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Organic Bioelectronics for Neurotransmitter Release at the Speed of Life

Theresia Arbring Sjöström

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NEUROTRANSMITTER RELEASE
AT THE SPEED OF LIFE

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Faculty of Science and Engineering
Department of Science and Technology
Norrköping, 2020

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Theresia Arbring Sjöström

During the course of the research underlying this thesis, Theresia Arbring Sjöström was enrolled in Forum Scientium, a multidisciplinary doctoral program at Linköping University, Sweden.

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To my amazing children

Abstract

The signaling dynamics in neuronal networks includes processes ranging from lifelong neuromodulation to direct synaptic neurotransmission. In chemical synapses, the time delay it takes to pass a signal from one neuron to the next lasts for less than a millisecond. [1] At the post-synaptic neuron, further signaling is either up- or down-regulated, dependent on the specific neurotransmitter and receptor. While this up- and down-regulation of signals usually runs perfectly well and enables complex performance, even a minor dysfunction of this signaling system can cause major complications, in the shape of neurological disorders. The field of organic bioelectronics has the ability to interface neurons with high spatiotemporal recording and stimulation techniques. Local chemical stimulation, *i.e.* local release of neurotransmitters, enables the possibility of artificially altering the chemical environment in dysfunctional signaling pathways to regain or restore neural function. To successfully interface the biological nervous system with electronics, a range of demands must be met. Organic bioelectronic techniques and materials are capable of reaching the demands on the biological as well as the electronic side of the interface. These demands span from high performance biocompatible materials, to miniaturized and specific device architectures, and high dose control on demand within milliseconds.

The content of this thesis is a continuation of the development of organic bioelectronic devices for neurotransmitter delivery. Organic materials are utilized to electrically control the dose of charged neurotransmitters by translating electric charge into controlled artificial release. The first part of the thesis, Papers 1 and 2, includes further development of the resistor-type release device called the organic electronic ion pump. This part includes material evaluation, microfluidic incorporation, and device design considerations. The aim for the second part of this thesis, Papers 3 and 4, is to enhance temporal performance, *i.e.* reduce the delay between electrical signal and neurotransmitter delivery to corresponding delay in biological neural signaling, while retaining tight dosage control. Diffusion of neurotransmitters between nerve cells is a slow process, but since it is restricted to short distances, the total time delay is short. In our organic bioelectronic devices, several orders of magnitude in speed can be gained by switching from lateral to vertical delivery geometries. This is realized by two different types of vertical diodes combined with a lateral preload and waste configuration. The vertical diode assembly was further expanded with a control electrode that enables individual addressing in each of several combined release sites. These integrated circuits allow for release of neurotransmitters with high on/off release ratios, approaching delivery times on par with biological neurotransmission.

Populärvetenskaplig sammenfattning

Signaldynamiken i neuronala nätverk innefattar processer som sträcker sig från livslång neuromodulering till direkt synaptisk neurotransmission. I kemiska synapser tar det inte ens en millisekund att skicka en signal från en neuron till nästa. [1] Vid den postsynaptiska nervcellen, blir signaleringen antingen upp- eller nedreglerad, beroende på specifik neurotransmittor och receptor. Samtidigt som denna upp- och nedreglering av signaler vanligtvis fungerar perfekt och möjliggör komplexa prestationer, kan även en liten obalans i detta signalsystem skapa stora komplikationer, i form av neurologiska sjukdomar. Området för organisk bioelektronik har förmågan att koppla samman nervceller och elektronik för att monitorera och stimulera nervceller med hög precision. Lokal kemisk stimulering, *dvs.* lokal frisättning av neurotransmittorer, möjliggör artificiell förändring av den kemiska miljön i dysfunktionella signalvägar för att återfå eller återställa nervfunktionen. För att framgångsrikt kunna koppla samman det biologiska nervsystemet med elektronik, måste en rad krav uppfyllas. Dessa krav sträcker sig från högpresterande biokompatibla material, till miniaturiserad och specifik komponentdesign, samtidigt som leverans av neurotransmittorer ska ske både snabbt och med hög doskontroll. Organiska bioelektroniska tekniker och material kan uppfylla dessa krav från både den biologiska och elektroniska sidan av gränssnittet.

Innehållet i denna avhandling är en fortsättning på framtagningen av organiska bioelektroniska enheter för lokal leverans av neurotransmittorer. Organiska material används för att elektriskt kontrollera dosen av laddade neurotransmittorer, genom att översätta elektrisk laddning till kontrollerad artificiell frisättning. Den första delen innefattar vidareutveckling av den resistorbaserade leveranskomponenten som kallas organisk elektronisk jonpump. Detta inkluderar utvärdering av organiska material, integrering av mikrofluidik och avväganden angående komponent- och enhetsdesign. Syftet med den andra delen av denna avhandling är att förbättra den temporala prestandan, *dvs.* minska fördröjningen mellan elektrisk signal och frisättning av neurotransmittorer till motsvarande fördröjning i biologisk neural signalering, med bibehållen stram doskontroll. Transport av neurotransmittorer mellan nervceller är i sig en långsam process, men eftersom det är begränsat till korta avstånd blir den totala tiden kort. I våra bioelektroniska leveransenheter kan hastigheten minskas med flera storleksordningar genom att växla från lateral till vertikal leverans. Detta realiserades genom två olika typer av vertikala diodanordningar i kombination med en lateral transport av neurotransmittorer för uppladdning och utflöde. Denna vertikala diodsammansättning utvidgades vidare med en styrelektrod som möjliggör individuell adressering i vart och ett av flera kombinerade frisättningspunkter. Dessa integrerade kretsar möjliggör frisättning av neurotransmittorer med hög ratio mellan på och av, som närmar sig den leveranstid som är i nivå med biologisk neurotransmission.

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Introduction

Our versatile brains operate over a wide range of spatial and temporal resolutions where even the smallest and fastest neuronal signals contribute to who we are and how we perceive and interact with the world. The ability and responsibility to synchronize the orchestration of signals are placed on the cells and networks involved. This complex signaling pathways does, however, come with a great risk of complex disorders: the leading cause of disability and second largest contributor to deaths worldwide is attributed to neurological disorders. To this group belongs disorders such as stroke, brain cancers, spinal cord injury, Alzheimer's and Parkinson's disease, epilepsy, and motor neuron diseases. Over the last decades, the burden from these diseases has increased, and with an aging world population, this trend seems likely to persist. [2] Common for these disorders is dysfunctions or disruption of signal pathways within the nervous system and/or to other organs. Even though disruptions or dysfunctions in these pathways are challenging to restore or substitute, it is a major target for the field of bioelectronics. Interfacing the body with electronics has successfully been done with pacemakers and deep brain stimulators, increasing the quality of life for patients around the world. Restoring lost functions such as motion, vision, or memory is the aim for neuroprosthetic devices. To date, neuroprosthetics can, for example, connect brain electrodes to wheelchairs and robotic arms [3]. Additionally, restoring the ability to walk has successfully been performed by a brain-spinal interface in rhesus monkeys [4] and via epidural electrical stimulation for human patients suffering from spinal cord injury. [5]

Interfacing neurons with electronics

A successful interface between neurons and engineered devices are heavily dependent on a good physical and mechanical match between the devices and the neural tissue. The measure of elasticity, Young's modulus (measured in Pa), shows that traditional inorganic electronic materials remains far less elastic than the spinal cord and brain (GPa compared to kPa). [6] A better match from this point of view is organic materials, approaching the lower numbers in Young's modulus. The discovery of electrically conducting polymers led to a Nobel Prize in Chemistry in 2000, and more importantly for the work presented in this thesis, enabled a new organic bioelectronic interface. [7, 8] Another important aspect of the interface between electronics and neurons is the different charge carriers. The tradition within bioelectronics has been to interface cells and tissue with electrodes that polarize the cells directly by applied potentials. Even though this can be performed very locally and in a controlled manner, an even more seamless interface would be to mimic the signaling as it occurs naturally within the biological system. [9, 10] The term "animal electricity" had been around since Galvani's experiments during the 18th century. [11] This concept is still valid in the sense that

neuronal action potentials are referred to as electrical transmission, even though the charge carriers for these action potentials are ions rather than electrons. And while action potentials occur within nerve cells, the connection and transmission between different cells remained a mystery for many years to come. It was more than a century later, around 1900, that the term "synapse" was introduced and speculations about chemical transmission started. Even after 1936, when the Nobel Prize for the discovery of neurotransmitters was awarded, the dispute over how neurons communicate continued. The most widespread argument against chemical transmission was the speed. The general conception was that only electrical transmission was fast enough to activate skeletal muscles, and chemical transmission in brain synapses was both unthinkable and hard to study. [12] Today we know that signal transmission between nerve cells are conducted with both electrical and chemical synapses. However, the vast majority of synapses are chemical and the different chemicals acting as neurotransmitters in these chemical synapses number in the hundreds. [13] The neurotransmitters that appear in charged form are especially important in the context of organic bioelectronics. Since these ions can be manipulated by applied potentials, they provide the key that enables electrically controlled artificial release of neurotransmitters.

Spatiotemporal complexity

So even though we now know, to some extent, how neurons communicate, there is a lot left to learn about how they act together on both the smaller as well as the larger scale. The conceptional view of neuronal signaling networks are based on linear pathways through tangled networks. However, these networks allow interconnections and crosstalk between different pathways in the volumetric space in our bodies. Thus, the number of possible cascades and downstream processes increases exponentially from the amount of cells involved. Huge efforts have been made to map these networks in the volumetric space, over levels ranging from molecules and synapses, to neurons, neural circuits, and large-scale brain systems. [14, 15] The various size domains of these neural components and systems can be seen in Figure 1.

Figure 1: Neural system ranges over many orders of magnitude in the spatial scale. The smallest units in this system involve the chemical transmission in synapses, that occurs with transmitting ions and molecules in the scale of Ångströms to nanometers. [16, 17, 18]

High spatial resolution of signaling networks is not enough to provide a complete understanding. How these networks change over time, i.e. the time resolution, adds an extra dimension to the complexity. The different spatial units and

domains of neural systems operate over different time scales. [15, 19] A few examples in this spatiotemporal map can be seen in Figure 2. Generally, the fastest processes in time involves the smallest units. An example of that is the diffusional transport of molecules. The scientist that argued against chemical transmission in the 1950s was not wrong in the fact that diffusion is a slow process. But they were wrong about the distances. What they did not realize at the time is that the characteristic distances in the synapse are not on the scale of millimeters [12], but in the range of nanometers. Today we know that chemical synaptic transmission has a duration in the range of milliseconds, and that diffusion does not even account for the majority of the total synaptic delay. [1]

Figure 2: A spatiotemporal map of biological signaling processes (yellow) and today's stimulation and recording techniques (black). [16, 17, 18] As technology evolves, transitions of stimulation and recording techniques are moving further towards the lower left corner. Electrical, optical, and chemical recording techniques can monitor single cells, or parts of cells, with a sub-microsecond time resolution, while the stimulation techniques deviate more. In terms of temporal resolution, local chemical stimulation lags behind compared to both electrical and optical stimulation techniques. [18]

Bioelectronic devices can contribute to the understanding of this complex network by stimulating and recording biological events. And as the technologies evolve, the temporal and spatial resolution of the data is expanding, reaching towards the faster and smaller corner of Figure 2. The same path is followed by the technologies providing optical, electrical, and chemical recording and stimulation. [20, 18] Locally at the synapse, there is still a lot to learn both about the normal mechanisms of neurotransmitter release, as well as the dysfunctional processes of release. [21] To be able to contribute, it is up to the field of organic bioelectronics to strive to match this spatiotemporal complexity of neuronal signaling. And while doing so, provide an interface as seamless and gentle as possible.

Scope and outline of this thesis

Bioelectronic, or iontronic, devices for neurotransmitter release have been around for over a decade. When I started at the Laboratory of Organic Electronics, the foundation of the technology was already developed and was expanding quickly. However, the portfolio of ion conducting materials compatible with our micro-fabrication techniques was very limited. The aim for the first project was to complement the available material for cation conduction with a solution-based alternative. The result from this was a cross-linked polyelectrolyte processable on glass substrates, reported in Paper 1.

Another challenge was to transfer the iontronic technology from surfaces to free standing devices, and a few different strategies were tested. [22, 23, 24] Our approach, with the result in Paper 2, was to use capillary fibers and manufacture an iontronic tip at the end of that fiber. The drug reservoir was microfluidic in this design, and the device was therefore named the *hybrid microfluidic iontronic probe*. The coupling between microfluidic transport and iontronic transport in small compartments is non-trivial. Here, finite element modeling was a very convenient tool to unravel many of the possibilities and limitations with this design.

The final two papers had the mission to push the temporal performance for on demand delivery, aiming for synaptic speed dynamics. The result was two different vertical release diodes that enabled release of diffusing neurotransmitters across very short distances. This was accomplished by separating the loading dynamics and the release dynamics in two different time and length scales. The slow pre-loading of neurotransmitters took place in the lateral direction over millimeters to centimeters. The vertical diode prevented release of neurotransmitters from a local storage just micrometers from the interface. On demand, the neurotransmitters could be released by a switch of potentials. The *vertical bipolar membrane diode* was presented and evaluated in Paper 3. Several of these vertical diodes were also combined into a *chemical delivery array*, with individual addressing at each release point. In Paper 4, the vertical *polarization diode* is reported. Theoretical modeling of this device helped us investigate the possibilities of pushing temporal and spatial performance even further for local artificial release of neurotransmitters.

The first part of this thesis describes the background of the scientific work presented in the papers, followed by the included publications. Chapter 1 provides a brief overview of neural network signaling and different strategies developed for artificial release of neurotransmitters. The physics of charge transfer within these devices and circuits, including how ions can and cannot be manipulated is described in detail in Chapter 2. The materials and fabrication techniques needed to realize these devices are presented in Chapter 3. Chapter 4 covers considerations of device design and includes a brief introduction of the devices developed in the work of this thesis. The electrical, chemical, and theoretical evaluation techniques used to evaluate these devices are described in Chapter 5. The final, Chapter 6, includes some comments, thoughts, and future perspectives and concludes the book I write today. I am humble to the fact that this is soon out of date, and I sincerely hope we get to update Figure 2 several times in the years to come.

List of publications

1 **Cross-Linked Polyelectrolyte for Improved Selectivity and Processability of Iontronic Systems**

Theresia Arbring Sjöström, Amanda Jonsson, Erik Gabrielsson, Loïg Kergoat, Klas Tybrandt, Magnus Berggren, and Daniel T. Simon

ACS Applied Materials & Interfaces 9, 36, 30247–30252 (2017)

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2 **Design and Operation of Hybrid Microfluidic Iontronic Probes for Regulated Drug Delivery**

Theresia Arbring Sjöström, Anton Ivanov, Christophe Bernard, Klas Tybrandt, David J. Poxson, Daniel T. Simon, and Magnus Berggren

Advanced Materials Technologies, 20010060 (2020)

DOI: 10.1002/admt.202001006

3 **Chemical Delivery Array with Millisecond Neurotransmitter Release**

Amanda Jonsson*, Theresia Arbring Sjöström*, Klas Tybrandt, Magnus Berggren, and Daniel T. Simon

Science Advances 2, e1601340 (2016)

DOI: 10.1126/sciadv.1601340

*These authors contributed equally to this work

4 **Miniaturized Ionic Polarization Diodes for Neurotransmitter Release at Synaptic Speeds**

Theresia Arbring Sjöström, Amanda Jonsson, Erik O. Gabrielsson, Magnus Berggren, Daniel T. Simon, and Klas Tybrandt

Advanced Materials Technologies, 1900750 (2019)

DOI: 10.1002/admt.201900750

Related work

Patent

EP3429660A1 ION CONDUCTIVE DEVICE WITH CONTROLLED DELIVERY ELECTRODE

Amanda Jonsson, Theresia Arbring Sjöström, Daniel T. Simon and Magnus Berggren
2016-03-15

A Decade of Iontronic Delivery Devices

Theresia Arbring Sjöström, Magnus Berggren, Erik O. Gabrielsson, Per Janson, David J. Poxson, Maria Seitanidou and Daniel T. Simon*

Advanced Materials Technologies 3, 1700360 (2018), DOI: 10.1002/admt.201700360

Controlling Epileptiform Activity with Organic Electronic Ion Pumps

Adam Williamson, Jonathan Rivnay, Loïg Kergoat, Amanda Jonsson, Sahika Inal, Ilke Uguz, Marc Ferro, Anton Ivanov, Theresia Arbring Sjöström, Daniel T. Simon, Magnus Berggren, George G. Malliaras* and Christophe Bernard*

Advanced Materials 27, 20 (2015), DOI: 10.1002/adma.201500482

pH Dependence of γ -Aminobutyric Acid Iontronic Transport

Maria Seitanidou, Juan Felipe Franco-Gonzalez, Theresia Arbring Sjöström, Igor Zozoulenko, Magnus Berggren, and Daniel T. Simon*

The Journal of Physical Chemistry B 121, 30 (2017), DOI: 10.1021/acs.jpcc.7b05218

Wireless Organic Electronic Ion Pumps Driven by Photovoltaics

Marie Jakešová, Theresia Arbring Sjöström, Vedran Đerek, David Poxson, Magnus Berggren, Eric Daniel Głowacki and Daniel T. Simon

npj Flexible Electronics 3, 14 (2019), DOI: 10.1038/s41528-019-0060-6

Background

1

From natural to artificial neural signaling

Signaling within and between the cells in the nervous system is based on complex and well-regulated electrical and chemical signaling pathways. Direct signaling between neurons is illustrated in Figure 1.1. Electrical signals, *i.e.* action potentials travel at velocities of up to 150 m/s over long distances. [13] When the action potential reaches an axon terminal in the pre-synaptic neuron, the action potential is transferred into a chemical signal, carried by neurotransmitters.

