**UNIVERSIDADE DE SÃO PAULO
INSTITUTO DE FÍSICA DE SÃO CARLOS**

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**A universal platform for fabricating organic
electrochemical transistors and application in biosensing
technology**

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electrochemical transistors and application in biosensing
technology**

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Supervisor: Prof. Dr. Gregório Couto Faria

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ABSTRACT

CAVASSIN, P. **A universal platform for fabricating organic electrochemical transistors and application in biosensing technology**. 2019. 82p. Dissertation (Master of Science) - Instituto de Física de São Carlos, Universidade de São Paulo, São Carlos, 2019.

Organic bioelectronics is a fast-rising research field that takes advantage of the soft and conducting/semiconducting nature of conjugated polymers to create devices that communicate, interface and mimic biological systems. Bioelectronics encompasses many applications, including tissue engineering, neural interfaces and biosensors. A device that has been extensively explored for such applications is the organic electrochemical transistor (OECT). The main reason is due to its amplification nature and, thus, high fidelity transducer of biological events. Additionally, OECTs convert ionic signals to electronic ones, providing a direct link between biological ion fluxes and electronics. Even though they have been widely explored in the past 10 years, a major drawback that remains unsolved is the lack of hydrophilic polymers that are suitable for applications in biological environment. Hence, in the first part of this dissertation, we propose a novel and universal OECT architecture that enables the use of virtually any type of conjugated polymer. Using the proposed method, which was based on physical chemistry principles, we successfully fabricated transistors that exhibit very high transconductance, good stability and reproducibility, using traditional water-insoluble conjugated polymers. In the second part, we developed a biosensing application using the proposed architecture. In short, the OECT device was functionalized with a cellular membrane model, making it possible to gather quantitative data on the physical and chemical properties of the membrane. This is particularly useful for understanding how different compounds interact with cells. Additionally, we were able to study the working mechanism of lidocaine, a widely used local anesthetic. The concept presented here was then successfully extended to the fabrication of biosensors, enabling thousands of water-insoluble materials that have been developed over the last several decades to be used in organic bioelectronics devices.

Keywords: Organic bioelectronics. OECT. Lipid monolayer. Cell membrane model. Local anesthetics.

RESUMO

CAVASSIN, P. **Plataforma universal para a fabricação de transistores eletroquímicos orgânicos e aplicações em biossensores**. 2019. 82p. Dissertação (Mestrado em Ciências) - Instituto de Física de São Carlos, Universidade de São Paulo, São Carlos, 2019.

A bioeletrônica orgânica é um campo de pesquisa que cresce rapidamente. Se beneficiando da natureza condutora/semicondutora e flexível dos polímeros conjugados, seu principal objetivo é o desenvolvimento de dispositivos eletrônicos capazes de interfacear, mimetizar e se comunicar com sistemas biológicos. A bioeletrônica envolve diversos tipos de aplicações, dentre eles engenharia de tecidos, interfaces neurais e biossensores. Um dispositivo que tem sido extensivamente explorado para esses tipos de aplicações é o transistor eletroquímico orgânico (OECT). OECTs convertem correntes iônicas para eletrônicas, atuando como uma conexão direta entre fluxos iônicos, típicos de eventos biológicos, e a eletrônica. Apesar de terem sido amplamente explorados na última década, uma de suas desvantagens que permanece sem solução é a falta de polímeros adequados para os ambientes biológicos, que devem ser hidrofílicos. Por isso, na primeira parte dessa dissertação, nós propomos uma nova arquitetura universal de OECT, que permite o uso de virtualmente qualquer tipo de polímero conjugado. Utilizando o método proposto, baseado em princípios físico-químicos, fabricamos transistores com polímeros conjugados insolúveis em água que exibem alta trancondutância, boa estabilidade e reproduzibilidade. Em seguida, desenvolvemos uma aplicação em biossensores utilizando a arquitetura proposta. Em resumo, o OECT foi funcionalizado com um modelo de membrana celular, possibilitando a aquisição de informações quantitativas sobre propriedades físico-químicas da membrana. Isso é particularmente útil para o estudo de como diferentes compostos interagem com células. Além disso, utilizamos a plataforma para estudar o mecanismo de funcionamento da lidocaina, um anestésico local amplamente utilizado. Assim, o conceito aqui apresentado foi estendido para a fabricação de biossensores, permitindo que milhares de materiais insolúveis em água possam ser utilizados na bioeletrônica orgânica.

Palavras-chave: Bioeletrônica orgânica. OECT. Monocamada lipídica. Modelo de membrana celular. Anestésico local.

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LIST OF ABBREVIATIONS AND ACRONYMS

CP	Conducting Polymers
DCM	Dichloromethane
gA	Gramicidin A
ITIES	Interface between two immiscible electrolytes
ITO	Indium tin oxide
LA	Local anesthetics
LiPS	Liquid-liquid phase separated
MB	Methyl Benzoate
ML	Monolayer
OECT	Organic electrochemical transistor
P3HT	Poly(3-hexylthiophene-2,5-diyl)
PEDOT:PSS	Poly(3,4-ethylenedioxythiophene) polystyrene sulfonate
POPC	1-palmitoyl-2-oleoyl-sn-glycero-3-phosphatidylcholine

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1 INTRODUCTION

Conducting polymers were discovered in 1977 by Alan MacDiarmid, Hideki Shirakawa, and Alan J. Heeger when they demonstrated the increase in the conductivity of polyacetylene by seven orders of magnitude after doping it with iodine vapour.^{1,2} The importance and impact of this work was recognized in 2000 when they were awarded the Nobel Prize in Chemistry "*for the discovery and development of conductive polymers*".³ Their findings have led conjugated polymers into an important and multidisciplinary research field, that focus not only on the fundamentals aspects of these materials but also on novel and practical applications. Ever since this discovery, different materials such as polythiophene, polypyrrole, poly(p-phenylene) and their derivatives have been synthesized, and their properties have been extensively studied and optimized. But it was only after 1989, when these unsaturated polymers were demonstrated as active semiconductors in light-emitting diodes, that the Organic Electronics field started to experience rapid and solid development.⁴ Since then many different devices and applications have been proposed, such as field effect transistors (OFET),⁵ photovoltaic cells (OPV),⁶ thermoelectric generators,⁷ and electrochromic devices,⁸ to name a few. Today, OLEDs are the most well-established technology and have now been commercialized for over a decade, being part of the newest products launched by Samsung, Sony, and others.

Organic electronics is still a growing field thanks to unique properties conjugated polymers (CP) present, that combines the best of two worlds: they exhibit electrical characteristics of semiconductors or metals with the mechanical properties of plastics.⁹ As a result, CPs make flexible and lightweight electronic devices and also have facile solution processing, being usually deposited in films using techniques such as spin coating, roll-to-roll or screen printing.^{10–12} Even though most research in organic electronic remains in more traditional applications such as OPVs and transistors, there is an emerging trend of using these materials to interface biological systems.¹³ Conjugated polymers are ideal to interface cells and tissues because they are not only electronic conductors, but also efficient ionic conductors.^{14,15} The relatively large space between the molecules allows ions to be absorbed and to move inside the film, enabling new means of communication with biological systems, where ion fluxes play an important role.^{16,17} Furthermore, the soft nature of these materials and the oxide-free interface with aqueous electrolytes are two additional advantages of using organic materials instead of traditional electronic materials, such as silicon.¹⁸

This emerging field is known as organic bioelectronics, a term that has been introduced by Berggren and Richter-Dahlfors in their seminal review¹⁶ and that describes the coupling of organic electronics devices with systems of biological interest. The coupling

works in two directions: in one, a biological process transfers a signal to the device, while in the other, an organic electronic device triggers the biological process. Examples of the first are sensors and transducers being used to convert an ionic to an electronic signal.¹⁷ Examples of the second include actuators such as polymeric electrodes for tissue stimulation and organic ionic pumps for drug injection.¹⁹

Among the many different applications in bioelectronics, a device known as organic electrochemical transistor (OECT) has been receiving a lot of interest and is currently the device of choice for numerous sensing applications.^{20–22} The device was first introduced by Wrighton and coworkers in 1984²³ and used a conducting polymer film as the active channel. In a regular OECT, the film interfaces an aqueous electrolyte, and since it can absorb and transport ions, it yields a 3D interaction of the device with the ionic species from the biological media. The ions that penetrate the volume of the film change its conductance, resulting in a device that operates as an ion-electron transducer.

OECTs have been used for numerous successful applications, such as glucose or multianalyte detection,^{22,24} barrier tissue integrity sensing,^{25,26} and brain activity recording.²⁷ These biological applications, however, demand polymeric materials that are stable and operate in an aqueous environment, which is not the case for most conjugated polymers synthesized to date. Figure 1.1 shows a comparison between traditional water soluble and insoluble polymers. The number of water-insoluble polymer outnumber that of water soluble by orders of magnitude.¹⁵

Figure 1.1 – Examples of conducting polymers

Source: By the author.

Currently, the majority of the applications using OECTs use the conductive mixture of poly(3,4-ethylenedioxythiophene) doped with poly(styrene sulphonate) (PEDOT:PSS) as active material.^{24,28} Even though this material has good stability in water and is an efficient ionic and electronic conductor, it has numerous drawbacks. First, the details of the chemical formulation are often unknown due to the proprietary nature of commercially-available formulations, making fundamental studies on the device difficult to perform.²⁹ Second, because the pristine polymer blend is highly conductive, transistors are usually ON and consume electrical power.^{15,30} For these reasons, there is an effort to find alternative materials for OECT fabrication. Recently, synthetic chemistry group have developed new materials that operate in water by engineering the side chain of traditional conducting polymers.^{31–33} These polymers are naturally non-conductive and can be used in OECTs.

Nevertheless, in the past twenty years, organic electronics has developed and characterized various polymers that have a cheap, high-yield and straightforward synthesis.³⁴ They can not be used in traditional OECTs, however, because they are not able to swell water. For this reason, we have developed both device architecture and guidelines that enable the use of ideally any type of conducting polymers for bioelectronic applications. The device is called liquid-liquid phase-separated transistor (LiPS OECT), and it takes advantage of the interactions of conducting polymers in certain organic solvents and the formation of a liquid-liquid interface between such solvents and water. The details about the platform will be further discussed in chapter three.

The second part of this master dissertation is about the development of a biosensor using the proposed platform. The new design enables the integration of the device with lipid monolayers, something that is not yet possible using a conventional transistor. A lipid monolayer represents a simplified model for the cell membrane. In vitro screening methods using lipids can elucidate membrane-compounds interactions, supporting the design of new drugs.^{35,36}

For this purpose, we have coupled a lipid monolayer with our LiPS OECT. Unperturbed lipid layers are highly electrically insulating, and this property is very sensitive to small changes or disruptions in the membrane packing.^{37,38} These monolayers block ion flow when placed on the liquid-liquid interface of our device, resulting in a decrease of the current modulation in the channel. To validate our platform for monitoring membrane disruption, we used gramicidin A, a very well-studied compound that forms pores in lipid bilayers.³⁹ Finally, we have used our platform to understand the mechanism of interaction of the anesthetic drug lidocaine with cell membranes. The biosensor, lipids, and drugs used are described in details in [chapter 2](#).

This dissertation has been divided into five chapters. The first is the current introduction that motivates the work that will be presented. The second one is an overview of the theory necessary for understanding the achievements of this work. It is a general

introduction to fundamental concepts.

The third chapter introduces the concept of the LiPS OECT, followed by the description of the experimental methods and materials. Finally, the findings of the research are presented, followed by the analyses of the results and discussion.

In the fourth chapter, I present and discuss the biomimetic LiPS OECT, accompanied by the experimental procedures involved in the device fabrication and characterization. Next, the results for the operating biosensor are shown, followed by the discussions.

