Geometrically enhanced sensor surfaces for the selective capture of cell-like particles in a laminar flow field

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Medical wires inserted into the blood stream of patients offer an attractive perspective to capture rare cells such as circulating tumor cells *in vivo*. A major challenge in such systems is to achieve an efficient interaction of the desired cells with the sensing surface and avoid those cells that simply flow by the wire without any contact while floating in a laminar flow field at some small distance to the sensor surface. We describe a new strategy to increase the interaction of cells or cell-like particles to such wire-shaped sensor surfaces both from an experimental and a theoretical point of view. For model experiments, we use cell-like particles that are flowing past the profile wire in a blood-like liquid stream. In the fluid dynamics simulations, this sensor is inserted into small capillaries. The influence of geometry and orientation of the wire with respect to the surrounding capillary onto the capture behavior is studied. Parameters, such as wire diameter, profile shape, wire torsion, and orientation of it with respect to the liquid stream, induce in some cases quite strong crossflows. These crossflows enhance the contact probability compared to a straight line wire of the same length by factors of up to about 80. A general model connecting the wire geometry with the crossflow intensity and the particle capture behavior is developed. Particle capture experiments demonstrate that the identified geometric factors can improve the capture of cell-like particles in laminar fluid flows and enhance the performance of such cell sensors. *Published by AIP Publishing.* <https://doi.org/10.1063/1.5017714>

INTRODUCTION

Separation and enrichment of rare cells (e.g., circulating tumor cells, fetal cells, and stem cells) out of body fluids (e.g., blood, urine, and cerebrospinal fluid) is an important, yet challenging task in the field of *in vitro* diagnostics.^{1,2} The accumulation of such cells is especially critical when they have a very low abundance and are contained in a high background of non-specific cells. The problem becomes exacerbated, when cells with an ultra-low abundance (<1 target ml^{-1}) are to be analyzed.³ For example, when CTCs are viewed, the presence and detection of a specific single cell might change the whole diagnostic result.⁴ Analysis of such extremely rare cell requires the sampling of larger volumes of liquid in order to avoid false-negative results and to ensure sufficient statistics.^{5,6} In such cases, the volumes of the analyte need to be situated well in the milliliter range. This poses for typical microfluidic setups a challenge as microfluidic setups can hardly process more than 10 ml h^{-1} .⁷

In a recently published study, it was shown that rare circulating tumor cells can be captured directly out of the human blood stream with a functionalized medical wire inserted for 30 min into the circulatory system of a patient by a standard venous cannula.^{8,9} After the incubation time, the wires were withdrawn and the attached cells analyzed. From a principle point of view, the wire-based *in vivo* method could screen a larger sample blood volume compared with *in vitro* methods without all the problems connected to blood storage and transport required for

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in vitro-analysis.^{6,7} In a study with 50 lung cancer patients, the wire-based *in vivo* method resulted in higher positive tumor cell isolations and higher cell counts per positive result compared to a FDA-cleared system that analyses 7.5 ml of venous blood *in vitro*.⁹ In a recent publication, the surfaces of such wire-shaped cell collectors were modified with a multilayered highly selective coating that can improve the selectivity of the capture process.¹⁰

The movement of particles close to a solid wall such as the wire surface is governed by forces exerted onto them by the laminar flow profile. In such a situation, the flow of particles near the wall is very slow, especially under “no slip” conditions. This results in a low contact probability of particles with the capture surface, and the vertical flux of these particles towards the wall is limited by diffusion.^{11,12} This situation is especially problematic for larger particles and higher liquid viscosities, as under these conditions, the transport becomes very slow.

To overcome these limitations for the capture and displacement of particles between laminar layers in flow systems, dead-end filters,¹³ filter-like structures,¹⁴ and series of high-aspect ratio microchannels¹⁵ have been integrated into microfluidic devices. Such structures increase the overall interaction of the fluid with the capture surface, very similar to the stationary phase in fluid chromatography. Nevertheless, increasing the surface-to-volume ratios by such flow devices does not necessarily result in strong improvements.¹⁶ In other approaches, more sophisticated functionalized obstacle arrays were developed that increased the contact probability.^{17,18} These approaches were based on the principle called deterministic lateral displacement (DLD),¹⁹ which allows the separation of particles according to size in a laminar flow. Other examples for maximizing collision probabilities under laminar conditions are micro-vortex (mixing) structures^{20,21} and cross-flow membranes²² or generally systems that add external forces like dielectrophoretic²³ and magnetic²⁴ forces. Structures disrupting laminar flow profiles without turbulence in the rather macroscale range are also known for laminar static mixers (also motionless mixers), which reveal a highly efficient mixing of liquids only by flowing through a structure.^{25,26}

