Hydrogel-based pH-sensors
Development and characterisation of optical and electrical pH sensors based on stimuli-responsive hydrogels.

Krister Hammarling

Supervisors: Prof. Hans-Erik Nilsson
Dr. Magnus Engholm
Dr. Henrik Andersson
Department of Electronics Design in the
Faculty of Science, Technology, and Media
Mid Sweden University, SE-851 70 Sundsvall, Sweden
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Department of Electronics Design
Mid Sweden University, SE-851 70 Sundsvall, Sweden
Phone: +46 (0)10 142 80 00
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Acknowledgement

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My family has been a great support during this time. Many times, they had to make sacrifices in their life, so that I could do what I wanted. I love you all, you are the best, so thank you for everything.

Lastly there is an expression

Don’t close any doors
That simple sentence is something I try to live by (though it is hard sometimes). What does it then mean? It can be applied in almost any situation, say for example that I made an enemy recently and if I had then completely shut the door, we could not be friends later on. Or the failed experiment I made, may in the future have a solution if I only keep an open mind to it. So here is an advice from me; always leave the door open a little bit.

Thank you all
Krister Hammarling
Abstract

The ability to measure the chemical parameter pH is of high importance in many areas. With new government regulations and evolving markets, there is a strong motivation for improving such measurements and conducting research on new types of pH sensors and sensor materials. Stimuli-responsive hydrogels (a group of polymers) have attracted a lot of attention in recent decades, due to their ability to be customized to suit many applications. One specific area where they have attracted attention is pH sensor technology.

Two stimuli-responsive hydrogels are used in this thesis. One is a non-toxic hydrogel, 1,4-acryl-terminated oligo(β-amino esters) (1,4-AOBAE). Although it was previously used in drug- and DNA- delivery systems, it has not (to my knowledge) been used in a sensor configuration, and thus it is interesting to study. The second hydrogel, 1,3-acryl-terminated oligo(β-amino esters) (1,3-AOBAE), is an improved variant of the first one. This improved hydrogel was synthesized because the original hydrogel crystallizes at room temperature, which meant that it was not optimal for various coating techniques. This hydrogel was characterized and verified for pH responsivity in two sensor configurations: electrical and optical. Designing a hydrogel for a specific application can be a complex procedure due to the many synthesizing parameters. For example, increasing a hydrogel’s mechanical strength by introducing a higher degree of cross linking, leads to a smaller mesh size, which in turn leads to a lower diffusion rate and less solution absorption. The two hydrogels examined in this thesis respond to pH changes by absorbing or desorbing water; this change in the hydrogel’s water content also changes its effective refractive index and permittivity. These changes can be measured using optical or electrical sensor systems. Three types of sensor systems were used in this thesis to verify the hydrogel’s pH response and to ensure that they are suitable for use in thin-film techniques on various substrates (e.g. glass and plastic). The experimental results prove that these hydrogels are suitable for use in both electrical and optical sensor configurations. For electrical systems, a pH range of approximately 3-12 was achieved, and for optical, the range was approximately 2-12. These ranges can likely be improved, as the sensor film delaminated from the substrate at low pHs due to adhesion problems and as measurements above 12 were not conducted.

The findings of this thesis could, after more research, have strong implications for the development of improved pH-sensor configurations, especially for medical and healthcare applications and in environmental monitoring.
Sammanfattning

Möjligheten att mäta den kemiska parametern pH är av stor betydelse inom många områden. Nya regler från myndigheter och tillväxtmarknader gör att det finns det en stark motivation för förbättring av och forskning om nya typer av pH-sensorer och sensormaterial. Stimuli-responsive hydrogeler (en grupp polymener) är ett material som under de senaste årtiondena uppmärksammats på grund av deras förmåga att skråddarsys för att passa många olika applikationer. Ett specifikt område där det finns ett starkt intresse är pH-sensorteknik.


Resultaten från denna avhandling kan med ytterligare forskning ha en stark inverkan på utvecklingen av förbättrade pH-sensor konfigurationer, särskilt inom medicinska- och hälsovårds-applikationer samt miljöövervakning.
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Acronyms

ADC  analog to digital converter
AOBAE  acryl-terminated oligo(β-amino esters)
ASIC  application-specific integrated circuit
BDDA  butanediol diacrylate
EMI  electromagnetic interference
E_{PD}  electric field penetration depth
FBG  fiber Bragg grating
FPI  Fabry-Perot interferometer
FSR  free spectral range
FTIR  fourier-transform infrared spectroscopy
ISFET  ion sensitive field effect transistor
MM  multi-mode
MZI  Mach-Zehnder interferometer
NMR  nuclear magnetic resonance
OFDR  optical frequency domain reflectometer
OPD  optical path length difference
OSA  optical spectrum analyzer
OTDR  optical time domain reflectometer
PET  polyethylene terephthalate
PIP  piperazine
pK_a  logarithmic acid dissociation constant
RI  refractive index
SNR  signal-to-noise ratio
## List of Publications

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<td>Article I</td>
<td>Blood pH optrode based on evanescent waves and refractive index change</td>
<td>Krister Hammarling, Jöns Hilborn, Hans-Erik Nilsson and Anatoliy Manuilskiy</td>
<td><em>Optical Fibers and Sensors for Medical Diagnostics and Treatment Applications XIV</em>, 2014</td>
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<td>Article II</td>
<td>Dual parameter fiber optic sensor combining a Fabry-Perot and a Mach-Zehnder interferometer</td>
<td>Krister Hammarling, Harald I. Muri, Markus S. Wahl, Magnus Engholm and Dag R. Hjelme</td>
<td><em>IEEE, Sensors</em>, 2017</td>
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<td>Article III</td>
<td>Synthesis, Curing Behavior and Swell Tests of pH-Responsive Coatings from Acryl-Terminated Oligo(β-Amino Esters)</td>
<td>Krister Hammarling, Mats Sandberg, Magnus Engholm and Henrik Andersson</td>
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<td>Article IV</td>
<td>Broad-Range Hydrogel-Based pH Sensor with Capacitive Readout Manufactured on a Flexible Substrate</td>
<td>Krister Hammarling, Magnus Engholm, Henrik Andersson, Mats Sandberg and Hans-Erik Nilsson</td>
<td><em>MDPI, Chemosensor</em>, 2018</td>
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Article V  
A Bio-Compatible Fiber Optic pH Sensor Based on a Thin Core Interferometric Technique  
Magnus Engholm, Krister Hammarling, Henrik Andersson, Mats Sandberg and Hans-Erik Nilsson  
MDPI, Photonics, SI: Advanced Optical Materials and Devices, 2019

Related publications, not included in this thesis:

Printed Write Once and Read Many Sensor Memories in Smart Packaging Applications  
Hans-Erik Nilsson, Henrik A. Andersson, Anatoliy Manuilskiy, Tomas Undander, Krister Hammarling, Johan Sidén, and Mikael Gulliksson  
IEEE, Sensor Journal, 2011

Modified EAS Tag Used as a Resistive Sensor Platform  
Henrik Andersson, Krister Hammarling, Johan Sidén, Anatoliy Manuilskiy, Thomas Öhlund and Hans-Erik Nilsson  
MDPI, Electronics, 2012

Fiber Bragg Grating filter using Evaporated Induced Self Assembly of silica nano particles  
Krister Hammarling, R. Zhang, A. Manuilskiy, H. E. Nilsson  
SPIE, Optical Components and Materials XI, 2014
Publication summary

Article I

Blood pH optode based on evanescent waves and refractive index change
The aim of this article was to build a pH sensor that could also be used in distributed sensing, for example in an optical time domain reflectometers OTDR or optical frequency domain reflectometers OFDR. A pH sensor based on a MM optical fiber evanescent wave sensing was introduced. On a part of the fiber, the cladding is etched away so that only the core is left and thus will be susceptible to refractive index changes. On this bare core, a pH sensitive hydrogel is coated. Depending on the pH level it is submerged in, it will expand or contract, resulting in an effective refractive index change of the hydrogel. Depending on the effective refractive index, different amounts of light will leak out from the core. The remaining light in the core can then be correlated to which pH the sensor is submerged in.

Article II

Dual parameter fiber optic sensor combining a Fabry-Perot and a Mach-Zehnder interferometer
There is often a need to measure several parameters at once. This work shows a conceptual dual parameter fiber optic sensor small enough to be used in vivo for health care applications. The article describes the characterisation of a concept optical fiber sensor for two parameters, both as a two-fiber and a single-fiber configuration. The concept utilize a MZI and a FPI. The MZI is RI sensitive and is built as an inline sensor. The FPI is built on the tip of the fiber by polymerizing a hydrogel.

Article III

Synthesis, Curing Behavior and Swell Tests of pH-Responsive Coatings from Acryl-Terminated Oligo(β-Amino Esters)
New pH sensitive materials are needed that are tailored to suit coating and printing techniques. Also, material that is non-toxic and biocompatible is needed, therefore a new pH sensitive hydrogel has been synthesized. The article describes the characterisation of a pH sensitive material that can be used for optical fibers and printed electronic sensors. The coating is done without using solvents and then cross-linked into an insoluble pH-responsive coating.
Publication summary

via UV-curing. Characterisation includes synthesis, curing behavior and expansion tests.

**Article IV**

*Broad-Range Hydrogel-Based pH Sensor with Capacitive Readout Manufactured on a Flexible Substrate*

The aim of this article was to verify that the material in Article III is suitable for use as a pH sensitive material in flexible electronics, and to address the importance of sensing penetration depth for interdigital capacitive sensors. Characterisation of a flexible interdigital capacitive sensor coated with a pH sensitive hydrogel was performed. Characterisation includes both simulation and experimental verification.

**Article V**

*A biocompatible fiber optic pH sensor based on a thin core interferometric technique*

In this article, a conceptual biocompatible fiber optic pH sensor was characterized. The sensor utilizes the pH sensitive AOBAEs from Article I and III, which was coated upon a MZI. The working principle of the sensor is shown by a COMSOL multiphysics simulation. Promising results such as fast response (<15s), high sensitivity with a resolution of 0.008 pH units and a broad measurement range (response measured between pH 2-12) has been shown. Development challenges for these types of sensors are discussed regarding the hydrogel and physical sensor design.
Preface

This dissertation is mostly based on the experimental data from chemical, optical and electronics experiments, together with some simulations done in Comsol Multiphysics.

Article I is a collaboration with Samba Sensor AB (Gothenburg, Sweden) and Ångström laboratoriet (Uppsala, Sweden). Article II is a joint effort with Norwegian University of Science and Technology (NTNU) (Trondheim, Norway). Articles III-V are collaborations with Research Institutes of Sweden (RISE) (Norrköping, Sweden).

Krister Hammarling
Sundsvall, 2019
1 Introduction

The ability to accurately measure the chemical parameter pH is of high value in many areas (e.g. industrial, physiological and clinical practices) and acts as an important diagnostic tool or parameter [1–6]. For this purpose, pH meters are used to convert a liquid’s acidity/basicity into a readable and interpretable signal (most commonly electrical or optical).

The requirements for measuring pH vary based on the subject area. For example, a distributed sensor system is desired for the monitoring of large areas (lakes, cities, harbours etc.) [7–9], whereas portable and wearable devices are preferred in healthcare applications [10–12].

Arnold O. Beckman invented the commercial glass electrode pH meter in 1934 [13]. Since then, glass electrodes and litmus paper have been the most common ways to measure pH [1, 14]. However, the glass electrodes have some disadvantages, as they are fragile and difficult to miniaturize and require frequent calibration. These drawbacks, together with new government regulations (e.g. increased control of industrial waste water) and new market demands within the medical and healthcare fields, generated a strong motivation for improvements in pH measurement and spurred new research on pH sensors and sensor materials [15–21].