In the fifth chapter, I conclude the dissertation and list the primary outcomes and highlights of this work. I will also give an outlook and future perspectives.

2 THEORETICAL FRAMEWORK

2.1 Conducting and semiconducting polymers

Polymers are mostly known for their use as insulating materials. The insulating properties in polymers arises from the fact that each carbon atom at the backbone is generally bounded by other four distinct atoms. Therefore, in traditional insulating polymer, the main chain is simply composed by σ -bound.⁴⁰ A classical example is the polyethylene ($-CH_2-$), where each carbon is surrounded by two carbons and two hydrogen, and thus, just single bound are involved. Because of that, the transition between σ and σ^* orbital, also known as the material's band-gap, can be as large as 6 eV.⁴¹ Those energies are much higher than that of Boltzmann energy at room temperature. Therefore, there will be very few free charges in the excited state and the material's conductivity is negligible. Moreover, the σ -bound electrons are essential for the backbone cohesion. The excitation of σ -electrons by high-energy radiation, such as ultraviolet, might irreversibly damage the polymer structure. However, this is not the case for a class of unsaturated carbon chain backbone, also known as conjugated polymers.

Conjugated polymers (CPs), are unsaturated organic macromolecules that share a common structural feature: a backbone chain of alternating double and single carbon-carbon bonds. In order to understand the origin of the electronic properties in conjugated polymers, it is useful to think in terms of the most simple conjugated polymer example: polyacetylene $((C_2H_2)_n)$. Each carbon atom in this molecule form three covalent bonds with two carbons and one hydrogen. They are bonded through sp^2 hybridization because only three sigma bonds are formed per carbon atom. The non-hybridized p_z orbital forms a π -bond from overlapping of unpaired electrons of adjacent carbons.⁴² By increasing the number of carbons in the polymer chain, the overlapping π -orbitals extend, creating a system of delocalized π -electrons along the polymer backbone.^{43,44} Therefore, the discrete energy levels of each orbital sum up leading to the formation of a continuous band. In molecular orbital terminology the valence band, formed by the superposition of bonding π orbital, is called highest occupied molecular orbital (HOMO). The conduction band, on the other hand, is formed by the anti-bonding π^* orbitals and is known as highest occupied molecular orbital (LUMO).⁴³ In traditional conjugated polymers the band-gap between the HOMO and LUMO are normally in the range of 1 to 3 eV - so that, these materials are intrinsically semiconducting.⁴²

2.1.1 Solitons

An immediate consequence of bond-alternation are bond-defects, which leads to a break of one of the polymer chemical bounds, forming two consecutive single bond (or

double bounds). This generates a free radical, also known in solid-state physics as solitons. Actually, the definition of solitons are way broader than this and was first described in 1834 by John Scott Russell to describe solitary waves that would eventually propagate for an extended span of time in the narrows canals connecting Falkirk to Edinburgh, in Scotland. John S. Russell notice that those translation waves would maintain its shape within a localized region and normally propagate at constant velocity.⁴⁵ The properties of solitons have rapidly spread to various fields in science, being now a days associated to phenomena in optics, biology and solid-state physics, to name a few.^{44,46,47}

In solid-state physics, solitons can be first understood as lattice relaxation, due to an introduced defect. For instance, assume that a particular material has an equally spaced lattice as shown in Figure 2.1(a). Imagine now that one of the atoms is suddenly removed from the lattice, as illustrated by Figure 2.1(b). The system will respond to such stress by relaxing to a new arrangement where locally the atoms will be equidistant one another and, therefore, atoms around the prior vacancy will be in a region of enlarged interatomic distances. This situation is depicted in Figure 2.1(c). Note that the lattice distortion will vanish after few atoms and the defective region is well localized in space. In ideal conditions, i.e., low pinning energy, this lattice defect may propagate through the chain, forming a travelling defect wave that resembles a soliton-like defect.

Figure 2.1 – Schematics of the types of lattice distortions

Source: By the author.

In polymer physics, a similar defect can be found in chains with alternate single and double bounds. In a perfect conjugated chain, double bounds alternate regularly with the single ones. The soliton-like defect occurs when the aforementioned bound-defect happen, leading to a sequence of two single bounds (or two double bounds). Such bond alternation defect can be theoretically study and shows to have, in polyacetylene, a low

effective mass of approximately 6 electron mass and “pinning” energy as low as 2 meV . Therefore, except at very low temperatures, the defect is expected to be very mobile, conferring properties of true solitons.^{48,49} Consequently, such solitons may act as moving domain walls separating a dimerized region A from a dimerized region B, as shown in Figure 2.2(a). In the case of a sequence of single-single bounds, the topological defect creates a non-bonding electron state (or a free-radical, in the terminology of the chemistry community), known as “non-bonding pz orbital”. Such one-electron state has smaller energies than those in the valence band, being energetic localized in the middle of the material bandgap. In this case, the overall molecule is still neutral, and such soliton is said to be neutral, although it carries spin ($1/2$), as shown in Figure 2.2(b).

In case electrons are withdrawn from the chain, (by doping processes, for instance), the non-bonding electron will be the first to be removed, due to its lower bounding energy. In this situation, the bound-defect will still exist, but it will now be positively charged, but spinless (Figure 2.2(c)). On the other hand, if an additional electron is added to the polymer chain, the defect will become negatively charged (but still spinless – see Figure 2.2(d)). Formally, a negative soliton corresponds to bound-defect where two double bounds meet.

Figure 2.2 – a) shows a soliton in a polyacetylene in the transition of the dimerized state A to B. Energy levels of b) a neutral, c) a positive and d) a negative soliton.

Source: By the author.

As a final note, it is worth mentioning that solitons are not only created by bound-defects due to unintended byproducts from chemical synthesis. For instance, they can be created by charge injection by metal electrodes or, even, by light absorption. Actually,

depending on the radiation energy, light can break double bonds and, therefore, create solitons. Moreover, if the energy of the radiation match that of the material's bandgap, an electron-hole pair is also created. In case the pair undergoes dissociation, they can charge existing neutral solitons, producing negative and positive solitons.

2.1.2 Polarons

Can solitons be considered polarons? In order to answer this question, it is required that we understand the stability of solitons in complex conjugated polymer structure. So far, we have analyzed solitons in polyacetylene molecules. Polyacetylene has a symmetric conjugated chain, and this has a tremendous effect in the stability of solitons. For instance, the two dimerized portions a soliton separates in polyacetylene, (see [Figure 2.2\(a\)](#)), are mirror image of one another and, therefore, the two portions are energetically equivalent (inset of [Figure 2.3\(b\)](#)). However, for more intricate polymer structure, such as the poly(para-phenylene), this is no longer the case. If a soliton exist in a polyphenylene molecule, the bound-defect will generate a portion with benzonoid rings (region A in [Figure 2.3\(a\)](#)) and another with quinoid rings (region B in [Figure 2.3\(a\)](#)). Benzonoid and quinoid are known to be different molecules and, thus, have non-equivalent energies (indeed, the quinoid ground state energy is known to be higher than the benzonoid). Because of that, the soliton represented in [Figure 2.3\(a\)](#) is unstable and will tend to move to the end of the polymer chain. However, the conjunction of two solitons between one aromatic ring in polyphenylene would overcome the issue with the non-equivalent benzonoid-quinoid forms, generating an stable dual-soliton complex. This situation is illustrated in [Figure 2.3\(c\)](#).

How can we correlate it with polarons? Polarons are defined to be quasi-particles that comprises a charge, a spin and a lattice deformation.⁵⁰ Therefore, a simple structure of polarons in asymmetric polymer can be initially thought as being consisted of a neutral and a charged soliton.

The electronic structure associated with a polaron is shown in [Figure 2.4](#). The split levels can be thought as if they were the bonding and anti-bonding combinations of the two midgap states of the soliton pair that makes the polaron. Energy calculations show that a polaron is only stable in the absence of another polaron in the near range.⁵¹ In this case, we observe the formation of a bipolaron. Bipolarons have no spin, are doubly charged and form states in the band gap.

Solitons exist only in systems with exact ground state degeneracy, what is uncommon for most conducting polymers. Thus, polarons and bipolarons are much more relevant for electron and hole conductance in polymers.

Figure 2.3 – a) shows a polaron in polyphenylene, located in the transition between region A and B. b) shows the energy levels of the dimerized regions of polyacetylene. It is easy to see that both are energetically equivalents. And c) compares the energy levels of the benzonoid and quinoid molecules, that have non-equivalent energies.

Source: By the author.

Figure 2.4 – a) Band diagram for a polaron. Note that the two states are symmetric with respect to the gap center. Q stands for charge and s for spin. b) Representation of a negative polaron in polyacetylene.

Source: By the author.

2.1.3 Doping

The greatest advantages for using conjugated polymers in electronics, as opposed to inorganic materials, are their easy synthesizability, flexibility, light weight and, more importantly, the ability to tune their electronic property in a wide range of conductivity (10^{-6} to 10^4 S/cm). In the neutral stage (undoped), conjugated polymers normally have poor semiconducting properties, being necessary to dope them to achieve higher conduc-

tivities. In fact, not only the electrical properties are changed when conjugated are doped. Its optical, electrochemical and even mechanical properties can be tailored depending on the nature and quantity of dopant agents.⁵²

In polymer physics, the term “doping” is employed differently than that used in traditional inorganic semiconductor. There, doping is associated to incorporation of holes in the valence band (p-doping) or electrons in the conduction band (n-doping) due to the introduction of very low concentration of impurity atoms into a highly pure semiconductor. On the other hand, a doping process in polymer happens when a dopant ion is introduced and exchange electrons with the polymer, forming a polymeric organic salt (ionic complex). This means that, in order to maintain bulk neutrality, a positive or negative charge is induced in the organic semiconductor to counterbalance the injected dopant ions. Charge carriers induced by doping are usually solitons, polarons, and bipolarons, that create electronic states in the energy gap. When the dopant concentration increases, these states also increased leading to the merging of the lower and upper bands, resulting in a new unfilled valence band with the Fermi level below the edge of the band.^{53,54}

Changes in the electronic structure of the material also change its optical properties. After doping, states that are created in the band gap allow new electronic transitions in lower energies, and the absorption is shifted to higher wavelengths. The absorption spectrum defines the color of the material and therefore, a doped polymer has a different color than that of its pristine form. This effect is known as electrochromism and can be used to assess the doping process as polaron and bipolaron are created in the material.^{44,55}

The most relevant type of doping for this dissertation is the p-doping of P3HT (Poly(3-hexylthiophene)). By injecting anions (negatively charged dopants) in the polymer film, we induce the formation of polarons and bipolarons that affect its electronic structure and optical absorption. Figure 2.5 describes in detail the changes induced in the pristine P3HT by charge injection. The general electrochemical equation that governs this process is reproduced below, where Q is the anion,

2.2 Mixed conductivity in conjugated polymers: the rise of organic bioelectronics

In certain conditions, conjugated polymers may present mixed ionic and electronic conductivity. Due to their amorphous nature and capability to swell in a number of solvents,¹⁵ ions have excellent mobility inside polymers films, giving rise to numerous applications that are based on the ion/electron mixed conductivity.⁵⁷ Electrochromic windows, for example, rely on the ions injected from an electrolyte into the film, changing its color, due to polarons formation along the polymer chain. Batteries, on the other hand,

Figure 2.5 – Chemical structure of (a) P3HT, (b) positive polaron in P3HT, and (c) a positive bipolaron. A denotes the anion and R the C_6H_{13} . Energy level diagrams are shown for: (d)pristine P3HT; (e)positive polaron; f)positive bipolaron. The blue arrows represent possible electronic transitions. VB and CB is for valence and conduction band. The arrow in (e) represents an unpaired electron.

