Journées MAGNUM – Partie 1

An unbiased adaptive sampling algorithm for the exploration of RNA mutational landscapes under evolutionary pressure

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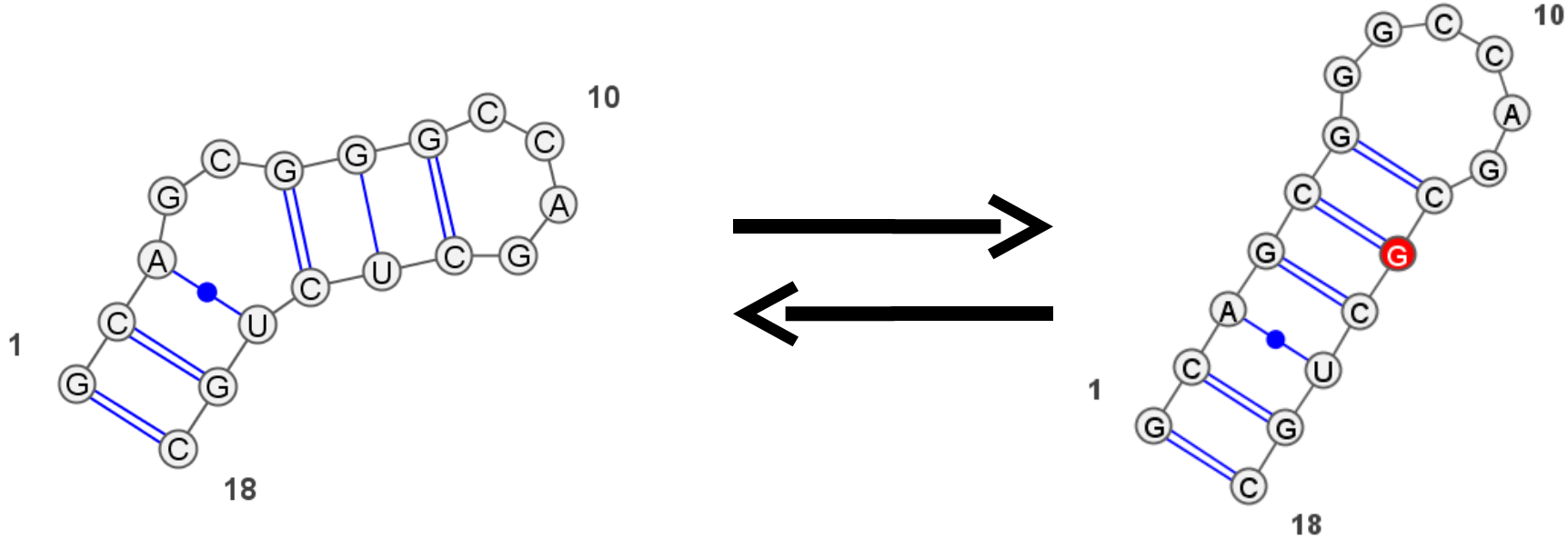
Overview

RNAmutants: Algorithms to explore the RNA mutational landscape



Understanding how mutations influence RNA secondary structures **AND** how structures influence mutations (Waldispühl et al., PLoS Comp Bio, 2008).

Sampling k-mutants

Seed

```
CAGUGAUUGCAGUGCGAUGC   (-1.20)
..((.(((((...)))))))
```

Classic: 0 mutation

```
CAGUGAUUGCAGUGCGAUcC   (-3.40)
..(.((((((...))))))
CAGUGAUUGCAGUGCGgUGC   (-0.30)
((.((....)).))......
CAGUGAUcGCAGUGCGAUGC   (-3.10)
.....(((((...)))))..
```

RNAmutants: 1 mutation

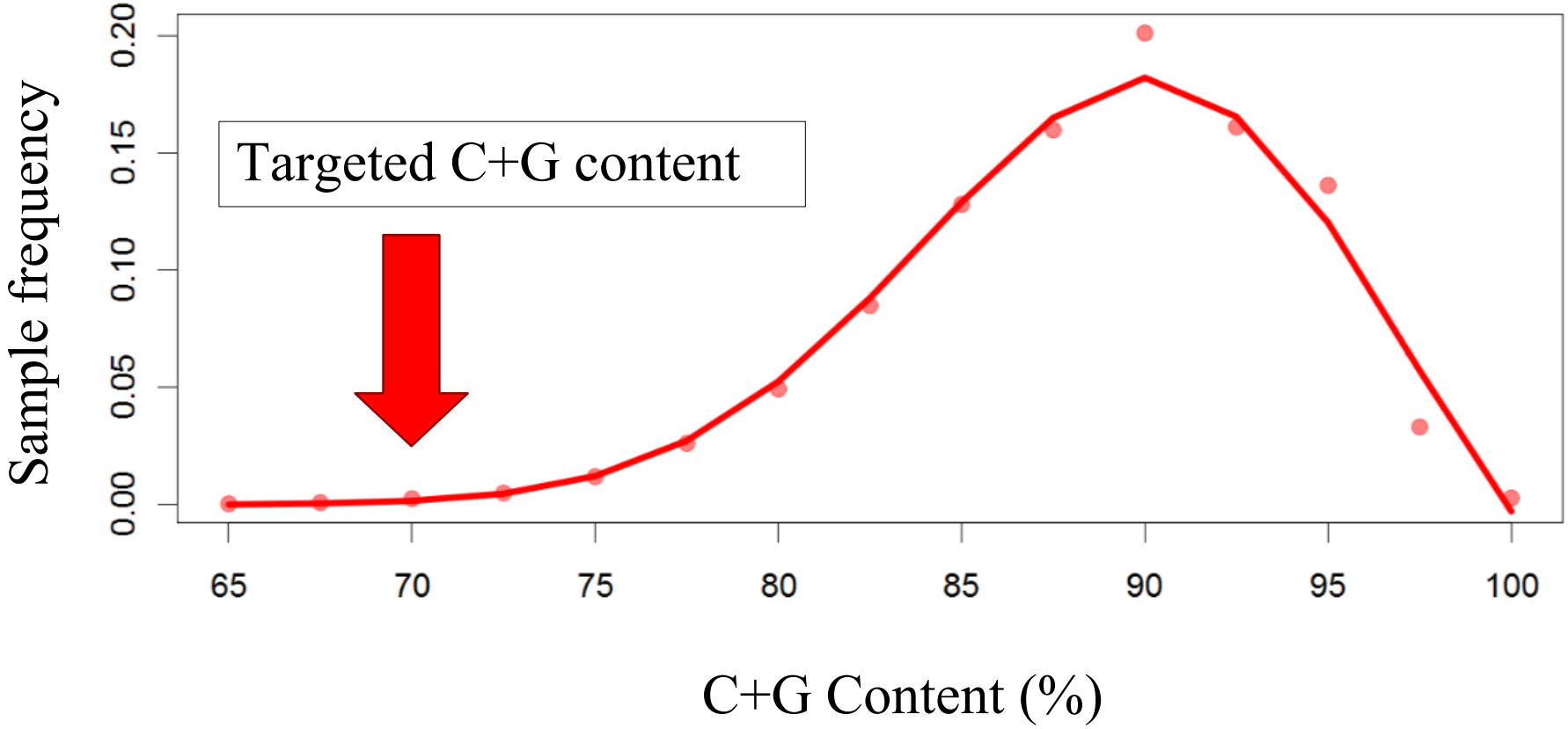
```
uAGcGccgGgAGacCGgcGC   (-18.00)
..(((((((....)))))))
CccUGgccGCAagGCcAgGg   (-20.40)
(((((((((....)))))))
CcGUGgccGCgagGCcAcGg   (-19.10)
(((((((((....)))))))
```

RNAmutants: 10 mutations

Sample k mutations increasing the folding energy

Consequence: Increase in C+G content

Objectives



How to efficiently sample sequences at arbitrary C+G contents … without introducing a bias!

