# Lab on a Chip

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# Optofluidic micro-sensors for the determination of liquid concentrations†‡

Emanuel Weber $*^{ab}$  and Michael J. Vellekoop<sup>a</sup>

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We present a novel optofluidic device for non-invasive and label-free determination of liquid concentrations. A microfluidic channel filled with the sample solution is hit by laser light in an angle close to the critical angle for total internal reflection. Due to the intentionally defined divergence of the incident beam, parts of the rays will experience total internal reflection while another part will be transmitted. Both reflected and transmitted light signals are recorded and the ratio of these signals is used for sample characterization. The stability compared to single signal analyses is significantly improved, resulting in a resolution of approximately 40 mmol  $L^{-1}$ . The typical working range of the device under investigation is between a few tens of mmol  $L^{-1}$  and 5 mol  $L^{-1}$  making it useful for applications in the food industry, for example to determine the amount of phosphates in liquid products.

# Introduction

For many biological and chemical applications, a precise control of concentrations is crucial for a successful execution of certain tasks. For example, ethanol,<sup>1,2</sup> protein,<sup>3,4</sup> and salt<sup>5</sup> content in liquid samples have to be monitored over time. This demand has fuelled a pursuit of microfluidic lab-on-a-chip devices performing such kind of analyses in a simple and fast manner on a miniature scale. For insoluble, solid components such as particles and cells, micro-flow cytometry is often utilized for the determination of concentrations.<sup>6-9</sup> Segerink et al. implemented an electrical impedance measurement circuit to determine spermatozoa concentrations in semen,<sup>10</sup> and Choi et al. have developed a device exploiting Raman spectroscopy for the detection of protein aggregates in solution.<sup>11</sup> Many of these analysis devices employ optical principles for the read-out. This has led to the fusion of microfluidics and optics and a new field called optofluidics has emerged.<sup>12,13</sup> Starting with the realization of liquid waveguides,<sup>14,15</sup> up to now optofluidic principles are embedded in different devices ranging from liquid micro-lenses<sup>16</sup> to on-chip laser systems.<sup>17</sup> Since most of the optical elements for those devices are non-solid and hence exchangeable, the flexibility and tunability are increased tremendously. In all these applications the refractive indices (n) of the employed liquids

<sup>b</sup>Institute of Sensor and Actuator Systems, Vienna University of

Technology, 1040 Vienna, Austria. E-mail: emanuel.weber@tuwien.ac.at; Fax: +43-1-58801-36699; Tel: +43-1-58801-76654 play an important role. Lenses would lose their focus and waveguides would stop guiding light if a mismatch in this property is evident.

In this paper we report an optofluidic sensor principle for the determination of the concentration of dissolved molecules in liquids. The investigated samples have an influence on the refractive index of the buffer solution which is exploited for sample characterization. In other work, different approaches for the determination of the refractive index of liquids on-chip have been presented. Lapsley et al.<sup>18</sup> have developed a planar, optofluidic Mach-Zehnder interferometer for the characterization of liquid samples. Chao et al.<sup>19</sup> have designed two different devices for the determination of refractive indices of liquids, one based on light refraction in a liquid filled prism and the second one using a refraction channel where light is coupled out of a liquid core waveguide in an angle corresponding to the refractive index of the core solution. Seow et al.<sup>20</sup> have exploited the principle of partial reflection to determine the refractive index of fluids. In this setup the reflectivity as well as the angle of the exiting light are used as a measure for the refractive index. Another device by Lapsley et al.<sup>21</sup> uses the reflection property of liquids with different refractive indices to build up a variable optical attenuator. Depending on the solution filled in the channel the optical output power can be adjusted.

