

Free energy calculation of modified nucleotides by molecular dynamics simulations

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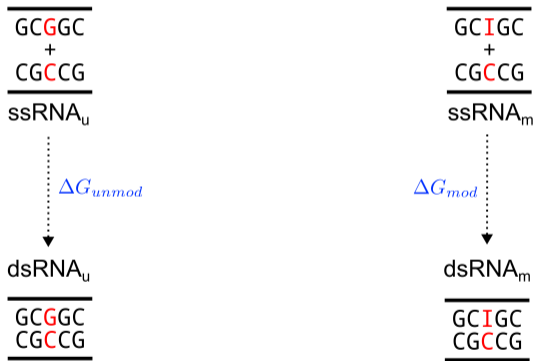
39th Winterseminar Bled
February 13, 2024

tbi



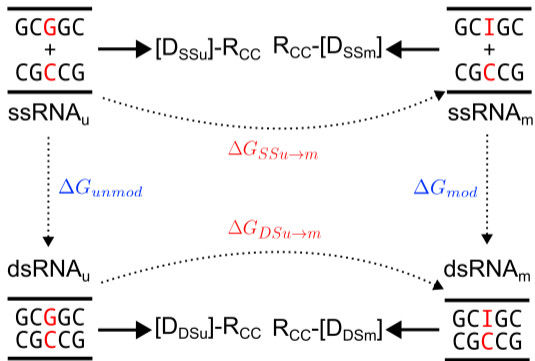
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Thermodynamic cycle from Transformato²



²Karwounopoulos et al. "Relative binding free energy calculations with transformato: A molecular dynamics engine-independent tool." *Frontiers in Molecular Biosciences* 9 (2022)

Thermodynamic cycle from Transformato²

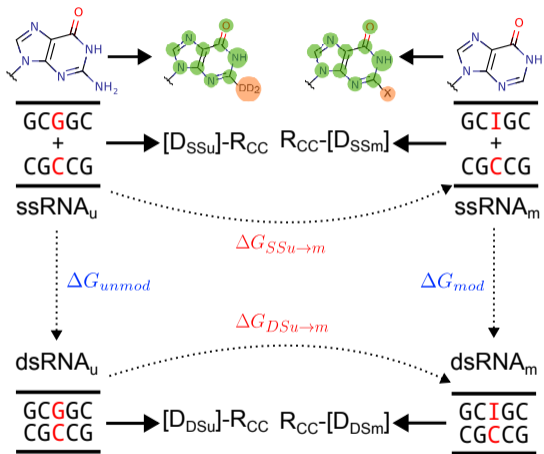


- Construction of an alchemical path

$$\begin{aligned} \Delta\Delta G_{unmod \rightarrow mod} &= \Delta G_{mod} - \Delta G_{unmod} \\ &= \Delta G_{DSu \rightarrow m} - \Delta G_{SSu \rightarrow Sm} \end{aligned}$$

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Thermodynamic cycle from Transformato²



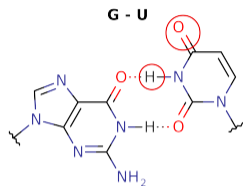
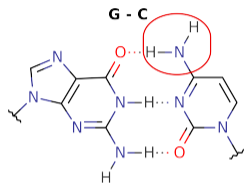
- Construction of an alchemical path
- Maximum common substructure

$$\begin{aligned} \Delta\Delta G_{unmod \rightarrow mod} &= \Delta G_{mod} - \Delta G_{unmod} \\ &= \Delta G_{DSu \rightarrow m} - \Delta G_{SSu \rightarrow Sm} \end{aligned}$$

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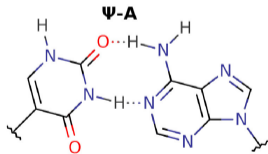
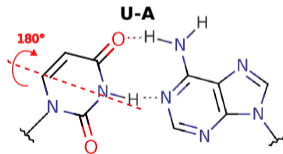
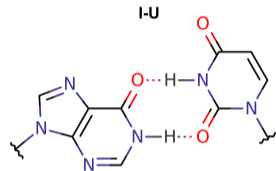
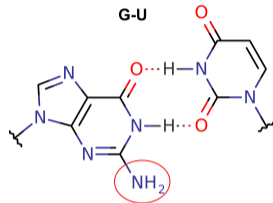
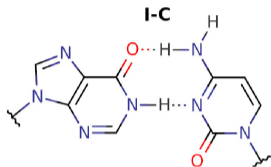
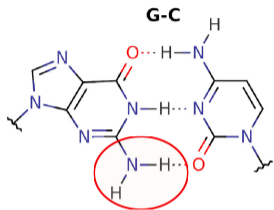
GC - GU

	MD	Lit	diff
GCUGC	2.72	2.20	0.52
CGGCG			
GCUAC	3.10	2.30	0.80
CGGUG			
GAUCC	2.02	2.60	-0.58
CUGGG			
GGUGC	1.73	1.90	-0.17
CCGCG			
GCUCC	3.53	3.00	0.53
CGGGG			
GGUAC	2.20	2.00	0.20
CCGUG			
GAUCC	1.64	2.60	-0.96
CUGGG			
GGUCC	2.64	2.70	-0.06
CCGGG			
GAUGC	0.78	1.80	-1.02
CUGCG			
GGUCC	2.79	2.70	0.09
CCGGG			



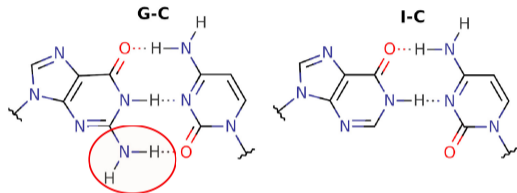
RMSE = 0.70
 std MD = 0.24
 std Lit = 0.14

