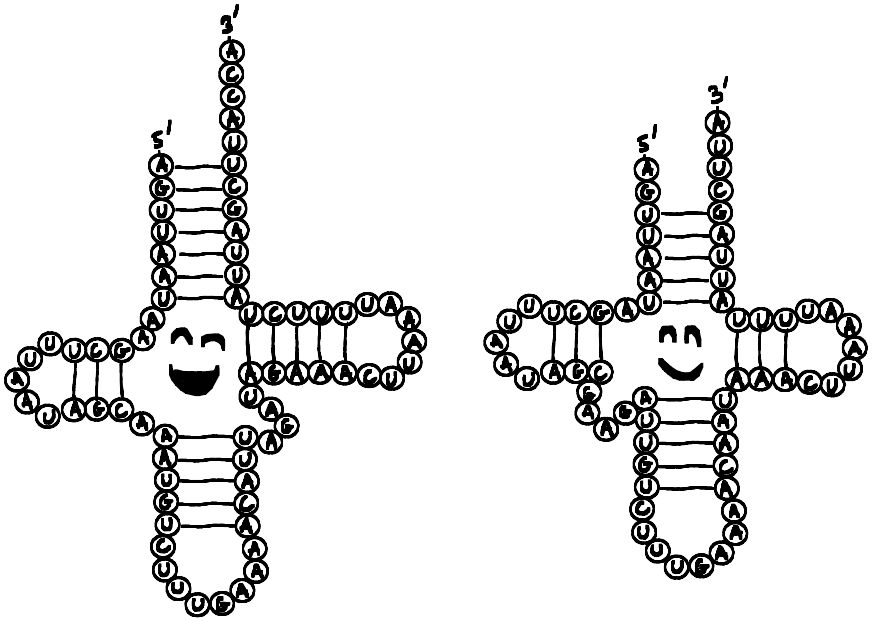
COUNTING, GENERATING AND SAMPLING TREE ALIGNMENTS

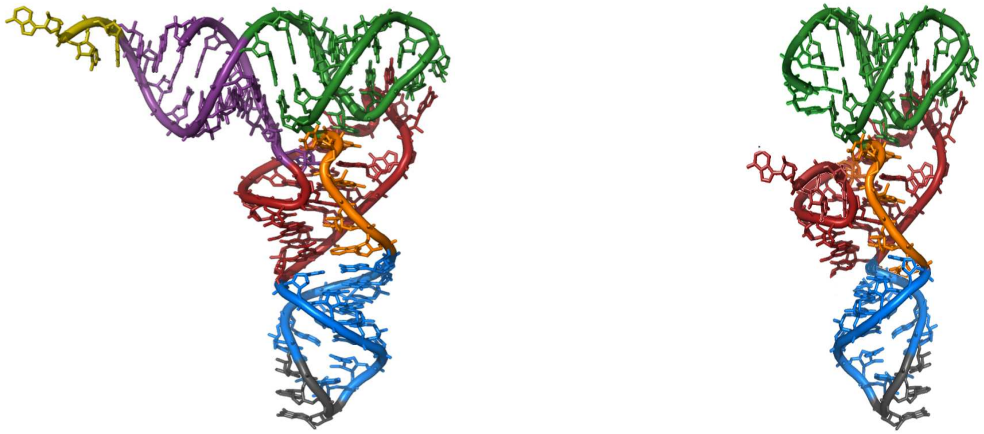
Cedric CHAUVE (Simon Fraser University, Vancouver)
Julien COURTIEL (PIMS/Univ. of British Columbia, Vancouver)
Yann PONTY (CNRS/LIX)



SeqBio 2015

MOTIVATION: RNA COMPARISON

Question: how to measure similarity between two RNAs?



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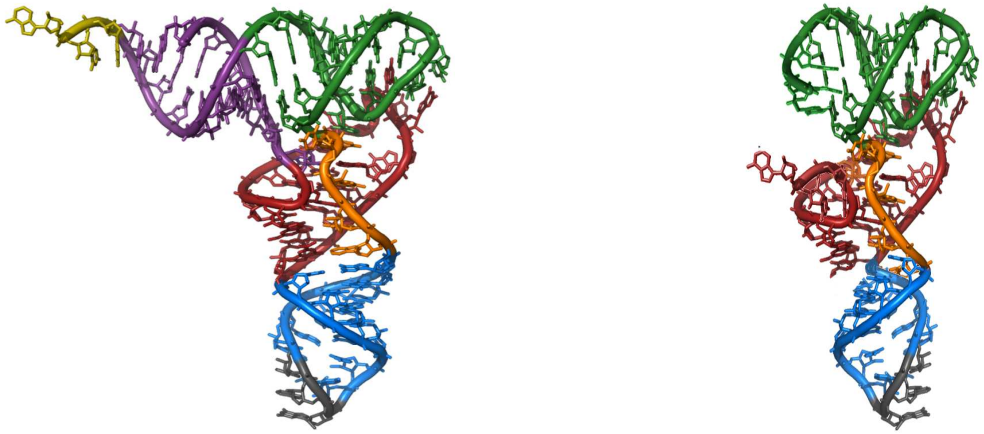

First idea: compare nucleic acid sequences.

RNA 1: AUUCGAUUA...

RNA 2: ACCAUGAUUA...

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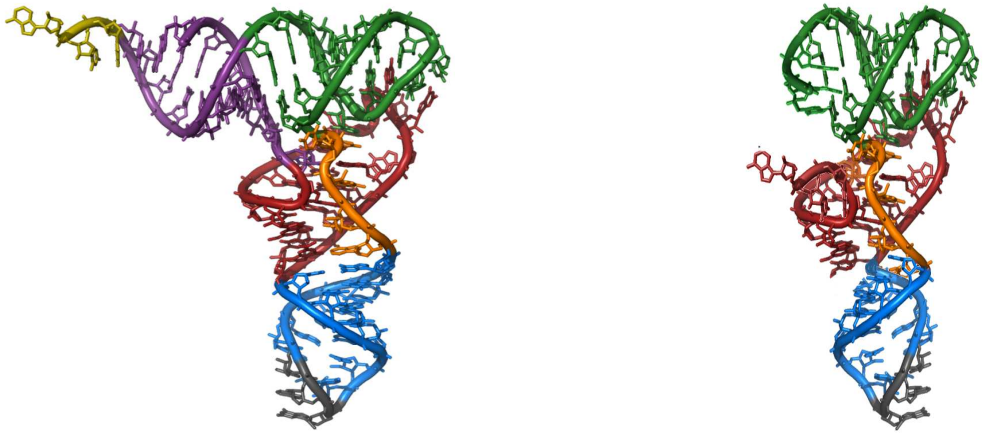

First idea: compare nucleic acid sequences.

→ sequence alignment

RNA 1: AUUCGAUUA...

RNA 2: ACCAUGAUUA...

alignment: $\binom{A}{A}\binom{U}{-}\binom{-}{C}\binom{U}{-}\binom{C}{C}\binom{-}{A}\binom{-}{U}\binom{G}{G}\binom{A}{A}\binom{U}{U}\binom{U}{U}\binom{A}{A}\ldots$

MOTIVATION: RNA COMPARISON

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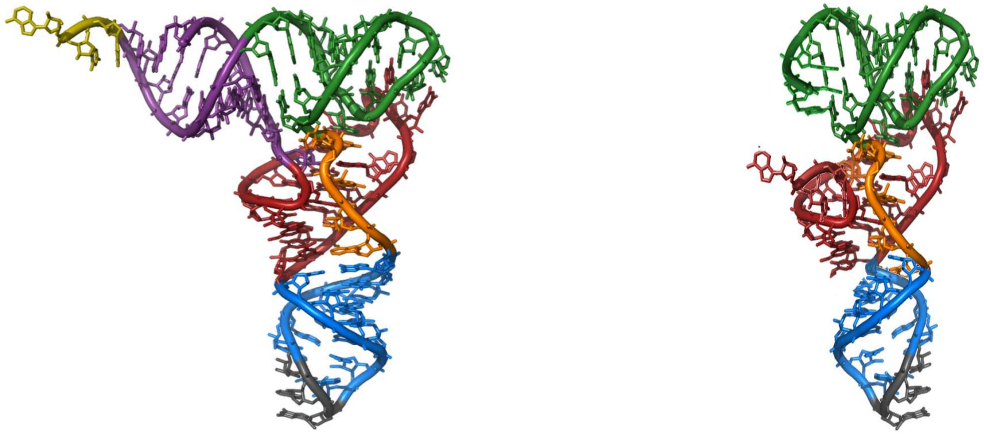
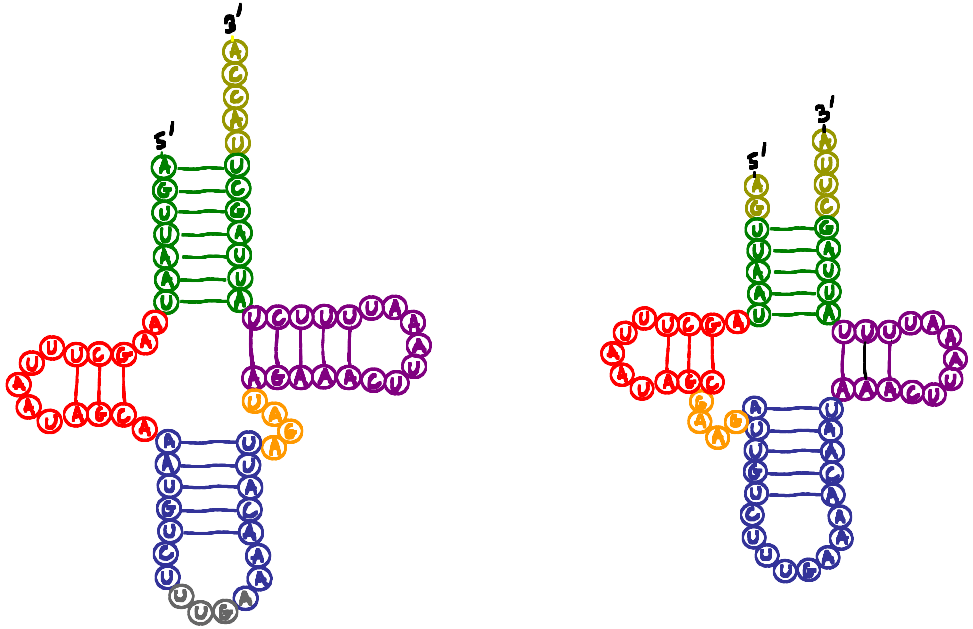
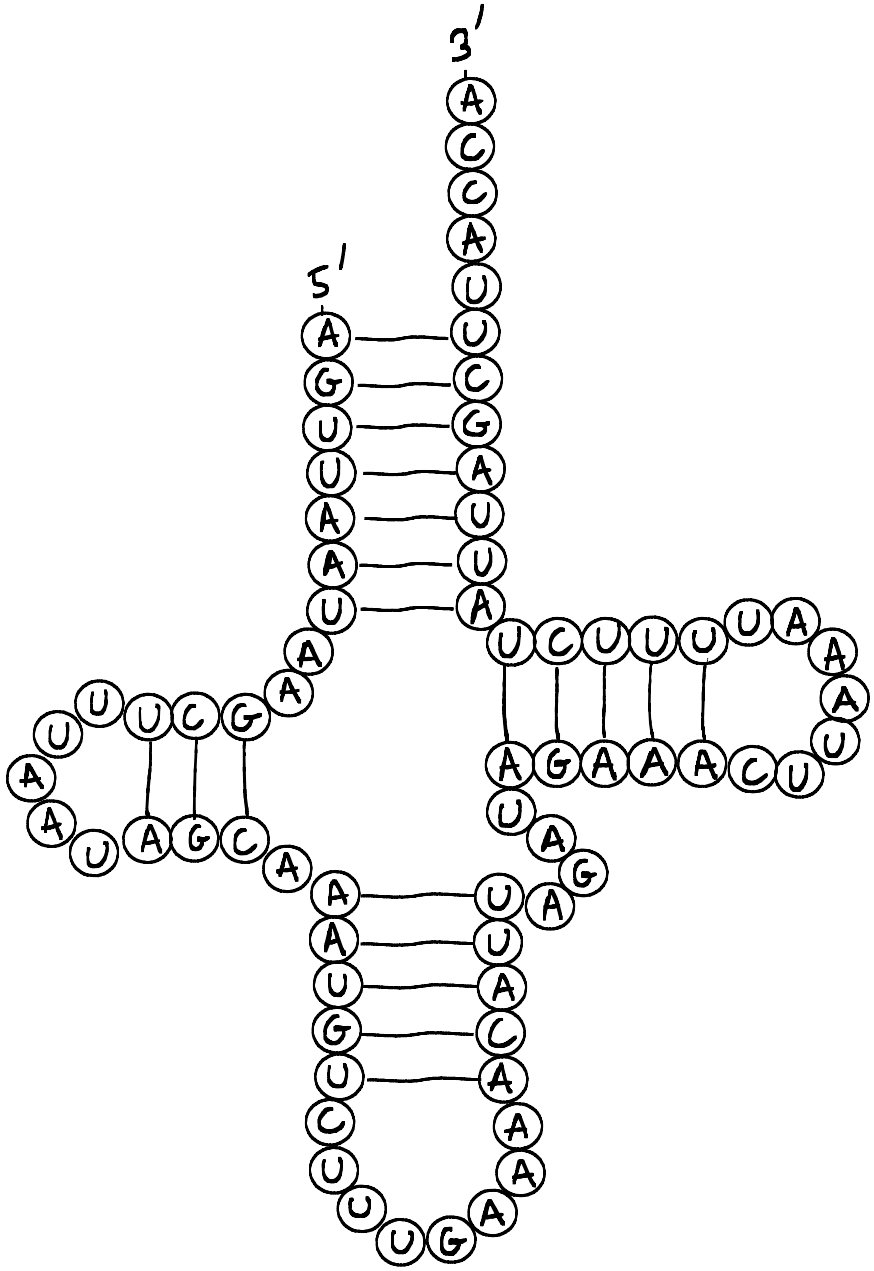


Second idea: compare secondary structures.



→ notion of tree alignment [Jiang, Wang, Zhang]

FROM SECONDARY STRUCTURES TO TREES



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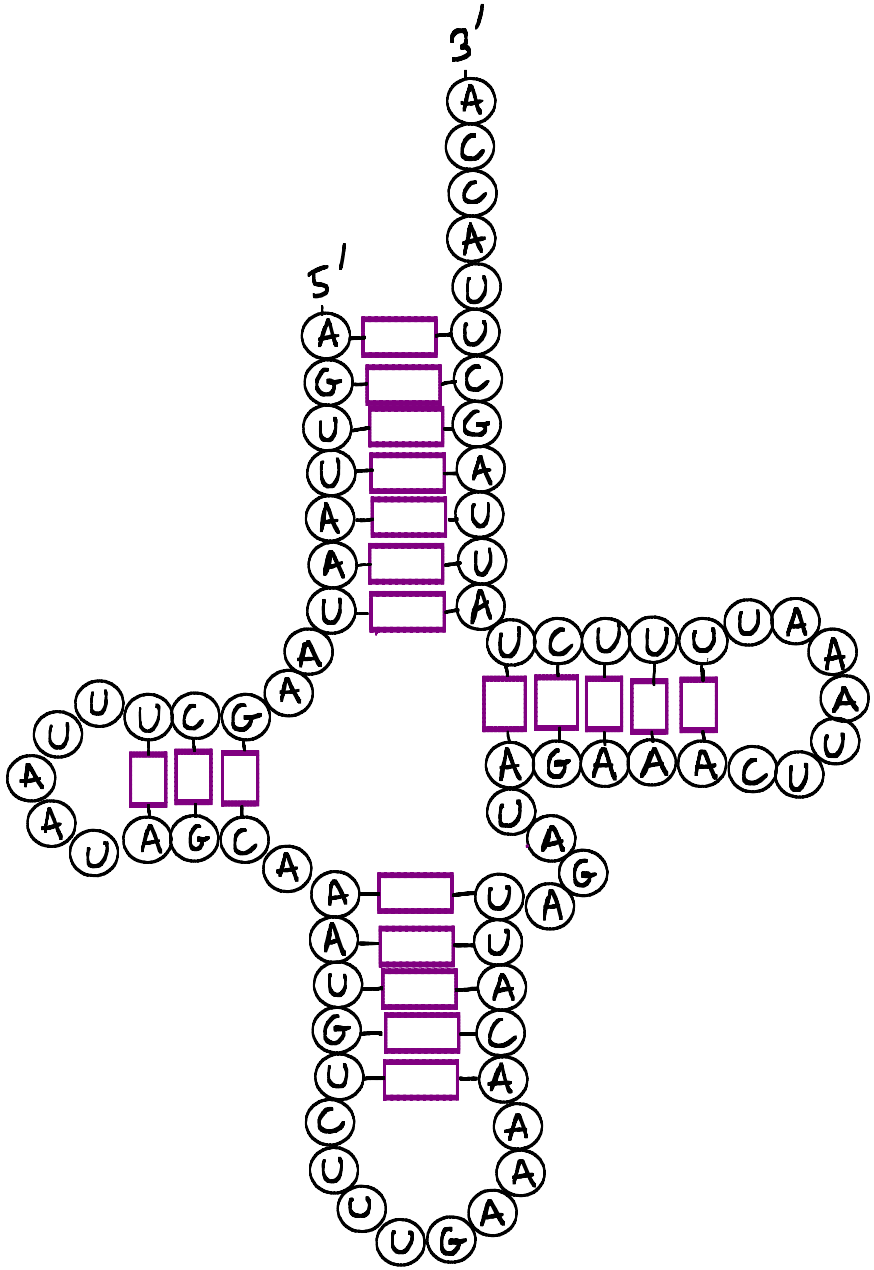

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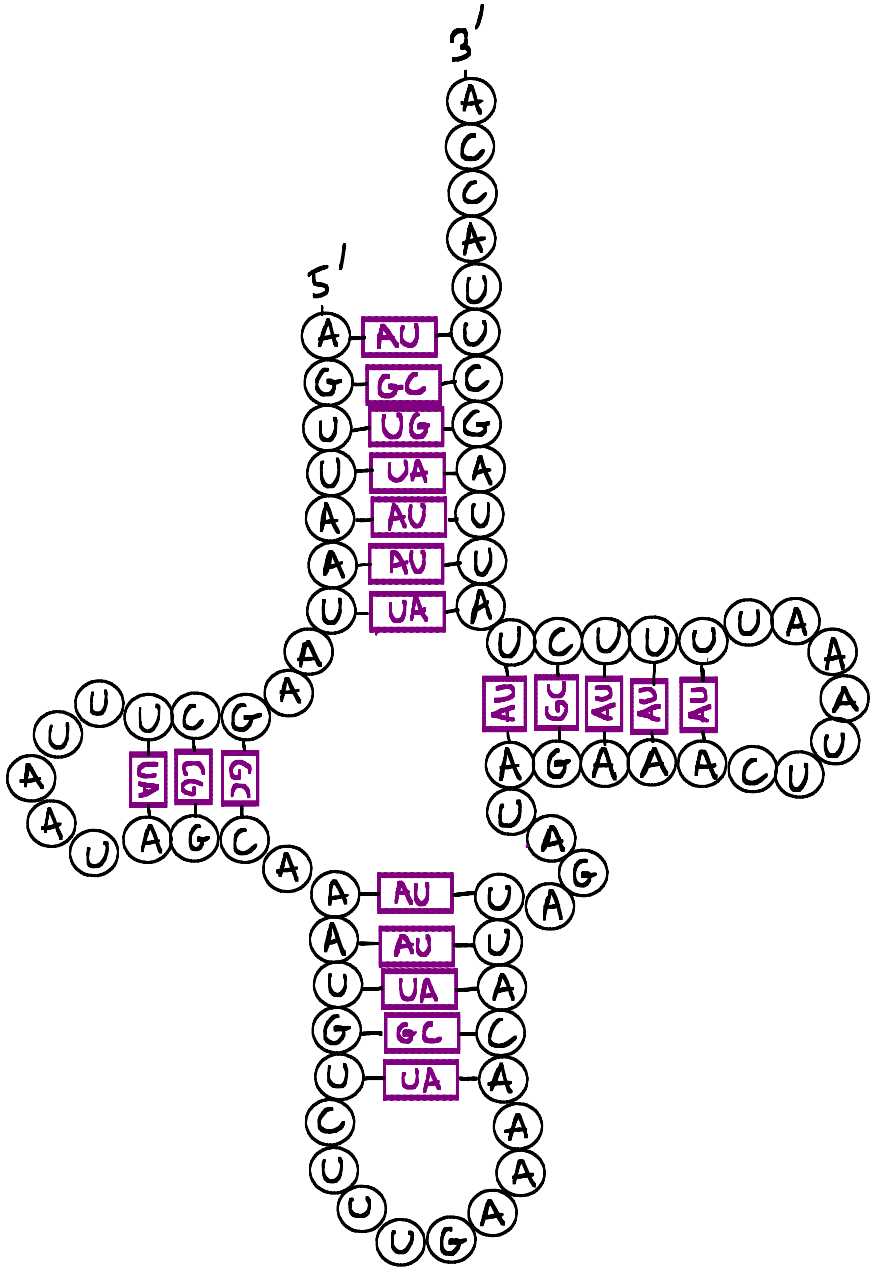

