1.3.22 Multiscale simulations of peptide-bilayer interactions

As highlighted by increasing scientific evidence, the crossing of biological membrane by cell penetrating peptides (CPPs) is governed by their self-association. We report a combined experimental and computational study showing that Tat_{11}, a CPP, is able to form dimers despite its sizeable positive charge. By extensive MD simulations, we unraveled the structural motives of Tat_{11} self-association, providing the basis to understand the membrane penetration mechanisms. Computational modeling of the peptide-aggregate interaction with the membrane can be greatly facilitated by using simplified coarse grain (CG) models. Here we also describe a strategy to build and optimize statistics-based analytical CG force fields, particularly suited to account for the common interaction motives between biopolymers.

Molecular dynamics (MD) simulations of aggregation phenomena become particularly challenging when dealing with intrinsically disordered proteins, such as the highly charged Tat_{11} peptide. The complexity of aggregation *per se* is compounded with the requirement of exhaustively sampling the numerous peptide conformations. Notwithstanding this complexity, the topic is of broad interest given its recurrence in several biological phenomena. One example is the mechanism of Tat_{11} internalization (across the biological membrane), being concentration dependent in a way that mirrors the aggregation state of the peptide in solution. Light scattering and NMR measurements of the diffusion coefficient (Fig. 1a) provide a picture suggesting the presence of a dimeric aggregate. These observations prompted us to investigate putative structure of Tat_{11} dimer by MD all-atom simulations. Starting configurations were obtained by maximizing the inter-peptide contacts by metadynamics, and unrestrained MD simulations at the μs timescale. The dimer structures were shown to be highly flexible with the inter-peptide interactions taking place mostly between the C-termini. In this arrangement the negatively charged carboxylic groups (COO^-) engages in salt bridges with the several charged side chains (see Fig. 1b). A notable feature is the presence of stacking between two or more Arg guanidinium groups close to the C-termini. Albeit keeping two positively charged groups in close contact, this motif optimized the geometry for the interaction with COO^- (Fig. 1b). The question whether this stacking is functional to the peptide interaction with the membrane will be the topic of further studies.

In spite of their increasing use, Coarse Grained (CG) models for biopolymers are still far from reaching the level of standard and validation currently available for all-atom models. This depends in part on the fact that the parameterization strategies are various and most often adjusted on the specific cases. We tried to design a general strategy to aid building and optimization of statistics based analytical force fields which we implemented in the software AsParaGS (Assisted Parameterization platform for Coarse Grained models, www.muscade-lab.it/project/asparags). The method relies on the exploration of the parameters space of the analytical interaction potential by combining different algorithms (i.e., relative entropy driven stochastic exploration and iterative Boltzmann inversion) and searching for optimal parameters set with respect to given score function, e.g., depending on the distance between the simulation and the experimental distribution of structural variables.

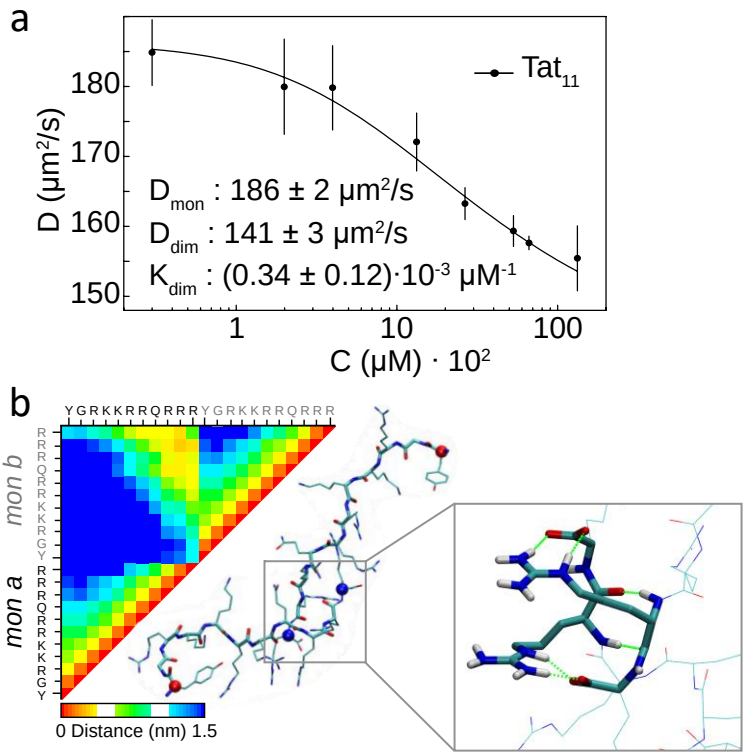

Figure 1. Panel a): Diffusion coefficients obtained by NMR DOSY experiments for increasing peptide concentrations. Monomer and dimer diffusion coefficients (D_{mon} and D_{dim}, respectively) with dimerization constant (K_{dim}) are obtained by fitting. Panel b): Tat_{11} inter and intra peptide contact map averaged during the simulation, and dimer representative structure. Single letter amino acids are indicated for each monomer. The inset shows the Arg-Arg stacking motif with salt bridges between C-termini and Arg side chains.

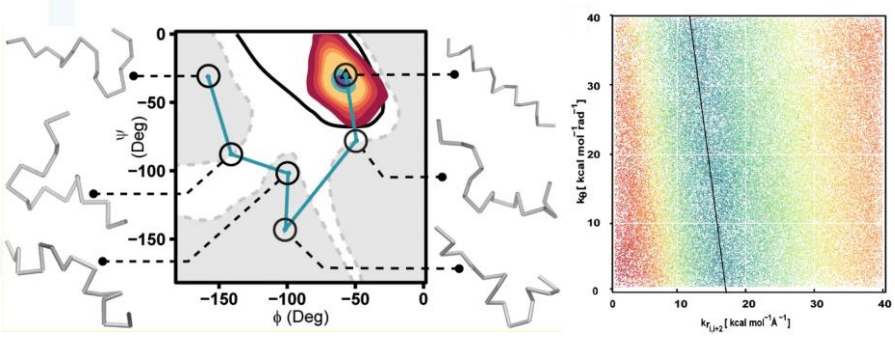

Figure 2. Illustration of the AsParaGS method on a test case (helical polypeptide). On the left: the parameters space is explored until the helical-stabilizing parameterization is reached, as shown in the Ramachandran Map. On the right: the methods reveal correlations between parameters: if two terms in the force filed are correlated (e.g., the bond angle and 1-3 interaction term), areas with similarly high scores appear in the parameters space (blue color), indicating that any combination of the two terms lying on the correlation line will give similarly good force fields.

References

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