

Impact Of The Energy Model On The Complexity Of RNA Folding With Pseudoknots

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

⊙ University of Florida, Gainesville, USA

♣ Albert Ludwigs University, Freiburg, Germany

• LIX, CNRS/Ecole Polytechnique, France

◇ AMIB Team-Project, INRIA, Saclay, France

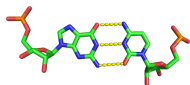
August 2nd – Benasque'12

Crossing interactions

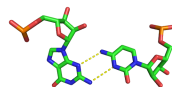
- **Non-canonical base-pairs:**

Any base-pair **other than** {(A-U), (C-G), (G-U)}

OR interacting in a non-standard way (WC/WC-Cis) [Leontis 01].

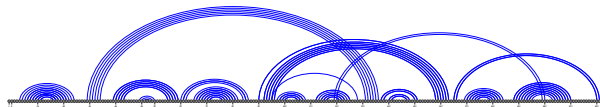


Canonical CG base-pair (WC/WC-Cis)



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

- **Pseudoknots:** Crossing sets of nested stable base-pairs



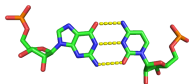
Group I Ribozyme (PDBID: 1Y0Q:A)

Crossing interactions

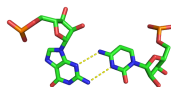
- **Non-canonical base-pairs:**

Any base-pair **other than** {(A-U), (C-G), (G-U)}

OR interacting in a non-standard way (WC/WC-Cis) [Leontis 01].

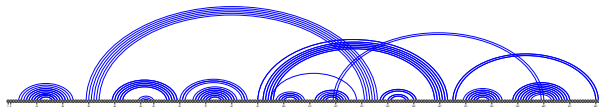


Canonical CG base-pair (WC/WC-Cis)



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

- **Pseudoknots:** Crossing sets of nested stable base-pairs



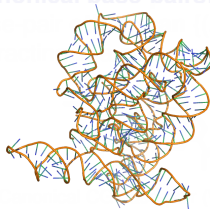
Group I Ribozyme (PDBID: 1Y0Q:A)

Crossing interactions

- **Non-canonical base-pairs:**

Any base

OR inter



(A-U), (C-G), (G-U)

standard Watson-Crick

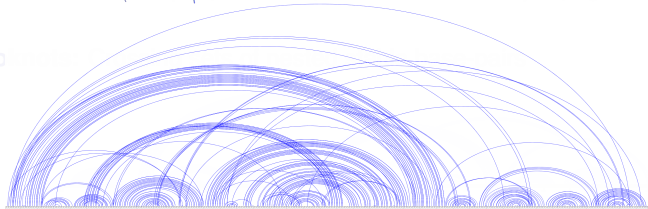
Crossing interactions, once ignored, are now **ubiquitous!**

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

VC/WC-Cis

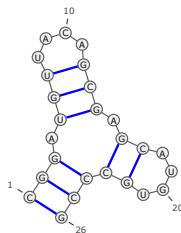
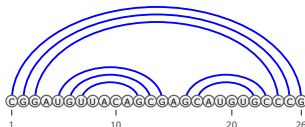
Non-canonical base-pair (Sugar/WC-Trans)

- **Pseudo**



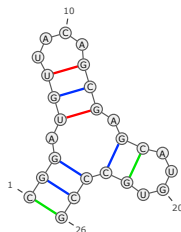
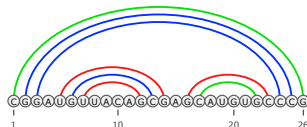
Group I ribozyme (PDB ID: 1RUC)

Problem statement



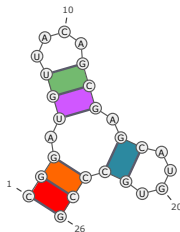
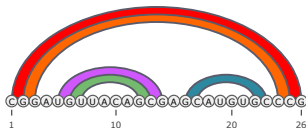
- **RNA structure S :** (Partial) matching of positions in sequence w
- **Motifs:** Sequence/structure features (e.g. Base-pairs, Stacking pairs, Loops...)
- **Energy model:**
 - Motif** \rightarrow Free-energy contribution $\Delta(\cdot) \in \mathbb{R}^- \cup \{+\infty\}$
 - Free-Energy $E_w(S)$:**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

Problem statement



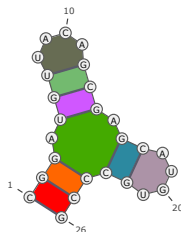
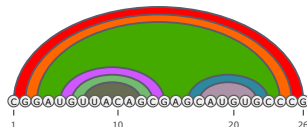
- **RNA structure S :** (Partial) matching of positions in sequence w
- **Motifs:** Sequence/structure features (e.g. Base-pairs, Stacking pairs, Loops...)
- **Energy model:**
 - Motif \rightarrow Free-energy contribution $\Delta(\cdot) \in \mathbb{R}^- \cup \{+\infty\}$
 - Free-Energy $E_w(S)$: Sum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

Problem statement



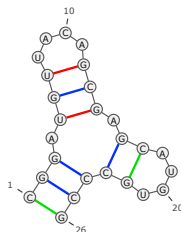
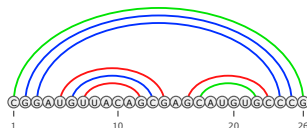
- **RNA structure S :** (Partial) matching of positions in sequence w
- **Motifs:** Sequence/structure features (e.g. Base-pairs, Stacking pairs, Loops...)
- **Energy model:**
 - Motif \rightarrow Free-energy contribution $\Delta(\cdot) \in \mathbb{R}^- \cup \{+\infty\}$
 - Free-Energy $E_w(S)$: Sum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

