Algorithmics and combinatorics of RNA sampling

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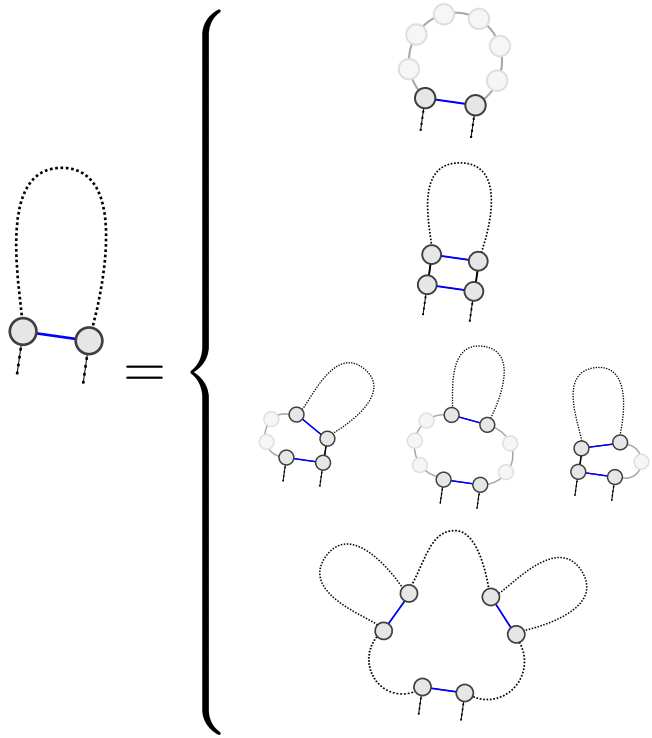
(Enumerative) Combinatorics helps:

- Counting conformations
- Analyzing features of null models
- Performing analysis of algorithms. . .
- . . . improving them?

MFE DP equations



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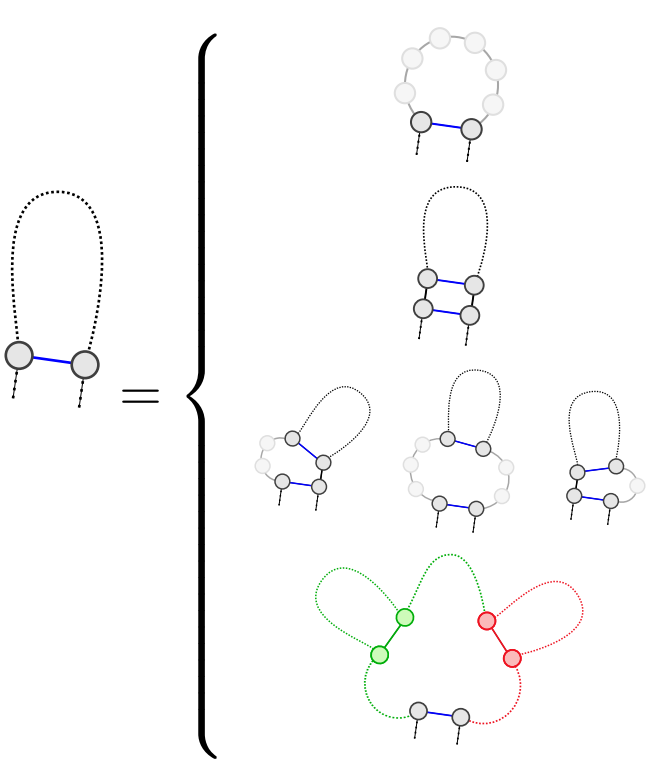

