Sequence-Structure RNA Alignments using Lagrangian Relaxation

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Discrete Math lecture WS 09

Rediscovery of RNA ...

nature

MARS'S ANCIENT OCEAN
Polar wander solves an enigma

THE DEPTHS OF DISGUST
Understanding the ugliest emotion

MENTORING
How to be top

NATUREJOBS
Contract research

DECODING THE BLUEPRINT
The ENCODE pilot maps human genome function

Rediscovery of RNA ...

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"It is beginning to dawn on biologists that they may have got it wrong. Not completely wrong, but wrong enough to be embarrassing." (The Economist, June 14th 2007)

RNA

- On the sequence level: string over the alphabet $\{A, C, G, U\}$

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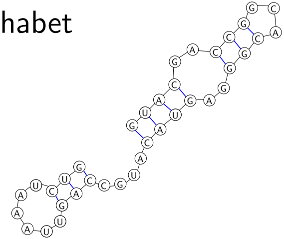
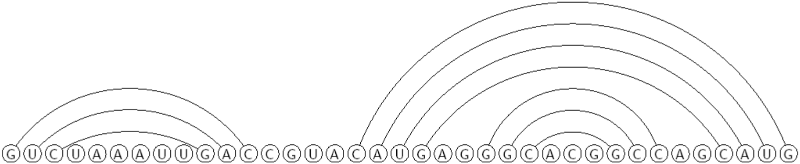
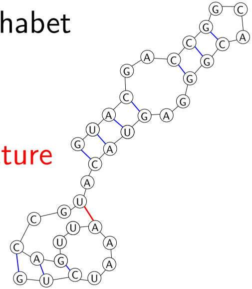
- Folds onto itself → secondary structure

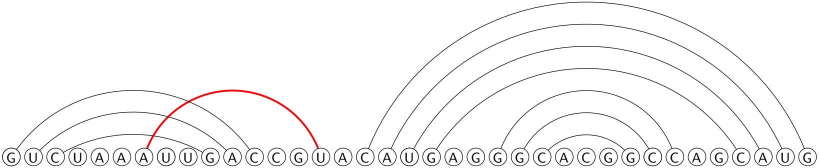




RNA

- On the sequence level: string over the alphabet $\{A, C, G, U\}$
- Folds onto itself → secondary structure
- Can contain pseudoknots → tertiary structure



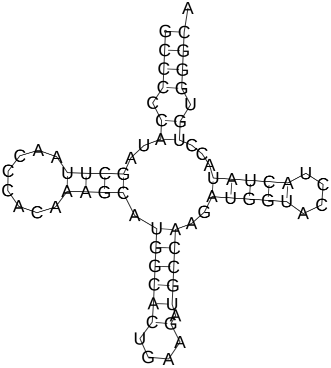


Real-world example: tRNA

- Tertiary structure:

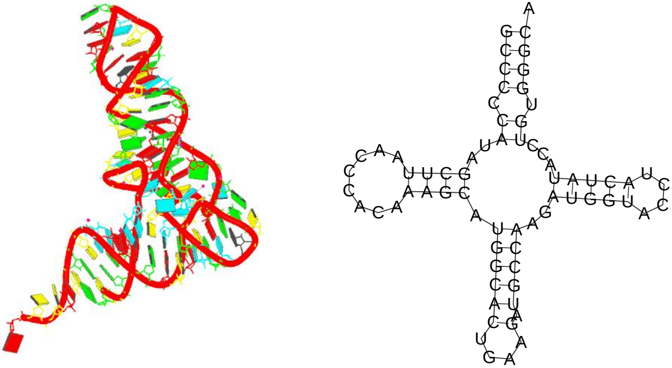
Real-world example: tRNA

- Secondary structure:



Real-world example: tRNA

- Primary structure:



GCCCCCAUAGCUUAACCCACAAAGCAUGGCACUGAAGAUGCCAAGAUGGUACCUACUAUACCUGUGGGCA

Sequence-structure alignments

- Function largely depends on structure
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  - Related functional RNAs often have low sequence but high structural similarity
- Similar function can often be detected by finding structural similarities → need to compute sequence-structure alignments
- Sequence-structure alignments serve as the basis for computing RNA consensus structures, finding RNA genes, structural clustering,. . .

