Combinatorial RNA Design: Designability and Structure-Approximating Algorithm Towards a theory of RNA design

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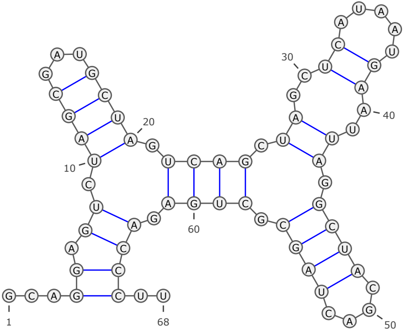
Benasque 2015

Results appear in **Combinatorial Pattern Matching'15** proceedings

Structure = Bunch of **non-crossing** base-pairs.



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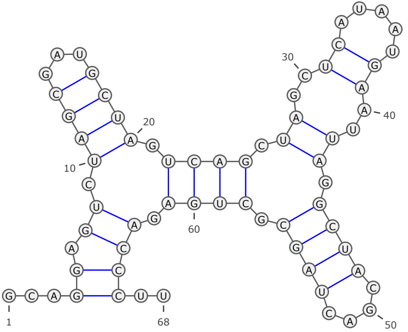

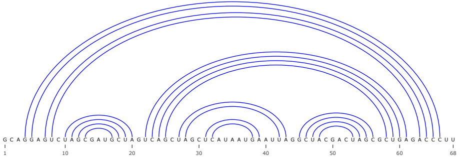

arc diagram

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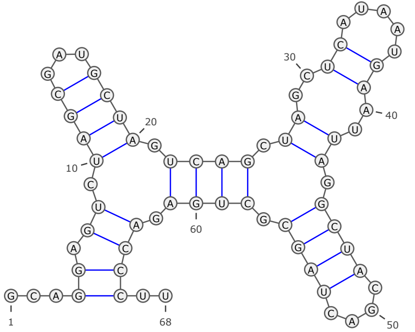

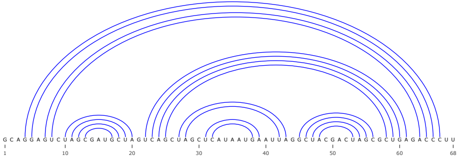

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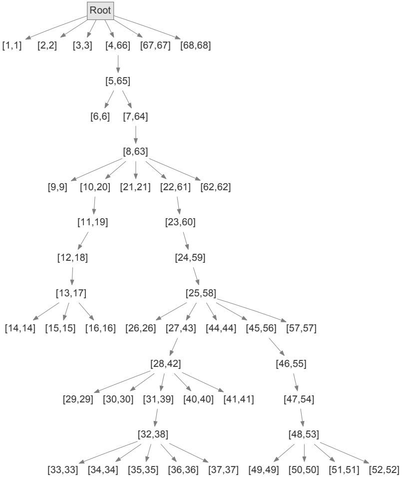
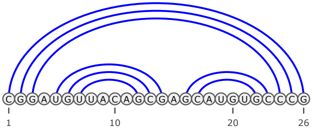
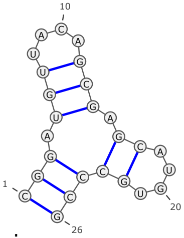


tree representation

RNA folding

Input: RNA sequence w, length $n := |w|$





- **RNA structure S:** (Partial) matching of positions in sequence w
- **Motifs:** Sequence/structure features (e.g. pairs, Stacking pairs, Nearest neighbor, ...)
- **Energy model.**

  Motif $\rightarrow$ Free-energy contribution $\Delta G(\cdot) \in \mathbb{R}^{-} \cup \{+\infty\}$

  Free-Energy $E_w(S)$: Sum over (independently contributing) motifs in S

Problem (RNA-FOLD$_{\mathcal{M}}$ problem)

Input: *RNA sequence w*

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RNA-FOLD$_{\mathcal{M}}(w)$ solved in time $O(n^3/\log(n))$ [Frid et al. (2010),etc.].