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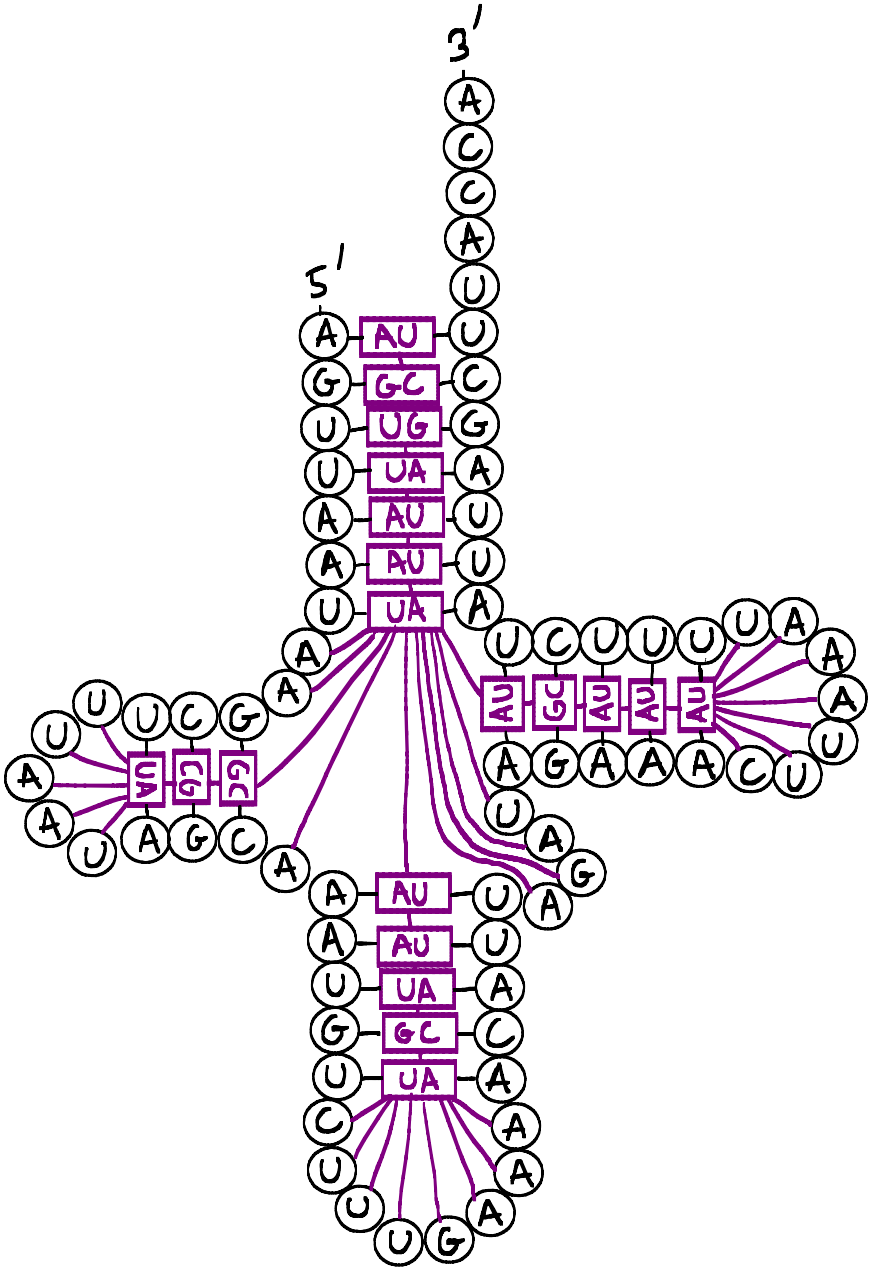

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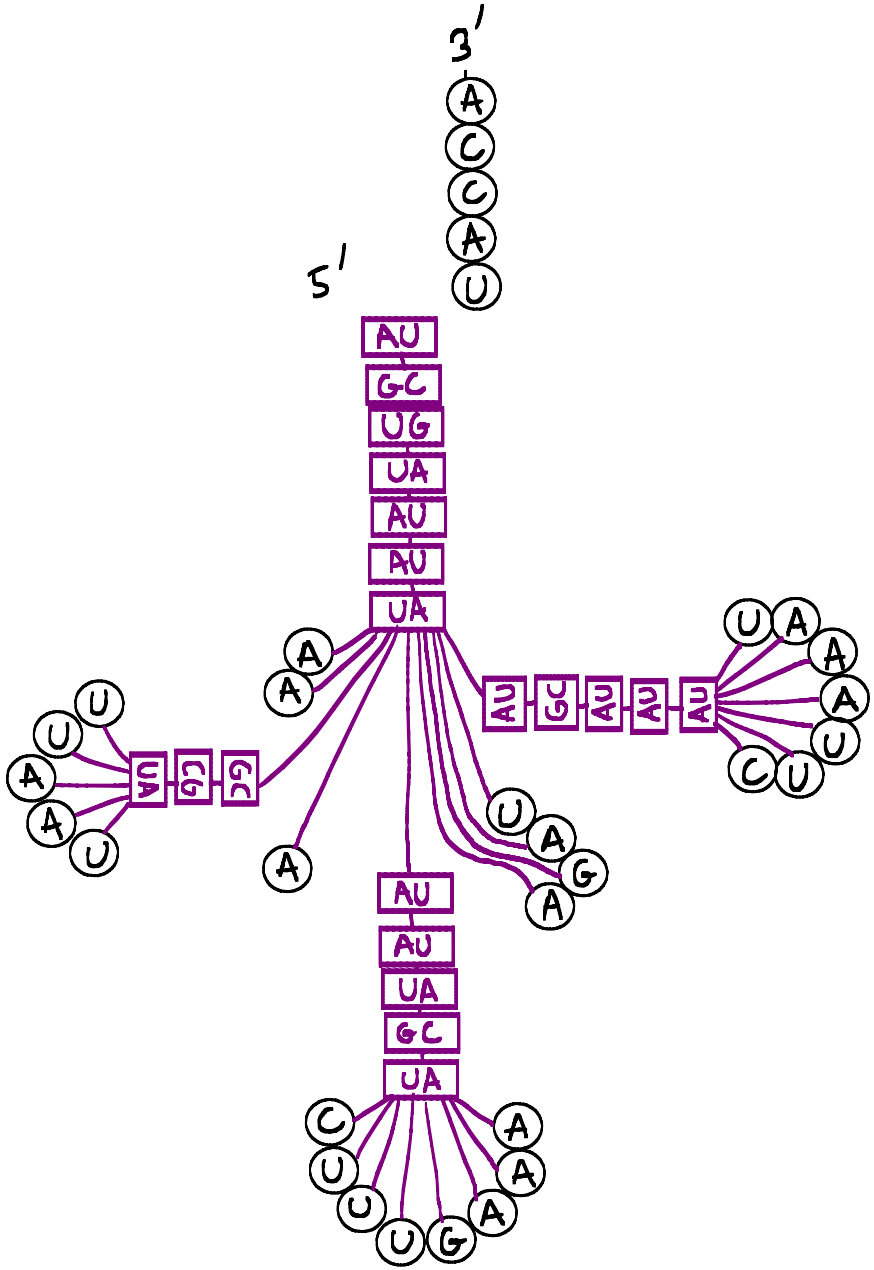

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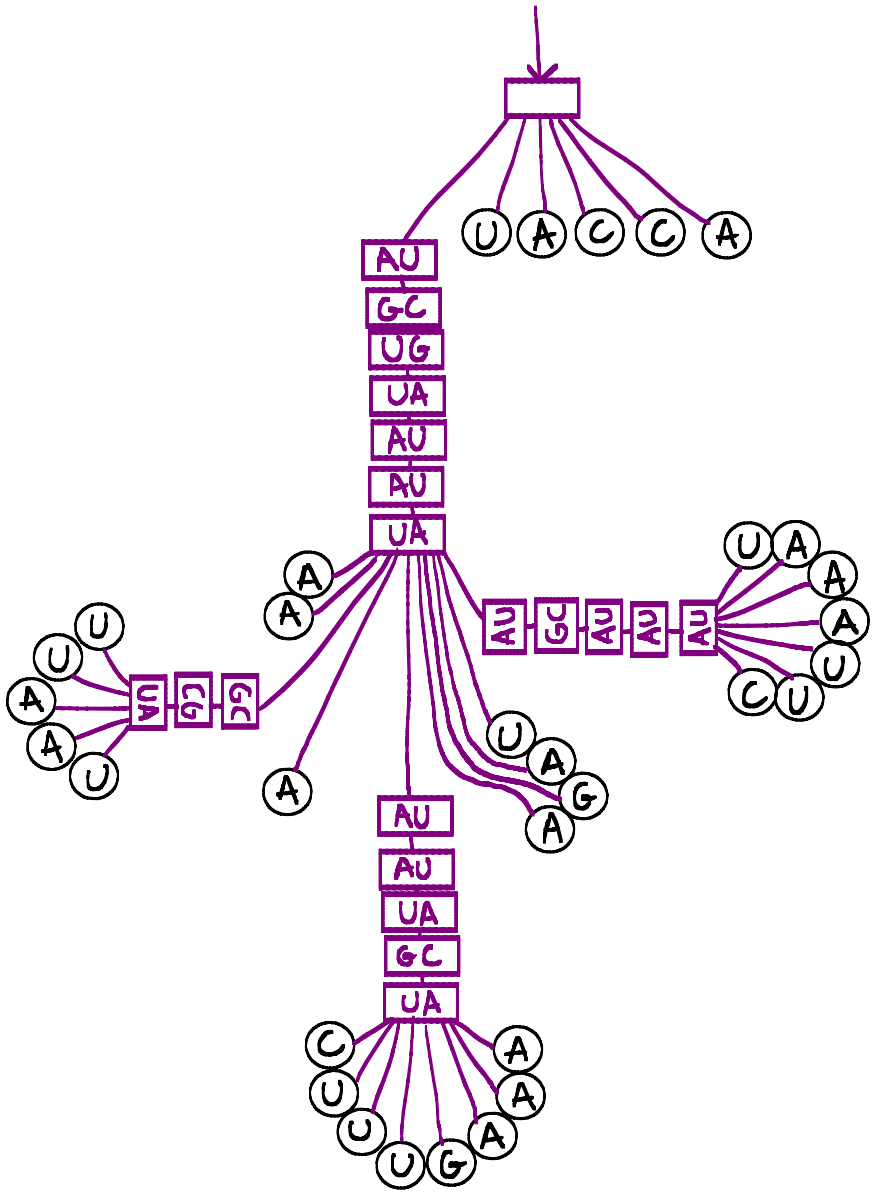
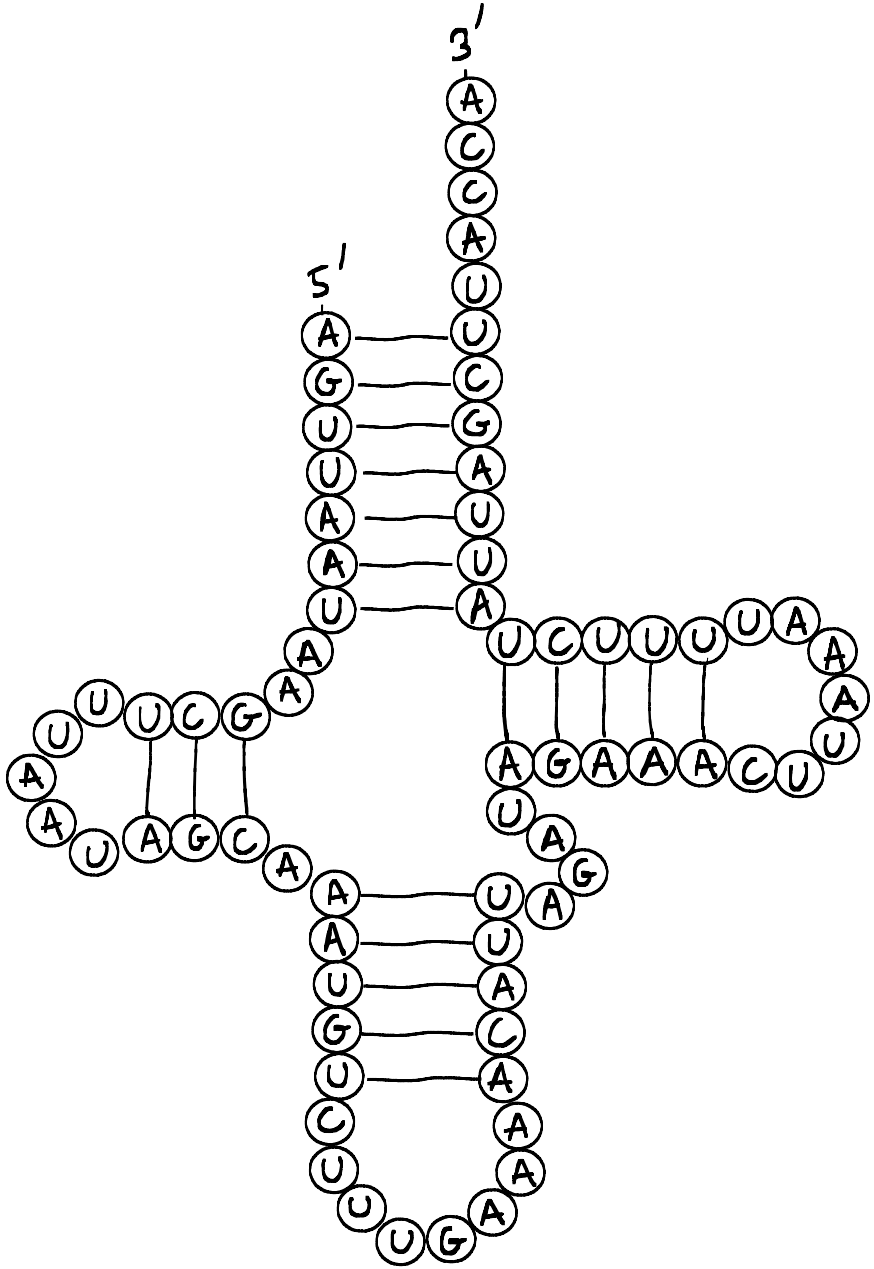
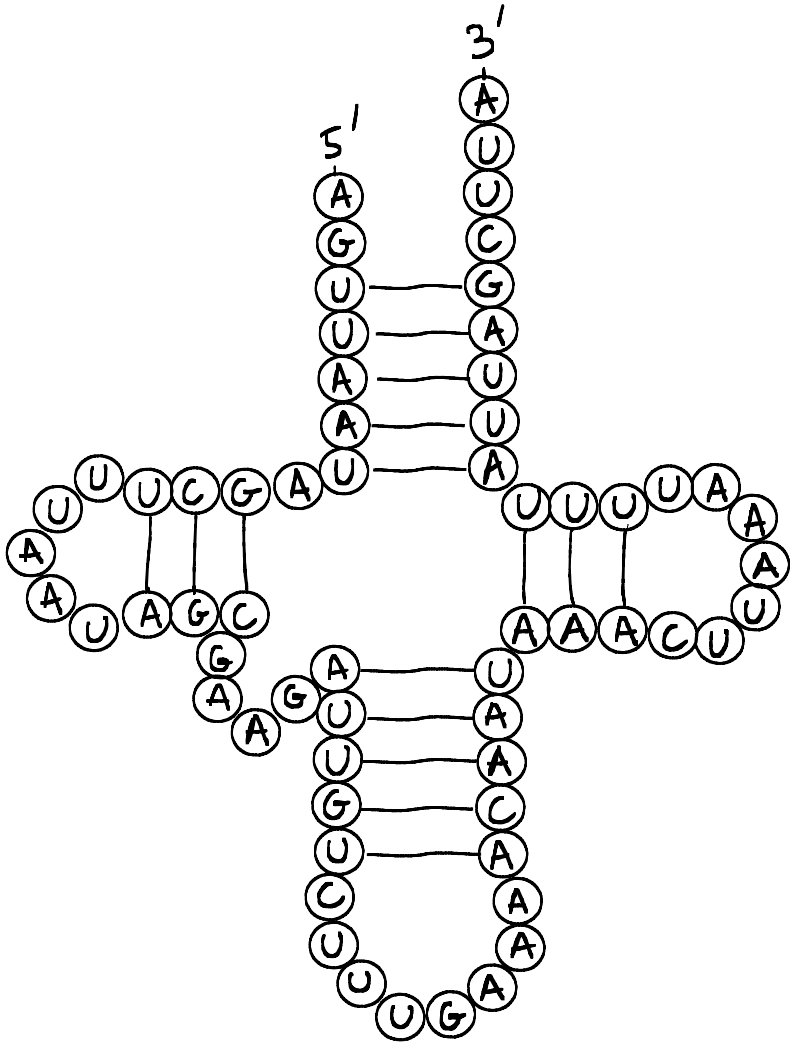


