Fixed-parameter tractable sampling for RNA design with multiple target structures

Stefan Hammer · Yann Ponty · Wei Wang · Sebastian Will

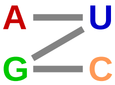
University of Leipzig · École Polytechnique · University of Vienna

RNA meeting Benasque 2018

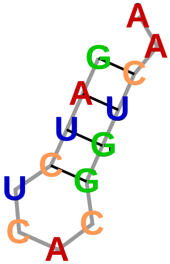
RNA Design

GAUCUCACGGUCAA

Structure prediction



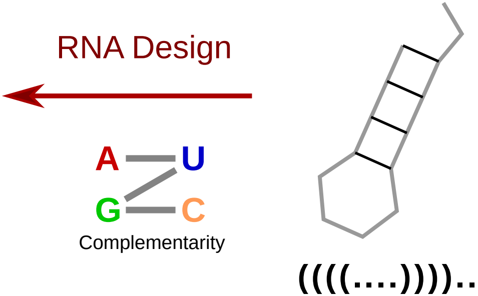
Complementarity



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

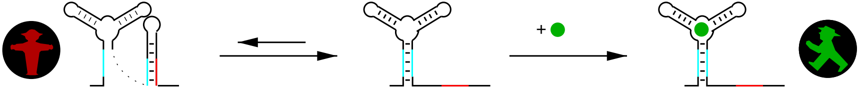
RNA Design

GAUCUCACGGUCAA



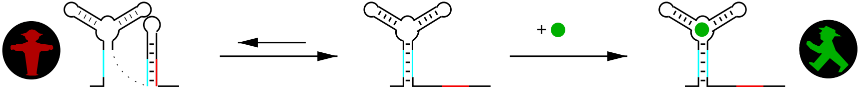
Multi-target design of RNA sequences

For example: design riboswitches for translational control

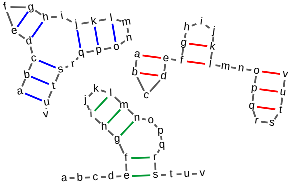


Multi-target design of RNA sequences

For example: design riboswitches for translational control



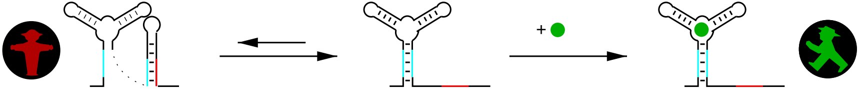
Multiple structures (=*multiple design targets*)



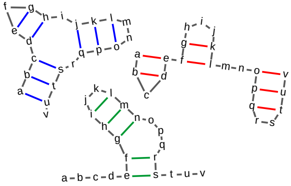
```
abcdefghijklmnopqrstuv
(((((.)).(((..))).))).
((.))((...))..(((..)))
....(((((..)))...)))...
```

Multi-target design of RNA sequences

For example: design riboswitches for translational control



Multiple structures (=*multiple design targets*)



```
abcdefghijklmnopqrstuv
(((((.)).(((..))).))).
((.))((...))..(((..)))
....(((((..)))...))...
```

Task: generate seq's with *specific* properties

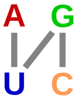
- low/specific energy for multiple structures
- specific GC content
- specific energy differences
- specific sequence/structure motifs

Approach:
***defined* sampling**

Uniform sampling for multiple structures

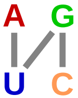
	1	2	3	4	5
S1	(	.	.	)	.
S2	.	(	(	)	)
S3	(	(	.	)	)
	A	A	A	U	U

- Complementarity



Uniform sampling for multiple structures

	1	2	3	4	5
S1	(	.	.	)	.
S2	.	(	(	)	)
S3	(	(	.	)	)
	A	A	A	U	U
	A	A	G	U	U
	A	G	A	U	U
	A	G	G	U	U
	G	A	A	U	C
	G	A	A	U	U
	G	A	G	U	C
	G	A	G	U	U
	G	G	A	U	C
	G	G	A	U	U
	G	G	G	C	C
	G	G	G	C	U
	G	G	G	U	C
	G	G	G	U	U
	⋮				

