M2 BIM/STRUCT - Lecture 2

Boltzmann equilibrium and RNA alignment

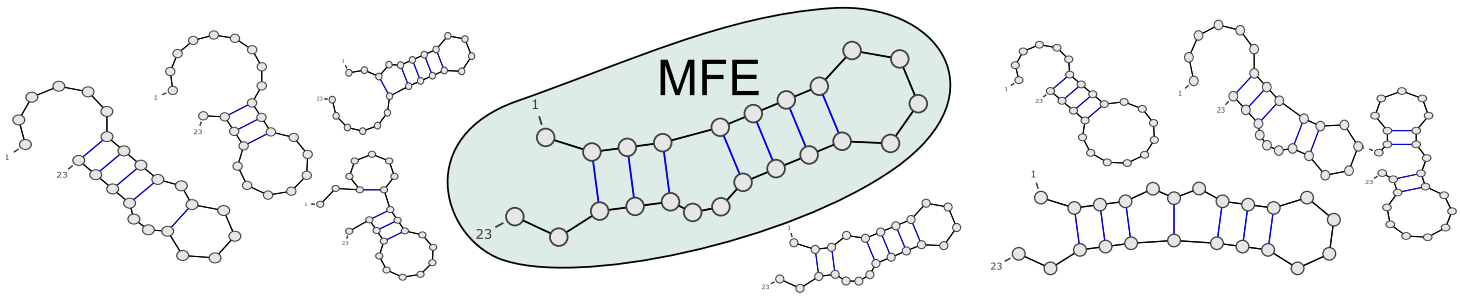
Yann Ponty

AMIBio Team
École Polytechnique/CNRS

RNA *breathes* $\Rightarrow$ There is no more than a single conformation.

New paradigm

The conformations of an RNA **coexist** in the **Boltzmann distribution**.



Consequence: The MFE probability can be arbitrarily small.
$\Rightarrow$ To understand how RNA acts, one must account for the set of alternative structures.

In particular, structurally close structures may *ally*, and become the most realistic candidate in the search for a functional conformation.

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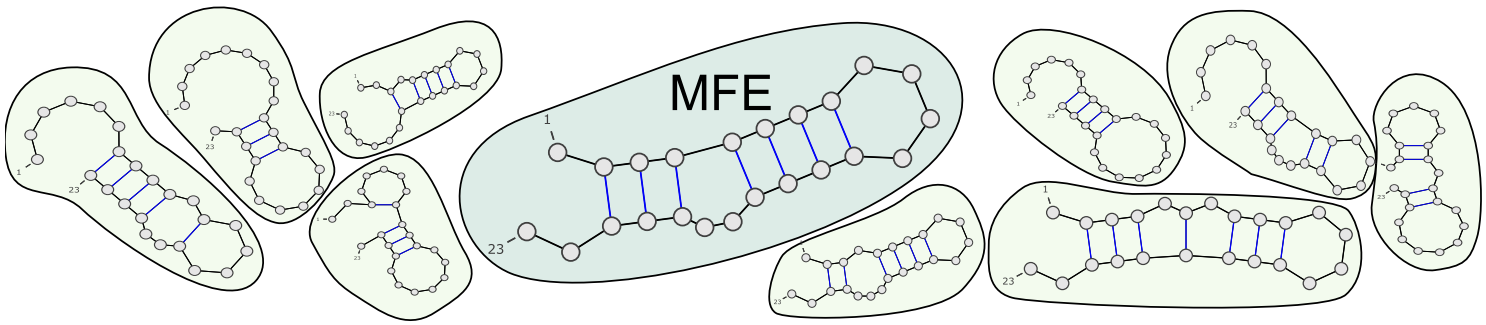


Consequence: The MFE probability can be arbitrarily small.
$\Rightarrow$ To understand how RNA acts, one must account for the set of alternative structures.

In particular, structurally close structures may *ally*, and become the most realistic candidate in the search for a functional conformation.

For each structure S compatible with an RNA ω, the Boltzmann distribution associates a **Boltzmann factor** $\mathcal{B}_{S,\omega} = e^{\frac{-E_{S,\omega}}{RT}}$, where:

- $E_{S,\omega}$ is the free-energy S (kCal.mol^{-1})
- T is the temperature (K)
- R is the perfect gaz constant (1.986.10^{-3} kCal.K^{-1}.mol^{-1})

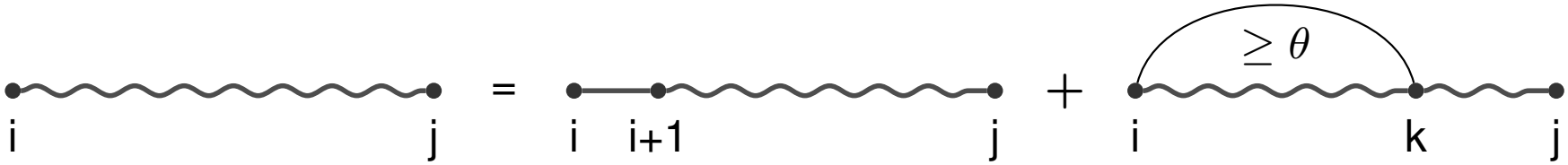
To obtain a distribution, one simply renormalizes by the **partition function**

$$\mathcal{Z}_\omega = \sum_{S \in \mathcal{S}_\omega} e^{\frac{-E_{S,\omega}}{RT}}$$

where $\mathcal{S}_\omega$ is the set of conformations that are compatibles with ω.

The **Boltzmann probability** of a structure S is simply given by

$$P_{S,\omega} = \frac{e^{\frac{-E_{S,\omega}}{RT}}}{\mathcal{Z}_\omega}.$$

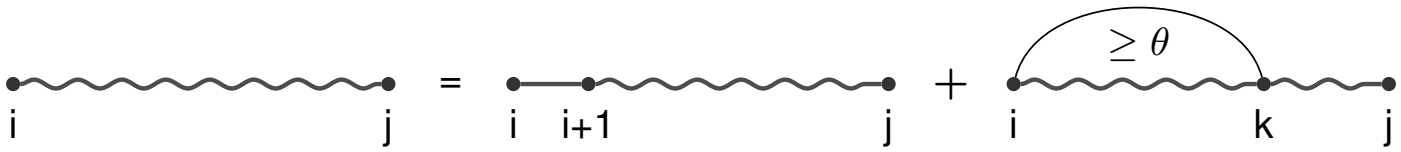


$$N_{i,t} = 0, \quad \forall t \in [i, i+\theta]$$

$$N_{i,j} = \min \begin{cases} N_{i+1,j} & i \text{ unpaired} \\ \min\limits_{k=i+\theta+1}^{j} \Delta G_{i,k} + N_{i+1,k-1} + N_{k+1,j} & i \text{ paired with } k \end{cases}$$

Ambiguity? Consider i: Either **unpaired**, or **paired** to k.
Sets of structures generated in these two cases are clearly disjoint.
(also holds for various values of k) $\Rightarrow$ **Unambiguous** decomposition

Completeness?True, since scheme explores every possible outcome for i.
+ Induction on interval length $\Rightarrow$ **Complete** decomposition



Recurrence for minimal free-energy of a fold :

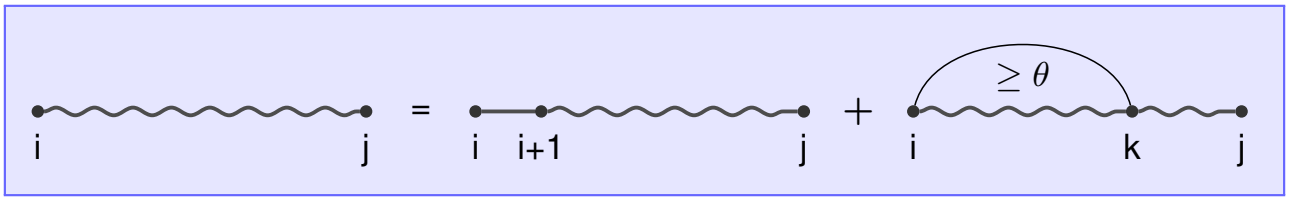
$$
\begin{aligned}
N_{i,t} &= 0, \quad \forall t \in [i, i+\theta] \\
N_{i,j} &= \min \begin{cases} N_{i+1,j} & (i \text{ unpaired}) \\ \min^{j}_{k=i+\theta+1} E_{i,k} + N_{i+1,k-1} + N_{k+1,j} & (i \text{ comp. with } k) \end{cases}
\end{aligned}
$$

Recurrence for counting compatible structures :

$$
\begin{aligned}
C_{i,t} &= 1, \quad \forall t \in [i, i+\theta] \\
C_{i,j} &= \sum \begin{cases} C_{i+1,j} & (i \text{ unpaired}) \\ \sum^{j}_{k=i+\theta+1} 1 \times C_{i+1,k-1} \times C_{k+1,j} & (i \text{ comp. with } k) \end{cases}
\end{aligned}
$$

Decomposition matters, and the rest (MFE, count. . .) follows!

