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Magnetically Enhanced Microflow Cytometer for Bead- and Cell-based Immunoaffinity Measurements in Whole Blood Samples

Scientific thesis for the attainment of the academic degree
Master of Science (M.Sc.)
of the Department of Electrical and Computer Engineering
at the Technical University of Munich.

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Contents

1. Theoretical Prequisites

The main measurement principle by a GMR (giant magneto resistance)-Sensor has been already described and characterized exhaustively by Helou [1], Reisbeck [2] and Brenner [3]. Therefore, this theoretical part will focus on (bio-)physical aspects of a cell rolling motion inside a microfluidic channel and surface modification chemistry.

1.1. Microfluidics

The main experiments of this work were carried out in microfluidic environments, which exhibit favorable properties compared to common turbulent systems. From a fluid-mechanical standpoint, shrinking the scales makes interfacial as well as electrokinetic phenomena much more significant, and reduces the importance of pressure and gravity.[4] However, electodynamics, chemistry and fluid dynamics are incetricably intertwined, so that fluid flow can create electric fields (and vice versa), with a degree of coupling driven by the surface chemistry. Many of the resulting phenomena arise or can explained by Cauchy-Momentum equation (eq. 1.3) and the resulting Navier-Stokes equation for incompressible fluids (eq. 1.4).

$$\frac{\partial}{\partial t}\iiint \rho \mathrm{dV} = -\iint \rho \mathbf{u}\cdot \vec{\mathbf{n}}\mathrm{dA} \tag{1.1}$$

$$\nabla \cdot \mathbf{u} = 0 \tag{1.2}$$

$$\rho\frac{\partial \mathbf{u}}{\partial t} + \rho\mathbf{u}\cdot\nabla\mathbf{u} = \nabla\cdot\boldsymbol{\tau} + \sum_i \mathbf{f}_i \tag{1.3}$$

$$\underbrace{\rho\frac{\partial \mathbf{u}}{\partial t}}_{\text{Transient}} + \underbrace{\rho\mathbf{u}\cdot\nabla\mathbf{u}}_{\text{Convection}} = \underbrace{-\nabla p}_{\text{Pressure}} + \underbrace{\eta\nabla^2\mathbf{u}}_{\text{Viscous}} + \underbrace{\sum_i \mathbf{f}_i}_{\text{Body Forces}} \tag{1.4}$$

conservation of mass, momentum reynolds number

Figure 1: 1
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Figure 2: 1
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Figure 3: 1
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1.1.1. Flow Field inside Microchannels

The foremost characteristic of a microchannel is the laminar flow behavior, which causes deterministic pathlines. Mathematically this is described by the reynolds number, which compares the intertia to shear forces. If it results below a certain threshold of 2000, laminar flow can be assumed. This holds true for the utilized microfluidic with the dimensions 12 000 µm x 700 µm x 150 µm (l x w x h) and aequous buffer solutions, where the channel width was used as characteristic length l. Hence, the Navier-Stokes equation can be applied to our system.

$$Re \;=\; \frac{2\rho|\overline{u}|l}{\eta} \tag{1.5}$$

The step from the Cauchy momentum equation to the Navier-Stokes equation is complex and harbors several sources of error. First, an incompressible newtonian fluid as well as channel is assumed. The used water suspensions can be approximated with negligible compressibility, which is not true for the real case. Also, for blood or other shear-thinning fluids some deviations are prone for high errors. This happens due to the fact that the $\boldsymbol{\tau}$ (surface stress tensor) is decomposed into pressure and viscous contributions as shown in the equations 1.6. Then, the divergence relation of the respective viscous stress (eq. 1.7) does not hold for non-uniform viscosity η.

$$\boldsymbol{\tau} = \boldsymbol{\tau}_{viscous} + \boldsymbol{\tau}_{pressure} = 2\eta\epsilon - p\mathbf{I}_{3\times3} \tag{1.6}$$

$$\nabla\cdot\boldsymbol{\tau}_{viscous} = \nabla\cdot 2\eta\epsilon = \nabla\cdot\eta\nabla\mathbf{u} \;\underset{uniform}{\overset{only\ if\ \eta}{=}}\; \eta\nabla^2\mathbf{u} \tag{1.7}$$

Second, the channel height varies in reality as a result of fabrication inaccuracies. In the model case of a flow through a rectangular channel, no analytical solution of the Navier-Stokes equation exists, but a Fourier Series expansion if channel width is larger than

