Molecular Simulation of Interactions between Structured Peptides and Biomaterial Surfaces

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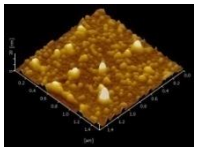
Introduction:


AFM image of proteins adsorbed to a surface.[1]

Protein-biomaterial interactions govern the biocompatibility of implanted materials.

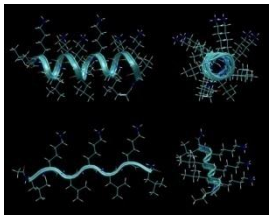
Controlling biocompatibility through material design begins with the study of these interactions at the atomic level, where all-atom molecular dynamics (MD) and replica-exchange (REMD) simulations serve as excellent research tools.

Current MD simulation methods and parameters are not designed to accommodate the unique types of atomic interactions involved in protein-biomaterial interactions, where nonbonded interactions dominate.

The purpose of this work is to evaluate the applicability of existing parameter libraries (CHARMM, AMBER, and OPLS-AA) for representing protein-surface interactions. We are simulating discrete protein structural components in the form of simple model peptide structures (α-helices and β-sheets), as they interact with hydrophobic and charged self-assembled monolayer (SAM) surfaces. These simulations are being run as a collaborative effort in parallel with experimental studies (ssNMR, XPS, ToF-SIMS, NEXAFS) of identical peptide-surface systems, which are being conducted by the Castner, Gamble, Stayton, and Drobny groups at the University of Washington.

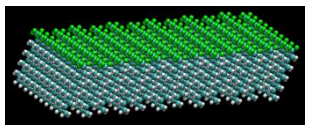
LKα and LKβ Model Peptides and SAM Surfaces:

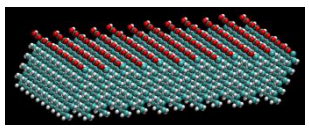
LKα14: (Ac-LKKLLKLLKKLLKL-NH_2)



LKβ7: (Ac-LKLKLKL-NH_2)

Peptides consisting of leucine (L) and lysine (K) serve as excellent peptide models because the periodicity of these amino acids can be arranged to provide distinct regions of hydrophobicity and positive charge, as desired.


-CH_3 hydrophobic surface

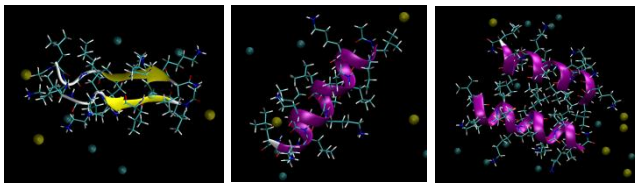

-COOH charged surface (50% deprotonated, pKa 7.4)

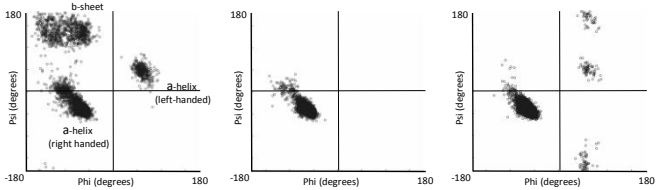
General Computational Approach:

- CHARMM[2] c34b2 simulation engine.
- CHARMM v27 FF, AMBER94 FF, OPLS-AA FF.
- MMTSB[3] toolset for managing REMD simulations.
- 10 ns-scale MD and REMD[4] simulations.
- Explicit TIP3P water with SHAKE algorithm for fixing X-H's.
- NVT ensemble w/Nosé-Hoover[5] thermostat.
- New Velocity Verlet[6] (VV2) integrator.
- Particle-mesh Ewald[7] (PME) for long-range electrostatics.
- Na^+ and Cl^- ions to achieve ~140 mM saline.
- All REMD runs are prepopulated with a variety of starting conformations (helical, extended, randomized, etc.).

