SPARSE: Quadratic Time SA&F of RNAs without Sequence-Based Heuristics

Beijing, RECOMB 2013

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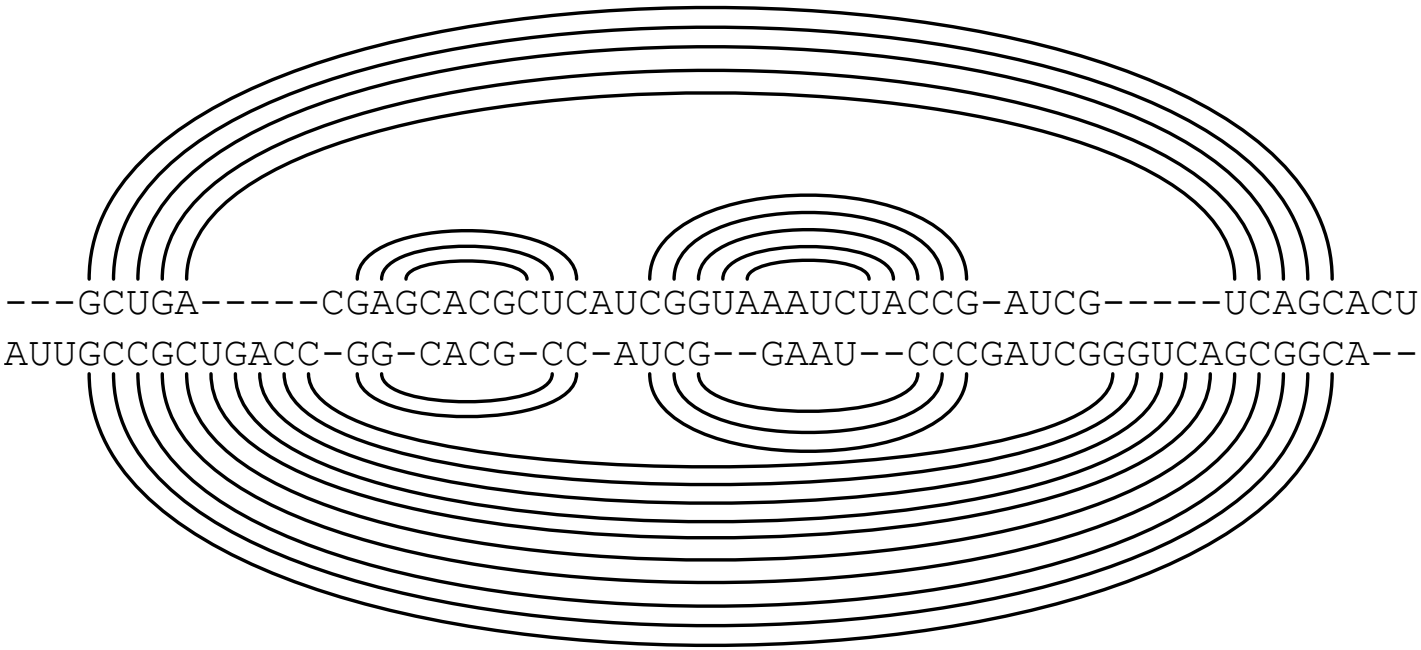
University of Leipzig
University of Freiburg

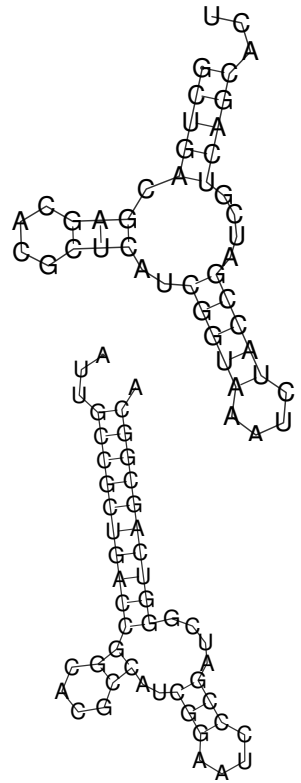
Simultaneous Alignment and Folding [Sankoff]

Given: A = GCUGACGAGCACGCUCAUCGGUAAAUCUACCGAUCGUCAGCACU

& B = AUUGCCGCUGACCGGCACGCCAUCGGAAUCCCGAUCGGGUCAGCGGCA

Find:





sequence similarity + energy A + energy B → opt

where alignment, structure A, & structure B are **compatible**

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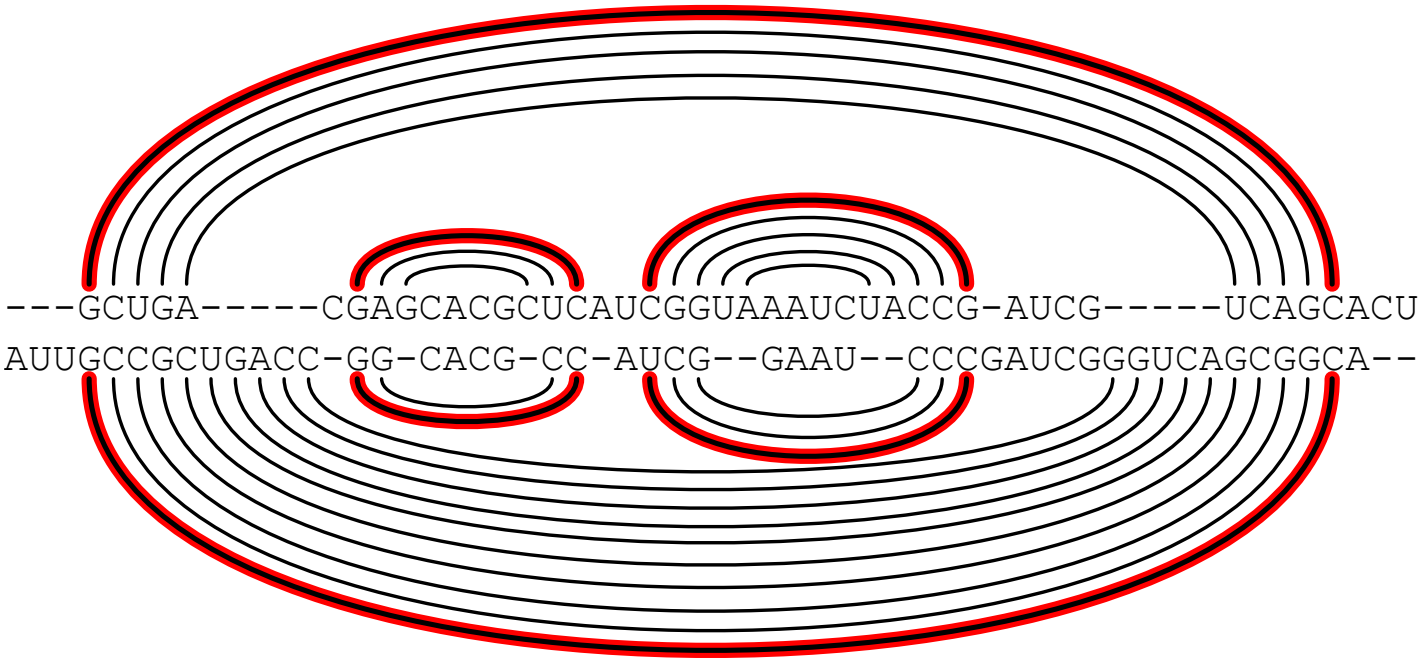

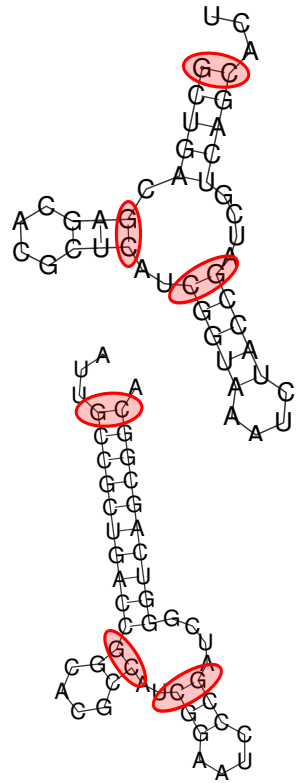

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Sankoff's Algorithm

Dynamic Programming

RNA Energy Minimization [Zuker]

$\times$

Sequence Alignment

$O(n^6)$ = **"extreme computational cost"**

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Sankoff-style Approaches

HEAVY

Dynalign
FoldAlign

- Sankoff implementations
- heavyweight energy model
- sequence-based heuristics

LIGHT

PMcomp

- lightweight energy model
- base pair probabilities

LocARNA

+ sparsifies structure space (ensemble-based)

- improves time and space

RAF

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SPARSE

- strong sparsification w/o sequence-based heuristics

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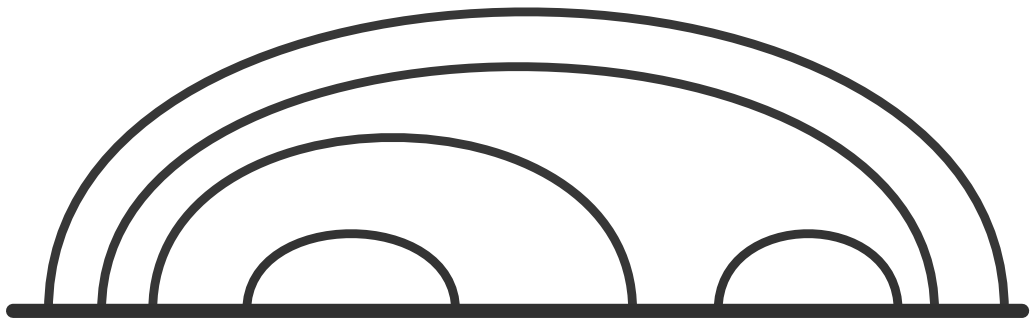
PMcomp's Trick – Lightweight SAF

Sankoff: **sequence similarity**
+ energies of A and B → **opt**

- **energies** composed of loop energies



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  Base Pair Maximization [Nussinov] × Sequence Alignment

- **cheaper but same complexity**

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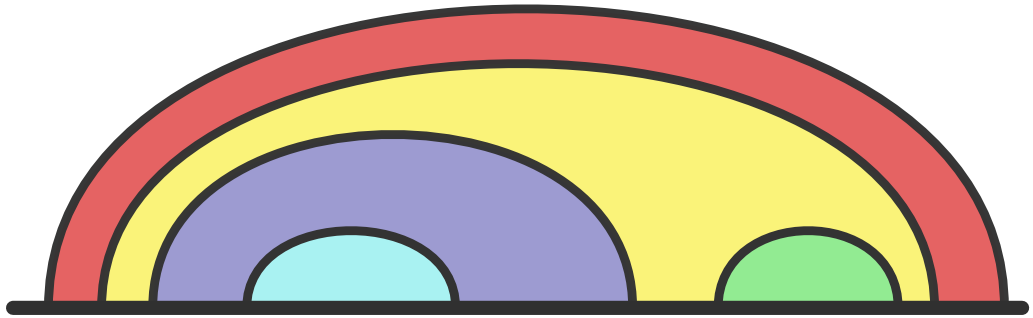