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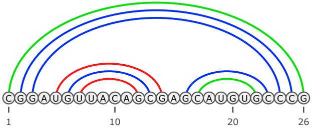

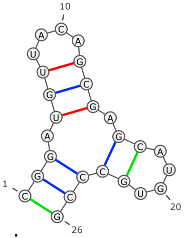

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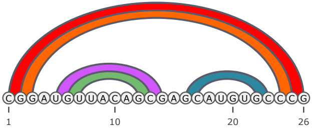

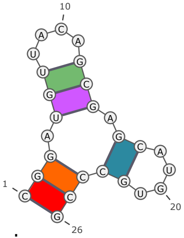

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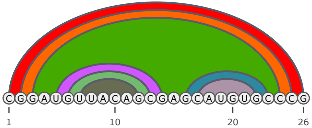

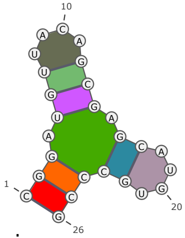

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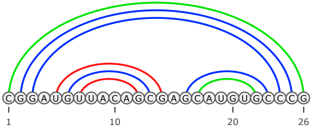

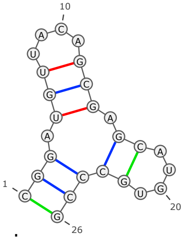

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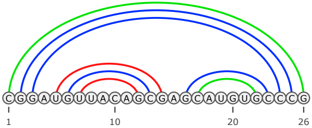

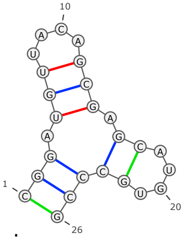

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RNA Design Problem

Let $\mathcal{M}$ be an energy model.

Problem (RNA-DESIGN$_{\mathcal{M},\Sigma.\Delta}$ **problem)**

Input: *Secondary structure S + Energy distance* $\Delta > 0$
Output: *RNA sequence* $w \in \Sigma^\star$ *— called a design for S — such that:*

$$\forall S' \in \mathcal{S}_{|w|} \setminus \{S\} : \; E_{\mathcal{M}}(w, S') \geq E_{\mathcal{M}}(w, S) + \Delta$$

or $\varnothing$ *if no such sequence exists.*

Difficult problem: No obvious DP decomposition

- Existing algorithms: Heuristics or Exponential-time
- Complexity of problem unknown (despite [Schnall Levin et al (2008)])
  Reason: Non locality, no theoretical frameworks, too many parameters. . .

$\Rightarrow$ **Stick to a simplified model!**

RNA Design Problem (simplified)

Simplified formulation for Watson-Crick model $\mathcal{W}$ and $\Delta = 1$:

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$$\text{RNA-FOLD}_{\mathcal{W}}(w) = \{S\}$$

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Designable(Σ)**:** All designable structures

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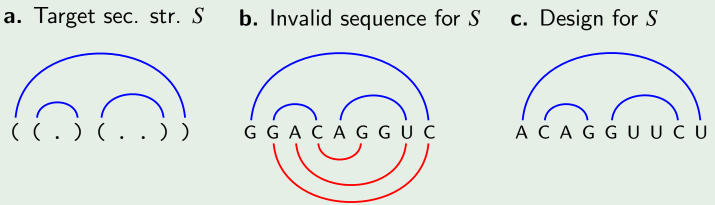

Our Results: Definitions and notations

Given a secondary structure S:

- Unpaired$_S$ = Set of all unpaired positions of S.
- S is **saturated** $\Leftrightarrow$ Unpaired$_S = \varnothing$.
  Saturated = Set of all saturated structures.
- **Paired degree of base-pair** = #Helices on the loop.
- $D(S)$ = Maximal *paired degree* of nodes in the tree representation of S.

