Conservation in Long Non-coding RNAs and other Updates

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Incongruent Evolution

```
CGUGGAAACCCACAG
.((((....))))..

CGUGGAAACC-CACAG
.((((....)-))).
.((-((....))))..
CGU-GAAACCUCACAG
```

```
CGUGAAACCUCACAG
.((((....))))..

.((((....))))..
CGUGGAAACCCACAG
CGUGAAACCUCACAG
.((((....))))..
```

exact conservation of the structure

Incongruent Evolution

Similar sequence, shifted structure

```
..((((.((((....)))).))))....
AAGGCUCUAUUAACUGGUAUCGGCUAUAG
**  *  ***** ***** **** *  *  ***
AAUGAUCUAUGAACUGUUAUCUGAUUUAG
...((((.((((....)))).))))...
```

```
..-((((.((((....)))).))))....
AA-GGCUCUAUUAACUGGUAUCGGCUAUAG
**  *          *           *   *  ***
AAUGAUCUAUGAACUGUUAUCUGAUU-UAG
...((((.((((....)))).))))-...
```

Is there really incongruent evolution?

Sequence and structure alignments mir-30a and mir-30b

```
consensus    ..U.AG....UGUAAACAUCCU..ACU...AGCUGU.A...CA....U.GGCU...A-GU.GGAUGUUUGC..C.GC...CU
mmu-mir-30a AGUGAGCGACUGUAAACAUCCUCGACUGGAAGCUGUGAAGCCACAAAUGGGCUUUCA-GUCGGAUGUUUGCAGCUGCCUACU
SS          ((((.(((.(((((((((((..(((((((((((.....))).....))))))))-)))))))))))))).))).))))
mmu-mir-30b -UUCAGUUCAUGUAAACAUCCUACACU--CAGCUGUCAU--CAUGCGUUGGCUGGGAUGU-GGAUGUUUACGUCAGCUGUCU
SS          -..(((((.((((((((((((.(((((--(((((..(..--.....)..)))))))).)))-)))))))))))).)))))...
consensus   ...[.[[[.[[[[[[[[[[[[.......[[[[[.............]]]]].......]]]]]]]]]]]].]]].]...

consensus    .....G....UGUAAACAUCCU.......A...........C........G..U.......GGAUGUUU.C....GC.U....
mmu-mir-30a AGUGAGCGACUGUAAACAUCCUCGACUGGAAGCUGUGAA-GCCACAAAUGGGCUUUCA-GUCGGAUGUUUGCAGCUGCCUACU-
SSi         ((((.(((.(((((((((((..(((((((((((..-..))).....)))))))-)))))))))))))).))).))))-
mmu-mir-30b UUCA-GUUCAUGUAAACAUCCU-ACACUCAGCUGUCAUCAUGCGUU-----GGCUGGGAUGUGGAUGUUUACGUCAGC-UGUCU
SS          ..((-(((.((((((((((((.-(((((((((..(.......)..-----))))))).)))))))))))))).)))-))...
consensus   ..[[.[[[.[[[[[[[[[[[[..[[[[[[[[[..[.......].......]]]]]]]].]]]]]]]]]]]]].]]].]]...
```

Incongruent Alignments

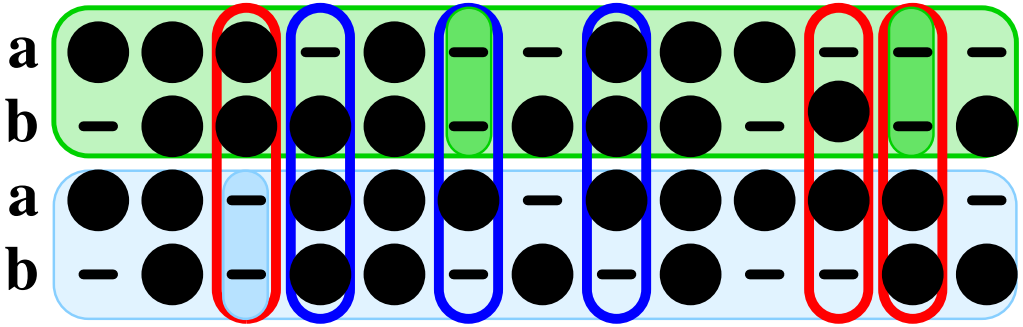
Basic idea: consider two or more alignments of the same objects (strings) simultaneously:

- implicitly defines alignments between the different copies of the same objects that do not allow mismatches
- Insertions and deletions in these same-object alignments correspond to *shifts* between the incongruent alignments
- scoring function:
  weighted scores of the consitutent alignments + scores for the "shifts"

... what exactly are "shifts"?