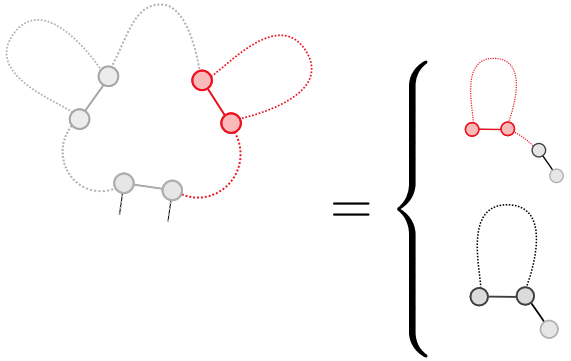

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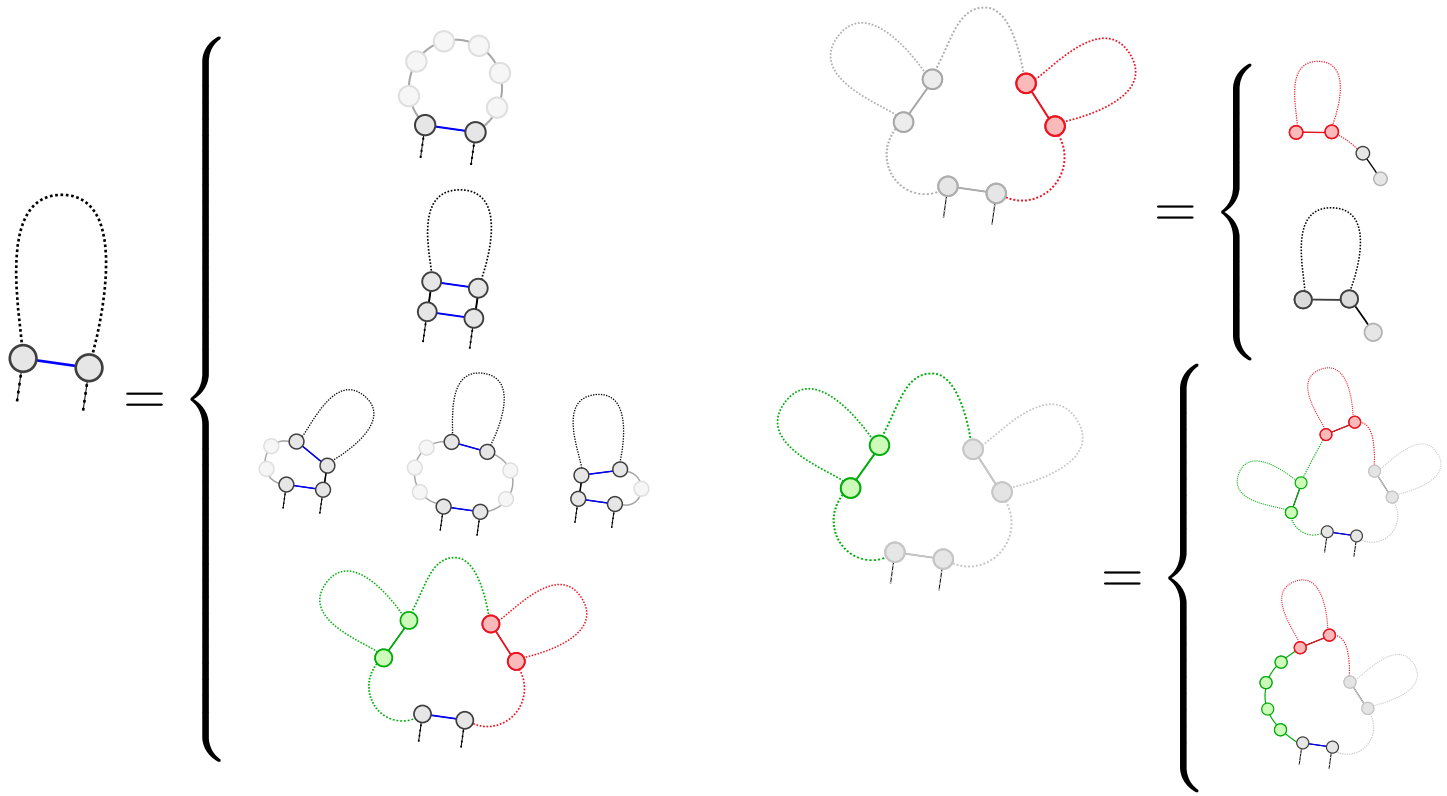
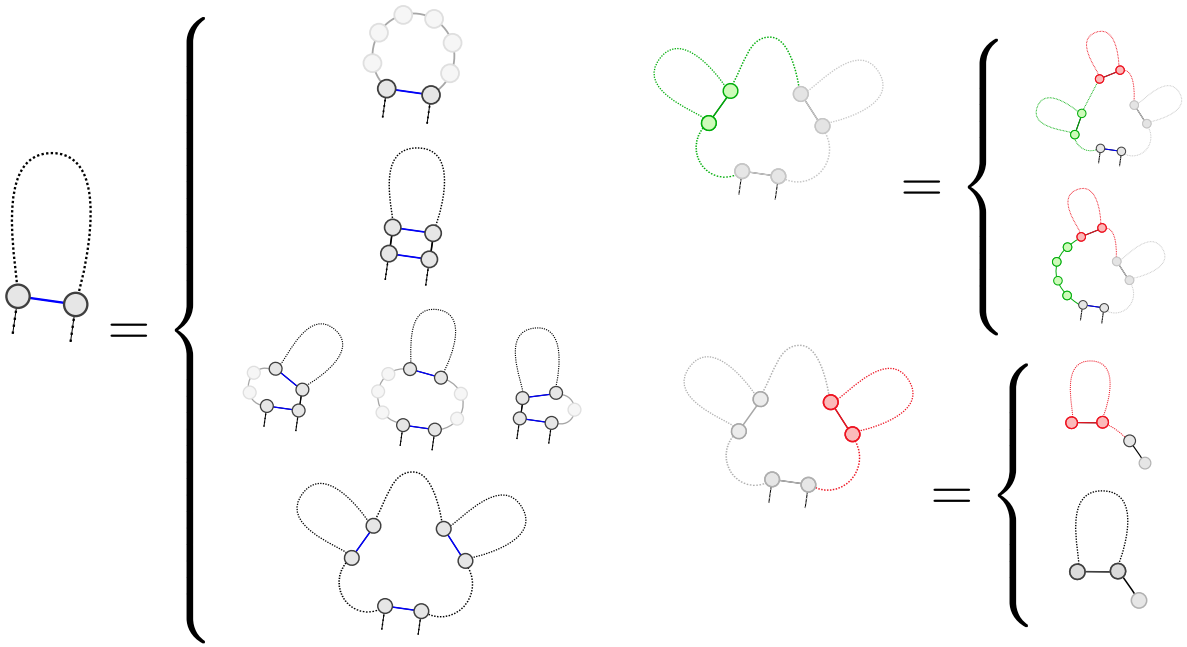


Completeness: Not too hard to check!
Unambiguity $\Rightarrow$ Enumerative combinatorics.

Validation



Validation

Generating function $\mathcal{T}(z) = \sum_{n \geq 0} t_n z^n$
With $t_n = \#$Secondary structures of size n

$$\mathcal{A}(z) = \begin{cases} \mathcal{S}(z) \\ z^2\mathcal{A}(z) \\ z\mathcal{S}(z)z^2\mathcal{A}(z) + z^2\mathcal{A}(z)\mathcal{S}(z)z \\ +z\mathcal{S}(z)z^2\mathcal{A}(z)\mathcal{S}(z)z \\ \mathcal{B}(z)\mathcal{C}(z) \end{cases} \qquad \mathcal{B}(z) = \begin{cases} \mathcal{B}(z)\mathcal{C}(z) \\ \mathcal{S}(z)\mathcal{B}(z) \end{cases}$$

$$\mathcal{C}(z) = \begin{cases} \mathcal{C}(z)z \\ z^2\mathcal{A}(z) \end{cases}$$

$$\mathcal{S}(z) = 1 + z\mathcal{S}(z)$$

Validation

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$$\mathcal{S}(z) = 1 + z\mathcal{S}(z)$$

Reminder: Waterman counted Sec. Str. [Wat78] and found the gen. fun.

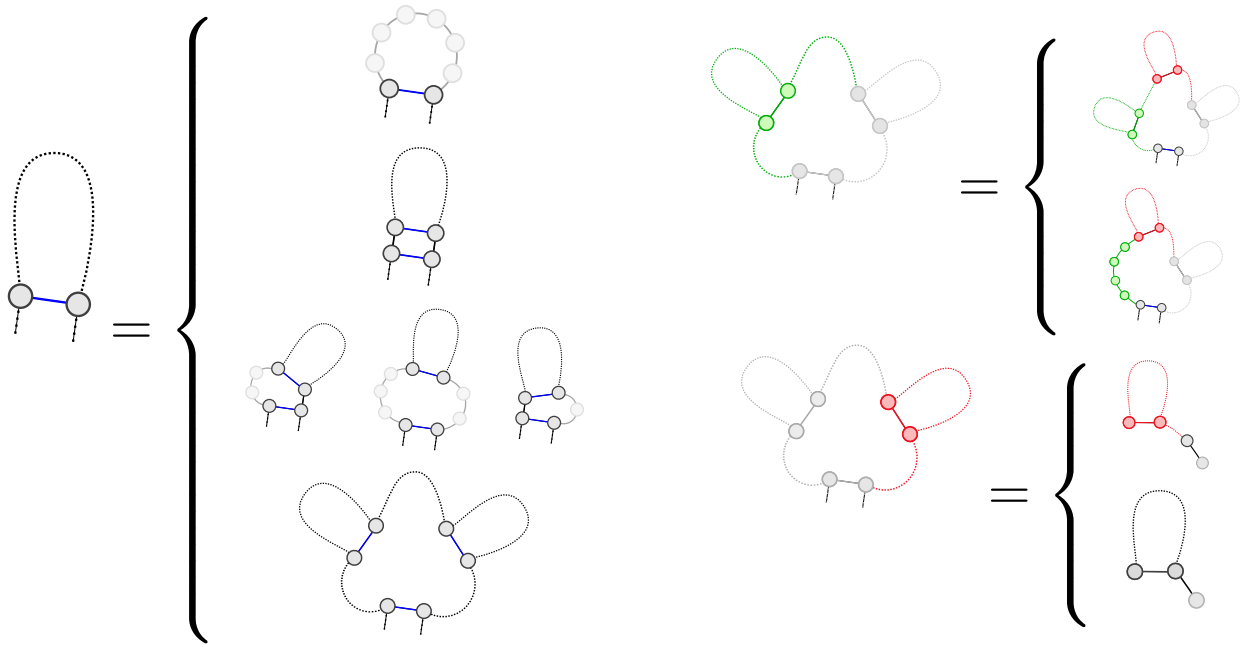
$$\mathcal{W}(z) = \frac{1 - z + z^2 - \sqrt{1 - 2z - z^2 - 2z^3 + z^4}}{2z^2}$$

