Parameterized approaches for the RNA energy barrier

Théo Boury[1,2,3], Laurent Bulteau[2], Bertrand Marchand[1,2], Yann Ponty[1]

[1] LIX, Ecole Polytechnique, Palaiseau, France
[2] LIGM, Université Gustave Eiffel, Marne-la-vallée, France
[3] ENS Lyon, Lyon, France

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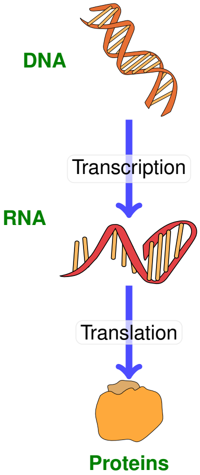
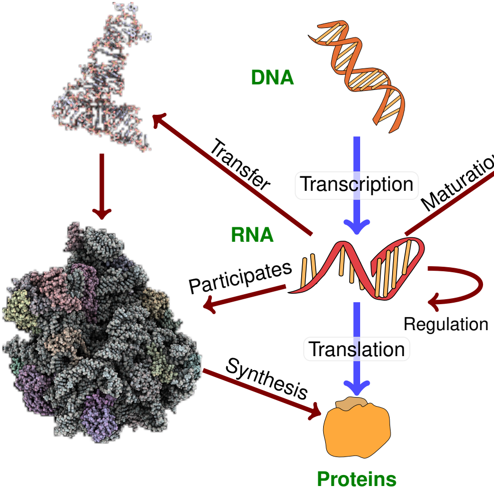
RNA: an interesting molecule?



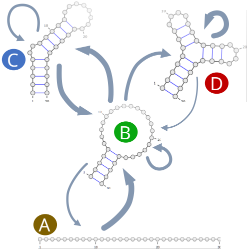
RNA: an interesting molecule!



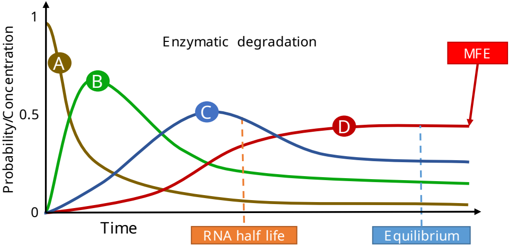
RNA functions

- Messengers
- Translation
- Regulation
- Enzymes
- Modifications
- Editing...

Kinetics: toward "real" RNA understanding?



A – Kinetic Landscape
Continuous-time Markov chain



B – Evolution of concentrations

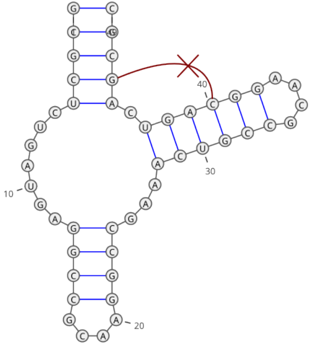
- At equilibrium, for a structure S: $\mathbb{P}(S)\ \alpha\ e^{-\beta\ \text{Energy}(S)}$
- How to compute the transition rates between the structures?

What is an RNA structure?

