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Predicting Domain Scale Mechano-reactivity in Human Blood Proteins via Coupled Machine Learning and Molecular Simulation.

Abstract: The von Willebrand Factor (vWF) is a blood protein that initiates clotting in humans and whose proper functioning is critical to human cardiovascular health. Approximately 2% of the world population suffer from some form of bleeding disorder associated with dysfunctional vWF. These macromolecules are essentially flow sensors in that, at lower shear rate conditions associated with healthy blood flow, vWF proteins adopt a compact conformation; however, when exposed to higher shear rate conditions near vascular injury, vWF molecules elongate and reveal sites all along the molecule to which binding of platelets in the blood and collagen exposed on injured blood vessel surfaces can occur. In this way, individual vWF proteins bind to multiple blood entities and initiate clotting. Inherent to the functionality of vWF is a reactivity that is somehow mediated by mechanical forces to which the protein is subject on the sub-monomer, domain scale. These forces are related to the overall protein conformation but that relationship is largely unknown. Results will be presented demonstrating the use of data from coarse-grain molecular simulations to train a Random Forest Algorithm (RFA) for predicting the reactivity of sub-monomer domains based on the protein conformation. The most pertinent data features in establishing highly accurate predictions will be discussed and considered in terms of their relationship (or lack thereof) to established polymer physics of macromolecule dynamics. Application of the RFA to results from microfluidic chamber-based experiments will be briefly discussed.