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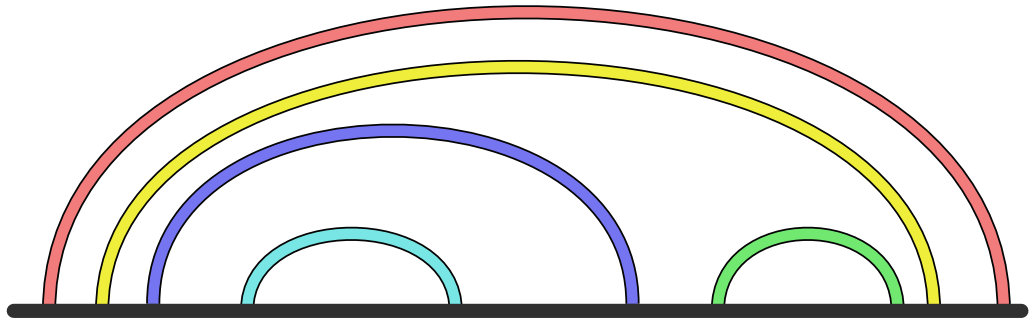

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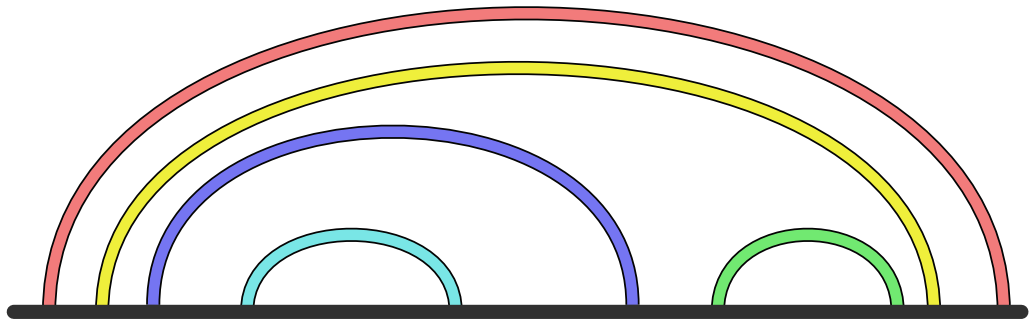

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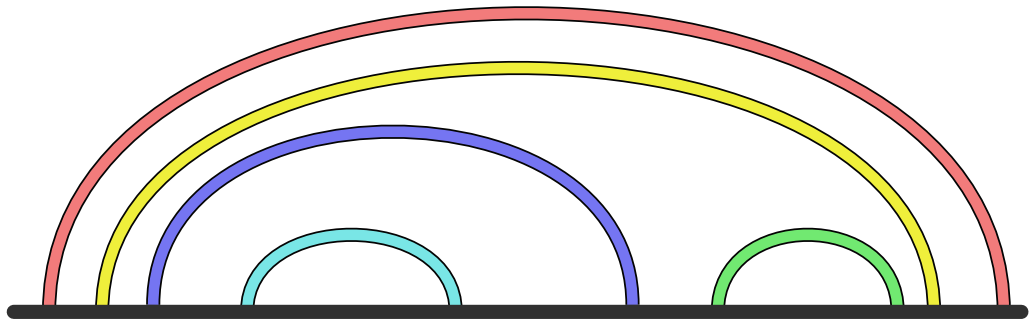

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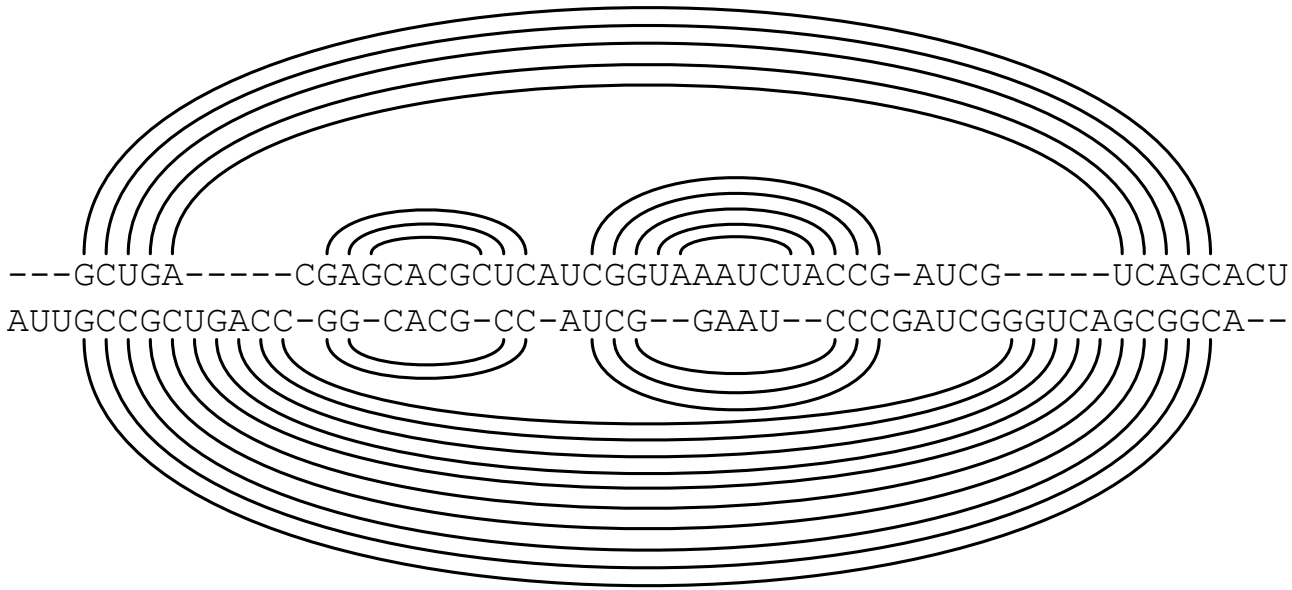

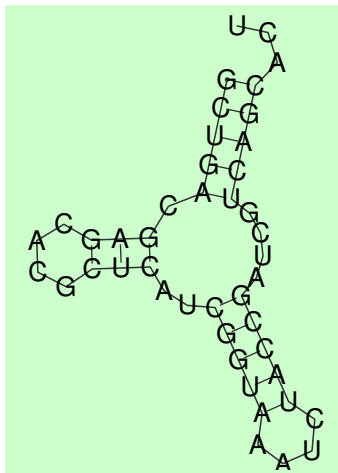

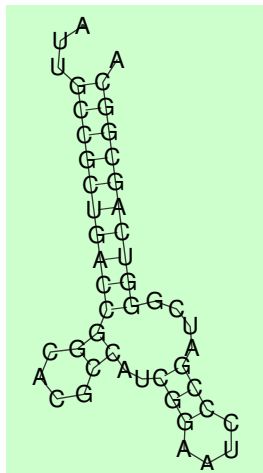

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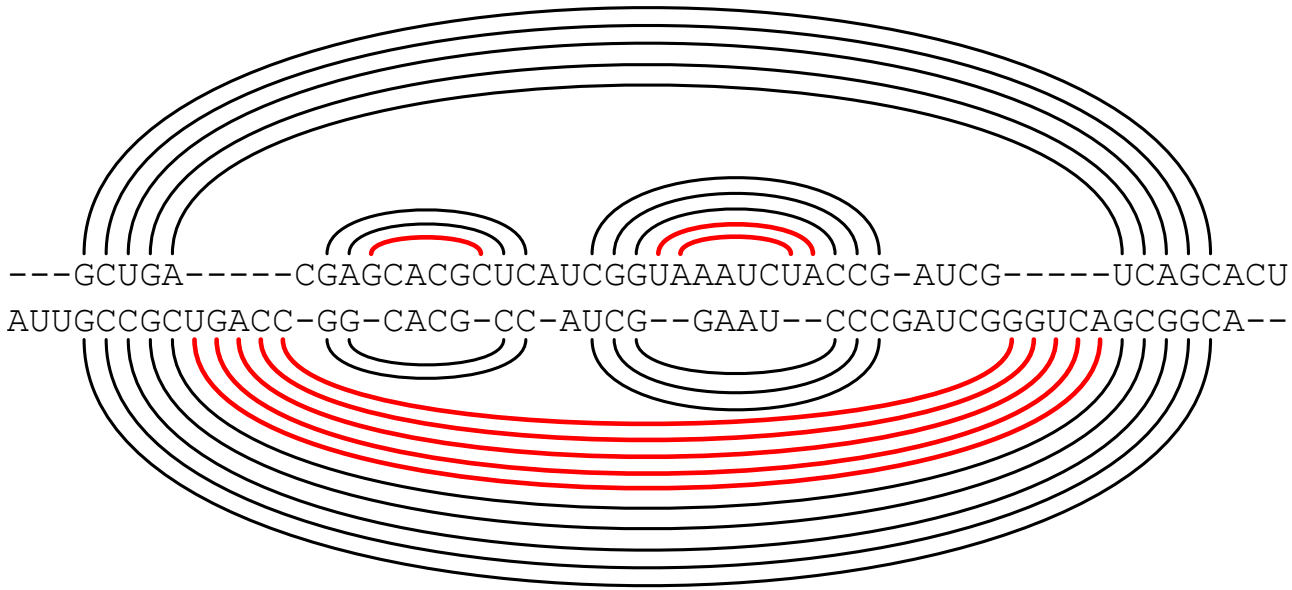