FROM SECONDARY STRUCTURES TO TREES

Objective: Align trees coming from RNA 2^{ary} structures





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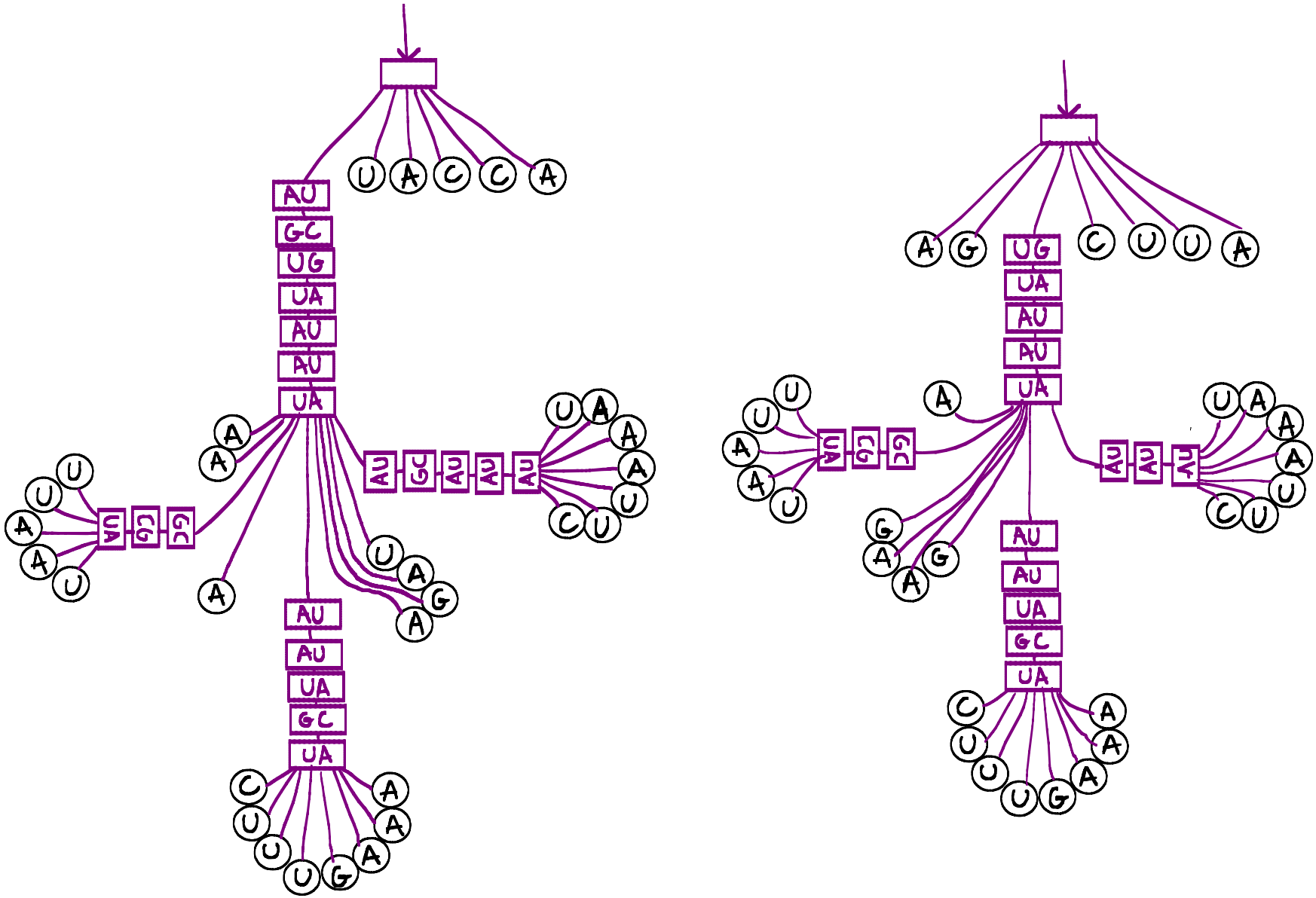
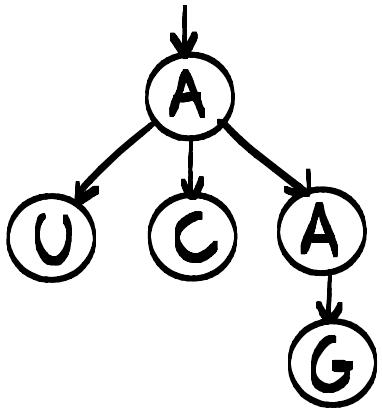


TREES AND SUPERTREES

Trees are plane, rooted, and vertices are labeled by an alphabet $\sum$.

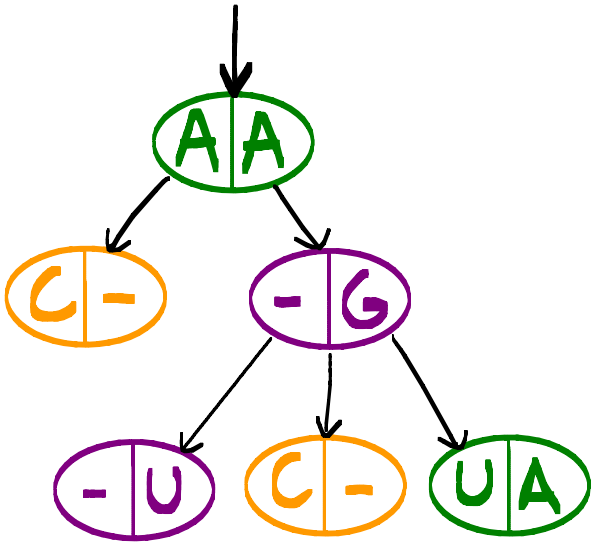


Supertree = tree with 3 types of vertices:

(mis)match

insertion

deletion



SUPERTREES INDUCE TREE ALIGNMENTS

Let A be a supertree,

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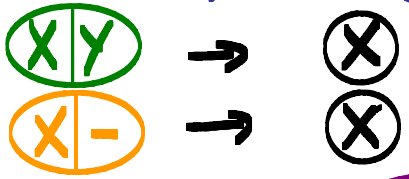

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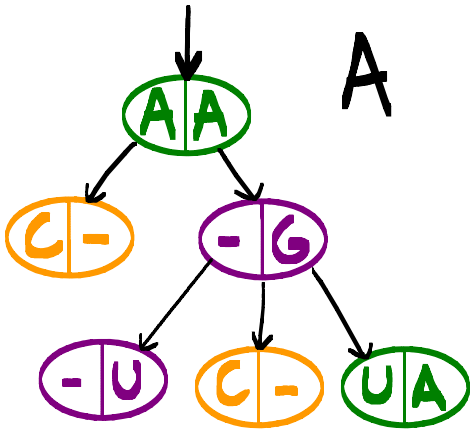

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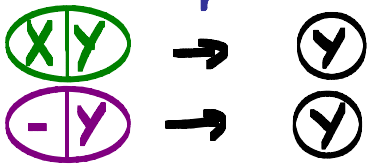

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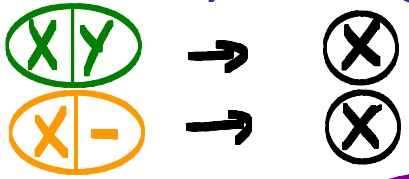

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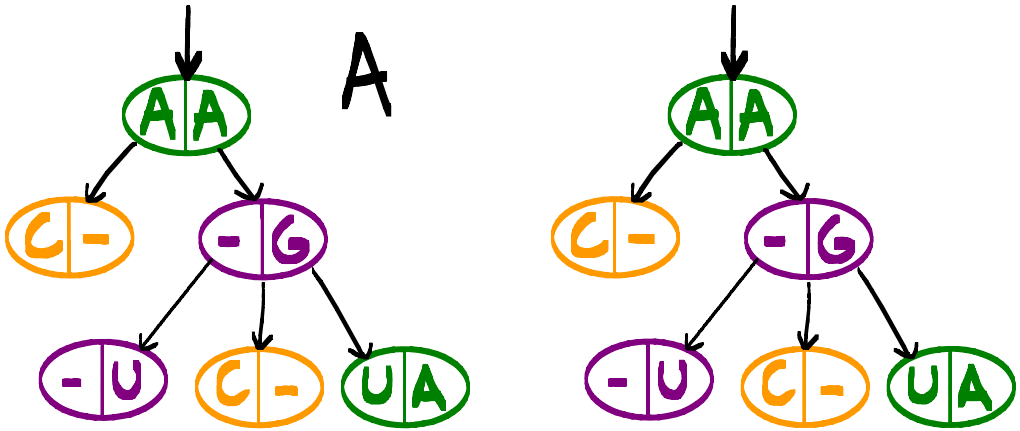

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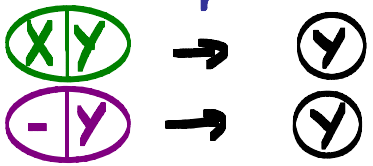

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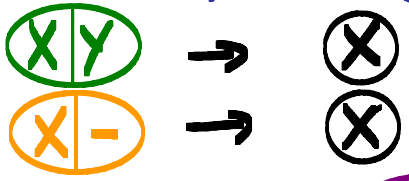

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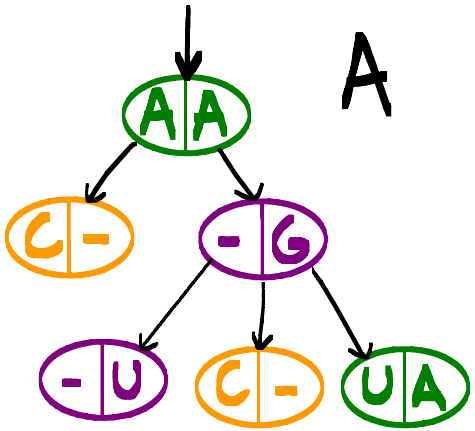

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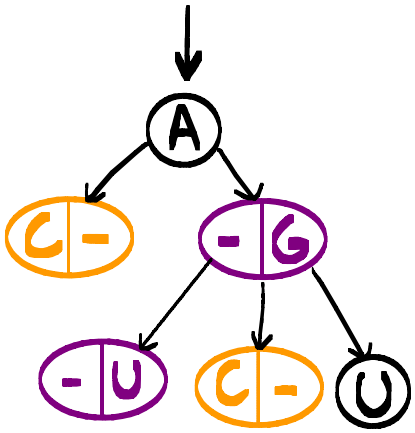

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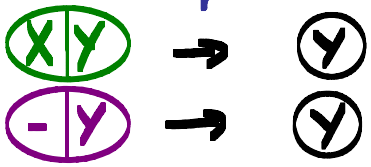

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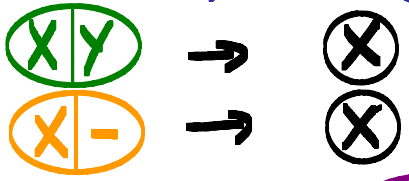

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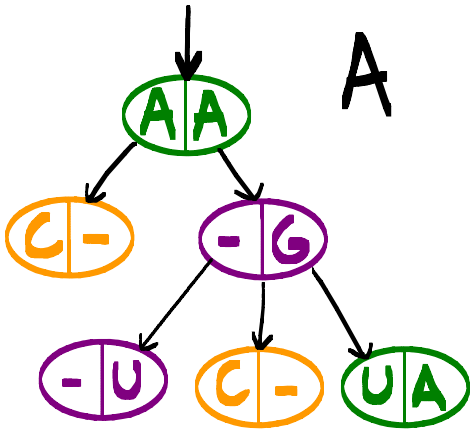

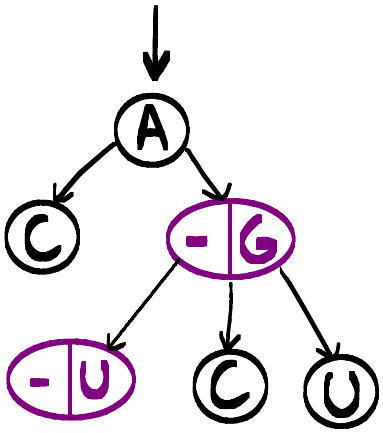

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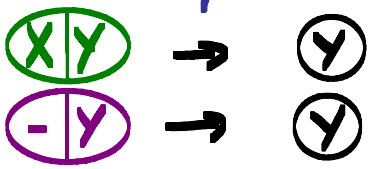

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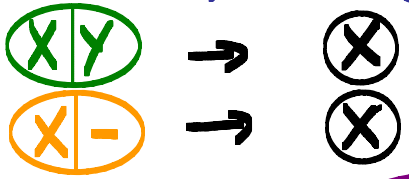

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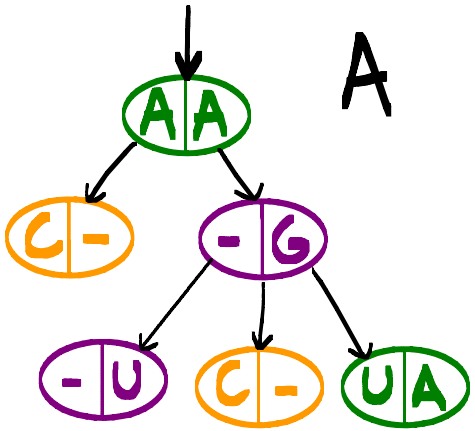

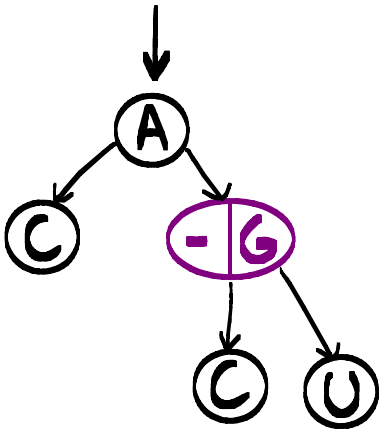

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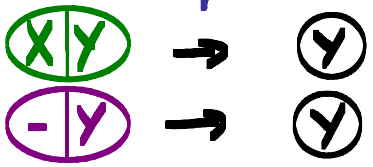

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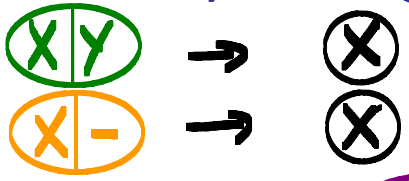

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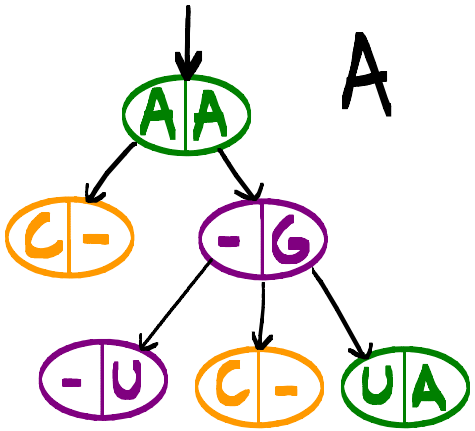

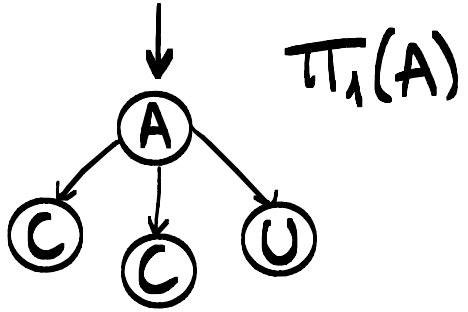

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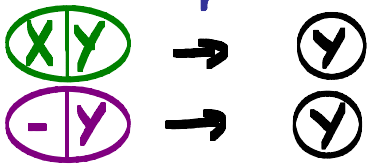

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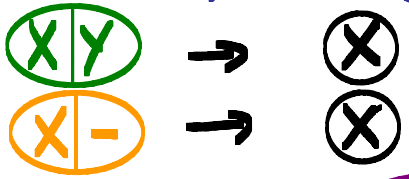

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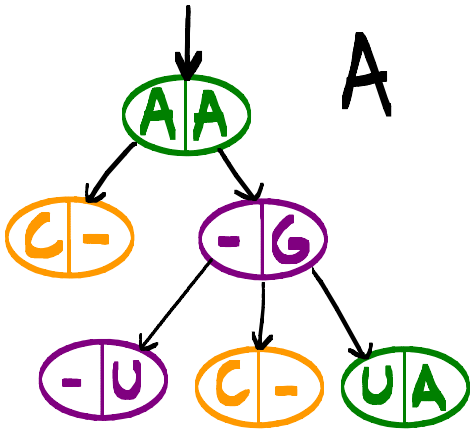

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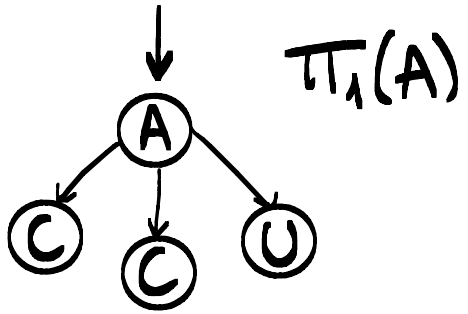

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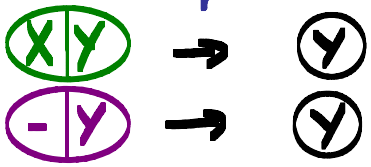

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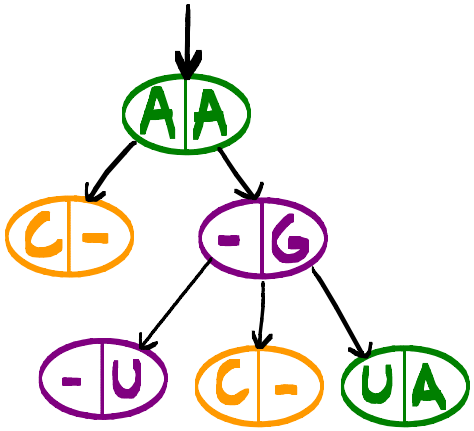

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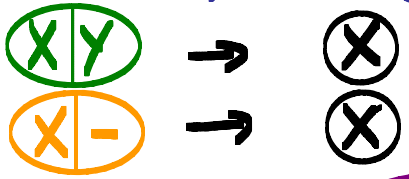

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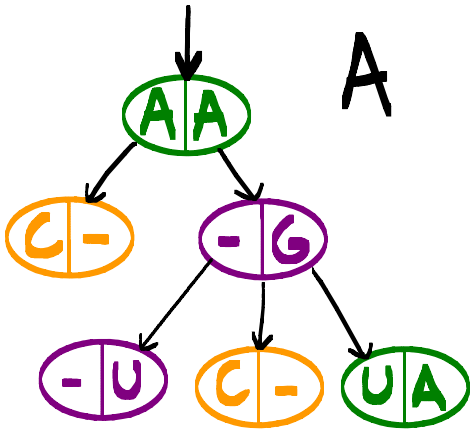

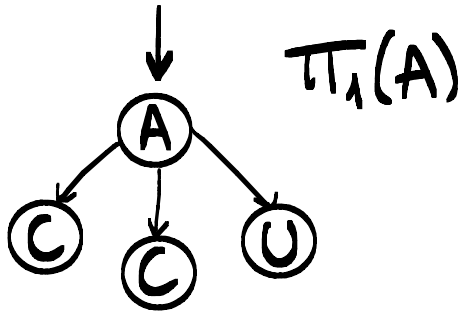

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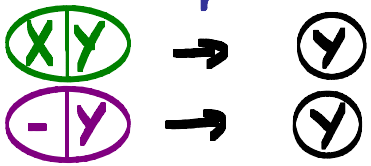

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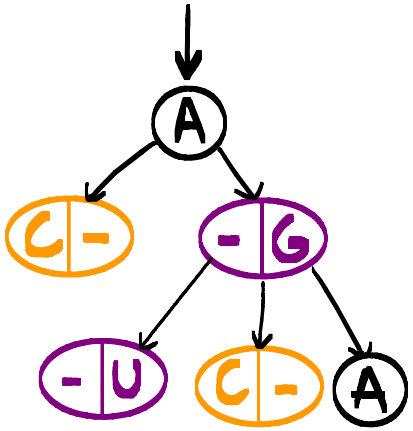

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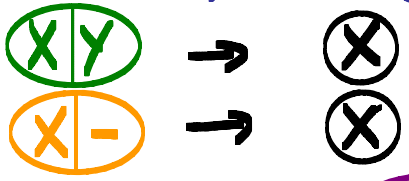

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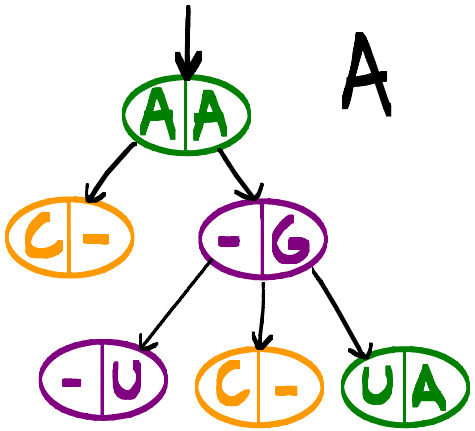

