Microrobotic Locomotion in Blood Vessels: A Computational Study on the Performance of Surface Microrollers in the Cardiovascular System

Journal Article

Author(s):
Bozuyuk, Ugur; Ozturk, Hakancan; Sitti, Metin

Publication date:
2023

Permanent link:
https://doi.org/10.3929/ethz-b-000617158

Rights / license:
Creative Commons Attribution 4.0 International

Originally published in:
Advanced Intelligent Systems, https://doi.org/10.1002/aisy.202300099

This page was generated automatically upon download from the ETH Zurich Research Collection. For more information, please consult the Terms of use.
Microrobotic Locomotion in Blood Vessels: A Computational Study on the Performance of Surface Microrollers in the Cardiovascular System

Ugur Bozuyuk, Hakancan Ozturk, and Metin Sitti*

Surface microrollers have emerged as a promising microrobotic platform for navigation in the circulatory system as future drug/gene delivery applications. The circulatory system comprises various vessels with different dimensions, blood flow velocities, and flow regimes. Therefore, the performance of surface microrollers would vary in blood vessels. Herein, the performance of surface microrollers, with diameters between 5 and 50 µm, inside vessels of the systemic circulation including veins, venules, capillaries, arterioles, and arteries is investigated with computational fluid dynamics simulations. The simulation environment consists of a simplified fluid with the viscosity and density of blood, without red blood cells, in a cylindrical pipe. The microrollers demonstrate successful upstream locomotion ability in veins and partially in arteries but fail to perform in smaller blood vessels due to significant confinement and flow effects. Overall, the results presented here establish a preliminary result for the future in vivo use of surface microrollers.

1. Introduction

Magnetic surface microrollers possess a significant potential for controlled navigation in blood vessels owing to their strong locomotion capability and minimized flow velocities at the vessel walls to revolutionize localized drug/gene delivery.[1] However, the circulatory system consists of many vessels significantly different from each other in terms of dimensions and flow speeds.[2] There are different flow regimes (i.e., laminar or turbulent), types (pulsatile or continuous), and dimensions (cell-sized or macroscopic), which render different fluidic effects in blood vessels.[3] Overall, understanding the navigation capability of surface microrollers in various types of vessels is crucial for the practical implementation of the system for future biomedical applications.

The human circulatory system mainly consists of pulmonary and systemic circulations.[4] The former is between the heart and lungs to oxygenate the blood, and the latter is between the heart and the rest of the body.[5] In a relevant drug/gene delivery scenario, surface microrollers would be implanted into the systemic circulation, likely from veins, to reach a target tissue to deliver the drug/gene to the tissue of interest. Therefore, it is crucial to understand the locomotion dynamics in any vessel of systemic circulation for any microrobot for a relevant drug/gene delivery scenario. Systemic circulation consists of hierarchical vessels that circulate oxygenated blood throughout the body, bringing the deoxygenated blood back to the heart.[5] First, the oxygenated blood comes from the aorta and then is transported into arteries, smaller arterioles, and capillaries, where oxygen exchange mainly occurs.[5] After the capillaries, deoxygenated blood is drained by venules, veins, and the vena cava, finally reaching the heart and pulmonary circulation. The flow speeds and types are different in the oxygenated and deoxygenated site of the body: 1) the flow speeds are usually higher in the oxygenated site of the circulation and 2) also, flow type is pulsatile in the oxygenated site, while the flow is continuous in capillaries, venules, and veins.[3] A summary of the systemic circulation is given Figure 1.[2-5]

Here, we investigated the upstream locomotion potential of surface microrollers inside different blood vessels with computational fluid dynamics (CFD) analyses. We studied all vessel types in the systemic circulation except the aorta and vena cava (Figure 1). We simplified the CFD conditions for the sake of the computational expense, especially for big vessels;[6] we omitted the effect of the presence of red blood cells and their interactions, as also non-Newtonian effects. Therefore, the simulation environment comprised fluid with the viscosity and density of blood, without red blood cells, in a cylindrical pipe. Based on the previous experimental studies, we modeled spherical...
microrollers with the size of 5, 10, 25, and 50 μm diameter with the feasible actuation settings.1a,b,7 Our results indicated that the upstream locomotion was entirely possible in venous flow, in agreement with our previous experimental results7 and partially in arterial flow. However, upstream locomotion was unsuccessful in smaller vessels in venule, arterioles, and capillaries due to significant confinement8 and increasing flow effects. Overall, our results provided an initial insight and better understanding of the navigation of surface microrollers in blood vessels for the practical application of surface microrollers in future endovascular applications.