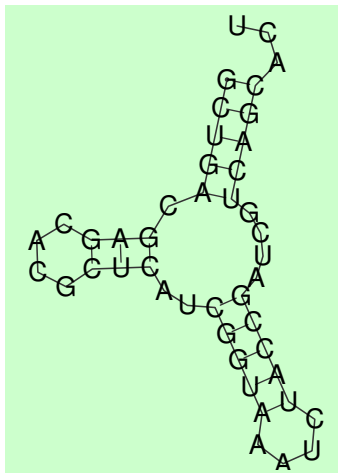

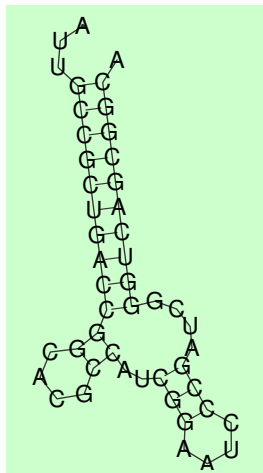

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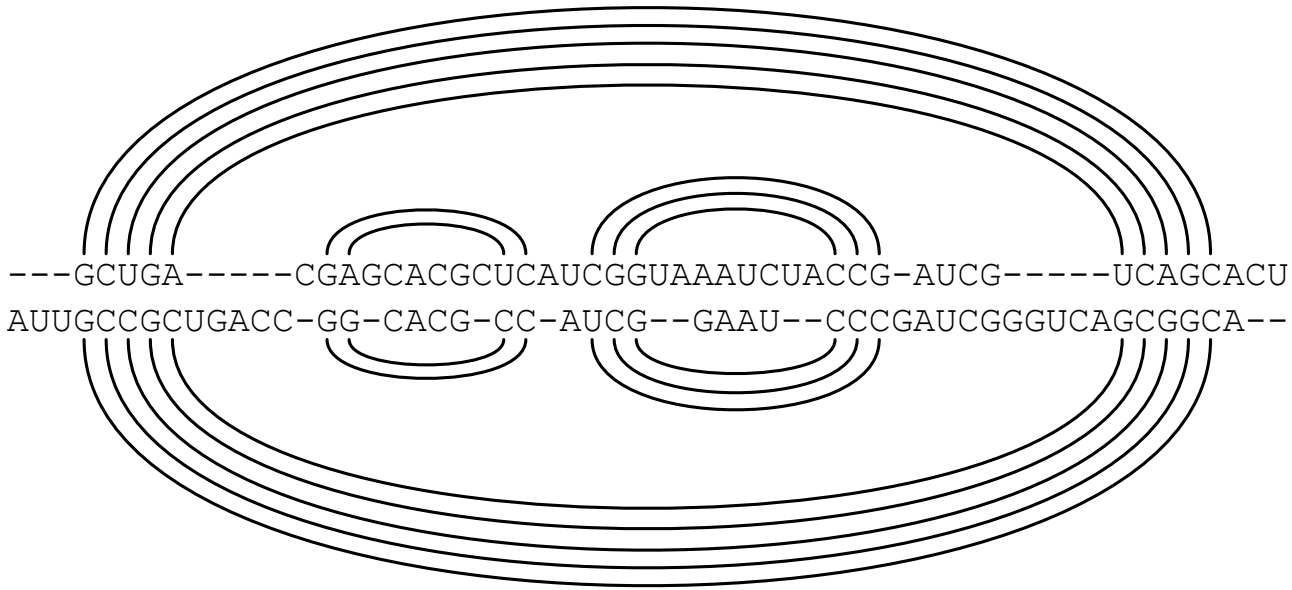

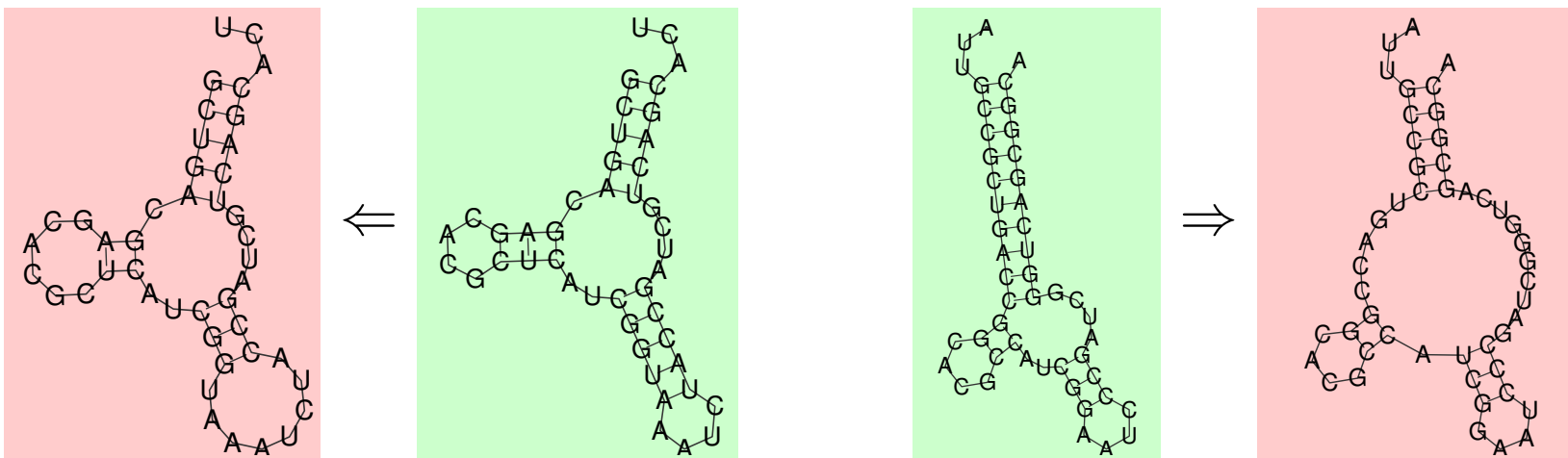

PARSE — THE Lightweight Sankoff Algorithm

(PARSE = Prediction and Alignment of RNAs using Structure Ensembles)

- **lightweight** (PMcomp pseudo-energy)

  & **complete** (Sankoff's compatibility)

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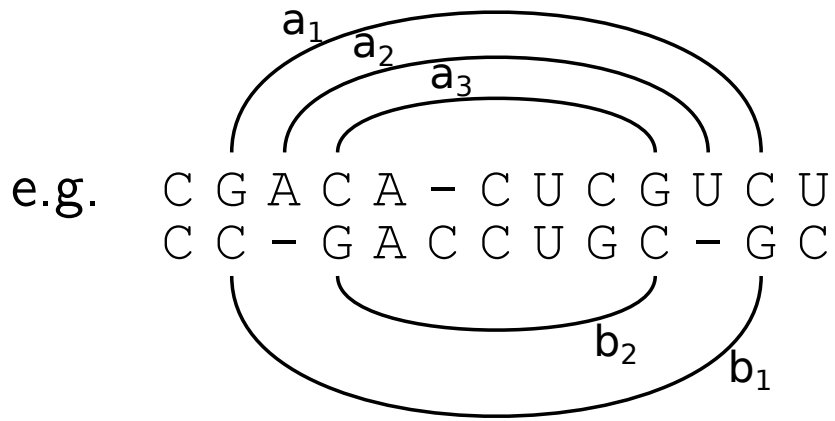

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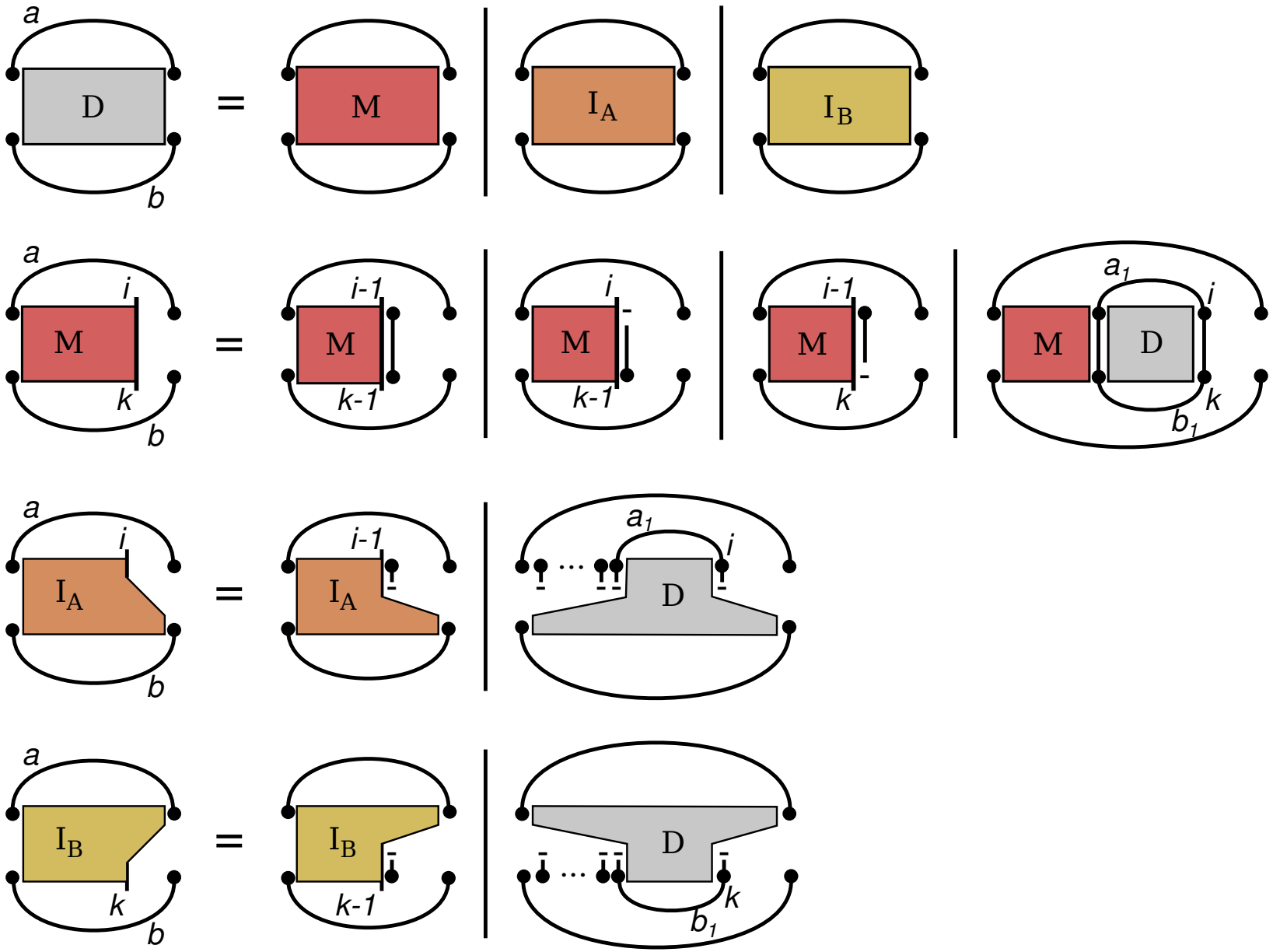