Figure 1.1: A simplified view of neural connections, where the pre-synaptic cell sends a chemical signal that is received by a post-synaptic dendrite. If the post-synaptic cell sends the signal further, it can do so via the electrical signaling known as action potentials in the axon.

The origin of these electrical and chemical signals will be described briefly in the first part of this chapter, zooming in on the small and fast units found in the neuronal networks responsible for synaptic transmission. The second part of this chapter describes the other side of the interface between neurons and electronics. Different techniques for recording and stimulation are described, mainly focusing on local chemical stimulation techniques.

1.1 Electrical and chemical neural signaling

The systems of neural networks are divided in two subsystems, where the brain and spinal cord belong to the central nervous system (CNS) that communicates with the rest of the body through the peripheral nervous system (PNS). The nervous systems are primarily based on two types of cells, neurons and glia cells. While neurons are capable of electric signaling, the glia cells are not. The glia cells greatly outnumber the neurons, but less is known about their function and purpose. It is nevertheless evident that glia cells interact closely with neurons to provide complex brain functions. [13] The neurons and glia cells are surrounded by extracellular space. The extracellular space, that in the brain occupies approximately 20% of the volume, is also essential for neuronal function and signaling. This space constitutes a source reservoir for the ions used during action potential propagation, and provides pathways for chemical signaling transmission between cells. [13, 25] Neurons are capable of transmitting electrical signals due to their polarizable cell membrane. The cell membrane contains protein-based pores called ion channels that are permeable to one or more ions and are selectively permeable to charge, *i.e* they are semi-permeable. Ions that are responsible for the electrical signaling are sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), and chloride (Cl^-).

Figure 1.2: The extracellular and intracellular space are separated by a cell membrane. The ion channels and ion pumps in the cell membrane are specialized protein structures used for passive and active transport of ions.

The membrane potential $\nabla\phi_{cell}$ is defined as the difference in potential between the inside ϕ^{intra} and the outside ϕ^{extra} of the cell membrane: [19]

$$\nabla\phi_{cell} = \phi^{intra} - \phi^{extra} \quad (1.1)$$

Neurons in their resting state have a membrane potential deviating from zero that balances a concentration difference between the inside and outside of the cell membrane. While the ion channels allow for transport of ions with concentration and electrical gradients, ion pumps in the cell membranes transport ions “uphill” the electrochemical gradient to maintain the concentration difference. [26] In this equilibrium state, no net current flows over the membrane.

The equilibrium potential ($\nabla\phi_{eq}$) is defined by the Nernst equation: [19]

$$\nabla\phi_{eq} = \frac{RT}{z_i F} \ln \frac{c_i^{extra}}{c_i^{intra}} \quad (1.2)$$

where z is the charge and c the concentration of the ion i , F is Faraday's constant, R is the universal gas constant and T is the temperature. ¹This membrane equilibrium potential is not only important for semi-permeable cell membranes, but also for semi-permeable ion exchange membranes, discussed in detail in Chapter 2. In neural networks, the electrical signaling is based on local and sudden spikes in the membrane potential. The membrane suddenly deviates from the equilibrium potential, as the different ion channels in the membrane change their permeability for the different ionic species and allows for transmembrane ionic currents. Thus the membrane potential depends on the concentration and permeability (P_i) for K^+ , Na^+ and Cl^- , as described in the Goldman equation: [13]

$$\nabla\phi_{cell} = \frac{RT}{z_i F} \ln \frac{P_K c_K^{extra} + P_{Na} c_{Na}^{extra} + P_{Cl} c_{Cl}^{extra}}{P_K c_K^{intra} + P_{Na} c_{Na}^{intra} + P_{Cl} c_{Cl}^{intra}} \quad (1.3)$$

During this spike, the membrane potential changes roughly from ≈ -65 mV to $\approx +40$ mV. [13] The spikes propagate further as new voltage-gated ion channels are opened. The chemical signaling within the neural system is carried by transmitting molecules that are responsible for both short-term and long-term plasticity of cells. [13, 19] Short-term plasticity refers to changes in synaptic strength over milliseconds to seconds, while long-term plasticity refers to modulations maintained over time, *e.g.* learning and memories. [19] Short-term signaling is carried by neurotransmitters. Over longer distances and longer time periods, the transmitting molecules are referred to as neuromodulators rather than neurotransmitters. [19, 15]

1.1.1 Synaptic transmission

In chemical synapses, synaptic transmission conveys signals from one neuron to another, but also from a neuron to a muscle or gland cell. There are two types of synapses, the electrical synapse and the chemical synapse. Electrical synapses are relatively rare but are found in instances where speed is most critical and where a high degree of electrical synchronization is needed, *e.g.* in the brain as well as in the heart. [27] In electrical synapses, seen in Figure 1.3, the pre-synaptic and post-synaptic cells are virtually connected by several connexons that forms hydrophilic channels, and this connection is referred to as a gap junction. These channels allow for direct passive transmission between the two cells. [27] This direct connection between the two cells' cytoplasm enables action potentials to be directly transmitted from one cell to another, meaning essentially no time delay between for transmission from the presynaptic to the postsynaptic cell. The gap junction also allows for direct transfer of larger molecules. In networks of glia cells, large signaling systems are formed by gap junctions by connecting the cytoplasm of many cells. [13]

¹Constant, variables and their units are found in the List of Symbols (p. 67)

Figure 1.3: The electrical synapse is formed by the connexons in a gap junction that form hydrophilic pores that directly connects of the cell membrane of two cells. This connection allows for direct transfer of signaling molecules and action potentials.

Compared to the connected gap junctions where the gap is virtually lacking, the chemical synapse is separated with a space known as the synaptic cleft, and the signal transmission over a chemical synapse exhibits a characteristic synaptic delay. [13] Signal transmission over a chemical synapse is governed by the incoming action potential that triggers the influx of Ca^{2+} through voltage-gated calcium channels. The increased level of Ca^{2+} triggers the synaptic release of neurotransmitters. Neurotransmitters are stored in vesicles containing a limited number of neurotransmitters. The vesicles for small-molecule neurotransmitters has a diameter of approximately 50 nm and contains thousands to tens of thousands of molecules each. [13, 28] On the millisecond scale, these vesicles are docked, activated, and fused with the cell membrane at the pre-synaptic cell. [21, 29]

Figure 1.4: The chemical synapse is separated by the synaptic cleft. Signaling occurs via vesicle release from the pre-synaptic neuron that diffuses to the post-synaptic neuron where a reaction is triggered. Here, neurotransmitters affects the ion channels that allow for ionic currents to change the membrane potential of the post-synaptic cell.

After the release, the neurotransmitters diffuse with the concentration gradient over the synaptic cleft, a distance in the range of a few tens of nanometers, to the postsynaptic cell. This diffusional transport that lasts for a few microseconds. [1, 27] At the post-synaptic cell membrane, ion channels are connected to receptors that specific neurotransmitters can bind to. The neurotransmitters, that can be either excitatory or inhibitory, affect the ion channels' permeability to ions that in turn affect the cell's membrane polarization, promoting or suppressing the probability of initiating a post-synaptic action potential.

1.1.2 Neurotransmitters

Molecules defined as neurotransmitters have a few characteristics in common. They are synthesized, stored, and released by neurons. When released, the neurotransmitter induces a specific behavior in the neuron (or target cell) receiving the signal. More than 100 different neurotransmitters have been identified, and the number is rising. Many of them are larger neuropeptides and others are referred to as small-molecule neurotransmitters. [13] A few of these small-molecule neurotransmitters, seen in Figure 1.5, are responsible for many excitatory and inhibitory events that occur in the neural signaling networks.

Figure 1.5: Acetylcholine, glutamate, and γ -aminobutyric acid (GABA) are three important small-molecule neurotransmitters. Together they are responsible for many of the excitatory and inhibitory events in the body.

A small and important neurotransmitter, also the first molecule recognized as a neurotransmitter, is acetylcholine (ACh). ACh is mostly an excitatory neurotransmitter but acts as an inhibitor in the heart. ACh is the main transmitter in neuro-muscular junctions, thus controlling muscle contractions. [13] While the role of ACh in muscle contractions has been fairly easy to study, its role in other parts of the nervous system is not as clear but has been associated with, *e.g.*, memory dysfunction in Alzheimer's disease. [30] In the central nervous system, the major excitatory neurotransmitter is glutamate (Glu). Glu is considered the most important neurotransmitter in normal brain function, due to its presence in a majority of all excitatory synapses and its role in neural circuits' ability to adapt their connectivity (plasticity). [30] Glu plays a major role in many signaling pathways and is highly associated with epileptic seizures [31] and is also associated with schizophrenia and dysfunctions in learning, memory, and vision. [30] Glu is a precursor to the major inhibitory neurotransmitter in the CNS, γ -aminobutyric acid (GABA). Due to its inhibitory properties, it can both suppress epileptic seizures as well as mitigate neuropathic pain, where both examples have been explored with iontronic devices. [32, 23] Both Glu and GABA are examples of amino acid neurotransmitters, which also include aspartate and glycine. [13] Neuromodulators are another type of important transmitting molecules. Signaling patterns with neuromodulators range over longer distances, last for longer periods of time, and allow for crosstalk and interconnections between different signaling pathways and groups of cells. [19, 15] To this group belongs ACh and Glu [33] as well as monoamines such as dopamine, norepinephrine (noradrenaline), histamine, and serotonin. Neuromodulators are involved in balancing behavioral states including sleep patterns, attention, and arousal and are also connected to a wide range of psychiatric disorders. [13, 19] Monoamines are also redox-active, *i.e.* easily oxidized, and can thus be recorded directly by electrochemical sensors. [20]

1.2 Recording and stimulation of neural networks

Complex and multilevel neuronal networks require complex and multilevel evaluation techniques. To get a full picture of neural function, it is desirable to combine stimulation and recording techniques and perform studies ranging from systemic down to local levels. To do so, it is reasonable to use all techniques available to complement each other's different strengths and weaknesses, including electrical, optical, and chemical techniques. The huge amount of data generated by these techniques can be collected, combined and investigated further using theoretical modeling. [19] Highly local stimulation and recording techniques are important for collecting details of healthy signaling as well as local pathogenic patterns. [21] Optical techniques for both stimulation and recording are capable of a broad range of spatiotemporal resolutions and can record single action potentials with sub-microsecond resolution. The techniques are usually based on light-sensitive reporters that provides high selectivity but are consequently limited by available reporters. [18] Electrical sensing techniques *e.g.* different types of patch clamp techniques, provide a temporal resolution below microseconds and provide excellent recording of fluctuating membrane potentials. Electrical stimulation techniques are highly developed and utilized in neural implants. They are however limited in the sense that they lack selectivity as the current spreads locally to all excitable cells surrounding the electrode. [18] Electrochemical sensing techniques can be used to detect electrochemically active neurotransmitters. If the sensors are additionally equipped with the proper enzymes, they can be used for highly sensitive and selective chemical recording of non-redox-active substances. [20, 18] Traditionally, chemical stimulation of the nervous system is performed systemically, but the interest and need for local chemical stimulation is rising. Local chemical stimulation and manipulation is recognized as the most challenging of these stimulation and recording techniques combined. While the gain is high due to the high chemical specificity, the general problem is the slow on/off kinetics and miniaturization of these systems. [18] To set the stage for the work presented in this thesis, the remaining sections of this chapter will cover the different strategies for local chemical stimulation with focus on artificial release of neurotransmitters.

1.2.1 Artificial release of neurotransmitters

Neurotransmitters can be released, actively and locally, either from liquid-based systems or from a range of organic materials such as hydrogels, polyelectrolytes, and conducting polymers. [18, 28, 34] The release can be controlled by *e.g.* pressure or potential gradients. In both directions, slow on/off kinetics can be problematic. The time delay for the on-state is limited by the transport from the storage in the device to the release site, followed by a time delay limited by the diffusion distance between the releasing device and target cell. And while there are many strategies for releasing neurotransmitters, the options for preventing leakage and turning the release off are far fewer. Thus, there are emerging needs of gating alternatives for neurotransmitter release technologies.

Fluidic-based systems controlled by pressure, *i.e.* micro and nano-injection, have the significant advantage of the range of molecules that can be delivered in terms of size and charge. On the other hand, the release cannot be performed without accompanying liquid and the pressure and volume gradients that follow. Injection techniques can also be combined with a membrane where molecules of certain sizes can pass from the device via diffusion. [20] Devices can be scaled down from microfluidics to nanofluidics to improve the spatial resolution, while preserving dose and release rates sufficient to trigger a cellular response. [28] Efforts to gate fluidic-based release devices have been made with, *e.g.*, hydrophobic switching, temperature, pH and magnetic fields [28, 35, 36].

Charged molecular compounds, *i.e.* ions, can be delivered from fluidic-based systems by the application of electrical potential gradients using a technique called iontophoresis, or microiontophoresis. Microiontophoresis generally involves the active transport of ions due to migration and electro-osmosis through micropipettes. It is hard to quantify the delivery of neurotransmitters, even though effort and improvements have been made by utilizing simultaneous recording techniques. [37, 38, 39]. Microiontophoresis devices have been used to mimic synaptic release [40, 28], where molecules can be delivered with high spatial resolution defined by the micro- or nanopipette tip. The small outlet also enables smaller retaining currents to prevent diffusional leakage. [40]

Another method of neurotransmitter release can be achieved using materials such as hydrogels and polymers loaded with the neurotransmitter. [6, 10] Molecules loaded in these materials can be released slowly by passive diffusion. If the molecule is an ion, active release can be performed from a conducting polymer, known as electrochemical release. The conducting polymer can be loaded with an ionic neurotransmitter during doping, followed by a switching of the potential that de-dopes the conducting polymer and thus releases the neurotransmitter. [41] Electrochemical release exhibits higher temporal resolution in the on-state compared to passive techniques but lacks any active prevention of diffusion via ion exchange in the off-state. [42]

Release of neurotransmitters from (or through) polyelectrolytes, that is polymers with fixed charges, is the approach utilized in iontronic devices covered in the final section of this chapter. Iontronic devices for neurotransmitter delivery can, as with other techniques, deliver a precise amount very locally via a well-defined release outlet. At the well-defined release site, a high concentration can be generated. Combining the high delivery concentrations with a gating functionality (ionic diodes) enables the potential of high on/off ratios. Using electrically controlled transport and release from porous membranes of polyelectrolytes (ion exchange membranes), the contribution of convection is minor [43, 44], resulting in negligible changes in extracellular volume and pressure in the target system. [45, 22]

1.2.2 Iontronic devices for neurotransmitter release

The most basic iontronic drug delivery device is called the organic electronic ion pump (OEIP). [45] In an OEIP, a polyelectrolyte forms an ion exchange membrane (IEM) that can transport charged compounds. The charged compound can

be smaller ions or larger ionic molecules, where the properties of the IEM restricts the possible transporters. Within the work of this thesis, the scope covers smaller ions and small-molecule ionic neurotransmitters. Cationic neurotransmitters can be transported in polyanions to compensate for fixed negative charges on the polyanion and anionic neurotransmitters can be transported in polycations, compensating the positive fixed charges. The basic OEIP circuit (illustrated in Figure 1.6) is based on two electrodes in two electrolytes connected/separated by an IEM. One electrolyte is called the source reservoir and the other one is called the target electrolyte. The source reservoir is loaded with the ion intended for transport and delivery and the ions are released to the target electrolyte. The IEM that the ions are transported through is referred to as the ion channel. The ion channel (often micro-fabricated) is covered with an encapsulating material which has openings for the inlet and outlet of the ion channel. The OEIP is a resistor version of an iontronic device where the IEM functions as an ionic resistor, typically with high resistance in the $M\Omega$ range. [46] When a potential difference is applied between the source reservoir and the target electrolyte, ions of a certain charge are actively transported – “pumped” – from the source to the target. How the charge flows through these iontronic circuits is described in detail in Chapter 2.

Figure 1.6: The basic design of the organic electronic ion pump (OEIP) and the delivery scheme (steps 1-3). The encapsulation defines the openings for the source reservoir and target electrolyte and protects the ion channel. Electrodes are placed in the electrolytes to control the transport in the ion channel. The ion exchange membrane in the ion channel, micro-fabricated on a carrier substrate enables selective transport of ions. This figure shows a cation-transporting OEIP with a polyanionic IEM.

Since its introduction in 2007 [45], the OEIP has been developed further into a range of different iontronic devices. [9, 47]. Figure 1.7 shows an overview of iontronic device development. With high resistance in the ion channels, the main mechanism for ion transport is the migration controlled by the potential gradients. However, the gating became more efficient when the resistor version was developed into iontronic diodes and transistors. [48, 49] These iontronic diodes and transistors were also combined into circuits and systems for more advanced ion-based circuits. [50] The design development includes surface-based and free-standing devices with different form factors and materials [22, 24]. As the technology evolved and more device designs were developed, the range of capabilities

and applications has also broadened over the years including pH regulating platforms [51], the regulation of neurological disorders such as epilepsy [32, 52] and neuropathic pain [23], to the regulation of plant physiology [53] to mention a few. The rest of this thesis will be dedicated to how these devices work (Chapter 2), how they are fabricated and designed (Chapter 3 and Chapter 4), evaluated (Chapter 5), as well as their limitations and possibilities for the future (Chapter 6).