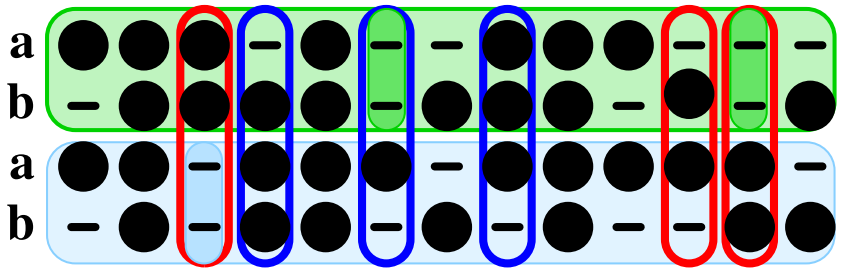
Formalization: Bi-Alignments

- two distinct alignments $\mathbb{U}$ and $\mathbb{V}$ of the same objects **a** and **b**
- an alignment $\mathbb{W}$ of the columns of $\mathbb{U}$ and $\mathbb{V}$
- score $= u(\mathbb{U}) + v(\mathbb{V}) + w(\mathbb{W})$
- Bi-alignment Problem: simultaneously optimize $\mathbb{U}$, $\mathbb{V}$, and $\mathbb{W}$.



Formalization: Shifts

- Gap patterns $c, d \in \binom{0}{1}$ in $\mathbb{U}$ and $\mathbb{V}$, respectively
- Congruent columns: $c_1 = d_1$ and $c_2 = d_2$.
- Incongruence $\|c - d\| = |c_1 - d_1| + |c_2 - d_2| \in \{0, 1, 2\}$
- score $w(\mathbb{W})$: proportional to the sum of the incongruences of the alignment columns.
- An alignment of alignments is again an alignment:
  $\mathbb{A} \simeq (\mathbb{U}, \mathbb{V}, \mathbb{W})$



- Number of in/dels between the two copies of **a** and **b**:
  $d(\mathbb{A}_{13}) = \sum_i |c_1(i) - d_1(i)|$ $\quad$ $d(\mathbb{A}_{24}) = \sum_i |c_2(i) - d_2(i)|$
- Columnwise scoring of $\mathbb{A}$:
  score of the projected alignments $\mathbb{U} \simeq \mathbb{A}_{12}$ and $\mathbb{V} \simeq \mathbb{A}_{34}$ plus the in/del-only scores $d(\mathbb{A}_{13})$ and $d(\mathbb{A}_{24})$.

Scoring Shifts

$$A \to A\binom{\bullet}{\bullet} \mid A\binom{\bullet}{-} \mid A\binom{-}{\bullet} \mid \cdots \mid A\binom{\bullet}{-} \mid A\binom{-}{\bullet} \mid A\binom{-}{-} \mid \varepsilon\,.$$

	$\binom{\bullet}{\bullet}$	$\binom{\bullet}{-}$	$\binom{-}{\bullet}$	$\binom{-}{-}$
$\binom{\bullet}{\bullet}$	0	Δ	Δ	2Δ
$\binom{\bullet}{-}$	Δ	0	2Δ	Δ
$\binom{-}{\bullet}$	Δ	2Δ	0	Δ
$\binom{-}{-}$	2Δ	Δ	Δ	-

$$M(0) = 0$$

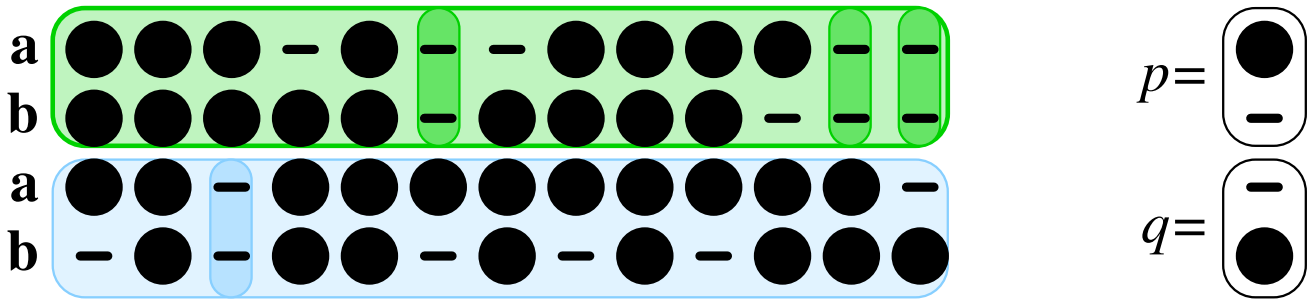
$$M(x) = \max_{c \in \mathcal{C}} M(x - c) + s(x, c)$$