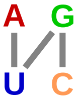
- Complementarity 

- For uniform: choose first position
  A : **C** : **G** : **U** = 4 : 4 : 10 : 10
  Then, e.g. after **G**, choose second
  A : **G** = 4 : 6, . . .
- → **counting**

Uniform sampling for multiple structures

	1	2	3	4	5
S1	(	.	.	)	.
S2	.	(	(	)	)
S3	(	(	.	)	)
	A	A	A	U	U
	A	A	G	U	U
	A	G	A	U	U
	A	G	G	U	U
	G	A	A	U	C
	G	A	A	U	U
	G	A	G	U	C
	G	A	G	U	U
	G	G	A	U	C
	G	G	A	U	U
	G	G	G	C	C
	G	G	G	C	U
	G	G	G	U	C
	G	G	G	U	U
	⋮				

- Complementarity



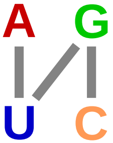
- For uniform: choose first position
  A : **C** : **G** : **U** $= 4 : 4 : 10 : 10$
  Then, e.g. after **G**, choose second
  A : **G** $= 4 : 6, \ldots$
- → **counting**

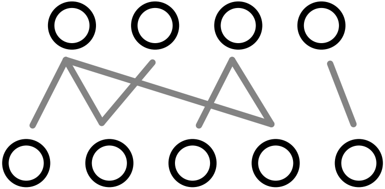
- **Theorem: Counting of sequences for multiple targets is #P-hard.**

Counting is #P-hard

Proof (sketch):

- Counting bipartite independent sets is #P-hard.
- Sequence counting is *equivalent* to counting **independent sets**.

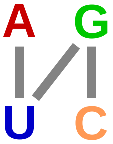


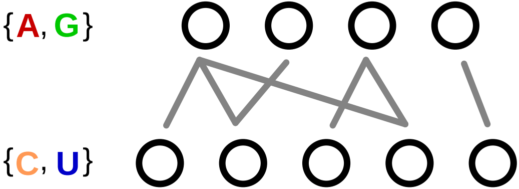


Counting is #P-hard

Proof (sketch):

- Counting bipartite independent sets is #P-hard.
- Sequence counting is *equivalent* to counting **independent sets**.

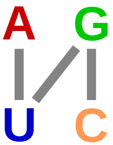


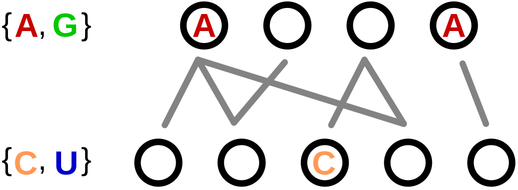


Counting is #P-hard

Proof (sketch):

- Counting bipartite independent sets is #P-hard.
- Sequence counting is *equivalent* to counting **independent sets**.

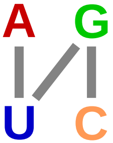


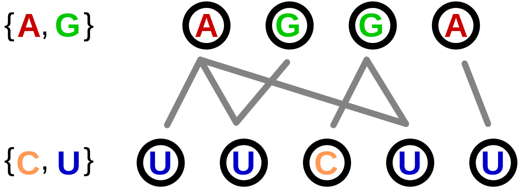


Counting is #P-hard

Proof (sketch):

- Counting bipartite independent sets is #P-hard.
- Sequence counting is *equivalent* to counting **independent sets**.

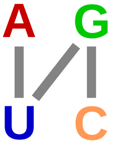


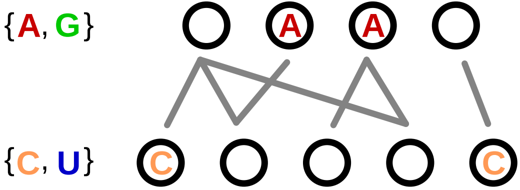


Counting is #P-hard

Proof (sketch):

- Counting bipartite independent sets is #P-hard.
- Sequence counting is *equivalent* to counting **independent sets**.