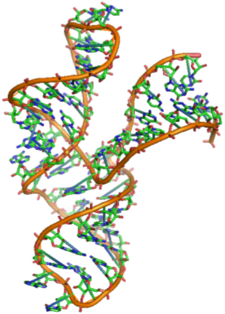
Sequence

GCGCUCUGAUGAG
GCCGCAAGGCCGA
AACUGCCGCAAGG
CAGUCAGCGC

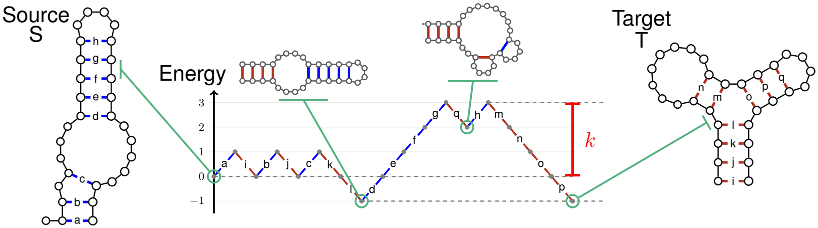
Secondary structure



3D conformation

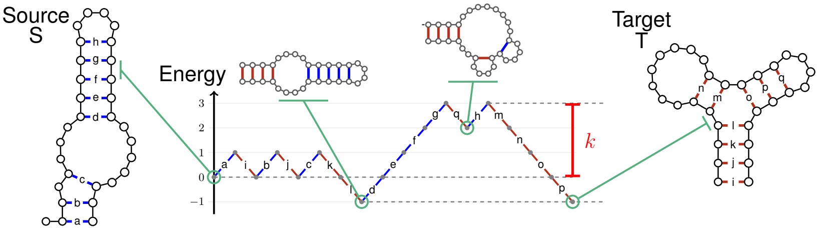


A kinetics cornerstone: the energy barrier problem



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

The energy barrier problem formalism



THE RNA ENERGY BARRIER

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

Output: $S_0 \cdots S_l$, sequence of secondary structures if

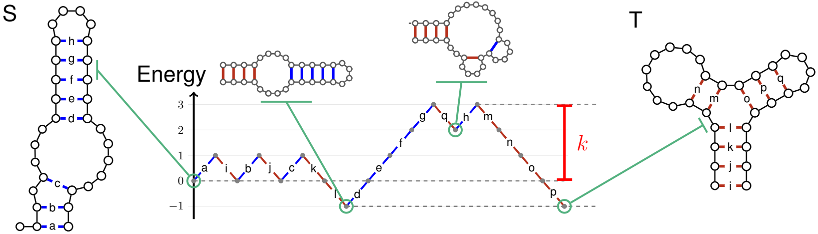
- $S_0 = \text{S}$ and $S_l = \text{T}$;
- $|S_i| \geq |L| - k, \forall i \in [0, l]$;
- $|S_i \triangle S_{i+1}| = 1, \forall i \in [0, l-1]$.

NP-HARD

Manuch et al, 2011

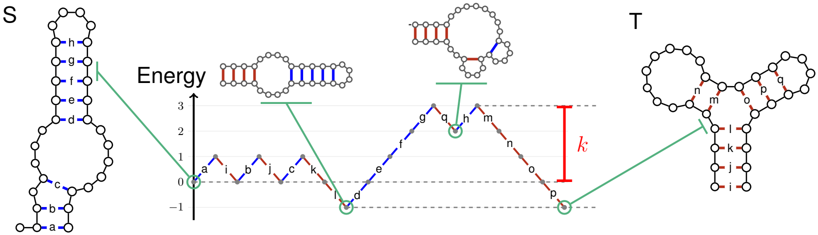
- Which parameter p for an algorithm in $O(n^p)$ or $O(f(n)c^p)$?

The natural parameter: barrier k as a parameter



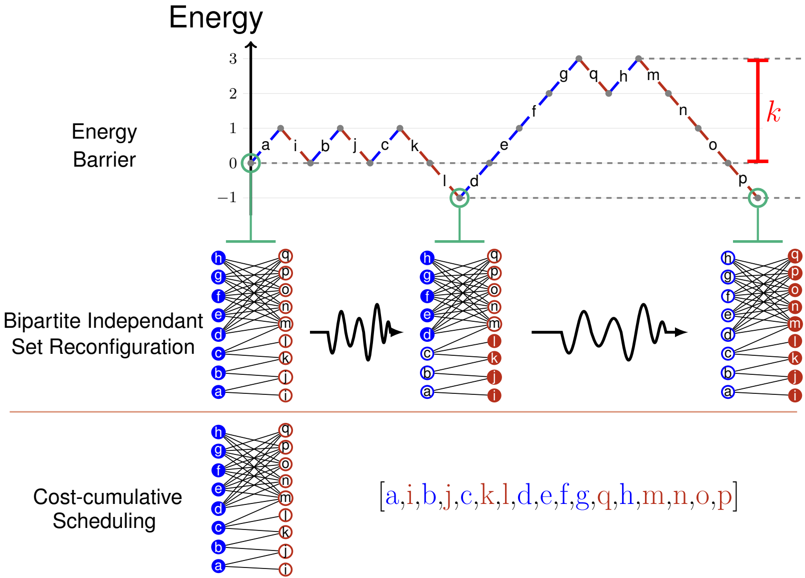
- Which parameter p for an algorithm in $O(n^p)$ or $O(f(n)c^p)$?