Source: ENENGL et al.⁵⁶

benefit from the ability to transport and accumulate ions in the bulk of the polymer film.

Among many different applications, those focused on biological sensing and actuation have been gaining attention in the past few years. Thanks to the material's ability to transport ions, they can efficiently interface with biological systems, which communicate through ionic flux. The device of choice for fabricating biosensors using semiconducting polymer is the organic electrochemical transistor (OECT). This device and its operational details and conditions form the core of this dissertation and will be further discussed in the next subsection.

2.3 Organic electrochemical transistor

The organic electrochemical transistor is a three-terminal device that consists of two pre-patterned electrodes (source and drain) deposited on a glass substrate, connected through a semiconducting polymer. The organic active layer is in contact with an electrolyte, where a third electrode (gate) is immersed. Figure 2.6 shows a schematics of the device. During operation, application of a gate voltage induces charge injection from the source and drain electrodes, which can either dope or de-dope the active channel, leading to a change in the source-drain current upon application of a constant drain voltage.^{30,58}

It is worth mentioning that there are two types of electrolyte-gated transistors and that the two can not be mistaken. In the first case, the polymer film is impermeable to ions of the electrolyte, and the application of a voltage to the gate causes migration and accumulation of ions at the gate-electrolyte and semiconductor-electrolyte interfaces.⁵⁹ The double-layer formed at the semiconductor interface produces a large electric field at the semiconductor interface, causing charge carrier accumulation or depletion, similar to the gating mechanism in field-effect transistors. On the other hand, with ion permeable semiconductors, the ions diffuse into the bulk of the film and electrochemically dope or de-dope the polymeric channel.⁵⁹ Because OEECTs always employ semiconductors that are permeable to ions of the electrolyte, leading to large interfacial areas, OEECT devices typically exhibit extremely large capacitances and display among the highest transconductance values in published literature.^{27,60}

Most OEECTs studies to date use the polymer mixture PEDOT:PSS as the active material.³³ PEDOT (poly(3,4-ethylenedioxythiophene)) is a conjugated polymer that is mixed with PSS (poly(styrenesulfonate)) which is a sulfonated salt. PSS is negatively charged and dopes the PEDOT, forming a highly conductive mixture.⁶¹

Figure 2.6 – OEECT schematics and PEDOT:PSS molecule.

Source: By the author.

The mode of operation of PEDOT:PSS OEECTs is the following: when a positive voltage is applied in the gate electrode (gate voltage, V_g), cations from the electrolyte penetrate the film and compensate the sulfonate anions, de-doping the polymer. This results in a decrease in the current that flows through the channel (drain current I_d). In other words, when the gate-source voltage is zero, the device is in its ON state, and when higher voltages are applied, the device is turned OFF. This is known as depletion mode operation.³⁰ Fundamentally, OEECTs act as ion-to-electron translators, in which an ionic current in the electrolyte (gate current I_g) changes the electronic drain current proportionally. Figure 2.7 presents the typical electrical characterization of a PEDOT:PSS OEECT.

Figure 2.7 – a) Output curves, (b) transfer curves and (c) transconductance of a PEDOT:PSS OECT.

Source: By the author.

The output curve shows the drain-current behavior of the transistor when the voltage applied in the gate is kept constant while the drain voltage (V_d) is changed. From the graph, we can identify two operation regimes in the transistor: linear and saturation. The linear regime occurs for lower values of V_d , where the current linearly increases with the potential. The saturation regime is where the current is independent of the applied bias.

The transfer curve, on the other hand, presents the behavior of the device when a constant bias is applied at the drain while varying the gate voltage. What stands out in the graph is how higher voltages in the gate can completely de-dope the channel, basically switching off the device. Another interesting feature is the threshold value. It can be seen in the curves that even at gate voltages close to zero one can see a modulation of the drain current, which means that the threshold voltage (V_{th}) for PEDOT:PSS is practically zero. The transfer curve is given by Equation 2.2, where W , L and d are the channel width, length, and thickness. The volumetric charge capacity (C^*) defines the ability of the film to accumulate ions into the bulk of the polymer film, and is measured in F/cm^3 , whereas μ is the electronic mobility.³⁰ Combined, their product is considered the materials/system figure of merit, since OECTs requires both efficient electronic transport and facile ion

injection.¹⁴

$$I_d = \frac{W}{2L} d\mu C^* (V_{th} - V_g)^2 \quad (2.2)$$

Another value that is commonly used to benchmark the system is the transconductance (g_m), which is the derivative of the transfer curve and is described in Equation 2.3. The concept can be understood as the ratio between the ON and OFF current, and interestingly, as we can observe in Figure 2.7, the maximum transconductance value does not necessarily happen for higher gate voltages. In fact, given that the transconductance depends on the device geometry, it can be engineered to present a maximum even at zero gate voltages, as already published by Rivnay et al.⁶⁰

$$g_m = \frac{Wd}{L} \mu C^* (V_{th} - V_g) \quad (2.3)$$

OECTs have been used for the most diverse applications in bioelectronics. By taking advantage of their unique ability of sensing and amplifying biological signals simultaneously, groups have been using OECTs for glucose or multianalyte detection,^{22,24} barrier tissue integrity sensing,^{25,26} and brain activity recording.²⁷ Figure 2.8 shows two very successful uses of OECT interfacing biology. First, the transistors are used to sense brain signals and are compared with common surface electrodes. Thanks to the OECT's high transconductance and, therefore, higher sensitivity, it generates a superior signal to noise ratio. This opens up a number of non-invasive record and treatment of several brain conditions.^{27,62} The second application incorporates human cells in a transistor and the differences in the electrical output can help detect the tissue integrity. This could allow the fabrication of an easy-to-operate point-of-care sensor to diagnose food-poising and/or to monitor the quality of perishable food, among many other useful applications.^{26,63,64}

2.3.1 PEDOT:PSS

PEDOT:PSS is the material of choice for organic bioelectronics for various reasons, but water solubility, biocompatibility and high conductivity are probably among the most important ones.¹⁸ Moreover, devices using PEDOT:PSS operate at voltages below that of the hydrolysis threshold, which is also important for biosensing application, since biological tissues that are often degraded by the application of high voltages. To avoid the dissolution of the films in aqueous environments, the PEDOT:PSS ink is generally mixed with a crosslinker in an optimal concentration that protects the film integrity, while maximizing the water uptake.^{66,67} This is especially important for OECTs, for example, because the polymer film must be able to efficiently swell the electrolyte in order to achieve complete de-doping.

Figure 2.8 – a) Optical micrograph of an electrocorticography probe placed over the somatosensory cortex and b) showing the OECT on top and a surface electrode on the bottom of the probe. c) Recordings from the OECT (pink), and a PEDOT:PSS surface electrode (blue). The transistor was biased with $V_d = -0.4V$ and $V_g = 0.3V$. Observe the superior signal to noise ratio of the OECT as compared with the surface electrode. d) Cartoon showing polarized Caco-2 (human epithelial colorectal adenocarcinoma) cells with tight junctions (left) and without (right), sitting on a porous cell culture membrane, above a PEDOT:PSS transistor channel. Tight junctions are shown in yellow. e) OECT I_d transient response with cells before (left) and after (right). OECT transient response in the absence of cells is overlaid in dashed lines.

Source: Adapted from STRAKOSAS; BONGO; OWENS.⁶⁵

On the other side, PEDOT:PSS has also important disadvantages. A major drawback is that the solution composition is often unknown, due to the proprietary nature of commercially available formulations.²⁹ Additionally, because the pristine mixture is highly conductive, PEDOT:PSS devices operate in depletion mode rather than accumulation mode, which is inconvenient for some applications, mainly because of the high consume of electrical power. In fact, recent synthetic efforts have led to the development of new materials with water soluble side chains containing, for example, sulfonates and alkoxy groups.^{31–33} These polymers are naturally nonconductive and can be used to make OECTs. However, their synthesis are often complex, yielding very small amounts of materials. On the other hands, the vast majority of traditional semiconducting polymers do not efficiently uptake water, nor are they easily electrochemically oxidized or reduced in aqueous environments, and therefore do not exhibit high-performance operation as water-based devices. The game changer question is: can we use fundamentals on physical-chemistry along with creative application to enable the use in organic bioelectronics of water-insoluble materials that have been developed over the last several decades for traditional thin film electronics?

In the next section, aspects on solubility of polymer in distinct solvents are discussed, in order to start answering the previous question.

2.4 Hansen solubility parameters

Hansen solubility parameters (HSP) were introduced by Charles Hansen in 1967 as a way to anticipate if a compound will dissolve in another one to form a solution. In this section I will introduce HSP that were used in this work to help identify which solvents would suit better for our application, as will be further described in Chapter 3. This section was written based on Hansen’s book, *Hansen Solubility Parameters: A User’s Handbook*.⁶⁸

Basically for each molecule is given three parameters: δ_h , δ_d , and δ_p . These parameters are treated as coordinates and form a 3-dimensional space known as Hansen space. Molecules are represented as points and the closer they are in the space, than more likely they dissolve each other. To understand what each parameter means it is more accurate to define cohesive energy first. Cohesive energy (E) of a solvent, for example, is how much energy is necessary to break it apart into gas molecules. E is defined in terms of the latent heat of evaporation H_V , the universal gas constant R and absolute temperature T as shown in Equation 2.4,

$$E = H_v - RT. \quad (2.4)$$

The total cohesion energy of a liquid can be divided into at least three separate parts. In the three-parameter Hansen approach these parts quantitatively describe the nonpolar, atomic (dispersion) interactions, E_d , the permanent dipole interactions, E_p , and the hydrogen bonding interactions, E_h ; as it can be seen in Equation 2.5. These are the three major types of interactions in organic materials.

$$E = E_d + E_p + E_h \quad (2.5)$$

Dividing Equation 2.5 by the molar volume, V , gives the respective Hansen cohesion energy (solubility) parameters. Equation 2.6.

$$\frac{E}{V} = \frac{E_d}{V} + \frac{E_p}{V} + \frac{E_h}{V} \quad (2.6)$$

Finally, we define the solubility parameter δ where $\delta^2 = E/V$ and we can rewrite Equation 2.6 as Equation 2.7, the equation for Hansen solubility parameters, where the total parameter δ is described in terms of δ_d , δ_p , and δ_h . The unit of the parameters is usually $MPa^{1/2}$.

$$\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \quad (2.7)$$

An important and widely used application of the HSP is to determine the solubility of organic semiconductors. For this purpose, the Hansen parameters of the solute are determined by analyzing the solubility of this solute in different solvents with known HSP. The solubility zone is determined by fitting a sphere into the Hansen space, in which good solvents are placed inside it and non-solvents or poor solvents are outside. The more

solvents are taken into account in the calculations, than the more precise the sphere center and radius will be. The center coordinates are the HSP and the radius (R_0) defines the solute's solubility space. Solvents that are located closer to the center are better solvents than the ones closer to the border and poor solvents stand outside the sphere. Finally, an equation for the HSP distance between two compounds can be defined via [Equation 2.8](#), where R_a is the distance between solute and one solvent, index 2 stands for the solvent and 1 for the solute.⁶⁹

$$R_a^2 = 4(\delta_{d2} - \delta_{d1})^2 + (\delta_{p2} - \delta_{p1})^2 + (\delta_{h2} - \delta_{h1})^2 \quad (2.8)$$

The factor 4 is controversial, but it has been introduced by Hansen because it conveniently makes the solubility space spherical and experimental evidence further confirms it. A simple affinity parameter is the relative energy difference (RED), which is the measure for the distance of a solvent from the center of the sphere in Hansen space and is given by

$$RED = \frac{R_a}{R_0}. \quad (2.9)$$

The RED is a simple way to compare solvents and to first screen how efficient they are. A solvent with RED equal to 1 will be located on the surface of the solubility sphere. Good solvents will have RED smaller than 1 and are inside the sphere, while bad solvents are outside. The worse the solvent, the higher RED will be.⁶⁹

Finally, HSP is a powerful screening method because the only information necessary to obtain a solute solubility sphere is how well a few solvents dissolve a particular solute. Once the sphere is determined, we have a straightforward method to test the solubility of the solute in any solvent with known HSP.

