M2 AMI2B - Lecture 2
Boltzmann ensemble

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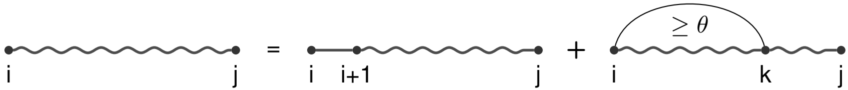
Outline

1. **Foreword**

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



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

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

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

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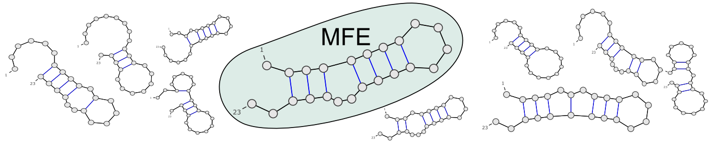
The canonical Boltzmann Ensemble

RNA *breathes* ⇒ 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.
⇒ 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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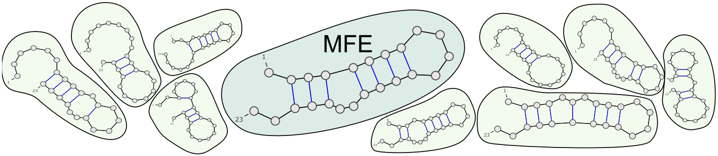

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Boltzmann Distribution: Definition

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**

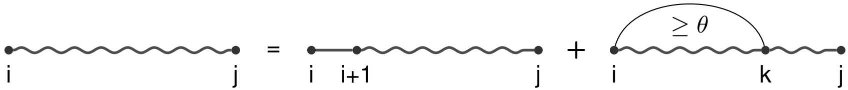
$$\mathcal{Z}_\omega = \sum_{S\in\mathcal{S}_\omega} e^{\frac{-E_{S,\omega}}{RT}}$$

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

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

Nussinov/Jacobson DP scheme



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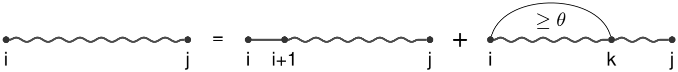


Recurrence for minimal free-energy of a fold :

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

$$N_{i,j} = \min \begin{cases} N_{i+1,j} & (i \text{ unpaired}) \\ \min_{k=i+\theta+1}^{j} E_{i,k} + N_{i+1,k-1} + N_{k+1,j} & (i \text{ comp. with } k) \end{cases}$$

Recurrence for counting compatible structures :

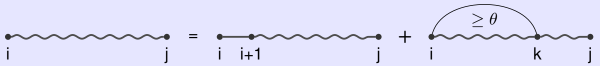
$$C_{i,t} = 1, \quad \forall t \in [i, i+\theta]$$

$$C_{i,j} = \sum \begin{cases} C_{i+1,j} & (i \text{ unpaired}) \\ \sum_{k=i+\theta+1}^{j} 1 \times C_{i+1,k-1} \times C_{k+1,j} & (i \text{ comp. with } k) \end{cases}$$

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

Partition function

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



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

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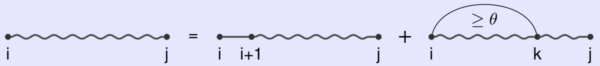

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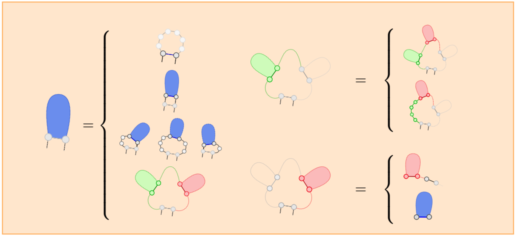