We present a device, which is based on the principle of partial total internal reflection occurring at the solid–liquid interface when the center incident angle of a slightly diverging light beam is close to the critical angle. On the device, both signals, the reflected and the transmitted, are recorded. Compared to approaches performing the analysis using a single signal, a drastically increased stability is obtained. Furthermore, two signals provide a permanent verification of the measurement results, allowing changes in the signals generated by laser power instabilities to be discarded. The improved stability allows for a

<sup>&</sup>lt;sup>a</sup>Institute for Microsensors, -actuators and -systems (IMSAS), MCB, University of Bremen, 28359 Bremen, Germany

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<sup>‡</sup> Electronic supplementary information (ESI) available: parameters of integrated optical components, incident beam optical power distribution, theoretical comparison of fully collimated and slightly diverging laser beam, dependency of results on the flow rate, temperature dependency, scanning electron microscope images of the fabricated devices, cross-section of the chip assembly. See DOI: 10.1039/c2lc40616k

more accurate analysis and has different practical applications. In the food industry, for example, various phosphates play an important role as additives. The maximum amounts of additives for certain food products in Germany are regulated in the "Zusatzstoff-Zulassungsverordnung"(ZZulV).<sup>22</sup> For different phosphates, a span between 0.5 g kg<sup>-1</sup> and 50 g kg<sup>-1</sup>, corresponding to a mono-phosphate concentration of approximately 3 mmol L<sup>-1</sup> and 0.3 mol L<sup>-1</sup>, respectively, is defined. Using the proposed design, concentrations in the range of tens of millimol per liter can be identified, making this principle a promising approach for control applications in this area.



# Fig. 1 True-to-scale schematic of operation principle and fluorescence ray-tracing photographs illustrating real behavior of the device. Width of the microfluidic channel is 70 $\mu$ m. At samples having a) for a relatively low refractive index, a larger amount of light is reflected and results in a high signal in output 1 and a low signal in output 2. b) for a relatively high refractive index, more light is transmitted and produces a high signal in output 2 and a low signal in output 1.

# **Optofluidic chip design**

The operation principle of the design is depicted in Fig. 1. The microfluidic channel filled with the analyte is hit by slightly diverging laser light. An integrated waveguide ensures precise on-chip light positioning. The core of this waveguide has a width of 100 µm, allowing most of the light exiting the peripheral glass fiber to be collected. An air micro-lens arranged after the integrated waveguide defines the divergence  $(\pm 3^{\circ})$  of the laser beam hitting the microfluidic channel. Two collecting lenses on the chip are responsible for focusing the reflected as well as the transmitted light which are consecutively coupled into two separate peripheral glass fibers. These lenses are bigger in size to counter beam broadening due to the divergence of  $+3^{\circ}$ . In this way, the major part of the reflected and transmitted light can be collected. To keep absorption losses to a minimum the lenses were placed as close as possible to the microfluidic channel, limited only by the fabrication method. The lens on the transmission side has a small lateral offset with respect to the incident light to compensate for light deflections by the microfluidic channel. Parameters of the integrated optical components can be found in the electronic supplementary information (see S1, ESI<sup>‡</sup>). The angle of the incident light is adjusted to result in partial total internal reflection at the solidliquid interface. For a given chip material the critical angle,  $\theta_c$ , is defined by

$$\sin(\theta_c) = \frac{n_{\text{analyte}}}{n_{\text{material}}}$$

where  $n_{\text{analyte}}$  and  $n_{\text{material}}$  are the refractive indices of the analyte and the chip material, respectively. After focusing the laser light on-chip, the incident angles vary approximately  $\pm 3^{\circ}$  around the center angle. The center incident angle and the span of  $\pm 3^{\circ}$ defines the working range of the design and can be optimized for the desired specifications. For device fabrication a dry resist with a refractive index of approximately 1.52 was used. This value was determined in a separate experiment using an air-prism in a layer of dry resist. For de-ionized (DI, n of 1.33) water as the analyte, the critical angle is calculated as 61.04°. If the center angle of the incident light is set in the vicinity of this value, a part of the light is totally reflected and subsequently results in a signal in output 1, whilst, at the same time, the other part is transmitted according to the Fresnel equations which increases the signal in output 2 if the analysis channel is filled with DI water. A correlation of these two signals is then used to deduce the composition of the sample being analyzed.

