A Common Framework for Linear and Cyclic Multiple Sequence Alignment

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Bioinformatics, University Leipzig

WABI 2014

Comparing Linear and Circular RNAs

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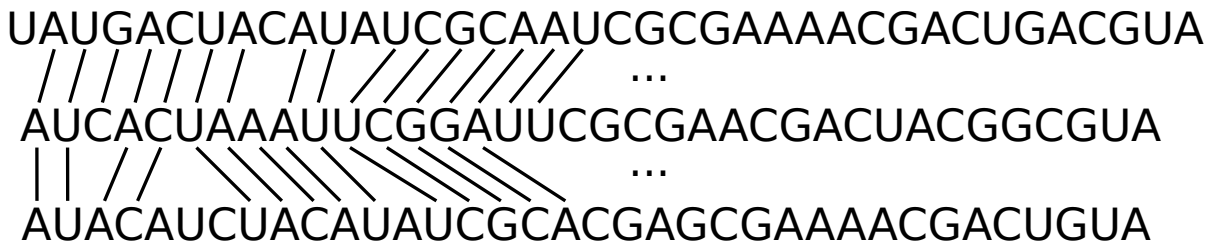
Comparing Linear and Circular RNAs



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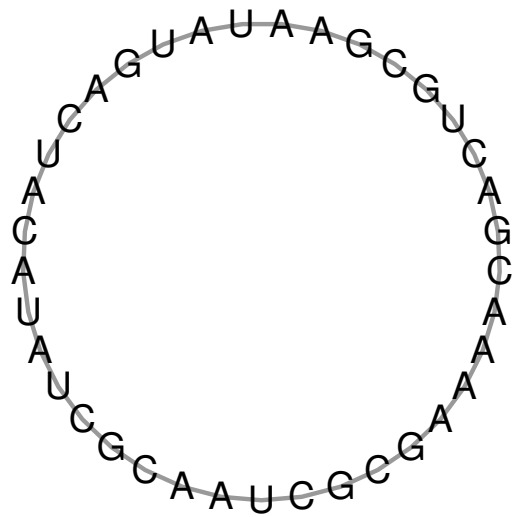

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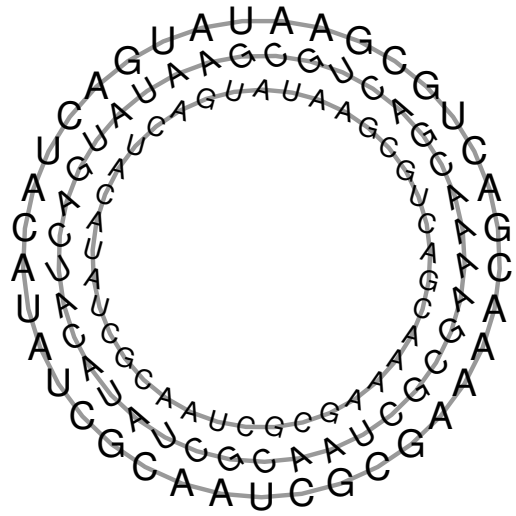

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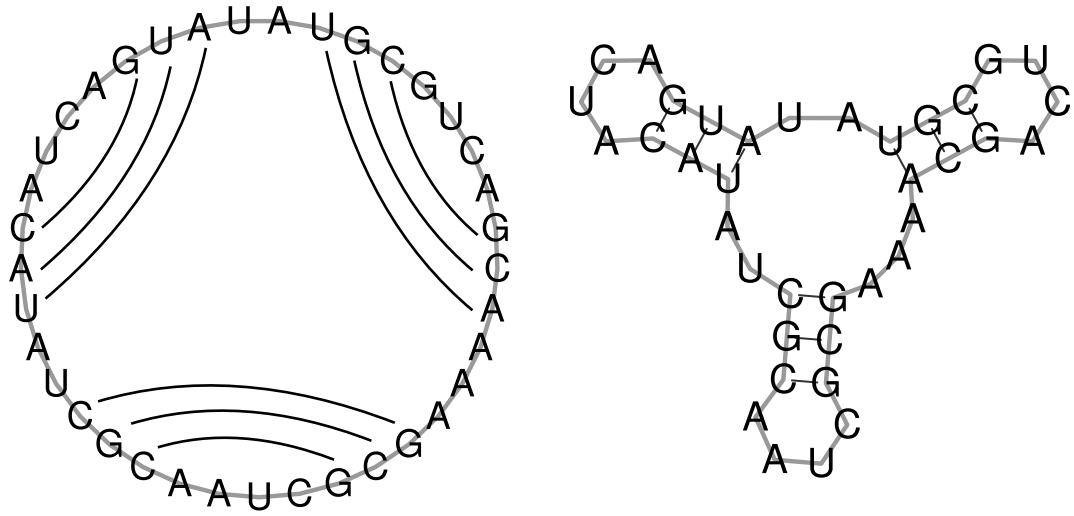