Sequence-structure alignments: previous work

- Polynomial algorithms (mainly based on DP) exist for the nested pairwise case, *e.g.*, [Sankoff, 86],[Tai, 79],[Jiang, 95],[Eddy, 94],. . .
- NP-complete in the multiple case and in the general unnested case ([Reinert, 98])

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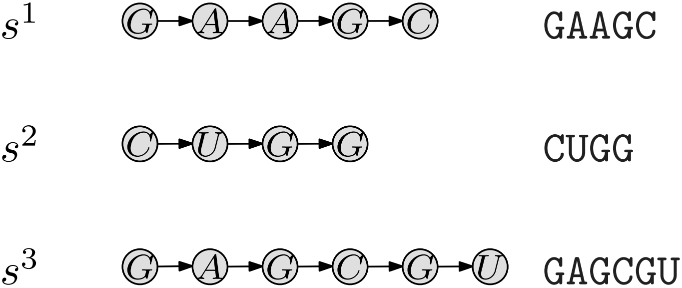
Two lines of research

- A novel formulation for exact multiple sequence-structure alignments of known and unknown structures (combining models from [Althaus, 06] and [Bauer, 04])
- Computing fast multiple sequence-structure alignments based on the pairwise alignment case

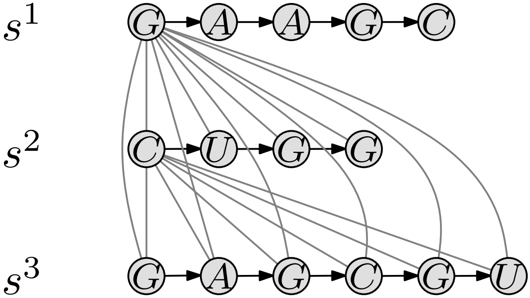
Graph-based formulation 1/5

- Vertices:



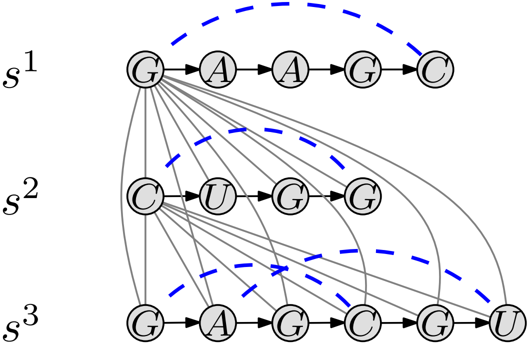
Graph-based formulation 2/5

- Alignment edges:



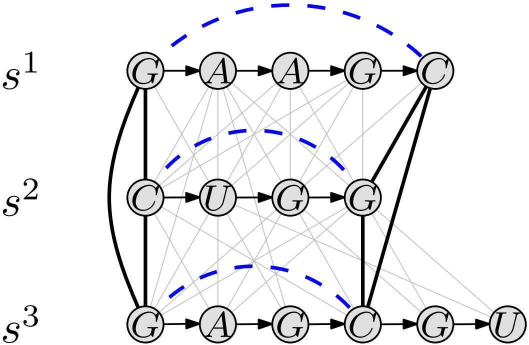
Graph-based formulation 3/5

- Interaction edges:



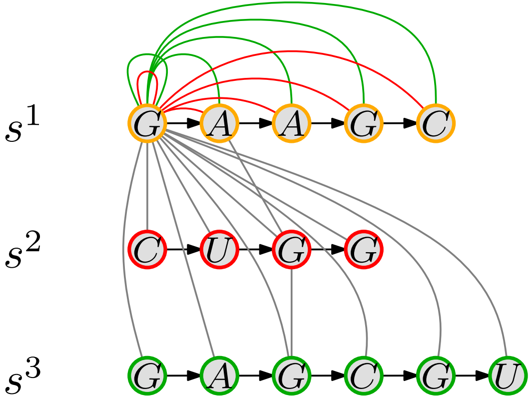
Graph-based formulation 3/5

- Interaction match:



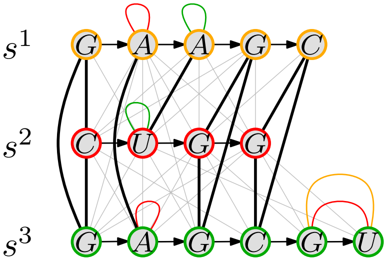
Graph-based formulation 4/5

- Gap edges:



Graph-based formulation 4/5

- Realized gap edges:



```
GAAGC--
C-UGG--
GA-GCGU
```

Graph-based formulation 4/5

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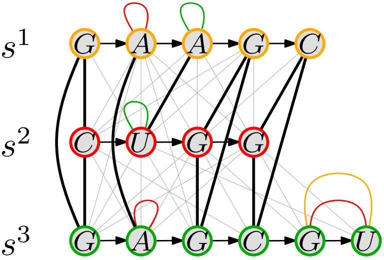

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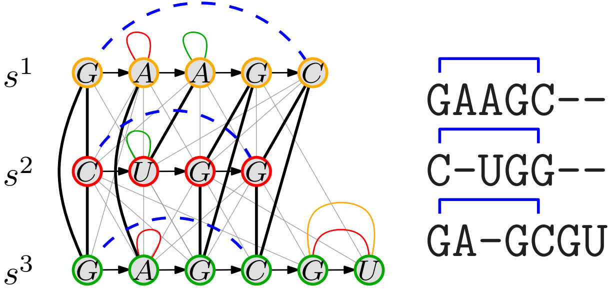
- Summary of the different edges:
  - alignment edges (alignment)
  - interaction edges (structure)
  - gap edges (gaps)

