Structures of Intrinsically Disordered Polypeptides

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Introduction

The folding of intrinsically disordered peptides is often difficult to elucidate by traditional experimental techniques because of the rapid conversion of these peptides between many low free energy states. Molecular simulations are one tool to resolve the structures of proteins on the angstrom and picosecond scales that can be applied to a diverse set of systems. This poster discusses how advanced sampling techniques such as bias exchange metadynamics and replica exchange solute tempering were used to determine the important conformations of proteins in a variety of environments. For example, the aggregation of the peptide human amylin has been associated with the formation of type II diabetes. Oligomers of amylin are suspected to cause the death of insulin producing cells in the pancreas; however, their transient nature has made them difficult to identify experimentally. As a first step towards understanding the aggregation of these intrinsically disordered peptides, molecular simulations were used to probe the conformations of single peptides in solution and on membranes. The fraction of peptides in a β-hairpin, α-helix, or random coil state was determined for human and rat amylin. Different force fields and their resulting ensembles of structures were then evaluated on their ability to reproduce experimentally measured NMR chemical shifts. Another project presented is the role of the chirality of peptides in forming coacervates, a liquid-liquid phase separation with applications in drug delivery, gene therapy, food sciences, and cosmetics. While homochiral peptides form precipitates, achiral systems instead form coacervates. Molecular simulations were performed to understand the effect of chirality on the strength of interactions between pairs of these peptides.

Bias Exchange Metadynamics

Metadynamics was used to sample high energy states not accessible using traditional molecular dynamics. This technique adds a small amount of energy to the state that is being sampled. As the simulation progresses, these energies fill the free energy minima, helping the system explore other regions. The force each particle experiences is modified to the below equation using the correction described in reference 1:

$$F_i(s) = -\frac{\partial V(s)}{\partial r_i} - \frac{\partial}{\partial r_i}\sum_{t'<t} \frac{W \exp\left(-\sum_i \frac{(s_i(t')-s_i)^2}{2\sigma_i^2}\right)}{\prod_{i=1}^{N}\left[erf\left(\frac{s_i - L_i}{\sqrt{2}\sigma_i}\right) + erf\left(\frac{U_i - s_i}{\sqrt{2}\sigma_i}\right)\right]}$$

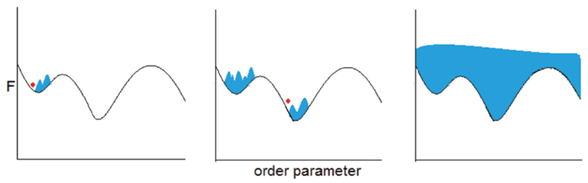
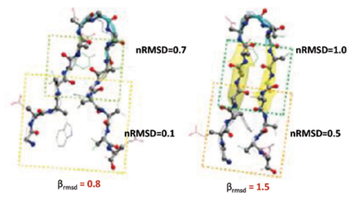


Figure 1. Diagram depicting the process by which metadynamics samples a free energy surface.

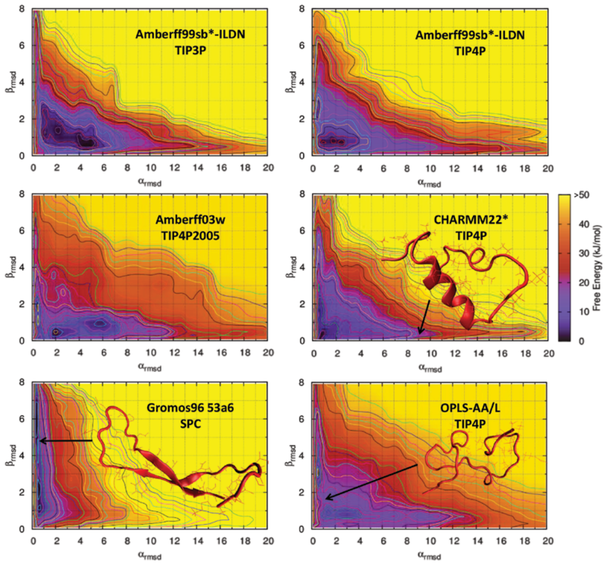
Residue Number	1 5 10 15 20 25 30 35
hIAPP Sequence	KCNTATCATQRLANFLVHSSNNFGAILSSTNVGSNTY-NH_2
rIAPP Sequence	KCNTATCATQRLANFLVRSSNNLGPVLPPTNVGSNTY-NH_2
Charge Used	++ +