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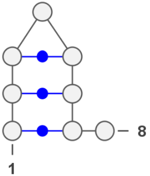

Unpaired$_S = \{4, 8\}$

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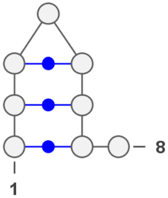
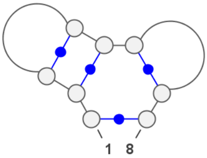


not saturated



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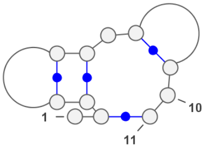

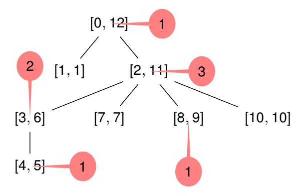

$D(S) = 3$

Our Results: Designability over Restricted Alphabets

$\Sigma_{c,u}$ = Alphabet with *c* pairs of complementary bases and *u* unpairable bases.

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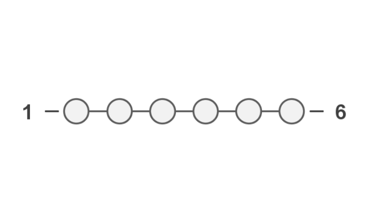

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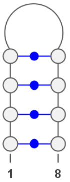

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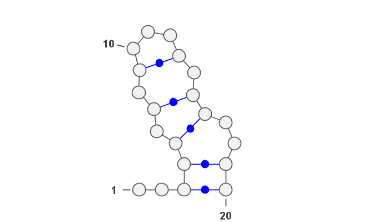

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Question: Why not degree 3?

Proof.

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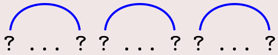

— we can only use C · G or G · C □

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C . . . G G . . . C C . . . G — one of them has to repeat □

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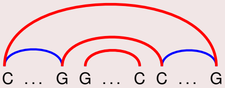

— there is an alternative fold □

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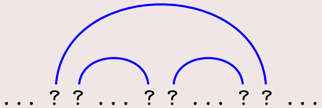

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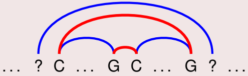

— either we get a repeat, or... □

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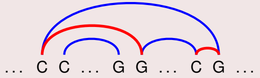

— ...or, the parent has the reversed base pair of a child □

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This can be easily generalized to:

Lemma

For any structure S in $\text{Designable}(\Sigma_{c,u})$, $D(S) \leq 2c$.

Our Results: Designability over the Complete Alphabet

$\Sigma_{2,0} = \{A, U, C, G\}$ + $\{G - C, A - U\}$ base pairs.

Without unpaired position $\rightarrow$ complete characterization:

R4 Designable($\Sigma_{2,0}$) $\cap$ Saturated $= \{S \mid D(S) \leq 4\} \cap$ Saturated.

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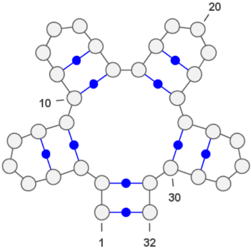
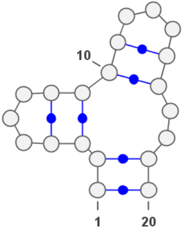


m5



m3o

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From the tree representation T_S of structure S, color every paired node of T_S:

- black $\rightarrow$ G $\cdot$ C;
- white $\rightarrow$ C $\cdot$ G;
- grey $\rightarrow$ A $\cdot$ U or U $\cdot$ A.

Proper coloring:

1. each internal node has at most one black, one white and two grey children;
2. a grey node has at most one grey child;
3. a black node does not have a white child; and
4. a white node does not have a black child.

Level of a node = #black nodes $-$ #white nodes on the path to the root.