Graph-based formulation 5/5

- Objective function of sequence-structure alignments:



maximize the sum of realized sequence plus structure scores, *i.e.*, award matches, penalize mismatches and gaps

Gapped Structural Traces

- Not all possible subsets of alignment, interaction, or gap edges correspond to proper alignments
- Adding constraints leads to the notion of a gapped structural trace
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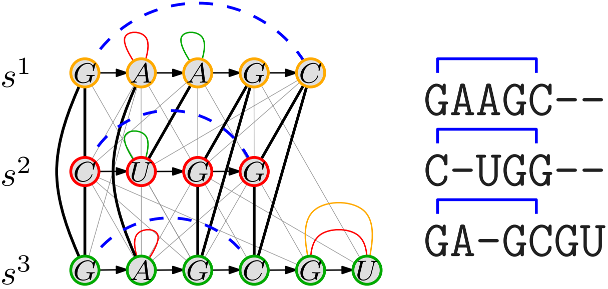

```
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```
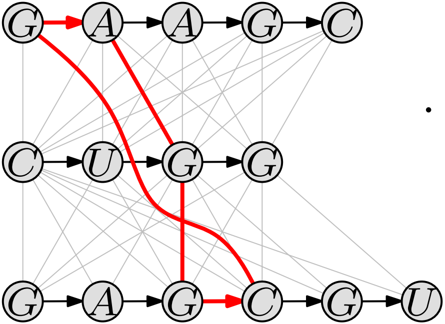

Gapped Structural Traces 1/5

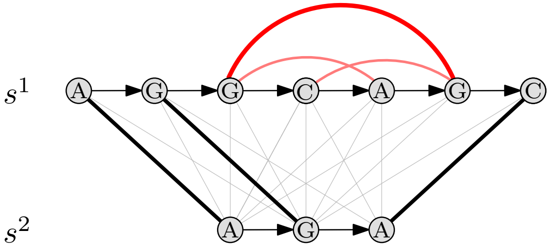
- We do not allow mixed cycles:



```
··· G A ···
  ··· G ···
  ··· G C ···
```

Gapped Structural Traces 2/5

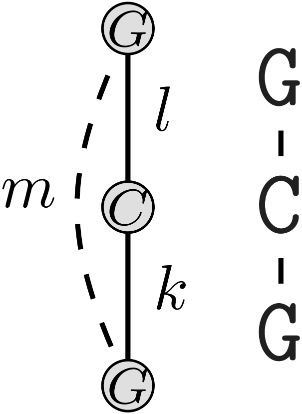
- We do not allow conflicting gap edges, *i.e.*, gaps are realized by one single gap edge:



```
AGGCAGC
AG----A
```

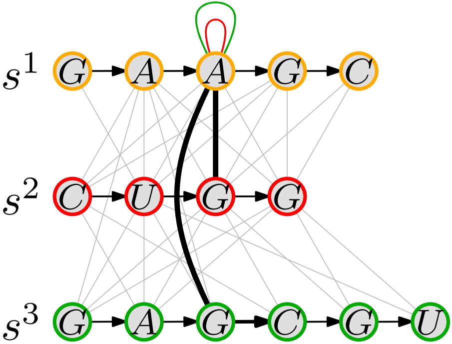
Gapped Structural Traces 3/5

- We have to realize transitive edges:



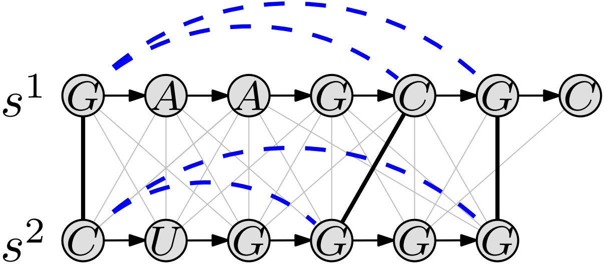
Gapped Structural Traces 4/5

- Every vertex has to be incident to an alignment or gap edge:



Gapped Structural Traces 5/5

- At most one interaction match counts:



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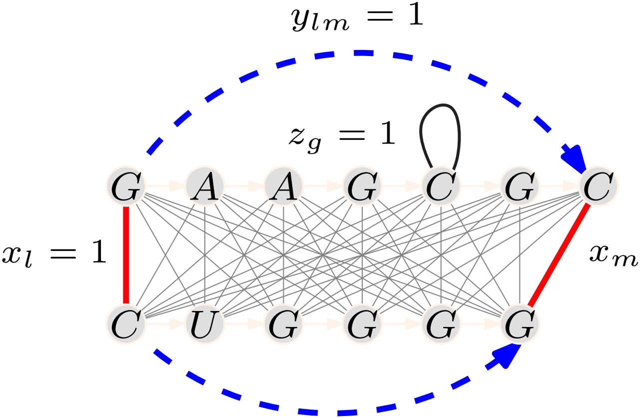
- We have a graph-based framework modelling multiple sequence-structure alignments
- But: we do not have an algorithm yet for determining the subsets of alignment, interaction, and gap edges
- Combinatorial optimization deals with determining the best solution out of a finite set of feasible solutions
- Integer linear programs are one of the main tools to solve combinatorial optimization problems
- The graph-based formulation gives rise to such an integer linear program

Integer linear program variables

Variables $x \in \{0,1\}^L, y \in \{0,1\}^{L\times L}, z \in \{0,1\}^G$

$$x_l = \begin{cases} 1 & l \in \mathcal{L} \\ 0 & \text{else} \end{cases} \quad y_{lm} = \begin{cases} 1 & \text{(l,m) match realized} \\ 0 & \text{else} \end{cases} \quad z_g = \begin{cases} 1 & g \in \mathcal{G} \\ 0 & \text{else} \end{cases}$$



Gapped structural traces

Given a weighted alignment graph $G = (V, L \cup I \cup G, w)$, we aim at finding the sequence-structure alignment of maximal weight, *i.e.*, select $\mathcal{L} \subseteq L$, $\mathcal{I} \subseteq I$, and $\mathcal{G} \subseteq G$ with

$$\max \sum_{l \in \mathcal{L}} w_l x_l + \sum_{l \in \mathcal{L}} \sum_{m \in \mathcal{L}} w_{lm} y_{lm} + \sum_{g \in \mathcal{G}} w_g z_g$$

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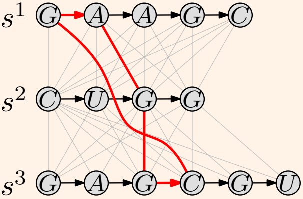
- There is no mixed cycle induced by the alignment:



$$\sum_{l \in L \cap M} x_l \leq |L \cap M| - 1$$

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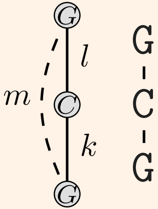

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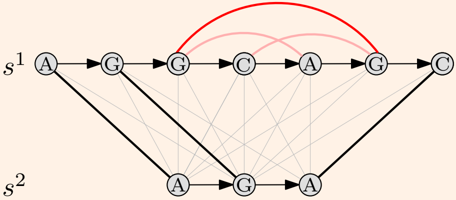
- There are no two gap edges in conflict with each other:



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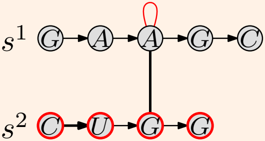
- Each vertex is incident to an alignment edge or spanned by a gap edge (w.r.t. every other input sequence):



$$\sum_{l \in L^{ij}_{s(m)}} x_l + \sum_{a \in G^{ij}_{s(l) \leftrightarrow s(l)}} z_a = 1$$

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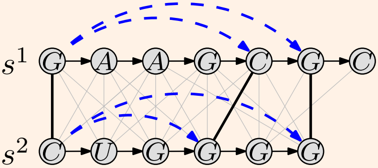

$$\sum_{m \in L} y_{lm} \leq x_l$$