The natural parameter: barrier k as a parameter

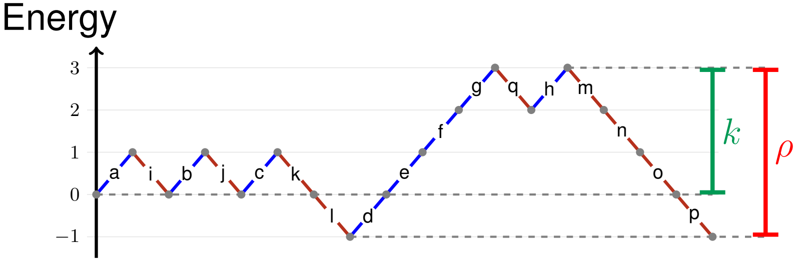


- Which parameter p for an algorithm in $O(n^p)$ or $O(f(n)c^p)$?
- Despite barrier k appearing as a natural parameter candidate, energy barrier was shown NP-hard even if $k = 0$

One problem, numerous useful formalisms!

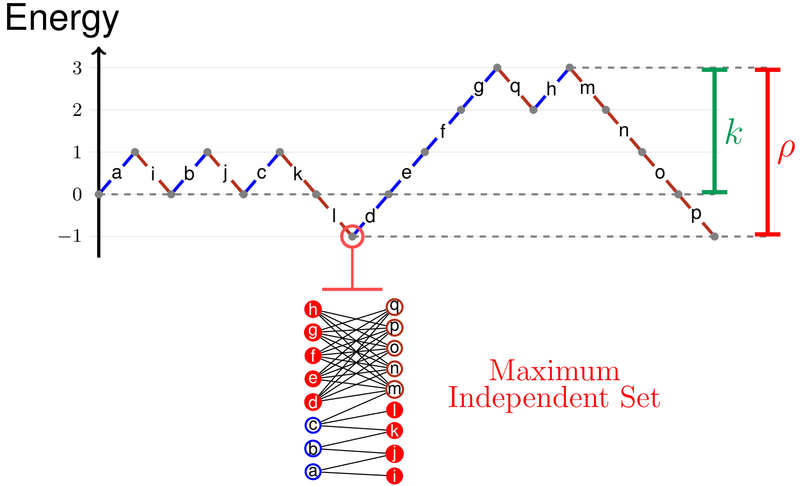


The range parameter ρ



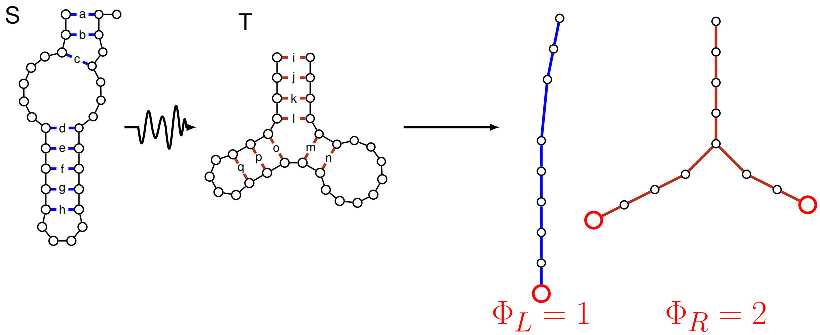
- Range $\rho = \min\limits_{P,\ \text{pathway}} \left(\max\limits_{p \in P} \text{Energy}(p) - \min\limits_{p \in P} \text{Energy}(p) \right)$
- $\rho \geqslant k$