In this study, we describe a strategy where wires used for such capture purposes are shaped in such a way that the structures induce crossflows in the liquid and this way enhance the cell/particle contacts with the wire surface itself. The influence of the wire geometry on the number of contacts, which the spherical cell models have with the wire surface, is studied by fluidic simulations. The results are compared with the experimental capture results using wires that are modified with a highly selective capture surface.¹⁰ In these experiments, polystyrene particles having the same size as the cells are chosen as a model to simplify the experimental effort. Additionally, in such experiments, we have chosen a transparent liquid which has about the same viscosity as venous flowing blood in order to allow an *in-situ* optical readout of the system. We describe a model on how geometric parameters can optimize the interaction of wire-shaped sensor surfaces with a solution containing cell-like particles under laminar flow conditions.

EXPERIMENTAL

Engineering design and fluidic simulations

Twelve different series of profile wires having varying cross-sectional shapes were used and the corresponding three-dimensional (3-D) twisted models were constructed using the CAD-Software SolidWorks 2013. All cross-sectional geometries were axially symmetric. The final twisted profile wires were 40 mm long with a torsion along the central axis. The tubular diameters varied in the different series of wires between 0.25, 0.5, and 1.0 mm.

Fluidic simulations were performed using COMSOL Multiphysics 4.3, using the stationary laminar flow and the time dependent particle tracing modules. STEP-files of 3-D twisted wire models were imported and incorporated into the model of a capillary ($\varnothing$ 2.3 mm) which was generated directly in the simulations software. In the model of the system, all wires were placed at two distinctive orientations inside of the capillary. The wires were placed at a distance of 200 μ m from the wall at the capillary outlet. In one case, the wire was placed parallel to the tube without any inclination, in the other with a 1–2° inclination against the central axis

depending on the wire diameter. The ends of the tubular flow systems were cut to the effective length of the wires, which were 40 mm for 0° inclination and 38 mm for 2° inclination, respectively. The geometric setup is shown in Figs. 1(a) and 1(b). For simulation of the liquid flow, mean inflow velocities of 1 cm s^{-1} and 3 cm s^{-1} were applied at the inlet without pressure at the outlet. The blood was treated as a non-Newtonian fluid according to the Carreau model with the viscosity-shear rate relation as described.^{27,28}

The resulting stationary flow at no slip conditions was then used to simulate the time dependent behavior of particles that were homogeneously distributed over the capillary cross-section at the inlet. All particles were released at once and the drag forces acting on the particles were calculated. This way, the particle flow was coupled to the static flow and allowed simulations of the movement of the particles through the capillary as a function of time. The mass density of the particles was assumed to be equal to the mass density of blood at about 1066 kg m^{-3} ²⁹ so that no sedimentation occurs. The standard set used for the particle tracing experiments was 3000 particles having a diameter of $20 \mu\text{m}$. Control experiments were also conducted with 750 particles and particle diameters of $10 \mu\text{m}$ or $1 \mu\text{m}$. Particles that got into contact with the wire surface while passing the capillary were set to freeze in space and time and were counted at the end of each simulated experiment.

Twisting and coating of profile wires for capturing biotinylated beads

Flat and square profile wires were twisted and coated as described previously.^{10,30} Briefly, the wires were vertically fixed between a screw clamp (Model 303 + 300, PanaVise Products, Inc., NV, USA) and a laboratory stirrer (RZR 2021, Heidolph Instruments GmbH & Co. KG, Germany) at a length of 40 mm. The wires were twisted while applying a vertical force of 1 N (Zwick BZ2.5/TN1S; Zwick GmbH & Co. KG, Germany).

FIG. 1. Basic model setup for laminar flow computer simulations with 2-D central cut planes. Setup for wires ($\text{Ø } 0.5 \text{ mm}$; length of 40 mm) (a) without inclination and (b) with an inclination of 2° inside of a capillary ($\text{Ø } 2.3 \text{ mm}$). Two-dimensional central cut planes from the three-dimensional simulated blood flow (3 cm s^{-1}) through the capillary containing different wires are shown. The cut planes represent the local pressure differences (gray scale) and the resulting velocity field (black arrows; length proportional to velocity) for (c) a round wire without inclination (d) a round wire with 2° inclination, (e) a 4-edged flat wire (aspect ratio 5:1; torsion 2 turns cm^{-1}) without inclination, and (f) the same flat wire with an inclination of 2° .

