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Large-scale molecular dynamics simulation of flow under complex structure of endothelial glycocalyx

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ABSTRACT

In this research, large-scale molecular dynamics (MD) simulations were conducted to study the fluid dynamics inside the endothelial glycocalyx layer. A work flowchart regarding constructing the flow/glycocalyx system, undertaking production simulation using the MD method and post-processing was proposed. Following the flowchart, physiological and accelerating flow cases were simulated to reveal velocity and shear stress distributions over the dendritic (tree-like) structure of the glycocalyx, thereby contributing to understanding of the influence of biomolecular complex structures on flow profiles. Besides, the selection of thermostat algorithm was discussed. Results have shown that when the forcing is below a critical value, the velocity fluctuates around a zero mean along the height in the presence of the dendritic glycocalyx. When the forcing is larger than a critical value, the bulk flow was accelerated excessively, departing from the typical physiological flow. Furthermore, distributions of shear stress magnitude among three sub-regions in the ectodomain indicate that shear stress is enhanced near the membrane surface but is impaired in the sugar-chain-rich region due to the flow regulation by sugar chains. Finally, comparisons of velocity evolutions under two widely used thermostats (Lowe-Andersen and Berendsen thermostats) imply that the Lowe-Andersen algorithm is a suitable thermostat for flow problems.

1. Introduction

Human metabolism requires exchange of materials between circulating blood and tissues. The material exchange occurs across a thin layer of endothelial cells located in the luminal surface of the blood vessels, known as the endothelium. The endothelium cells line the entire vascular network, from the wide heart arteries to the smallest capillaries [1]. The glycocalyx, a network of membrane-bound proteoglycans and glycoproteins, is located on the apical surface of vascular endothelial cells and is the first barrier in direct contact with blood [2]. The endothelial glycocalyx layer is related to many cardiovascular and renal diseases or illness, such as diabetes [3], ischemia/reperfusion [4], and atherosclerosis [5].

Electron micrograph of endothelium shows that the endothelial glycocalyx features its dendritic (tree-like) structure [6,7] and is exposed to the blood flow. To better understand the pathologies of glycocalyx-related cardiovascular diseases, the flow profile under the dendritic structure of the glycocalyx should be resolved. However, few firm conclusions about flow profiles in the presence of complex structures can be obtained from classic fluid mechanics and experiments. Therefore, researchers turn to computational methods for new insights.

One of the most powerful computational *in silico* techniques is molecular dynamics (MD) simulation, which can provide the trajectories of all atoms by solving Newton's Second Law of Motion. Although MD simulations have contributed to contemporary understanding of the glycocalyx, the lack of structural information of the glycocalyx has impeded the field for a long period. Not until recently was the most detailed structural information of the glycocalyx [8] published, which provides the feasibility to thoroughly study the flow structures in the presence of the complex configurations of the glycocalyx.

In this research, large-scale molecular dynamics simulations will be conducted to study the flow profile under the dendritic structure of the endothelial glycocalyx. Work flowchart regarding procedure of establishing flow/glycocalyx system, conducting simulations using the MD method and post-processing will be first proposed. Following the flowchart, physiological and accelerating flow cases will be undertaken to provide new insights into the influence of biomolecular structural configurations on flow profiles. Finally, selection of thermostat algorithm will be discussed.

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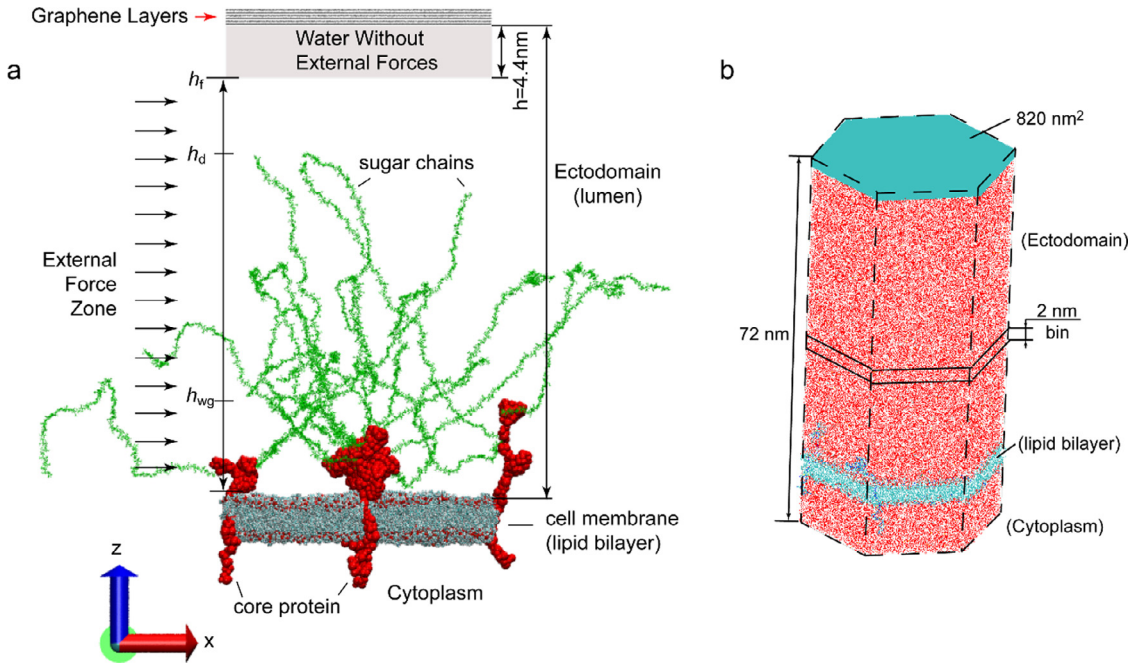