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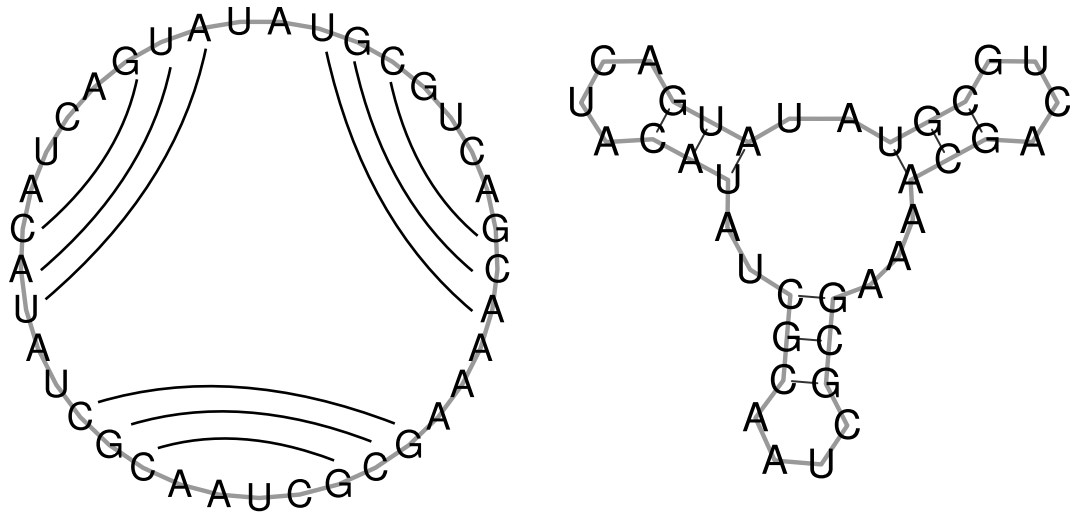
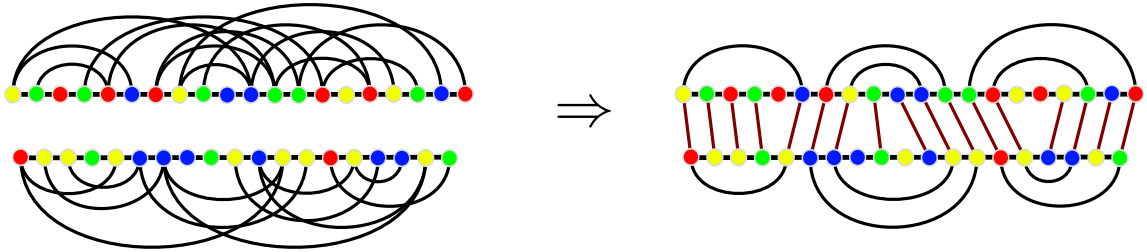


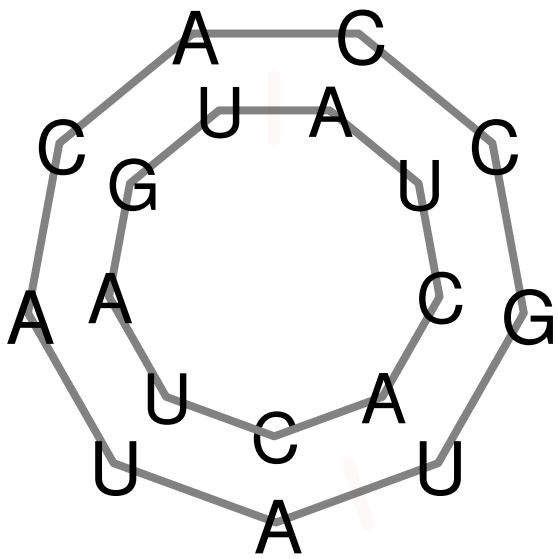
Structure-based alignment of RNAs:

e.g. [Will et al., 2007]: **two linear RNAs**



Here: **multiple circular RNAs**

(Pairwise) Cyclic Alignment (vs. Linear)



UAUCACUAG

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Pairwise: Dynamic Programming + find best rotation/cut.

Pairwise cyclic sequence alignment [Mosig et al., 2006].