2. CFD Setup

The geometrical setup of our model is demonstrated in Figure 2. We solved Newtonian laminar flow physics in steady state (i.e., Re number is lower than a threshold and no turbulence effects) in a geometry described by Cartesian coordinates in three dimensions (3D). The microrollers were modeled as perfect spheres with a radius of a. The surface microrollers are not in contact with the nearby wall,9 separated by a lubrication distance, δ = δ/a, as they mainly perform rolling/slipping locomotion rather than pure rolling.8,9b,10 The microrollers were placed with different δ and rotated with a certain angular velocity, Ω = 2πf, f = 180 Hz, in three dimensions (3D). f = 180 Hz is the highest actuation frequency we could achieve in our previous experimental works.1a,b,7 The diameter and the average flow speed were altered for a specific vessel (Table 1). The length of the vessel (L) is picked as L = 25D, where D is the diameter of the vessel. The simulations were performed in steady state and without the presence of red blood cells because the dynamic simulations are computationally expensive and practically not possible to perform in our case due to the high number of cases. Also, the presence of red blood cells brings extreme complexity to our problem due to the complex physics of red blood cell deformation,6e,11 which would make it practically impossible to solve vessels that require big workspaces such as arteries and veins.

In the simulations, the forces acting on the microrollers’ boundary were quantified in steady state. The upstream locomotion ability of the microrollers was determined by the generated force direction by the microroller body (Figure 2).8 The microroller rotated clockwise generates the force in the +x direction, also called propulsion force (Fp) (Figure 2). In the presence of a flow to the −x direction, the microroller generates less force in the +x direction in the flow case, and the direction of the force may even be reversed in the presence of a severe flow or physical confines.8 Overall, our criterion for upstream locomotion was the force generation of a microroller in the +x direction. The forces acting on the microrollers in simulations were normalized according to the Reynolds number (Re).

Figure 2. The summary of the CFD simulations. Microrollers, the diameter of 2a and a lubrication distance of δ', placed in a cylindrical channel with a diameter of D and length of L = 25D. Microrollers were rotated clockwise with an angular velocity of Ω, generating force in the +x and +z directions, propulsion and lift force, Fp and Fl, respectively. The flow, \( \mathbf{V}_{\text{flow}} \), was applied to the −x direction, and the Fp generated by the microroller determined the upstream locomotion ability. +Fp implied the upstream locomotion.
to those generated by a microroller in stagnant fluid and semi-infinite conditions at $f = 180$ Hz, also demonstrated as $|F_T| = 1$. The microrollers also generate a perpendicular force to the $x-y$ plane, called lift force in $+z$, $F_L$, due to rotational motion and flow (Figure 2). As stated earlier, the microrollers were rotated for different $\delta$, namely, $\delta' = 0.005, 0.01, 0.05, 0.1, 0.2$ which is a broad and realistic range for successful microroller locomotion. $\delta'$ is mainly dependent on the density of the microroller; microrollers with higher density would have smaller $\delta'$. We also modeled passive beads, without any translational motion, in the same flows to clearly see the contribution of rotational motion to upstream locomotion, and added to each result as a control group.