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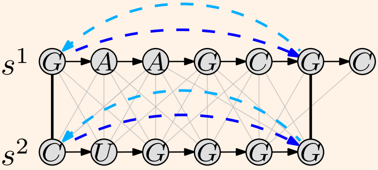
- Directed interaction matches have to match, *i.e.*, they have to be realized from both sides:



$$y_{lm} = y_{ml}$$

ILP modelling gapped structural traces

Variables $x \in \{0,1\}^L, y \in \{0,1\}^{L \times L}, z \in \{0,1\}^G$

$$\max \quad \sum_{l \in L} w_l x_l + \sum_{l \in L} \sum_{m \in L} w_{lm} y_{lm} + \sum_{g \in G} w_g z_g$$

$$\text{s. t.} \quad \sum_{l \in L \cap M} x_l \leq |L \cap M| - 1 \qquad \forall M \in \mathcal{M}$$

$$x_l + x_k - x_m \leq 1 \qquad (x_l, x_k, x_m) \text{ forming a cycle}$$

$$\sum_{a \in C} z_a \leq 1 \qquad \forall C \in \mathcal{C}$$

$$\sum_{l \in L^{ij}_{s(m)}} x_l + \sum_{a \in G^{ij}_{s(l) \leftrightarrow s(l)}} z_a = 1 \qquad 1 \leq i, j \leq k, i \neq j, \forall m \in L^{ij}$$

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$$y_{lm} = y_{ml} \qquad \forall\, l, m \in L$$

Computing optimal solution for ILPs

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- Lagrangian relaxation:
  - we are able to divide the constraints into good and bad constraints
  - dropping the bad constraints makes the problem easier to solve
  - move the bad constraints into the objective function associated with a penalty vector

Integer linear program

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Solving the relaxation intuitively. . .

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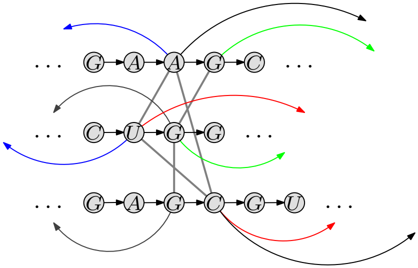

- Each line chooses its highest scoring interaction match

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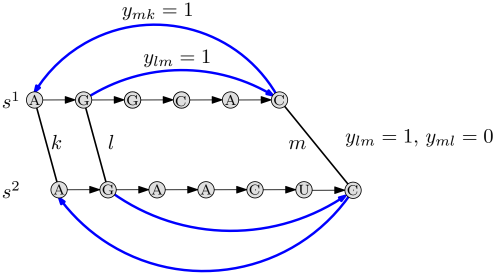
- Vector λ acts as a penalty vector to punish violations:



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- We incorporate the weight of structure edges in the weight of the alignment edges
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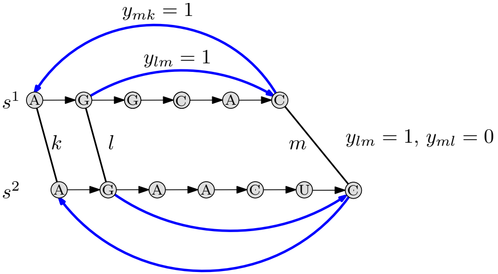

- The relaxation gives an upper bound on the original formulation

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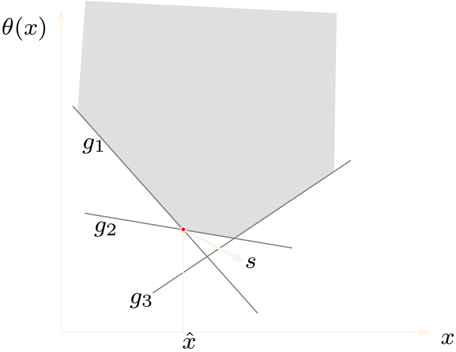

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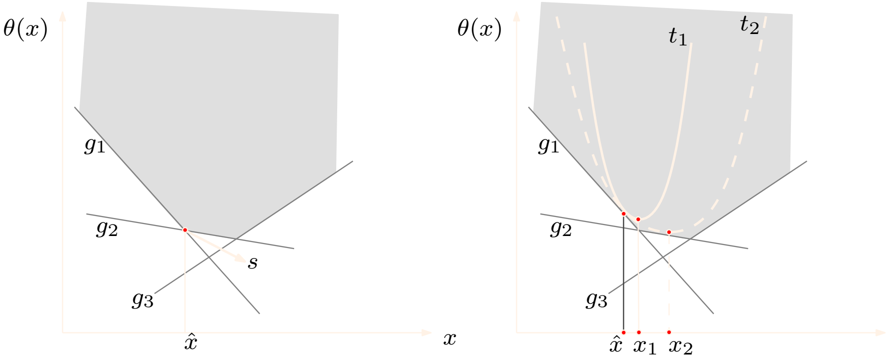

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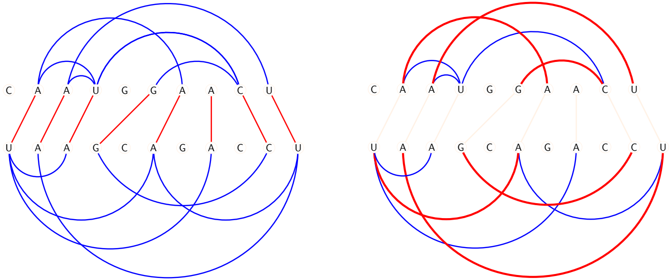
Need good upper and lower bounds z_U and z_L.

Computing the lower bound

Given: Lines from the solution of the last iteration
Find: Best interaction matches



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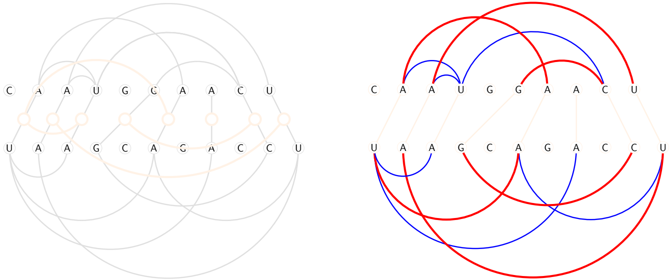