Stainless steel wires (EPflex Feinwerktechnik GmbH, Germany) and brass wires (Hassler-Profile, Liechtenstein) were cleaned and incubated for 1 h in a solution of 1 mM octadecylphosphonic acid (ODP; Sigma–Aldrich, Germany) in ethanol to generate a self-assembly monolayer (SAM) on the surface of the wires. SAM modified wires were then dipcoated at 30 mm s^{-1} with benzophenone containing copolymer solutions. The concentrations were set to polystyrene (PS), $c = 10\text{ mg/ml}$ and polydimethylacrylamide (PDMAA), $c = 5\text{ mg/ml}$. The coatings were sequentially dried in air and cross-linked by UV irradiation (3 J cm^{-2} at 360 nm on each side) in a Bio-Link UV-cross-linker (VWR International GmbH, Germany). For the immobilization of receptors (i.e., streptavidin) on top of the multilayer coating, a second layer of PDMAA was applied by dipcoating followed by a deposition technique where a droplet containing the streptavidin molecules rolls over the surface during deposition and drying. The droplet was brought into contact with the whole twisted surface area by a rotation of the wire along the central axis combined with an intermitted pivoting of the rotating axis from one side to the other. Partial wetting leads to homogeneous deposition of small amounts of the polymer solution. Good distributions of receptors on the surface of the wires were achieved by applying at least a volume of $8\text{ }\mu\text{l}$ onto wires that were 40 mm long and had a diameter of 0.5 mm. Finally, the dried receptors were bound to the surface of the wire by UV irradiation (3 J cm^{-2} at 360 nm on each side), which crosslinks the second PDMAA layer and attaches contacting receptor molecules simultaneously. The functionalized wires were stored in 10 mM PBS buffer at 4°C until usage for capturing biotinylated beads. The complete coating procedure is depicted schematically in Fig. 2.

Microfluidic setup for capturing biotinylated beads in laminar flow by functionalized wires

The flow chamber used in the fluorescence microscopy experiments consisted of a home-made three-layer composite construction with transparent top and bottom layers for observation and counting of fluorescently labeled and biotinylated beads as shown in Fig. 3(a). As a top layer, a commercially available open channel slide was used containing Luer inlet and outlet ports (sticky-Slide I 0.4 Luer, ibidi GmbH, Germany). The bottom layer was a commercial microscope plastic slide (PMMA). The intermediate layer was a 1 mm thick butyl-rubber gasket, which allowed for a reusable and tight sealing of the composite structure and which was cut to the appropriate shape to form the chamber. The streptavidin coated profile wires ($\varnothing$ 0.5 and 1 mm) were incorporated into the chamber and fixed such that they were freely hanging inside of the chamber by small pieces of silicone tubings. The tubings were put over both wire ends and clamped between the top and intermediate layer so that the wires did not contact the channel surface and that a flow directly against the ends or other parts of the wire was avoided. The different profile wires were functionalized with $8\text{ }\mu\text{g}$ streptavidin (Carl Roth, Germany).

Preparation of fluorescently labeled and biotinylated beads

Fluorescent (DY-648P1) polystyrene micro-particles with carboxylated surface ($15\text{ }\mu\text{m}$, 25 mg/ml, Kisker Biotech GmbH & Co. KG, Germany) were modified using the PolyLink Protein Coupling Kit for COOH Microspheres (Polysciences Europe GmbH, Germany). The kit was used as recommended by the supplier with the only exception that the washing step was done with the coupling buffer. This allows measuring the protein concentration of the supernatant by a colorimetric Bradford assay. The surface of the beads was modified with biotinylated BSA (Sigma-Aldrich, Germany) with each 8–16 biotin per BSA. The resultant protein surface concentration for all microfluidic bead experiments was $7.2 \times 10^5\text{ BSA molecules}/\mu\text{m}^2$.