Problem statement



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

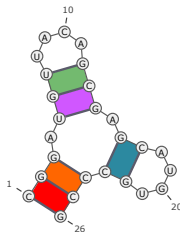
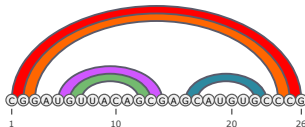
Problem statement



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

$$E_S = 2 \cdot \Delta \left(\begin{array}{c} \textcircled{U} \\ | \\ \textcircled{G} \end{array} \right) + 4 \cdot \Delta \left(\begin{array}{c} \textcircled{G} \\ | \\ \textcircled{C} \end{array} \right) + 2 \cdot \Delta \left(\begin{array}{c} \textcircled{C} \\ | \\ \textcircled{G} \end{array} \right)$$

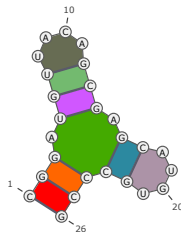
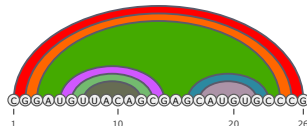
Problem statement



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

$$E_S = \Delta \left(\begin{array}{cc} \text{C} & \text{G} \\ | & | \\ \text{G} & \text{C} \end{array} \right) + \Delta \left(\begin{array}{cc} \text{G} & \text{G} \\ | & | \\ \text{C} & \text{C} \end{array} \right) + \Delta \left(\begin{array}{cc} \text{U} & \text{G} \\ | & | \\ \text{G} & \text{C} \end{array} \right) + \Delta \left(\begin{array}{cc} \text{U} & \text{G} \\ | & | \\ \text{G} & \text{C} \end{array} \right) + \Delta \left(\begin{array}{cc} \text{U} & \text{G} \\ | & | \\ \text{G} & \text{C} \end{array} \right)$$

Problem statement



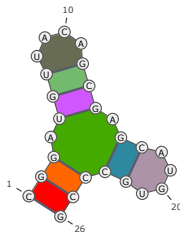
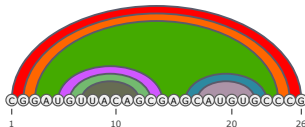
- **RNA structure S :** (Partial) matching of positions in sequence w
- **Motifs:** Sequence/structure features (e.g. Base-pairs, Stacking pairs, Loops...)
- **Energy model:**

Motif \rightarrow Free-energy contribution $\Delta(\cdot) \in \mathbb{R}^- \cup \{+\infty\}$

Free-Energy $E_w(S)$: Sum over (independently contributing) motifs in S

$$\begin{aligned}
 E_S = & \Delta \left(\begin{array}{c} \text{C} \quad \text{G} \\ | \quad | \\ \text{G} \quad \text{C} \end{array} \right) + \Delta \left(\begin{array}{c} \text{G} \quad \text{G} \\ | \quad | \\ \text{C} \quad \text{C} \end{array} \right) + \Delta \left(\begin{array}{c} \text{U} \quad \text{G} \\ | \quad | \\ \text{G} \quad \text{C} \end{array} \right) + \Delta \left(\begin{array}{c} \text{U} \quad \text{G} \\ | \quad | \\ \text{G} \quad \text{C} \end{array} \right) + \Delta \left(\begin{array}{c} \text{U} \quad \text{G} \\ | \quad | \\ \text{G} \quad \text{C} \end{array} \right) \\
 & + \Delta \left(\begin{array}{c} \text{A} \quad \text{C} \quad \text{A} \\ / \quad | \quad \backslash \\ \text{U} \quad \text{G} \end{array} \right) + \Delta \left(\begin{array}{c} \text{A} \quad \text{C} \quad \text{A} \\ / \quad | \quad \backslash \\ \text{U} \quad \text{G} \end{array} \right) + \Delta \left(\begin{array}{c} \text{C} \quad \text{A} \\ / \quad \backslash \\ \text{U} \quad \text{G} \end{array} \right)
 \end{aligned}$$

Problem statement



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

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

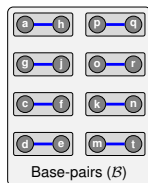
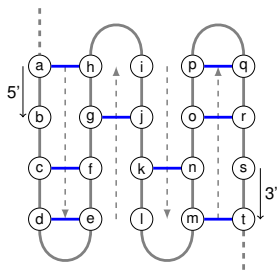
Input: RNA sequence $w \in \{A, C, G, U\}^*$.

Output: Matching S^* , having Minimal Free-Energy $E_w(S^*)$.

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 \emptyset)
 $\rightarrow \Delta_{\mathcal{N}}(w_i, w_j, w_{i+1}, w_{j-1}, w_{m_{i+1}}, w_{m_{j-1}})$
- **Stacking pairs model \mathcal{S}** : Nucl. at (i, j) and $(i+1, j-1)$ **only if latter paired**
 $\rightarrow \Delta_{\mathcal{S}}(w_i, w_j, w_{i+1}, w_{j-1})$



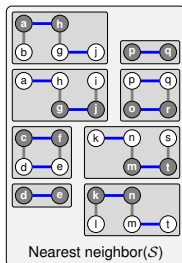
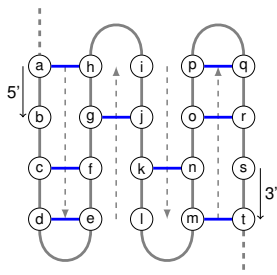
Solved in $\mathcal{O}(n^3)$ [Tabaska 98]
(Max-weighted matching)

Unrealistic!