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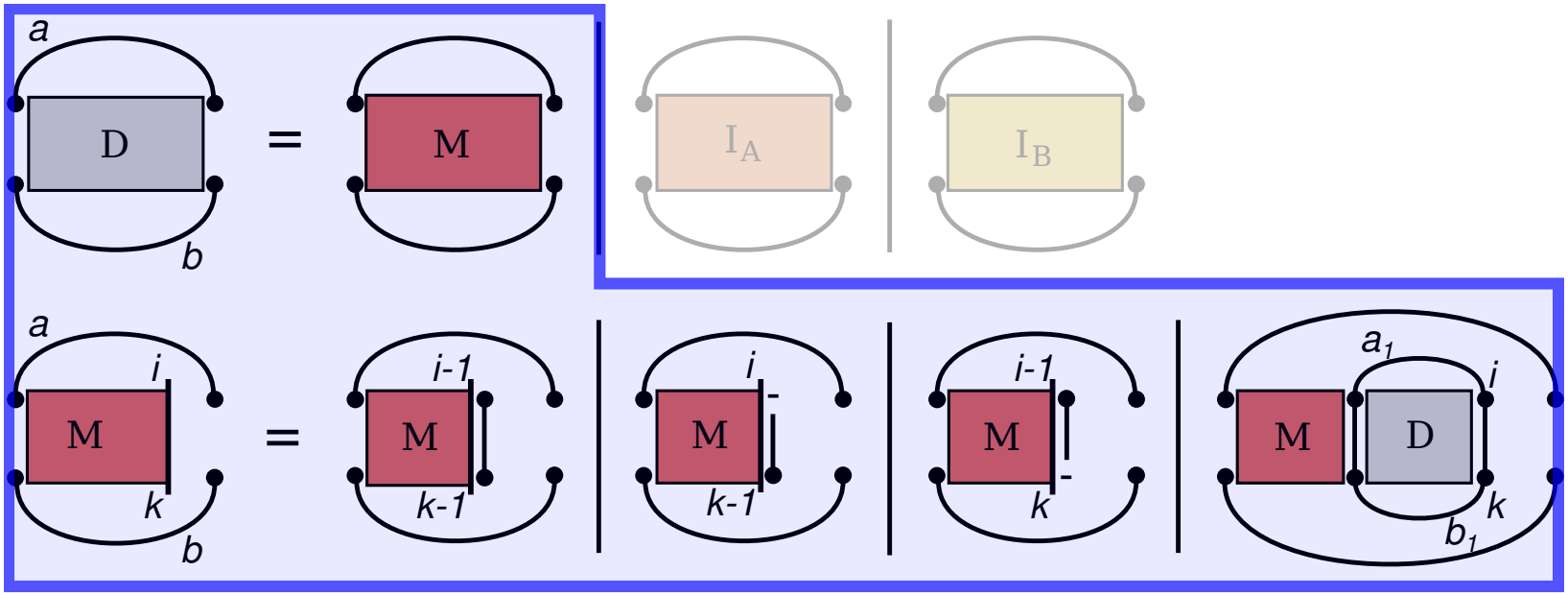
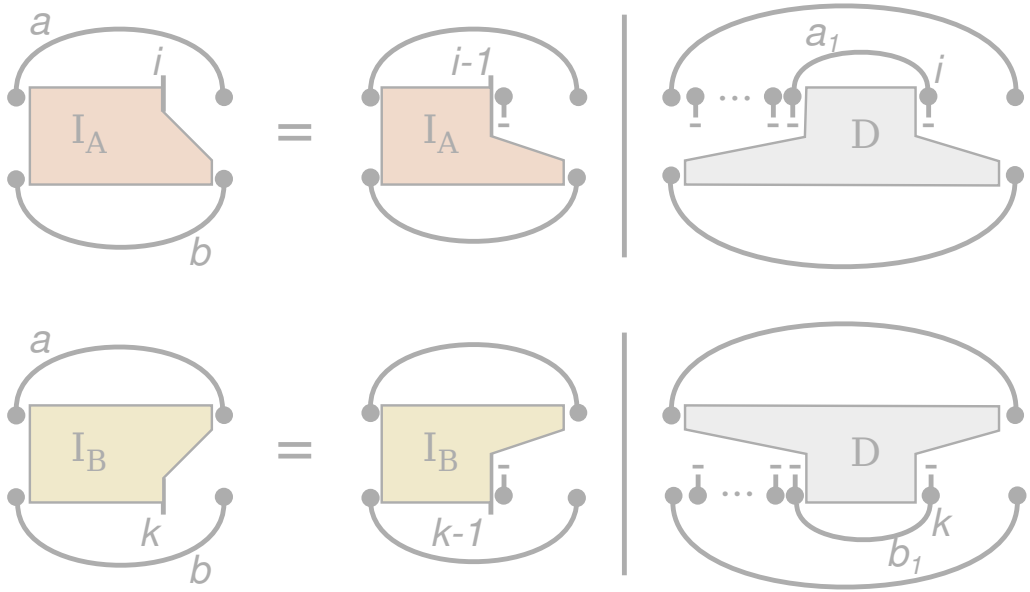


PMcomp/ LocARNA-like core



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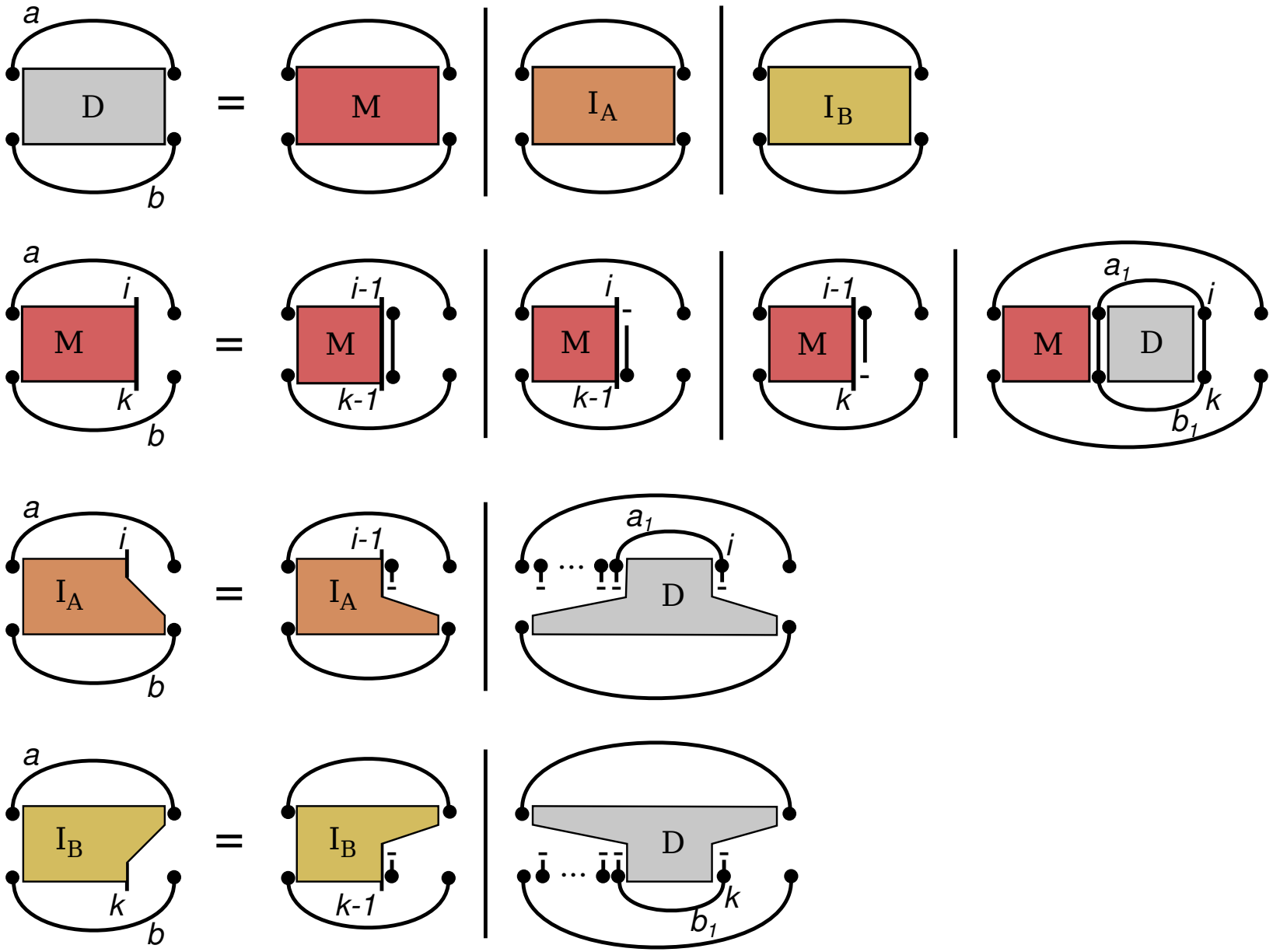
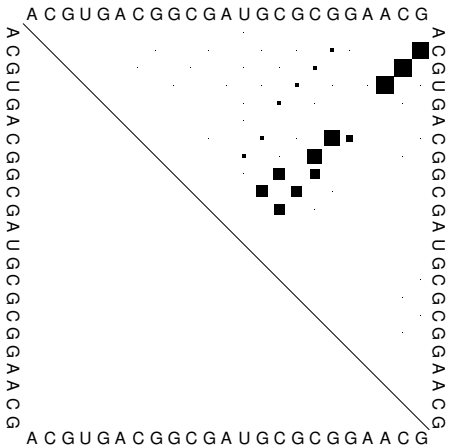


LocARNA's Trick: Ensemble-based Sparsification

- **Sparsify structure ensemble**



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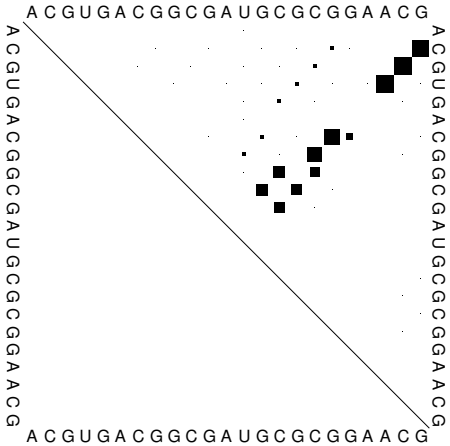

