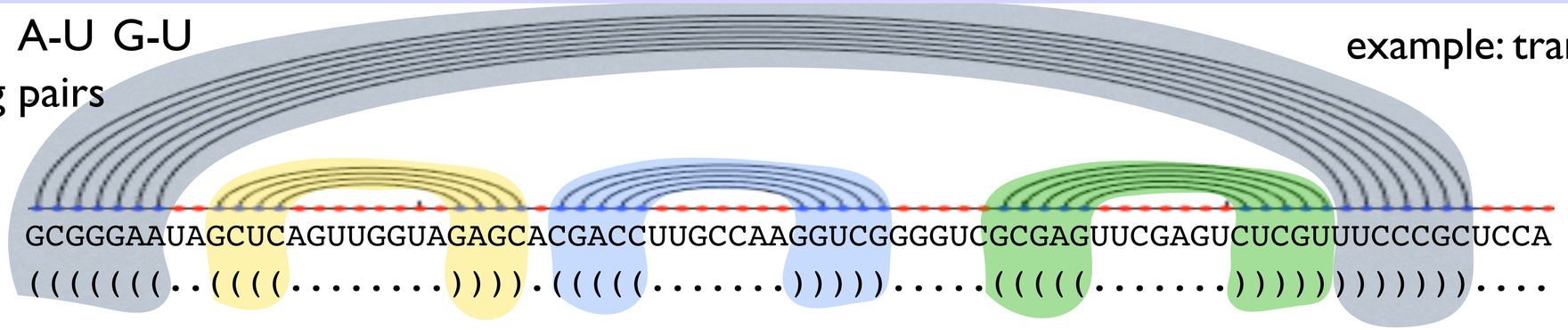

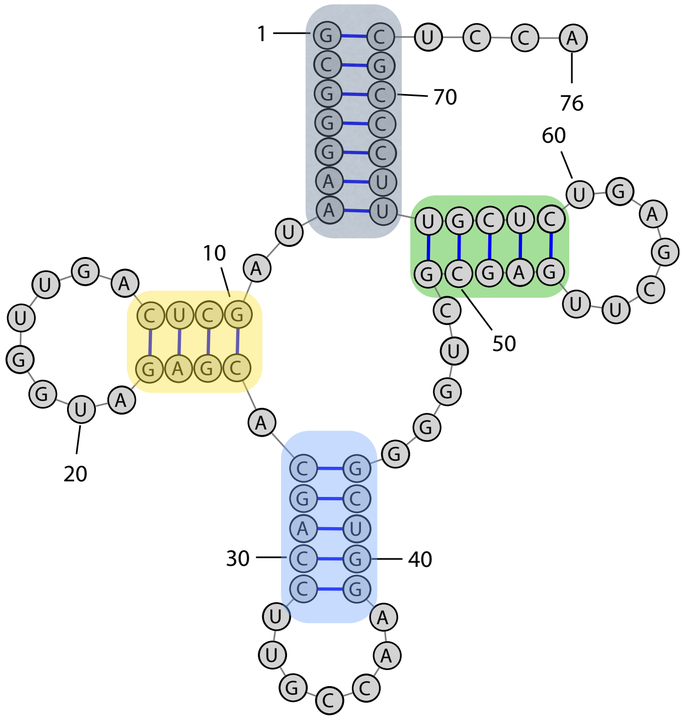

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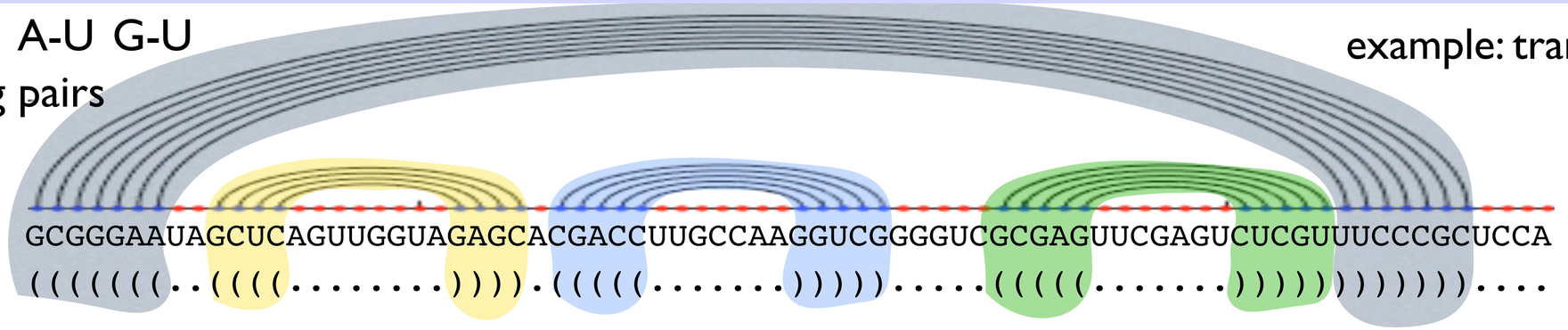

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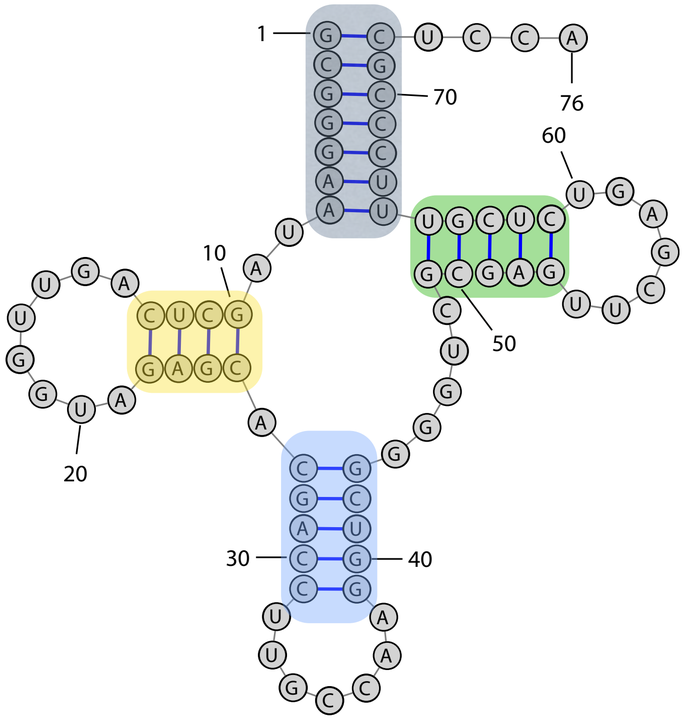

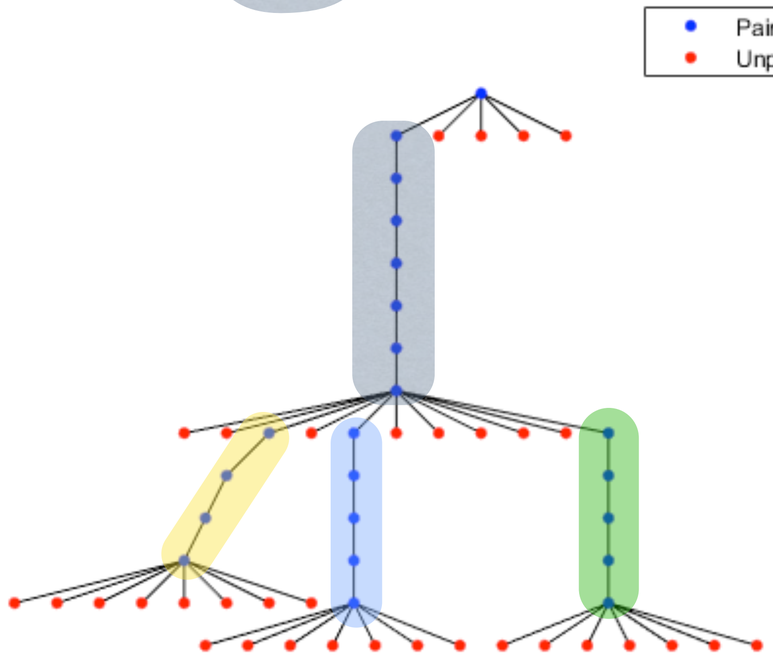

parse tree

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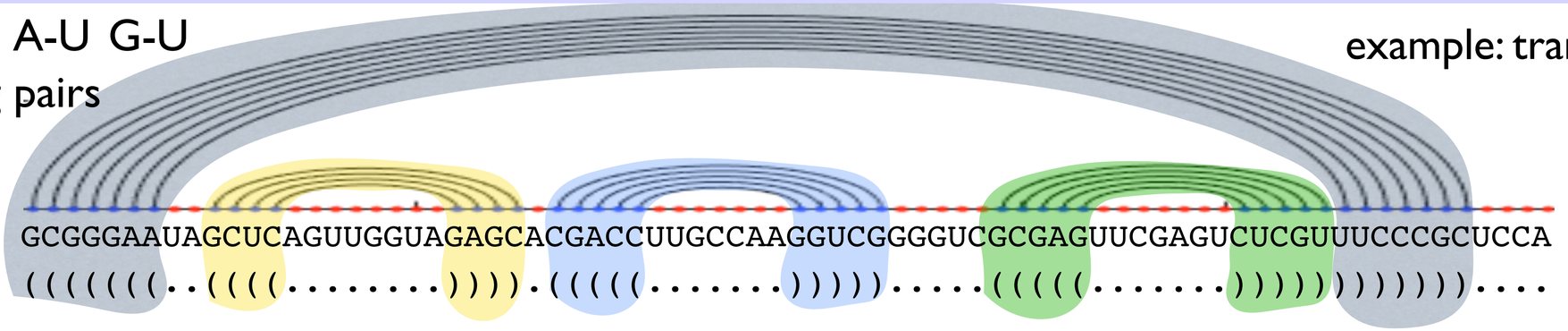
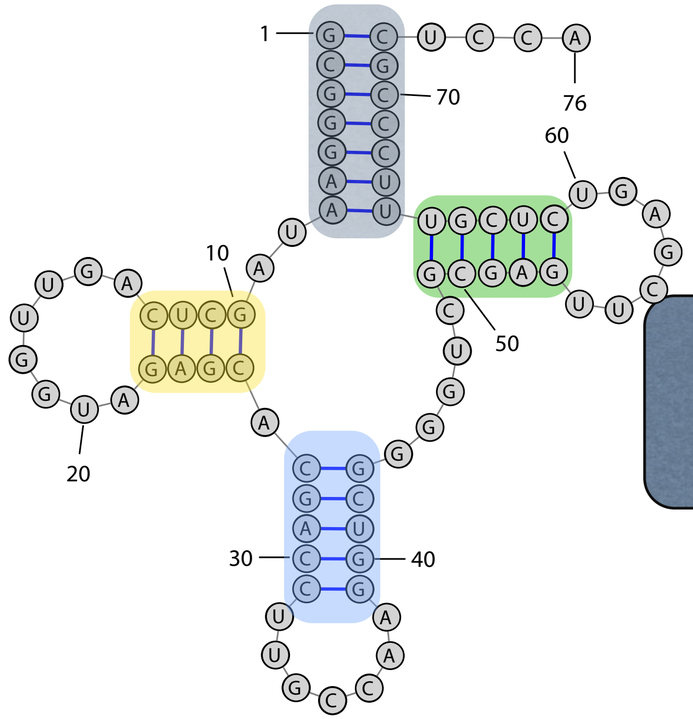
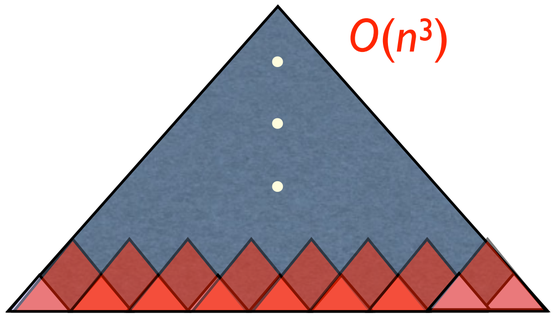
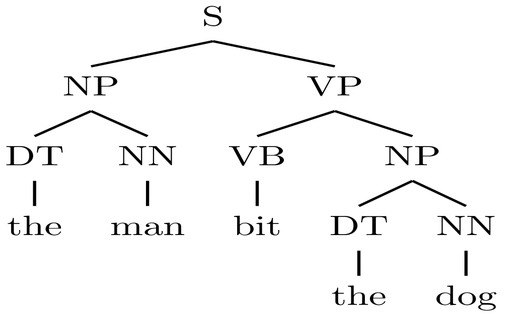
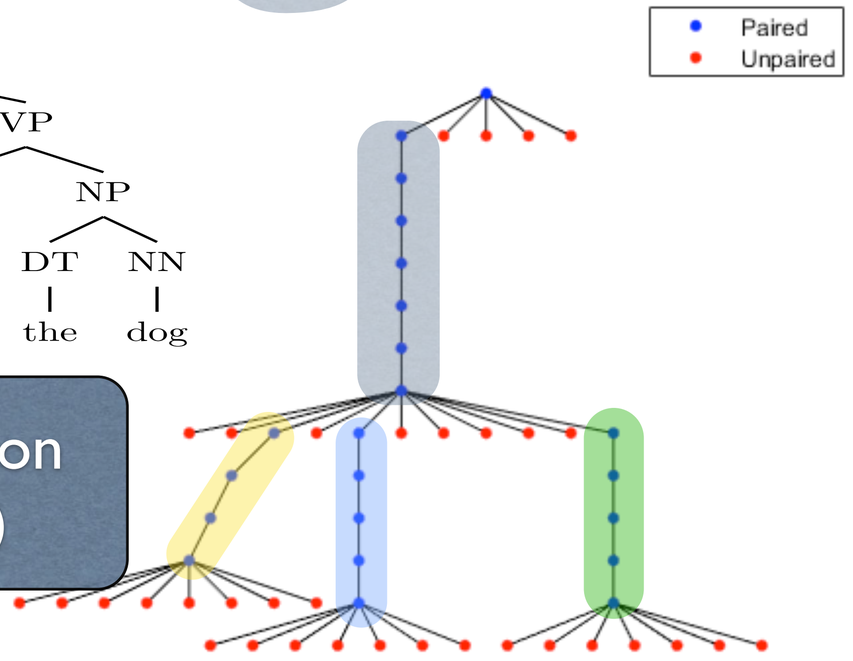








problem: standard structure prediction algorithms are way too slow: $O(n^3)$



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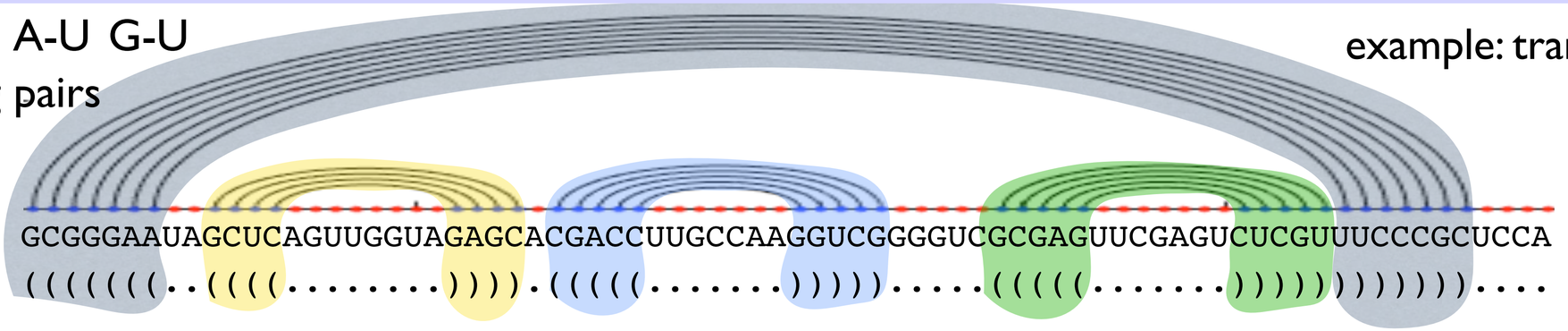
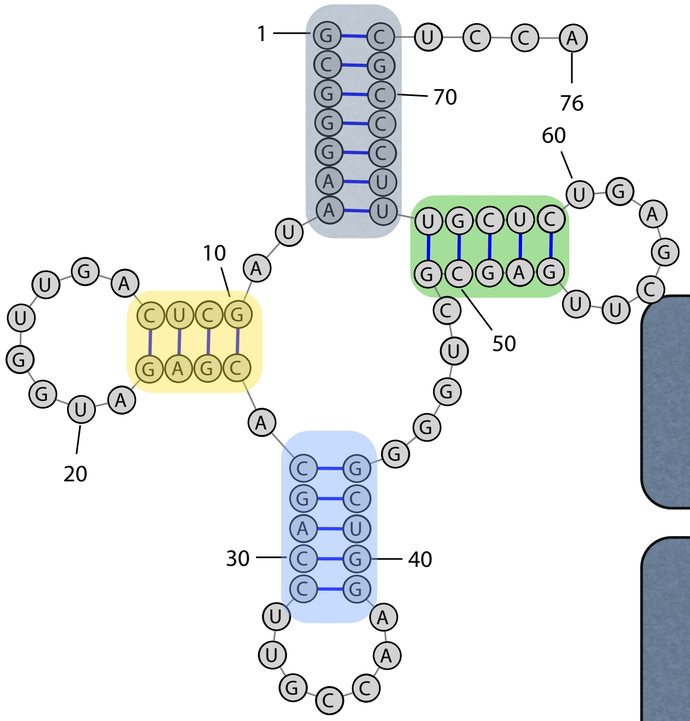
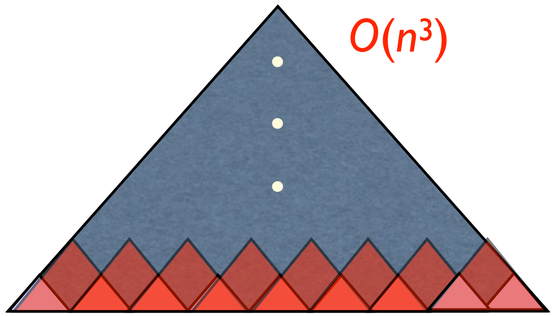
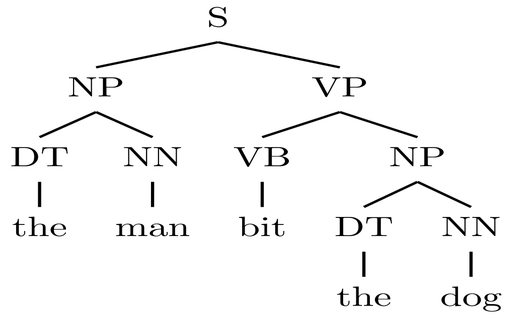
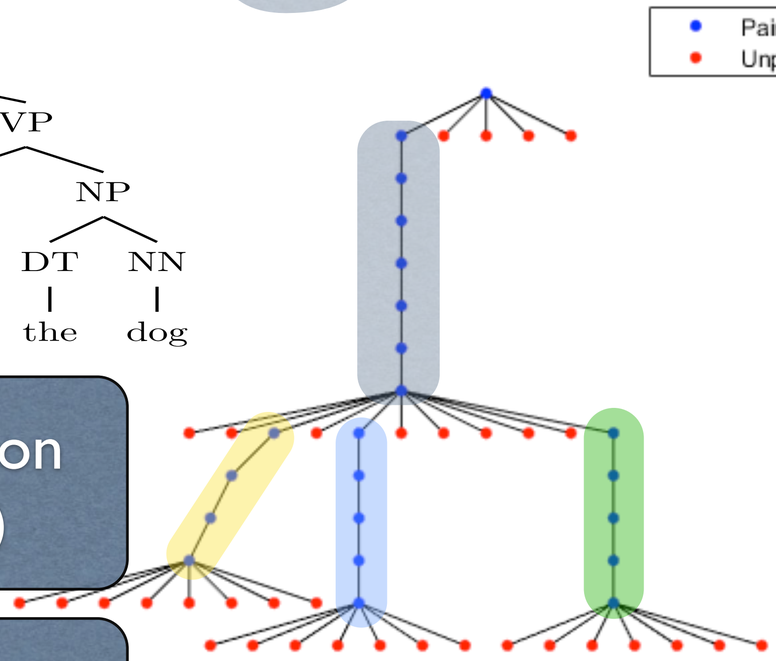










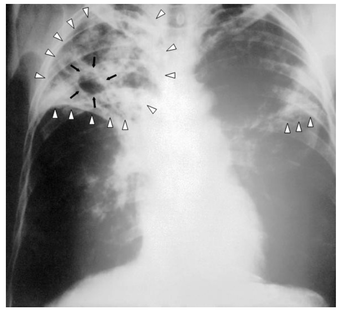
parse tree

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

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

Fast Structure Prediction Enables RNA Design

detecting active TB using RNA design
which needs our fast RNA folding



Professor **Rhiju Das**
Stanford Medical School

EteRNA game
(RNA design)

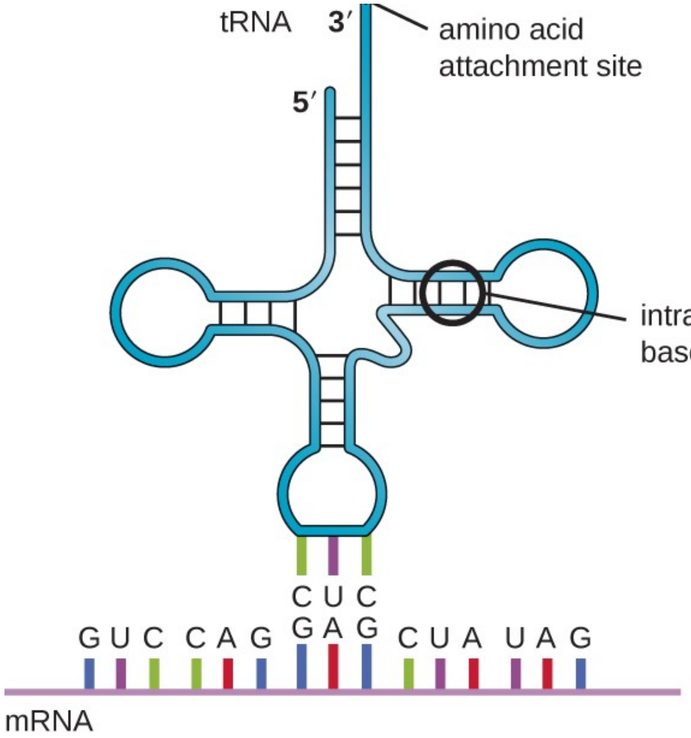
RNA sequence

GCGGGAAUAGCUCAGUUGGUAGAGCACGACCUUGCCAAGGUCGGGGUCGCGAGUUCGAGUCUCGUUUCCCGCUCCA

structure prediction ("folding")

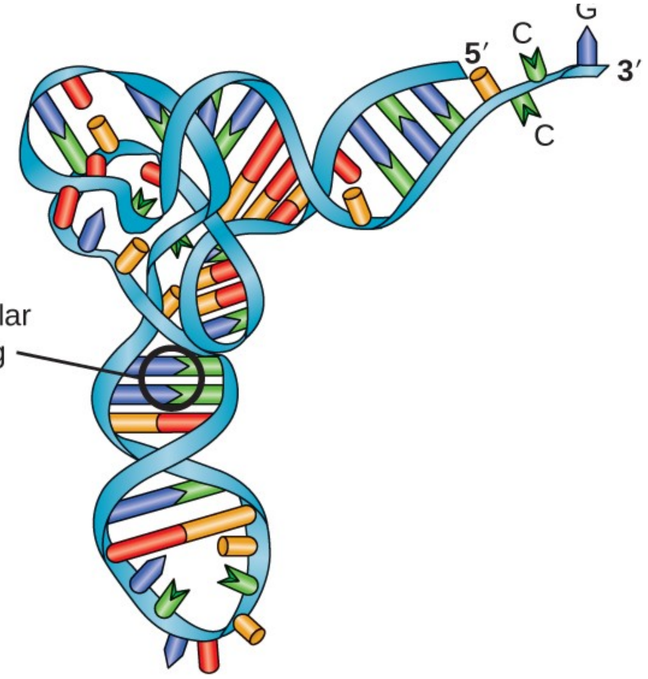
design

RNA secondary structure



tRNA 2-dimensional structure

RNA 3D structure



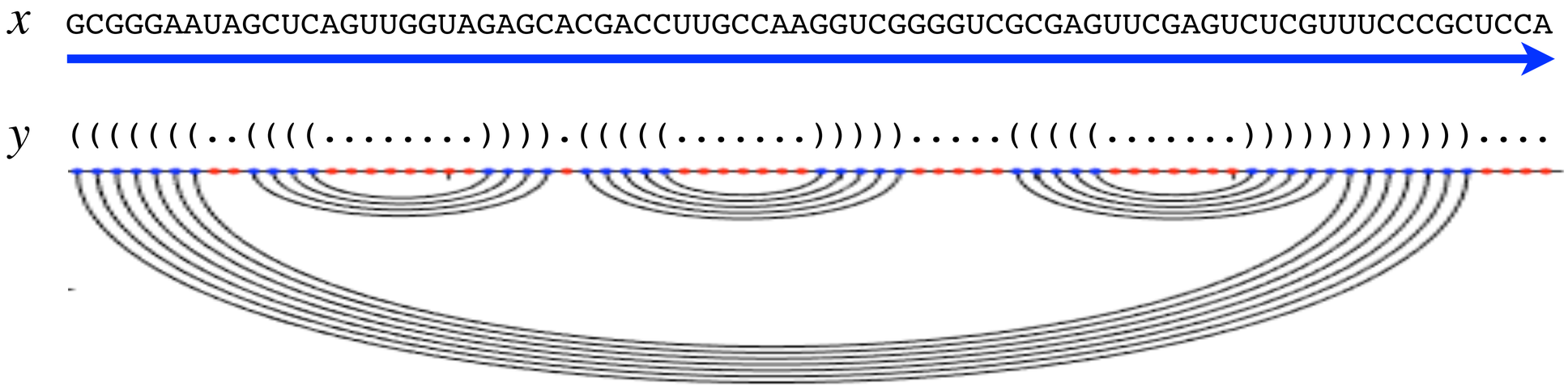
tRNA 3-dimensional structure

From Linguistics to Biology

x GCGGGAAUAGCUCAGUUGGUAGAGCACGACCUUGCCAAGGUCGGGGUCGCGAGUUCGAGUCUCGUUUCCCGCUCCA

y ((((((..((((........))))).((((.......)))).....((((.......))))))))))....

From Linguistics to Biology



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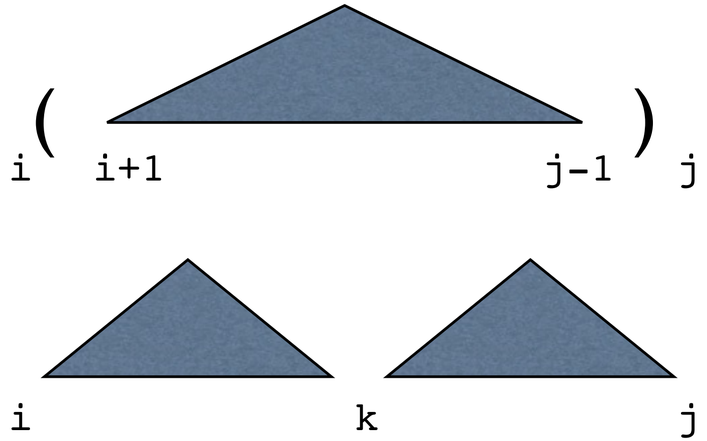

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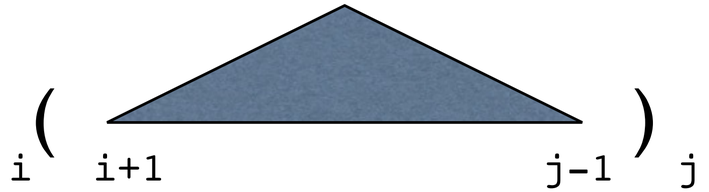

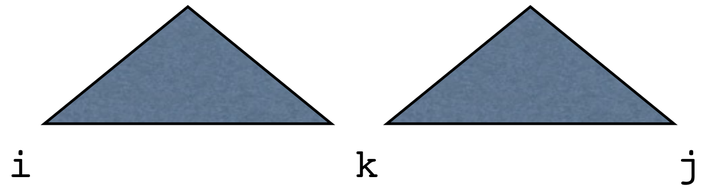

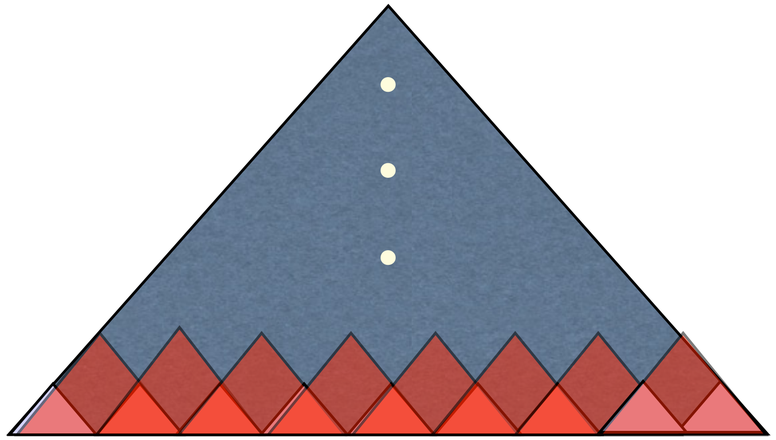

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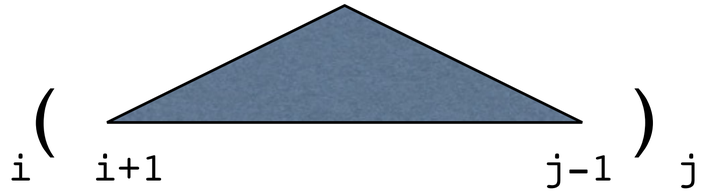

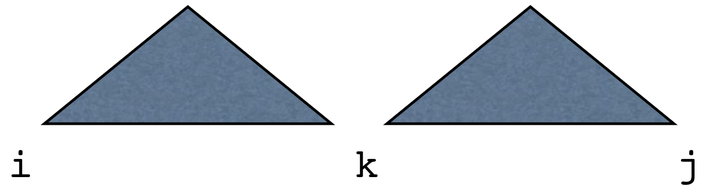

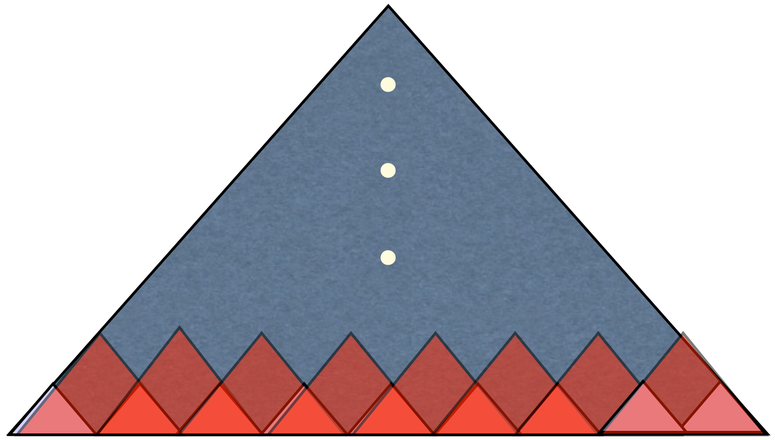

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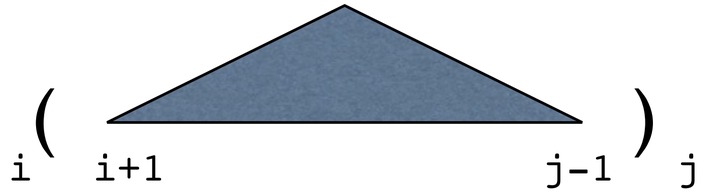