Figure 1.7: An overview of the technologies developed during the first decade of iontronic delivery devices. The development has proceeded from ionic resistors to diodes, transistors, and vertical release devices. Different form factors and multimodal designs combining stimulation and sensing have been developed to broaden the variety of interfacing opportunities. Figure adapted from Ref. [9].

2

The flow of charge

The aim for iontronic drug delivery devices is to deliver and release a specific dose of specific ions at a certain time and place, by controlling the current through the iontronic circuit. The current through the iontronic circuit is carried by a variety of electrons, holes, cations and anions as charge carriers, distributed differently over different domains. This chapter describes how the charge distribution and potential variations take place in these different domains in the iontronic circuit.¹ The circuit consists of different combinations of i) electrodes that enable electronic contact and constitute the electronic - ionic interface; ii) electrolytes, *i.e.* solutions of dissolved ions; and iii) ion exchange membranes (IEMs), *i.e.* the ionic conductors. The most basic iontronic circuit is the organic electronic ion pump (OEIP) that includes electrodes immersed in electrolyte solutions with an IEM separating the electrolyte solutions from each other, as seen in Figure 2.1.

This is an iontronic circuit:

Figure 2.1: The full iontronic circuit. The electrodes generate an ionic current, controlled by the power source. The ionic current passes through the electrolyte where both cations and anions contribute to the current. In the ion exchange membrane (IEM), the majority of the current is carried by counterions. Here, a cationic current is transported through a cation exchange membrane (CEM), and delivered to the target electrolyte. The source reservoir is the electrolyte loaded with the ion intended for transport.

¹Constant, variables and their units are found in the List of Symbols (p. 67)

To provide the background needed for the chapters following, a step-by-step description of the different domains and interfaces of this circuit will be covered in this chapter. First, the interface between ionic and electronic conductors in the electrodes will be described, where anions and cations take over the charge transport from the electrons or holes. Secondly, the mass transfer of ions in electrolytes including diffusion, migration, and convection will be covered. The mass transfer characteristics differ from unselective ionic transport in the electrolytes, and transitions into selective transport in the IEM, where the majority of the current is carried out by either cations or anions (but not both). The final section of this chapter covers how the applied voltage affects the current response in iontronic circuits. This response is discussed for both monopolar and bipolar membranes, where a monopolar membrane is one type of IEM, while a bipolar membrane (BM) is the combination of two types of IEMs: a cation exchange membrane (CEM) and an anion exchange membrane (AEM).

2.1 Bulk domains and interfaces

In the bulk volume of the electrolytes and IEMs, *i.e.* the volume away from the interface boundaries, it is often appropriate to assume that all charges are compensated by another charge of the opposite sign. That implies that the sum of the charge z and the concentration c of each species i is approximately zero:

$$\sum z_i c_i \approx 0 \quad (2.1)$$

The sum from Equation 2.1 multiplied by Faraday's constant ($F = 96\,485 \text{ C/mol}$) translates the sum of moles per m^3 to C per m^3 and defines the local electric charge density (ρ_e):

$$\rho_e = F \sum z_i c_i \approx 0 \quad (2.2)$$

Equation 2.2 is known as the local electroneutrality assumption. [43] At the interfaces between the different domains, some interesting phenomena arise (Figure 2.2). The charge density in the electrode and IEM differs from the charge density in the electrolyte and is compensated by a non-linear distribution of charge carriers in the close vicinity of the interfaces. The region where this non-linear arrangement occurs is called the electric double layer (EDL). [43]

Figure 2.2: Non-electroneutral electric double layers (EDLs) are formed in all interfaces in the circuit. The bulk volumes on the other hand can be assumed to be electroneutral.

The charge distribution in this arrangement deviates from the electroneutrality assumption in Equation 2.2. The term "double layer" refers to the fact that the charges on each side of the interface are mirrored on the other side of the interface, *i.e.* equal in size and opposite in charge. In the EDL, Poisson's equation for electrostatics can be used to relate the non-zero charge density to the local and non-linear electric potential (ϕ):

$$\nabla^2 \phi + \frac{\rho_e}{\epsilon_0 \epsilon_s} = 0 \quad (2.3)$$

where ϵ_0 is the vacuum permittivity and ϵ_s is the dielectric constant of the solvent. For the ionic charge carriers in the electrolyte, Poisson's equation of electrostatics can be rewritten (using Equation 2.2) to: [43]

$$\nabla^2 \phi + \frac{F}{\epsilon_0 \epsilon_s} \sum z_i c_i = 0 \quad (2.4)$$

EDLs appear at all interfaces throughout the iontronic circuit (Figure 2.2). The thickness of the double layer is restricted to the Debye (screening) length, which is typically in the range of nanometers. [54] Since these interfaces between the domains are extra interesting from a device point of view, they will be discussed in detail in this chapter.

2.2 Electrodes

The interface between an electronic conductor and an electrolyte, where electric current leaves or enters, is called an electrode. For the electric current to flow and cross this interface, an electrochemical potential difference between two electrodes with electrolytic contact is needed. An overview of a circuit with electrodes and electrolytes can be seen in Figure 2.3.

Figure 2.3: An iontronic circuit includes a mix of ionic and electronic conductors. At the interface between these conductors, *i.e.* at the electrodes, a conversion between electronic and ionic current is possible.

These two electrodes are contacted by a metal contact (*e.g.*, probe, alligator clip) and wired to a power supply that controls the applied potential difference between them. From this power supply, through the wiring and metal contacts

to the electrode, the current is based on the flow of electrons and is therefore referred to as an “electronic” branch of the iontronic circuit. In the electrolyte and any present IEMs, the charge is instead carried by ions, and these are referred to as “ionic” branches of the iontronic circuit. However, some materials, can carry both ionic and electronic current, and are therefore called mixed ionic-electronic conductors. At the electrode, *i.e.* at the interface between an ionic and an electronic conductor or in the bulk of the mixed conductors, that conversion between electronic current and ionic current is possible. This current transition can either be generated from electrochemical reactions involving charge transfer between the electrolyte and the electrode material, or from capacitive charging involving charge storage in the form of EDLs at the electrode surface. [55] Generally, electrode materials based on redox couples are electrochemical, while metals and many mixed ionic-electronic electrode materials can store charge in EDLs. The charge storage capacity of electrodes is an important parameter for iontronic components in prolonged experiments, and critical if the target application includes implantable devices. In the following section, the different processes of the flow of charge from electrode to electrolyte phase – and back – are discussed, including surface and volumetric capacitive charging and electrochemical reactions.

2.2.1 Capacitive charging with electric double layers

Capacitive charging takes place at the electrode surface in the electrolyte without any charge carriers moving across the interface boundary. When a voltage is applied, electrons or holes are redistributed, generating a charged electrode surface. Ions in the electrolyte solution compensates this charged surface electrostatically by rearranging the ions in the EDL. If the electrode surface is negatively charged, positive ions will accumulate close to this boundary and the density of negative ions will decrease. In the EDL, there is an exponential change in ion concentration towards the bulk concentration, called the diffusive double layer, as seen in Figure 2.4.²

Figure 2.4: Electric double layer (EDL) formed at the electrode-electrolyte interface, creates characteristic charge and non-electroneutral distribution locally at the electrode surface.

²The concentrations of cations and anions in Figure 2.4 are generated from a tutorial model "Diffuse double layer" in COMSOL Multiphysics v5.5, with 10 mV and -10 mV applied to the left and right side respectively. Electrolyte concentration is 1 mM, and the diffusion coefficients are equal for the two species.

Current will flow until the double layer is fully formed and will have an exponential decay with time after a voltage step is applied. During the formation of these double layers, mass transport of compensating ions in the electrolyte is needed. Once the EDLs are fully formed, no current will flow, and the entire voltage drop occurs over the EDL and not over the electrolyte.

2.2.2 Volumetric capacitive charging

The charge capacity of a flat metal surface, such as a gold surface, will be very limited and the current generated by a voltage step will not last for very long. The charge capacity can, however, be increased if the effective surface area is increased. If this is achieved by using the bulk of the electrode material instead of increasing the geometrical surface, the resulting charge capacitance can be viewed as a volume rather than an area. Practically, this can be achieved, *e.g.* by porous or nanostructured surfaces. [56] Another approach is to use organic mixed ionic-electronic conductors, *e.g.* conducting polymers in electrolyte. [57] In these heterogeneous materials, the ions can penetrate and reach deeper into the material, where they can interact with internal interfaces between the electrode and the electrolyte. In conducting polymer-based materials, the ions balance electronic carriers on the polymer by a process referred to as doping. A material where holes are responsible for charge transport, doped with anions, is referred to as a p-type material (positively doped). Materials with electrons as charge carriers, doped by cations, are referred to as n-type materials (negatively doped). [58, 59] Figure 2.5 illustrates an example of an organic mixed ionic-electronic conductor with holes as charge carriers, doped and de-doped by anions.

Figure 2.5: Mixed ionic-electronic conductors are one example of volumetric capacitance where ions can penetrate the material and form internal EDLs. This is an example of a p-doped polymer where the injection of holes (removal of electrons) gives room for a compensating anion at the positively biased electrode, while the negatively biased electrode is de-doped and releases ions.

2.2.3 Electrochemical reactions

Electrochemical reactions allow for current based on charge transfer induced by electrode reactions. These reactions can occur in different forms, usually with

mass transfer from the bulk to the electrode surface followed by an electrode reaction with electrons crossing the interface. This can be combined with other chemical reactions and surface reactions. [60] Figure 2.6 shows a direct charge transfer between redox molecules in the oxidized (O) and reduced form (R), dissolved in the solution. A reduction takes place at the negative electrode, where an electron is transferred from the electrode to the species O, that gets reduced into R. At the positive electrode, an oxidation of species R, that gets oxidized into O, takes place when an electron is transferred from the electrolyte to the electrode. [61, 62] The electrode reaction rate (r) of these reactions follows Faraday's law, and they are also often referred to as Faradaic processes:

$$r = \frac{I}{nF} \quad (2.5)$$

where I is the current density, n is the number of transferred electrons per reaction, and F is Faraday's constant. The rate limiting processes can be restricted from the mass transport of reactants in electrolyte to the electrode or by the reaction kinetics. [43] The mass transport can include diffusion, migration, and convection, covered in the following section. The degree of capacitive charging differs significantly between different materials, ranging from ideally non-blocking surfaces where no capacitive charging takes place to ideally polarizable surfaces with no reactions.

Figure 2.6: Electrochemical reactions at the electrode interface allow for charge transfer from the solution to the metal contact. R and O are redox molecules in the reduced and oxidized form, respectively. The figure shows an example of a partially polarized surface, where in addition to the electrochemical reactions, some capacitive charging takes place.

A widely used electrochemical reaction, often used in reference electrodes, is the Ag/AgCl redox couple where Ag and AgCl are solid on the electrode surface and Cl^- is dissolved in the solution:

Due to the fast reaction kinetics, stable potential and the possibility to provide high charge capacity from a liquid paste, Ag/AgCl is an excellent electrode material for characterization of iontronic components, as long as Cl^- ions are present in the electrolyte phase. [63, 64]

2.3 Electrolytes

Cations and anions dissolved in water are called an electrolyte. In water, ions can be transported by a combination of three main processes: diffusion, migration, and convection. [43] Which of these processes dominate the transport depends on the specific circumstances, but all three processes play important roles in both biological signaling as well as in iontronic circuits. The combined contribution of diffusion, migration, and convection to the total flux will be explained in this section by the Nernst-Planck approach, starting with diffusion, followed by migration and convection.

2.3.1 Ionic diffusion

Diffusion is governed by concentration differences and is the main transport mechanism for short-range molecular transport in the extracellular space for distances below 100 μm and time-scales under a minute. [25] Also, the final transport from iontronic device outlets to the target system is diffusional by nature.

Figure 2.7: Ions diffuse in the direction of the concentration gradient, from higher to lower concentration.

The diffusive ionic flux ($\vec{J}_{i,\text{diffusion}}$) for each ion species (i) depends on the magnitude of the concentration gradient (∇c) and the diffusion coefficient (D), as formalized in Fick's first law:

$$\vec{J}_{i,\text{diffusion}} = -D_i \nabla c_i \quad (2.7)$$

Diffusion coefficients generally scale with the effective molecular size (including hydration shells of ions), where a smaller molecule diffuses faster than a larger one.³ If the viscosity (η) of the (homogenous) phase (α) and the radius of the (spherical) particle (r) is known, D can be determined by the Einstein-Stokes relation: [17]

$$D_i^\alpha = \frac{RT}{6\pi\eta^\alpha r N_A} \quad (2.8)$$

where R is the universal gas constant, T is the temperature, and N_A is Avogadro's constant. For spherical particles, D is approximately inversely proportional to the cube root of the molecular mass. [17] Another commonly used property is the (electrochemical or mechanical) mobility (u) of ion i , that can be translated from the diffusion coefficient via the Nernst-Einstein relation:

$$u_i = D_i RT \quad (2.9)$$

³A few examples can be seen in Table 4.1, Chapter 4.

Diffusion coefficients (and ionic mobilities) are phase specific. For example, ions diffuse approximately 10 times faster in a free solution compared to their diffusion within IEMs. [65] In the extracellular space, small molecules have a diffusion coefficient 2-5 times lower compared to free solution. [25]

2.3.2 Ionic migration

While any type of molecule can be transported by diffusion and convection processes, migration is a movement of charged molecules (ions) in the presence of electric potential gradients. In these potential gradients, cations migrate towards lower potential and anions migrate towards higher potential (Figure 2.8). Migration is the main transport mechanism utilized for controlled transport in iontronic devices.

Figure 2.8: A positive potential attracts anions, while cations migrate towards lower potential.

The migrational flux ($\vec{J}_{i,\text{migration}}$) is proportional to the electric potential gradient ($\nabla\phi$) and can be described by:

$$\vec{J}_{i,\text{migration}} = -\frac{z_i F}{RT} D_i c_i \nabla\phi \quad (2.10)$$

where z is the charge and c the concentration of the ion, F is Faraday's constant, R is the universal gas constant, and T is the temperature. All electrolytes and polyelectrolytes (such as IEMs) have the ability to conduct electricity, where the total electrolytic conductivity (κ) is a sum of all conductivities of contributing species (i). Each ionic species contributes differently dependent on its charge (z), phase specific diffusion coefficient (D), and concentration (c): [43]

$$\kappa = \sum_i \kappa_i = \frac{F^2}{RT} \sum_i z_i^2 D_i c_i \quad (2.11)$$

The degree to which each ionic species contributes to the total current is measured by the transport number, t_i :

$$t_i = \frac{\kappa_i}{\kappa} \quad (2.12)$$

where all transport numbers sum to unity. For an binary electrolyte, composed of just two ionic species, one cationic and one anionic, the transport numbers can be defined as:

$$t_- = \frac{z_- D_-}{z_- D_- + z_+ D_+} = 1 - t_+ \quad (2.13)$$

where t_+ and t_- are the transport numbers for the cation and anion, respectively.

2.3.3 Convection

Convection is motion of molecules due to a solvent in motion, as seen in Figure 2.9. For long range transport is convection a much more potent transport mechanism than both diffusion and migration. Convection is for this reason utilized for e.g. transport of cells and hormones in the blood stream, as well as for microfluidic transport from a drug reservoir to a short range iontronic delivery device. Movement of the solvent can be caused and controlled by pressure gradients, but can appear as natural convection due to density or temperature differences. Electric fields can also induce fluidic movement if the solution is in contact with charged walls, creating a double layer with mobile charges affected by the potential gradient. This movement is referred to as electro-osmosis. [43]

Figure 2.9: Convection makes all ions move with the solvent motion.