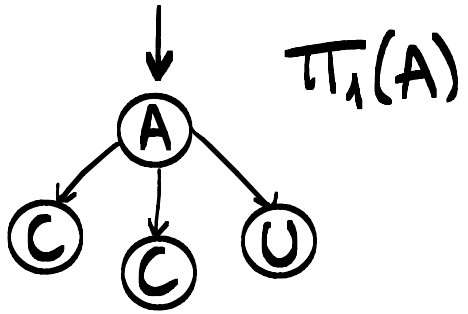

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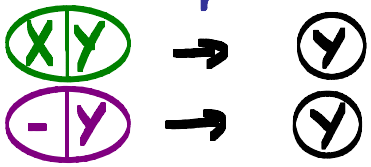

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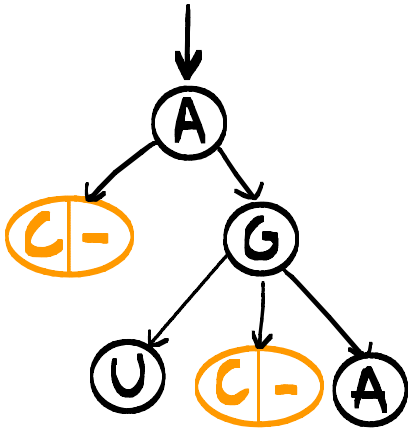

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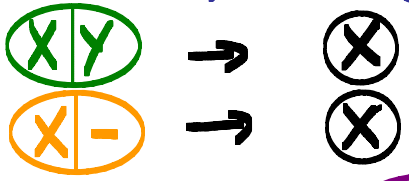
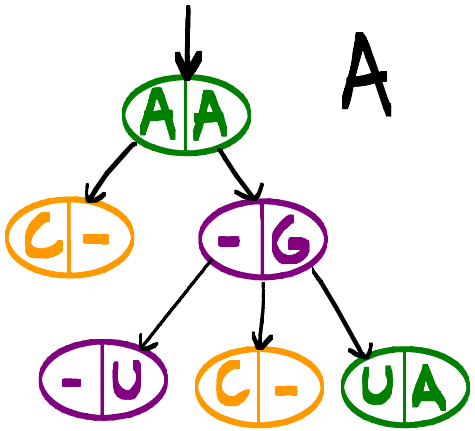
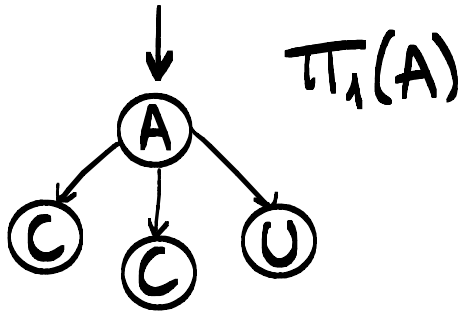


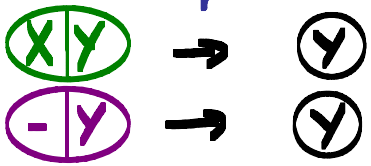
and removing 

.





$\Pi_2(A)$ = tree obtained by changing



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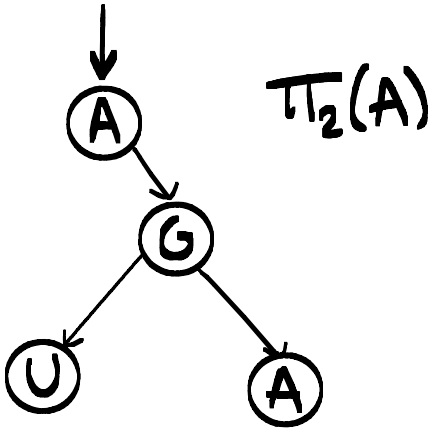
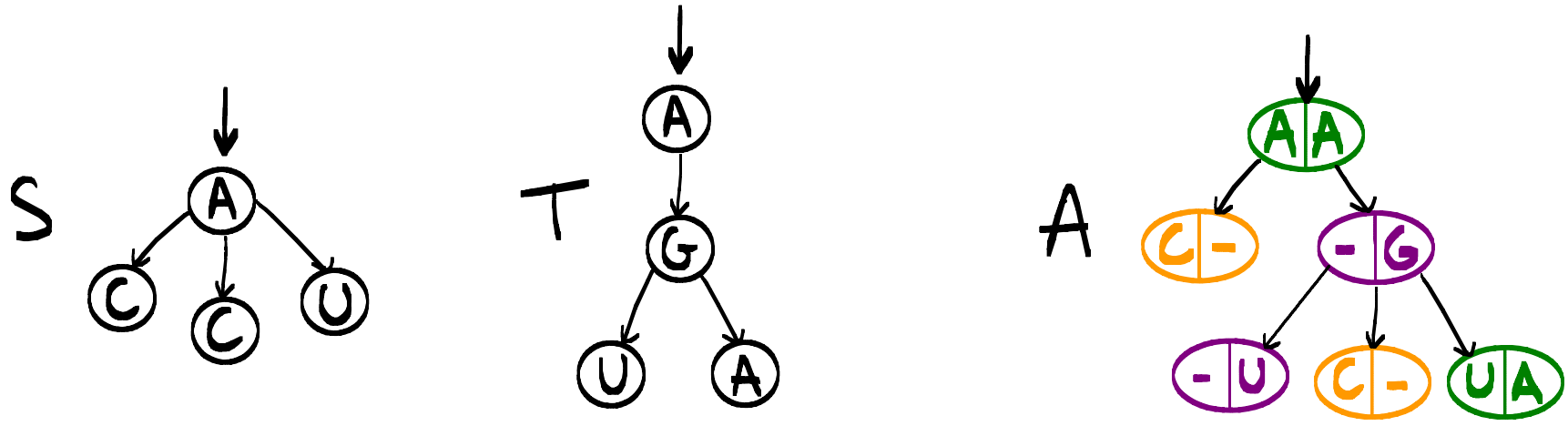


SUPERTREES INDUCE TREE ALIGNMENTS



Given two trees S and T,
a supertree A defines an alignment between S and T
if $\pi_1(A) = S$ and $\pi_2(A) = T$.

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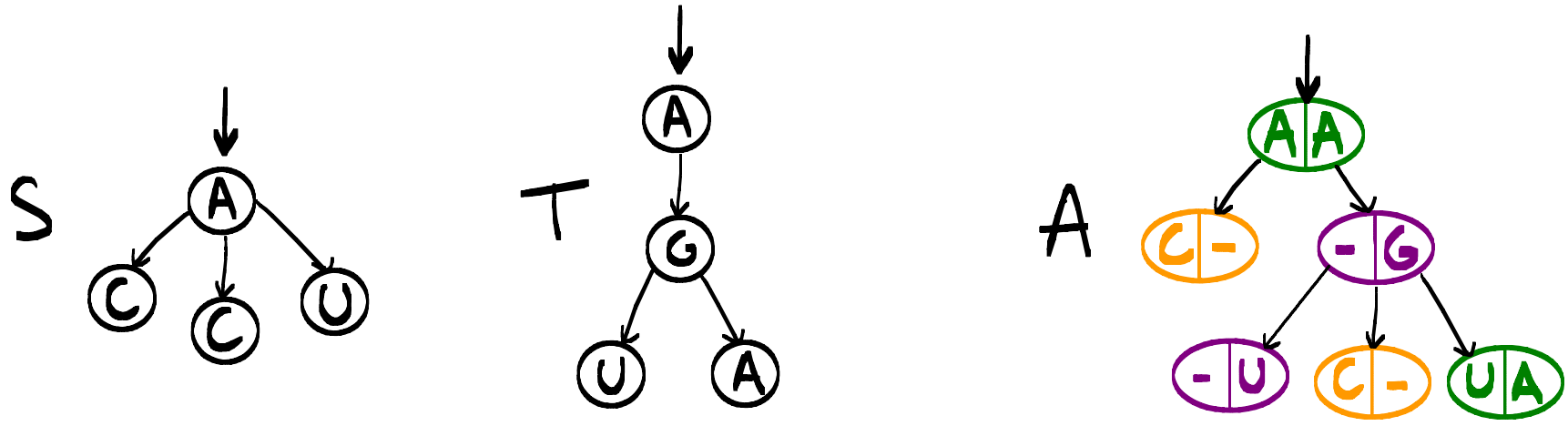


Given two trees S and T,
a supertree A defines an alignment between S and T
if $\pi_1(A) = S$ and $\pi_2(A) = T$.

cost(A) = nb of insertions + deletions + mismatches

(can be changed more complicated models)

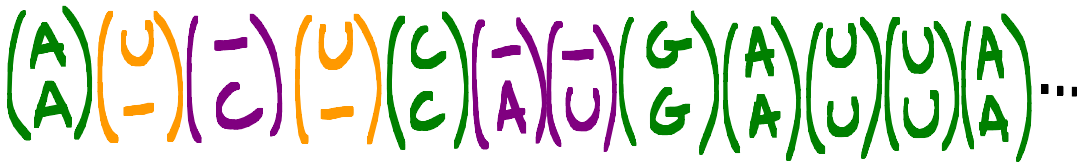
CONNECTION WITH SEQUENCE ALIGNMENTS

Tree alignments generalize sequence alignments.

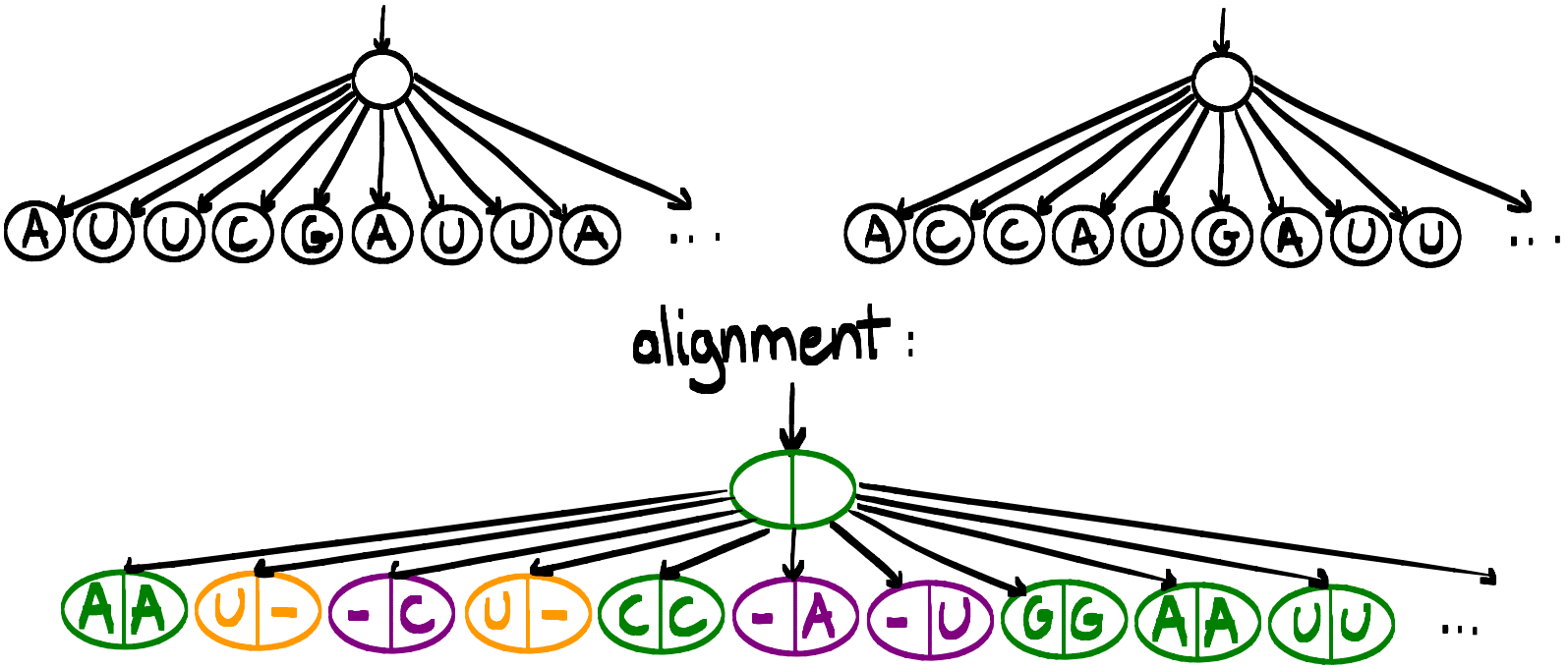
SEQUENCE

AUUCGAUUA... ACCAUGAUUA...

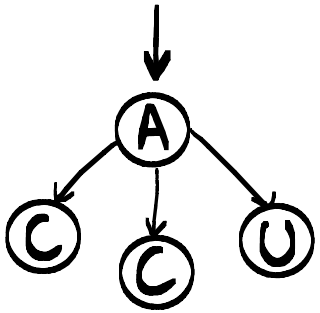
alignment:

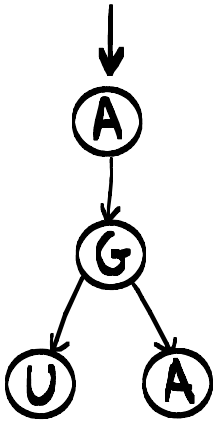


TREE



SPACE OF ALIGNMENTS

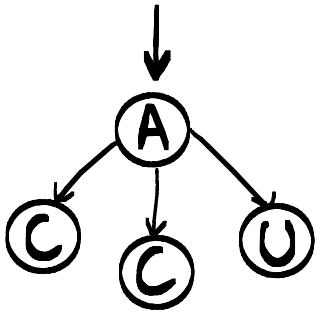
Which alignment between 

and 

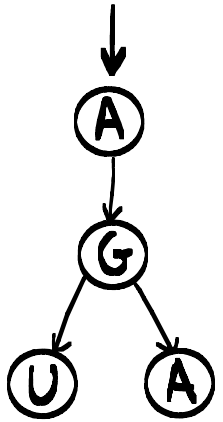
is the most likely?

SPACE OF ALIGNMENTS

Which alignment between



and

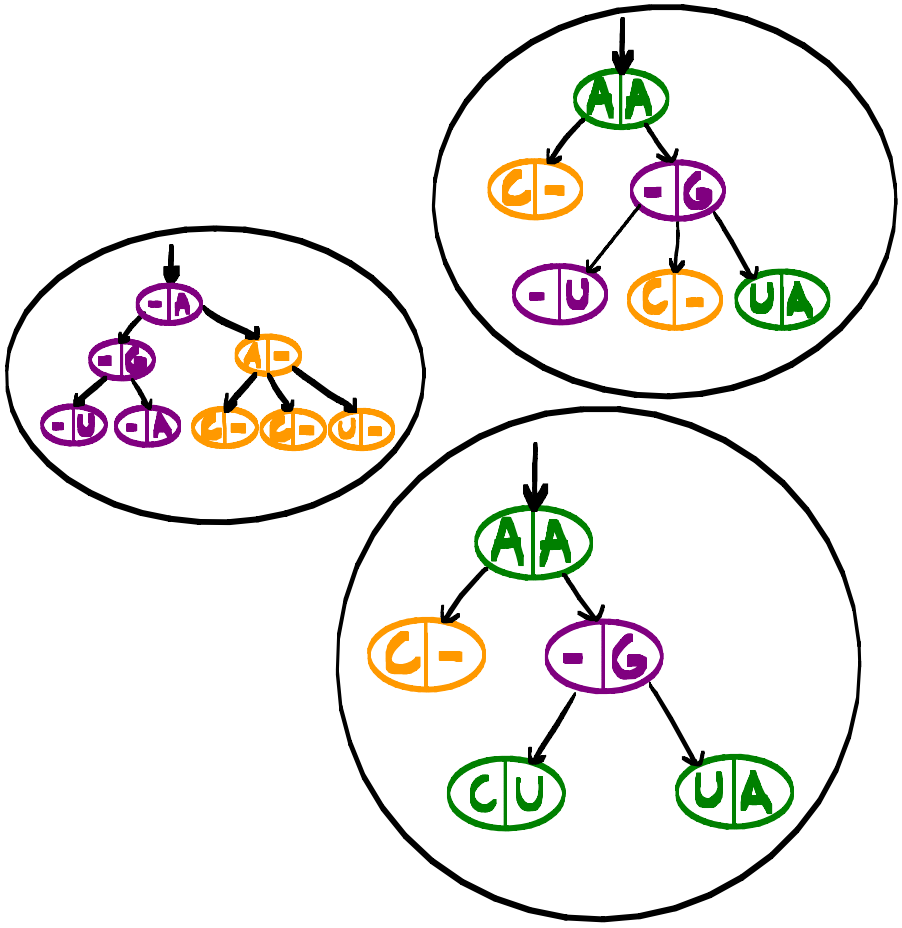


is the most likely?

probability of an alignment A

$$\propto e^{-\frac{cost(A)}{K}}$$

(Gibbs-Boltzmann distribution)



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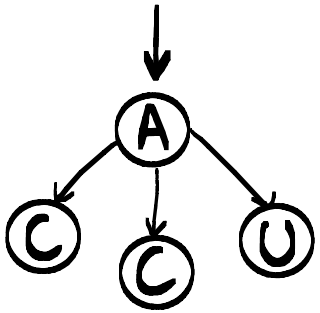
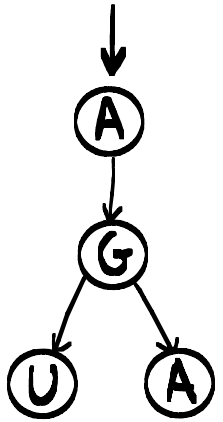


and



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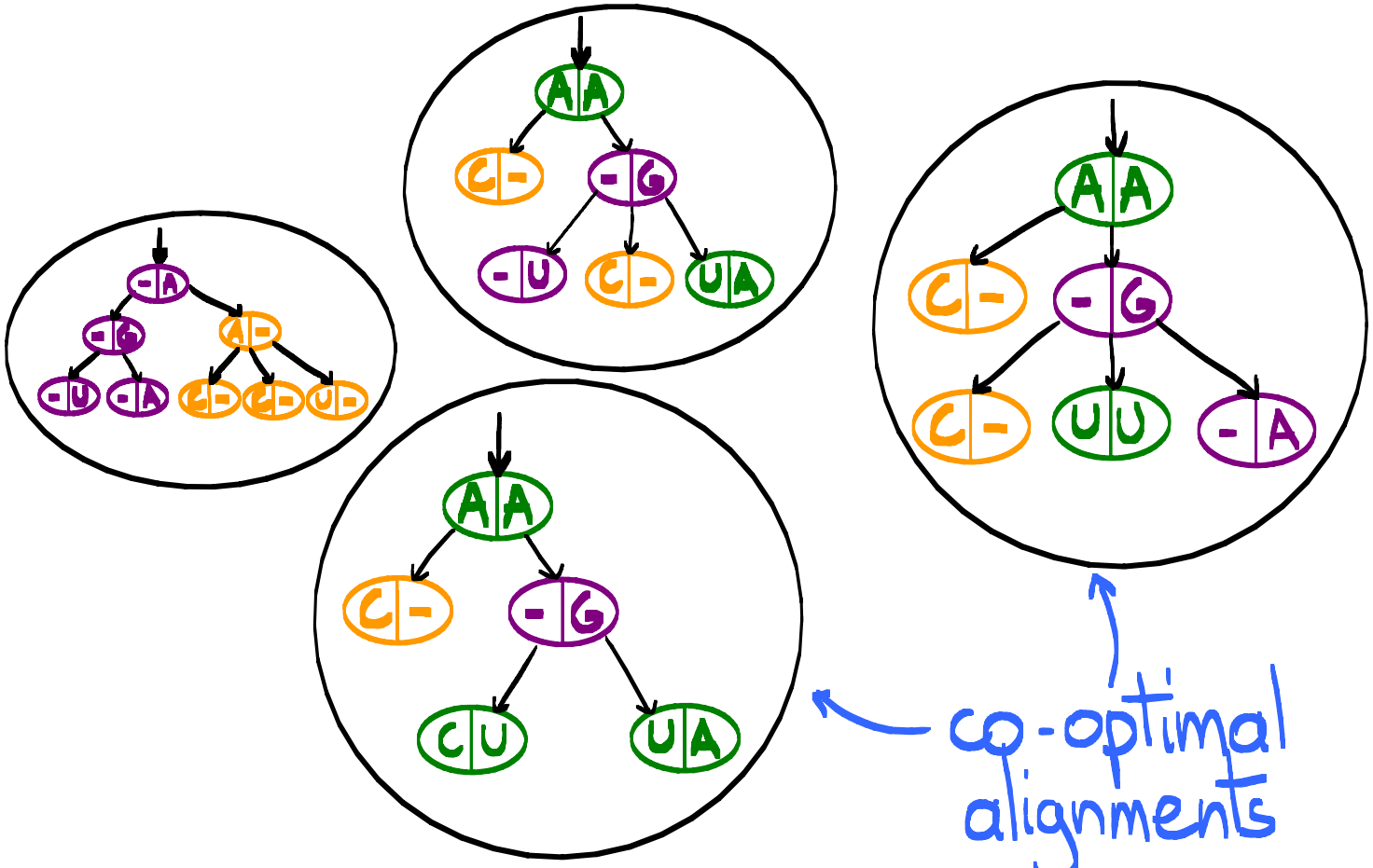


Space of alignments

Why finding one optimal alignment may be inadequate:

- Co-optimal alignments can be very different.
  (see for instance [Vingron, Argos, 1990])

- Exploring the space of alignments enables the detection of high probability features.