In the results section, we presented the upstream locomotion ability of different microrollers for given $\delta'$ values to give the whole picture; however, at the end of the analysis, we also estimate the value of $\delta'$ for a Janus experimental system; the thicknesses of the Ni films were 1000 nm for 5 and 10 $\mu$m microrollers and 1800 nm for 25 and 50 $\mu$m microrollers, and 50 nm Au for all sizes (Figure S1, Supporting Information). After calculating the density of the microrollers, we computed the gravitational force, $F_G$

$$F_G = \frac{4}{3}\pi (\rho_f - \rho_p) a^3 g$$

(1)

where $\rho_f$ is the density of the fluid, $\rho_p$ the density of the particle, and $g$ is the gravitational constant. We compared the values of $F_G$ with $F_L$ taken from simulations to estimate the $\delta'$. $F_G$ is a permanent force, but $F_L$ is dependent on $\delta'$ and the flow itself. From simulation results, the force acted on the microroller in $-x$ direction ($F_D$) was sensitive and always followed a pattern; however, the forces on $+z$ ($F_L$) were less sensitive and sometimes followed an irregular pattern (Figure S2–S5, Supporting Information). Typically, $F_L$ increases with decreasing $\delta'$ but the finite element simulations lose the sensitivity for $F_L$, especially for smaller microroller diameters, which was previously referred to in the literature. Because of that, for a specific vessel and flow speed, we gathered all the $F_L$ values for $\delta' = 0.005, 0.01, 0.05, 0.1, 0.2$, and estimated the $\delta'$ for the following relation

$$F_{L,\text{max}} < F_G \Rightarrow \delta' < 0.005$$

(2)

$$F_G < F_{L,\text{min}} \Rightarrow \delta' > 0.2$$

(3)

where $F_{L,\text{min}}$ and $F_{L,\text{max}}$ are the minimum and maximum lift forces obtained for different $\delta'$ on specific cases. The flows were modeled as continuous for capillary, venules, and veins. For arteries and arterioles, the pulsatile flow was applied. The pulsatility of the flow was tuned according to Womersley number ($Wo$)

$$Wo = \left( \frac{D}{2} \right) \left( \frac{\rho f}{\mu} \right)^{0.5}$$

(4)

where $(D)$ is the diameter of the vessel, $\omega$ is the angular frequency of the oscillations, $\rho$, and $\mu$ are the density and dynamic viscosity of the fluid, which is $\rho_t = 1050$ kg $m^{-3}$ and $\mu = 4.5$ cP, for all simulations done in the study. The arteries’ flow is more pulsatile than the arterioles, and then the pulse effect completely disappears in capillaries, postcapillary venules, and veins due to compliance of the vessel walls$^{[15]}$. Womersley numbers of 3.5 and 0.1 were used for arteries and arterioles, respectively$^{[16]}$, and the pulsatility function was defined as follows$^{[17]}$

$$V_{\text{flow}}(t) = V_{\text{flow}} \times (1 + A \sin(\omega t) - A \cos(2\omega t))$$

(5)

where $V_{\text{flow}}$ is the average flow speed (Table 1), $t$ is the time step, and $A$ defines the amplitude of the waves. We performed quasistatic simulations; we discreted one pulse cycle/period to 32 time points and then calculated the total force acting on the microroller over one cycle to determine the upstream locomotion ability. As performing time-dependent simulations is computationally expensive and not feasible for the case presented here, we used the quasi-steady-state approximation to model pulsatile flows.$^{[18]}$ Even though we acknowledge that quasistatic simulations are an approximation and may not capture all important features, it is still the best approximation to simulate such a high number of cases in our CFD environment. Other than that, in the literature, different $A$ were used depending on a specific case.$^{[17,19]}$ We picked $A=1.50$ as a generic value for both arteries and arterioles to reduce the computational expense, and to make $V_{\text{peak}} / V_{\text{flow}}$ relatively high$^{[17b,19]}$ to render more challenging simulation environment for microrobots.

3. Results

3.1. Inside Veins

Veins are accessible and convenient vessels in the body, and most drugs are given from veins using catheters/needles, also called intravenous (IV) injection.$^{[20]}$ They carry oxygen-poor blood to the lungs to oxygenate the blood. Veins seem to be the apparent deployment route for microrobots. Therefore, thorough navigation of the microrobots in such vessels is needed to perform endovascular applications (e.g., filling aneurysms in veins or drug delivery).