Here we have

$$\begin{aligned} \Rightarrow \mathcal{A}(z) &= \frac{1 - z - z^2 - \sqrt{1 - 2z - z^2 - 2z^3 + z^4}}{2z^2} \\ &= \mathcal{W}(z) - 1 \quad \text{(Woops, we forgot the } \textit{empty} \text{ RNA)} \end{aligned}$$

MFE folding

- $E_H(i,j)$: Energy of hairpin loop with closing pair (i,j)
- $E_{BI}(i,j)$: Energy of bulge or internal loop with closing pair (i,j)
- $E_S(i,j)$: Energy of stacking pairs $(i,j)/(i+1,j-1)$
- a,c,b: Penalties for multiloop, hairpins and unpaired bases in multiloop.



Message #1

Treating search space as a combinatorial object saves time and trouble!

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\begin{aligned}
\mathcal{M}'(i,j) &= \text{Min}\left\{\begin{array}{c} 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}(\mathcal{M}'(i+1,k-1)+\mathcal{M}^1(k,j-1)) \end{array}\right\} \\
\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\} \\
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Treating search space as a combinatorial object saves time and trouble!

Partition function: Beyond m.f.e. hypothesis

Partition function/Boltzmann probability

- Let ω be an RNA sequence
- $\mathcal{S}_\omega$ be the set of sequences compatible with ω,

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

where T is temperature in Kelvin and R is the universal gas constant.

$$\textbf{Boltzmann probability} \quad P_{S,\omega} = \frac{e^{\frac{-E_{S,\omega}}{RT}}}{\mathcal{Z}_\omega}$$

$P_{S,\omega}$ is the probability of observing ω in conformation S.

$\Rightarrow$ Offers a more dynamic view of the folding process

$\Rightarrow$ Gives a model for computing various probabilities (BP, Motifs ...)

$\Rightarrow$ Unified algorithmic framework for subopts and mfe ($RT \to \infty$)

$\Rightarrow$ Very easy to embed into any existing DP equations

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Partition function: Beyond m.f.e. hypothesis

From m.f.e. folding to partition function [McC90]:

- Atomic energy increment $E \rightarrow$ Boltzmann factor $e^{\frac{-E}{RT}}$
- Energies contr. move to the exponent:
  Sums $(+) \rightarrow$ Products $(\times)$
- Summing instead of minimizing: Min $\rightarrow$ Sums $(\sum)$

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\begin{aligned}
\mathcal{M}'(i,j) &= \text{Min}\left\{\begin{array}{c} 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{array}\right\} \\
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Message #2

From **unambiguous description** partition function (and then statistical sampling) is just one algebra switch $(\text{Min},+) \rightarrow (+,\times)$ away.

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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{array}
\right\} \\
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Statistical sampling through stochastic traceback

Algorithm `SFold` [DL03]:

1. Generate a random number in $[0, \mathcal{Z}'(i,j))$
2. Subtract to r individual contributions to $\mathcal{Z}'(i,j)$, until $r < 0$
3. Recurse over substructures

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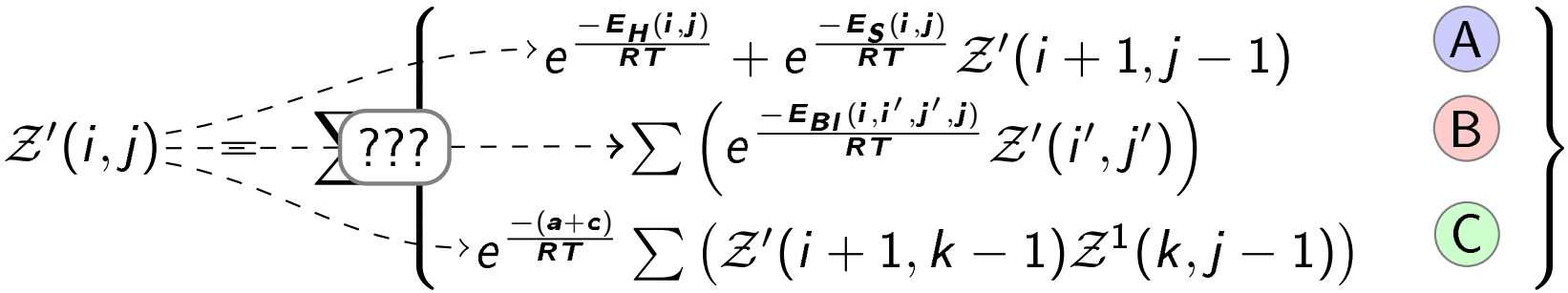

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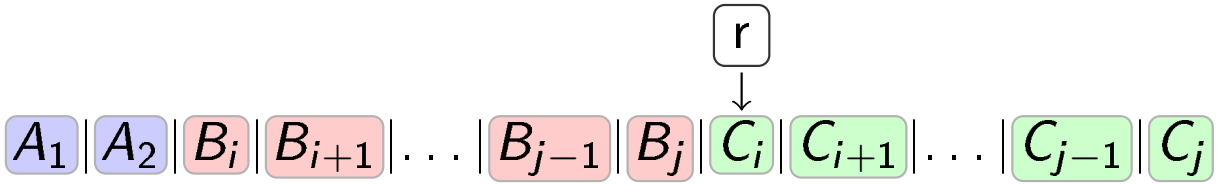

After $\Theta(n)$ operations, recurse over size $n-1$ interval
$\Rightarrow$ Worst-case time complexity for k samples in $\mathcal{O}(n^2 k)$

Remark: This is a weighted instance of the so-called recursive random generation of decomposable objects [DRT00].