Energy models

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 \emptyset)
 $\rightarrow \Delta_{\mathcal{N}}(w_i, w_j, w_{i+1}, w_{j-1}, w_{m_{i+1}}, w_{m_{j-1}})$
- **Stacking pairs model \mathcal{S}** : Nucl. at (i, j) and $(i+1, j-1)$ **only if latter paired**
 $\rightarrow \Delta_{\mathcal{S}}(w_i, w_j, w_{i+1}, w_{j-1})$

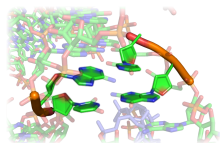
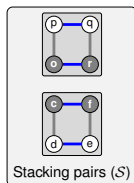
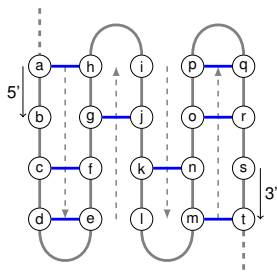


NP-hard [Lyngsø 00, Akutsu 00]
Too expressive?

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 \emptyset)
 $\rightarrow \Delta_{\mathcal{N}}(w_i, w_j, w_{i+1}, w_{j-1}, w_{m_{i+1}}, w_{m_{j-1}})$
- **Stacking pairs model \mathcal{S}** : Nucl. at (i, j) and $(i+1, j-1)$ **only if** latter paired
 $\rightarrow \Delta_{\mathcal{S}}(w_i, w_j, w_{i+1}, w_{j-1})$




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 [leong 03]	P [Zuker 81]
Non-crossing	Approx.	–	–	–
	Comp.	???	NP-Hard [leong 03]	NP-Hard [leong 03]
Planar	Approx.	2-approx. \approx [leong 03]	2-approx. [leong 03]	???
	Comp.	P [Tabaska 98]	NP-Hard [Lyngsø 04]	NP-Hard [Lyngsø 00, Akutsu 00]
General	Approx.	–	ϵ -approx. $\in \mathcal{O}(n^{4^{1/\epsilon}})$ [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 ($\exists \mathcal{M}$)?


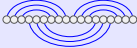
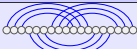
→ Dishonest

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

→ Honest

Under reasonable assumptions + \forall parameterization? → Almost honest

State of the art

		Base-pairs	Stacking-Pairs	Nearest-Neighbor
	Comp.	P [Nussinov 80]	P [leong 03]	P [Zuker 81]
Non-crossing	Approx.	–	–	–
	Comp.	???	NP-Hard [leong 03]	NP-Hard [leong 03]
Planar	Approx.	2-approx. \approx [leong 03]	2-approx. [leong 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 ($\exists \mathcal{M}$)?



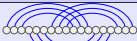
→ Dishonest

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

→ Honest

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

State of the art

		Base-pairs	Stacking-Pairs	Nearest-Neighbor
	Comp.	P [Nussinov 80]	P [leong 03]	P [Zuker 81]
Non-crossing	Approx.	–	–	–
	Comp.	???	NP-Hard [leong 03]	NP-Hard [leong 03]
Planar	Approx.	2-approx. \approx [leong 03]	2-approx. [leong 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 ($\exists \mathcal{M}$)?



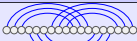
→ **Dishonest**

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

→ **Honest**

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

State of the art

		Base-pairs	Stacking-Pairs	Nearest-Neighbor
	Comp.	P [Nussinov 80]	P [leong 03]	P [Zuker 81]
Non-crossing	Approx.	–	–	–
	Comp.	???	NP-Hard [leong 03]	NP-Hard [leong 03]
Planar	Approx.	2-approx. \approx [leong 03]	2-approx. [leong 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 ($\exists \mathcal{M}$)?


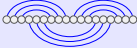
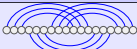
→ **Dishonest**

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

→ **Honest**

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

State of the art

		Base-pairs	Stacking-Pairs	Nearest-Neighbor
	Comp.	P [Nussinov 80]	P [leong 03]	P [Zuker 81]
Non-crossing	Approx.	–	–	–
	Comp.	???	NP-Hard [leong 03]	NP-Hard [leong 03]
Planar	Approx.	2-approx. \approx [leong 03]	2-approx. [leong 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**

(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] \rightarrow 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.

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.

$$x_{a_j} + x_{b_j} + x_{c_j} = K, \forall j \in [1, m].$$

Proof. Reduction from 3-PARTITION:

- Let $w_X := C^{x_1} A C^{x_2} A C^{x_3} A \dots A C^{x_n} \underbrace{A G^K A G^K A \dots A G^K}_{m \text{ times}}$ and $\delta := \Delta_S(C, G, C, G)$
- Best matching S^* for w_X has free-energy $E(S^*)_{w_X} \leq E^* := \delta \cdot (K - 3) \cdot m$.
- If X 3-partitionable, then matching induced by partition gives $E(S^*)_{w_X} = E^*$.
- If $E(S^*)_{w_X} = E^*$, then S^* saturates each G^K block, using three blocks (C^a, C^b, C^c).
- Since $|w_X| \in \mathcal{O}(n \cdot P(n))$, then $\text{RNA-PK-FOLD}(S) \in P \Rightarrow 3\text{-PARTITION} \in P$.

Reminder: 3-PARTITION is **strongly** NP-Hard [Garey 75], i.e. still hard if $x_i < P(n)$.