We start characterizing the upstream locomotion performance of microrollers from veins. We placed the microrollers for different $\delta'$ values and assessed the upstream locomotion performance at $f = 180$ Hz. The simulation results for veins are summarized in Figure 3. The first important consideration for the locomotion in the veins was that the vessel diameters are too big compared to the size of the microrollers, which provided a significant advantage for microroller locomotion. Due to the parabolic flow profile,
the flows on the vessel’s walls were significantly lower than the vessel’s center (Figure 3a), which also enabled the upstream locomotion capability of the microrollers. At the smallest $V_{\text{flow}}$ value (Figure 3b), the microrollers generated almost $|F_p|=1$, which is the force generated under stagnant and semi-infinite conditions for $f=180$ Hz, indicating that there was almost no flow on the surface of the tubing. The passive beads, as expected, were dragged with the flow (Figure 3b), and negative force values were computed due to dragging flow conditions. At higher flow velocities, such as $V_{\text{flow}}=25 \text{ mm s}^{-1}$, the microrollers generated relatively smaller forces but still were able to perform upstream locomotion (Figure 3c). As expected, the microrollers generated less force at higher $\delta'$ values due to less symmetry breaking, thus slower locomotion. The passive beads at higher flow speeds experienced more drag force; the exerted forces increased with increased $\delta'$ values because the magnitude of the flows was far higher from the wall boundary due to the parabolic profile of the flow.

At the highest average flow speed $V_{\text{flow}}=50 \text{ mm s}^{-1}$, microrollers were unable to perform upstream locomotion at higher $\delta'$ values (Figure 3d). Determination of $\delta'$ values depends on the microroller materials; the denser particles will lead to smaller $\delta'$ values, therefore better performance. The predictions of a previously used microroller system will be shown at the end of the results section. Another important consideration from the results is that the microroller size had little effect on the performance in veins, probably mainly due to the microroller/vein diameter ratio being too small for all sizes and under a critical threshold. In other words, even for the biggest microroller, 50 $\mu$m, the magnitude of the flows was still too small, and the size effect could not be felt. As a result, all sizes’ results overlapped (Figure 3b–d, S6, Supporting Information). Overall, we
concluded that microrollers of all sizes could perform upstream locomotion in vein flows and have good navigation capability in such environments. Our previous experimental results also demonstrated that the microrollers could perform upstream locomotion in venous flow in similar settings.[7]

### 3.2. Inside Venules

Venules drain the deoxygenated blood from the capillaries (Figure 1). In other words, the microrollers would reach venules only after the successful upstream locomotion in the veins. Furthermore, the venules are essential for the penetration of nanoparticles and drugs; for example, it was recently discovered that the blood–brain barrier could be crossed only in postcapillary venules by transcytosis-mediated delivery.[21] Therefore, targeting venules can be an important goal for microrollers. The previous section demonstrated that upstream locomotion in veins could be possible; thus, locomotion in venules would occur after successful locomotion in veins.

We only investigated the microroller size of 5 and 10 μm in diameter because bigger microrollers would not fit in the venule (20 μm). This time, the microrollers were subjected to a higher relative fluidic force due to an increased microroller diameter/vessel diameter ratio. The microroller 5 μm microroller even perturbed the parabolic flow (Figure 4a) due to its relatively more significant size. The CFD results demonstrated that the microrollers could not upstream locomotion at any flow speeds (Figure 4b–d). The interesting consideration was that the 10 μm microroller has shown worse performance than passive beads for all speeds (Figure 4b–d), indicating that it was affected by the confinement effect to a severe extent.[8] As shown here, we also previously showed that the spherical microrollers reverse their locomotion direction in circular confinements.[8] Therefore, in addition to more prominent flow effects, the confinement effect also played a significant role in the upstream locomotion of microrollers in small vessels like venules. On the other hand, even though 5 μm also could not perform upstream locomotion, its performance in smaller values was better than the passive beads, demonstrating that it was less affected by the confinement effect (Figure 4b–d). Overall, the upstream locomotion ability of microrollers was unsuccessful in venule due to prominent flow and confinement effects.