The movement of fluids can be described by the Navier-Stokes equation. For a stationary flow of an incompressible Newtonian fluid, with pressure (p) and an electrostatic force ($\rho_e \vec{E}$) applied, the Navier-Stokes equation reads:

$$\nabla p - \rho_e \vec{E} = \eta \nabla^2 \vec{v} - \rho(\vec{v} \cdot \nabla) \vec{v} \quad (2.14)$$

where $\vec{v}$ describes fluid velocity of the solvent, ρ the density, and η the viscosity. Any magnetic or gravitational forces are neglected in Equation 2.14. [66] The Navier-Stokes equation can be simplified further in the case of low flow rates and small dimensions – where the inertial forces represented by $(\vec{v} \cdot \nabla) \vec{v}$ are much smaller than the viscous term $\eta \nabla^2 \vec{v}$ – that are often the case in microfluidic flows. To estimate whether the flow is turbulent or laminar is usually decided by the Reynolds number (Re), that is a ratio between inertial effects and viscous effects:

$$Re = \frac{\rho v L}{\eta} \quad (2.15)$$

where ρ is the density, v is the apparent average velocity of the fluid, η is the dynamic viscosity of the fluid, and L is the characteristic length. For pipes, L is the inner diameter. [36, 17] $Re > 2000$ is defined as turbulent, while flow with Re below these values are assumed to be laminar. [66, 67] Flows with extremely low Re , $Re \ll 1$, are sometimes referred to as Stokes flows or creeping flows. The rule of thumb is that the inertial term can be neglected for these creeping flows. [67, 66] Thus, for a stationary flow driven by pressure (no electro-osmotic convection) with low Re , Equation 2.14 simplifies to:

$$\nabla p = \eta \nabla^2 \vec{v} \quad (2.16)$$

For convection movement, an appropriate approximation is that the ionic species moves fixed with the movement of the solvent. [43] Thus, the convective flux ($\vec{J}_{i,\text{convection}}$) can be described by:

$$\vec{J}_{i,\text{convection}} = c_i \vec{v} \quad (2.17)$$

2.3.4 The Nernst-Planck equation

The Nernst-Planck approach can be used to explain the mass transport of ionic species by combining the fluxes from diffusion, migration, and convection in the (extended) Nernst-Planck equation: [65]

$$\vec{J} = -D_i \nabla c_i - \frac{z_i F}{RT} D_i c_i \nabla \phi + c_i \vec{v} \quad (2.18)$$

This approach includes approximations, such as the lack of any cross-phenomenological coefficients for short-range interactions, and is therefore most accurate at dilute concentrations. Also, any deviations from the Nernst-Einstein relation (Equation 2.9) are neglected. [43] The degree to which diffusional, convective, and migrational fluxes contribute to the total flux varies significantly in different situations. Many times, one or two terms of Equation 2.18 can be neglected. When convection is excluded, the Nernst-Planck equation gets its most common form, also called the diffusion-migration equation or the drift-diffusion-equation:

$$\vec{J}_i = -D_i \nabla c_i - \frac{z_i F}{RT} D_i c_i \nabla \phi \quad (2.19)$$

By combining the contributions from the chemical gradient and the electric potential gradient, into an electrochemical gradient, the term electro-diffusion can be used. According to the Nernst-Planck approach, the ions move in the direction of their respective electrochemical gradient regardless of whether the chemical or electrical gradient is dominating. In biological cell membranes, active transport can take place against the electrochemical gradient. [43]

2.4 Ion exchange membranes

Ion exchange membranes (IEMs) are called semi-permeable membranes since they are only permeable under certain conditions. Specifically, IEMs are selective by charge either for cations or anions, but also selective by size related to their effective pore size. IEMs are based on a polymer network or matrix with charged groups fixed on these polymer chains and the sign of these fixed charges decides the selectivity. Mobile ions in the membrane phase are referred to as counterions if they have the opposite charge to the fixed charge. Mobile ions in the membrane with the same charge as the fixed charges are referred to as coions. The ratio of these ions depends on the fixed charge concentrations in relation the surrounding electrolytes. Lower fixed charge concentration or higher surrounding electrolyte concentration leads to more coions in the membrane phase. Due to the local electroneutrality condition (Equation 2.2), all fixed charges and coions are compensated by mobile counterions in the bulk of the membrane phase (m):

$$\sum z_i c_i^m + z_{fix}^m c_{fix}^m = 0 \quad (2.20)$$

where $z_{fix}^m c_{fix}^m$ denotes the charge and concentration of fixed charges in the membrane. Membranes selective for cations are called cation selective or cation exchange membranes (CEM). Membranes selective for anions are referred to as anion selective or anion exchange membranes (AEM). Both types are illustrated in Figure 2.10. An AEM or CEM immersed in an electrolyte is referred to as a monopolar membrane. The combination of a CEM and an AEM sandwiched together is also interesting for the design of iontronic components. This combination is called a bipolar membrane (BM). [68] While a single IEM acts as an ion resistor, the BM acts as an ion diode. The origin of their different current-voltage behaviors is discussed in detail in Section 2.5.

Figure 2.10: An overview of the two types of IEMs, the cation exchange membrane (CEM, in blue to the left) and the anion exchange membrane (AEM, in yellow to the right). The charge of the fixed ions, counterions, and coions are opposite in relation to the other type of IEM.

The fluxes through the IEM can be expressed with Equation 2.18 (extended Nernst-Planck), here with membrane phase-specific denotations:

$$\vec{J}_i = -D_i^m \nabla c_i^m - \frac{z_i F}{RT} D_i^m c_i^m \nabla \phi + c_i^m \vec{v} \quad (2.21)$$

When a potential gradient is applied, the contribution of the first diffusional term compared to the second migrational term is low and in many cases can be neglected. [43] Thus, the main contributor to the flux through an IEM is the migration during an applied potential gradient. The crosslinking density and shape of the polymer network give pore sizes that limit permeability by size. IEMs are usually dense with pore sizes ranging from 0.5-100 nm. [65] The effective diffusion coefficient in an IEM (D_i^m) is affected by the structure of the membrane and differs from the diffusion coefficient in free solution (D_i). The so-called structure factor is defined as the ratio between the porosity (ϵ_p) and the tortuosity factor (τ) of porous membranes. The tortuosity factor is a measure of the increased pathway due to hinderance. [25, 69] A common theoretical model for the relation between τ and ϵ_p is the Bruggeman model where $\tau = \epsilon_p^{-1/2}$. For ions transported in porous media using the Bruggeman model, the estimation of the effective diffusion coefficient in the IEM is given by: [69, 70]

$$D_i^m = \frac{\epsilon_p}{\tau} D_i = \epsilon_p^{3/2} D_i \quad (2.22)$$

From experimental data, the effective scaling factor for charged molecules in iontronic devices varies significantly [71, 64, 24]. For theoretical studies, an estimation of $D_i^m \approx 0.1 \cdot D_i$ is used as a standard approximation for monovalent ions. [65, 72] This scaling factor combines all the effects from membrane interaction, and counterions and coions are treated equally. Nevertheless, the pore walls inside the IEM are charged and a double layer is formed in the solution, with opposite charge. The model in Equation 2.22 does not consider how the electrostatic interactions with the fixed charges in the IEMs affect the diffusion coefficient. In addition, these electrostatic interactions, as well as the electric field, are likely to affect the diffusion coefficients of counterions and coions differently. Counterion condensation is such a case, where a fraction of the counterions appears to be immobile or slowed down by concentration to the fixed charges, while appearing mobile along the polymer chain during applied potentials. [73]

Water in the hydration shell bound to ions (vehicular transport) moves (in most cases) with the ions in the IEM with the same velocity. The movement of ions due to electrostatic interactions with the fixed charges at applied potentials can also cause an electro-osmotic flow in the same direction as the flow of the counterion. [43, 74] This contribution is generally small but increases with increasing pore size in combination with highly charged walls. [44, 43, 74]. The transport number in the membrane is affected by the transport of water. When water transport is neglected, the transport numbers are referred to as apparent transport numbers instead of true transport number. [44, 74]

Modeling of potentials and ion concentrations

Throughout the rest of this section, potential variations and concentration distributions are exemplified using a simple axis-symmetric model in COMSOL Multiphysics v5.5. Steady state simulations are performed by the use of the Nernst-Planck-Poisson equations without any type of convection. In this model a CEM is used as an example of a monopolar membrane, and the solutions contain two monovalent ions, where $D_+ = D_- = 2.0 \cdot 10^{-9} \text{ m}^2/\text{s}$. The ion concentrations are fixed at the outer boundaries of the electrolytes defined as half-spheres with a 100 μm radius, and everything outside this region is referred to as the bulk electrolyte. The Bruggeman model is used to set the effective transport parameter correction for the diffusion coefficient. The porosity of these membranes is set to 0.2, to generate $D_i^m = 0.1 \cdot D_i$. The data presented is a line along the z-axis, the same axis used for rotation. Each figure contains experiment-specific parameters and boundary conditions. The potentials are set as boundary conditions in the electrolytes, *i.e.* any resistance from the electrode interface is neglected. A more detailed descriptions of these types of models are described in Chapter 5.

2.4.1 Donnan equilibrium

In the boundary region between the electrolyte phase and the IEM (Figure 2.11), the difference in concentration of ions in the electrolyte (c_i^e) and the ion concentration in the membrane (c_i^m) give rise to an EDL with a very steep concentration gradient which is stabilized by a potential difference at this interface. This poten-

Figure 2.11: The electric potential difference in the membrane and electrolyte give rise to the Donnan potential at their interface. The electrochemical potentials in the two phases are however equal.

tial difference is called the Donnan potential, $\nabla\phi_D$. The summed electrochemical potential ($\tilde{\mu}_i$), on the other hand, is the equal on the membrane side ($\tilde{\mu}_i^m$) and the electrolyte side ($\tilde{\mu}_i^e$) of this interface and can be expressed as following: [75]

$$\tilde{\mu}_i = \mu_i^o + RT \ln(\gamma_i c_i) + \phi z_i F \quad (2.23)$$

where μ_i^o is the standard chemical potential and γ_i is the molar activity coefficient, and the two can be assumed equal for the two phases for membranes with high water content [43]. This equilibrated state between concentration gradients and potential drops is called the Donnan equilibrium state. And by rearranging $\tilde{\mu}_i^m = \tilde{\mu}_i^e$ the following Nernst equation for the Donnan potential is reached: [75]

$$\nabla\phi_D = \phi^m - \phi^e = \frac{RT}{z_i F} \ln \frac{c_i^e}{c_{fix}} \quad (2.24)$$

in similarity with the equilibrium potential from cell membranes (Equation 1.2, Chapter 1). In IEMs, $\nabla\phi_D < 0$ for cation exchange membranes (CEMs) and $\nabla\phi_D > 0$ for anion exchange membranes (AEMs). Figure 2.12 shows the magnitude of the Donnan potential for three different fixed charge concentrations (0.5-2M).⁴

Figure 2.12: The magnitude of the Donnan potential ($\nabla\phi_D$) will increase with higher concentration of fixed charges in the membrane compared to the concentration in the surrounding electrolyte. The transition of the potential is very steep but zoomed in to five nanometers on each side of the interface. For a CEM as illustrated in the figure, $\nabla\phi_D < 0$.

⁴The CEM consists of a 100 μm long cylinder with a 10 μm radius, with a fixed space charge is set to $\rho_{fix} = -c_{fix} \cdot F$. The electrolyte domains are defined as half-spheres with a 100 μm radius.

The Donnan potential is responsible for the exclusion of coions, and the phenomena is sometimes called Donnan exclusion. The magnitude of the Donnan potential, and thus how effective coions will be excluded, increases with higher concentration of fixed charges in the membrane compared to the concentration in the surrounding electrolyte. An effective exclusion of coions together with the inclusion of counterions will lead to a highly selective transport of counterions in the IEM (as long as the counterion is in fact permeable to the membrane).

In an ideal IEM, the transport of charge is carried by the counterions alone. In the case of an ideal CEM, the transport number of the positive counterion is $t_+^m = 1$ and the transport number for the negative coion is $t_-^m = 0$. In practice though, IEMs are not ideally selective, and a measure of the membrane selectivity is given by the membrane permselectivity, S . The permselectivity is based on the transport number of the counterion, how it differs in the membrane phase (m) compared to the electrolyte (e), and the ratio to the transport number of the coion. The permselectivity for a CEM can be evaluated by:

$$S = \frac{t_+^m - t_+^e}{1 - t_+^m} \quad (2.25)$$

The permselectivity of the membrane can range from 0, when $t_+^m = t_+^e$, to 1 for an ideally selective membrane, where $t_+^m = 1$. [43] An example of the concentration distribution of a CEM with 1 M fixed charges can be seen in Figure 2.13. Here, ≈ 10 mM anions are present in the CEM. Comparable numbers are ≈ 20 mM and ≈ 5 mM coions at 0.5 M and 2 M fixed charge concentration, respectively.

Figure 2.13: Concentration distribution over a cation exchange membrane (CEM) in electrolyte. The concentration gradient is high at the interfaces between the CEM and electrolyte. The total amount of cations in the CEM is just above the amount of fixed charges, since it also compensates for mobile coions in the membrane, for total electroneutrality in the CEM bulk.

2.4.2 Membrane potential

Previously in this chapter, the two electrolytes on each side of the membrane have been assumed to include the same ionic species with equal concentration. A concentration difference between the electrolytes (denoted electrolyte α and electrolyte β) introduces two different effects on the total membrane potential.

The concentration difference will give different magnitudes of the two Donnan potentials, one on each side of the membrane:

$$\nabla\phi_D^\alpha = \frac{RT}{F} \ln \frac{c_+^\alpha}{c_{fix}} \quad \nabla\phi_D^\beta = \frac{RT}{F} \ln \frac{c_+^\beta}{c_{fix}} \quad (2.26)$$

Figure 2.14 shows how the impact of how different concentrations in the α and β phases affects the Donnan potentials.⁵

Figure 2.14: The concentration difference between the α and β phases results in a difference in magnitude for the two Donnan potentials for each interface ($\nabla\phi_D^\alpha$ and $\nabla\phi_D^\beta$). In this example, no diffusion potential present ($D_+ = D_-$), thus the membrane potential ($\nabla\phi_M$) is the difference between the two Donnan potentials.

If the ions in the solutions also have different diffusion coefficients, another potential is introduced, called the diffusion potential ($\nabla\phi_{dif}$). The diffusion potential arises since there is a coupling between the ions that strive to maintain local electroneutrality while moving with the concentration gradient. This coupling will affect the speed of the separate ions. A slow ion will slow down a faster ion, and vice versa. [43] The total membrane potential ($\nabla\phi_M$) across an IEM separating two electrolyte phases (α and β) is the difference of the two Donnan potentials plus the diffusion potential: [43, 76]

$$\nabla\phi_M = \nabla\phi_D^\alpha - \nabla\phi_D^\beta + \nabla\phi_{dif} \quad (2.27)$$

The contribution of these potentials, in a scenario where $D_+ \neq D_-$ and $c^\alpha \neq c^\beta$, depends on the concentration of fixed charges. The Donnan potentials $\nabla\phi_D$ will be heavily reduced in weakly charged membranes. In uncharged membranes, $\nabla\phi_D$ will not exist at all, and $\nabla\phi_M = \nabla\phi_{dif}$. On the other hand, for strongly charged membranes, the contribution of $\nabla\phi_{dif}$ will decrease in comparison with $\nabla\phi_D$. $\nabla\phi_{dif}$ will also be negligible if $D_+ = D_-$. [43]

2.4.3 Bipolar membranes

IEMs of one polarity, either CEM or AEM, is referred to as monopolar membranes due to their single polarity. Bipolar membranes (BM) refers to the combination of two exchange membranes with opposite polarities, *i.e.* an AEM combined with an

⁵This data is collected for open circuit conditions ($I = 0$), with $D_+ = D_- = 2.0 \cdot 10^{-9} \text{ m}^2 \text{ s}^{-1}$.

CEM. [77] When an AEM and a CEM are sandwiched together, a new interface is formed between the two. When immersed in an electrolyte, this results in three interfaces where equilibrium is formed between the fixed and mobile ions and the Donnan potentials. This results in high concentration gradients and rapid potential drops at all three interfaces. In Figure 2.15 the concentration distribution can be seen in two equally charged membranes forming the BM.⁶

Figure 2.15: The concentration distribution of a BM with no externally applied potential. Due to the different polarities of the membranes, they have different types of counterions.

Since $\nabla\phi_D < 0$ for CEMs and $\nabla\phi_D > 0$ for AEMs, the largest potential drop will occur at their interface, as can be seen in Figure 2.16. Both monopolar and bipolar membranes play significant roles in the design of iontronic drug delivery devices and circuits, especially due to their different response vs. applied potentials. [68, 78] These responses and following limitations will be discussed in Section 2.5. How monopolar and bipolar membranes are incorporated into different device designs, will be explained in Chapter 4.

Figure 2.16: The opposite polarities generate Donnan potentials with equal magnitudes, oppositely directed. This gives a doubled potential drop at the AEM-CEM interface.

⁶In the model generating this data, the fixed space charge in the CEM is set to $\rho_{fix} = -c_{fix} \cdot F$, and $\rho_{fix} = c_{fix} \cdot F$ for the AEM. The membrane dimensions are for both membranes a 100 μm long cylinder with a 10 μm radius. c_{fix} is equal between the two. The electrolyte domains are defined as half-spheres with a 100 μm radius.

2.5 Applied potentials and current response

Migration can occur due to the internal electric fields correlated with *e.g.* concentration gradients and differences in diffusion coefficients for the ionic species. Conduction on the other hand, requires an applied electric field. Conduction in an iontronic circuit will cause a current where both electrons (or holes) and ions can act as charge carriers, called electronic and ionic current respectively, or electric current combined. The contribution of all fluxes combined in the electrolyte (Nernst-Planck, Equation 2.18) gives a net ionic current density $\vec{i}$: [43]

$$\vec{i} = F \sum z_i \vec{J}_i \quad (2.28)$$

where z_i comprises the cationic (z_+) and anionic (z_-) fluxes. Current (I) is defined as the flow of charge (Q) per time through a cross sectional area of the conductor: [79]

$$I = \frac{\partial Q}{\partial t} \quad (2.29)$$

The current scales with the applied voltage (U) and resistance (R) according to Ohm's law: [79]

$$I = U/R \quad (2.30)$$

where R will depend on the resistivity (ρ) and spatial parameters of the different domains according to: [79]

$$R = \rho l/A \quad (2.31)$$

where l is the length and A the cross-section area of the conductor. The inverse of electric resistivity gives electric conductivity ($\sigma = 1/\rho$). The total resistance in the iontronic circuit can be divided into contributions from the electrodes, contacts, electrolyte solution, and IEMs. The resistance for electronics currents (R_e) and resistance for ionic currents (R_i) often differ significantly in these types of circuits, where $R_i \gg R_e$. In general, for iontronic components the IEMs are designed to have very high resistance (long and narrow), and electrodes are designed to have low resistance. Phrasing this differently, the goal is to have as much of the applied potential drop over the IEM as possible.

2.5.1 Current regimes in monopolar membranes

Applied potentials over the IEMs will rearrange the distribution of ions compared to the distribution in resting state. Migration will cause cations to move towards lower potentials and anions to move towards higher potentials. The counterions will move from one electrolyte to the other across the IEM in one direction, while a small portion of coions will move in the opposite direction. The potential drop will occur mainly over the IEM, as seen in Figure 2.17.⁷

As a response to this applied potential, the local ion concentration will decrease at the side where ions enter the membrane and increase at the side where ions are leaving the membrane. If the applied voltage is increased, the current

⁷The concentration distribution and potential variation data in this section are from a capillary shaped IEM in an electrolyte, 500 μm long.