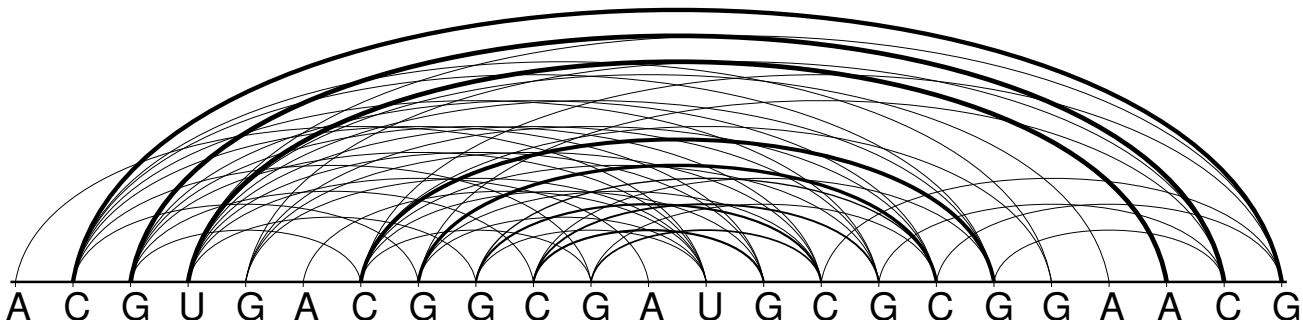

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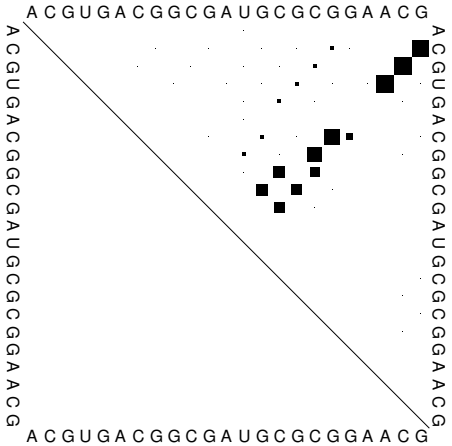

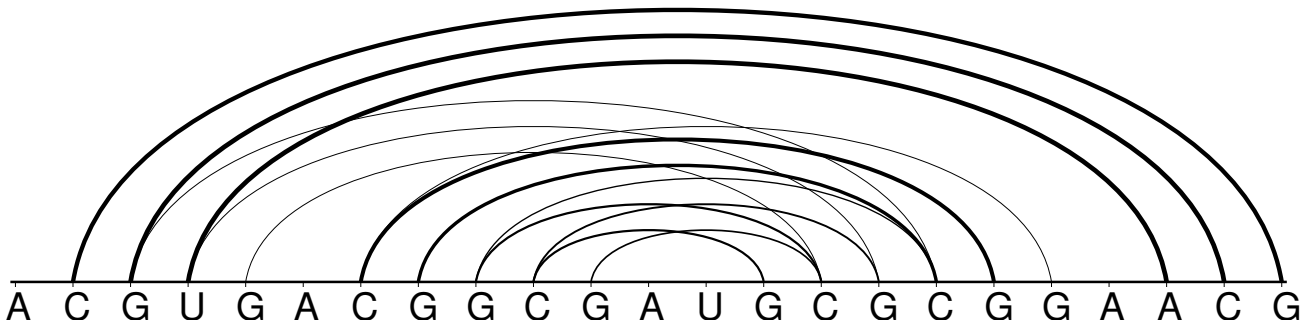

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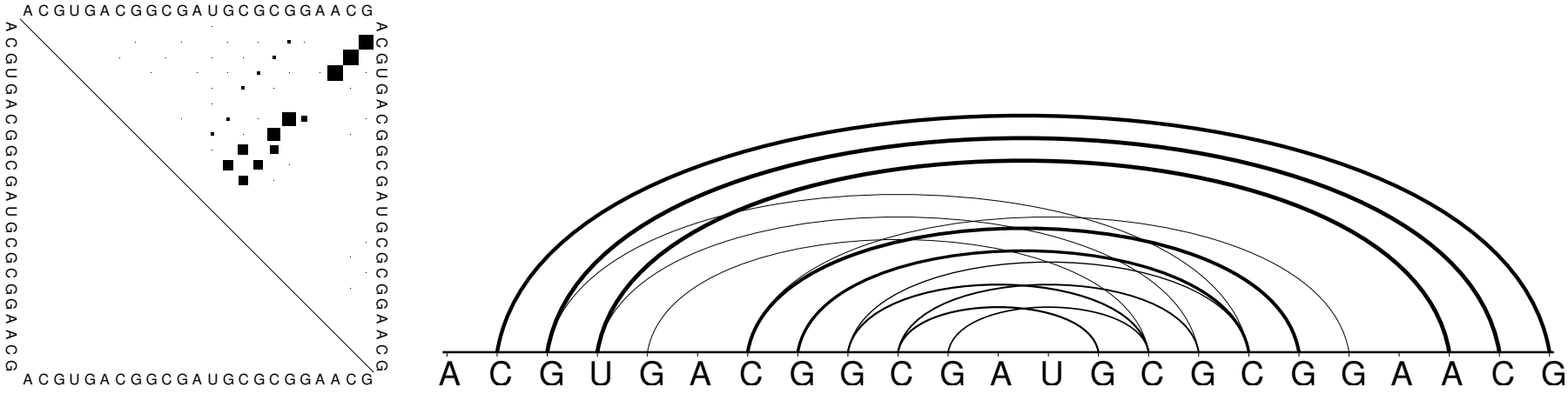

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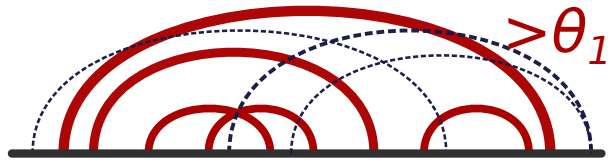
SPARSE: Novel Ensemble-based Sparsification*



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(*) confer LocARNA's "old" sparsification:

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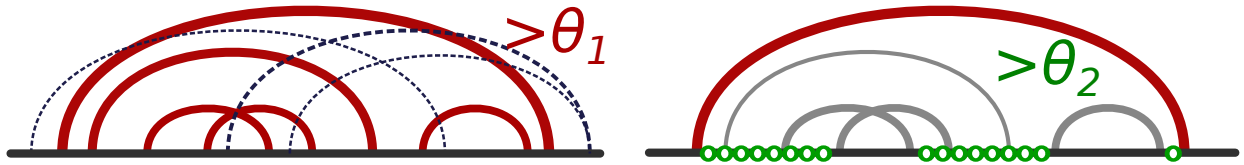

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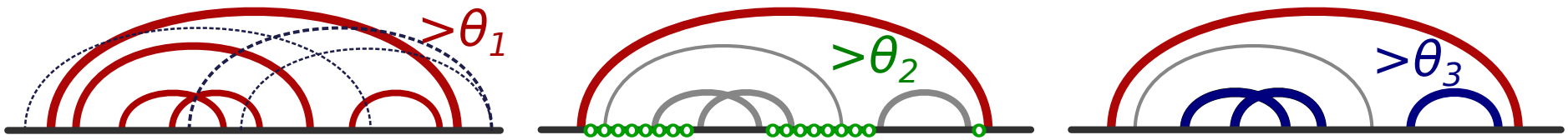

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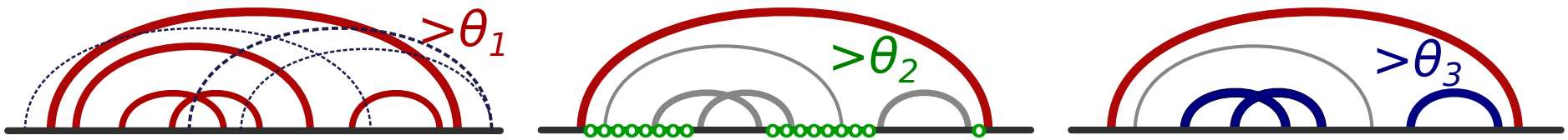

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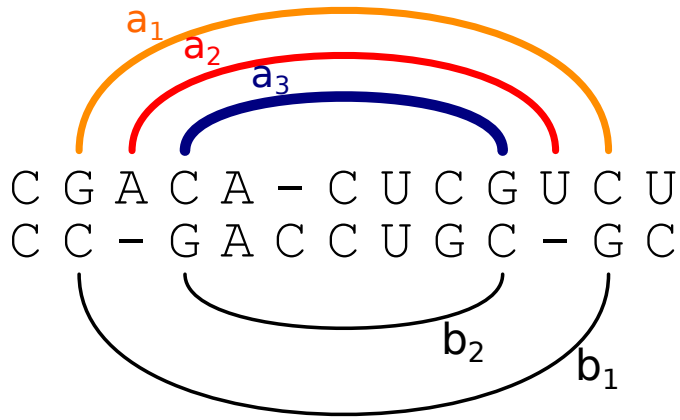
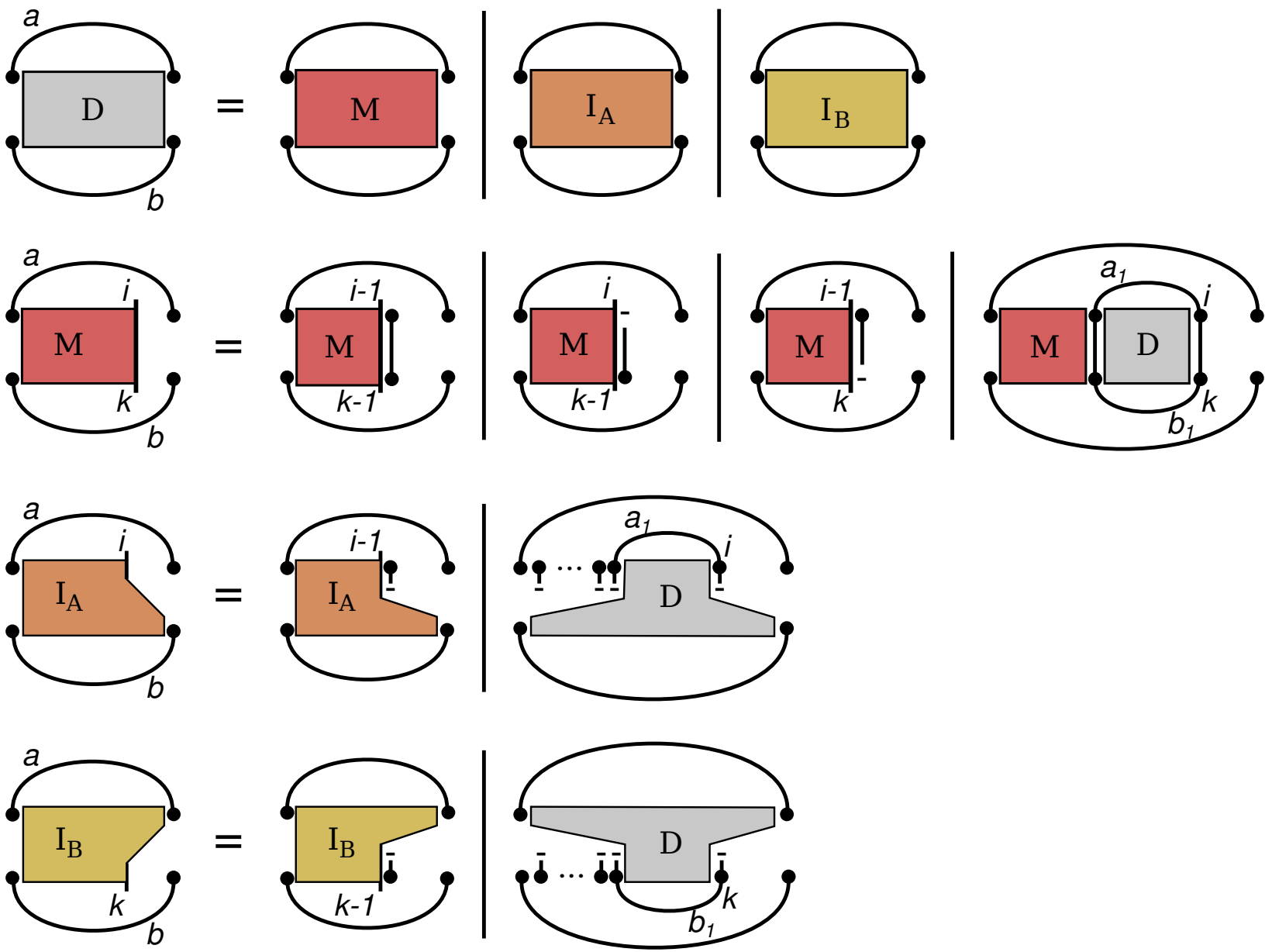


