DEVELOPING EFFICIENT TRANSFER FREE ENERGY CALCULATION METHODS FOR HYDROPHOBICITY PREDICTIONS

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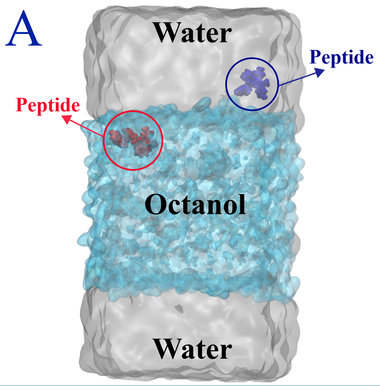
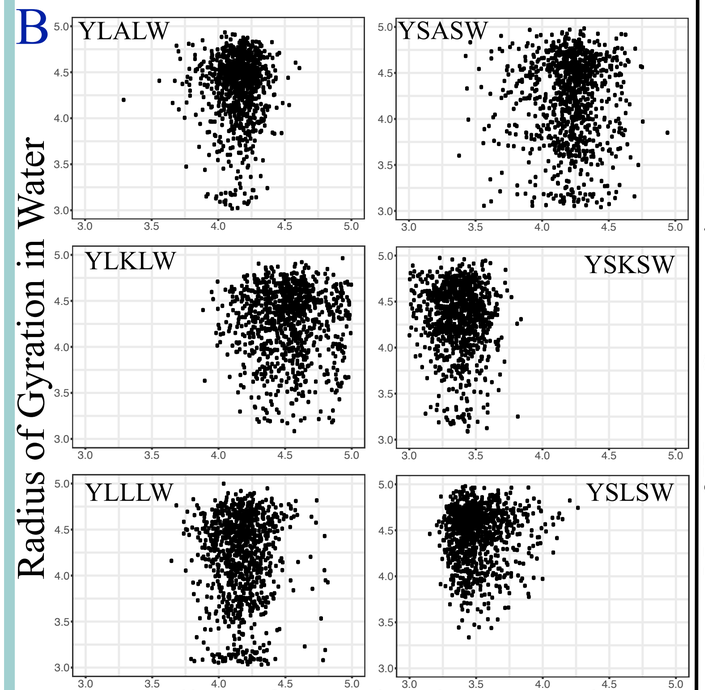
Abstract

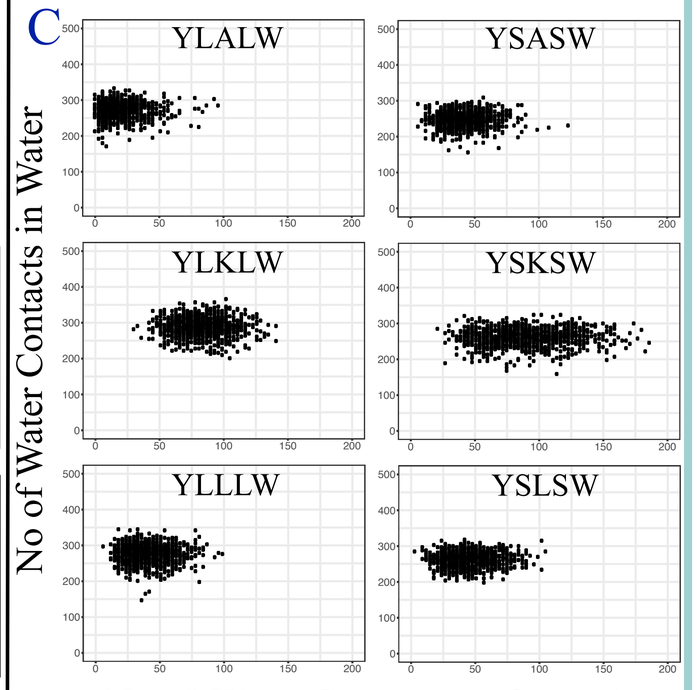
The interaction of peptides with membrane lipids is significant in the biological processes. Short peptides are an excellent alternative to the immune response antibodies, and they play a very crucial role in binding, insertion, and folding of membrane proteins. The characterization of solvent dependent conformational ensemble of the peptides is required for a molecular-level understanding of the thermodynamic hydrophobicity scale. To characterize the solvent-peptide interactions, we have developed a computational procedure that allows us to accurately model the peptides in both aqueous and organic solvent conditions and determine their properties at a thermodynamic level. This study evaluates the peptide conformational dynamics at different temperatures using molecular dynamics (MD) in the explicit solvent of water and octanol to estimate the transfer free energies accurately and to predict the partition coefficients. We have used a series of equilibrium MD simulations, and alchemical free energy calculations to measure the transfer free energies within various approximations. This study sheds light on the efficiency and accuracy of several different computational strategies for the study of transfer free energies.