Several sensor technologies can be used to measure pH [22, 23], including ion sensitive field effect transistor (ISFET) [23, 24], fluorescent [25], cantilever [26], imaging [27–29], interferometric [30], conductimetric [31], ratiometric [32] and magneto-elastic pH sensors [33, 34]. Appendix I contains a list of some common pH-sensor techniques with pH ranges, sensitivities and other properties. A majority of these types of pH sensors can use hydrogels as sensing material [23, 25–34].

Hydrogels are polymer/oligomer networks that can absorb water [35–37]. They are versatile and used in many areas, including biomedicine, pharmaceuticals, biotechnology, bioseparation, biosensors, agriculture, oil recovery, cosmetics, microfluidics and waste water treatment [36–38]. Stimuli-responsive hydrogels is one subgroup of hydrogels; these hydrogels which respond to certain environmental stimuli through changes in volume, mechanical strength, refractive index and/or permittivity. The stimuli that trigger these responses can be chemical (pH, ions, glucose, chemical agents etc.), physical (light, pressure, temperature, electric and magnetic fields etc.) or biological (ligand, enzyme, antigen, and other biochemical agents) [37–39]. The ability to respond to many types of parameters makes these stimuli-responsive hydrogels interesting candidates for use in sensor configurations. Therefore, research on such hydrogels is important, so as to improve their sensitivity, stability, repeatability and other
1 Introduction

characteristics [22,40,41].

Two common ways to use hydrogels for pH sensing are as stimuli-responsive hydrogels or as a passive material. Stimuli-responsive hydrogels can respond to pH either in terms of volume change (expansion/contraction) [42–44] or with conductance/resistance changes within the material [45,46]. As a passive material the hydrogel absorbs and transports water into the network, which is doped with pH sensitive dyes or fluorescent molecules [14,47,48].

1.1 Problem motivation

The aim of this work has been to investigate the properties of a special type of stimuli-responsive hydrogel, that is intended for use as a pH-sensitive coating material compatible with common electrical and optical sensor configurations. To my knowledge, this hydrogel, 1,4-acryl-terminated oligo(β-amino esters) (AOBAE), has not been considered for use in sensor applications prior to this investigation. It has several desirable properties, such as being bio-compatible and non-toxic and is therefore an interesting candidate, especially for use in medical and healthcare applications. The initial experiments in this study revealed that the 1,4-AOBAE crystallizes at room temperature and thus is not optimal for coating applications. Therefore, an improved variant denoted 1,3-acryl-terminated oligo(β-amino esters) (1,3-AOBAE) was synthesized. The 1,3-AOBAE’s curing behaviour and pH response were then characterized. A major part of the investigation involved experimental work to identify appropriate parameters such that thin films of the hydrogel could be coated and cured for use on various sensor platforms. The behaviour of these hydrogels as a pH-sensitive material has been studied by using capacitive and a fiber optic sensor configurations. Theory and simulations have been performed to identify appropriate design parameters and to support the experimental observations.

The motivation for the work presented in this thesis is to increase the knowledge and understanding of pH-responsive hydrogels and how they can be used in electrical- and optical sensor configurations. The findings can have a strong implication for the development of improved pH sensors configurations, especially within medical and healthcare applications and environmental monitoring.

1.2 Outline

This thesis is divided into five chapters and three appendixes as follows:

1. Introduction The thesis’s background and hypothesis are presented in this chapter.
2. Theory  
Contains theory and discussions about pH, hydrogels, response characteristics of hydrogels, optical and electrical measurement techniques, two coating techniques, and adhesion.

3. Experimental  
This chapter features the processes used to synthesize the hydrogel and the manufacturing of the optical and electrical sensors, including some processes that were used in these experiments but have not previously been published.

4. Results  
This chapter includes discussions about linearity, error etc. for various sensors in Articles I, II, IV and V.

5. Discussion  
This chapter summarizes the theoretical and experimental aspects of this thesis and covers some of the crucial parameters that can be changed regarding the hydrogel and sensor configurations.

6. Summary and conclusions  
The final chapter presents the thesis’s primary conclusions and suggestions for future work. It also includes the author’s contributions to the articles.

Appendix I  
This appendix comprises a table of various kinds of pH sensor technologies.

Appendix II  
This appendix comprises a mindmap of some synthesizing parameters for hydrogels.

Appendix III  
This appendix comprises a table of hydrogels that are commonly used as pH-sensing material.
2 Theory

Chapter 2 focuses on the theory behind pH, hydrogels (including their response characteristics), some optical and electrical measurement techniques, and two coating techniques.

2.1 pH

The acidity or basicity of an aqueous solution is measured in the logarithmic scale $pH$, which is a measure of the hydrogen ion activity $H^+$ [49, 50].

$$pH = -\log_{10}(a_{H^+}) = \log_{10}\left(\frac{1}{a_{H^+}}\right)$$  \hspace{1cm} (2.1)

The Henderson-Hasselbalch approximation, Eq. (2.2), provides $pH$ [51].

$$pH = pK_a + \log\frac{A^-}{a_{H^+}}$$  \hspace{1cm} (2.2)

where $K_a$ is the equilibrium constant for the acid dissociation reaction:

$$HA \leftrightarrow H^+ + A^-$$  \hspace{1cm} (2.3)

with

$$K_a = \frac{[H^+][A^-]}{HA}$$  \hspace{1cm} (2.4)

and

$$pK_a = \log(K_a)$$  \hspace{1cm} (2.5)

All equilibrium constants are a function of temperature ($T$) and are related to Gibbs free energy of the reaction ($\Delta G$), which is given by Eq. (2.6) [51]:

$$\Delta G = -RT\ln(k_a) = -2.303RT\log(K_a) = 2.303RTpK_a$$  \hspace{1cm} (2.6)

where $R$ is the gas constant. This is described in detail by Atkins et al. [51].

Hydrogels can also have an acid dissociation constant $pK_a$. This is especially important for pH-responsive hydrogels, as it determines how the gel reacts to $pH$. This is explained further in Section 2.2.1. Because $pK_a$ has a temperature dependency, both the liquid’s $pH$ and the hydrogel's $pH$ response change with the temperature.
2 Theory

2.2 Hydrogels

A hydrogel can be defined as a cross-linked polymeric network produced by the reaction of one or more monomers with the ability to expand and retain water, and should not dissolve in water. The ability to retain water comes from the hydrophilic functional groups attached to the polymer backbone, which becomes hydrated in aqueous media, while the resistance to be dissolved in water comes from cross-links in the polymeric network [35].

A hydrogel’s properties can be tailored to create the desired functionality, in terms of properties such as mechanical strength, diffusion rate and solution absorption [52]. However, altering one of these properties can induce a change in other properties. For example, the amount of water absorption is determined by the hydrogel’s molecular structure (source of molecules, mol ratio etc.), the preparation technique, cross-linking type and cross-linking degree. High water absorption can increase the time required to absorb a given volume of the measured liquid and can lower the hydrogel’s mechanical strength. Increasing the mechanical strength by introducing a higher cross-linking density, leads to a smaller mesh size, $\xi$ (see Fig. 2.1), and to a decrease in both the diffusion rate and the amount of solution absorption [53, 54]. Therefore, as the design parameter room for hydrogel’s is large and complex, the optimization of a hydrogel properties and functionality can be very complex. To visualize this complexity, Appendix II comprises a mindmap of some hydrogel synthesis and design considerations, as derived from [38, 55–60].

![Diagram of cross-links in a hydrogel matrix network and the definition of mesh size, $\xi$](image)

Figure 2.1: Cross-links in a hydrogel matrix network and the definition of mesh size, $\xi$ [41].

During synthesis (which often involves solvents) and before polymerization, safety precautions are required due to harmful chemicals. A table of some pH-sensitive hydrogels can be found in Appendix III, which also includes their hazard classification codes according to the globally harmonized system [61, 62].
and their uses as sensor materials. Three of these hydrogels have also been proven to have low toxicity according to cytotoxicity tests: number 9 [63], 12 [64,65] and 13 [66], the latter is the 1,4-AOBAE used in Articles I and V.

**Stimuli-responsive hydrogels**

A subcategory of hydrogels are stimuli-responsive hydrogels, also known as intelligent or smart hydrogels [39], change their physical and/or chemical properties in response to variations in environmental parameters, such as pH, temperature, moisture, current, ions, electromagnetic fields and biomolecules [40].

![Figure 2.2: Phase transition of stimuli-responsive hydrogels [37].](image)

Stimuli-responsive hydrogels can undergo phase transitions due to stimuli; the resulting changes in physical properties often involve volume and stiffness. Figure 2.2 shows the principle of these phase transitions. In the expanded phase (left), the dominant interactions are between the polymer and the solution to obtain the optimal mix of gel and solution. In the contracted phase (right), the dominant interactions are by internal forces that contract the gel, thus removing the solution from the gel. Small alterations of stimuli within the phase transition region, results in a hydrogel phase change [37].

Stimuli-responsive hydrogels are used in many application areas, for example sensors and biosensors [67], for controlled and triggered drug delivery [68], environmental remediation [69], wastewater treatment [36], chemomechanical actuators [70–72], nanocomposites [73], antioxidant materials [74] and optoelectronic coupling [75].
2 Theory

2.2.1 Hydrogels behaviour in water

When a conventional hydrogel is immersed in water, the first water molecules that enter the matrix hydrate the most polar hydrophilic groups and thus generate osmotic pressures $\Delta \pi_{\text{mix}}$ (acting expansively), denoted ‘primary bound water’. As the polar groups become more hydrated, the network expands, which exposes hydrophobic groups that interacts with the water molecules, denoted ‘secondary bound water’, thus leading to an elastic force, $\Delta \pi_{\text{elast}}$, that counteracts $\Delta \pi_{\text{mix}}$. Together, primary and secondary bound water are called ‘initial bound water’ [55]. Hydrogels that lack ionic moieties obtain their expanding equilibrium at the balance of these pressures, which can be described by Eq. (2.7) (phase one)

$$\Delta \pi = \Delta \pi_{\text{mix}} + \Delta \pi_{\text{elast}} = 0$$ (2.7)

These processes are described in detail by the Flory-Rehner theory [56, 76] and Flory-Huggins theory [50, 77].

A hydrogel can absorb water up to 1000 times its own weight in water [78].

Stimuli-responsive hydrogel behaviour

A stimuli-responsive hydrogel has two phase transition orders, so it behaves differently than a conventional hydrogel. The first phase transition is the same as for a hydrogel (i.e. the absorption of ‘initial bond water’). The second phase transition comes from the stimuli-responsive agent in the polymer; this agent changes the gel network by volume change. The following theoretical discussion is aimed at pH sensing, but also applies to other stimuli such as temperature, biomolecules and light.

A hydrogel can have three different stimuli transition behaviours, depending on whether the gel itself is acidic, basic or both. These are illustrated in Fig. 2.3, in which the red line (2) is acidic (anionic) hydrogels, the blue line (o) is basic (cationic) hydrogels and the green line (3) is amphiphilic hydrogels containing both acidic and basic groups.