Outline

- Background: RNAmutants in a nutshell
  Algorithms to sample RNA secondary structures and mutations.

- Our approach: Adaptive sampling
  Uniformly shifting the distribution of samples.

- Results: Evolutionary studies
  Insights on the evolutionary pressure stemming from an optimization of the thermodynamical stability.

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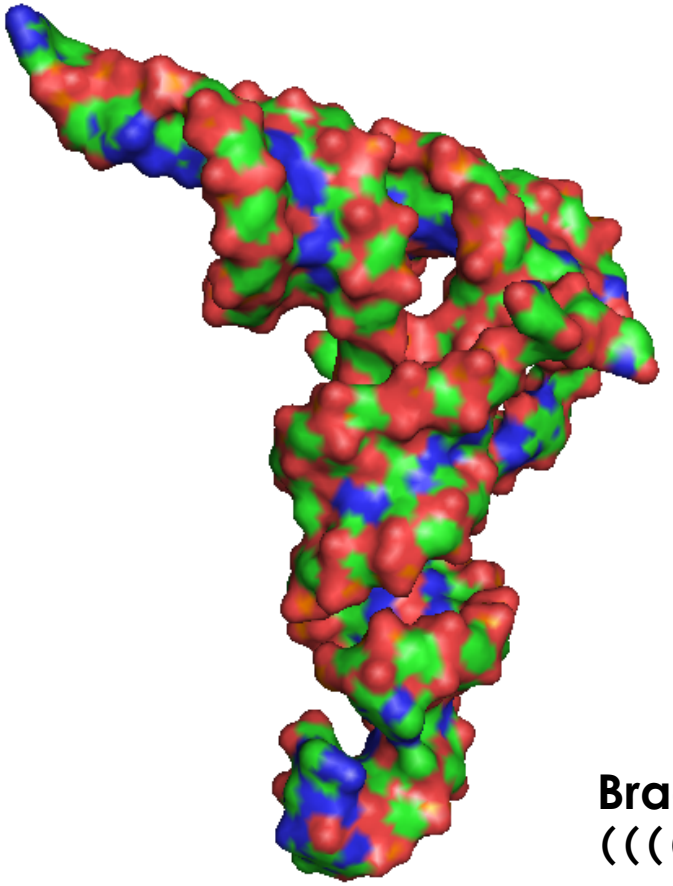
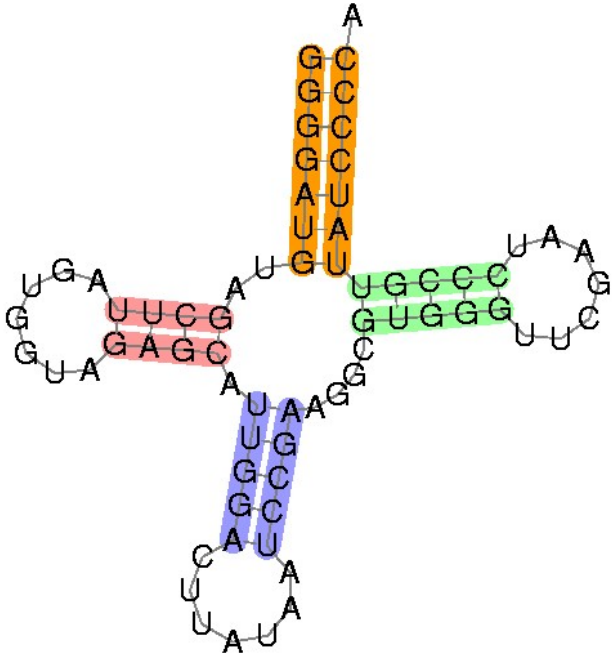
RNA secondary structure

The **secondary structure** is the ensemble of base-pairs in the structure.

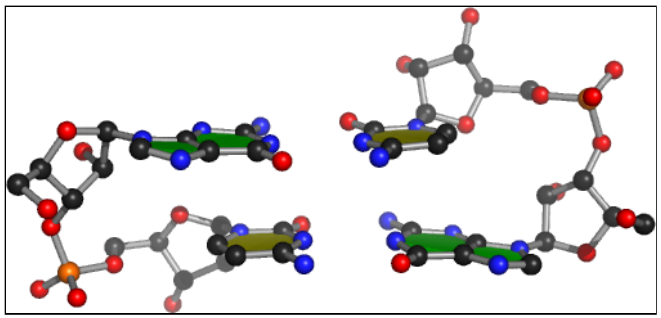




Bracket notation:

((((((((....))))..((((....))))).((((...))))..))))))