2.5 Cell membrane models

Cell membranes are the biological frontier between the cell and its exterior environment. They protect the cell and regulate the transport of certain ions and molecules in and out of the cell. For instance, they are the first point of interaction of drugs and pathogens with the cell and therefore exploring the membrane functional and physical properties is key to understand various diseases etiology and to develop novel drugs.^{70,71}

Traditionally, molecular processes occurring in the membrane have been studied using man-made models of biological membranes. The most accepted cell membrane framework model is the fluid mosaic of phospholipids, cholesterol, and proteins that displays fluidity and heterogeneity as shown in [Figure 2.9](#).^{72,73} Their increased complexity has led to the development of various reductionist model systems that have well-known conformation, geometry, and composition. To date, most studies have used supported lipid bilayers,^{37,74} black lipid membranes,⁷⁵ and vesicles.^{76,77} Lipids monolayers assembled on

an interface between two immiscible electrolyte solutions (ITIES) have also been used on several studies to mimic the outer leaflet of the membrane.^{78,79}

Figure 2.9 – Detailed diagram of a mammalian cell membrane. Phospholipids constitute about 50% of the mass of cell membranes. Cholesterol molecules account for approximately 20% of the lipids and nearly all of the remainder is protein. Protein channels are responsible for the exchange of molecules in and out of the cell and are also known as ionic channel.⁷⁰

Source: VILLAREAL.⁸⁰

Even though bilayers represent a more accurate model system, monolayers have significant advantages. For instance, they are much more stable and parameters such as temperature, ionic strength and composition are easily controlled.⁷⁹ Another advantage is the simplicity of how the membrane is formed: due to the distinct properties of the lipid head and tails, as shown in Figure 2.10, the lipids rapidly self-assemble on the interface between organic solvent and water.

The most common methods used to assess membranes at the ITIES are electrochemical. When a potential difference is applied at an ITIES, the charge is separated across it through the formation of electrical double-layers, which are affected by the presence of the ML formed at the interface. This affects the ion transfer rate and capacitance at the interface, which can be easily measured and used to investigate the membrane. In this context, monolayers are considered a well-suited model to mimic and elucidate cell membranes, and have been widely used for further understanding ionic exchange, drug delivery, and membrane activity.^{82,83}

2.6 Drug-membrane interactions

The first point of interaction of drugs with cells is the membrane, and therefore to fully understand a drug acting mechanism it is key to investigate how drugs interacts with

Figure 2.10 – a) The most common cell membrane model: lipid bilayer. b) Representation of a phospholipid molecule: hydrophobic tails (purple) and hydrophilic head (green). c) phosphatidylcholine (PC) is shown as an example; the hydrophilic head is composed of a choline structure (blue) and a phosphate (orange). The head is connected with the tails (purple) via a glycerol (green). The tails are also called fatty acids. d) atomic representation of a PC molecule.

Source: O'CONNOR; ADAMS.⁸¹

the membrane. Drugs may disrupt the membrane, change its fluidity and conformation, or simply won't affect it at all. Some types of antibacterial drugs, for example, are expected to completely disrupt bacterial membranes while leaving mammalian cells intact. In the next subsection we will explore the effects of local anesthetics on the membrane - an intriguing subject that has been on discussion for over a 100 years.⁸⁴

2.6.1 Local anesthetics

Local anesthetics (LA) act by suppressing the sodium ions exchange in the cell membrane, resulting in the blockage of the conduction of nerve impulses, and thus leading to anesthesia.⁸⁵ How the sodium ions are blocked, however, is still a topic of debate. While previous research has established that some local anesthetics, such as lidocaine, yield anesthesia through direct binding to ion channels,^{86,87} there is increased evidence that these anesthetics interact as well with the lipids of the cell membrane, perturbing the membrane structure and therefore causing the blockage of the sodium ion channels.^{88,89} Furthermore, data from several studies suggest that local anesthetics cause expansion

and increase the fluidity of model lipid membranes.^{88,89} These findings, however, are preliminary and the acting mechanism of LA is a debate that is still ongoing.

Further investigations on how LA interact with cell membranes are a fundamental issue and it has been gaining a lot of attention in the past few years. Elucidating the mechanism will also help minimize the toxicity and side effects related to the use of LA, since any changes in the physicochemical properties of cell membranes may compromise their well-functioning.

3 LIQUID-LIQUID PHASE SEPARATED OECTS

Most OECTs applications use PEDOT:PSS as active material, mainly because it is one of the few conjugated polymer that is hydrophilic and, therefore, water compatible. Although organic electronics has extensively synthesized hundreds of semiconducting polymers in the past few years, neither of them have been explored when it comes to interface biology. For this reason, we have proposed an architecture and general guidelines that allow the fabrication of electrochemical transistors using ideally any type of conducting polymer.

First, the guidelines to fabricate OECTs using any material are listed.

- The material must have at least two electrochemically accessible states: one conductive and one non-conductive state; in simpler word, it has to have an ON and an OFF state that can be switched by applying an electrochemical potential;
- The electrolyte must be able to penetrate the polymer film, enabling the reduction or oxidation of the bulk of the film. For this, the solvent of choice has to efficiently swell the polymer and dissolve salts;
- The polymer must be stable and not be dissolved by the solvent of choice.

First we applied the general requirements aforementioned to the polymer P3HT (Poly(3-hexylthiophene)), a prototype conjugated polymer, used with great success in several applications within organic electronics.⁹⁰ Pristine P3HT is a non-conductive polymer with conductivity in the range of 10^{-6} to 10^{-5} S/cm .⁹¹ When it is p-doped or electrochemically oxidized, it forms highly conductive polaronic and bipolaronic states with conductivities higher than 10 S/cm .⁹² P3HT, however, is a hydrophobic polymer, can not uptake water and therefore, can not be oxidized in aqueous environments. For this reason, in order to make it electrochemically active, we must choose a different solvent that meets the criteria established by the guidelines. We have used Hansen solubility parameters, described in [chapter 2](#), as a first screen analysis. The HPS calculation will be detailed in the next section.

However, most likely the HSP calculation would point to organic solvents, that are normally toxic to biological media and, therefore, not biocompatible. With that said, it is mandatory to maintain a water-electrolyte interface in the proposed OECT structure. That way, application of biological interested would be still possible even with a hydrophobic conjugated polymer as electrochemically active layer. Hence, in order to make biocompatible devices, we must also look for solvents that are immiscible and denser

than water. When choosing such a solvent, its electrolyte mixture with water will have two phases: a bottom phase solvent-rich solution that will be in direct contact with the polymer film, and a water-rich solution on top. The interface between two immiscible electrolyte solutions, usually abbreviated as ITIES, is polarizable and electrochemistry can occur across these interfaces.⁹³ By taking advantage of the ITIES we were able to build a Liquid-liquid Phase Separated (LiPS) OECT, in which the gate electrode is placed into the aqueous phase, and the semiconducting polymer channel is in the organic phase. A schematic of the device is shown in Figure 3.1. Upon application of a gate voltage, ions will either migrate to the interface and polarize the ITIES or to the other liquid phase. However, regardless of the ion transfer process, the gate bias is still able to oxidize the polymer channel across the interface.

Figure 3.1 – Schematic of a LiPS OECT and P3HT chemical structure.

Source: By the author.

Further details on the HSP method application, LiPS OECT fabrication and characterization are described in the next session, followed by the results and discussion.

3.1 Materials and Methods

3.1.1 HSP Calculation

One of the methods to compute the solute's HSP and interaction radius R_0 is based on solubility experiments with many solvents combined with computational methods. Here, the P3HT HSP were calculated with an algorithm based on testing the polymer's degree of interaction with many distinct solvents.

Machui, Roesing, and coworkers have experimentally determined the solubility of P3HT in 48 solvents with known HSP.^{94,95} Using this information, we listed each solvent (from $i = 0$ to $i = n$) and gave each one a solubility factor: 0 if it dissolves less than 1 *mg/ml* of P3HT and 1 otherwise. This table, that is listed in [Table A.1](#), is the input of the program. The algorithm is further detailed in [Figure 3.2](#), that is useful to follow the steps that will be described in the text. The program starts with a set of random values for the polymer’s HSP and R_0 , and for each set of HSP and radius the algorithm systematically evaluates the input data with a quality-of-fit function known as Desirability Function, which has the following form,

$$DataFit = (A_1 \times A_2 \times \dots \times A_n)^{1/n}, \quad (3.1)$$

where n is the total number of input solvents, and A_i is a quotient described by

$$A_i = e^{ErrorDistance}. \quad (3.2)$$

For good solvents (solubility factor 1) inside the sphere, and bad solvents outside the sphere (solubility factor 0), the ErrorDistance is 1. Otherwise, the ErrorDistance is the difference between the polymer R_0 and each solvent R_a (given by [Equation 2.8](#)), i.e., it is the distance between the solvent and the sphere boundary. As the fit improves, Datafit approaches 1, reaching this value when all the good solvents are inside the sphere and the bad ones outside. However, this function rarely reaches 1, so generally, a maximum tolerance for the difference between DataFit and 1 is considered, below which optimization stops.

The algorithm gives us the polymer’s HSP and R_0 . With this information, it is possible to predict the solubility of any solvent with known HSP.

3.1.2 Device Fabrication

3.1.2.1 Substrate Preparation

When this project was first started, we did not have an appropriate photolithography process to fabricate OECTs inside our laboratory. For this purpose, during the first months of my master, I have developed a simple, yet useful method to fabricate these devices, while using the equipment and consumables we had available in our lab.

First, glass slides were cleaned in 15 minutes ultrasonic bath of Extran detergent, water, acetone and isopropyl alcohol. Metal (55nm *Au*/5nm *Cr*) contacts were patterned using a metallic mask in a metal evaporator. Next, we exposed the substrates with UV-light for 10 minutes to treat their surface. The UV-light camera used is simply a commercially available mercury light without the bulb, placed into a homemade isolating camera. Next, the photoresist AZ 1512 was spin-coated on the glass slides (2000 *RPM* for 30 s). The

Figure 3.2 – Flowchart of the algorithm.

Source: Adapted from GHARAGHEIZI.⁹⁶

substrates were subsequently baked for 3 minutes at 125°C, covered with a PET printed mask (see Figure 3.3(a)), exposed in the UV-light camera for 4 minutes, and developed in AZ 300 MIF. At this point (see Figure 3.3(b)), the substrates are exposed to the oxygen plasma etcher from Plasma Etch Carson City for 180 seconds. This step cleans and prepares the glass surface for the polymer deposition. Next, the polymer is deposited following the parameters that will be described in subsection 3.1.2.2, resulting in Figure 3.3(c).

Since OECTs have an extra electrolyte layer that is added on top of the polymer channel, it is important that the gold contacts are insulated and not interacting with the media. For this reason, we deposit and pattern a negative photoresist that will serve as the insulating layer for the gold, as shown in Figure 3.3(f). The negative photoresist SU8 is spin-coated (3000 *RPM* for 30 *s*) on the substrate, softbaked at 60°C for 2

minutes, and hardbaked at 90°C for extra 2 minutes. The substrate is covered with a mask (see Figure 3.3(e) and UV-light exposed for 4 minutes. Finally, it is developed on 1-Methoxy-2-propyl acetate, resulting in the device shown in Figure 3.3(f).