A very preliminary scan survey

- small and medium-width `Rfam` seed alignments
  ($\leq$ 10 sequences, $\leq$ 120 columns)
  1181 `Rfam` families
- check if `Rfam` consensus-structure "oriented" Rfam alignment is significantly different from a `mafft` re-alignment of the sequences
  709 candidate families
- 10137 pairs of RNA sequences yield 143 cases in 72 families with prediced shifts in a sequence-based shift alignment

Affine Gap Costs in $\mathbb{U}$ and $\mathbb{V}$

- Gotoh's algorithm for each of $\mathbb{U}$ and $\mathbb{V}$
  scoring depending of the gap pattern of the penultimate column
- insufficient here: the penultimate column could be double-gap,
  i.e., an in/del of $\mathbb{W}$.
- remedy: keep *end gap pattern* defined for the last column that is **not** a double-gap:



Including secondary structure

$$A \rightarrow Ac \mid A\bar{c}Ac \mid \varepsilon$$

$$u(\mathbb{U}, \varphi_{\mathbb{U}}) + v(\mathbb{V}, \varphi_{\mathbb{V}}) + w(\mathbb{W})$$

$$M(x,y) = \max \begin{cases} \max\limits_{c \in \mathcal{C}} M(x, y-c) + s(y,c) \\ \max\limits_{\substack{(z,y)\in\mathcal{B}^* \\ (c,d)\in\mathcal{C}^*}} M(x,z-c) + M(z,y-d) + \tilde{s}(z,c;y,d) \end{cases}$$

$\mathcal{B}^*$ ... allowed index combinations, enforce base pairs

$$(c,d) \in \mathcal{C}' := \left\{ \begin{pmatrix} - \\ \bullet \end{pmatrix}, \begin{pmatrix} \bullet \\ \bullet \end{pmatrix}, \begin{pmatrix} - \\ \bullet \\ \bullet \end{pmatrix}, \begin{pmatrix} \bullet \\ \bullet \\ \bullet \end{pmatrix} \right\}^2$$

... Sankoff-style Bi-Alignments

Sankoff-style Bi-Alignments

- Complexity?
  $O(n^8)$ entries times $O(n^4)$ operations
- BUT: number of shifts is limited:

$$k\Delta \leq \delta^*(\mathbf{a},\mathbf{b}) := \max_{\mathbb{U}} u(\mathbb{U}) + \max_{\mathbb{U}} v(\mathbb{U}) - \max_{\mathbb{U}}[u(\mathbb{U}) + v(\mathbb{U})]\,.$$

  reduction to $O(n^4k^4)$ entries with $O(n^2k^2)$ operations, i.e., $O(n^6)$ like the Sankoff algorithm
- `locarna` approximation: only include $O(n)$ most frequent base pairs for each structure
- reduction to $O(n^2)$ space and time.
- Implementation: on the way

Matrices $M_{p,q}$ indexed by end gap patterns p and q for $\mathbb{U}$ and $\mathbb{V}$

$$M_{(p,q)}(x,y) = \max \begin{cases} \max\limits_{\substack{p'\neq 0\\ q'\neq 0}} M_{(p',q')}(x-q,y-q) + s(\binom{x}{y},\binom{p'}{q'},\binom{p}{q}) \\ \max\limits_{p'\neq 0} M_{(p',q)}(x-p,y) + s(\binom{x}{y},\binom{p'}{q},\binom{p}{0}) \\ \max\limits_{q'\neq 0} M_{p,q'}(x,y-q) + s(\binom{x}{y},\binom{p}{q'},\binom{0}{q}) \end{cases}$$

Collaborators

- Maria Waldl
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- Christoph Flamm
- Christian Höner zu Siederdissen
- Ivo L. Hofacker