Fig. 1. Initial configuration of the all-atom glycocalyx-flow system and perspective view of the simulation box. (a) Initial configuration. The system includes 3 Syn-4 dimers as proteoglycan, 18 sugar chains attached on the apexes of Syn-4 dimers and a lipid bilayer. External forces are imposed in the x direction on the water molecules in the ectodomain. Water molecules and ions are not shown. Graphene layers are added at the top to prevent the water molecules propagating from ectodomain to the cytoplasm due to the periodic boundary conditions. In Panel a, h_{wg}, h_d and h_f represent the heights of near wall region, dendritic region and flow region, respectively. (b) Perspective view of the simulation box. An illustration of a bin used for post-processing is also provided.

For the first time, the flow and glycocalyx interactions are studied under both typical physiological and accelerating (like in a disease situation) flow situations. This research will contribute to the study of fluid mechanics by unveiling the flow behaviour in the presence of complex boundaries with moving soft structures. It also contributes to biomedical research through a better understanding of flow under normal and diseased situations that would affect the function of glycocalyx, potentially leading to therapeutic strategies for glycocalyx-related cardiovascular diseases.

2. Methods

2.1. System construction

The current most detailed structure of glycocalyx [8] has been adopted to build the flow/glycocalyx system [9]. In the system, Syndecan-4 (Syn-4) proteoglycan and heparin sulfate (HS) sugar chains are selected to model the glycocalyx. The glycocalyx structure can be divided into three parts: Syn-4 ectodomain linked with sugar chains; Syn-4 transmembrane dimer embedded into a lipid bilayer; and Syn-4 cytoplasmic dimer.

The initial configuration of the glycocalyx-flow system is illustrated in Fig. 1a. The whole space is divided into two compartments by the lipid bilayer. Above the lipid bilayer is the ectodomain, representing the lumen where flow passes by. This region contains HS sugar chains, Syn-4 ectodomain in connection with HS sugar chains, water molecules and ions. Below the lipid bilayer is the cytoplasm, representing the inner space of the cell, which is filled with Syn-4 cytoplasmic protein, water molecules and ions. All the biomolecules are solvated and ionized to 0.1 M NaCl aqueous solution. In the follow-on simulations, the periodic boundary conditions are applied to all the three directions. The application of the boundary conditions would cause water molecules to propagate from the upper boundary of the ectodomain to the lower boundary of the cytoplasm, and vice versa. This propagation would disturb the micro environment of the ectodomain and the cytoplasm. Thus, to prevent the disturbance, fixed graphene layers are added on the top of ectodomain. This practice has also been adopted in Cruz-Chu's study [8].

In the system, three proteoglycans which individually consist of one Syn-4 dimer are embedded in the lipid bilayer. Each proteoglycan has six sugar chains attached on the dimer apexes. To mimic flow, external forces are imposed on the water molecules in the ectodomain. The simulation box is a hexagonal prism with an area of 820 nm^2 and height of 72 nm (Fig. 1b). The glycocalyx-flow system comprises 5,800,000 atoms in total.

2.2. Work flow

A typical work flow to study flow problems using MD simulations can be divided into three procedures, as illustrated in Fig. 2. Equilibrium should be first reached to ensure structural stability of the biomolecules, before flow simulations are conducted. External forces are then imposed to water oxygens in the ectodomain to mimic the blood flow in the lumen. The order of physiological values of velocities for endothelial glycocalyx layers is expected to be mm/s to cm/s [10]. Thus, to generate physiological velocity, iterations of forces are required. When the time-evolution of the resulting bulk flow velocities is in physiological ranges, post-processing including the distributions of velocities and shear stresses is conducted for further data analysis. The packages or platforms involved in the flowchart for this research are also listed in Fig. 2.

2.3. Protocol details

The TIP3P water model [11] was adopted to simulate water molecules. A CHARMM biomolecular force field [12] was applied on the proteins and the lipid bilayer. Force field parameters for sugar chains and graphene layers were adopted from a previous study [8].

In accordance with the work flow in Fig. 2, an equilibrium simulation with graphene layers being fixed was conducted at con-

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