The range ρ-algorithm



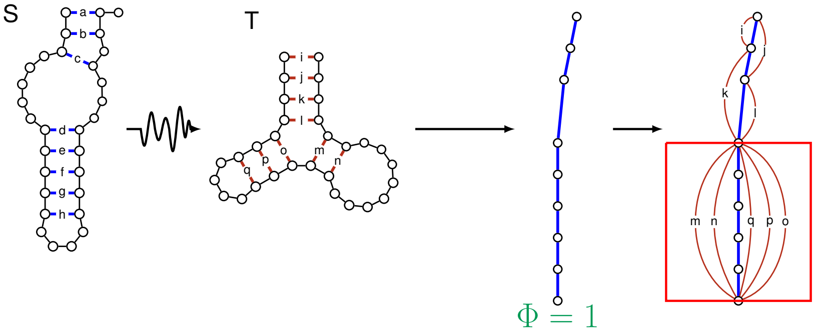
- **Core lemma:** The optimal pathways can always go through a Maximum Independent Set of both colors when it exists.
  Marchand et al, IPEC 2021
- **Complexity:** $O\left(n^2\right)$-space, $O\left(n^{2\rho+2.5}\right)$-time

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 $\Phi = \min(\Phi_S, \Phi_T)$

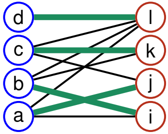
The arboricity Φ-algorithm

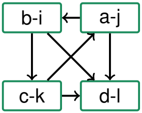


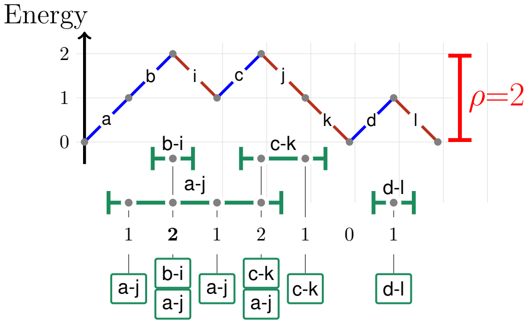
- **Core lemma:** Some subtrees are "safe" blocks schedulable first and next mergeable in linear time
- **Complexity:** $O\left(n^{\Phi+2}\right)$-space, $O\left(n^{\Phi+3}\right)$-time algorithm for the arboricity Φ

Parameters connection with other technique and biology

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

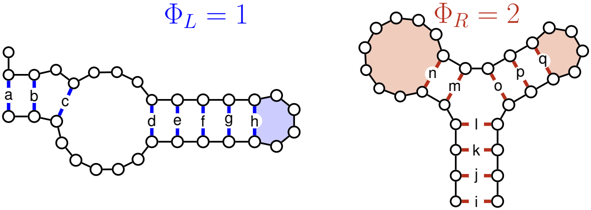






Parameters connection with other technique and biology

- **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.



Final words

- We proposed two slicewise polynomial $(O(n^{g(\rho,\Phi)}))$algorithms for the energy barrier problem.
- Range and arboricity: orthogonal yet complementary parameters

Parameter	ρ	Φ
Scope	Bipartite graphs	RNA instances only
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:**
  - An algorithm in $O(n^{\rho+c})$ for Directed Pathwidth to solve the barrier problem?
  - A fixed-parameter tractable algorithm $(O(f(n)c^{g(\rho,\Phi)}))$ combining range and arboricity?

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ERABLE team

You!

Link to the preprint

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