The theoretical situation for a center incident angle of  $65^{\circ}$  is examined in detail. Light rays will approach the microfluidic channel in angles between  $62^{\circ}$  and  $68^{\circ}$ . Partial total internal reflection starts once the refractive index of the sample exceeds

$$n_{\text{analyte,min}} = n_{\text{material}} \cdot \sin(62^\circ) = 1.34$$

Above a certain refractive index, no light ray will experience total internal reflection. This value is calculated using the largest incident angle

$$n_{\text{analyte,max}} = n_{\text{material}} \cdot \sin(68^\circ) = 1.41.$$

These two values define the working range of the device with a center incident angle of  $65^{\circ}$ . The Fresnel equations which give the amount

of reflected light at the solid-liquid interface for parallel and perpendicularly polarized light are

$$R_{\parallel} = \left| \frac{n_{\text{material}} \cdot \cos(\theta_t) - n_{\text{analyte}} \cdot \cos(\theta_i)}{n_{\text{material}} \cdot \cos(\theta_t) + n_{\text{analyte}} \cdot \cos(\theta_i)} \right|^2$$

and

$$R_{\perp} = \left| \frac{n_{\text{material}} \cdot \cos(\theta_i) - n_{\text{analyte}} \cdot \cos(\theta_t)}{n_{\text{material}} \cdot \cos(\theta_i) + n_{\text{analyte}} \cdot \cos(\theta_t)} \right|^2,$$

respectively, where  $\theta_i$  is the incident angle of the light. The exit angle of the transmitted light,  $\theta_t$ , can be calculated using Snell's law

$$\frac{\sin(\theta_i)}{\sin(\theta_t)} = \frac{n_{\text{analyte}}}{n_{\text{material}}}$$

The difference between  $n_{\text{analyte}}$  and  $n_{\text{material}}$  is intentionally kept small. In this case the reflectivity of parallel and perpendicularly polarized light does not significantly differ, justifying the use of an average value which is defined by

$$R = \frac{R_{\parallel} + R_{\perp}}{2}$$

The incident beam optical power distribution at the microfluidic channel was approximated as constant over the divergence of  $\pm 3^{\circ}$  (see S2, ESI<sup>‡</sup>). The comparison of the calculated averaged reflectivities of the proposed  $\pm 3^{\circ}$  divergent laser beam with a fully collimated incident beam (no partial total internal reflection occurs) at a center incident angle of 65°, shows remarkable differences (see S3, ESI<sup>‡</sup>). An increased working range and an almost linear relation between the refractive index and reflectivity over a huge range are obtained with the slightly diverging laser beam. For the derivation of the transmittance an analogous procedure can be applied.

In order to characterize its performance, we have tested the device with calcium chloride (CaCl<sub>2</sub>) samples. Table 1 summarizes the refractive indices of CaCl<sub>2</sub> solutions of different concentrations at a measuring wavelength of 589 nm.<sup>23</sup> With the given working range, CaCl<sub>2</sub> concentrations between 0.5 mol L<sup>-1</sup> and 3.5 mol L<sup>-1</sup> can theoretically be differentiated. It should be mentioned at this point that the wavelength used for measurements in the following sections was 531 nm. This differs from 589 nm, which was used for the determination of the refractive indices of the CaCl<sub>2</sub> solutions in Table 1. Although a significant difference is not expected, these absolute values should not be compared with the measurement results and are simply given to provide the reader with a feeling for the impact of CaCl<sub>2</sub> on the refractive index.

Table 1 Refractive indices of calcium chloride solutions at different concentrations, measured at a wavelength of 589 nm and a temperature of 20  $^\circ C^{23}$ 

Concentration (mol $L^{-1}$ )	Refractive index
0.045	1.3342
1.191	1.3625
2.122	1.3839
3.179	1.4066
4.062	1.4242
5.030	1.4420

### **Materials**

Chips were fabricated in dry film resist (Ordyl SY330 and SY317; ElgaEurope, Italy). Ordyl developer was composed of xylene, 2-butoxyethylester, and ethylbenzene (56/30/14, v/v/v; Sigma-Aldrich, USA). Calcium chloride (CaCl<sub>2</sub>), monosodium phosphate (NaH<sub>2</sub>PO<sub>4</sub>), and monopotassium phosphate (KH<sub>2</sub>PO<sub>4</sub>) were purchased from Carl Roth (Germany). A 531 nm diode pumped solid state laser (20 mW, linear polarization, Roithner LaserTechnik, Austria) was used as external light source. Peripheral light guiding was managed with reduced cladding glass fibers ( $50 \mu$ m core diameter,  $70 \mu$ m cladding diameter, numerical aperture of 0.22; Polymicro Technologies, USA) and pre-amplified silicon photodetectors (Thorlabs, USA) were used for the read-out.

