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ORGANIC ELECTRONICS FOR PRECISE DELIVERY OF
NEUROTRANSMITTERS

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Description of the cover image:

The photography on the cover was taken by Thor Balkehed, LiU, and depicts a multi-outlet delivery device developed within the thesis.

Organic electronics for precise delivery of neurotransmitters

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During the course of the research underlying this thesis, Amanda Jonsson was enrolled in Forum Scientium, a multidisciplinary graduate school at Linköping University, Sweden.

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Abstract

Organic electronic materials, that is, carbon-based compounds that conduct electricity, have emerged as candidates for improving the interface between conventional electronics and biological systems. The softness of these materials matches the elasticity of biological tissue better than conventional electronic conductors, allowing better contact to tissue, and the mixed ionic-electronic conductivity can improve the signal transduction between electronic devices and electrically excitable cells. This improved communication between electronics and tissue can significantly enhance, for example, electrical stimulation for therapy and electrical recording for diagnostics.

The ionic conductivity of organic electronic materials makes it possible to achieve ion-specific ionic currents, where the current consists of migration of specific ions. These ions can be charged signalling substances, such as neurotransmitters, that can selectively activate or inhibit cells that contain receptors for these substances. This thesis describes the development of chemical delivery devices, where delivery is based on such ion-specific currents through ionically and electronically conducting polymers. Delivery is controlled by electrical signals, and allows release of controlled amounts of neurotransmitters, or other charged compounds, to micrometer-sized regions.

The aims of the thesis have been to improve spatial control and temporal resolution of chemical delivery, with the ultimate goal of selective interaction with individual cells, and to enable future therapies for disorders of the nervous system. Within the thesis, we show that delivery can alleviate pain through local delivery to specific regions of the spinal cord in an animal model of neuropathic pain, and that epilepsy-related signalling can be suppressed *in vitro*. We also integrate the delivery device with electrodes for sensing, to allow simultaneous electrical recording and delivery at the same position. Finally, we improve the delay from electrical signal to chemical delivery, approaching the time domain of synaptic signaling, and construct devices with several individually controlled release sites.

Populärvetenskaplig Sammanfattning

Vårt nervsystem använder både elektrisk och kemisk signalering för att skicka signaler mellan olika delar av kroppen. Tack vare att nervsystemet använder elektriska signaler kan man skicka signaler till kroppen med hjälp av implanterade elektroder, tex. om kroppens egna signalering har rubbats pga. sjukdom eller skada. Detta utnyttjas i tex. pacemakers för reglering av hjärtrytmen, cochleaimplantat för förbättring av hörseln, deep brain stimulation för att lindra Parkinsons sjukdom, och ryggmärgsstimulering för smärtlindring.

En begränsning med elektrisk stimulering är att alla nervceller i närheten av elektroden påverkas, och att det kan vara svårt att styra om man vill stimulera eller inhibera en grupp av celler. Om man vill aktivera en typ av nervceller till att skicka signaler, kan man istället leverera kemiska substanser, *neurotransmittorer*, som binder in selektivt till dessa celler och aktiverar dem. Vill man minska cellernas signalering, kan man skicka ut andra inhiberande neurotransmittorer.

Kemisk stimulering är således mer specifik än elektrisk stimulering, men också mer komplex i och med att det behövs reservoarer för substanserna man vill leverera. Dessa reservoarer kräver plats och får inte läcka, och bör av plats- och säkerhetsskäl placeras på avstånd från leveranspunkterna. Det är också en svår utmaning att kunna leverera små och exakta doser i mycket små volymer, och med en tidsupplösning som matchar kroppens egen signalering.

Den här avhandlingen beskriver utveckling av komponenter som kan användas för frisättning av kontrollerade mängder laddade kemiska substanser, *joner*, exempelvis neurotransmittorer, till små volymer. Komponenterna är uppbyggda av jonledande och elektroniskt ledande polymerer, eller plaster, och frisättningen styrs med en elektrisk signal. Vissa av polymererna leder bara positivt laddade joner, medan andra bara leder negativt laddade joner, och dessa material kan användas för precis kontroll av mängden frisatta positiva respektive negativa joner. Genom att kombinera material som leder positiva och material som leder negativa joner kan mer komplexa komponenter konstrueras, vilket vi använt för att bygga en komponent med flera individuellt styrda frisättningspunkter. Dessa komponenter har också bättre tidsupplösning än tidigare varianter, och kan frisätta substanser på tiotals millisekunder. Vidare har vi konstruerat en komponent där kemisk leverans sker genom en elektrisk sensor, så att kemisk leverans sker lokalt till just de celler som sensorn läser av. Dessa kombinerade leverans-och-sensor-komponenter användes i en modell för epilepsi, där vi visade att vi kan minska epilepsi-relaterade signaler lokalt med kemisk leverans, och samtidigt läsa av hur signalerna minskar. I avhandlingen ingår också ett

projekt där vi uppvisade en terapeutisk smärtlindrande effekt i råttor. Smärtlindringen åstadkoms genom lokal leverans av en inhiberande neurotransmittor från en komponent placerad i ryggmärgen.

Acknowledgments

Although only my name appears on the cover of this thesis, the thesis is the result of the combined efforts of many individuals. Science is a collaborative, and typically slow process, where knowledge is added little by little. I believe that in order to contribute to this process, you need not only creativity, but a thorough understanding of previous work. Obviously, this is made a lot easier if you have the opportunity to be guided by intelligent, inspiring and experienced people.

I would like to sincerely express my gratitude to all the people that have made this work possible. First of all, I would like to thank my main supervisor, Magnus Berggren, and my co-supervisor, Daniel Simon. Magnus, thank you for giving me the opportunity to do a PhD in this interesting area of research, for involving me in highly interesting collaboration projects with other research teams, and for your never-ending enthusiasm! Thank you Daniel, particularly for your optimism, your open mind, for your help and support at all stages of the projects, and for transforming some of the manuscripts within the thesis through your amazing writing skills!

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Part I

Background

Introduction

1.1 Conductive polymers and organic electronics

Inorganic metals and semiconductors are the traditional electrically conducting materials of our society and are used in a vast array of engineering applications. In these materials, the atomic nuclei are typically arranged in a crystalline structure and are essentially immobile. The electronic charges of these materials can move rather freely, which render these materials conductive and electroactive. Polymers, or plastics, on the other hand, were for a long time regarded as electrical insulators, and it was not until the 1970's that it was discovered that polymers could be given electrical conductivities similar to the values of semiconductors [13, 79]. This discovery opened up the field of organic electronics, a field defined by that organic, that is, carbon-based, compounds are used as conductors and semiconductors in electronic components. Conductive polymers and other conductive organic materials are now used or being explored in, for instance, organic light emitting diodes (OLEDs), in digital displays, and as the energy converter material in organic solar cells. A major advantage with organic electronic materials, as compared to conventional inorganic electronic materials, is the possibility of low-cost fabrication processes, such as printing techniques, which is possible since the organics can be processed from solutions. Furthermore, many of the organic materials are relatively much softer than metals and semiconductors, which makes it possible to use them on flexible and even on stretchable carriers [64]. Conductive polymers are also different to conventional inorganic electronic materials in that they do not only conduct *electronic charge carriers*, *i.e.* conduct electrons and holes; they also allow ions to

pass through their porous structure, giving them an additional *ionic* conductivity. The combination of ionic and electronic conductivity together with the soft nature of conductive polymers suggests that these materials can offer unique opportunities when interfacing electronics with biological systems such as the cells, tissues and organs of the human body [71, 81].

1.2 Interfacing the body with electronics

In the 1780s the Italian philosopher, physician, physicist and biologist Luigi Galvani performed experiments using frogs and metal wires. He found that when he applied metal electrodes to detached frog legs, the legs started to twitch. Although it was not understood *how* electricity affected the body, it was clear that it did, and Galvani coined the term "animal electricity".

Today, it is known that body fluids contain charged compounds, *ions*, that migrate and polarize and thus give rise to ionic currents when electric fields are applied between electrodes in contact with the body fluids. Many cells, particularly cells of the nervous system, are sensitive to these ionic currents. The ionic currents cause changes in the ion concentrations in the vicinity of the cells, and thereby change the local electric potential. This change in electric potential is sensed by specialised proteins located within the cell membranes, and the cells respond by sending signals to other cells, for example to the cells of a muscle, causing the muscle to contract [8].

A signal is transported along a nerve cell in the form of an *action potential*, which is a pulse of increased electrical potential resulting from a wave of cation inflow and anion outflow through the cell membrane that spreads along the cell's axon. The axon ends by forming contact points, *synapses*, with other cells, and at these contact points, the signal can be transduced from an ion flux to chemical messengers, or neurotransmitters, that are released to the second cell.

Nerve cells fire action potentials spontaneously without any neurotransmitters being released at their synapses. It is the firing pattern, or the frequency of action potentials, that decides whether neurotransmitters should be released from the presynaptic terminal so that the signal is passed on to the next cell or not [62].

1.2.1 Electrical stimulation and electrical recording

In nature, sensory input or chemical messengers, generated from a presynaptic neuron, triggers action potentials. However, electrical stimulation provided by implanted electrodes may initiate signalling, and can, for instance, restore dysfunctional signalling pathways, or cancel out disease-related signalling. Such technologies are used to treat several neurological diseases today; electrodes are

implanted into the heart to regulate heart rate, into the brain to reduce tremor in Parkinson's disease, into the spinal cord to alleviate pain and into the inner ear to improve hearing.

For electrically triggered signalling, the resulting effect on a particular neuron depends on the position of the electrode, relative to the neuron itself, and on the amplitude and frequency of the electric stimulation current [24, 29, 70]. It may be possible to select between activating and inhibiting a group of neurons by considering the stimulation currents and electrode placement [10]. Also, by reducing the electrode dimensions, a smaller number of neurons, possibly even single cells, can be affected. Scaling down electrode areas means that the electrode must support higher charge storage per area, however [16], and for planar electrodes and capacitive charging, the capacity is limited by the double layer capacitance at the electrode/electrolyte interfaces. One route to improve the charge capacitance is to make electrodes porous, so that the effective area over the projected area increases. Another way is to coat the electrode surface with an electrochemical polymer that can conduct both electronic and ionic charges. The polymer gives a volumetric capacitance, thus the capacitance is increased simply by increasing the thickness of the electrochemical polymer [16, 72].

Implanted electrodes cannot only be used to transfer signals to the biological systems, they can also pick up and record signals. The ionic fluxes across the cell membrane that are associated with an action potential changes the extracellular potential in the vicinity of the nerve cell. Recording electrodes can thus be used to record such variations in ion concentrations, and thereby have potential to be used, for example, to predict epileptic seizures [36], and to aid paralyzed patients to attain cognitive control of external prostheses [23], by detecting specific activity patterns in the brain. To record action potentials from many cells individually, individual electrodes should be small, electrodes should be densely packed, and preferably placed directly onto the tissue. Contrary to stimulating electrodes, recording electrodes do not need a high capacity per area, since only small and short-lasting currents pass the electrode. However, to achieve high signal-to-noise ratio recordings, the electrode *impedance*, which is a measure of the electrical resistance and the lag between current and voltage, should be low. One way that can substantially lower the impedance of an ordinary metal electrode is to coat the electrode surface with a conducting polymer [78].

As described above, coating metal electrodes with conducting polymers can improve electrode performance for both recording and stimulating devices. Since the polymers are soft, they can also form better interface characteristics with soft biological tissue, especially if built on soft, stretchable, or conformable substrates [44, 46], and thereby possibly decrease reactions to artificial materials,

thus improving biocompatibility.

1.3 Local chemical delivery

Electrical stimulation by scaled-down electrodes can selectively stimulate cells in a small volumes. However, it cannot discriminate between different cell types in close proximity; all cells having voltage-sensitive proteins in their membranes will be affected. Also, it is difficult to select between activating and inhibiting a group of cells, since the outcome depends on the cells' orientation [10], and it is often a trial-and-error process to find the adequate electrode placement and stimulation protocols for a required outcome [24].

To only affect one cell type, a device that mimics the way cells communicate with each other at chemical synapses could be used. The device should release specific signalling molecules that bind to receptors expressed only by the target cells. To restrict the chemical stimulation to a smaller volume, the chemicals should be released locally, only to the specific volume of the targeted cells. To selectively affect individual cells, this means that the released chemicals should not spread in high concentrations beyond tens of micrometers.

There are several approaches to achieve local chemical delivery. These can be subdivided into passive and active delivery. Passive delivery implies that the release rate is predetermined, and active delivery means that delivery is controlled by an external signal [89]. For passive delivery, the predetermined release rate can depend on material compositions or geometries of the implants, and the compound can be released for example by slow diffusion from a semi-sealed compartment, or by swelling or degradation of an encapsulating material. Implants exhibiting passive delivery are used in, for example, birth control devices, where the release rate is controlled by diffusion through a membrane [22, 60]. Intrathecal pumps that deliver drugs directly to the spinal fluid is an example of active delivery, where the release rate depends on electric signals sent to the pump [47]. Other ways than electrical signals to control active delivery include light, for instance in optogenetics [68], magnetic fields [89], exemplified by local conversion of magnetic into thermal energy by magnetic nanoparticles [52], and pressure. Devices based on microfluidics specifically use pumps and valves to finely regulate the pressure that controls liquid delivery through micrometer-sized channels [54, 77].

1.4 Electronically controlled chemical delivery

Electronically controlled delivery has an advantage in that no external pumps, mechanical systems, lasers or magnets are needed to control delivery. Instead,

implanted batteries powering control circuits can supply the electronic signals necessary to control the release. Potentially, the batteries can even be replaced by energy-harvesting devices. These devices can, for example, exploit energy from natural movements within the body, such as the mechanical energy of the heart beat, using piezo-electric materials [20]. Approaches to electrically controlled delivery include multiple sealed compartments, where an electrical signal is used to open a compartment. One such study demonstrated successful delivery of drugs, locally, to the eye in an animal model, *ex vivo*. The applied electrical field created gases by dissociating water into hydrogen and oxygen gas, which increased the pressure in a drug-loaded compartment, then leading to active release of drugs [55].

1.4.1 Conductive polymers for controlled delivery

Conductive polymers can be used in devices for electronically controlled delivery in several different ways. For example, electrically controlled redox reactions of a conductive polymer can cause the polymer to swell or shrink, due to uptake or release of ions and water, respectively. This has been used to control the release rate of drugs loaded into conducting polymer nanotubes [1]. Here, electrically induced shrinking of the tubes caused release of drugs. An alternative method is to incorporate the drug as ions inside the conducting polymer; when the polymer is redox switched the ionic drugs are released and exchanged with ions from the electrolyte into which the polymer is immersed [91, 97].

Our approach to achieve electronically controlled delivery of biochemical compounds, using conductive polymers, aims at reaching a relatively higher spatial and temporal control of delivery as compared to other and previously explored methods. The goal is to via *electronic addressing and control deliver specific amounts of substances to micrometer-sized volumes within milliseconds*. The prime goal of this effort aims at precise and efficient communication with the nervous system. We base our research for this high-resolution delivery on a device called the organic electronic ion pump (OEIP).

1.4.2 Organic electronic ion pumps

OEIPs use electric fields across cation- or anion selective channels to electrophoretically transport cations, or anions, respectively, through the channels to a tissue, cells, or any system under study. The main advantages of OEIPs, in comparison to other local delivery techniques are that: (1) no liquid is released along with the delivery of ions or biomolecules. This is important since a liquid flow may disrupt the local chemical environment, and cause stress to the cells. Instead of delivering the ions or molecules by convection, they are released at the OEIP outlet, and spread to the surrounding only by diffusion. (2) the

amount of ions or biomolecules released is directly proportional to the time-integrated current that is passed through the circuit, which gives an excellent control of the amount of released substance. (3) The on-off-ratio can be very high, that is, passive leakage when no current is applied can be very low.