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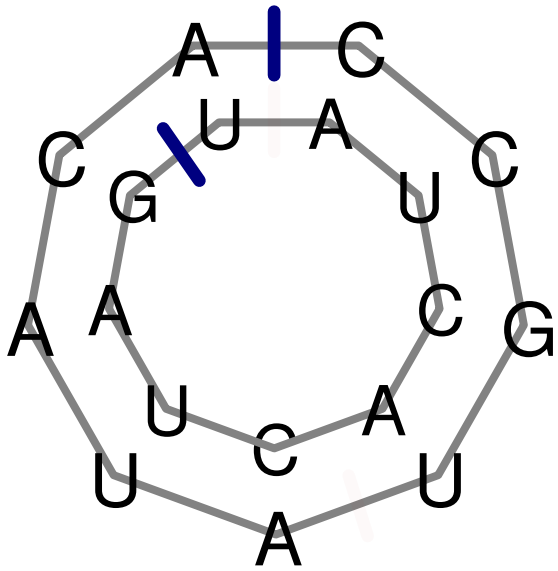

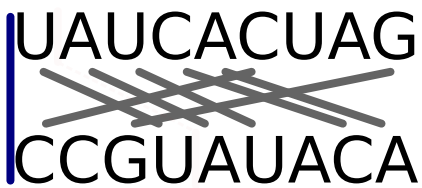

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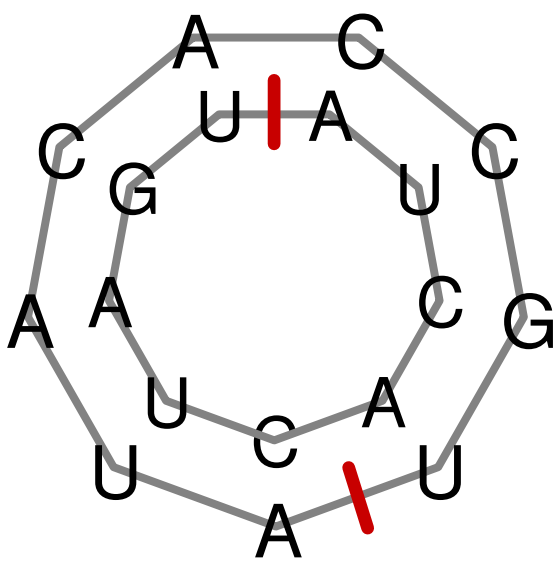

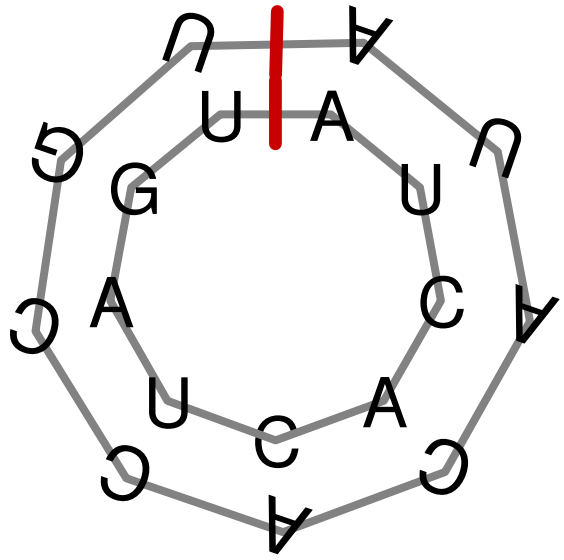

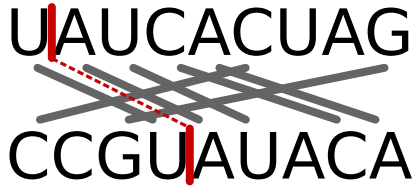

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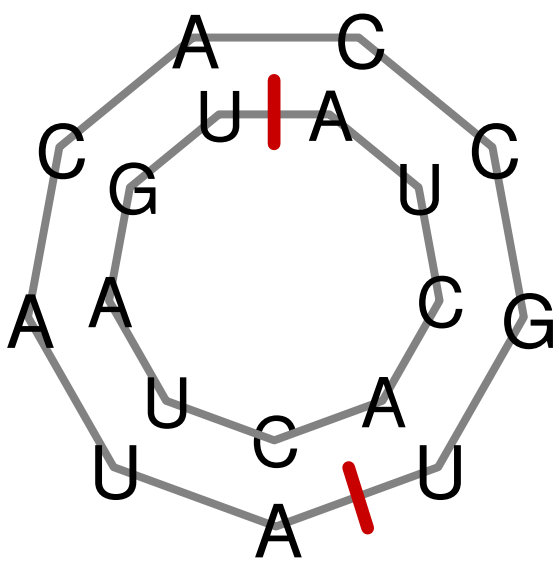