Figure 2.17: Potential drop over an electrolyte-CEM-electrolyte system, for current densities below and above the limiting current (I_{lim}). At current densities $< I_{lim}$, an extended potential drop will occur at the depleted zone near the electrolyte membrane interface.

density increases linearly along with the potential, and the concentration at the electrolyte - membrane interface decreases further. On the target side, ions will instead accumulate, resulting in a polarization of ions on the opposite sides of the IEM. This phenomenon is called ion concentration polarization (ICP). The region where these concentration gradients occur, that differs from the bulk concentration, is referred to as the diffusion boundary layer. For a controlled thickness of the diffusion boundary layer, stirring of the electrolyte is needed. [43]

At low voltages, the current response of the electrolyte - IEM system is linear. This region of the current vs. voltage plot is called the ohmic regime. In this regime, the electrolyte volume and concentration are enough to provide a sufficient supply of ions to the membrane inlet. As the voltage, and thus also the current density, in the system increases, the concentration decreases near the membrane inlet. Finally, the concentration drops to zero at the electrolyte-membrane inlet interface. This creates a region where the interface is depleted, leading to a very high local resistance. [54] At this point, the system is dependent on new ions diffusing to the interface. The current response plateaus as the applied potential is increased. The current density at which this full depletion occurs is called the limiting current density, and the corresponding regime in the current vs. voltage plot is called the current limiting regime. [80] The modeled ion concentration distribution, and associated ICP, from a capillary shaped IEM in an electrolyte below and above the limiting current can be seen in Figure 2.18.

Figure 2.18: Concentration distribution over an electrolyte - CEM - electrolyte system, for current densities below (solid lines) and above (dashed lines) the limiting current (I_{lim}). A zoom in at the inlet and outlet can be seen in Figure 2.19a.

A zoom in at the inlet and outlet from Figure 2.18 is found in Figure 2.19a for a range of voltages. Figure 2.19b shows the corresponding current response. The linear (ohmic) current response can be seen for the lower voltages, followed by a characteristic plateau in the limiting current region. When this iontronic circuit is in a resting state ($V = 0$), ions are available at the inlet. After a voltage step is applied to the circuit, the depletion zone will not form immediately, but after the available ions have been transported away. This time lag makes these current vs. voltage plots dependent on scan rate. This data is generated by steady state simulation, meaning infinite times between the voltage increase. Figure 2.17 shows the potential drops for voltages below and above the limiting current density (I_{lim}). For voltages that above the limiting current, the potential will drop very rapidly at the high resistance depleted zone.

Figure 2.19: a) Zoom in at inlet and outlet from Figure 2.18 illustrating the ion concentration polarization for a voltage range from 0-5 V. An ion depletion zone can be seen in the α electrolyte, where the ions enter the membrane. At 5 V a fully depleted zone ($c^\alpha = 0$) can be seen near the IEM surface. An ion enrichment zone can be seen in the β electrolyte, where the ions leave the membrane. Arrows indicate increasing voltage. b) Current vs. voltage response for the same model for 0-5 V, showing the transition to the limited current regime (solid line). The dashed line is an approximated response for the overlimiting regime.

Increasing the voltage further after ion concentration depletion extends the depleted region further into the electrolyte, as can be seen at the inlet for 5 V in Figure 2.19a. After this transition, as the voltage is increased even further, other processes are introduced that gives another increase in current response. This is the final overlimiting current regime. [81] The most important mechanism for the current increase in the overlimiting current regime is convection induced by the rapid potential drop near the electrolyte - membrane interface, called electroconvection. [82, 81] Another contribution, although less pronounced, is the splitting of water into protons and hydroxide ions. This process is known as water splitting or water dissociation and is much more pronounced at the AEM-CEM interface. [80] The model used to generate this data does not include any overlimiting phenomenon and will thus not provide a second current increase. The dashed line in Figure 2.19b is an approximation that exemplifies such an overlimiting behavior.

2.5.2 Forward and reverse bias in bipolar membranes

The current response in monopolar membranes is linear and symmetric within the ohmic current region in the current vs. voltage plot. The symmetry relates to the fact that the direction of the potential gradient will affect the direction of the current, but not the magnitude. Although, a perfectly symmetric response also requires symmetric geometries and electrolytes on each sides of the membrane. Bipolar membranes (BM) on the other hand, will respond asymmetrically to the direction of the applied potential. Thus, the response is non-linear. The non-linear behavior is one-directional and generates a current predominant in one direction, *i.e.* either $<0V$ or $>0V$. The BM stack can therefore be referred to as an ionic BM diode. [48] The direction of the potential gradient that generates the higher current is referred to as forward bias, while the low-current-generating bias is called reverse bias. As exemplified with a BM stack in Figure 2.20, forward bias is obtained for positive potential in the α electrolyte, while a reverse bias is obtained for a negative potential, when the β electrolyte is defined as $0V$.⁸ This diode effect is achieved due to different concentration distributions at the interface between the CEM and AEM in the two different biases.

Figure 2.20: Concentration distribution during forward (solid lines) and reverse bias (dashed lines). In reverse bias, the AEM-CEM interface is depleted. At forward bias, ions accumulate in high concentration due to Donnan failure at the AEM-CEM interface.

In reverse bias, the mobile ions in each of the membranes will move away from the CEM - AEM interface. This will generate a depleted region between the two membranes, with high electrolytic resistance due to lack of mobile charge carriers, that in the ideal case cuts the current completely off. However, in the non-ideal case, a current known as back-current is generated in reverse bias. The magnitude of the back-current reveals the current needed to remove diffusing coions to maintain a depleted interface. In forward bias, the ions will instead move towards the CEM - AEM interface, causing an accumulation of ions in both membranes. When the concentration is high enough, the membranes will lose their selectivity due to Donnan failure. A close magnification of the CEM - AEM interface can be seen together with the associated ionic BM diode's current vs. voltage response in Figure 2.21. The ions in forward bias will move unselectively from both electrolytes across the membranes with anions moving towards higher

⁸Data in the figures in this section comes from a model where the AEM/CEM bipolar membrane together forms a $500\ \mu m$ long capillary ion channel, with a $10\ \mu m$ radius.

potentials and cations towards lower potentials. Due to this unselective transport, BMs are not affected by the ICP phenomena during forward bias, at least not in a symmetrical stack as exemplified here.

Figure 2.21: a) Zoom in at inlet and outlet for reverse and forward bias. Over a few nanometers, the CEM-AEM interface is depleted. In a steady state simulation for a forward bias, the concentrations of both anions and cations exceed the fixed charge concentration of 1 M. b) Corresponding current vs. voltage response for reverse and forward bias. In the model, no water splitting effect is included, and the dashed line is an approximation.

The potential drop in forward bias tends to drop equally as it would over a non-selective membrane stack, while the potential in reversed bias will mainly drop over the AEM - CEM interface. A few examples of potential drops can be seen in Figure 2.22. The potential drop at the AEM - CEM interface in reverse bias will increase with increased voltages. This high potential drop will eventually cause water splitting at the AEM - CEM interface. Water splitting in reverse bias will also generate a current that will increase with increasing potential. The model used to generate the data in Figure 2.20 - Figure 2.22 does not take water splitting into account and will thus not provide a current increase in reverse bias. In Figure 2.21b, the dashed line illustrates an approximation of such a behavior. The voltage level where water splitting is initiated, as well as its magnitude, are dependent on the material and surface properties. [83, 48, 81]

Figure 2.22: Potential drop during forward and reverse bias. Increasing voltages in the reverse bias will increase the potential drop at the AEM - CEM interface.

3

Materials and microfabrication methods

Iontronic devices are composed of three types of materials: the ion conducting material, *i.e.* the ion exchange membranes (IEMs), the electrode material and the encapsulation material. Additionally, the devices are many times fabricated on another carrier substrate. For a device to work as intended, all materials and interfaces between them, need to be reliable. While electrode and ion conducting materials are responsible for electron to ion transfer and charge transport, encapsulation is needed to seal the device and ensure proper transport without any shortcuts. Material selection is not only important for device performance, the choice of materials is also crucial for a successful interface between device and tissue, especially when the device is to be implantable. [10, 34] For materials and devices to be fully biocompatible, their surface as well as mechanical properties must be accepted by surrounding tissues and their cells. The materials also need to endure the biological environment over the intended timeframe to maintain a stable and reliable device performance. A widely used and versatile class of material for bioelectronic devices is organic polymers. Organic polymers are carbon-based materials that consist of subunits called monomers, linked together to long chains. Due to their softer mechanical properties organic polymers can provide a more body-friendly interface compared to classic inorganic materials. [6, 10] Organic polymers are widely used in medicine, for example in drug delivery applications and as coating on stents. [84] In this chapter, the materials used to fabricate iontronic devices are presented, starting with IEMs and electrode materials, followed by a description of microfabrication techniques. The microfabrication techniques includes surface preparations of the carrier substrate, material deposition and photolithography. The a final step of fabrication, covered in the last section of this chapter, is the materials and methods for device encapsulation.

3.1 Ion conducting materials

Polyelectrolytes are polymer where negative or positive ions are present in the chain of repeating monomer units. When polyelectrolytes form a membrane, they are called ion selective or ion exchange membranes (IEMs). [43] IEMs are the core materials for iontronic delivery devices that defines device function and performance. To achieve a stable and reliable performance through device fabrication as well as during operation, high demands are placed on the IEMs. The IEMs needs to be hydrophilic and charged enough to selectively conduct ions, but at the same time not swell excessively due to water uptake when immersed in electrolytes or rinsed in deionized water. Two types of IEM polymers that are used iontronic components will be covered in this section, the linear and the hyperbranched polymers. An overview of these membranes can be seen in Figure 3.1.

Figure 3.1: Two types of linear polyelectrolytes, one polycation (qPVBC) and a crosslinked polyanion (PSS-co-MA/PEG). Hyperbranched polyglycerol can be functionalized into hyperbranched polyelectrolytes. In this example, the HPG is functionalized into a polycation (C-HPG).

The fixed charges on the polymer chains in IEMs are either negative in the case of cation exchange membranes (CEMs) or positive in the case of anion exchange membranes (AEMs). A common negatively charged group for CEMs is sulphonic acid ($-\text{SO}_3^-$), often bound with to styrene to form poly(4-styrenesulfonic acid) (PSS⁻). Chemical crosslinking of the polyelectrolyte chains can significantly improve the mechanical properties and the ability to endure the fabrication process. A crosslinked PSS-derivative can be accomplished by using poly(4-styrenesulfonic acid-co-maleic acid) (PSS-co-MA) together with poly(ethylene glycol) (PEG), an CEM material presented and evaluated for use in iontronic devices in Paper 1. PEG is an hydrophilic polymer that can form hydrogels, can swell extensively in water and is an excellent ion conductor. PEG is widely used in several biological applications, including drug delivery applications. [84, 10] In PSS-co-MA, the maleic acid groups can form ester bonds with the alcohol groups on either end of the PEG, thus crosslinking PSS-co-MA chains. For this reaction to take place, as illustrated in Figure 3.2, PSS-co-MA needs to be in proton form, accomplished by dialysis in HCl. The crosslinked PSS-co-MA provides a reliable and patternable linear CEM with high permselectivity. [63] PSS-co-MA/PEG was used as a cation conductor in Paper 3 and Paper 4, as well as in other related papers [32, 85, 86]. Complementary ionic charge groups used in AEMs are typically amines (NR_4^+) or phosphonium (PR_4^+). The linear AEM poly(vinylbenzyl chloride) quaternized by dimethylbenzylamine (qPVBC) have been used in iontronic com-

Figure 3.2: The reaction between PEG and maleic acid from PSS-co-MA provides a crosslinked IEM.

ponents, mainly as one half of a BM for various applications [87, 88, 48] including the vertical BM diode presented in Paper 3. [89] Dense and tightly crosslinked linear IEM perform well in terms of stability, but can be too dense to efficiently conduct bigger molecules. An alternative group IEMs, based on hyperbranched polymers, addresses this issue by offering a more porous structure. [90] Hyperbranched polyglycerol (HPG) can be crosslinked either by heat or UV and functionalized into polyelectrolytes, by the addition of either cationic groups for AEMs (C-HPG) or anionic groups for CEM (A-HPG). [90, 24] The choice of material including the trade-off between selectivity and permeability is discussed in Chapter 4.

3.2 Electrode materials

Electrodes serve as the interface between the ionic and electronic realm of bioelectronics. A key electrode material is the conducting polymer poly(3,4-ethylenedioxythiophene) combined with the polyelectrolyte poly(styrene sulfonate) (PEDOT:PSS), seen in Figure 3.3. [57, 91, 92] By removing electrons from the conjugated bonds in PEDOT, positive charges (holes) are formed that can move along the backbone, giving electrical conduction. The positive holes are compensated by negative PSS⁻. When the doping state of PEDOT changes, mobile cations move in or out of the film, to provide charge balance to PSS⁻.

Figure 3.3: PEDOT doped with the polyelectrolyte PSS⁻. PSS⁻ can compensate a PEDOT⁺ or be compensated by a small positive ion that is mobile in the PSS⁻ film.

While PEDOT:PSS is the most commonly used and investigated derivate of PEDOT, PEDOT can also be compensated with other ions, such as tosylate (Tos). [92] In contrast to the mechanical mismatch between tissue and metal electrodes, PEDOT:PSS have mechanical properties closer to tissue. The tissue-like Young's modulus provides a good interface to tissue, resulting in reduced inflammation response towards the material when implanted. [93, 10] The list of biological applications of PEDOT:PSS is long, ranging from sensing [94, 95] to different types of drug delivery systems [96, 41, 9]. Sensing capability of PEDOT:PSS is possible due to the change in conductivity dependent on the doping state of the polymer. Sensing electrodes coated with PEDOT:PSS gives a neural interface with low impedance that enables high signal-to-noise ratio recordings. [94]

3.3 Surface preparations

A challenge with multilayer microfabrication is compatibility between layers, especially regarding adhesion. For iontronic devices, this problem becomes especially evident during the combination of swellable hydrogels (such as IEMs) together with more rigid substrates and encapsulants, resulting in a mechanical mismatch at the interface. This mismatch, *e.g.* between an organic and inorganic interface, often lead to delamination issues. [97] A well-known solution to this issue is the use of a coupling agent as an adhesion promoter. The coupling agent creates a chemical link between two materials, such as between a glass substrate and a polymer IEM. Alkoxysilanes ($R-Si-OR$) is such a linker, containing a hydrolyzable alkoxy group (OR) and a silane linker functionalized with a reactive organic group (R) (Figure 3.4). After hydrolyzation of the alkoxy group the resulting silanol can form hydrogen bonds to the inorganic surface, while the linked reactive group can form chemical bonds to the organic surface. One commonly used alkoxysilane is 3-glycidypropyl trimethoxysilane (GOPS), where the R-group is a hydrophobic, highly reactive epoxy. [98] GOPS can be used both as interface linker and, when mixed into the polymer solution, as a crosslinker. Mixing GOPS in polymer solutions limits the polymers ability to swell, and decreases the ionic conductivity in IEMs and PEDOT:PSS films. [99] For PEDOT:PSS, the addition of GOPS decreases also the electronic conductivity. [100]

Figure 3.4: The addition of an adhesion promoter prevents delamination of the polymer film and enables patterning of the polymer on glass substrates.

To bind GOPS to a glass substrate, the alkoxy groups needs to be hydrolyzed (requires presence of water) and OH groups needs to be present at the glass surface. While OH groups appear naturally on glass substrates, the density can be

increased by oxygen plasma or ozone treatment. There are several ways to deposit a GOPS layer to the surface, including immersion in a bathing solution or vapor phase deposition. Immersion in bathing solution containing GOPS is a quick and rough method that usually provides sufficient adhesion. Here, the silanol groups form oligomers, a structure with a few repeating units, through a condensation reaction. After drying and heating, these oligomers can covalently bind to the surface. In vapor phase deposition GOPS is evaporated in a closed chamber by heating, and the GOPS gas can bind to the substrate and later couple together through condensation. Vapor phase deposition is more time consuming but forms higher quality monolayers on the glass substrate surface. [98]

3.4 Material deposition

To build iontronic devices, several layers of different materials need to be deposited onto the substrate. Even though the function of iontronic devices are primarily dependent on polymers, layers of both organic and inorganic materials are typically used. Contacts between the device and electronic equipments are for example usually formed by a patterned gold layer. Metal layers are also convenient as alignment marks, used to successfully align the different layers in a multi-layer device. This section describes deposition techniques used for both metals and polymers.

3.4.1 Thermal metal evaporation

Metals such as gold can be deposited onto substrates by a physical vapor deposition technique called thermal evaporation. The metal to be deposited is placed in a crucible (a tiny boat) inside a vacuum chamber. The crucible is heated by an applied current (resistive heating, Joule's effect) and when the temperature is above the evaporation temperature for the metal, metal atoms vaporize in the chamber. When the vaporized atoms reach a surface, such as a substrate, they condense to form a thin film. The thickness and uniformity of the film can be controlled and reproduced to a high degree, especially if the substrate is rotated during the process. [101] A convenient thickness for gold contacts and alignment marks is around 50 nm, thin enough to be easily patterned and patterned on top of, while still thick enough to give low resistance for contacting and good optical contrast for visual alignment. A layer of a few nm of chrome or titanium is often deposited prior to gold to improve the adhesion of the gold film to the substrate. The deposited metal film can be further patterned, commonly by photo-patterning, followed by either etching or lift off.