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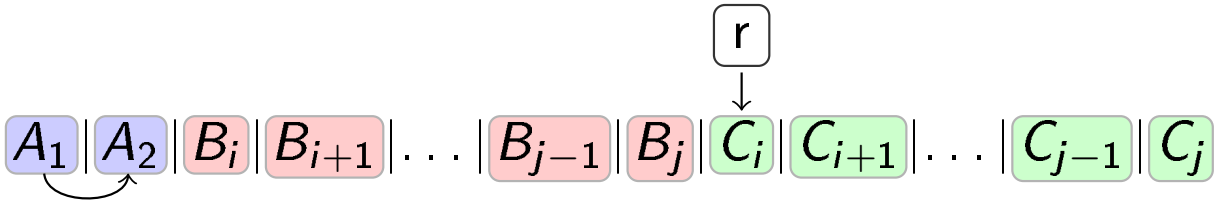

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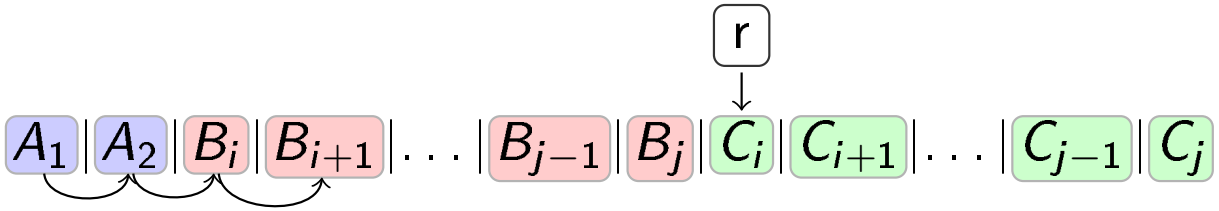

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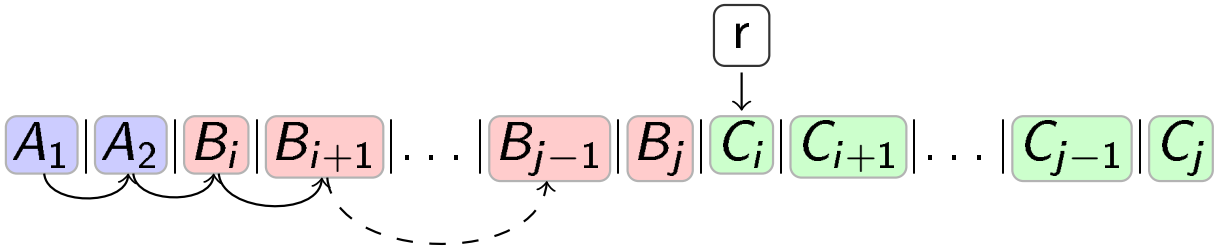

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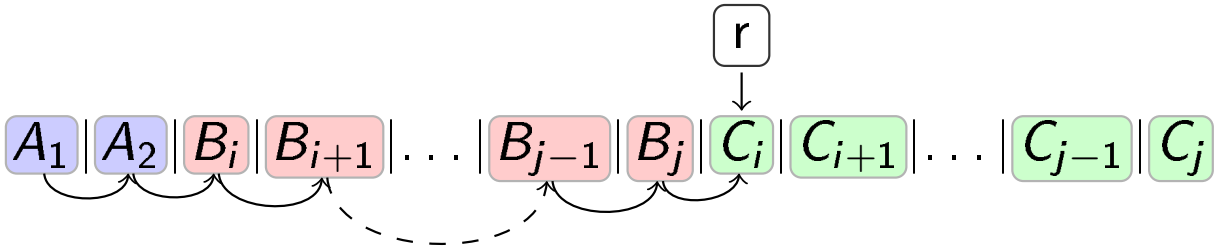


After $\Theta(n)$ operations, recurse over size $n-1$ interval
$\Rightarrow$ Worst-case time complexity for k samples in $\mathcal{O}(n^2 k)$

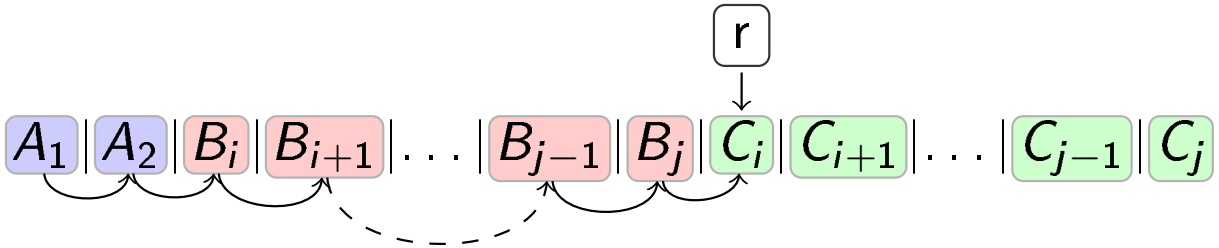
Remark: This is a weighted instance of the so-called recursive random generation of decomposable objects [DRT00].

Statistical sampling through stochastic traceback

Algorithm `SFold` [DL03]:

1. Generate a random number in $[0, \mathcal{Z}'(i,j))$
2. Subtract to r individual contributions to $\mathcal{Z}'(i,j)$, until $r < 0$
3. Recurse over substructures

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



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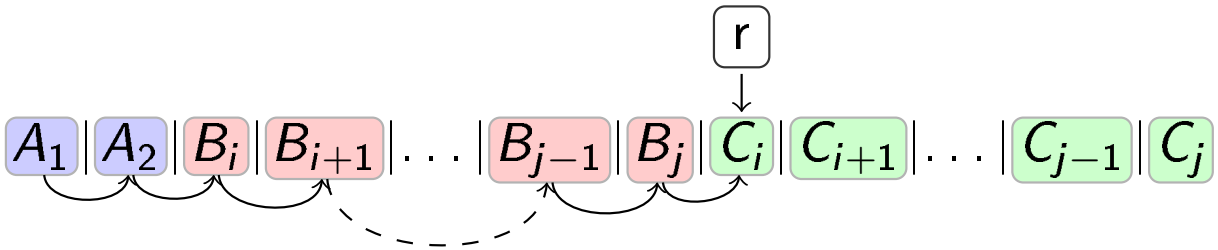
Efficient statistical sampling

How to improve statistical sampling?