### 3.3. Inside Capillaries

Capillaries are the most abundant vessels in the body with the highest surface area; the primary function of the capillaries is to transport oxygen and nutrients to tissues.[5] As molecular transport takes place in capillaries in the body, it is crucial to investigate the locomotion capability of microrollers in such vessels. In an intravenous administration scenario of passive beads, they first go to the heart and then pulmonary circulation. The microrollers/passive beads may end up in lung capillaries and also in capillaries in the systemic circulation. In addition,

![Figure 4. The upstream locomotion performance assessment inside venules. a) A representative cross-sectional CFD caption for \( V_{flow} = 2 \text{ mm s}^{-1} \) for a 5 μm diameter microroller. The colors show the magnitude of the flow, and the arrows indicate the direction of the flow. b–d) The diagrams for the microrollers and passive beads for different \( V_{flow} \). The green regions show upstream locomotion, and the red areas show the case where the microroller/particles drag with the flow direction.](https://example.com/figure4.png)
the microrollers can also be driven to capillaries in the scenario of achieving upstream locomotion in venules. The capillary analysis is given in Figure 5. We only analyzed the microroller with 5 μm due to the size limitation of the capillary vessel in the CFD environment. It must be anticipated from the “venule” section that the confinement and flow effects would be more drastic for capillaries (Figure 5a). It was indeed the case: the 5 μm microroller in the capillary vessel could not perform upstream locomotion; the microroller locomotion even worsened due to the confinement effect.[8] Namely, the performance of microrollers was worse than the passive beads, having more force on the flow direction (Figure 5b–d). The analyses here indicate that locomoting in smaller vessels would be highly challenging due to physical limitations. In addition, the model presented here is simplified; essential effects such as the presence of red blood cells and non-Newtonian effects were omitted. On top of this, red blood cells will also worsen the locomotion because they are highly packed in the capillaries. Overall, we can conclude that locomotion in capillaries is a highly challenging task requiring further research with different locomotion settings.

3.4. Inside Arterioles

Arterioles are small vessels transporting oxygenated blood to capillaries. Even though it is a small vessel type, the relative flow speeds are very high compared to venule and capillary (Figure 1). From the previous sections, we can conclude that travelling in small vessels is challenging due to increased flow and confined effects, which was also the case for arterioles.

The flow is pulsatile in arterioles, and the previously mentioned pulsatility function was used for arterioles (Figure 6a).

The forces acting on a microroller were quantified and reported over a period/cycle. We simulated 5, 10, and 25 μm microrollers inside of a 30 μm arteriole (Figure 6b). The most drastic results were obtained for the arteriole case because both confinement and flow effects were the most severe. The 25 μm microroller case faced severe confinement effects and severe flow magnitudes, which made upstream locomotion practically impossible in such vessels for that microroller size (Figure 6b). The only condition that a microroller was able to perform upstream locomotion was \( \nabla_{\text{flow}} = 1 \text{ mm s}^{-1}, \delta = 0.005 \) (Figure 6c). The force generated by the microroller was just above zero, implying that the microroller would barely perform upstream locomotion in that condition.

Other than that, there was no other group that performed upstream locomotion. The microroller locomotion did not create any positive effect than passive beads at high flow conditions \( \nabla_{\text{flow}} = 50 \) and 100 mm s\(^{-1}\) (Figure 6d,e); the results of microroller and passive beads virtually looked the same (Figure 6d,e), proving that rolling locomotion is insignificant in such a regime. Besides that, 25 μm experienced a significant confinement effect (Figure 6b), and performance worsened. The force magnitudes experienced by the microrollers were the most drastic in arteriole cases, demonstrating that it is highly challenging to control microobjects in such vessels.

3.5. Inside Arteries

Arteries carry fully oxygenated blood from the aorta to other body vessels. Its size is comparable to the vein; however, the blood flow is pulsatile, contrary to veins, and average flow velocities are much higher (Figure 1).[22] Even though the flow speeds are

---

**Figure 5.** The upstream locomotion performance assessment inside capillary. a) A representative cross-sectional CFD caption for \( \nabla_{\text{flow}} = 1 \text{ mm s}^{-1} \) for a 5 μm diameter microroller. The colors show the magnitude of the flow, and the arrows indicate the direction of the flow. b–d) The diagrams for the microrollers and passive beads for different \( \nabla_{\text{flow}} \) in capillaries.
higher, the microroller diameter/artery diameter ratio is minimal, which favors microroller locomotion due to significantly decreased flow velocities on the vessel walls, and no confinement effect is expected.