1.5 Coupling chemical delivery to sensors

An implanted device capable of local chemical release on demand, is preferably coupled to input signals that form the decision protocol to control when, where and how much of a specific chemical that should be released. This decision can be taken by the patient, if, for example, a pain alleviating compound is released by the implant. In other cases, an electrical or chemical sensor that is located at the site of chemical delivery can be used to probe the microenvironment and, via auto-decision-making electronics, determine whether delivery should be on or off, and at what release rate. For example, the activity of nearby neurons can be measured and used to control the delivery of a substance that induces or inhibits neuronal activity. Electrical stimulation and recording can be done from the same device [5, 17], however coupling chemical delivery to sensors requires more elaborate structures. For example, silicon probes with microfluidic chemical delivery outlets in close proximity to electrodes for recording and stimulations have been reported [12].

1.6 Contributions of this thesis

All work presented in this thesis involves biological/medical applications of OEIPs, or technical advancements of the OEIP technology. The main outcomes of this work are related to:

- development of the OEIP technology into an implantable device targeting the spinal cord, to demonstrate, for the first time, a therapeutic effect in an animal model (Paper A)
- development and evaluation of a new material for OEIPs possible to use on glass substrates, and development of a method for comparing new materials with previously used materials (Paper B)
- demonstration of the ability of OEIPs to control epileptiform activity in an animal model *in vitro* (Paper C)
- integration of the OEIP delivery technology with recording electrodes, resulting in an array of co-localized chemical delivery - recording electrode pixels, and demonstration of combined recording/delivery *in vitro* (Paper D)
- improvement in the speed of OEIP delivery to tens of milliseconds (Paper E)

- engineering of OEIPs exhibiting several individually addressable chemical release sites (Paper E)

1.7 Thesis outline

The thesis consists of two parts, where the intention of Part I is to provide the reader with the background necessary to read the publications that are presented in Part II. Part I is divided into different chapters, where Chapter 2 deals with conducting polymers, which is the foundation to the research field of organic electronics, and thus to the material in the thesis. Chapter 3 discusses ion transport processes and ion exchange membranes, which are the basis for the OEIP devices. Since OEIPs need electrodes for translation between electronic and ionic current, since the OEIP was integrated with a sensing electrode in paper D, and since the device in paper E includes a delivery electrode, Chapter 4 discusses electrodes. Chapter 5 briefly discusses nerve cells and nerve cell signalling, which is one target system for the OEIP technology. In Chapter 6, the devices developed in the thesis are presented. Chapter 7 describes fabrication and characterization of the devices presented in Chapter 6, and Chapter 8 gives a brief conclusion and future perspective.

1.7.1 Overview of the publications

Paper A: Therapy using implanted organic bioelectronics

Summary: In this project, we developed a fully implantable OEIP. The OEIP was specifically designed to be implanted onto the spinal cord of rodents, with delivery points where the sciatic nerve couples the spinal cord. The novelty of the design included a sealed reservoir containing the neuro-inhibitory substance and an approx. 4 centimeter-long ion conducting channel leading up to four delivery points. Devices were implanted in animals with a sciatic nerve injury, resulting in a condition similar to neuropathic pain, and by delivering the inhibitory neurotransmitter γ -aminobutyric acid (GABA), we could observe a decrease in pain-related behaviour. The project was a collaboration with Bengt Linderöth's group at Karolinska Institutet, where the *in vivo* study was performed. It was a proof-of-concept that OEIP technology may be useful in reducing the dosage by delivering drugs locally in future therapies.

Contributions: I contributed to the design, developed fabrication techniques, performed nonbiological device characterization, analyzed results, and contributed to writing the manuscript.

Paper B: In situ evaluation of materials for iontronic applications

Summary: A new material for cation transporting devices that can be processed from solution, and therefore be used on glass and other substrates, was developed and characterized. Specifically, the material's ability to preferentially

transport positive, rather than negative ions, was estimated by different methods.

Contributions: I assisted in the development of fabrication processes using PSSA-co-MA, and adapted the emf method for our devices.

Paper C: Controlling Epileptiform Activity with Organic Electronic Ion Pumps

Paper D: Bioelectronic neural pixel: Chemical stimulation and electrical sensing at the same site

Summary: The project leading to paper C and D was a collaboration project between our group and the group led by George Malliaras at the Department of Bioelectronics, Ecole Nationale Supérieure des Mines, Gardanne, France. The aim was to merge our OEIP technology with their recording electrodes. The group led by Christophe Bernard at Aix Marseille University, Inserm, INS, Institut de Neurosciences des Systèmes, Marseille, France, was responsible for the *in vitro* tests of the device. We developed fabrication methods for the devices combining OEIPs with co-localized recording electrodes. The devices were used first to deliver K^+ , to induce hyperexcitability in a brain slice. Then, epileptiform activity was induced using three different models (high K^+ , low Mg^{2+} , and added AP4), and the neuroinhibitor GABA was delivered to stop the epileptic events (paper C). The integrated recording electrodes were used to record the suppression of epileptic events at the GABA delivery sites (paper D).

Contributions: I contributed to the design, developed new materials and fabrication methods, analyzed results, and contributed to writing the manuscripts.

Paper E: Chemical delivery array with millisecond neurotransmitter release

Summary: In this publication OEIP-based devices with several addressable outlets are demonstrated, allowing independent on-off switching of the delivery sites. The devices use potential gradients in directions perpendicular to the substrate plane as well as in the substrate plane, instead of only in the substrate plane, which has been the case for previous devices. Along with addressability, we also demonstrated release within tens of millisecond, possible thanks to the out-of-the-plane-delivery. Delivery was also done through bipolar membrane diodes, which helped prevent passive leakage when delivery was off. The project was a close collaboration with Theresia Arbring Sjöström.

Contributions: I conceived of the project idea, designed devices, developed fabrication and characterization methods, analyzed results, modelled the device and contributed to writing the manuscript.

Conductive polymers and electronic conduction

Plastics, or *polymers*, are generally electrically insulating materials. Indeed, polymers are used to coat electrical wires to insulate the surrounding from electrical conductivity. However, in the 1970's, Alan Heeger, Alan G. MacDiarmid and Hideki Shirakawa discovered that by *doping* the polymer polyacetylene with halogens, its electrical conductivity was significantly increased [79]. The demonstration awarded them the Nobel prize in chemistry in 2000 "for the discovery and development of electrically conductive polymers". In part, this triggered the research field of organic electronics, in which *organic*, or carbon-based, molecules that are electronically conducting are used in electronic components.

Using organic materials in electronic devices has several potential advantages, compared to devices made from conventional inorganic electronic materials. One advantage relates to the low cost of the materials, and another advantage is that many organic materials can be processed from solutions, in the form of dispersions, or as dissolved materials in, for instance, water or ethanol. The solutions can be used to form thin films that can later be patterned using photolithography, or as inks, allowing additive patterning using various printing techniques. Two additional advantages of organic materials include that they can be soft, and therefore used on flexible [33], or even stretchable substrates [64], and that they can be transparent. The transparency/colour state of the polymer can often be controlled by varying the oxidation state of the polymer; this process is termed electrochromism.

Organic conductors are used in an increasing number of applications [26]. For example, they are included as the light harvesting and energy converting material in organic solar cells [103]. They are also used in organic light emitting diodes (OLEDs), and in organic field effect transistors (OFETs). The electrochromic properties of some organic conductors make the materials useful in smart windows, where an applied potential changes the transparency of the window

2.1 Electrical conductivity

Electrical conductivity is defined by Ohm's law:

$$V = IR \quad (2.1)$$

where V is the voltage, or the electric potential difference (given in Volts, V), applied over a resistor R (in Ohm, Ω) resulting in the electric current I (in Ampere, A). This law applies to so called Ohmic materials, for which the resistance also scales with the length l and the cross sectional area a , over which the potential is applied, such that:

$$R = \frac{\rho l}{a} \quad (2.2)$$

where ρ is a material property called the resistivity (in $\Omega \cdot \text{m}$). The reciprocal of ρ gives the material property conductivity, σ , (in Siemens $\cdot \text{m}^{-1}$, $\text{S} \cdot \text{m}^{-1}$):

$$\sigma = \frac{1}{\rho} \quad (2.3)$$

The conductivity depends on the density of charge carriers, n , their mobility, μ , and the charge of the charge carries, q :

$$\sigma = n\mu q \quad (2.4)$$

When we think of electrical conductors, we generally think of metals and semiconductors, but any material that contains mobile charged species will conduct current. For example, your body is an electrolytic conductor, since it contains a variety of charged dissolved compounds, ranging from small

monatomic ions to large proteins. The conductivity of a system depends directly on the mobility of the charged species in the system (equation 2.4), and the mobility of the charge carriers depends strongly on their size. Small species, like electrons, typically reach high mobilities, whereas larger species, like ions, in particular polyatomic ions, possess lower mobilities.

To distinguish the conductivity of metals, semiconductors, and other materials where electrons or holes are the charge carriers, from the generally lower conductivities of materials where ions carry the charge, the term *electrical* conductivity, as opposed to *ionic* conductivity can favourably be used.

Electrical conductivity in metals and semiconductors

Metals exhibit high electrical conductivity because of their high density of freely moving electrons. In a metal, the atomic nuclei are generally arranged in a crystalline structure, and some of the outer shell electrons move freely within the material. Semiconductors do not possess a high density of freely moving electrons, and therefore exhibit rather low conductivities. However, they can be "doped" by the addition of small amounts of atoms with a different number of electrons, compared to the semiconductor. Incorporation of these other atoms into the crystal lattice introduces charge carriers, and thus increases the conductivity. Metal conductivities are normally found in the order of 10^2 to $10^6 \text{ S} \cdot \text{cm}^{-1}$, whereas semiconductor conductivities range from about 10^{-8} to $10^2 \text{ S} \cdot \text{cm}^{-1}$ [27]. Neither metals nor semiconductors include ions, and therefore show only electronic, not ionic, conductivity.

2.2 Intrinsically conducting polymers

The word polymer stems from the Greek language, and is composed by *poly*, meaning many, and *mer*, meaning parts. Indeed, a polymer is a large molecule, composed of many smaller parts. Some polymers occur naturally, like silk, proteins and DNA, and some polymers are chemically synthesized, like polyethylene terephthalate (PET) and nylon. A polymer can be linear, meaning that it consists of one long chain, or it can be branched. Several polymer molecules can be linked to each other by chemical or physical bonds, something that is commonly referred to as cross-linking.

In general, polymers do not conduct electricity. However, there is a class of polymers, referred to as conductive polymers, or *intrinsically conducting polymers*, that conduct electricity. The word *intrinsically* is here prefixed to distinguish these polymers, whose backbone is *conjugated*, that is, it consists of alternating single and double bonds between the carbon atoms, from insulating polymers that have been mixed with conducting material to obtain a conductive blend.

To obtain an intrinsically highly conductive polymer, charge carriers, *i.e.* electrons or holes, must be introduced. These charge carriers can be introduced by a process called doping. Instead of replacing atoms in the crystal lattice with atoms of a different valence characteristics, like in semiconductor doping, doping of conductive polymers means that electrons are transferred to (n-doping) or from (p-doping) the polymer chain. The electrons can be transferred to, or from, an electrode (electrochemical doping), or to, or from, a chemical compound (chemical doping). For both electrochemical and chemical doping, the charges that are introduced along the polymer must be stabilized by counter-ions, so that the system remains neutral. When electrochemical doping is used, the stabilizing ions come from the electrolyte, whereas in chemical doping, the chemical compound that accepts or donates an electron becomes the stabilizing ion [61]. Through doping, conductive polymers can reach conductivities above $10^3 \text{ S} \cdot \text{cm}^{-1}$ [103]. Since electrons are transferred to or from the polymer when it is doped, a redox reaction takes place; electron transfer *from* the polymer is equivalent to oxidizing the polymer, and electron transfer *to* the polymer means that the polymer is reduced.

2.3 Electronic structure

To understand why some materials are good conductors while others are electrical insulators one can preferably study their *electronic band structures*, which describes the energy states that electrons within the material can occupy. Basically, for a conductor there must exist electrons within the material, of high enough energy, to enable the migration of charges.

2.3.1 Atomic orbitals

An atom consists of a positively charged nucleus surrounded by negatively charged electrons. The state of the electrons cannot be distinctly determined, instead their positions are related to a quantum mechanical wave function, $\psi(\mathbf{r}, t)$, where $|\psi(\mathbf{r}, t)|^2$ represents the probability of finding the electron at location $\mathbf{r}$, relative to the nucleus, at time t . Only wave functions that are solutions to the Schrödinger equation are allowed, and these solutions are termed *atomic orbitals*. Each atomic orbital is characterized by a unique set of the three quantum numbers n , l , and m_l . n is called the principal quantum number and describes the energy level of the electron, and can take the values $n = 1, 2, 3, \dots$, whereas l and m_l describe the electron's angular momentum around the nucleus. The value of n determines the maximum value of l : $l = 0, 1, 2, \dots, n - 1$, and l determines the possible values of m_l : $m_l = 0, \pm 1, \pm 2, \dots, \pm l$. There can be

a maximum of two electrons in each orbital, and these need to be of opposite *spin*, one spin up and the other spin down.

All orbitals with the same n -value form what is called a *shell*, where $n = 1$ is called the K-shell, $n = 2$ the L-shell, $n = 3$ the M-shell, and so on. The K-shell is closest to the nucleus and it has therefore the lowest energy. Orbitals with $l = 0$ are referred to as s-orbitals, those with $l = 1$ as p-orbitals, and those with $l = 2$ as d-orbitals. S-orbitals are spherical in shape, while p-orbitals consist of two lobes separated by a nodal plane that passes through the nucleus.

As stated above, the energy of an electron is determined by the principal quantum number n . For a 1-electron atom of atomic number Z the allowed energy levels, E_n are proportional to $-\frac{Z^2}{n^2}$ [3]. Since n is an integer, this leads to a discrete set of allowed energy levels.

Electrons occupy the orbitals of lowest energy first. Thus, the electronic configuration of a H atom is $1s^1$, that of He is $1s^2$, and that of Li $1s^2 2s^1$, where the numbers denote the value of the principal quantum number of the orbitals, the letter indicate orbital type (s-, p-, d-, etc.), and the superscript denote the number of electrons that reside in the respective orbital. A carbon atom has six electrons, and its electronic structure is $1s^2 2s^2 2p^2$.

For $n = 2$, four orbitals exist: one is an s-orbital with $l = 0$ and $m_l = 0$, and three are p-orbitals with $l = 1$ and $m_l = -1, 0, +1$, respectively. The three p-orbitals are differently oriented in space and are therefore denoted p_x , p_y and p_z . To minimize energy, the electrons occupy different p-orbitals if possible, and a more specific description of the electronic structure of the carbon atom is therefore $1s^2 2s^2 2p_x^1 2p_y^1$.

Figure 2.1: Illustration of the bonding orbitals of a carbon atom. Reused with permission of Erik Gabrielsson.

2.3.2 Molecular orbitals and chemical bonds

The electrons in the outermost shell of an atom, the *valence electrons*, can form a bond to a neighbouring atom by interacting with the valence electrons of that atom. When atoms approach each other, the atomic orbitals of the valence electrons start to overlap and may combine to form *molecular orbitals*, which are linear combinations of the atomic orbitals. One linear combination of the atomic orbitals is constructive and leads to a higher probability of finding the electrons between the atomic nuclei, and the other linear combination is destructive, and thus leads to a lower probability of finding the electron between the nuclei. The linear combination with constructive interference of the atomic orbitals has a lower energy than the initial atomic orbitals, and is a *binding orbital*, whereas the combination with destructive interference has a higher energy than the original atomic orbitals, and is an *antibonding* molecular orbital, denoted with a *. There is thus a splitting of the energy levels when atomic orbitals combine to form molecular orbitals, and the electrons fill the molecular orbitals of lowest energy first. If the total energy of the molecule is lower than that of the separate atoms, a more or less stable bond is formed. The highest energy level containing electrons is called the *highest occupied molecular orbital (HOMO)*, and the lowest energy level without electrons is called the *lowest unoccupied molecular orbital (LUMO)*, and the energy gap between the HOMO and the LUMO is commonly called *the band gap*.

Just like atomic orbitals, molecular orbitals come in different shape, where σ -orbitals are rotationally symmetric along the bond axis, whereas π -orbitals are not. π -orbitals also have a nodal plane passing through the nuclei. σ bonds are stronger than π bonds due to the high probability of finding the electrons between the nuclei.