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\begin{aligned}
\mathcal{M}'_{i,j} &= \text{Min}\begin{cases} E_H(i,j) \\ E_S(i,j) + \mathcal{M}'_{i+1,j-1} \\ \text{Min}(E_{BI}(i,i',j',j) + \mathcal{M}'_{i',j'}) \\ a + c + \text{Min}\left(\mathcal{M}_{i+1,k-1} + \mathcal{M}^1_{k,j-1}\right) \end{cases}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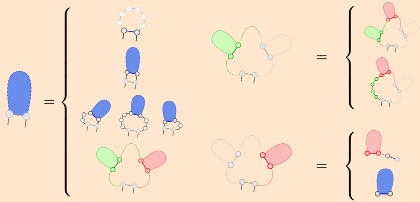

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\text{Min}\left(e^{\frac{-E_{BI}(i,i',j',j)}{RT}} + \mathcal{M}'_{i',j'}\right) \\
e^{\frac{-(a+c)}{RT}} + \text{Min}\left(\mathcal{M}_{i+1,k-1} + \mathcal{M}^1_{k,j-1}\right)
\end{cases}
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\mathcal{M}_{i,j}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

$$
\mathcal{M}^1_{i,j} = \text{Min}\left\{e^{\frac{-b}{RT}} + \mathcal{M}^1_{i,j-1}, e^{\frac{-c}{RT}} + \mathcal{M}'_{i,j}\right\}
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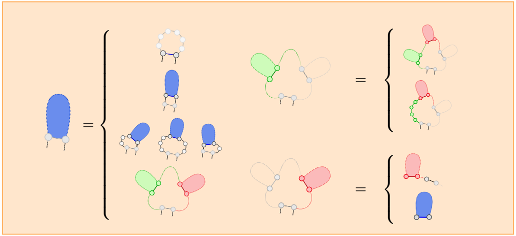

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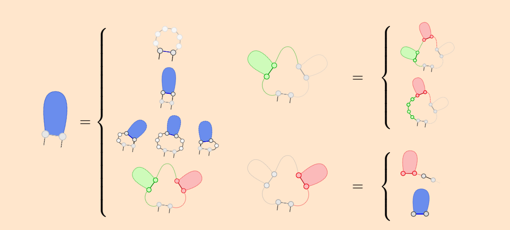

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\begin{aligned}
\mathcal{Z}'(i,j) &= \sum \begin{cases} e^{\frac{-E_H(i,j)}{RT}} \\ e^{\frac{-E_S(i,j)}{RT}} \mathcal{Z}'(i+1,j-1) \\ +\sum \left(e^{\frac{-E_{BI}(i,i',j',j)}{RT}} \mathcal{Z}'(i',j') \right) \\ +e^{\frac{-(a+c)}{RT}} \sum \left(\mathcal{Z}(i+1,k-1)\mathcal{Z}^1(k,j-1) \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)
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Partition function = **Weighted count** over compatible structures

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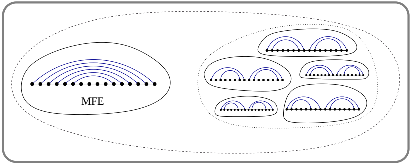
MFE ($\Leftrightarrow$ Max probability) may be **heavily dominated** by a set $\mathcal{B}$ of **structurally similar** suboptimal structures.
$\Rightarrow$ Functional conformation probably closer to $\mathcal{B}$ than to MFE.



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 $r < 0$
3. Recurse over associated regions/matrices

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

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r ↓

$A_1 | A_2 | B_i | B_{i+1} | \ldots | B_{j-1} | B_j | C_i | C_{i+1} | \ldots | C_{j-1} | C_j$

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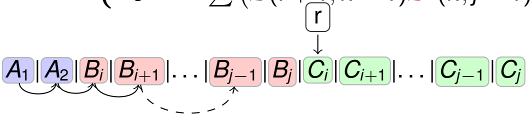

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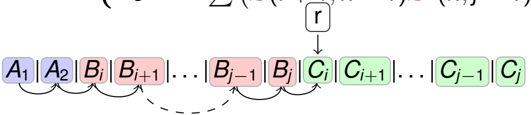