Modifications



Energy predictions GC - IC

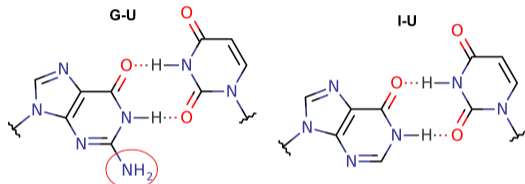
	MD	Lit	diff
GCCICGC	2.41	2.05	0.36
CGGCGCG			
GCGICGC	2.44	2.19	0.25
CGCCGCG			
GCGIGGC	2.71	1.75	0.96
CGCCCCG			
GCUIUGC	2.43	2.32	0.11
CGACACG			
GCGIAGC	2.39	1.90	0.49
CGCCUCG			
GCUICGC	2.32	2.65	-0.33
CGACGCG			
GCUIGGC	2.63	2.21	0.42
CGACCCG			
GCAICGC	1.84	2.04	-0.20
CGUCGCG			
GCAIGGC	2.08	1.60	0.48
CGUCCCG			
GCAIUGC	1.68	1.71	-0.03
CGUCACG			
GCCIAGC	2.29	1.76	0.53
CGGCUCG			
GCGIUGC	1.97	1.86	0.11
CGCCACG			
GCCIUGC	2.43	1.72	0.71
CGGCACG			



RMSE = 0.47
 std MD = 0.23
 std Lit = 0.55

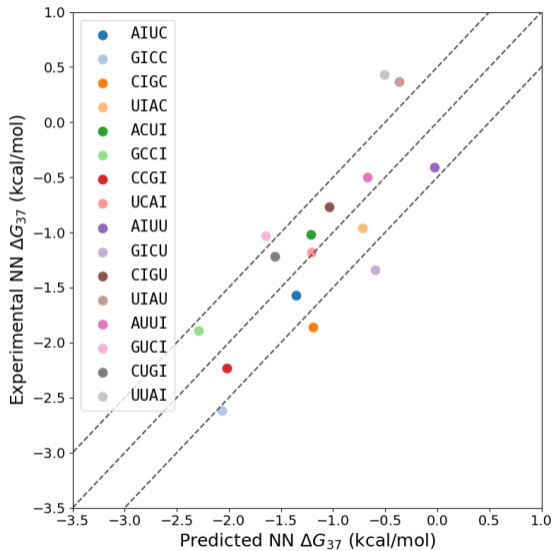
Energy predictions GU - IU

	MD	Lit	diff
GCCIAGC	0.94	2.36	-1.42
CGGUUCG			
GCCIICGC	1.27	2.10	-0.83
CGGUGCG			
GCUIGGC	1.33	2.25	-0.92
CGAUCCG			
GCUICGC	1.34	2.84	-1.50
CGAUGCG			
GCGIGGC	1.57	1.04	0.53
CGCUCGG			
GCCIUGC	0.95	1.53	-0.58
CGGUACG			
GCUIUGC	1.18	2.27	-1.09
CGAUACG			
GCGIAGC	1.65	1.89	-0.24
CGCUUCG			
GCGICGC	1.60	1.63	-0.03
CGCUGCG			
GCGIUGC	1.42	1.06	0.36
CGCUACG			
GCAIAGC	1.55	1.92	-0.37
CGUUUCG			
GCAIUGC	1.33	1.09	0.24
CGUUACG			
GCAIGGC	0.98	1.07	-0.09
CGUUCGG			



RMSE = 0.85
 std MD = 0.23
 std Lit = 0.56

Energy parameters Inosine



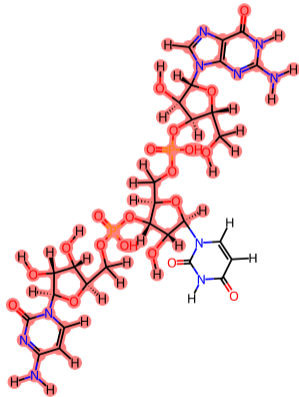
RMSE = 0.48

IC RMSE = 0.37

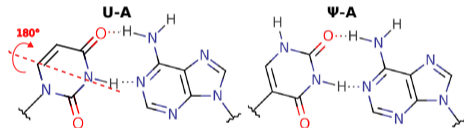
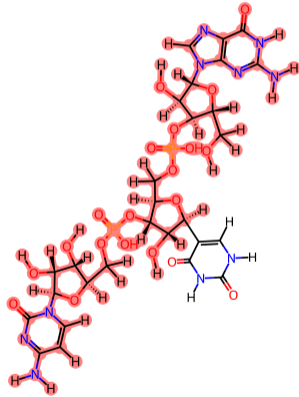
IU RMSE = 0.58

Common Core U to Ψ

GUC



G Ψ C



Ongoing Work

- Implementation for the Amber forcefield instead of Charmm
- Analysis of the common core
 - Base pair distances
 - Energy differences between the two CC states
- Construction of the common core

Conclusion and Outlooks

- Promising results with Inosine
- New NN parameters predicted for $I \bullet C$ and $I \bullet U$ next to $G \bullet U$
- Pipeline for NN parameters with modifications
- Not only stacking base pairs, but also larger loops

Acknowledgments

Ivo Hofacker
Ronny Lorenz
Yuliia Varenik

Stefan Boresch
Johannes Karwounopoulos

The whole TBI team

Thank you for your attention

The logo for TBI (Theoretical Biophysics Institute) is written in a stylized, lowercase, black cursive font.

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Base pair distances GC - GU

	MD	Lit	diff
GAUGC	0.78	1.80	-1.02
CUGCG			
GGUCC	2.79	2.70	0.09
CCGGG			