- Improve time complexity:
  Average-case time complexity in $\Theta(kn\sqrt{n})$ [Pon08]
  ($\Theta(n^2)$ arises from recursing on $n - \mathcal{O}(1)$ after $\Theta(n)$ ops)
  - Interleaving Bulges (B) and Multiloops (C) contributions
  - Boustrophedon [FZV94]
    Investigate uneven decompositions first, then even ones !
- Non-redundant generation



Message #3

Boustrophedon search saves $\Theta(\frac{n}{\log n})/\Omega(\frac{\sqrt{n}}{\log n})$ worst/average case.

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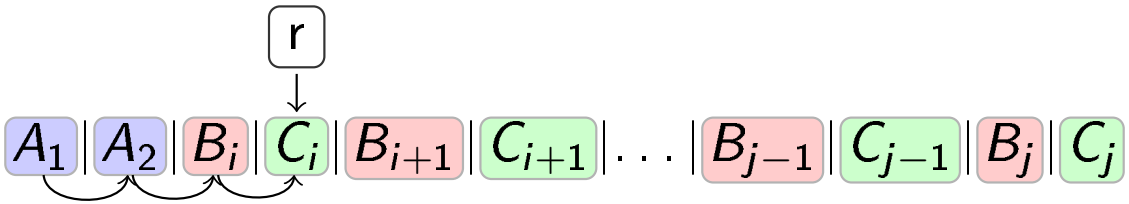

$\Rightarrow$ Some terms from B and C are reached in $\mathcal{O}(1)$

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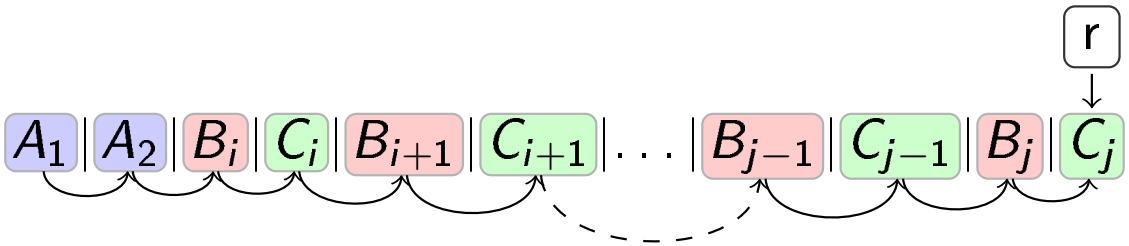

$\Rightarrow$ Some terms from B and C are reached in $\mathcal{O}(1)$
But still $\Theta(n^2)$, since $\mathcal{Z}'(i,j) \rightarrow (\mathcal{Z}'(i+1,k-1), \mathcal{Z}^1(k,j-1))$

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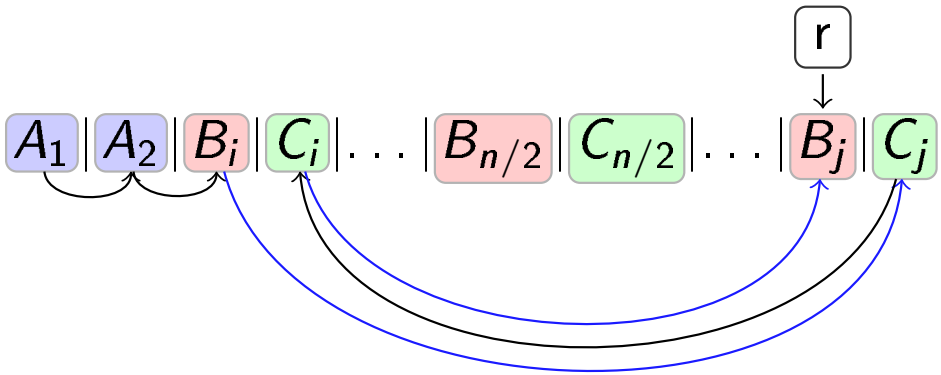

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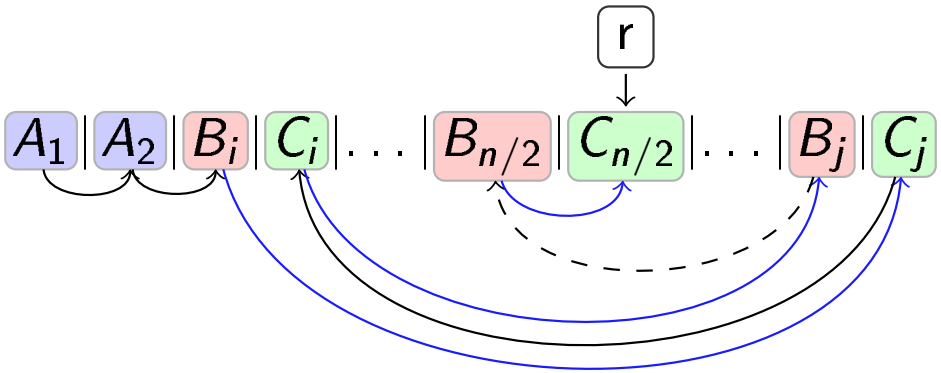

Worst-case: Divide evenly at each step [GK81] $\Rightarrow \Theta(n \log(n))$

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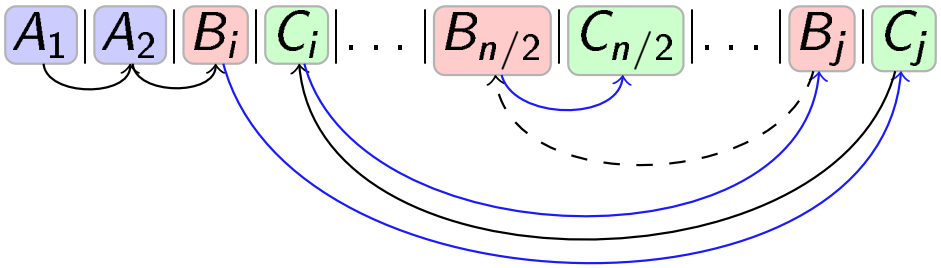