Figure 4: 1
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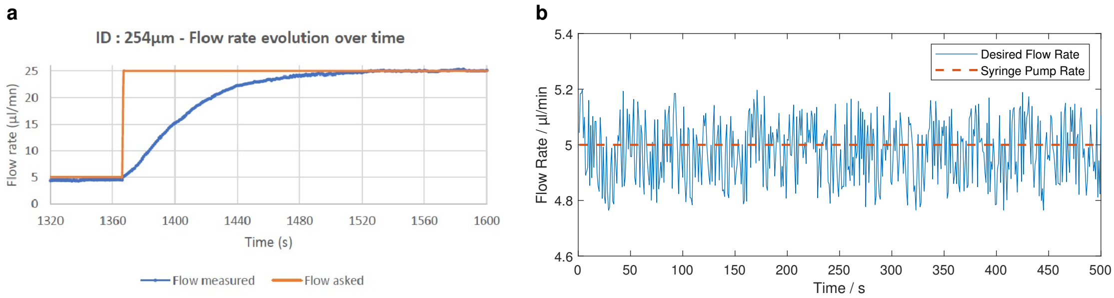


Figure 5: Syringe Pump error sources
Set flow rate: , Real Flow Rate: **a,** Transient step answer of a syringe pump through a microtube with 254 µm inner diameter. **b,** Steady state flow rate error around the desired 5 µL min^{-1} dispensing rate. A sinusoidal behaviour caused by the microstepping can be observed. [6]

channel height. [5] The equation 1.8 shows that height deviations can have prominent influence on a channel velocity simulation as it is proportional to h^2. Further, the flow rate (which is the velocity integral over the channel cross section) depends even on h^3.

$$u_x(y,z) = \frac{4h^2 \Delta p}{\pi^3 \eta l} \sum_{n,odd}^{\infty} \frac{1}{n^3} \left(1 - \frac{\cosh(n\pi \frac{y}{h})}{\cosh(n\pi \frac{w}{2h})}\right) \sin(n\pi \frac{z}{h}) \quad (1.8)$$

Third, the transient term (eq. 1.4) was neglected in all simulations, but a connected syringe pump possesses a slow rise time (Fig. 5a) and a remaining “pulsation error” in steady state (Fig. 5b). In effect, another error adds to the simulation, which is only valid after several ten seconds of the last flow rate change.

For later studies in a matlab model, the flow velocity and shear stress computations were carried out with the error sources considered.

1.1.2. Particles in Microfluidics

Stokes Drag Force Gravity Electro-static interaction Magnetic Force Friction Interface-Forces

1.1.3.

1.2. Surface Chemistry

Molecules can be immobilized through various mechanisms on surfaces to achieve a biological or chemical functionality. The most simple is physisorption. Here, a biomolecule is bonded only by weak elektrostatic, van-der-Waals or dipole-dipole interaction with a adsorption enthalpy below $50\,\mathrm{kJ\,mol^{-1}}$. In contrast, this yields fast reaction rates, because no activation energy has to be overcome. Although a large number of molecules can be captured with this method, several drawbacks have been identified. [7], [8] For example, immobilized receptors can start to desorb or change their position, which in turn reduces sensitivity or causes false-positive results. [9], [10]
Therfore, most functionalization approaches rely on chemisorption where molecules are covalent bound to a surface. Due to the higher activation energy barrier this bonding mechanism works slower in comparison to physisorption though higher temperatures or catalysators can promote an equilibrium. One of the most well-known strategies to bring reproducible thin films on surfaces is the formation of SAMs (self-assembled monolayers) where a dense layer of single molecules with high internal order forms upon dipping into a surface-active substance. [11]

1.2.1. Silane Chemistry

By the use of silane chemistry a surface is rendered organofunctional with alkoxysilane molecules. Since glass, silicon, alumina, titania, and quartz surfaces, as well as other metal oxide interfaces, are rich in hydroxyl groups, silanes are particularly useful for modifying these materials. [12]
The general formula for a silane coupling agent (Fig. 6) typically shows the two classes of functionality. X is a hydrolyzable group typically alkoxy, acyloxy, halogen or amine.
Following hydrolysis, a reactive Si−OH (silanol) group is formed, which can condense with other silanol groups to form Si−O−Si (siloxane) linkages. (Fig. 7) Stable condensation products are also formed with other oxides such as those of aluminum, zirconium, tin, titanium, and nickel. Less stable bonds are formed with oxides of boron, iron, and carbon, whereas alkali metal oxides and carbonates do not form stable bonds with siloxanes at all. The R group (Fig. 6) is a nonhydrolyzable organic radical that may posses a functionality that imparts desired characteristics. One of the more common silanes is APTES ((3-