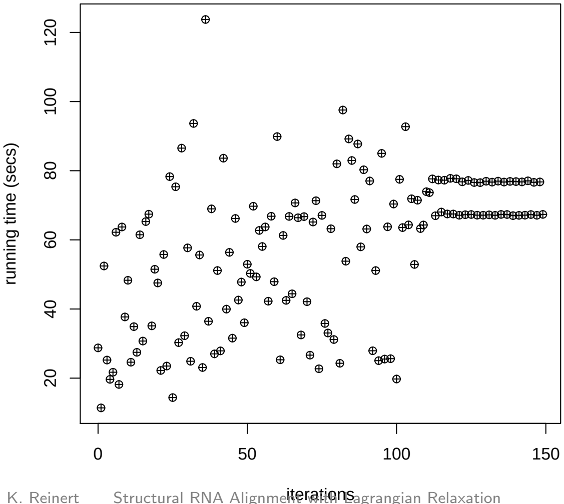


This is a matching problem!

Computing the lower bound



A stripped-down ILP for the pairwise case

Variables $x \in \{0,1\}^L, y \in \{0,1\}^{L \times L}$

$$\begin{aligned}
\max \quad & \sum_{l \in L} w_l x_l + \sum_{l \in L} \sum_{m \in L} w_{lm} y_{lm} & \\
\text{s.t.} \quad & \sum_{l \in C_L} x_l \leq 1 & \forall C_L \in \mathcal{C}_L \\
& \sum_{m \in L} y_{lm} \leq x_l & \forall\, l \in L \\
& y_{lm} = y_{ml} & \forall l, m \in L \\
& x \in \{0,1\}^L \quad y \in \{0,1\}^{L \times L} &
\end{aligned}$$

Branch-and-Bound framework

- Use the best upper and lower bounds in a branch-and-bound setting
- Branching on the x variables, *i.e.*, the possible alignment edges, yields the enumeration tree
- Results are similar to a branch-and-bound implementation for the quadratic knapsack problem:

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- Results are similar to a branch-and-bound implementation for the quadratic knapsack problem:
  - Bounds have to be very tight to solve problem to optimality
  - Large number of variables has to be fixed to close the gap between lower and upper bound
  - Small improvement of the best lower bound and the optimal solution

Results for Branch-and-Bound

APSI	♮ vars	lb	ub	opt	ratio	time
35	679	181.93	185.18	182.24	(1.00)	1907.45
36	432	194.32	197.43	194.62	(1.00)	252.66
37	597	141.78	142.62	142.17	(1.00)	164.38
38	711	166.01	168.05	166.03	(1.00)	1545.21
39	782	164.40	169.33	165.78	(0.99)	2084.61
40	664	171.74	172.84	171.74	(1.00)	350.71
41	647	190.95	194.16	192.20	(0.99)	1713.44
42	737	167.84	169.31	167.87	(1.00)	816.75
43	873	163.88	165.40	163.93	(1.00)	1782.08
44	682	189.58	192.04	190.05	(1.00)	967.01
45	740	167.33	170.59	168.04	(1.00)	1178.52
46	601	188.49	189.95	188.53	(1.00)	537.22
47	791	183.21	185.76	183.59	(1.00)	1920.89
48	669	181.73	183.55	182.05	(1.00)	1135.23
49	844	177.13	178.73	177.28	(1.00)	1020.95

Computational results

Two main parts:

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- B: Fast computation of heuristic multiple alignments (using T-COFFEE or in a progressive fashion)

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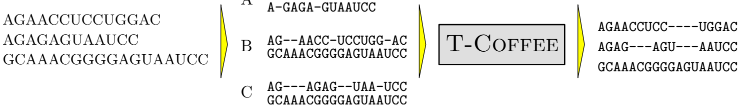
B: Heuristic multiple alignments

- Compute multiple alignments based on the pairwise case (which is solvable in $\mathcal{O}(n^2)$)
- `LaRA` and `sLaRA` use T-COFFEE:



AGAACCUCCUGGAC
AGAGAGUAAUCC
GCAAACGGGGAGUAAUCC

A
```
AGAACCUCCUGGAC
A-GAGA-GUAAUCC
```

B
```
AG--AACC-UCCUGG-AC
GCAAACGGGGAGUAAUCC
```

C
```
AG---AGAG--UAA-UCC
GCAAACGGGGAGUAAUCC
```

T-COFFEE