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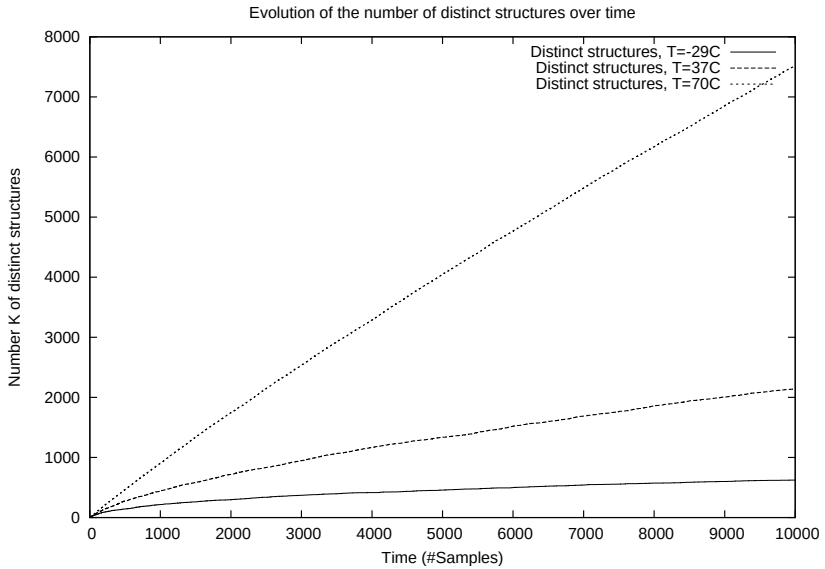
Efficient statistical sampling

How to improve statistical sampling?

- Improve time complexity
- Non-redundant generation (with D. Gardy and A. Lorenz)

For each sampled structure one can compute the actual probability

$\Rightarrow$ It does not make any sense to sample it twice!



How long will it take to get k **distinct** samples?

Efficient statistical sampling

How to improve statistical sampling?

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  How long will it take to get k distinct samples?

Full collection (k = #structures): $E[C] \approx \mathcal{Z}'.n$
Way larger than #structures $\Rightarrow$ Exponential number of collisions.

Numerical values (Homopolymer/Nussinov energy/T=37):

$$E[C] \sim K \cdot 4.332^n/\sqrt{n} \text{ and \#structures: } S_n \sim K' \cdot 2.618^n/n\sqrt{n}$$

$\Rightarrow$ Each structure is sampled $1.65^n \cdot n$ times ($\neq \Theta(n)$ uniform dist.)

Message #4

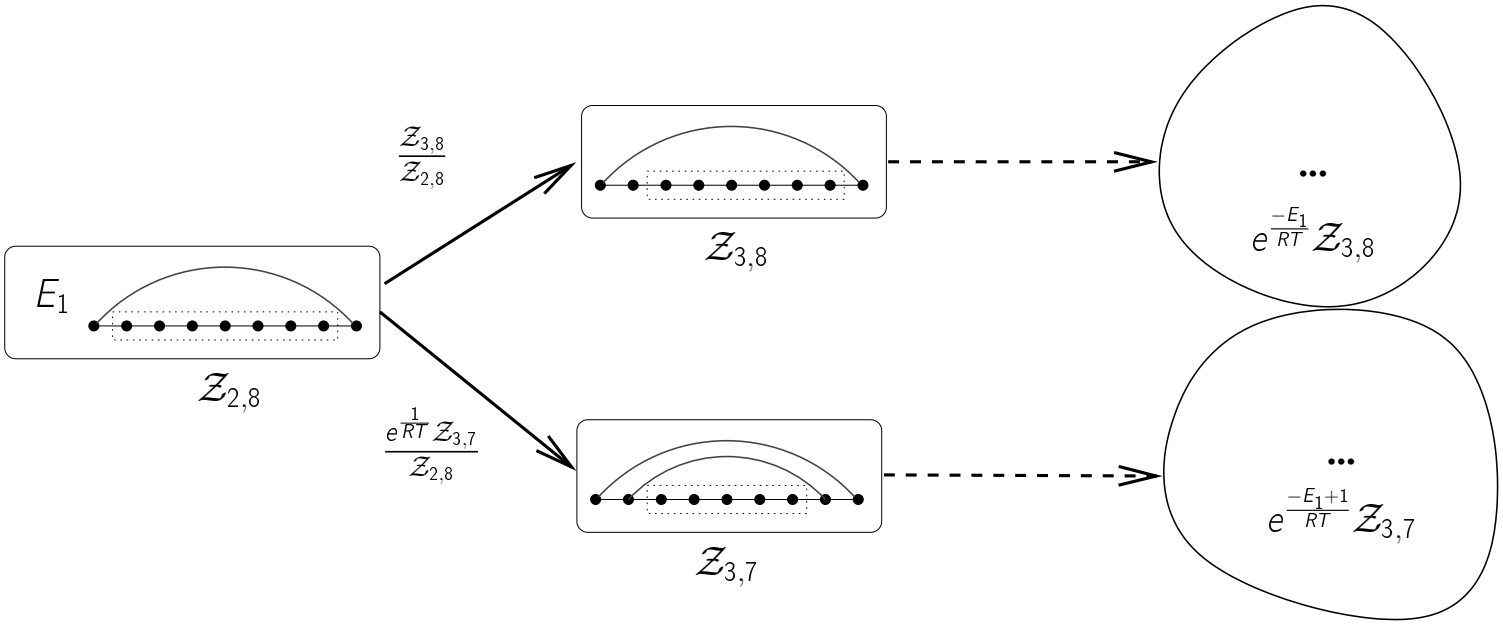
For any RNA there exists k such that the time for sampling k **distinct** sec. str. is **heavily dominated** by the cost of collisions.

k depends on the length $\Rightarrow$ Still need to push further our analysis...

Efficient statistical sampling

How to improve statistical sampling?

- Improve time complexity
- Non-redundant generation (with D. Gardy and A. Lorenz)
  - Build prefix tree for parse traces, storing in each node the contributions $K = \sum_{S \in \mathcal{R}} e^{\frac{-E_S}{RT}}$ of already sampled structures $\mathcal{R}$
  - During traceback, modify contributions of terms using K [Pon08]