Bead capture experiments

Bead capture experiments were done under an inverted fluorescence microscope (ECLIPSE TS100, Nikon GmbH, Germany). The flowrate of a peristaltic pump (ISMATEC, IDEX Health & Science, Switzerland) was adjusted to a mean flow velocity of 1 cm s^{-1} inside of the flow

FIG. 2. Schematic illustration of the coating procedure of profile wires for capturing biotinylated beads. (1) A self-assembly monolayer (SAM) for surface priming is applied by incubation. (2) A photoreactive polystyrene (PS) copolymer layer is deposited by dipcoating. (3) The PS-layer is crosslinked by UV-irradiation. (4) A photoreactive hydrogel (PDMAA) layer is deposited by dipcoating. (5) The PDMAA-layer is crosslinked by UV-irradiation. (6) A second PDMAA layer is deposited by dipcoating. (7) A receptor solution (i.e., streptavidin) is applied to the non-irradiated second hydrogel layer. (8) The streptavidin solution is air-dried on the hydrogel, while the wire is rotated and tilted simultaneously. (9) The surface dried receptors are bound to the hydrogel surface by UV-irradiation. (10) The coated and streptavidin modified wire surface capture and bind biotinylated beads.

chamber. Modified beads with a particle concentration of $\approx 17.000 \text{ ml}^{-1}$ were dispersed in water, whose viscosity was adjusted by adding 1.25% (w/v) polyvinylpyrrolidone K 90 (Carl Roth, Germany) (dynamic viscosity $\approx 3.25 \text{ mPa s}$). The time for capture was set to 10 min and counting of beads sticking to the wire surfaces was performed only on the bottom side. For particle concentrations of $\approx 17.000 \text{ ml}^{-1}$ and incubation times of 10 min, it was calculated that $\approx 680\,000$ particles pass through a channel cross-section of $\approx 7 \text{ mm}^2$ ($5 \text{ mm} \times 1.4 \text{ mm}$).

RESULTS AND DISCUSSION

The streamlines of laminar flow fields are usually parallel to the surfaces that guide the liquid so that particles contained in this liquid can reach the surface only by diffusion [Fig. 4(a)]. The number of particle contacts with the sensor surfaces in such flow fields can be improved when cross-flows are introduced, which target the surface of the structure itself. To induce such lateral fluid movements, a flat-shaped wire is twisted along the long axis of the flat surface [Fig. 4(b)].

To investigate the influence on streamlines and the particle capture performance of different twisted wire profiles in laminar flow fields, a model setup was established as shown in Figs. 1(a) and 1(b). For this, computational fluid dynamics (CFD) simulations were performed on twelve different 3-D wire-shaped, computer generated structures that were introduced into a

FIG. 3. Experimental results for counting captured fluorescence labeled beads on the surface of functionalized twisted profile wires. (a) Fluidic setup with a twisted flat wire that is fixed freely hanging at two tubings, which are clamped between the top slide and the intermediate layer. The effective capture length of tested wires is about 3 cm. Fluorescence pictures of captured particles (black points) on a functionalized 4-edged 5:1 flat wire for (b) stainless steel (Ø 0.5 mm) and (c) brass (Ø 1 mm). Focal changes must be done while counting all particles. (d) Comparison of normalized particle numbers between experimental results and the linear master plot functions of simulations with wire inclinations of 0° (dashed line) or 1–2° (dotted line) plotted against the shape factor $A_C^2 \cdot f \cdot R$. The normalized individual results ($n = 30$) for wire diameters with 1.0 mm (cross) and 0.5 mm (plus) for each five measurements per three different shapes are shown.

capillary (Ø 2.3 mm). The investigations were focused on the cross-sectional profile, the number of cross-sectional turns per unit length (torsion), the angle of wire inclination, and the relative diameter of the wire structure in relation to the capillary dimension.

In a first step, the fluid flow was studied on central cross-sections of the 3-D simulation model as shown in Fig. 1. Profile wires with a varying shape (i.e., round, triangular, rectangular, etc.) were used and placed at a fixed location. Additionally, slightly different tilt angles with respect to the capillary were employed. For all different geometries, the local flow fields and the local fluid velocities were calculated. The obtained vectors of the velocities of the crossflows are indicated by arrows in Fig. 1 and the pressure differences are depicted using grey scales.

In a second step of these simulations, homogeneously distributed particles were released through the inlet of the capillary. Particles which struck the wire surface were set to freeze and stick and were counted at the end of the simulation run.

FIG. 4. Schematic representation of flat wire-shaped sensor surfaces in a flow field. (a) Flat surface and (b) a twisted flat surface of the same size that are placed in a laminar flow of a viscous fluid.

