Mesoscopic simulation of the membrane disrupting activity of the cyclotide Kalata B1

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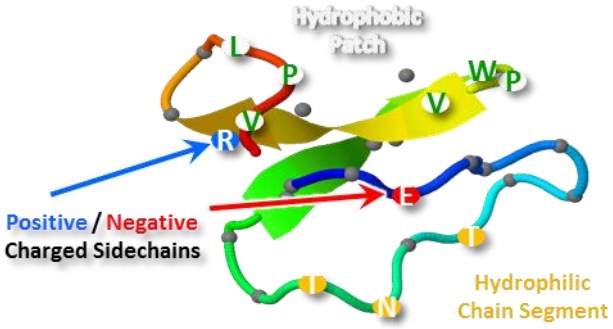
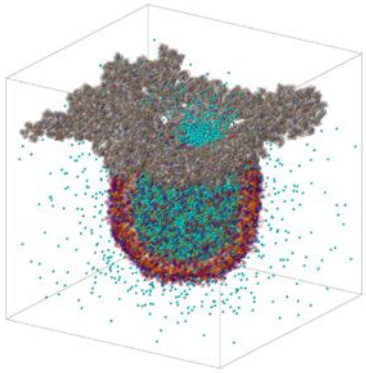
Dissipative Particle Dynamics (DPD) is an established simulation technique to study condensed matter systems on mesoscopic scales. Whereas its coarse-grained interacting units (beads) may not necessarily be identified with distinct chemical compounds at all, the DPD variant Molecular Fragment Dynamics (MFD) makes use of specific small molecules to represent all molecular species of interest. MFD has been successfully applied for studying surfactant systems at the water-air interface [1] and for phospholipid membranes, peptides and proteins [2].





Recent studies with the MFD technique demonstrate the membrane disrupting activity of the cyclotide Kalata B1 (left figure), a 29 amino acid self-defense associated peptide expressed in plants [2]. This work aims at establishing better test systems for membrane pore formation due to Kalata B1 activity like a 30 nm 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC) bilayer vesicle filled with water molecules (right figure). The effects of single and multiple amino acid replacements within Kalata B1 on membrane pore formation are compared to experimental results and may finally be utilized to predict the bioactivity profiles of specifically mutated cyclotids. These studies may support the understanding of pharmaceutical active peptides with cyclotide scaffold which are applied e.g. for anti-HIV treatment [3].

[1] Truszkowski, A.; Epple, M.; Fiethen, A.; Zielesny, A.; Hubert, K. Molecular fragment dynamics study on the water-air interface behavior of non-ionic polyoxyethylene alkyl ether surfactants. *J. Colloid. Interface. Sci.* **2013**, 410, 140–145.
[2] Truszkowski, A.; van den Broek, K.; Kuhn, H.; Zielesny, A.; Epple, M.: Mesoscopic Simulation of Phospholipid Membranes, Peptides and Proteins with Molecular Fragment Dynamics. *Journal of Chemical Information and Modeling* **2015**, 55: 983-997.
[3] Sangphukieo, A.; Nawae, W.; Laomettachit, T.; Supasitthimethee, U.; Ruengjitchatchawalya, M.: Computational design of hypothetical new peptides based on a cyclotide scaffold as HIV gp120 inhibitor. *PLoS One* **2015**;10: 1–15