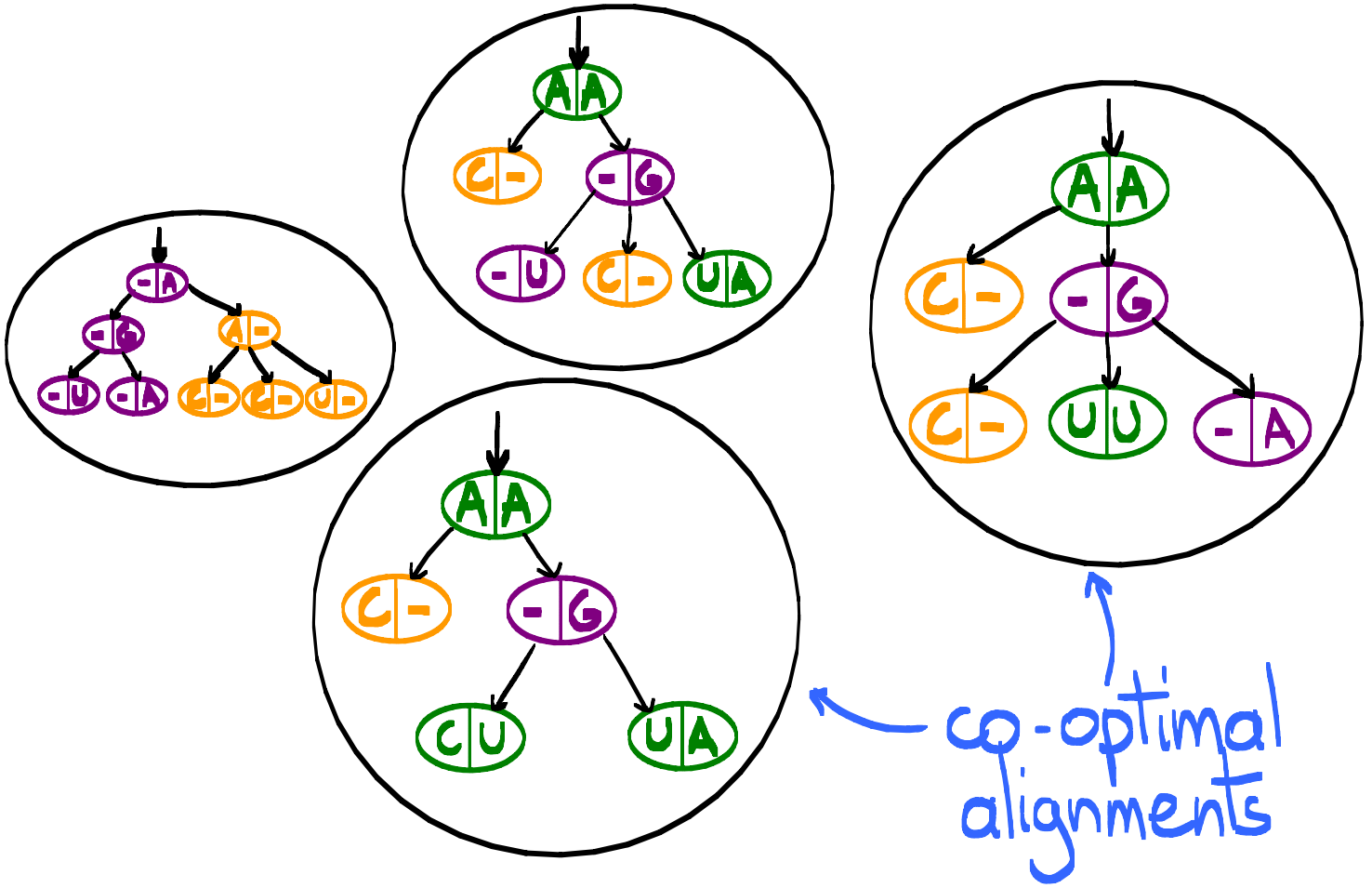
SPACE OF ALIGNMENTS

Objective: Sampling alignments under the Gibbs-Boltzmann probability distribution.

probability of an alignment A

$$\propto e^{-\frac{cost(A)}{K}}$$

(Gibbs-Boltzmann distribution)



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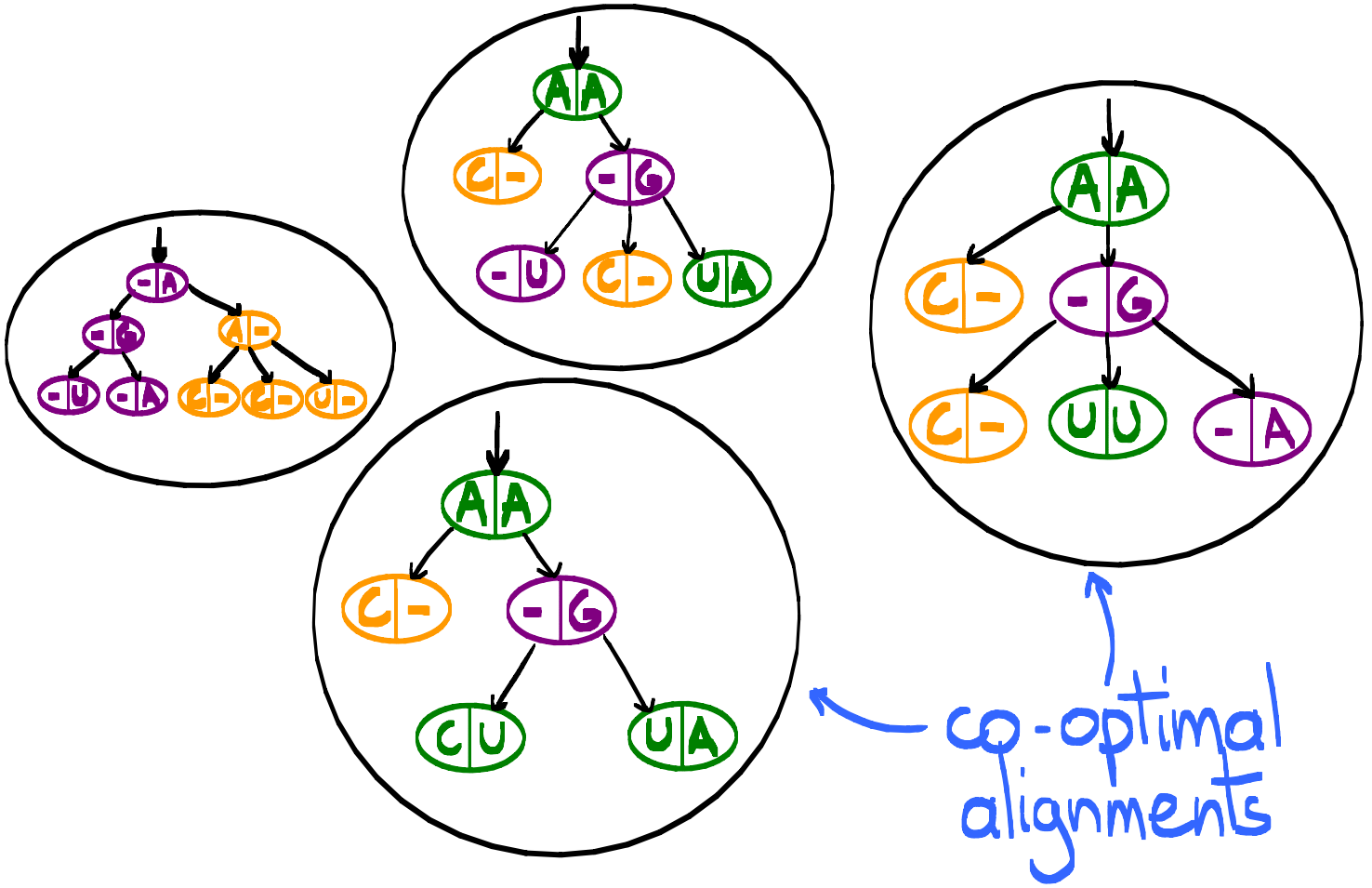
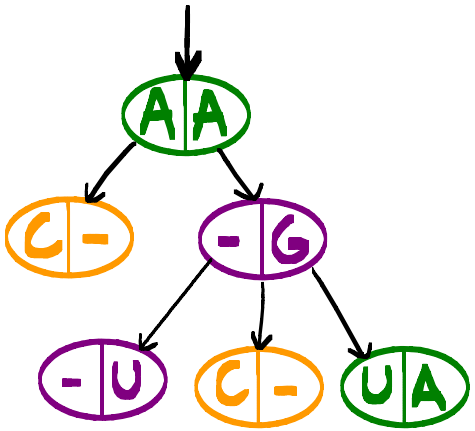
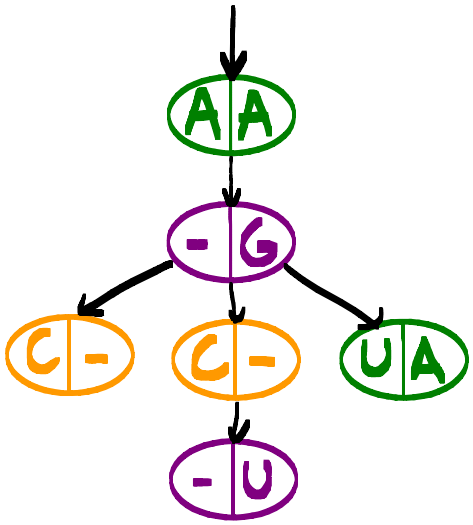


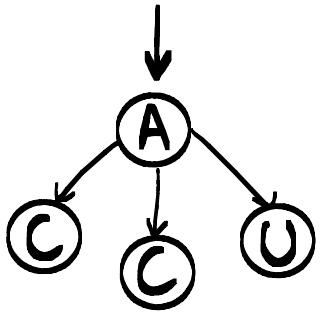
AMBIGUITY OF ALIGNMENTS

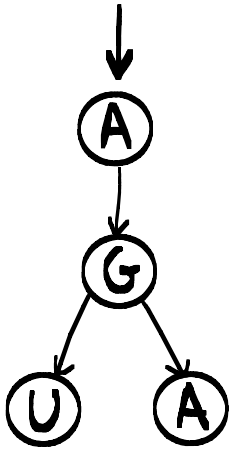
The two supertrees





induce the same alignment between the trees





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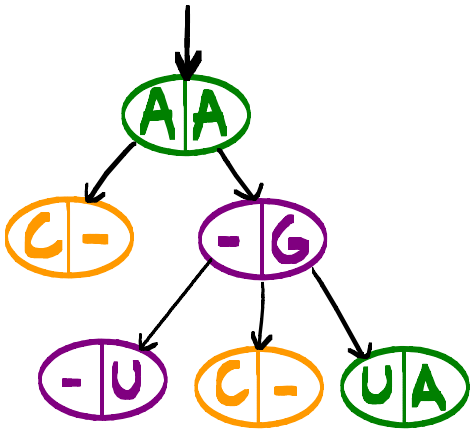
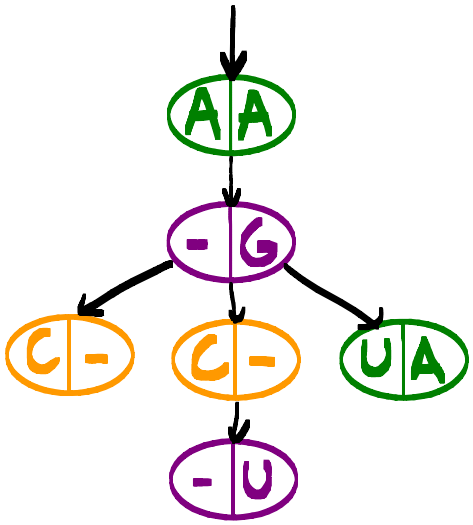
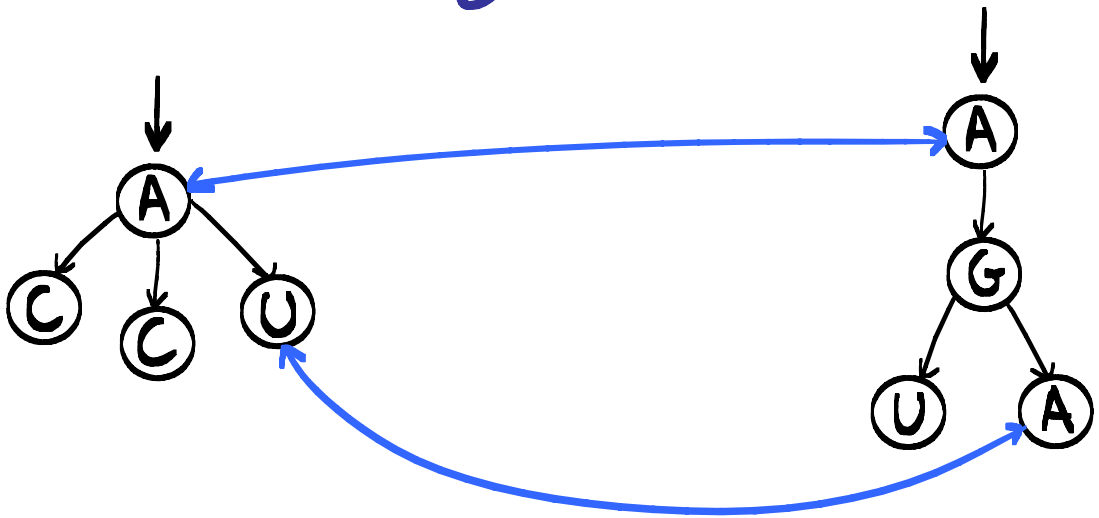




induce the same alignment between the trees



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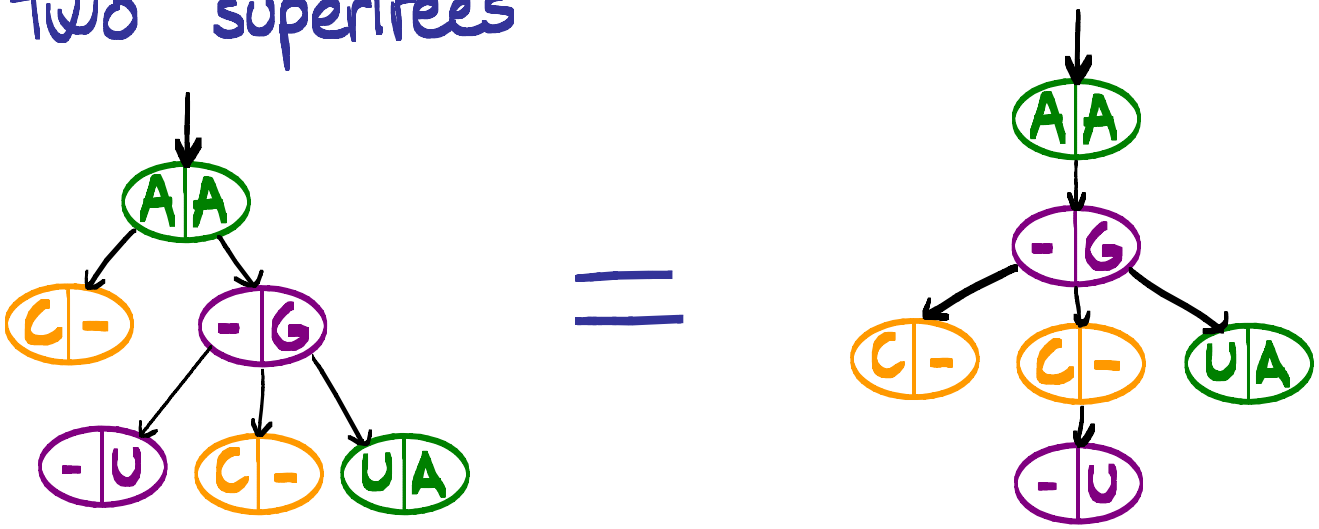

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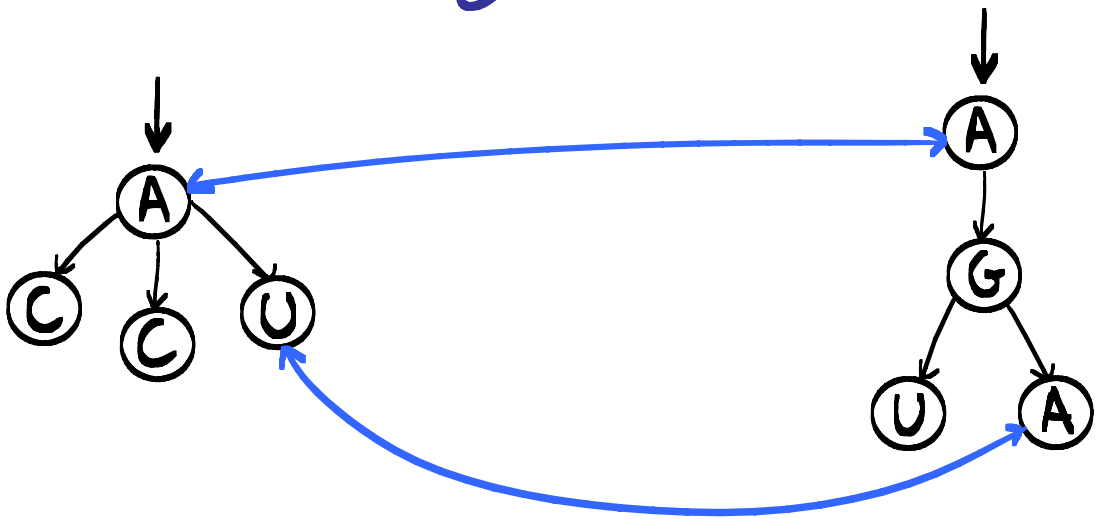
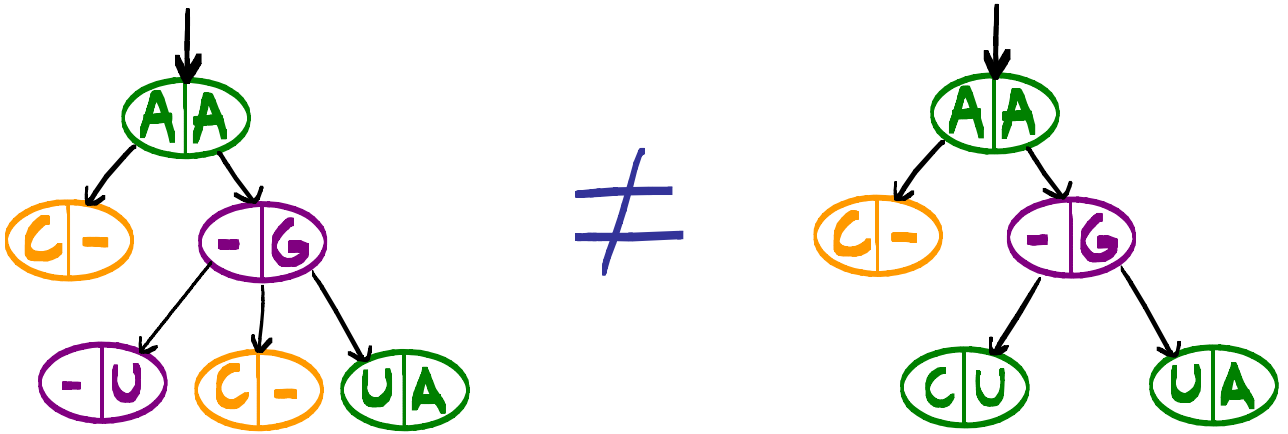


