Tar-MD in NMR-based structure determination as a tool for handling local flexibility: application to a linear heptapeptide.

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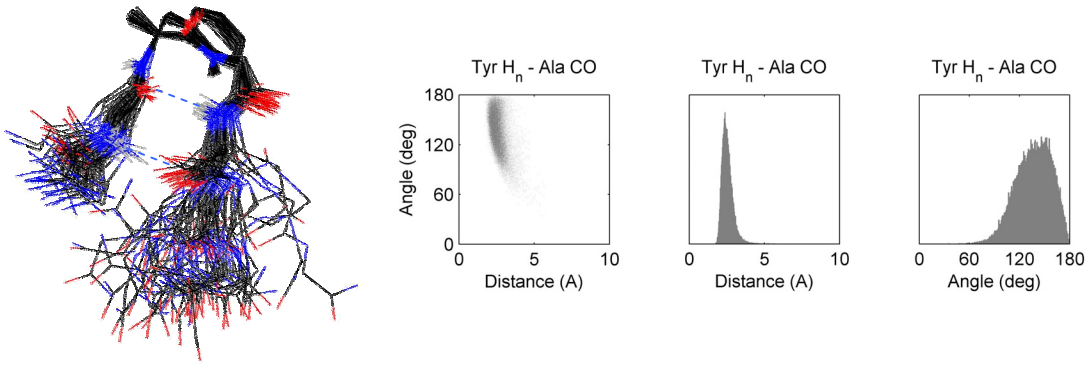
Over the years, NMR has been proven an excellent spectroscopic technique for the structure determination of many different types of organic compounds. These kind of determinations are generally based upon experimentally determined proton-proton distances, accessible from 2D NOESY spectra. Due to the dipolar nature of the measured interactions from which these distances can be calculated, only proton-pairs that reside close in space (<5Å) can be correlated. As this leads to a sparse set of distance data, molecular modeling schemes are used to aid the structure determination process. Classically, such molecular modeling schemes are designed to yield a single conformation that should agree with all proton-proton distances determined experimentally, simultaneously.

In (partially) flexible molecules however, these NMR derived proton-proton distances are averaged over all conformations accessible to the molecule. Forcing these distances onto the molecule using the classical modeling schemes may therefore lead to erroneous results. To overcome this, a recently developed scheme using time-averaged restraints (tar) in a molecular dynamics simulation (MD) can be used to allow for some flexibility.



We present a case-study of a linear opioid heptapeptide from the dermorphin class, that has been shown to be partially flexible in DMSO solution. Classical and tar-MD modeling schemes were used to obtain the molecule's conformation. Both yield a conformation with a turn centered over the central Phe-3 and Gly-4 residues. However, only application of the tar-MD modeling scheme resulted in the generation of conformations consisting a hydrogen bond as predicted by independent NMR data. While the tar-MD procedure is computationally more demanding, it can now routinely be applied using desktop CPU power within an acceptable time. Therefore it should be considered a valid alternative for NMR-based structure determination in flexible systems.