Definition of Order Parameters

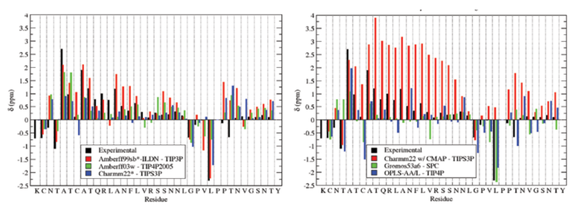
- α_{rmsd}: define an ideal subunit of α-helix. Then count the number of 3 residues blocks that are similar to this ideal structure.[2]
- β_{rmsd}: similar to α_{rmsd}, but instead compares blocks of 6 residues with three residues from each strand to an ideal β-hairpin.



Structural Propensities of Amylin



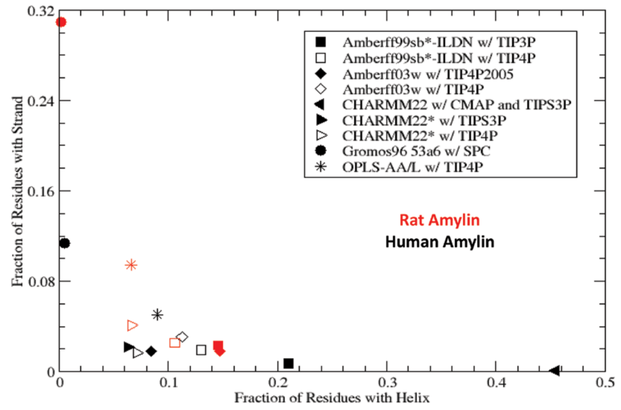
Comparison with NMR

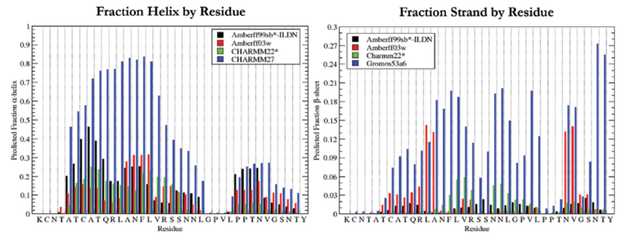


Force Field	Water Model	C_α	C_β	H_α	H_N	N
Amberff99sb*-ILDN	TIP3P	0.48	1.08	3.15	2.82	2.74
Amberff99sb*-ILDN	TIP4P	0.41	0.91	3.13	1.77	1.97
Amberff03w	TIP4P2005	0.49	0.67	3.70	1.57	0.92
Amberff03w	TIP4P	0.65	1.14	4.27	1.50	0.81
CHARMM22/CMAP	TIPS3P	2.61	1.19	2.62	2.49	2.28
CHARMM22*	TIPS3P	0.54	0.76	3.79	1.66	0.66
CHARMM22*	TIP4P	0.33	0.55	2.82	1.16	0.81
Gromos53a6	SPC	0.61	1.28	7.07	2.36	0.39
OPLS-AA/L	TIP4P	0.52	1.09	5.96	2.09	1.58

$$Error = \sqrt{\sum_{i}^{NumResidues}\left(\frac{\delta_{i,experimental} - \delta_{i,predicted}}{J_{i,experimental}}\right)^2}$$