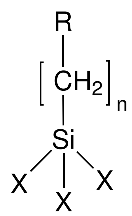


Figure 6: Trialkoxysilane Structure of a typical trialkoxysilane, X: hydrolyzable group, R: non-hydrolyzable organic radical, n: methylene chain-length

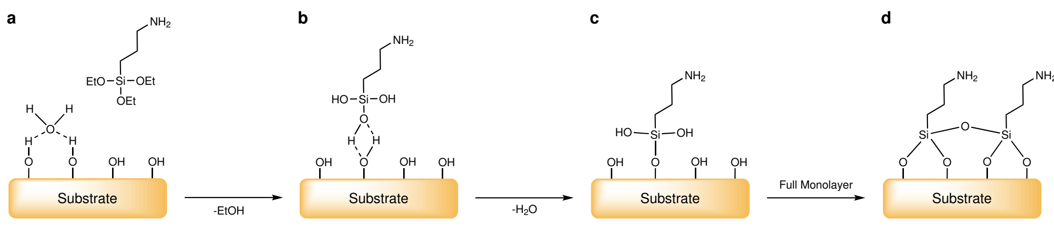


Figure 7: APTES Modifcation of an oxidized surface
a Before the condensation reaction, the oxidized surface forms hydrogen bonds with water molecules. The silane molecules are in the bulk solution. **b** The hydrolyzed Si—OH group adsorbs onto the surface and forms hydrogen bridges with it. **c** In a condensation reaction, under the loss of water, a covalent bond to the surface forms. **d** After the SAM assembly the surface is saturated with a covalent-bound, crosslinked silane film. [18]

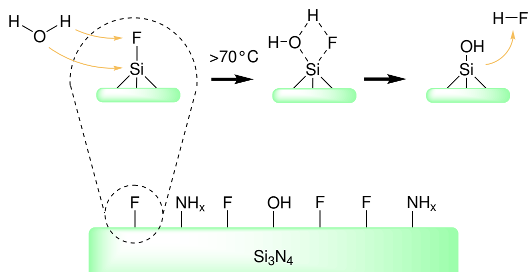
aminopropyl)triethoxysilane), where the X group consists of an $-O-CH_2-CH_3$ (ethoxy) group, the organic rest R is substituted by an $-NH_2$ (amine) and the 3 $-CH_2-$ (methylene) groups alter n to 3. [13] The final result of reacting an organosilane with a substrate ranges from altering the wetting or adhesion characteristics of the substrate, utilizing the substrate to catalyze chemical transformation at the heterogeneous interface, ordering the interfacial region, and modifying its partition characteristics. Significantly, it includes the ability to effect a covalent bond between organic and inorganic materials. Especially in optical or biological sensors, silane modifications open a broad range of applications.

However, the silanization reactions bear a few drawbacks which are often neglected. For instance, silane chemistry is strongly temperature and pH-dependent. [14], [15] Further, in a process to build SAMs out of APTES, the reaction has to be catalyzed by water. But already small changes in the water content cause dramatic deviations in layer thickness. [16] Additionally, silanes can crosslink to themselves through possible side reactions. (Fig. 7 D) [17]

Oxidation
To modify a surface by silanization, oxidized sites ($-OH$ (hydroxyl) resp. $Si-OH$ groups) have to be present. To increase the presence of those reactive groups on differing substrates, various activation methods such as HF (hydrofluoric acid) dip, Piranha (H_2O_2:H_2SO_4) or O_2 (oxygen gas) - plasma treatment can be chosen. [19]

1.2.2. Carbodiimide Crosslinker Chemistry

The in the previous manner produced $-NH_2$ (amine) terminated films form the



basis of many reactions and open the possibility to various applications, such as the direct attachment of biofunctional molecules by carbodiimide crosslinking chemistry.[20] EDC-NHS-Activation sulfo-NHS vs. NHS

1.2.3. Microscopic Particle Surface Physics

1.2.4. The Biotin-Avidin-System

1.3. MRCyte

Short intro over MRCyte Foto of setup with arrows to necessary parts Microscope Stages PEEK holder Helmholtz coils Kepco MFLI DAQ