Surface inclination against the laminar flow profile

When a smooth round wire is brought into contact with a laminar stream in a capillary, the influence of this structure on the flow depends on the orientation of the structure compared to the streamlines. If a round wire is placed parallel to the capillary [Fig. 1(a)], no influence of the wire on the streamlines around the wire is observed and the cross-sectional pressure profile and velocity field are homogeneous along the wire [Fig. 1(c)]. However, when the same wire is inserted into the capillary with a small inclination of 2° [Fig. 1(b)], the fluid flow at the wire surfaces is not parallel to it and causes a positive pressure above the wire/in front of it and a negative pressure below/behind the wire which serves essentially as an obstacle. This pressure difference results in a unidirectional cross-flow that is symbolized by black arrows in Fig. 1(d). For comparison, the pressure and transversal flow vectors induced by a twisted 4-edged 5:1 flat wire with 2 turns cm^{-1} are investigated in the same two cases (i.e., with and without inclination). In contrast to the situation with the round wire, the flat wire induces multidirectional transversal flows induced by the twisted structure as shown in Fig. 1(e). These flows are the result of the clockwise torsion and the pressure differences around the cross-sectional profile as shown in Fig. 1(e). The pressure differences were more pronounced at the center of the capillary where higher fluid velocities are found and the highest values of them were observed at the edges. In case of an inclination of the twisted flat wire, it produced a (clockwise) rotating flow profile (due to the direction of twisting), similar to the 0° position but much stronger [Fig. 1(f)].

Influence of torsion of profile wires on laminar cross-flows and particle collisions

In a set of simulations, the effect of the extent of twisting on the induced laminar cross-flows was studied using 4-edged 5:1 flat wires. The resulting number of particle collisions with the wire were investigated [Fig. 5(a)]. In Fig. 5(b), the maximum lateral flow velocities measured on slice planes close to the center are plotted against the number of turns per length. It was observed that the maximum lateral flow velocities increased with the extent of wire torsion. Furthermore, the wire inclination resulted in significantly higher flow values compared to parallel wires for all objects that have less than 1 turn cm^{-1} . This can be explained by the strong

FIG. 5. Effect of cross-sectional turns of a twisted flat wire on the maximum lateral flow, the number of captured particles, and the resulting contact enhancement in a simulated laminar blood flow with a mean velocity of 3 cm s^{-1} . (a) 3-D drawings of eight 4-edged 5:1 flat wires ($\varnothing 0.5 \text{ mm}$; 4 cm in length) with different numbers of turns cm^{-1} . The different wires were exposed to the laminar blood flow in a capillary ($\varnothing 2.3 \text{ mm}$) of computer simulations. (b) Maximum cross-flow velocities measured on central cut planes are plotted against the wire torsion. (c) Particles ($\varnothing 20 \mu\text{m}$; $n = 3000$) released in the simulated blood stream, which were contacting the wires are plotted against the wire torsion. (d) A factor of contact enhancement compared to a non-twisted wire was calculated and plotted against the torsion.

unidirectional flow due to the inclination, which did not simply add to the clockwise directional flow caused by flat wire torsions [Fig. 5(b)].

In a next step, 3000 homogeneously distributed particles were released at once from the inlet. When the number of contacting particles are plotted against the torsion (with a constant wire profile), it can be observed that the collisions increase with the number of turns cm^{-1} . Additionally, it is higher in the case of 2° compared to 0° inclination [Fig. 5(c)]. The number of particles for the non-twisted wire was more than twice at 2° (11 particles) compared to 0° (5 particles). Furthermore, enhancement factors were calculated taking the non-twisted wires as a reference [Fig. 5(d)]. It is interesting to see that the enhancement of the particle contacts due to the wire torsion is slightly higher for wires having no (i.e., 0°) inclination.

Influence of cross-sectional geometries and wire sizes on the cross-flow and surface contacts

In a new set of simulations, the influence of the shape profiles of the wires on the induced cross-flows was investigated [Fig. 6(a)]. To this, the tubular diameter ($\varnothing 0.5 \text{ mm}$) and the torsion (2 turns cm^{-1}) of the wires were kept constant. The maximum cross-flows are plotted against the differences in areas of wire cross-sections and their identical circumcircle [Figs. 6(b) and 6(c)]. This area difference is visualized as the gray area in Fig. 6(a), which is zero for a round wire shape. For further considerations, the area difference is divided by the area of the circumcircle and termed A_C [Fig. 6(a)]. It can be observed that the maximum cross-flows increase almost linearly with the values of A_C at mean velocities of 1 cm s^{-1} and 3 cm s^{-1}

FIG. 6. Effect of differences in the cross-sectional geometry of twisted profile wires on the cross-flow. (a) Calculations of 12 different cross-sectional wire geometries and their corresponding normalized differences in areas (gray) between the cross-section (black) and their circumcircle denoted by A_C . Plotting of maximum cross-flow velocities from central cut planes induced by the 12 different wire shapes in a laminar blood flow simulation at mean velocities of (b) 1 cm s^{-1} and (c) 3 cm s^{-1} plotted against the corresponding number of A_C .