Partition function = **Weighted count** over compatible structures



$$\mathcal{Z}_{i,t} = 1, \quad \forall t \in [i, i+\theta]$$

$$\mathcal{Z}_{i,j} = \sum \left\{ \sum_{k=i+\theta+1}^{j} 1 \times \mathcal{Z}_{i+1,k-1} \times \mathcal{Z}_{k+1,j} \right.$$

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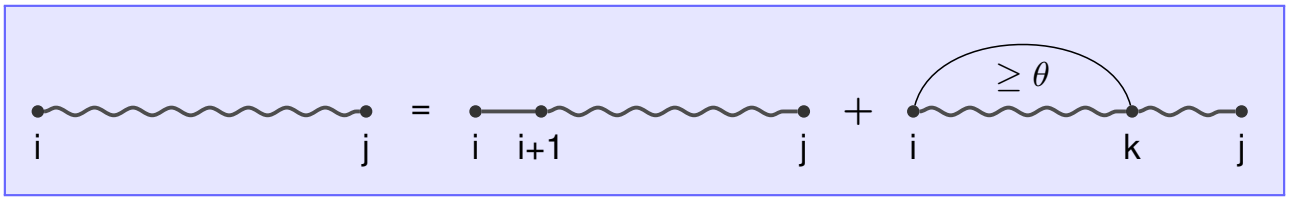

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$$\mathcal{Z}_{i,j} = \sum \begin{cases} \mathcal{Z}_{i+1,j} \\ \sum_{k=i+\theta+1}^{j} e^{\frac{-E_{bp}(i,k)}{RT}} \times \mathcal{Z}_{i+1,k-1} \times \mathcal{Z}_{k+1,j} \end{cases}$$

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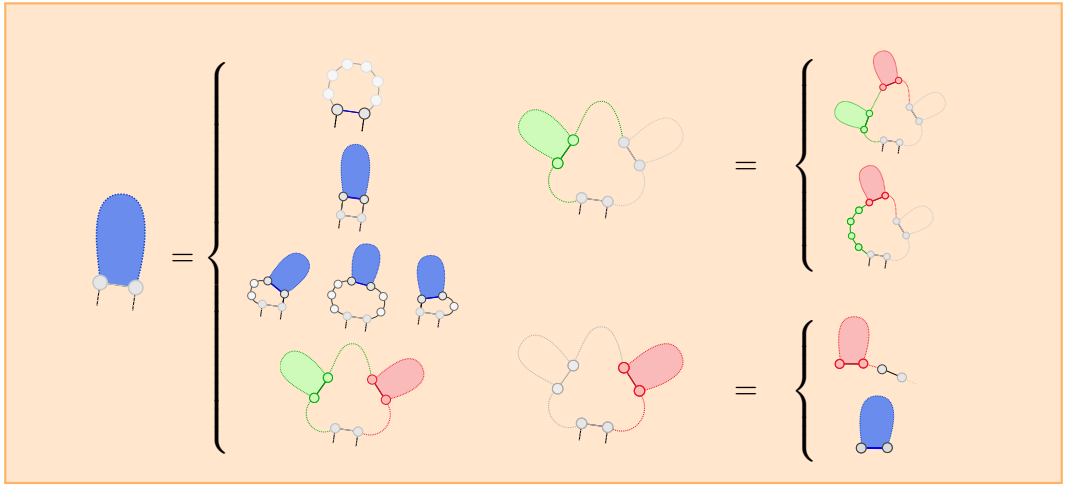

$$
\begin{aligned}
\mathcal{M}'_{i,j} &= \text{Min}\begin{cases} E_H(i,j) \\ E_S(i,j) + \mathcal{M}'_{i+1,j-1} \\ \text{Min}(E_{BI}(i,i',j',j) + \mathcal{M}'_{i',j'}) \\ a + c + \text{Min}\left(\mathcal{M}_{i+1,k-1} + \mathcal{M}^1{}_{k,j-1}\right) \end{cases} \\
\mathcal{M}_{i,j} &= \text{Min}\left\{\text{Min}\left(\mathcal{M}_{i,k-1}, b(k-1)\right) + \mathcal{M}^1{}_{k,j}\right\} \\
\mathcal{M}^1{}_{i,j} &= \text{Min}\left\{b + \mathcal{M}^1{}_{i,j-1}, c + \mathcal{M}'_{i,j}\right\}
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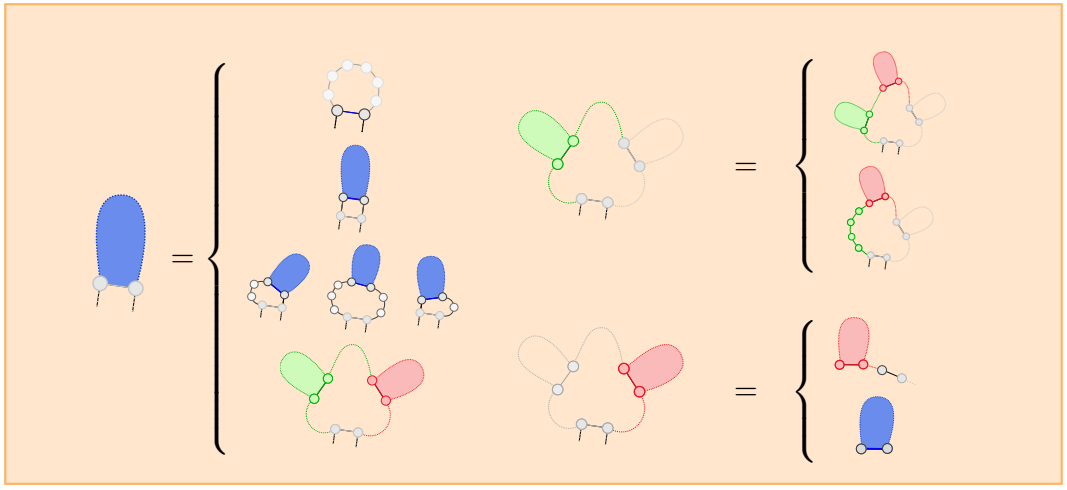

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\text{Min}\left(e^{\frac{-E_{BI}(i,i',j',j)}{RT}} + \mathcal{M}'_{i',j'}\right) \\
e^{\frac{-(a+c)}{RT}} + \text{Min}\left(\mathcal{M}_{i+1,k-1} + \mathcal{M}^1{}_{k,j-1}\right)
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\right. \\
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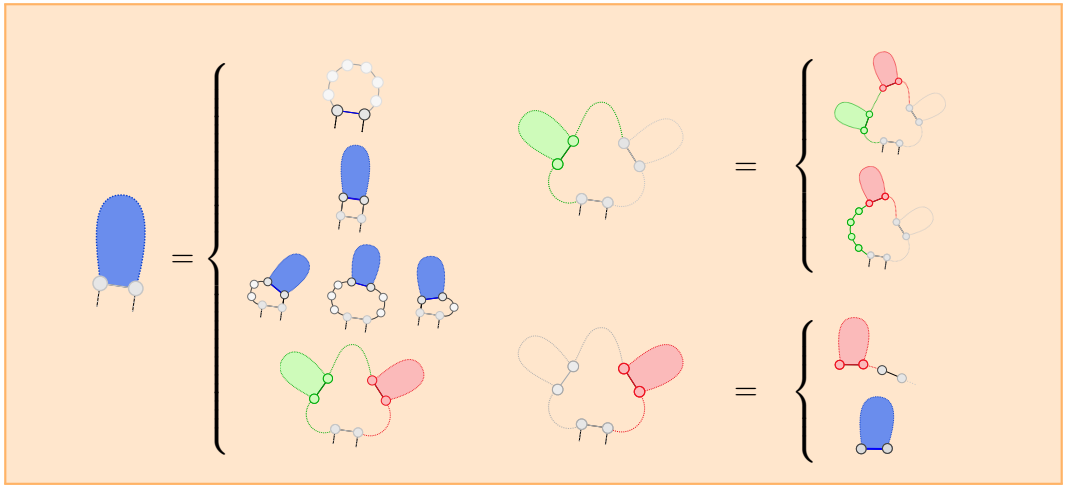

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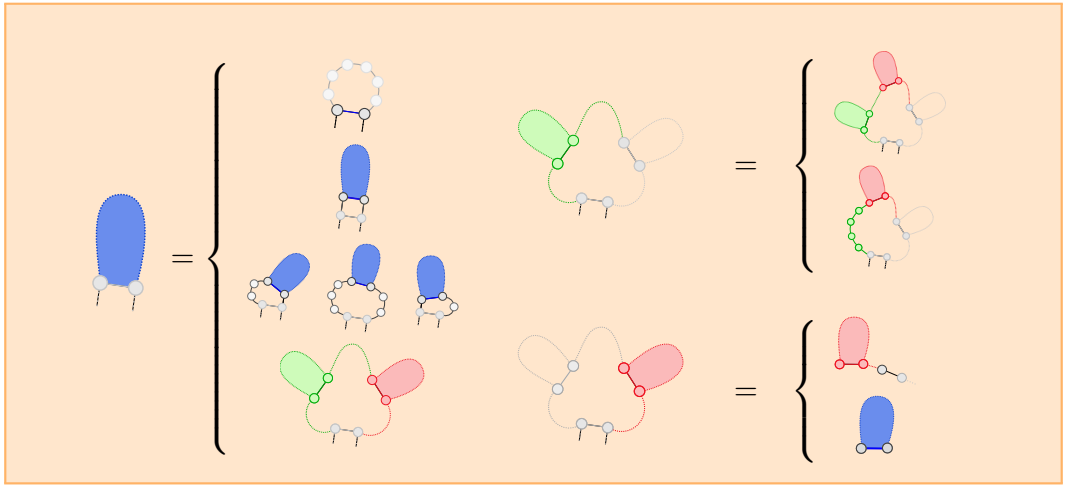

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\mathcal{Z}'(i,j) &= \sum \begin{cases} e^{\frac{-E_H(i,j)}{RT}} \\ e^{\frac{-E_S(i,j)}{RT}}\,\mathcal{Z}'(i+1,j-1) \\ +\sum\left(e^{\frac{-E_{BI}(i,i',j',j)}{RT}}\,\mathcal{Z}'(i',j')\right) \\ +e^{\frac{-(a+c)}{RT}}\sum\left(\mathcal{Z}(i+1,k-1)\mathcal{Z}^1(k,j-1)\right) \end{cases} \\
\mathcal{Z}(i,j) &= \sum\left(\mathcal{Z}(i,k-1)+e^{\frac{-b(k-1)}{RT}}\right)\mathcal{Z}^1(k,j) \\
\mathcal{Z}^1(i,j) &= e^{\frac{-b}{RT}}\,\mathcal{Z}^1(i,j-1)+e^{\frac{-c}{RT}}\,\mathcal{Z}'(i,j)
\end{aligned}
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$$\mathcal{Z}_{i,j} = \sum \left\{ \sum_{k=i+\theta+1}^{j} e^{\frac{-E_{\text{bp}}(i,k)}{RT}} \times \mathcal{Z}_{i+1,k-1} \times \mathcal{Z}_{k+1,j} \right.$$

Validity of a partition function computation:

- Completeness/Unambiguity of decomposition scheme
- Correctness of Boltzmann factor

