Breakup of shear activated nano-therapeutics in a microfluidic device by a CFD - Stokesian Dynamics approach

BREAKUP OF SHEAR ACTIVATED NANO-THERAPEUTICS IN A MICROFLUIDIC DEVICE BY A CFD-STOKESIAN DYNAMICS APPROACH

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Summary The treatment of arterial obstructions can be strongly improved by the development of drug carriers with a highly localized action. Our research focuses on the investigation of Shear Activated Nano-Therapeutics, a novel class of drug carriers consisting in aggregates of nanoparticles, which are locally activated by the breakup induced by the viscous stress acting on them as they travel in obstructed blood vessels. We adopted a coupled Computational Fluid Dynamics - Stokesian Dynamics technique able to compute the history of the viscous shear forces experienced by the aggregates and to study the dynamics of breakup. We investigate the behaviour of different potential morphologies of the aggregates, in order to identify the most suitable for such a delivery strategy and to identify the critical structural properties to be taken into account when designing such carriers.

INTRODUCTION

Arterial obstructions represent one of the main causes of disease and death worldwide [1]. When treating this disease, the dose of active agent that can be administered to the patient has to be carefully chosen in order to limit the potential adverse effects due to the free circulation of the drug in the blood stream. For this reason, targeted drug delivery techniques have received considerable attention over the last years. One of the most promising delivery strategy is based on the observation that in obstructed blood vessel abnormally large shear stress are present. This feature of the hemodynamic condition has therefore pushed research towards the development of Shear Activated Nano-Therapeutic (SANT) particles [2]. SANTs are micro-metric agglomerates of polymeric primary nanoparticles on which a clot-lysing drug is deposited. As the nanoparticles are held together mainly through relatively weak Van-der-Waals forces, SANTs can be engineered in such a way that they break up into smaller fragments when they enter a high shear zone; these fragments, because of their smaller size, experience lower hydrodynamic drag forces, thus they are more likely to adhere to the obstruction and to perform their clot-lysing action.

In this work we use a coupled Computational Fluid Dynamics - Stokesian Dynamics approach able to investigate the breakup dynamics of aggregates of primary particles [3, 4]. We tested our method on a microfluidic device designed in such a way as to mimic a pathological vessel obstruction. CFD simulations are performed to compute the flow field in the device and to extract a set of particle trajectories including the history of experienced shear stresses. Stokesian Dynamics simulations are instead carried out to compute the distribution of mechanical stress inside the aggregate structure, from which the occurrence of breakup can be predicted. We investigate different potential SANTs morphologies by comparing them in terms of conditions for the onset of breakup and size distribution of the generated fragments.

METHODS

Computational Fluid Dynamics

We used ANSYS Fluent 19.2 to simulate the flow field of a Newtonian fluid with viscosity $\mu = 1 \times 10^{-3}\,\mathrm{Pa \cdot s}$ flowing in a rectangular microchannel. The presence of the clot is modelled by introducing a 90% lumen obstruction. The domain is divided in 10^5 hexahedrical cells (left panel in Figure 1). The flow rate is adjusted in order to obtain the typical values of shear stress in a blood vessel (10 Pa in the unrestricted vessel and 100 Pa in the obstructed vessel).

The computed flow field is used to extract the trajectories of a set of 1000 aggregates. Being their Stokes and Reynolds numbers much lower than the unity, the aggregates can be treated as tracer particles, i.e. massless particles with negligible inertia; their equation of motion therefore reads as:

$$\dot{\mathbf{x}}_\mathbf{p}(t) = \mathbf{u}(\mathbf{x}_\mathbf{p}(t)) \tag{1}$$

where $\dot{\mathbf{x}}_\mathbf{p}(t)$ is the velocity of the particle and $\mathbf{u}(\mathbf{x}_\mathbf{p}(t))$ is the velocity of the flow at the particle position.

Stokesian Dynamics

In Stokesian Dynamics (SD) simulation, the morphology of the aggregates is taken into full account. This technique, by using a first order approximation of the flow field, allows one to evaluate the hydrodynamic forces acting on each primary particle composing the aggregate and, based on these, to evaluate the normal stress acting at each inter-particle contact [4]. In order to identify the most suitable morphology for our delivery strategy, three classes of clusters characterized by different shape and porosity are studied; we analyze the behaviour of aggregates obtained by a diffusion limited aggregation (DLCA), Random Close Packing aggregates (RCP) and hollow RCP aggregates. In order to get statistically robust results, for every class we studied 100 aggregate realizations. Therefore, a statistical analysis has been conducted in order to count for the variety of aggregate morphologies and aggregate trajectories.