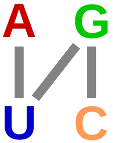


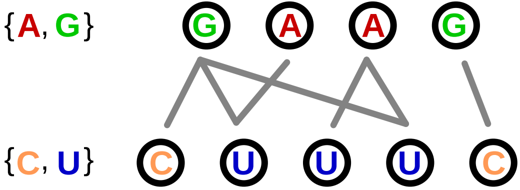


Counting is #P-hard

Proof (sketch):

- Counting bipartite independent sets is #P-hard.
- Sequence counting is *equivalent* to counting **independent sets**.

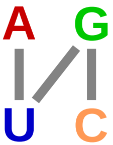


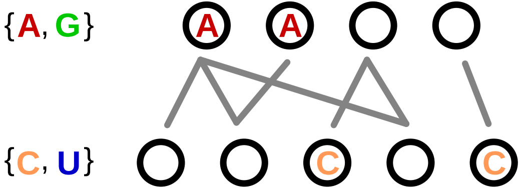


Counting is #P-hard

Proof (sketch):

- Counting bipartite independent sets is #P-hard.
- Sequence counting is *equivalent* to counting **independent sets**.





Systematic counting and sampling

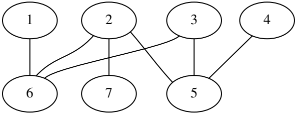
Recipe:

1. Decompose dependency graph
2. Apply **dynamic programming** ↑
3. **Sample** ↓

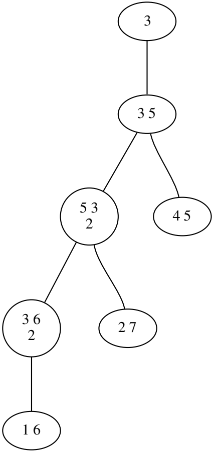
```
1  2  3  4  5  6  7

(  (  .  .  )  )  .
.  (  (  (  )  )  )
.  (  (  .  )  )  .
```

target structures



dependency graph



tree decomposition

Systematic counting and sampling

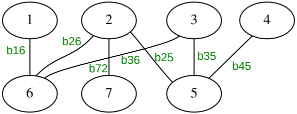
Recipe:

1. Decompose dependency graph
2. Apply **dynamic programming** ↑
3. **Sample** ↓

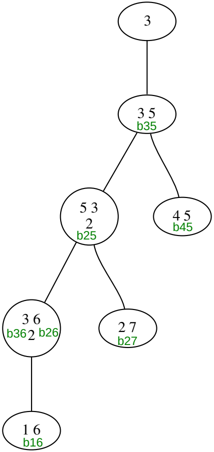
```
1 2 3 4 5 6 7

( ( . . ) ) .
. ( ( ( ) ) )
. ( ( . ) ) .
```

target structures



dependency graph



tree decomposition

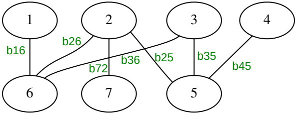
Systematic counting and sampling

Recipe:

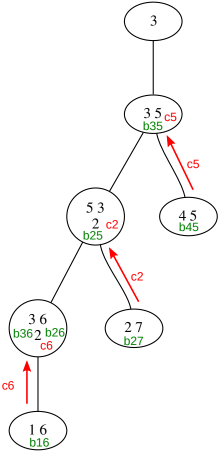
1. Decompose dependency graph
2. Apply **dynamic programming ↑**
3. **Sample ↓**

1	2	3	4	5	6	7
(	(	.	.	)	)	.
.	(	(	(	)	)	)
.	(	(	.	)	)	.

target structures



dependency graph



tree decomposition

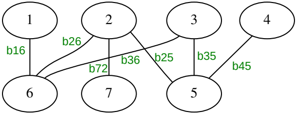
Systematic counting and sampling

Recipe:

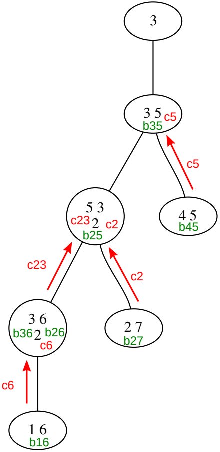
1. Decompose dependency graph
2. Apply **dynamic programming** ↑
3. **Sample** ↓

1	2	3	4	5	6	7
(	(	.	.	)	)	.
.	(	(	(	)	)	)
.	(	(	.	)	)	.

target structures



dependency graph



tree decomposition

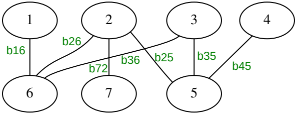
Systematic counting and sampling

Recipe:

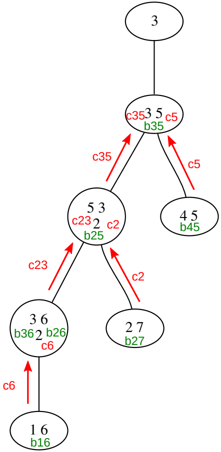
1. Decompose dependency graph
2. Apply **dynamic programming** ↑
3. **Sample** ↓

```
1  2  3  4  5  6  7
(  (  .  .  )  )  .
.  (  (  (  )  )  )
.  (  (  .  )  )  .
```

target structures



dependency graph



tree decomposition

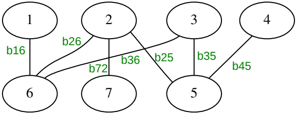
Systematic counting and sampling

Recipe:

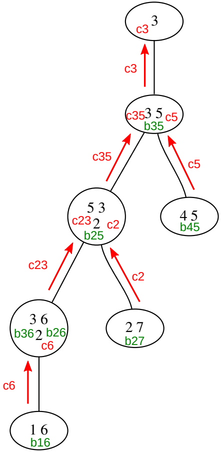
1. Decompose dependency graph
2. Apply **dynamic programming** ↑
3. **Sample** ↓

```
1  2  3  4  5  6  7
(  (  .  .  )  )  .
.  (  (  (  )  )  )
.  (  (  .  )  )  .
```

target structures



dependency graph



tree decomposition

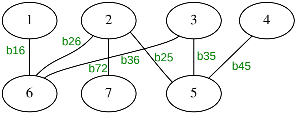
Systematic counting and sampling

Recipe:

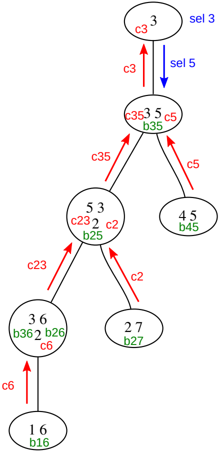
1. Decompose dependency graph
2. Apply **dynamic programming ↑**
3. **Sample ↓**

```
1 2 3 4 5 6 7
( ( . . ) ) .
. ( ( ( ) ) )
. ( ( . ) ) .
```

target structures



dependency graph



tree decomposition

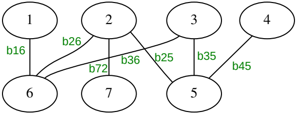
Systematic counting and sampling

Recipe:

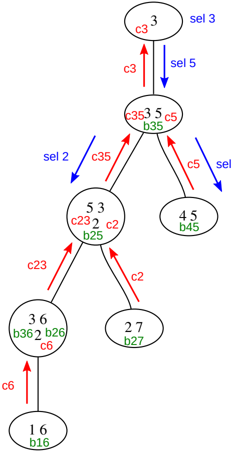
1. Decompose dependency graph
2. Apply **dynamic programming** ↑
3. **Sample** ↓

```
1  2  3  4  5  6  7
(  (  .  .  )  )  .
.  (  (  (  )  )  )
.  (  (  .  )  )  .
```

target structures



dependency graph



tree decomposition

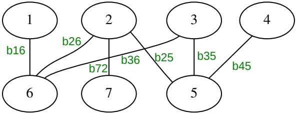
Systematic counting and sampling

Recipe:

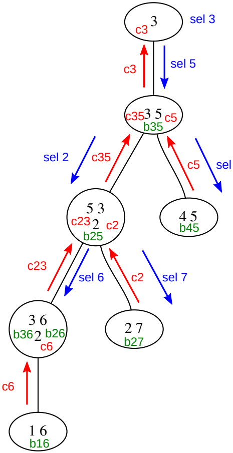
1. Decompose dependency graph
2. Apply **dynamic programming** ↑
3. **Sample** ↓

```
1 2 3 4 5 6 7
( ( . . ) ) .
. ( ( ( ) ) )
. ( ( . ) ) .
```

target structures



dependency graph



tree decomposition

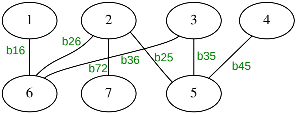
Systematic counting and sampling

Recipe:

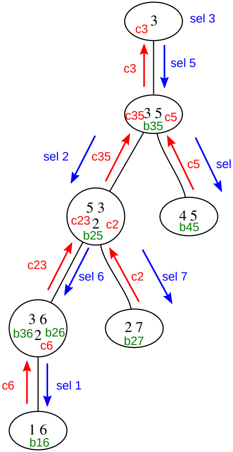
1. Decompose dependency graph
2. Apply **dynamic programming** ↑
3. **Sample** ↓

```
1 2 3 4 5 6 7
( ( . . ) ) .
. ( ( ( ) ) )
. ( ( . ) ) .
```

target structures



dependency graph



tree decomposition

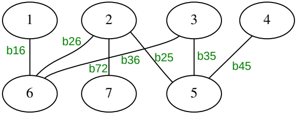
Systematic counting and sampling

Recipe:

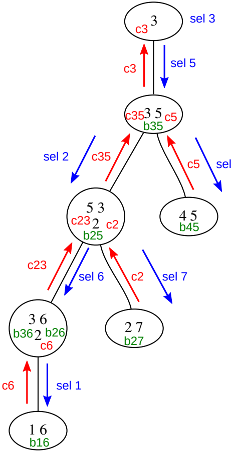
1. Decompose dependency graph
2. Apply **dynamic programming** ↑
3. **Sample** ↓

1	2	3	4	5	6	7
(	(	.	.	)	)	.
.	(	(	(	)	)	)
.	(	(	.	)	)	.

target structures



dependency graph



tree decomposition

Theorem: Counting and sampling is efficient for fixed tree width

$$\mathcal{O}(n\,k\,\mathbf{4^w} + t\,n\,k)$$

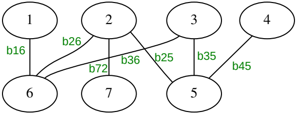
Systematic counting and sampling

Recipe:

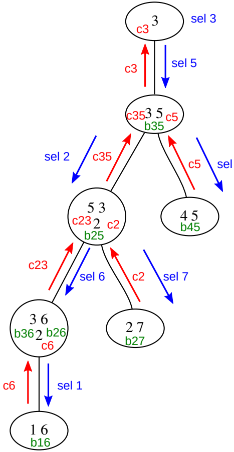
1. Decompose dependency graph
2. Apply **dynamic programming** ↑
3. **Sample** ↓

```
1  2  3  4  5  6  7
(  (  .  .  )  )  .
.  (  (  (  )  )  )
.  (  (  .  )  )  .
```

target structures



dependency graph



tree decomposition

Theorem: Counting and sampling is efficient for fixed tree width

$$\mathcal{O}(n\,k\,\mathbf{4^{w}} + t\,n\,k) \longrightarrow \mathcal{O}(n\,k\,\mathbf{2^{w+c}} + t\,n\,k)$$