2.3.3 Metals, semiconductors and insulators

In metals the orbital energy levels overlap, reducing the band gap to zero. This implies that hardly any energy is needed to excite the electrons of highest energy to levels where they are not bonded, but mobile (*i.e.* from the valence band to the conduction band). Typically, at room temperature, enough electrons are excited to yield a high conductivity. When the temperature increases, more electrons are excited, and one would expect an even higher conductivity. Instead, for metals, an increase in temperature reduces the conductivity. This is explained by that thermally excited vibrations of the atoms cause collisions between the nuclei and the electrons, which slows down the electrons and thus reduces the conductivity. Semiconductors and insulators do have a band gap, and the distinction between the two depends on the value of the band gap and is not absolute. When the temperature is increased, electrons get excited across

Figure 2.2: Energy levels of the molecular orbitals 1σ and $1\sigma^*$ formed from the linear combination of two $1s$ atomic orbitals. The linear combination with constructive interference, *i.e.* an increased electron density between the nuclei has a lower energy than the initial atomic orbitals, and is a bonding orbital, 1σ . The linear combination resulting in a decrease in electron density is an antibonding orbital, $1\sigma^*$, with a higher energy than the individual atomic orbitals. The electrons occupy the bonding, lower-energy orbital, as indicated by the arrows. Image courtesy of Erik Gabrielsson.

the band gap, which means that they will transfer from the valance band to the conduction band, leading to an increase in conductivity with temperature. The smaller the band gap is, the more likely it is that electrons get excited, and the higher the conductivity becomes. As mentioned in the beginning of the chapter, semiconductors can be doped by the addition of atoms with a different number of electrons. These dopant atoms introduce new energy states, that is, new allowed energy levels appear within the band gap, which is why the conductivity increases.

2.3.4 Hybridization and the carbon atom

The ground state of the carbon atom $1s^2 2s^2 2p_x^1 2p_y^1$ only has two unpaired electrons; the ones in the p -orbitals, and should therefore only be able to form two bonds with other atoms. From chemistry we know, however, that a carbon atom can bond to both three and four other atoms (for example in ethene C_2H_4 and ethane C_2H_6 , respectively). To explain this, valence bond theory dictactes that electrons can be *promoted* to higher energy levels [3]. If one $2s$ electron is promoted to a $2p$ orbital, the electronic configuration of carbon becomes $1s^2 2s^1 2p_x^1 2p_y^1 2p_z^1$ with four unpaired electrons in separate orbitals,

which explains how carbon can form four bonds. This excited electronic structure suggests that three of the bonds, formed by the p-orbital electrons, are different from the fourth bond, formed by the s-orbital electron, something that we know is not true from for example methane CH_4 , where one carbon atom binds four hydrogen atoms with equivalent bond configurations. To account for this, the concept of *hybridization*, or *hybrid orbitals* is introduced. Hybrid orbitals are formed by the interference between the $2s$ and $2p$ orbitals, and a specific linear combination of the three p-orbitals and the s-orbital results in four equivalent hybrid orbitals, called sp^3 -orbitals, since they are built from one s- and three p-orbitals. Thus, an sp^3 hybridized carbon atom forms four equivalent bonds, resulting in for example a tetrahedral CH_4 molecule. If instead the s-orbital and only two of the p-orbitals are used to form hybrid orbitals, three equivalent sp^2 hybrid orbitals are formed. The sp^2 -orbitals lie in a plane with 120° angles between the orbital lobes, and the p-orbital not included in the hybridization has its axis perpendicular to this plane. In ethene, the two carbon atoms contribute one electron each from a hybridized sp^2 orbital, and one electron each from the non-hybridized p-orbital to bond the carbon atoms together. Thus, there are four electrons involved in the C-C bond, resulting in a double bond that consists of a σ -bond and a π -bond.

2.3.5 Electronic structure of conjugated polymers

A conjugated molecule has a chain of alternating double and single bonds between carbon atoms. A simple example of a conjugated polymer is polyacetylene, $(\text{C}_2\text{H}_2)_n$, where each carbon atom is sp^2 hybridized, and binds to three other atoms (Figure 2.4a). The non-hybridized p-orbitals of the carbon atoms are perpendicular to the plane of the carbon chain and interact to form π -bonds. The π -bonded electrons are not localized to any specific bond but can move along the carbon chain. As the number of carbon atoms in a polyacetylene molecule is doubled, the energy levels of the π and π^* orbitals are split, resulting in one π and one π^* level for C_2H_4 , two π and two π^* levels for C_4H_6 , and $\frac{n}{2}$ π and $\frac{n}{2}$ π^* levels for a polyacetylene chain of n carbon atoms (Figure 2.3). In polyacetylene, all bonding π -orbitals are filled with electrons, whereas all antibonding π^* orbitals are empty, thus the highest energy level of the π levels coincides with the HOMO, and the lowest energy level of the π^* levels coincides with the LUMO. As the length of the carbon chain increases, the HOMO and LUMO approach each other, thus reducing the band gap. There is one π electron for each carbon atom in the chain. If these were distributed homogeneously along the chain, that would create equally long distances between the carbon atoms. For infinitely long chains, the band gap would disappear, and a metallic-type of conductivity should be achieved. According to Peierls' theorem, however, a chain with alternating single and double bonds is more

stable than a chain with equally spaced atoms [27]. Therefore, the band gap remains, and dictates that polyacetylene stay a semiconductor.

Conducting polymers typically have band gaps of 1 - 4 eV [38]. For very long chains, the difference between the π levels, and the difference between the π^* levels become so small, that the levels can be treated as continuous π bands and π^* bands, respectively. The filled π band and the empty π^* band are called the *valence band* and the *conduction band*, respectively.

Figure 2.3: As polyacetylene grows in length, molecular orbitals are formed from atomic orbitals, which leads to a splitting of the energy levels. This reduces the band gap E_g . Image courtesy of Klas Tybrandt.

2.4 Charge transport and doping

2.4.1 Solitons

Conjugated polymers, in which two different bond length alternations result in identical molecules are said to have a degenerate ground state. Transpolyacetylene is an example of a conjugated polymer with a degenerate ground state, where the two different structures, or the two phases, have identical energy (Figure 2.4). If the two ends of the polyacetylene have different phases, for example, there will be a boundary between the two phases, somewhere along the chain, and this boundary is referred to as a soliton. A soliton introduces an energy level in the middle of the band gap [9] and contributes to the electrical conductivity of degenerate conjugated polymers.

Figure 2.4: Polyacetylene can exist in two equivalent configurations; A and B. If one end of the polymer is in the A configuration, and the other end is in the B configuration, there will be a transition zone between the configurations somewhere along the chain. The altered electronic structure in the transition zone introduces energy levels in the band gap. Image courtesy of Erik Gabrielsson.

2.4.2 Polarons and bipolarons

Unlike polyacetylene, most conjugated polymers do not have a degenerate ground state, and do not include solitons. However, the mobile π -electrons typically imply that several conformations are possible. Polythiophenes, for instance, come in an aromatic and a quinoid form, where the aromatic form has a relatively lower energy than the quinoid form. When a positive charge is introduced into a polythiophene chain, this creates a local conformational change from the lower-energy aromatic structure to the higher-energy quinoid form. This introduced charge and the related structural deformation is termed a polaron (Figure 2.5 c). Two polarons can form a bipolaron, a structure that can be energetically more favourable than two separate polarons [9]. Like solitons, polarons and bipolarons introduce energy levels within the band gap, and thereby increase the conductivity of the polymer.

2.4.3 Charge transport

Solitons and polarons can move along a polymer chain, and thus transport charge within the polymer chain. However, to reach macroscopic electronic conduction over longer distances in polymer solids, charges must also be able to move between polymer chains. This intermolecular charge transport in organic materials can be explained by thermally activated "hopping" of the charges between localized states. Polymers are generally disordered, which

Figure 2.5: A polythiophene can exist in an aromatic (a) and in a quinoid (b) form. When a positive charge is introduced into a polythiophene, this results in a local conformational change from the lower-energy aromatic structure to a quinoid form, called a polaron (c). Introduction of a second charge can result in a bipolaron (d). Image reused with permission of Erik Gabrielsson.

makes hopping between molecules difficult. The hopping can be facilitated if the polymer has ordered, crystalline domains, where π -orbitals from adjacent molecules overlap [82].

2.5 PEDOT:PSS

Due to its chemical stability and its high electronic conductivity, poly(3,4-ethylenedioxythiophene), PEDOT, is one of the most studied and explored conductive polymers. Like most conductive polymers, PEDOT is not soluble in water. However, if PEDOT is polymerised from its 3,4-ethylenedioxythiophene monomer with a water soluble polyanion present, for example poly (styrenesulfonate) (PSS), a dispersion of PEDOT with the polyanion as a counter-ion (or dopant ion) is formed. This aqueous dispersion can be used in various coating

and printing methods to form thin films of the polyelectrolyte complex, where the positive charges of the PEDOT thiophene groups are compensated by the negative sulfonic acid groups of PSS (Figure 2.6). The ratios of PEDOT to PSS in commercially available dispersions are such that the negative charge of the PSS is about 6 to 46 times the maximum charge of PEDOT [27]. Thus, only a small fraction of the negative charges of PSS is compensated by positive charges from the PEDOT. This implies that the polyelectrolyte complex must contain additional cations to make it neutral. The excess of PSS and the mechanism by which PEDOT polymerizes along the PSS chains creates a composition which can be described as PEDOT:PSS islands in a PSS sea (Figure 2.6).

Applying a positive potential to PEDOT increases its charge (dopes it), and introduces quinoid domains in the aromatic structure (Figure 2.5), thus increases its conductivity, while applying a negative potential reduces its charge (dedopes it), which leads to a decreased conductivity. The doping level of PEDOT can therefore be used to modulate its conductivity, which is a property that is exploited in electrochemical transistors [63], for example used for electrical [45] and chemical sensing [43]. The doping introduces positive charges into the polymer, and as a consequence, cations are repelled from the film. Dedoping the PEDOT in PEDOT:PSS is instead associated with cation migration into the film.

PEDOT:PSS is not highly conductive per se, but by adding conductivity enhancement agents, also referred to as secondary dopants, the conductivity can be increased by several orders of magnitude. For example, ethylene glycol and dimethyl sulfoxide have been reported to increase the conductivity of PEDOT:PSS by two orders of magnitude [27, 65]. The increased conductivity is accompanied by conformational changes of the PEDOT, which increases interaction between the PEDOT chains. Secondary dopants have been shown to reduce ionic conductivity [73], however. This can be explained by the fact that an increased connectivity between PEDOT regions may cause less connectivity between the PSS regions, which is where ion conduction takes place.

PEDOT:PSS as an electrode material is further discussed in section 4.5.

Figure 2.6: The morphological structure of PEDOT:PSS can be described as PEDOT:PSS islands in a PSS sea (top). Chemical structure of PEDOT and PSS (bottom) showing a positive charge in PEDOT compensated by a negative charge from PSS. Sodium ions are present in the film to compensate for the excess charge of PSS. Positive charges are marked with red dots and negative charges are marked with blue dots

Ion exchange membranes and ionic conduction

While the previous chapter dealt with electronic conduction, particularly in conductive polymers, this chapter discusses ionic conduction in electrolytes and in charged membranes, ion exchange membranes. A major difference between ionic conductivities and electronic conductivities, is that there is always a transport of mass related to the ionic conduction, whereas the mass of an electron is very small (for example, the mass of Na^+ is 40 000 times the mass of an electron). This makes ionic conductivities significantly lower than electronic conductivities.

3.1 Electrical conductivity in an electrolyte

An electrolyte is electrically conducting because it contains mobile ions. Dissolving a salt in a solvent, so that the salt dissociates into positive and negative ions, results an electrolyte. Depending on the degree of dissociation, electrolytes are classified as strong or weak, where the ions are more or less completely dissociated in a strong electrolyte.

As an example, an electrolyte is formed when MgCl_2 is added to water: MgCl_2 dissociates to magnesium and chloride ions, Mg^{2+} and Cl^- . Since every MgCl_2 unit gives rise to one magnesium ion and two chloride ions, the stoichiometric coefficients, v_i , of the ions are $v_{\text{Mg}^{2+}} = 1$ and $v_{\text{Cl}^-} = 2$, respectively. There are thus twice as many chloride ions as magnesium ions, but the magnitude of the

charge number of a chloride ion, is only half that of a magnesium ion; $z_{Mg^{2+}} = 2$ and $z_{Cl^-} = -1$.

Electrical conductivity was defined in section 2.1 by Ohm's law, eq. 2.1, and applies to electronic as well as ionic conduction, although ionic conductivities are several orders of magnitude lower than the conductivities of metals. For example, the proton conductive polymer Nafion, widely used in fuel cells, exhibits conductivities in the $10\text{-}200 \text{ mS} \cdot \text{cm}^{-1}$ range [14, 58]. Because ions have different mass, shape and charge, they contribute differently to the electrolyte conductivity. The total electrolytic conductivity, κ , can be written:

$$\kappa = \sum_i z_i \mu_i v_i c F \quad (3.1)$$

where z_i , μ_i and v_i are the charge number, the mobility, and the stoichiometric coefficient of ion i , respectively. c is the electrolyte concentration, and F is the Faraday constant $96\,485 \text{ C mol}^{-1}$. The mobility of an ion is directly proportional to its diffusion coefficient, D , and the two are related by:

$$\mu = \frac{D}{k_B T} \quad (3.2)$$

where k_B is the Boltzman constant $1.38 \cdot 10^{-23} \text{ m}^2 \text{ kg s}^{-2} \text{ K}^{-1}$, and T is the temperature in Kelvin (K). Diffusion coefficients for a few ions are given in table 3.1 [56]. However, diffusion coefficients depend on concentration [93], and the given numbers are valid at low concentrations.

Table 3.1: Diffusion coefficients

Ion	Diffusion coefficient at infinite dilution [$\text{cm}^2 \cdot \text{s}^{-1}$]
Na^+	$1.4 \cdot 10^{-5}$
K^+	$2.0 \cdot 10^{-5}$
H^+	$9.3 \cdot 10^{-5}$
Cl^-	$2.0 \cdot 10^{-5}$
OH^-	$5.3 \cdot 10^{-5}$

3.1.1 Transport numbers

As described above, different ions contribute differently to the conductivity of an electrolyte due to their different mobilities. The fraction of the ionic current

due to the transport of ion i , is called the transport number, t_i , of that ion. As an example, when current flows through an electrochemical cell of NaCl (aq) electrolyte, the transport number of Na^+ and the transport number of Cl^- can be estimated from their diffusion coefficients, and sum to 1:

$$t_{\text{Na}^+} = \frac{D_{\text{Na}^+}}{D_{\text{Na}^+} + D_{\text{Cl}^-}} = 0.4 \quad \text{and} \quad t_{\text{Cl}^-} = \frac{D_{\text{Cl}^-}}{D_{\text{Na}^+} + D_{\text{Cl}^-}} = 0.6 \quad (3.3)$$

However, the transport numbers depend on concentration and temperature.

3.2 Diffusion, migration, convection

The previous section discussed how electric potential differences in an electrolyte causes ions to move, with ionic currents as a result. This process is termed migration, and implies that cations and anions move in opposite directions. However, ions in electrolytes move not only by migration, but also by convection and diffusion. Convection means that parts of the fluid move, and that ions move along with the solvent. Convection can arise due to stirring of the liquid or because of density gradients, *e.g.* caused by temperature variations. Diffusion results from the random motion of particles, and leads to an evening out of concentrations; thus diffusion spreads the ions down their concentration gradient.

Figure 3.1: Ions in an electrolyte can move by (a) diffusion, that is, down their concentration gradient, by (b) convection - following the movement of the solvent, or by (c) migration, when an electric field is applied. Image courtesy of Erik Gabrielsson.