3.4.2 Polymer deposition techniques

Polymers can be deposited by a range of techniques such as spin-coating, drop-casting, spray-coating, ink-jet printing, lamination, electropolymerization etc. The main polymer deposition techniques used for iontronic devices can be seen in Figure 3.5. Spin coating is a common, reliable and reproducible method when the

bottom layer or carrier substrate is very flat. The solution of the material is dispensed on the substrate, and the spin-coater initially spreads the solution across the substrate by spinning the substrate at first a slow speed, followed by an acceleration reaching a final spin speed. During this time, the solution forms a very uniform film due to the centrifugal force and solvent evaporation. The viscosity of the polymer solution, initial acceleration, spin speed and spin time are parameters that can be varied to control the final thickness of the film. If the viscosity of the solution is too high to spread well, one can decrease the concentration or slightly increase the temperature of the solution. [101] Drawbacks for spin-coating is the large amount of wasted material and difficulty to form uniform films on uneven surfaces.

Figure 3.5: Material deposition using spin coating, drop-casting on pre-patterned carrier substrates and lamination as a sealing layer.

In the situations where spin-coating is not an option, drop-casting or spray-casting can be an alternative. Drop-casting, in contrast to spin-coating, benefits of uneven, pre-patterned surfaces. An already patterned surface can then define a chamber for the material, where the capillary force acts to pull the material to its intended area. While spin-coating covers bigger areas where several devices can be patterned next to each other, drop-casting is a serial (time-consuming) process with poorer possibility to control the thickness. Printing techniques using inkjet is an alternative to drop-casting that can be set up to be more automatic than manual drop casting. [68] Spin-coating, drop-casting, spray-coating, and ink-jet printing all deposit the material from solution, and are usually followed by a baking step to remove excess solvent. In some cases, crosslinking by UV or heating can also take place before further processing steps. Some polymer materials are not acquired in solution form, but in pre-made films. These can be added to the carrier substrate or material stack by lamination. Additionally from being deposited from solution, materials such as PEDOT:PSS and PEDOT:Tos can be directly polymerized onto surfaces either by electropolymerization or vapor phase polymerization. For electropolymerization, soluble monomers are mixed together with their counter-ion and polymerized directly on a contacted metal surface by application of an electrical bias. [102, 103]

3.5 Photolithography

To interface an iontronic device with neurons, where features are in the nano to micrometer scale, at high resolution requires highly sophisticated microfabrication or nanotechnology techniques. In iontronic devices the electrodes, ion conductors, and encapsulants are usually based on thin films ranging from tens of nanometers to hundreds of micrometers. To avoid contamination of the device during manufacturing, the fabrication takes place in a cleanroom where particles in the micrometer scale is controlled. [101] In general, the manufacturing process is composed of multiple iterations of surface preparation, material deposition and patterning. Often, the patterning is based on UV photolithography. Photolithography is a patterning technique that transfer a pattern from one master substrate to another substrate, by using photo patterning with UV beams and etching techniques. [101] The final step of fabrication includes sealing of the device with an encapsulant to ensure only the inlets and outlets of the device are exposed.

3.5.1 Photo-patterning

The first step in photolithography is photo-patterning where a pattern is transfer from a photomask to a photosensitive polymer, called photoresist, coated on the substrate. The pattern on the photomask is defined by opaque and transparent areas. Photomask are typically made from chrome-coated glass substrates, and the pattern produced through point-wise exposure of a photoresist and the subsequent etching of the chrome layer. These chrome-patterned glass masks offer very high resolution (with features as small as 10 nm). [101] For each device design, several different patterned layers, and thus masks, are needed. To successfully place several layers of patterns on-top of each other, special alignment marks are patterned on the first layer that can be used to align the masks belonging to the following layers. The alignment between layers (*i.e.* between photomask and previous layers on the substrate) is performed in a mask aligner, that also after alignment exposes the substrate with UV light, for example to 365 nm light (i-line of a high pressure mercury-vapor lamp). After exposure of UV light, the substrate with the exposed photoresist is immersed in a developer solution that dissolves either the exposed or the non-exposed areas. A photoresist that gets soluble by UV exposure is called a positive photoresist.

Figure 3.6: Side view of a photolithographic process for a positive photoresist. The opaque area of the photomask protects the layer underneath, and transparent areas is exposing the photoresist underneath that gets soluble in the developer solution. After photo-patterning, the layer underneath, not covered by the photoresist, can be etched away in a following step.

The opposite type, the negative photoresists, gets polymerized or crosslinked by UV (sometimes in combination with heat), and the non-exposed areas are then soluble to their developer. [104] Positive photoresists and non-permanent negative resists are commonly used to pattern polymers, and then functions to protect areas from removal during a following etching step (Figure 3.6). Such protective photoresists are usually removed from the substrate after the polymer is etched. In contrast, the strong polymerization or crosslinking of some negative photoresists, such as SU8, enables them to be as permanent protection or encapsulating layer in the component (Figure 3.9). The resolution achievable with photolithography is restricted by the parallelity and wavelength of the UV light, the photoresist type and thickness and mask resolution. High resolution and well-shaped patterns also require an optimal exposure dose in mJ cm^{-2} (exposure time (s) multiplied with the lamp power (mW cm^{-2})). The dose needs to be adjusted for the photoresist type and thickness and the substrate material, to avoid under- or over-exposures. [105]

3.5.2 Etching

Etching is a technique for removal of material. Generally, a protective layer (such as the patterned photoresist from the previous section) protects the areas of the material to be kept while exposing the areas meant to be removed. There are two main categories of etching techniques, dry etching and wet etching. Dry etching is a process where gaseous species is used to remove material. The etching chamber is filled with one or a mixture of gases and an alternating electromagnetic field is applied to ionize the gas molecules and create a plasma. One type of dry etching is reactive ion etching, where the material is removed by both physical and chemical effects as the ions in the plasma interacts with the substrate. While the physical (sputter) removal is non-selective, chemical reactions between reactive ions and the material at the surface can gives a selective etching process. Polymers can *e.g.* be etched by oxygen or oxygen/flouorocarbon plasma. The etching rate is dependent on the substrate material and plasma parameters such as applied power, pressure and gas mixture. [68] The applied electromagnetic field in the plasma chamber directs the reactive ions towards the substrate. Thus, this process can be highly anisotropic, *i.e.* predominantly directed in one direction that can result in patterns with close to vertical side walls. [101]

Figure 3.7: In the etching step, areas not protected by the photoresist is exposed to etching and removed, and the pattern from the mask is transferred to the bottom layer. Polymer etching by dry reactive ion etch gives vertical side walls by anisotropic etching (left). Wet etching of gold is directed in all directions, with a characteristic isotropic etching profile (right). After this step, the photoresist can be removed, and the substrate is ready for a cleaning step before the addition of sequential layers.

Wet etching is a process where the substrate is immersed in an etching solution that selectively react with, or dissolves and removes a specific material on the substrate. Wet etching, *e.g.* the etching of gold with iodine, is many times isotropic, *i.e.* equal in all directions. [106] The etching rate is controlled by the combination of material and etching chemistry in combination with factors such as concentration, solution temperature and solution movement. [68]

3.5.3 Lift-off

Lift-off patterning occurs in the reverse order compared to patterning by etching. First the photoresist is deposited, exposed, and developed directly on the sample, followed by deposition of the material to be patterned, typically an evaporated metal layer (Figure 3.8). After the evaporation, the photoresist is dissolved, thereby also removing the material deposited directly on top of it. The photoresist thus act as a so called sacrificial layer, that is removed for the purpose of removing something else. Although a perfectly vertical photoresist sidewalls are preferable for best resolution, a slight over-exposure of the photoresist is typically used for lift-off patterning to produce a slightly undercut profile. For lift-off of metals, the undercut profile shadows the photoresist walls from the deposition, allowing better access for the solvent used for removal. [104]

Figure 3.8: A patterning of metals with the lift-off technique starts off with patterning of a photoresist, with an over-exposure that gives an undercut shape of the side walls. The substrate with the patterned photoresist is placed in a vacuum chamber, where the metal is evaporated. Removal of the photoresist leaves a patterned layer attached to the substrate surface.

3.6 Encapsulation materials

The third important material class for iontronic components are the non-permeable materials used for encapsulation. The encapsulant covers the IEM and acts as a barrier between the drug reservoir and channel and the target system, and defines openings such as inlets and outlets. The function of the encapsulant is important since it assures that ion currents travels along the intended pathways, *i.e.* through IEMs and inlets and outlets. Any minor cracks or pinholes in the encapsulant will cause an ionic short circuit and cause failure of the device. The encapsulant should thus be a good insulator. It is also important that the encapsulant adhere well to the carrier substrate and the IEM to prevent the formation of unwanted water pathways. Since the IEM is highly hydrophilic and therefore swells when immersed in water (*e.g.* during operation of a device) proper adhesion can be quite

challenging. A material that performs well as an encapsulant is the negative photoresist SU8. SU8 is a high-density epoxy-based photoresist that can be used to pattern high resolution structures with high aspect ratio and is widely used in biological applications. [107] An example of a patterning process using SU8 can be seen in Figure 3.9. SU8 is deposited from solution and is usually spin-coated. After the deposition, the polymer is exposed and crosslinked by a photoinitiated polymerization of the epoxy groups. Even though the polymerization is initiated by UV, a post-exposure bake accelerates the process to produce a full crosslinked polymer. The non-crosslinked areas (shadowed by the mask during exposure) are rinsed away in a developer solution after the post-exposure bake. [107]

Figure 3.9: Photo-patterning of a negative photoresist, used as an encapsulation layer. The transparent areas of the mask allow exposure of the areas underneath, that is crosslinked by the UV exposure. The development solution removes the un-exposed parts of the polymer film, thus finalizing this patterning step. For process optimization, fine-tuned baking steps takes place after deposition, after exposure and after development.

The photo-patterning of SU8 is considered an art in the sense that optimization and many tricks can be applied during the several steps of spinning, pre-baking, exposure, post-exposure baking, and final hard bake for a successful patterning. This is especially important if the goal is high aspect ratio (height/width) structures. [108] A dry film alternative for encapsulation is the negative photoresist Ordyl SY300 (Resistech). [109] Ordyl SY300 can be laminated on top of uneven surfaces (Figure 3.5) and is rigid enough to allow sealing of hollow voids, such as microfluidic channels. In Paper 2, Ordyl SY300 is used as the carrier substrate as well as encapsulant for the hybrid microfluidic-iontronic tip of a microfluidic capillary. The target application for Ordyl SY300 is MEMS applications and complex biochips and initial tests for biocompatibility are encouraging. [110, 109]

4

Device and circuit design

The development of new iontronic devices or circuits requires considerations from many point of views. This chapter covers these different considerations and highlights some important tradeoffs and restrictions with respect to operation and design of devices. The physics of mass transport, as discussed in detail in Chapter 2, gives us a crucial platform to develop and explore device designs for various applications. On the other hand, theory sets design rules and boundaries for what the iontronic technology can in fact provide and deliver in terms of device specifications and performance. Fundamentally, we can control the drift of ions upon applying a potential and we can also, to a large degree, control the transport of the electrolyte fluid. Diffusion on the other hand, is a spontaneous movement of species that will occur as long as there are concentration gradients. How to utilize these transport phenomena, to achieve iontronic devices that operates in the most optimal manner for a dedicated application, will be discussed in this chapter. Target experiments (specific or more hypothetical) sets the requirements for device design and dictate also the level of complexity. While added complexity can increase device performance, *e.g.* on/off ratio, delivery time or spatial addressability, it can however result in device architecture that are very hard to manufacture and/or to operate. This chapter focus on designs considerations within the scope of the iontronic devices of this thesis, with specific experiments and applications as a target. Towards the end of the chapter, an overview of all the specific devices developed and reported in this thesis are presented. Future directions and consideration will be discussed in Chapter 6.

4.1 Device requirements

The device and circuit design such as properties of materials and the architecture of the final iontronic device design impact the device characteristics. How these factors and properties are coupled are reviewed and summarized in Figure 4.1. For an iontronic device to serve as an adjustable complement to an already existing end-application setup, *e.g.* an electrophysiology setup for patch clamp recordings,

a free-standing probe design might be favorable and desired. For such free standing probes, the list of materials available to realize complete devices is shorter than for planar devices. For the purpose to encapsulate our free-standing probes, a dry photoresist was used for the devices in Paper 2. For this probe, the encapsulation serve both as the supporting substrate during the manufacturing process and also as the final carrier and as the top encapsulant. In other applications, various planar device configurations that acts as a bottom layer in an experimental setup is accepted or even preferred. For successful evaluation using optical techniques in experiments with planar devices, glass support substrates are preferred over polymer-based substrates, since the latter often are non-transparent. Planar devices on glass substrates requires an ion exchange membrane (IEM) that can be patterned by photolithography and that at the same time adhere well to the glass surface. Both material evaluation of PSS-*co*-MA/PEG and its processing on glass substrates was performed in Paper 1.

The specific targeted experiment sets the criteria for device dimensions, all from the smallest dimensions of e.g. the outlet to the overall device dimensions of the ion channel and reservoirs. Specific dimensional properties affects then specific device performance parameters, see Figure 4.1. For example, we can use the spatial properties to tune the resistance of the ion channel. The resistance in a resistor depend on the resistivity, length and area, $R=\rho l/A$ (Equation 2.31), meaning that a longer ion channel will thus have higher resistance than a shorter one, and a thinner ion channel will have higher resistance while comparing to a thick channel. Resistivity is a fundamental material property that we can adjust, via chemistry, but on the other hand we can also compensate for high or low resistivity via spatial and dimensional properties.

4.1.1 Miniaturization

In general, it is advantageous if the over-all device dimensions are as small to guarantee minimal invasiveness. Both from a fabrication and device design point of view, miniaturization can be utterly challenging, with respect to carrier substrate, manufacturing and encapsulation. Physical forces act very differently on small-sized objects as compared to large devices and systems, as the volume to surface ratio changes. [101] An example of this is obvious for fluidic behavior, explained by the Navier-Stokes equations (Equation 2.14), where large scale systems are more affected by inertial forces (mass and volume), but for small-scale system friction forces (surface properties) is dominating. [66]

Scaling down the ion channel outlet and the source reservoirs are other examples where miniaturization will affect device behavior. As discussed in Chapter 2, the ohmic regime is to one extent restricted by experimental conditions such as potentials, concentrations and convection of the electrolyte. [54] Also, geometrical conditions such as minimized inlet areas and source reservoirs will add on limitations to the ohmic regime, even further. How ion concentration polarization (ICP), that causes ion depletion in the source reservoir limits device operation, and how to extend the ohmic regime versus operational potentials, is investigated both in Paper 2 of this thesis, as well as in the work from Seitanidou et al. on miniaturized capillary-based devices [64].

4.1.2 Transport of the neurotransmitter

The neurotransmitter supposed to be released, driven by its specific charge, dictates whether an AEM or an CEM is needed as the ion channel in the OEIP. The choice of IEM, along with its inner structure and morphology, is also correlated to the size of the molecule intended for release. There is a clear tradeoff between the permeability and the selectivity of the IEM. [111] The charge selectivity of the IEM is directly dependent on the fixed charge density, where higher density typically gives higher selectivity. The fixed charges are placed on the pore walls, and electrostatic interactions are restricted by the Deybe length. The pore size, related to water uptake and cross-linking density, limits the permeability by size. As the pore size is increased, the charge density is decreased, while the range of the electrostatic interactions remains constant. Thus, an increased pore size increases the permeability but allows for an increased inclusion of coions. As a consequence, this leads to a higher permeability and conductivity of the membrane, by sacrificing selectivity. [112] Ideally, this would be balanced, where pore size is big enough to transport the ion of interest, while dense enough to provide as high fixed charge density as possible in the ion channel.

4.1.3 The released dose

The aim for the delivered dose is to tune it until it is high enough to generate desired effects, while at the same time staying below the limit for harmful side effects, *i.e.* well within the therapeutic window. The dose from an iontronic device can be tuned by the magnitude and duration of a voltage pulse. The voltage pulse generates migration of ions in the IEM, leading to increased concentration at the target side. Due to the high resistance in the ion channel, no significant potential drop takes place beyond the Donnan potential drop at the interfaces (see Figure 2.17, Chapter 2). Ionic transport outside the membrane channel, within the target electrolyte, is typically pure diffusional. Diffusion is a dynamic process dependent on the concentration gradient and the diffusion coefficients of the ionic species (reminder from Equation 2.7, Chapter 2):

$$\vec{J}_{i,\text{diffusion}} = -D_i \nabla c_i \quad (4.1)$$

The concentration gradient reveals that the distance from the release point to the site of stimulation is important for the diffusion range. The delivered dose will be levelled out and will, at a certain distance, reach concentration levels below the activation threshold. This was exemplified by Tybrandt et al. in an experiment with a lateral OEIP releasing ACh⁺ to neuronal cells. [113] A cell located 50 μm from the ion channel outlet (10 μm wide) responds to short delivery pulses (200 ms). However, the cell located at 150 μm away from the outlet needs a relatively longer pulse to in order to respond (800 ms). Thus, the dose decreases with distance, following Equation 4.1. The same behavior can be observed while releasing charged species from vertical diodes. Figure 4.2 shows a simulated pulse propagation, where it is found that the concentration levels out quickly already over the 10 μm travel distance from the IEM to the end of the encapsulation thickness.