Methods

Initial atomic models of 6 different sequence (YLALW, YLKLW, YLLLW, YSASW, YSKSW, and YSLSW) of penta-peptides were generated using VMD molefacture[1]. The system was solvated with TIP3P water and octanol, then energetically minimized and equilibrated for 50 ns under constant pressure and temperature of 1 atm and 300 K respectively with timestep of 2 fs. For simulations CHARMM36 forcefield were used. For minimization and system production simulations were performed using NAMD 2.13[2]. Following equilibration simulations of all peptides, we constructed 1000 peptides models solvated in water and octanol binary film placing peptide in both water and octanol layers and equilibrated the models for another 10 ns. Free energy calculations were done using In Silico Alchemy free energy perturbation (FEP) method. All visualizations of protein system and free energy calculations are done using VMD. We performed the solvation free energy calculation of peptide in water and octanol solution of 20 individual systems for each peptide. The average solvation free energy values were used for calculating partition coefficient of peptide in octanol solution.







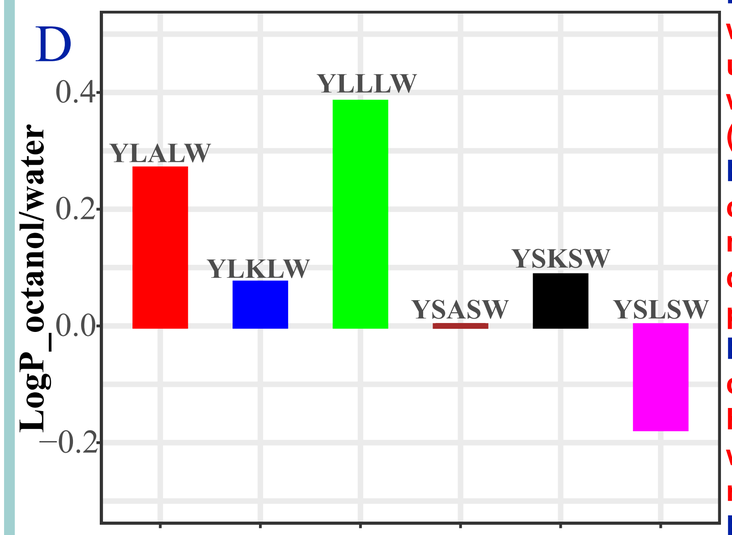


Fig A. Snapshot of MD equilibrium simulation with water (gray) and octanol (cyan). To understand the structural behavior of peptide we solvated in both water (blue) and octanol (red).

Fig B. Hydrophobicity is the significant contributor to peptide stability. Even minor modulation in the hydrophobicity scale could directly Affect the structural behavior of the peptide.

Fig C. The water interaction with peptide could be a critical variable to estimate the hydrophobicity of the peptides. The peptides with a lower hydrophobic scale have a higher no of water interaction in octanol.

Fig D. Our Logp calculations shows that peptides with higher hydrophobicity scale have higher Logp value in octanol.

CONCLUSION

We have demonstrated that the exact connection between the octanol-water partition coefficient of a peptide and its structure can be effortlessly estimated by properties of the peptide, for example, radius of gyration and interaction with an aqueous solvent. Based on our observations the peptide's conformational dynamics are dependent on the hydrophobic nature of the peptide. Peptides with a similar range of hydrophobicity have relatively similar behavior in the respective solvent for example, simulations of YLALW and YLLLW (with 80% hydrophobicity) have a significantly similar radius of gyration (Rg) in octanol and water solvents. Even minor modulation in the hydrophobicity scale could directly affect the structural behavior of the peptide, YLKLW peptide which is 60% hydrophobic has a very distinct behavior compared to the others (YLALW & YLLLW). The water interactions in octanol/water solvent with peptide could be a significant variable to estimate the hydrophobicity of the peptides. As expected, the peptides with a lower hydrophobic scale have a higher no of interactions with water in octanol solvent. The parameters obtained in our analysis could be used as a hydrophobicity scale for peptides. Finally, the calculated LogP of peptides using solvation free energy perturbation (FEP) of the peptide in water and octanol clearly support our predictions from our equilibrium simulation parameters. In this study, we have demonstrated that partition coefficients of peptides can be predicted reliably by using either by equilibrium simulations model or FEP model.

Reference

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