Figure 3.3 – Details of the device fabrication. a) The photoresist is deposited and b) developed, exposing the channel area. c) The polymer is deposited on the channel and d) the photoresist and polymer excess are removed in a toluene and methanol solution. To insulate the gold electrodes, e) the SU8 photoresist is deposited on the substrate and, finally, f) is removed from the top of the channel.

Source: By the author.

The method that has been described is being used by students in our laboratory to fabricate OEECTs, and it enables the fabrication of devices with a channel resolution of $5\text{ mm} \times 5\text{ mm}$. Even though it is a simple and yet efficient photolithography method that has helped me to get started with my project, further experiments required faster and smaller devices. For this, our collaborators at Stanford University fabricated and sent us devices that were patterned using the state of the art microfabrication techniques. The methods they used will be further described here, but I would like to stress that I have not been involved in the fabrication of these devices.

First, metal contacts were patterned by photolithography. The photoresist SPR3612 was spin-coated on clean glass substrates, exposed with a Heidelberg MLA 150 aligner and developed in MF-26, followed by electron beam evaporation of titanium/gold (5/50 nm). Metal liftoff was done in acetone followed by a rinse with acetone/isopropyl alcohol. Two $1.5\text{ }\mu\text{m}$ layers of Parylene C were deposited with an SCS Labcoater 2 system. To promote adhesion of the first layer, the surface was treated with 3-(trimethoxysilyl)propyl methacrylate, and a diluted soap solution was spin coated in between them to prevent adhesion of the second layer. To serve as a hard mask, a 75 nm layer of titanium was evaporated and lithographically patterned using the same process described above. Sub-

sequently, the entire substrate was etched using a PlasmaTherm Versaline LL-ICP to remove the Parylene-C (PaC) layers of the unprotected parts and, therefore, defining the transistor channel. Figure 3.4 presents all the steps of the fabrication method.

Figure 3.4 – Details of the device fabrication. a) After the photoresist patterning, a thin layer of gold is deposited on the surface and lifted off, leaving b) the gold electrodes, source and drain, patterned on the glass slide. c) The two layers of Parylene-C are evaporated and etched d) creating the transistor channel. e) The polymer solution is spin coated and f) the second layer of PaC is peeled off leaving the polymer film confined inside the channel. The first layer of PaC insulates the gold electrodes so that they do not interact with the electrolyte that will be added on top of the device.

Source: By the author.

3.1.2.2 Materials and film deposition

Regioregular P3HT was purchased from Sigma Aldrich, and 10 *mg/ml* solutions were made in dichlorobenzene and stirred overnight at 80°C. The thin films were formed by spin coating the solution on the prepared substrates for 3 minutes at 1000rpm. They were soft baked at 120°C for 1 minute, followed by the mechanical peel off of the second PaC layer. Finally, the substrates were hard baked for 20 minutes at 120°C. The resulting films were on average 80 *nm* thick. All processes were performed inside a glovebox in an N₂ controlled environment. The fabrication steps are shown in details in Figure 3.4.

Finally, a glassy well (*area* = 0.287cm²) was glued onto the surface of the substrate with a commercially available tape from 3M in order to confine the electrolyte mixture. The final device structure is shown in Figure 3.7.

Electrodes for electrochemical measurements were fabricated by spin coating (under the same conditions described above) the polymer solution onto indium tin oxide (ITO)

coated glass. ITO is a transparent oxide commonly used in optoelectronics devices, due to its high conductivity ($10\text{-}10^3\text{ S/cm}$) and excellent transmittance of visible light.

3.1.2.3 Electrolyte

A solution of 0.1 M NaCl in milli-q water and a solution of $TBAPF_6$ in either dichloromethane or in methyl benzoate were used as electrolyte (as we will show in [subsection 3.2.1](#), those chemicals were the best swelling solvent for P3HT).

3.1.3 Electrochemical characterization

Electrochemical measurements were performed using a standard three-electrode configuration: working (WE), reference (RE), and counter electrode (CE). In this setup, the working electrode is the ITO coated glass, which is in direct contact with P3HT film; the reference is Ag/AgCl immersed in a saturated solution of the chosen electrolyte; and the counter is a platinum plate with 2 cm^2 . The electrolyte is $TBAPF_6$ in either dichloromethane or methyl benzoate.

Experiments in this setup control the potential of the working electrode while measuring the resulting current that flows between the CE and the WE. While the WE is being oxidized, for example, the CE is reduced, and it is extremely difficult for an electrode to maintain a constant potential while being reduced/oxidized. To avoid this problem, the RE is introduced. It has a well-defined equilibrium potential, and its only role is to control the potential in the WE. No current flows through the reference electrode.⁹⁷

Figure 3.5 – Three-electrode cell diagram

Source: By the author.

3.1.4 Cyclic voltammetry and chronocoulometry

In a cyclic voltammetry, the potential applied in the working electrode is linearly ramped over time, with a fixed rate - in our case 50mV/s - while the current response is recorded. Generally, the voltage increases until a certain point and decreases linearly until the start point, closing the cycle. The current is plotted versus the applied potential, and the curve gives information on the redox reactions happening on the working electrode. The materials redox potentials can be inferred directly from the experimental curve, as well as the reversibility of the process. This technique also allows the study of the electron transfer kinetics.

On the other hand, in a chronoamperometry, a potential step is applied in the WE, while the current response is monitored over time. Integrating this curve results in the amount of charge that has passed during the applied voltage and is useful to observe double-layer charge and absorbed charge on the WE. This experiment is known as chronocoulometry. In order to normalize the injected charge by the electrode size, we introduce the injected carrier density (p) that is calculated using:

$$p = \frac{Q}{eAt}. \quad (3.3)$$

where the A is the electrode area, t is the film thickness, Q is the injected charge and e the electron charge. It is worth mentioning that the film thickness was measured on a dried, undoped polymer film. It is known that upon electrochemical doping, the active polymer swells, changing its momentary thickness, introducing a systematic error in the charge density. On the other side, the polymer swelling does not affect the estimation of the charge per thiophene unit, and for this reason, we use this value to evaluate the polymer doping. To estimate the charge per thiophene ring, the injected carrier density was multiplied by the volume of the crystalline P3HT unit cell ($1.00 \times 10^{-21}\text{cm}^{-3}$) and divided by the number of thiophene rings in each cell, considered here 4.⁹⁸

$$\text{charge/thiophene ring} = \frac{pV_{\text{cell}}}{4} \quad (3.4)$$

The cyclic voltammetry and chronocoulometry were performed by connecting the three-electrode cell with a Palmsens 4 potentiostat and its embedded software. The electrode sizes are given for each result, and the film thickness is 80 nm .

3.1.5 Optical characterization

To evaluate the doping levels of the P3HT we use the fact that when oxidized, the polymer has a different absorption spectrum than when it is pristine (due to polaron and bipolaron formation). A three-electrode cell with plane surfaces was used, employing the same electrodes and electrolytes described. Figure 3.6 is an illustration of the setup. The area of the P3HT on ITO is 1.15 cm^2 .

Absorption spectra were recorded with a Ocean Optics spectrometer and software. Spectra were taken while applying a gate bias for at least 10 seconds, followed by complete dedoping of the polymer by application of 0.4 V gate voltage for 10 seconds.

Figure 3.6 – Setup for spectroelectrochemistry measurements. RE and CE are not represented in the diagram.

Source: By the author.

3.1.6 Electrical characterization

The transistor was gated through an Ag/AgCl electrode (Harvard Apparatus) and wired in a configuration where the drain electrode is the common ground of the source and the gate (see Figure 3.1). The terminals were biased, and the response was measured using either a Keithley 2636B or a Keithley 2612B via a customized LabVIEW software. More details are shown in Figure 3.7, and three types of measurements were performed with this setup: transient response, output, and transient.

Figure 3.7 – Experimental setup for LiPS OEET electrical characterization. The gate electrode is partially immersed in the aqueous phase and the needles are in contact with the drain and source gold electrodes. To facilitate the visualization of the interface, water was colored with red colorant, as can be seen in the detailed image.

Source: By the author.

The transient curve of the device is the record of the drain current over time while applying a constant drain bias and a pulsed gate voltage. This curve provides essential

information: it shows the ON and OFF currents of the transistor, the time it takes to reach the steady state, to discharge back to the off state, and also the resistivity of the electrolyte. The output and transfer curves have been discussed in details in [chapter 2](#).

3.2 Results and Discussion

3.2.1 HSP and electrochemical measurements

In order to find the appropriate solvent for the P3HT LiPS OECT, we used Hansen solubility parameters. Some of the results obtained using the algorithm are listed on [Table 3.1](#), and a more complete version of the table is shown in [Table C.1](#).

Table 3.1 – Hansen solubility parameters and RED for P3HT in several solvents

Material	δ_d	δ_p	δ_h	R_a	RED	Density (gcm^{-3})	Solubility in water (gL^{-1})
P3HT ($R_0 = 3.78$)	18.25	4.34	5.73	-	-	-	<0.0001
acetone	15.5	10.4	7	8.29	2.19	0.7845	miscible
acetonitrile	15.3	18	6.1	14.89	3.94	0.7857	miscible
benzene	18.4	0	2	5.73	1.52	0.8765	1.8
chlorobenzene	19	4.3	2	4.01	1.06	1.1058	0.5
chloroform	17.8	3.1	5.7	1.54	0.41	1.4788	7.95
cyclohexane	16.8	0	0.2	7.60	2.01	0.7739	0.055
dichloromethane	18.2	6.3	6.1	2.00	0.53	1.3266	17.5
ethanol	15.8	8.8	19.4	15.20	4.02	0.789	miscible
methanol	14.7	12.3	22.3	19.71	5.22	0.791	miscible
methyl benzoate	18.8	8.2	4.7	4.14	1.10	1.0837	2.1
toluene	18	1.4	2	4.77	1.26	0.867	0.5
water	15.5	16	42.3	38.78	10.26	0.998	-

Source: By the author.

Solvents with RED significantly higher than 1, such as water, methanol, and ethanol, weakly interact with P3HT and, therefore, can not efficiently swell the polymer. For this reason, we look for intermediate solvents with RED around 1. We also want solvents that are denser than water, which allows us to eliminate many solvents listed on the table. At this point, we are left with chlorobenzene, chloroform, dichloromethane, methyl benzoate, and toluene. From those, chlorobenzene, chloroform, and toluene are eliminated due to their low polarity and inability to efficiently dissolve salts. Finally, we are left with dichloromethane (DCM) and methyl benzoate (MB), that are our solvents of choice.

After this first screening, we immersed thin P3HT films in these solvents and left them soaked for several hours. We do not observe any degradation or dissolution of the film in either solvent. To confirm whether the DCM and MB electrolytes can swell and

dope the polymer and to further understand the doping processes, we performed cyclic voltammetry (CV) and chronocoulometry on the P3HT films deposited on ITO. The results are shown in the next sections.

3.2.1.1 P3HT in dichloromethane electrolyte

Figure 3.8 – a) Cyclic voltammogram of a thin film P3HT in DCM. b) The experimental data can be fitted by using 4 different oxidation processes, each one described by Gaussian functions. The sum of these processes is represented in red and it fits the data with a R^2 coefficient of 0.999. Note that the voltage is applied in the working electrode versus the reference. Positive voltages mean that anions are being injected in the polymer, oxidizing it. Area of the electrode is 1.15 cm^2 .

Source: By the author.

Figure 3.8(a) not only further confirms the electrochemical doping of the polymer, but also shows at least three oxidation peaks. The first oxidation starts at 0.3 V , reaching its maximum at 0.4 V , whereas the second and the third start at around 0.5 V and 0.7 V and reach their maximums at approximately 0.6 V and 0.83 V . However, in the re-reduction of the film we can easily identify not only these three peaks but also a shoulder close to 1 V .