```
AGAACCUCC----UGGAC
AGAG---AGU---AAUCC
GCAAACGGGGAGUAAUCC
```

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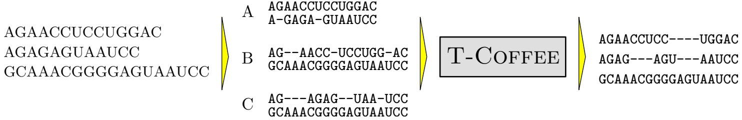

AGAACCUCCUGGAC
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B
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C
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T-COFFEE

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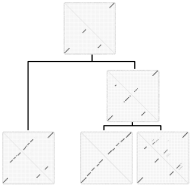
- pLaRA and psLaRA are progressive tools:



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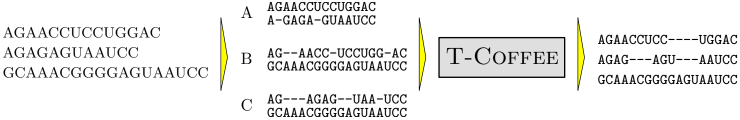

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T-Coffee

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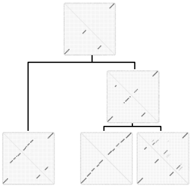
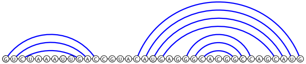


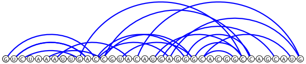
- Currently C^{++} using LEDA, part of the LiSA-framework (`http://www.planet-lisa.net`)

Input and training

- Interaction edges. Two modes:
  - Known structure:



  - Weights based on base pair probabilities [McCaskill, 90], similar to PMCOMP [Hofacker, 04]:



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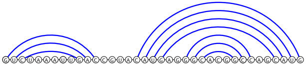

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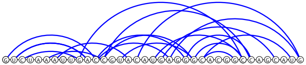
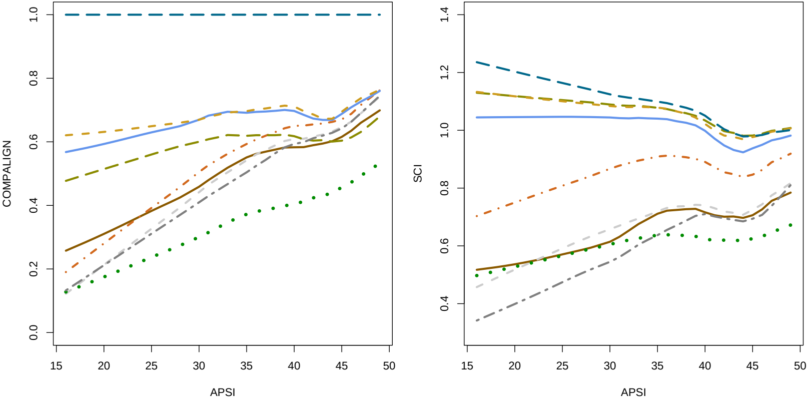


- Computational experiments performed on the BRAliBase 2.1 benchmark dataset, the MASTR data set [Lindgreen, 07] serves as the training set
- We only consider instances of an average pairwise sequence identity $< 50\%$