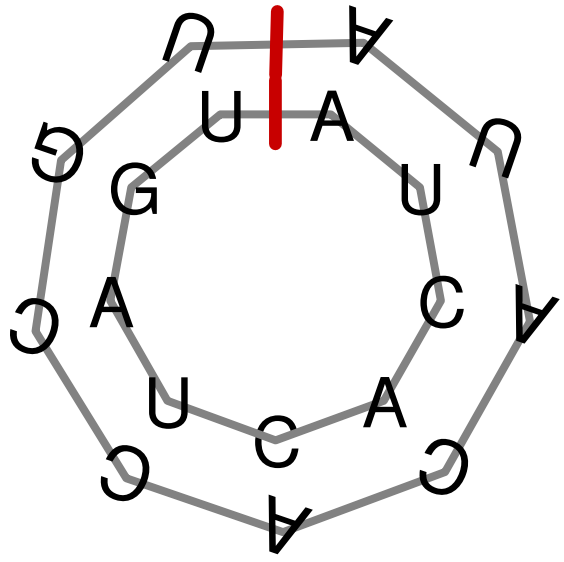

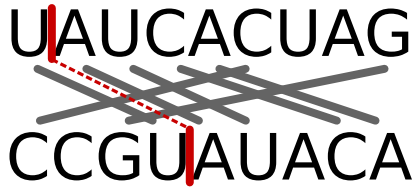

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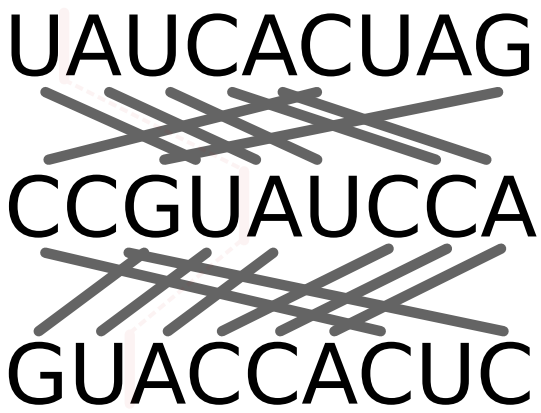
Multiple Cyclic Sequence Alignment

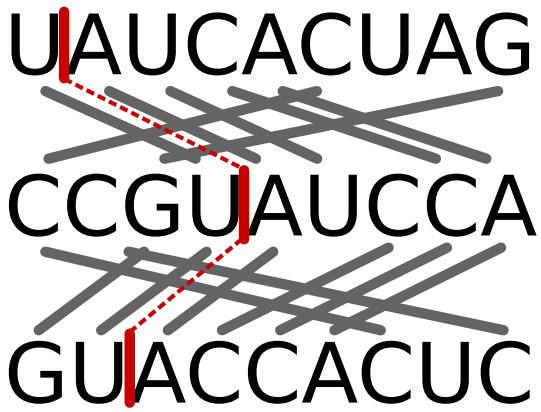


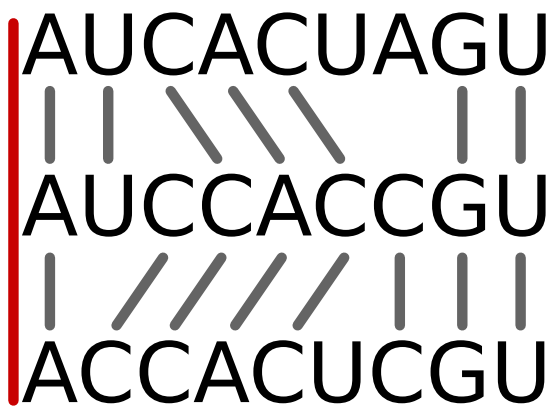
Two major problems at once

1) (Linear) multiple sequence alignment is NP-hard.

2) Search over all cuts is exponential!

Multiple Cyclic Sequence Alignment





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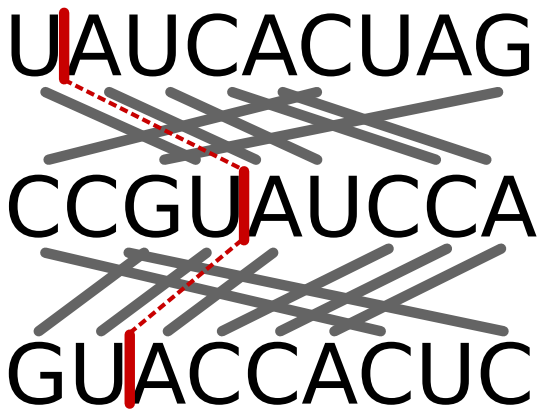