The electric potential, ϕ , at a certain position in space is defined by the electrostatic energy that a positive unit point charge would have, if situated at that position, and can be found by summing up the contributions of all surrounding charges. The electric field, $\vec{E}$, is a vector field that in each position points in the direction of most decreasing potential, with a magnitude that reflects the change in potential:

$$\vec{E} = -\nabla\phi \quad (3.4)$$

Given that there is no convection in a fluid, the ionic flux density $\vec{J}$, given in $\text{mol} \cdot \text{s}^{-1} \cdot \text{m}^{-2}$, for an ion can be described by the Nernst-Planck equation [48]:

$$\vec{J} = \underbrace{-D\vec{\nabla}c}_{\text{ionic diffusion}} + \underbrace{zDcf\vec{E}}_{\text{ionic migration}} \quad (3.5)$$

where D is the diffusion coefficient of the ion and c its concentration. $f \equiv \frac{F}{RT}$, where F is the Faraday constant with the value $96\,485 \text{ C} \cdot \text{mol}^{-1}$, R is the ideal gas constant with the value $8.3144 \text{ J} \cdot \text{mol}^{-1} \text{K}^{-1}$, T is the temperature in K, and z is the charge number of the ion.

The Nernst-Planck equation assumes that there are no short-range interactions between ions, and therefore works well in dilute solutions, but not as well in concentrated solutions when ions come close.

As seen in eq. 3.5, the flux of an ionic species is determined by its diffusion coefficient, concentration gradient, charge, concentration, and the electrical potential gradient. The movement of a specific ionic species is affected by the movement of other ions through their effect on the electrical potential. This is described in section 3.2.1.

The change in concentration at a specific location can found by considering the flux *from* the location and the flux *to* the location, and is given by the negative gradient of the flux:

$$\frac{\partial c}{\partial t} = -\nabla J \quad (3.6)$$

The Poisson equation relates the Laplacian of the electrical potential (or equivalently, the divergence of the electric field) to the local charge density ρ by:

$$-\nabla^2\phi = \nabla \cdot \vec{E} = \frac{\rho}{\epsilon_0} \quad (3.7)$$

Thus, electric fields diverge from positive charges and converge at negative charges, and where the local net charge is zero, the electric field is constant and the gradient of the electric potential is constant. In the bulk of a material, the local net charge is typically close to zero, whereas charge can build up at interfaces between materials.

3.2.1 Potential differences at electrolyte boundaries

At a boundary between two electrolytes, a *liquid junction*, there will be diffusional forces that act to even out the concentrations. As an example, a neutral membrane may separate two different electrolytes, or two electrolytes consisting of the same ions but of different concentrations. If there are ions with different mobilities in the system, the ions with higher mobility will initially move more rapidly than the ions with lower mobility. This will create a charge imbalance, and thus a potential difference, referred to as a diffusion potential, or a liquid junction potential, that slows down the high-mobility ions and speeds up the low-mobility ions, so that the net movement is charge neutral [4].

A few different situations can occur. For example, a high and low concentration of HCl gives rise to an excess positive charge at the low concentration side since protons move more easily across the membrane than chloride ions (Figure 3.2). Similarly, if a HCl and a NaCl electrolyte of the same concentration are in contact, the NaCl side will get a net positive charge, and be at a higher potential. The diffusion potential E_j for a 1:1 electrolyte of different concentrations c_1 and c_2 can be estimated from [4]:

$$E_j = (t_+ - t_-) \frac{RT}{F} \ln \frac{c_1}{c_2} \quad (3.8)$$

and is thus strongly dependent on the difference in transport number of the two ions. Since K^+ and Cl^- ions have similar mobilities, the diffusion potential at a liquid junction between two KCl electrolytes of different concentrations is small. For example, the diffusion potential between two KCl electrolytes, where one electrolyte is ten times more concentrated than the other one, is only 1.2 mV [4].

3.3 Ion-exchange membranes

Membranes are barriers that separate electrolytes, and let some of the electrolyte species pass the membrane, whereas other species are retained. For example, a membrane with a defined pore size may let small, but not large, species pass through the membrane. The cell membrane is another membrane that separates the interior of a cell to the outside world. The cell membrane is more permeable to non-polar, than to polar or charged compounds, due to its hydrophobic core.

An ion-exchange membrane (IEM) is yet another membrane that contains either positive, negative, or both positive and negative fixed charges. An IEM can be made by cross-linking a charged polymer, a *polyelectrolyte*. A positively charged membrane repels positive ions but attracts negative ions, and is called

Figure 3.2: The different mobilities of protons and chloride ions create a potential difference, called a diffusion potential, at a junction between two HCl electrolytes of different concentrations.

an anion-exchange membrane (AEM), whereas a negatively charged membrane is referred to as a cation-exchange membrane (CEM). Ions with the same charge as the fixed charges of the membrane are called co-ions, and ions with opposite charge are called counter-ions.

Ion exchange membranes (IEM) are commonly used in electrodialysis to desalinate water. In this process, a salt solution is supplied to an electrodialyzer, across which an electrical potential is applied. This allows the electrolyte to be separated into one desalted and one concentrated solution. The electrodialyzer consists of (up to 2000) stacks of CEM and AEM arranged between two electrodes. As a potential difference is applied between the electrodes, cations and anions move in opposite directions and pass CEMs and AEMs, respectively, but are trapped when they encounter an AEM or a CEM, respectively. Thus, ions get concentrated between some membranes and diluted between other membranes [92].

3.3.1 Ion-exchange equilibrium and Donnan potential

An IEM repels co-ions but attracts counter-ions. Thus, when an IEM is in contact with an electrolyte, an equilibrium with an uneven ion distribution in the membrane will form, where the net charge concentration is zero:

$$z_{\text{fixed}}c_{\text{fixed}} + z_{\text{co}}c_{\text{co}} + z_{\text{counter}}c_{\text{counter}} = 0 \quad (3.9)$$

where z is the charge number and c the concentration of the respective ions. The distribution of co- and counter-ions in an IEM with a high concentration

of fixed charges, relative to the electrolyte concentration, sandwiched between two electrolytes is visualized in Figure 3.3. At the interface between a CEM and an electrolyte, diffusion will tend to move counter-ions (cations) away from the membrane to the electrolyte, and co-ions (anions) from the electrolyte into the membrane. This creates a net positive charge immediately outside the membrane, and a net negative charge immediately inside the membrane. The charge separation implies that an electric field is established at the interface, acting opposite to diffusion; it keeps counter-ions in the membrane and co-ions in the electrolyte. The potential of the membrane relative to the electrolyte is called the Donnan potential, φ_D (Figure 3.3), and its magnitude increases with an increased concentration of fixed charges of the membrane, relative to the electrolyte concentration. The Donnan potential is negative for CEMs, and positive for AEMs, and is related to the concentration of fixed charges in the membrane and the electrolyte concentration by eq. 3.10 [90]:

$$c_{fixed} = c_{electrolyte} (e^{-f\varphi_D} - e^{f\varphi_D}) \quad (3.10)$$

where $f = \frac{RT}{F}$, and F is the Faraday constant with the value $96\,485 \text{ C} \cdot \text{mol}^{-1}$, R is the ideal gas constant with the value $8.3144 \text{ J} \cdot \text{mol}^{-1} \text{K}^{-1}$ and T is the temperature in K.

As an example, the Donnan potential is about 60 mV when $c_{fixed} = 10 \cdot c_{electrolyte}$ for monovalent ions, and about 40 mV when $c_{fixed} = 5 \cdot c_{electrolyte}$.

The higher the concentration of fixed charges of the membrane, relative to the electrolyte concentration, the more pronounced will the effect of inclusion of counter-ions and exclusion of co-ions be. For monovalent ions, the concentration of counter-ions and the concentration of co-ions in the membrane are given by the relation [48]:

$$c_{counter} = c_{fixed} + c_{co} = \left(\frac{c_{fixed}}{2} \right) + \left(\left(\frac{c_{fixed}}{2} \right)^2 + (c_{electrolyte})^2 \right)^{\frac{1}{2}} \quad (3.11)$$

This can be rearranged to show the fraction of counter-ions in the membrane:

$$\frac{c_{counter}}{c_{counter} + c_{co}} = \frac{1}{2} + \frac{1}{4 \sqrt{\frac{1}{4} + \left(\frac{c_{electrolyte}}{c_{fixed}} \right)^2}} \quad (3.12)$$

If c_{fixed} is 1 M and $c_{electrolyte}$ is 0.1 M, the concentration and fraction of co-ions in the membrane should be 1.01 M and 0.99, respectively.

Figure 3.3: The concentration of ions, the electric field (in the x -direction), and the electric potential across an electrolyte - CEM - electrolyte system. Diffusional forces give an excess positive charge just outside the membrane, and an excess negative charge just inside the membrane. This creates an electric field at the interface, pointing towards the membrane. The electric field can also be visualized by the electric potential, since the electric field is the negative of gradient of the potential. The potential in the membrane is lower than the potential in the electrolyte; cations are attracted to the membrane while anions are repelled. The potential difference between a charged membrane and an electrolyte is called the Donnan potential, φ_D . Image courtesy of Erik Gabrielsson.

3.3.2 Permselectivity

As described in section 3.1.1, the different mobilities, or the different diffusion coefficients, of different ions, make the ions contribute unequally to the conductivity of an electrolyte. In an IEM, not only the mobility, but also the concentrations of co-ions and of counter-ions are different, which also affects how the ions contribute to the conductivity. As seen in eq. 3.1, the product of the concentration, mobility and valence is proportional to that ion's contribution to the total conductivity in the membrane. K^+ and Cl^- have similar diffusion coefficients, and contribute equally to the current when dissolved in,

for example, water. In a CEM with a concentration of fixed charges ten times higher than the electrolyte concentration, the concentration of K^+ will be 100 times the concentration of Cl^- , however, and the transport number of K^+ should be approx. 0.99, thus 99 % of the current is carried by K^+ .

The *permselectivity*, S , of an IEM describes how much of an ionic current passed through the membrane that is carried by counter-ions, and is related to the transport numbers by [32]:

$$S \equiv \frac{t_{counter}^M - t_{counter}^w}{1 - t_{counter}^w} = \frac{t_{counter}^M - t_{counter}^w}{t_{co}^w} \quad (3.13)$$

where M denotes the membrane phase and w the electrolyte phase. Thus, the higher the transport number of the counter-ion is in the membrane *compared to in water*, the larger is the membrane's permselectivity, and if the transport number in the membrane is the same as in water, the permselectivity is zero. If all current is carried by counter-ions, the permselectivity is 1, and the membrane is said to be perfectly permselective.

3.3.3 Concentration polarization

When electrodes are immersed in two electrolytes that are separated by an IEM, and a potential difference is applied, ions migrate across the membrane and a current results. This alters the concentration profile (Figure 3.3 and 3.4). For a CEM, the electrolyte concentration decreases adjacent to the membrane on the side where cations enter the membrane, *the feeding side*, since the electric field moves cations into the membrane and anions away from the membrane. At the other side of the membrane, cations leave the membrane, and anions migrate toward the membrane, thus the electrolyte concentration is increased at this side (Figure 3.4). As a result of this increased ion concentrations at the membrane-electrolyte interface, the concentration of both counter- and co-ions in the membrane increases as well. The different electrolyte concentrations on the two sides of the membrane is referred to as *concentration polarization*.

For low current densities, the system behaves like an ionic resistor, and the current increases linearly with the applied potential. However, as the current density is increased, the electrolyte concentration at the feeding side of the membrane drops, and when the current density is so high that the electrolyte concentration approaches zero at the membrane, the resistance of the system increases. The current at which this occurs is called the limiting current, i_{lim} . When the current is increased above i_{lim} , the zero-concentration extends further out into the electrolyte, and a high-resistance region is formed. For some membranes, increasing the current density even more above i_{lim} can result in a high

Figure 3.4: Ion concentrations in and adjacent to an IEM for different current levels (left), and the current-voltage behaviour of an IEM (right). As the current density is increased, the electrolyte concentration on the feeding side of the membrane will fall, approaching zero as the limiting current is reached. Below the limiting current, the system behaves like a resistor, with a current that is a linear function of voltage. Above the limiting current a plateau is reached.

conductivity [51], (Figure 3.4). This overlimiting current has been proposed to occur due to electrically induced convection, electroconvection, at the feeding side of the membrane. According to this theory, inhomogeneities of the membrane causes an inhomogeneous electric field that interacts with the "extended space charge", that builds up due to an excess of counter-ions adjacent to the membrane at current densities above the limiting current density [74]. This "stirs" the layers at the membrane and transports ions towards the membrane, enabling a higher current density.

3.3.4 Bipolar membranes

A CEM and an AEM together form a bipolar membrane (BM), with current rectification properties, that is, diode-behaviour, similar to a semiconductor pn-junction. The concentration profile and the resulting potential profile of an electrolyte-BM-electrolyte system where the fixed charge concentrations of the CEM and AEM are equal and higher than the electrolyte concentration is given in Figure 3.5. A BM rectifies an ionic current because its ionic conductivity depends on the polarity of the applied potential. If the polarity is such that the counter-ions from the two IEM migrate towards the CEM-AEM interface, the

ion concentration becomes so high that the permselectivities of the membranes are lost, and cations move into the AEM and anions into the CEM. This polarity is called forward bias, and since both co-ions and counter-ions contribute to the current, this bias implies a high conductivity. In the opposite polarity, which is called reverse bias, the counter-ions are instead withdrawn from the CEM-AEM interface into their respective membrane, and the junction between the membranes is depleted of ions; thus reverse bias conductivity is low. If a reverse potential above a certain threshold is applied, this can result in electric field-enhanced water dissociation; water molecules in the junction are dissociated into H^+ and OH^- , which are transported through the CEM and AEM, respectively. This gives a high current, and a decrease / increase in pH at the CEM-electrolyte and AEM-electrolyte interface, respectively [75, 85].

Figure 3.5: Concentration and potential profile across an electrolyte-BM-electrolyte system. Positive ions are present at high concentrations in the CEM (C_+), and negative ions are present at high concentrations in the AEM (C_-).

Figure 3.6: When a BM is forward biased, ions accumulate at the CEM-AEM interface, and the membranes loose their permselectivity, which leads to a high conductivity. When the BM is reverse biased, the interface gets depleted of ions, and the conductivity is low.

3.4 Evaluation of IEMs by the emf-method

Ideally, all current passed though a CEM (AEM) is due to cation (anion) transport, and the membrane is perfectly permselective. However, in practice, a certain degree of co-ion transport occurs across the membrane. A direct way of assessing a membrane's permselectivity, or the transport number of the ion intended for transport, is to integrate the current passed through the membrane, and compare the resulting charge to the change in ion concentration on the two sides of the membrane. Another method, called the emf-method, measures the open circuit potential difference that arises when electrolytes of different concentration are placed on either side of the membrane.

To understand how this open circuit potential can be related to ionic transport numbers in the membrane, we need to understand how potential differences arise. In section 3.2.1 it was described how electrolytes on two sides of a membrane containing ions of different mobilities could give rise to a diffusion potential and in 3.3.1 we described how the distribution of ions at an IEM-electrolyte gave rise to a potential difference called the Donnan potential, eq. 3.10, at an electrolyte-membrane interface.

The open circuit potential that is measured across an electrolyte-IEM-electrolyte system consists of electrode-electrolyte diffusion potentials at the electrode-electrolyte interfaces, diffusion potentials across the membrane, and Donnan potentials at the IEM-electrolyte interfaces. By using KCl (aq) electrolytes and Ag/AgCl/KCl electrodes the diffusion potentials at electrode-electrolyte interfaces, and the diffusion potential across the membrane become close to zero, and the measured potential is the sum of the two Donnan potentials at

the electrolyte-membrane interfaces. The Donnan potential will be larger at the interface with the lower concentration, and smaller at the interface with the higher concentration. Since the Donnan potentials are larger for IEMs with higher concentrations of fixed charges, and thus higher transport numbers for counter-ions, the measured membrane potential can be used to estimate the transport numbers. Transport numbers measured by the emf-method are typically underestimates, however. The reason for this is that ions migrating across a membrane move some solvent molecules along, resulting in some degree of convection in the direction of the majority charge carriers, increasing their flux [53]. Therefore, emf-derived transport numbers are referred to as apparent transport numbers t_{app} . The relation between the apparent counter-ion transport number $t_{+(app)}$ and the measured potential for a CEM, E , is given by equation 3.14. For an AEM, the same equation but with a minus sign before the right hand term and $t_{+(app)}$ substituted for $t_{-(app)}$ applies.

$$E = \left(1 - 2t_{+(app)}\right) \frac{RT}{F} \ln \frac{c^{high}}{c^{low}} \quad (3.14)$$

Electrodes and transduction between electronic and ionic conductivity

An electronically conducting material, like a metal or a conductive polymer, that is placed in an ionically but not electronically conducting material, *i.e.* an electrolyte, is called an *electrode*. Electrodes are used for interfacing electronics with the electrolytes of biological systems, as in electrical recording and stimulation, but also in various other systems for several different purposes. For example, electrodes are used in batteries and fuel cells, where chemical energy is converted into electrical energy. They are also used in electrolysis where an electric current drives a non-spontaneous chemical reaction, for example to purify metals in the metal industry.