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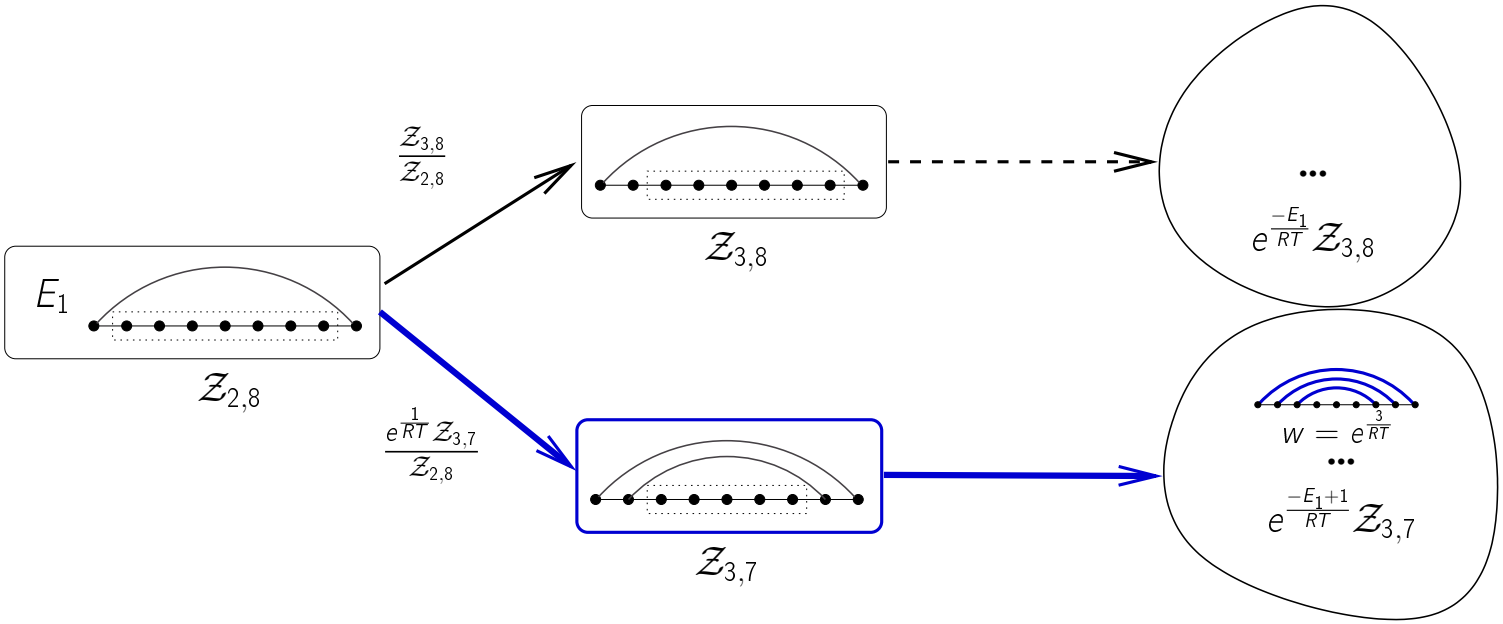

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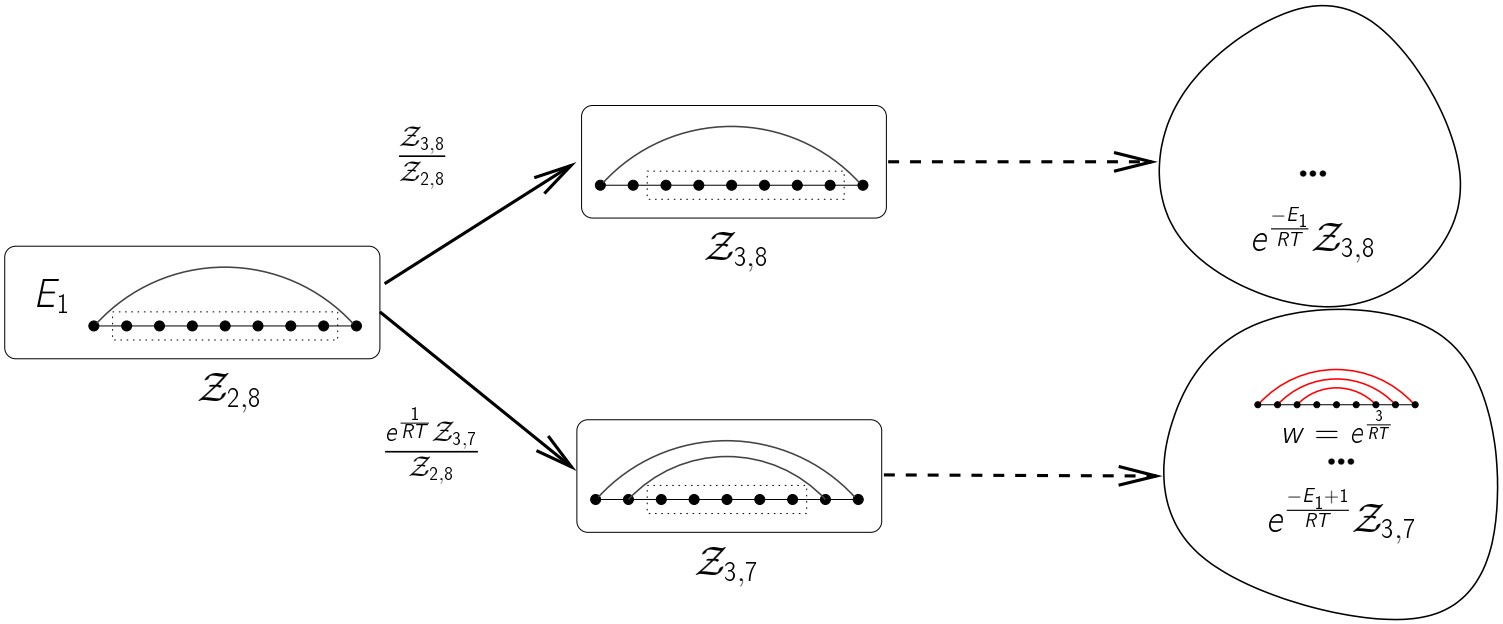