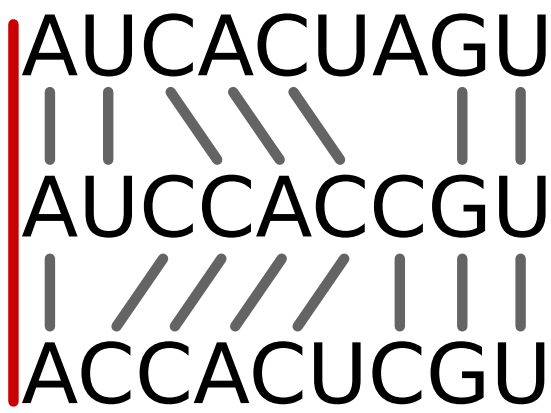

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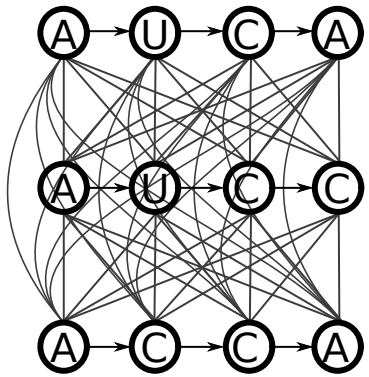
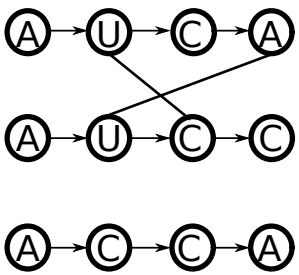
Graph-based Model: Maximum Weight Trace
(for linear alignment)

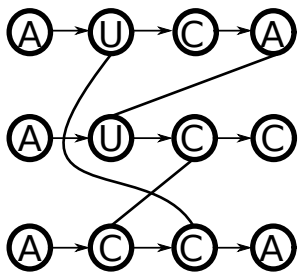
Alignment graph for input sequences (a =AUCA, b =AUCC, and c =ACCA)



MWT-problem: find trace of maximum weight, where *trace* := set of edges that corresponds to a valid MSA

Mixed cycle constraints





There are **exponentially many** mixed cycles!

Branch-and-cut: mixed cycles as cuts [Reinert et al., 1997]

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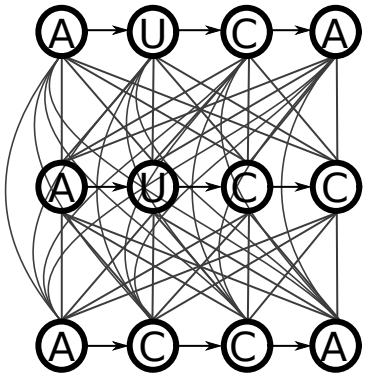

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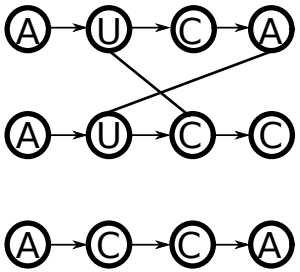

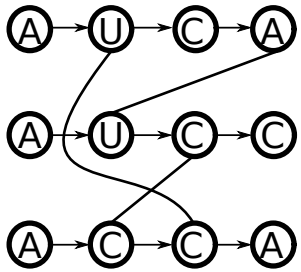

Transfer to cyclic MSA!?

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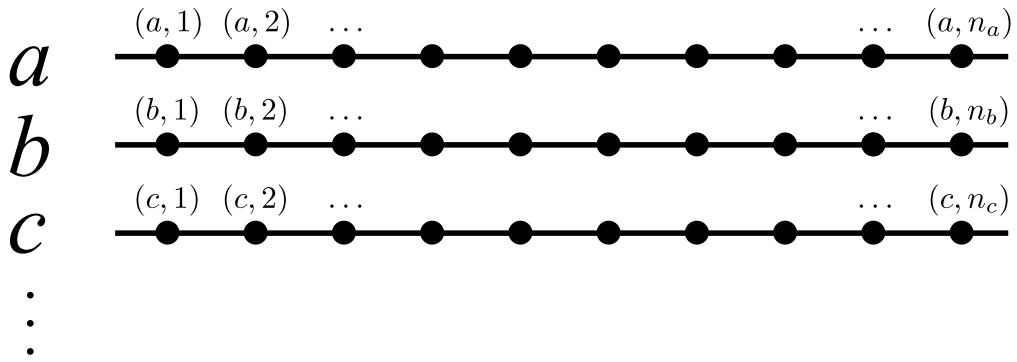
Set-theoretic Model of Linear MSA



$X :=$ set of all positions (a, k) of all sequences

Define linear order relation on classes $A, B \subseteq X$: $A \prec B$ iff

- $A \neq B$ (irreflexive)
- $\exists\, (a,i) \in A, (a,j) \in B$: $i < j$ (ordered for at least one sequence)
- $\nexists\, (a,i) \in A, (a,j) \in B$: $i > j$ (no conflicts)

Definition [Morgenstern et al., 1999]: A partition $\mathcal{A}$ is called *multiple sequence alignment* iff

