Complexity aspects of RNA folding on complex conformation spaces

Saad Sheikh[⊙,◇] Rolf Backofen[♣] Yann Ponty[•,◇]

[⊙] Bloomberg RD, New York, USA

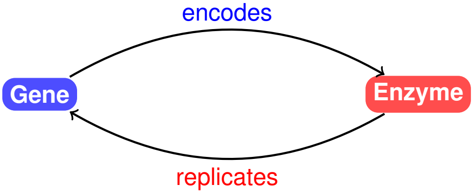
[♣] Albert Ludwigs University, Freiburg, Germany

[•] LIX, CNRS/Ecole Polytechnique, France

[◇] AMIB Team-Project, INRIA, Saclay, France

Sep 30th – MBI workshop’15

RNA world: Resolving the *chicken vs egg* paradox at the origin of life...



A gene big enough to specify an enzyme would be too big to replicate accurately without the aid of an enzyme of the very kind that it is trying to specify. So the system *apparently cannot get started*.

[...] This is the RNA World. To see how plausible it is, we need to look at why proteins are good at being enzymes but bad at being replicators; at why DNA is good at replicating but bad at being an enzyme; and finally why *RNA might just be good enough at both roles to break out of the Catch-22.*

R. Dawkins. *The Ancestor's Tale: A Pilgrimage to the Dawn of Evolution*

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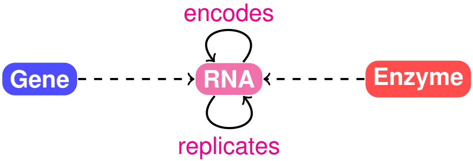

The RNA World
THIRD EDITION
PROTEIN
mRNA
RNA
RNA
DNA
RNA
Edited by Raymond F. Gesteland
Thomas R. Cech
John F. Atkins

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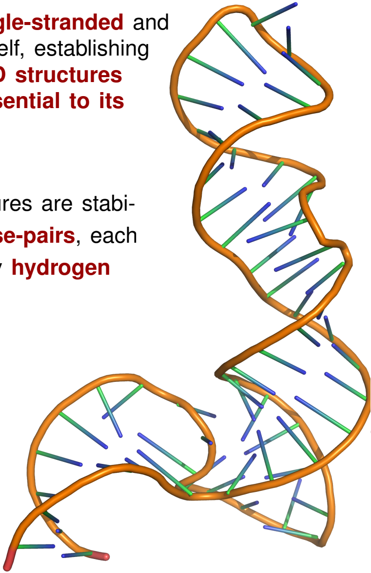
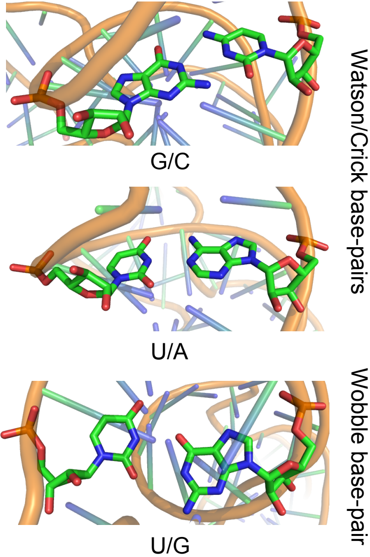
RNA folding

RNA is **single-stranded** and **folds** on itself, establishing **complex 3D structures** that are **essential to its function(s)**.

RNA structures are stabilized by **base-pairs**, each mediated by **hydrogen bonds**.