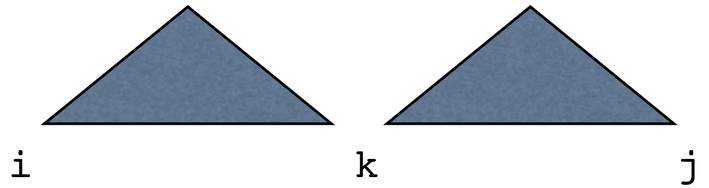

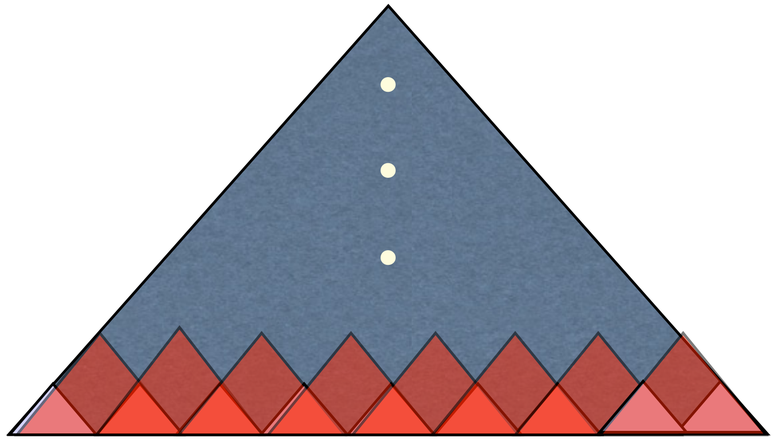

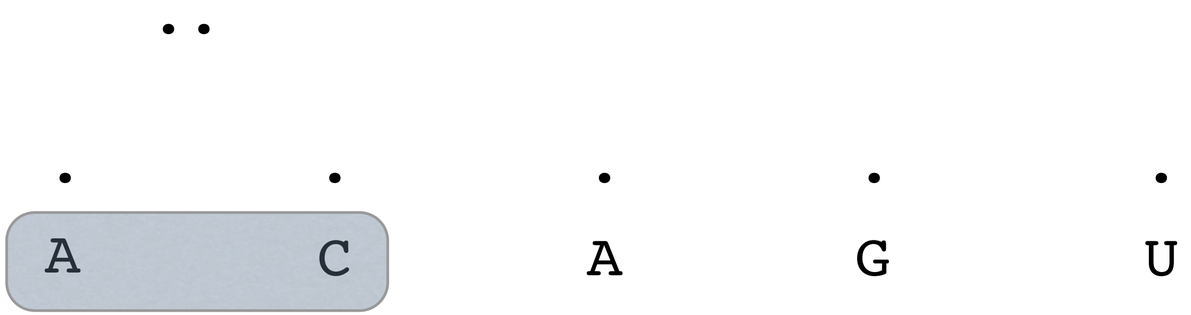

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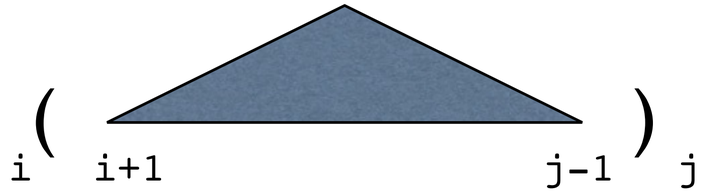

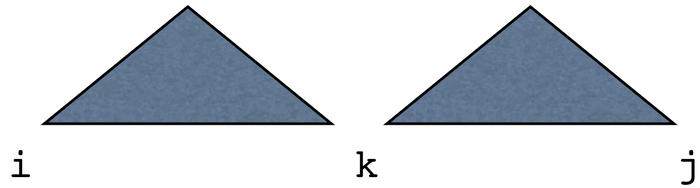

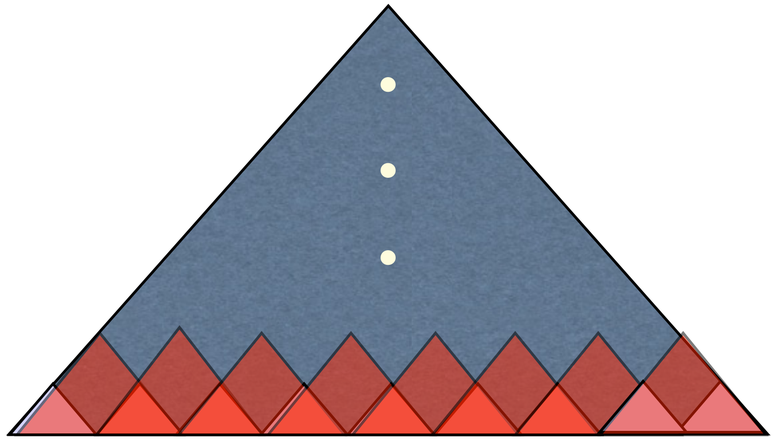

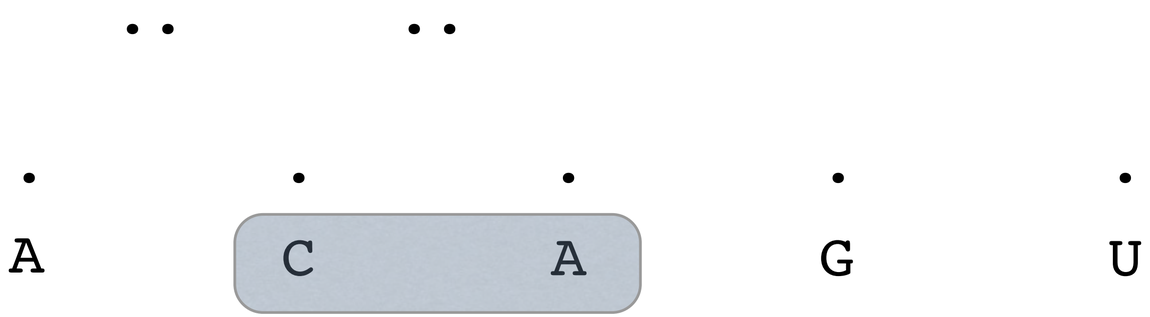

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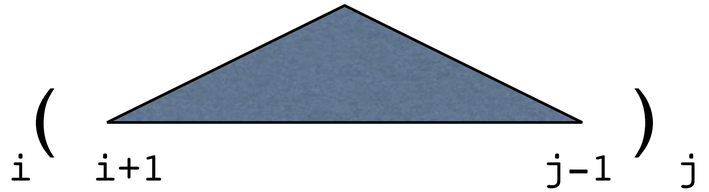

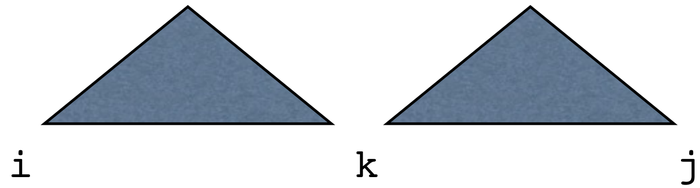

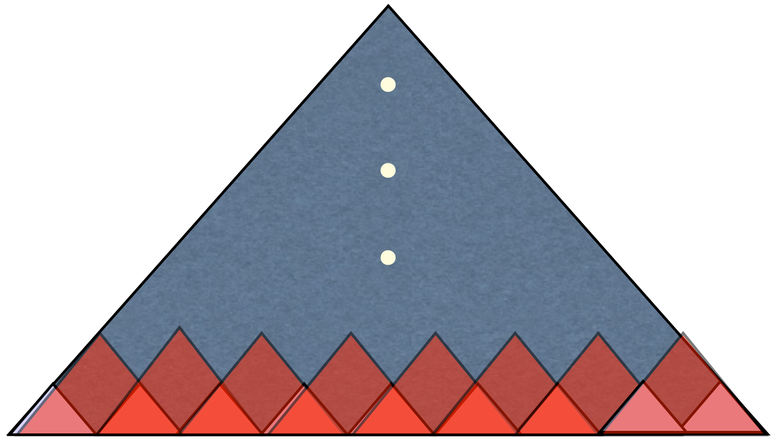

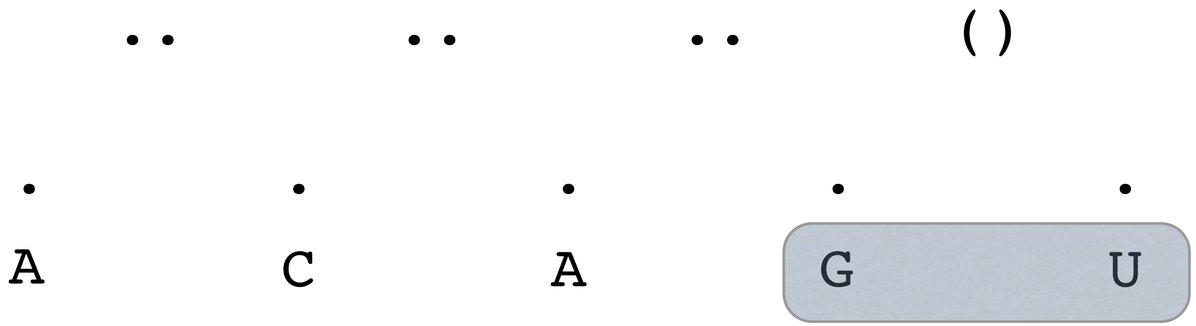

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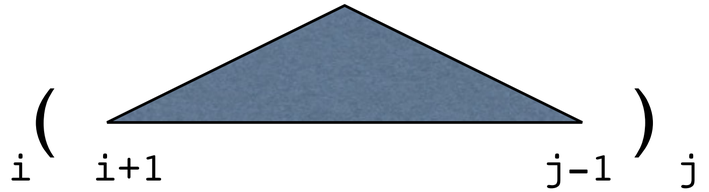

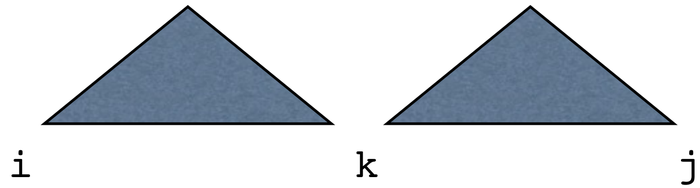

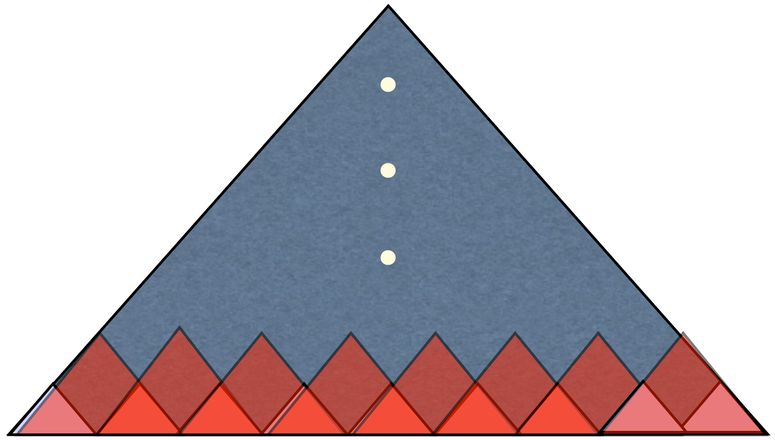

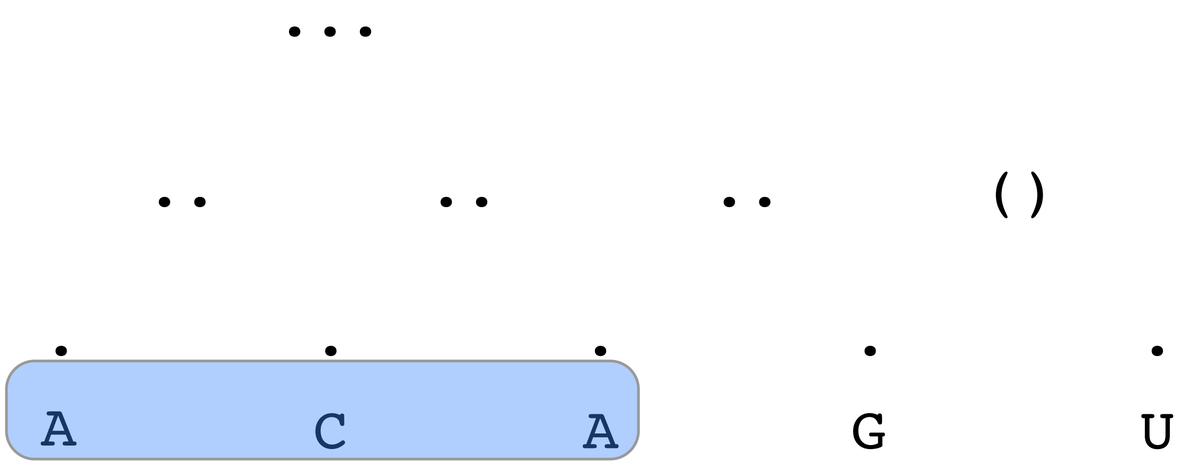

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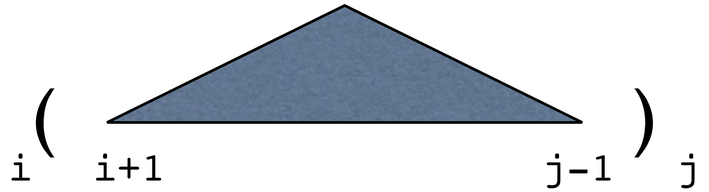

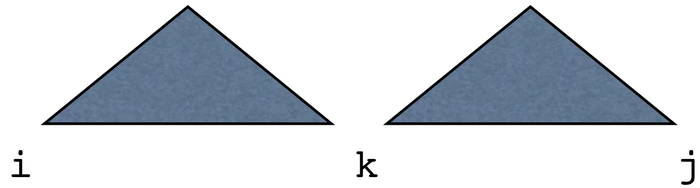

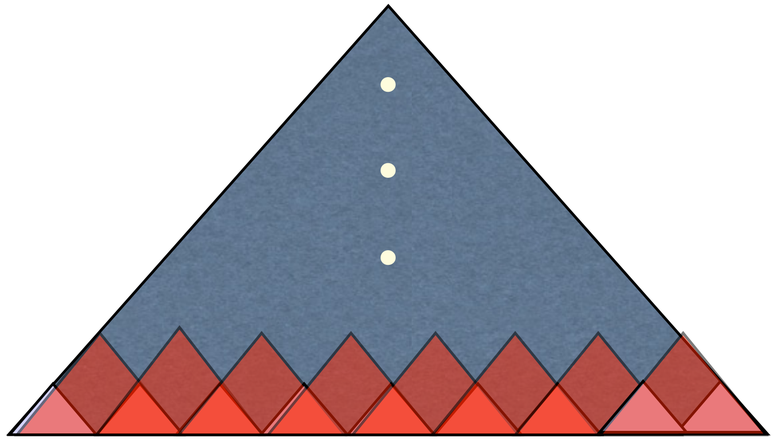

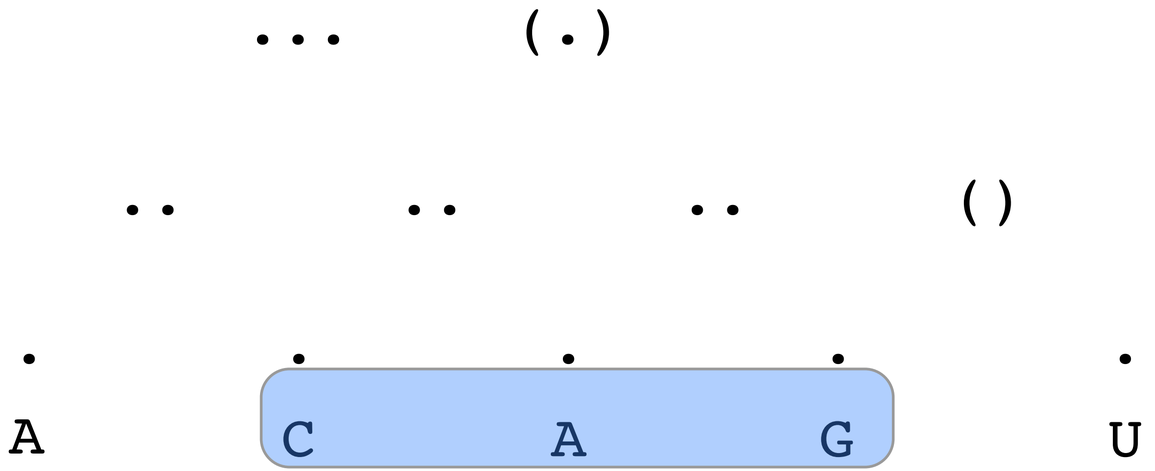

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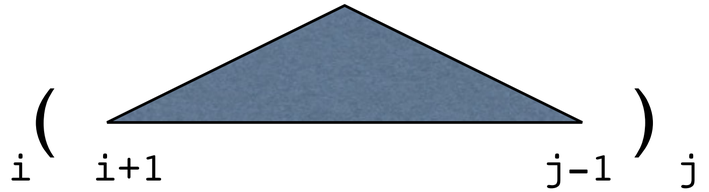

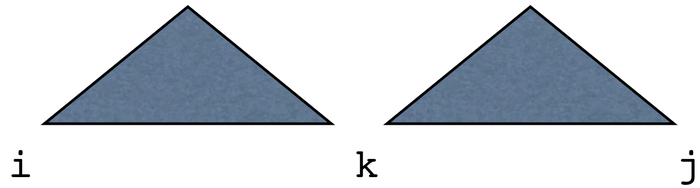

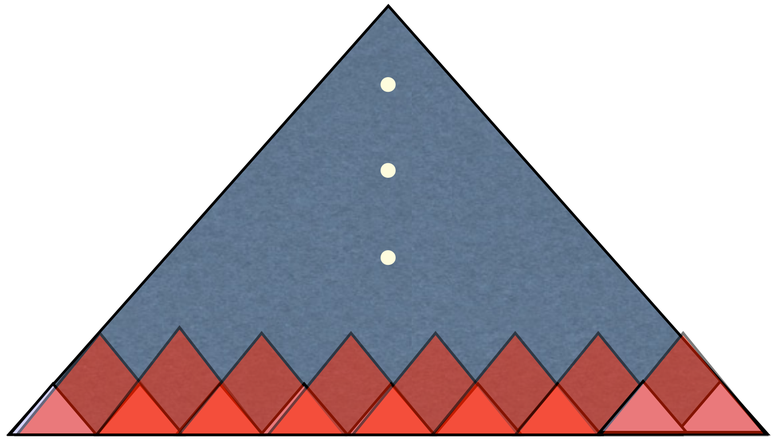

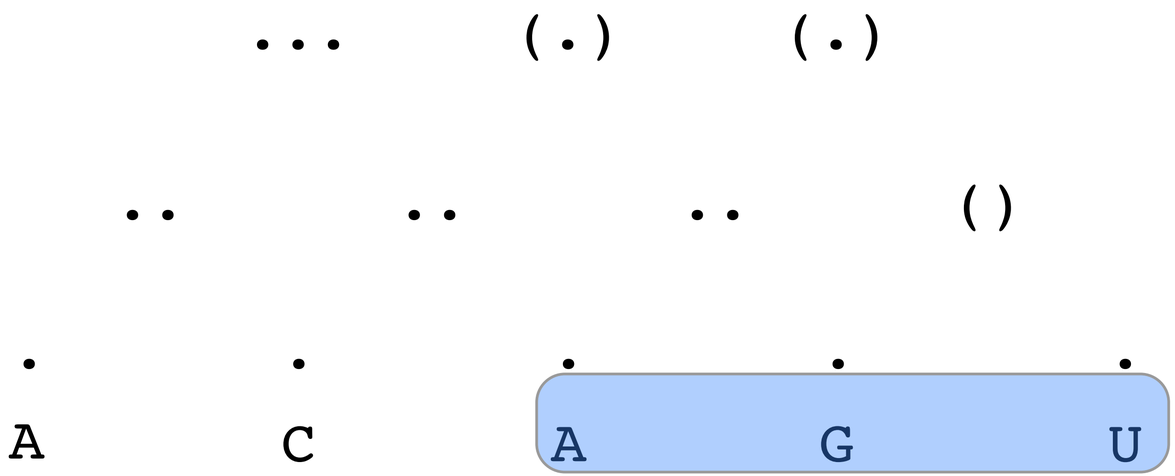

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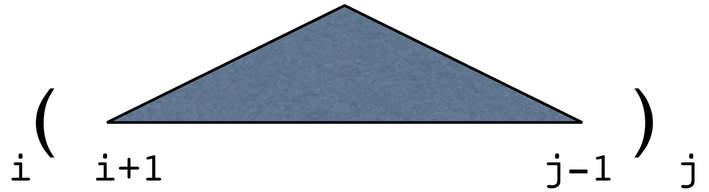

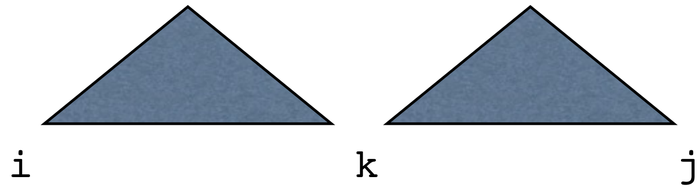

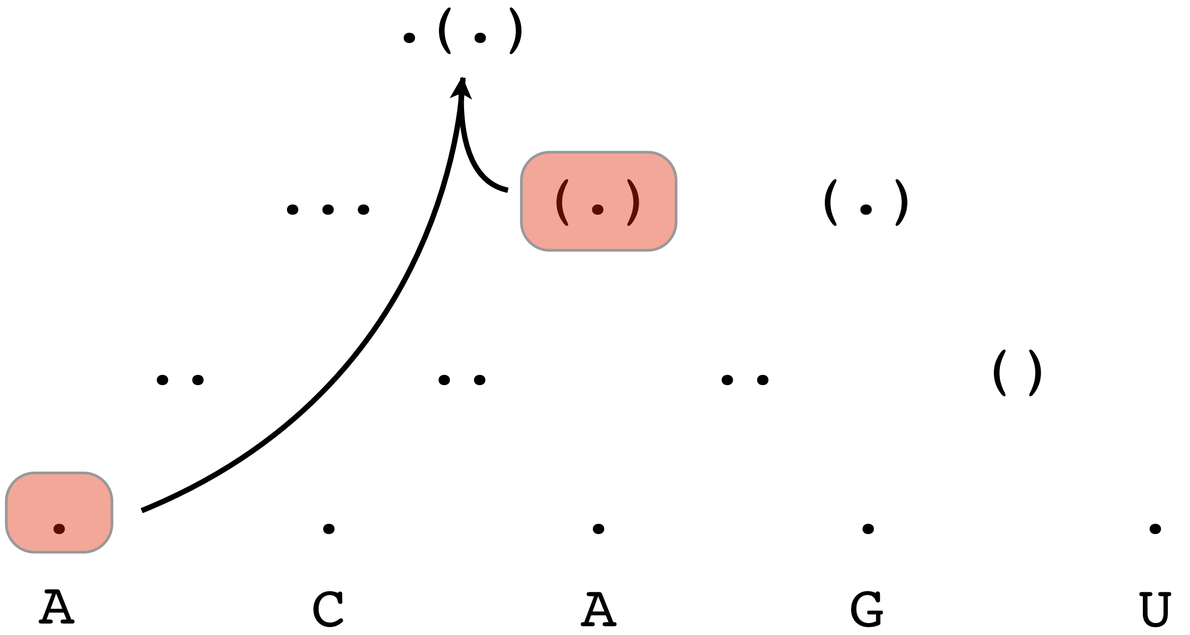

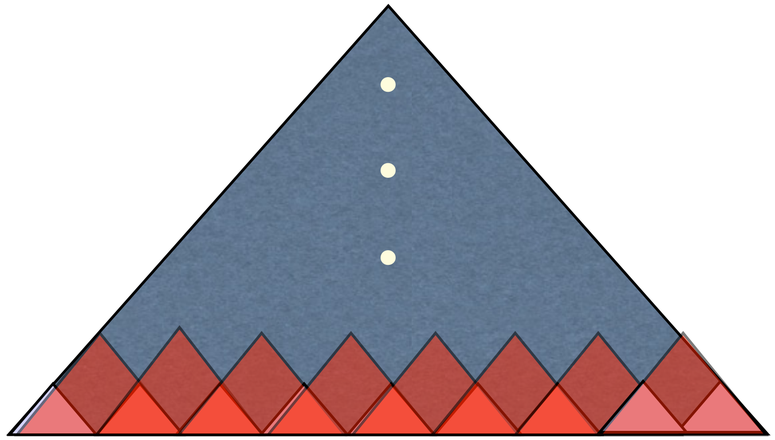

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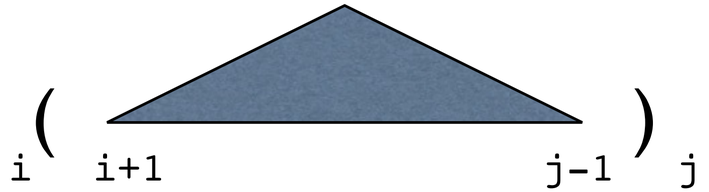

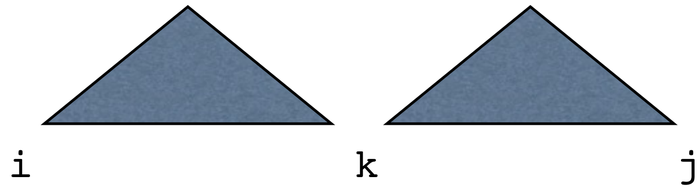

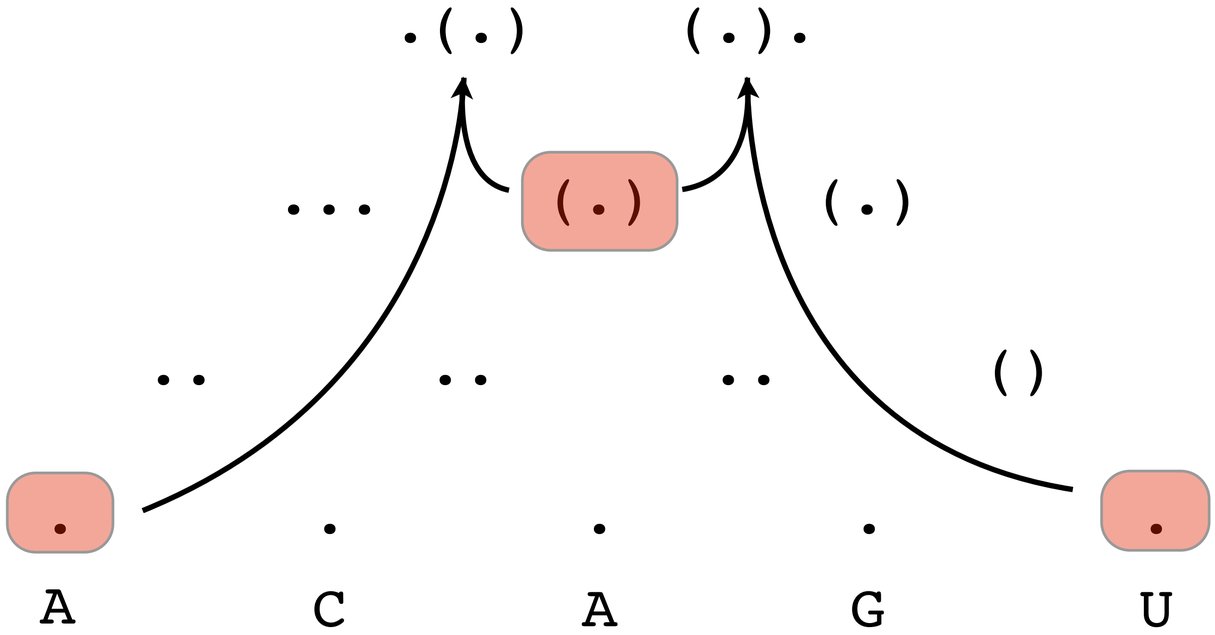

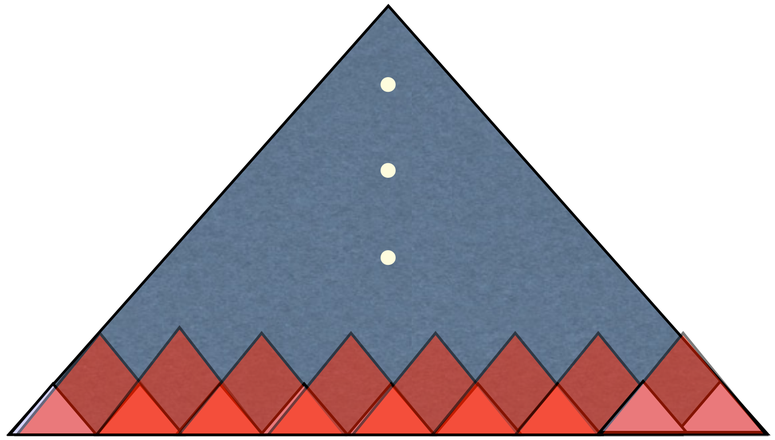

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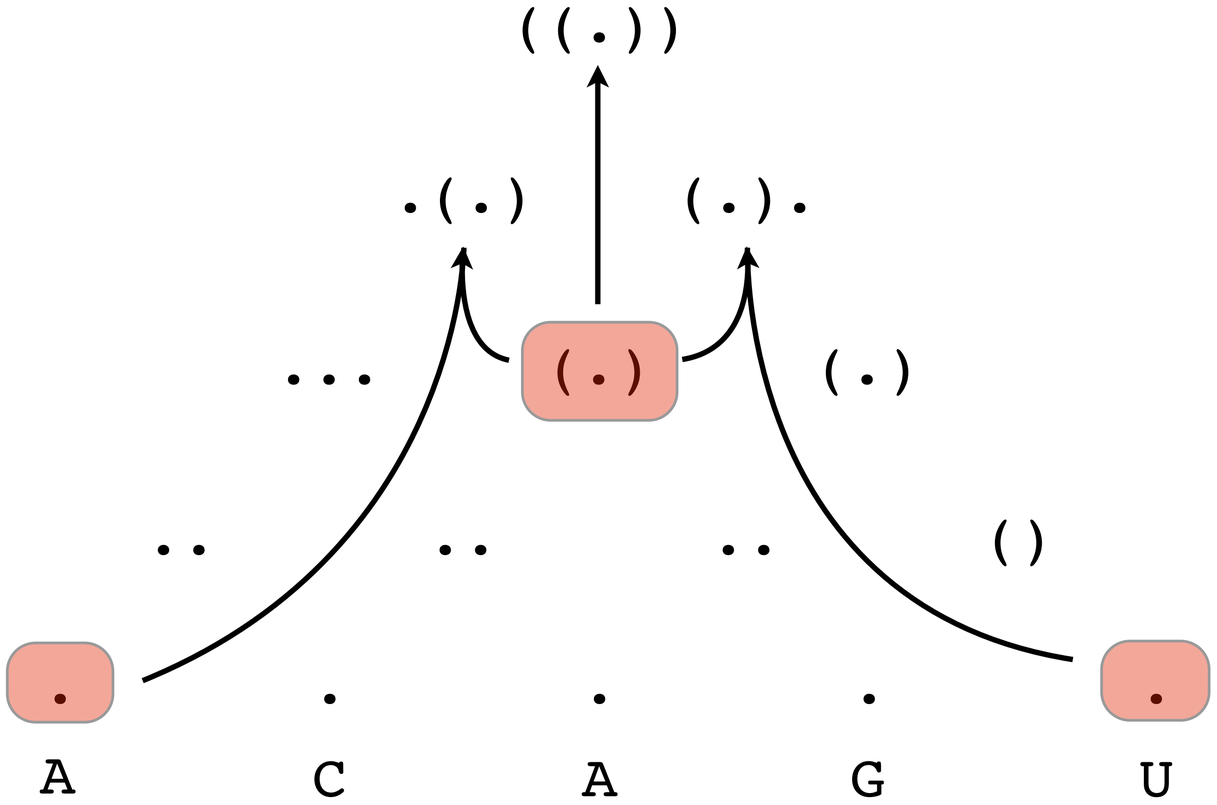
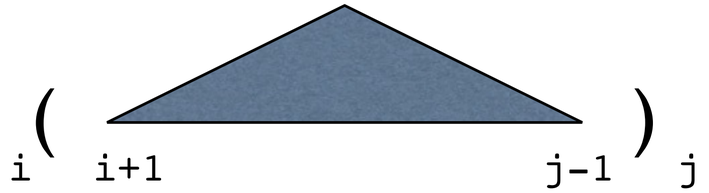
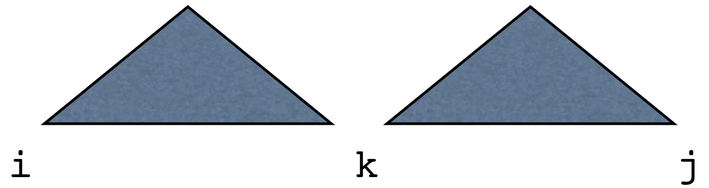
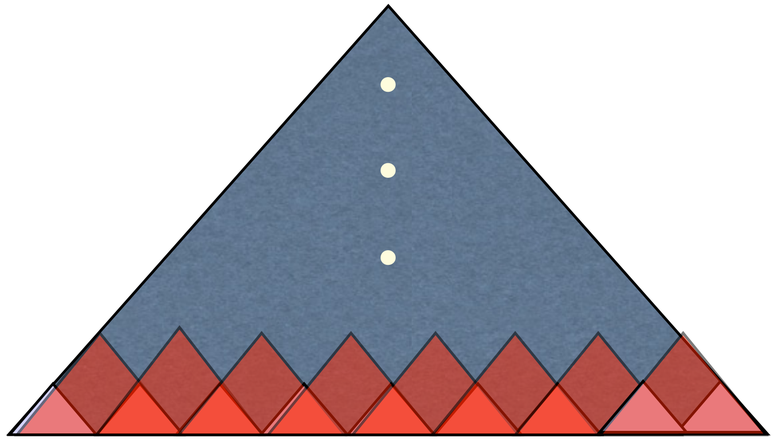




