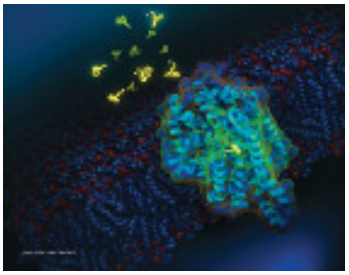

Contribution ID: **48** Type: **not specified**

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 RRPs 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 RRPs 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 eld 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 inuence of acid-base equilibria and chain length on the energetics of RRPs membrane permeation.

REFERENCES

1R. Brock, \The uptake of arginine-rich cell-penetrating peptides: Putting the puzzle together," Bioconjugate Chemistry 25, 863{868 (2014).

2S. Macchi, G. Signore, C. Boccardi, C. D. Rienzo, F. Beltram, and F. Cardarelli, \Spontaneous membrane-translocating peptides: inuence of peptide self-aggregation and cargo polarity," Scientic Reports 5, 16914 (2015).

3G. Tesei, M. Vazdar, M. R. Jensen, C. Cragnell, P. E. Mason, J. Heyda, M. Skepo, P. Jungwirth, and M. Lund, \Self-association of a highly charged arginine-rich cell-penetrating peptide," Proceedings of the National Academy of Sciences 114, 11428{11433 (2017).

Author: Mr TESEI, Giulio (Chemistry, Lund university)

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