Canonical base-pairs

RNA structure(s)

```
UUAGGCGGCCACAGC
GGUGGGGUUGCCUCC
CGUACCCAUCCCGAA
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CGAGCCUCUGGGAAA
CCCGGUUCGCCGCCA
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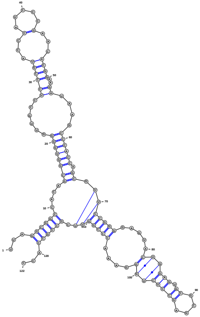

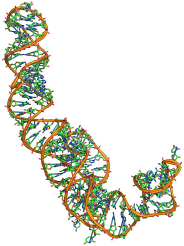

Primary structure

Secondary structure

Tertiary structure

Source: 5s rRNA (PDBID: 1K73:B)

Definition (Secondary Structure)

A **secondary structure** S for an RNA w is a set of **base-pairs** $(i,j) \in [1,n]^2$ such that:

- **Monogamy:** Each position $x \in [1,n]$ involved in **at most** one base-pair;
- **Non-crossing base-pairs:** $\nexists (i,j),(k,l) \in S$ such that $i < k < j < l$;
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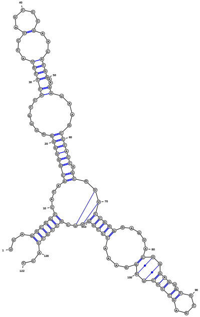

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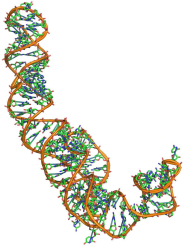

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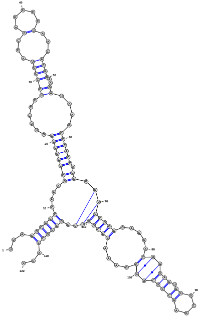

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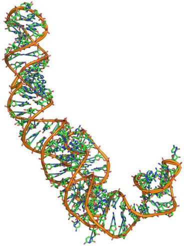

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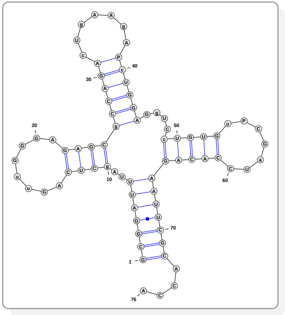
Various representations for a versatile biomolecule



Outer-planar graphs

Hamiltonian-path, $\Delta(G) \leq 3$, 2-connected*

Diversity supports intuitions

Different representations

Common combinatorial structure

*Additional steric constraints

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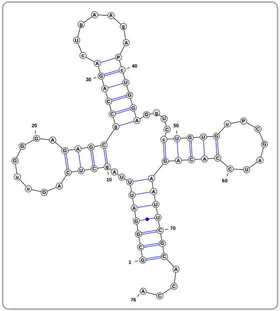

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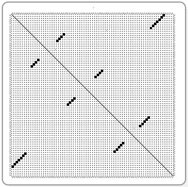

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Adjacency matrices*

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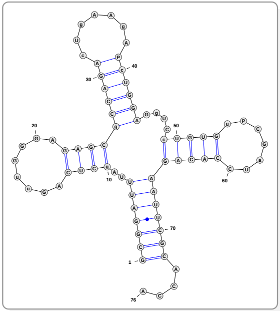

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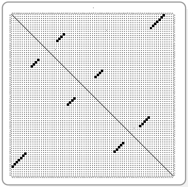

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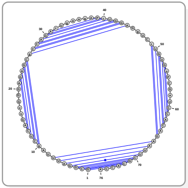

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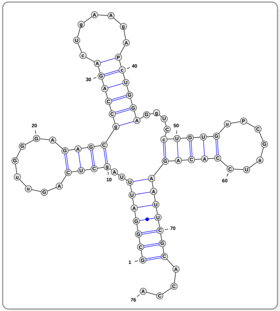

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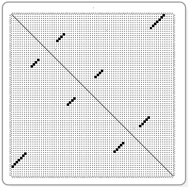
Motzkin words*



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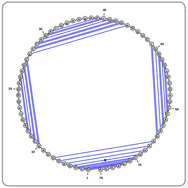

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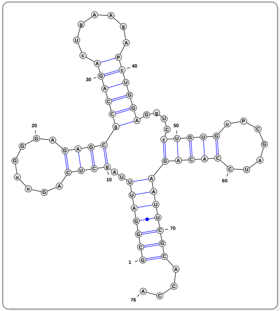

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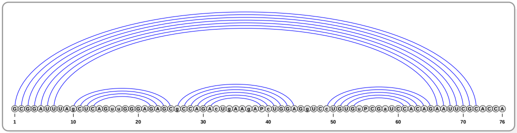
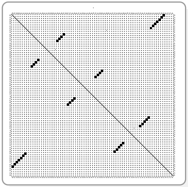


Non-crossing arc-annotated sequences*



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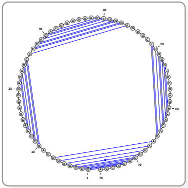

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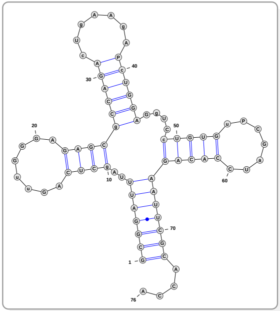

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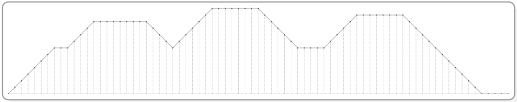
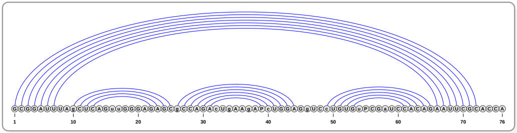


Positive 1D meanders* over $\mathcal{S} = \{+1, -1, 0\}$



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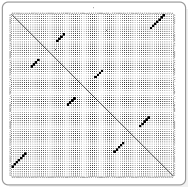

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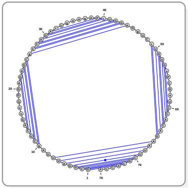

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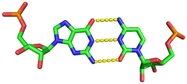
Crossing interactions