The hydrogel’s phase transition occurs in a small range around the hydrogel’s logarithmic acid dissociation constant ($pK_a$). Approximately at $pK_a$, the ionization starts resulting in expansion and water absorption. When the ionization is complete, the expansion stops. If there is any further increase in pH after the ionization reaches its maximum, the extra pH will only increase the ionic strength [37]. This extra increase of ionic strength leads to a decrease in the osmotic pressure, which causes the hydrogel to contract (see Fig. 2.3, acidic hydrogel). The extra contribution of osmotic pressure needs to be treated as an expansive force, $\Delta \pi_{\text{ion}}$. Equation (2.7) is therefore rewritten as

$$\Delta \pi = \Delta \pi_{\text{mix}} + \Delta \pi_{\text{elast}} + \Delta \pi_{\text{ion}} = 0$$ (2.8)

Within the hydrogel, the counter-ions must have freedom so that they can
2.2 Hydrogels

Figure 2.3: Phase-transition behaviour of polyelectrolyte hydrogels. The red line (○) represent acidic (anionic) hydrogels, the blue line (□) represent basic (cationic) hydrogels and the green line (△) represent amphiphilic hydrogels containing both acidic and basic groups [37].

be released into the surrounding solution. However, the gel can only exchange them with other ions from the surrounding medium, as it must preserve charge neutrality. This ionic exchange can affect the osmotic pressure balance of both the gel and the surrounding solvent, leading to changes in the expansion equilibrium. If the ionic strength is low, the influence on expansion is negligible, since the ion exchange is marginal. If it is increased to medium strength, the hydrogel begins to exchange the mobile counterions with the surrounding ions. This, in turn, increases the hydrogel’s internal osmotic pressure, causing it to expand. If the solution has high ionic strength, this process will result in polyelectrolyte shielding that reduces the osmotic pressure, thus causing the hydrogel to contract [79]. This contribution of ionic strength, $\Delta \pi_{bath}$, needs to be accounted for, adding $\Delta \pi_{bath}$ to the osmotic pressure in Eq. (2.8) results in Eq. (2.9) [80]:

$$\Delta \pi = \Delta \pi_{mix} + \Delta \pi_{elast} + \Delta \pi_{ion} + \Delta \pi_{bath} = 0$$ (2.9)

Polyelectrolyte hydrogels

The molecules of polyelectrolyte hydrogels (a group of stimuli-responsive hydrogels) can be ionized, which causes the hydrogels to expand, mainly due to the electrostatic repulsion among the charges present on the polymer chain. This expansion is influenced by conditions that alter the electrostatic repulsion, which include pH, ionic strength, and other types of counter-ions [81].

Depending on whether the pH sensitive hydrogel is cationic or anionic, the expansion is a response to either an acidic or a basic medium, respectively [59]. For example, hydrogels containing cationic groups are protonated in acidic
2 Theory

conditions, as described in Eq. (2.10) and deprotonated in basic conditions, as described in Eq. (2.11).

\[
[RNH_2]_{gel} + [H^+]_{aq} \rightarrow [RNH_3^+]_{gel} \quad (2.10)
\]

\[
[RNH_3^+]_{gel} + [OH^-]_{aq} \rightarrow [RNH_2]_{gel} + [H_2O]_{aq} \quad (2.11)
\]

Equation (2.10) shows that increasing the density of charged groups induces a phase transition due to electrostatic repulsion of \([RNH_3^+]_{gel}\) and the expansion of the hydrogel. In a basic ambient environment, the cationic hydrogel deprotonates, as described in Eq. (2.11), resulting in decreased charge density and reduced content of mobile counter-ions within the gel, leading to gel contraction, as shown in Fig. 2.4.

Figure 2.4: Cationic hydrogel response to deprotonation and protonation. Due to the adhesion between the substrate and the hydrogel, no size differences occur at that interface.

Figure 2.5 shows an example in which a cationic hydrogel absorbs water with \(H^+\) ions. When the \(H^+\) ions protonate the network charge that is carrying the pendant groups, as described in Eq. (2.10), ions start to repel each other, thus stretching the hydrogel network, as shown in Fig. 2.5. This leads to increased mesh size, \(\xi\), which allows the hydrogel to contain more water.

Figure 2.5: Absorption of water with \(H^+\) ions in a pH-sensitive cationic hydrogel. The \(H^+\) ions attach to the cationic groups and start to repel each other. The network stretches, thus increasing the mesh size, \(\xi\), and allowing the hydrogel to absorb more water.
Expansion kinetics

Conventional and polyelectrolyte hydrogels have different expansion kinetics. For a hydrogel to expand or shrink, matter must be transported in or out of the hydrogel. This process is time-consuming and there are two transport mechanisms to be considered.

The time constant, $\Gamma$, for a spherical hydrogel is expressed as in Eq. (2.12), where the mechanisms $D_{\text{stim}}$ (primary bound water) and $D_{\text{solv}}$ (secondary bound water) force the network’s polymer chains to move and obtain new positions. [82, 83]

$$\Gamma = \frac{\Delta r^2}{D_{\text{stim}}D_{\text{solv}}} = \frac{\Delta r^2}{D_{\text{coop}}}$$

In Eq. (2.12) $\Delta r$ is the difference between the final radius and the characteristic dimension: $D_{\text{stim}}$ is the initial stimulus from the solvent, which is associated with the difference in osmotic pressure between the hydrogel and the solution. The second mechanism, $D_{\text{solv}}$, tends to equalize the internal osmotic pressure, by expanding or contracting the network. These two mechanisms together are called $D_{\text{coop}}$ (initial bound water). This simplified theory describes the expansion process without the influences of the surrounding area, such as temperature, pressure and radiation.

For a polyelectrolyte gel, the characteristics of the expansion kinetics time constant are different than for a conventional hydrogel. According to Lesho and Sheppard [84], the characteristic time constant, $\Gamma_{\text{bdr}}$, that describes a “buffer-mediated diffusion reaction” is given by Eq. (2.13):

$$\Gamma_{\text{bdr}} = \frac{\delta^2}{\pi^2 D_{\text{HB}} [1 + \frac{\beta_{\text{gel}}}{(1 + H_0)\beta_{\text{HB}}}]^2}$$

where $\delta$ is gel thickness, $D_{\text{HB}}$ is the diffusivity of the buffer molecule in the hydrogel, $H_0$ the hydration, $\beta_{\text{gel}}$ the buffer capacity of the hydrogel and $\beta_{\text{HB}}$ the buffer capacity of the buffer solution. This simplified theory describes the process without external influences such as temperature, pressure and ionic strength.

An analysis of the time constants in Eq. (2.12) and Eq. (2.13), reveals that both have a squared dependency to the thickness of the hydrogel. Therefore, for the hydrogels to respond quickly, they need to have polymer layers that are as thin as possible. For polyelectrolyte gels, Eq. (2.13) also reveals that an increase in the buffer capacity, $\beta_{\text{gel}}$, gives a higher time constant, whereas an increase in the solution’s buffer capacity, $\beta_{\text{HB}}$, lowers the time constant.

A hydrogel’s response rate can be changed by altering its size, shape, cross-linking density, number of ionic groups or composition [59]. For example, the response rate can be increased by increasing the pore size or the number of ionic groups, as well as by decreasing the cross-linking density [41].

Because the time constant depends on the square of the thickness, it might induce an impractically for sensors with large electric field penetration depth,
2 Theory

$E_{PD}$, since it can give response times over several hours (see Article IV). In this case, one solution is to have the hydrogel layer be thinner than the electric field penetration depth ($E_{PD}$). The sum of the layer thickness ($D$) + max expansion ($\Delta D$) must then be less than $E_{PD}$, $D + \Delta D < E_{PD}$ or else there is a risk of signal folding, as seen in Article V Fig. 8. When the sensor signal folds back, the same sensor output occurs for two measured values. However, Article IV, Figs. 4 and 9, show that as the hydrogel layer thickness changes, the expected responses are in opposite directions. A risk of using an $E_{PD}$ that is larger than the hydrogel thickness is that because $E_{PD}$ reach out into the surrounding, the sensor also measures upon any contaminants within the range of $E_{PD}$.

2.3 Hydrogel sensor readout techniques

Although it is not possible to measure the pH directly, it is always correlated to some physical parameter that is measurable. For example, a glass electrode can be used to measure the pH through a voltage difference based on a known reference [22]. However, pH responsive hydrogels can change one or more physical parameters in regard to pH, such as RI, permittivity, resistivity, stiffness, mass and volume [37]. Many sensor configurations, both optic and electric, can detect these parameter changes. Some of these techniques are presented below.

2.3.1 Optical sensor techniques

When a pH responsive hydrogel is subjected to pH change, its RI and volume can change. These changes can be detected with optical measurements, such as intensity measurements, which can detect absorbency differences. Interference and phase techniques such as those used by the MZI and FPI can reveal constructive and destructive wavelength patterns due to changes in RI and/or volume.

Refractive index

RI is a dimensionless unit that describes how light propagates in a medium. It is defined as $n = c/\nu$, where $c$ is the speed of light and $\nu$ the phase velocity. The most common way to measure RI is by using a refractometer, this usually means a critical angle refractometers such as the Pulfrich and Abbé types [85]. RI can also be measured with an optical fiber through a MZI [86].

Mach-Zehnder interferometer technique

Ludwig Mach and Ludwig Zehnder invented the Mach-Zehnder interferometer (MZI) in 1891-92 [87,88]. The MZI measures the relative phase shift variations between two collimated beams that are split off from a single light source (see Fig. 2.6).
2.3 Hydrogel sensor readout techniques

Figure 2.6: The principle of an MZI. At the first beam splitter, the input ray is split into two beams: a reference beam and a measurement beam. The second beam splitter recombines the beams into two measurement rays. Any changes in the measurement rays can be detected as an interference pattern in the output rays.

There are two ways to build a fiber-optic MZI, with fiber-optic couplers (see Fig. 2.7) or as an inline MZI (see Fig. 2.8). With optical couplers, the light in one fiber is split into two fibers, which then work on the same principle as the MZI in figure Fig. 2.6. In an inline fiber-optic MZI, a part of the core light energy is decoupled out into the cladding, thus forming cladding modes. The induced cladding modes are after a length L recoupled into the core. The cladding modes experience a different effective RI than the core mode, thus having a different propagating constant. There are multiple construction techniques that can be used to build a fiber-optic MZI, as shown in Fig. 2.8.

![Diagram of fiber MZI with couplers](image)

Figure 2.7: Configuration of fiber MZI built with couplers. Coupler 1 splits the light in the fiber into two arms, reference and sensing arm. Coupler 2 recombines the two signals.

The Mach-Zehnder interference can be expressed as $I = I_1 + I_2 + 2\sqrt{I_1 I_2 \cos \phi}$, where $I_1$ and $I_2$ are the light intensity transmitted in the fiber core and fiber cladding, respectively, and where $\phi$ is the phase difference [89] between the core and cladding, which can be approximated as $\phi = 2\pi \Delta n_{eff} L / \lambda$, where $n_{eff}$ is the difference in the effective RI between the core and cladding modes ($\Delta n_{eff} = n_{eff, core} - n_{eff, clad}$), $\lambda$ is the operating
2 Theory

Figure 2.8: Configuration of various optical MZIs (a) fiber Bragg grating, (b) sandwich with coreless fiber, (c) core offset, (d) sandwich with MM fiber, (e) thin core fiber, (f) tapered fiber, and (g) coreless fiber. Derived from [86].

wavelength. The MZI has an attenuation peak when the phase condition $\phi$ satisfies $\phi = (2m + 1)\pi$, where $m$ (an integer) is the order of the MZI. The attenuation peak wavelength, $\lambda_m$, can be found at $\lambda_m = 2n_{eff}/(2m + 1)$. The spacing between adjacent attenuation peaks $\Delta\lambda_m$ is $\Delta\lambda_m = \lambda_{m+1} - \lambda_m = 4n_{eff}L/((2m - 1)(2m + 1))$ [90]. If a change occurs in either the RI of the medium surrounding the MZI or the temperature of the MZI, the effective RI of the cladding modes also change. This induces changes in the propagating constants of the cladding modes, thus causing a shift in the attenuation peak.

If an MZI is bent, then the path for the cladding modes changes, which also changes the wavelength at which the attenuation peaks appear. Therefore, the length of the MZI is an important factor and can be utilized to minimize the bending and temperature dependency.