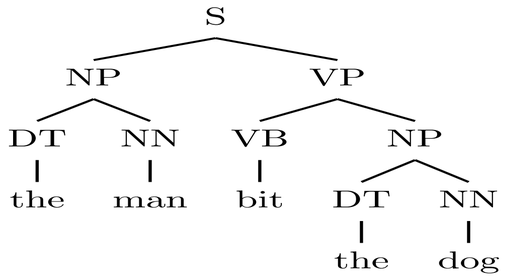




Computational Linguistics => Computational Biology

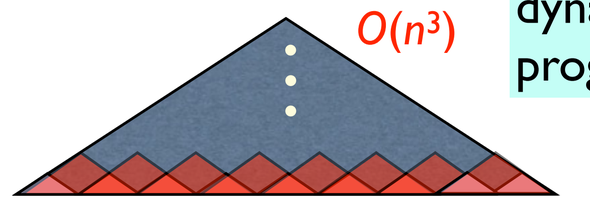
linguistics | **compiler theory** | **comp. linguistics** | **computational biology**

1955 Chomsky: context-free grammars (CFGs)

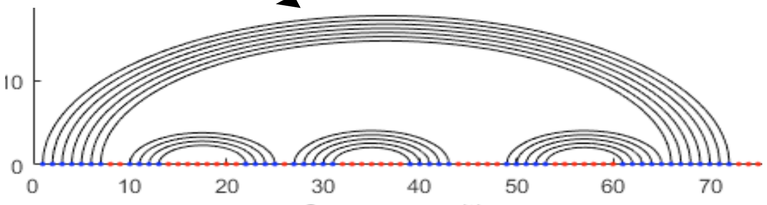


1958 Backus & Naur: CFGs for program, lang.

1964 **C**ocke \ bottom-up
1965 **K**asami - **CKY** $O(n^3)$
1967 **Y**ounger / for all CFGs



dynamic programming



1978: Nussinov $O(n^3)$ RNA folding
1981: Zuker & Siegler

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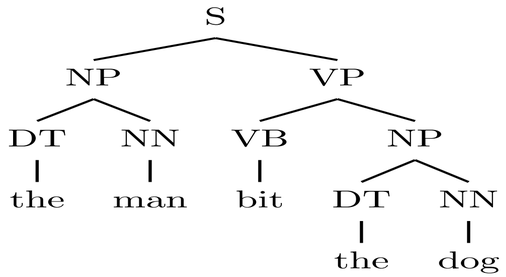

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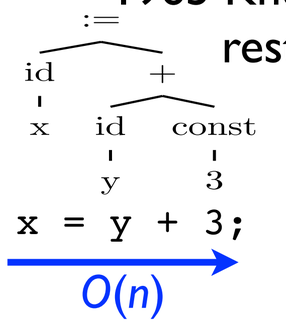

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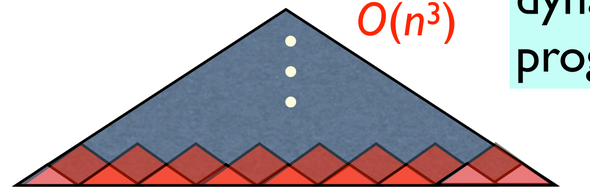
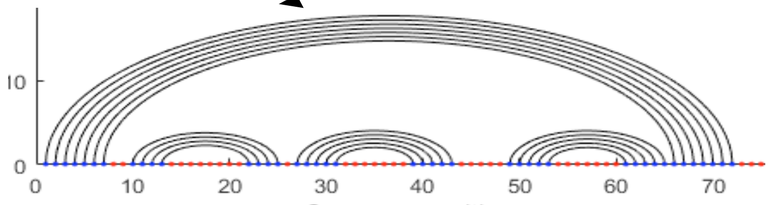


dynamic programming



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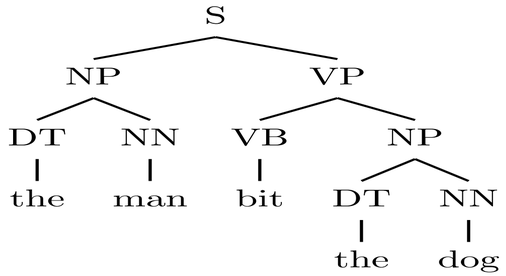

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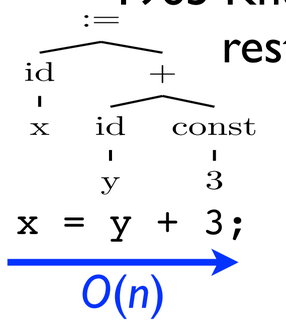

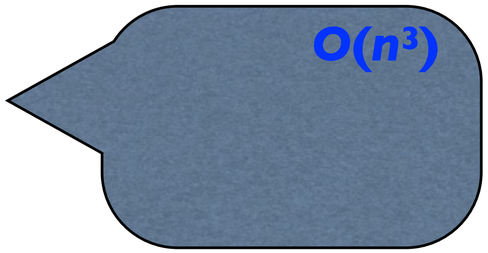

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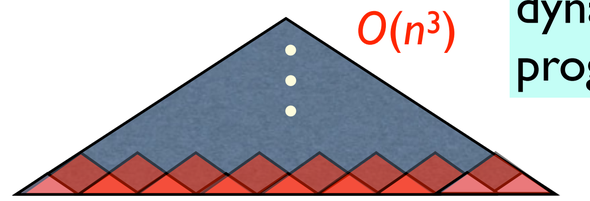

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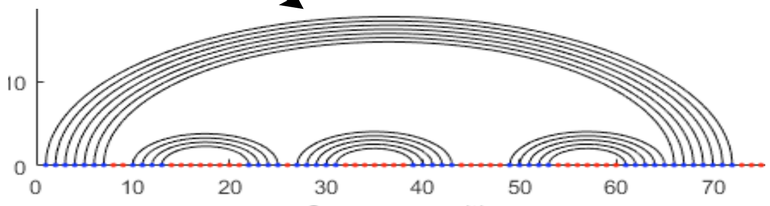

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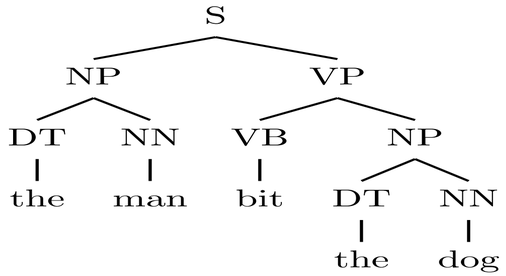

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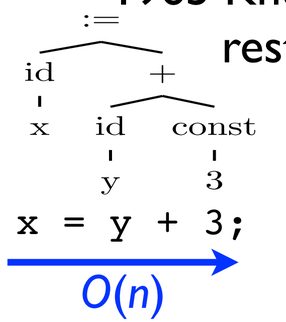

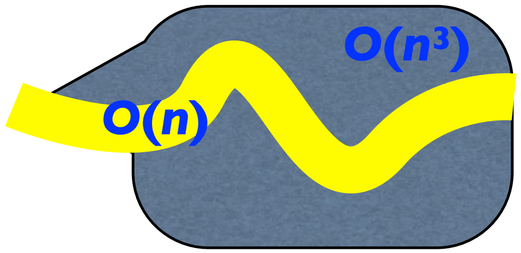

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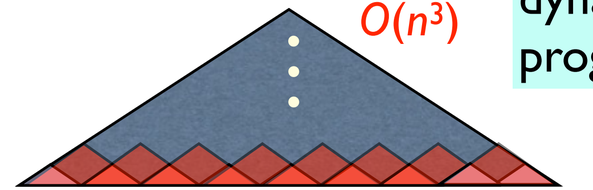

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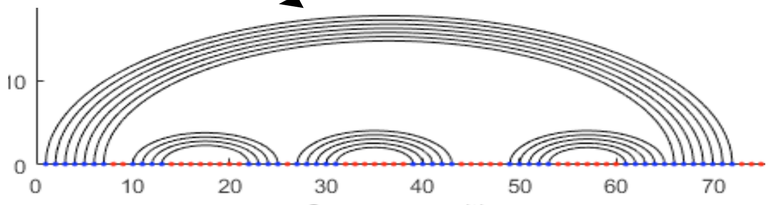

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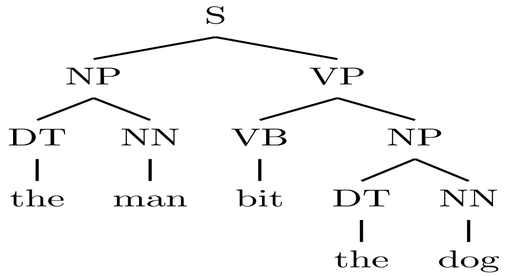

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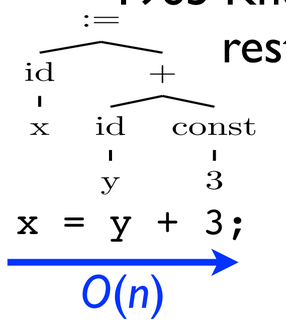

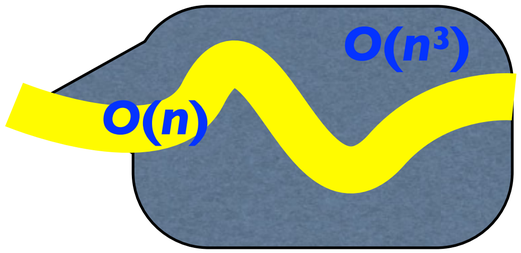

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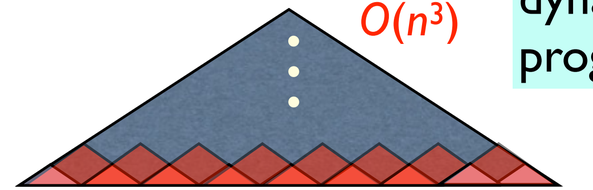

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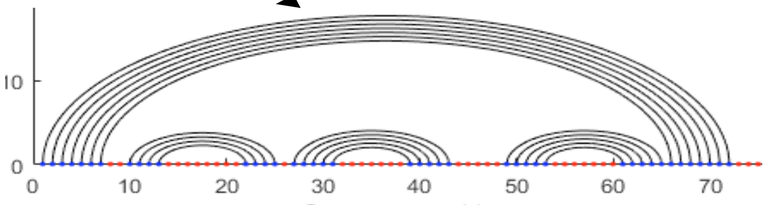

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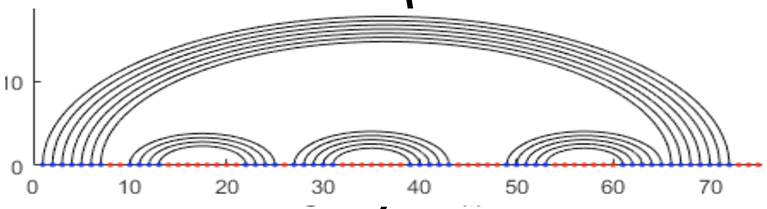

2019: LinearFold O(n) (approx.) RNA folding

How to Fold RNAs in Linear-Time?

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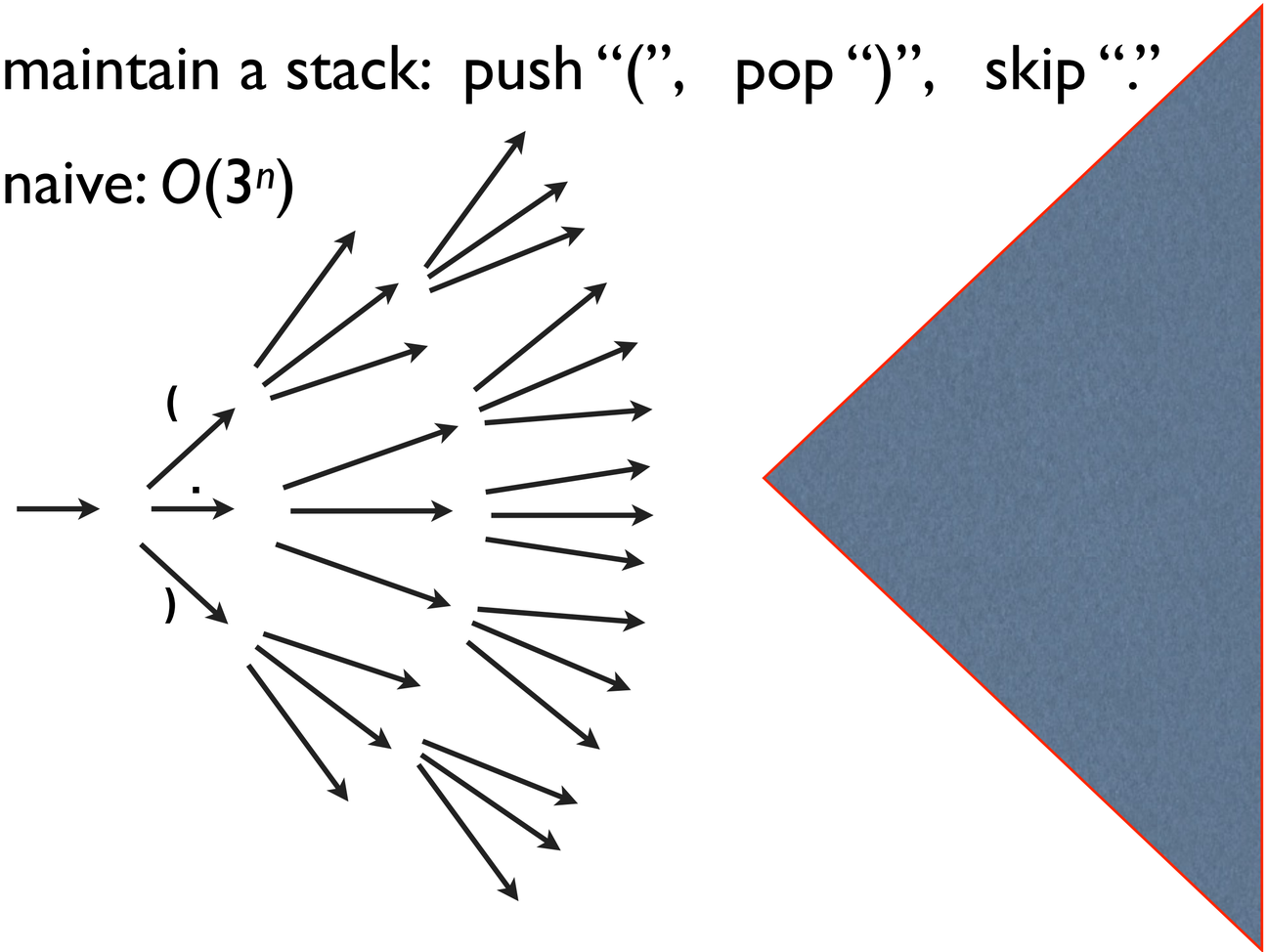
- idea 0: tag each nucleotide from left to right
  - maintain a stack: push "(", pop ")", skip "."
  - naive: $O(3^n)$



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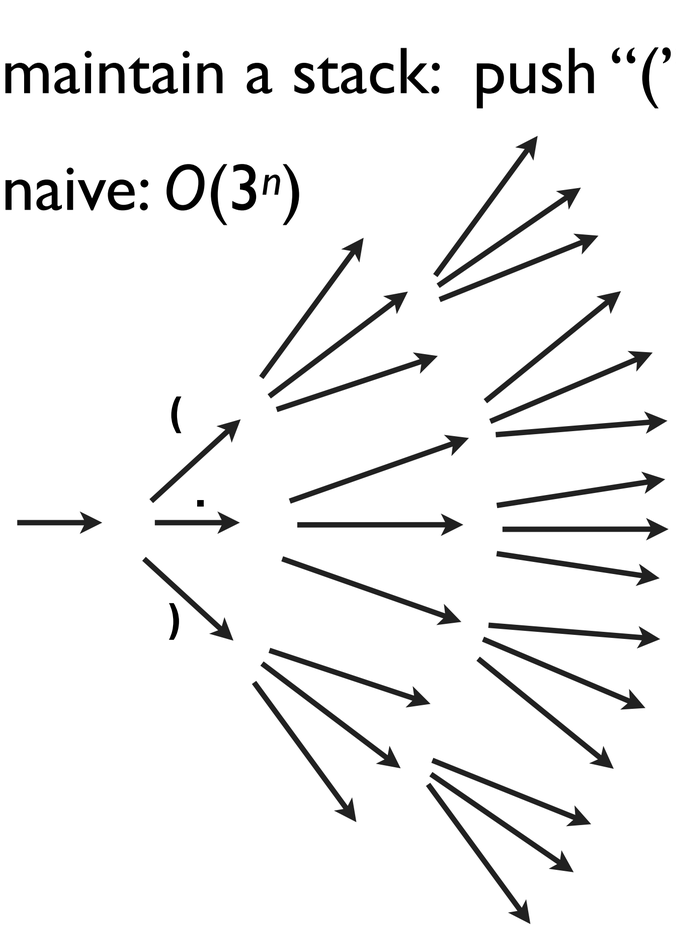

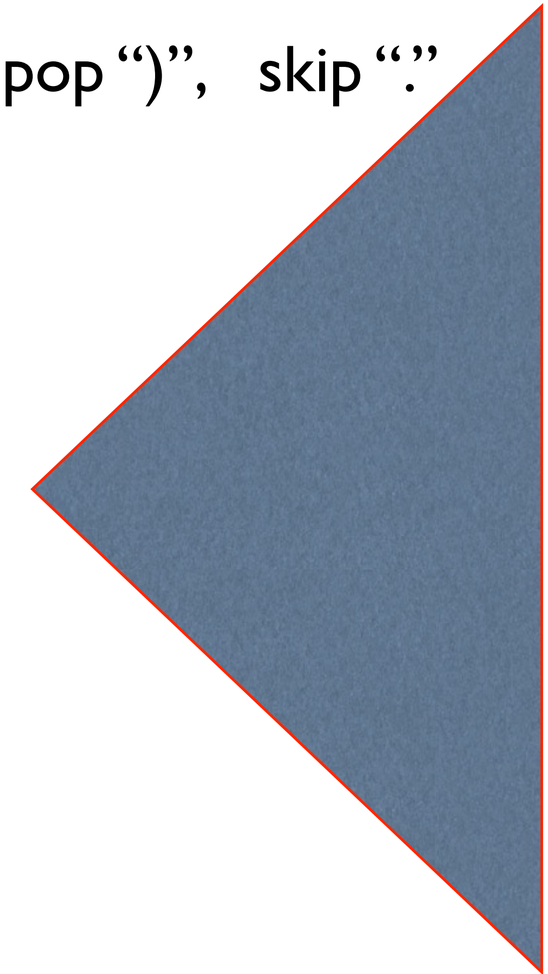

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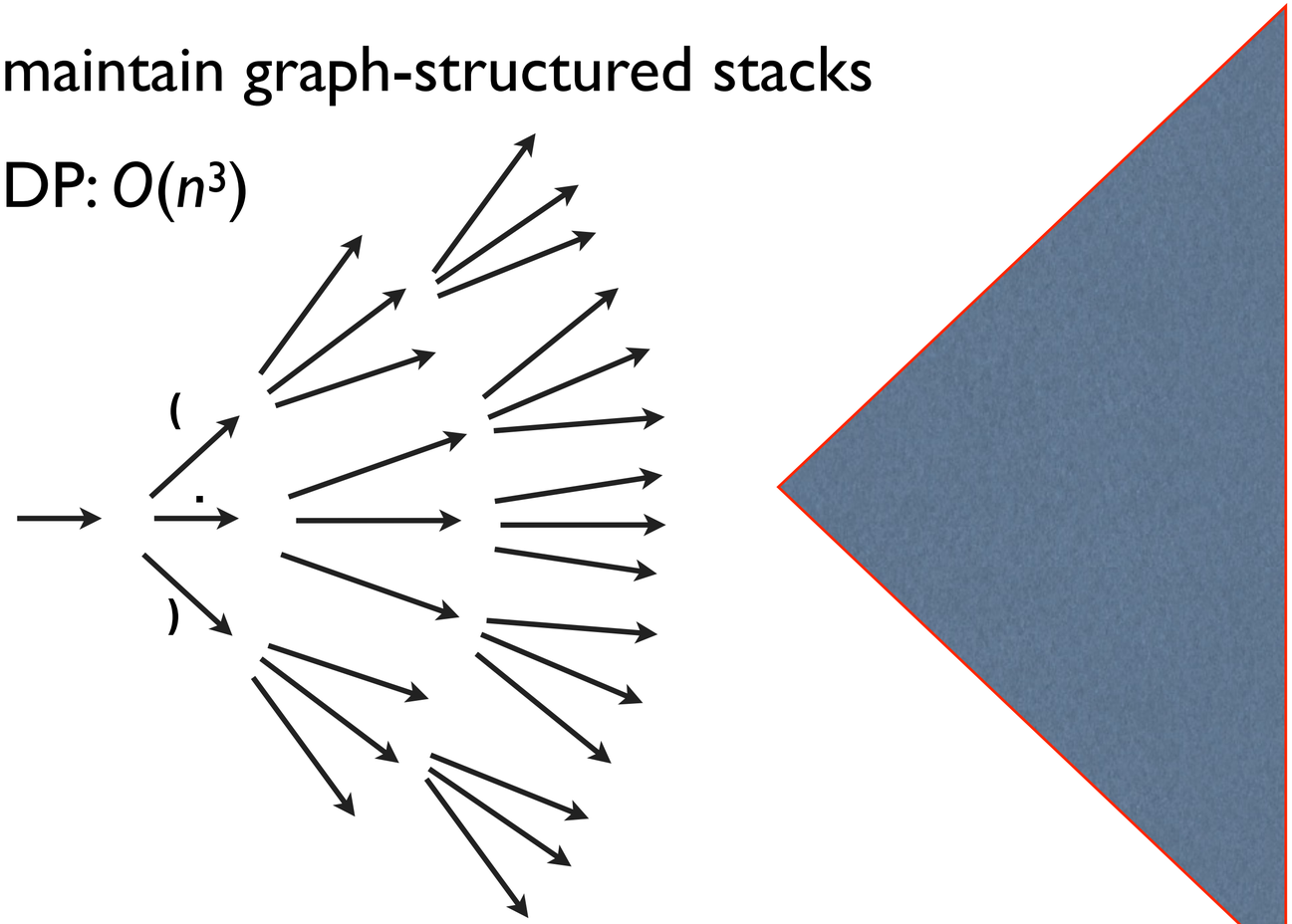

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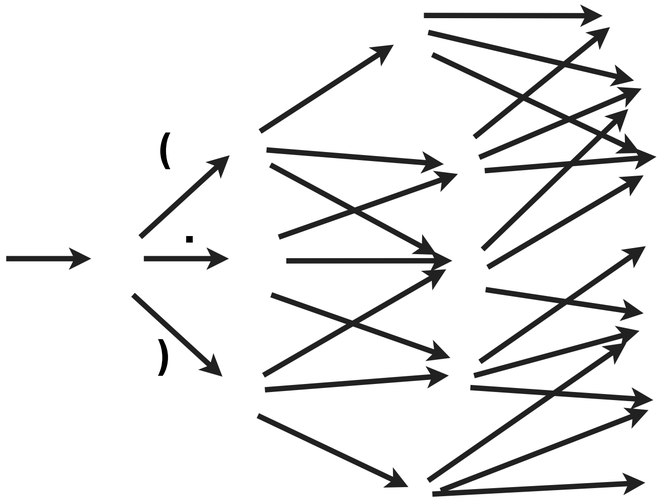

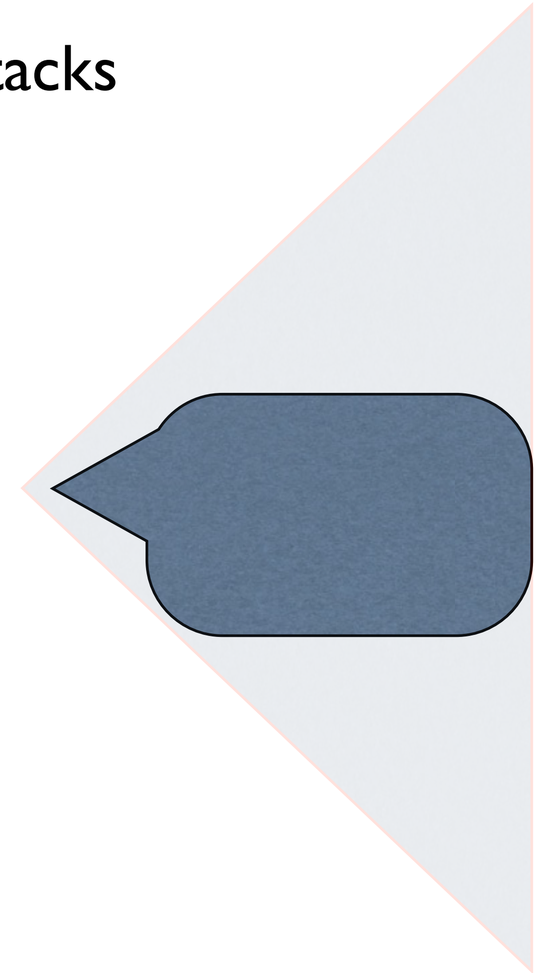

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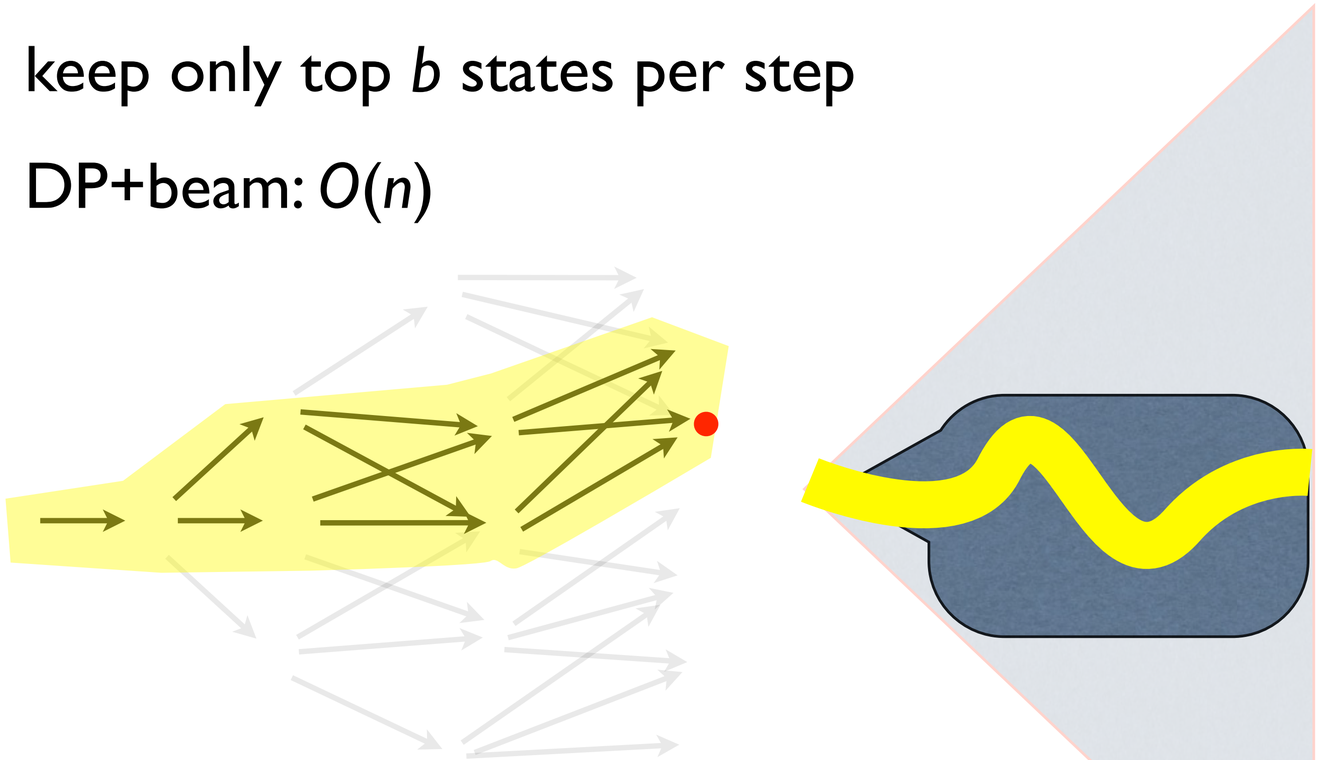

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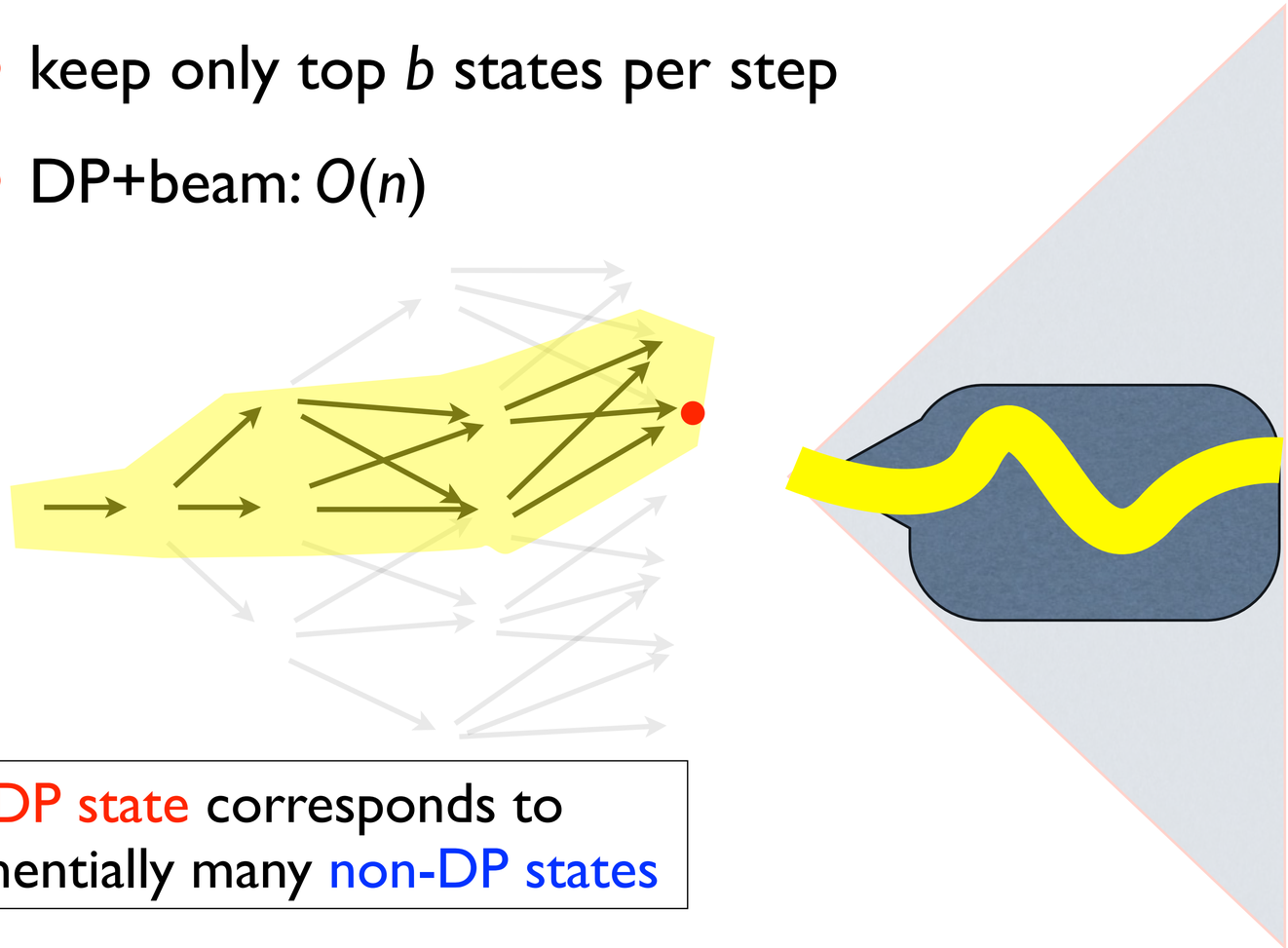