Separated coloring: Levels of grey nodes $\cap$ Levels of unpaired nodes $= \varnothing$

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Descendant restrictions: Any node $\rightarrow \leq 1$ black & ≤ 1 White & ≤ 2 Grey;
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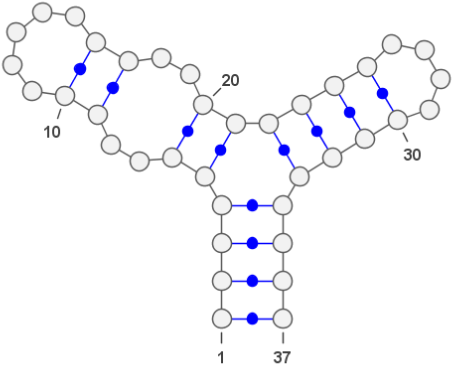
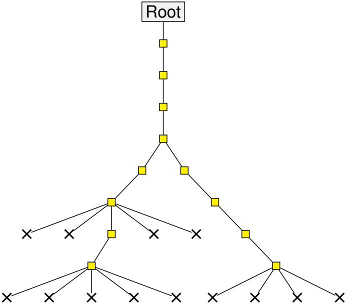
(● → GC ○ → CG ◉ → AU|UA × → U)





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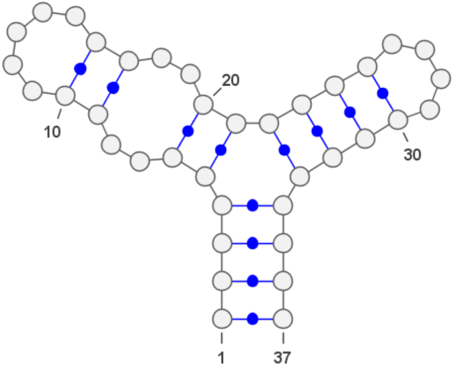

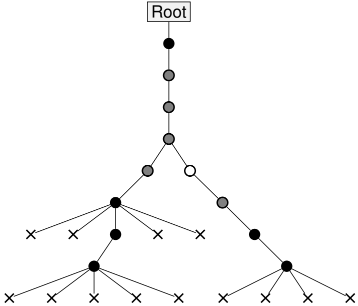

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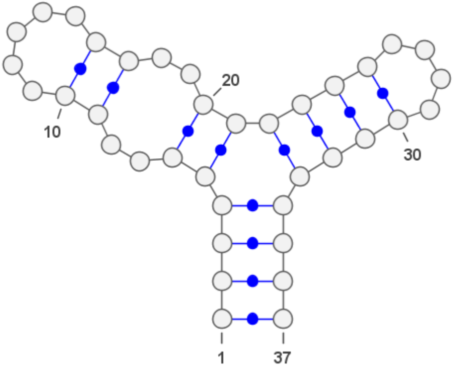

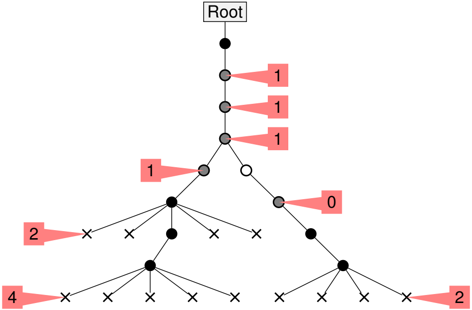

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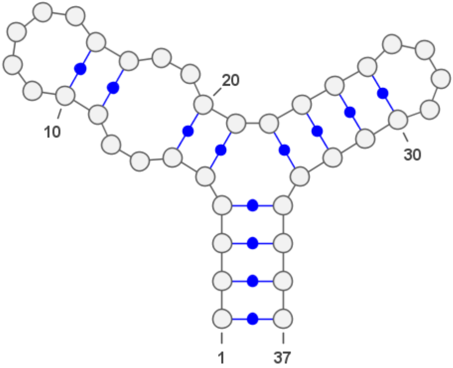