Loop decomposition



Stacking pairs

Hairpin loop

Bulge loop

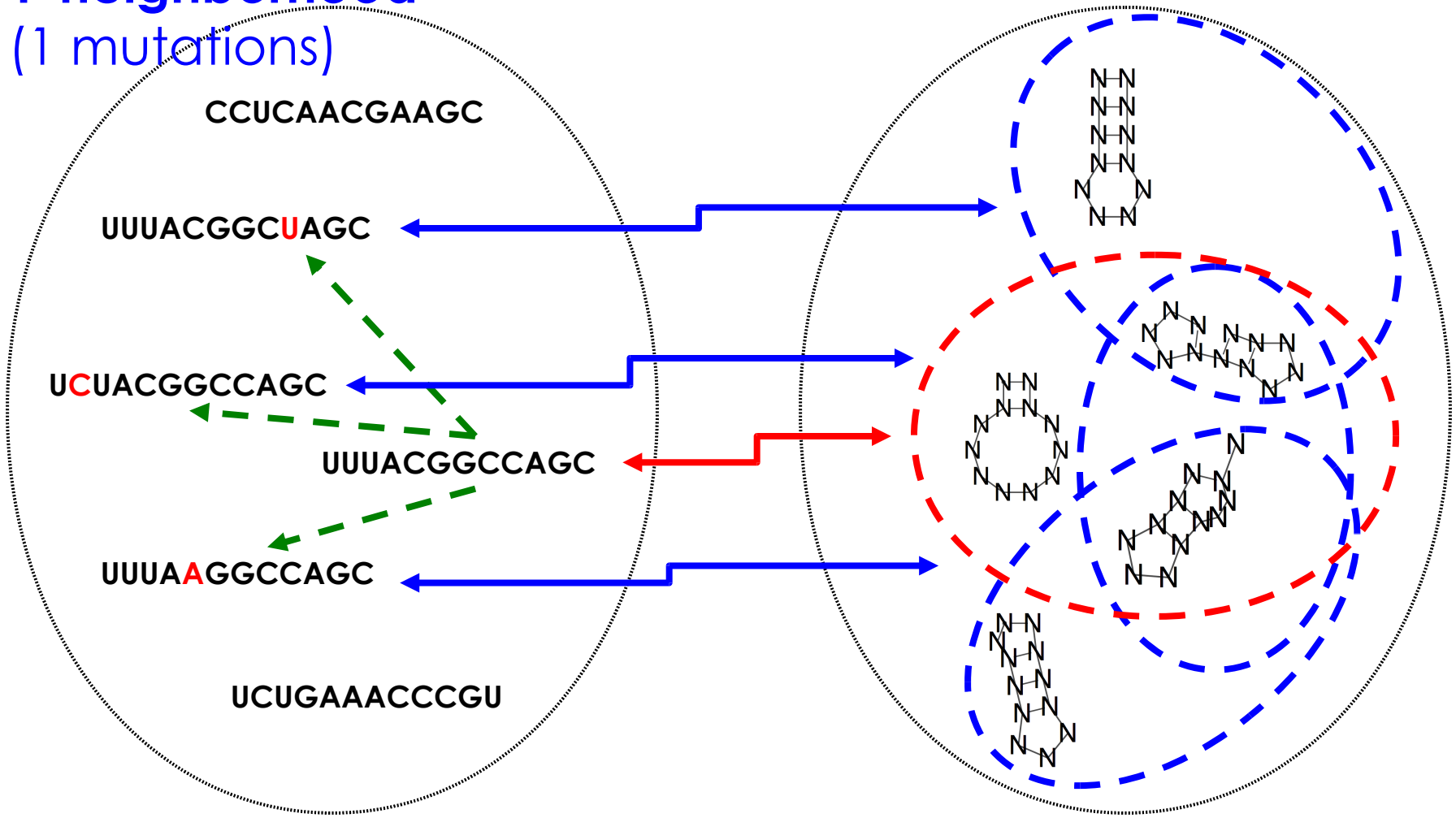
Interior loop

Multibranched loop

Unconstrained single-stranded region

Parameterization of the mutational landscape

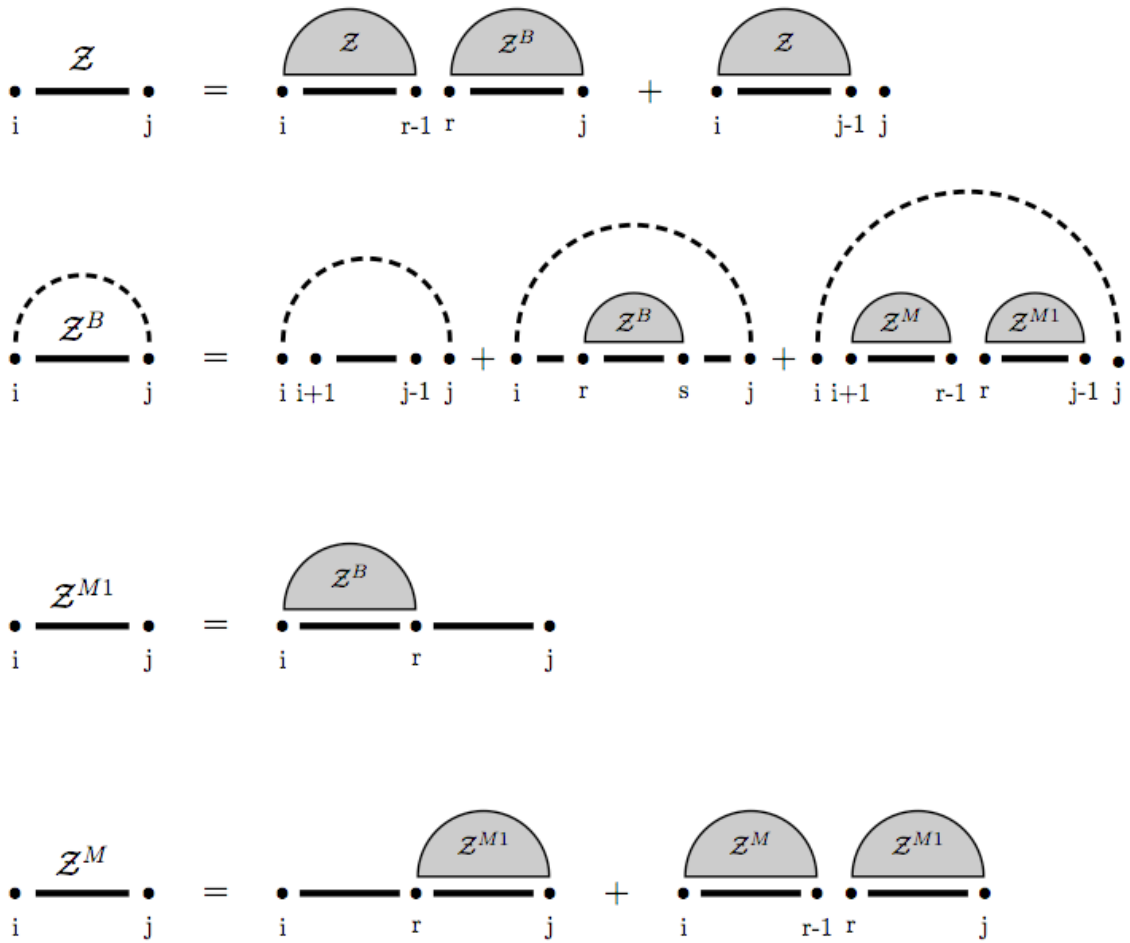
1-neighborhood
(1 mutations)