The pulsatility is higher in arteries than arterioles due to its higher order to the heart in the blood vessel hierarchy; thus, $Wo$ number is bigger than the arteriole (Figure 7a), meaning that $T_{\text{period,artery}}$ is smaller than $T_{\text{period,arteriole}}$. As expected, the relative flow magnitudes again were very low where the microroller was located (Figure 7b), which could facilitate microroller locomotion. The results in the artery showed that the microrollers could perform upstream locomotion for $V_{\text{flow}} = 100\, \text{mm s}^{-1}$ for a $25\, \mu\text{m}$ diameter microroller. The colors show the magnitude of the flow, and the arrows indicate the direction of the flow. c–e) The diagrams for the microrollers and passive beads for different $V_{\text{flow}}$ in arteriole.

Figure 6. The upstream locomotion performance assessment inside arteriole. a) A complete cycle of arteriole used in simulations. The overall force over a cycle is calculated and reported. b) A representative cross-sectional CFD caption for $V_{\text{flow}} = 100\, \text{mm s}^{-1}$ for a $25\, \mu\text{m}$ diameter microroller. The colors show the magnitude of the flow, and the arrows indicate the direction of the flow. c–e) The diagrams for the microrollers and passive beads for different $V_{\text{flow}}$ in arteriole.

Thus far, the performance results have been given as $\delta$ against the generated force by the microrollers. $\delta$ is a critical parameter for microroller locomotion and having smaller $\delta$ values facilitate better microroller performance. It is not easy to determine $\delta$ because it depends on the material properties and the fluidic forces exerted on the microroller. Microrollers with higher densities would be closer to the lower boundary, thus having smaller $\delta$. At the same time, stronger fluidic forces would lead to increased lift forces and try to increase $\delta$. Therefore, $\delta$ depends on multiple factors and would have different values for each vessel example.
The upstream locomotion performance assessment inside the artery. a) A complete flow cycle of the artery used in simulations. The overall force over a cycle is calculated and reported. b) A representative cross-sectional CFD caption for \( \dot{V}_{\text{flow}} = 100 \text{ mm s}^{-1} \) for a 5 \( \mu \text{m} \) diameter microroller. The colors show the magnitude of the flow, and the arrows indicate the direction of the flow. c,d) The diagrams for the microrollers and passive beads for different \( \dot{V}_{\text{flow}} \) in artery.

4. Discussion

Microrobots were proposed to replace passive drug/gene delivery agents to overcome inherent limitations of passive systems, such as nonspecific distribution in the body.\(^{[25]}\) Toward that goal, magnetic surface microrobots demonstrated great potential, produced strong propulsion, and overcame high fluid flow in microfluidic chips.\(^{[1a−c,7−8]}\) Furthermore, their locomotion relies on a boundary effect, which is advantageous for upstream locomotion; they utilize the decreased flow velocities on the vessel walls and evade strong fluidic effects. However, their performance in different types of vessels was unknown, which is the primary motivation of the study. The microrobots in CFD analyses have demonstrated great upstream locomotion capability in veins and arteries to some extent. They failed to perform in smaller vessels mainly due to the confinement effect\(^{[8]}\) and amplified fluidic flow effects due to the increased microroller diameter/vessel diameter ratio. However, the confinement effect can be tackled by using anisotropic-shaped microrobers, rendering safer hydrodynamic interactions with the confinement.\(^{[8]}\) Alternatively, integrating alternative flow generation schemes to microrobers, such as acoustic locomotion, could also be useful to generate favorable interactions with confinements. Additionally, microrobers could perform upstream locomotion utilizing significantly decreased flow velocities on the vessel walls, which was not the case in smaller vessels. Overall, despite the findings presented here, experimental validation is required, and a separate report will be dedicated to this purpose in the future. Nevertheless, we performed a brief experimental demonstration of microrollers of 25 \( \mu \text{m} \) in venous flow in phosphate-buffered (PBS) saline,
3, 25, and 50 mm s\(^{-1}\) in a 4.76 mm diameter plastic tubing. We actuated microrollers against the flow and characterized their upstream locomotion ability (Video S1, Supporting Information). The 25 μm swarming microrollers were able to perform upstream locomotion in 3 and 25 mm s\(^{-1}\) flows but failed in 50 mm s\(^{-1}\), probably they worked in high δ\(^0\) regime (Figure 3d), consistent with the CFD results. A detailed research report will be fully dedicated to validate the findings presented here, as a future work.