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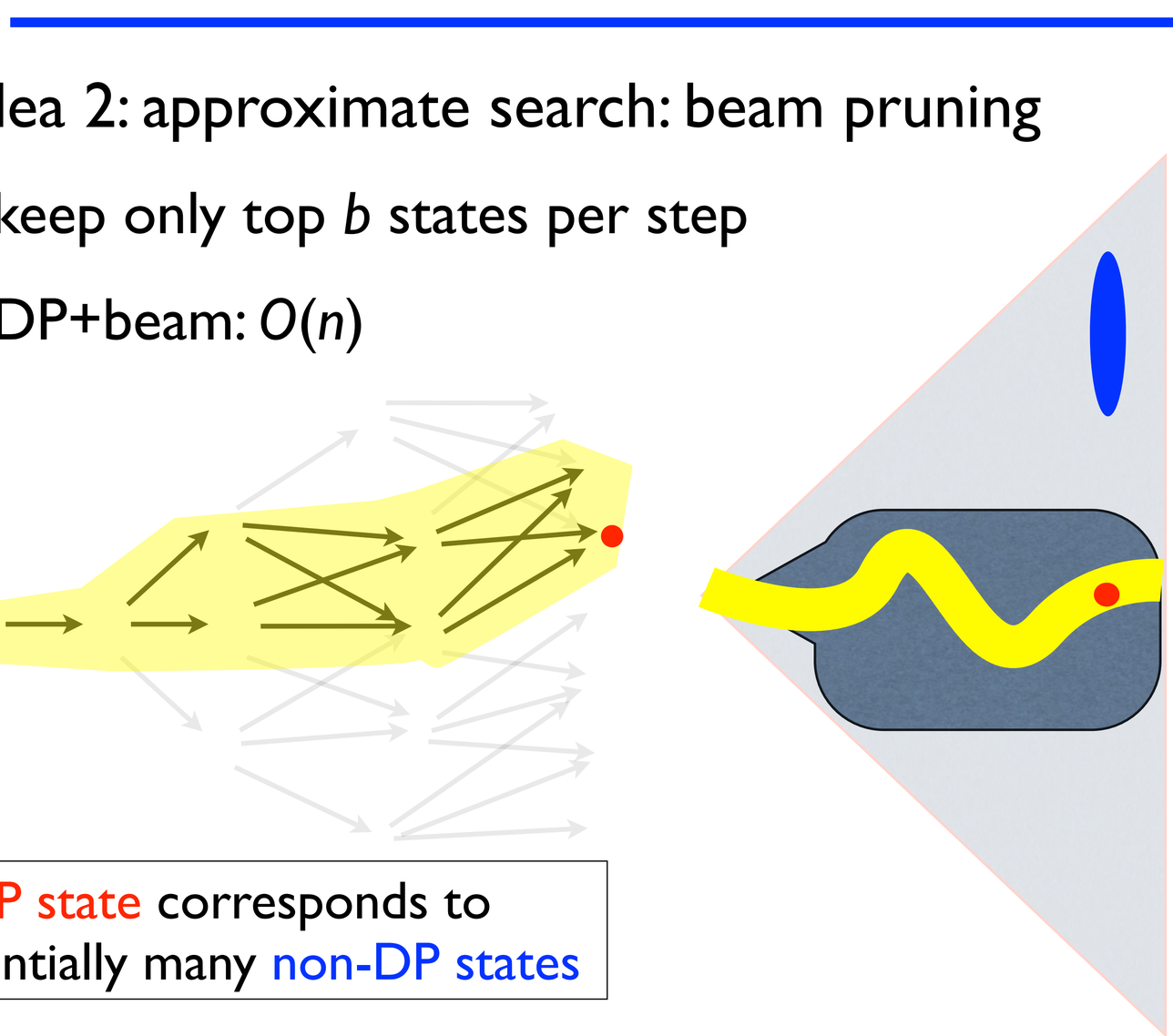

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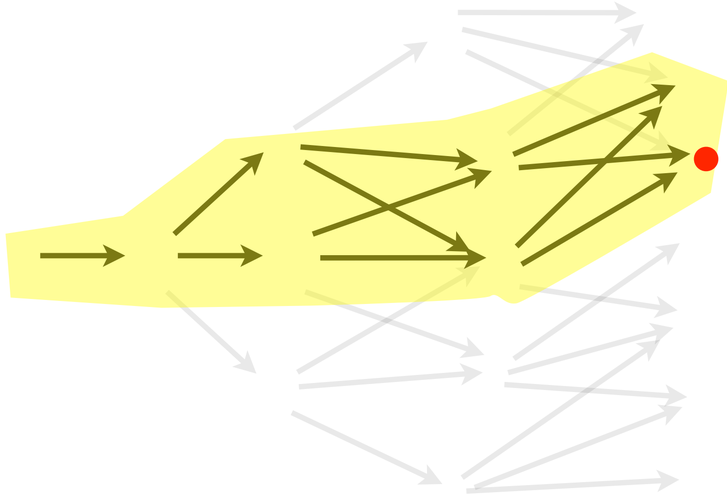

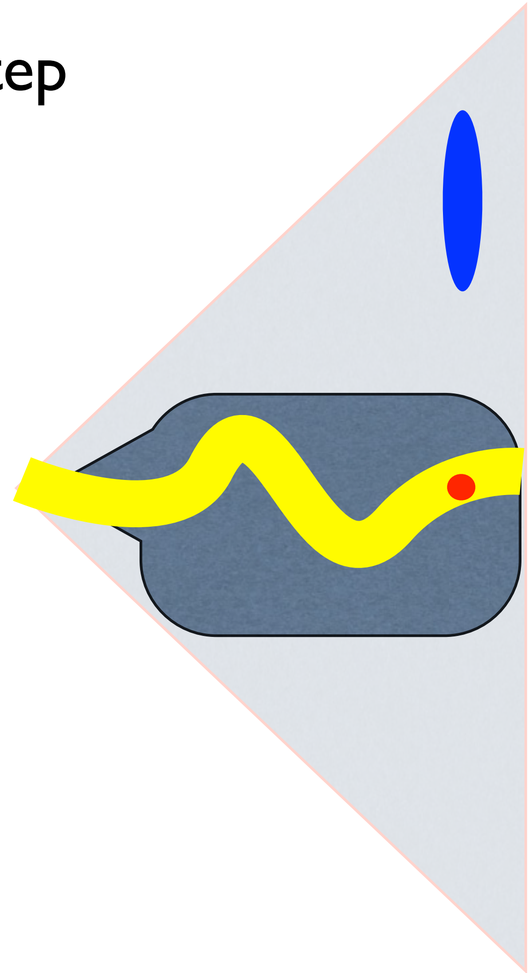

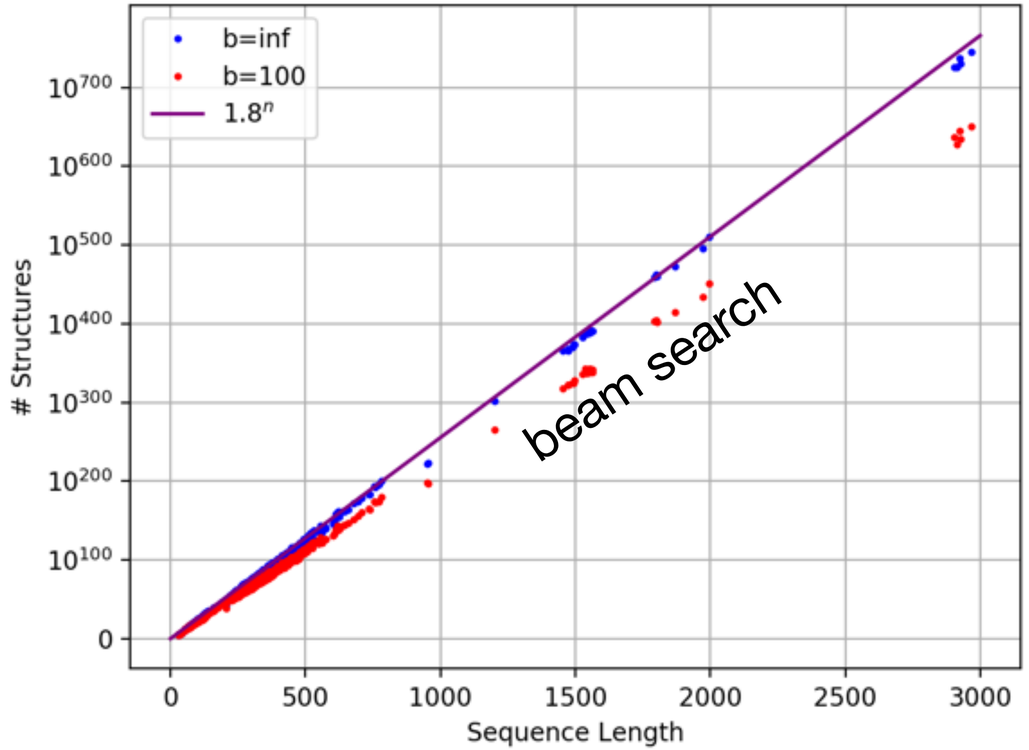

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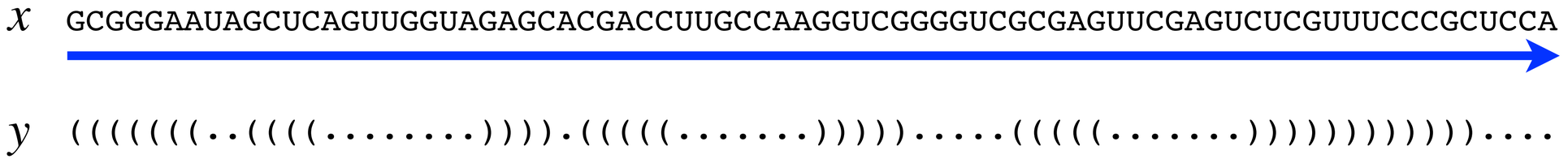

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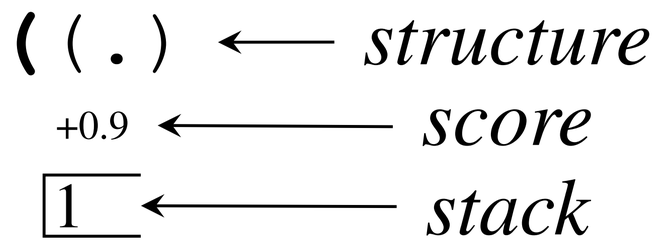

Nussinov-style scoring model:
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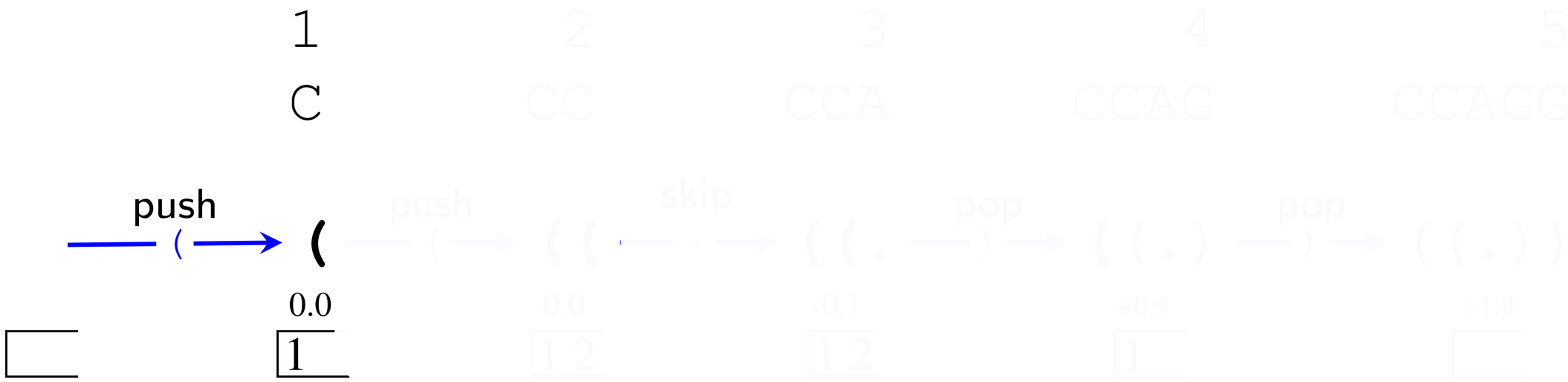

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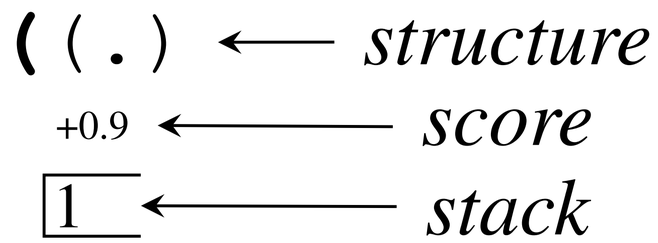

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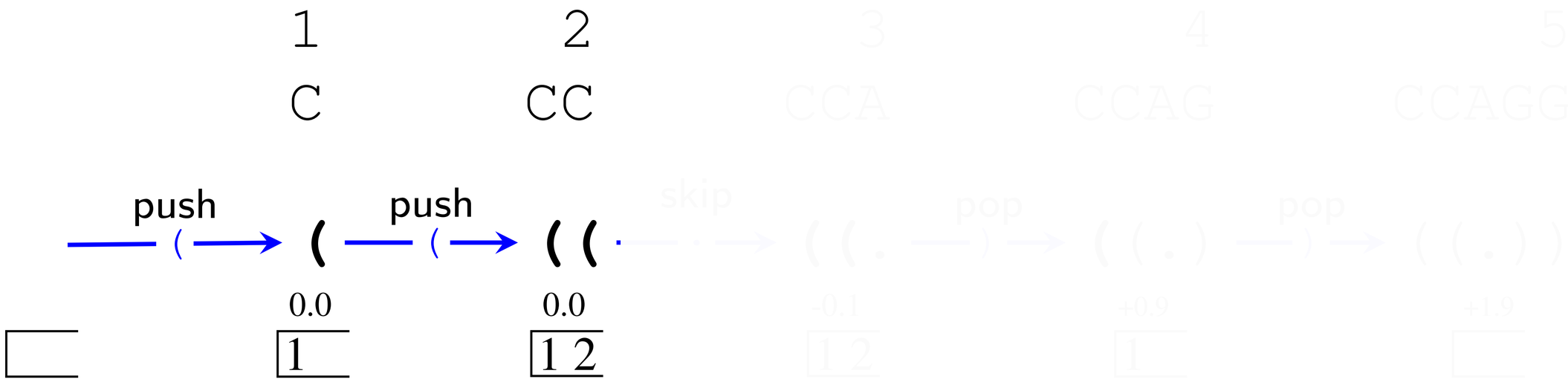

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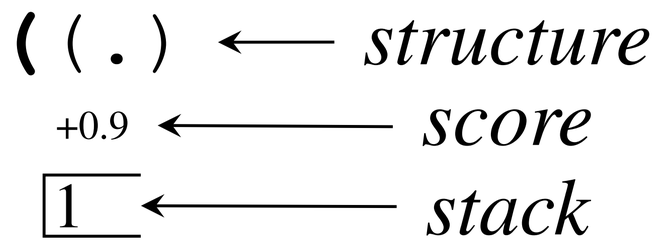

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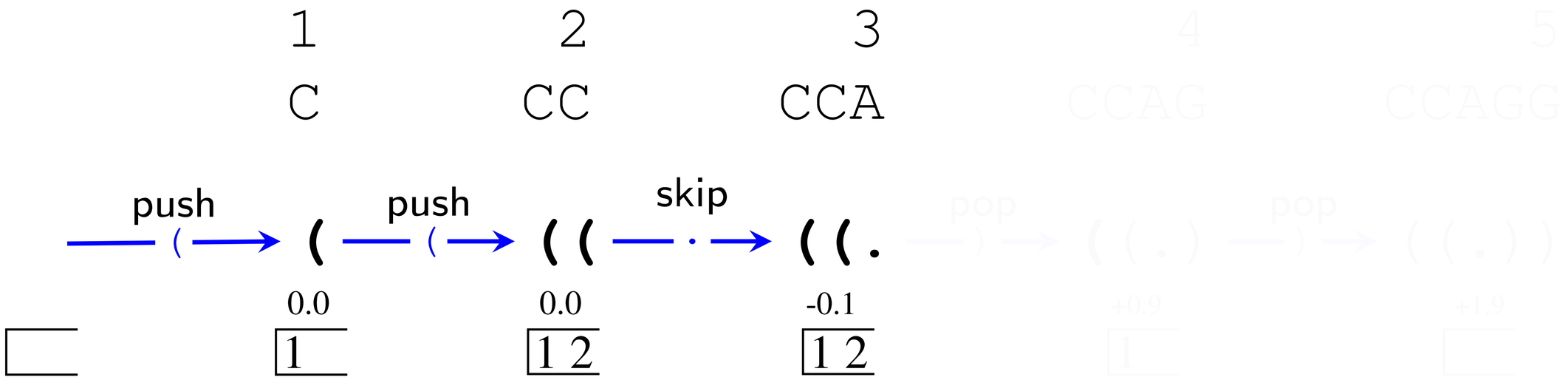

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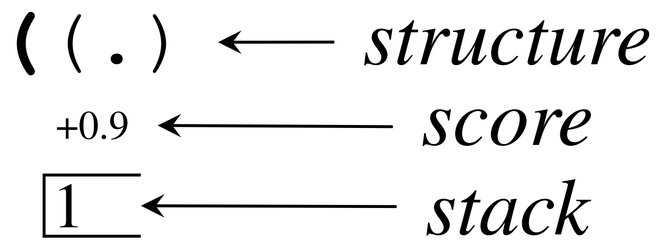

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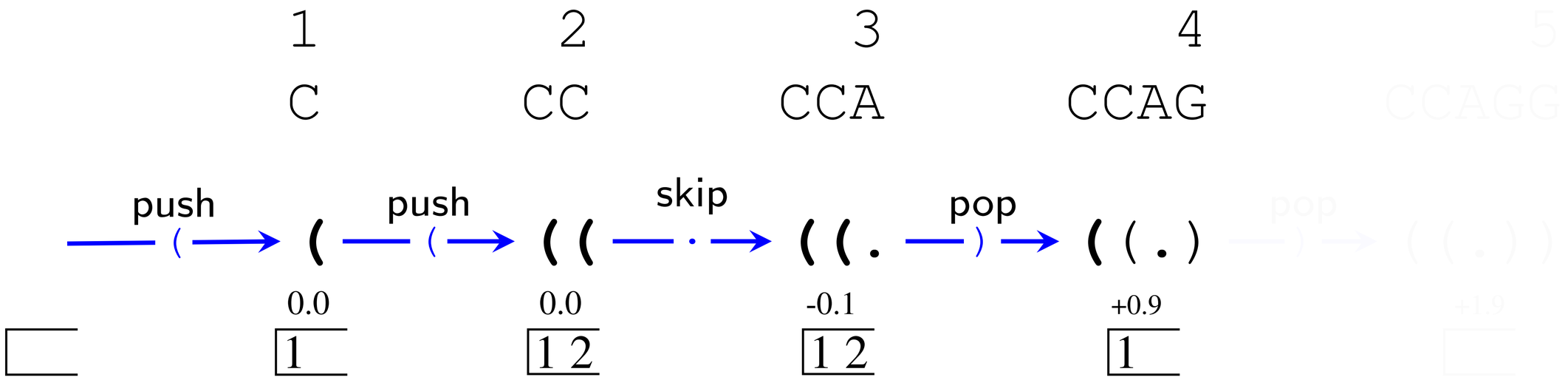

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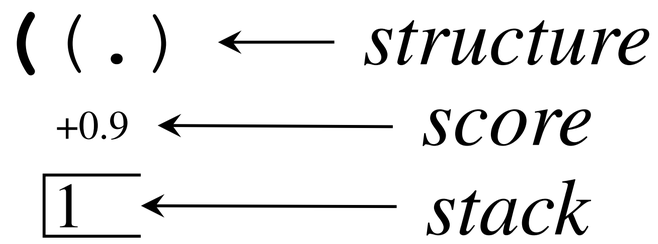

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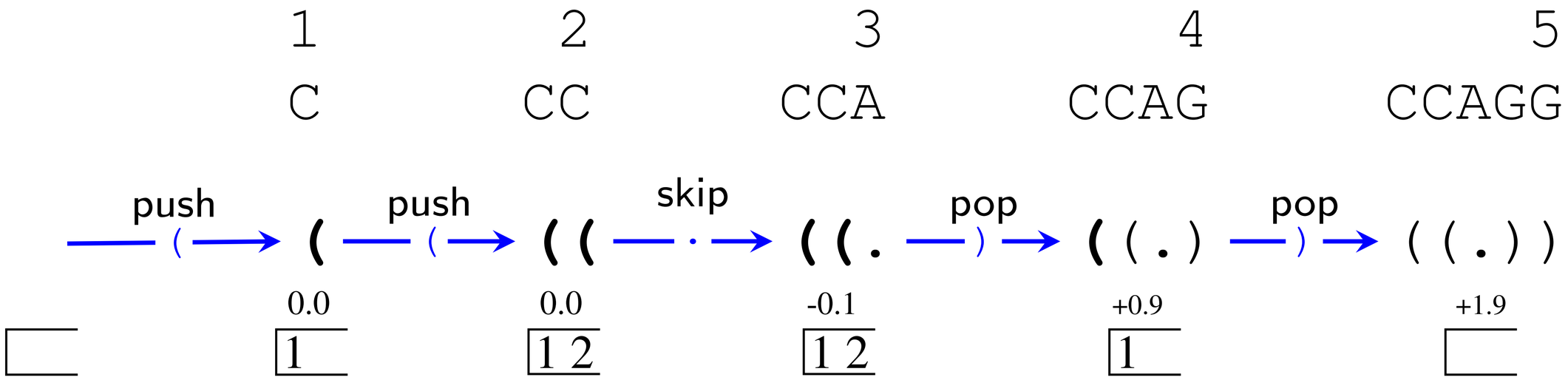

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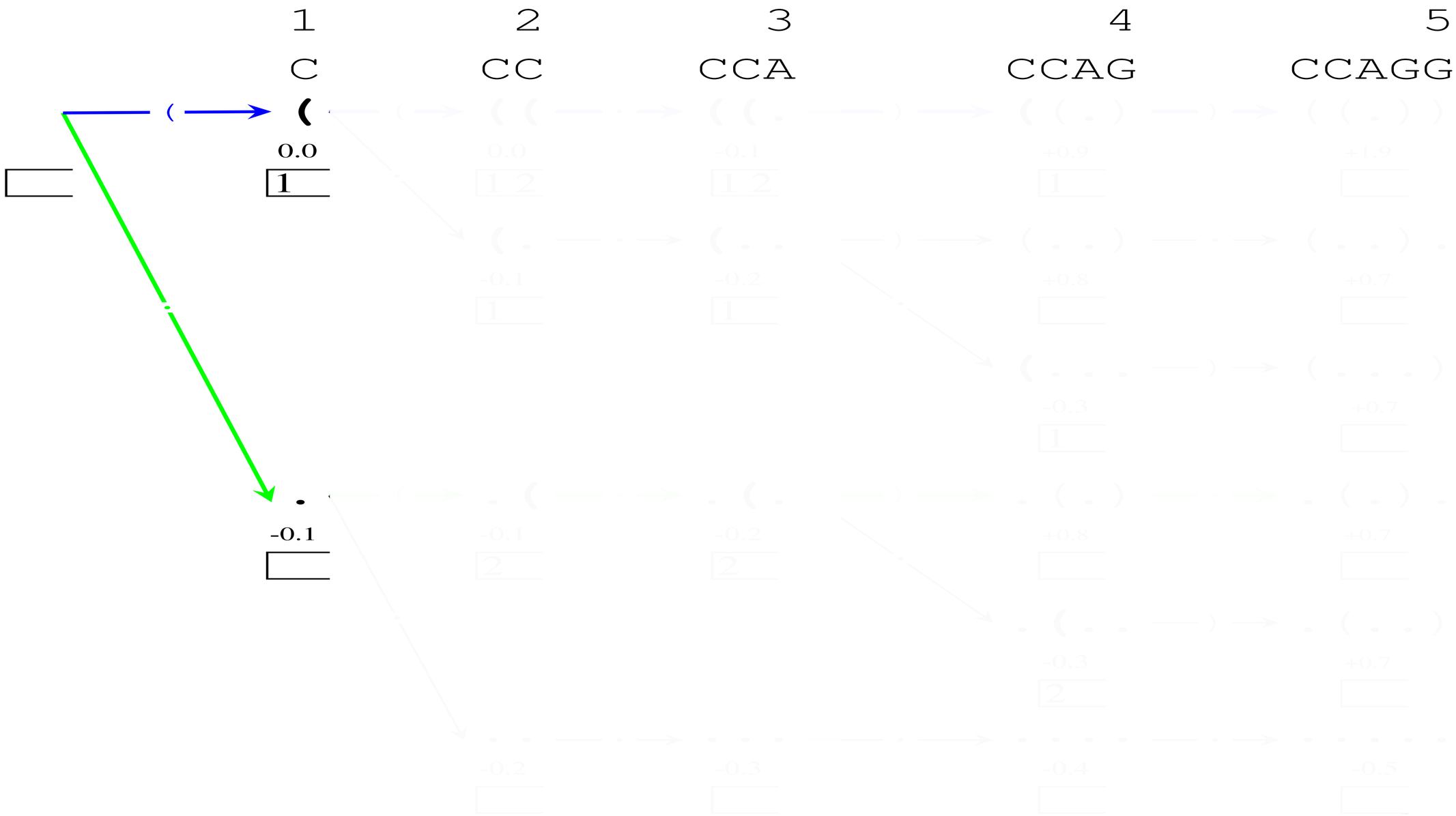

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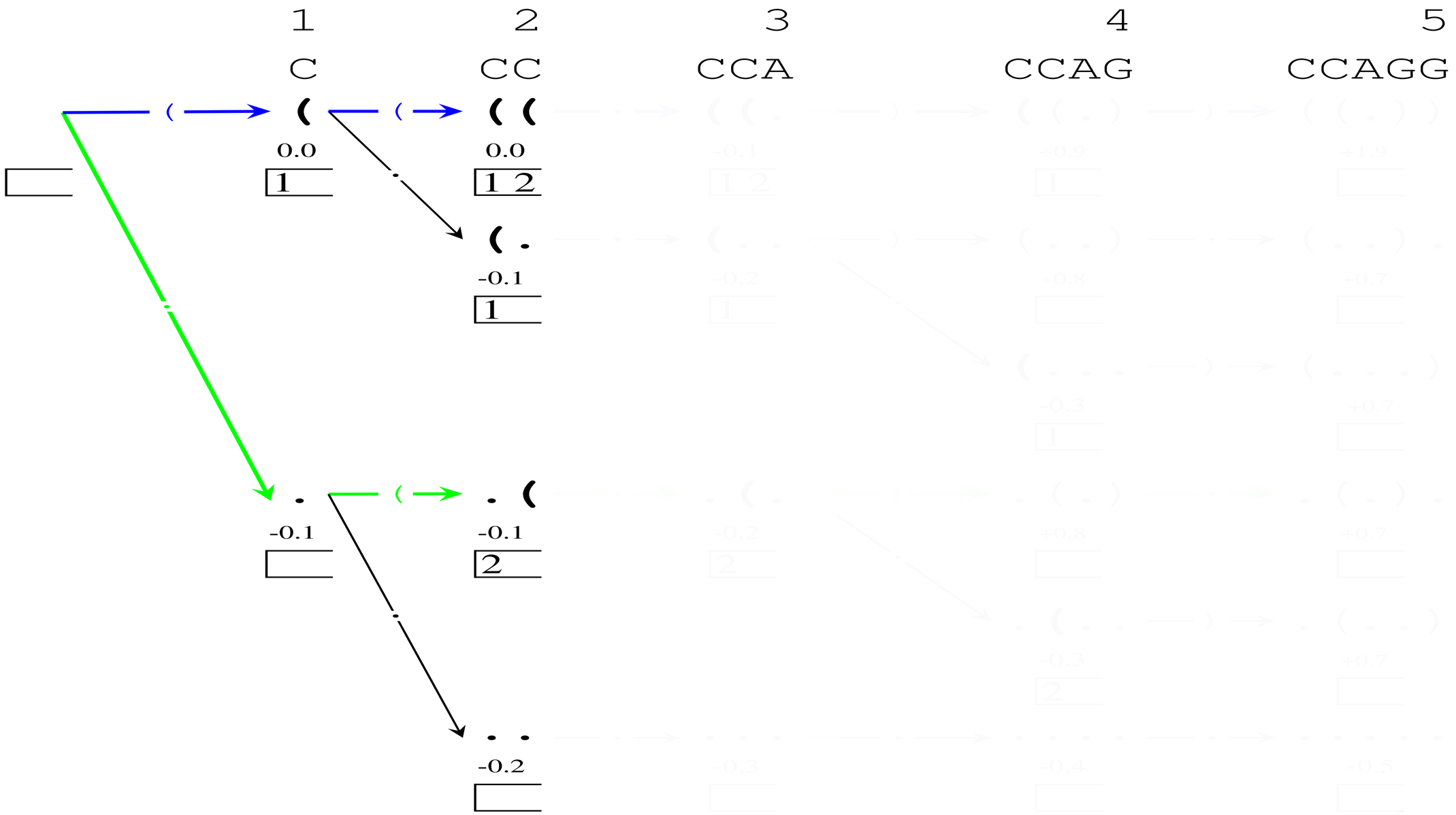

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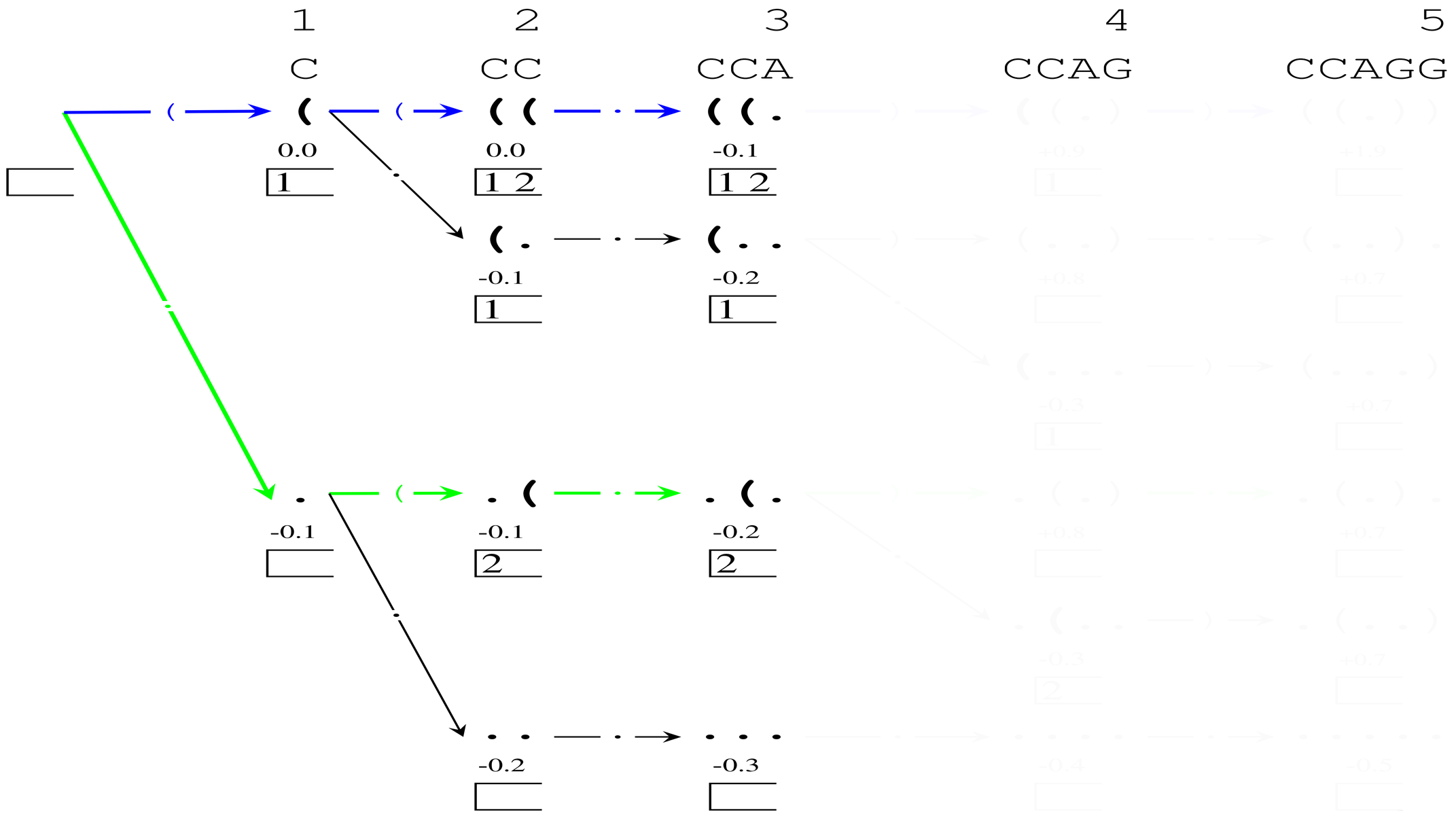

