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NORTH CAROLINA AGRICULTURAL AND TECHNICAL STATE UNIVERSITY

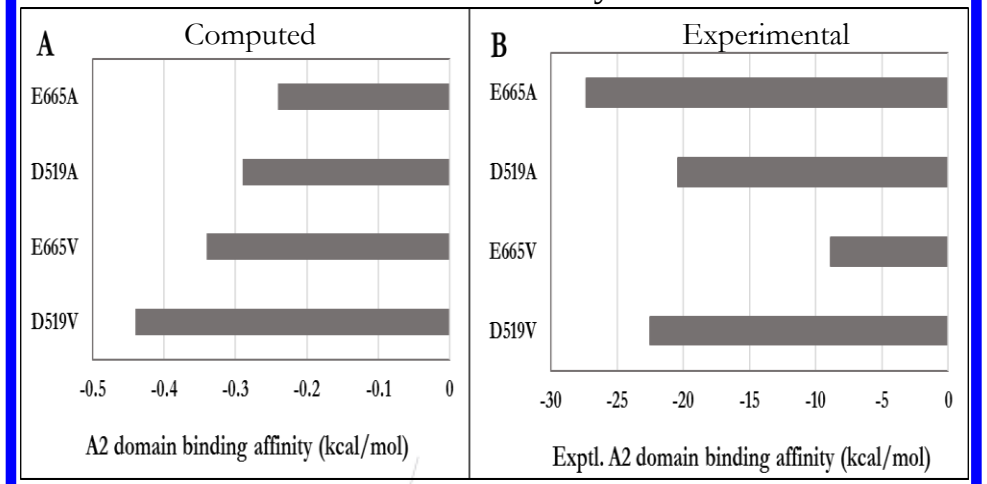
Shenna Marie Shearin

Computational Science and Engineering

Title: *"Computational Investigation of the Structure, Stability, and Function of Human Blood Coagulation Factor VIIIa"*

Major Professor: *Dr. Divi Venkateswarlu*

Benchmark study



RESEARCH QUESTIONS / PROBLEMS:

- Can we use the solvent-explicit Molecular Dynamics (MD) based Molecular Mechanics Poisson Boltzmann Surface Area (MM-PBSA) method as a reasonably accurate approach for reproducing experimental activity decay rates? If so, is this method accurate enough in reproducing mutational binding free energy data for protein-protein interactions (PPI)?

METHODS:

- *In-silico* based mutagenesis and solvent-explicit MD based MM-PBSA methods were employed to assess the binding affinity and structural stability of each hydrophobic mutation.

RESULTS / FINDINGS:

- We were able to mutate 9 polar/charged residues (S268, R282, A284, S285, E287, D519 Q645, T646, E665) to hydrophobic ones to test the binding affinity and mutational outcome based on MM-PBSA method.
- E287, D519, E665, Q645 residues are predicted to be promising hotspot residues for structural modification and may be considered for testing in recombinant FVIIIa variants for improving the binding affinity of the A2 domain and overall stability of FVIIIa.

SIGNIFICANCE / IMPLICATIONS:

- Solvent explicit MD based MM-PBSA is reliable for reproducing similar qualitative trends for experimental activity decay data and is therefore accurate enough to predict the mutational binding free energy for PPI. This research provides insight that could lead to genetic engineering of better, more desirable therapeutic drugs for Hemophilia patients.