  Weight induced by backtrack = Product of derivations weights

  $e^{-E/RT} \rightarrow$ Weight products $\Leftrightarrow$ Summing energy terms

$$e^{-E_{\text{bp}}(i,k)/RT} \times \mathcal{Z}_{i+1,k-1} \times \mathcal{Z}_{k+1,j} = \cdot \sum_x e^{-E(x)/RT} \cdot \sum_y e^{-E(y)/RT}$$

$$= \sum_{x,y} e^{-a/RT} \cdot e^{-E(x)/RT} \cdot e^{-E(y)/RT}$$

$$= \sum_{x,y} e^{-(E_{\text{bp}}(i,k)+E(x)+E(y))/RT}$$

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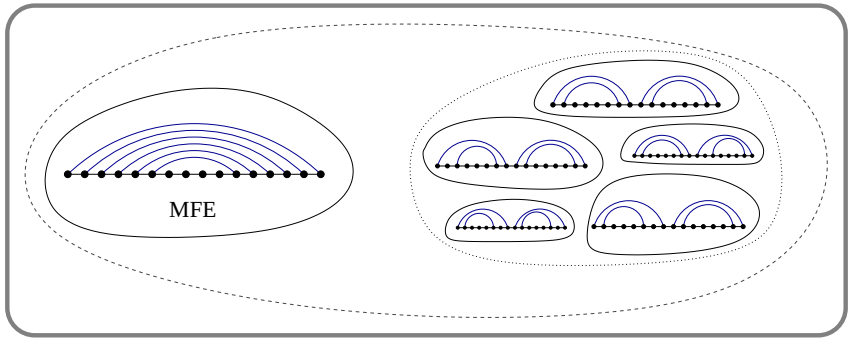
MFE ($\Leftrightarrow$ Max probability) may be **heavily dominated** by a set $\mathcal{B}$ of **structurally similar** suboptimal structures.
$\Rightarrow$ Functional conformation probably closer to $\mathcal{B}$ than to MFE.



Proof-of-concept: [DCL05]

- Sample structures within Boltzmann probability
- Cluster structures
- Build and return consensus structure of the heaviest cluster

$\Rightarrow$ Relative improvement for specificity (+17.6%) and sensitivity (+21.74%, except group II introns)

Problem

How to sample from the Boltzmann ensemble?

Goal [DL03]: From sequence ω, draw S with prob. $e^{-E_S/RT}/\mathcal{Z}$

Principle: Choose derivation with prob. prop. to its contribution to part. fun.
Precomputation: Compute part. fun. versions of matrices ($\mathcal{Z}, \mathcal{Z}', \mathcal{Z}^1$).
Stochastic backtrack:

1. Draw uniform random number $r \in [0, \mathcal{Z}'(i,j))$
2. Subtract from r the contributions of $\mathcal{Z}'(i,j)$ until $r < 0$
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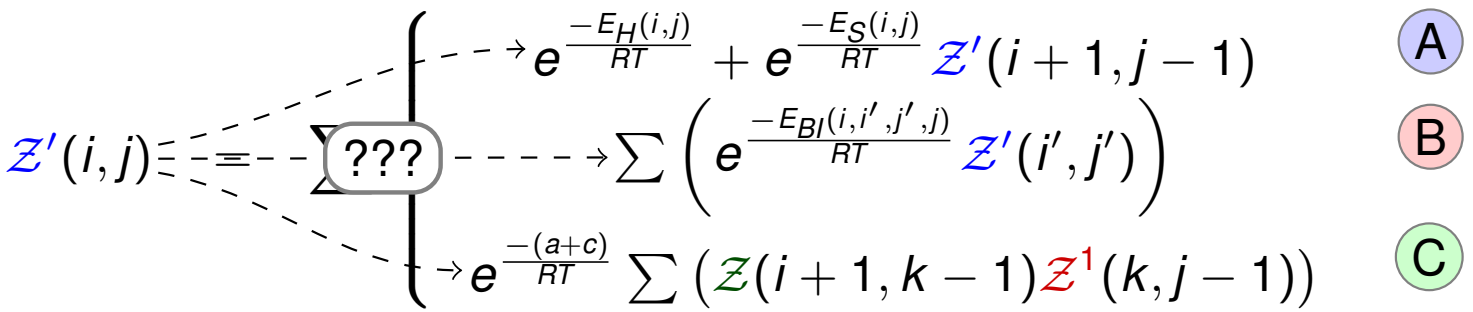

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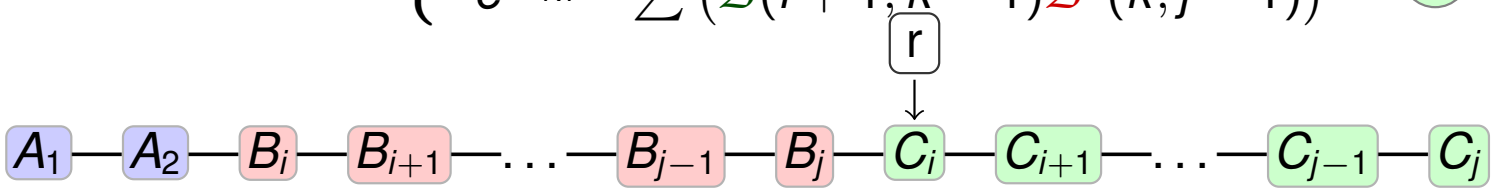

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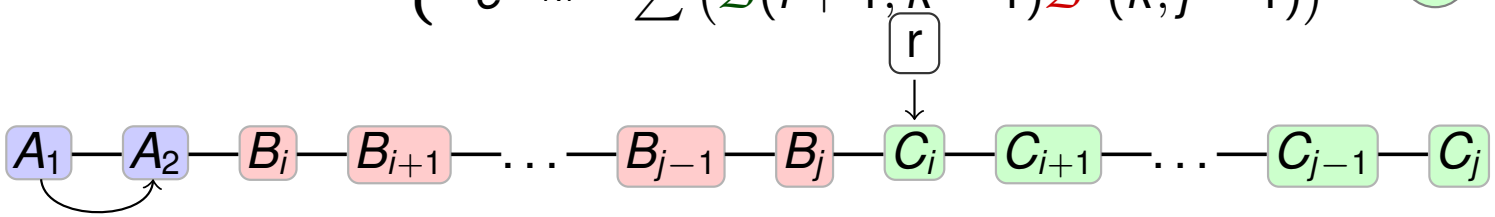

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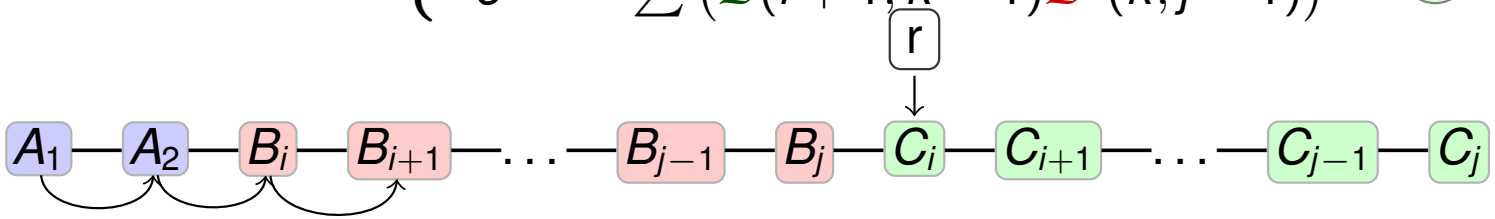

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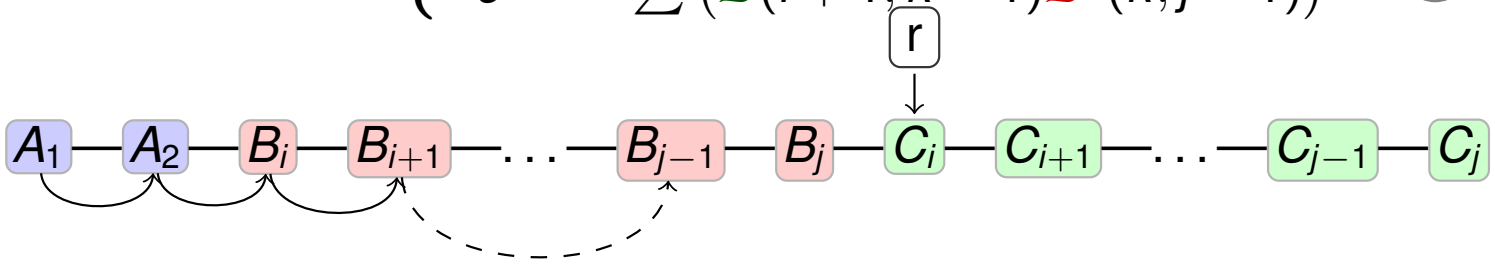

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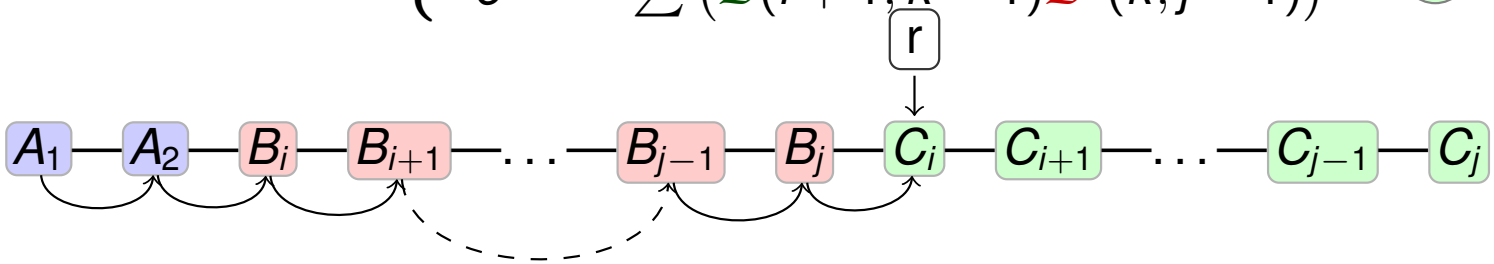