To further understand the redox reactions in the material, we fitted the experimental data by using four different oxidation processes, each one described by a Gaussian function, as shown in Figure 3.8(b). The sum of these curves fit the data with a R^2 coefficient of 0.999. These same peaks have been previously identified in the literature in a slightly different setup, using acetonitrile, a solvent typically used in the electrochemical characterization of polymers.⁵⁶ The oxidation process four is related to an interfacial capacitive current or to irreversibility, that comes from the material over-oxidation. This process has its maximum at $V = 1.01 \text{ V}$ and will not be further discussed here. In order to have a

more accurate description of the other three oxidation peaks, we will now look into the chronoamperometry measurements and UV-VIS absorption spectra.

The oxidation processes have their peaks at 0.39 V, 0.62 V, and 0.84 V. By performing chronocoulometry measurements after each peak, we can compare the amount of charge that goes through the working electrode during each oxidation process. Figure 3.9 shows the injected carrier density in the polymer film and the total number of charge carriers per thiophene ring.

Figure 3.9 – Charge injected in the P3HT film. The curves were measured at constant bias. The voltages were chosen based on the three oxidation processes previously identified, and it allow us to compare the amount of charge injected during each process. Area of the electrode is 1.15 cm^2 .

Source: By the author.

After the first oxidation process, there are approximately 0.05 charges per thiophene ring, which means that there is about one charge due to the doping process every twenty thiophene units. The charges are spread along the polymer backbone and are known as polarons. After the second oxidation, there is about 0.2 charge per thiophene, which means that every 5 units have a polaron. At this point, there is no significant bipolaron formation. This will be further demonstrated when discussing the UV-VIS absorption spectra. The fact that the polaron formation may happen in two separate processes and at distinct voltages has been already reported in the literature.⁵⁶ Possible explanation can be related to the polymer morphology. Conjugated polymers are known to be semicrystalline materials. While in the amorphous region, the polymer swells easy, in the crystalline domains it is required more energy to push ions in between crystalline lamella. Based on this explanation, the lower voltage oxidizing state can be associated to redox processes occurring in the amorphous regions, whereas the second oxidation is taking place at the crystalline domains. Moreover, it has been argued that longer polymer chains are oxidized

at a lower potential than shorter chains.⁹⁹ In fact, longer conjugation lengths are associated to the amorphous region, while shorter ones tend to crystallize.¹⁰⁰

Finally, in the third process, there is about 0.4 charge per unit, or 5 charges every 10 units. However, theoretical calculations show that two polarons located in the range of 5 thiophenes are not stable and will form a bipolaron.¹⁰¹ Therefore, after the third oxidation, there is one bipolaron every 5 rings, and 40% of the film is doped. Literature shows typical maximum doping values of 25%-40%.⁵⁶

The UV-VIS absorption spectra corroborate the assumptions made regarding the oxidation reactions, and are shown in Figure 3.10. As already demonstrated in chapter 2, the electronic transition allowed in pristine P3HT is 2.41 eV. A positive polaron has two, one at 0.52 eV and the other at 1.68 eV, while a bipolaron has only one at 0.35 eV. From the graph in Figure 3.10 we can see that the doping process starts at 0.4 V and that beyond this point, as the applied potential increases, the peak at 2.4 eV (pristine P3HT band gap transition) decreases until it reaches about 20% of its initial value. Simultaneously, a broader peak around 1.6 eV increases until 0.8 V and then slightly decreases while applying a potential of 0.9 V and 1 V.

Figure 3.10 – Spectroelectrochemical measurements of P3HT films in DCM. Spectra were obtained while applying constant bias from 0 V do 1 V, in steps of 0.1V. Lighter red represents 0 V and darker 1 V. Area of the electrode is 1.15 cm².

Source: By the author.

Qualitatively, between 0.4 V and 0.8 V there are no significant changes in the

shape of the curves, which further confirms the assumptions we made about the first and second oxidation processes. Besides that, the decrease in the 500 nm peak while the broad peak arises is in exact agreement with the transformation of the pristine P3HT in oxidized P3HT. As the voltage increases to 0.9 V, the decrease in the broad peak suggests that the polarons are now combining to form bipolarons.

A comparison between the two methods - electrochemical and spectroelectrochemical - to monitor doping in the P3HT is demonstrated in Figure 3.11. The graph shows the relation between injected charge and the bleach factor, i.e., the ratio between the absorption at 500 nm of the doped and the pristine film. It can be seen that there is a good correlation between the two methods. First, at lower doping levels, the factor increases linearly. For higher doping, the function changes and tends to reach saturation. It is interesting to note that at 40% doping levels the peak at 500 nm has decreased to approximately 80% of its initial value.

Figure 3.11 – Absorption ratio versus injected charge density.

Source: By the author.

3.2.1.2 P3HT in methyl benzoate electrolyte

CV measurements of P3HT thin films in methyl benzoate were carried out to measure the oxidation potentials and reversibility of the redox reaction. As shown in Figure 3.12, the onset of P3HT in this setup is around 0.4 V - 0.5 V. It is clear that in this electrolyte, the turn-on voltage is much higher than it was in DCM, and that there is

a positive shift in the voltages where the reactions are happening. Instead of 4 different oxidation process, we can now identify only 3.

Figure 3.12 – a) Cyclic voltammogram of a thin film P3HT in MB. b) The experimental data was fitted by using 3 different oxidation reactions, each one described by Gaussian functions. The sum of these processes is represented in red and it fits the data with an R^2 coefficient of 0.999. Electrode area: 0.0025 cm^2

Source: By the author.

To get further insight into the doping process of P3HT, chronocoulometry measurements were performed. Comparing the results in Figure 3.13 with the ones in Figure 3.9, it is easy to see that the amount of charges injected in the polymer film in MB is much smaller than in the one in DCM. If we continue with the explanation of polaron formation as for the previous section, when a voltage of 1 V is applied, a polaron would be localized every 5 thiophenes unit. In DCM, while applying the same voltage, the polymer had a double amount of dopant charges. These findings may suggest that, in this setup, we observe no bipolaron formation in the thin film while applying voltages smaller than 1 V. While the first two peaks are shown in Figure 3.12(b) are in agreement with the first two peaks described in Figure 3.8, the third one seems to be related with an irreversible current coming from the material over-oxidation. Furthermore, during the experiments in MB, we noticed that the polymer film did not show reproducible results after being subjected to a voltage bias higher than 0.8 V.

These experiments confirmed that P3HT can be electrochemically doped either in dichloromethane or in a methyl benzoate environment. This study has found that generally, DCM is a more appropriate solvent for our purposes, because it allows for a much higher doping rates while applying lower polarization voltages. We will now look into the transistor characterization experiments and data.

Figure 3.13 – Chronocoulometry of a P3HT film in MB. The curves were measured at constant bias. Area of the electrode is 0.070 cm^2 .

Source: By the author.

3.2.2 Electrical characterization

Typical transistor characterization was carried in two different setups, one with DCM, and one with MB. The results will be shown and discussed in the next subsections.

3.2.2.1 LiPS OECT with dichloromethane

Figure 3.14 shows the transfer and output curves for our LiPS OECT. Upon application of an increasing negative bias in the gate electrode, the polymer is p-doped and the magnitude of the drain current increases. It is easy to see that the device operates in accumulation mode, in which the current is normally OFF and it turns ON upon application of gate bias. This is good for sensing applications because they consume low power when compared to common OECTs with PEDOT:PSS as active material (or any other depletion mode OECT). As a typical OECT, it operates at low gate voltages ($< 0.8 \text{ V}$) and the current saturates as the drain voltage magnitude is increased.

Another interesting feature of the LiPS OECT is its threshold voltage. On the contrary of a typical PEDOT:PSS OECT, the LiPS transistor only turns on after a certain potential. Figure 3.14(b) shows that in this setup, the threshold voltage is around -0.2 V . The presence of a threshold is important and very useful for many sensing applications, as will be demonstrated in the next chapter.

As discussed in the previous chapter, the derivative of the transfer curve, which is

Figure 3.14 – a) Output characteristics, where the gate voltage step between each curve is of 0.05 V, and transfer characteristics (black curve) of a LiPS OEET with DCM. The curve represented in red is the transconductance of the device.

Source: By the author.

described by Equation 2.3, carries important information about the operation of the device. Figure 3.14(b) simultaneously shows the transfer and transconductance of the device. Note that the peak of the transconductance is around 0.5 V and that it decreases for higher values. The maximum transconductance obtained for this device and condition was 5.5 mS, which is among the highest numbers obtained for OEETs. From the electrochemical measurements, one would expect that the transconductance would indefinitely increase with the doping levels. However, the transconductance is also dependent on the electronic mobility of the polymer film, meaning that the more charges are injected into the polymer, and the more "wet" it is than the worst is the electronic mobility.

Looking back to Equation 2.3, it is clear that μC^* is the only factor that is non-related to geometry and bias, but rather to the polymer-system. μC^* expresses the mixed ionic-electronic transport properties of the polymer, and for this reason, it is commonly used to benchmark novel OEET architectures.¹⁴ To extract the μC^* product, the transconductance data can be plotted as g_m versus $\frac{W}{2L}d|V_{th} - V_g|$, where the slope is μC^* . This is shown in Figure 3.15(b), in which the linear coefficient for the curve is $224 \text{ F cm}^{-1} \text{ V}^{-1} \text{ s}^{-1}$. The μC^* product for the LiPS OEET is plotted in Figure 3.16, where we can compare our system with others reported in the literature. As we can see from the graph, the LiPS OEET gives not only a chance to explore novel materials but also to fabricate state-of-art devices that show excellent results when compared with different systems.

Figure 3.15 – Transconductance of the LiPS device.

Source: By the author.

Figure 3.16 – Comparison map of previously reported materials.¹⁴ The LiPS OEET with P3HT and DCM is represented with a star, and is among the best results reported in the literature.

Source: By the author.

3.2.2.2 LiPS OECT with methyl benzoate

Figure 3.17 shows the transfer and output characteristics of the LiPS OECT with methyl benzoate as the electrolyte. It is straightforward to see that the drain current is much smaller when compared with the DCM system and that the threshold voltage is also higher, between 0.55 V and 0.60 V. These results are consistent with the electrochemical measurements.

Figure 3.17 – a) Output characteristics, where the gate voltage step between each curve is of 0.05 V b), and transfer characteristics of a LiPS OECT with MB.

Source: By the author.

Figure 3.18 demonstrates the doping reaction happening real-time, while a square pulse voltage is applied at the gate. The increase in the magnitude of the gate bias followed by the immediate increase in current is consistent with the injection of anions from the electrolyte into the P3HT film, which is compensated by the injection of carriers from the source.

3.2.2.3 LiPS OECT working mechanism

In order to understand the transfer mechanism that happens in the interface between the two solvents, we measured a LiPS OECT using only methyl benzoate and $TBAPF_6$, followed by the addition of pure milli-Q water on top of the organic electrolyte. We expected that both setups would lead to similar responses. However, as demonstrated in Figure 3.19, after the addition of water the drain current slightly increases. We have repeated this measurement a number of times and similar trend were observed. At this point, we can not explain why this happens, and more experiments are necessary to allow for further conclusion. However, it confirms that even without ions in the top phase, the device is normally gated. This result suggests that the working mechanism of our transistor involves TBA ions movement from the bottom solvent layer to the top aqueous layer.

Figure 3.18 – Transient drain curve of the LiPS OECT with MB. Initially, the gate voltage is equal to 0. After 5 seconds, a negative voltage is applied for 10 seconds, when it goes back to 0 again. The applied voltage values are shown in the graph.

Source: By the author.