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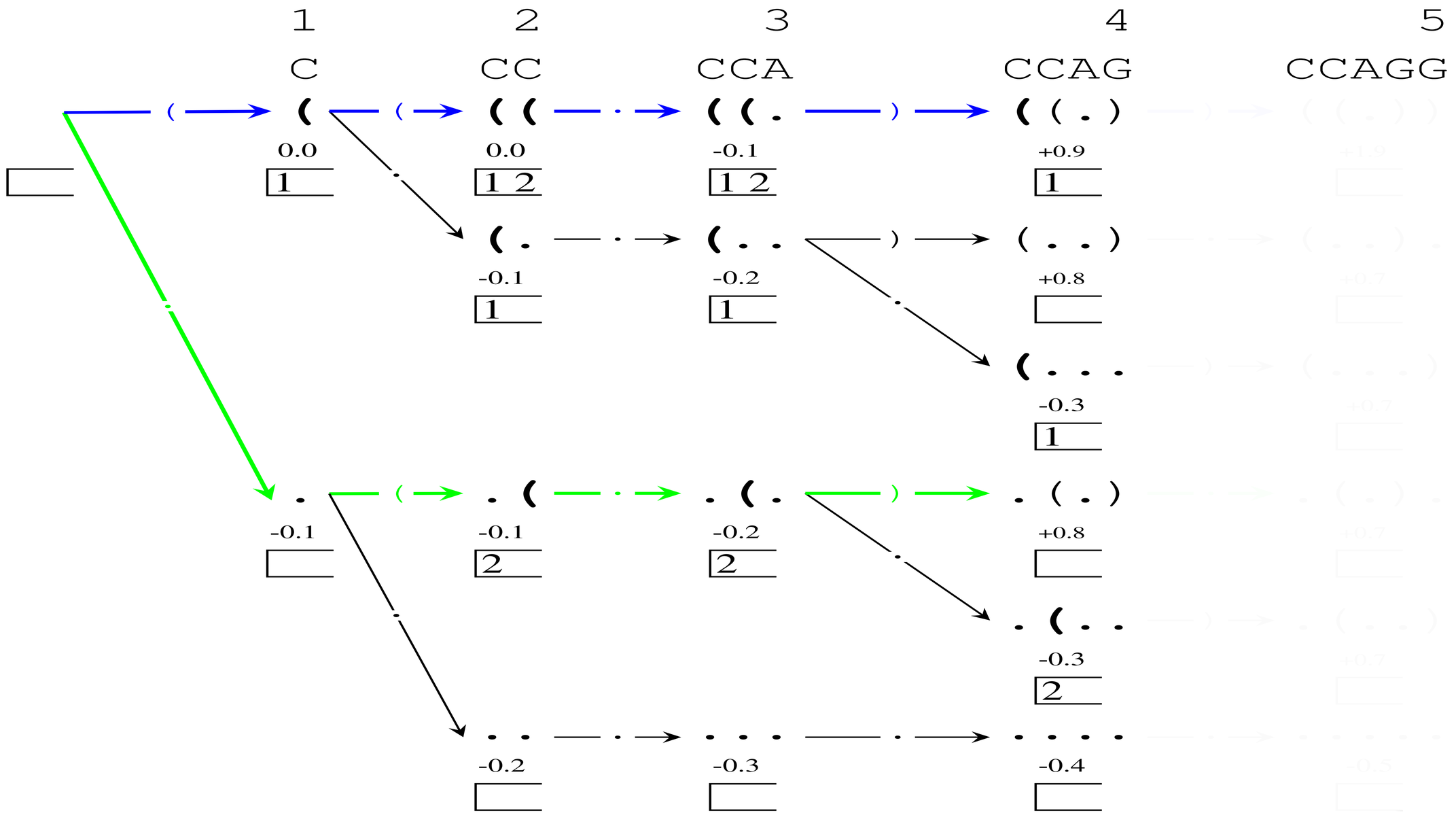

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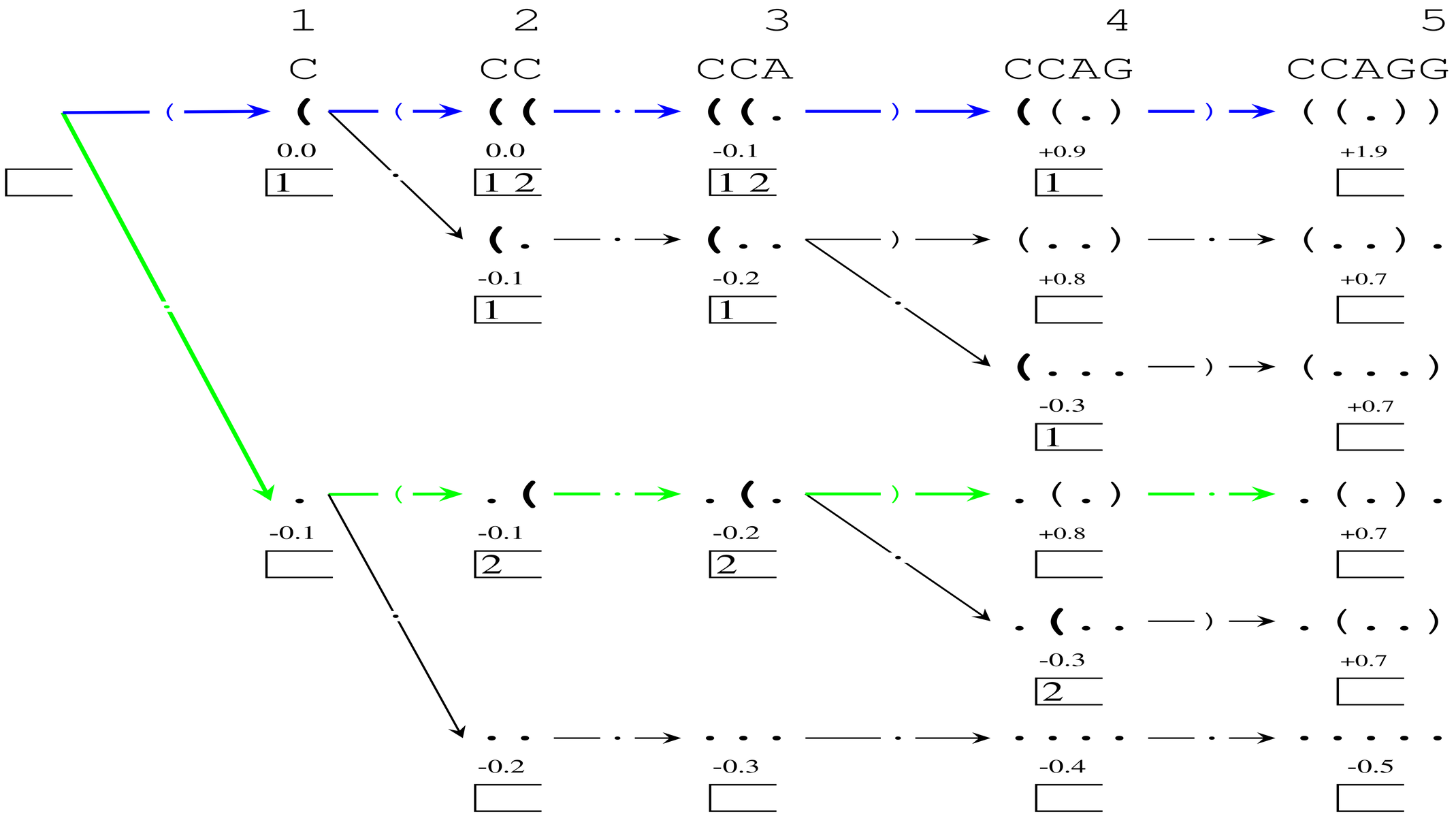
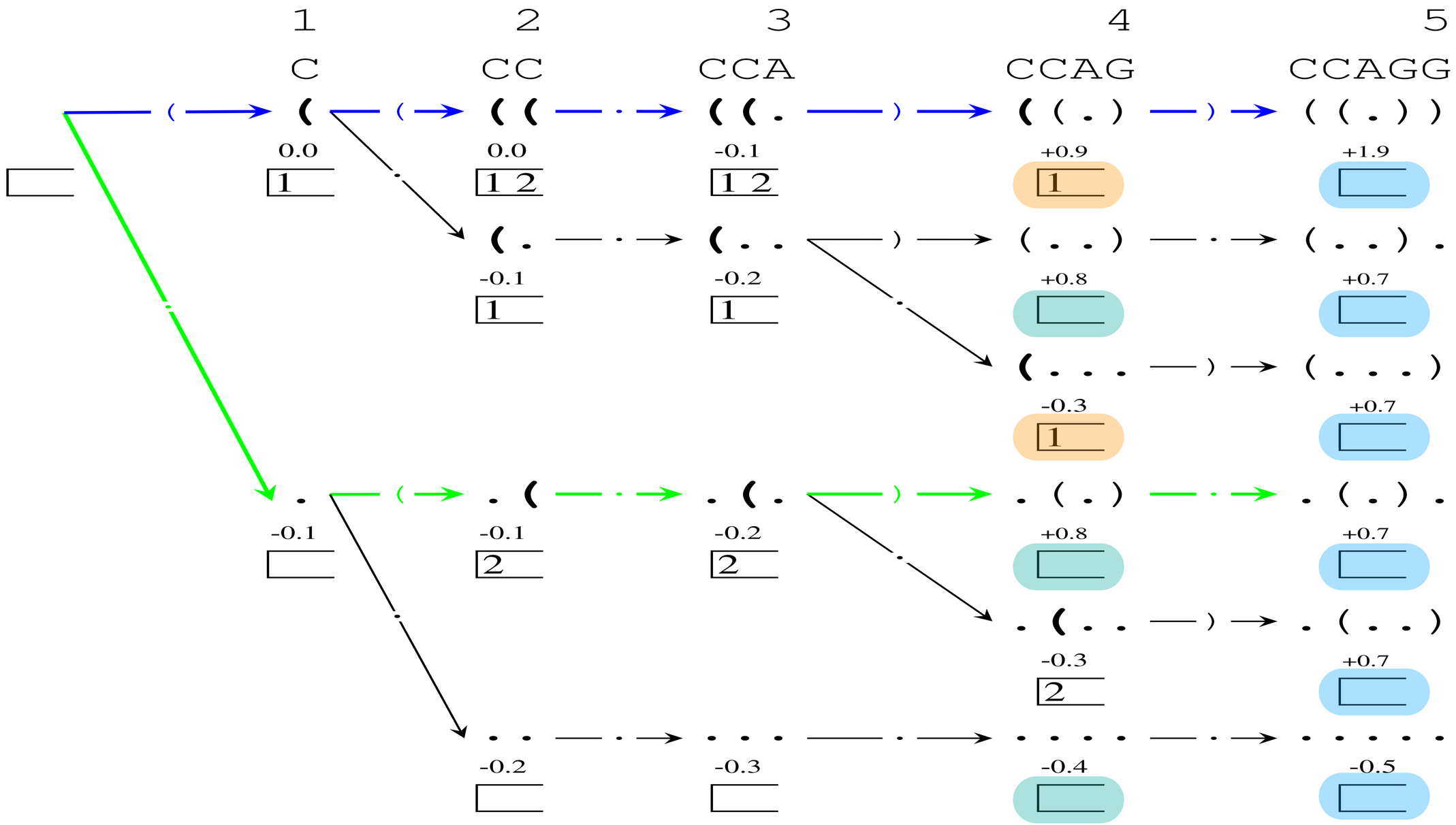


Idea 1: Merge Identical Stacks => Version 2: $O(2^n)$



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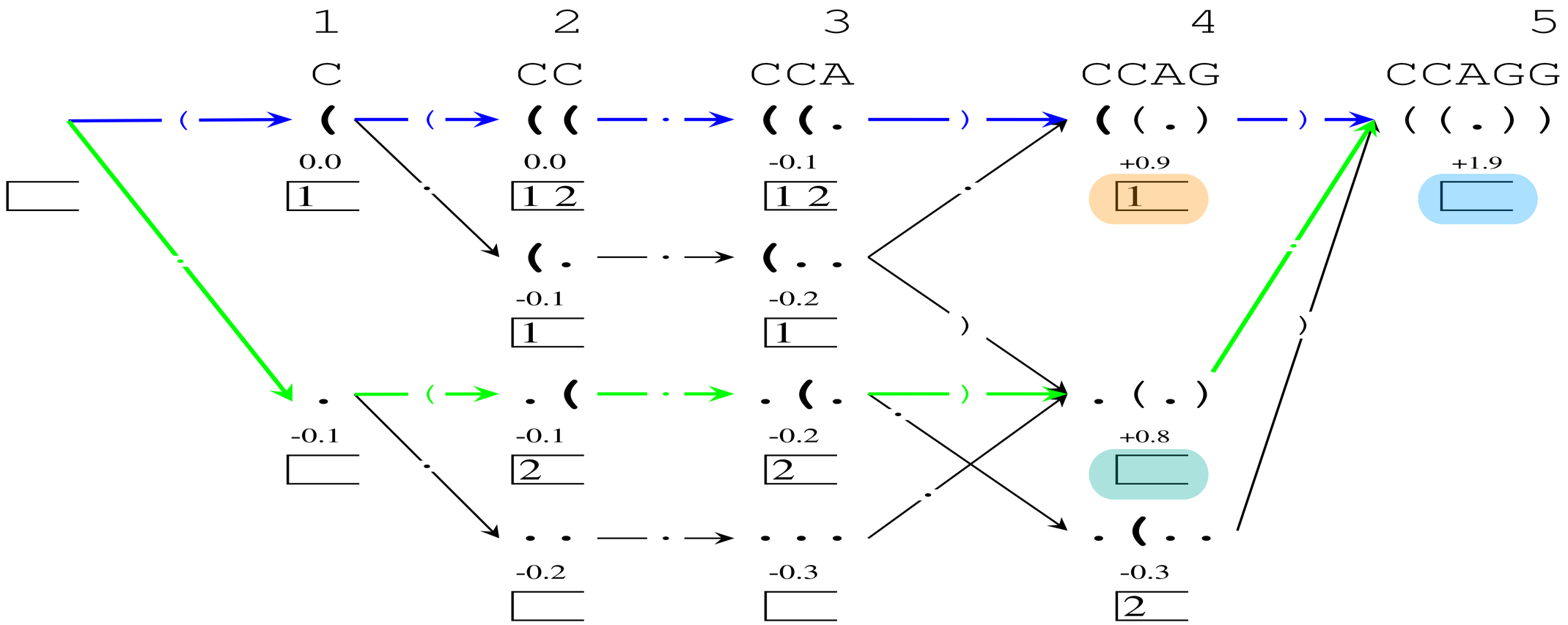
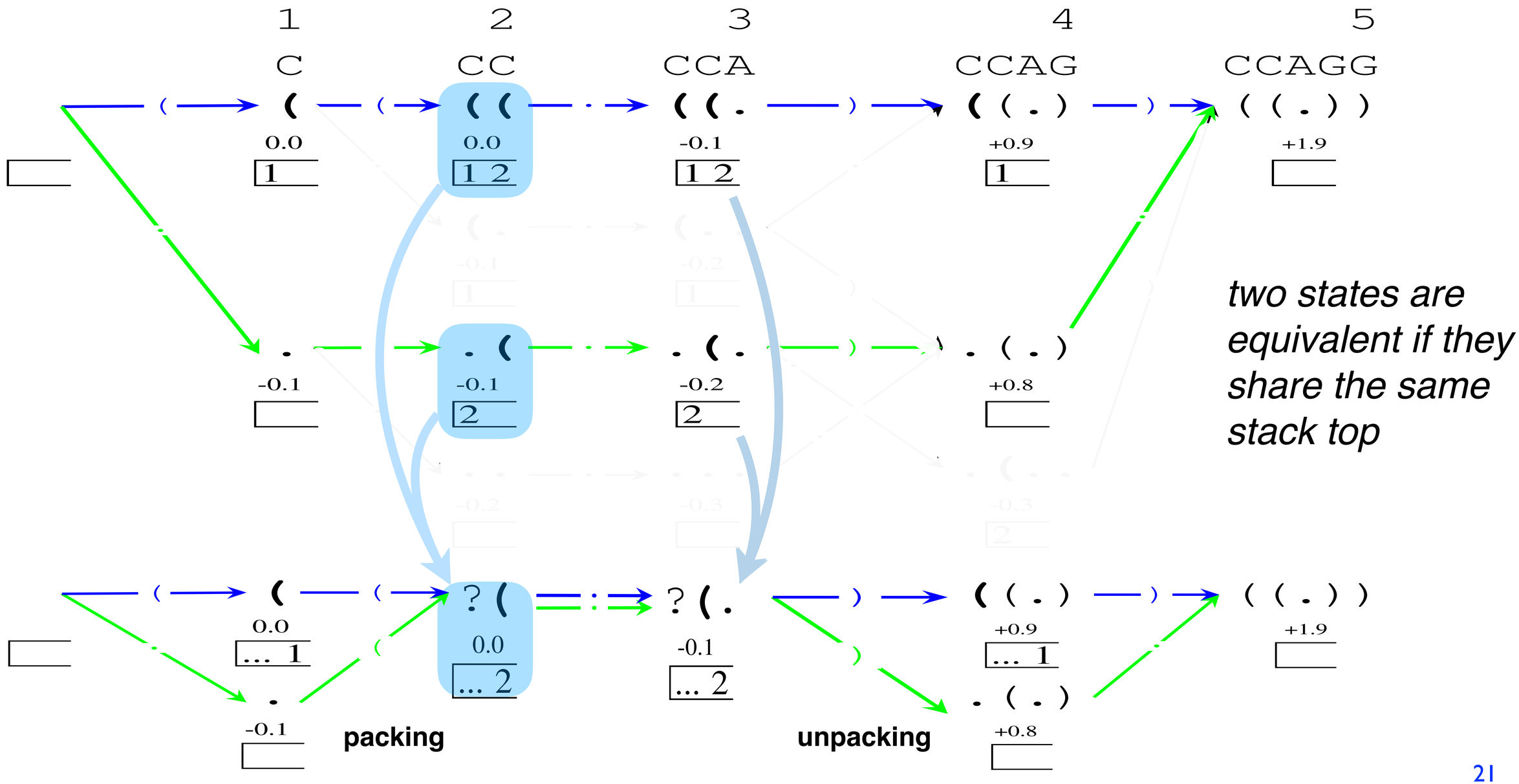


Details: Pack "Equivalent" States => $O(n^3)$



two states are equivalent if they share the same stack top

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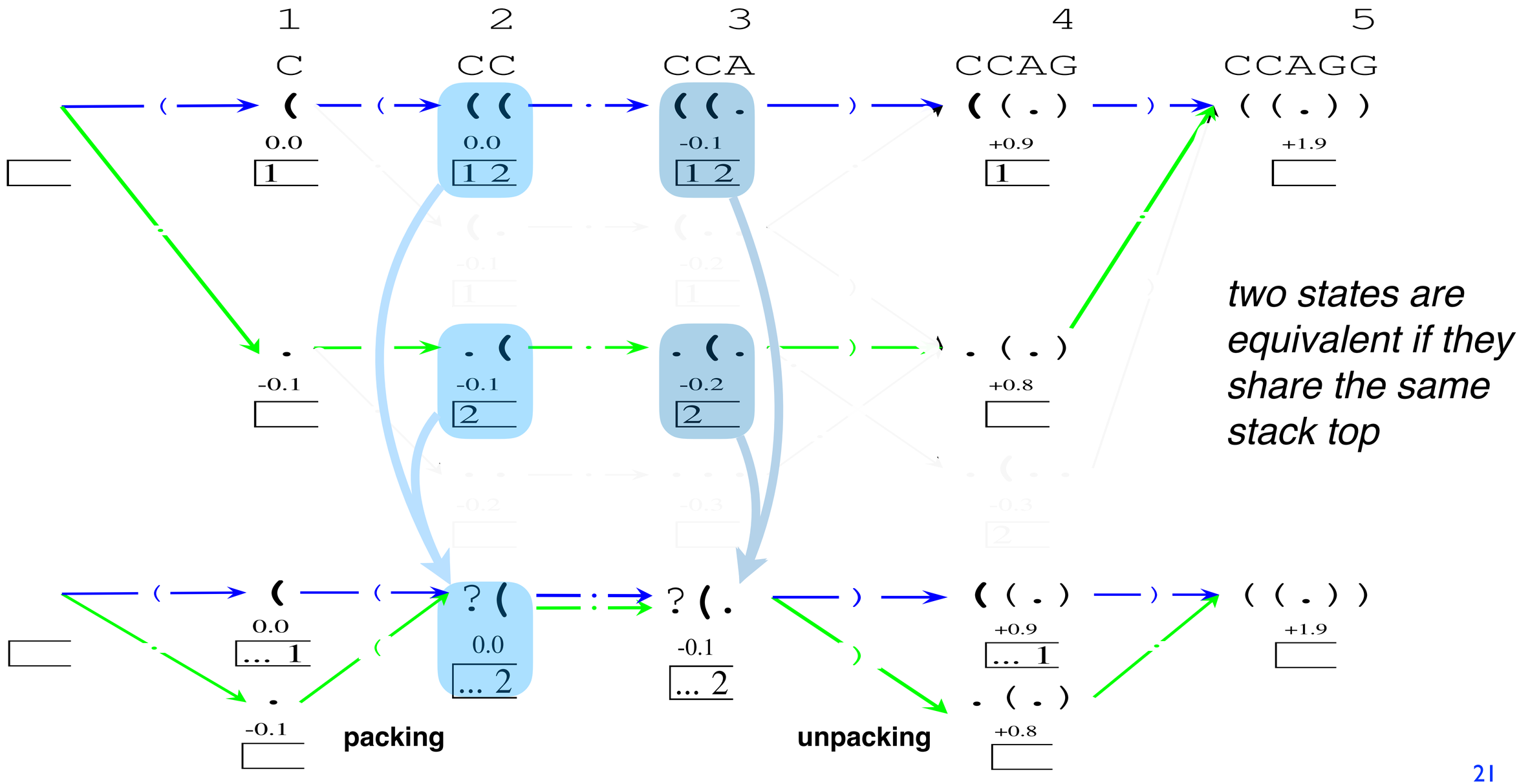

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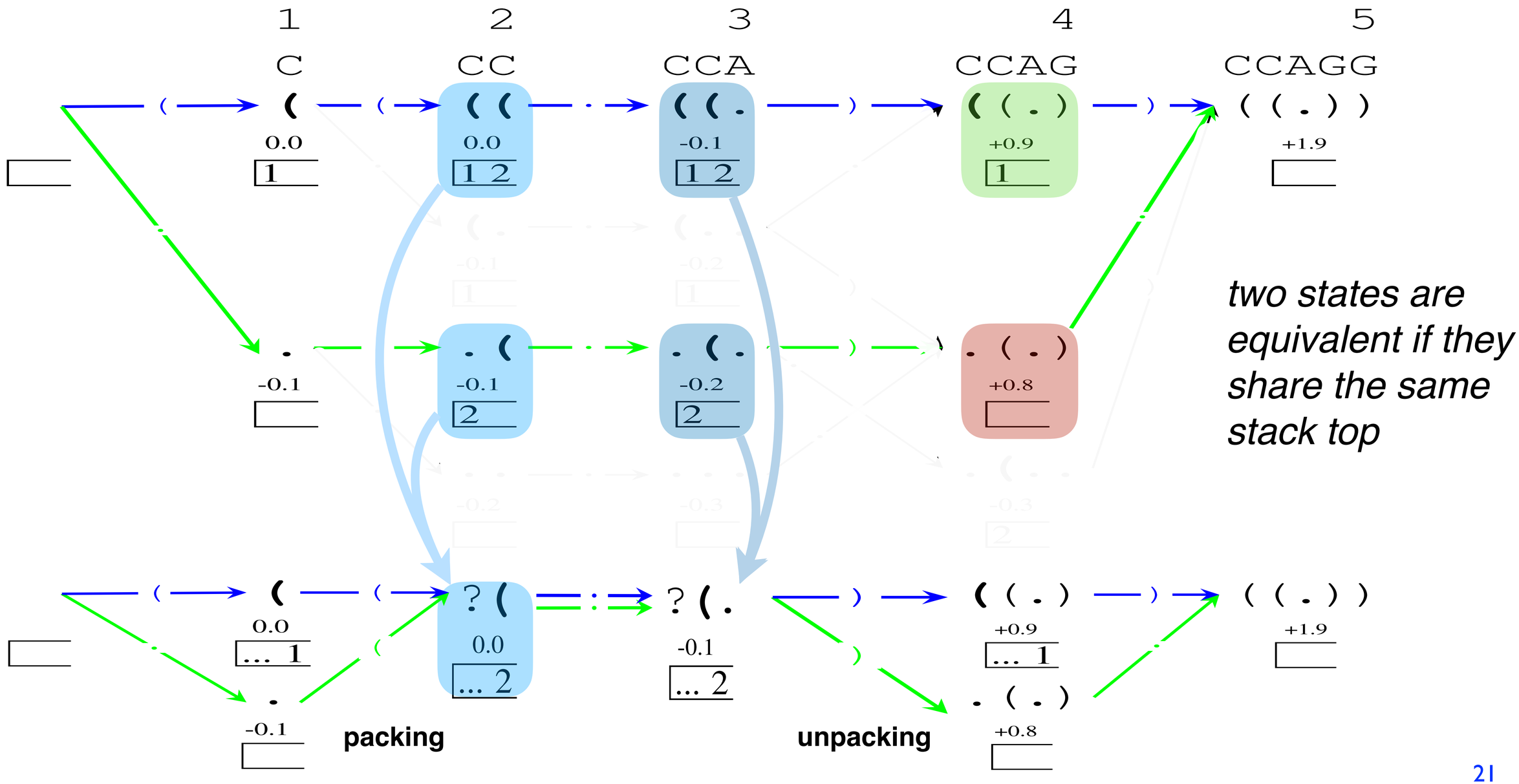

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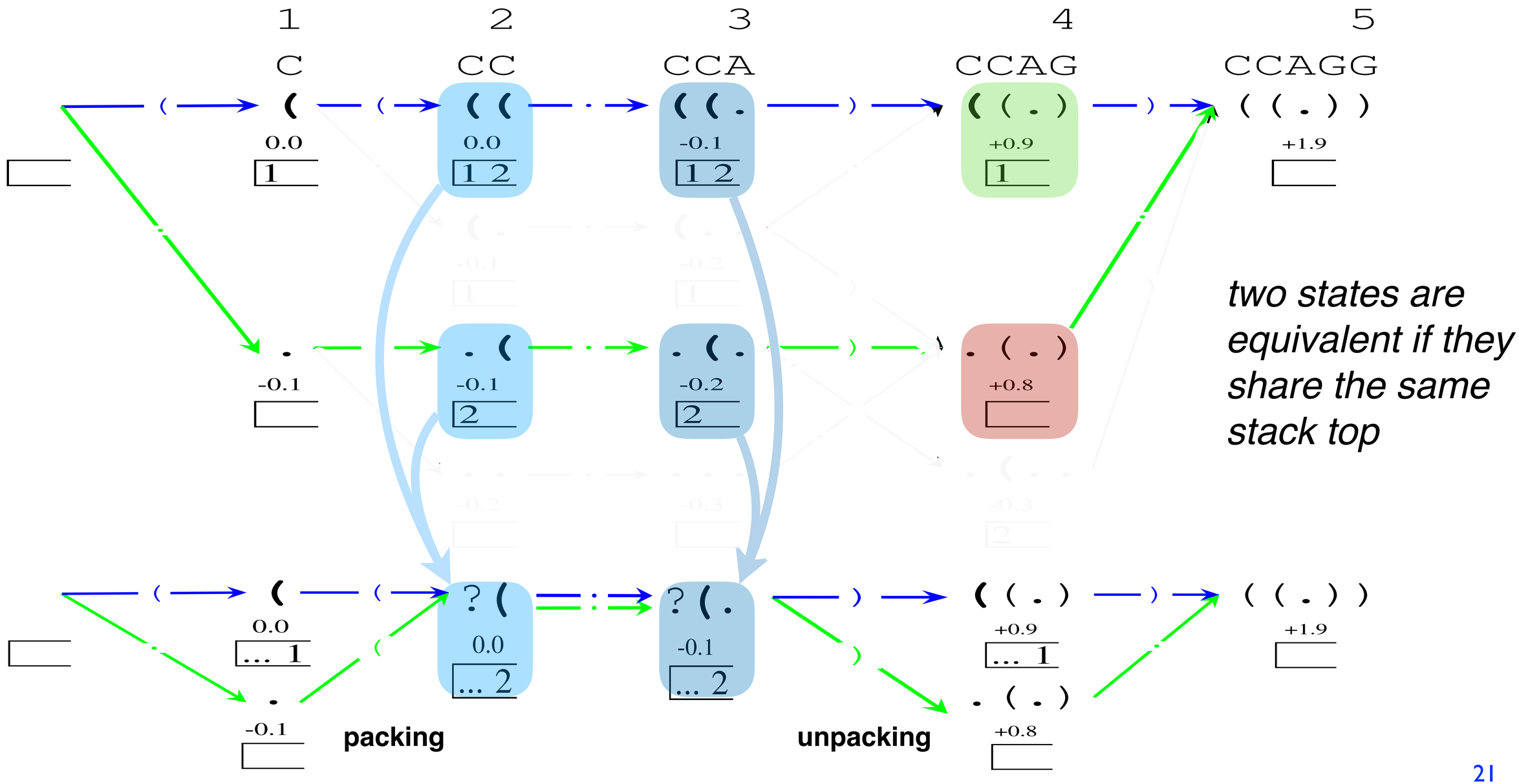

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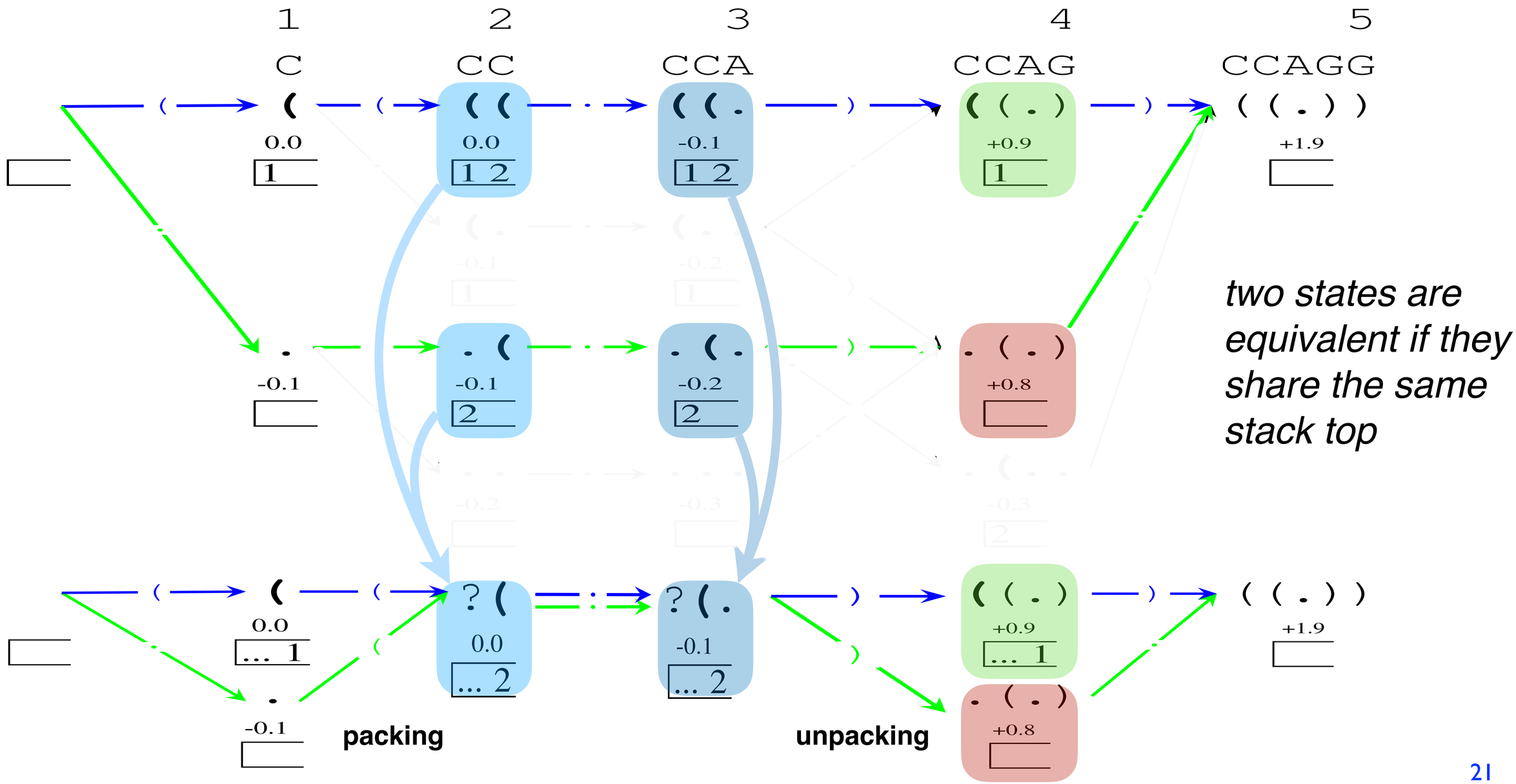

two states are equivalent if they share the same stack top

Details: Packing "Temporarily Equivalent" States

- two states are "temporarily equivalent" if they share the same stack top index
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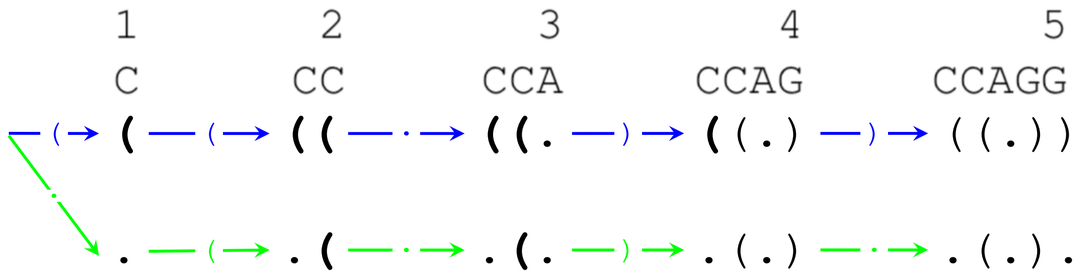
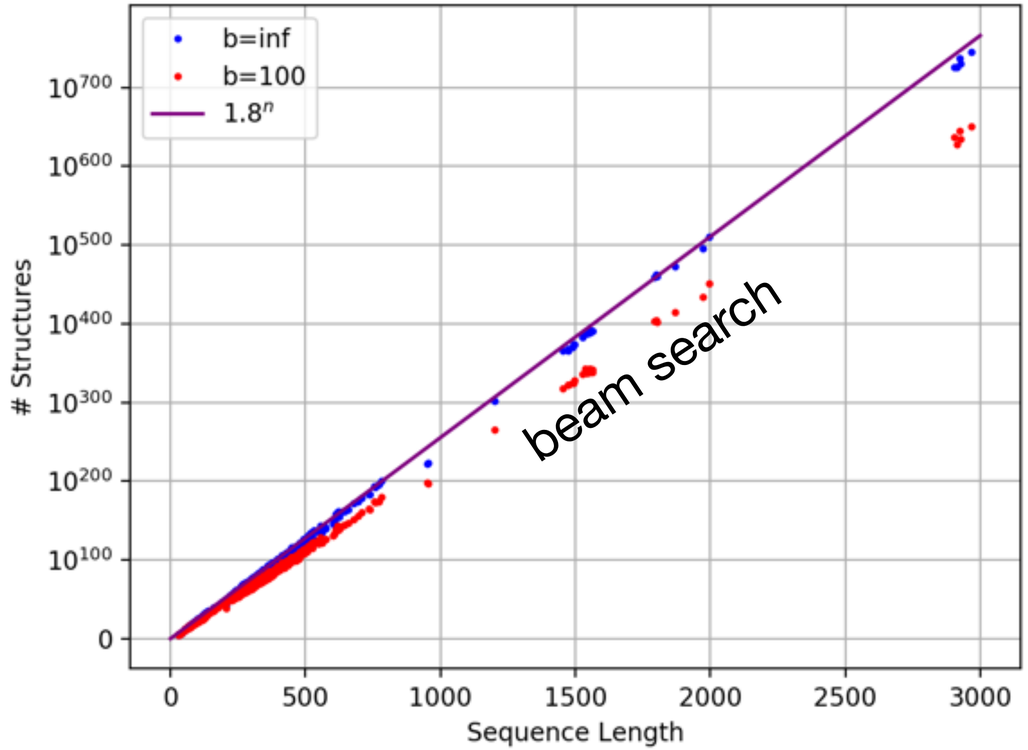
  - this is how we can explore exponentially many structures in linear time