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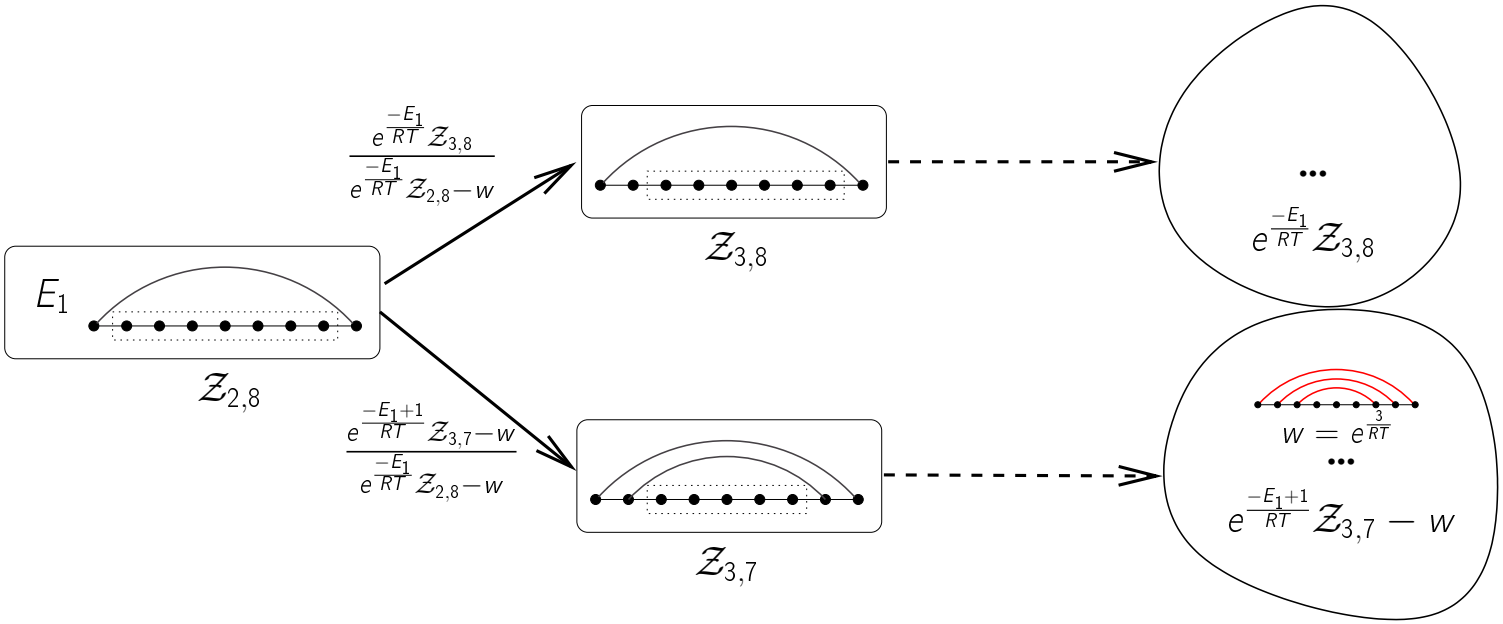

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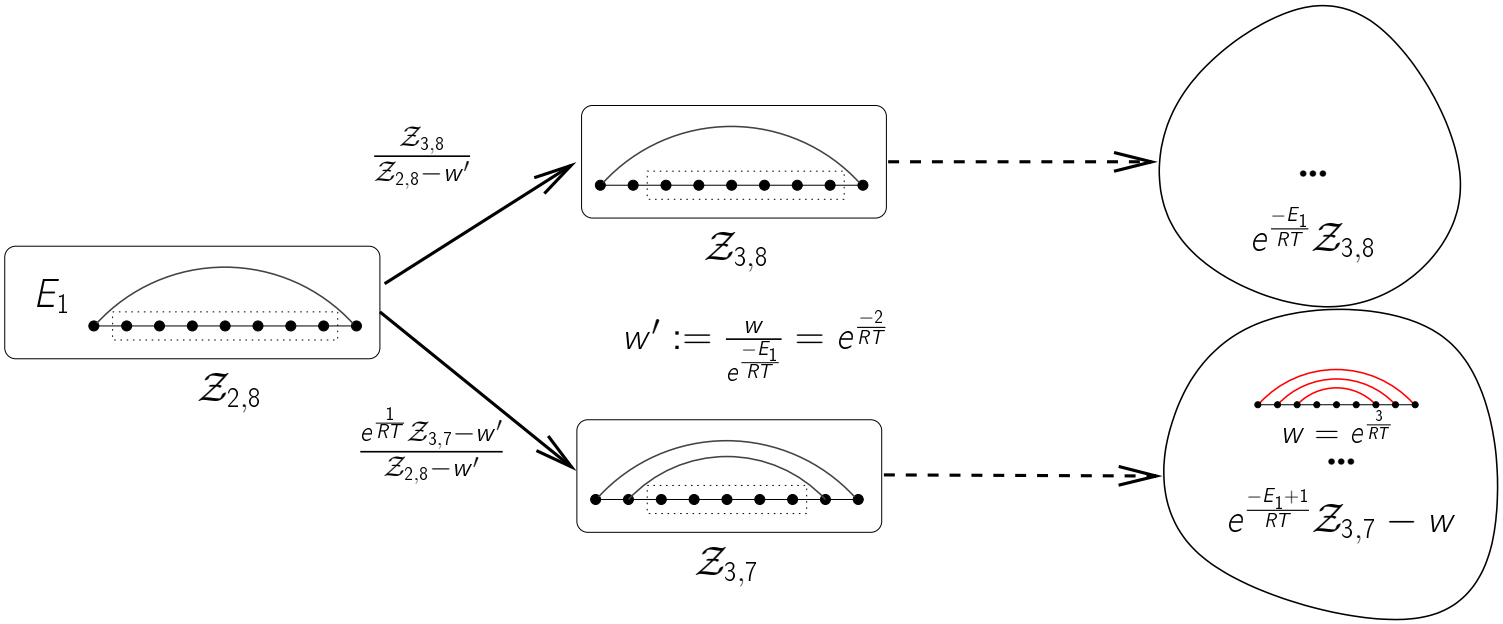

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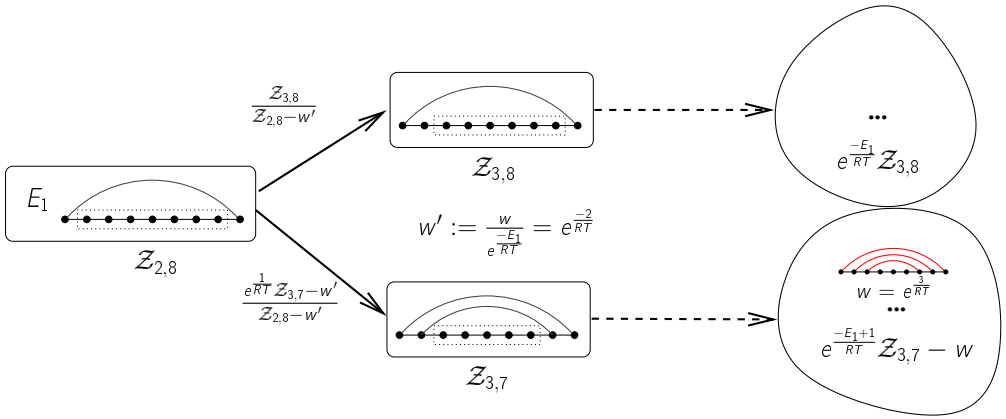

Message #5

Storing parse trees and biasing local choices, one can perform non-redundant sampling in $\mathcal{O}(kn\log(n))$ time.

Conclusions

- Combinatorics gives a convenient framework for validating/analyzing/improving dynamic programming algorithms
- Statistical sampling = (Weighted) random generation of combinatorial structures + constraints
- During stochastic traceback, reordering comparisons saves time!
- One does not benefit from redundancy $\Rightarrow$ Non-redundant sampling

Open questions:

- When do collisions overcome the complexity of sampling?
- Does there exist sequential alternatives to RNASubopt?

Thanks for E. Rivas and E. Westhof!!!

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