CMET Seminar

UNIVERSITY OF DELAWARE

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DATE:
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TIME:
10:00 am
LOCATION:
366 CLB

David got his B.S. in Biology from the California Institute of Technology in 2009. He joined Prof. Angel Garcia's lab in 2010 as a graduate student in the Biology department at RPI. His research in the Garcia lab focuses on the use of molecular dynamics and nuclear magnetic resonance techniques to characterize the conformational ensemble of the Aβ peptides implicated in Alzheimer's disease.

"Finding Order in the Chaos: Toward a Generalized Characterization of the Ensembles of Aβ Monomers"

Amyloid β (Aβ) peptides are a primary component of fibrils and oligomers implicated in the etiology of Alzheimer's disease (AD). However, the intrinsic flexibility of these peptides has frustrated efforts to investigate the secondary and tertiary structure of Aβ monomers, whose conformational landscapes directly contribute to the kinetics and thermodynamics of Aβ aggregation. Here, *de novo* replica exchange molecular dynamics (REMD) simulations on the μs/replica timescale are used to characterize the structural ensembles of different isoforms (Aβ42, Aβ40, and M35-oxidized Aβ42) and familial AD-linked mutants (E22Δ, D23N, and E22K in Aβ40) with substantially different aggregation properties. Further, to assess the generalizability of our simulations, we compare the ensembles simulated with two different force fields (OPLS-AA/L and TIP3P, AMBER99sb-ILDN and TIP4P-Ew). Despite this fundamental change in simulation parameters, we find that these ensembles demonstrate a strong convergence in structural properties. Prominent in the C-terminus for both force fields are antiparallel β-hairpins between L17-A21, A30-L36, and V39-I41, similar to oligomer and fibril intrapeptide models, which expose these hydrophobic side chains to solvent and may serve as hotspots for self-association. In particular, antiparallel β-hairpin structure between L17-A21 and A30-L34 is prevalent in ensembles of Aβ40 in both force fields, while residues A21-A30 forms an interceding region that rarely interacts with the majority of the protein. Further, Aβ42 contributes new β-hairpin motifs involving V40-I41, regardless of force field. However, the structural flexibility of the central region and the electrostatic interactions that characterize it are notably different between the two conditions. Further, the effects of FAD-linked mutations in this region are much more subtle in the ILDN set. This said, both force fields produce ensembles that have good quantitative agreement with experimental chemical shifts and J-couplings, and yield a structural model that is consistent with the observed sensitivity of backbone chemical shifts to changes in sample pressure. Subtle differences aside, the large degree of agreement between these simulation sets across force fields provides a generalizable characterization of Aβ that is also highly consistent with experimental data and models.