Dissertation Defense - Christopher M. Siwy, PhD Bioinformatics and Computational Biology April 1,
April 16, 2021 1:00 - 3:00 PM
VIEW EVENT
All are invited to attend the defense. For more information please contact Graduate Coordinator at kharrism@gmu.edu

Candidate: Christopher M. Siwy
Program: PhD Bioinformatics and Computational Biology
Date: Friday, April 16, 2021
Time: 01:00 PM Eastern Time (US and Canada)

Place: Join Zoom Meeting
https://gmu.zoom.us/j/94582381906?pwd=dVlJUGMyNWhPQ21zeXFNTW9zYVhXQT09

Title: Molecular Dynamics Study into the Passive Transport of Amyloid-β Inhibitors Permeating the Blo od-Brain Barrier Targeting Alzheimer's Disease

Committee Chair: Dr. Dmitri K. Klimov
Committee Members: Dr. Iosif Vaisman, Dr. Amarda Shehu

ABSTRACT:
Alzheimer's disease is a progressive neurodegenerative disorder linked to gradual oligomerization and accumulation of soluble amyloid Aβfragments into diffuse plaques within the central nervous system. Clearance of Aβfragments from brain tissues proceeds through blood-brain barrier (BBB), which therefore plays a critical role in preventing aggregation of neurotoxic Aβvariants. The primary purpose of this work is to study *in silico* the structural characteristics and molecular interactions associated with the passive permeation through human BBB of Aβaggregation inhibitors, such as small drug compounds or peptides involved in transcytotic behavior. Additionally, to evaluate potential modeling artifacts this dissertation probes the force field dependence of Aβpeptides conformational ensemble. To execute this research plan, we first applied parallel tempering replica exchange (REMD) molecular dynamics simulations to compare the conformational ensembles of amino-truncated Aβ10-40 peptides using four protein parameterizations (CHARMM36, CHARMM22*, CHARMM22/cmap, and OPLS-AA) and two water models (standard and modified TIP3P). Then, using an all-atom explicit water model and replica exchange umbrella sampling (REUS) simulations, we investigated the molecular mechanisms of benzoic acid (BA) partitioning into two model lipid bilayers, a homogeneous, pure DMPC and BBBmimetic bilayers. Finally, our REUS studies evaluated the molecular mechanisms of permeation of Aβfragments, polar Aβ16-19 (KLVF) and apolar Aβ39-42 (VVIA), through BBB-mimetic bilayer.

The results of our investigations are as follows. We found that CHARMM36 force field followed by CHARMM22 produce the most accurate representation of Aβconformational ensemble. Comparative analysis of BA partitioning into the DMPC and BBB bilayers has revealed significant similarities. Partitioning into both bilayers is thermodynamically favorable, although insertion into the former lowers the BA free energy by *1 kcal/mol*. Partitioning energetics is largely similar based on the balance of BA interactions with apolar fatty acid tails, polar lipid headgroups, and water. In both bilayers BA retains residual water until reaching the bilayer midplane, where it experiences nearly complete dehydration. Upon insertion BA undergoes several rotations primarily determined by the interactions with the lipid headgroups. Nonetheless, besides the depth of free energy minimum, the BBB bilayer differs from the DMPC counterpart by a much deeper location of free energy minimum and appearance of high free energy barrier and BA positioning near the midplane. DMPC and BBB bilayers also exhibit different structural responses to BA insertion. We surmise that BBB-mimetic bilayer is preferred for accurate description of partitioning.

Our REUS simulations reconstructed the mechanism of partitioning of the two Aβfragments into the BBB-mimetic bilayer. Despite dissimilar sequences, their permeation shares common features. Computations of free energies and permeabilities show that partitioning of both peptides are highly unfavorable ruling out passive transport. The peptides experience multiple rotational transitions within the bilayer and typically cause considerable lipid disorder and bilayer thinning. Near the midplane they lose almost entirely their solvation shells and interactions with lipid headgroups. The peptides cause complex bilayer reorganization. Upon insertion they induce striking cholesterol influx reversed by its depletion and the influx of DMPC when the peptides reach the midplane. The differences in partitioning mechanisms are due to much higher polarity of KLVF peptide, the permeation of which is more unfavorable, and which exclusively assumes vertical orientations within the bilayer. In contrast, VVIA positions itself flat between the leaflets causing minor disorder and even thickening of the BBB-mimetic bilayer. Due to the high density of cholesterol-rich BBB bilayer, the unfavorable work associated with the peptide insertion provides a significant, but not dominant contribution to the partition free energy, which is still governed by dehydration and loss of peptide-headgroup interactions. Comparison with experiments indicates that KLVF and VVIA permeation is similar to that of proline tetrapeptide, mannitol or cimetidine, all of which exhibit no passive transport. Taken together, this dissertation demonstrates that molecular dynamics has become a valuable research tool for exploring the molecular mechanisms of permeation through cellular membranes.