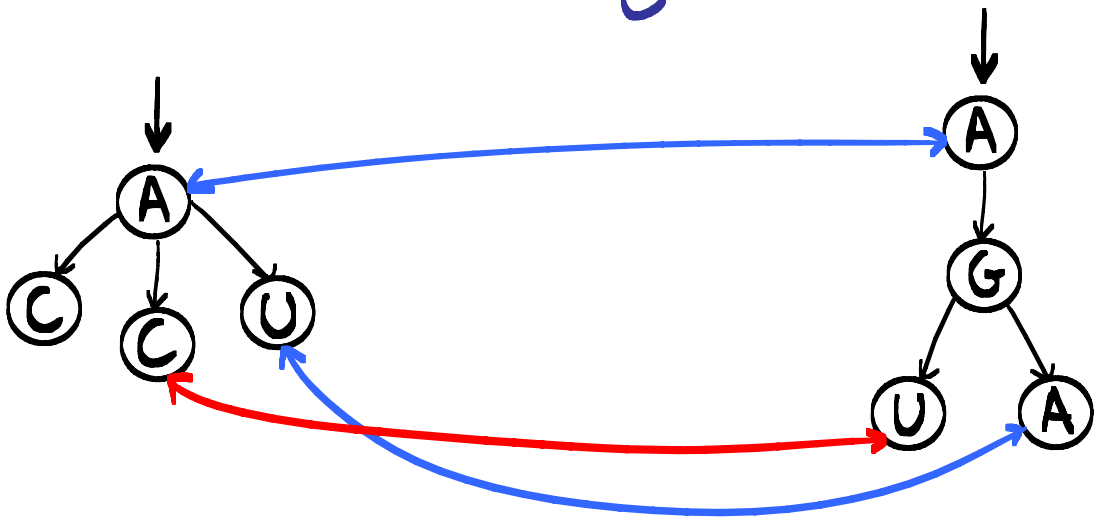
They are the same!

AMBIGUITY OF ALIGNMENTS

The two supertrees



do not induce the same alignment between the trees



A GRAMMAR FOR ALIGNMENTS

Strategy: Build a context-free grammar that generates every alignment exactly once

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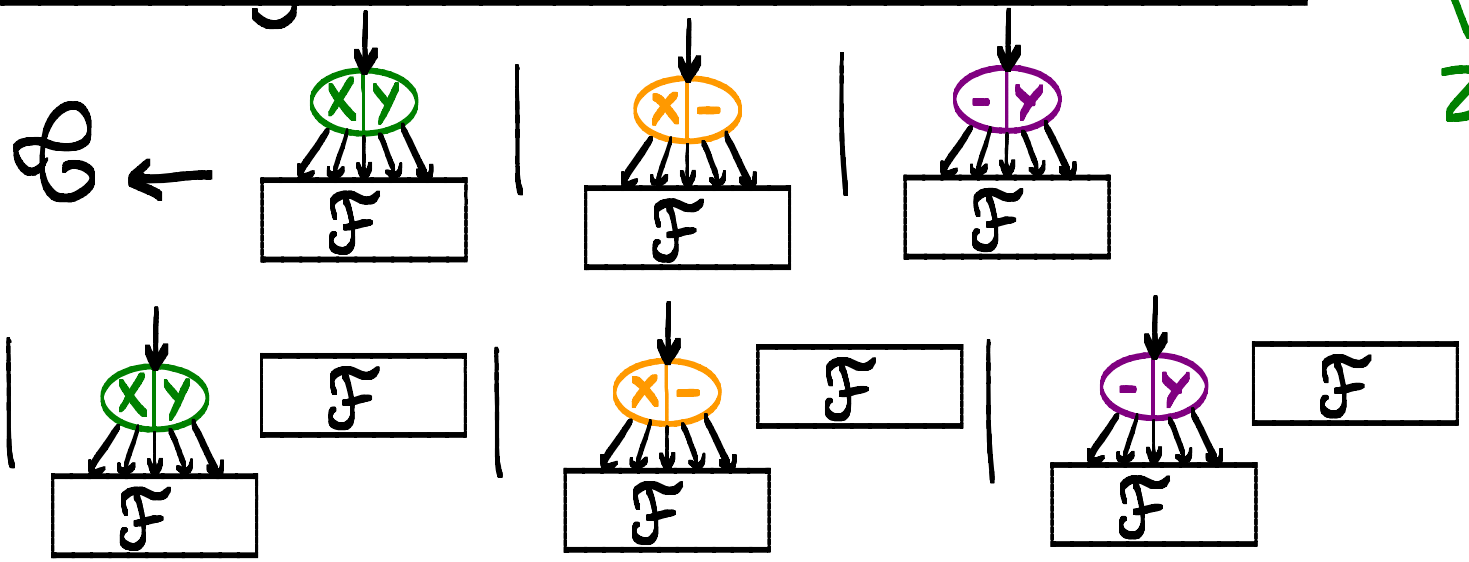
An example of grammar that does not work: [Jiang, Wang, Zhang]



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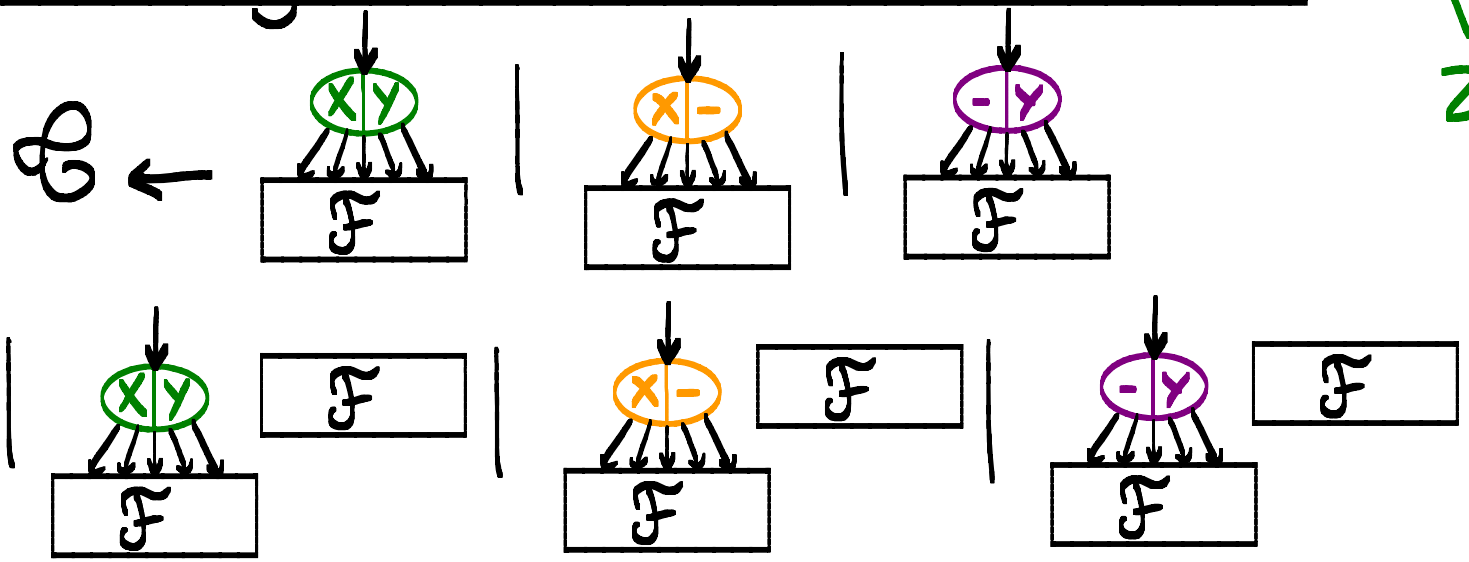

Ex:

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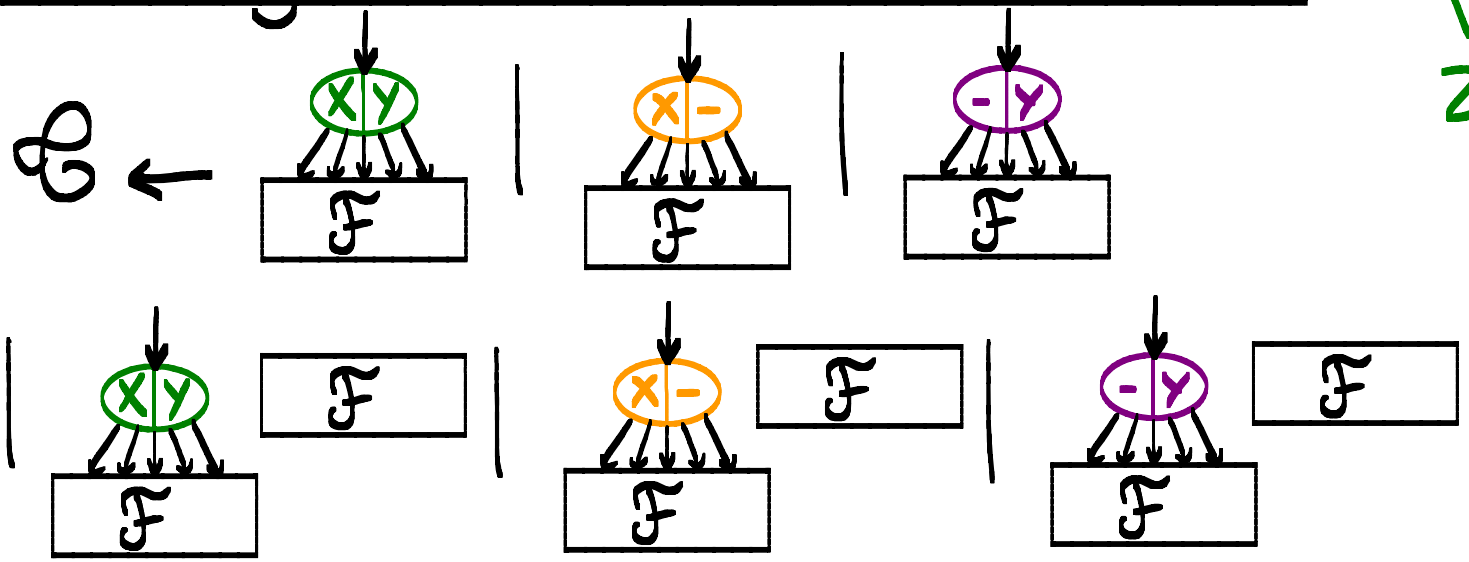

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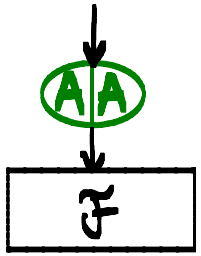

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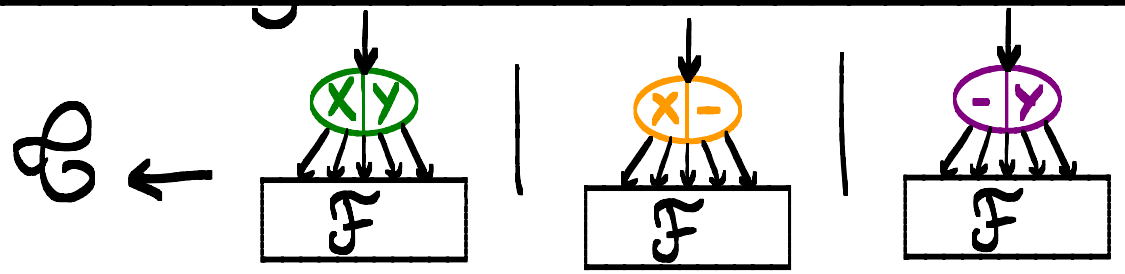

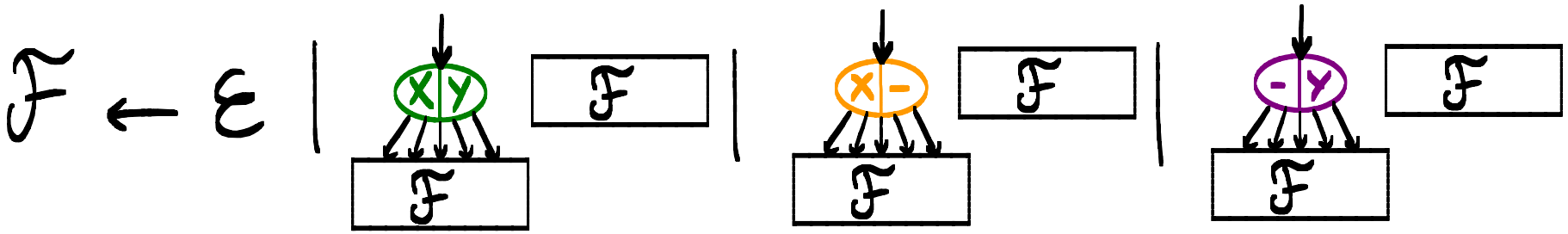

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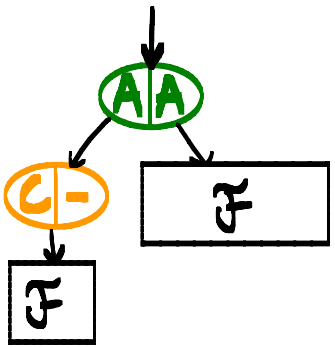

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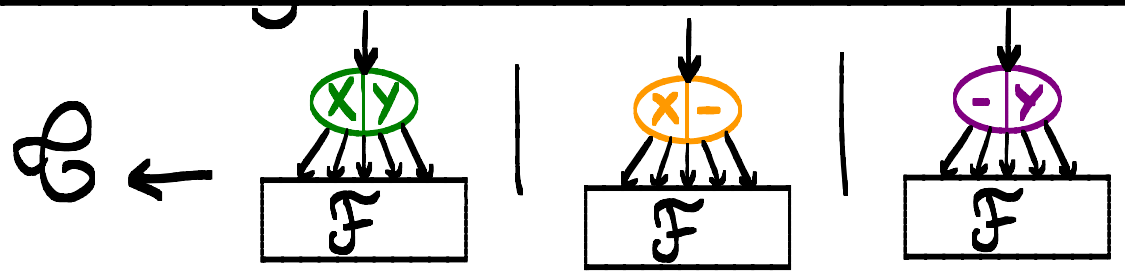

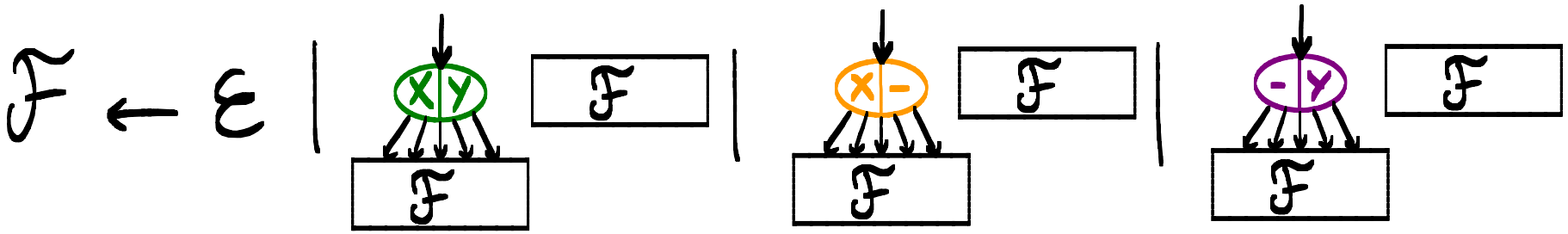

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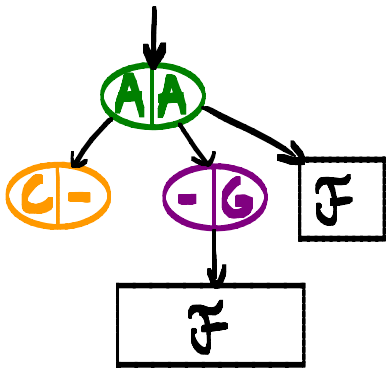

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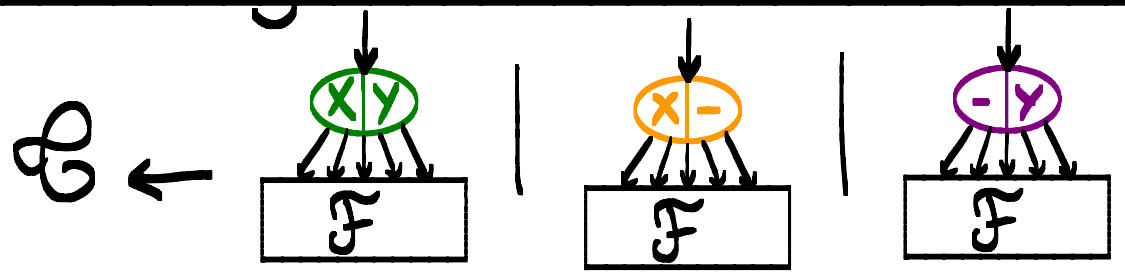

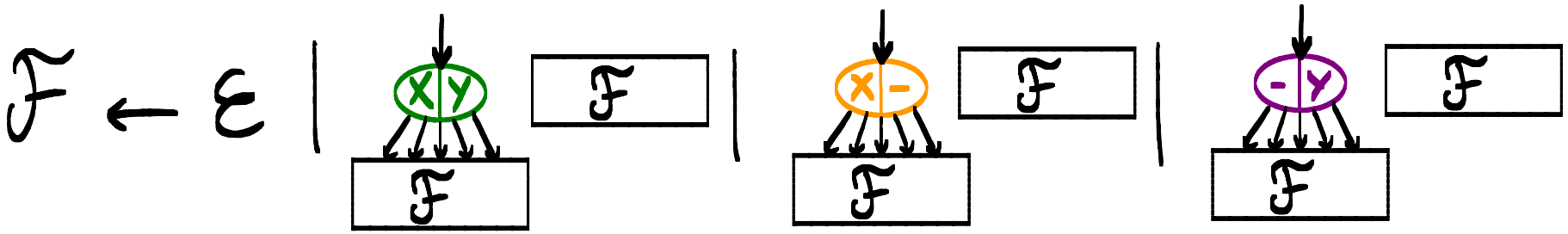

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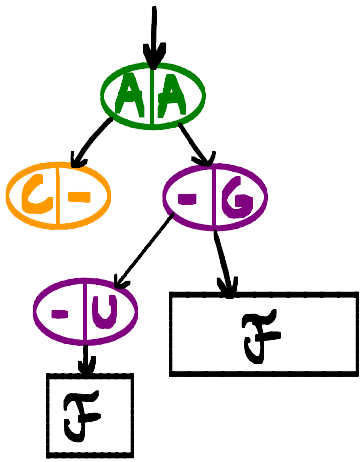