[Figs. 6(b) and 6(c)]. This correlation between cross-flow velocities and area differences is the result of a local pressure gradient with positive pressure in front of the edges and negative pressure behind them. It should be noted that, as the flow rates were rather small, changing the fluid flow from blood to a Newtonian liquid such as water at 20°C resulted in negligible changes of these findings (data not shown).

In additional experiments, the influence of the wire diameter (studied here for 0.25, 0.5, and 1.0 mm) at constant capillary dimensions ($\varnothing 2.3 \text{ mm}$) was investigated. It should be noted that the thickest wires ($\varnothing 1 \text{ mm}$) could only be inclined by 1° as stronger inclinations of the thicker samples led to surface contact with the capillary wall. The wire thickness has a strong influence on the maximum cross-flow values [Fig. 7(a) and 7(b)]. Larger wire diameters result in larger “free space” between circumcircle and cross-sectional area as the whole system is scaled up. Thus, the generated cross-flows correlate also to the absolute area difference between circumcircle area and cross-section of the wire [Fig. 7(c)]. It should be noted that the data in Fig. 7(c) are generated from multiplying the data from Figs. 7(a) and 7(b) with the wire diameter. The fact that all data collapse onto one master curve (one for each angle of inclination) demonstrates the tight correlation between wire size and strength of the cross-flow.

In a next step, the particle capture performance of different profile shapes was tested. The general goal was to identify geometries (i.e., wire shapes) that can enhance the number of surface contacts. To predict the particle contact probability of different twisted profile wires, it is considered that the relative number of particles, which can contact the surface, will be

FIG. 7. Influence of the wire diameter and the absolute area difference between a cross-sectional profile and its circumscribed circle on the wire induced cross-flows. Maximum lateral flow velocities in dependence of the relative area difference (A_C) for 3 different wire diameters (0.25, 0.5, and 1.0 mm; 2 turns cm⁻¹) at mean flow velocities of (a) 1 cm s⁻¹ and (b) 3 cm s⁻¹. All wires were in parallel to the capillary ($\varnothing = 2.3$ mm). (c) Maximum lateral flow velocities in dependence of the absolute area difference at mean velocities of 1 cm s⁻¹ (open circles) and 3 cm s⁻¹ (open squares). Linear regression analyses are depicted by dotted and dashed lines.

proportional to the free volume ratio A_C . The larger this volume, the more particles will be contained in it and the more particles hit the surface in the course of the flow. This situation is not unlike that of a rotor, where the particles hitting the rotor blades are contained in the volume between the blades. Additionally, as shown above, the number of contacting particles will be proportional to the cross-flow velocity, which in turn is also proportional to A_C . A third factor influencing the flow behavior will be the number of rims R contained in the structure. The number of rims will determine the number of walls with which the particle flow can interact. Every such rim and the wall connected with it will represent an obstacle with which the flowing particle can collide. Such obstacles induce a local increase of the shear rates that is the result of a compression of the streamlines due to the presence of the obstacles. A compression of streamlines results in a pushing of the (incompressible) particles towards the wire surface. We thus obtain a two parameter shape factor ($A_C^2 \cdot R$) that describes the number of contacting particles N_P^s as a function of the shape in relation to the number of particles contacting a round wire N_P^r [Fig. 8(a)]

$$N_P^s = N_P^r (1 + a \cdot (A_C^2 \cdot R)), \quad (1)$$

where a is a constant which reflects all geometric factors not included in $A_C^2 \cdot R$.

FIG. 8. Function of cross-sectional shape factors and correlation to the particle contacts. (a) Derivation of the shape factor $A_C^2 \cdot f \cdot R$ that correlates with the number particles that strike the wire surface. (b) 12 different cross-sectional wire geometries with their corresponding calculated number of $A_C^2 \cdot f \cdot R$ are shown. (c) Percentage of particles ($\phi=20$ mm; $n=3000$) and equivalent processed blood volume ($\approx 150 \mu\text{l h}^{-1}$ per particle) striking 12 different wire shapes ($\phi=0.5$ mm) in a laminar blood flow simulation at a mean velocity of 3 cm s^{-1} plotted against the number of $A_C^2 \cdot f \cdot R$.