Article V includes some Comsol Multiphysics simulations of a MZI. The simulated structure is not a full-scale fiber, because Comsol recommends using a mesh resolution that is at minimum ten times smaller than the shortest wavelength [91]. To further validate the simulation, additional graphs are presented here. Figure 2.9 shows the electric field comparison between a single wavelength (1.8 $\mu$m) and the sum of seven wavelengths (1.2 to 1.8 $\mu$m). The sum of the seven wavelengths is more representative to a broadband light (normally used in MZI) than a single wavelength. As can be seen in Fig. 2.9, the sum of the seven wavelengths has fewer minimas, as all the energies are summed. A combined minimum appears only in positions where all individual wavelengths have local minima.

Fig. 2.10 shows the output end of the simulated structure from Article V, where the light is to be recoupled into the SMF28. In agreement with Snell’s law, fewer modes are contained when the outer RI is closer to the RI of the cladding. This means that, with a higher outer RI, fewer modes propagate within the fiber and that the output power is much lower than the input power. This can lead to low signal-to-noise ratio (SNR), making the interpretation of the signal harder.
2.3 Hydrogel sensor readout techniques

Figure 2.9: Comsol Multiphysics simulation of a coreless MZI. The plot shows the results of the simulations from Article V. A comparison of the electric field for a single wavelength (1.8 $\mu$m) and that for the sum of seven wavelengths (1.2 to 1.8 $\mu$m), reveals that a single wavelength has more and deeper minimas than when seven wavelengths are added together.

Figure 2.10: Comsol Multiphysics simulation of the output part of a coreless MZI. The plots are deducted from the results of the simulations from Article V. The input light has the wavelength 1550 nm, and the external RI is 1.33 to 1.45. When the external RI increases and thus gets closer to the cladding RI, more modes decouple and are lost, and less energy is contained within the fiber.
2 Theory

Fabry-Perot cavity

Each FPI consists of two parallel reflecting surfaces that are separated by a certain distance $L$, thus forming a cavity. Multiple superpositions of both reflected and transmitted beams at the two parallel surfaces cause interferences. Fiber-optic FPI sensors can be classified into two categories: extrinsic and intrinsic. The extrinsic FPI sensor uses the reflections from an external cavity formed outside of the measuring fiber, as shown in Fig. 2.11a. However, intrinsic FPI fiber sensors have reflecting components within the fiber itself, as shown in Fig. 2.11b. The local cavity of the intrinsic FPI can be formed by methods such as micromachining, fiber Bragg grating (FBG), chemical etching and thin film deposition [86].

![Figure 2.11: Fiber-optic FPI examples. (a) an extrinsic FPI with an air cavity and (b) an intrinsic FPI with two reflecting components, R1 and R2. L is the length of the cavity.](image)

The FPI output spectrum is a wavelength dependent intensity modulation of the input light spectrum; this is caused by the optical phase difference between two reflected or transmitted beams. The maximum and minimum peaks of the modulated spectrum at that particular wavelength are in phase and out-of-phase, respectively, in the modulus of $2\pi$. The phase difference of the FPI is given as $\phi_{FPI} = \frac{4\pi n L}{\lambda}$, where $\lambda$ is the wavelength of the incident light, $n$ is the RI within the cavity, and $L$ the physical length of the cavity. The phase

![Figure 2.12: Typical Fabry-Perot signal. FSR is the distance between two adjacent peaks.](image)
difference is influenced by the variation in \( n \) or \( L \), which changes the interferometer’s optical path length difference (OPD). The spacing between adjacent interference peaks in a spectrum is called the FSR, as shown in Fig. 2.12. FSR is influenced by variations in OPD and shorter OPD gives larger FSR. Even though a large FSR provides a wide dynamic range to a sensor, it gives a poor resolution due to blunt peak signals. Therefore, it is important to design the OPD of the FPI for the target application, such that it satisfies both the dynamic range and the resolution [86].

The round-trip time, \( t_{RT} \), of light travelling in the cavity with speed \( c = c_0/n \), where \( c_0 \) is the speed of light in vacuum, is given by \( t_{RT} = 2L/c \). FSR as expression of \( t_{RT} \) then becomes FSR = \( 1/t_{RT} = c/(2L) \) [92].

**Evanescent wave**

![Figure 2.13: Sensor principle and evanescent wave field (for the first order mode) in an optical fiber. The picture shows how the evanescent wave field penetrates into the polymer and the surrounding area.](image)

Even though there is total internal reflection within a fiber, a part of the light energy travels outside the core as an evanescent wave, as shown in Fig. 2.13. Where it can also be seen that the power decays exponentially in the outer medium. The penetration depth of the evanescent wave is defined as the distance in the outer optical medium, such that the amplitude of the evanescent wave has decreased to 1/e of its initial value, it is typically in the order of the wavelength of the propagating light. The penetrating depth \( (d_p) \) can be calculated with equation Eq. (2.14) [93].

\[
d_p = \frac{\lambda}{2\pi (n_1^2\sin^2\theta - n_2^2)^{1/2}} \quad (2.14)
\]

Where \( n_1 \) and \( n_2 \) are the core and cladding RI, respectively; \( \theta \) is the incident ray angle; and \( \lambda \) is the wavelength. In evanescent wave measurements, the light is altered by refraction losses, the molar absorptivity and the concentration of the absorber. The sensing length and number of light interactions also affects
2 Theory

the sensor output. These theories are described in detail in [94–97]. Figure 2.14 shows how the penetration depth $d_p$ as a function of the angle $\theta$ for two different wavelengths, 1500 and 1700 nm. In the figure it can be seen that close to the critical angle, the penetration depth increases quickly towards infinity.

Figure 2.14: Evanescent wave penetration depth, $d_p$, at various angles for two wavelengths, 1500 and 1700 nm, calculated with cladding RI 1.436 and water RI of 1.33.

2.3.2 Capacitance sensor techniques

The most common way to measure capacitance is by using an electrical wave, squared or sine wave. With a square wave, the measurement is a voltage over time measurement, while for a sine wave it is the reactance that is measured. It is also common to use an RLC circuit to make frequency measurements to calculate the capacitance.

Permittivity

Permittivity is a material’s ability to store an electric field, and it describes the amount of charge needed to generate one unit of electric flux (F/m). In dielectric spectroscopy, a sample’s loss factor and relative permittivity are measured through frequency sweeps. If a material changes its relative permittivity based on stimuli (e.g. temperature, humidity, pressure), then that material can be used as a sensor in capacitance measurements.

Interdigital capacitance

An interdigital capacitor consists of two electrodes with interspersed “fingers”, with length $L$ and electrode width $W$ and gap $G$, as shown in Fig. 2.15. The
2.3 Hydrogel sensor readout techniques

Figure 2.15: The principal layout of an interdigital capacitor, where W is the width of the electrode, G is the gap between two electrodes, and L is the length of the electrodes.

The capacitance is given by Eq. (2.15)

\[ C = \frac{\epsilon_r \epsilon_0 A}{G} \]  

(2.15)

where \( \epsilon_r \) is the relative permittivity of the medium: \( \epsilon_0 \) is the dielectric constant; \( A \) the effective electrode area \( (A = LW_n/2) \), where \( n \) is the number of electrodes in the capacitance and \( G \) the effective spacing between the electrodes [98].

When using interdigital capacitance, the penetration depth \( E_{PD} \) must be considered. The \( E_{PD} \) is defined as the depth at which (at a distance \( z \)) the capacitance \( C(z=E_{PD}) = 0.03*(C(z=0) - C(z=\infty)) \), as shown in Fig. 2.16. The distance \( E_{PD} \) can be estimated as the sum of one third of the electrode width and the electrodes gap, \( E_{PD} = (W + G)/3 \) [99].

Figure 2.16: The relation between capacitance and the distance to a material being tested, which is placed at a distance, \( z \), from an interdigital capacitance. The distance, \( z \), is orthogonal to the capacitance x-y plane.

As discussed in detail in Article IV, there is a need to adjust the \( E_{PD} \) according to the sample thickness. For example, if the \( E_{PD} \) is larger then the sample
2 Theory

thickness, then the sensor also measures some of the space above the sample (i.e. the air or water), which can affect the measurements.

2.3.3 Sensor-field penetration and film thickness

The relation between the sensor penetration depth and the hydrogel film thickness is important to know, because it affects the sensor response. This applies to both the optical sensors based on evanescent wave penetration and the interdigital capacitance sensor.

![Figure 2.17: Evanescent wave principle for a MM wave. In (a), the evanescent wave reaches farther out than the hydrogel layer, and in (b), the evanescent wave is completely contained within the hydrogel.](image)

![Figure 2.18: Electric field principle for an interdigital capacitance. (a) shows the electric field beyond the hydrogel film thickness, and (b) the electric field when it is completely contained within the hydrogel.](image)

Sensors will behave differently depending on whether they are built with hydrogel layers thinner than the sensor field penetration, as shown in Fig. 2.17(a) and Fig. 2.18(a), or if the sensor field is completely contained within the film, as in Fig. 2.17(b) and Fig. 2.18(b). When the sensor field is contained within the film, the sensor will only respond to the film’s internal changes, such as the RI or permittivity changes. However, when the field reaches beyond the film thickness, it is more complicated to predict the sensor response. Because
2.4 Printing and coating techniques used in sensor manufacturing

the hydrogel used expands and contracts in response to pH changes, the film thickness will also differ, which implies that changes in RI and permittivity will occur in the film, but the change in film thickness also changes the ratio between the film and water in the sensing field. This ratio change can have a large impact on the sensor’s behaviour. For example, water has a relative permittivity of $\sim 80$ and the hydrogel’s permittivity is $\sim 5.5$. Therefore, pure water has around $\sim 15$ times larger impact on the sensor output than pure hydrogel (for the same volume). Another issue is that if the hydrogels are thinner than the sensor field and than swells to become larger than it, the sensor signal may fold, as in Article V Fig. 8. A more detailed explanation of these sensor behaviours can be found in Articles IV and V.

2.4 Printing and coating techniques used in sensor manufacturing

A wide variety of printing methods is commonly used for flexible electronics fabrication, including screen, inkjet, gravure, flexo and offset printing. Two other commonly used coating techniques are dip coating and blade coating, which will be described here. Depending on the nature of the flexible electronics products, suitable choices regarding the ink, substrate, device design structure, pattern geometry, manufacturing speed, yield, quality and production cost must be made. Some common printing parameters are accuracy, resolution, uniformity, wetting control, adhesion, interface formation and compatibility of the printing material with printing techniques [100].

Dip coating

Dip coating is the oldest commercially applied coating process [101]. The principle is simple: a substrate is immersed into a precursor, then removed, thus leaving a film of the precursor on the substrate. Dip coating can be divided into three categories: deposition and drainage, when the substrate is pulled upward at a constant speed, a thin layer of precursor solution is deposited onto the surface of the substrate; immersion and dwell time, a substrate is immersed into the precursor solution, followed by a certain dwell time until the substrate is completely wetted by the precursor; and evaporation, the solvent evaporates from the fluid, forming the as-deposited thin film.

Dip coating seems rather simple at first glance. However, by understanding the processes involved, it is possible to tailor the final film’s thickness and structure [102].