If two electrodes are placed in an electrolyte, and a potential difference is applied between the two electrodes, this can result in a current through the system. For a current to occur, the electronic current must be transduced into an ionic current, and vice versa, at the electrode-electrolyte interface. The (material) properties of the electrodes, the composition of the electrolyte, and the magnitude of the potential difference between the electrodes determine the extent to which electronic-to-ionic transduction occurs [4] and the level of the resulting current.

There are two basic mechanisms for how electronic current can be transduced into ionic current at the electrode-electrolyte interface, called faradaic and nonfaradaic processes. Nonfaradaic processes are characterized by the lack of charge-transfer between the electrode and electrolyte, and typically give rise to

exponentially decaying currents when a step voltage is applied [4]. Faradaic processes, on the other hand, imply electron-transfer, and typically result in currents as long as there is enough oxidizable and reducible species present at the electrodes. These processes are described in detail below.

4.1 Nonfaradaic processes

As stated above, nonfaradaic processes are defined by the absence of electron-transfer between the electrode and the electrolyte, meaning that no chemical reactions take place at the interface. Instead, charge builds up at the electrode-electrolyte interface, resulting in an *electric double layer*. An electrode where no charge-transfer can occur, regardless of the applied potential, is called an ideal polarizable electrode. In reality, no ideal polarizable electrodes exist, but some electrode-electrolyte systems behave like ideal polarizable electrodes for a limited potential range.

4.1.1 Electric double layer

When the potential of a metal electrode, immersed in an electrolyte, is different from the potential of the electrolyte, an electric double layer will form (Figure 4.1). The electric double layer consists of a less than 0.1 Å thin layer of excess electronic charge on the electrode and an equivalent amount of oppositely charged ions in the electrolyte. Whereas the charge of the electrode is confined to a thin layer, the charge of the electrolyte can be described as consisting of several layers. The layer closest to the electrode consists of specifically adsorbed molecules and ions, and is termed the *inner layer*, or the *Helmholtz layer*. Outside the inner layer, there is a layer of solvated ions that interact with the electrode through long-range electrostatic forces. Because of their size, and the size of the solvent molecules, the solvated ions cannot approach the electrode surface closer than to a specific distance, defining the *outer Helmholtz plane*. The solvated ions also extend out into the electrolyte tens to hundreds of Å, depending on the ionic strength of the electrolyte. The solvated ions make up what is called the *diffuse layer*. The Gouy-Chapman-Stern theory models the layers as two capacitors in series, and suggests a linear potential drop from the electrode surface to the outer Helmholtz plane, since the charge density in this region is zero. Outside the outer Helmholtz plane the potential is suggested to decay exponentially [4].

4.1.2 Charging an electrode

If two ideal polarizable electrodes are immersed in an electrolyte, and a potential difference is applied between the electrodes, ions in the electrolyte will start

Figure 4.1: When an electrode in contact with an electrolyte is positively biased, negative ions will accumulate at the electrode surface, creating an electrical double layer. There will be specifically adsorbed ions and molecules directly on the electrode surface, whereas solvated ions only can approach the metal to a distance that defines the outer Helmholtz plane. Image courtesy of Erik Gabrielsson.

to rearrange, and will eventually balance the charge of the electrodes by the build-up of electric double layers. At short timescales, before the ions have had time to establish double layers, the electrolyte will behave like a non-conducting dielectric material, and there will be a uniform potential drop across the electrolyte. Then, as the ions migrate, and as the electric double layers build up, the potential drop shifts from the electrolyte to the electrode-electrolyte interfaces. Once the electric double layers have established, the potential of the electrolyte will be constant, and the entire potential drop will occur across the interfaces. When this happens, current will cease to flow through the system (Figure 4.2). The amount of current that can flow thus depends on the amount

of charge that is possible to store at the electrode-electrolyte interface, that is, the *capacitance*.

Figure 4.2: As a potential difference V is applied between two polarizable electrodes in an electrolyte (time = 1), an electric field E is created across the electrolyte, and ions start to migrate towards the electrodes (time = 2). The electric field remains in the electrolyte until enough ions have accumulated at the electrodes, so that their charge is balanced. Then, all potential drop occurs across the electric double layer (time = 3). Image courtesy of Henrik Toss.

4.1.3 Capacitance of electrode-electrolyte interface

The double layer at an electrode-electrolyte interface is similar to a parallel plate capacitor, which is a device that stores charge when a subjected to a potential difference. Such classical capacitor consists of two electronic conductors of area A separated a distance d by an insulator.

The capacitance, C , of the system, which is defined by how much charge, q , it can store as a result of an applied electrical potential difference, V , is then given by:

$$C \equiv \frac{q}{V} = \epsilon \frac{A}{d} \quad (4.1)$$

where ϵ is the permittivity of the insulating material, a property that relates to how easily the material polarizes as the electric field is applied, and thus its ability to oppose, or screen, the electric field. In such a classical capacitor, the charge is separated by the thickness d of the dielectric.

In the electrode-electrolyte double layer, the charge separation instead depends on how close the solvated ions can approach the electrode surface, and is thus related to the outer Helmholtz plane (Figure 4.1). For electrolytes with concentrations above 0.01 M, d is typically less than 10 nm. Since d is so small, the double layer capacitance, C_d , is rather large, and a typical electric double layer capacitance is 10 - 40 $\mu\text{F} \cdot \text{cm}^{-2}$ [4]. However, the capacitance of a double layer is a function of electrolyte concentration and applied potential, which is not the case for a traditional, dielectric-based, capacitor.

4.2 Faradaic processes

While no chemical reactions take place during nonfaradaic processes, faradaic processes are defined by the electron transfer between the electrode and some species in the electrolyte. Faradaic processes are governed by Faraday's law (thereof the name), eq. 4.2, that relates the amount, N , in moles, of chemical reaction taking place per second to the current, i , in Ampere by:

$$\frac{dN}{dt} = \frac{i}{nF} \quad (4.2)$$

where n is the stoichiometric number of electrons involved in the reaction and F is the Faraday constant with the value $96\,485 \text{ C} \cdot \text{mol}^{-1}$.

In section 4.1 an ideal polarizable electrode was defined as an electrode at which no charge transfer could occur. Conversely, an ideal nonpolarizable electrode is an electrode where charge is easily transferred between the electrode and the electrolyte, and no electric double layer builds up. An ideal nonpolarizable electrode therefore stays at a fixed potential, irrespective of the current passed through it, and can therefore be used as an electrochemically stable "reference" electrode. Such reference electrode can be achieved by keeping the species that participate in the redox reaction at a constant concentration. The internationally accepted reference electrode is the *standard hydrogen electrode* (SHE) which consists of a platinum electrode immersed in a H^+ solution bubbled with H_2 gas, where the activity coefficients of H^+ and H_2 are both unity. $\text{Ag}/\text{AgCl}/\text{KCl}$ (saturated in water) is another commonly used reference electrode.

The potential at which faradaic currents can flow at an electrode are related to the standard potentials and the concentrations of the oxidizable and reducible chemical substances in the electrolyte. The reduction potential for the redox reaction $O + ne \rightleftharpoons R$ can be calculated from the Nernst equation:

$$E = E_0 + \frac{RT}{nF} \ln \frac{c_O}{c_R} \quad (4.3)$$

where O and R are the oxidized and reduced species, respectively, c_O and c_R their concentrations. R is the ideal gas constant with the value $8.3144 \text{ J} \cdot \text{mol}^{-1} \text{K}^{-1}$, T the temperature in K, F the Faraday constant, e denotes an electron, and n is an integer. For some reactions and electrode materials, a higher potential than the potential estimated by the Nernst equation is needed for the reaction to occur. This extra potential is then referred to as an *overpotential*.

4.2.1 Avoiding faradaic processes

While faradaic processes are key reactions for galvanic and electrolytic cells, where chemical energy is converted into electrical energy, and vice versa, faradaic processes are often undesirable, for example in electrical stimulation and in other situations when an electrode is in contact with a biological system. Reactions that may occur in such situations include electrolysis of water, which alters the pH and produces gases, and oxidation of biochemical compounds such as glucose [16]. These redox reactions can be avoided by carefully controlling the potential of the electrode, and keeping it within the range where the electrode behaves as an ideal polarizable electrode.

4.3 Electrode characterization methods

There are several techniques that can be used to characterize an electrode and the electrode-electrolyte reactions. These typically involve controlling the potential of the electrode of interest, "the working electrode", with respect to a reference electrode by allowing current to flow between the working electrode and a counter electrode. The potential of the working electrode can be held constant, it can be changed in steps, it can be swept over time, or it can be varied in more complex ways. Alternatively, the current can be controlled, and the potential measured. Cyclic voltammetry, CV, and Electrochemical Impedance Spectroscopy (EIS) are two popular methods that are briefly discussed below. CV can reveal information about the presence of redox reactions, and reveal the amount of charge available for a stimulation pulse from a stimulation electrode, whereas EIS can be used to assess the recording capabilities of recording electrodes.

4.3.1 Cyclic voltammetry

In CV, the potential of the working electrode is swept at a constant rate, "cycling" repeatedly between two set voltages, while current is allowed to flow between the working electrode and a counter electrode. The current as a function of potential can reveal electrochemical reactions, since the current increases at potentials where these reactions take place. The integrated current also gives a measure of the charge-injection capacity of the electrode. However, the sweep rate has a high impact on the current-voltage response, and thus the estimated charge-injection capacity, since at high sweep rates, less accessible areas of the electrode (for examples the pores in a porous electrode) do not have time to react [16]. Nonfaradaic processes give a box-shape in a cyclic voltammogram (Figure 6.7 a), whereas faradaic processes give peaks in the current-voltage curves around the potential at which the redox reactions take place (Figure 6.7 b) [4].

Figure 4.3: For completely nonfaradaic processes, ramping the potential leads to a constant current (a). If redox reactions take place at the electrodes, this gives peaks in the current-voltage curve (b). As the potential is swept towards more negative values it reaches a potential where electrons transfer to electron-acceptors (denoted O) in the electrolyte, which increases the current. Continuing the scan towards even more negative potentials, electron-acceptors at the electrode/electrolyte interface are consumed, and their concentration falls. Thus, the reduction reaction is limited by the mass transport of electron-acceptors to the interface, and the current decreases. The same reasoning applies to the sweep in the positive direction, but for the electron-donor (R), and an oxidation reaction.

4.3.2 Electrochemical impedance spectroscopy

In CV, the potential of the electrode is driven far away from equilibrium. In electrochemical impedance spectroscopy, EIS, the electrode is instead only slightly perturbed from its equilibrium by means of a low amplitude ac voltage,

$v = V \sin \omega t$, where ω is the angular frequency and V is the voltage amplitude. The frequency of the ac voltage is varied, and the phase shift, ϕ , and the magnitude, I , of the resulting current $i = I \sin(\omega t + \phi)$ are measured. The current and the voltage are thus described by two sinusoidal signals with the same frequency. Alternatively, they can be represented by two *phasors*, *i.e.* two vectors with a common origin that rotate in the complex plane at the same angular frequency. These rotating vectors, $\dot{V}$ and $\dot{I}$, can be related by the complex number Z by $\dot{V} = \dot{I}Z$, which is a generalized form of Ohm's law, eq. 2.1, with Z , termed the impedance, being a generalized resistance.

The impedance varies with varying frequency, and the magnitude, $|Z|$, and the phase angle, ϕ , are often plotted against frequency in a Bode plot (Figure 4.4). Impedance data can be rather complex and are often interpreted by modelling the electrode - electrolyte with an equivalent electrical circuit. In general, the phase angle tells us about the resistive versus capacitive behaviour of the cell, since resistive elements don't give any phase shift, whereas a capacitor shifts the current by up to $\frac{\pi}{2}$.

Assuming no charge transfer occurs between an electrode and an electrolyte, the system can be described as a resistor R and a capacitor C in series, where the resistor describes the solution resistance and other resistive elements in the system, and the capacitor describes the capacitance of the electrode-electrolyte double layer. The total impedance of such system is then given by:

$$Z_{tot} = Z_R + Z_C = R + \frac{1}{j\omega C} \quad (4.4)$$

where j is the imaginary unit and $j^2 = -1$. Coating a metal electrode with a conductive polymer, or another porous material that increases the effective surface area of the electrode, increases the capacitance of the system. At high frequencies, the impedance of the system is dominated by the resistance, and the capacitance of the electrode does not play a major role. However, at lower frequencies, the capacitor becomes more and more dominating, and a high capacitance decreases the magnitude of the impedance. A high capacitance also shifts the transition from mainly resistive to mainly capacitive behaviour towards lower frequencies (Figure 4.4). The magnitude of the impedance is related to a low charge-injection resistance, and for recording electrodes this implies better signal-to-noise ratio and improved recording capabilities.

Figure 4.4: Typical Bode plot of the magnitude and phase angle of the impedance of a metal electrolyte (black), and the same metal electrode coated with a conductive polymer (red). The coating increases the capacitance of the electrode - electrolyte system. This decreases the magnitude of the impedance for low frequencies, and shifts the transition from resistive to capacitive behaviour towards lower frequencies.

4.4 Electrical stimulation and recording electrodes

4.4.1 Electrical stimulation

Electrical stimulation can affect the activity of neurons, or other voltage sensitive cells, by altering the electric potential in the vicinity of an electrode. The potential is altered by passing ionic currents between two or more electrodes, and typically square-wave charge-balanced current waveforms are used. Using charge-balanced waveforms reduces the risk of irreversible reactions that damage the electrode or the tissue, since the electrodes may be kept within potentials where these reactions don't occur. Currents levels for electrical stimulation usually fall within 1 μA to tens of mA with durations of 50 μs to a few ms,

depending on application and electrode size [16].

Electrodes for electrical stimulation are commonly made from platinum or stainless steel. As an example, stimulation for improved hearing in cochlear implants uses platinum electrodes. However, for small area electrodes, the charge-injection capacity of platinum, or other bare metal electrodes, which are typically below $1 \text{ mC} \cdot \text{cm}^{-2}$, is not enough for a stimulating effects. By making the electrodes porous, as exemplified by fractal titanium nitride, the charge-injection capacities can be improved somewhat [99]. Porous electrodes do have relatively high charge storage capacities, but at high frequency currents, all this capacity is not available, due to the pore resistance. To avoid highly resistive pores, small-dimension structures such as carbon nanotubes can instead be added onto the electrodes [98].

An alternative approach to increase the charge storage capacity of an electrode is to coat it with a material that contains a redox couple, for example iridium oxide where the redox reaction $\text{Ir}^{3+} \leftrightarrow \text{Ir}^{4+} + \text{e}^-$ allows fast and reversible charge injection [16]. Conductive polymer coatings where the charge state of the polymer can be altered, can similarly be used to improve the charge-injecting capacity by allowing faradaic reactions between the metal and the polymer. Thus, both iridium oxide and conducting polymer electrodes behave as polarizable electrodes with respect to the electrolyte. However, faradaic reactions take place *within the electrode materials*, and the "electric double layer" is formed throughout the electrode volume.

4.4.2 Electrical recording

Neuronal activity can be recorded by probing either the intracellular or extracellular potential [86]. An action potential consists of ionic currents through the cell membrane and therefore changes the cell's potential, as well as the potential immediately outside the cell (see section 5.2).