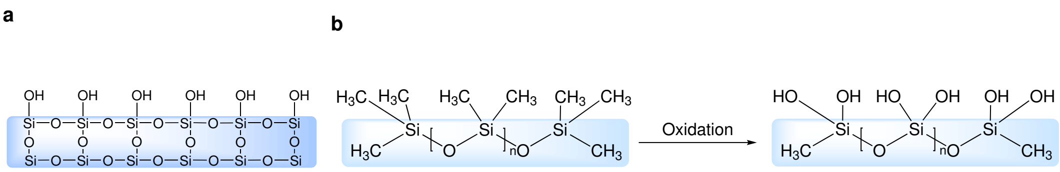


Figure 8: Different substrate surfaces: glass and PDMS
Surface groups and internal structure of quartz glass (**a**) and PDMS (poly(dimethyl siloxane)) (**b**). After an oxidation step, the methyl groups are changed to hydroxyl.

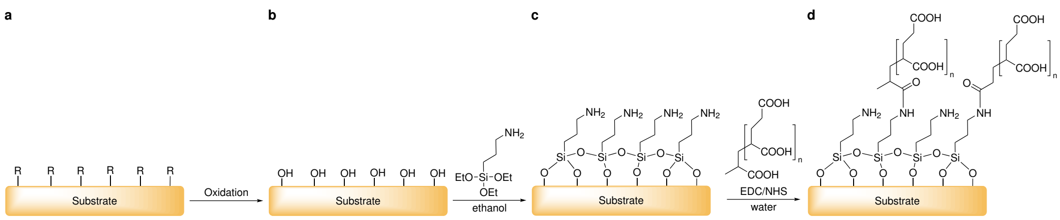


Figure 10: General process chain of chemical surface modification
Any substrate with various surface groups R (**a**) is oxidized to exhibit hydroxyl groups.(**b**). Then a silane SAM is attached (**c**) and subsequently modified by carbodiimide chemistry with Poly(acrylic) Acid. (**d**)

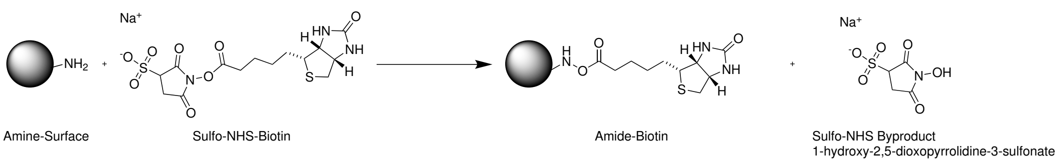


Figure 11: Amine bead modification with Sulfo-NHS-Biotin
An amine terminated bead is incubated with sulfo-NHS-Biotin to cover its surface by amide-Biotin. As byproduct the sulfo-NHS-ester 1-hydroxy-2,5-dioxopyrrolidine-3-sulfonate splits off.