Figure 2.19 shows that when the substrate is withdrawn from the precursor, some of the precursor will adhere to the substrate with a thickness of $h_0$, and the rest will return to the bath. If the precursor contains solvents or water, then $h_0$ may become even thinner during evaporation/curing/drying [103].
2 Theory

According to Scriven [104], the thickness, \( h_0 \), of the deposited film is related to \( S \) in Fig. 2.19, which is the streamline dividing the upward- and downward-moving layers. When the withdrawal speed, \( U_0 \), and the liquid viscosity, \( \eta \), are high enough to decrease the curvature of the gravitational meniscus, the deposited film thickness, \( h_0 \), balances the viscous drag (\( \eta U_0 \)) and gravity force (\( \rho g \)) according to Eq. (2.16)

\[
h_0 = c_1 \left( \frac{\eta U_0}{\rho g} \right)^{1/2}
\]

where \( \rho \) is the liquid density; \( g \) is the acceleration of gravity; and the constant, \( c_1 \), is about 0.8 for a Newtonian liquid. When the substrate speed (typical range of \( \sim 1-10 \text{ mm/s} \)) and the liquid viscosity, \( \eta \), are low (< 100 cP), as often occurs in sol-gel film deposition, Eq. (2.16) is modulated by the ratio of viscous drag to liquid-vapour surface tension, \( \gamma_{LV} \), in Eq. (2.17), according to the relationship Landau and Levich derived for a Newtonian and non-evaporating fluid [105].

\[
h_0 = 0.94 \left( \frac{\eta U_0}{\gamma_{LV} \rho g} \right)^{1/3}
\]

This is the cases for the 1,4-AOBAE (mol ratio 11:3, 28 cP at 23°C), because the AOBAE does not contain any water or solvents (\( \gamma_{LV} = 1 \)), see Articles I and V.

Blade coating

Blade coating is also known as knife coating or doctor blade coating. The principle is simple: a blade is positioned a distance, \( h_0 \), above a surface, as shown in Fig. 2.20. In front of the blade, the precursor is added; then either the substrate

Figure 2.19: Flow patterns (streamlines) during the dip-coating process. \( U_0 \) is the draw speed, \( S \) the stagnation point and \( h_0 \) is the thickness of the entrained fluid film. Derived from [104]
or the blade moves with a constant speed, leaving a defined layer thickness behind. The mathematical estimation of the final coated layer, $t_{\text{dry}}$, can be expressed as [106]

$$t_{\text{dry}} = \frac{1}{2} \left( h_0 \rho_l \rho_s \right)$$

where $\rho_l$ is the concentration of the solids in the precursor in g/cm$^3$ and $\rho_s$ is the density of the material in the final film in g/cm$^3$.

![Figure 2.20: Two blade coating techniques. In (a), the blade is elevated by two supports (i.e. $h_0$), and in (b), a roll-to-roll principle is shown.](image)

As can be seen in Eq. (2.18) the final thickness, $t_{\text{dry}}$, is not dependent on the draw velocity, but draw velocity is closely related to the leakage of the coated precursor. The leakage and overflow of the precursor is a critical problem in the knife-over-edge coating. This problem has been handled by changing the knife length and shape, and installing a solution bath for high-viscosity solutions [107].

### 2.4.1 Adhesion between substrate and hydrogel

The adhesion on a surface can be increased in several ways, such as through mechanical, wet chemical and plasma treatments. The basic objective is to remove surface contaminations, thus providing intimate contact between two materials [108]. Mechanical treatment is done mostly to remove solid particles, such as dust and coating residues. It can be done with, for example, pressure air, wipes and sandpaper. Mechanical treatment can also roughen the surface, thereby enhancing the mechanical interlocking and the total contact area [109]. Several chemical methods are available to remove all organic residues. J.J Cras et al. studied eight methods and concluded that a 1:1 methanol (MeOH)/hydrochloric acid (HCl) wash followed by a bath in concentrated sulfuric acid (H$_2$SO$_4$) most effectively removes any surface contaminants [110]. Plasma treatments can be classified into two categories: atmospheric and low-pressure. Atmospheric treatments are generally used to treat larger substrates. Plasma can remove organic residues and introduce chemical functional groups on the surface. For example, oxygen-containing plasmas introduce hydroxyl groups, which makes the surface more hydrophilic [111].
2 Theory

The AOBAE used in Articles I, III and V is amorphous, therefore, if it was free floating in a solution, any volume increase would be equal in the x, y and z directions. The AOBAE can only make strong covalent bonds with the substrate surface (or primer) via any free double bonds on the 1,3- or 1,4-BDDA (see Figs. 3.1 and 3.2). The 1,3- and 1,4-BDDA are insensitive to pH; therefore, no lateral (x-y) forces can occur at the bonding points. The first pH-sensitive PIP molecule is therefore always found a distance $z > 0$ from the surface. When the PIP molecules are charged via H$^+$ ions, they start to repel each other. Because the substrate is solid, they cannot move in the $-z$ direction, leaving the x-y and $+z$ directions for movement. The x-y direction is to some extent also blocked by other molecules (except at the edges), which makes movement in the $+z$ direction easiest. Therefore, each charged molecule that moves in the $+z$ direction will exert a force in that direction on the bond between the hydrogel and the substrate. When the combined force from these molecules exceeds the bonding strength to the surface, the bond breaks. In a thick hydrogel layer, more charged molecules are striving in the $+z$ direction (i.e. greater force), so it will delaminate more easily than a thinner. Strong adhesion between the hydrogel and the substrate is therefore an important factor in sensor manufacturing.
3 Experimental

In this chapter, differences between 1,3- and 1,4-AOBAE are shown, together with some results from pH response and the translational diffusion effect. Some manufacturing techniques for the optical and electrical sensors are also shown.

3.1 Synthesizing and characterizing 1,x-AOBAE

Specific data on reagents, instrumentation and measurement setups for Section 3.1 “Synthesizing 1,x-AOBAE” can be found in Articles I and III.

Synthesizing 1,x-AOBAE

The base of the AOBAE is either 1,4-BDDA or 1,3-BDDA, which are copolymerised with PIP. The reaction between 1,x-BDDA and PIP was made by dissolving PIP into 1,x-BDDA while stirring it at 60 °C without the use of any solvents; as shown in Figs. 3.1 and 3.2 for the synthesis of 1,4-AOBAE and 1,3-AOBAE. Stirring continued until no visible PIP crystals were visible in the solution and then for another 30 min, for a total of 180 and 120 min, respectively. The AOBAE was then left to cool to room temperature before any further processing. For all curing, the photoinitiator Diphenyl(2,4,6-Trimethylbenzoyl)phosphine oxide (TPO) was used.

![Figure 3.1: Synthesis of oligo(β-amino ester) from 1,4-BDDA and PIP. The diamine nitrogen breaks the double bond on the diacrylate and forms a secondary (β-amino ester). Note that 1,4-BDDA and PIP has a symmetrical structures.](image-url)
Article III discusses characterisation of the 1,3-AOBAE regarding curing behaviour and clarifies the asymmetric structure of 1,3-AOBAE compared to 1,4-AOBAE. Fourier-transform infrared spectroscopy (FTIR) was used to monitor the UV-curing process of 1,3-AOBAE in air and a nitrogen atmosphere (N\textsubscript{2}) by examining the peaks at 810 and 1408 cm\textsuperscript{-1}. Nuclear magnetic resonance (NMR) was used to show the asymmetric structure of 1,3-AOBAE compared to that of 1,4-AOBAE.

**Sensor response time to pH and hydrogel thickness**

For the pH response experiments, 1,3-AOBAE was spin coated onto a Si-wafer, forming films with thicknesses between 1.4 and 12 µm. To measure the film thicknesses, an interferometric thin film measurement setup was used.

In the experiments, it was challenging to measure thicker films (>3 µm) due to the larger physical force that a thicker film exerts on the adhesion points between film and substrate, than what a thinner film exerts. Because the mechanism of a hydrogel’s expansion is a diffusion process, a film that expands more will have a longer time constant to equilibrium than a thinner film [37,83]. This effect can be seen in Fig. 3.3, where the pH values of 5.53 and 5.70 (more expanded) have longer time constants than pH 5.95 (less expanded): ~60 and ~10 s, respectively.

**Translational diffusion effect**

An interesting effect noticed but not discussed in Article III is that curing viscous material can cause a translational diffusion effect [112–114]. Specifically, in a viscous material, the time for two propagating radicals to reach each other and therefore be able to bond is longer. This effect is more pronounced when a material is cured in air, because the polymerization of the polymer also is
3.1 Synthesizing and characterizing 1,\textsubscript{x}-AOBAE competing with oxygen termination, as Fig. 3.4 shows. Therefore, when viscous materials are cured in air, a prolonged curing time might be necessary.

Figure 3.3: The behaviour of 1,3-AOBAE with mole ratio 2:1 that was exposed to various pH values, 5.53, 5.70 and 5.95. A value of 0% on the Y-axis equals the film’s dry thickness before any pH solution is added.

Figure 3.4: Polymerization conversion of 1,3-AOBAE, mole ratio 5:4, showing the difference between air and N2. Polymerization of a 300 \( \mu \)m thick film with 2.5\% photoinitiator and 11.9 mW/cm\(^2\) of curing power. The air curve (red) shows the translational diffusion effect.
3 Experimental

3.2 Manufacturing fiber-optic sensors

In tests conducted with dip coating on optical fibers, cleaning the surface with only acetone and ethanol was not always enough. Even with a primer between the fiber and the polymer, strong adhesion was no guarantee. Possibly, because residues from the coating may remain on the fiber after cleaning. One way to improve the cleaning of a fiber is to clean it with acetone and ethanol, burn away possible acrylate residues with a butane flame and clean it with acetone and ethanol again.

Surface priming with a molecule that can covalently bind to the substrate and the polymer resulted in the samples with the best adhesion. In the experiments, 3-(trimethoxysilyl) propyl acrylate was used, where the 3-(trimethoxysilyl) part can tether to the fiber thereby leaving the acrylate group to tether to the polymer. To have strong adhesion with optical fibers, the primer should be an even monolayer. To achieve this condition, the surface must be clean from organic residues so the hydroxyl (OH) groups are exposed.

The polymer coating of the fibers was done with a dip-coating technique. With a motorised translation stage, the fiber was drawn into the quartz tube with a constant speed and simultaneously coated with hydrogel. The curing was then performed in the quartz tube (flooded with N\textsubscript{2} gas). A more detailed approach of the manufacturing process can be found in Article V.

Fiber-optic Mach-Zehnder interferometers

Coreless MZI does not have a linear dependency towards RI, as Fig. 3.5 shows, where the sensitivity nm/RIU (refractive index unit) is higher the closer to the RI of the fiber cladding the surrounding RI is (measurement data is taken from unpublished work by Hammarling). Therefore, for a sensor system working in region 1, the average sensitivity is \( \sim 100 \) nm/RIU, and for region 2 \( \sim 500 \) nm/RIU.

End mirror on fiber

Articles I and V use inline sensors, but it should be possible to manufacture them as single-strand sensors. The reflection power from a fiber end surface in water is \( \sim 0.2\% \), resulting in a low SNR level. With a mirror placed on the end, the signal could be increased up to 500 times (i.e. reflection 100\%). Experiments have been conducted on the MZI sensor, but no data have been published.

Experiments have been conducted by making a mirror with silver nanoparticles, which can improve the strength of the return signal by more than 20 dB. The used Ag ink was ANP Silver Jet Ink DHG. Two methods have been tested to make the mirrors. The first method was dipping the end of the fiber directly into the ink, then sintering the particles with heat (100 °C). The second method was soaking a piece of tissue with the ink, then touching the tip of the fiber onto that tissue and then sintering the ink. For both methods, up to three
3.3 Manufacturing of interdigital capacitive sensors

Figure 3.5: Sensitivity plot of an MZI when measuring refractive index.

repetitions were needed before a useful mirror (>20 dB increase of reflection power) was manufactured. The drawback of the first method is that it is very easy to get ink on the side of the fiber due to capillary forces and accidentally dipping too deeply. With the second method, ink is placed only on the fiber tip, not the sides. However, the drawback is that considerably more ink is required because the tissue needs to be soaked.