a_3 in loop a_2 ✓
but a_3 in loop a_1 ✗

a_2 ✗ $\Longrightarrow$ a_3-b_2 ✗

Thresholds in Recursions Cases



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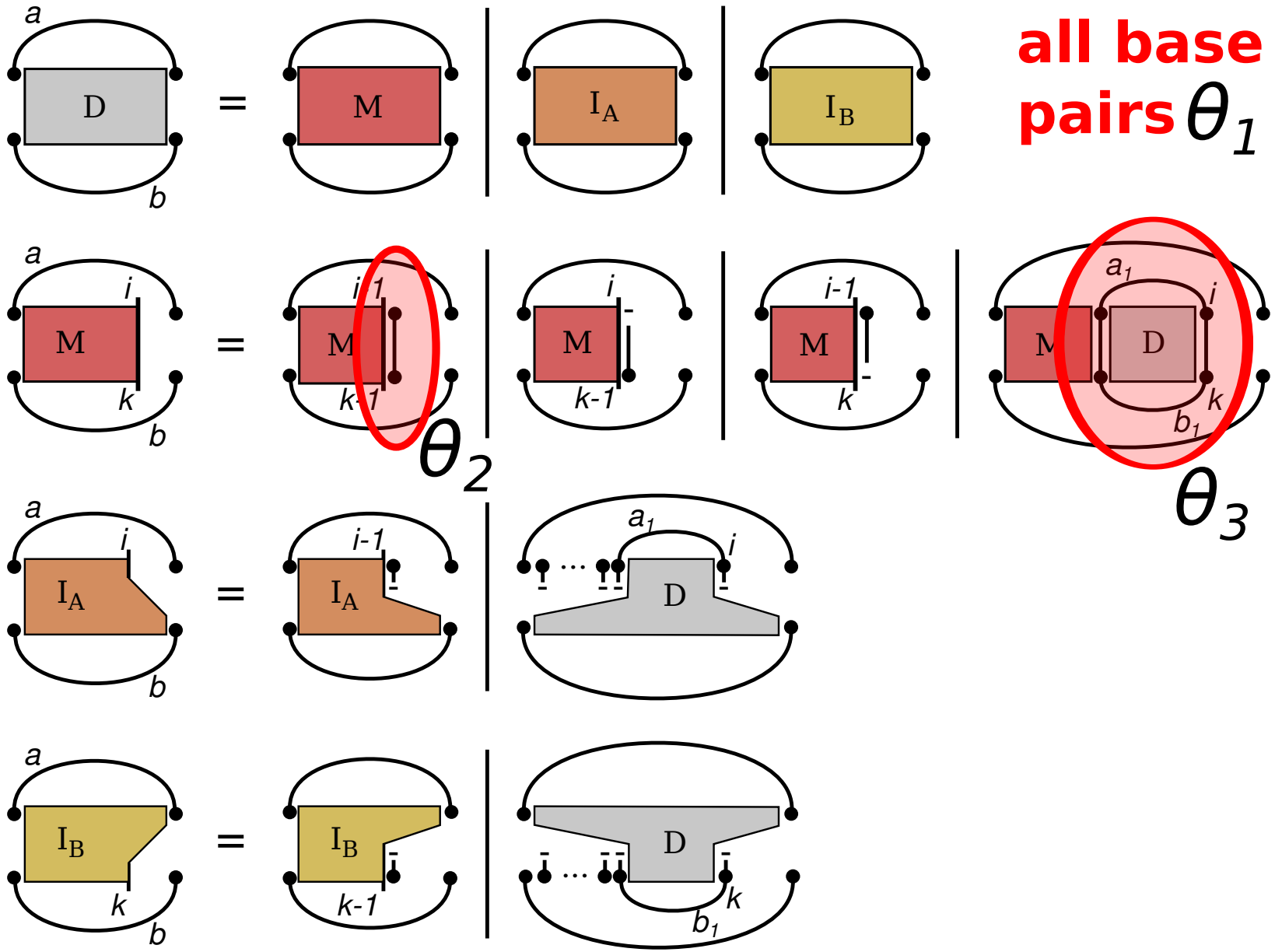
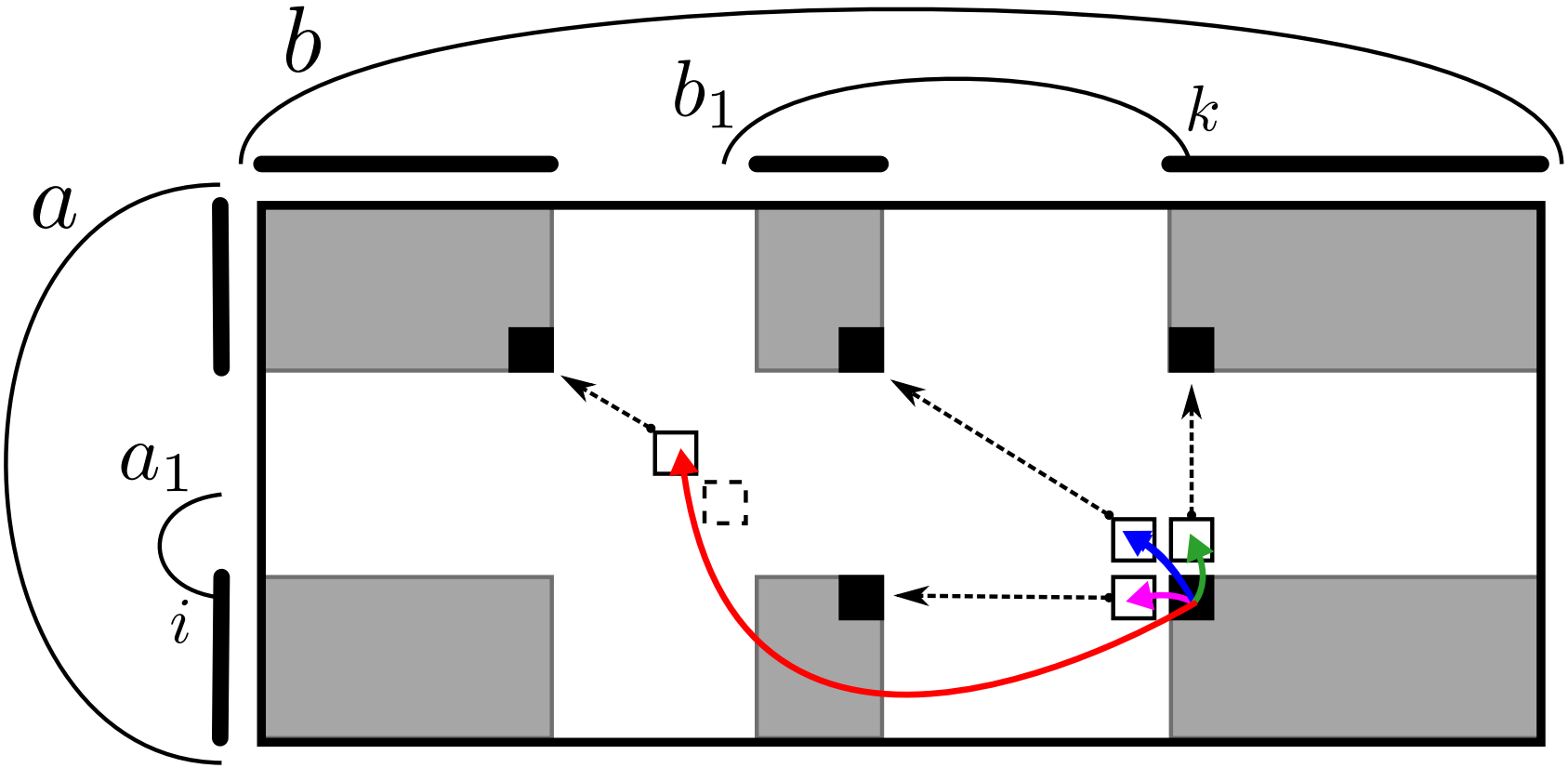
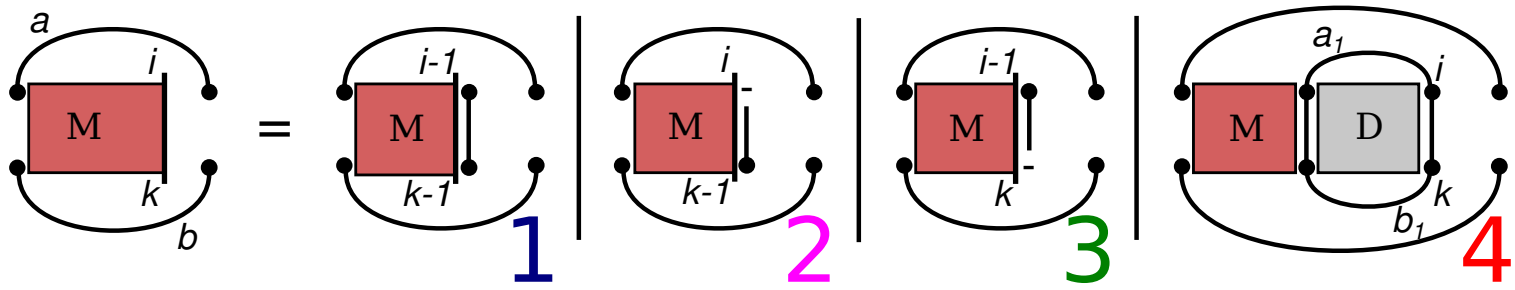