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Correctness: Each $S \in \mathcal{S}_\omega$ uniquely generated (DP scheme unambiguity)
Therefore the probability of generated S is

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

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2. Subtract from r the contributions of $\mathcal{Z}'(i,j)$ until $r < 0$
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

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

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:

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Therefore the probability of generated S is

$$p_S = \frac{\mathcal{B}(\{S\})}{\mathcal{B}(\mathcal{S}_w)} = \frac{e^{-E_s/RT}}{\mathcal{Z}} = P_{S,\omega}$$

Complexity

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

Stochastic backtrack:

1. Draw uniform random number $r \in [0, \mathcal{Z}'(i,j))$
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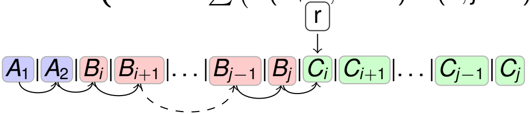
$$\mathcal{Z}'(i,j) = \sum ??? \begin{cases} e^{\frac{-E_H(i,j)}{RT}} + e^{\frac{-E_S(i,j)}{RT}}\mathcal{Z}'(i+1,j-1) & \text{(A)} \\ \sum \left(e^{\frac{-E_{BI}(i,i',j',j)}{RT}}\mathcal{Z}'(i',j') \right) & \text{(B)} \\ e^{\frac{-(a+c)}{RT}} \sum \left(\mathcal{Z}(i+1,k-1)\mathcal{Z}^1(k,j-1) \right) & \text{(C)} \end{cases}$$



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].

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

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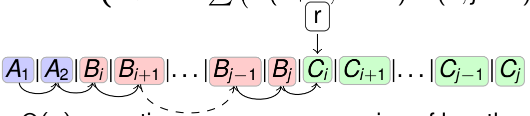
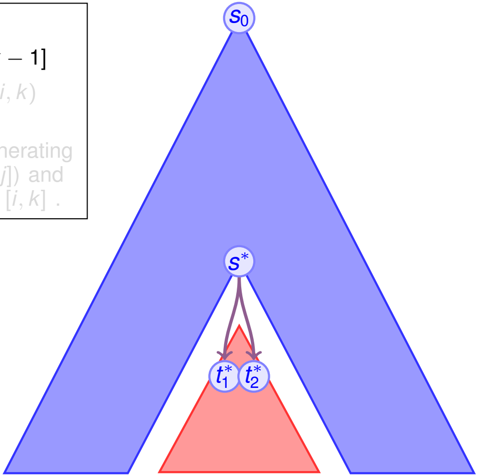


After $\Theta(n)$ operations, recurse over region of length $n-1$
$\Rightarrow$ Worst-case complexity in $\mathcal{O}(k \times n^2)$ for k samples

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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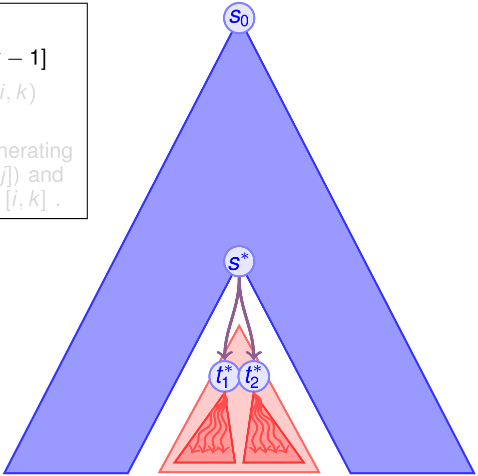

Algorithme Inside/outside

Structure including base pair (i, k):