MFE structure, part. func.... computed exactly in $\Theta(n^3)$ time in the absence of:

- **Non-canonical base-pairs:**
  Any base-pair **other than** {(A-U), (C-G), (G-U)}
  OR interacting in a non-standard way (WC/WC-Cis) [Leontis 01].



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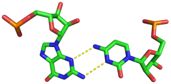
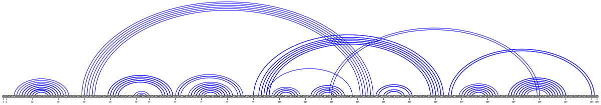


Non-canonical base-pair (Sugar/WC-Trans)

- **(Pseudo?)knots:** Crossing sets of nested stable base-pairs



Group I Ribozyme (PDBID: 1Y0Q:A)

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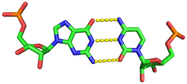

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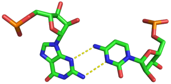

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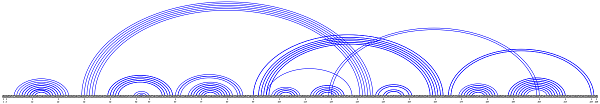

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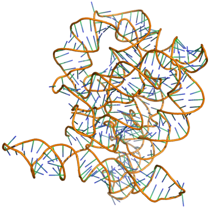
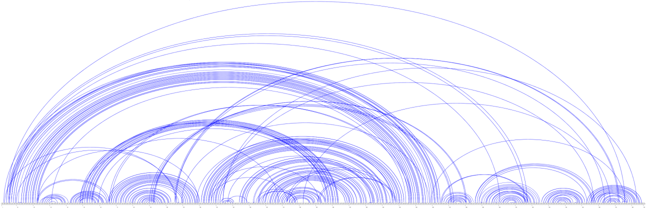
  Any ba
  OR int



Crossing interactions, once ignored, are now **ubiquitous**!

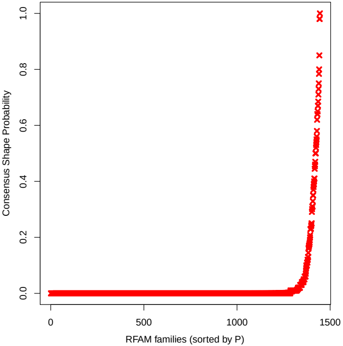
Example: Group II Intron (PDB ID: 3IGI)

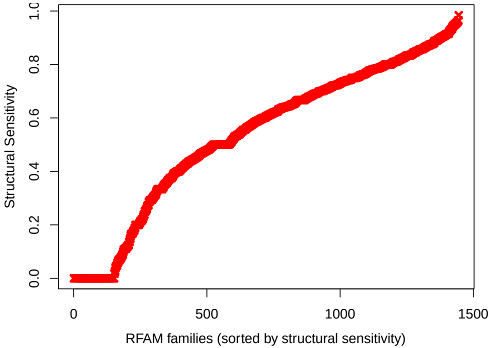


- **(Pseu**

(Pseudo)-knots: They Walk Amongst Us…

…and are responsible for (some of) the shortcomings of predictive tools.





Software: RNAFold **Database:** RFAM Release 10.1

Many of **those** families feature pseudoknots (RFAM consensus or predictions)

⇒ **Include pseudoknots to folding space of structure prediction algorithms**

Looks tough (this talk) but restricting the search space helps (Orland's talk)

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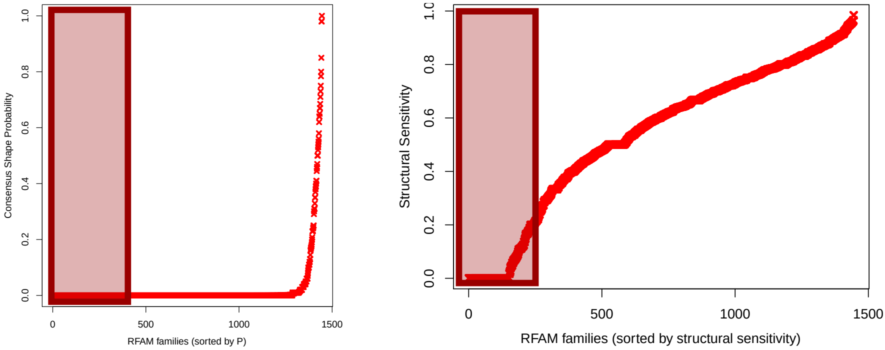

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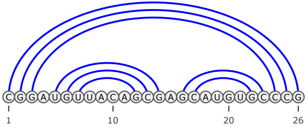

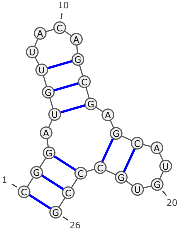

- **RNA structure *S*:** (Partial) matching of positions in sequence *w*
- **Motifs:** Sequence/structure features (e.g. Base-pairs, Stacking pairs, Loops. . .)
- **Energy model:**
  Motif → Free-energy contribution $\Delta(\cdot) \in \mathbb{R}^- \cup \{+\infty\}$
  Free-Energy $E_w(S)$: Sum over (independently contributing) motifs in S

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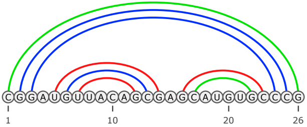

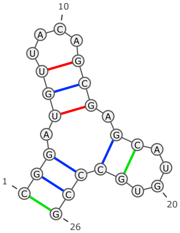

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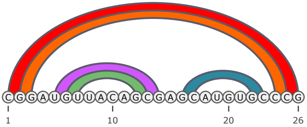

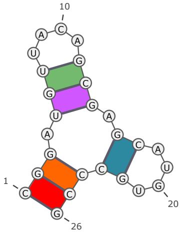

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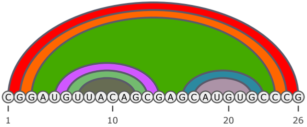

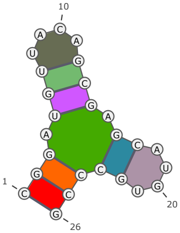

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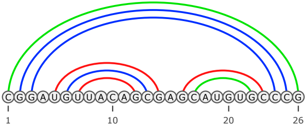

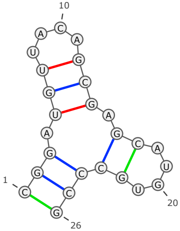

- **RNA structure *S*:** (Partial) matching of positions in sequence *w*
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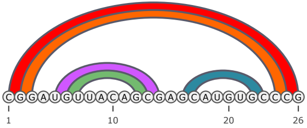
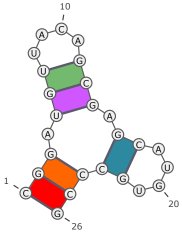
  Motif $\rightarrow$ Free-energy contribution $\Delta(\cdot) \in \mathbb{R}^{-} \cup \{+\infty\}$
  Free-Energy $E_w(S)$: Sum over (independently contributing) motifs in S

$$E_S = 2 \cdot \Delta\begin{pmatrix} U \\ | \\ G \end{pmatrix} + 4 \cdot \Delta\begin{pmatrix} G \\ | \\ C \end{pmatrix} + 2 \cdot \Delta\begin{pmatrix} C \\ | \\ G \end{pmatrix}$$