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.

$$x_{a_j} + x_{b_j} + x_{c_j} = K, \forall j \in [1, m].$$

Proof. Reduction from 3-PARTITION:

- Let $w_X := C^{x_1} A C^{x_2} A C^{x_3} A \dots A C^{x_n} \underbrace{A G^K A G^K A \dots A G^K}_{m \text{ times}}$ and $\delta := \Delta_S(C, G, C, G)$
- Best matching S^* for w_X has free-energy $E(S^*)_{w_X} \leq E^* := \delta \cdot (K - 3) \cdot m$.
- If X 3-partitionable, then matching induced by partition gives $E(S^*)_{w_X} = E^*$.
- If $E(S^*)_{w_X} = E^*$, then S^* saturates each G^K block, using three blocks (C^a, C^b, C^c) .
- Since $|w_X| \in \mathcal{O}(n \cdot P(n))$, then $\text{RNA-PK-FOLD}(S) \in P \Rightarrow 3\text{-PARTITION} \in P$.

Reminder: 3-PARTITION is **strongly** NP-Hard [Garey 75], i.e. still hard if $x_i < P(n)$.

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.

$$x_{a_j} + x_{b_j} + x_{c_j} = K, \forall j \in [1, m].$$

Proof. Reduction from 3-PARTITION:

- Let $w_X := C^{x_1} A C^{x_2} A C^{x_3} A \dots A C^{x_n} \underbrace{A G^K A G^K A \dots A G^K}_{m \text{ times}}$ and $\delta := \Delta_S(C, G, C, G)$
- Best matching S^* for w_X has free-energy $E(S^*)_{w_X} \leq E^* := \delta \cdot (K - 3) \cdot m$.
- If X 3-partitionable, then matching induced by partition gives $E(S^*)_{w_X} = E^*$.
- If $E(S^*)_{w_X} = E^*$, then S^* saturates each G^K block, using three blocks (C^a, C^b, C^c).
- Since $|w_X| \in \mathcal{O}(n \cdot P(n))$, then $\text{RNA-PK-FOLD}(S) \in P \Rightarrow 3\text{-PARTITION} \in P$.

Reminder: 3-PARTITION is **strongly** NP-Hard [Garey 75], i.e. still hard if $x_i < P(n)$.

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.

$$x_{a_j} + x_{b_j} + x_{c_j} = K, \forall j \in [1, m].$$

Proof. Reduction from 3-PARTITION:

- Let $w_X := C^{x_1} A C^{x_2} A C^{x_3} A \dots A C^{x_n} \underbrace{A G^K A G^K A \dots A G^K}_{m \text{ times}}$ and $\delta := \Delta_S(C, G, C, G)$
- Best matching S^* for w_X has free-energy $E(S^*)_{w_X} \leq E^* := \delta \cdot (K - 3) \cdot m$.
- If X 3-partitionable, then matching induced by partition gives $E(S^*)_{w_X} = E^*$.
- If $E(S^*)_{w_X} = E^*$, then S^* saturates each G^K block, using three blocks (C^a, C^b, C^c) .
- Since $|w_X| \in \mathcal{O}(n \cdot P(n))$, then $\text{RNA-PK-FOLD}(S) \in P \Rightarrow 3\text{-PARTITION} \in P$.

Reminder: 3-PARTITION is **strongly** NP-Hard [Garey 75], i.e. still hard if $x_i < P(n)$.

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.

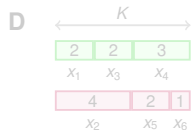
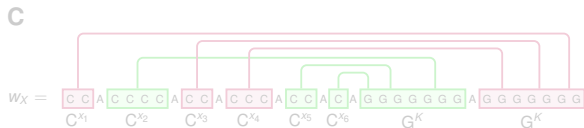
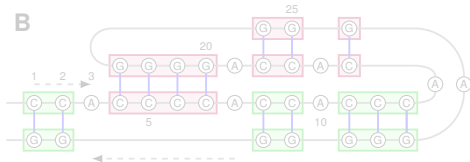
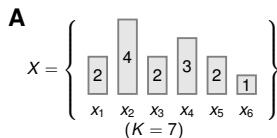
$$x_{a_j} + x_{b_j} + x_{c_j} = K, \forall j \in [1, m].$$

Proof. Reduction from 3-PARTITION:

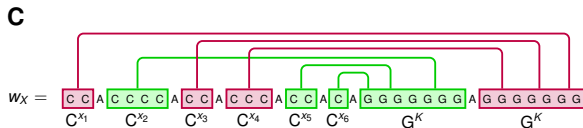
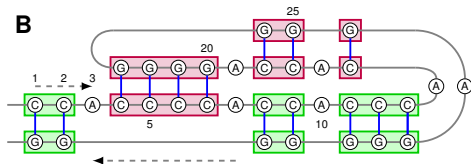
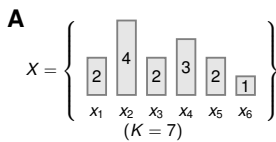
- Let $w_X := C^{x_1} A C^{x_2} A C^{x_3} A \dots A C^{x_n} \underbrace{A G^K A G^K A \dots A G^K}_{m \text{ times}}$ and $\delta := \Delta_S(C, G, C, G)$
- Best matching S^* for w_X has free-energy $E(S^*)_{w_X} \leq E^* := \delta \cdot (K - 3) \cdot m$.
- If X 3-partitionable, then matching induced by partition gives $E(S^*)_{w_X} = E^*$.
- If $E(S^*)_{w_X} = E^*$, then S^* saturates each G^K block, using three blocks (C^a, C^b, C^c) .
- Since $|w_X| \in \mathcal{O}(n \cdot P(n))$, then $\text{RNA-PK-FOLD}(S) \in \mathcal{P} \Rightarrow 3\text{-PARTITION} \in \mathcal{P}$.

Reminder: 3-PARTITION is **strongly** NP-Hard [Garey 75], i.e. still hard if $x_i < P(n)$.

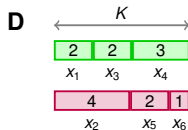
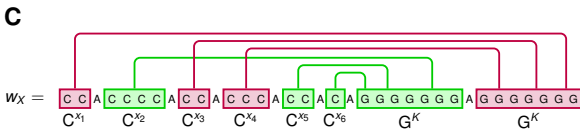
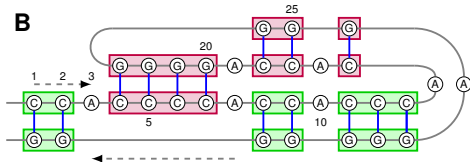
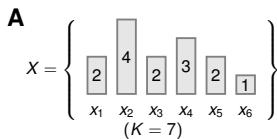
Example



Example



Example

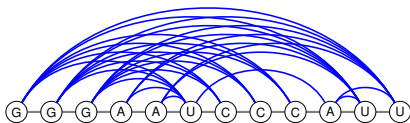


Honest $\mathcal{O}(n^3)$ 5-approximation for RNA-PK-FOLD(S)

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

Algorithm:

- 1 Build weighted adjacency graph $G = (V, E)$
 - Vertices: Pairs of consecutive pos. $(i, i + 1)$
 - Edges: $(i, i + 1) \rightarrow (j - 1, j)$ with weight $-\Delta_S(w_i, w_j, w_{i+1}, w_{j-1})$
- 2 Compute maximal-weighted matching m' .
- 3 Loop over $p = (i, i + 1), (j, j - 1) \in m'$, ordered by decreasing weight:
 - Add result to output m , remove any $p' \in m'$ conflicting with p
- 4 Return m



Honest $\mathcal{O}(n^3)$ 5-approximation for RNA-PK-FOLD(S)

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

Algorithm:

- 1 Build weighted adjacency graph $G = (V, E)$
 - Vertices: Pairs of consecutive pos. $(i, i + 1)$
 - Edges: $(i, i + 1) \rightarrow (j - 1, j)$ with weight $-\Delta_S(w_i, w_j, w_{i+1}, w_{j-1})$
- 2 Compute maximal-weighted matching m' .
- 3 Loop over $p = (i, i + 1), (j, j - 1) \in m'$, ordered by decreasing weight:
 - Add result to output m , remove any $p' \in m'$ conflicting with p
- 4 Return m

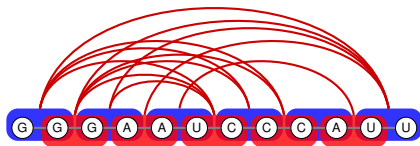


Honest $\mathcal{O}(n^3)$ 5-approximation for RNA-PK-FOLD(S)

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

Algorithm:

- 1 Build weighted adjacency graph $G = (V, E)$
 - Vertices: Pairs of consecutive pos. $(i, i + 1)$
 - Edges: $(i, i + 1) \rightarrow (j - 1, j)$ with weight $-\Delta_S(w_i, w_j, w_{i+1}, w_{j-1})$
- 2 Compute maximal-weighted matching m' .
- 3 Loop over $p = (i, i + 1), (j, j - 1) \in m'$, ordered by decreasing weight:
 - Add result to output m , remove any $p' \in m'$ conflicting with p
- 4 Return m

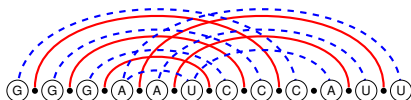


Honest $\mathcal{O}(n^3)$ 5-approximation for RNA-PK-FOLD(S)

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

Algorithm:

- 1 Build weighted adjacency graph $G = (V, E)$
 - Vertices: Pairs of consecutive pos. $(i, i + 1)$
 - Edges: $(i, i + 1) \rightarrow (j - 1, j)$ with weight $-\Delta_S(w_i, w_j, w_{i+1}, w_{j-1})$
- 2 Compute maximal-weighted matching m' .
- 3 Loop over $p = (i, i + 1), (j, j - 1) \in m'$, ordered by decreasing weight:
 - Add result to output m , remove any $p' \in m'$ conflicting with p
- 4 Return m

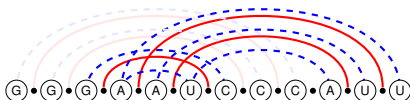


Honest $\mathcal{O}(n^3)$ 5-approximation for RNA-PK-FOLD(S)

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

Algorithm:

- 1 Build weighted adjacency graph $G = (V, E)$
 - Vertices: Pairs of consecutive pos. $(i, i + 1)$
 - Edges: $(i, i + 1) \rightarrow (j - 1, j)$ with weight $-\Delta_S(w_i, w_j, w_{i+1}, w_{j-1})$
- 2 Compute maximal-weighted matching m' .
- 3 Loop over $p = (i, i + 1), (j, j - 1) \in m'$, ordered by decreasing weight:
 - Add result to output m , remove any $p' \in m'$ conflicting with p
- 4 Return m

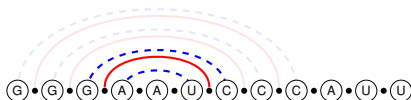


Honest $\mathcal{O}(n^3)$ 5-approximation for RNA-PK-FOLD(S)

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

Algorithm:

- 1 Build weighted adjacency graph $G = (V, E)$
 - Vertices: Pairs of consecutive pos. $(i, i + 1)$
 - Edges: $(i, i + 1) \rightarrow (j - 1, j)$ with weight $-\Delta_S(w_i, w_j, w_{i+1}, w_{j-1})$
- 2 Compute maximal-weighted matching m' .
- 3 Loop over $p = (i, i + 1), (j, j - 1) \in m'$, ordered by decreasing weight:
 - Add result to output m , remove any $p' \in m'$ conflicting with p
- 4 Return m

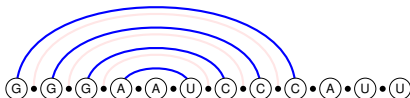


Honest $\mathcal{O}(n^3)$ 5-approximation for RNA-PK-FOLD(S)

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

Algorithm:

- 1 Build weighted adjacency graph $G = (V, E)$
 - Vertices: Pairs of consecutive pos. $(i, i + 1)$
 - Edges: $(i, i + 1) \rightarrow (j - 1, j)$ with weight $-\Delta_S(w_i, w_j, w_{i+1}, w_{j-1})$
- 2 Compute maximal-weighted matching m' .
- 3 Loop over $p = (i, i + 1), (j, j - 1) \in m'$, ordered by decreasing weight:
 - Add result to output m , remove any $p' \in m'$ conflicting with p
- 4 Return m

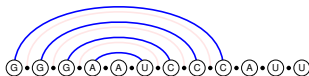


Honest $\mathcal{O}(n^3)$ 5-approximation for RNA-PK-FOLD(S)

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

Algorithm:

- 1 Build weighted adjacency graph $G = (V, E)$
 - Vertices: Pairs of consecutive pos. $(i, i + 1)$
 - Edges: $(i, i + 1) \rightarrow (j - 1, j)$ with weight $-\Delta_S(w_i, w_j, w_{i+1}, w_{j-1})$
- 2 Compute maximal-weighted matching m' .
- 3 Loop over $p = (i, i + 1), (j, j - 1) \in m'$, ordered by decreasing weight:
 - Add result to output m , remove any $p' \in m'$ conflicting with p
- 4 Return m



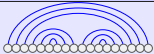

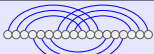
Complexity: At most $\mathcal{O}(n^3)$ (Max-weighted matching)

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 ($\forall S \rightarrow$ Honest)

Half-time 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. \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. $\in \mathcal{O}(n^{4^{1/\epsilon}})$ [Lyngsø 04] 1/5 (any Δ model)	???

How hard is it to approximate the nearest neighbor model?

(Dishonest!) Inapproximability of Nearest-Neighbor model

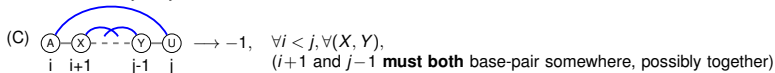
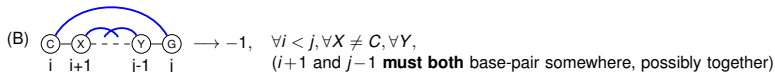
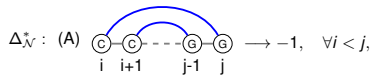
Theorem

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

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

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

and the energy model:



Lemma: 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

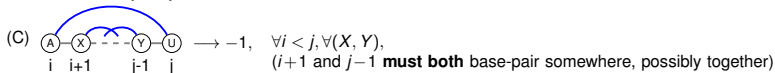
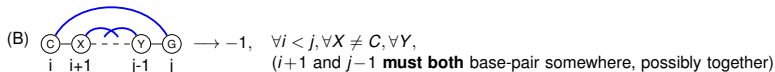
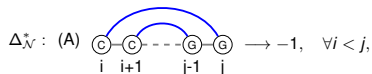
Theorem

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

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

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

and the energy model:



Lemma: 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).

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 matching**

$$X = \left\{ \begin{array}{cccccc} \boxed{2} & \boxed{4} & \boxed{2} & \boxed{3} & \boxed{2} & \boxed{1} \\ x_1 & x_2 & x_3 & x_4 & x_5 & x_6 \end{array} \right\}$$

$(K = 7)$

$W_X =$ 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

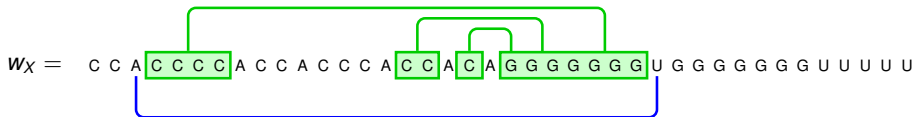
Three choices

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 matching**

$$X = \left\{ \begin{array}{cccccc} \begin{array}{|c|} \hline 2 \\ \hline \end{array} & \begin{array}{|c|} \hline 4 \\ \hline \end{array} & \begin{array}{|c|} \hline 2 \\ \hline \end{array} & \begin{array}{|c|} \hline 3 \\ \hline \end{array} & \begin{array}{|c|} \hline 2 \\ \hline \end{array} & \begin{array}{|c|} \hline 1 \\ \hline \end{array} \\ x_1 & x_2 & x_3 & x_4 & x_5 & x_6 \\ \end{array} \right\}$$

$(K = 7)$



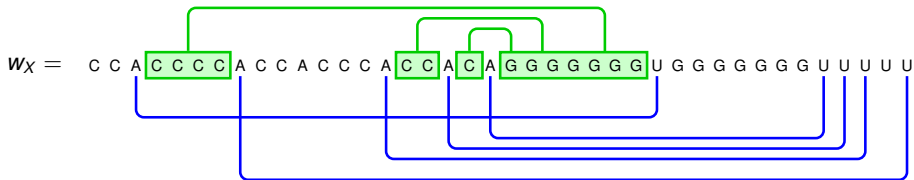
Three choices

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 matching**

$$X = \left\{ \begin{array}{cccccc} \boxed{2} & \boxed{4} & \boxed{2} & \boxed{3} & \boxed{2} & \boxed{1} \\ x_1 & x_2 & x_3 & x_4 & x_5 & x_6 \end{array} \right\}$$

$(K = 7)$



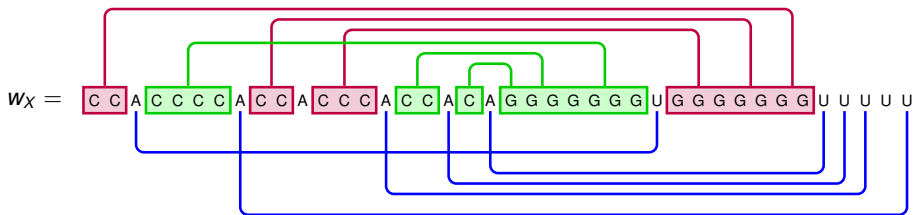
Three choices

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 matching**

$$X = \left\{ \begin{array}{cccccc} \boxed{2} & \boxed{4} & \boxed{2} & \boxed{3} & \boxed{2} & \boxed{1} \\ x_1 & x_2 & x_3 & x_4 & x_5 & x_6 \end{array} \right\}$$

$(K = 7)$



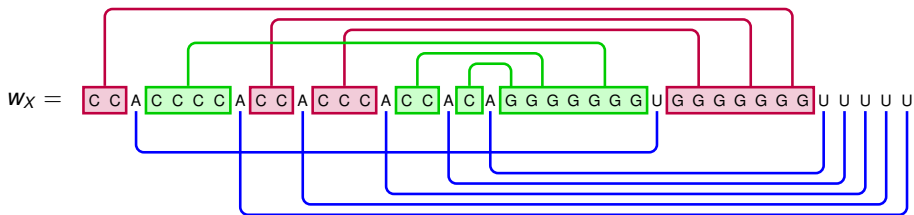
Three choices

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 matching**

$$X = \left\{ \begin{array}{cccccc} \boxed{2} & \boxed{4} & \boxed{2} & \boxed{3} & \boxed{2} & \boxed{1} \\ x_1 & x_2 & x_3 & x_4 & x_5 & x_6 \end{array} \right\}$$

$(K = 7)$



(Dishonest!) Inapproximability of Nearest-Neighbor model

Theorem

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

Proof (continued).

- The energy of **any matching** of w_X under \mathcal{N} is either 0 (no base-pair), $-|w_X| < 0$ ($\Rightarrow X$ is 3-partitionable) or $+\infty$ (any other case).
 - **Reminder:** Polynomial-time $1/f(n)$ -approximation algorithm bound to produce solution having free-energy $\leq f(n) \cdot \text{OPT}$.
 - Any $1/f(n)$ -approx. algorithm, $f(n) > 0$, produces a matching of **negative free-energy** $\leq f(n) \cdot E^* < 0$ iff a matching of energy $E^* < 0$ exists...
 - ... i.e. iff X is 3-partitionable!
- \Rightarrow Unless $P = NP$, there is no **polynomial-time approximation algorithm of (non-necessarily constant) positive ratio** for $\text{RNA-PK-FOLD}(\mathcal{N})$.

(Dishonest!) Inapproximability of Nearest-Neighbor model

Theorem

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

Proof (continued).

- The energy of **any matching** of w_X under \mathcal{N} is either 0 (no base-pair), $-|w_X| < 0$ ($\Rightarrow X$ is 3-partitionable) or $+\infty$ (any other case).
 - **Reminder:** Polynomial-time $1/f(n)$ -approximation algorithm bound to produce solution having free-energy $\leq f(n) \cdot \text{OPT}$.
 - Any $1/f(n)$ -approx. algorithm, $f(n) > 0$, produces a matching of **negative free-energy** $\leq f(n) \cdot E^* < 0$ iff a matching of energy $E^* < 0$ exists...
 - ... i.e. iff X is 3-partitionable!
- \Rightarrow Unless $P = NP$, there is no **polynomial-time approximation algorithm of (non-necessarily constant) positive ratio** for $\text{RNA-PK-FOLD}(\mathcal{N})$.

(Dishonest!) Inapproximability of Nearest-Neighbor model

Theorem

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

Proof (continued).

- The energy of **any matching** of w_X under \mathcal{N} is either 0 (no base-pair), $-|w_X| < 0$ ($\Rightarrow X$ is 3-partitionable) or $+\infty$ (any other case).
 - **Reminder:** Polynomial-time $1/f(n)$ -approximation algorithm bound to produce solution having free-energy $\leq f(n) \cdot \text{OPT}$.
 - Any $1/f(n)$ -approx. algorithm, $f(n) > 0$, produces a matching of **negative free-energy** $\leq f(n) \cdot E^* < 0$ **iff a matching of energy** $E^* < 0$ **exists...**
 - ... i.e. iff X is 3-partitionable!
- \Rightarrow Unless $P = NP$, there is no **polynomial-time approximation algorithm of (non-necessarily constant) positive ratio** for $\text{RNA-PK-FOLD}(\mathcal{N})$.

(Dishonest!) Inapproximability of Nearest-Neighbor model

Theorem

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

Proof (continued).

- The energy of **any matching** of w_X under \mathcal{N} is either 0 (no base-pair), $-|w_X| < 0$ ($\Rightarrow X$ is 3-partitionable) or $+\infty$ (any other case).
- **Reminder:** Polynomial-time $1/f(n)$ -approximation algorithm bound to produce solution having free-energy $\leq f(n) \cdot \text{OPT}$.
- Any $1/f(n)$ -approx. algorithm, $f(n) > 0$, produces a matching of **negative free-energy** $\leq f(n) \cdot E^* < 0$ **iff a matching of energy $E^* < 0$ exists...**
- ... i.e. iff X is 3-partitionable!

\Rightarrow Unless $P = NP$, there is no **polynomial-time approximation algorithm of (non-necessarily constant) positive ratio** for $\text{RNA-PK-FOLD}(\mathcal{N})$.

(Dishonest!) Inapproximability of Nearest-Neighbor model

Theorem

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

Proof (continued).

- The energy of **any matching** of w_X under \mathcal{N} is either 0 (no base-pair), $-|w_X| < 0$ ($\Rightarrow X$ is 3-partitionable) or $+\infty$ (any other case).
 - **Reminder:** Polynomial-time $1/f(n)$ -approximation algorithm bound to produce solution having free-energy $\leq f(n) \cdot \text{OPT}$.
 - Any $1/f(n)$ -approx. algorithm, $f(n) > 0$, produces a matching of **negative free-energy** $\leq f(n) \cdot E^* < 0$ **iff a matching of energy** $E^* < 0$ **exists...**
 - ... i.e. iff X is 3-partitionable!
- \Rightarrow Unless $\text{P} = \text{NP}$, there is no **polynomial-time approximation algorithm of (non-necessarily constant) positive ratio** for $\text{RNA-PK-FOLD}(\mathcal{N})$.

Conclusion

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

Nearest Neighbor model:

- **Dishonest** unapproximability → Hardness of approximating within ratio $f(r)$?
where r is largest ratio between contributions of motifs.

Stacking model:

- **Honest** + **efficient** polynomial-time approximation scheme
- **Approximations** do not guarantee **any** overlap with best solution.
→ Polynomial k -overlap algorithm? (Seems unlikely...)

Thanks for listening
Questions?

Thanks to



Conclusion

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

Nearest Neighbor model:

- **Dishonest** unapproximability → Hardness of approximating within ratio $f(r)$ where r is largest ratio between contributions of motifs.

Stacking model:

- **Honest** + **efficient** polynomial-time approximation scheme
- **Approximations** do not guarantee **any** overlap with best solution.
→ Polynomial k -overlap algorithm? (Seems unlikely...)

Thanks for listening
Questions?

Thanks to



Conclusion

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

Nearest Neighbor model:

- **Dishonest** unapproximability \rightarrow Hardness of approximating within ratio $f(r)$ where r is largest ratio between contributions of motifs.

Stacking model:

- **Honest** + **efficient** polynomial-time approximation scheme
- **Approximations** do not guarantee **any** overlap with best solution.
 \rightarrow Polynomial k -overlap algorithm? (Seems unlikely...)

Thanks for listening
Questions?

Thanks to



Conclusion

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

Nearest Neighbor model:

- **Dishonest** unapproximability \rightarrow Hardness of approximating within ratio $f(r)$ where r is largest ratio between contributions of motifs.

Stacking model:

- **Honest** + **efficient** polynomial-time approximation scheme
- **Approximations** do not guarantee **any** overlap with best solution.
 \rightarrow Polynomial k -overlap algorithm? (Seems unlikely. . .)

Thanks for listening
Questions?



Thanks to



References I



Tatsuya Akutsu.

Dynamic programming algorithms for RNA secondary structure prediction with pseudoknots.
Discrete Appl. Math., vol. 104, no. 1-3, pages 45–62, 2000.



M. R. Garey & D. S. Johnson.

Complexity Results for Multiprocessor Scheduling under Resource Constraints.
SIAM Journal on Computing, vol. 4, no. 4, pages 397–411, 1975.



Samuel leong, Ming yang Kao, Tak wah Lam, Wing kin Sung & Siu ming Yiu.

Predicting RNA Secondary Structures with Arbitrary Pseudoknots by Maximizing the Number of Stacking Pairs.
Journal Of Computational Biology, vol. 10, no. 6, pages 981–995, 2003.



N. Leontis & E. Westhof.

Geometric nomenclature and classification of RNA base pairs.
RNA, vol. 7, pages 499–512, 2001.



R. B. Lyngsø & C. N. S. Pedersen.

RNA Pseudoknot Prediction in Energy-Based Models.
Journal of Computational Biology, vol. 7, no. 3-4, pages 409–427, 2000.



Rune Lyngsø.

Complexity of Pseudoknot Prediction in Simple Models.
In Proceedings of ICALP, 2004.



R. Nussinov & A.B. Jacobson.

Fast algorithm for predicting the secondary structure of single-stranded RNA.
Proc Natl Acad Sci U S A, vol. 77, pages 6903–13, 1980.



Jesse Stombaugh, Craig L. Zirbel, Eric Westhof & Neocles B. Leontis.

Frequency and isostericity of RNA base pairs.
Nucleic Acids Research, vol. 37, no. 7, pages 2294–2312, 2009.

References II



J. E. Tabaska, R. B. Cary, H. N. Gabow & G. D. Stormo.

An RNA folding method capable of identifying pseudoknots and base triples.
Bioinformatics, vol. 14, no. 8, pages 691–699, 1998.



M. Zuker & P. Stiegler.

Optimal computer folding of large RNA sequences using thermodynamics and auxiliary information.
Nucleic Acids Res., vol. 9, pages 133–148, 1981.