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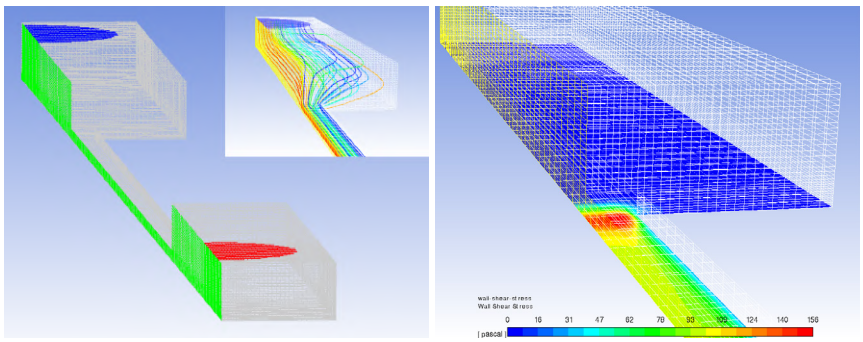

Figure 1: Left) Microchannel with inlet (blue surface), outlet (red surface), symmetry plane (green surface) and walls (grey surfaces). The inset shows the trajectories of a subset of tracer particles. Right) Wall shear stress on the bottom wall of the microchannel.

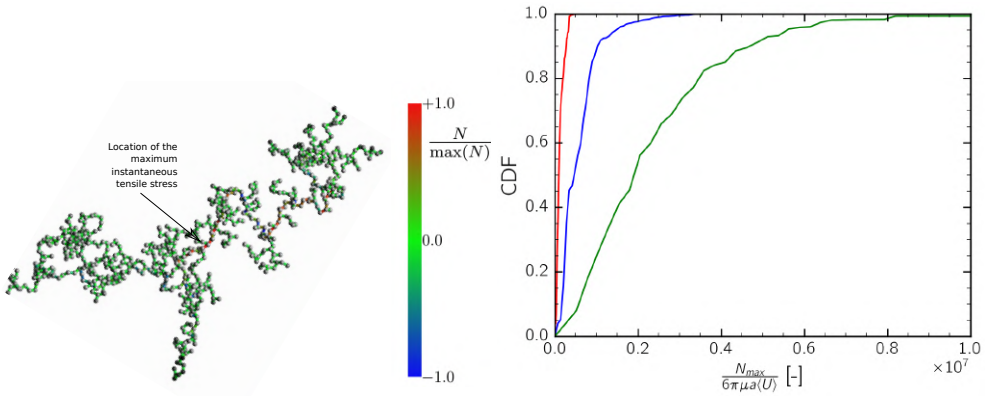

Figure 2: Left) Distribution of normal force in a DLCA cluster. A ball and stick representation has been used to highlight the inter-particle bonds. Right) Cumulative Distribution Function of the maximum tensile force experienced by RCP clusters (red), DLCA (blue) and hollow RCP (green). On the x-axis, a is the radius of the NPs, $\langle U \rangle$ is the average velocity in the constricted section.

RESULTS

The flow field in the microdevice and the trajectories of a set of tracer particles were obtained by running CFD simulations. Figure 1 right) reports the contour plot of the shear stress evaluated at the bottom wall of the microchannel. It can be noticed that the shear stress is relatively mild ($\approx$ 10 Pa) in the unrestricted section, it reaches a peak value ($\approx$ 150 Pa) at the entrance of the constricted section and then goes down to a value of 100 Pa in the narrowed region.

By Stokesian Dynamics we computed the distribution of the normal forces at the inter-particle contacts of the aggregates, as they move along the microchannel. A sample instantaneous distribution for a DLCA cluster is shown on the left side of Figure 2. For this class of aggregates, the highest tensile forces are observed in the internal region, thus suggesting that the expected dominant mechanism of breakup should be the fragmentation in two almost equally sized fragments. On the contrary, in the case of RCP and hollow RCP clusters, the highest tensile forces are observed in the external region, so that a progressive erosion of the cluster should instead be expected [4]. In the right plot of Figure 2 the mechanical responses of three different populations of aggregates are compared through the Cumulative Distribution Functions of the maximum experienced tensile stress. Hollow RCP aggregates emerged as the most fragile structure (i.e. the highest internal tensile force were observed for this class), RCP aggregates as the most resistant, whereas DLCA aggregates had an intermediate behaviour.

Results are encouraging and show the feasibility of such a deliver strategy. The CFD-Stokesian Dynamics approach appears as a promising tool to identify the fundamental properties of the aggregates to take in account when designing shear-activated drug carriers.

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