Problem statement





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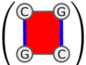
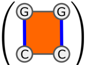
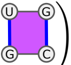
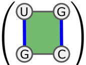
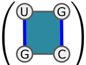
$E_S = \Delta\Bigg($  $\Bigg) + \Delta\Bigg($  $\Bigg) + \Delta\Bigg($  $\Bigg) + \Delta\Bigg($  $\Bigg) + \Delta\Bigg($  $\Bigg)$

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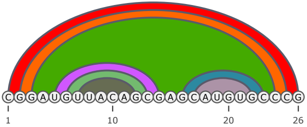

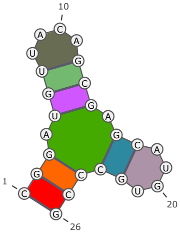

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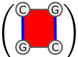
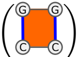
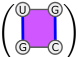
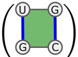
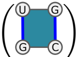
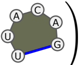
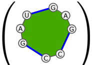
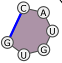
$E_S = \Delta\Bigg($  $\Bigg) + \Delta\Bigg($  $\Bigg) + \Delta\Bigg($  $\Bigg) + \Delta\Bigg($  $\Bigg) + \Delta\Bigg($  $\Bigg)$

$+ \Delta\Bigg($  $\Bigg) + \Delta\Bigg($  $\Bigg) + \Delta\Bigg($  $\Bigg)$

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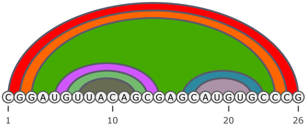

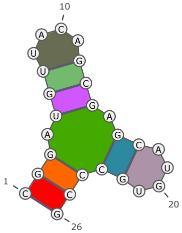

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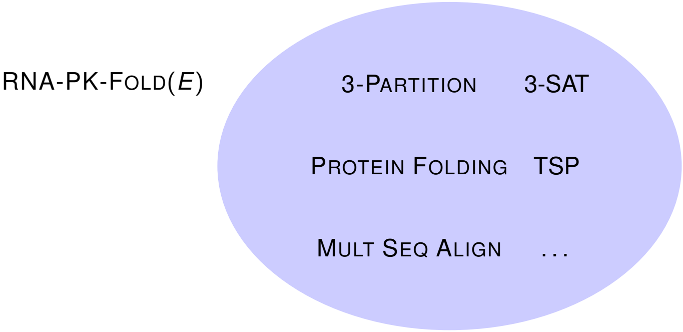
Definition (RNA-PK-FOLD(E) problem)

Input: RNA sequence $w \in \{\mathrm{A}, \mathrm{C}, \mathrm{G}, \mathrm{U}\}^*$.
Output: Matching S^*, having Minimal Free-Energy (MFE) $E_w(S^*)$.

Are there **efficient** algorithms to predict MFE with **arbitrary** (pseudo)knots?
With **restricted** pseudoknots? On which **energy models**?

NP-hardness: Characterizing the difficulty of algorithmic problems

Question(s): Is RNA-PK-Fold(E) intrinsically difficult?



RNA-PK-Fold(E)

3-Partition

3-SAT

Protein Folding

TSP

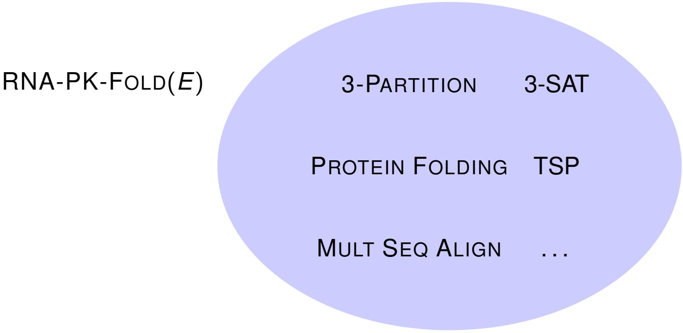
Mult Seq Align

...

NP-Complete problems

NP-hardness: Characterizing the difficulty of algorithmic problems

Question(s): ~~Is RNA-PK-FOLD(E) intrinsically difficult?~~
Is RNA-PK-FOLD(E) **as hard as** some reference **hard problem(s)**?



RNA-PK-FOLD(E)

3-PARTITION 3-SAT

PROTEIN FOLDING TSP

MULT SEQ ALIGN . . .

NP-Complete problems

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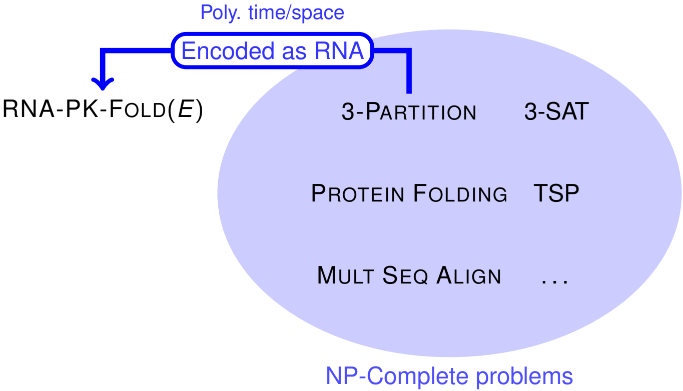

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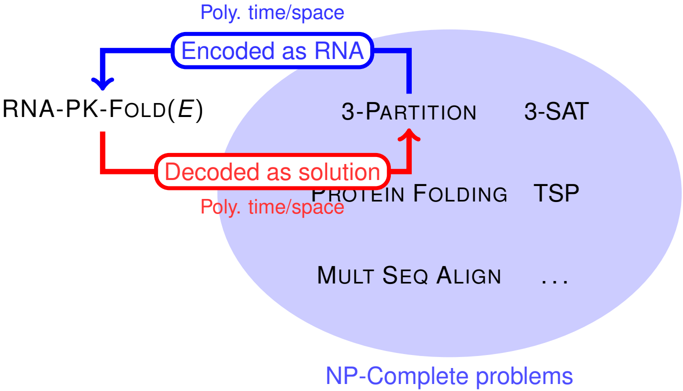

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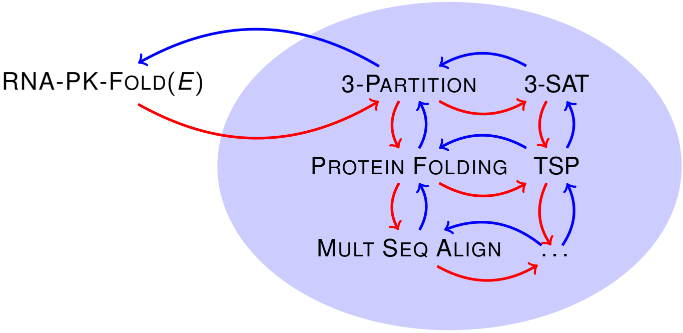

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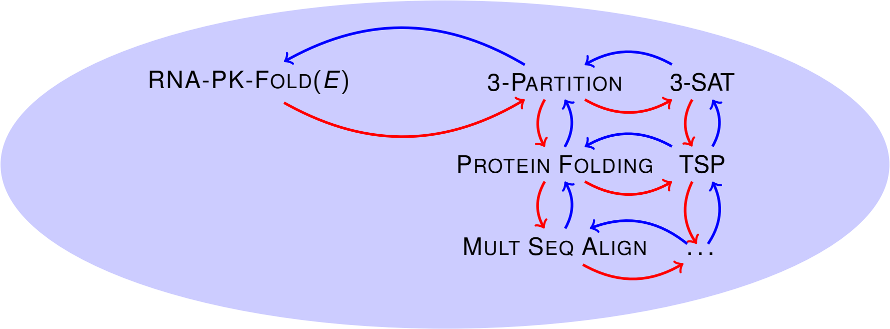
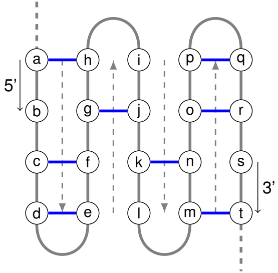


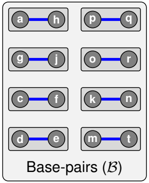
NP-Complete problems

Energy models

Three models, based on interacting positions (i,j):

- **Base-pair model $\mathcal{B}$**: Nucleotides (w_i, w_j) at (i,j) $\rightarrow \Delta_{\mathcal{B}}(w_i, w_j)$
- **Nearest-neighbor model $\mathcal{N}$:** Nucl. at (i,j) and $(i{+}1, j{-}1)$ + partners (or $\varnothing$) $\rightarrow \Delta_{\mathcal{N}}(w_i, w_j, w_{i+1}, w_{j-1}, w_{m_{i+1}}, w_{m_{j-1}})$
- **Stacking pairs model $\mathcal{S}$:** Nucl. at (i,j) and $(i{+}1, j{-}1)$ **only if** latter paired $\rightarrow \Delta_{\mathcal{S}}(w_i, w_j, w_{i+1}, w_{j-1})$