The magnetic properties of microrollers are a crucial factor that determines their efficacy in physiological fluid flows. Higher rotational speeds lead to increased translational velocities in unconfined environments, but their motion is impeded in confined regions.\(^{[8]}\) Thus, higher rotation rates are advantageous for optimal performance in larger vessels. In our study, we selected a rotation frequency of 180 Hz, the highest frequency that could be safely generated by our custom-made coil system, based on our prior investigations.\(^{[1a,b,e,8]}\) However, previous studies have demonstrated that microrollers can achieve rotation frequencies beyond 180 Hz through the use of unique magnetic materials,\(^{[1e]}\) provided that magnetic coil systems are capable of handling such actuation frequencies. In summary, the development of high-performance magnetic coil systems is necessary for the effective implementation of microrollers in larger blood vessels, such as high-flow arteries.

The swarm mode of microrobots is necessary for the human body due to increased imaging contrast and sufficient drug dose.\(^{[26]}\) On the other hand, the CFD simulations included only a single microroller which would not be the case for real applications. The swarming effect would also increase the performance of microrollers due to helpful hydrodynamic couplings between single units of the swarm. We tested the performance of swarming five microrollers next to each other in CFD simulations in venules with 1 mm s\(^{-1}\) flow and found out that the swarming microrollers were able to locomote upstream in contrast to the single microroller for small δ\(^0\) (Figure 9). Due to increased mesh complexity, the CFD simulations could not handle more than five microrollers in the current settings. However, in practical applications, there will be more than five microrollers, further increasing the overall success. Therefore, future work includes a detailed investigation of swarming microrollers in feasible CFD settings for such applications.

It must be pointed out that the CFD analyses given here are simplified. For example, the effect of red blood cells is neglected in simulations. It was previously shown that the presence of red blood cells brings extra resistance and significantly affects the upstream locomotion of surface microrollers.\(^{[1c]}\) This situation may revert the successful cases in reverse. Still, the computational investigation of such cases is highly challenging and may be practically impossible for big vessels due to the demanding computational power.\(^{[11]}\) Such cases require solving computational fluid dynamics physics and solid physics to capture the deformability of the red blood cells.\(^{[11]}\) In addition, the non-Newtonian effects are also neglected in our model for simplicity and feasibility. The shear-thinning behavior of blood may bring unexpected effects, especially in smaller vessels such as capillaries.

Another important consideration is the margination of the microrollers to the vessel walls.\(^{[27]}\) In this work, we simulated microrollers on the vessel walls; however, the margination capability of microrollers to the blood vessel walls is currently unknown and needs further research, which will be investigated.
in a similar simplified model for the initial assessment. The density of microrollers is an important factor that influences their ability to marginate in blood vessels. Higher microroller densities promote margination capability and reduce the lubrication distance of the microrollers. A smaller lubrication distance can lead to better performance, as heavier microrollers tend to stay closer to the vessel wall. Therefore, the density of the microrollers is a critical consideration in designing them for optimal margination and performance in physiological flows.

The inner walls of the blood vessels consist of packed endothelial cells that introduce surface microtopographies on the vessel walls. Surface microtopographies significantly impede the locomotion of spherical surface microrollers,[1b] which is omitted in the simulations here. However, the surface microtopography effect is expected to disappear after a certain size threshold for spherical microrollers; in a way, the surface microtopography becomes just roughness, and therefore, not felt. This effect for smaller microrollers can also be tackled by using anisotropic-shaped microrollers for the small size of microrollers.[1b] Anisotropic microrollers also improve the upstream locomotion performance in smaller vessels.[8] Future work will investigate the performance of anisotropic microrollers in all blood vessels.