Sequence ensemble

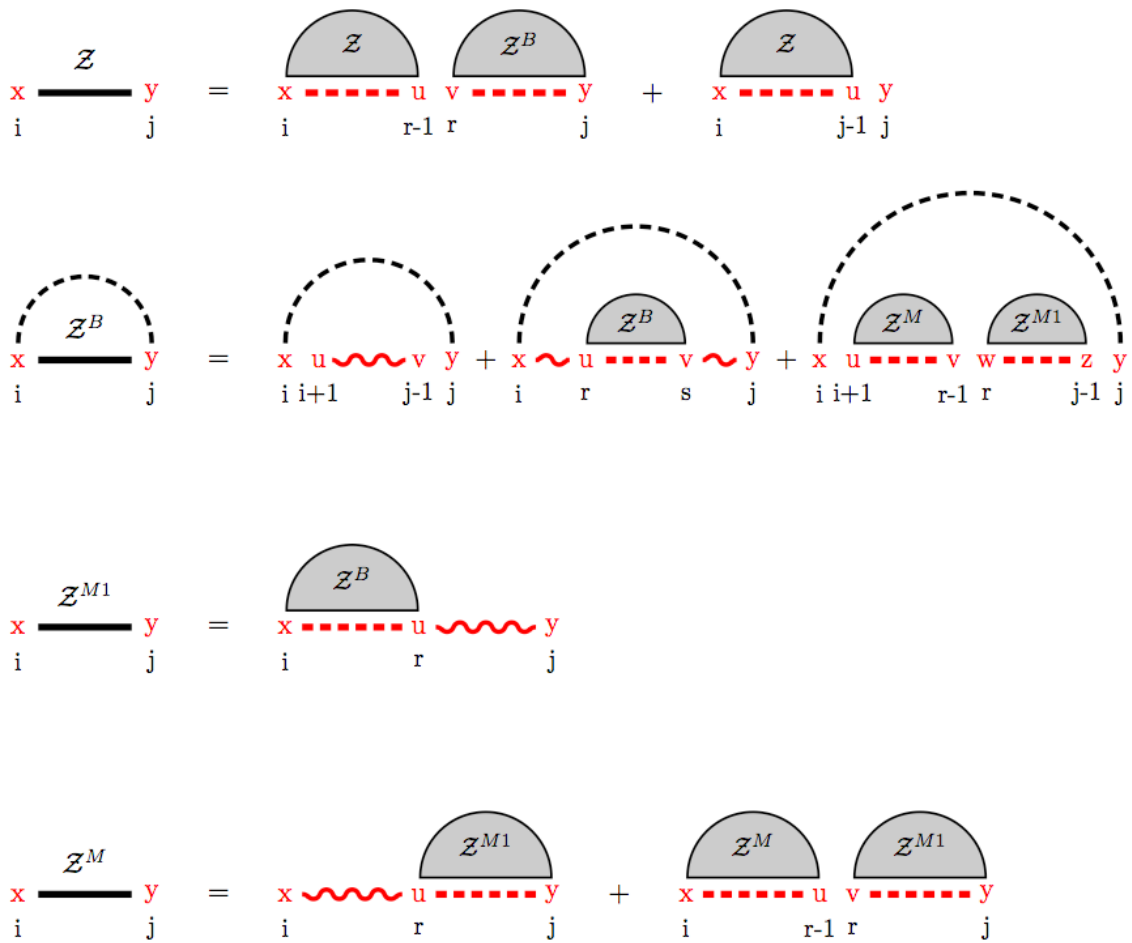
Structure ensemble

Classical Recursions (Zuker & Stiegler, McCaskill)



Enumerate all secondary structures

RNAmutants Generalize Classical Algorithms



Enumerate all secondary structures over all mutants

(Waldispuhl et al., *ECCB*, 2002)

Our approach

RNAmutants

- Explore the complete mutation landscape.
- *Polynomial* time and space algorithm.
- Compute the partition function for all sequences:

RNAmutants:

$$Z = \sum_{s} \sum_{S} \exp\left(-\frac{E(s,S)}{RT}\right)$$

Single sequence:

$$Z(s) = \sum_{S} \exp(b \times E(s,S))$$

- Sample by backtracking in dynamic prog. Tables.

  => Weighted random generation (recursive method)

(Waldispuhl et al., *PLoS Comp Bio*, 2008)

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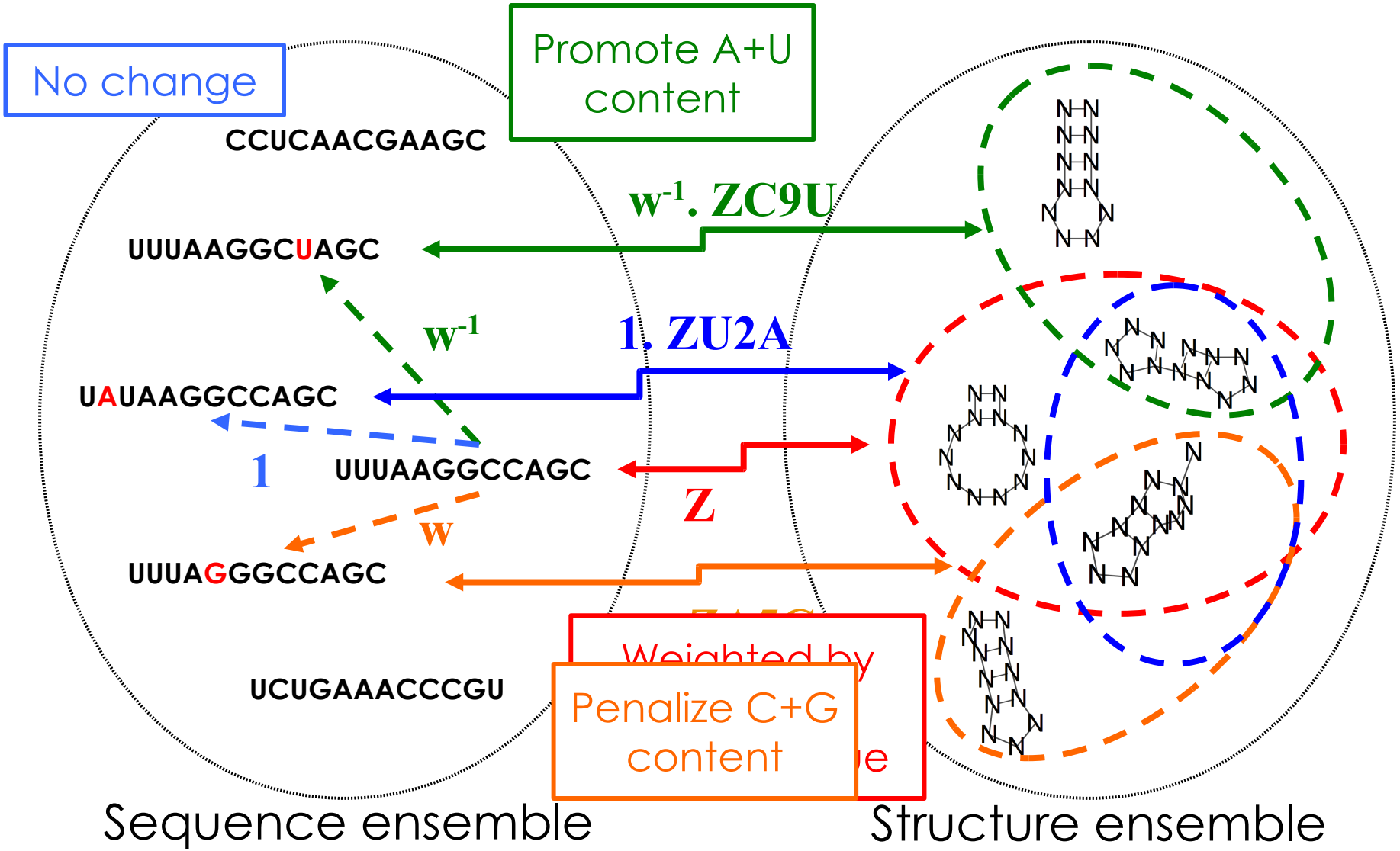
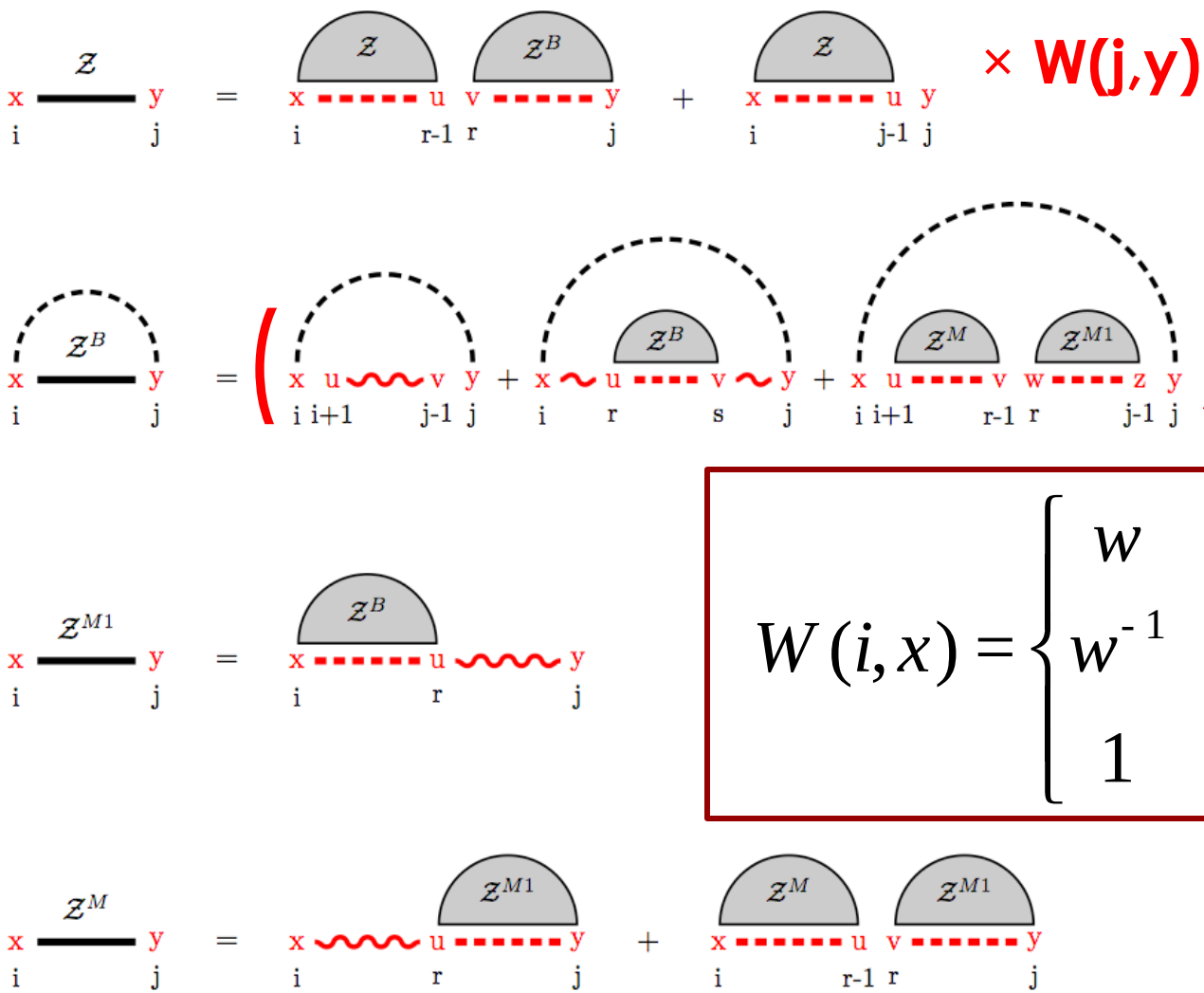
Our approach: Weighting mutations