Peptide Stability and Interaction Studies:

MD and REMD simulations of single and multiple peptides with various starting orientations (including random conformations) were used to establish model peptide behavior in solution in the absence of a surface.

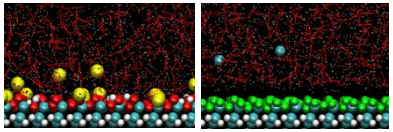

LKβ7 pair (10 ns REMD) | LKα14 (10 ns REMD) | LKα14 pair (10 ns REMD)

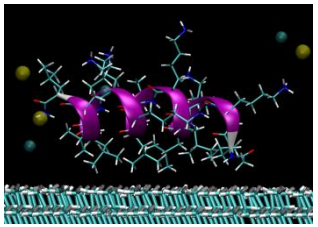


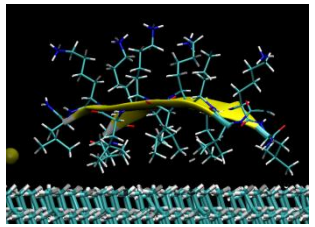
Ramachandran plots characterizing peptide secondary structure (phi & psi dihedral angles of backbone)

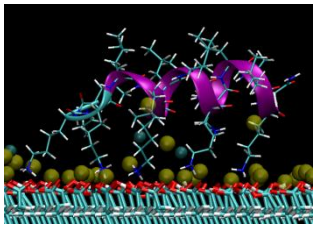
Complete Production Systems:

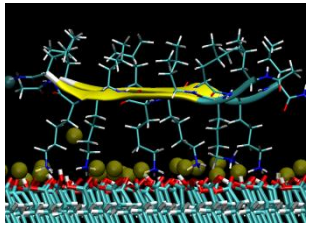
An initial round of MD and REMD simulations of peptides with surfaces has revealed distinct behavioral characteristics of the peptides and of the water structure over these two different surfaces. (Note low density of water over CH_3-SAM)

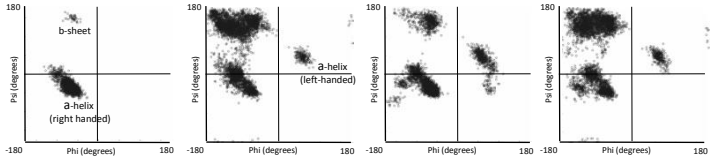



LKα14 over hydrophobic -CH_3 SAM surface (10 ns REMD, CHARMM)


LKβ7 pair over hydrophobic -CH_3 SAM surface (10 ns REMD, CHARMM)


LKα14 over charged -COOH SAM surface (10 ns REMD, CHARMM)


LKβ7 pair over charged -COOH SAM surface (10 ns REMD, CHARMM)



LKα14, -CH_3 SAM | LKβ7 pair, -CH_3 SAM | LKα14, -COOH SAM | LKβ7 pair, -COOH SAM

Ramachandran plots characterizing peptide secondary structure (phi & psi dihedral angles of backbone)

Concluding Remarks:

- The LKα14 peptide retains its helical structure in solution and when it is adsorbed to either surface (with adsorption to the CH3 surface predicted to be more stable).
- The pair of LKβ7 peptides maintain an antiparallel configuration in solution and when adsorbed to either surface.
- Adsorption of the charged residues on the oppositely charged surface represents an entropy-driven ion-exchange process in which the multivalent peptide displaces multiple monovalent ions from the surface.
- Simulations with the CHARMM force field are providing results that appear to closely represent the realistic behavior of this peptide adsorption system.

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1) http://nanotech.sc.mahidol.ac.th
2) J. Mol. Graph. Model. 22, 377-395 (2004).
3) Comp. Chem. 4, 187-217 (1983).
4) Chem. Phys. Lett. 314, 141-151 (1999).
5) J. Chem. Phys. 119, 3025-3039 (2003).
6) Mol. Phys. 87, 1117 (1996).
7) J. Chem. Phys. 103, 8577 (1995).