From uniform to Boltzmann sampling

uniform sampling ⟵ **counts**
Boltzmann sampling ⟵ **partition functions**

$$\textit{Boltzmann sampling}: \quad \mathrm{P}(S) \;\propto\; \exp(-\beta E(S)).$$

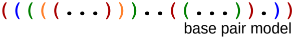
From uniform to Boltzmann sampling

uniform sampling ⟵ **counts**
Boltzmann sampling ⟵ **partition functions**

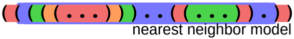
$$\textit{Boltzmann sampling}: \quad \mathrm{P}(S) \ \propto \ \exp(-\beta E(S)).$$

Energy $E(S) := \sum$ weighted energies of single structures

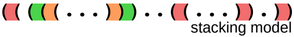
- **energy models**
  - **Base pair model**
    "like counting"



  - **Nearest neighbor model (Turner)**
    requires multi-ary dependencies:
    constraint framework*



  - **Stacking model**
    "in-between", scores stacks

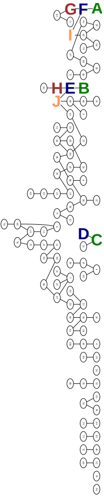


[*] Constraint networks / cluster tree elimination [Rina Dechter]

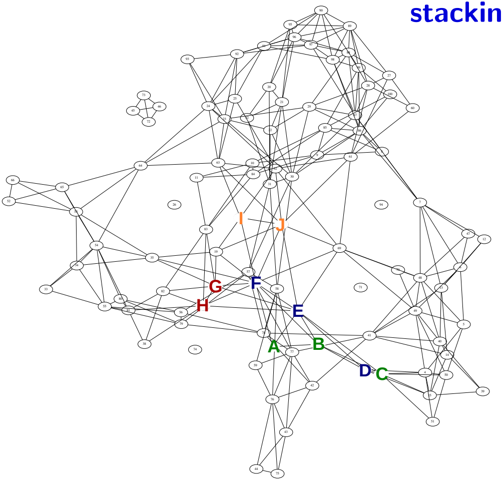
Dependency graphs

```
((((.((....)).))))).((.(((.((((.....(((..((((((.((..(((.(.....).)))..)).)).))))..)))..)))).))).))....
..(((((.....(((.((((((((.....))))..))).))).....)))))..((((((((((...))).)....))))))...((((((....))))))
......(((((.....(((...(((.((.((.(((....((......))...))).)).)))))..)))............))))).((((...)))).
ABC                 DEF                 GH                                IJ
```

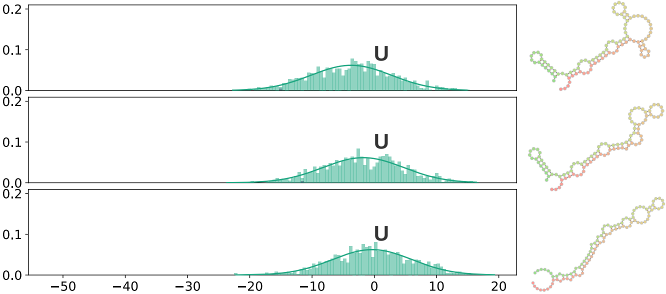
base pair



stacking



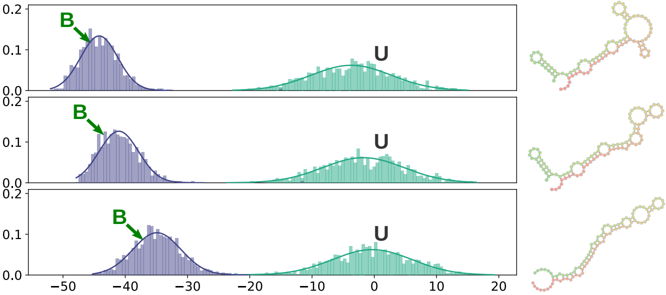
Targeting specific properties: multi-dimensional Boltzmann sampling