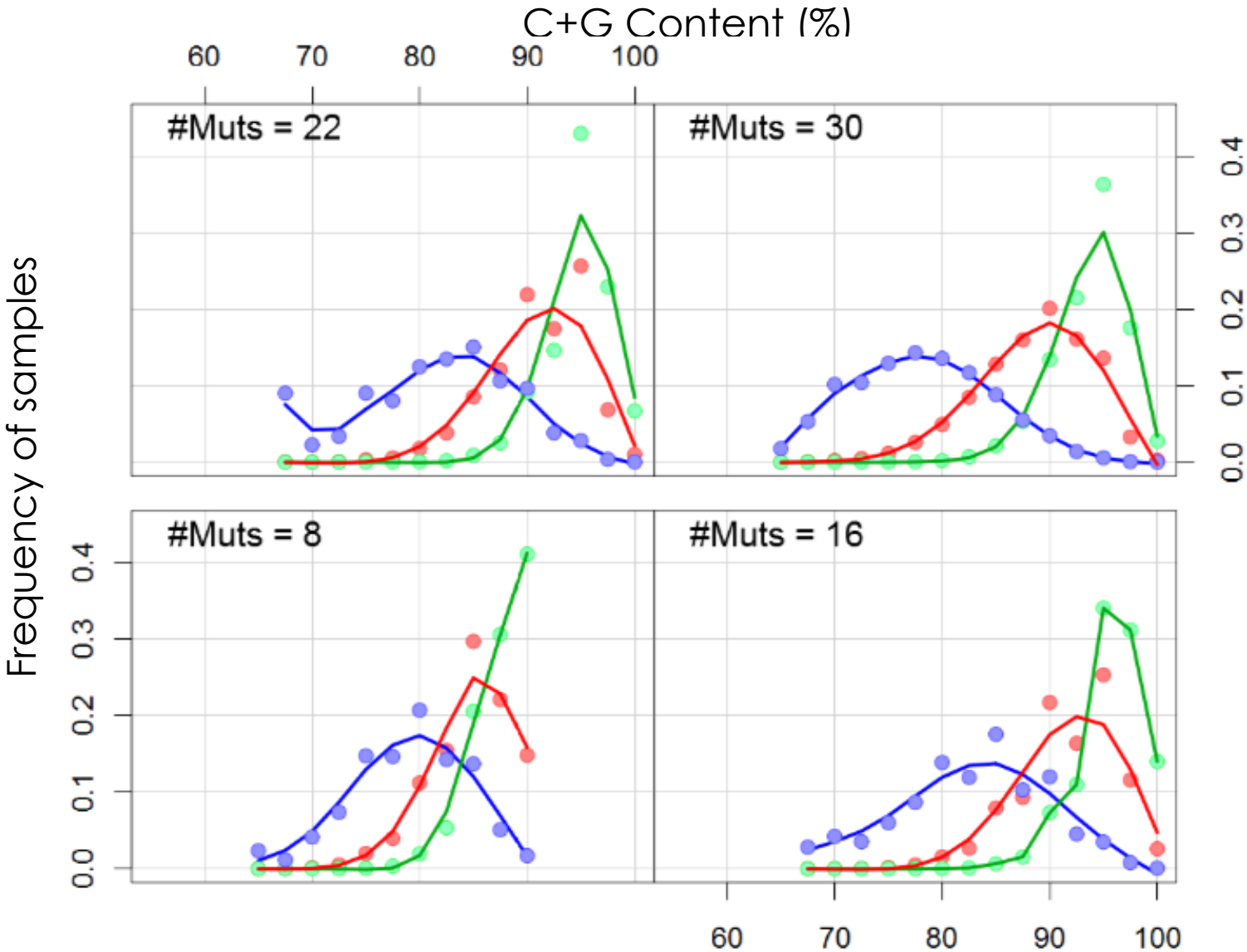


Weighting recursive equations



$$W(i,x) = \begin{cases} w & \text{If } A,U \rightarrow C,G \\ w^{-1} & \text{If } C,G \rightarrow A,U \\ 1 & \text{Otherwise} \end{cases}$$

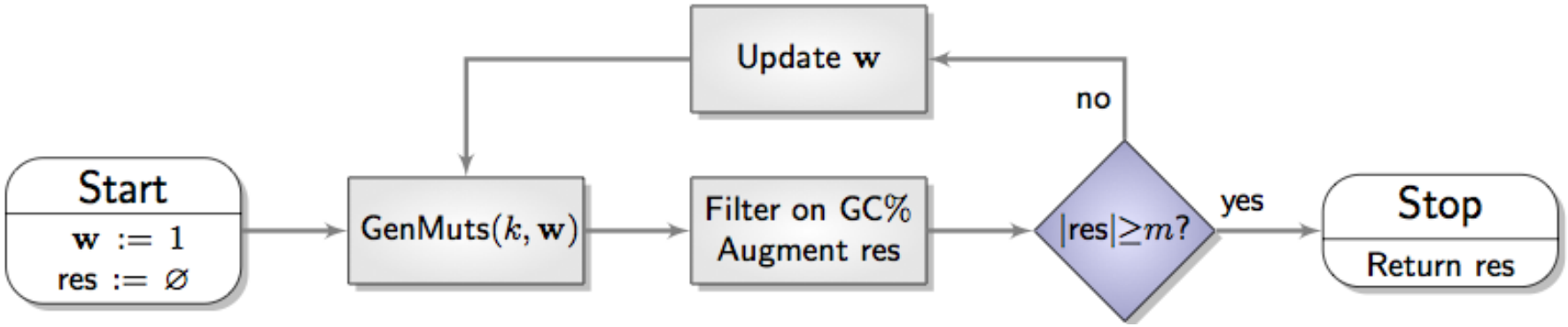
Effect of weighted sampling



■ Unweighted sampling ■ weighted (**w**=1/2) ■ weighted (**w**=2)

An Adaptive Sampling approach

Idea: Figure out a suitable weight *on the fly*.