Modify Evaluation to Save Time





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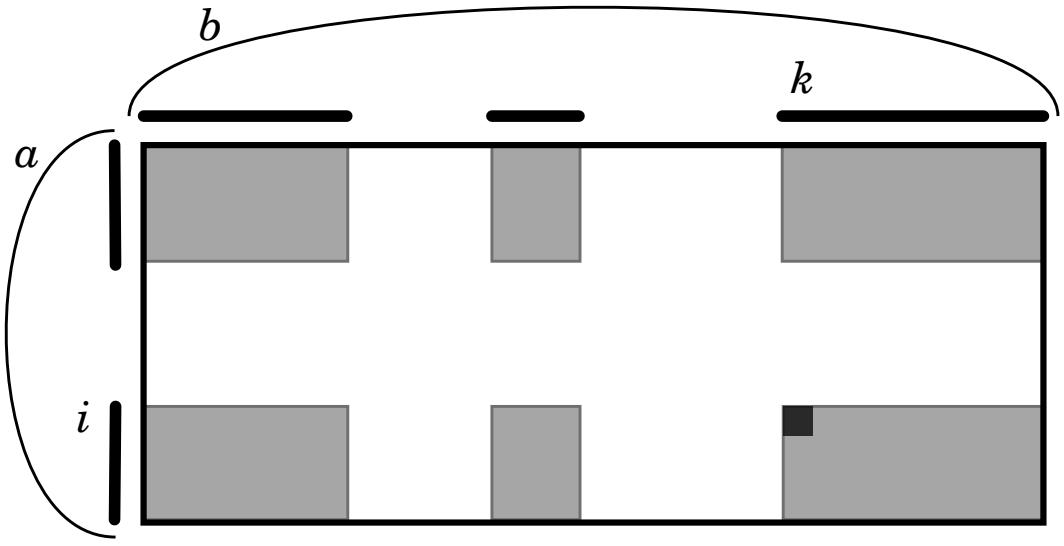

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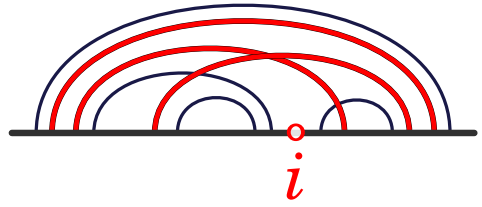

$\Rightarrow$ less than $1/\theta_2$

A: each (i, k) in only constant number of matrices $\square$

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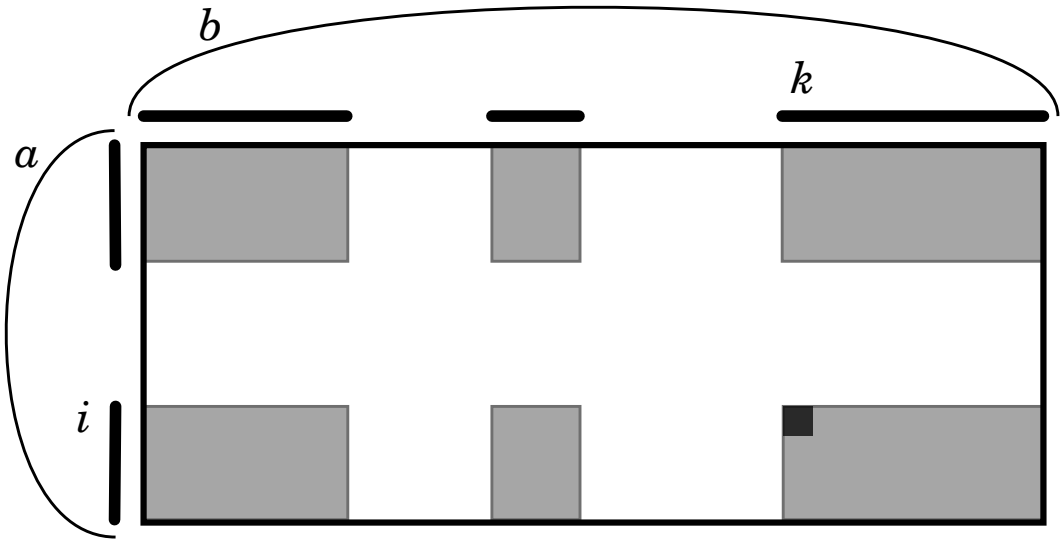

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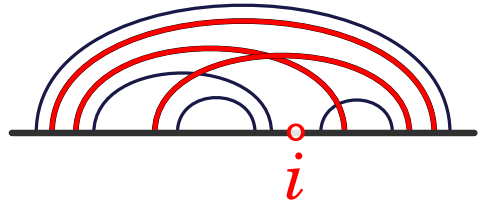

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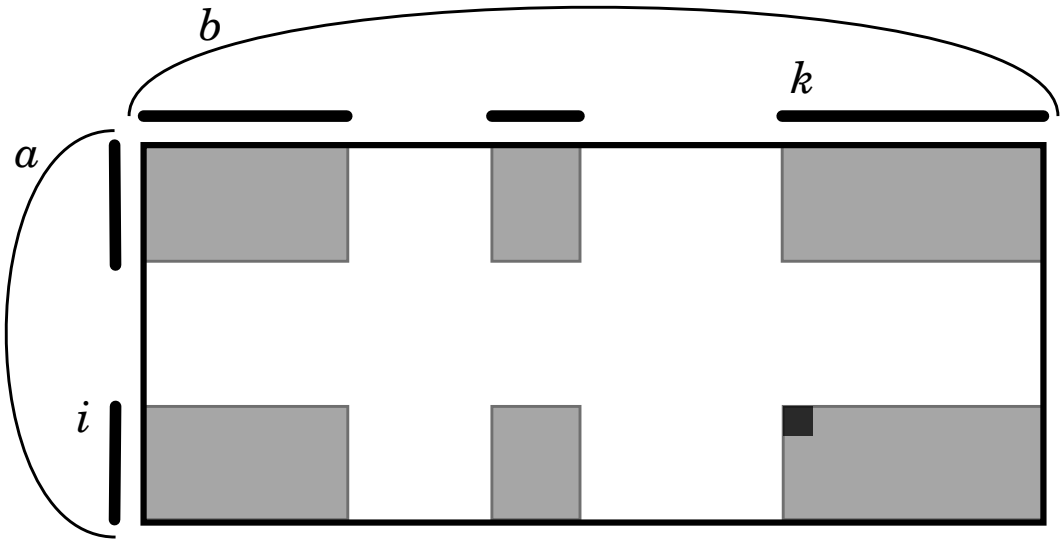

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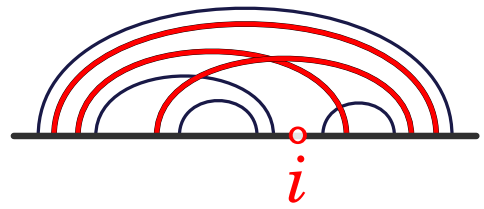

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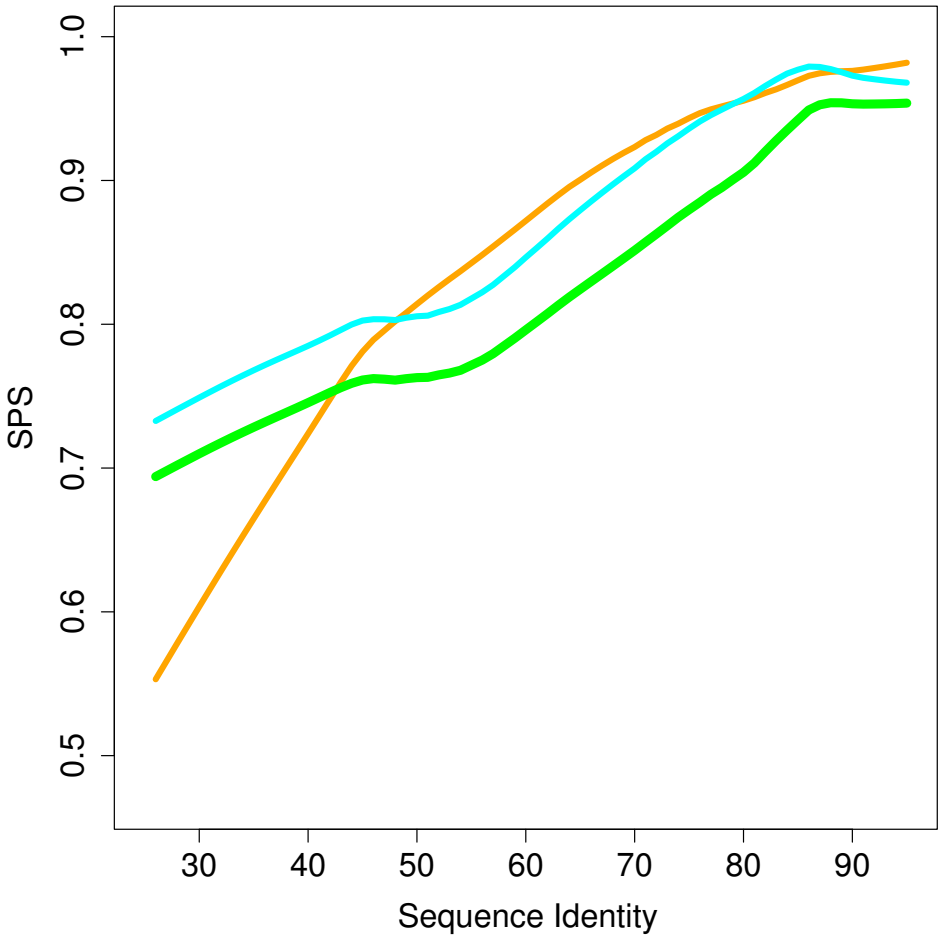
Run-times and Speedup