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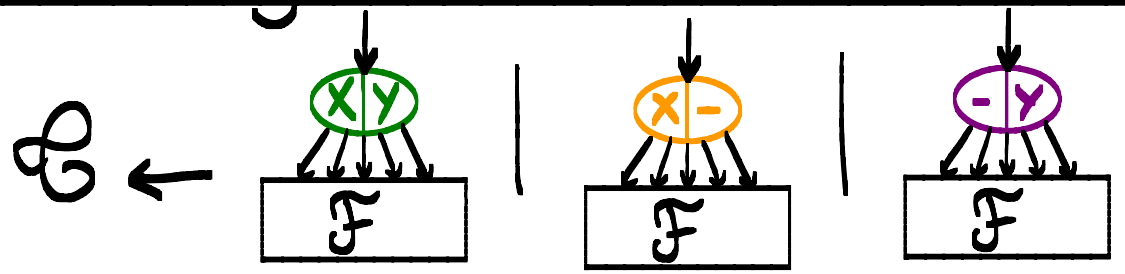

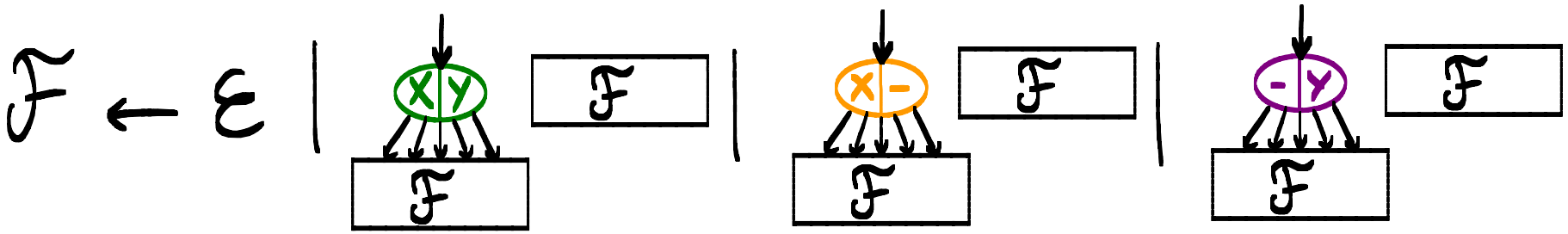

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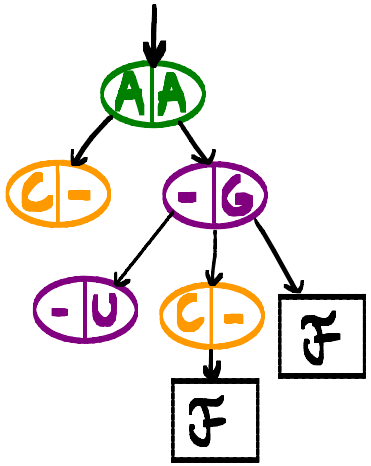

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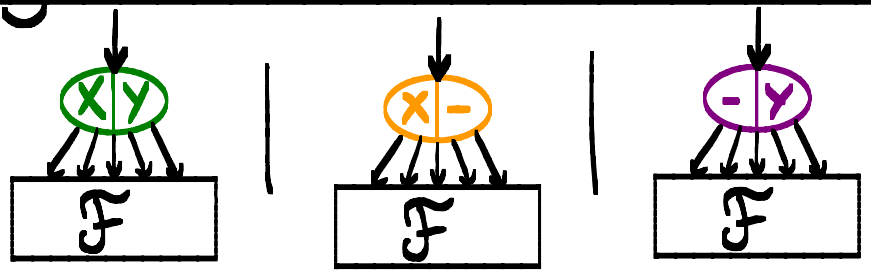
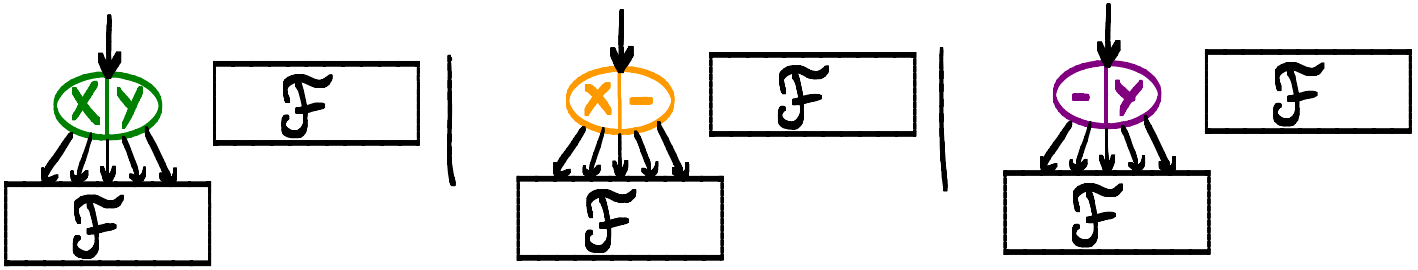
$\mathcal{G} \leftarrow$ 

$\mathcal{F} \leftarrow \varepsilon \mid$ 

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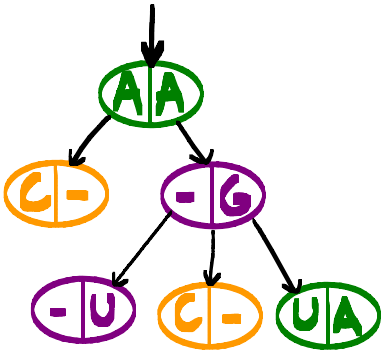

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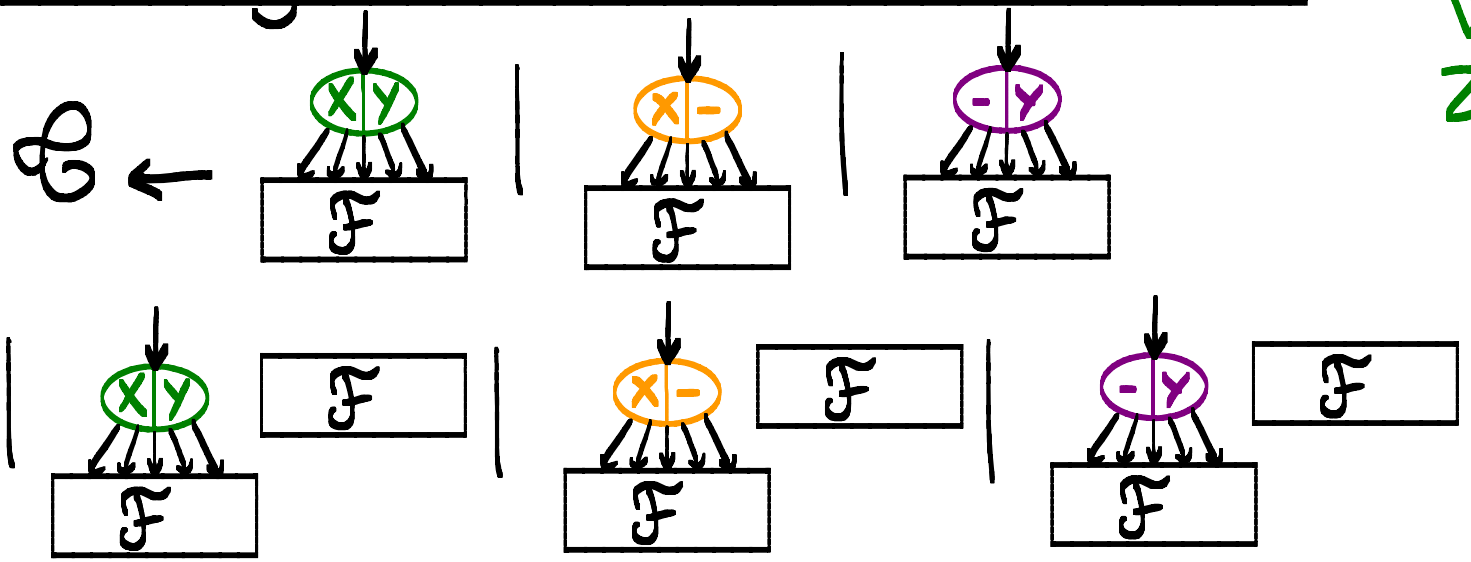

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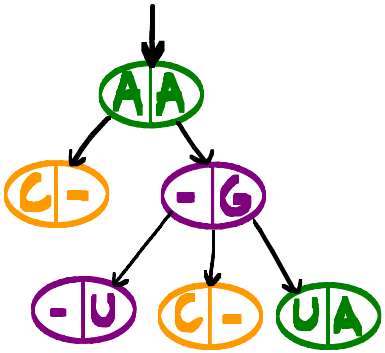

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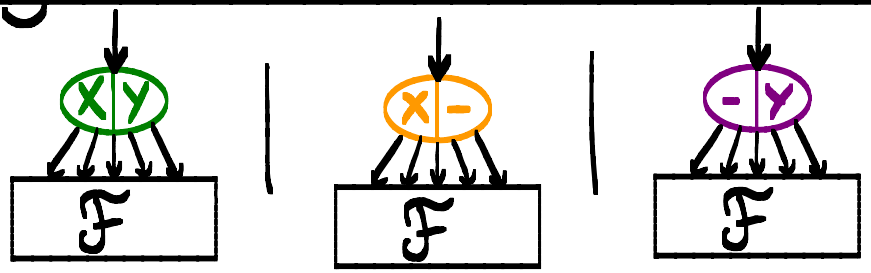
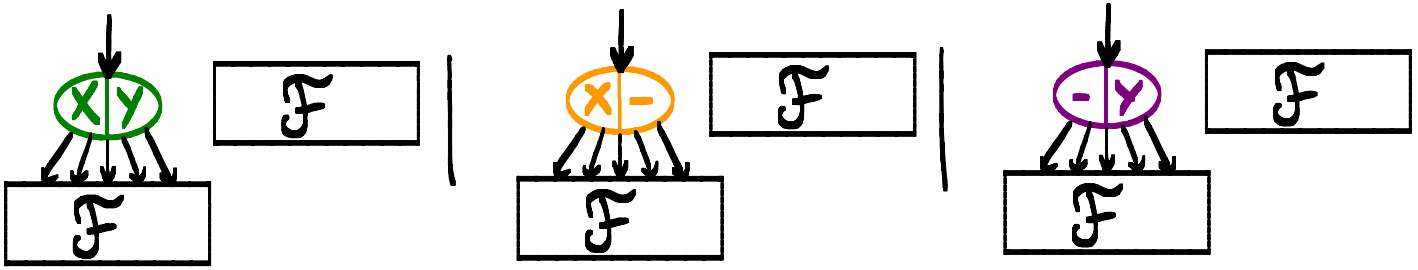
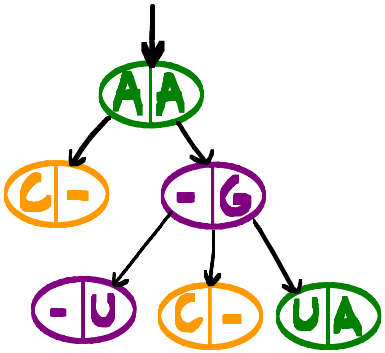
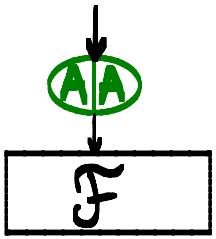
$\mathcal{G} \leftarrow$ 

$\mathcal{F} \leftarrow \varepsilon \mid$ 

Ex:

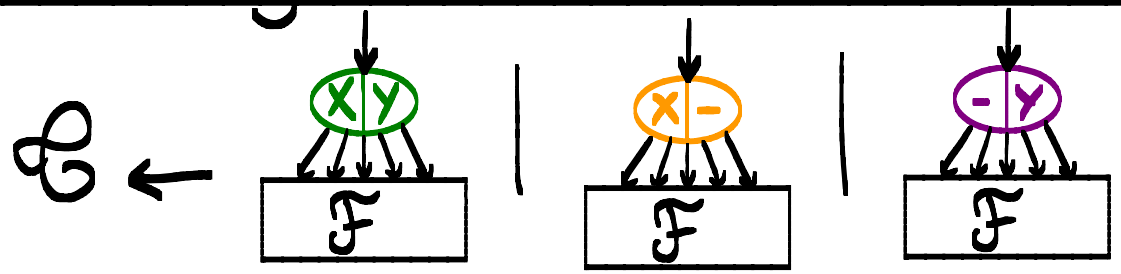


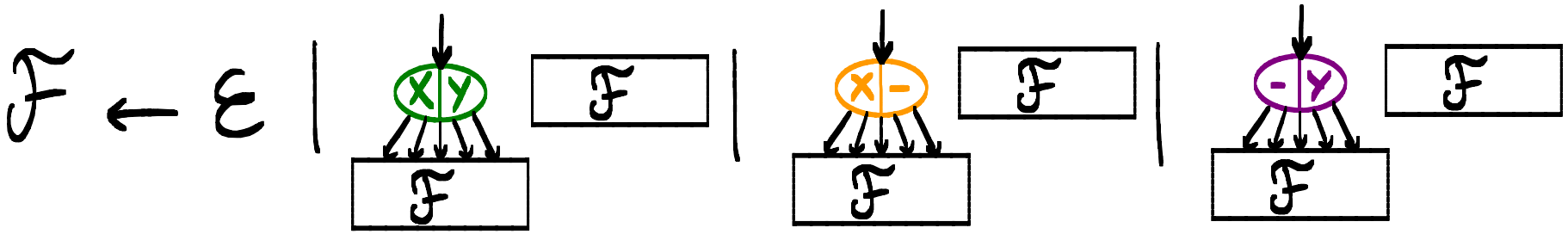


A GRAMMAR FOR ALIGNMENTS

Strategy: Build a context-free grammar that generates every alignment exactly once

An example of grammar that does not work: [Jiang, Wang, Zhang]





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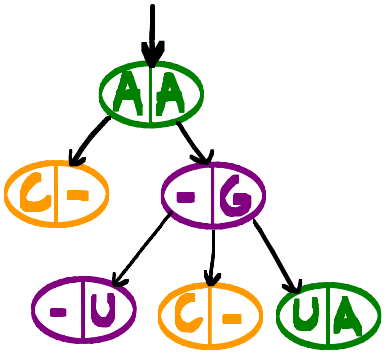

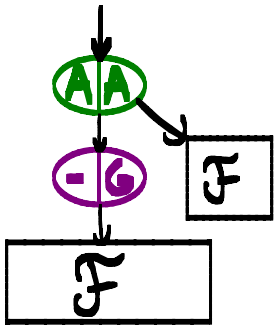

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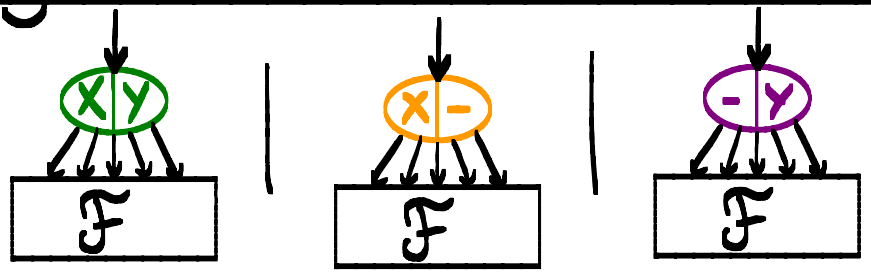
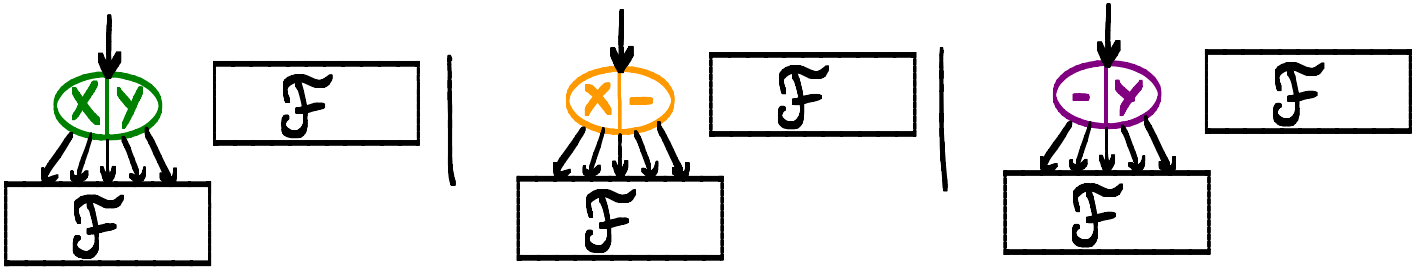
$\mathcal{G} \leftarrow$ 

$\mathcal{F} \leftarrow \varepsilon \mid$ 

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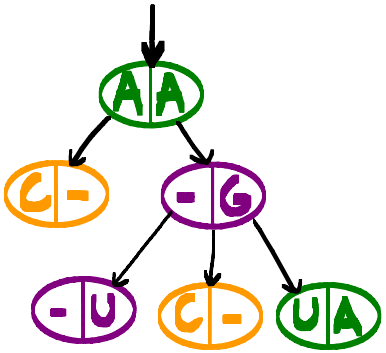

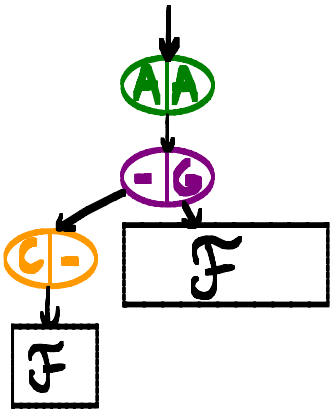

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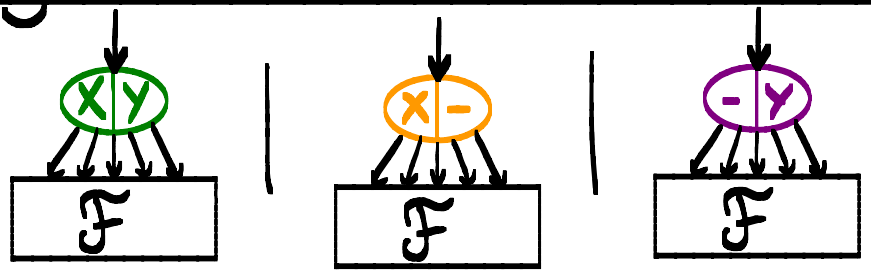
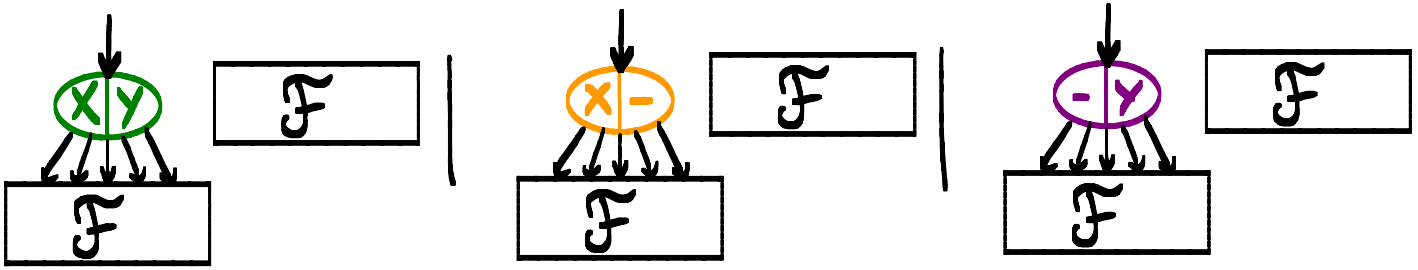
$\mathcal{G} \leftarrow$ 