- Keep all samples at targeted C+G% and reject others.
- Update **w** at each iteration using a bisection strategy.
- Stop when enough samples have been stored.

Algorithmic aspects

· After rejection, the weighted schema only impacts performance, not the probability distribution.

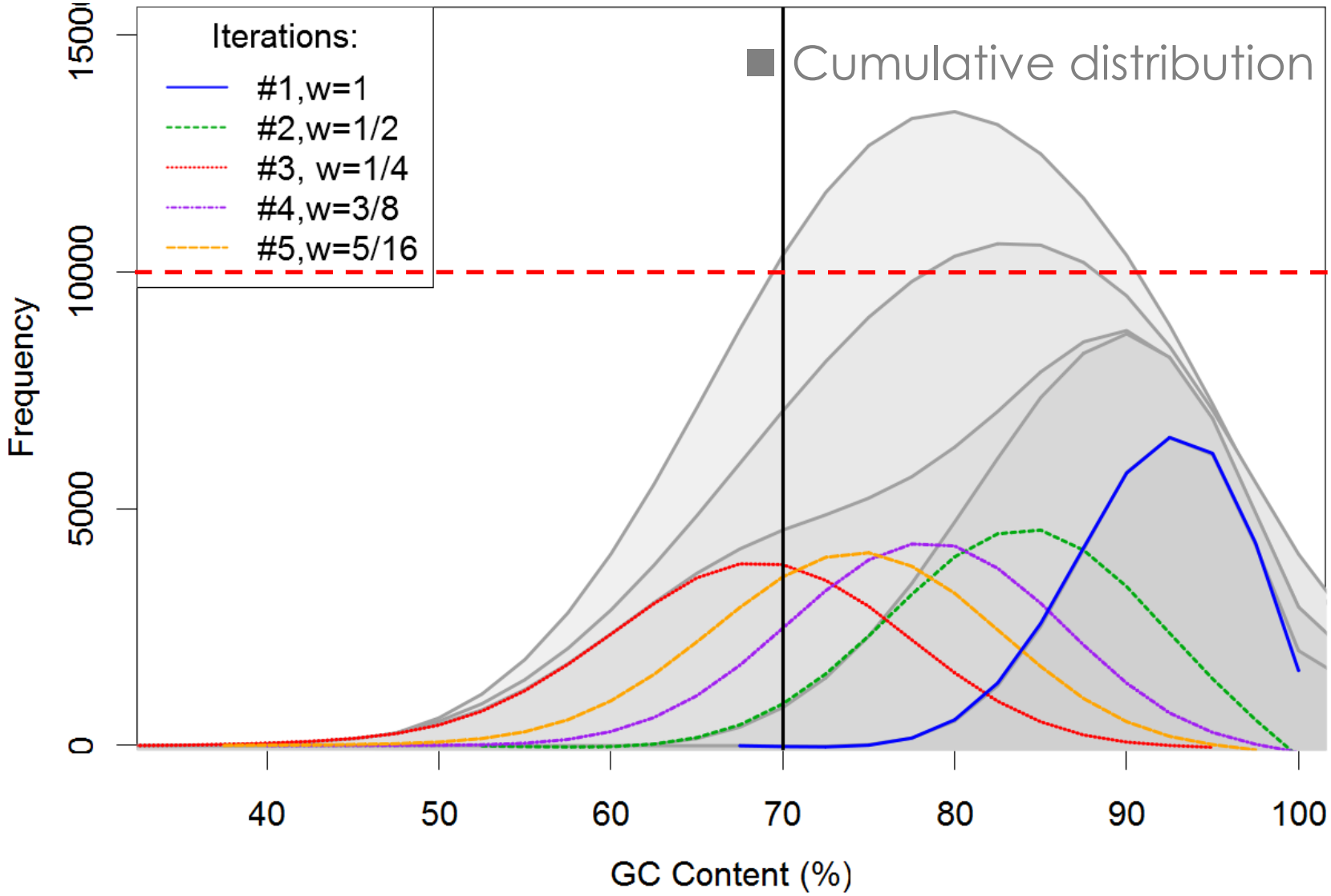
· Partition function can be written as a polynomial:

$$Z = \sum_{i=0}^{n} a_i \times w^i$$

After *n* iterations one can compute all a_i through interpolation and *invert* the polynomial to compute optimal weight *w* (Gröbner base).

Remark: In practice, few iterations are necessary

Example: 40 nt., 10000 samples, 30 mutations, 70% C+G content



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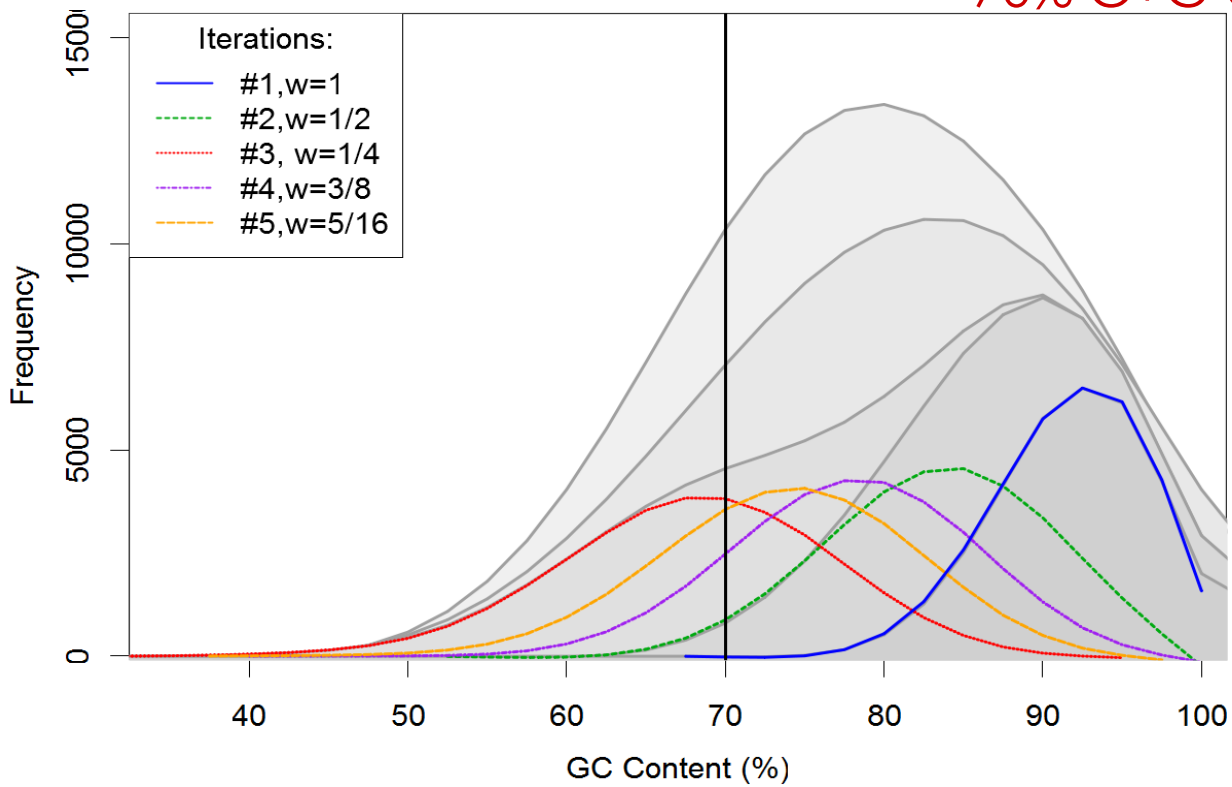

Overall, 150 000 samples required.
Naïve rejection: ~30 000 000 samples!
+ Ratio grows exponentially on length (gen. Fun.)