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Correctness: Each $S \in \mathcal{S}_\omega$ uniquely generated (DP scheme unambiguity)
Therefore the probability of generated S is

$$p_S = \frac{\mathcal{B}(E_1)}{\mathcal{B}(\mathcal{S}_w)} \cdot \frac{\mathcal{B}(E_2)}{\mathcal{B}(E_1)} \cdot \frac{\mathcal{B}(E_3)}{\mathcal{B}(E_2)} \cdots \frac{\mathcal{B}(\{S\})}{\mathcal{B}(E_m)}$$

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3. Recurse over associated regions/matrices

$$\mathcal{Z}'(i,j) = \sum \begin{cases} e^{\frac{-E_H(i,j)}{RT}} + e^{\frac{-E_S(i,j)}{RT}} \mathcal{Z}'(i+1,j-1) & \text{A} \\ \sum \left(e^{\frac{-E_{BI}(i,i',j',j)}{RT}} \mathcal{Z}'(i',j') \right) & \text{B} \\ e^{\frac{-(a+c)}{RT}} \sum \left(\mathcal{Z}(i+1,k-1) \mathcal{Z}^1(k,j-1) \right) & \text{C} \end{cases}$$

Correctness: Each $S \in \mathcal{S}_\omega$ uniquely generated (DP scheme unambiguity)
Therefore the probability of generated S is

$$p_S = \frac{1}{\mathcal{B}(\mathcal{S}_w)} \cdot \frac{1}{1} \cdot \frac{1}{1} \cdots \frac{\mathcal{B}(\{S\})}{1}$$

Goal [DL03]: From sequence ω, draw S with prob. $e^{-E_S/RT}/\mathcal{Z}$

Principle: Choose derivation with prob. prop. to its contribution to part. fun.
Precomputation: Compute part. fun. versions of matrices ($\mathcal{Z}, \mathcal{Z}', \mathcal{Z}^1$).
Stochastic backtrack:

1. Draw uniform random number $r \in [0, \mathcal{Z}'(i,j))$
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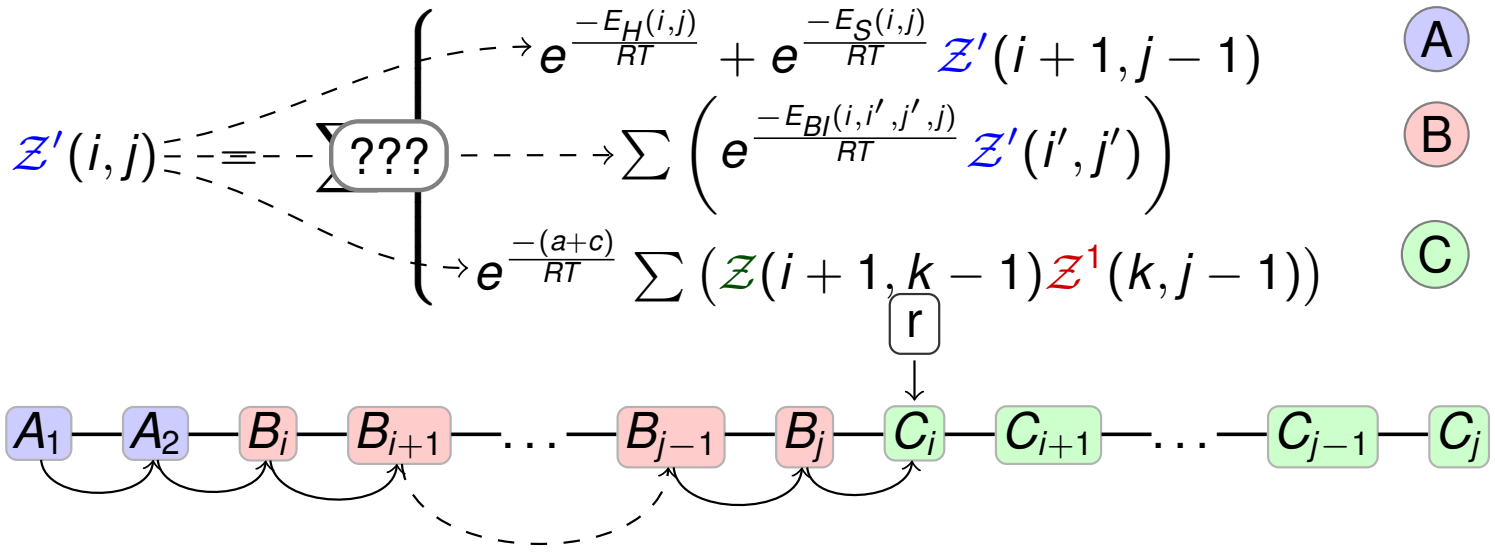

Average-case complexity in $\Theta(k \times n\sqrt{n})$ (homopolymer model) [Pon08].
Boustrophedon search $\Rightarrow \mathcal{O}(k \times n \log n)$ worst-case [Pon08].

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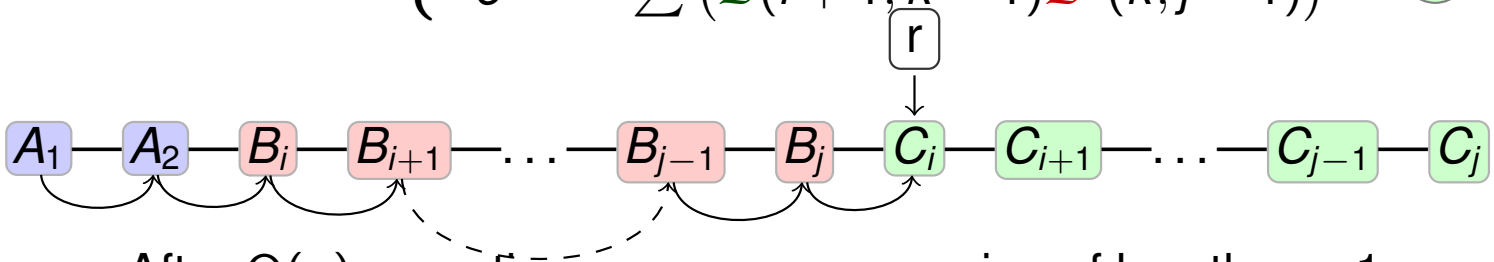
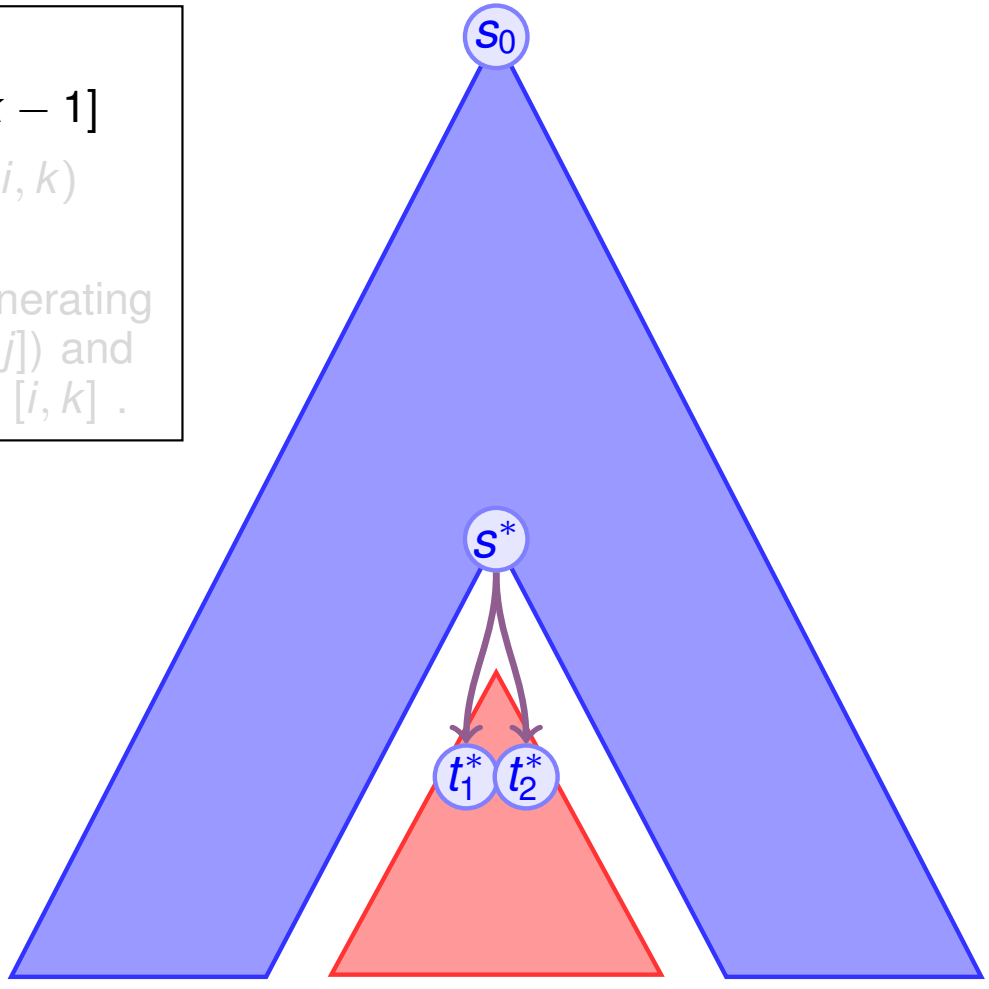


After $\Theta(n)$ operations, recurse over region of length $n-1$
$\Rightarrow$ Worst-case complexity in $\mathcal{O}(k \times n^2)$ for k samples

Average-case complexity in $\Theta(k \times n\sqrt{n})$ (homopolymer model) [Pon08].
Boustrophedon search $\Rightarrow \mathcal{O}(k \times n \log n)$ worst-case [Pon08].

Structure including base pair (i, k):

- Inside: Structures over $[i + 1, k - 1]$
- Outside: **Contexts** of interval (i, k)
  - $\forall$ interval $[i, j], i < j \leq k$
  - **Complete** structure by generating **brother intervals** ($[k + 1, j]$) and recurse over the **father** of $[i, k]$.