$\mathcal{F} \leftarrow \varepsilon \mid$ 

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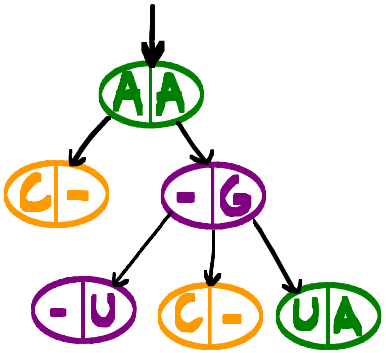

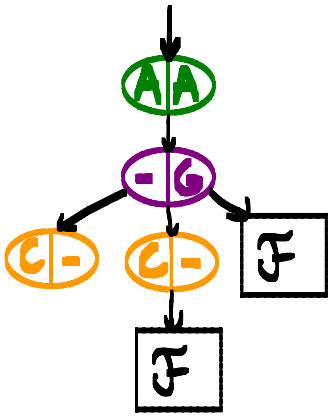

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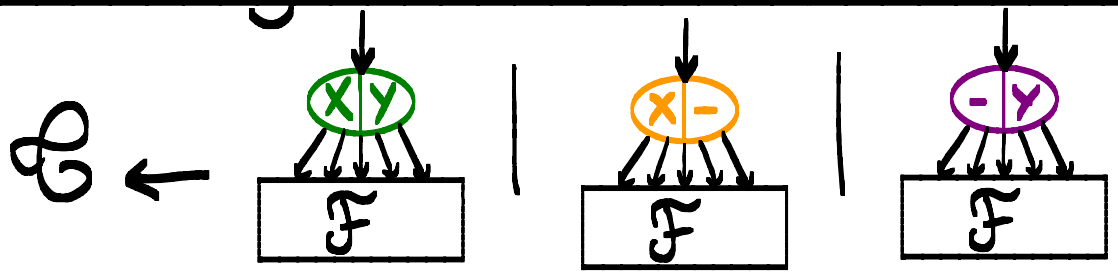

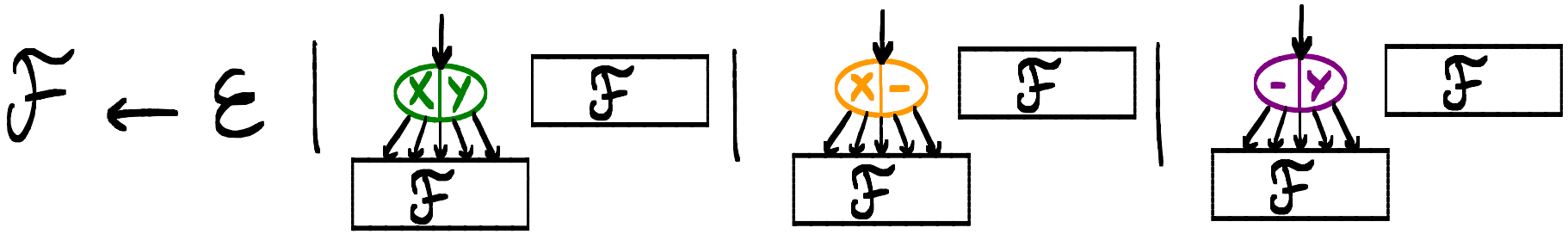

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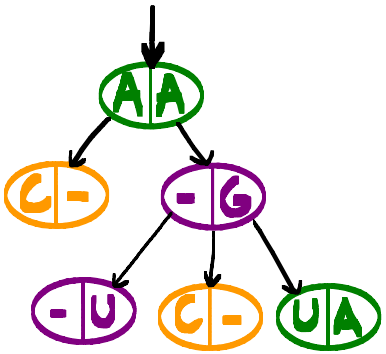

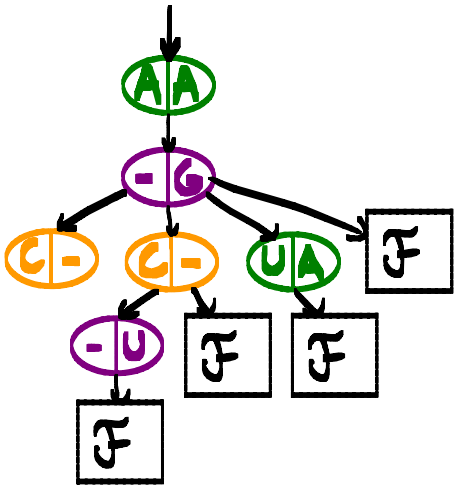

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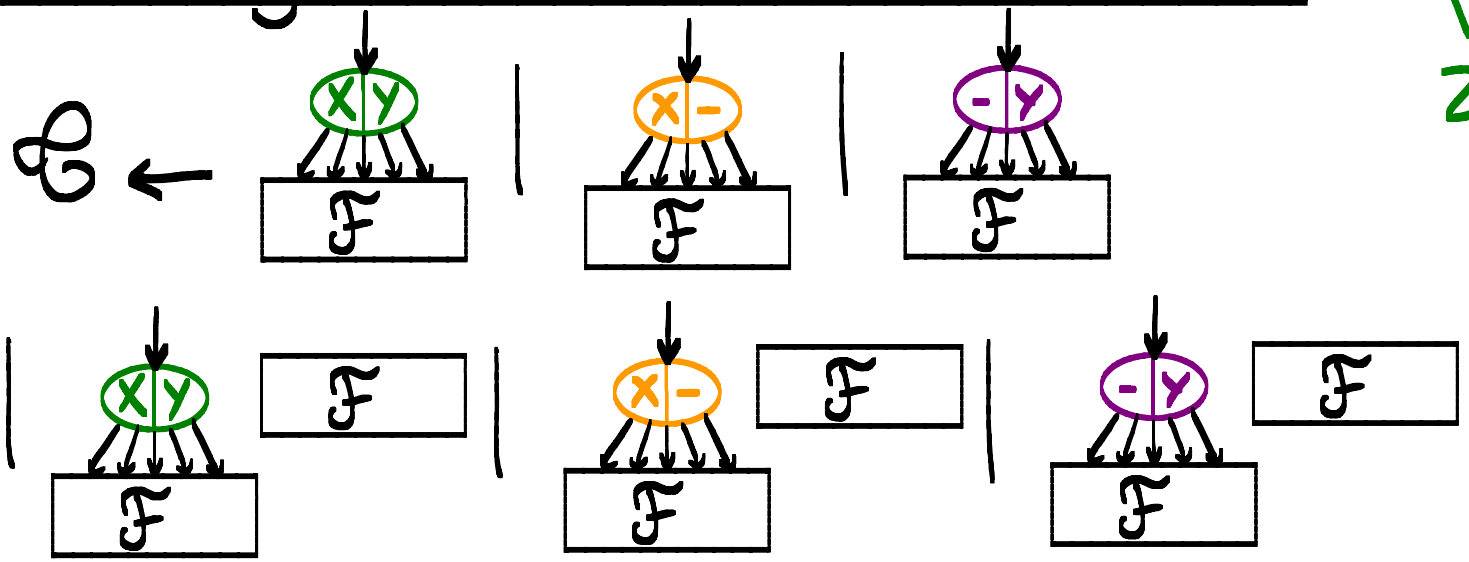

Ex:

A GRAMMAR FOR ALIGNMENTS

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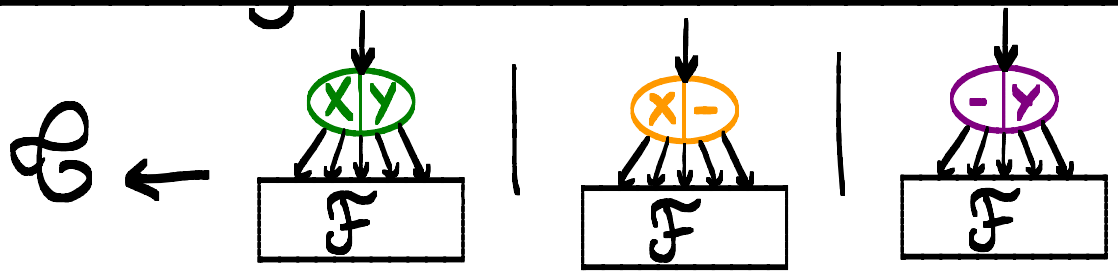

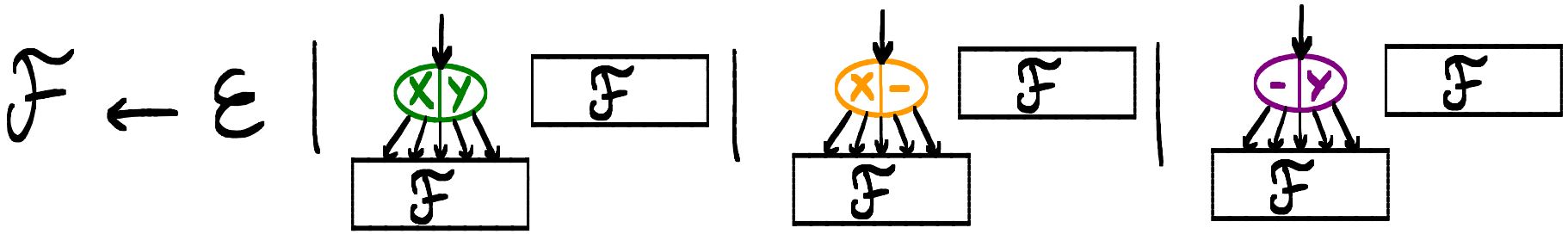

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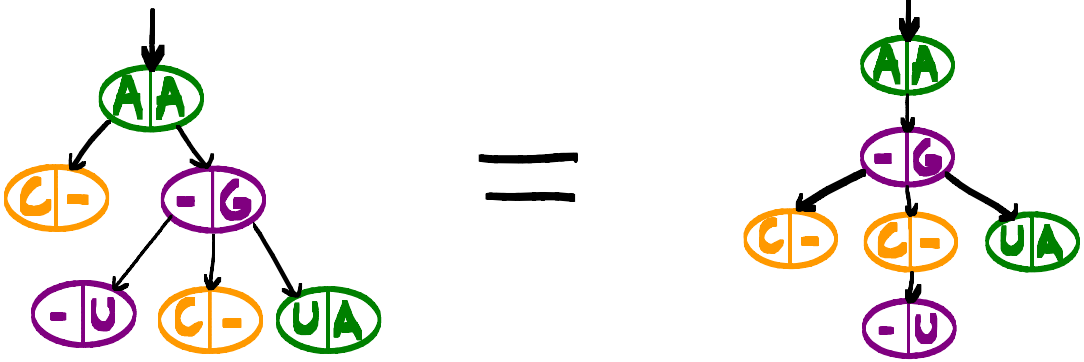


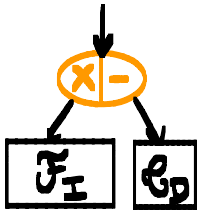
ambiguous grammar

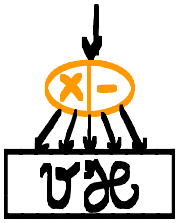
A GRAMMAR FOR ALIGNMENTS

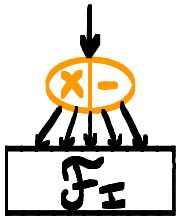
Theorem: The set $\mathcal{A}$ generated by the following grammar contains every tree alignment exactly once.

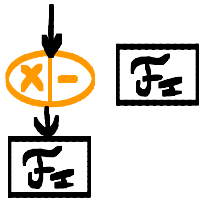
A GRAMMAR FOR ALIGNMENTS

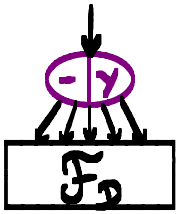
Our (complicated) non-ambiguous grammar:

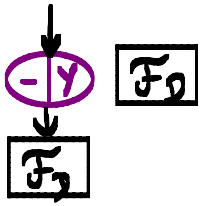
$$\mathcal{A} \leftarrow \mathcal{V}^{\phi} \mid \mathcal{C}_I \mid \mathcal{C}_D \mid$$ 

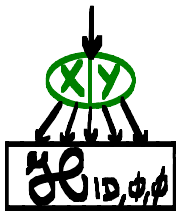
$$\mathcal{V}^{\phi} \leftarrow \mathcal{V}^{\uparrow} \mid$$ 

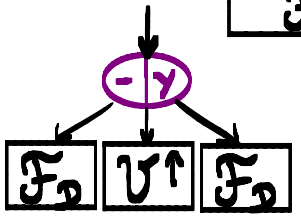
$$\mathcal{C}_I \leftarrow$$ 

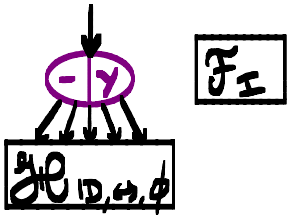
$$\mathcal{F}_I \leftarrow \varepsilon \mid$$ 

$$\mathcal{C}_D \leftarrow$$ 

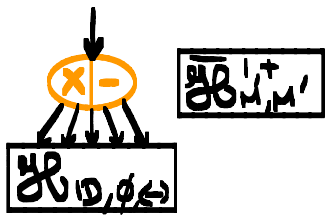
$$\mathcal{F}_D \leftarrow \varepsilon \mid$$ 

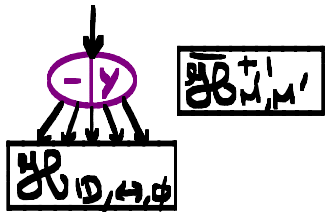
$$\mathcal{V}^{\uparrow} \leftarrow$$ 

$\mid$ 

$$\mathcal{V}\mathcal{H} \leftarrow \mathcal{F}_I\ \mathcal{V}\mathcal{H} \mid \mathcal{V}^{\phi}\ \mathcal{F}_I \mid$$ 

For $J \in \{D, \underline{D}\}$, $(M, M') \in \{\phi, \rightarrow, \leftrightarrow\}^2$:

$$\mathcal{H}_{J,M,M'} \leftarrow \varepsilon \mid \mathcal{C}_I\ \mathcal{H}_{J,M,M'} \mid \mathcal{C}_D\ \mathcal{H}_{\underline{D},M,M'} \mid \mathcal{V}^{\phi}\ \overline{\mathcal{H}}^{J,J}_{M,M'} \mid$$ 

$\mid$ 

only if $(M,M') = (\phi,\phi)$

only if $J \neq D$ and $M \neq \leftrightarrow$

only if $M' \neq \leftrightarrow$

no room for $\overline{\mathcal{H}}^{i,j}_{M,M'}$...

SOME STATISTICAL PROPERTIES

Theorem There are on average $C \times 1.5^n$ alignments between two random trees of cumulative size n where $C = 0.299\ldots$

Corollary: A same alignment was repeated $\sim 0.875 \times 1.412^n$ times on average in the previous ambiguous grammar.

SAMPLING

Theorem Let S and T be two trees of size n_1 and n_2. Sampling alignments between S and T under the Gibbs-Boltzmann distribution can be done with worst-case time and space complexities $O(n_1 n_2 (n_1 + n_2)^2)$ and with average-case time and space complexities $O(n_1 n_2)$.

Strategy:

→ Filter the grammar to obtain a new grammar that only generates alignments between S and T

→ Use dynamic programming.

SAMPLING

Theorem Let S and T be two trees of size n_1 and n_2. Sampling alignments between S and T under the Gibbs-Boltzmann distribution can be done with worst-case time and space complexities $O(n_1 n_2 (n_1 + n_2)^2)$ and with average-case time and space complexities $O(n_1 n_2)$.

Proof inspired by

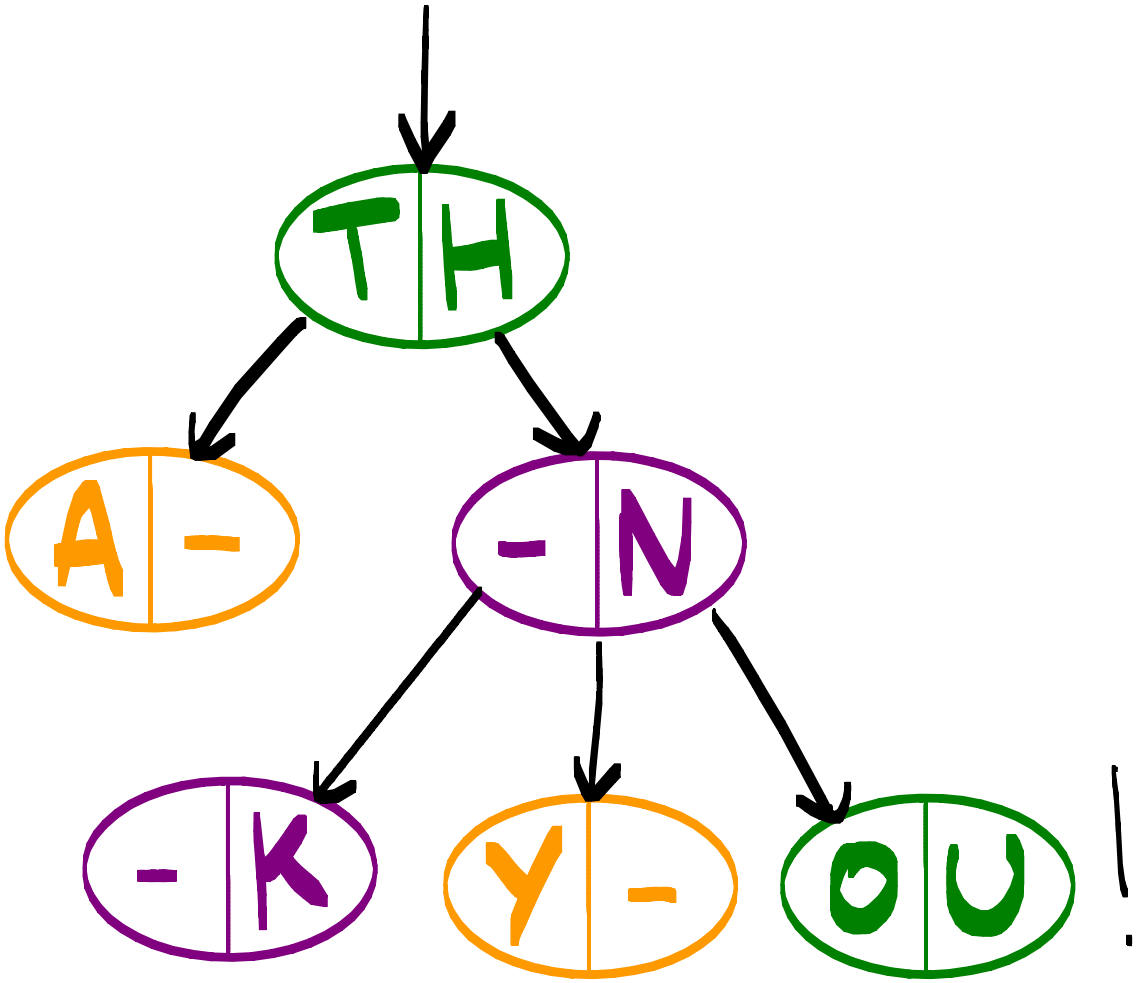
[Herrbach, Denise, Duluca]

CONCLUSION

→ We are using our grammar and adapted dynamic programming algorithms to revisit the 3D alignments of RNA structures.

→ more general method ?

new way to design dynamic programming algorithms ?


TH
A-
-N
-K
Y-
OU
!