# **Experimental setup**

A schematic of the overall setup, consisting of an external light source, three reduced cladding glass fibers, two pre-amplified silicon photodetectors, a digital storage oscilloscope, the sample solution (DI, CaCl<sub>2</sub> dissolved in DI, or a phosphate solution), a fluidic waste box, and the optofluidic chip is shown in Fig. 2. The flow velocity of the analyte in the microfluidic channel does not have any influence on the results (see S4, ESI<sup>‡</sup>). Therefore, a stop-and-go flow profile was applied in all the experiments to keep sample consumption at a minimum. All experiments were conducted at room temperature (22 °C)  $\pm 1$  °C. Temperature variations have only a minor impact on the results (see S5, ESI<sup>‡</sup>).



**Fig. 2** Overall experimental setup consisting of an external light source, three reduced cladding glass fibers (green lines), two pre-amplified silicon photodetectors, a digital storage oscilloscope, the sample solutions (DI, CaCl<sub>2</sub> dissolved in DI, or a phosphate solution), a fluidic outlet, and the optofluidic chip on the PMMA microscope slide. A light microscope having a CMOS camera attached is used for visual inspection.

One end of all three glass fibers is equipped with an SMA connector for direct connection to the light source as well as to the photodetectors. The bare other end is clamped onto the optofluidic chip using integrated fiber-grooves. The signals of the two photodetectors are recorded simultaneously using a digital storage oscilloscope. A syringe pump is used to manage the supply of sample solution through PTFE tubings into the microfluidic channel. The outflow is collected in a waste box. To allow for visual inspection of the on-goings in the microchannel the optofluidic chip is placed under a light microscope having a CMOS camera attached.

# **Results and discussion**

The devices presented in the next sections were all fabricated in dry resist following the protocol described by Weber *et al.*<sup>24</sup> Advantages of this technique are fast prototyping (production of devices within a few hours) and cost efficiency. Aspect ratios of two are achievable which qualifies this technology for the given application. The wall surface smoothness, which is of importance for optical aspects, can still be improved (see scanning electron microscope images in S6, ESI‡) allowing to further enhance the performance of the devices by employing other fabrication techniques.

The sidewalls of the microfluidic channels are made from dry resist with a refractive index of 1.52. The bottom is a polymethyl methacrylate (PMMA) microscope slide, with a refractive index of 1.49.<sup>25</sup> On the top of the channels a 17 µm thick layer of dry resist (n of 1.52) is bonded on a polyester foil (n in the range of 1.6). Keeping the optical aspect of waveguiding in mind, the used chip assembly is not entirely optimized in the z-direction (see schematic of cross-section in S7, ESI<sup>‡</sup>). Although having full light control in 2 dimensions (x-y plane), in particular the top border does not allow light confinement within the microfluidic layer. Using SU-8 as chip material (*n* exceeding  $1.60^{26}$ ) sandwiched between two layers of borosilicate glass (n in the range of 1.50) would further improve the optical yield of such devices. Nevertheless, the use of dry resist allows for fast and cost effective prototyping and was chosen to demonstrate the functionality of the proposed system.

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Fig. 3 Offset corrected and normalized reflected (output 1) and transmitted (output 2) light signals for all four devices at different CaCl<sub>2</sub> concentrations. Solid lines represent reflected and dashed lines represent transmitted light signals recorded by external photodetectors. For different incident angles, different working ranges are evident.

# Optimization of incident angle

As mentioned before, the presented principle can be optimized for various ranges of interest. To cover  $CaCl_2$  concentrations from 0 mol  $L^{-1}$  up to 5 mol  $L^{-1}$ , four designs with different incident angles were investigated. The angles were set to 60°, 62.5°, 65°, and 67.5°. All the designs were optimized using raytracing simulations (ZEMAX, USA). The first angle was chosen to be sensitive for very low concentrations and the last one for CaCl<sub>2</sub> concentrations close to 5 mol  $L^{-1}$ .