However, upon a closer inspection, it becomes evident that for some geometries a correction factor must be included as not only the number of rims but also the distance between the rims plays an important role. When two rims are placed so closely together that no crossflow can develop between them and capture areas overlap, they will effectively act as one rim. Accordingly, the number of rims R needs to be replaced by the number of effective rims $f \cdot R$, so that we obtain

$$N_p^s = N_p^r (1 + a \cdot (A_C^2 \cdot f \cdot R)). \quad (2)$$

Here, f represents an efficiency factor for the rims and is constant for a given geometry. The number of effective rims is equal to the number of edges of the cross-sectional geometries in cases where the edges are uniformly, i.e., equidistantly distributed on the circumference. When some of the rims are getting too close to each other, f will become smaller than unity ($0 < f < 1$). In the [supplementary material](#), a calculation of the number of effective rims is performed for some of the most commonly used wire structures, i.e., 4-edged or rectangle wires with a non-uniform edge distribution as a function of the aspect ratios of the wires.

The obtained Eq. (2) shows that a good strategy to enhance the number of particle contacts with the surface is to increase the “free space” between the rims as much as possible and at the same time to increase the number of rims. For very “airy” structures, where A_C approaches

$A_C \approx 1$, the number of rims becomes the determining factor and structures that contain a large number of rims will generate very efficient capture devices. However, while increasing the number of rims, one has to pay attention that they are not placed too closely together, because then the rim efficiency factor will decrease. Thus, for many geometries, A_C and $f \cdot R$ point into different directions and the choice of an advantageous geometry is not trivial.

The enhancement of the capture efficiency of a certain geometry in relation to that of a round wire can be described by an efficiency factor E

$$E = \frac{N_P^s}{N_P^r} = \frac{N_P^r (1 + a \cdot A_C^2 \cdot f \cdot R)}{N_P^r} = 1 + a \cdot A_C^2 \cdot f \cdot R. \quad (3)$$

The efficiency factor E describes how many more particles are captured by a certain geometry compared to a round wire.

To investigate the capture performance of model, profile wires with a torsion of 2 turns cm^{-1} were generated and 3000 particles were released from the inlet of the capillary to count particles that hit the surface. Figure 8(c) shows that the percentage of these particles that strike the wire surface increases with the shape factor $A_C^2 \cdot f \cdot R$. Additionally, a small inclination by only 2° doubles the number of particle contacts in many cases. The number of contacting particles is also used to describe the actual processed fluid volume by the sensor surface in the simulations. To calculate this, it should be considered that the 3000 particles were homogeneously distributed at the inlet of the capillary over a cross-section of 4.15 mm^2 . Accordingly, roughly $1400 \text{ } \mu\text{m}^2$ of the cross-sectional capillary area is allocated to each particle. Multiplying the allocated area per particle with a mean flow rate of, e.g., 3 cm s^{-1} results in an estimated flow rate of $\approx 150 \text{ } \mu\text{l h}^{-1}$ per each particle. Based on these assumptions, the equivalent processed blood volume can be calculated and is plotted on the secondary y-axis in Fig. 8(c). It can be seen that some of the wires interact with liquid volumes of more than 10 ml h^{-1} , whereas a simple round wire contacted only 0.15 ml h^{-1} at 0° inclination and 1.0 ml h^{-1} at 2° inclination.

For further comparison, we normalized the numbers of colliding particles of all data sets to the wire shape of the 4-edged 5:1 flat wire with a shape factor value of $A_C^2 \cdot f \cdot R = 1.11$ which is set a value of 1. The resulting master plot comprises all simulated results at a constant torsion of 2 turns cm^{-1} (Fig. 9). The master plot includes also computed experimental data sets for varying wire diameters (0.25, 0.5, and 1.0 mm), varying particle diameters (1, 10, and $20 \text{ } \mu\text{m}$), varying particle amounts (750 and 3000 particles) and for simulations with water instead of blood (latter not shown in detail). It can be shown that all normalized particle numbers are linearly correlated to the shape factor. The normalized particle contacts were then converted to efficiency factors based on the calculated parameters of the linear regression functions. The results show that an enhancement of the contact efficiency factors of about 80 (0° inclination) and 12 ($1\text{--}2^\circ$ inclination) could be obtained by using an appropriate profile wire instead of a round wire.

