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Flow-induced conformational change of von Willebrand Factor multimer: Results from a molecular mechanics informed model

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ABSTRACT

The von Willebrand Factor (vWF) is a large multimeric protein that aids in blood clotting. Hydrodynamic forces trigger conformational changes of vWF that regulate its binding to clotting agents in the blood. A coarse grain molecular model is proposed for the vWF multimer that incorporates observed mechanical properties of vWF monomers. Each monomer is represented by a finitely extensible nonlinear elastic (FENE) spring connecting two beads. The FENE spring represents the A2 domain in the central region of vWF monomers and it permits extensive elongation to mimic domain unfolding. The beads at each end of the FENE spring represent relatively rigid domains adjacent to A2 in vWF monomers. The spring constant and maximum extended length of the FENE spring are optimized to reproduce force-extension experimental data for the A2 domain in vWF monomers. Multimers in the model are formed by connecting beads on adjacent monomers via a stiff harmonic spring. The bead–bead interaction parameters are optimized to reproduce observed packing of vWF globules in poor solvent at zero flow experimental conditions. Brownian dynamics simulations using this model are performed to understand vWF multimer response to shear flow in both free-draining (FD) and hydrodynamic interactions (HI) cases. Results from the new model are in excellent agreement with available experimental data as well as previous coarse grain modeling predictions for vWF response to shear flow. Unique to this work, the conformation of the model A2 domains (i.e. the FENE springs) are examined in response to flow. For dimensionless Wiessenberg number $Wi < 10$, model A2 domains are fully coiled and this shows no dependence on the number of monomers in the molecule N. For $Wi > 10$, the model A2 domain size increases with increasing shear rate and this effect is greater for smaller N. This N dependence is opposite to what is observed for the conformation of the vWF multimer, where the increase in molecular extension with shear rate is more pronounced for larger N. The inverse N dependence for model A2 domain response to increasing flow is due to greater overall molecular alignment with the flow direction for larger N; increased molecular alignment manifests forces that cause less intra-monomer elongation. Fluctuations in model A2 domains were shown to increase significantly at high flow, including periodic complete extension of the domain.

1. Introduction

In human bodies, bleeding is stopped by forming a clot at the site of vascular damage. Crucial in the process is the aggregation of platelets at the damaged vessel wall, forming platelet "plugs". Under rapid flow conditions such as in arteries and arterioles, however, platelets cannot adhere to vessel walls due to the strong hydrodynamic force imposed by the flowing fluid. In such scenarios the plasma protein von Willebrand Factor (vWF) plays an indispensable role in sticking to both platelets and collagen on damaged vessel walls, allowing the formation of platelet plugs.

vWF is a very large plasma protein that can be stretched by shear flow and extended to tens of microns. After synthesis and removal of the signal peptide, pro-vWF subunits associate in the endoplasmic reticulum in "tail-to-tail" dimers by the formation of disulfide bonds between CK domains. Following this, dimers further polymerize by forming "head-to-head" disulfide bonds between the amino-terminal cysteine-rich D3 domains before secretion (Fig. 1(A)). With such significant length, multimeric vWF carries many binding sites for platelets and collagen, and experiences non-trivial hydrodynamic forces in the circulating

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system. It has been reported that vWF has force-sensing capability: the protein adopts a compact shape in normal circulatory status where shear rates range from hundreds to a few thousand per second. For shear rates greater than 5000 s^{-1}, vWF changes conformation to an elongated shape, increasing its interaction with platelets and collagen (Fig. 1(C)) [1]. Proper functioning of vWF is critical to human health; at least two human diseases are related to the conformational states of vWF. Type 2 von Willebrand Disease (vWD), a commonly seen coagulation abnormality, is caused by genetically mutated and structurally abnormal multimeric vWF. Thrombotic thrombocytopenic purpura (TTP), another hereditary blood disorder caused by vWF multimer dysfunctionality, causes thrombus formation and blood clots throughout the body [2,3]. Thus, great potential for benefit to human welfare can be had by developing intimate understanding of the mechanisms by which biopolymers like vWF achieve flow sensitivity.