Solved in $\mathcal{O}(n^3)$ [Tabaska 98]
(Max-weighted matching)
Unrealistic!

Energy models

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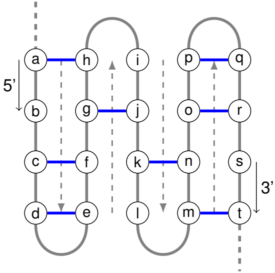

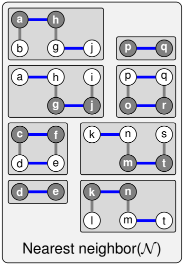

NP-hard [Lyngsø 00, Akutsu 00]

Too expressive?

Energy models

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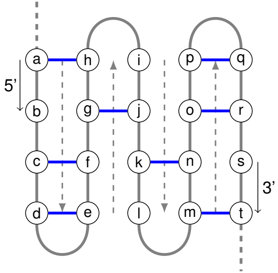
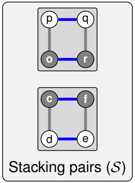
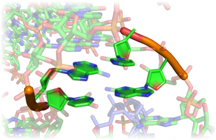




Stacking pairs ($\mathcal{S}$)

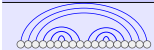
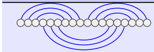
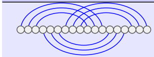


Captures stablest motifs

Still NP-hard [Lyngsø 04]

. . . but PTAS [Lyngsø 04]

State of the art

		Base-pairs	Stacking-Pairs	Nearest-Neighbor
	Comp.	P [Nussinov 80]	P [Ieong 03]	P [Zuker 81]
Non-crossing	Approx.	–	–	–
	Comp.	???	NP-Hard [Ieong 03]	NP-Hard [Ieong 03]
Planar	Approx.	2-approx. ≈[Ieong 03]	2-approx. [Ieong 03]	???
	Comp.	P [Tabaska 98]	NP-Hard [Lyngsø 04]	NP-Hard [Lyngsø 00, Akutsu 00]
General	Approx.	–	ε-approx. $\in \mathcal{O}(n^{4^{1/\varepsilon}})$ [Lyngsø 04]	???

Missing:

- Qualitative difference between Stacking-pairs and Nearest-Neighbor models?
- Influence of $\mathcal{M}$ on hardness/approx. ratio (only unit-valued studied)

Biologists demand (Biology deserves) **honest hardness results**:

- Energy model as input: Pandora's box (e.g. RNA folding on infinite alphabet!)
- Model as parameter: Is problem hard…

  Sometimes ($\exists\mathcal{M}$)? → **Dishonest**

  Always ($\forall\mathcal{M}$)? Almost surely (w. p. 1)? → **Honest**

  Under reasonable assumptions + $\forall$ parameterization? → **Almost honest**

State of the art

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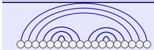	Comp.	P [Nussinov 80]	P [Ieong 03]	P [Zuker 81]
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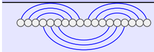	Comp.	???	NP-Hard [Ieong 03]	NP-Hard [Ieong 03]
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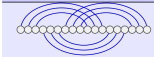	Comp.	P [Tabaska 98]	NP-Hard [Lyngsø 04]	NP-Hard [Lyngsø 00, Akutsu 00]
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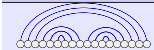
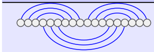
	Comp.	P [Nussinov 80]	P [Ieong 03]	P [Zuker 81]
Non-crossing	Approx.	–	–	–
	Comp.	???	NP-Hard [Ieong 03]	NP-Hard [Ieong 03]
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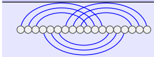	Comp.	P [Tabaska 98]	NP-Hard [Lyngsø 04]	NP-Hard [Lyngsø 00, Akutsu 00]
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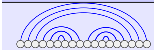	Comp.	P [Nussinov 80]	P [Ieong 03]	P [Zuker 81]
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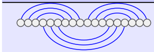	Comp.	???	NP-Hard [Ieong 03]	NP-Hard [Ieong 03]
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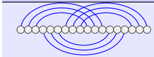	Comp.	P [Tabaska 98]	NP-Hard [Lyngsø 04]	NP-Hard [Lyngsø 00, Akutsu 00]
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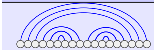
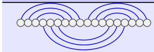