Weight and combine single structure energies and features

Learn weights (adaptively) → target specific energies and GC content

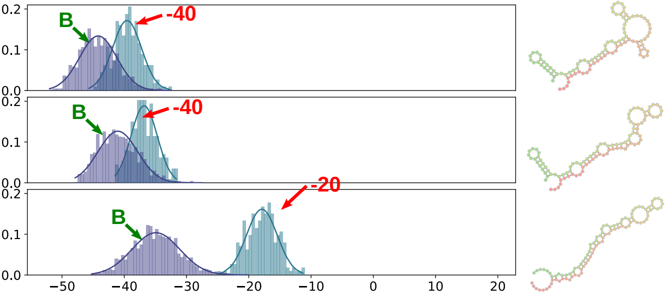
Targeting specific properties: multi-dimensional Boltzmann sampling



Weight and combine single structure energies and features

Learn weights (adaptively) → target specific energies and GC content

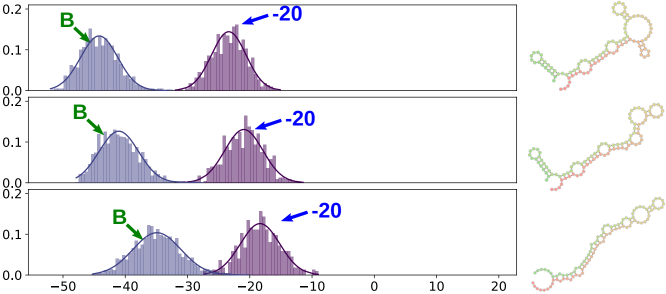
Targeting specific properties: multi-dimensional Boltzmann sampling



Weight and combine single structure energies and features

Learn weights (adaptively) → target specific energies and GC content

Targeting specific properties: multi-dimensional Boltzmann sampling



Weight and combine single structure energies and features

Learn weights (adaptively) → target specific energies and GC content

Boltzmann vs. uniform sampling for multi-target RNA design

	Dataset	RedPrint	Uniform	Improvement
Seeds	2str	21.67 (±4.38)	37.74 (±6.45)	73%
	3str	18.09 (±3.98)	30.49 (±5.41)	71%
	4str	19.94 (±3.84)	32.29 (±5.24)	63%
Optimized	2str	5.84 (±1.31)	7.95 (±1.76)	28%
	3str	5.08 (±1.10)	7.04 (±1.52)	31%
	4str	8.77(±1.48)	13.13 (±2.13)	37%

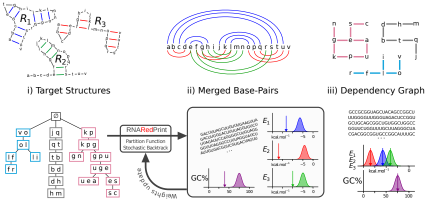
Multi-target design objective[*Blueprint*] on the **Modena benchmark**

https://github.com/yannponty/RNARedPrint

[Modena] Taneda. *BMC Bioinformatics*, 2015.
[Blueprint] Hammer et al. *Bioinformatics*, 2017.

Summary

- FPT Boltzmann sampling for multi-target RNA design (counting is #P-hard)
- Targets specific properties
- Versatile framework w/ multi-ary constraints
- Supports complex RNA design scenarios and various RNA energy models (NN, PKs)
- Perspectives: towards FPT negative design; Riboswitch design



i) Target Structures

ii) Merged Base-Pairs

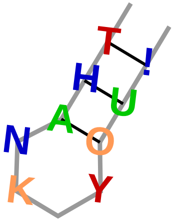
iii) Dependency Graph

iv) Tree Decomposition

v) Weight Optimization (Adaptive Sampling)

vi) Final Designs

(workflow for the base pair energy model; our approach supports complex models and scenarios by *n*-ary constraints)



Co-authors

Stefan Hammer

Yann Ponty

Wei Wang

Team

TBI at universität wien

Funding

AGENCE NATIONALE DE LA RECHERCHE ANR

Federal Ministry
of Education
and Research

FWF

SEVENTH FRAMEWORK
PROGRAMME