Many studies have used coarse grain molecular models to understand macromolecule behavior, including specific mechanisms by which vWF senses flow. These models typically employ some form of bead-spring description of the biopolymer. In such models, a single bead may represent a monomer or part of a monomer and adjacent beads in a polymer are connected by finitely extensible non-linear elastic (FENE) springs [4]. Beads, including those not connected by springs, typically interact via a pair potential such as the Lennard-Jones. Instead of springs, one can utilize a pair potential description between bound beads where the bound interaction is much stronger than the un-bound bead–bead pair potential. Such an approach is useful if molecular scission is relevant to the phenomenon being modeled. This approach was described as the potential model (PM) in a recent review [5]. An alternate method for defining binding between beads was described as the reactive model (RM) and, in such descriptions, bonds between beads are formed and broken stochastically based on proximity and parameterized binding and unbinding energies. This latter approach is particularly appealing for describing binding between vWF and relevant biological species, like platelets and tissue walls. For both PM and RM approaches, it is typical practice to parameterize the model such that, at zero and low flow conditions, molecules assume compact globule conformations in accord with being in poor solvent conditions.

Alexander-Katz and his coworkers [6,7] used PM methods to investigate the unfolding phenomenon of polymers under the influence of both shear flow and elongational flow. They found unfolding is regulated very strongly by elongational flow fields, compared to shear flow. Schneider et al. [8] utilized the same kind of model in their simulations. They observed flow-induced conformation changes both in experiments and simulations, and concluded there is a critical shear rate to unfold vWF in bulk, which triggers surface adsorption in the presence of a collagen substrate. A reactive model approach was used by Sing and Alexander-katz to investigate the force-extension behavior of self-associating homopolymers [9]. They utilized the same RM technique as implemented in the Bell model to describe the interaction between A3 domains on vWF multimers and collagen. Using this method, they were able to study vWF adsorbing and immobilizing platelets at sites of injury under high-shear-rate conditions [10]. Those results showed the expected shear-induced adsorption behavior and the adhesion rate quantitatively matched experimental observations. Other important simulation work was done by Ibáñez-García et al. [11]. They studied the effect of attractive surfaces on the stretching of confined tethered polymers under shear flow and found that adsorption is enhanced by the shear flow strength; this was in agreement with simulations of adsorbed non-tethered polymers. Results described here provide a sampling of work already present in the literature. It is obvious that distinct benefit can be had from applying molecular simulation to the study of flow sensitive biopolymers and that much has been learned about underlying mechanisms dictating molecular response to flow.

Descriptions of vWF such as the one at the start of this introduction are a result of a large body of experimental work that has been performed investigating the structure and functionality of the protein. The recent review by Alexander-Katz provided a distinction of blood clotting stages based on the role played by vWF; in particular, stages were distinguished based on when vWF exhibits different types of what can be considered highly sought-after molecular behavior [5]. This naturally motivates consideration of different architectural length scales for vWF. The overall molecule, in an unraveled state where repeat units can be envisioned to roughly line up, can span tens of microns. This scale is associated with molecular function in the sense that vWF proteins must have at least ten repeat units to express blood clotting functionality. At a smaller length scale of order tens to one hundred nanometers are the individual repeat units; these monomers consist of a collection of folded domains, each with a specific chemical binding affinity. Collectively, these domains help unraveled vWF molecules execute necessary binding to platelets and tissue walls (as well as many other complex biochemical reactions). Thus, when considering the mechanical response of vWF, two scales of unfolding must be

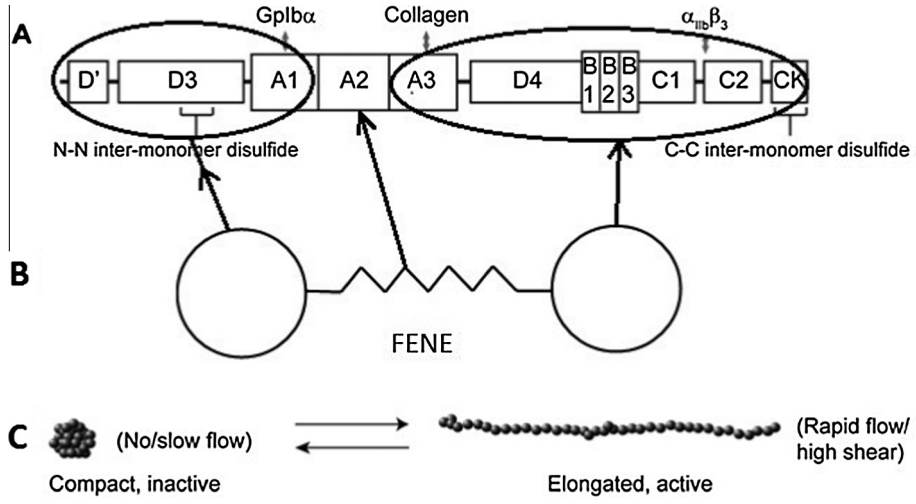

Fig. 1. (A) Schematic illustration of vWF's domains. (B) The vWF monomer model containing two rigid beads connected by a highly flexible FENE spring. (C) Possible mechanism of flow-induced conformational change.