Figure 4.2: A delivery pulse creates a steep concentration gradient that over space reduces quickly. Initially after the release pulse, the concentration increases until it reaches a maximum concentration at the delivery outlet. In this simulation the maximum concentration reaches approximately 800 μM at a distance of 10 μm , after a 4 ms long release pulse from an IEM with 1.5M fixed charge concentration. Figure adapted from Paper 4. [114]

At the other side of the release dynamics we find timing effects and characteristics. We aim to control, not only what, but also when the fine-tuned dose is actively delivered. However, the time duration between the active on-state, is termed the off-state. The off-state of the ionic resistor OEIP is defined as the state when the device is not operated, *i.e.* a 0 V potential bias is applied, *i.e.* no migration from applied potentials occurs (reminder from Equation 4.3, Chapter 2):

$$\vec{J}_{i,\text{migration}} = -\frac{z_i F}{RT} D_i c_i \nabla \phi \quad (4.2)$$

The lack of applied potential does not hinder diffusional fluxes, *i.e.* the passive delivery. During the off-state, the aim is to keep the passive delivery below any activation thresholds. The ratio between the states is referred to as the on/off ratio. The on/off ratio of a device can be considered by comparing the migrational flux from applied potentials and the diffusional flux.

$$\frac{\vec{J}_{i,\text{migration}}}{\vec{J}_{i,\text{diffusion}}} = \frac{z_i F}{RT} \phi \quad (4.3)$$

where F is Faraday's constant, R is the universal gas constant and T is the temperature. $(FR/T) \approx 40$, *i.e.* the on/off ratio is approximately 40 times the applied potential for monovalent ions. [113] Accordingly, we can tune the on/off ratio of with the resistance in the ion channel for OEIPs, to reach higher operational voltage for the on state.

In the case where the magnitude of the passive delivery from an OEIP resistor is still too high for the target system, other approaches can be utilized to counteract passive delivery. This can be achieved by for instance applying a diode to the device configuration which is operating in the reverse mode, a feature which actively prevents passive delivery (Paper 3 and 4). Another setting that includes an active off-mode is when an iontronic circuit is included, which contains multiple separately addressable release sites. The diodes are then responsible for keeping some outlets off, while addressing others to actively release ions. For individual addressing, a more complicated circuit design is required, including considerations of the placement and contacting of individual control electrodes.

4.2 The speed of iontronics

The level of control as well as the speed of transport varies drastically between the three discussed transport processes: diffusion, migration and convection (Chapter 2). We can adapt to these differences by taking advantage of the best suited transport process at different stages of transportation. Additionally, the total period of time used to cause delivery can in fact be divided into two separate steps, which allows us to separate the time of loading from the actual time of release and it's dynamics.

4.2.1 Time of loading

The distance between the source reservoir and the target system sets the delay from when the OEIP is completely turned from off to on. For basic OEIP resistors, this off-to-on transition agrees to filling the total length (volume) of the ion channel. This period of time is referred to as the loading time. The loading of an ion channel is traditionally governed by migration. The speed acquired by migration, referred to as drift speed (v), that depends on the specific diffusion coefficient (D_i^m) of the transport phase and the potential gradient ($-\nabla\phi$). In an IEM (phase m), the average drift speed (for each ion i) with respect to the solvent can be decided as:

$$v_i = -\frac{z_i F}{RT} D_i^m \nabla\phi \quad (4.4)$$

where F is Faraday's constant, R is the universal gas constant, and T is the temperature. Applying 10 V over a 1 cm long ion channel for transport of ACh^+ (where $D_{\text{ACh}}^m \approx 0.1 \cdot D_{\text{ACh}}$) gives a drift velocity in the range of $2 \mu\text{m s}^{-1}$. For a specific device, the total volume of the ion channel and its fixed charge density will determine the time, or rather the amount of charge, it takes to load and reload the ion channel with the specific ion intended for transport and release. Over longer distances, it can be desirable to decrease this loading time. Fluidic motion can easily transport high concentrations of dissolved ions in the range of mm s^{-1} in microfluidic channels [36]. This is a rather swift transport mechanism while comparing to the $\mu\text{m s}^{-1}$ transport rates achieved by migration through IEM channels. A faster loading and reloading also enables faster switching between different neurotransmitters and/or buffer solutions during running experiments. Using fluidic motion for loading was utilized in a hybrid microfluidic iontronic device, presented in Paper 2.

To instead circumvent the period of time devoted for loading, a local source reservoir in the IEM can be achieved by the addition of a waste channel that is connected to a third electrolyte. In this way, pre-loading can occur before the first delivery pulse. This was first utilized in a lateral version where the final target channel was shorter and thinner than the source to waste channel. [113] This strategy was further evolved and explored in the work reported in Paper 3 and Paper 4.

4.2.2 Time of release

While the range of diffusion sets limits to how far the signal can reach (Figure 4.2), the diffusion time sets limits on how fast a signal can reach a target after the addressing bias has been applied. Einstein showed that diffusion in one dimension, the time (t) it takes for a particle in a random walk event to travel a distance (x), is expressed as the mean square displacement (x^2) for an ensemble of similar particles and is also inversely dependent on the diffusion coefficient (D) for the specific ion (i): [17]

$$t = \frac{x^2}{2D_i} \quad (4.5)$$

The diffusion coefficients of ions in water is on the order of $10^{-9} \text{ m}^2 \text{ s}^{-1}$, and a few examples can be seen in Table 4.1. Protons H^+ extreme on the high range due to proton hopping (Grotthus mechanism), and large ions can be very slow. [115] According to Equation 4.5, a traveling distance of 50 nm, that is the distance range of the synaptic cleft, would thus take approximately 1 μs for Na^+ , and 2.3 μs for ACh^+ .

Table 4.1: Diffusion coefficients at 25° C at infinite dilution¹, 100 mM² and 1 mM³.

	Dif. coeff. ($\text{m}^2 \text{ s}^{-1}$)	Ref.		Dif. coeff. ($\text{m}^2 \text{ s}^{-1}$)	Ref.
K^+	$1.957 \cdot 10^{-9}$	[116] ¹	1/2 Ca^{2+}	$0.792 \cdot 10^{-9}$	[116] ¹
H^+	$9.311 \cdot 10^{-9}$	[116] ¹	ACh^+	$0.544 \cdot 10^{-9}$	[117] ²
Cl^-	$2.032 \cdot 10^{-9}$	[116] ¹	GABA	$0.765 \cdot 10^{-9}$	[118] ²
Na^+	$1.334 \cdot 10^{-9}$	[116] ¹	NaHGlu	$0.836 \cdot 10^{-9}$	[119] ²
OH^-	$5.273 \cdot 10^{-9}$	[116] ¹	indigo carmine	$0.314 \cdot 10^{-9}$	[120] ³

To get a more complete picture of specific concentration levels and time frames for ions released by specific iontronic devices, finite element modeling of the Nernst-Planck-Possion equations can be utilized. [113, 72] In Figure 4.3 the time resolution from Figure 4.2 is added, showing a release pulse of 4 ms from the polarization diode in, reported in Paper 4. The maximum concentration of 800 μM was reached after approximately 20 ms but reached a threshold level (set to 100 μM to match physiological values [121, 113]) already after approximately 6 ms. Increasing the pulse width to 6 ms, increases the released dose and decreases the time until the threshold is reached to 5 ms, with a maximum concentration of 1.9 mM reached after 20 ms.

Figure 4.3: Release pulse propagation over time. A threshold limit at 100 μM was reached after 6 ms at 10 μm distance from the CEM, reached a maximum concentration at 20 ms followed by a decay. Figure adapted from Paper 4. [114]

4.3 Overview of developed devices

This final section of this chapter aims to give an overview of the devices designed and developed within this thesis, utilizing the design principles described above. The evaluation techniques used to establish their performance details are described in the next chapter, Chapter 5. A full description of the devices and their specific evaluation experiments are found in Paper 2, 3 and 4, respectively.

4.3.1 Hybrid microfluidic iontronic probe

The hybrid microfluidic iontronic probe, seen in Figure 4.4 was designed to be a user-friendly free-standing probe, combining microfluidics and iontronic technology within the same device setting. The hybrid probe operates at reasonable dynamics and transient characteristics, by utilizing the different transport phenomena available in a well-balanced way.

Figure 4.4: The hybrid microfluidic iontronic probe utilizes fluidic, migration as well as diffusional transport, during different stages of ionic transport from a source reservoir to the target system.

The capillary microfluidic system is responsible for the pre-loading as well as for the waste handling. The transport is shifted from microfluidic transport to migrational transport in the region denoted to as the transfer chamber. The ions migrate through a short, low-resistance ion channel based on a C-HPG membrane, according to the potential gradient between an PEDOT:Tos electrode, located in the transfer chamber and a target electrode, located on the outside (Figure 4.4). By using the fluidic motion for long range transport, the pre-loading step and time is decreased while the source reservoir is miniaturized. Migrational transport are utilized in the short-range ion channel, followed by a diffusional delivery at the ion channel outlet.

4.3.2 Vertical bipolar membrane diode

As discussed in this chapter, the transport distance together with the transport mechanism and transport speed limits how fast a neurotransmitter can be delivered at the outlet site. When aiming for faster delivery, migration combined with diffusion are desirable transport mechanisms to keep to retain high control and pressure-free release. Thus, the key to faster delivery, *i.e.* to reduce the time delay from decision to release, is to reduce the dimensions.

The general idea for these fast delivery devices is to divide the transport in the two steps, as presented in Ref. [113] and as described above. By using the lateral direction for pre-loading and utilizing the vertical distance available and defined by the thickness of thin films for release, the delivery is separated both in time and dimension. Thus, the pre-loading takes place over millimeters to centimeters, while the actual release is governed by vertical addressing which is defined by layers being a few micrometers in thickness. In Paper 3, a fast release OEIP with a vertical bipolar membrane diode is presented, also here in Figure 4.5.

Figure 4.5: In this device, designed for fast release, pre-loading of neurotransmitters occurs in the lateral direction from the source reservoir to the waste electrolyte. Between delivery pulses, the vertical diode is kept in a reverse bias. The PEDOT:PSS control electrode is used to switch the diode from the reverse bias to forward bias to initiate vertical release. After a release pulse, the diode is switched back to reverse bias. When operating the device in the reverse bias in between the release pulses, the control electrode can be re-loaded with new neurotransmitters provided from the source reservoir.

As a first step, cations are loaded in the lateral ion channel (PSS-co-MA/PEG) by a potential gradient between the source reservoir (with source electrode potential V_s) and the waste electrolyte (with waste electrode potential V_w). A control electrode (potential V_{CE}), placed vertically underneath the outlet is made by PEDOT:PSS. The PSS^- in the control electrode forms together with a thin film of qPVBC a vertical bipolar membrane diode.

The PEDOT:PSS control electrode is kept at a negative potential relative to the target electrolyte $V_T = 0V$. The negative potential keeps the vertical diode in reverse bias, while simultaneously loading it with cations ready to be released in the next step. When the pre-loading is done, ions can be released vertically by switching the control electrode to positive potentials, and thus switching the vertical diode to forward bias relative to V_T . After a release pulse is generated, the potential is switched back to negative, stops the release and re-loads the PEDOT:PSS with new cationic neurotransmitters ready for release in the next release pulse.

4.3.3 Polarization diode

In Paper 4, another version of a vertical diode is presented, illustrated in Figure 4.6. In this polarization diode, the reverse bias is also based on ion depletion at the membrane interface, but here this effect is due to a restricted outlet geometry that generates ICP and a following local ion depletion region in the target electrolyte at the site of the outlet.

Figure 4.6: A high aspect ratio outlet in the encapsulation layer, *i.e.* the outlet channel, defines the vertical polarization diode. As in Figure 4.5 pre-loading takes place in the lateral film underneath the outlet before and after the releasing events.

Depletion will occur in this miniaturized outlet channel, at a limiting current directed towards the waste electrolyte, dependent on the concentration and diffusion coefficient of the ion (c_i and D_i) and the dimensions and geometry of the outlet channel. Assuming an ideal permselectivity of the membrane, the limiting current I_{lim} can be estimated by the Equation 2.19 (Nernst-Planck eq.) to: [46]

$$I_{lim} = \frac{-2D_i c_i F A}{d} \quad (4.6)$$

where F is Faraday's constant, A is the outlet channel area and d the outlet channel distance, *i.e.* the encapsulation thickness. Accordingly, a higher aspect ratio in the outlet channel that is fabricated for this diode, the lower back-current is thus needed to maintain a depleted outlet in reverse bias. Migrational pre-loading of cations takes place in the lateral ion channel (PSS-co-MA/PEG) by a potential gradient established between the source reservoir (with source electrode potential V_S) and the waste electrolyte (with waste electrode potential V_W). In this vertical diode configuration, in a device with a single release site, no control electrode is neither incorporated, nor needed. Switching from reverse to forward bias is instead entirely performed by altering the V_W in relation to V_T in the target electrolyte. In forward bias, a high current density will cause Donnan failure at the outlet interface, which promote accumulation of ions in the device in a similar manner as the mode of operation of ion bipolar membrane diodes.

4.3.4 Chemical delivery array

In Paper 3, the vertical membrane diodes were connected together into a chemical delivery array for release of cations with high spatiotemporal addressability. The individual addressing is possible due to the control electrodes, placed vertically below the release outlets. Figure 4.7 shows a simplified overview of this array. In this device, pre-loading was performed in six parallel ion channels connected to a common source reservoir (and source electrode potential V_S) and common waste electrolyte (and waste electrode potential V_W). Every release site has one dedicated PEDOT:PSS control electrode (potential V_{CEi} each, where i is release site $i=1-6$). Release is performed by individually switching the vertical diodes from reverse to forward bias by the control electrodes relative the target potential at 0 V. The different potentials was set in the order of $V_S > V_{CEi}$ (off) $> V_T = 0 > V_{CEi}$ (on) $> V_W$ to achieve a constant pre-loading of diodes at reverse bias and instant delivery pulses of selected diodes temporarily switched to forward bias.

Figure 4.7: A chemical delivery array with individually addressed vertical release sites. Pre-loading takes place in the lateral direction from a common source reservoir to a common waste electrolyte. The control electrode dedicated to each vertical bipolar membrane diode allows release from one or several release sites while preventing release from others by active reverse biasing.

5

Device evaluation

To evaluate the performance of developed materials, devices, and circuits, several different evaluation techniques are used together. During device fabrication, most evaluation is performed with optical techniques based on microscopes and surface profilers. The fabricated devices are later characterized both in terms of electrical characteristics and chemical output, *i.e.* released dose quantification. Additionally, theoretical investigations of device behavior with numerical simulations can be used to complement the electrical and chemical characterization techniques. These techniques are used in different combinations within this work, all contributing to an overview of device behavior. In this chapter, these characterization techniques will be explained in general terms together with some specific examples from the Papers.

5.1 Electrical characterization

Using a source meter, either a constant voltage or a constant current can be sourced while measuring the other (current or voltage). The measurement technique is called amperometry when potential is sourced (measuring current), and potentiometry when current is sourced (measuring potential) and can be performed in real time during loading and release of ions. Following these measurements, the resistance of the device and resistivity of the IEM can be determined (from Equation 2.30 and Equation 2.31, Chapter 2). Resistance of the IEM can be determined from the resistivity together with ion channel geometry set by the mask design and thickness measured with profile measurements during fabrication. The resistivity will vary depending on the phase-specific mobility of the ionic charge carriers in the IEM. Other phenomenon affecting the resistivity of the channel is the water content and level of hydration. [115, 57] The majority of the current is conducted by counterions, while coions contribute to a lesser degree (Figure 5.1). Thus, the mobility of the counterion will affect the total resistance to a larger degree than the coion.

Figure 5.1: An overview of the iontronic circuit. Both counterions and coions can contribute to the total current, where the majority of current is carried by the counterions. The measured resistance depends on the charge carriers and the ion channel properties.

The change in resistivity can be measured during the transition from transport of i) a high mobility counterion to ii) a low mobility counterion. The resistivity will evolve from a higher constant level, decrease during the transition, and level out at a lower level when the ion channel is filled. By integrating the current (I) over the time span for transition from a high mobility ion to a lower mobility ion (t_0 to t in Equation 5.1), we get information about the total charge (Q) transferred in the circuit:

$$Q = \int_{t_0}^t I(t)dt \quad (5.1)$$

The charge used in this transition equals the ion exchange for the entire bulk of the ion channel and can thus be translated to the total amount of fixed charge in the ion channel membrane. The total amount of fixed charge together with volume specifications of the ion channel gives an estimation of the fixed charge density. [24] If the volume measurements are performed in a dry state, the fixed charge density also reflects that dry state. The fact that the measured resistivity changes with the mobility of the ion can also be used to evaluate selectivity properties, as demonstrated in Paper 1.

If the mobility, and thus the diffusion coefficient, of ions in the channel is assumed to scale with the mobility in water, the total current should scale linearly with the diffusion coefficient of the major charge carrier. Since IEMs are also size-selective, this assumption is only valid as long as the ions are small enough compared to the effective pore size of the specific IEM. If the membrane is highly selective, and thus with a negligible inclusion of coions, the total current should show a minor or negligible dependence on the mobility of the coion loaded in the target reservoir. In Paper 1, cations were loaded in the source reservoir in contact with a CEM and the current response was investigated by the use of different ion pairs with different mobilities in the source reservoir and target electrolyte.