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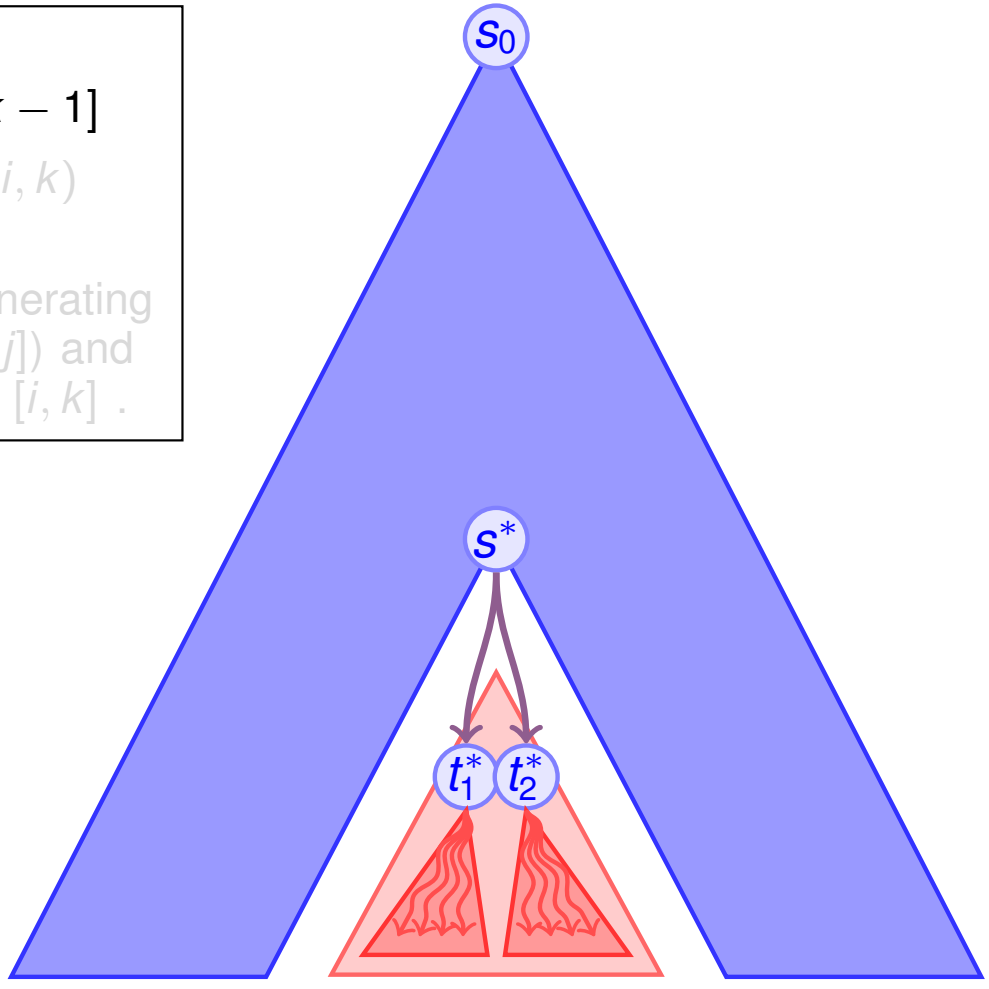

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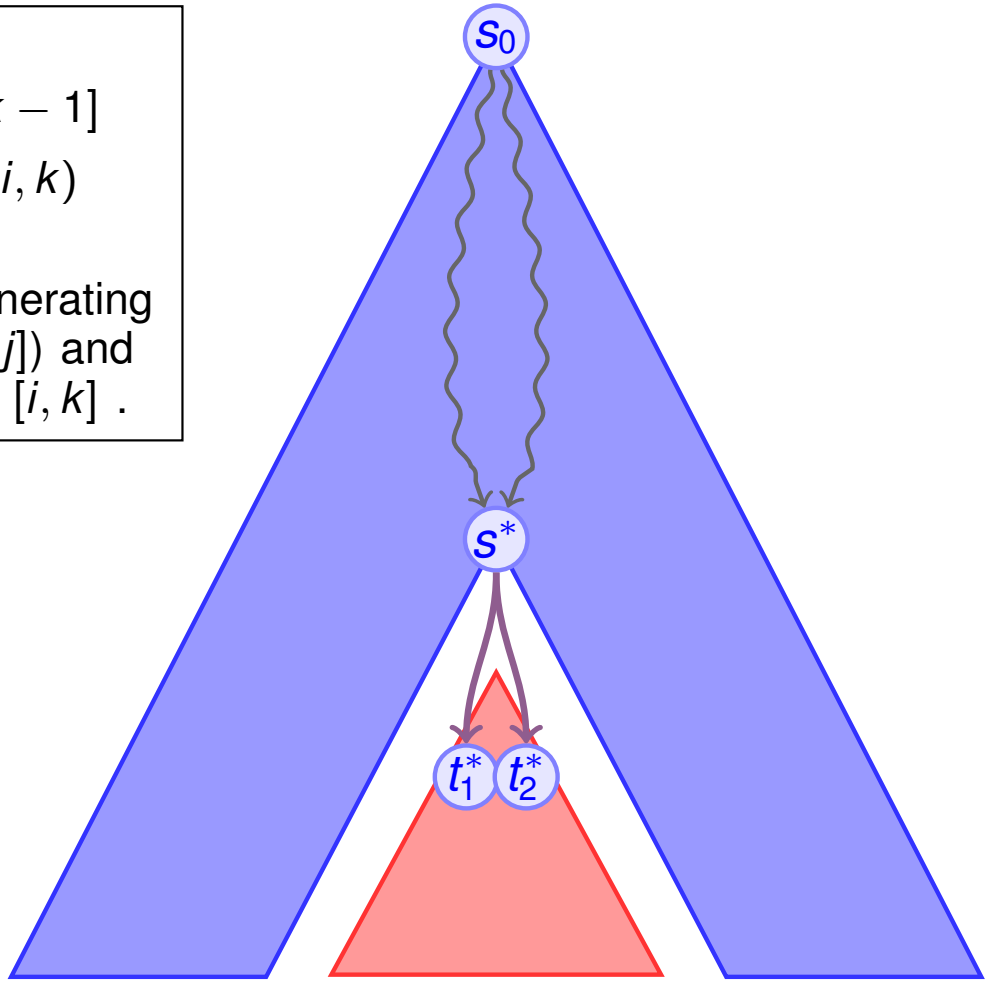

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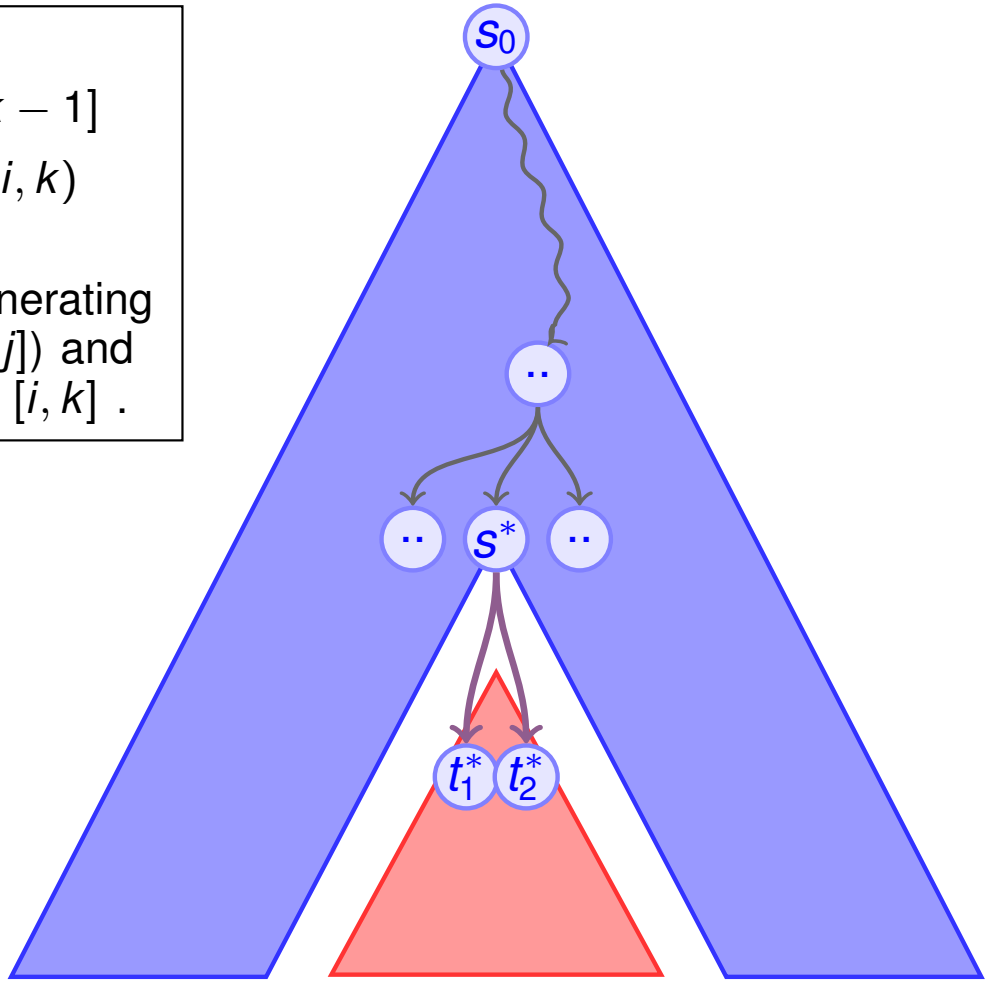

