Dissecting von Willebrand Factor Subdomain Dynamics in Hyperglycemia Using Molecular Simulations

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Introduction

Global diabetes cases are expected to reach 693 million by 2045 [1]. von Willebrand factor (VWF) is a crucial glycoprotein for platelet adhesion and coagulation. Hyperglycemia alters the solvent quality of blood, which may affect the shear-activation threshold of VWF, impairing hemostasis and cause bleeding disorders.

VWF operates as a multimer, where the A1 and A2 domains are essential for platelet adhesion and shear-induced unfolding, respectively [4]. We hypothesize hyperglycemia can inhibit these domain functions, altering VWF activity.

To test this hypothesis, we model VWF subdomain dynamics using all-atomistic molecular dynamics, including explicit solvent-particle intermolecular interactions.

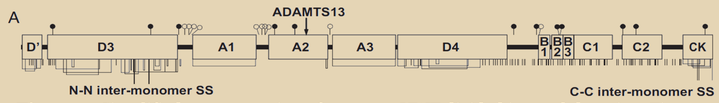


Figure 1. Simplified representation of a mature VWF divided into subdomains. Figure borrowed from reference [11]

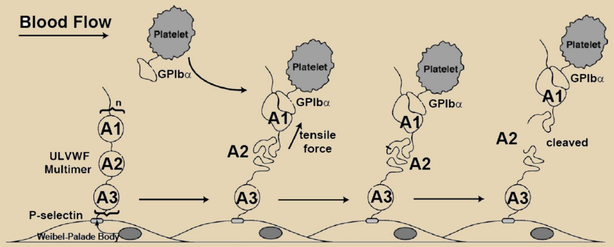


Figure 2. Molecular dynamics simulations of binding, unfolding, and global conformational changes of signaling and adhesion molecules. Figure borrowed from reference [2]

Methods

Computational Framework

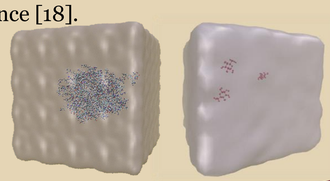
Explicit water, VWF A1 domain solvation, and glucose solution MD simulations were conducted using LAMMPS [6, 17, 19].

Intermolecular Potential Modification

CHARMM36M [20] was applied to VWF and glucose, paired with the TIP3P water model. TIP3P was selected as it is parameterized for compatibility with CHARMM force fields, ensuring accurate solvent-protein interactions.

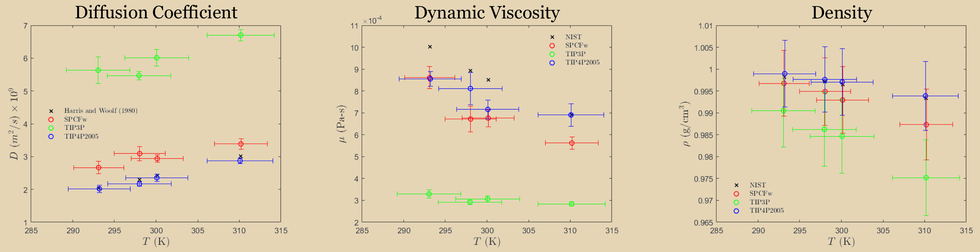
System Setup & Parameters

All-atomistic glucose and VWF molecules were placed in water using reference [18]. VWF verification was solvated and neutralized with NaCl ions in TIP3P water. Glucose validation was performed with three molecules in deionized TIP3P water. CHARMM36M, and TIP3P parameters came from reference [18].

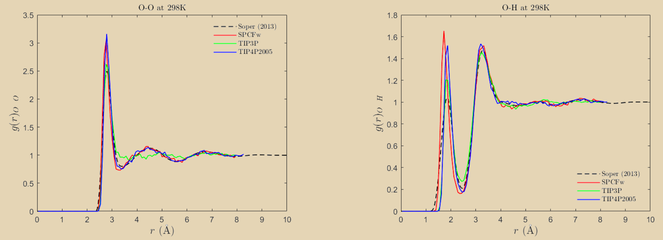


Data & Results

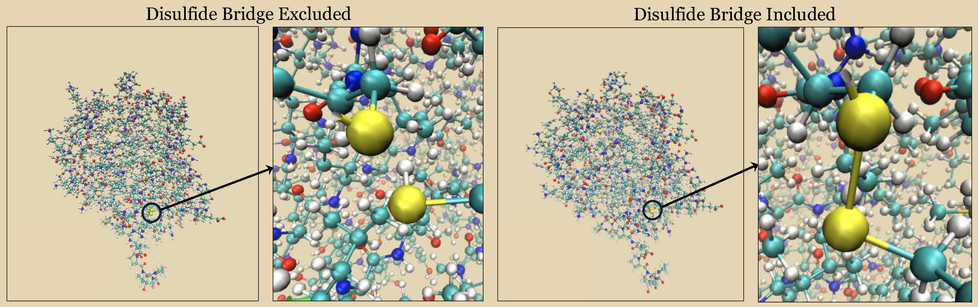
Water Validation



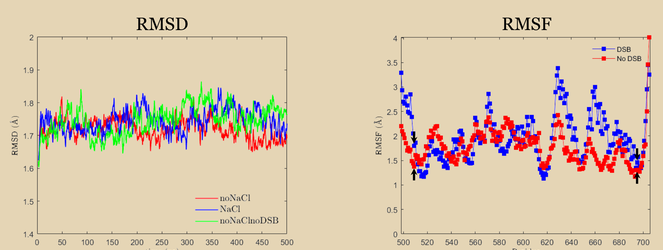
Radial Distribution Functions



VWF Protein Structure



VWF Protein Verification



Water and VWF A1 domain simulations were conducted via LAMMPS and visualized via MATLAB and VMD, respectively. Two versions of the protein were modeled with and without the disulfide bridge (images shown above). Black circles indicate the broken or bonded disulfide bridge. RMSD data collected from the equilibration runs indicate that simulations are viable for production runs. Black arrows indicate the 509 and 695 cysteine residues.

Conclusions

The TIP3P model was used for simulating VWF protein in water. Although there are more accurate water models such as TIP4P/2005, TIP3P is parameterized for CHARMM forcefield compatibility.

Simulations modeling the A1 domain of the VWF protein were completed with and without the disulfide bridge. Collective variables [15] were used to calculate RMSD data for the equilibration phase. A plateau in the RMSD graph suggests that the simulation reached equilibration and was viable for production runs.

RMSF data was collected using VMD. The graph represents the RMSF of each alpha-Carbon atom in the protein averaged over the entire equilibration run. Slight differences in RMSF data fluctuations were observed in the A1 domain when including and excluding the disulfide bridge.

Although the simulations were equilibrated, the VWF A1 domain and glucose simulations require further verification and validation, respectively, before drawing any significant conclusions.

Future Directions

- Extensive VWF verification and glucose validation
- Combine verified VWF A1 domain and validated glucose to explore dynamics under fluctuating glucose levels
- Parameterize the LJ 12-6 framework for use in an LB-LD model with implicit potentials for more accurate mesoscale VWF representation in hyperglycemic conditions

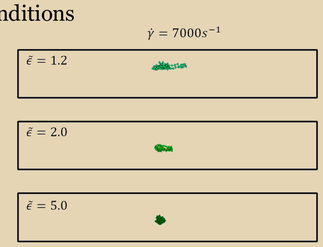


Figure 3. APS Presentation. Figured borrowed from reference [16]

References