IMPRS on Multiscale Biosystems

Title: Investigating the role of fluorinated amino acids on protein structure and function using simulation
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In collaboration with: Prof. Dr. Beate Koksch (FU)

Project description: Proteins containing fluorine atoms are inexistent in nature, but over the past decade many fluorine-substituted protein analogues have been created. We now know that substituting even a single C-H by a C-F group may alter the protein's function, resistance to degradation by proteases or conformational stability with respect to temperature or denaturants. Fluorine substitution is thus a promising tool to enhance the properties of proteins. Presently, we have limited understanding of the molecular scale mechanisms by which fluorination induces particular changes in proteins. This project aims to build this understanding, by using molecular simulations to investigate how fluorinated amino acids differ from natural ones in their interactions with other amino acids, water, or ions. First we will investigate how C-H to C-F mutations alter the intrinsic structural properties of amino acids and those of their water of hydration. In a second stage we will mutate amino acids in small peptides with known structure - e.g. coiled-coils, see Fig. 1 - and will build on what was learned in the first stage to determine the molecular scale origin of differences in the properties of natural and fluorinated peptides. The project will involve frequent discussions with the Koksch group at the FU, benefiting from the group's expertise and on-going work synthesizing and experimentally evaluating fluorinated peptides[1].

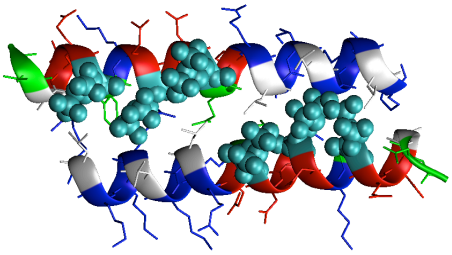

Figure 1: Structure of a coiled-coil; the blue spheres are fluorinated leucines.

The student will address these issues using multiple particle-based simulation methods, with emphasis on classical molecular dynamics. Enhanced sampling techniques will be systematically used to calculate, e.g., binding free energies and transition rates for rare events. Ab initio methods will be used to parameterize new compounds for classical simulations. This project is mainly computational but has a strong interdisciplinary component: the student will have the chance to do experiments (e.g. dynamic light scattering, titration) on model systems, gaining a level of insight into these techniques that will be valuable for his/her future career.

Required background: Strong knowledge of chemical physics, physical chemistry and physics. Prior experience with particle-based simulation techniques (atomistic or coarse-grained molecular dynamics, Monte Carlo, ab initio calculations) is an advantage.
Paper to read before the interview: Buer, B.C. & Marsh, E.N.G. *Fluorine: A new element in protein design Protein Science,* **2012***, 21*, 453-462

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[1] Nyakatura, E.K.; Reimann, O.; Vagt, T.; Salwiczek, M. & Koksch, B. *Accommodating fluorinated amino acids in a helical peptide environment*, Rsc Advances, **2013***, 3*, 6319