- $\forall\, A \in \mathcal{A}$: at most one position per sequence,
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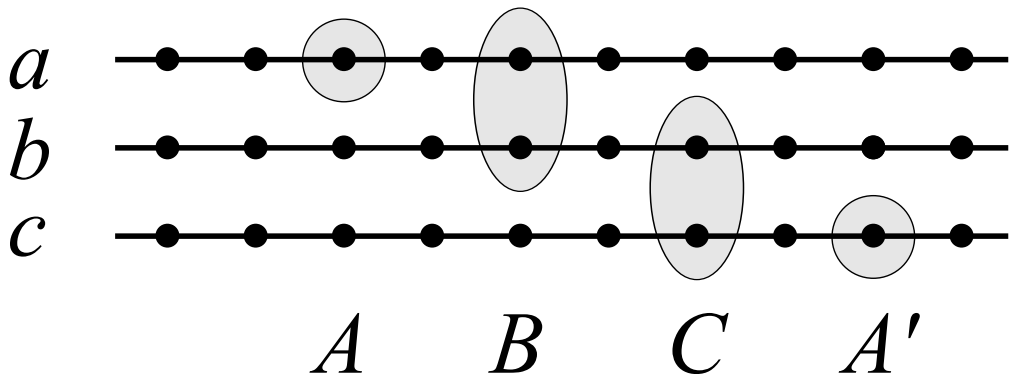

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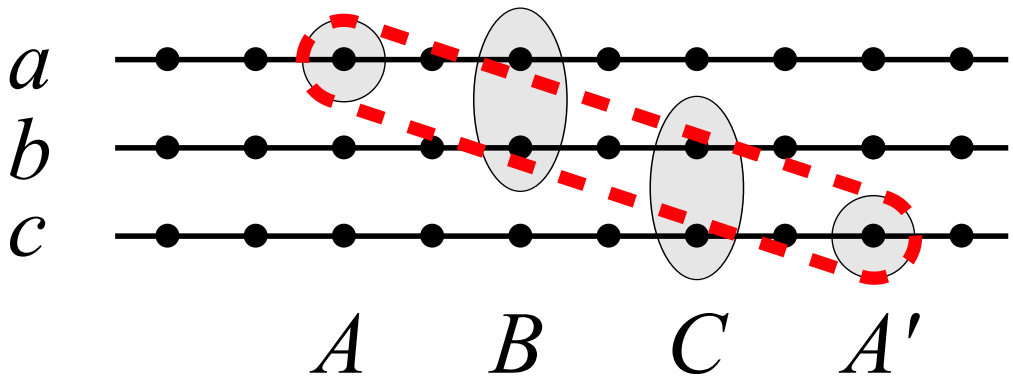

$A^+ = A \cup A'$

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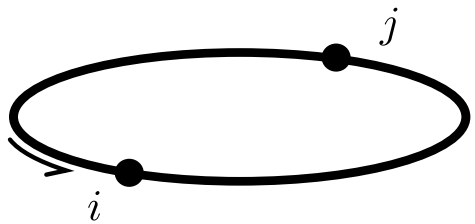
Towards a Set-theoretic Model for Cyclic MSA

Key idea: use cyclic order (in place of linear order)



The ternary relation $\lhd$ is a *cyclic order* iff

- $\lhd i\ j\ k$ implies i, j, k pairwise distinct (irreflexive)
- $\lhd i\ j\ k$ implies $\lhd k\ i\ j$ (cyclic)
- $\lhd i\ j\ k$ implies $\neg\lhd k\ j\ i$ (antisymmetric)
- $\lhd i\ j\ k$ and $\lhd i\ k\ l$ implies $\lhd i\ j\ l$ (transitive)
- If i, j, k are pairwise distinct then $\lhd i\ j\ k$ or $\lhd k\ j\ i$ (total)

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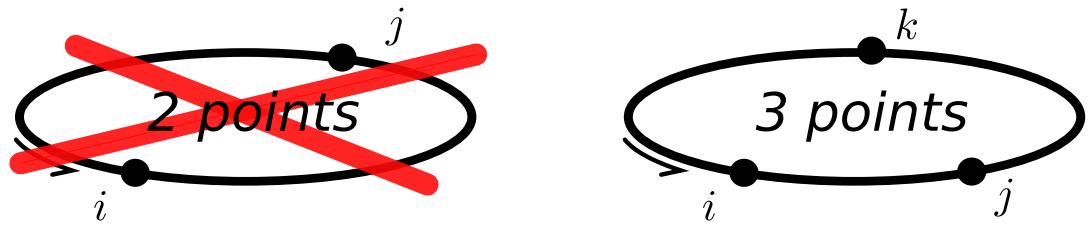

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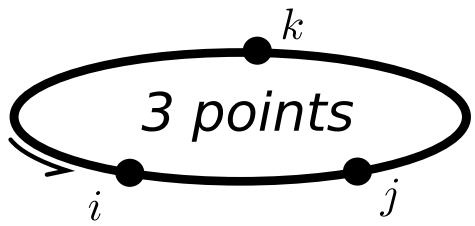