- Inside: Structures over $[i + 1, k - 1]$
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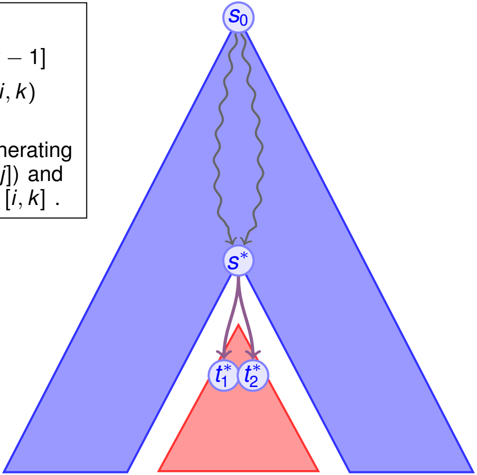

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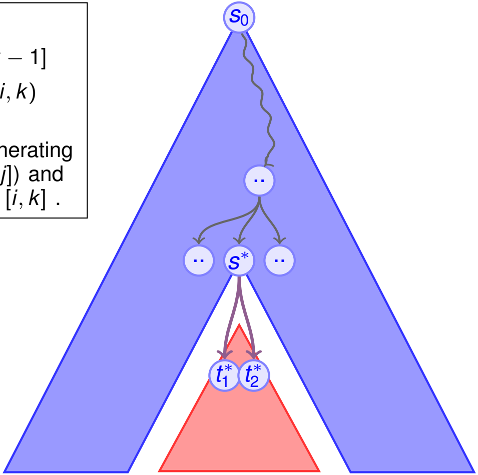

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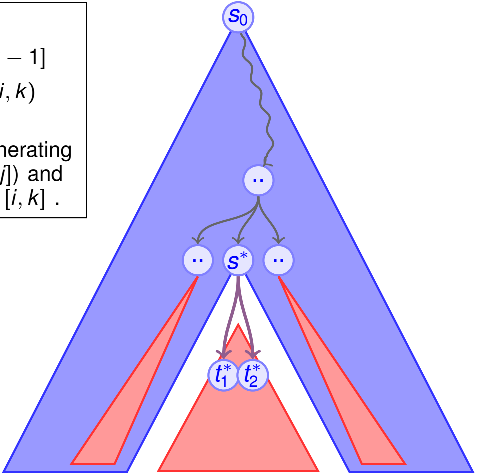

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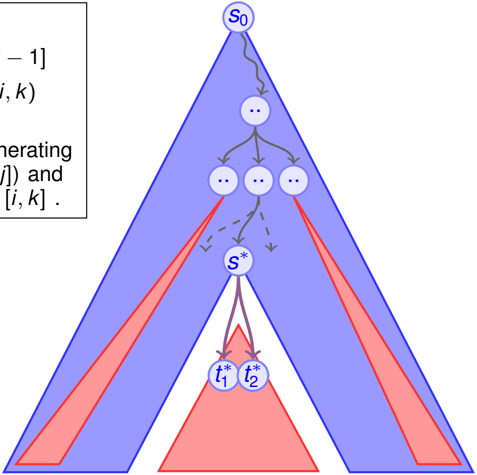

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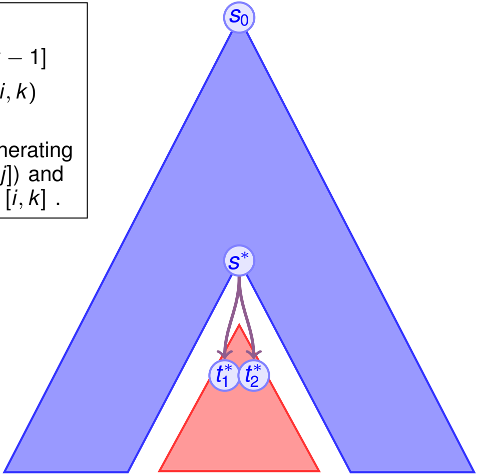

Whenever some further **technical conditions** are satisfied, this decomposition is **complete** and **unambiguous**, and implies a ***simple recurrence*** for computing the base pair probability matrix in $\Theta(n^3)$.

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