Missing:

- Qualitative difference between Stacking-pairs and Nearest-Neighbor models?
- Influence of $\mathcal{M}$ on hardness/approx. ratio (only unit-valued studied)

Biologists demand (Biology deserves) **honest hardness results**:

- Energy model as input: Pandora's box (e.g. RNA folding on infinite alphabet!)
- Model as parameter: Is problem hard...
  Sometimes ($\exists\mathcal{M}$)? → **Dishonest**
  Always ($\forall\mathcal{M}$)? Almost surely (w. p. 1)? → **Honest**
  Under reasonable assumptions + $\forall$ parameterization? → **Almost honest**

State of the art

		Base-pairs	Stacking-Pairs	Nearest-Neighbor
	Comp.	P [Nussinov 80]	P [Ieong 03]	P [Zuker 81]
Non-crossing	Approx.	–	–	–
	Comp.	???	NP-Hard [Ieong 03]	NP-Hard [Ieong 03]
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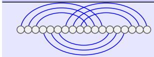	Comp.	P [Tabaska 98]	NP-Hard [Lyngsø 04]	NP-Hard [Lyngsø 00, Akutsu 00]
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(Almost!)-honest hardness of RNA-PK-FOLD($\mathcal{S}$)

For any **stacking energy model $\mathcal{S}$,** such that:

- Only G/C, A/U and G/U pairs are allowed
- Any other X/Y pair forbidden

$$\Rightarrow \Delta_{\mathcal{S}}(X, Y, *, *) = +\infty$$

(Such BPs are rarely observed [Stombaugh 09]$\longrightarrow$ Unstable)

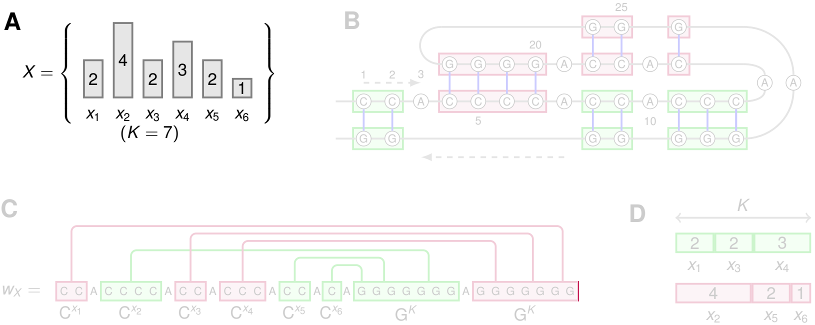
- Arbitrary energies associated with valid stackings

$$\Rightarrow \Delta_{\mathcal{S}}(X, Y, X', Y') < 0$$

Theorem

RNA-PK-FOLD($\mathcal{S}$) *is* NP*-hard.*

Example


A
X =
2
4
2
3
2
1
x1 x2 x3 x4 x5 x6
(K = 7)
B
25
20
1 2 3
5
10
C
wX =
C C A C C C C A C C A C C C A C C A C A G G G G G G G A G G G G G G G
C^x1 C^x2 C^x3 C^x4 C^x5 C^x6 G^K G^K
D
K
2 2 3
x1 x3 x4
4 2 1
x2 x5 x6

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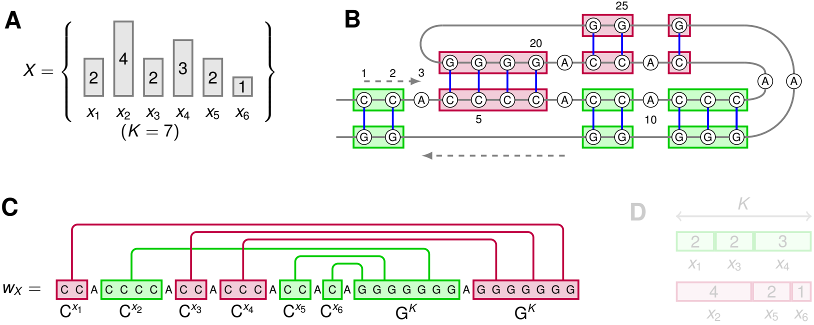
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G G G
G G G G A C C A C
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A A
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C
w_X =
C C A C C C C A C C A C C C A C C A C A G G G G G G G A G G G G G G G
C^x1
C^x2
C^x3
C^x4
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C^x6
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D
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2
2
3
x1
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x4
4
2
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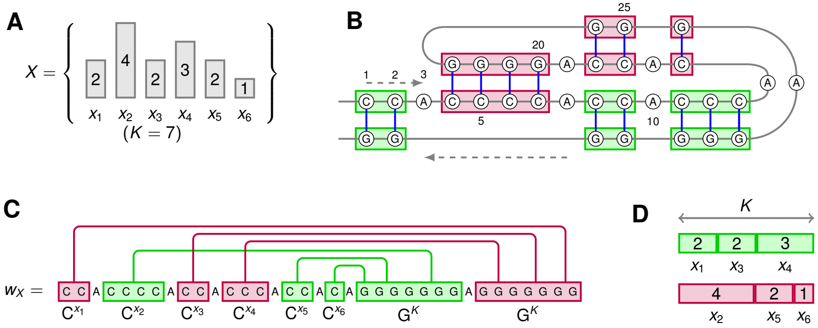
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$X = \{ 2, 4, 2, 3, 2, 1 \}$
x_1 x_2 x_3 x_4 x_5 x_6
$(K = 7)$
B
1 2 3
5
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G G G G A C C A C
C C A C C C C A C C A C C C
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G G G
A A
C
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C^{x_1} C^{x_2} C^{x_3} C^{x_4} C^{x_5} C^{x_6} G^K G^K
D
K
2 2 3
x_1 x_3 x_4
4 2 1
x_2 x_5 x_6

Proof

Definition (3-PARTITION problem)

Input: Sequence of integers $X = \{x_i\}_{i=1}^{n}$, summing to $n/3 \cdot K$, $K \in \mathbb{N}$.
Output: `True` iff X can be split into $m := n/3$ triplets $\{(x_{a_j}, x_{b_j}, x_{c_j})\}_{j=1}^{m}$ s. t.

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Proof. Reduction from 3-PARTITION:

- Let $w_X := \mathrm{C}^{x_1}\mathrm{A}\mathrm{C}^{x_2}\mathrm{A}\mathrm{C}^{x_3}\mathrm{A}\cdots\mathrm{A}\mathrm{C}^{x_n}\underbrace{\mathrm{A}\mathrm{G}^{K}\mathrm{A}\mathrm{G}^{K}\mathrm{A}\cdots\mathrm{A}\mathrm{G}^{K}}_{m\text{ times}}$ and $\delta := \Delta_{\mathcal{S}}(\mathrm{C},\mathrm{G},\mathrm{C},\mathrm{G})$
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Reminder: 3-PARTITION is **strongly** NP-Hard [Garey 75], i.e. still hard if $x_i < P(n)$.

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- Existence of polynomial time approximation scheme (in $\mathcal{O}(n^{4^{1/\varepsilon}})$) [Lyngsø 04]
- Base-pair maximization (unit cost) ⇒ Arbitrary energies???

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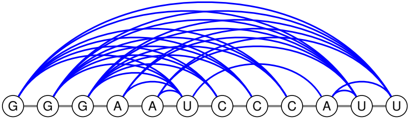

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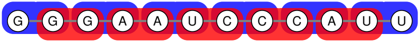

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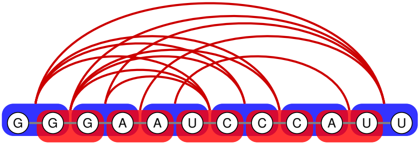

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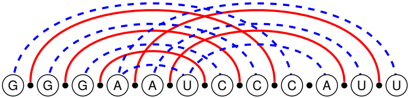

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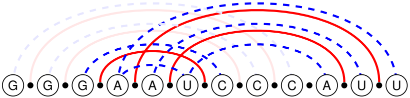

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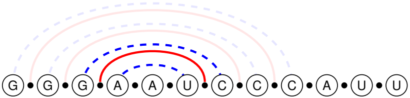

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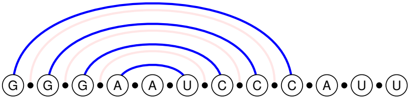

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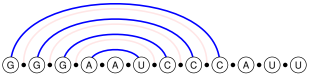
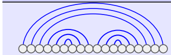


Complexity: At most $\mathcal{O}(n^3)$ (Max-weighted matching)

Approx. ratio: Initial matching m' has total energy smaller than OPT.
Loop 3: Each stacking pair p conflicts with ≤ 4 **pairs** in m', **having greater energy**.

$\Rightarrow$ Returned matching has free-energy $\leq 1/5$ of OPT ($\forall \mathcal{S} \to$ **Honest**)

Half-time summary

		Base-pairs	Stacking-Pairs	Nearest-Neighbor
	Comp.	P [Nussinov 80]	P [Ieong 03]	P [Zuker 81]
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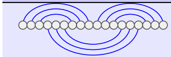
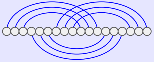
	Comp.	???	NP-Hard [Ieong 03]	NP-Hard [Ieong 03]
Planar	Approx.	2-approx. ≈[Ieong 03]	2-approx. [Ieong 03]	???
	Comp.	P [Tabaska 98]	NP-Hard [Lyngsø 04] **(any* Δ model)**	NP-Hard [Lyngsø 00, Akutsu 00]
General	Approx.	–	ε-approx. $\in \mathcal{O}(n^{4^{1/\varepsilon}})$ [Lyngsø 04] **1/5 (any Δ model)**	**???**

How hard is it to approximate the nearest neighbor model?

(Dishonest!) Inapproximability of Nearest-Neighbor model

Theorem

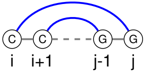
For some nearest-neighbor model $\mathcal{N}$, one has $\text{RNA-PK-F}\textsc{old}(\mathcal{N}) \notin APX$.

Proof. Consider the RNA seq. built from some 3-PARTITION instance X:

$$w_X = \text{C}^{x_1}\text{AC}^{x_2}\text{A}\cdots\text{AC}^{x_{3m}}\text{A}\,\underbrace{\text{G}^K\text{UG}^K\text{U}\cdots\text{G}^K\text{U}}_{m\text{ times}}\,\text{U}^{2m}$$

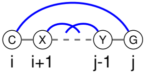
and the energy model:

$\Delta^*_{\mathcal{N}}$: (A)



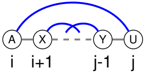
$\longrightarrow -1, \quad \forall i < j,$

(B)



$\longrightarrow -1, \quad \forall i < j, \forall X \neq C, \forall Y,$
($i+1$ and $j-1$ **must both** base-pair somewhere, possibly together)

(C)