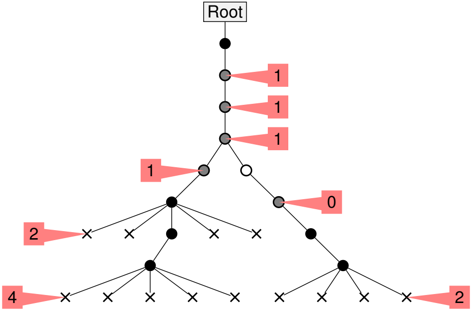

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Levels of leaves: 2,4
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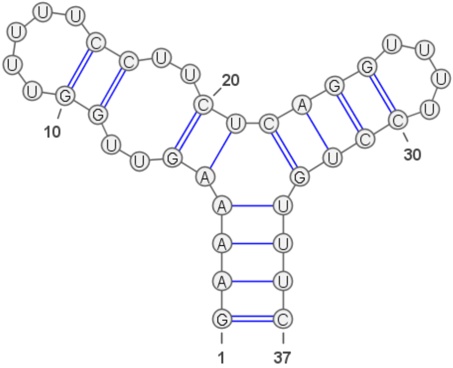

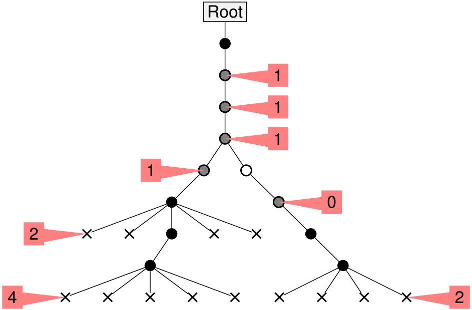

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$\Rightarrow$ **Design:** GAAAAGUUGGUUUUUCCUUCUCAGGUUUUCCUGUUUC

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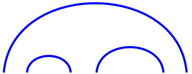
Our Results: *k*-Stutter (example)



Designable structure: ((.) (. .))

Then 2-stutter is designable as well:

Proof idea: Use König's Theorem (size of max. matching = size of min. vertex cover) to show that an MFE structure of the stutter sequence can't connect a region to two different regions.

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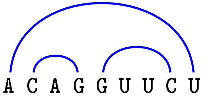

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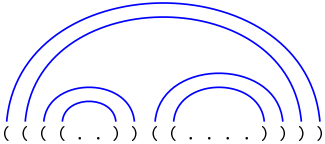

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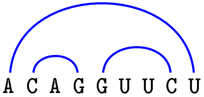

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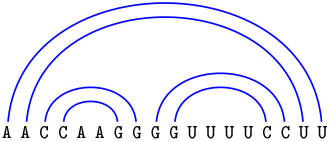

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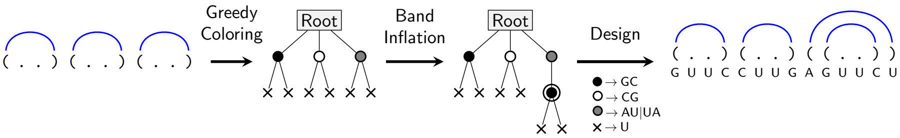

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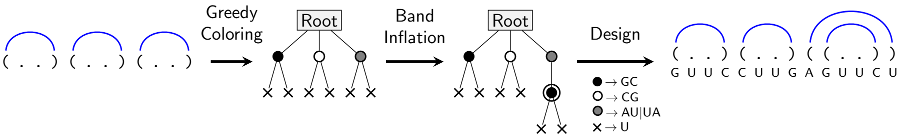

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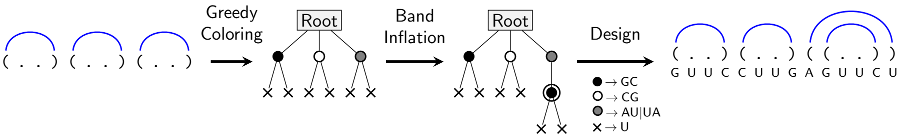

