Subject: Dissertation Defense - Bryan M. Delfing, PhD Bioinformatics & Computational Biology
Date: Tuesday, April 9, 2024 at 10:20:06 AM Eastern Daylight Time
From: SSB Faculty List on behalf of Diane St. Germain
To: SSB-FACULTY-LIST-L@LISTSERV.GMU.EDU

Dissertation Defense Announcement
To: The George Mason University Community

Candidate: Bryan M. Delfing

Program: PhD Bioinformatics & Computational Biology

Date: Tuesday April 23, 2024

Time: 3:00 PM Eastern Time (US and Canada)

Location: Via Zoom

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Committee chair: Dr. Dmitri Klimov
Committee members: Dr. Iosif Vaisman, Dr. M. Saleet Jafri, Dr. Kylene Kehn-Hall
Title: "Predicting the Effects of Chemical Modifications in Biomolecules on Their Binding Affinities Using All-Atom Molecular Dynamics"

Abstract:

Although Venezuelan Equine Encephalitis Virus (VEEV) is a life-threatening pathogen with potential for epidemic outbreaks, it lacks an FDA-approved antiviral for human treatment. This dissertation studies the binding of VEEV's capsid protein nuclear localization signal (NLS) fragments to nuclear transport importin-α protein and analyze the effectiveness of the inhibitors against the virus. These goals were accomplished by probing atomistic binding using Replica Exchange Molecular Dynamics with solute tempering (REST). Overall, our investigation included three studies. In the first, we examined the binding of three inhibitors, G281-1485 (I0), as well as its congeners (I1 and I2), to the major NLS binding site of importin-α. We saw that I0 did not form a well-defined binding pose, binding diffusively to importin-α. I1

also formed distributed biding poses, but all of them were confined to the VEEV NLS binding site on importin-α (an “on-target” binding). Finally, I2 bound via a well-defined binding pose that only partially overlapped the NLS binding site (an “off-target” binding). In the second study, we explored the binding of NLS peptide fragments, the minNLS KKPK, and the coreNLS KKPKKE, to the major NLS binding site. We saw that the minNLS exhibited a diverse ensemble of non-native poses, while the coreNLS had a high probability of adopting a native-like pose. We also showed that the coreNLS sequence is absent among human proteins involved in nuclear traffic. Our final study combines elements of the first two to perform competitive binding simulations of I1 or I2 alongside the coreNLS. We found that both inhibitors severely disrupted the peptide’s native binding pose. The abrogation of native pose is largely due to masking of the coreNLS residues, rather than caused by specific interactions between the inhibitors and importin-α. These results were supported through the free energies computations that showed both inhibitors reducing the free energy gain from coreNLS binding. Our finding that I1 is a stronger inhibitor than I2 agrees with the experimental evaluations of their IC50 values. Through these results, we hypothesize that I1 and I2 may exhibit inhibitory action that is specific to the NLS of VEEV’s capsid.

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