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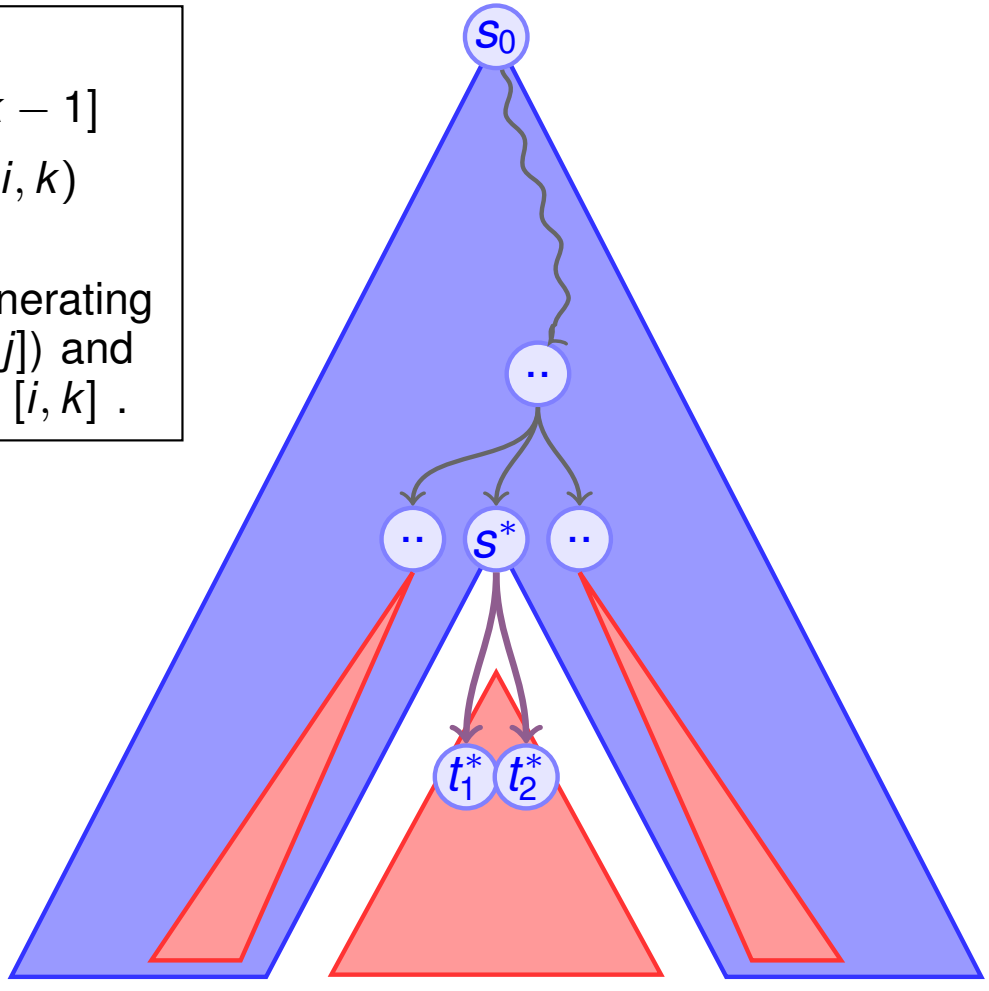

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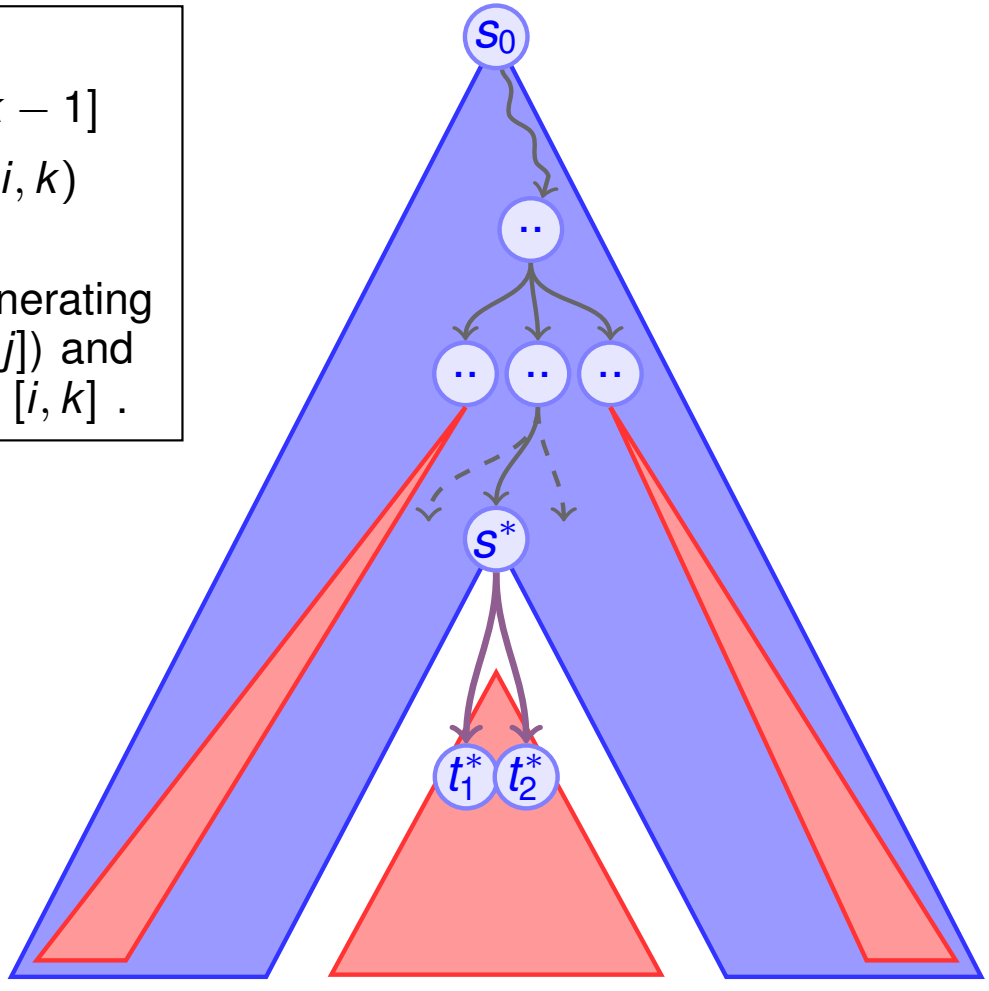

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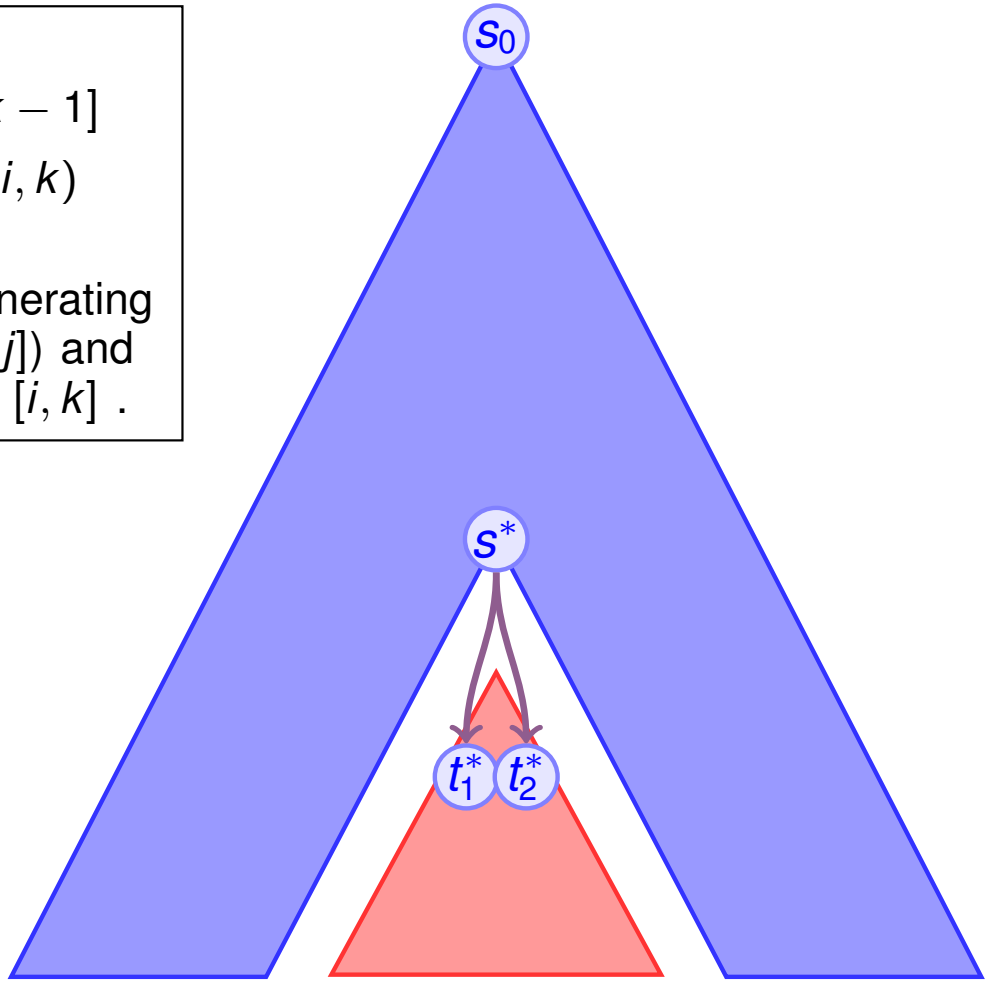


Whenever some further **technical conditions** are satisfied, this decomposition is **complete** and **unambiguous**, and implies a ***simple recurrence*** for computing the base pair probability matrix in $\Theta(n^3)$.

1. Boltzmann ensemble
   - Nussinov: Minimisation $\Rightarrow$ Counting
   - Computing the partition function
   - Statistical sampling
   - Inside/outside

2. **Extensions**
   - What is a good dynamic programming scheme?
   - Suboptimal structures
   - Pseudoknots

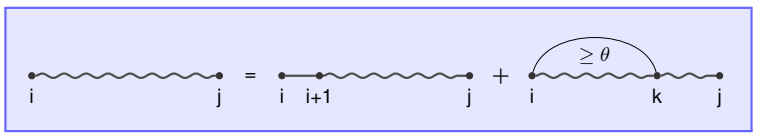
What is a good dynamic programming scheme?

Correction of a (Ensemble) dynamic programming scheme:

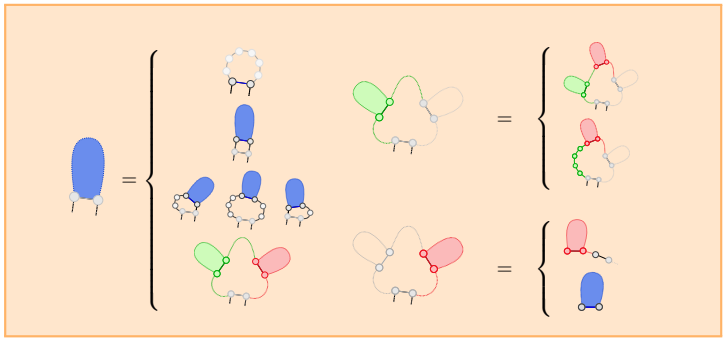
Objective function correctly computed/inherited at local level

\+ All the conformations can be obtained

$\Rightarrow$ Correct algorithm (Induction)



$\Leftrightarrow ?$



Enumerating search space helps **but** does not constitute a proof.