Note: Dynamic programming alternative in $O(n^7)$

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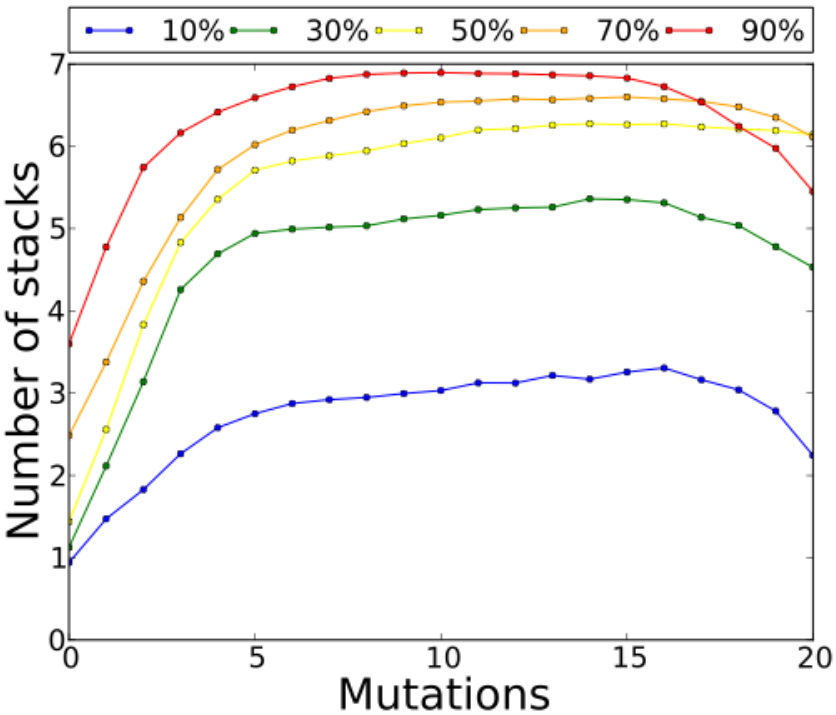
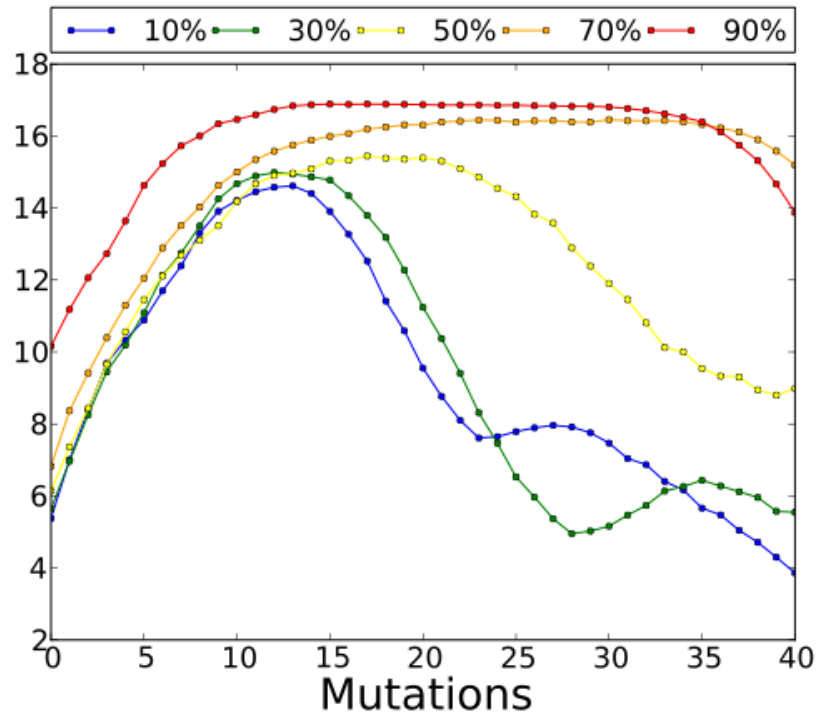
Low CG-contents favor structural diversity

