Kinetic models of the Cyclosporines A and E

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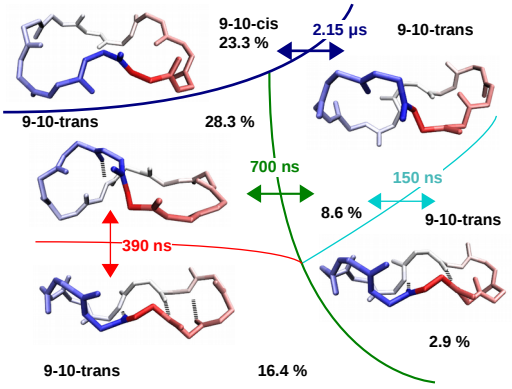

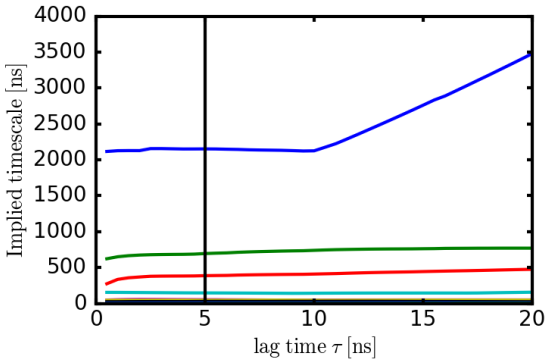

Cyclic peptides have gained high interest as potential drug candidates. However, they often suffer from a low bioavailability due to their size and complexity. One exception is the undecamer Cyclosporine A (CsA), which can passively diffuse through the membrane. The reason for this is most likely found in its dynamic behavior as it can change between an „open“ and a „closed“ conformation. Cyclosporine E (CsE) is a synthetic derivative of CsA, missing a backbone methylation in Val-11. Its membrane permeability, however, is one order of magnitude smaller [1,2].

To get a better understanding of the dynamics of both molecules and their kinetic differences MD-simulations in water (polar solvent) and chloroform (apolar solvent) have been performed [1,2], which are analyzed using core-set Markov-State-Models (cs-MSMs). In cs-MSMs one focuses on the metastable states of the system, called core sets. This has the advantage that only a small number of states is needed to describe the dynamics accurately [3,4]. We showed that using this kind of analysis recrossing can be reduced and disconnection of metastable states within the data set can be pointed out. In addition, we analyzed the influence of the cis-trans isomerization of the 9-10 peptide bond, which seems to be an important factor for the conformational changes of CsA and CsE, and compared both molecules using a combined discretization.

[1] J. Witek, B.G. Keller, M. Blatter, A. Meissner, T. Wagner, S. Riniker, *J. Chem. Inf. Model.*, **2016**, *56*, 1547-1562
[2] J. Witek, M. Mühlbauer, B.G.Keller, M. Blatter, A. Meissner, T. Wagner, S. Riniker, *ChemPhysChem*, **2017**, *18*, 3309-3314
[3] M. Sarich, R. Banisch, C. Hartmann, C. Schütte, *Entropy*, **2013**, *16*, 258-286
[4] O. Lemke, B.G. Keller, *J. Chem. Phys*., **2016**, *145*, 163104