

Constrained folding simulations of RNA-RNA Interaction in 3D

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wien

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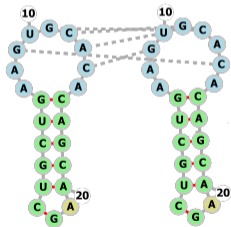


FWF

Computational analysis in 3D

2D

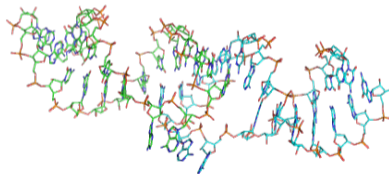
- ▶ Based on secondary structure and the nearest neighbour model
- ▶ Well established
- ▶ Computational efficient
- ▶ Steric effects **not** visible



[1,2]

3D

- ▶ Steric effects are taken into account
- ▶ Not applicable in large scale wide screens or transcriptome wide data



[1,3]

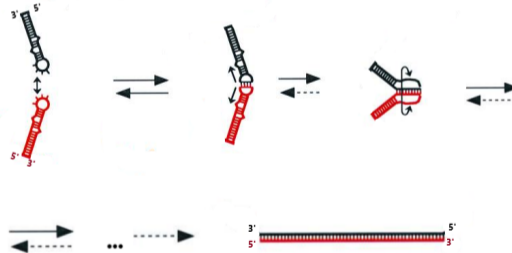
[1] Ennifar, E. et al.(2006) J.Mol.Biol.

[2] Visualized via Forna: Kerpedjiev, P. et al.(2015) Bioinformatics

[3] Visualized via Pymol: The PyMOL Molecular Graphics System, Version 2.0 Schrödinger, LLC.

Research Questions

- ▶ Which RNA-RNA interactions are **sterically** possible?
- ▶ Which RNA-RNA interactions are **kinetically** reachable?
- ▶ Can we identify **general properties**?



[1]

GGGCCCGGUAUUCUUUUCGUACUCGCCAAAGUUGAAGAUAUUCGGGGUUU CCCCGAUAAUCUUUC AACUUUGGCGAGUACGAAAAGAUUACCGGGG
 1 ((((((((((((((((((.....))))))))).....)))))) ((((((((((((((((((.....))))))))).....))))))
 **UU** **UU**

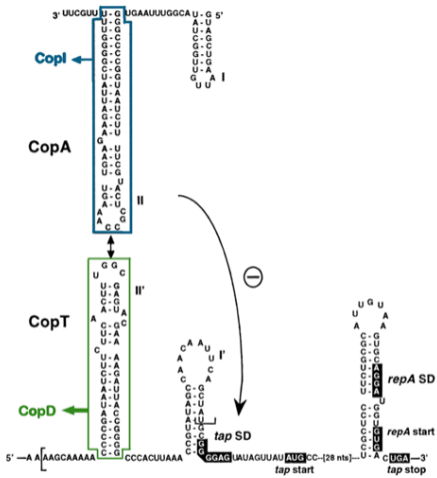


Figure modified from Kolb, F. A. et al. (2000) RNA

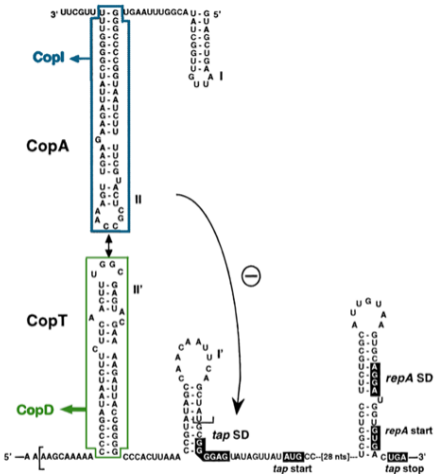
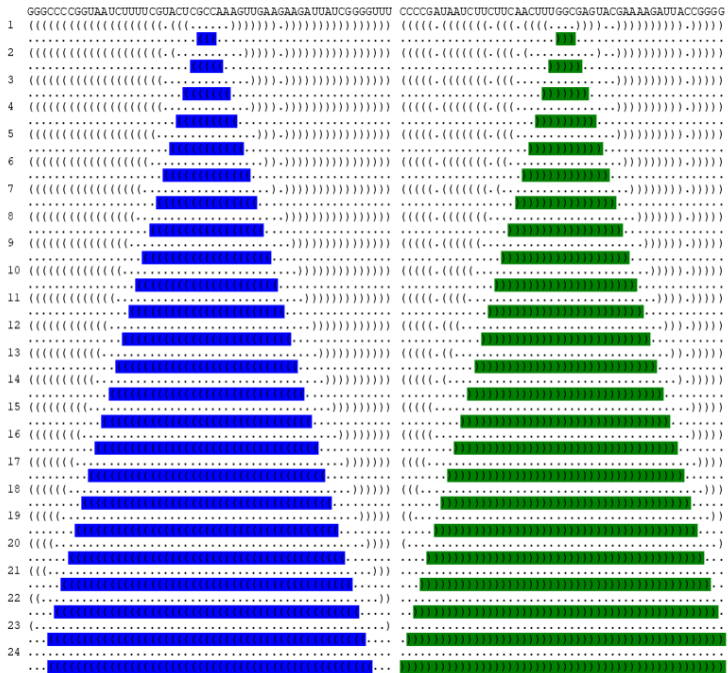
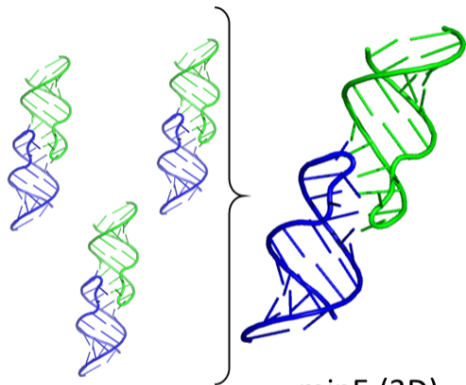