The simulations were compared to experiments using four different wire profiles with two different wire diameters (0.5 mm and 1.0 mm) as representative examples. These examples cover more or less the whole range of shape factors of wires available. For these experiments, the twisted profile wires were previously coated with covalently bound streptavidin as described in the Experimental section. The samples were then fixed at the center of the flow chamber. The complete setup is shown in Fig. 3(a).

The capture experiments showed an instantaneous binding of beads directly at contact without visible surface rolling. The wire contacting particles became immobilized through binding of the biotin units present at their surface with the streptavidin on the wires. The major portion of the particle capture was observed at the rims [Figs. 3(b) and 3(c)], which is the predominant contact area, which agreed well with simulation results (data not shown). The resultant number of adherent particles on the wire surface was counted only from the bottom side of the flow chamber in order to eliminate effects of sedimentation. The experimental results of each wire diameter was normalized to the mean value ($n=5$) of the 4-edged 5:1 flat wire ($A_C^2 \cdot f \cdot R = 1.11$). The

FIG. 9. Wire inclination dependent master plots for the normalized particle numbers and corresponding efficiency factors in dependence of the shape factor $A_C^2 \cdot f \cdot R$. The normalized numbers of particles striking wire surfaces in different laminar flow simulations plotted against the geometric shape factor of 12 wire profiles are shown. Individual data sets from experiments were normalized to the particle numbers of the 4-edged 5:1 flat wire. The results of simulations at mean flow velocities of 1 cm s⁻¹ (open circles, n=46) and 3 cm s⁻¹ (open squares, n=46) are shown for wires that had (a) no inclination within the capillary and (b) a size dependent inclination of 1–2°. The dashed lines show linear regression functions over all data sets.

experimental values were then plotted against the numbers of $A_C^2 \cdot f \cdot R$ and compared to the linear regression functions from the normalized simulation results [Fig. 3(d)]. Here, it is seen that the simulated particle–wire contacts and the experimental particle captures by the wires gave similar results. This indicates that the shape factor can predict the relative performance of a wire-shaped sensor surface and that maximizing this shape factor will generate efficient wire-based sensor surfaces for particles or cells in laminar fluid flows of capillaries.

CONCLUSIONS

When a wire-based sensor is brought into a capillary through which a laminar flow passes, containing suspended cells or model particles representing such cells, most of the particles contained in the fluid never contact the sensor surface. Even when their distance to the surface is rather low, they follow the laminar flow and simply pass by the wire without any contact. The contact probability between particles and the wire-shaped sensor can be improved by moving towards twisted profile wires. The rims of these wires represent obstacles for the flow of the liquid and induce lateral (laminar) flows. These lateral flows lead to a local mixing of the analyte and thus increases strongly the probability for particles or cells contained in the liquid to contact the wire.

The extent of the generated cross-flows depends on profile shape, torsion, diameter, and orientation of the wire. Even a small inclination of the wires by 1–2° with respect to the axis of capillary results in an increase in particle contacts by a factor of about 2 for many geometries. Torsion and wire diameter can increase the fluid volume contacting the wire by factors ranging each between roughly 1.5 and 8. When all these factors are considered, an optimal geometry is chosen, and the number of surface-contacting particles can be enhanced by a factor of about 80 in comparison to the number captured on a simple round wire. When a mean flow rate of 1–3 cm s⁻¹ is applied, a simple round wire probes only a very small sample volume (in the range of 0.1–1 ml h⁻¹) and suspended particles can only reach the surface by Brownian motion. In contrast to this, the optimized wire geometries presented here allow the sampling of easily more than 4–10 ml h⁻¹.

In summary, the geometrically enhanced sensor surfaces presented here offer an interesting perspective for an efficient *in vivo* sensing of cells in laminar fluid flows of venous blood capillaries. The presented data show that the shape of functionalized medical wires has an important influence on the capture efficiency when they are used as collectors for rare cells in the blood stream of a patient. A further optimization of the cell capture efficiency could be achieved by parallelization of wire-like sensor setups. However, in doing so, one has to watch that such structures integrated into the circulation do not obstruct the blood flow and cause problems with blood cell coagulation as this would generate thromboses. Such improved wire structures would open the pathway to a very efficient *in-vivo* screening for rare cells.

SUPPLEMENTARY MATERIAL

See [supplementary material](#) for details on the calculation of the effective rim number (R) from rectangular cross-sections with different aspect ratios.

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