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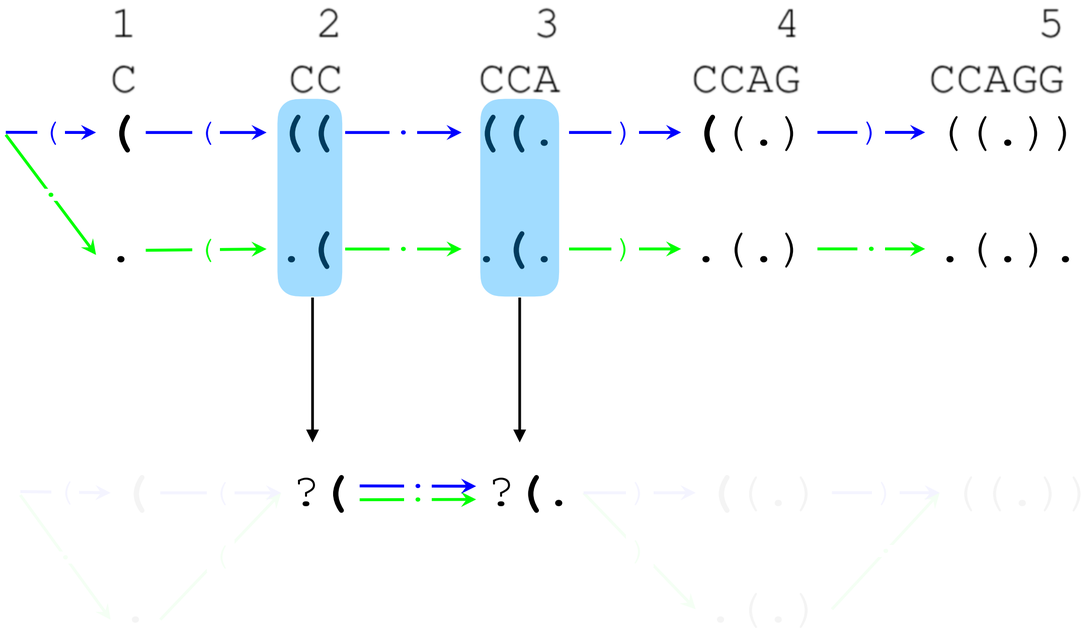

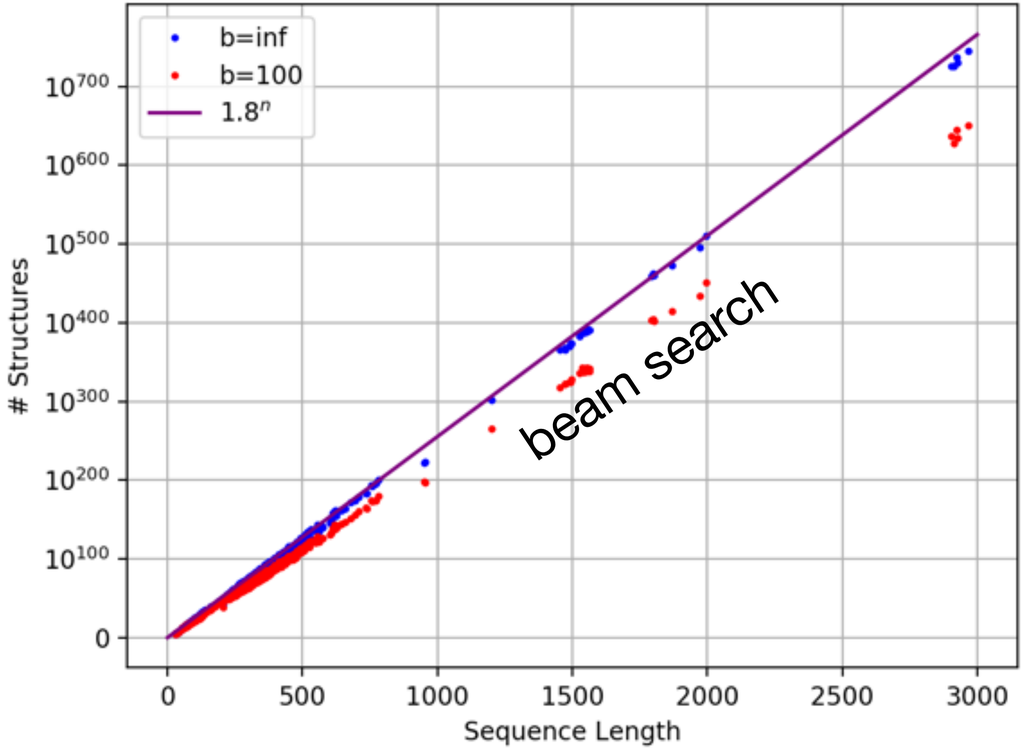

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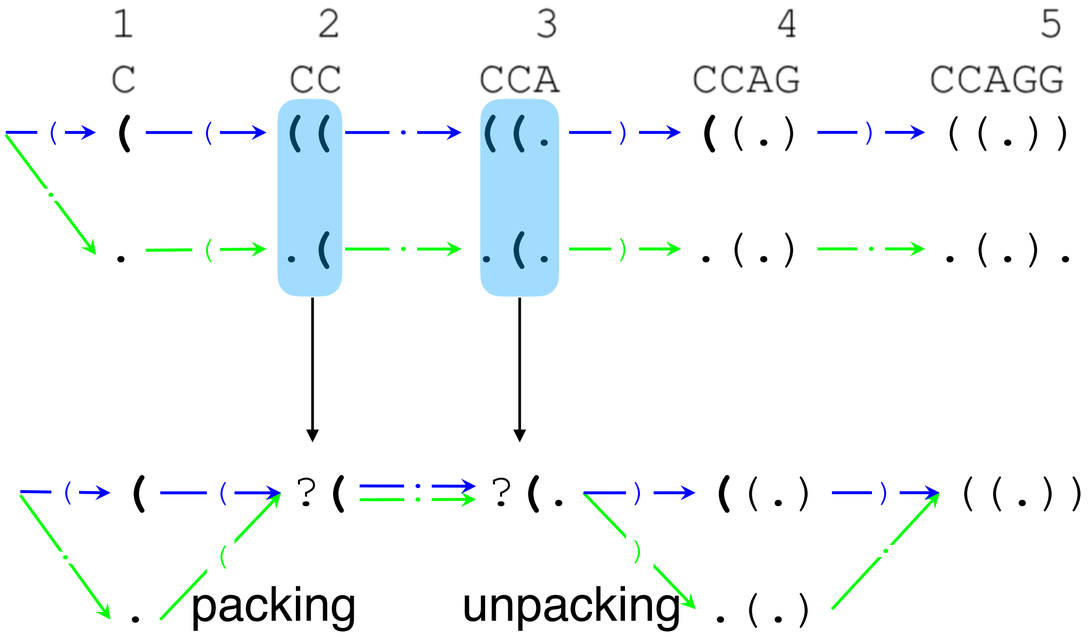
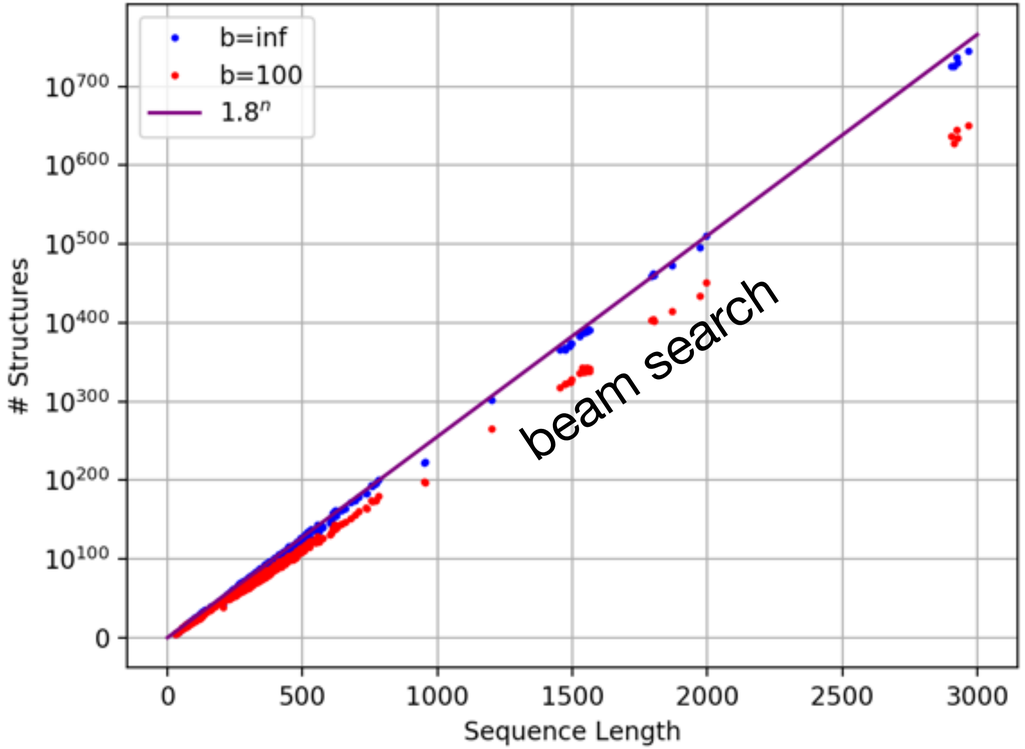
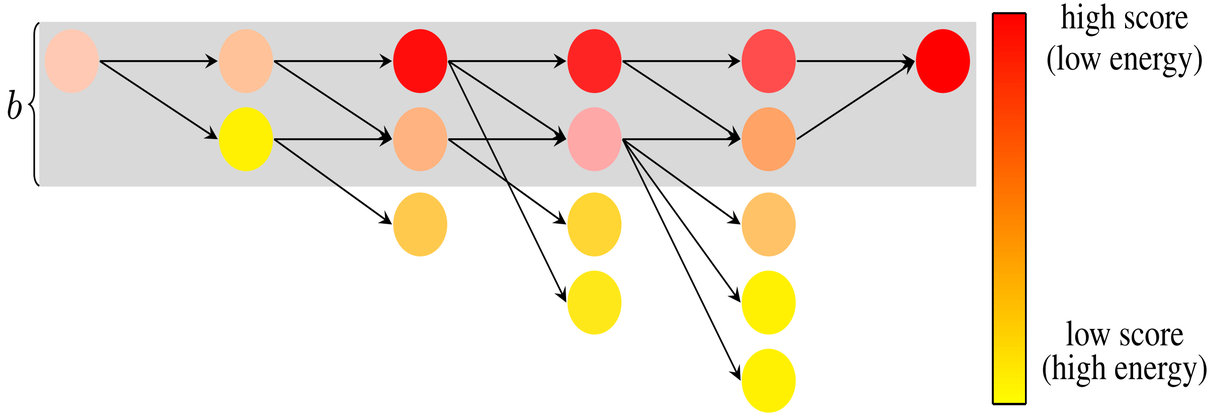
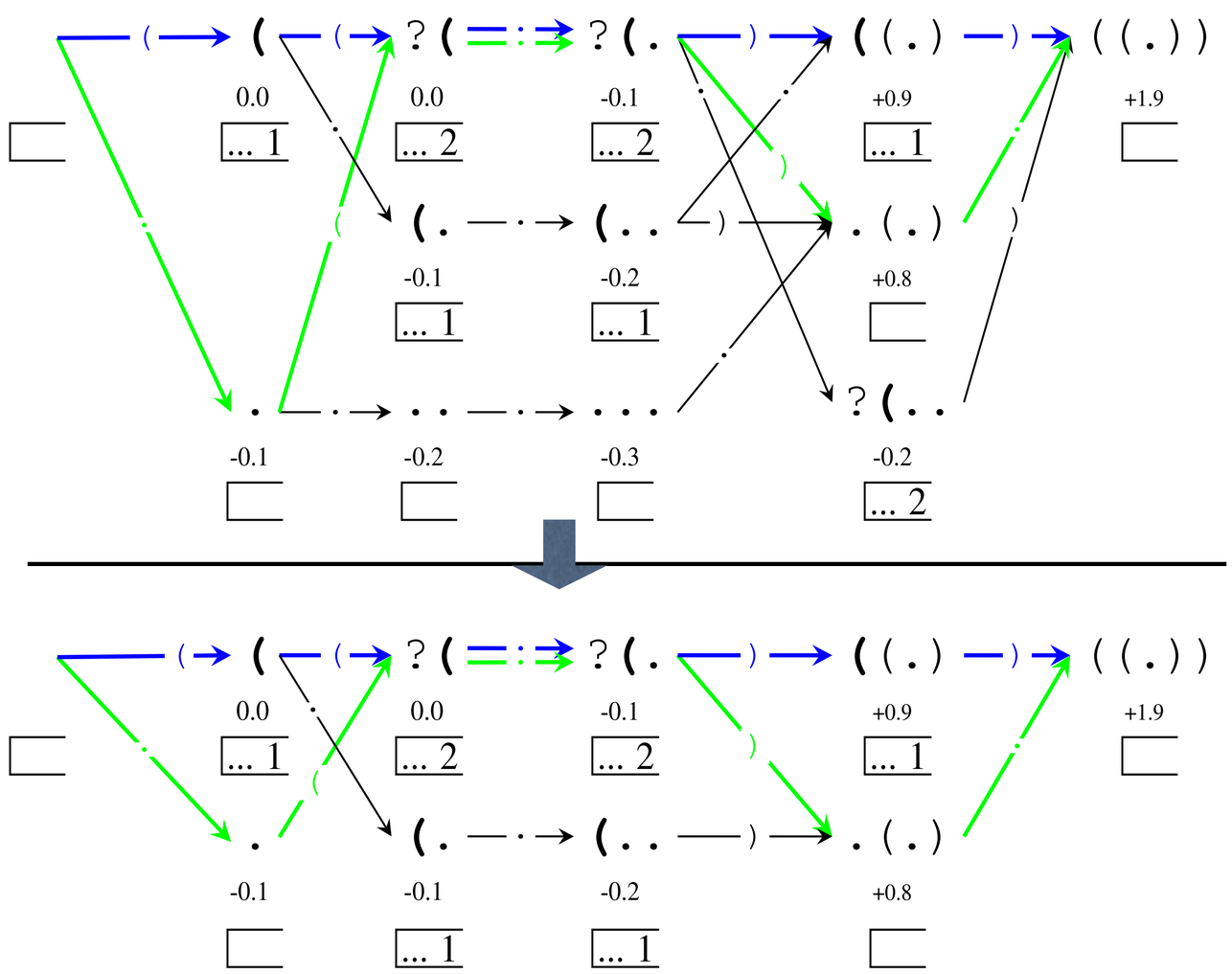




Idea 3: Beam Search => Version 4: $O(n)$, approx.





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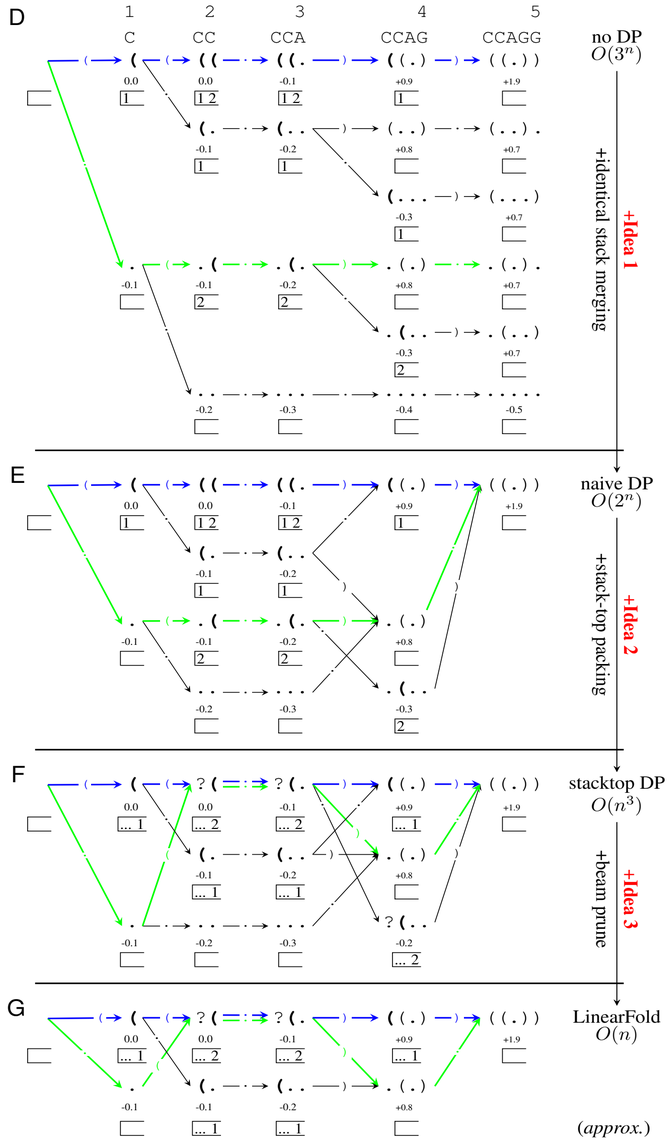
  - our real systems have full scoring functions



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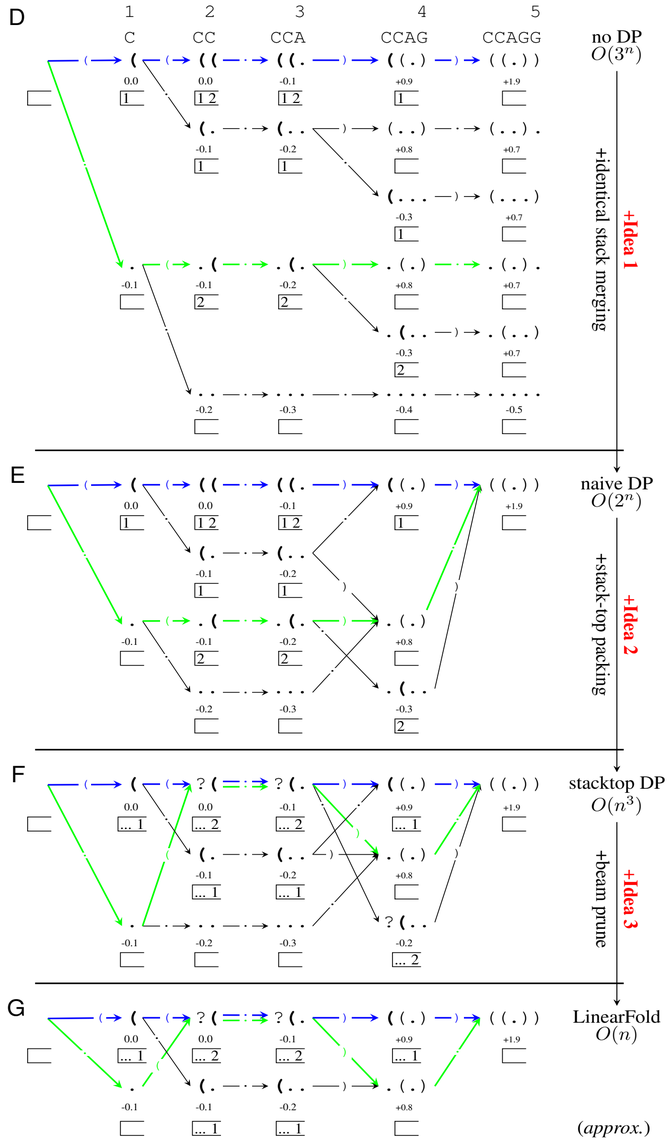

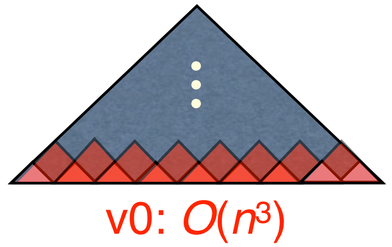

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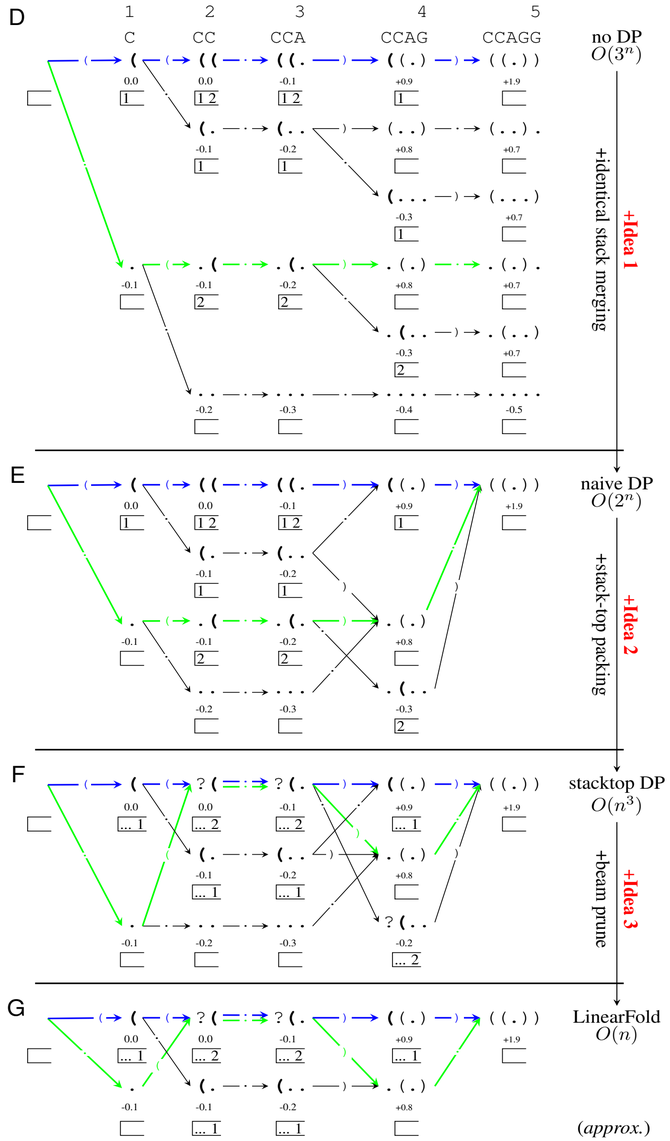

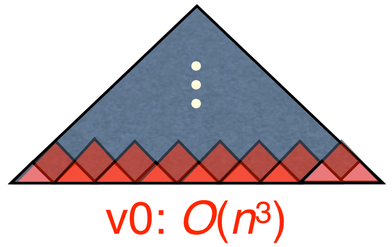

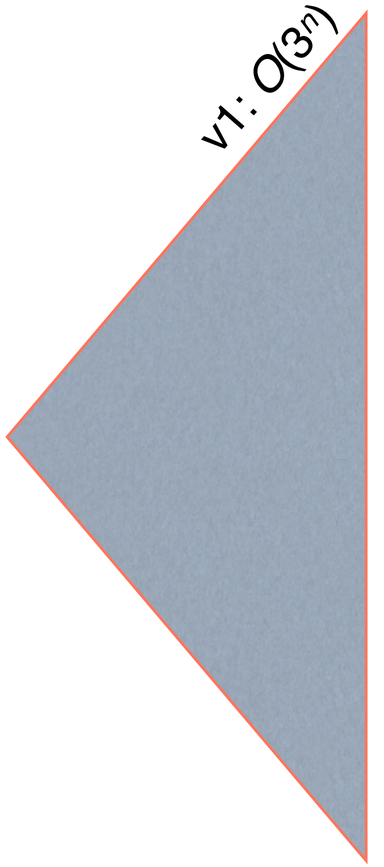

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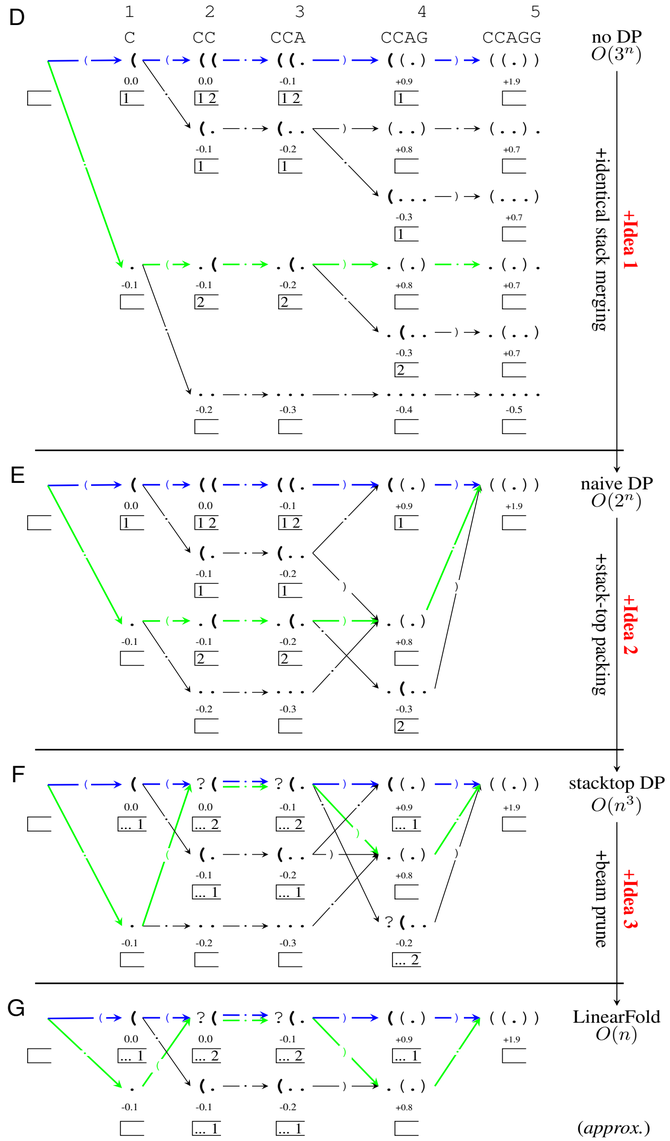

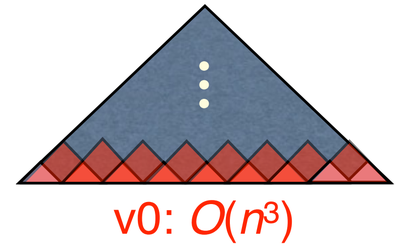

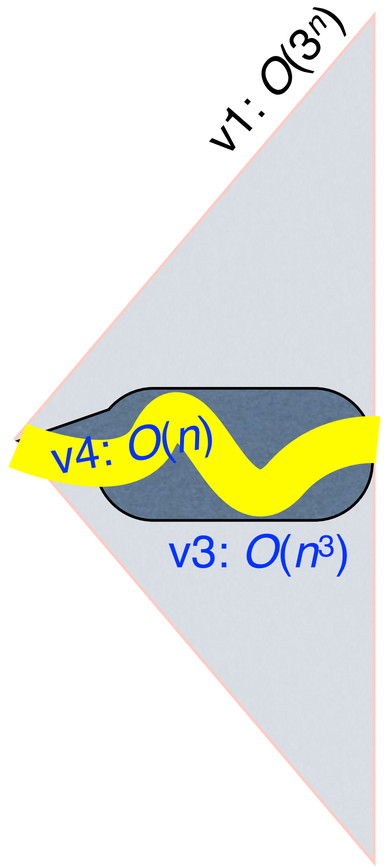

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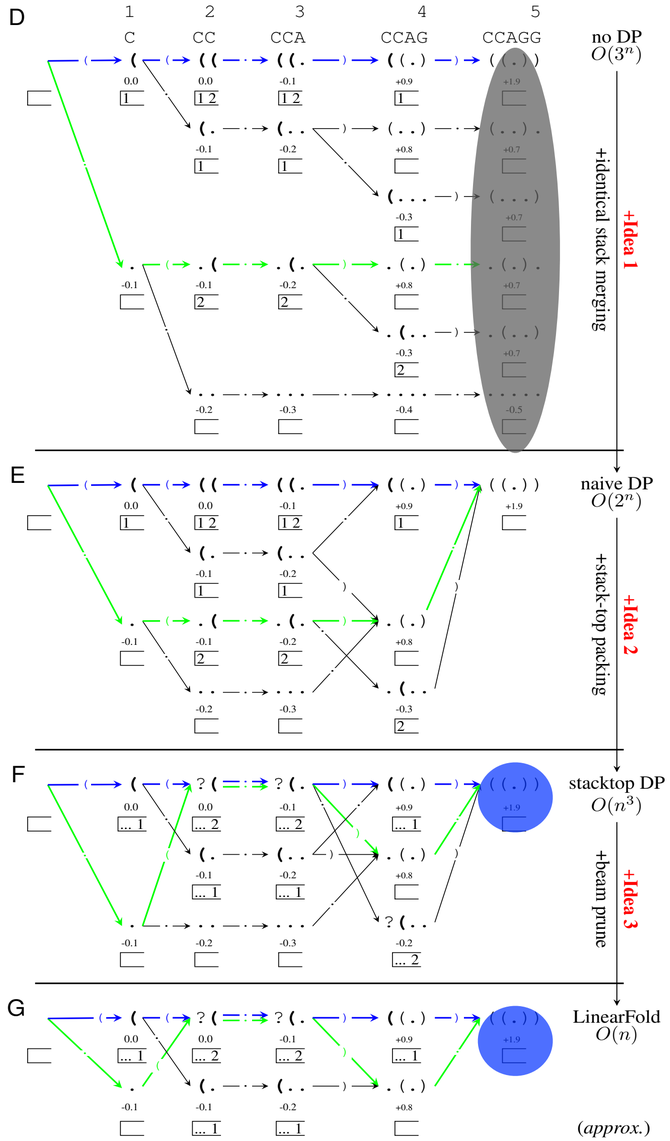
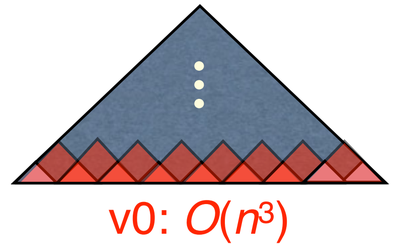
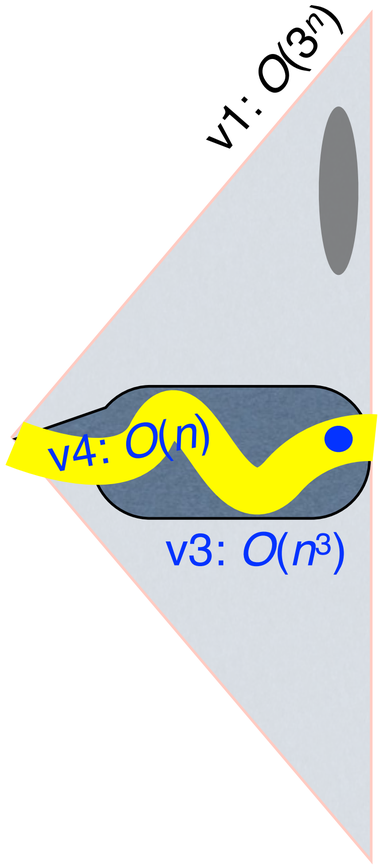


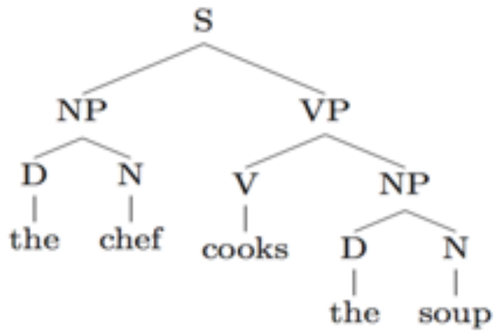




Computational Linguistics => Computational Biology

linguistics | **compiler theory** | **comp. linguistics** | **computational biology**

1955 Chomsky: context-free grammars (CFGs)



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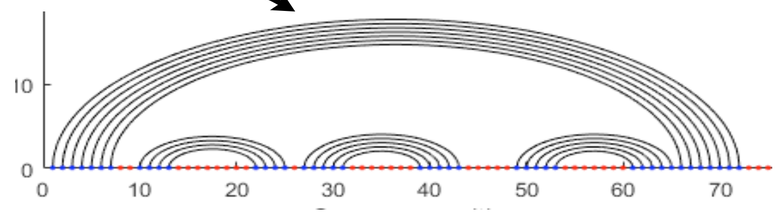

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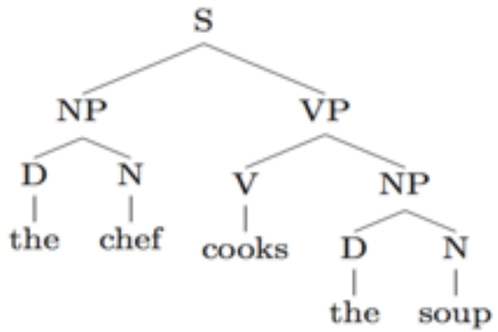

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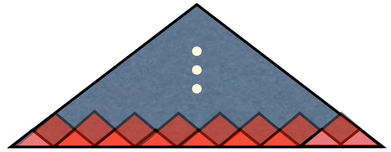

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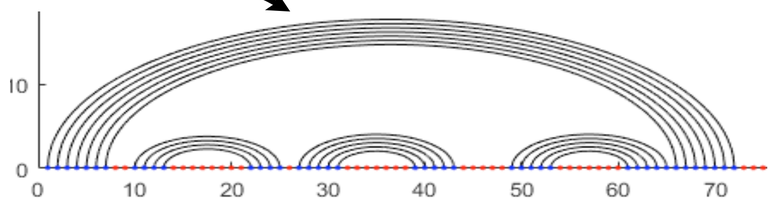

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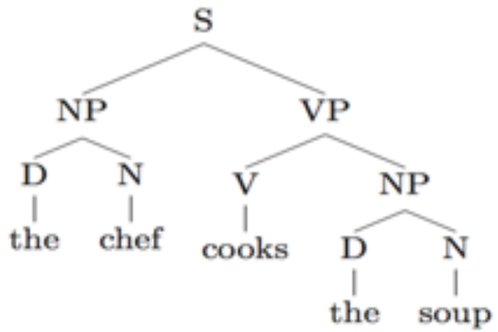

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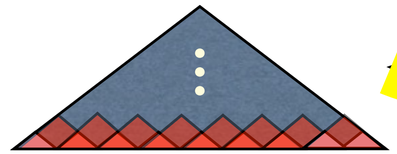

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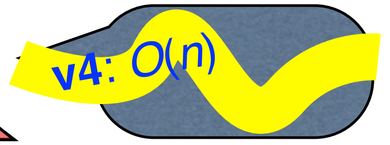
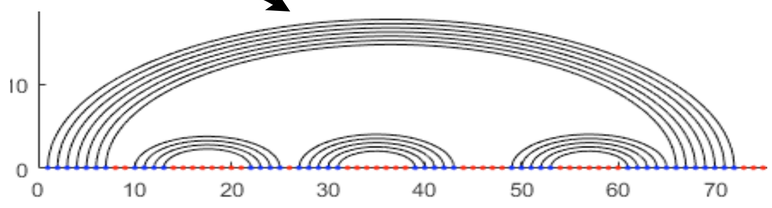


v3: $O(n^3)$



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  - pack non-crucial local ambiguities along the way
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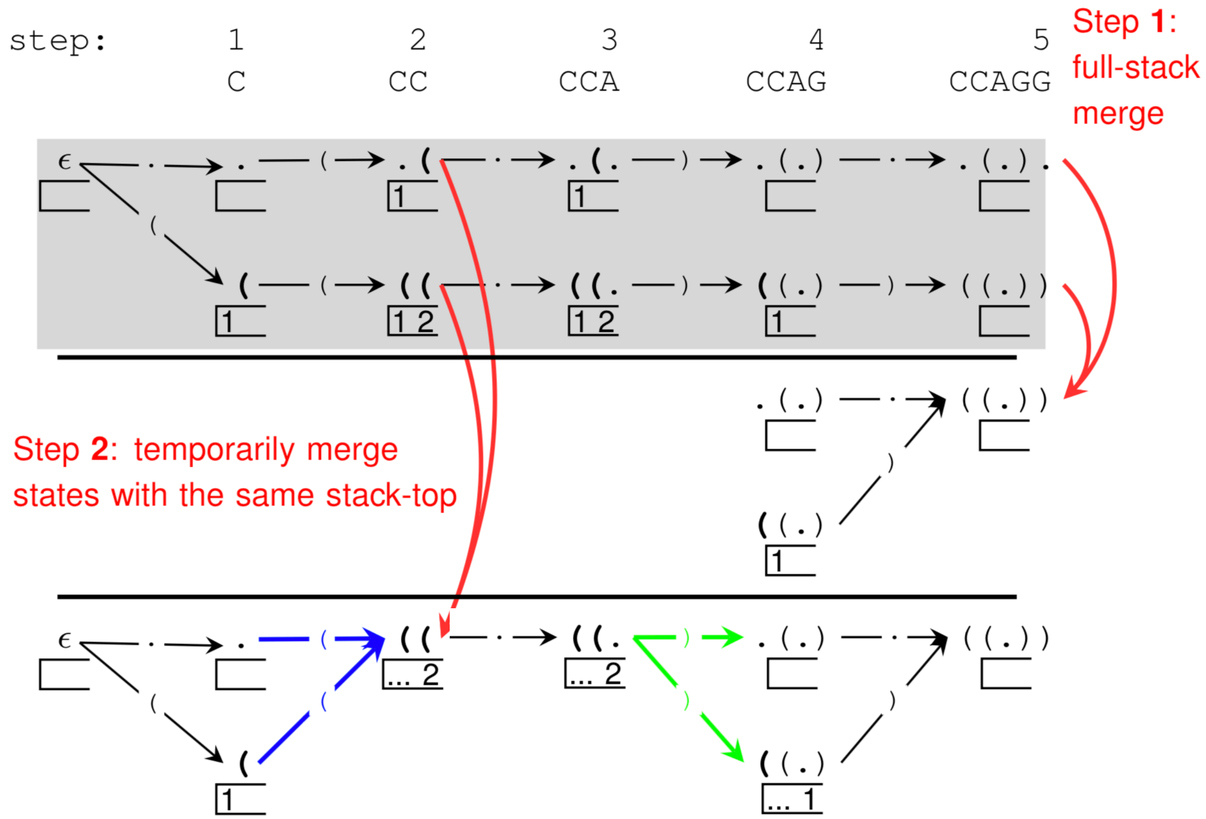

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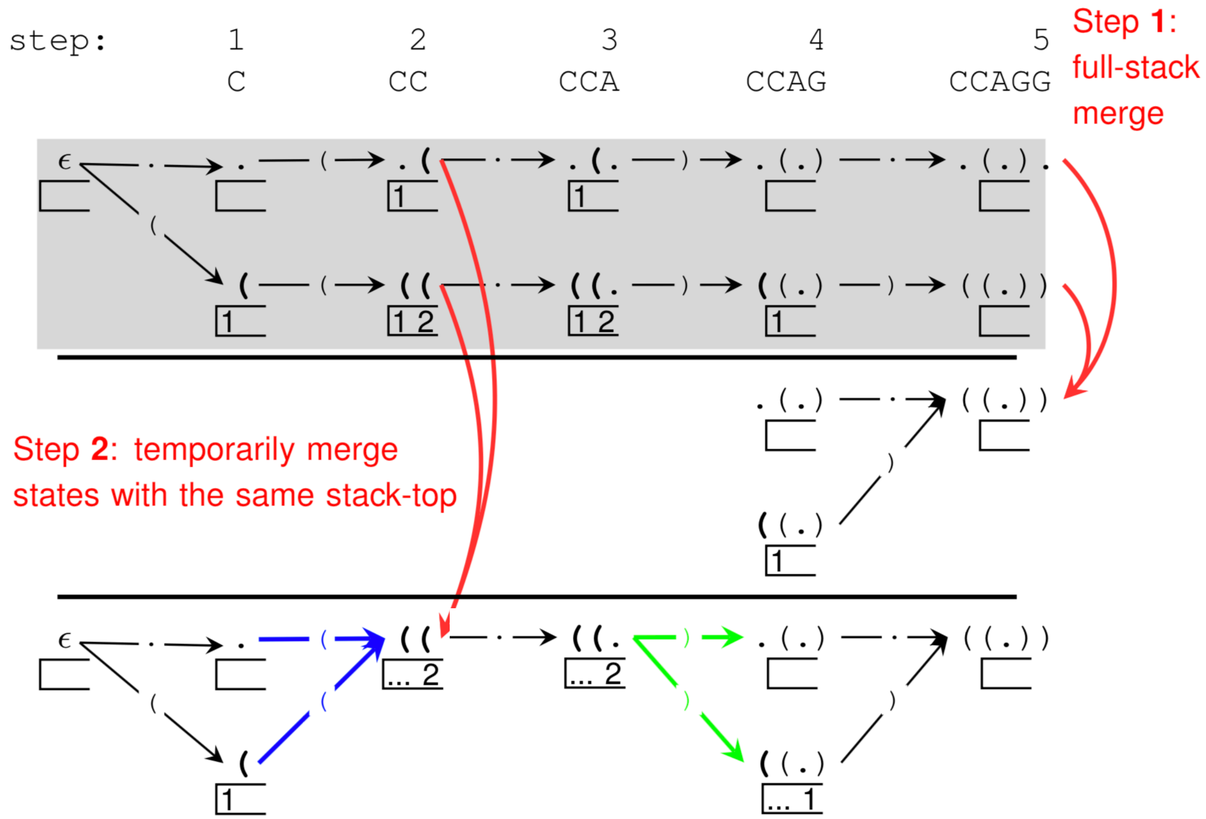

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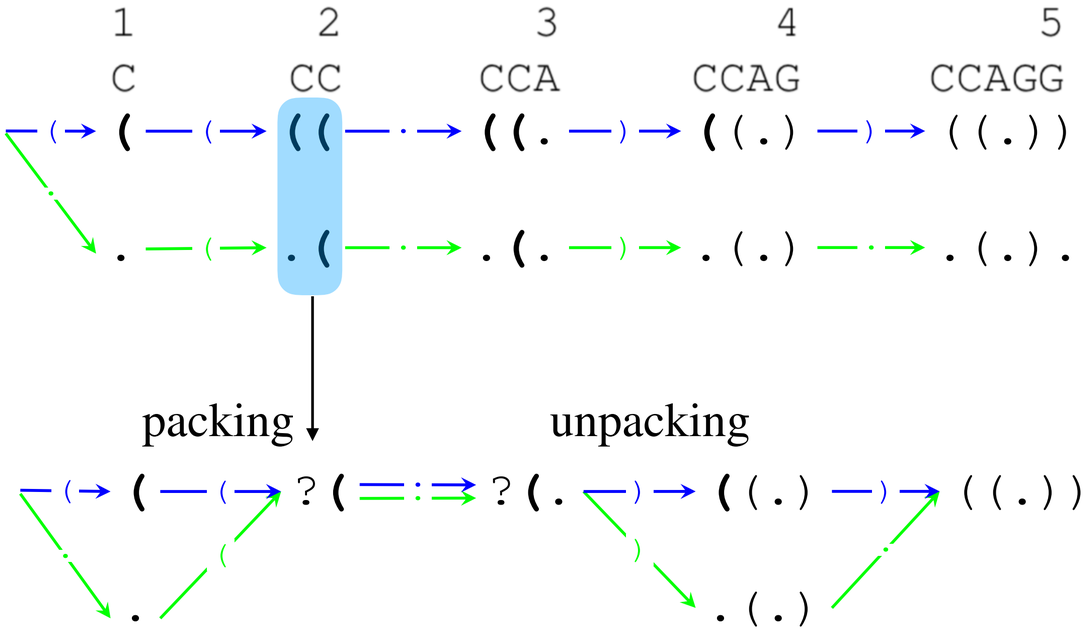

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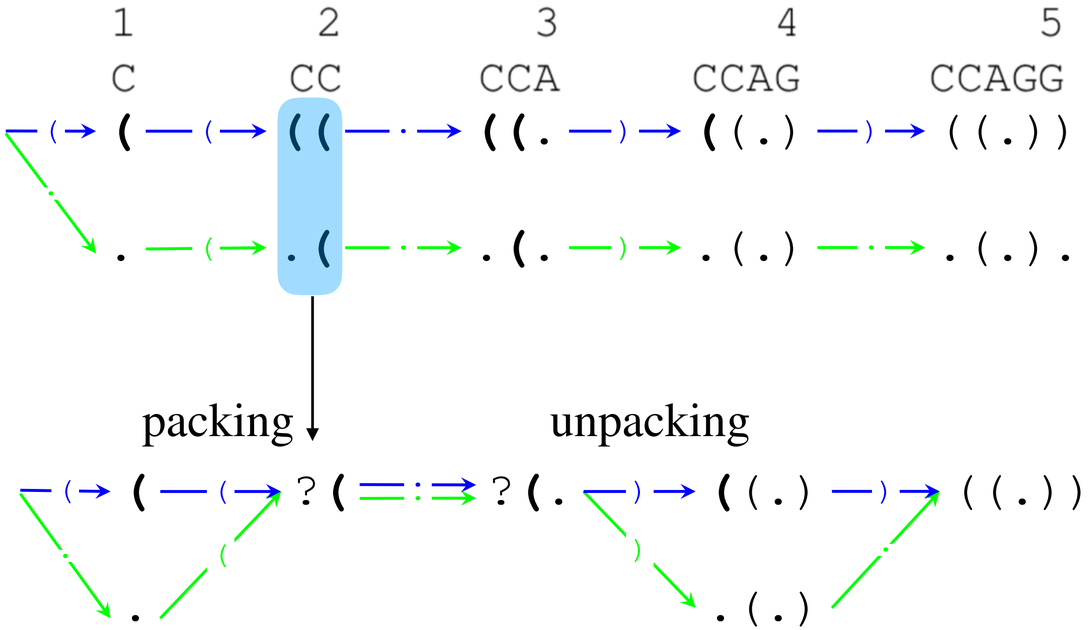
  - pack non-crucial local ambiguities along the way
  - unpack (in a reduce action) only when needed



psycholinguistic evidence
(eye-tracking experiments):

delayed disambiguation

John and Mary had 2 papers each
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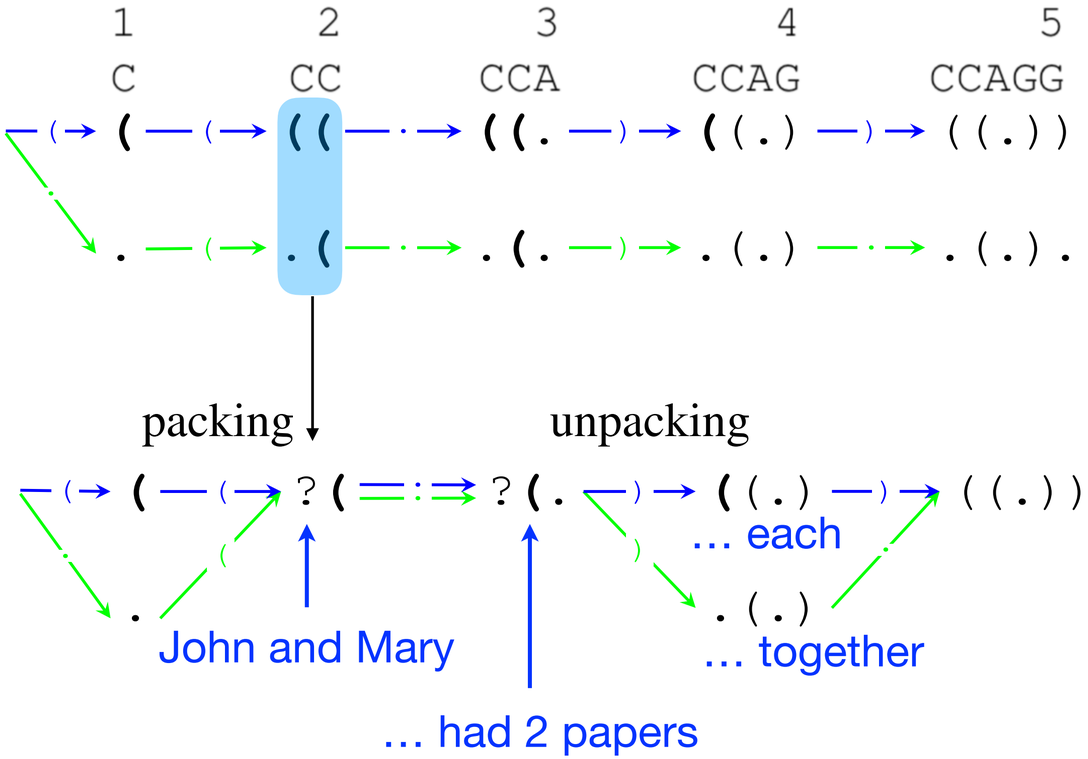

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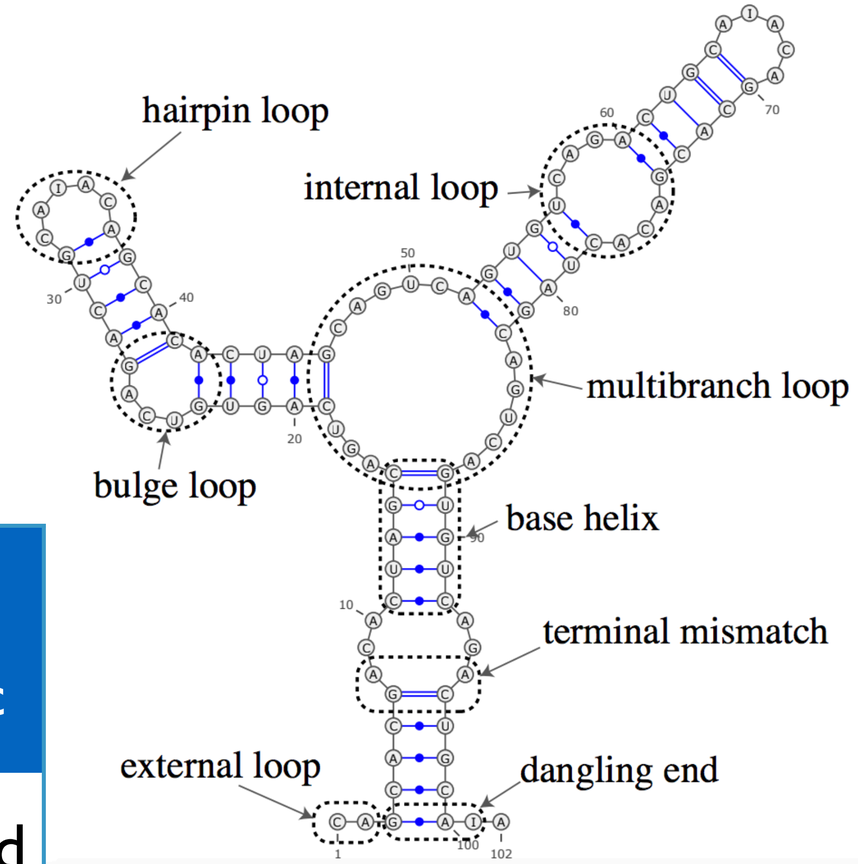
Results

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 $O(n)$



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	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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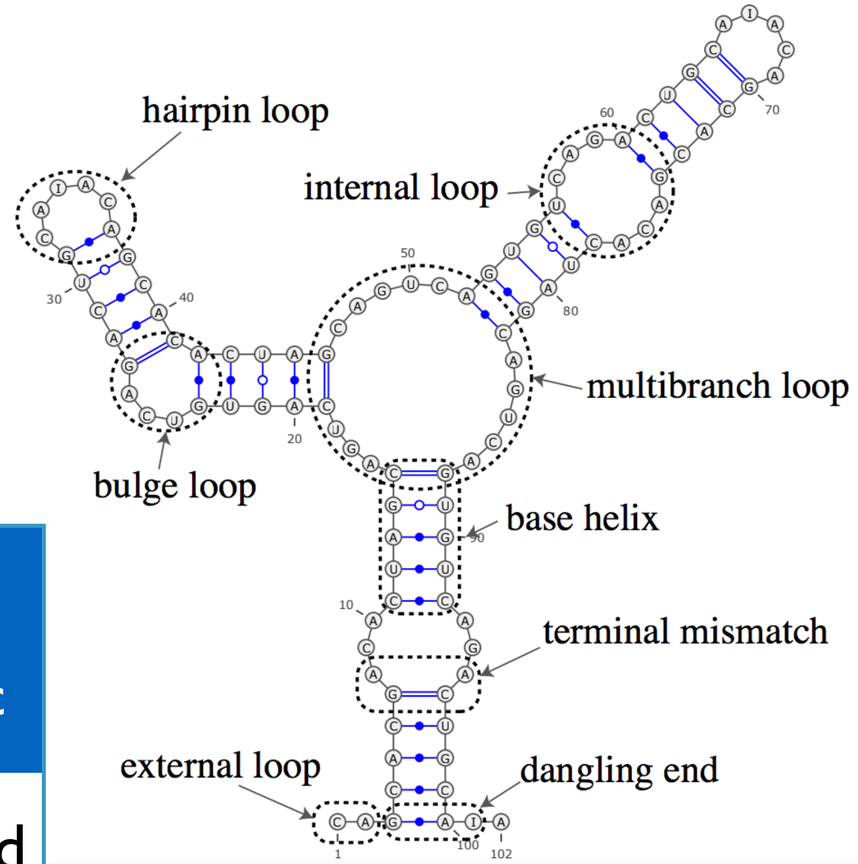

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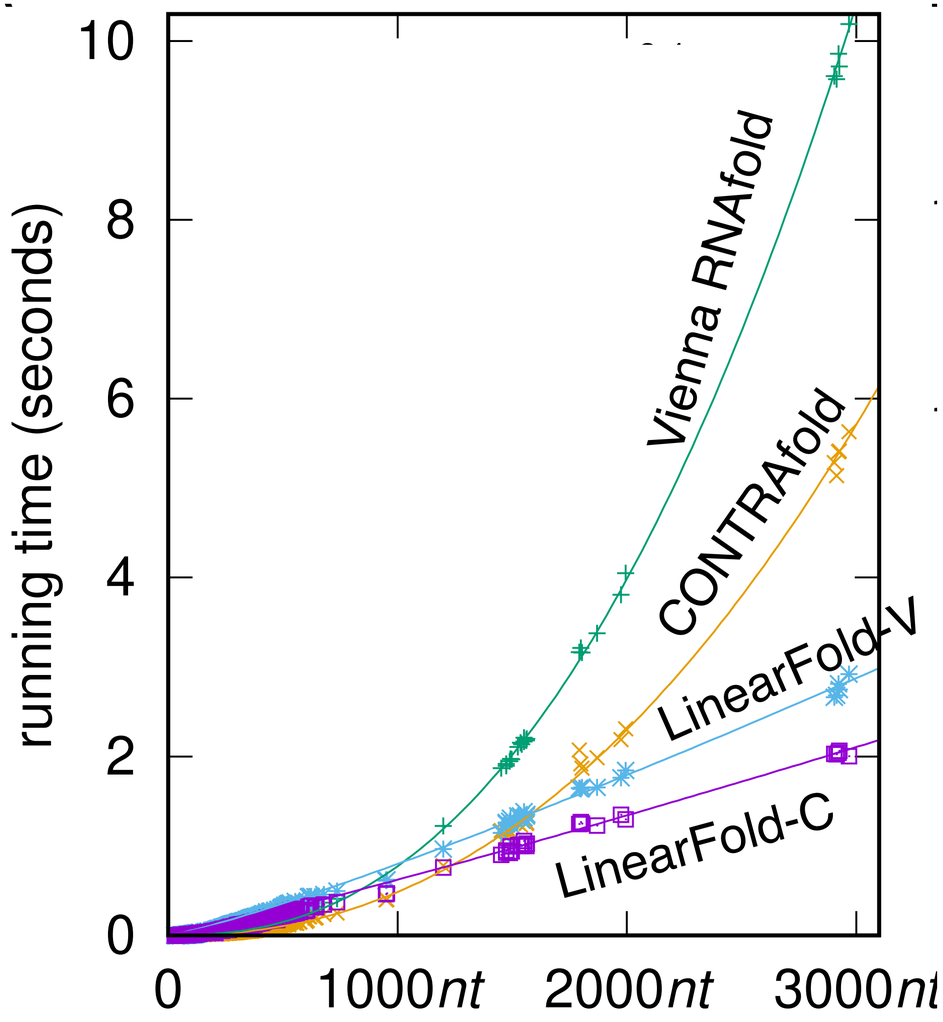
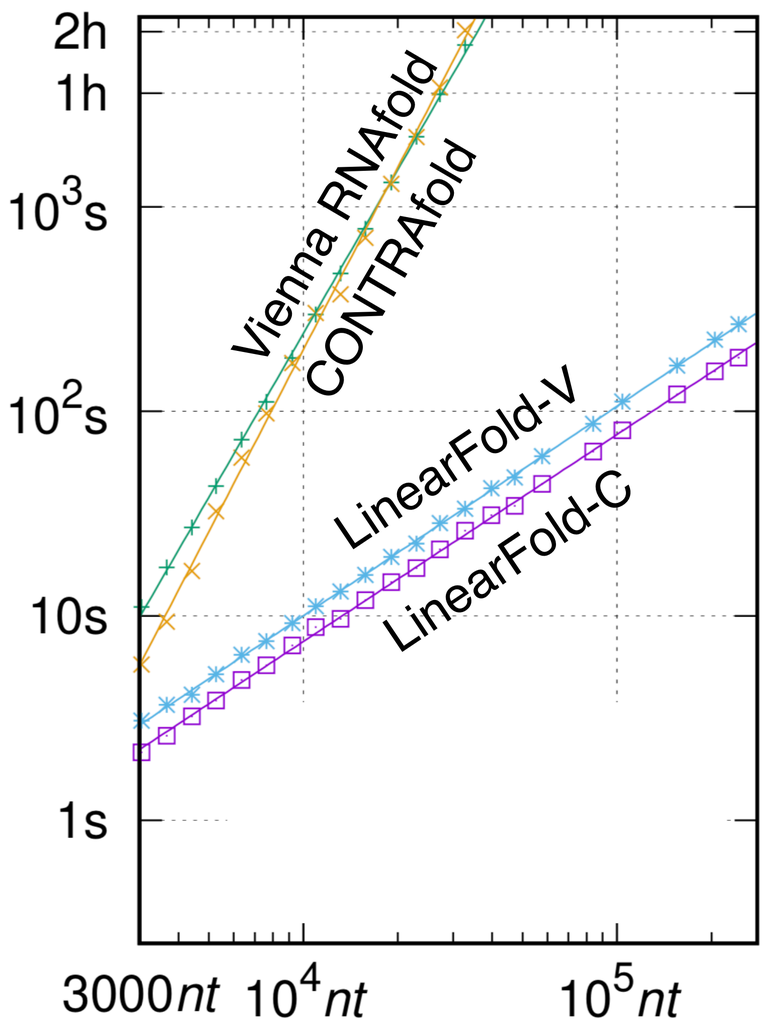
Efficiency & Scalability: *O*(*n*) time, *O*(*n*) memory



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



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

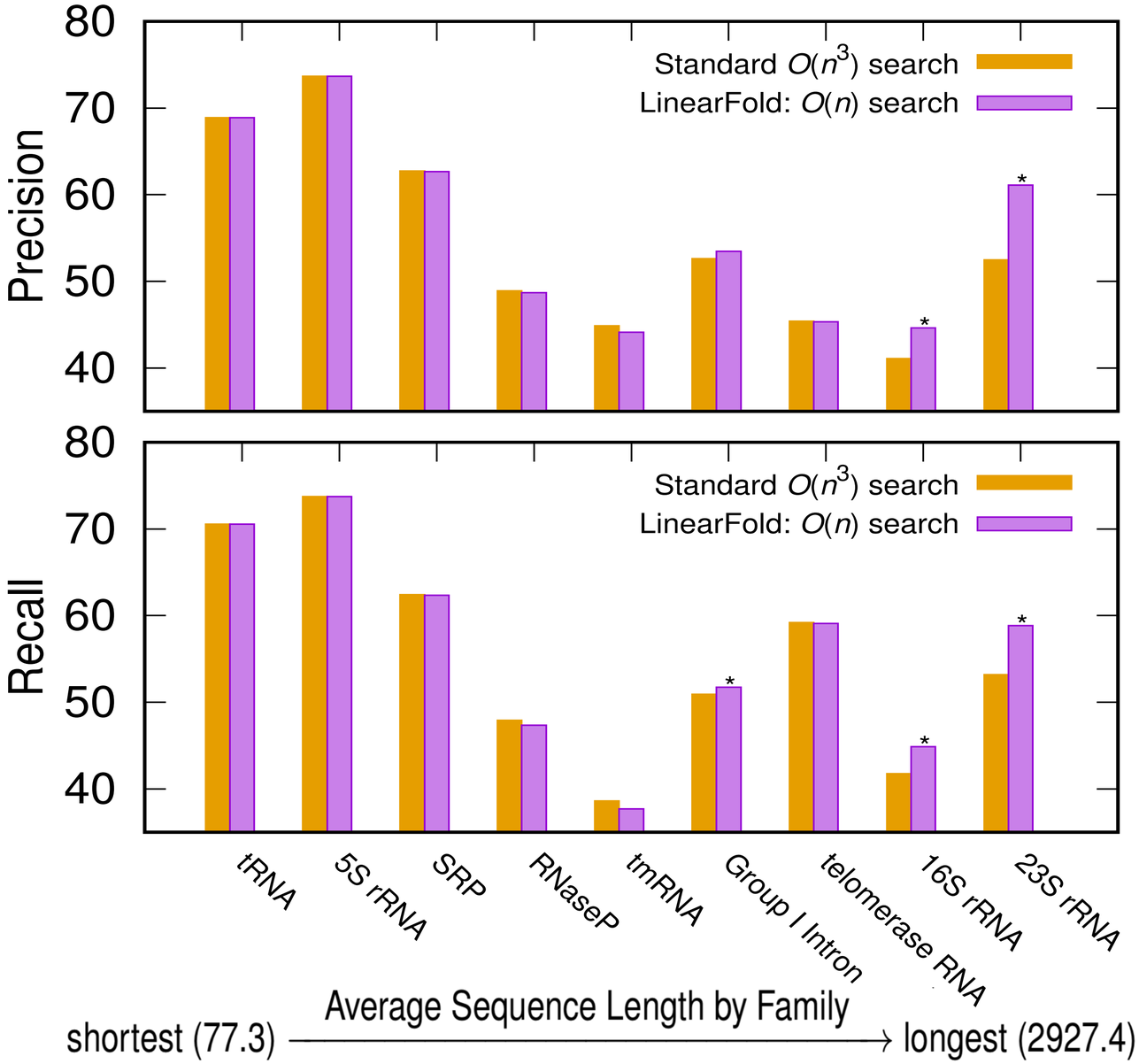
10,000*nt* (~HIV)
4min → 7s

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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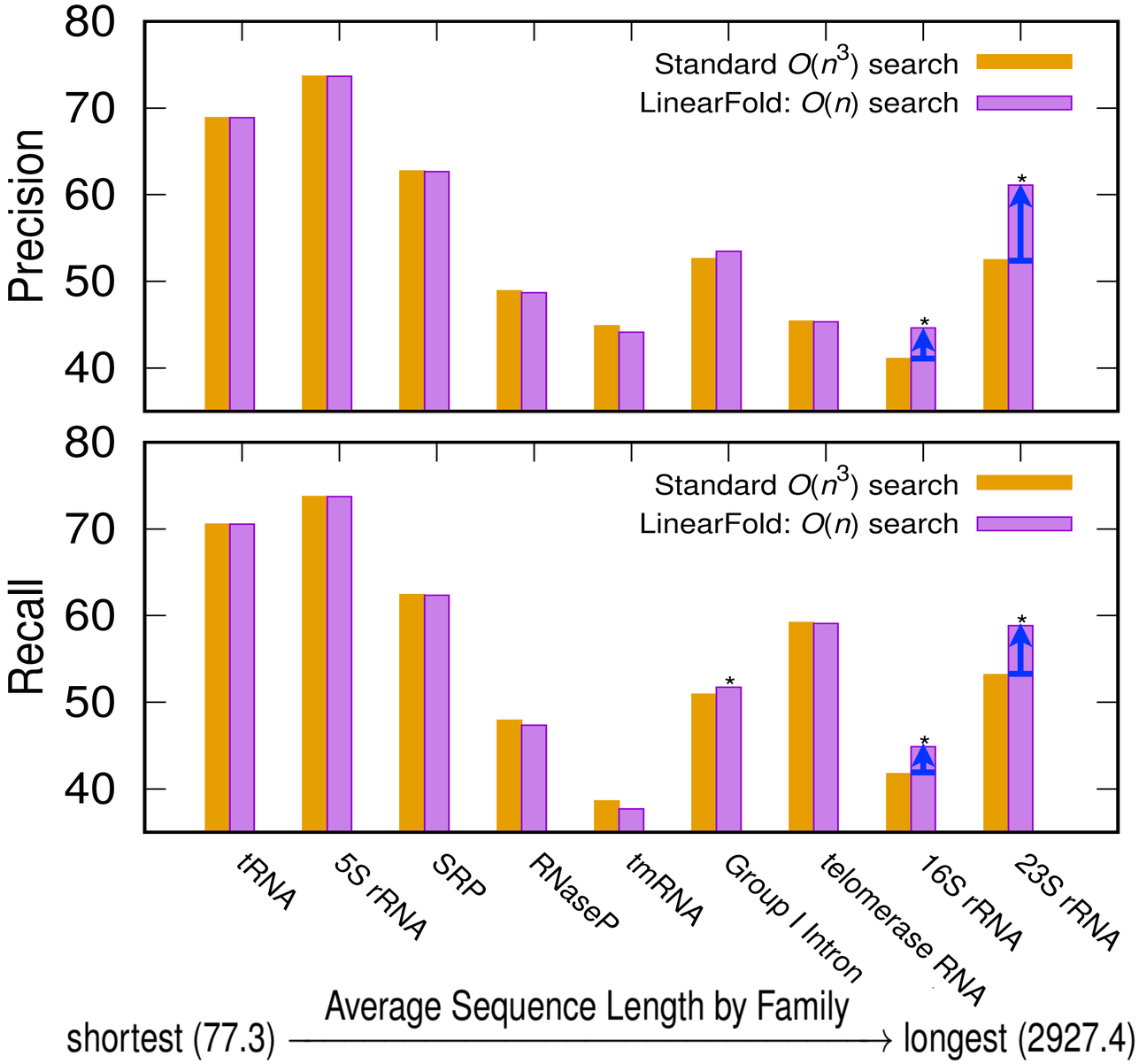
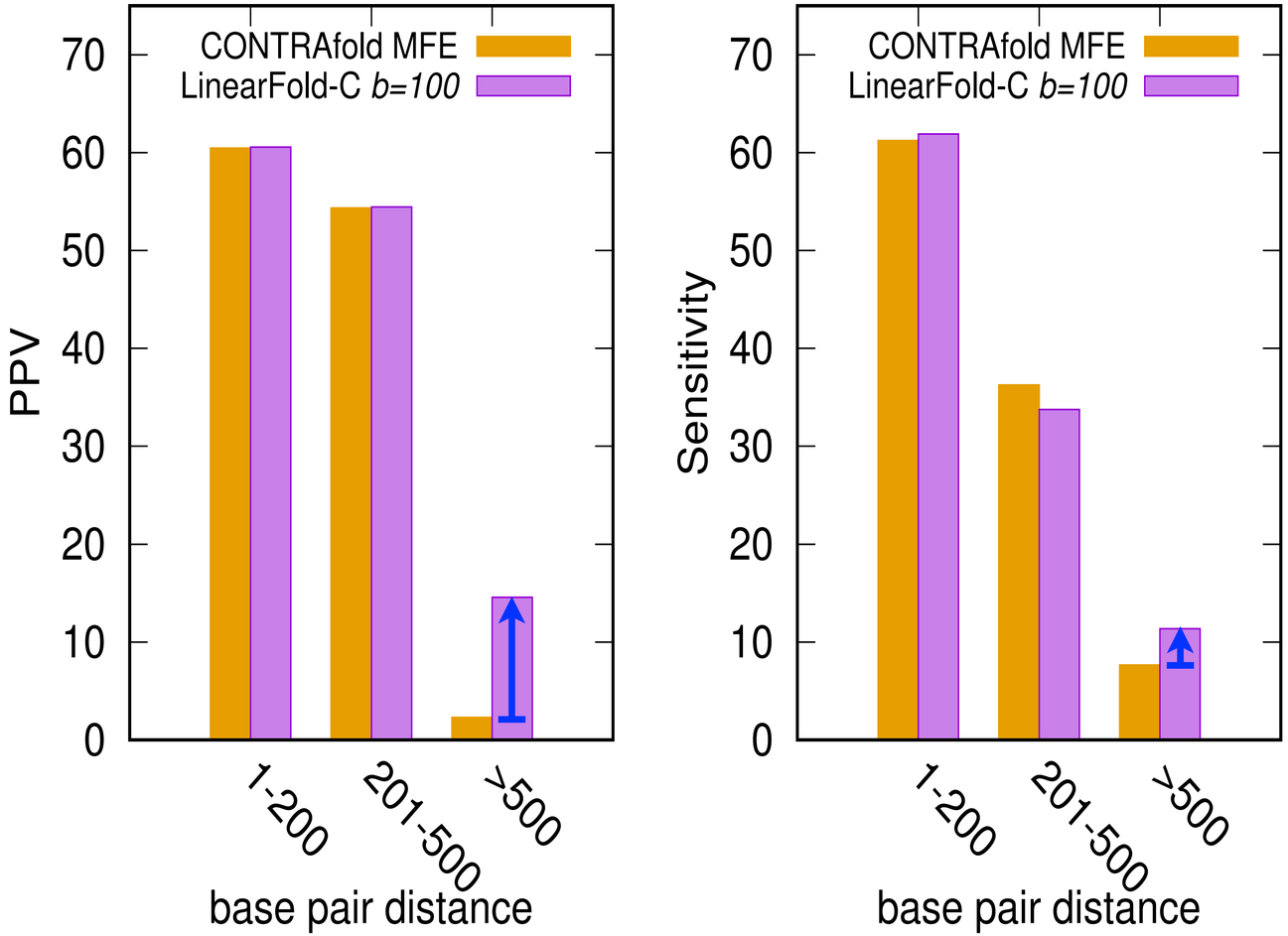


Improvements on Long-Range Base Pairs

- 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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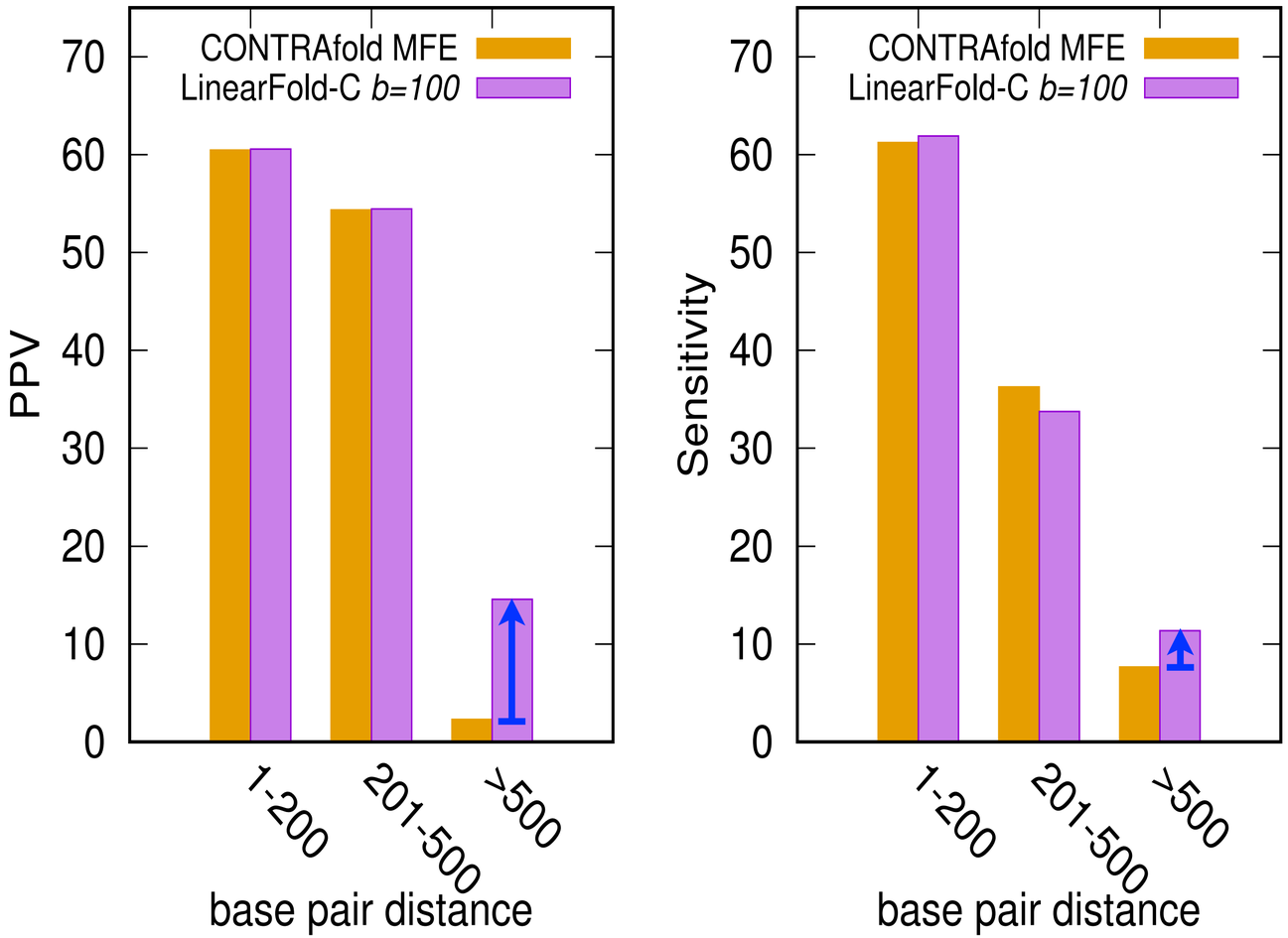
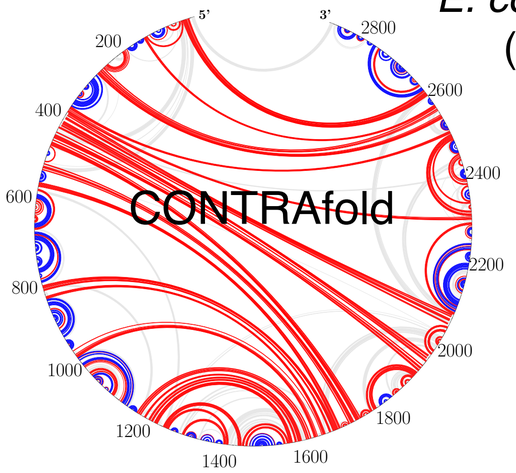
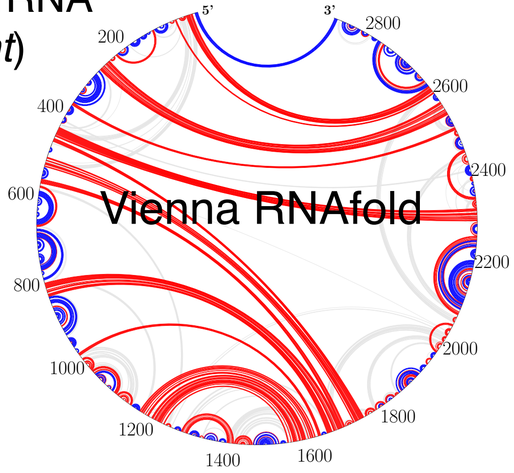


E. coli 23S rRNA
(2,904 *nt*)





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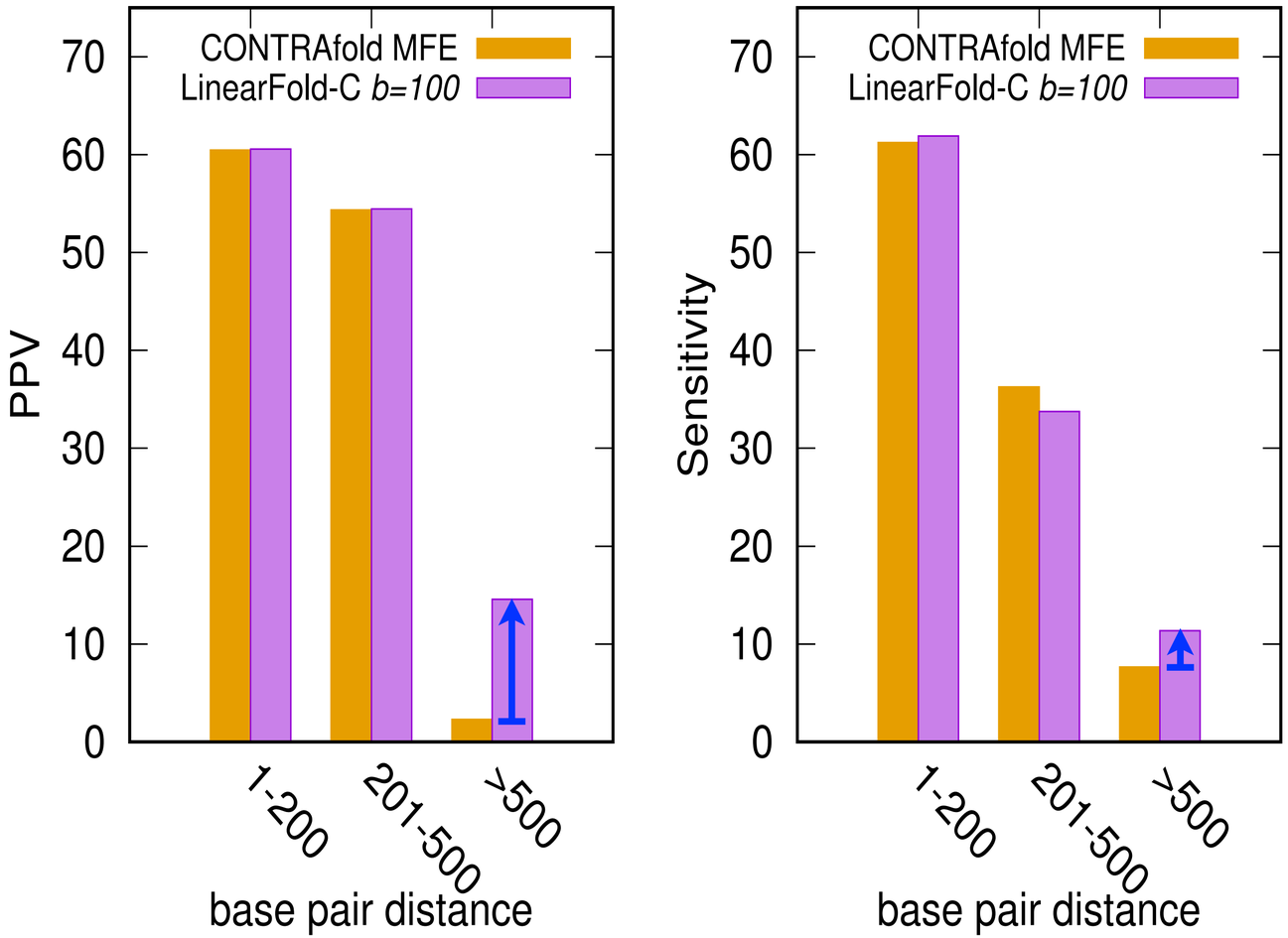

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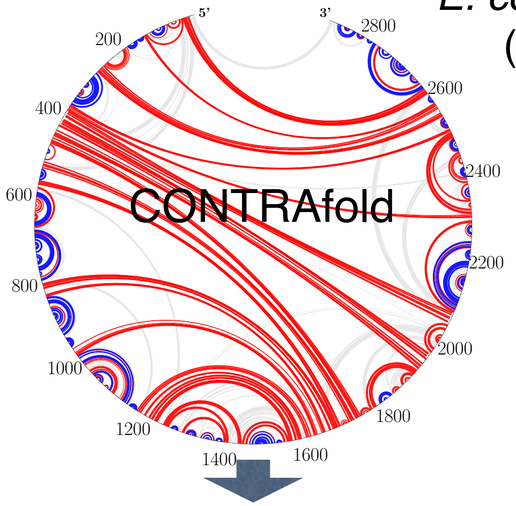
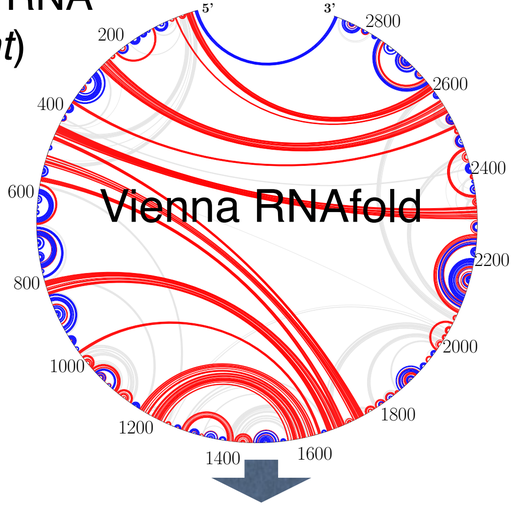
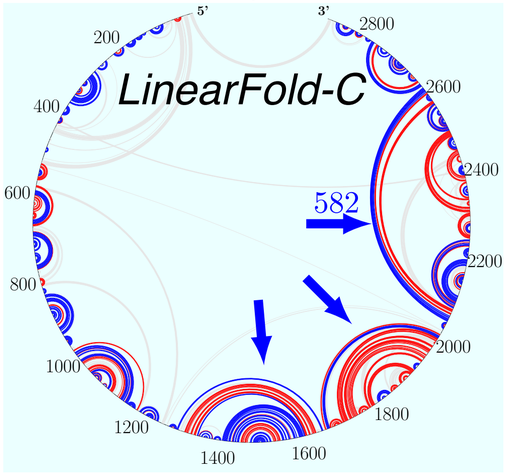
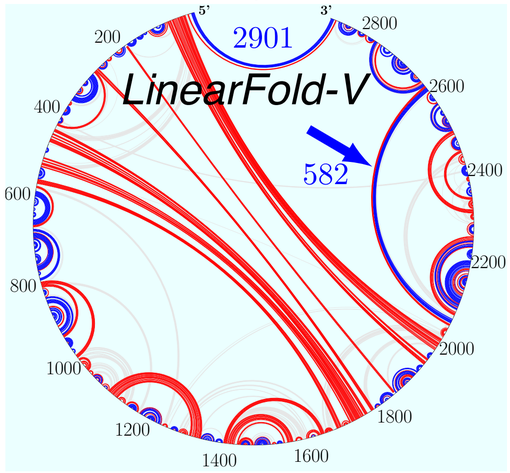


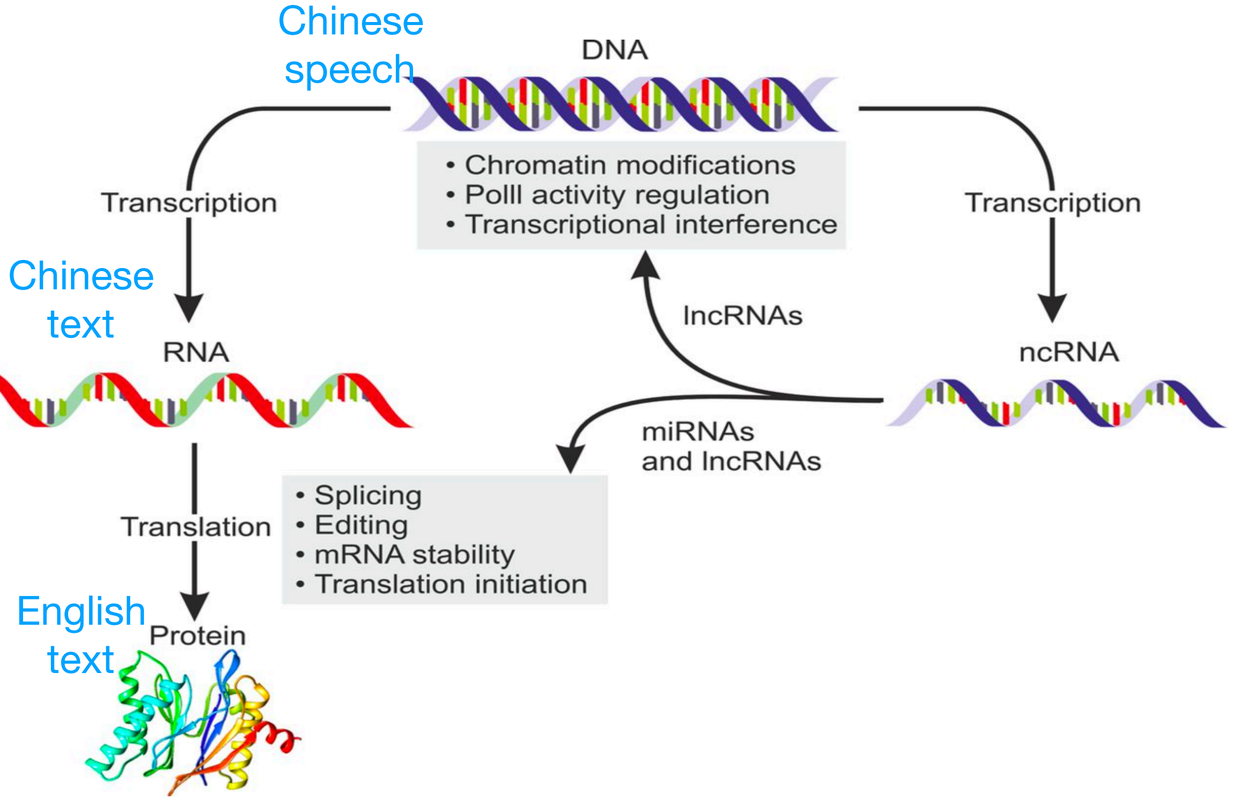


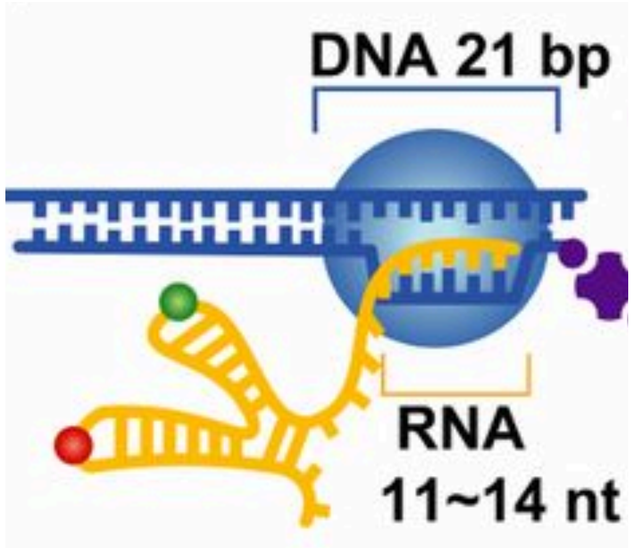


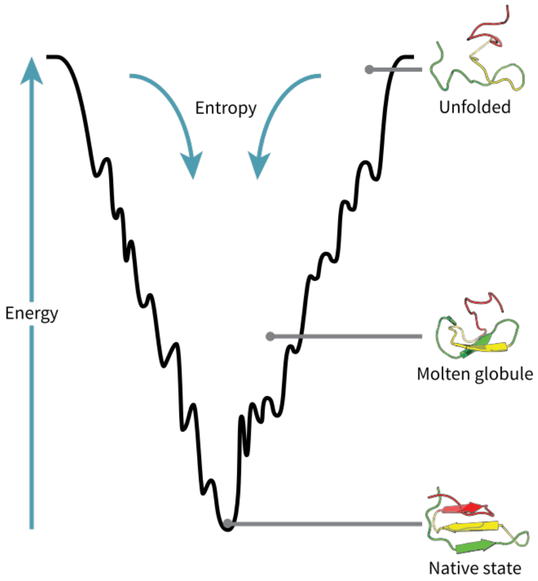


Incremental Parsing <=> Incremental Folding

- humans process sentences incrementally
- human language sentences *evolve* to be incrementally parsable
- RNAs & proteins fold while being assembled
- RNA & protein sequences evolve to be incrementally foldable
- these might explain why linear-time search performs better than exact search

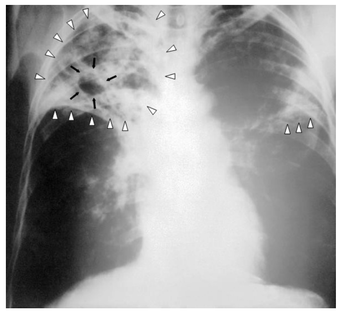






Fast Structure Prediction Enables RNA Design

detecting active TB using RNA design
which needs our fast RNA folding



Professor **Rhiju Das**
Stanford Medical School

EteRNA game
(RNA design)

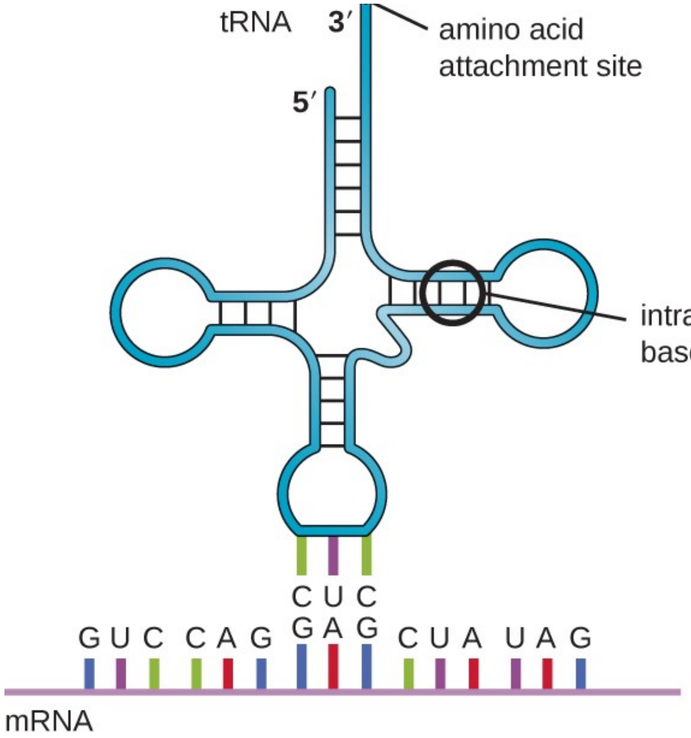
RNA sequence

GCGGGAAUAGCUCAGUUGGUAGAGCACGACCUUGCCAAGGUCGGGGUCGCGAGUUCGAGUCUCGUUUCCCGCUCCA

structure prediction ("folding")

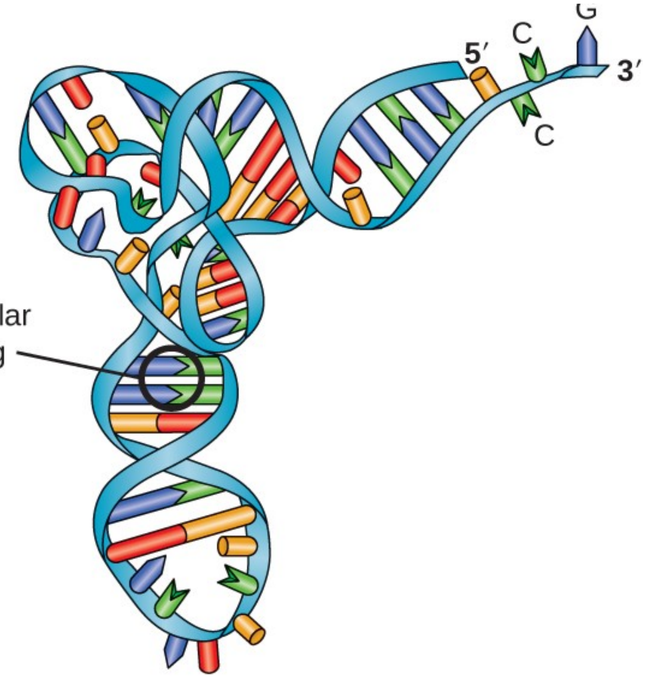
design

RNA secondary structure



tRNA 2-dimensional structure

RNA 3D structure



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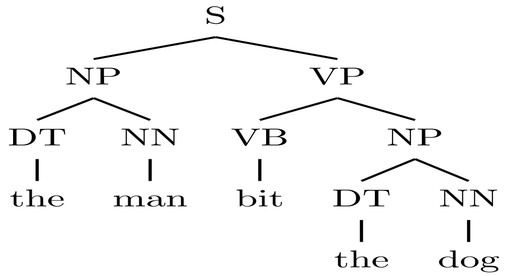
Computational Linguistics => Computational Biology

linguistics | **compiler theory** | **comp. linguistics** | **computational biology**

1955 Chomsky: context-free grammars (CFGs)



1958 Backus & Naur: CFGs for program, lang.

1964 **C**ocke \ bottom-up
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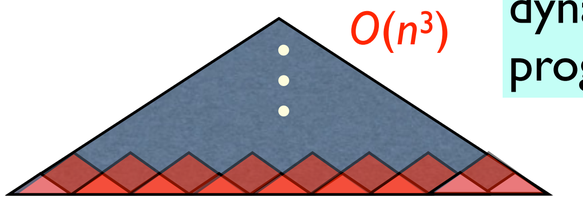
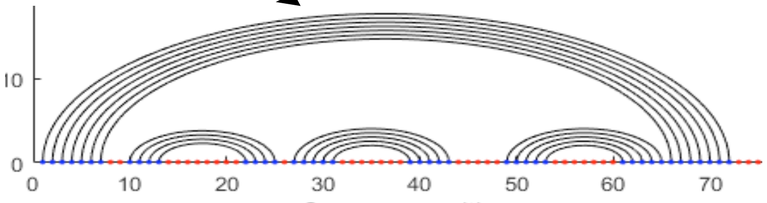


dynamic programming

1965 Knuth: **LR** parsing for restricted CFGs: $O(n)$



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

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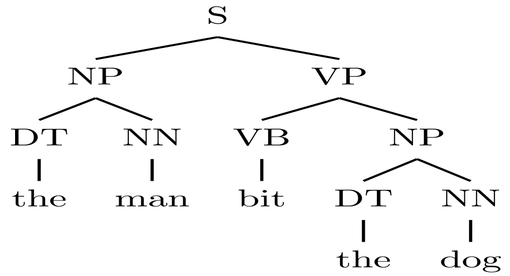

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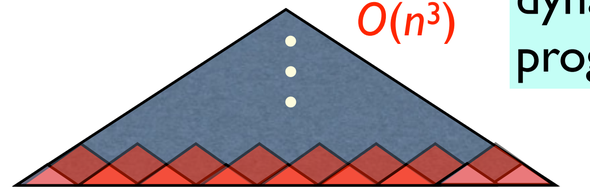

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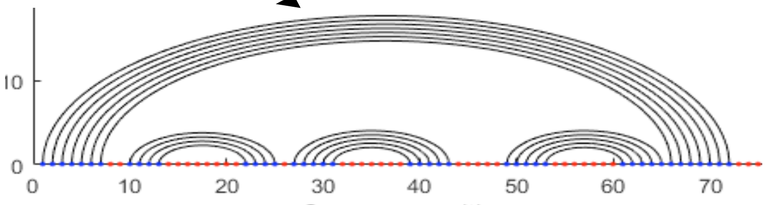

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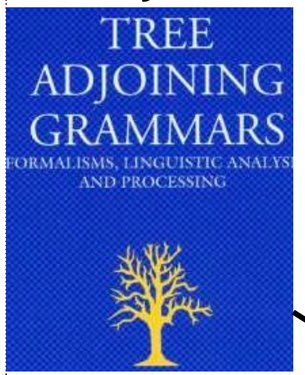

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Swiss-German:
...mer em Hans es huss hälfed aastriiche

English:
...we helped Hans paint the house

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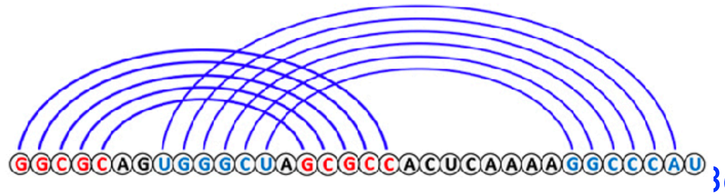
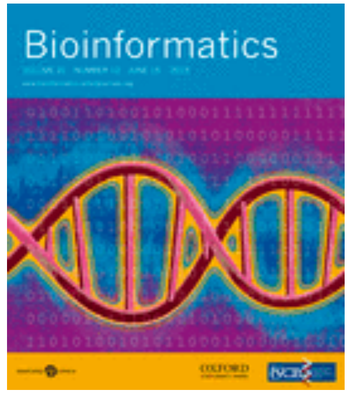
1990s TAGs for RNA pseudoknots





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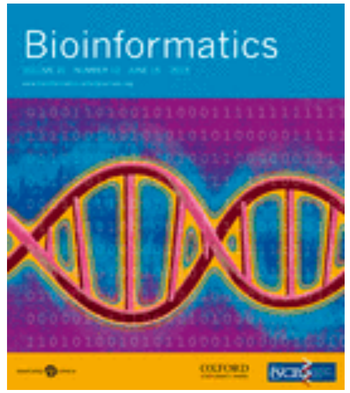

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Oregon State University

Baidu Research

UNIVERSITY of ROCHESTER