PASSAGE OF A DDS NANO-PARTICLE THROUGH THE CLEFT OF CAPILLARY WALL WITH GLYCO-CHAINS

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Summary
A novel drug delivery system (DDS) such as using a biomimetic carrier is awaited the practical use. In particular, the transportation of DDS nano-particles through the cleft of blood capillary wall is of crucial importance in understanding its fundamental aspects and in developing the application technique. In this paper, we shall present numerical calculations in the following two cases: (i) the particle is deformable but the wall is rigid, and (ii) the particle is rigid but the wall is covered by deformable glycocalyx.

BACKGROUND

The drug transportation only to the body part affected by illness is very important to increase the drug efficacy and to reduce adverse drug reactions. Biomimetic drug delivery carrier is one of the expectations awaited the practical use. The development of such drug delivery system (DDS) presents a multi-scale and multi-physics problem which consists of (a) the design of the DDS nano-particles (the complex of the liposome and the ligand) which incorporate a drug molecule, (b) the molecular design of the ligand which recognizes the receptors in the capillary wall near the diseased part, and (c) the design of the transport process of the DDS nano-particles in the blood vessel. In recent years, Yamazaki *et al.*[1] have made a drug delivery carrier of a liposome, the surface of which is coated with the same cell-surface marker molecules as a leukocyte (i.e., white blood cell) to mimic the behavior of the leukocyte in an inflammatory process. Such a liposome is expected to be transported with the blood flow, finally reach the capillary tube, then transmigrate from the lumen to the extravascular tissue through the cleft of capillary wall. On the other hand, anatomical findings reveal that the wall is covered not only with the receptors but also with glycocalyx bushes.[2] A glycocalyx bush is a layer of membrane-bound macromolecules such as proteoglycans and glycoproteins, the so-called glyco-chains. Nieuwdorp *et al.*[3] revealed that the glycocalyx is likely to serve as barrier against the passage of a leukocyte through the cleft of the wall when the dimension of the glycocalyx exceeds that of the receptors. A lot of hydrodynamical studies on the transport of particles through the glycocalyx layer have already been made for the past decade.[4, 5, 6] But the *local* interaction of the leukocytes and/or liposomes with the glyco-chains near the cleft of the capillary wall, which can be decisive to the transmigrations, has to our knowledge not been studied from the view point of the hydrodynamics. In this paper, we shall present fundamental aspects to transport DDS nano-particles in blood capillary.

METHOD OF CALCULATION

We deal with the motion of a liposome of the size about 100 nm, in a capillary blood flow of order 0.01 cm/s, so that the Stokes approximation is relevant.

(i) Passage of a droplet under shear flow and suction

In the first part, we simulate the motion of an initially spherical drop of radius $a(= d/2)$ and viscosity μ' in a viscous fluid of viscosity μ (viscosity ratio λ being defined as μ'/μ). The drop is placed in the shear flow (shear rate $\dot{\gamma}$) along the wall with a cleft of width $2w$, from which a given amount of fluid is sucked with pressure gradient p_y. The translational velocity of the droplet is determined by the fluid mechanical force, whereas the shape of the drop is determined self-consistently by taking into account the surface tension σ and the flow field under given boundary conditions. In analyzing these processes, we employ an integral representation of the Stokes equation that involves the boundary values of the velocity and surface force over the relevant boundary.[7] The numerical approach we adopted was the boundary element method (BEM).

(ii) Passage of a sphere through a cleft of endothelial cells with glyco-chains

In the second part, the liposome is assumed to be a rigid sphere and we simulate the hydrodynamic interaction in terms of the beads model. We employ the Cartesian coordinate system, where the 6 larger rigid spherical beads representing the cells are arranged in the xy plane encircling the cleft, and the z axis is taken along the center of the cleft. Each glyco-chain is described by the 12 beads arranged in line, whose *base* bead is attached to the cell bead. The angle between the line elements connecting neighboring beads of the chain is allowed to change by the exerted fluid mechanical force. The motion of the sphere that is driven by a constant force is simulated.

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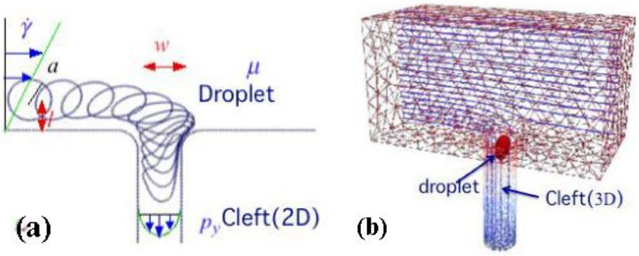

Figure 1. Passage of a droplet under shear flow and suction.

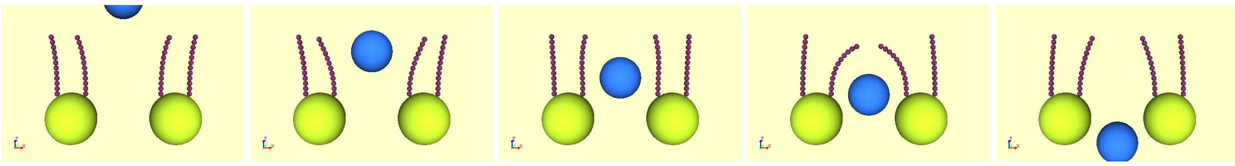

Figure 2. Passage of a sphere through a cleft of endothelial cells with glyco-chains.

RESULTS

(i) Passage of a droplet under shear flow and suction

We show an example of motion and deformation of a drop in Fig.1(a). Similar calculation for three-dimensional configuration is also given in Fig.1(b). We found that the suction of the droplets into the cleft region is expected when

$$\tilde{\alpha} = \frac{w^{D+2} p_y}{\mu \dot{\gamma} l^{D+1}} > C,$$

where l is the distance of the particle from the wall, D is the dimension of the system and C is a certain constant. Roughly speaking, $\tilde{\alpha}$ characterizes the ratio of the Poiseuille flow (or sink flow) to the shear flow. The relative importance of the surface tension is given by the normalized surface tension $\tilde{\sigma} \equiv \sigma/(\mu\dot{\gamma}a)$, whereas the relative importance of the suction flow is given by $\tilde{p} \equiv p_y a/(\mu\dot{\gamma})$.

(ii) Passage of a sphere through a cleft of endothelial cells with glyco-chains

Figure 2 shows the time evolution of the beads captured in the xz plane. In our previous paper[8], where the chains are assumed rigid, we found that the influence of the inner chains of the glycocalyx to the velocity of the rigid sphere is dominant over that of the outer ones. A qualitatively similar tendency is confirmed in the present calculation. The magnitude of the velocity of the sphere decreases much more in the vicinity of the cleft than the case without glycocalyx.

CONCLUSIONS

We have examined the fundamental process of the passage of a DDS particle through the cleft of the capillary wall. In the first part, we found that the passage of the droplet through the cleft is greatly enhanced by increasing the cleft width or decreasing the distance from the wall, and the dependence is w^4/l^3 or w^5/l^4 for two-dimensional or three-dimensional cleft, respectively. The dependence on w agrees with the enhanced permeation and retention (EPR) effect, which is qualitatively known in physiology. In the second part, we proposed a bending glyco-chain model and found that the passage of the rigid sphere through the cleft is greatly affected by the existence of the glyco-chains. Whether the glycocalyx prevents or enhances the passage of a liposome should be verified through further physiological evidences.

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