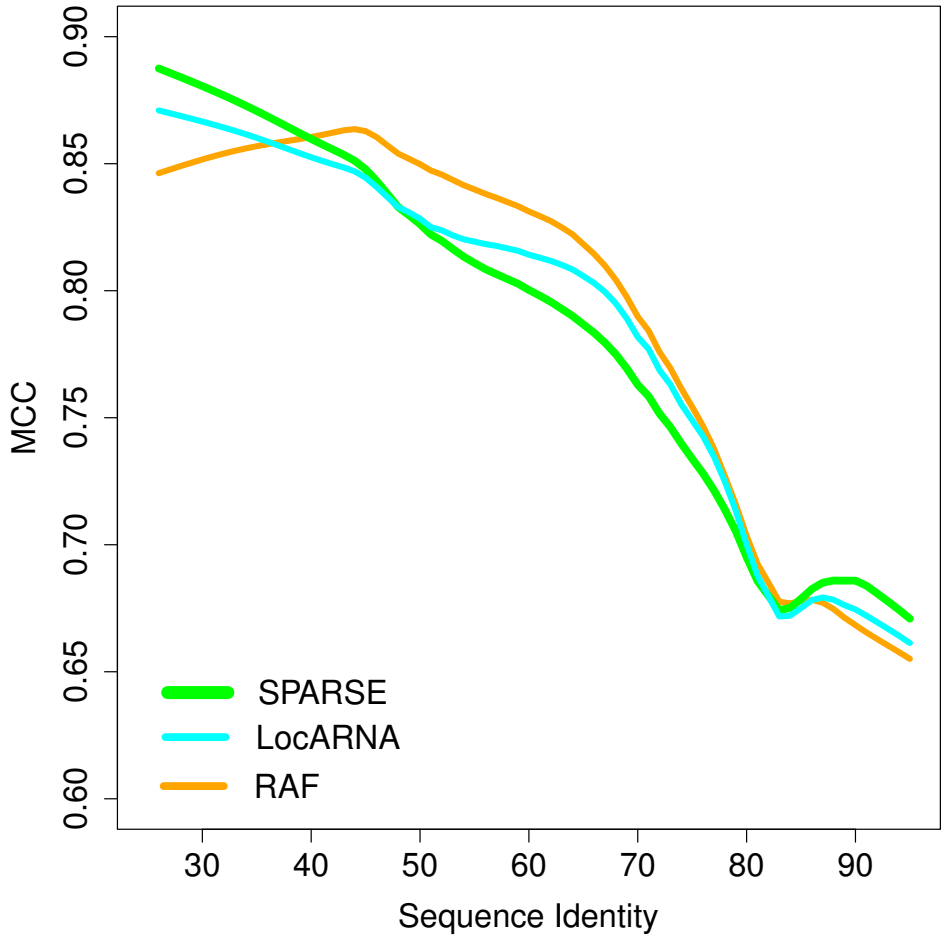
Tool	Sparsification			Mean Time per Instance	Speedup vs. LocARNA
	θ_1	θ_2	θ_3		
LocARNA	1e-3	-	-	2.02s	1.0
SPARSE	1e-3	1e-5	1e-4	0.92s	2.2
RAF	2e-3	-	-	0.37s	5.5

Bralibase 2.1, pairwise alignments

Alignment and Prediction Accuracy (Bralibase 2.1, 3-way alignments)



SPS: alignment quality



MCC: prediction quality

Conclusions

SPARSE: very efficient RNA alignment without sequence-based heuristics

- PARSE is ***THE*** lightweight Sankoff-variant (cf. PMcomp)
  - predicts deleted/inserted base pairs; like original SAF
- SPARSE = **Sparsified** PARSE
  - Novel **ensemble-based sparsification** (*in-loop* probabilities)
  - No sequence-based heuristics
  - Speeds up SAF: **Quadratic Time** [$\leftarrow O(n^6)$]

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Thanks

. . . for your attention

. . . to my coauthors

- Christina Schmiedl 
- Milad Miladi 
- Mathias Möhl 
- Rolf Backofen 

. . . and the German Research Foundation DFG

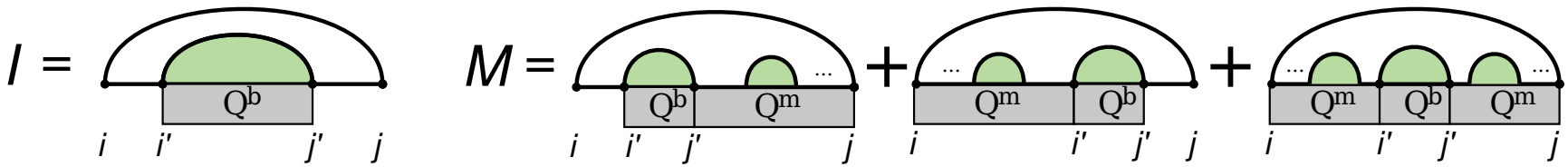
Appendix

Computing "In Loop" Probabilities

from McCaskill matrices: Q_b, Q_m

Pr[(i',j') base pair in loop of (i,j)]

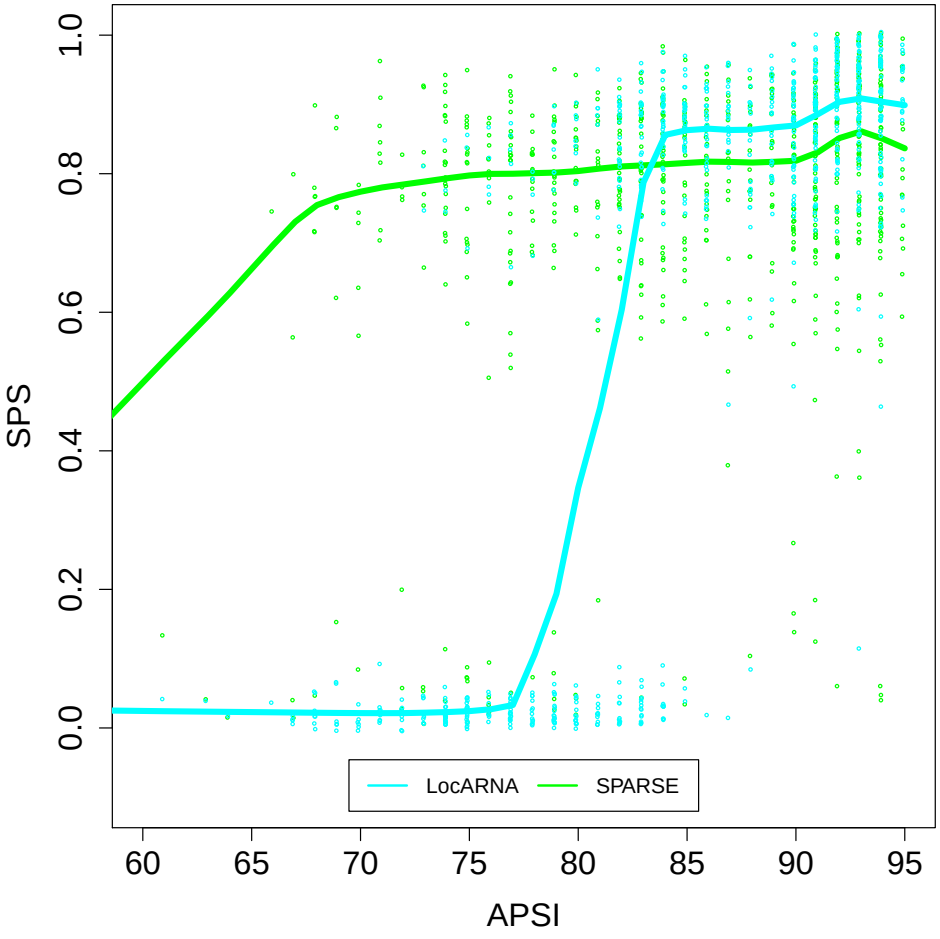
$$=(I+M)/Q$$

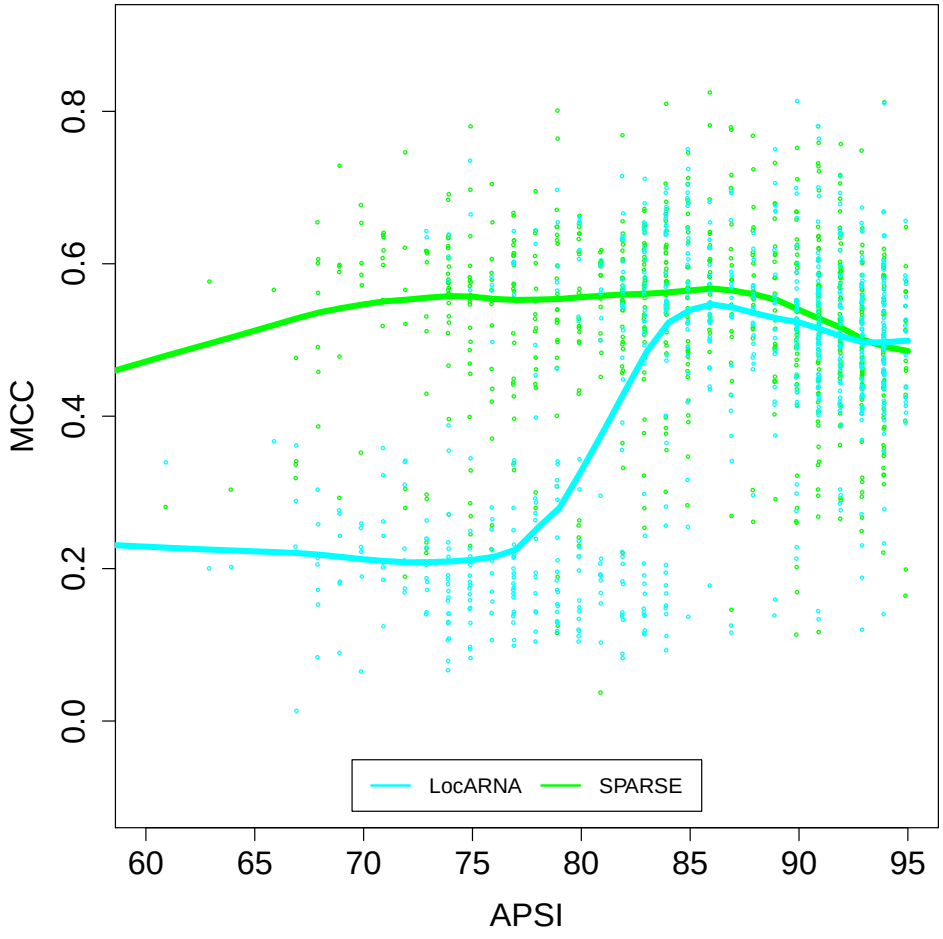


similar: **Pr[k unpaired in loop of (i,j)]**

[ExpARNA-P; Schmiedl et al., RECOMB 2012]

SPARSE Improves Over LocARNA for Specific Families





(shown: IRES HCV, pairwise)