Figure 3.19 – Comparision of the transient curve with and without the aqueous electrolyte.

Source: By the author.

3.3 Conclusions

The results in this chapter indicate that it is possible to fabricate OECTs while using materials that do not uptake water. We investigated the P3HT electrochemical doping in two different electrolytes and showed that our proposed platform, the LiPS OECT, is an elegant, albeit robust solution to develop novel transistors using any type of material. Even though both solvents were a good fit for our purposes, methyl benzoate is much less toxic and less volatile than DCM, and therefore, it makes more stable and user-friendly devices. The next chapter we move on to discuss a biosensor application using the methyl benzoate LiPS OECT.

4 BIOMIMETIC LIPS OECTS FOR MONITORING MEMBRANE-DRUG INTERACTIONS

Cellular membranes are fundamental for the cell's integrity and well-functioning, and exploring their chemical and physical properties is an urgent matter.^{102–104} To elucidate these properties, artificial models that mimic the membrane are typically used. Indeed, lipid layers represent a simplified replica for a cell membrane, and these unperturbed layers are highly insulating.^{37,38} Some drugs, for example, act by changing the membrane's packing or fluidity (and even breaking its cohesion forces), drastically affecting the layer's insulating property. These physical changes in the membrane can be assessed and characterized by coupling it with an electronic transducer, like an OECT. Assembling stable lipid layers directly on the device, however, is quite challenging, since the polymer surface is rough and can be electrically charged, conditions that interfere with the lipids organization.

In fact, researches in the field of bioelectronics have dedicated a lot of efforts to deposit lipid membranes on PEDOT:PSS films without success.⁷⁴ Only recently Zhang et al. managed to disrupt lipid membranes on top of solid-state PEDOT:PSS film.¹⁰⁵ However, in non-ideal surfaces, the vesicles only disrupt in very specific conditions of temperature, PH, shear stress and so on. This makes it challenging for replicating experiments, suggesting that the development of new methods and strategies are very much welcome. For this reason, we propose here a different solution: depositing a lipid monolayer on the organic-aqueous interface of our LiPS OECT. As mentioned in the literature review, lipids form stable monolayers on an ITIES. We take advantage of this to build our biomimetic transistor, which is illustrated in [Figure 4.1](#).

Since lipid membranes are highly insulating, we expect that the layer will block the ionic flux from the bottom phase electrolyte to the top phase, inhibiting the gating of the device, as shown in [Figure 4.1\(b\)](#) and (c). There are many different types of phospholipids that can be used to mimic different cell membrane types. For instance, the type of lipid used to mimic mammalian cells is the 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphatidylcholine (POPC).¹⁰³ Here, we couple a POPC ML with a LiPS OECT with the main goal of creating a platform that will help improve our general understanding of drug-membrane interactions, and as a consequence, help the development of novel drugs.

We use the proposed device to study interactions between membrane and drugs, especially with lidocaine, a widely used local anesthetic. As discussed, the working mechanisms of local anesthetics are still on debate. To elucidate them is not only an important step for our current drug mechanisms understanding but also a way to minimize side effects caused by their use. In this chapter, further details of the fabrication of the biomimetic devices will be described, followed by the results and discussion.

Figure 4.1 – a) Schematic of a biomimetic LiPS OECT and chemical structure of a POPC molecule. b) device operating before the membrane incorporation and c) after the coupling. Note that the lipid monolayer blocks the ionic flux, inhibiting the gating of the device.

Source: By the author.

4.1 Materials and Methods

4.1.1 Device fabrication

The devices were fabricated as described in the previous chapter, apart from the glassy well that received the following surface treatment before being glued onto the substrate. A 3 *mM* solution of perfluorodecyltrichlorosilane (FDTS) in toluene was prepared and placed into a small container. The solution and the glassy well were then placed into a vacuum desiccator chamber for 3 hours. The silane treatment is important because it makes the surface hydrophobic, inhibiting the lipids from sticking on the glass.

4.1.2 Materials and film deposition

The film deposition and polymeric material used followed the same protocols previously described in [subsubsection 3.1.2.2](#).

4.1.2.1 Electrolyte

We used 0.1 *M* *TBAPF*₆ in methyl benzoate as the organic electrolyte (the one that interfaces the polymer film), and 0.1 *M* *NaCl* in milli-Q water on the top.

4.1.2.2 Phospholipids

POPC and cholesterol suspended in chloroform were purchased from Avanti Polar Lipids. Aliquots of POPC and POPC:Cholesterol (4:1) were prepared, and the bulk of the chloroform removed under a stream of nitrogen. To ensure that there was no residual solvent left, the samples were left in a vacuum chamber for 2 hours. The compounds were resuspended in methyl benzoate, forming a 5 *mM* concentration solution.

4.1.2.3 Drugs

Gramicidin A and lidocaine were purchased from Sigma Aldrich. A 3 *mM* stock solution of gramicidin A in 4:1 MB:EtOH was diluted 100 times in MB and a 1:1 v/v mixture with the POPC lipid solution was made. For the experiments using lidocaine, a 12 *mM* stock of lidocaine in MB was diluted 2, 3, 20, 200 times in MB and 1:1 v/v mixtures with the POPC lipid solution were made.

4.1.3 Monolayer formation

In all experiments, the lipid mixtures or the drugs and lipid mixtures were injected through a pipette at the organic electrolyte, after the liquid-liquid interface was formed.

4.1.4 Electrical measurements

Electrical measurements were performed as described in [subsection 3.1.6](#). Additionally to measuring the drain current over time, here we also measured the transient gate current. The time-dependent current was then integrated to give us the total amount of injected charge in the film, a number that is useful to account for the ionic flux through the device.

The OECT without any ML was characterized measuring the transfer, output and transient curves, and will be referred here as OECT control. To have accurate control of the ML formation, the lipids were always added while a very low square pulse potential (close to the threshold voltage) was applied at the gate (≈ 0.5 V), and the transient response was being measured. After the ML formation, further characterization was performed after 20 minutes. It is necessary to wait for 20 minutes to obtain stable and consistent results, as will be discussed in the next section.

Device sizes and applied potentials are given for each measurement. Experiments with lidocaine were performed using different devices and the response was normalized according to its control OECT response.

4.1.5 Permeability factor

We defined a permeability factor to assess the potency of the compound.¹⁰³ First, it was defined that an intact lipid membrane would have a permeability factor (p) of 0

whereas the absence of any membrane (control OECT) would have a permeability factor of 1. We normalized each measurement/experiment based on the following equation

$$p = \frac{\frac{I_{\text{lidocaine}}}{I_{\text{lipid}}} - 1}{\frac{I_{\text{OECT}}}{I_{\text{lipid}}} - 1}, \quad (4.1)$$

where $I_{\text{lidocaine}}$ is the saturated current of the device functionalized with lidocaine, I_{lipid} is the saturated current of the device with an intact lipid membrane, and I_{OECT} is the saturated current of the device without the membrane.

4.2 Results and Discussions

The first set of experiments aimed to demonstrate the successful incorporation of the lipid monolayer and to characterize the biomimetic device. Figure 4.2 presents the output characteristics of the transistor, with and without the monolayer. As expected, the membrane formation is followed by an expressive decrease in the magnitude of the drain current, due to the lipid monolayer highly-insulating property.

Figure 4.2 – Output characteristics of the biomimetic OECT. Note the decrease in the drain current after the formation of the monolayer. Device characteristics: $L = 50\mu\text{m}$, $W=2\text{mm}$ and $d=80\text{nm}$.

Source: By the author.

After the addition of the lipid mixture at the bottom phase electrolyte, the ML is immediately formed, as seen in Figure 4.3(a). However, in order to obtain a better sealing and more consistent results, we notice that it is necessary to wait at least 20 minutes after the layer formation. The LiPS OECT transfer characteristics right before and right after the ML formation show that the modulation of the channel (induced by

the gating) is suppressed in the presence of the ML. Interestingly, in order to obtain reproducible and consistent results, it was necessary to wait for a certain time. This is expected since the lipids have a slow dynamic and it normally takes some time to reach a stable monolayer. The difference between the sealing of a recently formed layer and the same one after 90 minutes is presented in Figure 4.3(b). At 90 minutes, we observe a decrease of approximately 70% of the current. Later on, we optimized the waiting time and concluded that 20 minutes was sufficient to achieve similar results.

Figure 4.3 – a) shows the transient drain current over time, while a square pulse was applied in the gate. While the gate is applied we observe an increase in the magnitude of the drain current. When it is off, we observe it decreasing to zero. The arrow points at the exact moment the lipid mixture was injected in the bottom phase and is followed by a suppressing in the drain current. b) Shows a comparison between the transfer curves of the OECT without any membrane, right after its formation, and after waiting 90 minutes. Device characteristics: $L = 50\mu\text{m}$, $W=2\text{mm}$ and $d=80\text{nm}$.

Source: By the author.

Overall, these results indicate the successful incorporation of the ML on the OECT transducer. We now turn to investigate how different compounds interact with the membrane, and whether or not our device is sensitive enough to detect the presence of different compounds. First, we used the disrupting compound gramicidin A (gA). Gramicidin A is a bacterial peptide that is known to interact with lipid bilayers by forming pores.¹⁰⁶ Since its working mechanism is well established we use it here to test our device sensibility to subtle changes in the membrane. Figure 4.4 shows a comparison between the electrical properties of the membrane with and without addition of gA. The drain current seems to be partially recovered when adding gA, confirming that the membrane becomes "leakier" due to the incorporation of such compound. In part (b), the injected charge, calculated by integrating the gate curve while applying a square pulse, is presented. The result further confirms our assumptions that the ionic flux is first blocked by the

presence of the ML, and that the addition of the gA disrupts the membrane, making it leakier to ions. In fact, we have successfully built an impedance biosensor that is capable of measuring the integrity of the biological membrane.

Figure 4.4 – a) Output curves of the OEET and b) injected charge in the film without any layer, with the lipid membrane and after addition of gramicidin A. Device characteristics: L:20 μm W:2mm d: 80nm.

Source: By the author.

Indeed, our biomimetic device proved to be sensitive enough to capture changes in the membrane. To further validate our device as a platform for studying membrane-drug interactions, we moved on to test the local anesthetic lidocaine (LA).

Five different concentrations of the LA were used, and the output characteristics for each one is shown in Figure 4.5. Our simplistic lipid-only cell membrane model was able to show the distinct effect of anesthetics on the lipid packing. As seen in Figure 4.5, as the concentration of lidocaine increases, the electrical response recovers back to its initial value. We further introduce a concentration-dependent permeability factor (Figure 4.6 and Equation 4.1) as a tool to quantify ionic permeability using our device data.

This preliminary finding supports the evidence that lidocaine expands the monolayer.¹⁰⁷ If the area per lipids increases, it is expected that more ions will be able to penetrate the ML, and hence, the conductivity of the device will be recovered. Furthermore, the present results are significant because they are in agreement with recent findings that the anesthetics indeed interact with the lipids, changing the conformation/physicochemical properties of the membrane and thus affecting its permeability. This finding can also explain the toxicity and side effects related to the use of lidocaine, since any changes in the permeability of cell membranes may compromise their well-functioning.¹⁰⁸

Figure 4.5 – a) Output curves of the OECT and b) injected charge in the film without any layer, with the lipid membrane and after addition of gramicidin A.

Source: By the author.

Figure 4.6 – Permeability factor versus lidocaine concentration. Device characteristics: $L = 50\mu\text{m}$, $W=2\text{mm}$ and $d=80\text{nm}$.

Source: By the author.

