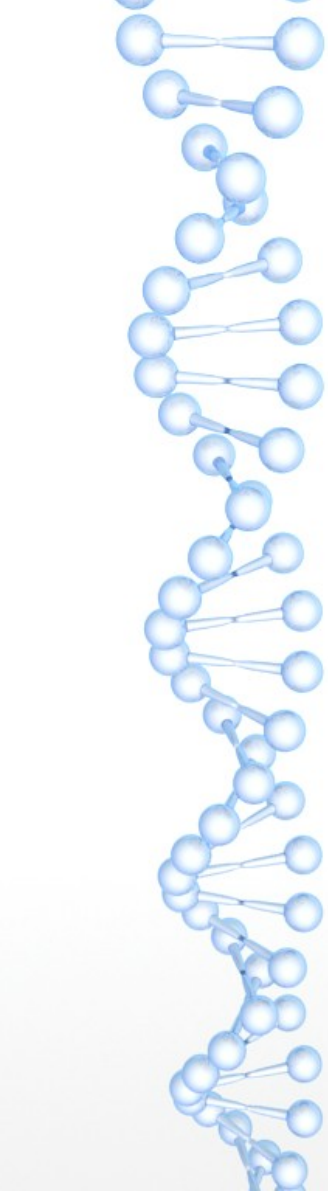

Developing an accurate force field for simulating modified RNA

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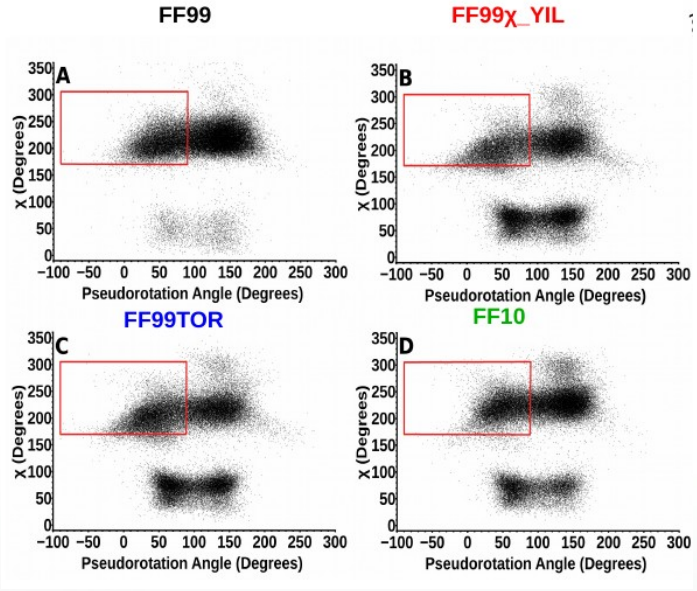
Motivation and Aim

- Post-transcriptional modifications occur extensively in RNA and provide an additional layer of chemical coding that presumably alters the chemistry, structure and dynamics of the molecules
- Currently the RNA modification database Modomics (http://genesilico.pl/modomics/) has more than 140 modified nucleosides listed
- What are the structural and dynamical consequences of these modifications?
- Molecular dynamics simulation can be a useful technique to answer this question **provided we have a well-validated force field for all the modifications**

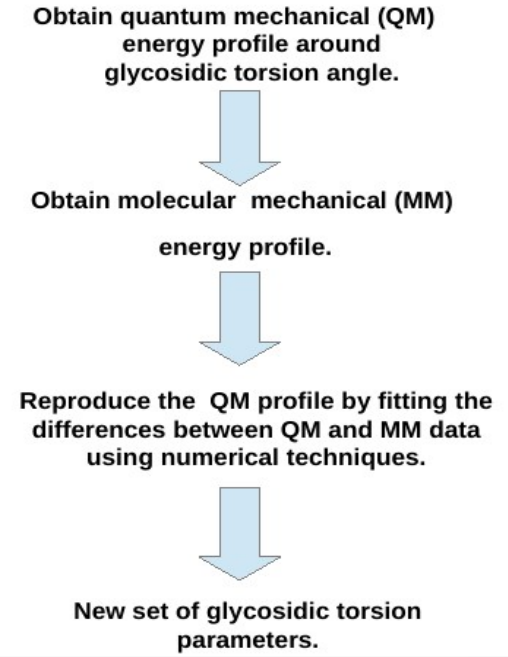
Methods and Algorithms

We have shown that many of the AMBER force fields for RNA do not work in the case of modified residues (Deb et al. JCIM 2014).

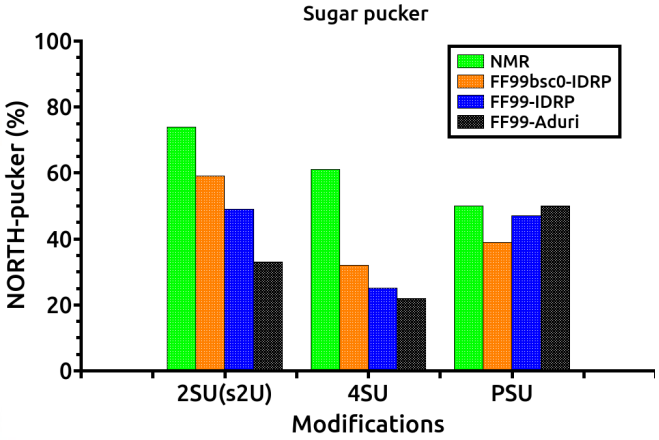


E.g., the conformational distribution for 2-thiouridine does not match with NMR observation (red rectangle)

Our protocol (IDRP) for force field revision (Deb et al. JCC 2016)



Results



Our protocol (IDRP) provides better agreement with NMR data compared with the current AMBER force field (*Aduri et al. J. Chem. Theory Comput. 2007*)

Our force field parameters are also transferable, e.g. 2-thiouridine parameters can be transferred to its C5-derivatives
Sarkar et al. JPCL 2020

% of C3' endo (NORTH) sugar pucker

Residues	Single letter code	FF99bsc0-χ_IDRP	FF99bsc0-Aduri	FF99-Aduri
5-methylaminomethyl-2-thiouridine	ESU	57	41	31
5-Methyl-2-thiouridine	52U	60	46	33
5-aminomethyl-2-thiouridine	SAU	57	43	34
5-taurinomethyl-2-thiouridine	STU	42	29	29
5-methoxycarbonylmethyl-2-thiouridine	SMU	60	43	33

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- Dutta, N., Deb, I., Sarzynska, J., & Lahiri, A. (2022). Data-informed reparameterization of modified RNA and the effect of explicit water models: application to pseudouridine and derivatives. Journal of computer-aided molecular design, 36(3), 205-224.

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