3.3 Manufacturing of interdigital capacitive sensors

In Article IV an interdigital pH-sensitive capacitance was manufactured and evaluated. The interdigital capacitance was made by laser ablating the pattern
3 Experimental

out of a 30 nm thick gold film that had been sputtered upon a polyethylene terephthalate (PET) film. After patterning of the electrical structure, an insulation layer and the pH sensitive AOBAE was coated, as shown in Fig. 3.6. The electrical protection layer should be as thin as possible to avoid lowering the sensitivity (preferably less than 10% of the sensor’s penetration depth, in this case <3 $\mu$m), and the hydrogel thickness should be in the order of $E_{PD}$ (30 $\mu$m). Sensors made from etched aluminium foil on plastic, reduction of copper oxide (CuO) to copper (Cu), inkjet printed patterns, laser-burning of polyimide to graphene and screen printing have also been made and evaluated. In Sections 3.3.1 to 3.3.5, these experiments are discussed.

3.3.1 Inkjet-printed silver

Silver nanoparticles were printed into an interdigital pattern on polyimide with an inkjet printer (Dimatix 2831) and sintered in an oven at 160 ºC. Then SU8 (2000.5) was inkjet-printed, baked and cured to act as an isolation layer. The last step was done by blade coating the AOBAE as a sensing layer. We faced two big challenges with this type of sensor. First, the SU8 cured into an uneven surface, as Fig. 3.7 shows, possibly due to the poor wetting ability between the polyimide and SU8. Second, the AOBAE’s wetting ability and adhesion on SU8 was not good. Therefore, these sensors were easily delaminated between these two layers when they were immersed in acid. Inkjet printing is a slow process compared to, for example, screen printing and etching.

Figure 3.7: Silver nanoparticles sintered as electrical tracks with SU8 as an electrical insulation layer and AOBAE as sensing layer.
3.3 Manufacturing of interdigital capacitive sensors

3.3.2 Etched alumina foil on plastic

Interdigital capacitors were etched out of 40 µm thick alumina foil on PET support and then coated with an electrical protection layer and hydrogel. During manufacturing, two challenges were encountered. First, because the etched grooves were 40 µm deep and the calculated hydrogel layer should be 30 µm, the coating of the 30 µm thick hydrogel layer became uneven, as it also sank into the grooves, as shown in Fig. 3.8a. Second, when this hydrogel layer absorbs water and starts to expand, it exerts a lateral physical force on the alumina bars, thus trying to push them apart and bending the flexible structure as Fig. 3.8b shows, making the response of the sensor hard to predict. This technique has been successful in other sensor configurations. See, for example, the humidity sensor in [115].

![Cross section of an interdigital capacitance with hydrogel and electrical insulation layers. Picture (a) shows the principle sensor. Picture (b) shows the lateral forces of the hydrogel work when it expands, thus bending the flexible substrate.](image)

3.3.3 Intense pulsed light processing of CuO to Cu

Copper oxide (CuO) can be reduced to Copper (Cu) with a high-intensity light and a reduction agent [116]. This reduction can be achieved with either flash sintering or laser processing [116, 117]. Experiments using this method to make laser-written electrical patterns on plastics have been conducted, but during the experiments, the physical forces from the hydrogel swelling caused the copper tracks to delaminate from the substrate.

3.3.4 Laser-induced graphene on polyimide

Graphene has gained attention for its use in flexible electronics [118, 119]. One way to make graphene for flexible electronics is using the direct laser engraved graphene method, which can be done directly on polyimide [120]. The heat from the laser forms graphene directly from the polyimide, but the heat also induces deformations in the polyimide. These deformations could be up to 30 µm in height, thus it was difficult to deposit even films of electrical insulation and AOBAE.
3 Experimental

3.3.5 Screen printing

Screen printing is a method that is very fast and can be used in roll-to-roll processes. Printing resolution is limited to $\sim 70 \mu m$ using conventional screen printing meshes [121]. In the experiments, the thickness of the electrical tracks was $\sim 20 \mu m$, thus it was difficult to deposit even films of electrical insulation and the AOBAE. In the design, the track (W) plus the gap (G) measured 200 $\mu m$, which gives a penetration depth of $\sim 70 \mu m$ of the electrical field [99]. The AOBAE needs to cover this depth, which resulted in a slow response time (hours) for the sensor compared to the other sensors (minutes) presented above.

3.4 Dual-parameter sensor

Many measurands depend on secondary parameters, for example, pH has a temperature dependency. Therefore, to accurately measure one parameter, it is often necessary to also measure the dependent value. In Article II, two dual-parameter sensor concepts for optical fibers that utilise the interferometric techniques, MZI and FPI are shown. This article is a preliminary study of a combined glucose-pH sensor to be used in vivo in intensive care units. The FPI sensor is manufactured from a glucose-responsive hydrogel based on 3-phenylboronic acid, which is also susceptible to pH changes [122]. By measuring the blood pH at the same time with the MZI, it is possible to adjust the measured glucose value accordingly. Because the temperature in a body is relatively constant, no temperature sensor was added. However, it would be possible to add a temperature-sensitive fiber Bragg grating [123] to the dual sensor, making it a triple sensor on one single-strand fiber.
4 Sensor results

In Article I, the intensity sensor works with a combination of refraction losses and evanescent wave absorption where refraction loss is the primary sensing response, due to the changed outer RI (mode leakage). Most of these refraction losses happen at the beginning of the sensor; the sensor then becomes more of an evanescent wave absorption sensor. This type of sensor has several benefits, for example, it has a simple design, making it possible to use simple photo detectors for the readout. The sensor works with almost all wavelengths (visible to IR is shown in the article); therefore, it is possible to use lasers and broadband light sources. Because intensity sensors are very sensitive to the input energy, a reference signal is needed so any input fluctuations can be compensated for. The highest sensitivity was reached for the sensor built with 1,3-AOBAE with a molar ratio of 5:4 and a sensitivity of $\sim 15$ dB between pH 6-7 over the wavelength range 600-1700 nm.

The sensors in Article II, which were designed as a pre-study to measure two parameters at once, were tested in two configurations. The first configuration was built with a 1310/1550 splitter (dual strand), after the splitter one fiber had an MZI (RI sensor) built on the end, and the other had an FPI (ethanol sensor). This technique ensures that the two sensor signals are separated in wavelength and therefore not interfering with each other. The second version was built as a single-strand sensor with the MZI and the FPI on the fiber end. In this case, the two return signals, MZI and the FPI, will interfere with each other. However, because the MZI returns a low-frequency signal and the FPI signal is a high-frequency signal, it is possible to separate them by using Fourier transform-based filtering algorithms. In the first configuration, the MZI had an error of $\sim \pm 0.5$ nm when the FPI was subjected to ethanol concentrations from 0 to 50% and the RI was held constant. The FPI had an error of $\sim \pm 1.5$ nm when the RI was changed from 1.3325 to 1.4346, and the ethanol concentrations was held constant at 30%. For the single-strand sensor, the MZI and FPI errors occurred in the same order as in the first configuration. Hence, it is possible to build a single-strand sensor with the error characteristics of a dual-strand sensor.

The interdigital capacitance structure in Article IV was laser-ablated with a pulsed laser system that had a spatial resolution of 10 $\mu$m. The average edge roughness for the structure was $\sim \pm 1$ $\mu$m because the pulsed system works by ablating one overlapping round spot at the time. This roughness can be neglected when calculating the effective capacitance surface area because the structure is 3 orders larger than the error. The sensor has two layers coated on top of the structure, the insulating layer (SU8) and the hydrogel (1,3-AOBAE). Both have some deviations in thickness from the coating. Experiments showed
that the insulating layer had a deviation of $\pm 1 \mu m$ and the hydrogel $\pm 3 \mu m$ for thin films ($<18.5 \mu m$). The deviation from the insulating layer will not affect the sensor performance, as it can be counted as a constant that is set when calibrating the sensor. However, deviations of the hydrogel will increase the time constant before the sensor is stable. Long-term stability tests (weeks, months) have not been conducted, but experiments have shown a stability of $\pm 0.65\%$ during 1 h from the stable value point. The stable value point was calculated as the point when the capacitance mean deviation stayed within $\pm 1\%$ for at least 10 min. Repeated experiments of the sensors resulted in a deviation of $< \pm 1.1\%$ when cycled in solutions of pH 7.12 and 8.38 ten times.

The optical MZI in Article V showed a nearly linear response of $\pm 1.25$ nm between pH values of 7.1-11.89, as shown in Fig. 4.1, where the errors are estimated as 0.5 nm from the optical spectrum analyzer (OSA), 0.5 nm from the Matlab script and 0.25 nm from ten consecutive deviation measurements. In theory, with the OSA set to a resolution of 0.05 nm, the error can be 0.35 nm, which would give a sensor resolution of $\sim 0.06$ pH in the pH range of 7.1 to 11.89. The linear region could be extended with an improved sensor design in which the signal is not folding back (see Article V, Fig. 8). The cycling measurements showed an error of $\pm 0.2$ nm after 10 min at each pH, 7.10 and 8.15, see Article V, Fig. 10.

![Figure 4.1: MZI with a linear fit between pH 7.1 and 11.89. The slope of the fitted line is $-5.69$ nm/pH, and the errors are $\pm 1.25$ nm.](image)
5 Discussion

1,3-AOBAE has the advantage over 1,4-AOBAE because even without solvents, it does not crystallise at room temperature (due to its asymmetrical molecular structure) and therefore has no need for any temperature-elevated process steps during manufacturing. In characteristics such as pH response, coatability and curing, no notable difference has been noticed between the two hydrogels. If solvents are used during synthesis of the hydrogel, up to three extra process steps are needed, separation, washing and drying [57]. The use of solvents can also be problematic if a non-toxic hydrogel is desired, because some solvents are hazardous and may leave residues in the hydrogel (despite separation and washing) [124]. It is therefore beneficial to avoid solvents.

From a manufacturing point of view, regarding sensor deviations, a hydrogel layer thickness greater than $E_{PD}$ is preferred because as long as the gel thickness plus any deviations is greater than $E_{PD}$, the sensor will give the same final output (although the time constant will change). When the gel thickness is less than $E_{PD}$, any deviations will alter the characteristics of the sensor. It is therefore more critical to have a well-defined gel thickness, if the sensor has an $E_{PD}$ greater than the gel thickness. Also, if the $E_{PD}$ is greater than the gel thickness, there is a risk that the sensor is also measuring any contamination in the $E_{PD}$ field.

There are some general differences between an electric and optical measurement system. Optical fibers are insensitive to all types of electromagnetic interference (EMI) and are more resistant to corrosion than copper cables, making them suitable for use in areas with high EMI (e.g., in the vicinity of high power lines or magnetic resonance imaging, MRI) and in harsh environments (e.g., salt and seawater). Also, there is no risk of sparks because no electric current is running in the fiber, so it is also suitable for use in areas with a fire or explosion risk. It is also possible to build optical fibers as distributed sensors, allowing for measurement of kilometers of fiber length at the same time using an optical time domain reflectometer (OTDR) or optical frequency domain reflectometer (OFDR) system [125]. Optical systems still need an electric readout system where the light signal is converted to an electric signal, such as with a photodiode or an OSA. An OSA (~$20,000) is expensive compared to many electrical systems (24-bit analog to digital converter (ADC) card ~$200), which can limit the use of these types of sensors in many applications. Regarding development time, electronic systems have an advantage over optical systems due to their variety of components and fast processes, such as application-specific integrated circuit (ASIC) and printing techniques. The hydrogels used have proven to be usable in electrical and optical sensor systems, due to the nature
5 Discussion

of the hydrogel’s effective RI and permittivity change in response to pH.