Simulation at **fixed G+C content** from random seeds



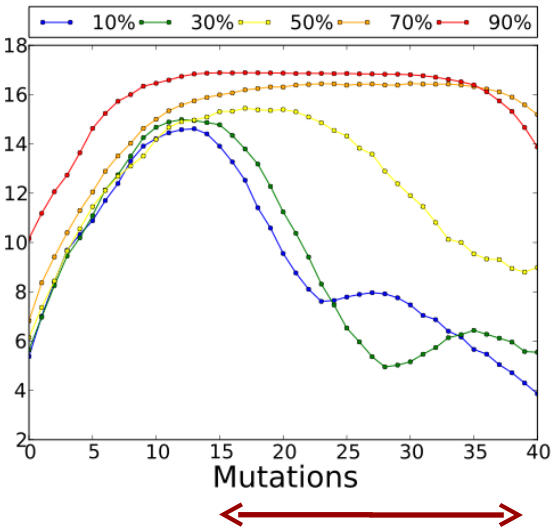
20 nucleotides

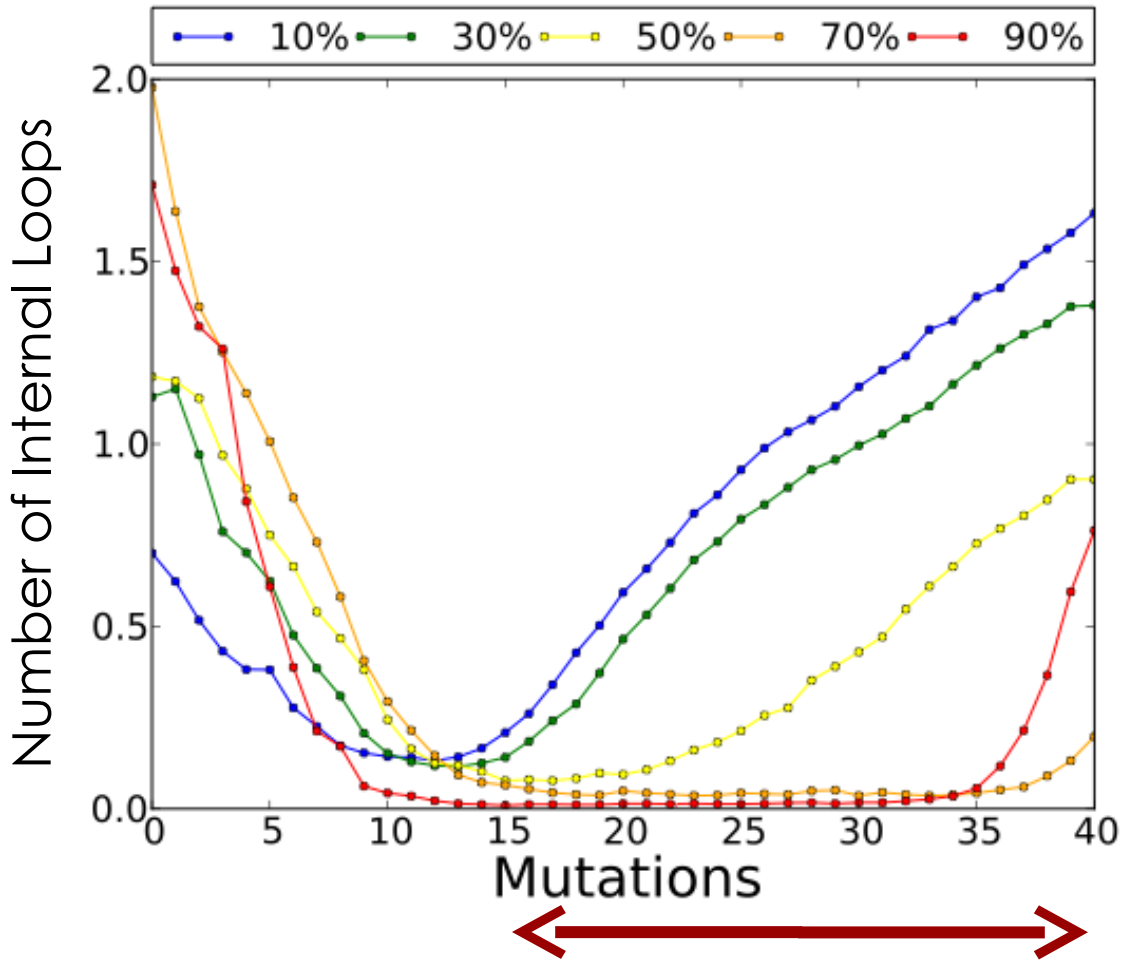


40 nucleotides

10% 30% 50% 70% 90%

Low C+G contents favor internal loop insertion

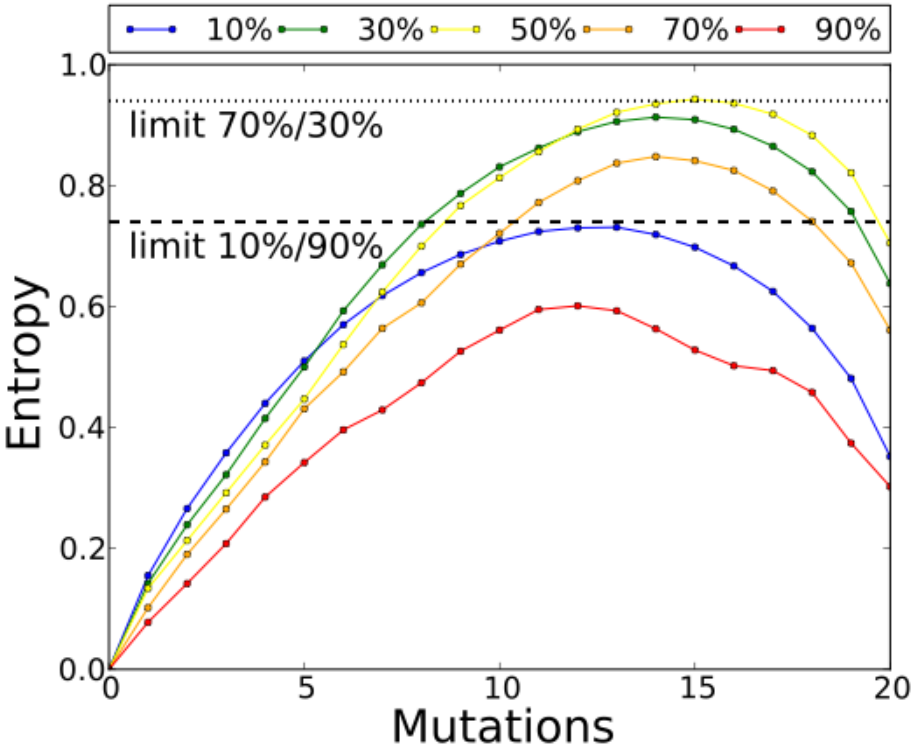




■ 10% ■ 30% ■ 50% ■ 70% ■ 90%

High G+C-contents reduce evolutionary accessibility

Simulation at **fixed G+C content** from random seeds



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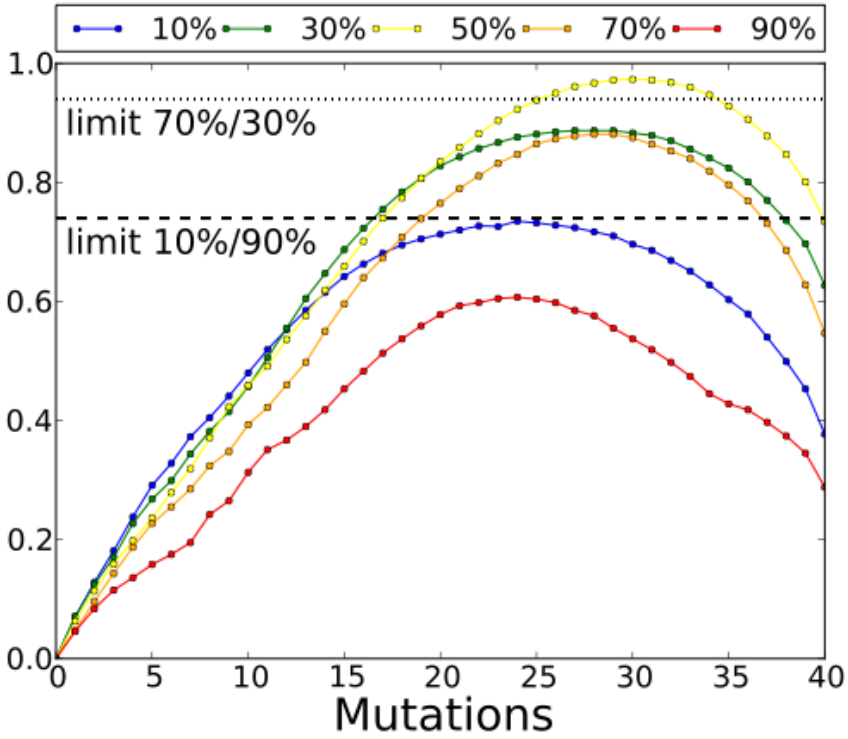

40 nucleotides

■ 10% ■ 30% ■ 50% ■ 70% ■ 90%

Perspectives

- More studies of Sequence-Structure maps.
- Applications to RNA design.
- Same techniques can be applied to other parameters (e.g. number of base pairs).
- Can be generalized to multiple parameters.

Acknowledgments

Jérôme Waldispühl

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Boston College
· Peter Clote

University of Paris 6
· Olivier Bodini

University of Paris 11
· Alain Denise

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Would you like to know more?

- O. Bodini, and Y. Ponty
Multi-dimensional Boltzmann Sampling of Languages,
Proceedings of AOFA'10, 49--64, 2010

- J. Waldispühl, S. Devadas, B. Berger and P. Clote,
Efficient Algorithms for Probing the RNA Mutation Landscape,
Plos Computational Biology, 4(8):e1000124, 2008.

http://csb.cs.mcgill.ca/RNAmutants