Figure modified from Kolb, F. A. et al. (2000) RNA



Sequence + 2D Structure

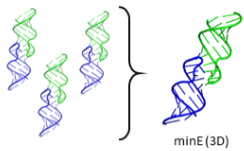
LONG CONSTRAINT
SIMULATION RUN



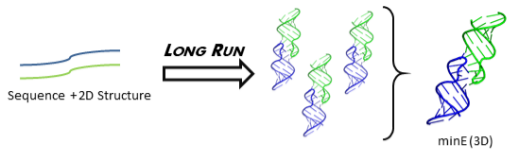
minE (3D)

Sequence + 2D Structure

LONG RUN

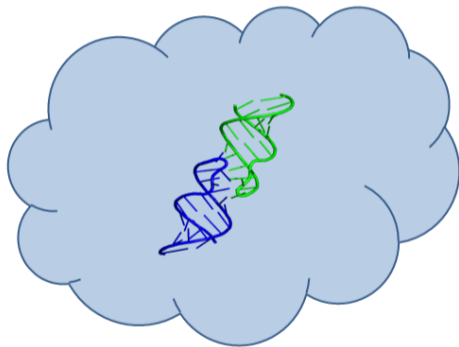


minE (3D)



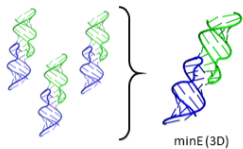
PREDICT A STRUCTURAL CLOUD

AROUND THIS STRUCTURE



Sequence + 2D Structure

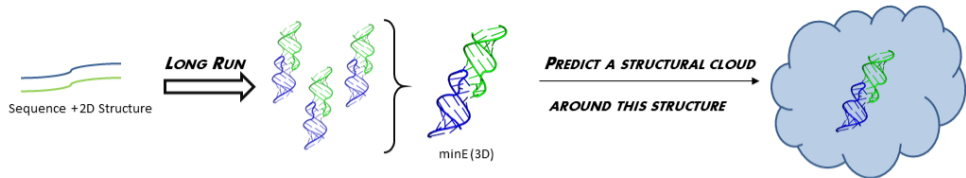
LONG RUN



minE (3D)

PREDICT A STRUCTURAL CLOUD
AROUND THIS STRUCTURE





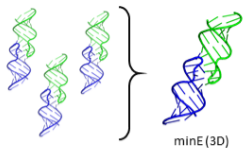
SELECT ONE STRUCTURE BASED ON:

- 2D | 1. Minimal basepair distance (constraint) within the interaction site
- 2D | 2. Minimal basepair distance (constraint) of the whole structure
- 3D | 3. minE

3D + 2D structure

Sequence + 2D Structure

LONG RUN



PREDICT A STRUCTURAL CLOUD
AROUND THIS STRUCTURE



SELECT ONE STRUCTURE BASED ON:

- 2D 1. Minimal basepair distance (constraint) within the interaction site
- 2D 2. Minimal basepair distance (constraint) of the whole structure
- 3D 3. minE

3D + 2D structure

INTERACTION

00

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

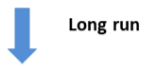
.....