5.1.1 Membrane potentials

The transport numbers (Equation 2.12, Chapter 2) can also be evaluated using purely electrical characterization techniques. Traditionally, evaluation of apparent transport numbers has been conducted for free-standing membranes, by measuring the membrane potentials over a range of different concentration differences across the membrane. [122, 65] In Paper 1, we tested this technique in our lateral OEIP to estimate the transport numbers of K^+ and Cl^- in a PSS-co-MA/PEG ion channel. As discussed in Chapter 2, the fixed charge density of the membrane affects the magnitude of the membrane potential. The total membrane potential across an IEM, measured in the two electrolyte phases (α and β) in an electrolyte is the sum of two Donnan potentials and the diffusion potential. [43, 76]

$$\phi_M = \phi_D^\alpha - \phi_D^\beta + \phi_{dif} \quad (5.2)$$

Since K^+ and Cl^- exhibit similar diffusion coefficients ($D_{K^+} = D_{Cl^-} \approx 2.0 \cdot 10^{-9} \text{ m}^2 \text{ s}^{-1}$, Table 4.1), the influence of ϕ_{dif} can be neglected, reducing the membrane potential to:

$$\phi_M = (t_+^m - t_-^m) \frac{RT}{zF} \ln \frac{c_i^\alpha}{c_i^\beta} \quad (5.3)$$

where t_+^m and t_-^m are the transport numbers of the ions in the membrane and $t_+^m + t_-^m = 1$. In an ideal membrane, the transport number of the counterion is 1 and the transport number of the coion is 0. [65] Thus, by measuring the membrane potential by an open circuit ($I = 0$) with known concentrations of KCl in both reservoirs, Equation 5.3 can be used to estimate the apparent transport numbers of K^+ and Cl^- in the IEM. The apparent transport numbers shows a small deviation from the true transport numbers, since apparent transport numbers neglect any water transport. [44]

5.2 Dose quantification

The other side of device characterization involves the verification and quantification of neurotransmitter or other substance release. Both glutamate (Glu) and acetylcholine (ACh) are examples of neurotransmitters that can be detected and quantified by the use of enzymatic reaction cascades (Figure 5.2). Glu can be oxidized directly by the enzyme glutamate oxidase (GluOx). ACh requires a two-step enzymatic process where first the enzyme, acetylcholinesterase (AChE), converts ACh to choline (Ch). In a second step, Ch is oxidized by the enzyme choline oxidase (ChO). [20, 123] In both enzymatic cascades with GluOx and ChOx, H_2O_2 is generated with a 1:1 molar ratio to the concentration of Glu/Ch, in the presence of O_2 . The concentration of H_2O_2 can later be detected by *e.g.* fluorometric or electrochemical techniques. [123] Fluorometric measurements of H_2O_2 can be performed by the combination of H_2O_2 , horseradish peroxidase (HPR), and *e.g.* the artificial substance Amplex Red [124], that generates a red-fluorescent product that can be quantified in a plate reader. [125] This quantification technique was used for the quantification of ACh in Paper 1 and Paper 3.

Figure 5.2: Enzymes can be used to quantify both glutamate and acetylcholine, by the generation of H_2O_2 through oxidation reactions. H_2O_2 can be detected by both fluorometric and electrochemical techniques.

Since H_2O_2 is an electrochemically active substance, it can also be quantified with amperometry. By an applied potential, electrons are transferred by an oxidation of H_2O_2 at the electrode surface. The amount of charge generated in the sensing circuit (Q_S) can be translated into the amount of H_2O_2 present (N_{sensed}), by using Faraday's constant:

$$N_{sensed} = \frac{Q_S}{nF} \quad (5.4)$$

where n is the number of electrons from the redox step. [20] The charge transfer measured in the iontronic circuit (Q_R , Equation 5.1) can be translated in a similar manner:

$$N_{released} = \epsilon \frac{Q_R}{z_i F} \quad (5.5)$$

where z_i is the charge number of the released ion. The modifier ϵ is a measure of the device efficiency, that is the ratio between sensed and released ionic neurotransmitters, i.e. $\epsilon = N_{sensed}/N_{released}$.

For the released doses to be detectable, they need to be considered in relation to the limit of detection (LOD) and limit of quantification (LOQ) of the detection technique. Even though the fluorometric quantification method used in Papers 1 and 3 is considered as a sensitive quantification technique, it requires 200 μ l solutions with samples with an LOQ of 0.3 μ M. [124] In terms of local neurotransmitter release, this dose is fairly high. Even at a 100% efficiency, such a dose would require approximately a release of ACh at a constant 100 nA current for a duration of 60 s. In Paper 3, we used multiple millisecond-duration release pulses to achieve a quantifiable dose.

Glu detection from the free-standing hybrid probe in Paper 2 was detected by electrochemical sensing at the surface of a microelectrode. By immobilizing enzymes at the electrode surface, this technique can be used for various non-electroactive neurotransmitters, including ACh and Glu. Microelectrodes can sense neurotransmitters in real time and provides high spatial and temporal resolution (μ m and sub-seconds). [126] The state-of-the-art microelectrodes provide impressively low detection limits as they are able to detect neurotransmitter content in single vesicles. [29]

5.3 Theoretical evaluation

Theoretical studies of iontronic devices offer a valuable complement to our other characterization techniques and enable another level of understanding of device behavior. These studies help us unravel issues with miniaturization and dose dynamics in a way that cannot be achieved from the electrical and chemical characterization alone. In the scope of this work, theoretical studies have been used both as a tool for device design as well as further evaluation of fabricated and characterized devices. The space- and time-dependent problems provided by iontronic and microfluidic systems can be studied as computational models by numerical analysis which provides well-adjusted approximate solutions to specific problems that cannot be solved analytically. By using appropriate boundary conditions and initial values, a numerical solver can iteratively solve the set of problems.

The most commonly used method in numerical analysis is the finite element method (FEM). By splitting the computational problem into small patches, *i.e.* mesh elements in space, local solutions to that element alone can be found. A global solution can be obtained by stitching together the local solutions. [127] The size of these mesh elements are adjusted to the magnitude of change of dependent variables in that specific location. In the case of iontronic systems, the dependent variables are generally potentials and concentrations of the ionic species. [70] The potential drops and concentration gradients are very steep within a few nanometers on each side of the electrolyte - IEM interface (in the EDL). To solve the Nernst-Planck-Poisson equations (Equation 2.18 and Equation 2.4, Chapter 2) at this interface, meshing structures need to be in sub-nanometer size. [70] The high density meshing at the interfaces can grow rapidly to low density meshing in the less dramatic bulk areas away from the interfaces. The meshing structure for one of the models used in Chapter 2 can be seen in Figure 5.3.

Figure 5.3: A finite element model of an electrolyte - IEM - electrolyte system. Interface between the different domains are meshed with high density.

The computational models in Paper 2 and Paper 4 are solved using FEM in COMSOL Multiphysics. COMSOL Multiphysics provides a platform where multiple physical problems can be solved within the same model by the combination of different physics interfaces. [67, 70] The model from Chapter 2 in Figure 5.3 is an example of an axis-symmetric model (rotational axis), that is solved as a 2D problem that generates 3D solutions. The IEM is treated as a porous membrane, with a fixed charge density where diffusion coefficients are reduced by the volume

fraction and tortuosity factor, compared to the solution phase in the electrolyte. The boundary conditions to this model are set in the outer electrolyte boundary where both the concentration as well as potential levels are fixed. By this, the extension of the diffusional boundary layer is restricted by the model geometry. Encapsulated areas are insulated, *i.e.* no flux or diffusion crosses these boundaries.

In the case when fluidic motion is present in the system, the Navier-Stokes equations (Equation 2.14, Chapter 2), with the velocity field (v) and pressure (p) as dependent variables, can be used to complement the Nernst-Planck-Poisson equations. [67] Figure 5.4 shows the fluidic capillary from the computational model used in Paper 4. In this axis-symmetrical capillary model, a no-slip condition is applied to the wall, *i.e.* no velocity at the walls. The largest changes in velocity will thus appear near the walls, requiring a higher mesh density than the areas in the middle of the capillary. The flow profile is assumed to be fully developed and will thus not change during the passage through this capillary. [128]

Figure 5.4: A finite element model of a fluidic capillary. The density of meshing is decreased with the distance from the capillary wall. The dashed line indicates the symmetric axis, where the 2D model can be rotated to generate a 3D solution.

Numerical models can be treated as stationary problem (steady state) or transient problem (time dependent). The steady state provides a balanced state for the model under a certain set of parameters. [43] Usually, a steady state solution is used to determine the initial values for a transient problem. To limit the size of the problems, theoretical models require assumptions and simplifications. Many of these assumptions, and when and where they are appropriate, are discussed in Chapter 2. When appropriate simplifications and assumptions are set together with appropriate boundary conditions, theoretical modeling can be a useful tool in two separate ways. Firstly, the model system can be used to optimize device geometries to decrease the number of iterations in the lab. Secondly, it can provide a detailed characterization of device behavior when matched with electrical and chemical characterization techniques.

6

Concluding remarks and future outlook

There is no doubt that much remains to be learned regarding the structure and function of neuronal signaling networks and that it offers many research possibilities ahead with respect to developing new techniques and to generate new knowledge. We need to understand the healthy system in much more details as well as how pathology is connected to the neuronal structure and spatiotemporal electrical and chemical states of signaling. And to do so, we need reliable techniques for recording and stimulation that complement each other's strengths and weaknesses. There is also no doubt that local artificial release of neurotransmitters is indeed challenging to achieve, especially if high demands are placed on the quality of the released signal, such as turn-on/off kinetics, high on/off ratios and miniaturization. [18] When studying the ion channels in the neural cell membrane and the ionic currents that carries the action potentials, it is obvious that they do not at all suffer from slow kinetics. As seen in Figure 6.1, the source reservoir of ions is situated within the extracellular matrix, separated from the target with the thickness of the cell membrane as the total distance.

Figure 6.1: The voltage-gated ion channels at the neuron cell membrane provides well-defined vertical diodes with the source reservoir extremely close.

Even though there is a concentration gradient across the cell membrane, and thus a chemical potential, the ions do not freely cross the cell membrane. Instead, signal processing occurs. This include the gating of signals using ion channels.

This gating assure that the ion channels are impermeable for ions over certain voltage ranges. [26, 19] From a device design point of view, the voltage-gated ion channels at the cell membrane can be considered as a vertical rectifier possessing diode characteristics. The same analogy can be used for the chemical synapse where voltage-gated Ca^{2+} channels initiates the neurotransmitter release.

The lack of addressing and gating of the ionic resistor version of the OEIP is the main limitation for its capabilities of spatiotemporal miniaturization. As the target cells are approached, the influence of the concentration levels from passive diffusion is increasing. To overcome this issue while keeping the source reservoir closed, a vertical gate was added to the OEIP and reported in Paper 3 and 4. The engineered vertical diodes do not, however, perform in agreement with the natural voltage gated ion channels of the neuron cell membrane. In particular, we are still far away from matching the spatial resolution and overall miniaturization. The thickness of the encapsulation, *i.e.* the distance from the source reservoir to the target, is typically $10\text{ }\mu\text{m}$ compared to the 50 nm that is an approximate dimension of a chemical synapse. In Paper 4, some investigation of further miniaturization was conducted in order to estimate how miniaturization can improve the turn-on speed of the vertical polarization diodes. In Figure 6.2 the critical dimension of the delivery devices are thus down-sized, keeping the aspect ratio between thickness and outlet area constant, which then leads to decreased delivery times while retaining the diode functionality. However, for the vertical polarization diode, the encapsulation layer will always be present as it defines the depleting interface.

Figure 6.2: Simulation of ACh release where the time of delivery decreases with encapsulation thickness. For encapsulation thickness of $2.5\text{ }\mu\text{m}$, ACh reaches the concentration threshold set to $100\text{ }\mu\text{M}$ within $100\text{ }\mu\text{s}$. Figure adapted from Paper 4. [114]

In simulations of the vertical bipolar membranes performed by Tybrandt [72], an optimal thickness of the anion exchange membrane covering the control electrode (see Figure 4.5, Chapter 4) was found at around 100 nm in size. In a design where any encapsulation or substrate do not add to that critical thickness, 100 nm can be seen as a lowest possible limit for vertical bipolar membrane diodes, at least to the best of our knowledge today.

Another drawback of these vertical diodes is that they only enable a leakage-free interface as long as they are biased in the reversed direction. This “active-off” mode of operation is effective but effectively consumes the capacity of included electrodes that are constantly biased. And, if the connection is lost for any reason, an undesired releasing event will take place. Nevertheless, it is important to emphasize that the vertical diodes provide an interface that overcomes many of the obstacles holding the local chemical stimulation technology back. The verti-

cal diodes offer a unique feature in that it provides a low-leakage off-state before and after a release pulse is applied, together with faster on/off kinetics compared to lateral resistor designs. This is of great importance when applying an artificial signaling interface to neuron systems.

Devices for local neurotransmitter release can provide several features, and future developing pathways for iontronic device design should be navigated towards different directions depending on the targeted application. Major attention in this thesis has been devoted to reach fast release of neurotransmitters, even though also slower signaling patterns are of great importance in neuronal systems. For the investigation of volumetric signaling, crosstalk and neuromodulation, lower demands are placed on speed of signaling as compared to real time neural by-passing. The desired device characteristics are also completely different if the aim is directed towards *in vitro* studies compared to neurological implants, especially in terms of materials and form factors. For *in vitro* studies, major inspiration can be found in the field of chemical sensing. In chemical sensing microelectrodes, chemical and electrical signals are combined and coupled using the same or similar type of materials as the ones used to manufacture iontronic devices. Often, these microelectrodes are shaped into rigid free-standing probes with impressive miniaturized probe tips. [29] Also micro-iontophoresis devices perform well with respect to spatiotemporal resolution as free-standing probes. [40] Since the vertical diodes, presented in this thesis, are realized on substrate surfaces, the natural next step is then to transfer this technology to free-standing rigid and miniaturized probes. Aiming at short-term *in vitro* studies without an exchangeable source reservoir brings the goal to such setup even closer. In this case, the loading time is not a restriction or an issue, and does not need to be miniaturized or further optimized.

Further down the road of iontronic devices and system, we find several possibilities of a biocompatible seamless interfaces between neurons and electronics, that can provide long term stimulation of drugs or real-time bypassing of nerve signals. At the site of the post-synaptic neuron cell membrane, chemical gating is achieved through ion channels that allows for post-synaptic firing of action potentials. A chemical input that generates an electrical signal, highly reminds of a chemical sensor. The work of uniting iontronic devices with microelectrode sensors has started. [85, 129] Even so, before the future of real-time neural by-passing is a reality, further efforts need to be combined. These efforts include further down-scaling of spatiotemporal resolution together with further development of iontronic materials and encapsulation systems aiming for soft, biocompatible long-term stability and stable operation. In addition, by addressing several of the minimized release outlets in the volumetric space enables possibilities to match the spatial complexity of neuronal networks. Careful multidisciplinary device evaluation needs to be performed in close collaboration with neuroscientists and medical clinicians for this technology to mature enough to be utilized in true applications as implanted prosthesis med-technology. Already today though, iontronic devices are ready to aid to investigate healthy and unravel pathologic patterns in neuronal signaling by its ability of highly controlled spatiotemporal artificial release of neurotransmitters.

List of Acronyms

From Chapter 1: From natural to artificial neural signaling

CNS	central nervous system
PNS	peripheral nervous system
ACh	acetylcholine
Glu	glutamate
GABA	γ -aminobutyric acid

From Chapter 2: The flow of charge

OEIP	organic electronic ion pump
IEM	ion exchange membrane
CEM	cation exchange membrane
AEM	anion exchange membrane
BM	bipolar membrane
EDL	electric double layer
ICP	ion concentration polarization

From Chapter 3: Materials and microfabrication methods

GOPS	3-glycidoxypopyl trimethoxysilane
PEDOT	poly(3,4-ethylene-dioxythiophene)
PSS	poly(styrene sulfonate)
PSS-co-MA	poly(4-styrene-sulfonic acid-co-maleic acid)
PEG	poly(ethylene glycol)
qPVBC	poly(vinylbenzyl chloride) quaternized by dimethylbenzylamine

List of Symbols

Constants¹

F	Faraday's constant, $N_A \cdot e = 96\,485\text{ C mol}^{-1}$
N_A	Avogadro's constant, $6.022 \cdot 10^{23}\text{ mol}^{-1}$
e	elementary charge, $1.602 \cdot 10^{-19}\text{ C}$
R	universal gas constant, $8.3144\text{ J mol}^{-1}\text{ K}^{-1}$
ϵ_0	vacuum permittivity, $8.854 \cdot 10^{-12}\text{ F m}^{-1}$
ϵ_s	dielectric constant for material s , 1
ϵ_{water}	dielectric constant for water, 78.5 (20° C))

Variables

z_i	charge number of ion i , 1
c_i	concentration of ion i , mol
T	temperature, K
ρ_e	local electric charge density, C m^{-3}
ϕ	potential, V
$\tilde{\mu}_i$	electrochemical potential for ion i
μ_i^o	standard chemical potential for ion i
J_i	flux of ion i , $\text{mol s}^{-1}\text{m}^{-2}$
D_i	diffusion coefficient of ion i , $\text{m}^2\text{ s}^{-1}$
u_i	mobility of ion i , s mol kg^{-1}
κ	electrolytic conductivity, $\Omega^{-1}\text{ m}^{-1}$
t_i	transport number for ion i , 1
S	permselectivity, 1
η	viscosity, Pa s
ρ	density, kg m^{-3}
p	pressure, Pa
v	velocity, m s^{-1}
Re	Reynolds number, 1
ϵ_p	porosity, 1
τ	tortuosity factor, 1
I	current, A
i	current density, A m^{-2}
Q	charge, C
U	voltage, V
R	resistance, Ω
ρ	resistivity, $\Omega\text{ m}$

¹Values from Ref. [79].

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