Patch pipettes, which are glass pipettes with micrometer-sized openings, can be used for intracellular recording. These pipettes can be used to measure ionic currents through single ion channels, as well as ionic currents from whole cells. In patch clamping, a glass pipette containing a Ag/AgCl electrode is used to form a tight seal with the cell membrane. To make whole cell recordings, the cell membrane is opened, so that the fluid within the pipette becomes continuous with the intracellular fluid. The Ag/AgCl electrode can then directly measure the intracellular potential of single cells. However, this and other intracellular recording methods generally disturb the intracellular milieu, and typically cause cell death [86], which make them unsuitable for *in vivo* chronic recordings.

The ionic currents associated with action potential firing can alternatively be picked up by recording electrodes placed outside the cell. Extracellular

recording electrodes will pick up signals by all nearby cells that change the potential at the electrode site, though, and it can thus be difficult to discern single cell activity. Also, to record from single cells, the electrode size should be similar to the size of the cells. However, scaling down electrodes increases their impedance, and thereby impairs the quality of recording. Since most neuronal activity occur at 300 - 1000 Hz, the electrode's impedance at 1 kHz is often used as a measure of the electrode performance [18]. It should be taken into account that even if recording electrodes perform well *in vitro*, signal quality from implanted electrodes may degrade over time because of foreign-body reactions to the implant.

In the future, chronically implanted recording electrodes could, for instance, aid patients to achieving cognitive control of external prosthesis [23] or paralyzed body parts [11, 34]. Such electrodes could also be used to treat various disorders to the nervous system, including epilepsy, where the signal from the recording electrodes could be used to control the output of stimulating electrodes, or the drug release from implanted devices [36].

4.5 PEDOT:PSS electrodes

Coating an electrode with a conductive polymer in general improves the electrode charge injection capacitance, lowers the magnitude of the impedance, and decreases the impedance phase shift by allowing faradaic reactions within the polymer [49], and as a result makes it possible to obtain high signal-to-noise ratio recordings from micrometer-sized electrodes [16, 44, 46]. The polymer coating also increases the lifetime of an electrode from which a direct current is run, while avoiding faradaic reactions with the electrolyte [6]. Furthermore, it has been hypothesized that soft and ionically conducting polymers can form a better contact with biological tissue, compared to hard metal electrodes [71], and that inflammation can be reduced due to a better match between the mechanical properties of the electrode surface and the tissue [37]. Reducing the inflammatory response may in turn reduce fibrous tissue encapsulation of the implant, so that high-quality recordings can be maintained over time.

The conductive polymer-polyelectrolyte blend poly(3,4-ethylenedioxythiophene):poly(styrenesulfonate), PEDOT:PSS, is one of the most investigated materials when it comes to conductive polymer coatings for implantable electrodes. Fundamentals of PEDOT:PSS and chemical structure can be found in section 2.5. To operate PEDOT:PSS within the capacitive regime, that is, to avoid electrochemical side reactions with the electrolyte, one needs to stay within an "electrochemically safe window". For example, oxygen is easily reduced if the potential of PEDOT is decreased [101], and PEDOT:PSS is therefore usually operated above -0.6 V vs Ag/AgCl. If a too positive potential is applied, PEDOT:PSS may lose its conductivity by being overoxidized [50].

The charge storage capacity is an important parameter if significant amounts of ions are to be moved over an electrode-electrolyte interface, and typically depends on the electrode area. It has been reported to be between 2 and 15 $\text{mC}\cdot\text{cm}^{-2}$ [16, 19] for PEDOT:PSS films. Since charge is stored throughout the volume of a PEDOT:PSS electrode, however, the volume rather than the area, determines the charge storage capacity. The volumetric capacitance has been reported to be $39\text{ F}\cdot\text{cm}^{-3}$ [72], indicating that changing the potential 1 V of a 1 cm^3 PEDOT:PSS electrode would lead to the uptake or release of 39 C of charge. However, the ions in the outermost part of a polymer electrode may move more quickly and with a lower resistance over the interface, whereas ions stored deeper inside the polymer are less accessible.

4.5.1 Drug delivery from conducting polymer electrodes

As described in section 2.5 the application of a potential to a conductive polymer is associated with ion migration to or from the polymer. This electrically driven ion movement, and the associated volume change, has been proposed for electrically controlled drug delivery applications: ionic drugs can be embedded in the polymer [91], and subsequently released, as a result of a changing potential. For example, cationic drugs incorporated into PEDOT:PSS can be released by the application of a positive potential to the polymer, as shown schematically in Figure 4.5.

Figure 4.5: Applying a positive potential to a PEDOT:PSS coated electrode, injects holes into PEDOT and increases its positive charge, which repels cations from the polymer

Nerve cell signalling

The cells in our bodies need to communicate with each other to coordinate body functions such as growth, movement, and defence against disease. This means that the cells must be able to receive and process signals and generate the appropriate response, and to send out their own signals to other cells and tissues.. The majority of these signals are chemical signals that bind to specific receptors in the cell membrane. The receptors change conformation and activate intracellular signalling pathways, where signals are amplified and integrated so the cell can respond. Some signals affect the cell by which they are released, while other signals affect nearby or distant cells. Hormones are released by endocrine glands and spread throughout the body via the circulatory system, and act on a timescale of hours to weeks, whereas neurotransmitters transmit signals between nerve cells across the 20 nm synaptic cleft within a few milliseconds [2].

The rapid and local signalling between cells of the nervous system makes interaction with it particularly challenging; systemic drug administration cannot restore a particular nerve cell signalling pathway that has been perturbed due to injury or disease. However, local on-demand release of signalling compounds in a fashion mimicking the function of nerve cells could potentially restore dysfunctional nerve cell signalling. This would require controlled release of neurotransmitters with high spatiotemporal resolution, which is the goal of the devices presented in this thesis. This chapter gives some fundamentals of nerve cell signalling and the diseases related to nerve cell signalling that could possibly be helped by the devices presented in the thesis.

5.1 The nervous system

The nervous system coordinates diverse actions in the body, both voluntary and involuntary ones. It transmits sensory signals (vision, hearing, touch, etc.) from the sensory organs to the brain, and sends out signals from the brain to the muscles and glands in the body.

The nervous system can be subdivided into the central and the peripheral nervous systems, CNS and PNS, respectively, where the CNS includes the brain and the spinal cord, and the PNS includes nerves. Nerves consist of bundles of axons, that are long protrusions of the nerve cells that connect all parts of the body with the CNS. Apart from nerve cells, or neurons, that are responsible for the fast long-range electrical signal transmission characteristic of the nervous system, the nervous system also comprises glial cells that repair, support, and control the regrowth where neurons have been damaged.

5.2 Intracellular signalling

Although neurons are not intrinsically electronically conducting, they conduct electricity by means of electrical potential waves. Due to the difference in ionic concentrations inside and outside the cell, and due to the fact that the cell membrane permeability is different for different ions, the inside of the cell is at a negative potential (typically -40 to -90 mV) relative to the outside when the cell is at rest. When the cell sends a signal, however, a *wave of positive potential*, an *action potential*, resulting from ionic currents through the cell membrane, spreads along its axon. This short-lived and local positive potential is created by ions that move across the cell membrane through specific ion channels and spread to neighbouring parts of the membrane where they open more voltage gated ion channels, that is channels that open or close according to the potential.

At rest, the Na^+ concentration is higher outside than inside the cells, while the K^+ concentration is higher inside the cells. The basis of an action potential relies on opening of Na^+ ion channels, which leads to influx of Na^+ and a raised membrane potential, and a subsequent closing of Na^+ ion channels together with an opening of K^+ ion channels, which causes outflux of K^+ and a return to the lower resting potential (top Figure 5.1). Thus, the ion movement is primarily perpendicular to the pathway along which an action potential spreads, which partly explains the high speed of action potential transmission. Myelin, a fatty insulation around the axons consisting of specialized glia cells, further increases the speed, and myelinated axons can reach conduction velocities of 150 meters per second [69].

The electrical nature of signal propagation within nerve cells makes it possible

to affect nerve cell signalling by sending currents to the cells from implanted electrodes (see section 4.4.1).

5.3 Signal transmission between neurons

Some nerve cells' intracellular fluids are interconnected, which means that action potentials can spread between cells, but most nerve cells need to pass on signals to other cells over a *chemical synapse*, which includes an extracellular synaptic cleft. A synapse is a point of contact between cells, where neurotransmitters are released by the first "presynaptic" cell, diffuse over the synaptic cleft, and bind to receptors on the second "postsynaptic" cell (bottom Figure 5.1). A single nerve cell can receive input from up to 100 000 synapses. This input is then integrated, and if the cell's membrane polarization exceeds a specific threshold, the cell generates another action potential at the origin of its axon (the "axon hillock"). The delay between a presynaptic action potential and the postsynaptic response is typically between a few hundred μs to a few ms [76]. A synapse can have either an excitatory or an inhibitory effect on the postsynaptic neuron, depending primarily on the type of neurotransmitter that is released. There are over 100 different neurotransmitters, but a few examples are the excitatory neurotransmitters acetylcholine and glutamate, with acetylcholine being the main neurotransmitter in neuromuscular synapses, and glutamate the main excitatory neurotransmitter in the brain. GABA and glycine are mainly inhibitory neurotransmitters, on the other hand, and inhibit postsynaptic neurons from firing action potentials.

5.4 Diseases and injury to the nervous system

The devices developed in this thesis aim at interacting with nerve cell signalling, for example to restore dysfunctional signaling in disorders of the nervous system. In paper A we inhibited abnormal firing of neurons leading to neuropathic pain *in vivo* by delivering the inhibitory neurotransmitter GABA, and in paper C and D epileptic activity was suppressed *in vitro* by delivery of the same compound. This section provides a brief description of neuropathic pain and epilepsy.

5.4.1 Neuropathic pain

When we are subjected to heat, cold, pressure or damaging chemicals, this stimulus is sensed by specialized sensory neurons, called nociceptors. The nociceptors pick up the signal about potential damage and transmit the signal to the spinal cord. At the spinal cord, the signals are relayed to a second set

Figure 5.1: A nerve cell (pink) with dendrites that receive input signals from another neuron or a sensory organ, and an axon that transmits the signal to a neuron, muscle or gland. The signal travels along the axon in the form of an action potential (top), and is transmitted between neurons by neurotransmitters that cross the synaptic cleft and bind to receptors on the next cell (bottom).

of neurons that take the message to the brain, where pain is experienced. Pain leads to behaviours that protect us from injury, and can thus be regarded as a friendly warning. However, if the pain signalling pathways get perturbed, pain may be experienced in the absence of noxious stimulus. This is exemplified by neuropathic pain, which means pain arising from nerve injury or disease. The pain persists after the injury is healed, and apart from spontaneous ongoing pain, patients often suffer from mechanical and thermal hypersensitivity. A complete understanding of the mechanisms behind neuropathic pain is lacking, but after injury, nerve cells at the injured site have been observed to increase

their action potential firing rate. Damaged myelination of axons, inducing crosstalk between neighbouring axons, is one explanation to the increased activity. At the spinal cord level, excitability has also been observed to increase, with a resulting increase in the release of excitatory neurotransmitters. Along with increased excitation, inhibition is decreased due to for example loss of GABAergic neurons, that is, neurons that signal using GABA, and a reduced level of GABA [102].

Current therapies for neuropathic pain include anti-inflammatory drugs and anti-convulsants [25], as well as electrical stimulation by implanted electrodes [57], but only give adequate pain relief in about half of the patients [35].

5.4.2 Epilepsy

Epilepsy is a brain disorder afflicting about 1% of people world-wide [59]. A characteristic of epilepsy is the occurrence of abrupt seizures that are often associated with convulsions and, sometimes, loss of consciousness. Such seizures are known to result from an imbalance between excitatory and inhibitory input. However, the reason behind this imbalance in epileptic patients is not understood [87], nor is the timing of seizure onset. When a seizure occurs, large groups of neurons fire in a coordinated, rhythmic pattern. The seizures are thought to start as abnormal activity in small areas in the brain, "epileptic foci", and then spread to connected areas [66].

There are two main strategies for pharmacological treatment of epilepsy: enhancement of inhibitory GABAergic synapses and limitation of action potential firing by affecting voltage-gated Na^+ channels. Both strategies decrease firing probability. However, existing therapies are only effective in two thirds of patients [59, 66]. An alternative approach would be seizure-triggered local electrical stimulation by implanted electrodes [7].

Devices developed in the thesis

This chapter describes the devices that were developed during this thesis work. The devices are all advancements of the Organic Electronic Ion pump (OEIP), which is an electrically controlled device that can deliver precise amounts of charged chemical species to micrometer-sized regions. OEIPs were first described in 2007 when Isaksson et al. used an OEIP to deliver K^+ to cultured cells and recorded cellular response in terms of intracellular Ca^{+} fluxes [39]. Since then the technology has been improved in terms of design, speed, and precision [31, 80, 95].

In paper A, *Therapy using implanted organic bioelectronics*, an implantable OEIP was developed (section 6.2.1), and we showed that the OEIP could be used to achieve a therapeutic effect in an animal model. In paper C, *Controlling epileptiform activity with organic electronic ion pumps*, we built OEIPs on glass substrates for the first time and showed that OEIPs could control epileptic events *in vitro*. In paper D, *Bioelectronic neural pixel: Chemical stimulation and electrical sensing at the same site*, we merged the OEIP outlet with a sensing electrode and showed that the combined device could be used for local delivery and recording (section 6.2.2). Finally, in paper E, *Chemical delivery array with millisecond neurotransmitter release*, we demonstrated high speed OEIPs/delivery diodes (section 6.3) arranged as an array with individually controlled delivery sites (section 6.4).

6.1 OEIP structure and function

To a first approximation, the OEIP can be regarded as a miniaturised electrochemical cell (Figure 6.1) with a specialized salt bridge made of a polymer with the properties of an ion exchange membrane (IEM). The IEM is permselective, that is, it allows the passage of either *only cations* or *only anions* (see section 3.3). When a potential difference is applied between the two electrolytes, cations (or anions) migrate across the IEM and close the electrical circuit. Therefore, ideally, all charge passed through the electronic branch of the circuit corresponds to cation (or anion) migration. Thus, the charge q that is passed through a device, found by integrating the current i over time t , can be correlated to the amount of transported ions, N , by:

$$N = \frac{q}{zeN_A} = \frac{\int_0^T i(t) dt}{zeN_A} = \frac{\int_0^T i(t) dt}{zF} \quad (6.1)$$

where e is the elementary charge with the value $1.602 \cdot 10^{-19}$ C, z the charge number of the transported ion, and N_A is Avogadro's constant $6.022 \cdot 10^{23} \text{ mol}^{-1}$. $F = eN_A$ is the Faraday constant $9.649 \cdot 10^4 \text{ C} \cdot \text{mol}^{-1}$. As an example, running a current of 100 nA for one minute should result in delivery of 60 picomole monovalent ions.

The electrolyte containing the ion to be delivered is called the *source* electrolyte, and the electrolyte to which ions are delivered is called the *target* electrolyte. For a cation-OEIP, a positive potential is applied to the source relative to the target to start cation migration toward the target, while the potential difference is reversed for an anion-OEIP.

Ion pumps are typically fabricated using microfabrication techniques, including spin coating, photolithography, and etching (see section 7.1). This means that we deposit and selectively remove thin films (typically 100 nm - 1 μm thick) of the polymer IEM material to make an *ion channel* of a certain length, l , width, w , and thickness, d . The ion channel is then partly encapsulated, leaving openings to the source and target electrolytes. The ionic resistance of the OEIP depends on its geometry, and on the ion that is being transported. Arbring measured the ionic sheet resistance for K^+ to be 0.56 M Ω /square in a CEM-based ion pump made from 250 nm thick overoxidized PEDOT:PSS [83], which gives resistances in the M Ω range for typical channel geometries. OEIPs exhibit a linear current - voltage relation, and thus behave like resistors.

Figure 6.1: An electrochemical cell (top) is compared with an OEIP (middle) and a typical potential profile of an OEIP with applied potential is shown (bottom). The salt bridge in an electrochemical cell allows both cation and anion transport, whereas the cation exchange membrane in the OEIP only allows cation transport.