CCC

GGG

Constraint Output

3 bp



00 CopStems minE Structure

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

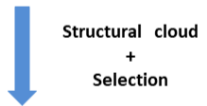
.....

CCCC

GGG

3 bp

5 bp



00 CopStems

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

.....

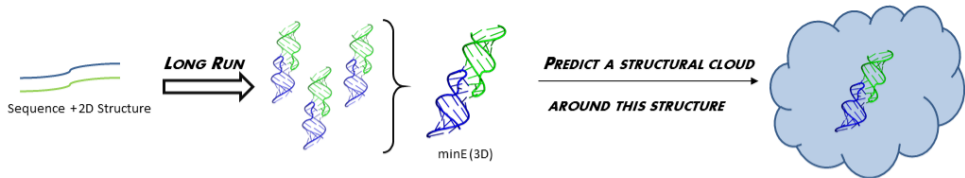
CC

GG

3 bp

3 bp





3D + 2D structure



EXPAND THE INTERACTION SITE (2D)

1. Left + Right

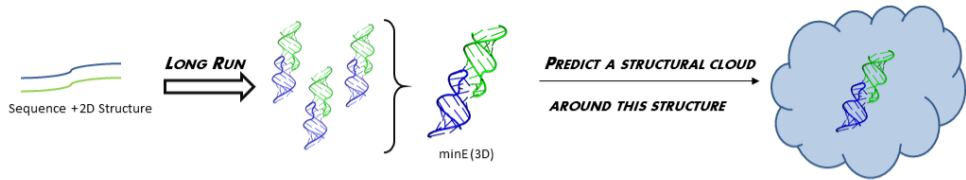
2. Linker region (2 bases)

„old“ 3D + new 2D constraint

SELECT ONE STRUCTURE BASED ON:

- 2D 1. Minimal basepair distance (constraint) within the interaction site
- 2D 2. Minimal basepair distance (constraint) of the whole structure
- 3D 3. minE

3D + 2D structure



SELECT ONE STRUCTURE BASED ON:

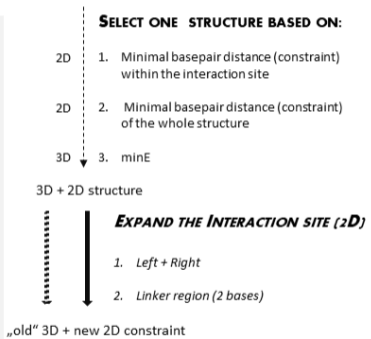
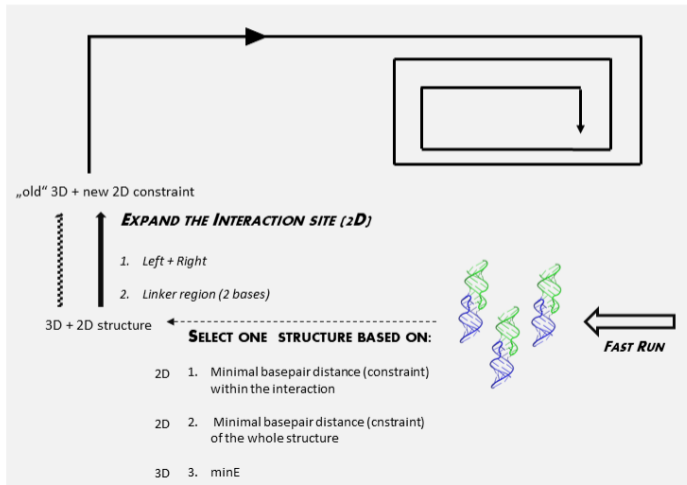
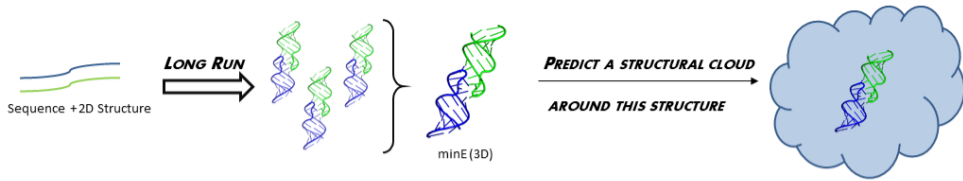
- 2D
1. Minimal basepair distance (constraint) within the interaction site
 2. Minimal basepair distance (constraint) of the whole structure
- 3D
3. minE