For the first characterization of the devices, the channels were filled with  $CaCl_2$  solutions of a known concentration and the signals of both outputs were recorded. Fig. 3 depicts the obtained results where reflected light signals of all four devices are illustrated by solid lines and the corresponding transmitted light signals by identical colored dashed lines.

The output signals of the external photodetectors were offset corrected to counter any dark currents and normalized by the maximum values before printing in the diagram. As expected, the device with an incident angle of 60° shows sensitivity already for DI water. Neither the reflected nor the transmitted signal at 0 mol  $L^{-1}$  CaCl<sub>2</sub> is at its maximum or minimum, respectively. This means that at this point, partial total internal reflections occurs. With increasing concentration the reflected signal converges to zero while the transmitted signal reaches its maximum and defines the end of the working range of the device. The situation for the other devices is similar but shifted towards higher concentrations. The device with an incident angle of 67.5° shows sensitivity for concentrations up to 5 mol  $L^{-1}$  and above. Due to the finite solubility of CaCl<sub>2</sub> in DI water the analysis was stopped at a concentration of 5 mol  $L^{-1}$ . Theoretically, these curves can be continued to any higher values.

The working ranges of the devices are summarized in Table 2. Each one can be used over approximately 2 mol  $L^{-1}$ . By changing the divergence of the laser beam hitting the micro-fluidic channel, this span can be either enlarged or further reduced. Depending on the application, a perfectly optimized design can be elaborated. The only limitations are the size of the device (larger divergences call for longer analysis channels), the incident optical power which has to be increased for higher divergences to obtain a similar sensitivity, and the length of the optical path on-chip causing absorption losses and beam expansion. Considering these parameters for the given device, an increase in working range by a factor of two is feasible.

### Determination of CaCl<sub>2</sub> concentration

Before starting with the determination of  $CaCl_2$  concentrations, a calibration curve for each device was recorded. Similar to the angle study described in the preceding section, channels were filled with know concentrations of  $CaCl_2$  solutions and the signals in output 1 and output 2 were measured. To increase the

Table 2 Working ranges of the investigated designs

Incident angle	Lower limit	Upper limit
60.0° 62.5° 65.0° 67.5°	$\begin{array}{c} 0 \ \text{mol} \ L^{-1} \\ 1 \ \text{mol} \ L^{-1} \\ 2 \ \text{mol} \ L^{-1} \\ 3 \ \text{mol} \ L^{-1} \end{array}$	$\begin{array}{c} 2 \ \text{mol} \ L^{-1} \\ 3 \ \text{mol} \ L^{-1} \\ 4 \ \text{mol} \ L^{-1} \\ 5 \ \text{mol} \ L^{-1} \end{array}$





**Fig. 4** Normalized ratio of reflected and transmitted light signal plotted against CaCl<sub>2</sub> concentration. Obtained data points for each device were fitted on a Boltzmann sigmoidal distribution.

accuracy of the calibration curve, the signals for each concentration were recorded over five seconds and an average value was calculated. The ratio of corresponding reflected and transmitted value was then taken, normalized, and plotted against the CaCl<sub>2</sub> concentration (Fig. 4).

For each individual device the collected data points were fitted on a curve using a best-fit algorithm (OriginPro, USA). The obtained best-fit function is a Boltzmann sigmoidal distribution defined by

$$y = \frac{A_1 - A_2}{1 + e^{\frac{x - x_0}{dx}}} + A_2$$

where  $A_1$ ,  $A_2$ ,  $x_0$ , and dx are constants obtained separately for each device (summarized in Table 3 for all four devices), x gives the  $CaCl_2$  concentration, and y stands for the absolute ratio of reflected and transmitted light signal. The obtained equations are then used to determine the CaCl<sub>2</sub> concentration from the ratios of reflected and transmitted light signals. For practical applications lower concentrations of dissolved molecules might be of more interest than higher quantities. Therefore, Table 4 gives obtained values and the observational errors for the device with an incident angle of  $60^{\circ}$ , having the lowest working range (0-2 mol  $L^{-1}$ ). The resolution amounts to approximately 40 mmol  $L^{-1}$ . The other devices gave similar results within their working ranges. For CaCl<sub>2</sub> concentrations approaching 5 mol  $L^{-1}$ , fluctuations in the signal occurred. These fluctuations can be attributed to scattering/diffusion effects within the sample solutions due to their increasing colloidal behavior.