Need to **show equivalence** of DP schemes, *e.g.* use one to simulate the other and vice versa.

(Generating functions may help)

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Objective function correctly computed/inherited at local level

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$$C_{i,t} = 1, \quad \forall t \in [i, i+\theta]$$

$$C_{i,j} = \sum \left\{ \sum_{k=i+\theta+1}^{j} 1 \times C_{i+1,k-1} \times C_{k+1,j} \right.$$

Homopolymère (Toute paire autorisée) + $\theta = 1$
$\Rightarrow C_{1,n} = \mathbf{1}, 1, 1, 2, 4, 8, 17, 32, 82, 185, 423, \ldots$

$\Leftrightarrow$?

$$\mathcal{C}'_{i,j} = \sum \left\{ \begin{array}{l} 1 \\ \mathcal{C}'_{i+1,j-1} \\ \sum_{i',j'} \mathcal{C}'_{i',j'} \\ \sum_{k} \mathcal{C}_{i+1,k-1} \times \mathcal{C}^1{}_{k,j-1} \end{array} \right.$$

$$\mathcal{C}_{i,j} = \sum_{k} \left((\mathcal{C}_{i,k-1} + 1) \times \mathcal{C}^1{}_{k,j} \right)$$

$$\mathcal{C}^1{}_{i,j} = \mathcal{C}^1{}_{i,j-1} + \mathcal{C}'_{i,j}$$

Homopolymère + $\theta = 1$
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Prob.: Simplified energy model (no pseudoknots, only canonical BPs)
$\Rightarrow$ **Native** structure (functional) could be **overthrown**.

$\Rightarrow$ Investigate suboptimal structures (`RNASubopt` [WFHS99]),
i.e. build all structures within Δ KCal.mol^{-1} of MFE:

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- Backtrack on any contribution within Δ of MFE;
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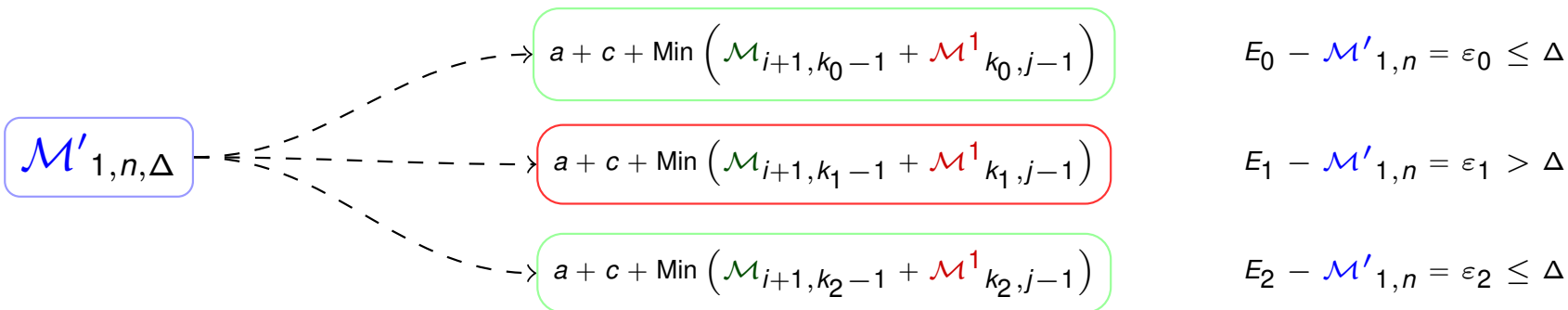

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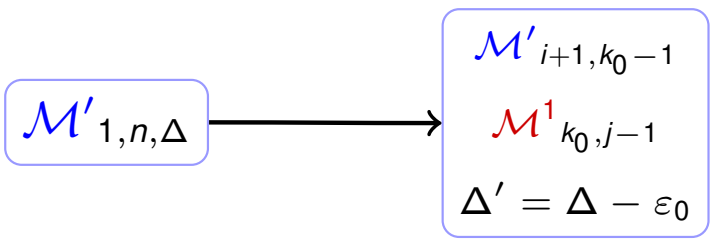

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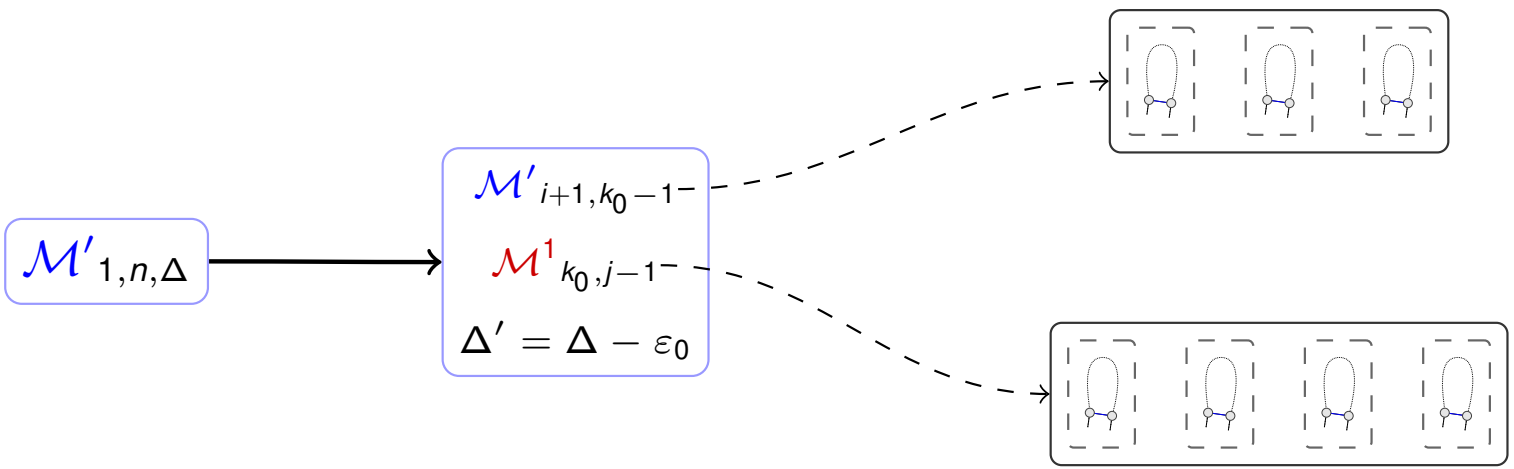

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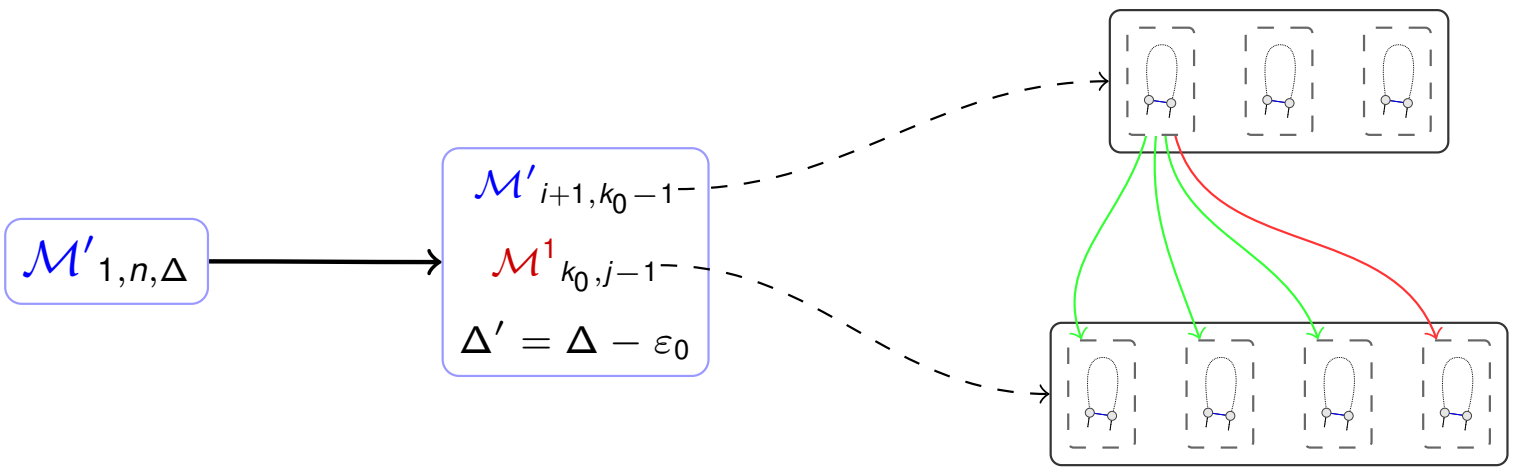