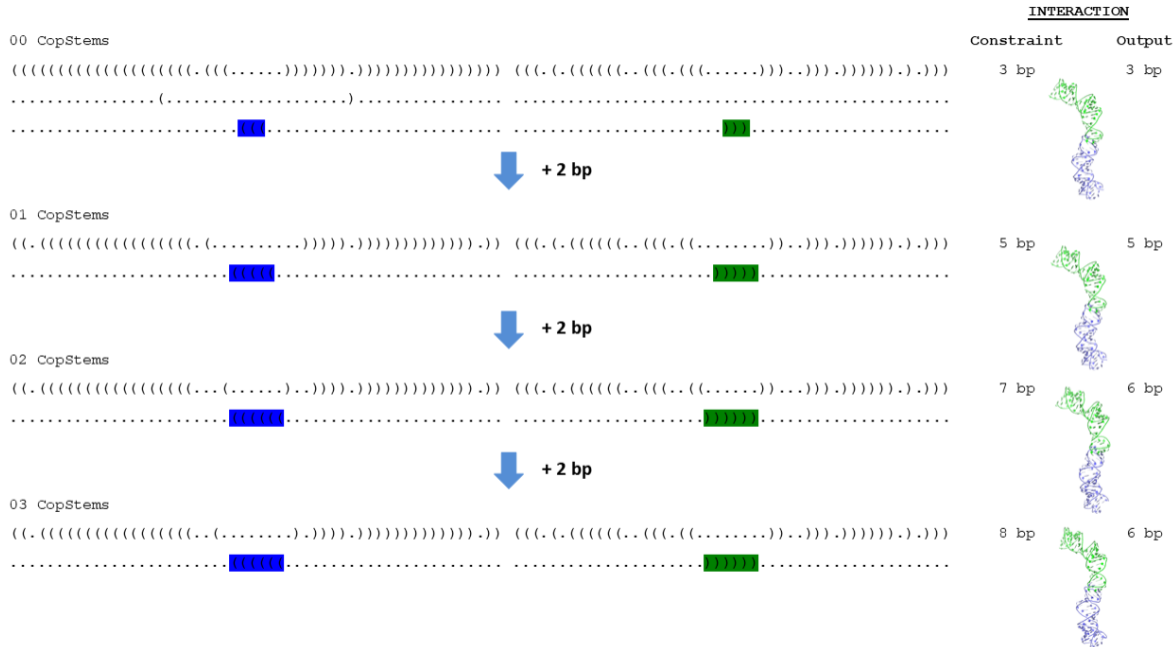
3D + 2D structure

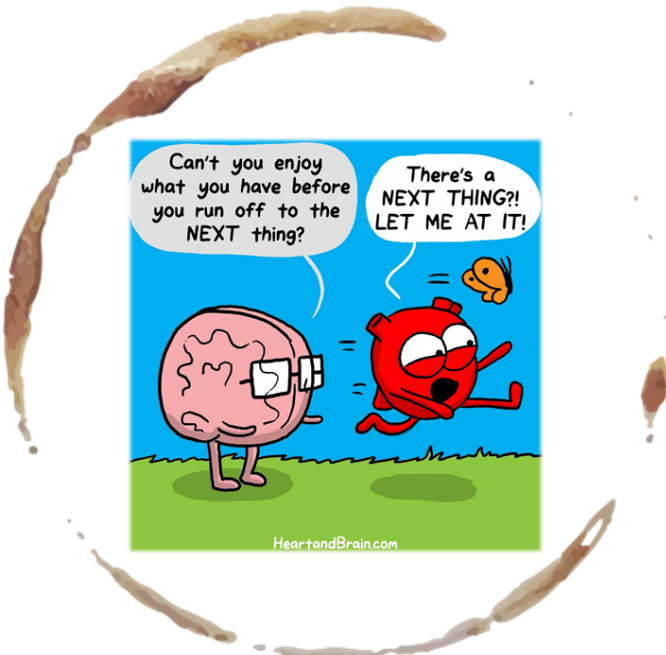
EXPAND THE INTERACTION SITE (2D)

1. Left + Right
2. Linker region (2 bases)

„old“ 3D + new 2D constraint





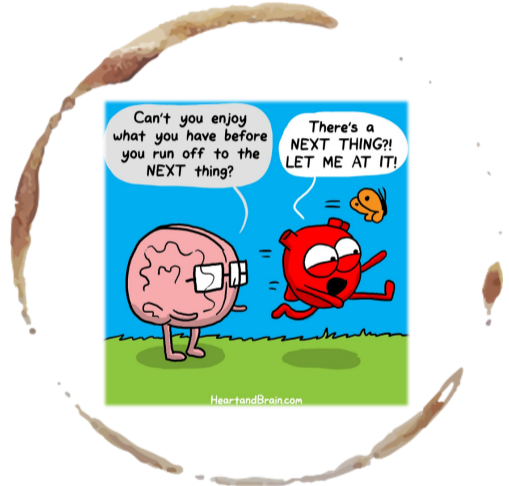


Can't you enjoy
what you have before
you run off to the
NEXT thing?