BRAliBase 2.1 - k2

- 2 input sequences per instance, 2251 instances:



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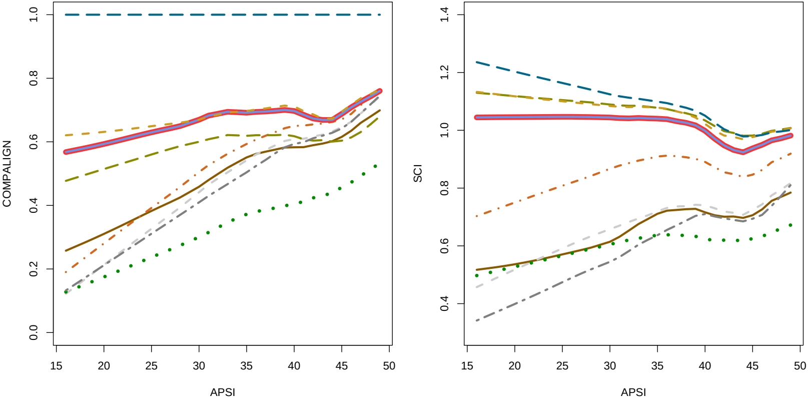
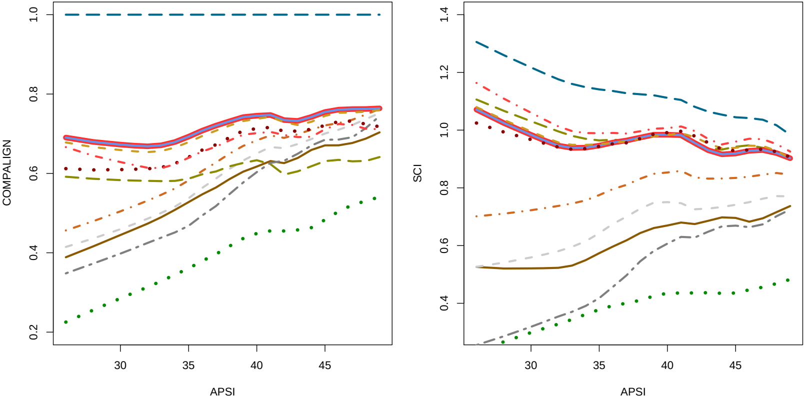


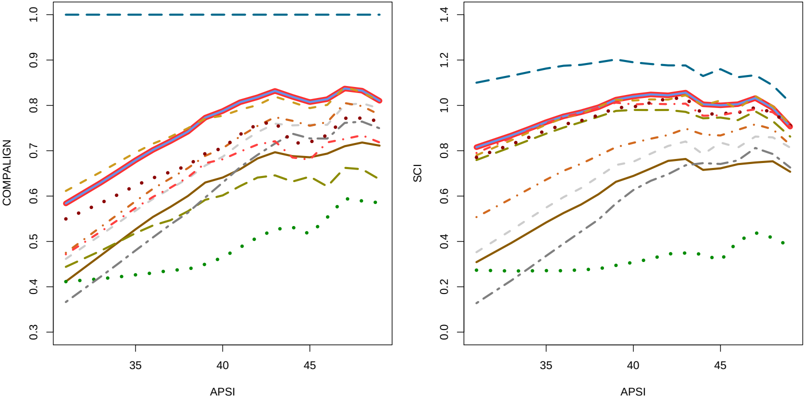
BRALIBASE 2.1 - k3

- 3 input sequences per instance, 1048 instances:



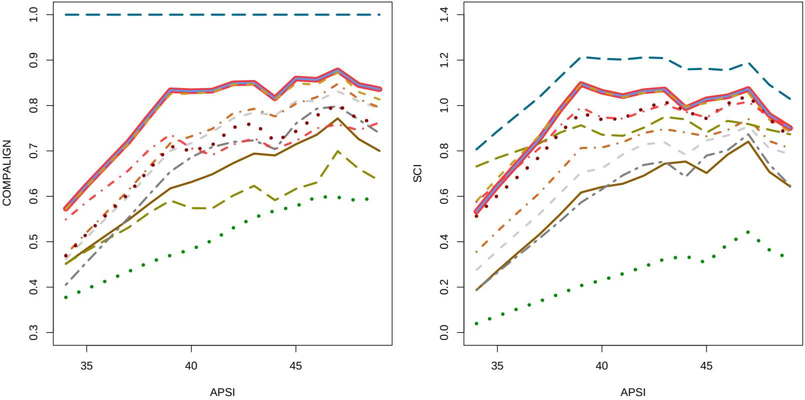
BRALIBASE 2.1 - k5

- 5 input sequences per instance, 512 instances:



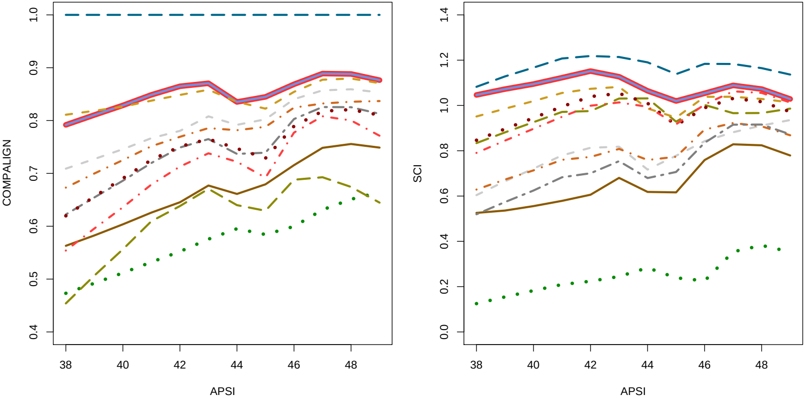
BRALIBASE 2.1 - k7

- 7 input sequences per instance, 323 instances:



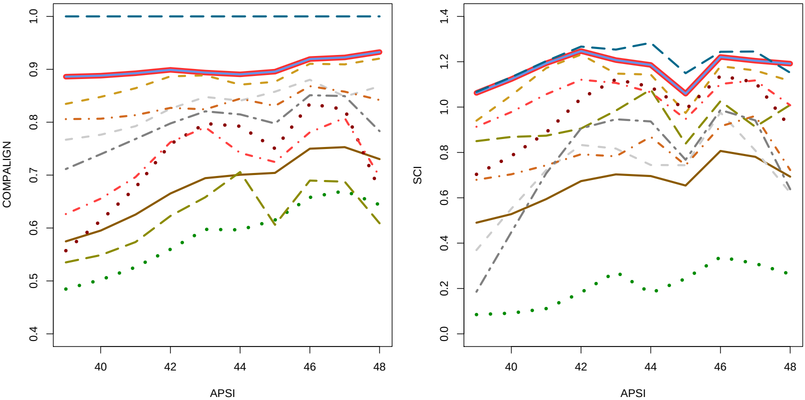
BRALIBASE 2.1 - k10

- 10 input sequences per instance, 189 instances:



BRALIBASE 2.1 - k15

- 15 input sequences per instance, 123 instances:



Comparison of running times

- Running time (in secs) for all 2251 pairwise alignment instances (k2) of the BRALIBASE dataset:

	running time	⌀ SPS	⌀ SCI
LARA	3157.74	0.68	0.98
sLARA	5234.15	0.69	1.01
FOLDALIGN	10360.44	0.61	1.02
MURLET	9575.54	0.60	0.73
MARNA	56434.11	0.42	0.63
MXSCARNA	478.74	0.64	0.87
STRAL	18.72	0.58	0.71

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  - we are lacking sound energy parameters
- We did not report on:
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  - the performance of our approach within a branch-and-bound framework

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- We implemented variants based on the bundle method and branch-and-bound

THANKS FOR YOUR ATTENTION!

Check out

`http://www.planet-lisa.net`