Fraction of Helix and Strand



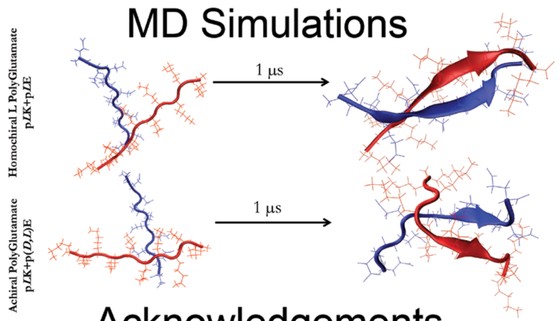


Coacervates

Coacervates can be created when polyglutamate and polylysine are combined. However, if both of the peptides have exclusively homochiral L C_α groups, then precipitates are formed.

LLLLL…LLL + LLL…LLL → precipitate
LDDLDLL… + LLL…LLL → coacervate

Why do racemic mixtures form coacervates but homochiral mixtures from precipitates?
- Do achiral backbones prevent β-hairpins and sheets?
- How deep is the energy minima associated with forming these secondary structures?



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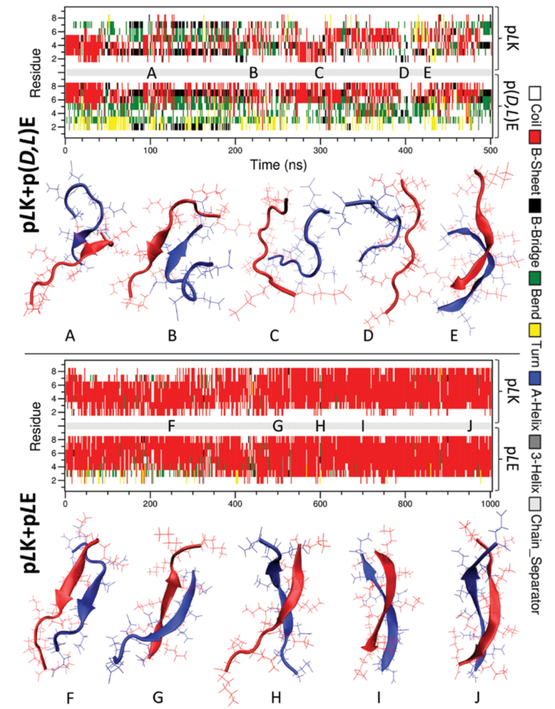
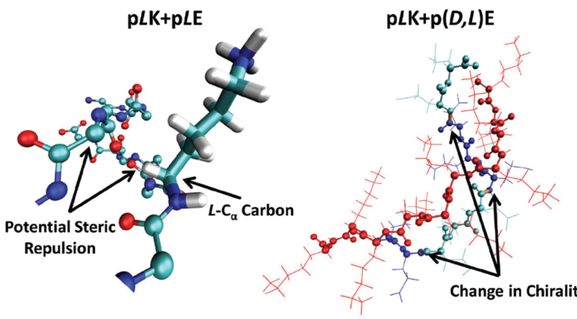
Difference in Free Energy

The order parameters needed to sample the free energy difference of peptides with D amino acids are unknown. However, we can use replica exchange solute tempering[3] to find the important structures. For this technique, several simulations are run simultaneously where the protein experiences different temperatures. The replicas can exchange allowing the proteins to travel to higher temperatures where they can more easily escape local minimum.





References

1. McGovern, M. et al. A boundary correction algorithm for metadynamics in multiple dimensions. *Journal of Chemical Physics* **139**, 084102 (2013).
2. Pietrucci, F. & Laio, A. A Collective Variable for the Efficient Exploration of Protein Beta-Sheet Structures: Application to SH3 and GB1. *Journal of Chemical Theory and Computation* **5**, 2197-2201 (2009).
3. Wang, L., Friesner, R. A. & Berne, B. J. Replica Exchange with Solute Scaling: A More Efficient Version of Replica Exchange with Solute Tempering (REST2). *J. Phys. Chem. B* **115,** 9431–9438 (2011).