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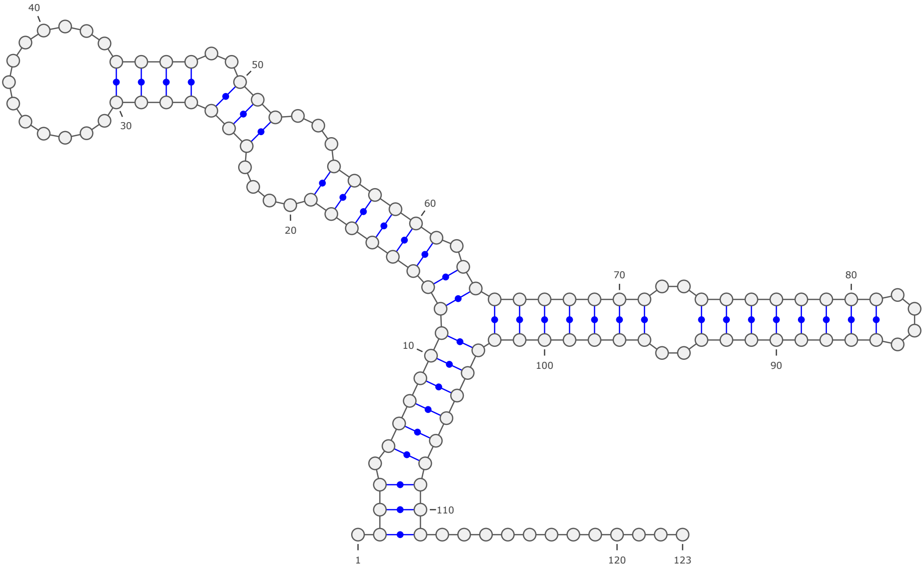

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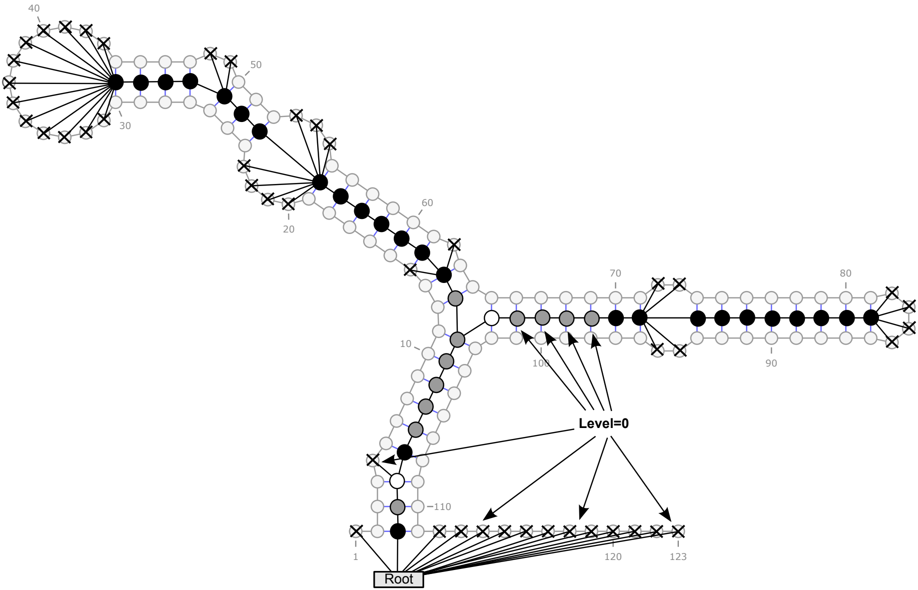