6.1.1 Transport numbers and permselectivity in OEIPs

Eq. 6.1 relates the integrated electrical current through an OEIP to the amount of delivered ions in the ideal case. In practice, the delivered amount does

not always reach the ideal amount, that is, each electronic charge does not correspond to exactly one of the intended ions being transported. This can be explained by co-ion transport in the opposite direction (see section 3.1.1 and 3.3.2), or that another counter-ion is present in the source electrolyte, apart from the ion intended for transport. In that case, the additional counter-ion will contribute to the current. For example, the pH may have been adjusted to yield a high proportion of an ion in its charged form, which increases the concentration of H^+ or OH^- .

The fraction of the ionic current due to intended ion transport through an IEM is called the transport number of that ion, t_i^M (section 3.3.2), where $t_i^M = 1$ is the ideal case.

6.2 OEIP resistor networks for multiple delivery points

In the work leading to paper A, C, and D, we developed multiple outlet-OEIPs. As described in section 6.1, an OEIP behaves like a resistor. Therefore, an ion pump with multiple outlets can be modelled as a network of resistors (Figure 6.2). To obtain equivalent currents through several outlets, for example $i_A = i_B = i_C = i_D$ in Figure 6.2, the resistors must be chosen so that:

$$R_A + R_1 = R_B$$

$$R_2 + R_{eq(RA, RB, R_1)} = \frac{R_C}{2}$$

$$R_3 + R_{eq(RA, RB, RC, R_1, R_2)} = \frac{R_D}{3}$$

where the equivalent resistances are given by:

$$R_{eq(RA, RB, R_1)} = \frac{1}{\frac{1}{R_A + R_1} + \frac{1}{R_B}}$$

$$R_{eq(RA, RB, RC, R_1, R_2)} = \frac{1}{\frac{1}{R_3 + R_{eq(RA, RB, R_1)}} + \frac{1}{R_D}} = \frac{1}{R_3 + \frac{1}{\frac{1}{R_A + R_1} + \frac{1}{R_B}}} + \frac{1}{R_D}$$

The resistance of an ion pump is mainly determined by the mobility of the ionic species and the geometry of the ion channel. We have observed that the OEIP resistance scales with length/width for a given material thickness [83], but there is also evidence that narrow channels (below approx. 50-100 μm) exhibit relatively higher resistances, particularly for larger ions (unpublished). However, given that resistance scales with length/(width · thickness), several geometries resulting in equivalent delivery currents through multiple outlets are possible. Two example geometries are shown in Figure 6.3.

Figure 6.2: An OEIP with several outlets (here 4) can be modelled as a resistor network. The relative currents, i_A , i_B , i_C , i_D , through the outlets depend on the relative resistances, which to a first approximation scale with the length/width of the different parts of the ion channel.

6.2.1 The implantable ion pump

The implantable ion pump-project (paper A) aimed at investigating whether pain derived from injury to the sciatic nerve could be alleviated by local neuro-inhibition at the four locations where the injured nerve couples to the spinal cord. The implantable ion pump was thus designed to allow simultaneous delivery of the endogenous neuro-inhibitor γ -aminobutyric acid (GABA) at these four locations (2.5 mm apart) along the spinal cord.

To fit the geometry of the rodent spinal cord, the device had to be built on a minimum 60 mm long, maximum 1.2 mm wide flexible support. Based on these geometric constraints, we designed an OEIP with the same length/width for R_A , R_B , R_C and R_D ($500 \mu\text{m} / 100 \mu\text{m}$), and the same length/width for R_2 , R_3 , R_4 ($2500 \mu\text{m} / 500 \mu\text{m}$), as defined in Figure 6.2. Thus, all the resistors have the same value, and about 40 % of the resulting current should come through

Figure 6.3: Two examples of multiple outlet OEIPs that should result in equal delivery currents through the outlets (outlets are marked with red circles) given that resistance scales with length/width. The numbers denote the length/width of the respective parts.

the closest delivery point (i_A). The simultaneous delivery through all outlets was confirmed by proton delivery into a pH-sensitive dye.

A major challenge in the development of the implantable ion pump was to find an encapsulation material that withstood the bending needed during implantation and while implanted. Although previous OEIPs had been reported to be built on flexible substrates (approx. 100 μm thin PET) they had not been bent, and the previously used encapsulation material (SU-8) cracked and delaminated during the handling of the implantable OEIP. Instead, we screen printed the material DuPont 5018 dielectric, which successfully encapsulated the ion channels.

6.2.2 Ion pump and integrated recording electrode

In the project leading to papers C and D, we set out to merge OEIPs with conducting polymer electrodes for sensing, in order to enable chemical delivery and electrical recording from the same micrometer-scale locations. To merge the two device technologies, it was necessary to fabricate OEIPs on glass, since the previous plastic OEIP substrate did not allow high quality recordings (*i.e.* low noise) from the electrodes. The resulting device consisted of an array of OEIPs, that is, several ion channels connecting a source electrolyte and a target electrolyte. At the OEIP delivery sites, conducting polymer recording electrodes were incorporated in such a way that ion transport occurred through the recording electrodes (Figure 6.4).

The reason for having several outlets was to increase the probability of finding a cell close to an outlet/delivery point when culturing cells on the device, and to have outlets/delivery points at relevant positions when placing a tissue slice on the device. To obtain delivery through the 32 outlets, the length/width was made substantially higher ($200\text{ }\mu\text{m}/20\text{ }\mu\text{m}$) for the 32 delivery fingers, (*i.e.* equivalent to the RA, RB, RC,... in Figure 6.2) than for the wide channel ($200\text{ }\mu\text{m}/1000\text{ }\mu\text{m}$)(equivalent to the R1, R2, R3,...) (Figure S1 in paper D [41]).

Figure 6.4: The OEIP with integrated sensors consists of CEM ion channels through which cations are transported from a source to a target electrolyte by an applied potential difference V_S . The ions are transported to the target electrolyte through a PEDOT:PSS recording electrode, thus chemicals can be delivered at the site of electrical recording.

6.3 Fast ion pumps

One of the main goals with the OEIP technology is to allow efficient communication with the nervous system, and eventually to replace dysfunctional neural communication and missing chemical synapses. To do so, the OEIPs must be able to match the speed of signal transmission between neurons and other cells, which occurs on the millisecond timescale. This motivated us to reduce the delay between the application of an electrical signal and the release of ions, which had been on the scale of seconds to minutes in previous devices. The results of this effort are detailed in paper E.

In order to rapidly release ions fast when a voltage is applied, the ions must be stored close to the release site. For a simple ion pump (Figure 6.5a), this could be achieved by shortening the ion channel length, d . However, shortening d

Figure 6.5: The switch-on speed of an ion pump depends on the distance the ions must migrate before reaching the delivery point. The speed can be increased by reducing the distance, d , between the source and target (a), or by incorporating a waste electrolyte so that part of the channel can be loaded with ions (b), which reduces d . To reduce d more efficiently, the fast ion pumps were made, where delivery occurs out of the plane of the device (c). The arrows indicate the delivery points

would increase the diffusive leakage of the ions when the voltage is off, which means that the ions in the part of the ion channel closest to the release site would be exchanged with ions in the target electrolyte. Also, shortening d would reduce the distance between the source and target electrolytes, which is impractical in some applications and not possible in others.

An alternative approach to increase the speed of delivery, other than shortening d , is to add a third electrolyte, a *waste electrolyte*, so that part of the ion channel can be loaded with the ions intended for delivery by running a source-to-waste current (Figure 6.5b) [95]. By running a target - waste current while the ion

channel is loaded with ions, leakage by diffusion can be prevented.

The fast ion pumps use a similar approach; they include a waste electrolyte - but the ions are transported *below* the target electrolyte when they migrate from source to waste to preload the channel. Delivery is subsequently done perpendicular to the plane of the substrate, into the target electrolyte. This vertical delivery simplifies the reduction of d , since layer thicknesses can easily be made a few hundred nanometers, whereas features below $1\ \mu\text{m}$ in the plane of the device are difficult to obtain. The release site in the fast ion pumps consists of a small hole (typically $40 - 400\ \mu\text{m}^2$) in the encapsulation material (Figure 6.5c). To prevent diffusive leakage of the ions through the hole during the preloading from source to waste, a reverse current can be applied across the hole. This means that the diffusion can be counteracted by migration. However, the reverse current implies that ions from the target will dilute the ions intended for delivery immediately under the hole, with a slower onset of delivery of the intended ions as a consequence. Therefore, it is ideal if the reverse current can be minimized.

To minimize the reverse current while allowing a high conductivity in the forward (delivery) direction, an ion-diode function can be added to the outlet. We created such diodes by adding an oppositely charged polymer at the outlet, thus creating a bipolar membrane (BM) diode (see Figure 6.6a and section 3.3.4). When the voltage is scanned between the source and target electrolyte, these devices show typical current-voltage behaviour of BM diodes [15] (Figure 6.7). The hysteresis in the reverse scan is due to ions that have accumulated in, and migrated across, the BM junction (during the forward scan), which need to be extracted before the low conductivity state is reached.

Designing the OEIPs so that the resistance between the source and the target equals the resistance between the target and the waste makes the potential under the delivery point the average of V_S and V_W , and V_T may be controlled relative to this value to determine the direction of the delivery current, i_T . However, when the ions in the source are exchanged, or when ions from the target enter the ion channel, parts of the ion channel will be filled with ions of different mobility. Thus different parts of the ion channel will have different conductivities, and the potential under the delivery point can no longer be assumed to be halfway between V_S and V_W . This makes it difficult to predict the exact potentials that result in reverse and forward bias.

The second version of fast OEIPs have a *control electrode*, CE, under the delivery point (Figure 6.6b) to enable better control of the potential across the BM-outlet. Delivery with this device architecture is not exclusively controlled by adjusting the potential of the electrolytes, which has been the case for previous OEIPs and related devices. Instead, changing the potential of the control electrode switches on the delivery. This makes it possible to build devices where the potentials of

Figure 6.6: In the fast OEIPs, ions are first transported from a source to a waste electrolyte to locate the ions close to the release site in the target electrolyte. To switch on delivery, a source - target current is run. (a) shows the first generation fast ion pumps, and (b) shows the second generation fast ion pumps that include a control electrode under the release site.

the electrolytes are kept constant, and the delivery from several release sites are controlled by their respective control electrode, as described in section 6.4.

6.4 Addressable rechargeable ion delivery array

As suggested above, the device structure depicted in Figure 6.6 b can be used to build arrays with several individually controlled delivery sites, which we did in the work leading to paper E. Figure 6.8 shows a photograph of such an array consisting of six parallel ion channels, where the control electrodes placed at each delivery site make individual addressing of these sites possible. The potential profile in Figure 6.9 explains how some of the delivery sites can be off (V_{CE} below V_T) while others are on (V_{CE} above V_T).

Figure 6.7: Current rectification through a CEM (PSSA-co-MA) fast ion pump with an AEM (polyphosphonium) under a $400\ \mu\text{m}^2$ outlet. The potential V_S was applied to the source relative to the target, with a scan rate of $25\ \text{mVs}^{-1}$. The arrows indicate the direction of the scan.

Figure 6.8: An addressable rechargeable ion delivery array with six parallel ion channels (highlighted in blue) connecting the three electrolytes. There are six $20\ \mu\text{m} \cdot 20\ \mu\text{m}$ release sites separated by $200\ \mu\text{m}$ in the center of the target electrolyte. Photograph by Thor Balkehed, Linköping University.

Figure 6.9: The lower figure shows the electrical potential experienced by a cation along the path in the upper figure. The potentials of the source, target and waste electrolytes, V_S , V_T , and V_W , are fixed, and set so that the potential of the PEDOT:PSS is lower than V_T unless addressed. This prevents diffusion of cations to the target. To switch on the delivery, the potential of the PEDOT:PSS control electrode is raised above V_T , causing the cation-migration to the target electrolyte.

Fabrication and characterization

The devices presented in the previous chapter all start with an idea. Based on the idea, the devices are sketched out and fabrication protocols are designed. Then, devices can be fabricated in the laboratory and tested, or characterized. Typically, this is an iterative process, where parts of the fabrication process and the design need to be changed in order to achieve devices with the desired characteristics. This chapter provides an overview of these fabrication processes and characterization methods.

7.1 Fabrication

All devices presented in the papers were made by adding and selectively removing thin films of different materials using microfabrication techniques. The techniques used involve spin coating, metal evaporation, photolithography, reactive ion etching and lift-off. Since we make micrometer-sized features, and 100 - 1000 nanometer-thin films, the fabrication processes are sensitive to dust and other particles. Therefore, most of the fabrication is done in a cleanroom where the amount of particles per volume is controlled and kept under a certain limit. This section provides a brief description of the fabrication methods.

7.1.1 Deposition of materials

Preparing the substrate

The first step in the fabrication of a device is to clean and prepare the substrate onto which the device will be built. We generally clean glass substrates by man-

ual scrubbing and ultrasonication in acetone, followed by rinsing in isopropanol and water to remove particles. Then, organic compounds are removed by a UV ozone cleaning step, which also activates the surface. Glass contains Si-O-H groups on the surfaces, and by applying a silane coupling agent, which is a compound that can bind both to inorganic and organic compounds, a link can be created between the glass and the polymer to be deposited. We typically use 3-glycidoxypyrpyl trimethoxysilane, GOPS, that forms silanol bonds to the glass and has epoxy groups that can react with the polymer.

Spin coating

After the substrate has been prepared, we start depositing material onto it. The main technique we use to deposit polymeric thin films from liquid solution onto planar substrates is spin coating. In spin coating, the substrate is first fixated onto a vacuum chuck. Then, the liquid is applied onto the substrate, which is rotated at a high speed (typically 1000 to 6000 rpm), which spreads the liquid over the substrate while the solvent starts evaporating. Films can be formed with thicknesses ranging from a few nm to hundreds of μm with this method with a good reproducibility. In general, increased concentration and viscosity of the solution and decreased rotational speed of the spin coater leads to thicker films. To obtain even films, the solution must wet the substrate and spread well on the surface.

Thermal evaporation

Thin films of metals can be deposited by thermal evaporation, in which a solid piece of metal is heated under vacuum. The metal atoms evaporate and spread onto a substrate (and to the whole evaporation chamber), where they condense to form a thin film.

7.1.2 Photolithography

When a film has been formed on a substrate, the film can be selectively removed, or patterned, so that the desired geometries of a device are obtained. Photolithography is a method to produce such patterns of thin films. In photolithography, a *photoresist*, which is a light-sensitive polymer, is used to transfer a pattern from a *photomask* to a substrate. Typically, the photoresist is applied by spin coating, and irradiated with UV light through the mask. The mask consists of opaque chromium patterns on a transparent glass, so that only the film under the transparent parts of the mask gets exposed (Figure 7.1 and 7.2). In a positive photoresist, the exposure initiates chemical reactions that render the photoresist soluble in a *photoresist developer*, and in a negative photoresist,

the exposure instead induces cross-linking of the photoresist, so that the exposed parts become insoluble in a developer. After exposure, the substrate is immersed in the developer solution, where parts of the resist are dissolved and the pattern of the mask appears.

If a material was deposited under the photoresist, the pattern can be transferred to that material by etching (Figure 7.1). Alternatively, a material can be deposited on top of the photoresist and the pattern can be formed by lift-off (Figure 7.2) (See section 7.1.4 and 7.1.3). After the pattern has been transferred to the material, remaining photoresist is usually removed, but in some cases the photoresist can remain and become a part of the device. SU-8 is a negative photoresist that is usually not removed. In OEIP devices SU-8 is often used as an insulating layer to encapsulate parts of the devices. Different formulations of SU-8 can be used to create various film thicknesses; from below a micrometer to a few hundred micrometers. SU-8 is also known for its ability to form structures with high thickness:width aspect ratios [21].

The resolution in photolithography is defined by the minimum attainable size features and gaps between features. It depends on the thickness of the photoresist and the wavelength of the UV light, and is typically 1 - 2 μm [28].

