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Arginine-rich Cell-penetrating Peptides: Solution Behavior and Membrane Permeation

Giulio Tesei,¹ a) Mario Vazdar,² and Mikael Lund¹

¹)Division of Theoretical Chemistry, Lund University, POB 124, SE-22100 Lund, Sweden

²)Division of Organic Chemistry and Biochemistry, Rudjer Boskovic Institute, POB 180, HR-10002 Zagreb, Croatia

Arginine-rich cell-penetrating peptides (RRPs) spontaneously traverse cell membranes and are promising candidates for drug delivery. The internalization mechanism has been suggested to involve a cooperative process initiated by the self-aggregation of RRP adsorbed onto the plasma membrane¹. Likewise, formation of aggregates in solution has been shown to be related to the efficiency of cellular uptake². Using small-angle X-ray scattering experiments and all-atom simulations, we study the solution behavior of arginine and lysine decapeptides. Despite its large positive charge, we find that deca-arginine self-associates in aqueous solution³. Simulations elucidate the molecular origin of the attraction, whereas inspection of the Protein Data Bank reveals that the mode of deca-arginine dimerization commonly occurs in protein crystal structures. To investigate the concerted interaction between multiple RRP and a lipid bilayer over large time and length scales, we develop a computationally efficient coarse-grained model which can be readily parametrized against all-atom simulations as well as experimental data. The force field is based on a granular representation of the mismatch between the dielectric constant of lipids and aqueous medium, combined with an accurate description of membrane elastic properties. Via constant-pH Monte Carlo simulations, the model is used to study the influence of acid-base equilibria and chain length on the energetics of RRP membrane permeation.

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Primary author(s) : Mr. TESEI, Giulio (Chemistry, Lund university)

Presenter(s) : Mr. TESEI, Giulio (Chemistry, Lund university)