There's a
NEXT THING?!
LET ME AT IT!

What next?

- ▶ More runs
- ▶ Longer runs
- ▶ Expand the interaction only at the left or the right interaction site
- ▶ Expand the interaction one additional time
- ▶ Enable a longer linker region



CONSTRAINT

```
((.((((((((((((((((((.....))))))))))))..)) ((.(.((((((.(.(((.....))))))..)))))..))  
.....(CCCCC).....(GGGG).....
```

Multiple runs

10x (10,000 iteration steps) → 3x

```
((.((((((((((((((((((.....))))))))))))..)) ((.(.((((((.(.(((.....))))))..)))))..))  
.....(CCCC).....(GGGG).....
```

Longer runs

20,000 iteration steps

```
((.((((((((((((((((((.....))))))))))))..)) ((.(.((((((.(.(((.....))))))..)))))..))  
.....(CCCC).....(GGGG).....
```

30,000 iteration steps

```
((.((((((((((((((((((.....))))))))))))..)) ((.(.((((((.(.(((.....))))))..)))))..))  
.....(CCCC).....(GGGG).....
```

Expand only one site

right

```
((.((((((((((((((((((.....))))))))))))..)) ((.(.((((((.(.(((.....))))))..)))))..))  
.....(CCCC).....(GGGG).....
```

left

```
((.((((((((((((((((((.....))))))))))))..)) ((.(.((((((.(.(((.....))))))..)))))..))  
.....(CCCC).....(GGGG).....
```

INTERACTION

Constraint Output

8 bp 6 bp



8 bp 6 bp



7 bp 6 bp



CONSTRAINT: Longer interaction - Expand interaction one additional time

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

↓ + 2 bp

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

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

CONSTRAINT: Longer Linker region

3 bases

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

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

4 bases

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

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

INTERACTION

Constraint Output

10 bp 6 bp



8 bp 6 bp



8 bp 6 bp



What next?

- ▶ More time for the rearrangement
- ▶ Longer linker region
- ▶ ...
- ▶ **Mix of several factors**



Summary and Outlook



Developing a pipeline that predict, expand and analyse an interaction



Run the pipeline within a reasonable short time



Method detects possible kinetic steric effects



Insert/automatise a "What next"-option



Identification of length restrictions in RNA-RNA interactions



Detection of further interaction conformations



Define rules for feasible RNA-RNA conformations



Improve 2D RNA-RNA interaction prediction tools

Acknowledgements

THANKS TO ...

Vienna TBI-Team

- ▶ Sebastian Will
- ▶ Maria Waldl
- ▶ Ivo L. Hofacker

Freiburg Team

- ▶ Rolf Backofen
- ▶ Martin Raden

... and you!

Funding: FWF I 2874

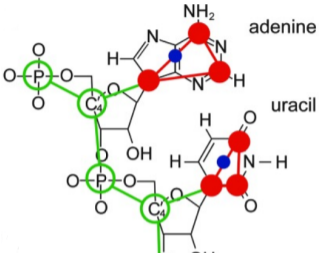


TBI

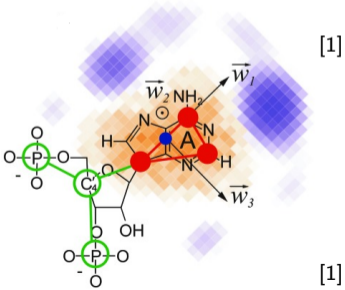


FWF

SimRNA



- Backbone: P, C4
- Bases: Pyrimidines: N1, C2, C4
Purine: N9, C2, C6
- Midpoint of each base

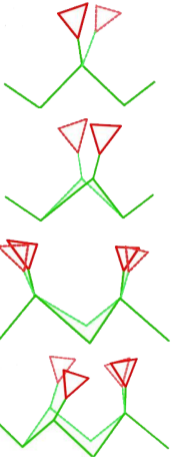


3D cubic grid

[1] Figures modified from: Boniecki, M. J. et al.(2015) Nucleic Acids Research

SimRNA

[1]



Change the Position of ...

... the base

... the backbone (C4)

... the backbone (P)

... two subsequent atoms of the backbone