The medical applications of microrollers include only endovascular applications because tissue penetration is not possible for the microroller size scale. The envisioned applications of microrollers are aneurysm treatment[28] and endovascular drug delivery applications could contain targeting cancer invasions to the blood vessels[29] or cancer-associated endothelial cells[30] through antibody receptor interactions[1b] and then release the drug to the cancer tissue. Overall, deployment workflow of the microrollers includes 1) medical imaging of the patient before the deployment, 2) injection of the microrollers with catheters, and 3) actuation of the microrollers to the diseased sites along with an imaging modality. Still, there needs to be more research effort on medical imaging of microrollers along with the biocompatibility aspect.[1e,31]

5. Experimental Section

**Numerical Simulations:** COMSOL Multiphysics 6.0 Simulation Software (COMSOL, Inc.) was used to simulate microrollers and calculate the forces acting on the microrollers in all conditions, using laminar interface physics by solving the Navier–Stokes equations. We used previously validated simulations with small modifications.[9] We defined two different mesh regions, the first one is in the vicinity of the microroller and the second one covered the remaining spaces in the simulation environment. The mesh around the microroller was cylinder with radius of the tubing and the second one covered the remaining spaces in the simulation environment. The circular diameter and average curvature factor, and the resolution of narrow regions were defined in Table 1 and the length of the tubings was taken as 3a, where minimum element size, maximum element size, maximum element growth rate, curvature factor, and the resolution of narrow regions were defined in COMSOL was a/50, a/5, 1.2, 0.05, and 1.5, respectively, for all sizes.

For the second mesh, “extremely fine” built-in mesh settings were used. The circular diameter and average flow velocities of the circular tubings were adjusted to Table 1 and the length of the tubings was taken as $L = 25D$. The density and the dynamic viscosity of the fluid were taken as $\rho_f = 1050 \text{ kg m}^{-3}$ and $\mu = 4.5 \text{ cP}$. The boundaries other than microrollers were defined as no-slip boundaries. The forces acting on the microrollers were calculated using
\[ F = \iiint_{\Omega} \sigma \cdot n \, dS \]  

(6)

where \( \sigma \) is the stress tensor, \( d\Omega \) is the microroller surface boundary in 3D, and \( n \) is the outward pointing normal vector. Generalized minimum residual (GMRES) method is used in COMSOL for all the simulations with the parameters in Table S1, Supporting Information.

Fabrication and Actuation of Surface Microrollers: Magnetically actuated, spherical Janus microrollers were fabricated by sequentially sputtering Ni and Au nanofilms on predried monolayer of silica (SiO₂) particles of 25 μm diameter (Microparticiles GmbH, Corpuscular Inc.) using benchtop sputter coating system (Leica EM ACE600, Leica Microsystems). 1800 nm was Ni used for surface microrollers while they also had 50 nm Au as passivating layer. After sputtering, magnetization direction of the Janus microparticles was oriented toward out of the cap by applying a 1.8 T uniform magnetic field in a vibrating-sample magnetometer (VSM; MicroSense, Lowell, MA). The microrollers were intensely washed and finally dispersed in PBS 1 x. The microrollers were actuated using a custom-made five-coiled electromagnetic coil system placed on a microscope. The microrollers were actuated using uniform rotating magnetic fields with an amplitude of 10 mT that enables surface rolling and steering control. The experiment is performed in PBS 1 x in 4.76 mm diameter tubing, while the flow was induced using a syringe pump.

Supporting Information

Supporting Information is available from the Wiley Online Library or from Project DEAL.

Acknowledgements

U.B. and H.O. contributed equally to this work. The authors thank Jack Saud for his assistance in CFD analyses. This work was funded by the Max Planck Society. Open Access funding enabled and organized by Projekt DEAL.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords

cardiovascular system, circulatory system, computational fluid dynamics, medical microbots, microparticles, microbots, surface microrollers

Received: February 22, 2023
Revised: April 23, 2023
Published online:


