Exact algorithms for the RNA energy barrier

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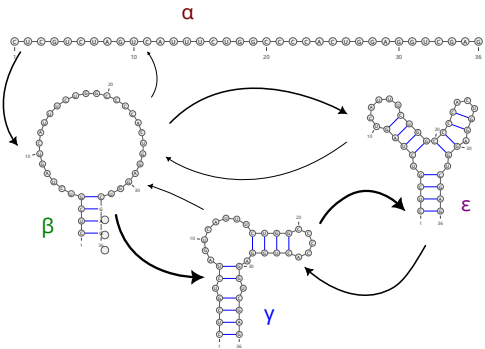
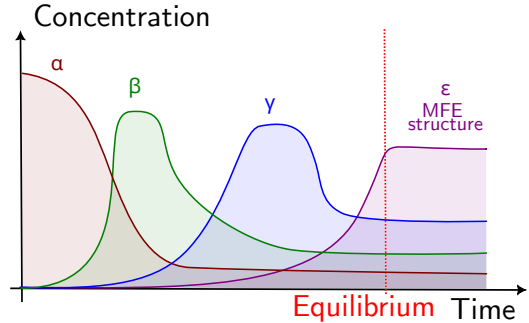
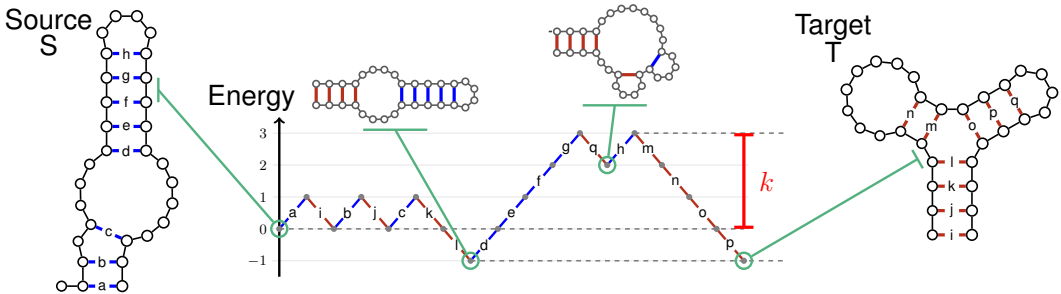
Kinetics motivation





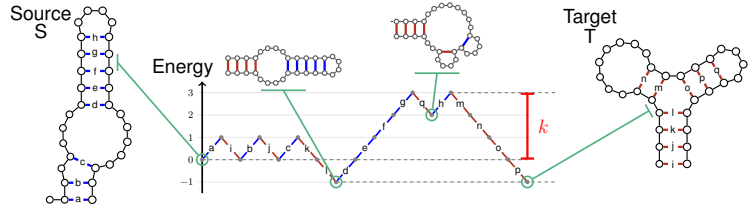
- At equilibrium, for a structure T: $\mathbb{P}(T) \propto e^{-\beta\ \mathrm{E}(\omega,T)}$
- How to compute the transition rates between the structures?
- Barrier k $= \min_{\mathrm{Path}=T_{\mathrm{start}}\to T_{\mathrm{end}}} \max_{S\in\mathrm{Path}} \mathrm{E}(\omega, T)$
- Transition rate between two structures $\propto \frac{1}{k}$

The energy barrier problem



- Barrier k $= \min_{P=S\to T} \max_{p\in P} \text{Energy}(p)$
- Transition rate $\propto \frac{1}{k}$

The energy barrier problem



Problem 1 (RNA Energy Barrier):

Input: Secondary structures S and T; Energy barrier $k \in \mathbb{N}^+$

Output: $P = [T_0 \cdots T_l]$, list of secondary structures if

- $T_0 = S$ and $T_l = T$;
- $|T_i| \geq |L| - k, \forall i \in [0, l]$;
- $|T_i \triangle T_{i+1}| = 1, \forall i \in [0, l-1]$.

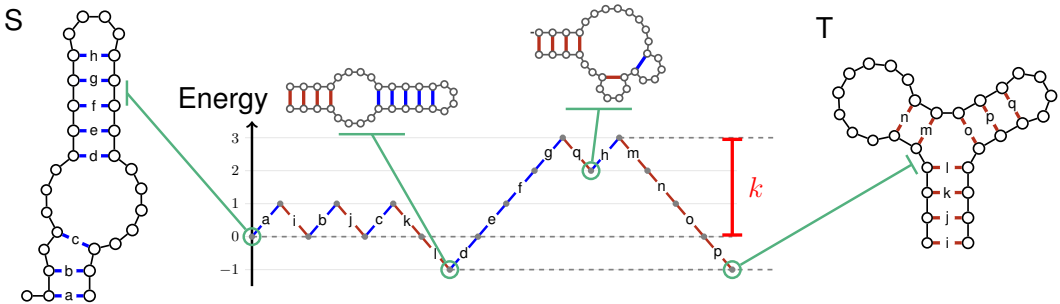
or $\perp$ if no such list exists

NP-HARD

[Maňuch *et al*, Natural Computing 2011]

- Which parameter p for an algorithm in $O(n^p)$ or $O(f(n)c^p)$?

The natural parameter: barrier k as a parameter



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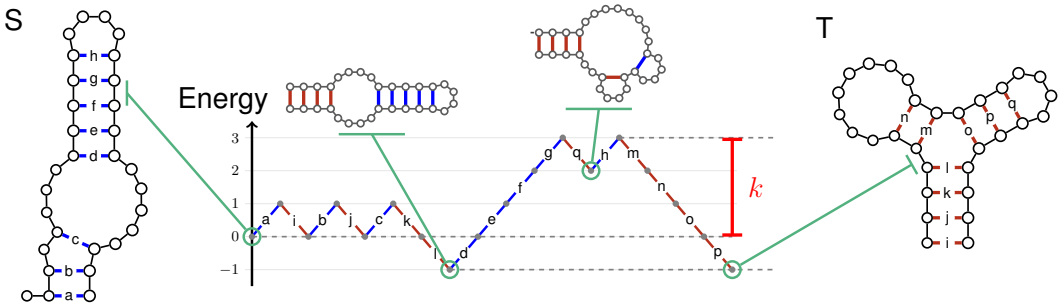
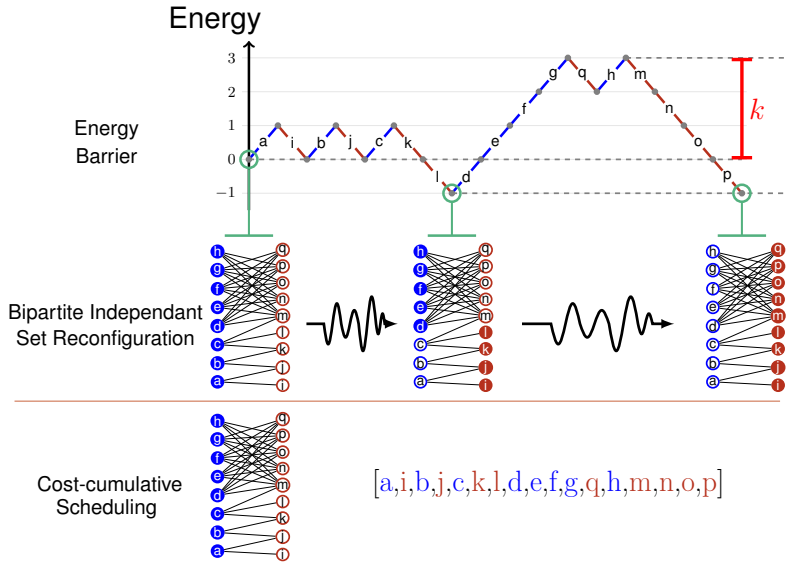
The natural parameter: barrier k as a parameter

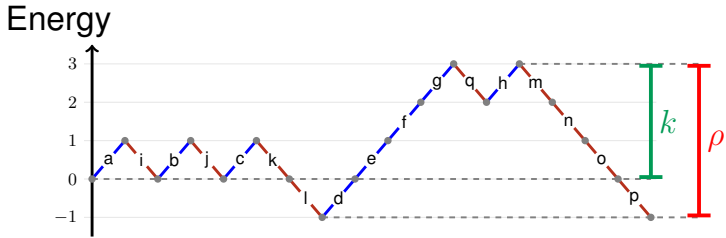


- Which parameter p for an algorithm in $O(n^p)$ or $O(f(n)c^p)$?
- Despite barrier k appearing as a natural parameter candidate, energy barrier was shown NP-hard even if $k = 0$

Energy barrier: one problem, numerous equivalents!

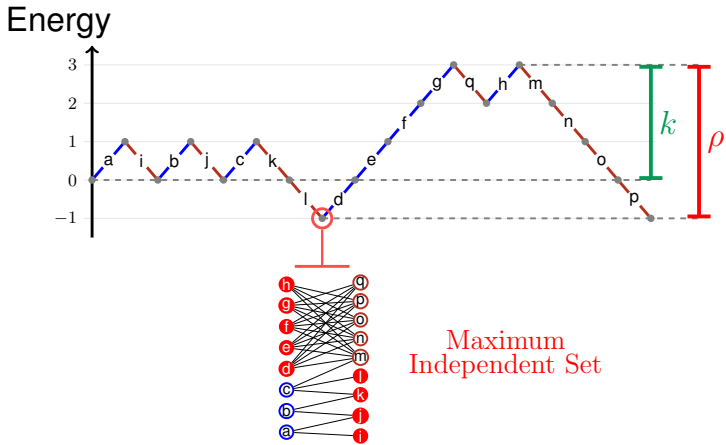


The range parameter ρ



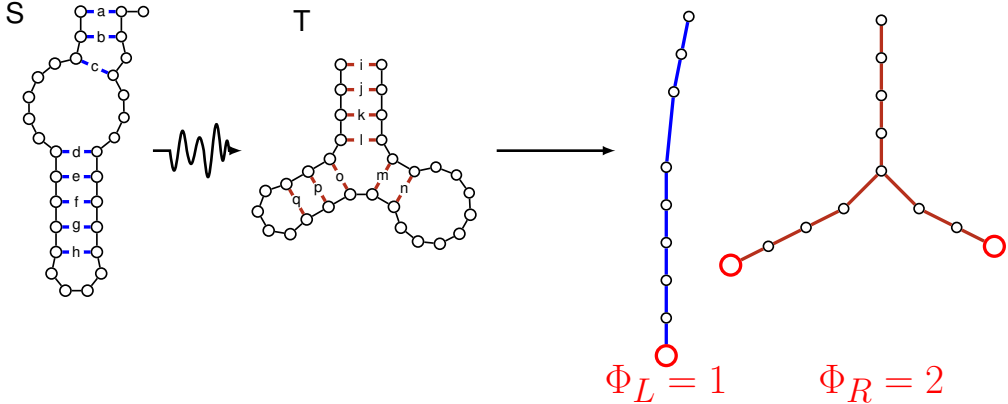
- Range $\rho = \min_{P,\ \text{pathway}} \left(\max_{p \in P} \text{Energy}(p) - \min_{p \in P} \text{Energy}(p) \right)$
- $\rho \geqslant k$

The range ρ-algorithm



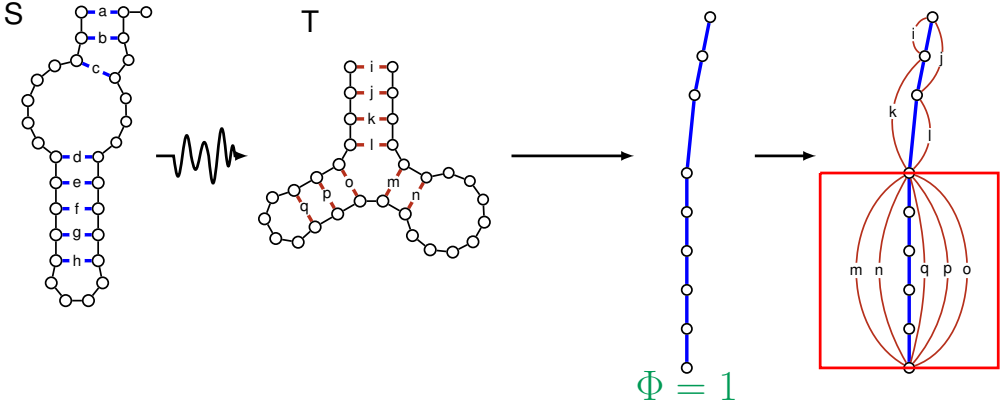
- **Core lemma:** The optimal pathways can always go through a Maximum Independent Set of both colors when it exists.
- **Complexity:** $O\left(n^2\right)$-space, $O\left(n^{2\rho+2.5}\right)$-time

The arboricity parameter Φ



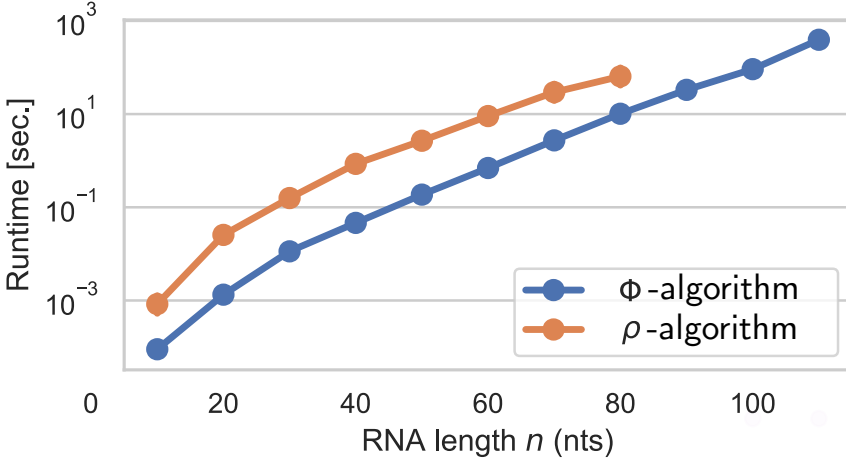
- Φ_S, Φ_T are the number of leaves in the trees inherited from the RNA structures S and T
- Arboricity $\Phi = \min(\Phi_S, \Phi_T)$

The arboricity Φ-algorithm



- **Core lemma:** Some subtrees are "safe" blocks schedulable first and next mergeable in linear time
- **Complexity:** $O\left(n^{\Phi+2}\right)$-space, $O\left(n^{\Phi+3}\right)$-time algorithm for the arboricity Φ

Our algorithms on synthetic datasets . . .



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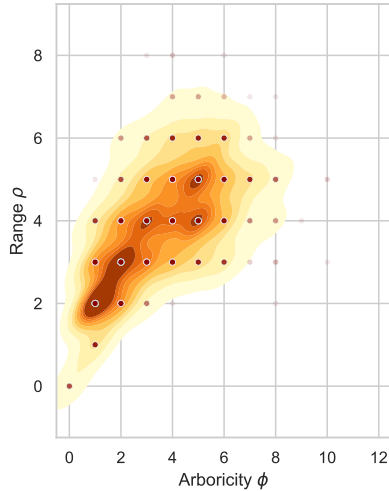
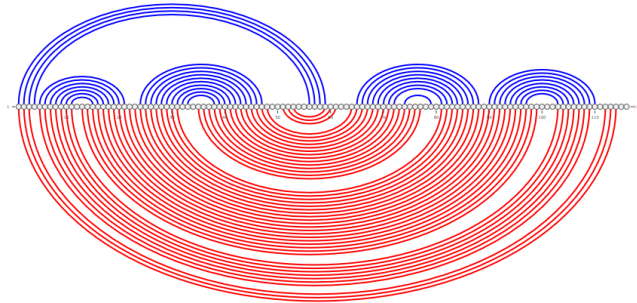


. . . And on more realistic instances

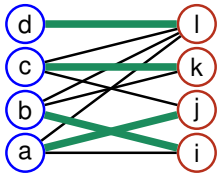


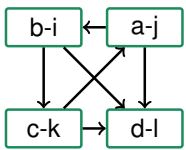
On a SV-11 riboswitch (115nts): [Biebricher *et al*, EMBO journal]

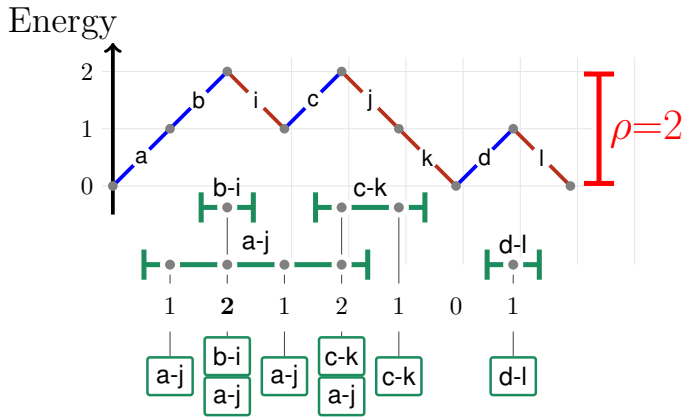
ρ	Φ	Time ρ-algo	Time Φ-algo
9	1	49.55 seconds	0.56 seconds

Parameters and their "meaning"

- **The Graph-parameter:** Range ρ is exactly the Directed Pathwidth of an associated graph.



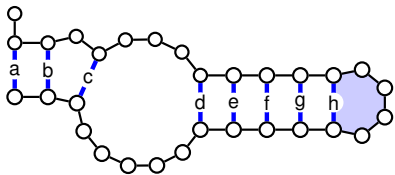




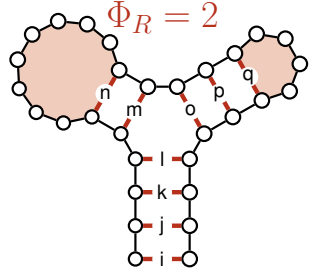
Parameters and their "meaning"

- **The Graph-parameter:** Range ρ is exactly the Directed Pathwidth of an associated graph.
- **The RNA-parameter**: Arboricity Φ is exactly the minimal number of hairpin of the structures.

$\Phi_L = 1$



$\Phi_R = 2$



Final words

- We proposed two exact parameterized algorithms for the energy barrier problem.
- Range and arboricity: orthogonal yet complementary parameters

Parameter	ρ	Φ
When computed?	After the algo	Beforehand
n exponent	$2 \times \rho$	Φ
Practical complexity	Often less than $O(n^{2\rho})$	Worst case always

- **Future work:**
  - A fixed-parameter tractable algorithm ($O(f(n)c^{g(\rho,\Phi)})$) combining range and arboricity?
  - Some algorithm extension toward the stack pair maximization energy

Acknowledgments

Thanks to...


Yann Ponty


Bertrand Marchand


Laurent Bulteau

Link to the paper

[B., Algorithmica 2026]