$\longrightarrow -1, \quad \forall i < j, \forall (X, Y),$
($i+1$ and $j-1$ **must both** base-pair somewhere, possibly together)

(D) Any other motif $\longrightarrow +\infty, \quad \forall i < j,$

Claim: The energy of **any matching** of w_X is either 0 (no base-pair), $-|w_X| < 0$ ($\Rightarrow X$ is 3-partitionable) or $+\infty$ (any other case).

(Dishonest!) Inapproximability of Nearest-Neighbor model

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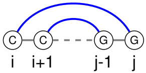

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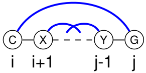
(B)



$\longrightarrow -1, \quad \forall i < j, \forall X \neq C, \forall Y,$
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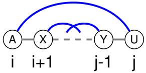
(C)



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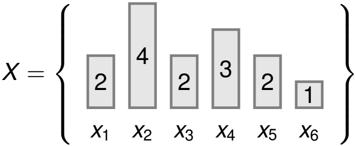
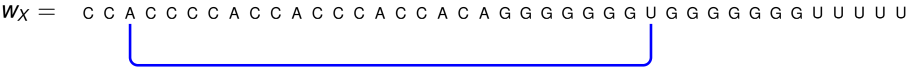
Three choices

Matching S^* is:

- **Empty** $\rightarrow \Delta_{\mathcal{N}}(S^*) = 0$
- **Invalid:** Some base-pair breaks some rule $\rightarrow \Delta_{\mathcal{N}}(S^*) = \infty$
- **Induces a 3-partition matching**



$(K = 7)$



$w_X =$ C C A C C C C A C C A C C C A C C A C A G G G G G G G U G G G G G G G U U U U U

Three choices

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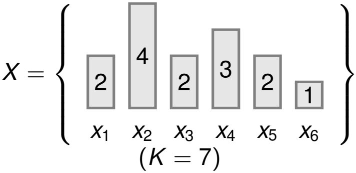

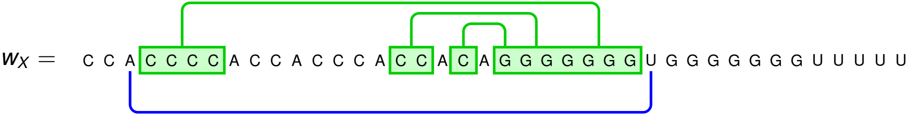
$w_X =$
C C A C C C C A C C A C C C A C C A C A G G G G G G G U G G G G G G G U U U U U

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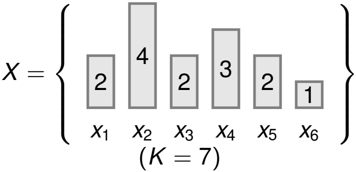
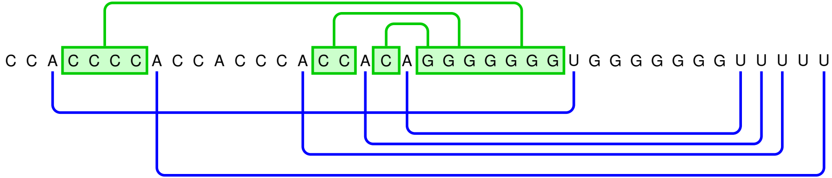


$w_X =$


C C A C C C C A C C A C C C A C C A C A G G G G G G G U G G G G G G G U U U U U

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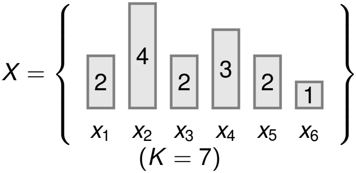

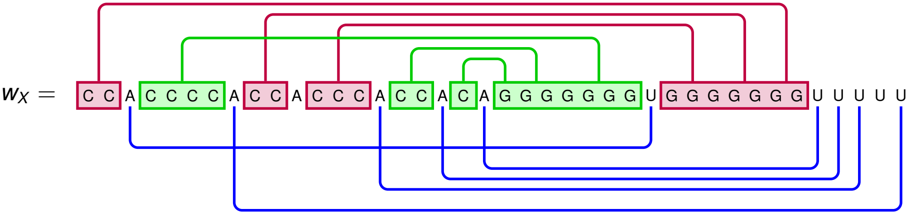
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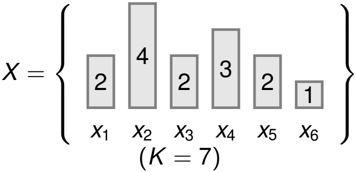
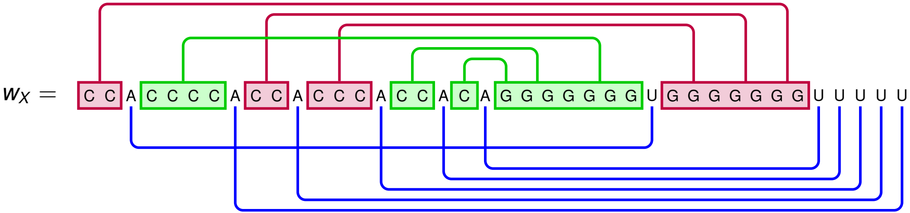
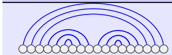
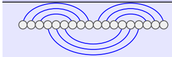
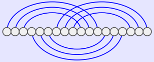



w_X =
C C A C C C C A C C A C C C A C C A C A G G G G G G G U G G G G G G G U U U U U

Final summary

		Base-pairs	Stacking-Pairs	Nearest-Neighbor
	Comp.	P [Nussinov 80]	P [Ieong 03]	P [Zuker 81]
Non-crossing	Approx.	–	–	–
	Comp.	???	NP-Hard [Ieong 03]	NP-Hard [Ieong 03]
Planar	Approx.	2-approx. ≈[Ieong 03]	2-approx. [Ieong 03]	???
	Comp.	P [Tabaska 98]	NP-Hard [Lyngsø 04] **(any* Δ model)**	NP-Hard [Lyngsø 00, Akutsu 00]
General	Approx.	–	ε-approx. $\in \mathcal{O}(n^{4^{1/\varepsilon}})$ [Lyngsø 04] **1/5 (any Δ model)**	**APX-Hard**

Conclusion

Incorporating pseudoknots is generally hard:

- **Dishonest** inapproximability result for nearest-neighbor model
- **Almost honest** general hardness result for stacking model
- **Honest** 5-approximation for stacking model

Still hope for **tractable exact algorithms** accounting for PKs:

- Parametrized approaches (*aka you get what you pay for. . .*)
- Topologically restricted sets of RNAs

Thanks for listening
Questions?

Job offers: PhD & Postdoc on RNA kinetics@Inria/Ecole Polytechnique

Funding

Agence Nationale de la Recherche ANR

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