When designing a pH sensor, it is important that one takes into account as many parameters as possible early in the design process, such as the required measuring range and resolution, electric or optic system, volume of measured liquid, size etc. Each parameter chosen for a sensor system will reduce the window for possible measurement techniques and usable materials. Healthcare parameters could be, for example, ability to measure in seconds (fast), disposable (one time use), non-toxic and small (fit inside the blood vessels of the body) [126].

In the work presented in this thesis, the hydrogels 1,3 and 1,4-AOBAE were used in two sensor configurations, one using optical and one using electrical readout. However, the hydrogels can be used in other sensor technologies because the pH response affects several parameters, such as volume, mass, RI, permittivity, resistivity and light absorbance. Some example techniques are acoustics and vibrations (mass sensitive), cantilever (volume) and resistivity systems. In general, hydrogels can also be made sensitive to a number of other physical and chemical parameters (glucose, temperature, chemical and biological agents etc.); therefore, it might be possible to utilise one measurement system to measure several other parameters by changing the sensing hydrogel layer to a hydrogel that can sense something else, such as glucose [127]. This possibility makes hydrogels and hydrogel-based systems in general very versatile.

Finally, this thesis problematised and discussed pH-responsive hydrogels and some of their many synthesizing parameters together with the importance of knowing the penetration depth of a sensor versus the thickness of the sensing layer. The knowledge gained from this work can be used to plan suitable hydrogel and sensor parameters for use in sensor development, especially in healthcare and environmental applications. Even though none of the sensors built has a specific area where it is to be used, the hydrogels may be useful in optical and electric sensor systems due to the broad pH range of the gel (pH 2-12), its non-toxicity and the coating possibility on various substrates. For example, the hydrogel could be used in an in vivo optical system, such as a dual sensor at intensive care units to measure pH and glucose [122,128] or an electric system that measures the pH level in a chronic wound bed [129].
6 Summary and conclusions

Development, synthesis, characterisation and verification experiments of an improved hydrogel, 1,3-AOBAE (related to 1,4-AOBAE), were conducted. The gel was characterised regarding chemical composition by NMR and curing behaviour with FTIR. The hydrogel-coating characteristics proved to be in the range that it is usable for blade- and dip-coating techniques (<100 cP for mol ratio 2:1, BDDA:PIP), which has been verified through manufacturing of sensors with these techniques. The response to pH was investigated by testing the AOBAE in optical and electrical pH-sensor systems, which proved that it alters both its optical and electrical characteristics regarding pH change. The electric interdigital pH sensor can measure pH between 2.9 and 11.9. Measurements above pH 11.9 were not performed, and problems with adhesion arose below 2.9. This broad range makes it suitable for use in environmental monitoring. The optical MZI pH sensor responded to pH changes in the range of 1.9-11.9, with a resolution of 0.008 pH and a nearly linear response between pH 7.1 and 11.9. Even though the sensor had a breaking point around a pH of 6, where the pH response reversed, as Article V, Fig. 8, shows, it is suitable for use in, for example, healthcare blood measurements. With an improved sensor design, it is believed that the sensor should be able to measure in the whole pH range (1.9-11.9) without the signal folding.

The optimization process of a hydrogel is a complex procedure, because many synthesizing parameters will affect the finalised gel. Some examples of synthesising parameters are chosen molecules, preparation method, ionic charge and cross-linking. The complexity arises from the fact that one synthesising parameter might induce changes in several gel properties. For example, altering the gel to have a smaller mesh size, $\xi$, by introducing higher cross-linking density also leads to a decrease in the diffusion rate, an increase in the mechanical strength and a decrease in solution absorption. Therefore, research is needed to optimise the hydrogel for the specific application in mind.

The need for new innovative pH sensors in our modern society is growing, which enhances the need for research that increases the knowledge and understanding of pH sensors and pH-sensing material. The resulting knowledge can then be used to open doors to new novel applications, which will benefit society in form of, for example, better healthcare and environmental monitoring.
6 Summary and conclusions

6.1 Future work

For future work, it would be interesting to characterise the 1,3-AOBAE described in Article III, regarding various ions, ionic strength susceptibility and long-term stability.

To find out how deviations in cut angles, cut length and bending changes the output spectrum of an MZI, a full-scale simulation should be performed (preferably with white light).

The MZI sensor is now working at around 1700 nm, but it would be preferable to redesign it to one of the telecommunication bands (e.g. C-band 1530-1565 nm), where the fiber-optic components are less expensive.

During the experiments, adhesion problems led to delamination of the films. This effect has to be addressed and more closely examined, to ensure more stable and correct sensors.

6.2 Social, ethical and environmental aspects

During the doctoral studies, social, ethical and environmental values have been considered and respected accordingly. No experiments on animals were conducted.
### 6.3 Author’s contributions

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1 Krister Hammarling, 2 Magnus Engholm, 3 Hans-Erik Nilsson, 4 Henrik Andersson, 5 Mats Sandberg, 6 Harald I. Muri, 7 Markus S. Wahl, 8 Dag R. Hjelme, 9 Jöns Hilborn, 10 Anatoliy Manuilskiy. M = main author, C = co-author.
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### Appendix I. pH sensors, derived from Khan [22]

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<th>Sensitivity per pH unit</th>
<th>Minimal response time</th>
<th>Accuracy of measurement (pH)</th>
<th>Pros and cons</th>
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<td>A few seconds</td>
<td>Acidic or basic</td>
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<td>Not applicable</td>
<td>a few seconds</td>
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</tr>
<tr>
<td>Glass electrode pH sensor</td>
<td>Potential measurement of an electrolyte comparing result with a reference electrolyte</td>
<td>2-12 (0-14)</td>
<td>59 mV</td>
<td>~20s</td>
<td>0.005</td>
<td>Pros: Accurate and reliable reading. Cons: Fragile materials, complex construction and frequent calibration is required, relatively large, need a reference.</td>
<td>[130–132]</td>
</tr>
<tr>
<td>Electrode modification by pH sensitive polymers</td>
<td>Organic conducting polymer modified electrodes</td>
<td>3-10</td>
<td>50 mV</td>
<td>&lt;1 s</td>
<td>Pros: Stability in air and being compatible with biological molecules in a neutral aqueous solution. Cons: Unstable due to defects and pinholes present in the structure of the film.</td>
<td>[133]</td>
<td></td>
</tr>
<tr>
<td>Optical fiber pH sensors</td>
<td>Adsorption of dyes</td>
<td>1-9</td>
<td>18 counts</td>
<td>&lt;1 s</td>
<td>0.001</td>
<td>Pros: Fast response, no contact measurements, no spatial storage conditions, continuous measurement capability, low energy consumption, low production cost, possibility of mass production, measurements in biological pH range, do not require reference sensor. Cons: Limited long-term stability because of photobleaching and dye leaching along with dependence on temperature.</td>
<td>[22, 47]</td>
</tr>
<tr>
<td>Fluorometric</td>
<td>Fluorescence</td>
<td>0-14</td>
<td>&lt;1 s</td>
<td>0.16</td>
<td>Pros: Can be miniaturized to submicron diameter, do not suffer from electromagnetic and electrical interferences. Cons: Rigged and fixed setup of fluorescent pH sensor is that of measuring a signal which depends on the ionic strength of the sample.</td>
<td>[14, 32]</td>
<td></td>
</tr>
<tr>
<td>Ratiometric</td>
<td>Intensity1 divided by intensity2</td>
<td>2-9</td>
<td>&lt;1 s</td>
<td>&lt;0.04</td>
<td>Pros: Very useful in accurate quantification of intracellular pH, minimally impacted by drift in the instrument or the fluctuations of the excitation source. Cons: Two squared signals measurements are required in ratio-metric detection, changes in light sources and filter sets may result in time-delayed recording. The leaching of the embedded dyes from the matrices is also a matter of concern.</td>
<td>[25, 134, 135]</td>
<td></td>
</tr>
<tr>
<td>Optical fiber pH sensors</td>
<td>Holographic</td>
<td>4-7</td>
<td>150 nm</td>
<td>&gt;10 min</td>
<td>Pros: Promising due to high sensitivity &amp; high enough accuracy, ease of operation and three-dimensional image. Cons: Expensive, still a developing technology.</td>
<td>[27, 42]</td>
<td></td>
</tr>
<tr>
<td>Optical fiber pH sensors</td>
<td>Interferometric</td>
<td>0-14</td>
<td>&lt;1 s</td>
<td>&lt;0.09</td>
<td>Pros: Flexibility to use computer software for quick analysis and the MS Excel sheet to process data compared to the more time-consuming analysis in conventional spectrophotometric techniques. Covers the whole pH range 0-14. Cons: Relatively large.</td>
<td>[28]</td>
<td></td>
</tr>
<tr>
<td>Optical fiber pH sensors</td>
<td>Interferometric</td>
<td>2-12</td>
<td>11 mm</td>
<td>~10 s</td>
<td>0.01</td>
<td>Pros: Not dependent on input power, high sensitivity. Cons: Requires broadband light source.</td>
<td>[30, 43, 136]</td>
</tr>
<tr>
<td>Sensor type</td>
<td>Technique for measuring</td>
<td>Working pH range</td>
<td>Sensitivity per pH unit</td>
<td>Minimal response time</td>
<td>Accuracy of measurement (pH)</td>
<td>Pros and cons</td>
<td>Ref.</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------------------------------------</td>
<td>------------------</td>
<td>-------------------------</td>
<td>-----------------------</td>
<td>----------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td><em>Evanescent wave adsorption</em></td>
<td>[14]</td>
<td>3-11</td>
<td>1.1 dB/2 mm</td>
<td>10 s</td>
<td></td>
<td>Pros: High sensitivity. Cons: Dependent on input power.</td>
<td>[44, 47]</td>
</tr>
<tr>
<td>Ion-sensitive field-effect transistor (ISFET)</td>
<td>[15]</td>
<td>0-14</td>
<td>160 mV</td>
<td>&lt; 10 s</td>
<td>0.01</td>
<td>Pros: Comparatively less expensive and smaller than glass electrode. Cons: Drift of the device response over time, requires a reference electrode.</td>
<td>[23, 30-40]</td>
</tr>
<tr>
<td>Image Sensor</td>
<td>[16]</td>
<td>2-10</td>
<td>475 mV</td>
<td>~ 5 s</td>
<td></td>
<td>Cons: Relatively large, requires a reference.</td>
<td>[29, 48]</td>
</tr>
<tr>
<td>Conductimetric</td>
<td>[17]</td>
<td>1.5-13</td>
<td>120 mV</td>
<td></td>
<td></td>
<td>Pros: Simple technique.</td>
<td>[22, 49, 50]</td>
</tr>
<tr>
<td>Potentiometric</td>
<td>[18]</td>
<td>2-10</td>
<td>76 mV</td>
<td>~2 s</td>
<td></td>
<td>Pros: Fast response time and are efficient at high pressure and temperature, good repeatability, one of the most sensitive methods of measuring pH from 0 to 14. Cons: Requires reference electrode.</td>
<td>[46, 141, 142]</td>
</tr>
<tr>
<td>Cantilever and micro-cantilever</td>
<td>[19]</td>
<td>4-10</td>
<td>40 nm</td>
<td>~100 s</td>
<td>5x10^-4</td>
<td>Pros: High sensitivity, low cost, non-hazardous procedure, quick response, low analyte requirement (in µL). Cons: Deflection resolution which may be in nm.</td>
<td>[26, 143]</td>
</tr>
<tr>
<td>Magnetoelastic</td>
<td>[20]</td>
<td>2-10</td>
<td>1290 Hz</td>
<td>~14 min</td>
<td>0.02</td>
<td>Pros: Relative cheap method. Cons: Sensors resonance frequency vary with ambient temperature and earth magnetic fields, it will reduce the accuracy and reliability of measurements.</td>
<td>[22, 35, 36]</td>
</tr>
<tr>
<td>Wireless</td>
<td>[21]</td>
<td>2-10</td>
<td>78 Hz</td>
<td>~1 min</td>
<td></td>
<td>Pros: Wireless and passive system that can allow measurement of long-term pH monitoring in otherwise inaccessible area. Cons: Cost competitiveness compared to wired systems.</td>
<td>[33]</td>
</tr>
</tbody>
</table>

Note that range, sensitivity, response time and resolution are the best values and not always correlated. For example, there can be a high sensitivity but in a small range or vice versa.
Appendix II. Hydrogel synthesising

Figure 1: Example of design considerations when synthesising hydrogels. The green groups are synthesising properties (before and during synthesising) and blue physical properties (after synthesising and curing is done). Dark blue properties represent the essential properties for pH sensors manufactured with stimuli-responsive hydrogels for this thesis.