To produce a device with several layers of patterned materials, the procedure of material deposition, patterning with photolithography, and selective removal is iterated with different materials and patterns. As an example, the fabrication of the addressable fast delivery array presented in paper E is illustrated in Figure 7.3. To position the different material layers correctly with respect to each other, the substrate must be correctly aligned with the mask for each exposure. This is facilitated by special *alignment marks* on the masks, outside the relevant pattern. The uncertainty in the alignment of different layers limits the resolution of a device containing several photolithographically patterned layers.

7.1.3 Dry etching

Etching transfers the photolithographic pattern from the photoresist to the material underneath. There are two classes of etching; wet etching and dry etching, also referred to as plasma etching. In wet etching a liquid etchant attacks the substrate and a soluble product is formed, while in dry etching a gaseous etchant attacks the substrate to form a volatile product.

Reactive Ion Etching, RIE, which is a form of dry etching, is used in the fabrication of OEIPs to selectively remove the IEM materials. Dry etching is performed in a vacuum chamber where reactive gases are excited by radio frequency electromagnetic fields applied between a top and a bottom metal electrode. The substrate to be etched is placed on the bottom electrode, and reactive gases are introduced into the chamber through the top electrode. Ionic

Figure 7.1: A material to be patterned is deposited as a thin film by for example spin coating. Next, a photoresist is deposited on top of the material, partially exposed by UV light through a mask, and developed. In the development, the photoresist that has been exposed to light is dissolved, while the unexposed photoresist remains (for a positive resist, the opposite is true for a negative resist). The substrate is then dry etched. The patterned photoresist protects portions of the material from being etched away in this step. After etching, remaining photoresist is typically removed, the substrate is cleaned, and the process can be repeated, with a new material and a new mask.

species get accelerated by the electromagnetic field, and positive ions bombard the electrode with the substrate to be etched. The electric field gives the etching directionality so that the substrate is mainly etched perpendicular to the electrode surface. Both chemical reactions and physical bombardment contribute to etching away material. Different gases are used for etching different materials, and to etch the polymers used in OEIP fabrication we typically use a mixture of CF_4 and O_2 . O_2 etches polymers, and CF_4 is added to increase the etch rate and to etch the silicon that is sometimes added to the polymers [67].

7.1.4 Lift-off

In lift-off, a photoresist is first patterned on a substrate, then a material is deposited on top of the resist. The substrate is then placed in a solvent that dissolves the resist but leaves the material intact. We used lift-off to pattern gold on glass, and lifted off the resist in acetone. Lift-off is facilitated by giving the photoresist a slight undercut profile, since this creates a gap between the metal to remain and the metal to be removed (Figure 7.2). Such undercut profile can be obtained by slightly overexposing a positive photoresist.

Figure 7.2: Metals can be patterned by a method called lift-off. A photoresist is first patterned to leave holes where the metal is to remain. Then, the metal is evaporated over the whole surface. Finally, the photoresist covered with metal is lifted-off in solution, leaving the metal where there is no photoresist underneath.

7.1.5 Photomask design

The fast delivery array, presented in paper E and described in Figure 6.6 b, was fabricated using spin coating, photolithography, lift-off and dry etching as described. A schematic overview of the fabrication is presented in Figure 7.3. To make these devices, a set of five different photomasks was needed. Although alignment marks are used to correctly position each mask relative to the substrate, the alignment can only be performed with a certain accuracy. Therefore, the error in alignment between layers must be taken into account when designing the masks. To account for the alignment error, we design the masks so that there is an overlap of a few micrometers between materials that should be in contact. This ensures no gaps occur between the materials. The overlap is illustrated in Figure 7.3, where there is an overlap of the polyanion and the gold (leftmost), and an overlap between the two layers of photoresist used to pattern the PEDOT:PSS and the polycation (center image).

7.1.6 Preparation of PSS-co-MA/PEG

The cation channel in previous OEIPs and the OEIP in paper A was obtained by chemically overoxidizing the PEDOT of poly(ethylene terephthalate) (PET) substrates precoated with a PEDOT:PSS formulation. The overoxidation, which is done by soaking the device in a sodium hypochlorite (NaClO) solution, breaks the conjugation bonds in PEDOT and makes it electronically insulating but leaves the PSS intact [94]. Thus an electronically insulating but cationically conducting material is formed.

To build OEIPs on glass, or on any other substrate, a new polyanion that

Figure 7.3: We fabricated the addressable fast delivery array by first patterning gold with lift-off (described in Figure 7.2) and the polyanion with dry etching (described in Figure 7.1). Then we deposited and patterned another layer of photoresist, deposited PEDOT:PSS and the polycation, and deposited and patterned another layer photoresist. After this, the substrate was etched, and remaining photoresist was removed. Finally, we deposited and patterned the encapsulation material SU-8.

could be deposited from solution was needed. The PSS-co-polymer, poly(4-styrenesulfonic acid-co-maleic acid) (PSS-co-MA), where the maleic acid groups can form ester bonds to a polyalcohol, was found to give stable films that withstood the fabrication processes well. We used polyethylene glycol (PEG) for cross-linking (Figure 7.4). PSS-co-MA was bought as a sodium salt, and sodium was exchanged for protons using dialysis in HCl(aq), to obtain the proton form needed for cross-linking.

Figure 7.4: PEG is used to cross-link PSSA-co-MA. Cross-linking is thought to occur due to the formation of ester bonds. This material is used as the CEM cation channel in OEIPs.

The polycations qPVBC and polyphosphonium were prepared as described in [96] and [30], respectively.

7.1.7 Fabrication challenges

Our ion transporting polymers need to be hydrophilic and able to contain a high amount of water to allow good ionic conductivities. This typically implies that the polymer films need to swell when exposed to water. However, swelling during fabrication can cause poor adhesion between different materials.

The main challenge I came across during fabrication was adhesion between different materials, especially adhesion to the glass substrate, and stability of the polymers in the fabrication process. Often, the polymer films delaminated or even dissolved, either during photoresist development, or when remaining photoresist was stripped in a remover after the etching step. Sometimes, the polymers instead reacted with the photoresists.

To solve the adhesion problem to glass, we first carefully cleaned the surface. Then the surface was activated using UV-ozone treatment or oxygen plasma etch, to expose hydroxyl groups that could then react with the adhesion promoter 3-glycidioxypropyltrimethoxysilane (GOPS), that was applied as an adhesion layer in the next step. When this was not enough, we mixed in GOPS with the polymers, although the addition of GOPS decreases the ionic conductivity [88].

To protect the polymers from reacting with photoresists and from damage from developer, we spin coated a thin layer of the polymer poly(methyl methacrylate), PMMA, between the polymer and the photoresist. After dry etching, the PMMA is removed along with remaining photoresist in acetone.

The main photoresists we use are from the Microposit S1800 G2 series. These resists have been developed for standard microfabrication on silicon wafers, with metals and semiconductors, not for fabrication of organic materials. Unfortunately organic materials are often soluble in the alkaline developers and sometimes in the solvent of the photoresists. An alternative to the use of protective layers would be to use another type of photoresists that are *orthogonal* to, that is not miscible with organic materials. Fluorinated photoresist have been proposed as orthogonal to organic materials [104], and may facilitate patterning of polymers. In some cases, a "peel-off" patterning method, similar in principle to lift-off, can be used. We used such peel-off in the fabrication in paper C, where the recording PEDOT:PSS electrodes were defined by peeling off an underlying layer of parylene C. By using peel-off, contamination of the electrode surface by e.g. photoresists is prevented.

7.2 Characterization

When a device has been fabricated, it can be examined by various method. A first inspection can be to study the different parts of the device using light microscopy. This inspection can for example reveal cracks in the encapsulation, swelling or partial delamination of the polymers, dust or particles, or errors in alignment. Next, the device is electrically characterized to investigate whether it is functioning properly.

7.2.1 Electrical characterization

The ion channels in OEIPs should behave as resistors, that is, they should have a linear current-voltage behaviour. Therefore, the first test we do in terms of electrical characterization of an OEIP is to check that we obtain a stable current for an applied potential difference between the source and target, and that the currents scales with the applied potential. The OEIP resistance should also depend on the ion that is transported, and be higher for less mobile ions. Thus, we verify that the current increases if the ion in the source is exchanged to an ion with higher mobility. Also, to verify that counter-ions are the major charge carriers, and that co-ions do not contribute substantially to the current, the co-ions in the target can be varied and the current response can be studied. If the current varies as the co-ions are exchanged, it is an indication of that co-ions contribute to the current, and that the OEIP does not function properly. This "ion pair method" was developed further and is described by T. Arbring Sjöström in paper B.

Emf-method

In paper B we also investigated an alternative method to estimate transport numbers and permselectivity in OEIP devices. We adapted the emf-method, described in section 3.4, which is a characterization method for membranes. The IEM in our devices can be regarded as thick (μm to cm) membranes with small cross sectional areas (typically tens of μm^2). In our emf-method, KCl (aq) electrolytes of different concentrations are placed on opposite sides of an OEIP. Ag/AgCl (KCl) electrodes are then immersed in the electrolytes, and the open circuit potential that results from the increased transport number of K^+ or Cl^- in the channel, is measured. The set-up is shown in Figure 7.5.

7.2.2 Chemical delivery characterization

To verify that the encapsulation has a good adhesion to the substrate, and that ions are released exclusively at the intended outlets, we typically load protons in the source electrolyte and pH indicator in the other electrolytes (paper A and

Figure 7.5: The set-up for emf-measurements include an OEIP with multiple 0.5 mm long parallel ion channels, KCl electrolytes of different concentrations and Ag/AgCl (KCl) reference electrodes. The measured open-circuit potential E is related to the apparent transport number by equation 3.14.

paper E) and apply a voltage to induce delivery. This proton-pH experiment also gives an idea of the time delay of delivery, and the spatial spread at the outlet. Protons are much more mobile than other ions, however, therefore they appear faster at the outlet, and spread more once released, compared to other ions.

To quantify the amount of ions that are released, we collect samples, and analyze the ion concentration using for example a plate reader or mass spectrometry. The measured concentration can then be compared to the integrated current (eq. 6.1) to obtain the transport number of the ion intended for transport.

Concluding remarks

Within my thesis, I have described and reported steps towards using the OEIP technology for alleviating pain and for suppressing epileptic seizures. The OEIP technology has been advanced in many respects, in part by integrating the release sites with electrical sensors, by improving the release-speed to milliseconds, and by constructing chemical delivery circuits with several individually controllable release sites. This chapter provides a brief comparison of the potential of the work of this thesis to alternative technologies, and discusses future challenges and also possible future work.

8.1 Limitations of OEIP technology

The technology described in this thesis is based on the selective electrophoresis of cations or anions through charged polymeric ion channels. This limits the deliverable substances to charged compounds only.

Today, ions up to the size of a few hundred grams per mole have been successfully transported in the OEIP devices. To allow transport of larger compounds, new, more porous and open materials that enable molecules with larger cross-sections to selectively migrate through its solid bulk are needed. However, the permselectivity to cations or anions requires the polymeric membranes to possess a certain concentration of negative or positive charge, respectively. Increasing the pore size inevitably decreases the charge density, and it will therefore be a trade off between charge concentration and porosity, *i.e.* the volume of voids, in emerging materials.

8.2 Advantages of OEIP technology

Electronic control over the delivery of precise doses of chemical compounds to micrometer-sized locations without convection at high temporal resolution represent the ensemble of characteristics making the OEIP technology unique. In most other delivery techniques, the temporal resolution and dosage control are either far worse than with OEIPs, or chemicals are dissolved and delivered along with their aqueous solvent. Delivering a compound via fluidic techniques drastically increases the number of deliverable compounds, since any soluble compound may then be delivered. However, solution-based delivery techniques always implies the addition of a certain volume of delivered liquid, which may for example perturb the microenvironment, or increase the local pressure within or in proximity to the target tissue, something that may not be tolerated by the biological system. Also, many alternative methods include mechanical bulky constructs and moving parts, or require external pumps, whereas OEIPs have the advantage of being entirely controlled electronically by miniaturized solid-state systems (see section 1.4).

8.3 Future work

If the OEIPs and related devices are to be used for therapy via electronically controlled local release of chemical compounds, it is necessary to evaluate the stability and biocompatibility of the included materials of the devices. For instance, it is not straightforward how to properly encapsulate a hydrated polymer network through which ionic currents will pass for extended periods of time, and no long-term studies have been performed so far. Design-wise, I see two possible future strategies; one is to develop the OEIPs on substrates that are flexible, or even stretchable, that interface with the biological system in a conformal fashion. The second approach aims at using substrates that are needle- or fiber-like, which would enable delivery deep inside tissues and organs.

The OEIP technology can potentially also be further developed to become a tool for *in vitro* studies. Tissue slices or cultured cells can either be placed onto planar devices, or a pipette-like version of the OEIPs may be applied to the biological system. The planar devices may potentially include a matrix of release sites, or the sites can be distributed following a pattern or the anatomy of the targeted tissue or organ. This would then allow experiments where the concentration of a compound is varied over space and time. The pipette-like version would typically not allow several release sites, but it would allow for precise positioning using micromanipulators. Also, since it would be similar in shape to a pipette, and particularly to patch-pipettes used for electrophysiology

studies, it could represent a convenient tool for the users. This type of tool could, for instance, give information on the number of molecules needed to elicit a certain biological event.

Below two examples are presented and illustrated, suggesting important next steps in order to advance the OEIP technology, hopefully taking the technology closer to applications.

8.3.1 Fiber ion pumps

The OEIP devices reported in this thesis are all built on two-dimensional substrates. However, if the location of delivery should occur within a tissue, for example inside the brain, these 2D substrates are not suitable. This motivates the development of OEIPs on thin fibers or similar linear structures that can penetrate the tissue and thus deliver chemicals deep inside a biological system.

To this end, a first step towards the development of a fabrication process for fiber-based OEIPs was taken. In this process, the IEM material and the encapsulation materials are dip-coated on glass fibers. With this method, similar materials and protocols, as used for planar substrates and spin coating can be used. Specifically, 125 μm -diameter glass fibers were coated with the anion exchange membrane (AEM) material qPVBC and the silicon-based encapsulation material ACC15. A heat shrink tubing comprising the source electrode and electrolyte was attached. Then, the tip was cut open to form a circular release area through which ions can be delivered (Figure 8.1) (unpublished results). The materials could potentially be patterned by photolithography to give, for example, several release sites along the fiber. An alternative approach to dip-coating is to fill hollow fibers, capillaries, with polymeric materials.

8.3.2 Diode-functionality from a high aspect ratio hole

To limit the reverse current in the fast OEIPs, a diode-functionality was built into the release site by the addition of an AEM capping the CEM, thus forming a bipolar membrane (BM) diode. This allows a high delivery current, while reducing the leakage-preventing current under reverse bias. However, the BM may further restrict the number of transportable species, since the charged molecules need to pass through both the AEM and the CEM materials in series. As an example, we found that we cannot deliver the neurotransmitter GABA through such BM diode configurations. This is possibly due to the pH-dependent charge of GABA; GABA is only positively charged below a certain pH, and we cannot control the pH within the IEMs.

Another option to achieve the desired diode-effect is to construct a small high aspect ratio hole. Within such hole, a quasi-one dimensional diffusion gradient

Figure 8.1: OEIPs can be built on fiber supports by dip-coating a layer of AEM material and a layer of encapsulation material.

is created. Assuming that the concentration at the top of the hole is constant, and equivalent to that of the electrolyte concentration, that the CEM at the bottom of the hole is perfectly permselective, and that concentration at a certain distance to the membrane is the same within the hole, the current at which the concentration will reach zero at the bottom of the hole can be calculated from the one-dimensional Nernst-Planck equation. This will then result in a limiting current, (section 3.3.3) at reverse potential bias.

The limiting current will depend on the diffusion coefficient D of the ion, the depth and the area of the hole (d and A), and the electrolyte concentration c , and is given by:

$$i_{lim} = -\frac{2DcFA}{d} \quad (8.1)$$

where F is the Faraday number with the value $96\,485\text{ C} \cdot \text{mol}^{-1}$. As an example, the limiting current will be approx. 4 nA for a $1\text{ }\mu\text{m}^2$ hole with $10\text{ }\mu\text{m}$ sidewalls and 0.1 M KCl electrolyte.

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