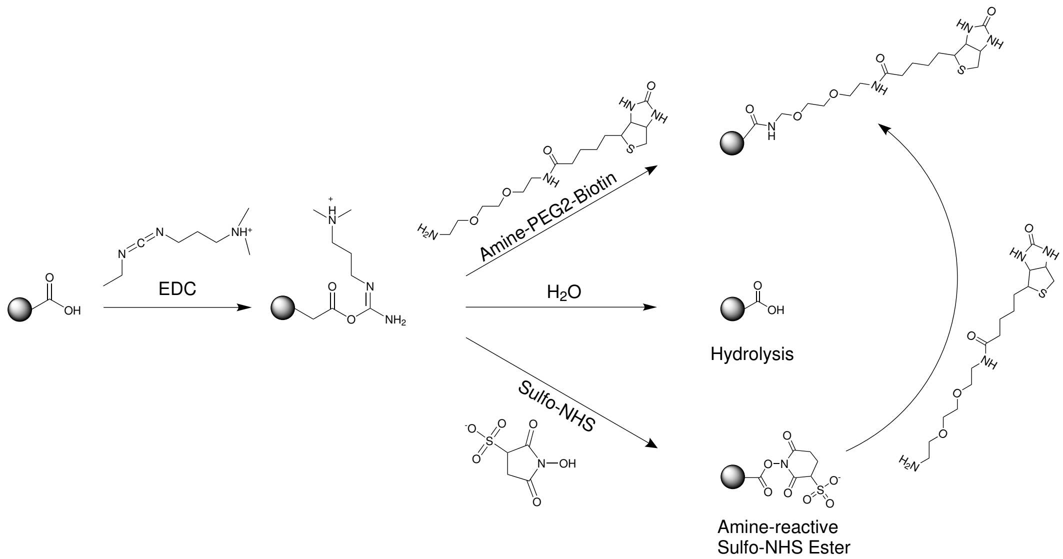


Figure 12: Carboxyl bead modification with EDC/NHS
The carboxy groups bead are activated with EDC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide) to an active O-acylisourea intermediate. This can then either be nucleophilicly attacked by a primary amine of the amine-PEG$_2$-biotin reactant or - due to its instability - hydrolzed back to a regenerated carboxyl surface. A present NHS-ester can also displace the O-acylisourea to form a considerably more stable intermediate which then itself reacts with any primary amine.

1.3.1. Focusing Structures

test,test Loss because of reduced velocity and magnetic drag

1.3.2. GMR

Different produced GMR stacks Wheatstone Bridge setup Magnet alignment

1.3.3. Electrical Circuit

Ground PCB Stacked PCBs with spacer

1.3.4. Electronic Readout

test,test

Hysteresis Alignment

test,test

Single GMR

test,test

Dual GMR

one MFLI supplies both at same freuqency. Aux Trigger tested, but no advantage.

2. Results

test,test

2.1. Signal Similarity For Cells With Varying Bead Coverages

Cross-Correlation between single dipole with sum magentic moment and surface covered with randomly distributed magnetic particles

2.1.1. Single Cell Signal

2.1.2. Cell Aggregates

2.2. Reference Bead Surface Functionalization

2.2.1. Amine-Surface Biotinylation

Streptavidin-Atto488 reference calibration Anti-Biotin-PE working? BNF-Dextran-Streptavidin unspecific binding?

Magnetic Polystyrene Bead

Non-Magnetic Polystyrene Bead

2.2.2. Carboxy-Surface Biotinylation

2.3. Concentration Measurements in MRCyte

2.3.1. Count Stability

Measurement over 1h Measurement of Syringe Tubing Losses

2.3.2. Velocity Measurement

2.3.3. 2-Chip-Setup for Macro Measurements

Sensitivity Calibration

Concentration Measurements

2.4. Protein Immobilization On The Microfluidic Channel Bottom

2.4.1. Physisorption

Quantification in Plate Reader Trial with Neutravidin + Sensor (Esthis Versuch)

2.4.2. Covalent Attachment

Plasma-Based Approach

Water-Based Approach

Sonicate in Acetone and Water 5’ 1:1 HCl (hydrochloric acid):Methanol H_2SO_4 (sulfuric acid) Treat for 30 min in light boiling water

List of Abbreviations

Symbols

$\boldsymbol{\tau}$ - surface stress tensor

η - dynamic viscosity

μF - microfluidic

ρ - density

$\sum_i \mathbf{f}_i$ - body forces

Si$-$O$-$Si - siloxane

$-CH_2-$ - methylene

$-NH_2$ - amine

$-$OH - hydroxyl

$-O-CH_2-CH_3$ - ethoxy

A

AAF - artificial Anti-Ferromagnet

AcOH - acetic acid

AFM - Anti-Ferromagnetism

APTES - (3-aminopropyl)triethoxysilane

D

diH_2O - deionized water

E

EDC - 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

EtOH - ethanol

F

FM - Ferrimagnetism

FWHM - full width at half maximum

G

GMR - giant magneto resistance

H

H_2O_2 - hydrogen peroxide

H_2SO_4 - sulfuric acid

HCl - hydrochloric acid

HF - hydrofluoric acid

I

IPA - isopropanol

M

MACS - MACS running buffer

MeOH - methanol

MES - 2-(N-morpholino)ethanesulfonic acid

MNP - magnetic nanoparticle

N

N_2 - nitrogen gas

NFM - non-ferro-magnetic

NHS - N-hydroxysuccinimide

O

O_2 - oxygen gas

P

PAA - Poly(acrylic) Acid

PBS - phosphate buffered saline

PCB - printed circuit board

PDMS - poly(dimethyl siloxane)

Piranha - H_2O_2:H_2SO_4

PM - Paramagnetism

S

SAM - self-assembled monolayer

Si_3N_4 - silicon nitride

Si$-$OH - silanol

SMA - styrene maleic anhydride

SPM - superparamagnetism

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Statement

I declare that I have authored this thesis independently, that I have not used other than the declared sources / resources, and that I have explicitly marked all material which has been quoted either literally or by content from the used sources.

Munich, December 4th, 2020, Signature