$\triangleleft\, i\, j\, k$

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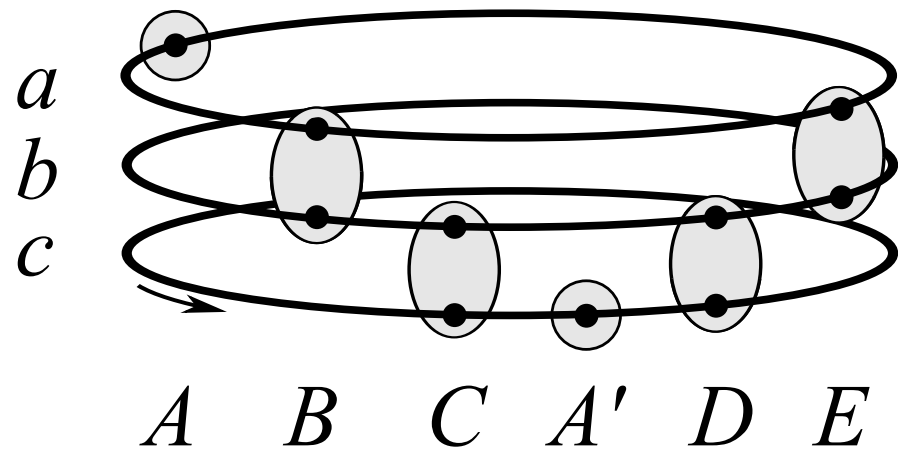
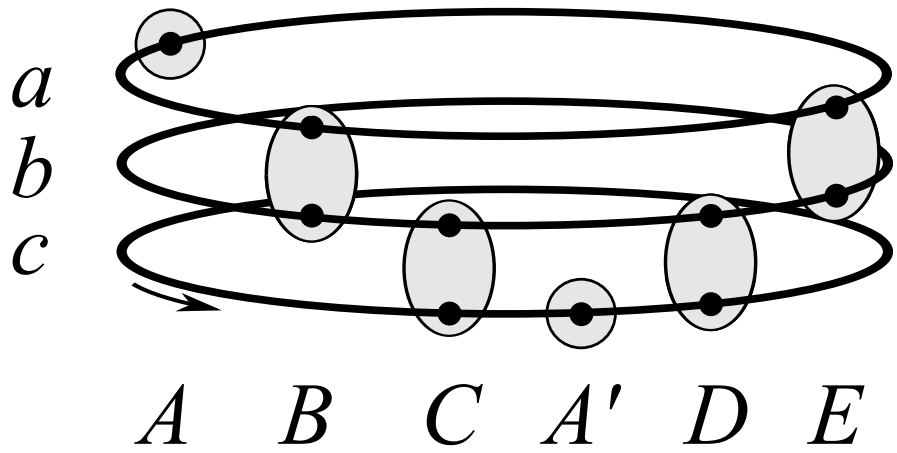
Towards a Set-theoretic Model for Cyclic MSA



Define relation $\blacktriangleleft$ on classes (of X); $\blacktriangleleft ABC$ iff

- A, B, and C are pairwise distinct (irreflexive)
- $\exists\, (a,i) \in A, (a,j) \in B, (a,k) \in C$: $\triangleleft\, i\, j\, k$ (comparable)
- $\nexists\, (a,i) \in A, (a,j) \in B, (a,k) \in C$: $\neg\triangleleft\, i\, j\, k$ (no conflicts)

Set-theoretic Cyclic MSA Model



Definition (Cyclic MSA)

A cyclic MSA is a partition $\mathcal{A}$ of X iff

- $\forall\ A \in \mathcal{A}$: at most one position per sequence,
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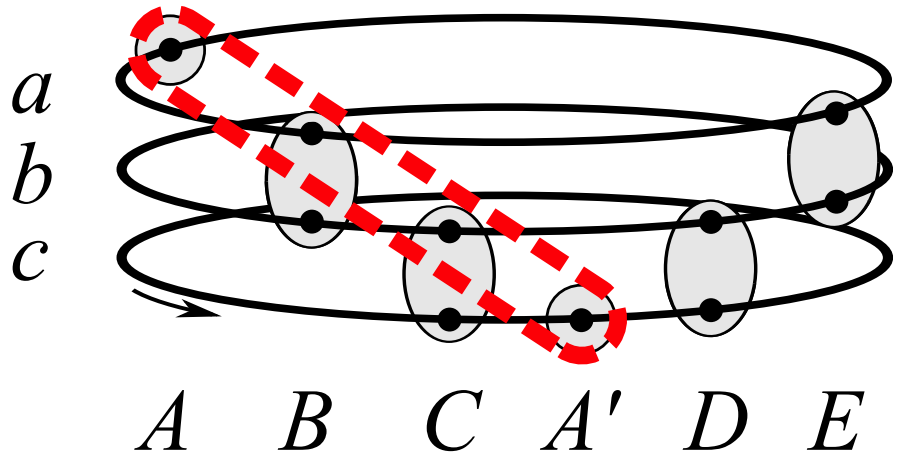

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Formal Linear MSA Model $\Rightarrow$ ILP Model

Model the linear MSA $\mathcal{A}$ by Boolean variables and linear inequations and maximize alignment score.

Variables:

- $\mathbf{P}x\alpha = 1$ iff $x = (a, i)$ is in class α of the partition $\mathcal{A}$
- $\mathbf{O}\alpha\beta = 1$ iff $\alpha \overline{\prec} \beta$
- ... (further variables for objective function: base matches: **E**, affine gap cost: **G**, **GO**, RNA structure matches **B**)

Integer Linear Program (ILP):

max alignment-score($\mathbf{E}, \mathbf{G}, \mathbf{GO}, \mathbf{B}$)

s.t.

- Variables $\mathbf{P}x\alpha$ represent a partition of $\mathcal{A}$
- Variables $\mathbf{O}\alpha\beta$ represent $\overline{\prec}$
- $\mathbf{O}\alpha\beta$ describe a partial order
- . . . (constrain the variables of the objective function)

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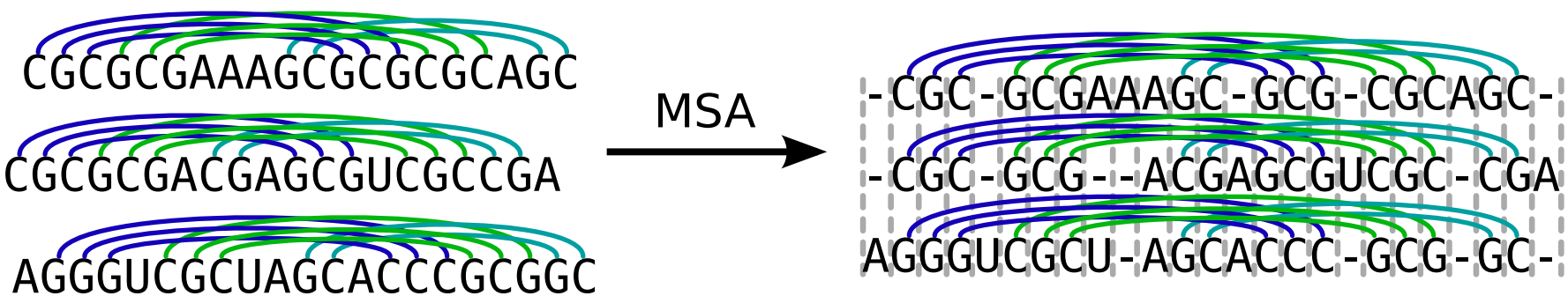
- ~~$\mathbf{O}\alpha\beta$~~ **$\mathbf{O}\alpha\beta\gamma$** describe a partial **cyclic** order
- . . . (constrain the variables of the objective function)

Preliminary Results with CPLEX Solver

Instance			Model	Solving Time (s)	
#seqs	length	structure		95% opt.	optimal
3	10	2-knot	linear	1.4	1.4
3	10	2-knot	cyclic	170	176
3	10	2-knot	cyclic	229	273
3	15	3-knot	linear	129	143
3	20	3-knot	linear	287	> 300
3	20	3-knot	linear $\Delta 3$	8.4	8.4
4	10	2-knot	linear	10	28
4	10	2-knot	linear $\Delta 3$	4.8	6.4



Conclusions

- Systematic analysis of cyclic MSA
- Framework for linear and cyclic MSA; single difference: **order**
- Only polynomially many constraints (graph-based: exponential)
- Model is flexibly extensible:
  structure-based alignment of circular RNAs
- Current ILP model: CPLEX solves only small instances
- Future work:
  - are other solvers more suitable?
  - "tricks" like variable reduction
  - transfer "critical mixed cycles" from linear to cyclic MSA (some reassuring theoretical results given in the paper)

  $\Rightarrow$ branch-and-cut or Lagrange relaxation for cyclic MSA

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- Systematic analysis of cyclic MSA
- Framework for linear and cyclic MSA; single difference: **order**
- Only polynomially many constraints (graph-based: exponential)
- Model is flexibly extensible:
  structure-based alignment of circular RNAs
- Current ILP model: CPLEX solves only small instances
- Future work:
  - are other solvers more suitable?
  - "tricks" like variable reduction
  - transfer "critical mixed cycles" from linear to cyclic MSA (some reassuring theoretical results given in the paper)

  $\Rightarrow$ branch-and-cut or Lagrange relaxation for cyclic MSA

Thank you!