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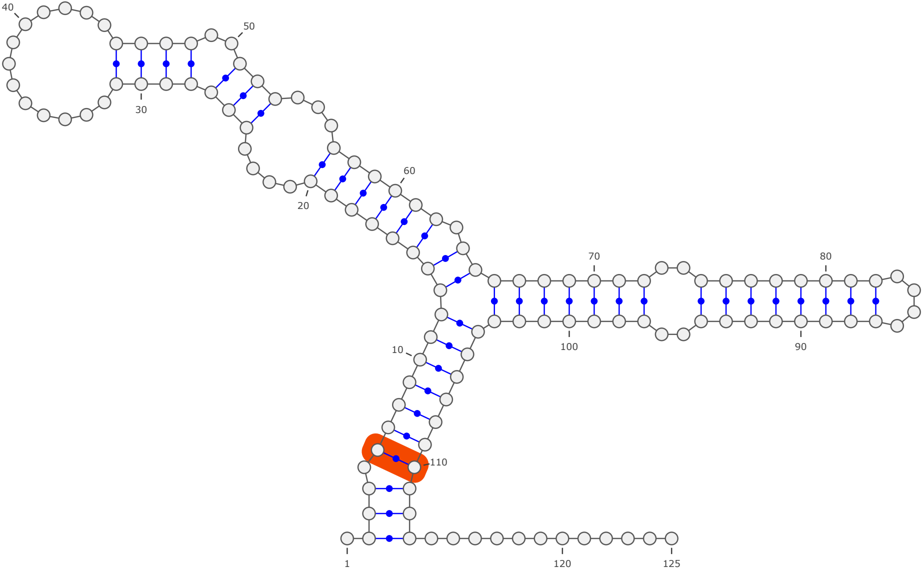

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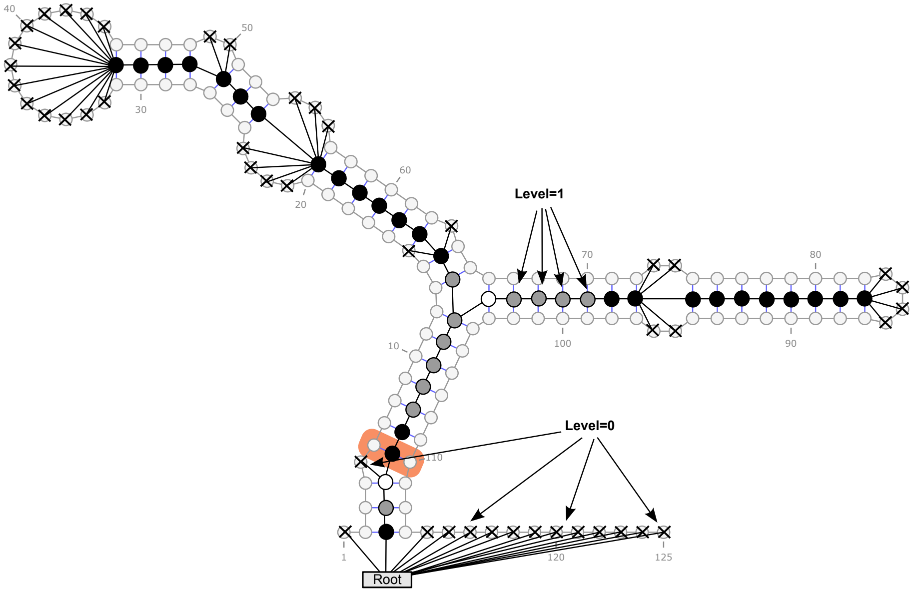
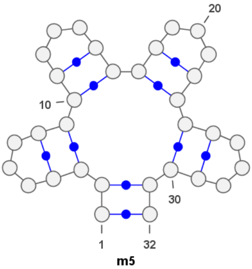


Remark: Breaking motifs



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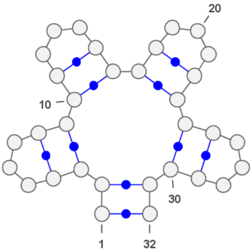

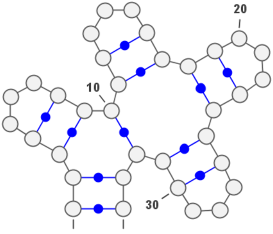

Open Problems and Future Work

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3. What's the complexity of determining if a structure has a separated coloring?
4. Extend the results to more complex energy models.
   Our results hold for the **Base-pair sum** model, as long as $-\delta_B(G, U)$ is smaller than $-\delta_B(C, G)$ and $-\delta_B(A, U)$.
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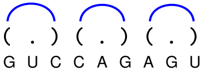

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