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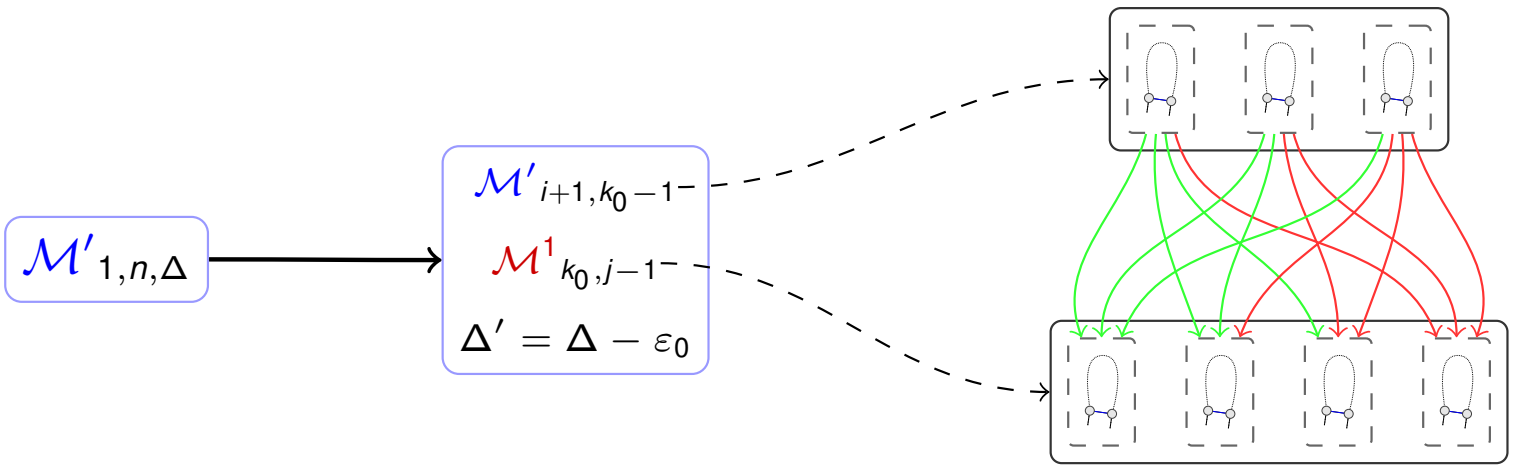

Suboptimal structures

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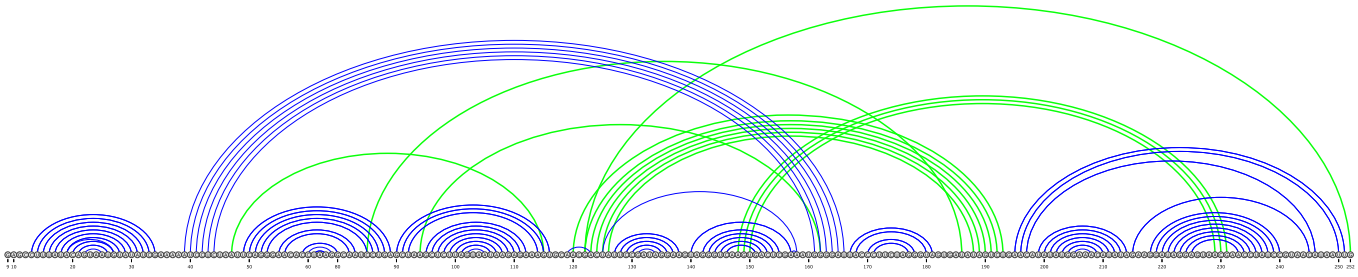
$$\Rightarrow \text{Time complexity (Sort)} : \mathcal{O}(n^3 + n \cdot k \log(k))$$

(k grows exponentially fast with Δ!)

Pseudoknots are essential to the folding and activity of multiple RNA families.



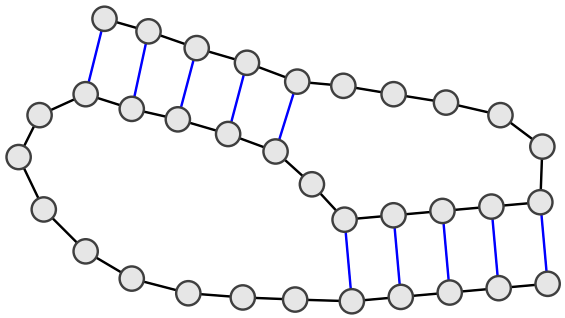
Groupe I Ribozyme

Their disregard within current folding algorithms stems both from **algorithmic** and **energetic** intricacies.

(**Pseudoknots =** Crossings $\Rightarrow$ foldings delimited by base-pair can no longer be assumed to be independent)

Type	Complexity	Reference
Secondary structures	$\mathcal{O}(n^3)$	[MSZT99]
L&P	$\mathcal{O}(n^5)$	[LP00]
D&P	$\mathcal{O}(n^5)$	[DP03]
A&U	$\mathcal{O}(n^5)$	[Aku00]
R&E	$\mathcal{O}(n^6)$	[RE99]
Unconstrained	NP-complete	[LP00]

Goal: Capture a category of **simple**, **yet** recurrent, pseudoknots.



Idea: When such a PK motif is **rotated**, one can deduce the MFE of a triplet (i, j, k) from the MFE of triplets **directly below** it.

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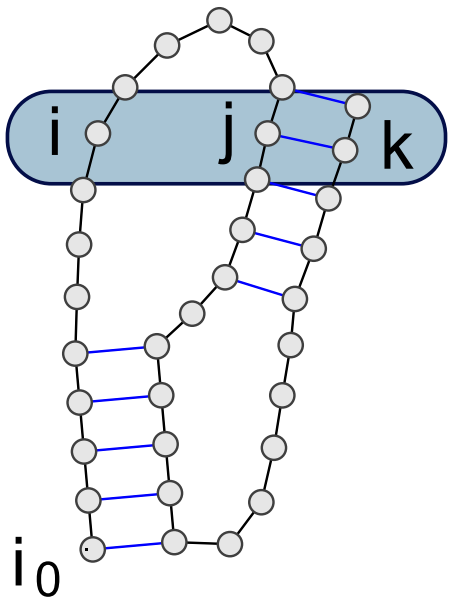

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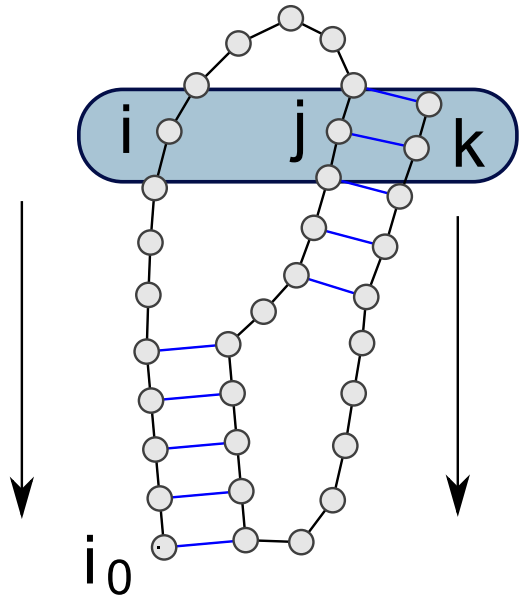

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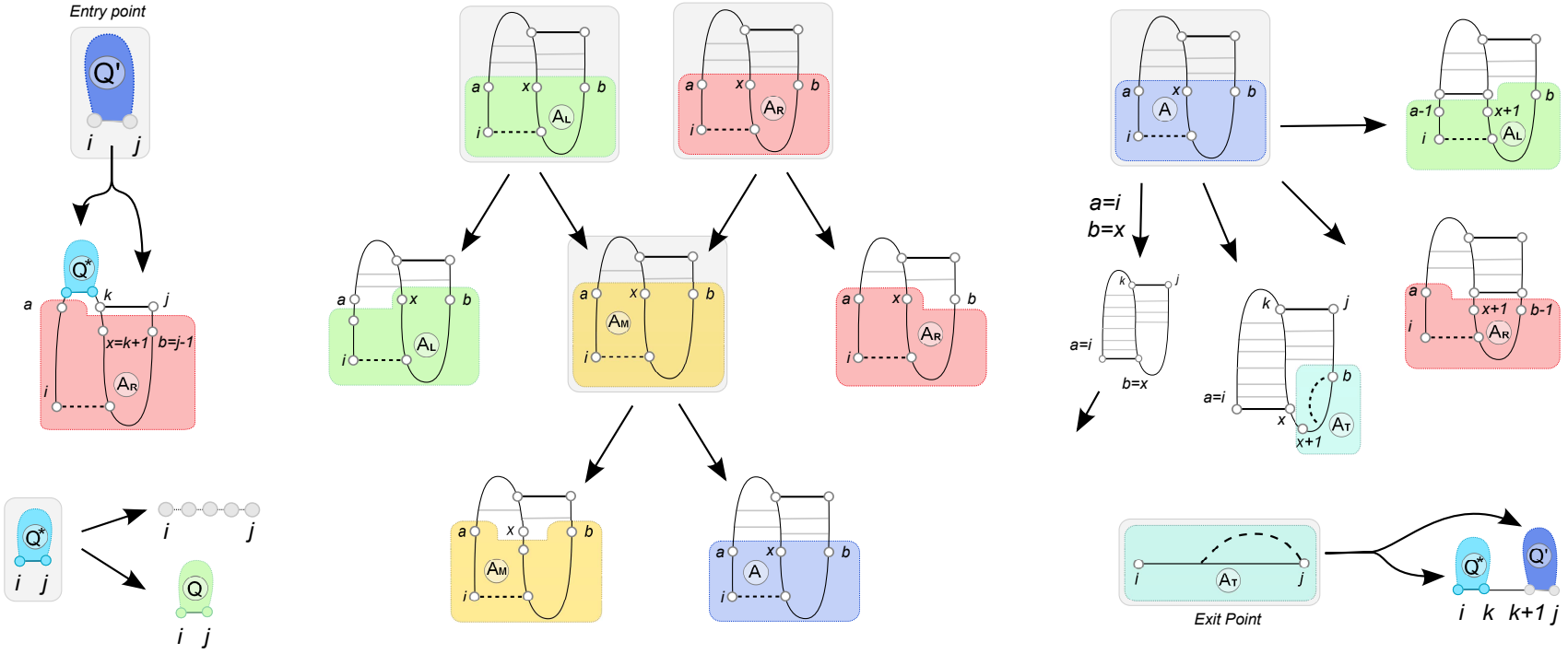

Application/Problem	Weight fun.	Time/Space	Ref.
Energy minimization	π_{bp}	$\mathcal{O}(n^4)/\mathcal{O}(n^4)$	[Aku00]
Partition function	$e^{\frac{-\pi_{bp}}{RT}}$	$\mathcal{O}(n^4)/\mathcal{O}(n^4)$	$\Theta(n^6)$[CC09]
BP probabilities	$e^{\frac{-\pi_{bp}}{RT}}$	$\mathcal{O}(n^4)/\mathcal{O}(n^4)$	–
Sampling (k-struct.)	$e^{\frac{-\pi_{bp}}{RT}}$	$\mathcal{O}(n^4 + kn\log n)/\mathcal{O}(n^4)$	–

Exercice: Write DP equation for MFE computation, counting and partition function.


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