### Detection of phosphates dissolved in DI water

Two monophosphates,  $NaH_2PO_4$  and  $KH_2PO_4$ , dissolved in DI water were used as the sample solutions. To evaluate the

 Table 3 Constants for fitted Boltzmann sigmoidal distributions

Device	$A_1$	$A_2$	<i>x</i> <sub>0</sub>	dx
60.0°	380.74639	0.5431	-6.91827	1.07977
62.5°	2.62706	0.26287	0.83892	0.56033
65.0°	1.84164	0.67093	2.1333	0.47561
67.5°	1.89455	0.52888	3.15032	0.42376

Table 4Measurement results of  $CaCl_2$  concentration determinationexperiments obtained with the  $60^{\circ}$  device

Reference value	Determined concentration	Observational error
1.05 mol $L^{-1}$ 0.70 mol $L^{-1}$ 0.35 mol $L^{-1}$ DI water	$\begin{array}{c} 1.04 \text{ mol } L^{-1} \\ 0.68 \text{ mol } L^{-1} \\ 0.31 \text{ mol } L^{-1} \\ -0.04 \text{ mol } L^{-1} \end{array}$	$\begin{array}{c} 0.01 \ \text{mol} \ L^{-1} \\ 0.02 \ \text{mol} \ L^{-1} \\ 0.04 \ \text{mol} \ L^{-1} \\ 0.04 \ \text{mol} \ L^{-1} \end{array}$



Fig. 5 Absolute ratio of reflected and transmitted light signal printed against phosphate concentration. Both phosphates,  $NaH_2PO_4$  and  $KH_2PO_4$ , show a similar influence on the measurement results. Imperfections in sample preparation leading to concentration errors explain small deviations from the fitted curve.

performance of the device (incident angle of  $60^{\circ}$ ), aliquots of the samples at different phosphate concentrations (0 mol L<sup>-1</sup> up to 1 mol L<sup>-1</sup>) were taken and analyzed. As for the CaCl<sub>2</sub> experiment, both signals, reflected and transmitted, were recorded and the ratio was calculated for each concentration. Fig. 5 depicts the obtained results.

As can be seen, both phosphates show similar characteristics. With increasing concentration the refractive index of the sample solution increases and results in a reduction of the reflected light signal and a concurrent increase in the transmitted one. The obtained data points were fitted on an asymptotic exponential curve. Deviations from the curve can be explained by imperfections in sample preparation, resulting in small concentration errors. For the lowest concentrations the magnitude of the sensitivity was 0.41 (mol  $L^{-1}$ )<sup>-1</sup>. Following the typical convention, the resolution is defined as three times the standard deviation of the noise in the system. Given that the mean standard deviation of the obtained ratios (reflected to transmitted light signal) for both phosphate experiments was 5.3 ×  $10^{-3}$ , a resolution of  $16 \times 10^{-3}$  can be approximated. Using these two values, the limit of detection can be calculated as

Limit of Detection = 
$$\frac{\text{Resolution}}{\text{Sensitivity}} = 39 \,\text{mmol/L}$$
.

# Conclusions

The presented device proved suitable for the detection of liquid concentrations in the range of a few tens of mmol  $L^{-1}$  to

5 mol  $L^{-1}$ . The typical resolution amounts to approximately 40 mmol  $L^{-1}$  which outperforms previous devices. The large working range provides high flexibility in potential applications of the device. The simultaneous detection of two signals, reflected and transmitted, gives a permanent verification of the results. In addition, the use of the signal ratio for the sample analysis compensates for fluctuations in the light intensity due to laser instabilities which would destroy any validity in single signal approaches. The detection of phosphates dissolved in DI water demonstrated the applicability of the device. A resolution of approximately 40 mmol  $L^{-1}$  is sufficient for control analyses in the food industry field.

The robustness, its simplicity and hence the ease in fabrication, and the tunability of the characteristics of the presented optofluidic analysis chip allow for sensitive, cost effective, flow-through, and non-invasive sensor implementations.

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