Figure 1 displays some synthesising and design considerations that can be
Appendix II

made when synthesising hydrogels, which has been derived from [38, 55–60]. The mindmap of a hydrogel is categorised in two phases, before/during synthesis (green group) and after synthesising (blue group), respectively. These phases, denoted as synthesising and physical group are then divided into properties and sub-properties (without any mutual weight). As can be seen, the many choices during synthesising will have a large impact on the hydrogels final physical characteristics. In Fig. 2 some dependencies are added to Fig. 1, such as pH susceptibility is dependent on which molecules that are used (source), and if these molecules are anionic or cationic by nature. Each bubble will have their own dependency.

Figure 2: Example of design considerations when synthesising hydrogels, together with some parameter dependencies. For example, toxicity is dependent on used source material, how the preparation is done, used cross linking type and if the hydrogel is degradable.
### Appendix III. pH polymers

<table>
<thead>
<tr>
<th>No</th>
<th>Material</th>
<th>Example method</th>
<th>Physics or Chemistry</th>
<th>Sensor advantages</th>
<th>Sensor disadvantages</th>
<th>Used in application(s)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PAA-co-iso styrylaketone, AA, N,N-methylenebis(acrylamide)</td>
<td>Mass-sensitive pH sensor</td>
<td>Resonance with a certain frequency</td>
<td>Easy to fabricate and low material cost</td>
<td>The swelling of pH responsive polymer is affected by the salt concentration of immersion solution</td>
<td>Sensing of biological, chemical and environmental conditions</td>
<td>F1902, F1903, G1907, G1909</td>
</tr>
<tr>
<td>2</td>
<td>Poly-m-phenylenediamine</td>
<td>Conducting polymer pH sensor</td>
<td>Linear response from pH 1-13 and slope of 56.7 mV/pH</td>
<td>Good potential stability and reproducibility</td>
<td>The complexity of construction, fragile materials involved, frequent calibrations</td>
<td>Medical and biological applications</td>
<td>G1906, G1908, G1909</td>
</tr>
<tr>
<td>3</td>
<td>PMMA with PEGDA</td>
<td>Nano-Constructed cantilever based pH sensor</td>
<td>Biparametric and reversible change in surface stress of micro-cantilever</td>
<td>Highly sensitive, low power, and compact transducers</td>
<td>Integration of cantilever arrays and microfluidic channel network is still under development, complex to manufacture</td>
<td>Biological applications</td>
<td>G1905, G1906, G1907, G1909</td>
</tr>
<tr>
<td>4</td>
<td>MHA and HDT</td>
<td>Nano-Constructed cantilever based pH sensor</td>
<td>Changes in interfacial stress between thiol-covered cantilevers and buffer solutions of various pH</td>
<td>Highly sensitive, low power, and compact transducers</td>
<td>Integration of cantilever arrays and microfluidic channel network is still under development, complex to manufacture</td>
<td>Semiconductor and integrated circuit design technology</td>
<td>G1907, G1909</td>
</tr>
<tr>
<td>5</td>
<td>MA, AAM, APS, BAAM and TEMED</td>
<td>Optical fiber based sensor</td>
<td>Interferometric and FPP</td>
<td>pH and temperature measurement in one sensor</td>
<td>Low resolution, long manufacturing time &gt;12 h</td>
<td>Sensing of biological, chemical and environmental conditions</td>
<td>G1905, G1906, G1907, G1909</td>
</tr>
<tr>
<td>6</td>
<td>PAA and PA</td>
<td>Optical fiber based sensor</td>
<td>Interferometric</td>
<td>Good resolution</td>
<td>Laser by layer deposition (25 layers), long in manufacturing time &gt;12 h</td>
<td>Sensing of biological, chemical and environmental conditions</td>
<td>G1907</td>
</tr>
<tr>
<td>7</td>
<td>PVA and PA</td>
<td>Optical fiber based sensor</td>
<td>Interferometric</td>
<td>Good repeatability</td>
<td>Saline dependent, many steps in manufacturing &gt;33 h manufacturing time</td>
<td>Sensing of biological, chemical and environmental conditions</td>
<td>G1907</td>
</tr>
<tr>
<td>No</td>
<td>Material</td>
<td>Sample detection method</td>
<td>Physics or Chemistry</td>
<td>Sensor advantages</td>
<td>Sensor disadvantages</td>
<td>Used in application(s)</td>
<td>GHS* Ref.</td>
</tr>
<tr>
<td>----</td>
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<td>------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>9</td>
<td>AAM, bisacrylamide, TEMED, APS, MAA, glacial acetic acid, sodium hydroxide</td>
<td>Optical fiber based sensor</td>
<td>Interferometric</td>
<td>Fast, stable</td>
<td>Low resolution, long manufacturing time +48 h</td>
<td>Sensing of biological, chemical and environmental conditions</td>
<td>GHS02, GHS03, GHS05, GHS06, GHS07, GHS08</td>
</tr>
<tr>
<td>9</td>
<td>PANI</td>
<td>Conducting polymer pH sensor</td>
<td>Voltage change</td>
<td>Cytotoxicity tested, easy method</td>
<td>Repeatability</td>
<td>Biological sensors</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>HEMA, AIBN, EGDMA, PQ and MAA</td>
<td>Holographic</td>
<td>Wavelength change, color shift</td>
<td>Good sensitivity</td>
<td>Slow, long manufacturing time +48 h</td>
<td>Biological monitoring, biological sensing</td>
<td>GHS02, GHS06, GHS07, GHS09</td>
</tr>
<tr>
<td>11</td>
<td>pHEMA-co-MAA, EGDMA</td>
<td>Holographic</td>
<td>Wavelength change, color shift</td>
<td>High sensitivity in the range pH 4-6.6</td>
<td>Manufacturing time not stated</td>
<td>Biological sensing</td>
<td>GHS05, GHS06, GHS07</td>
</tr>
<tr>
<td>12</td>
<td>PEGDA and acryloyl</td>
<td>Fluorescent sensor</td>
<td>Fluorescence</td>
<td>Small pores, cytocompatibility, non-toxicity, easy of use</td>
<td>Good sensitivity, cytocompatibility, non-toxicity, fast easy manufacturing</td>
<td>Biological sensing</td>
<td>GHS02, GHS05, GHS06, GHS07</td>
</tr>
<tr>
<td>13</td>
<td>1,3-BDDA, PIP</td>
<td>Optical fiber based sensor, flexible electronics sensor</td>
<td>Wavelength change, permittivity change</td>
<td>Good sensitivity, cytocompatibility, non-toxicity, fast easy manufacturing</td>
<td>Still under development</td>
<td>Sensing of biological, chemical and environmental conditions</td>
<td>GHS05, GHS07, GHS08</td>
</tr>
</tbody>
</table>

* GHS = Globally Harmonized System [62], GHS is pre polymerization.
## Appendix III

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Name</th>
<th>GHS code</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>Acrylic acid</td>
<td>GHS02, GHS05, GHS07, GHS09</td>
</tr>
<tr>
<td>AAM</td>
<td>Acrylamide</td>
<td>GHS07, GHS08</td>
</tr>
<tr>
<td>ABN</td>
<td>2,2-azobis (2-methyl propane)</td>
<td>GHS02, GHS07</td>
</tr>
<tr>
<td>APS</td>
<td>Ammonium persulphate</td>
<td>GHS05, GHS07, GHS09</td>
</tr>
<tr>
<td>BAAM</td>
<td>N,N'-methylene acrylic amide</td>
<td>GHS07</td>
</tr>
<tr>
<td>ICYMA</td>
<td>Icyryl methacrylate</td>
<td>GHS07</td>
</tr>
<tr>
<td>HAM</td>
<td>Hexadecane</td>
<td>GHS07</td>
</tr>
<tr>
<td>HEMA</td>
<td>Ethylene glycol dimethacrylate</td>
<td>GHS07</td>
</tr>
<tr>
<td>MAA</td>
<td>Meth-acrylic acid</td>
<td>GHS05, GHS06</td>
</tr>
<tr>
<td>MHA</td>
<td>Mercaptohexadecanoic acid</td>
<td>GHS09</td>
</tr>
<tr>
<td>FMA</td>
<td>Poly-acrylic acid</td>
<td>none</td>
</tr>
<tr>
<td>PANI</td>
<td>Polyamine (conductive polymer)</td>
<td>none</td>
</tr>
<tr>
<td>PEGDA</td>
<td>Polyethylene glycol diacrylate</td>
<td>GHS05, GHS07</td>
</tr>
<tr>
<td>pHEMA</td>
<td>Polydihydroxyethyl methacrylate</td>
<td>none</td>
</tr>
<tr>
<td>PEMA</td>
<td>Polyethylene methacrylate</td>
<td>GHS05, GHS06</td>
</tr>
<tr>
<td>PQQ</td>
<td>Phenanthrenequinone</td>
<td>GHS07, GHS09</td>
</tr>
<tr>
<td>PVA</td>
<td>Polyalcohol alcohol</td>
<td>none</td>
</tr>
<tr>
<td>TEMED</td>
<td>N,N-trimethylglycine</td>
<td>GHS02, GHS09, GHS07</td>
</tr>
<tr>
<td>PIP</td>
<td>Piperazine</td>
<td>GHS05, GHS09</td>
</tr>
<tr>
<td>1,3-BDDA</td>
<td>1,3-Butanediol diacrylate</td>
<td>GHS05, GHS07</td>
</tr>
</tbody>
</table>

### GHS Code Definitions

- **GHS02**: Flammable gases, category 1: Flammable aerosols, categories 1, 2: Flammable liquids, categories 1, 2, 3: Flammable solids, categories 1, 2: Self-reactive substances and mixtures, Types B, C, D, E, F: Pyrophoric liquids, category 1: Pyrophoric solids, categories 1, 2: Pyrophoric solids, categories 1, 2, 3: Organic peroxides, Types B, C, D, E, F

- **GHS03**: Oxidizing gases: oxidizing liquids

- **GHS05**: Corrosive to metals, category 1: Skin corrosion, categories 1A, 1B, 1C: Serious eye damage, category 1

- **GHS06**: Acute toxicity (oral, dermal, inhalation), categories 1, 2, 3

- **GHS07**: Acute toxicity (oral, dermal, inhalation), category 4: Skin irritation, category 2: Eye irritation, category 2: Skin sensitization, category 3: Specific Target Organ Toxicity – Single exposure, category 3

- **GHS08**: Reproductive toxicity, categories 1A, 1B, 2: Specific Target Organ Toxicity – Single exposure, categories 1, 2: Specific Target Organ Toxicity – Reproduced exposure, categories 1, 2: Aspiration hazard, category 1

- **GHS09**: Hazardous to the aquatic environment: - Acute hazard, category 1: - Chronic hazard, categories 1, 2