4.3 Conclusions

In this chapter, we proposed and built a platform that is capable of studying the acting mechanisms of drugs. We showed that our LiPS platform is a simple, yet elegant solution, that allows easy integration of lipid monolayers on the OECTs structure. Our biomimetic transistor can detect and amplify the biological signal with high sensitivity, and therefore, it can capture real-time and subtle changes in the membrane. Even though it is well-known that many drugs directly interact with the cell membrane, how they do it, and what is their acting mechanisms are still unknown. Our proposed device is a novel platform that will pave the roads for constructing biofunctionalized sensing platforms to obtain not only qualitative data of membranes-drugs interactions, but also to provide quantitative data regarding these fundamentals biological phenomena.

Future research might explore different lipid compositions in order to mimic different cell membrane types. For instance, adding cholesterol to the POPC mixture would create more realistic models. We tried to prepare ML that had 20% cholesterol in its content; however, the sealing was not as good as the ones without any cholesterol. It is well known that temperature and PH affect lipids packing, and therefore, these parameter have to be optimized in order to have a better sealing membrane, while using POPC:Cholesterol. Furthermore, it is unfortunate that the study did not include any optical measurements of the monolayer. Even though we have tried to use confocal microscopy, we could not obtain any relevant image on the membrane structure. Future work aims to find the means to visualize the ML by using atomic force microscopy.¹⁰⁹

5 CONCLUSIONS

This study set out to develop a new OECT architecture that enables the use of ideally any semiconducting polymer as the active material, something that is not yet possible using the traditional transistor structure. The second aim of this study was to use the proposed platform to build state-of-the-art impedance biosensor, that allowed the investigation of membrane-drugs interactions.

In the first part of this research, we have demonstrated a general method and guidelines to fabricate organic electrochemical devices using materials that do not swell water. We have successfully fabricated transistor while using P3HT as the active material, which is a hydrophobic polymer generally used for organic photovoltaics and organic field effect transistors. The devices operate in accumulation mode, show good stability, exhibit high transconductance, and its μC^* product is among the best values reported in the literature. An implication of this is the possibility of searching for even better materials to prepare more efficient transistors. A secondary result is the identification of two different solvents that are appropriate to electrochemically dope P3HT films (and probably, other conjugated polymers). One of them, methyl benzoate, is a non-toxic and non-volatile solvent that is largely used in the cosmetic industry, being the perfect choice to make stable devices and biosensors. Part of the development of this first part was published in the *Advanced Electronic Materials* magazine.¹⁵ A second manuscript is being written, and will include the optical measurement and comparisons between distinct organic solvent.

Moving on to the biosensor focused research, one of the more significant results to emerge from this study is the development of an elegant platform that detects and amplifies the biological signal. We were able to easily couple the device proposed in the first part of this project with a lipid monolayer that mimics mammalian cell membranes, and because the device can detect subtle changes in the layer fluidity or conformation, it can be used to understand the working mechanisms and delivery of different drugs. For instance, it has shown that lidocaine makes the membrane leakier to ions and that this effect is related to its concentration, something that could be used in order to minimize side effects caused by the anesthetic. Finally, the monolayer stability combined with the simplicity and sensitivity of our device results in a solution for drug-membrane studies that paves the road for robust and easy-to-manufacture lipid-functionalized impedance biosensor. A manuscript comprising this second part of my dissertation is being submitted to *Advanced Materials Technologies* magazine.

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Appendix

APPENDIX A – SOLVENT LIST WITH RESPECTIVE SOLUBILITY FACTOR

Table A.1 – Solvent list with their respective HSP and solubility factor.

Solvent	δ_d ($Mpa^{1/2}$)	δ_p ($Mpa^{1/2}$)	δ_h ($Mpa^{1/2}$)	Solubility Factor
1,2,4-trichlorobenzene	20.2	4.2	3.2	1
1,2-dichlorobenzene	18.3	7.7	2.8	1
1-butanol	16	5.7	15.8	0
1-pentanol	15.9	5.9	13.9	0
2,4-pentanedione	17.1	9	4.1	0
2-butanone	16	9	5.1	0
2-chlorophenol	19	5.5	13.9	0
2-chlorotoluene	19	4.9	2.3	1
2-propanol	15.8	6.1	16.4	0
3-chlorotoluene	18.9	3.9	2.9	0
acetone	15.5	10.4	7	0
acetonitrile	15.3	18	6.1	0
a-methylstyrene	18.5	2.4	2.4	0
aniline	20.1	5.8	11.2	0
a-pinene	17.3	2.4	3.1	0
benzaldehyde	19.4	7.4	5.3	0
benzene	18.4	0	2	0
benzyl alcohol	18.4	6.3	13.7	0
benzyl benzoate	20	5.1	5.2	0
b-pinene	17.1	3	2.7	0
bromobenzene	19.2	5.5	4.4	1
bromoform	20	5	7	1
chlorobenzene	19	4.3	2	1
chloroform	17.8	3.1	5.7	1
cyclohexane	16.8	0	0.2	0
cyclohexanol	17.4	4.1	13.5	0
cyclohexanone	19.2	6.3	3.3	0
cyclohexylbenzene	18.7	0	1	0
dichloromethane	18.2	6.3	6.1	0
dimethylsulfoxide	18.4	16.7	10.2	0
ethanol	15.8	8.8	19.4	0

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ethyl acetate	15.8	5.3	7.2	0
limonene	17.2	1.8	4.3	0
methanol	14.7	12.3	22.3	0
methyl acrylate	15.3	6.7	9.4	0
n-butyl acetate	15.8	3.7	6.3	0
n-hexane	14.9	0	0	0
octadecene	16.4	0	0	0
oleic acid	16	2.8	6.2	0
o-xylene	17.8	3.1	5.7	1
quinoline	20.5	5.6	5.7	0
styrene	18.6	1	4.1	1
tetrahydrofuran	16.8	5.7	8	1
tetrahydronaphthalene	19.6	2	2.9	0
tetrahydrothiophene	18.6	6.7	6	1
toluene	18	1.4	2	0
valeraldehyde	15.7	9.4	5.8	0
water	15.5	16	42.3	0

Source: By the author

APPENDIX B – ALGORITHM TO CALCULATE THE SOLUTE HSP AND R_a

The algorithm is programmed in Julia. The original input is [Table A.1](#) and the output is the solute HSP and R_a .

```
using Optim
using Statistics
using DataFrames
using CSV
using LinearAlgebra
using DelimitedFiles

# uploading input table
data = CSV.read("Input.csv", header=false)
δ_d = data[1]
δ_p = data[2]
δ_h = data[3]
solubility = data[4]
# calculation mean values
mean_delta = zeros(4)

for j in 1:4
    mean_delta[j] = mean(data[:,j])
end

mean_delta[4] = sqrt(dot(mean_delta[1:3],mean_delta[1:3]))

# our initial guess is the absolute value of mean delta
guess = mean_delta

# initial error
tol = 1

# number of solvents
n = size(data)[1]

# defining the function we want to minimize

function QFval(targets_delR, δ_d, δ_p, δ_h, solubility, n)

    δ_dp = targets_delR[1]
    δ_pp = targets_delR[2]
    δ_hp = targets_delR[3]
    R_o = targets_delR[4]

    R_a = sqrt.(
        4*(δ_d .- δ_dp).^2 + (δ_p .- δ_pp).^2 + (δ_h .- δ_hp).^2
    )
end
```

```
A = zeros(n)

for i = 1:n
    if R_a[i] > R_o
        if solubility[i] == 0
            A[i] = 1
        else
            A[i] = exp(R_o - R_a[i])
        end
    else
        if solubility[i] == 0
            A[i] = exp(R_a[i] - R_o)
        else
            A[i] = 1
        end
    end
end

DataFit = prod(A)^(1/n)

return abs(DataFit - 1)

end

QF(x) = QFval(x,  $\delta_d$ ,  $\delta_p$ ,  $\delta_h$ , solubility, n)

counter = 0
guess = mean_delta
guess = rand(4)
while tol > 1e-2
    global result = optimize(QF, guess, NelderMead())
    global tol = Optim.minimum(result)
    global counter += 1
    global guess = Optim.minimizer(result)
    println("The tolerance is $tol in step $counter.")
end

mini = Optim.minimizer(result)
d_d, d_p, d_h, R_o = mini[1], mini[2], mini[3], mini[4]

R_a = sqrt.(
    4*( $\delta_d$  .- d_d).^2 + ( $\delta_p$  .- d_p).^2 + (d_h .-  $\delta_h$ ).^2
)

RED = R_a./R_o

writedlm("Output.csv", RED)
writedlm("values_minimized.csv", mini)
```

APPENDIX C – SOLUTE AND SOLVENT LIST WITH RESPECTIVE HSP, R_a AND RED

Table C.1 – The solute HSP and R_0 , and the solvents R_a and RED. Here, 59 solvents are shown: the initial 49 used as the input together with 10 extra solvents we had no experimental data before and could only be included after optimizing the solute HSP.

Solvent	δ_d ($Mpa^{1/2}$)	δ_p ($Mpa^{1/2}$)	δ_h ($Mpa^{1/2}$)	R_a ($Mpa^{1/2}$)	RED
P3HT ($R_0 = 3.779$)	18.252	4.340	5.725	-	-
1,2,4-trichlorobenzene	20.2	4.2	3.2	4.645	1.229
1,2-dichlorobenzene	18.3	7.7	2.8	4.456	1.179
1-butanol	16	5.7	15.8	11.120	2.942
1-methyl naphthalene	19.7	0.8	4.7	4.687	1.240
1-pentanol	15.9	5.9	13.9	9.560	2.530
2,4-pentanedione	17.1	9	4.1	5.447	1.441
2-butanone	16	9	5.1	6.511	1.723
2-chlorophenol	19	5.5	13.9	8.391	2.220
2-chlorotoluene	19	4.9	2.3	3.779	1.000
2-propanol	15.8	6.1	16.4	11.879	3.143
3-chlorotoluene	18.9	3.9	2.9	3.139	0.831
acetone	15.5	10.4	7	8.285	2.192
acetonitrile	15.3	18	6.1	14.886	3.939
α -methylstyrene	18.5	2.4	2.4	3.881	1.027
aniline	20.1	5.8	11.2	6.765	1.790
α -pinene	17.3	2.4	3.1	3.779	1.000
benzaldehyde	19.4	7.4	5.3	3.849	1.018
benzaldehyde	19.4	7.4	5.3	3.849	1.018
benzene	18.4	0	2	5.727	1.515
benzyl alcohol	18.4	6.3	13.7	8.218	2.175
benzyl benzoate	20	5.1	5.2	3.616	0.957
b-pinene	17.1	3	2.7	4.032	1.067
bromobenzene	19.2	5.5	4.4	2.587	0.685
bromoform	20	5	7	3.779	1.000
chlorobenzene	19	4.3	2	4.014	1.062
chloroform	17.8	3.1	5.7	1.535	0.406

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cyclohexane	16.8	0	0.2	7.602	2.012
cyclohexanol	17.4	4.1	13.5	7.963	2.107
cyclohexanone	19.2	6.3	3.3	3.649	0.966
cyclohexylbenzene	18.7	0	1	6.478	1.714
dichloromethane	18.2	6.3	6.1	1.998	0.529
dimethyl formamide	17.4	13.7	11.3	11.027	2.918
dimethylsulfoxide	18.4	16.7	10.2	13.148	3.479
diphenyl ether	19.4	3.4	4	3.022	0.800
dipropylene glycol	16.6	12	19	15.679	4.149
ethanol	15.8	8.8	19.4	15.197	4.021
ethyl acetate	15.8	5.3	7.2	5.211	1.379
limonene	17.2	1.8	4.3	3.593	0.951
mesitylene	18	0.6	0.6	6.365	1.684
methanol	14.7	12.3	22.3	19.712	5.216
methyl acrylate	15.3	6.7	9.4	7.344	1.943
methyl Benzoate	18.8	8.2	4.7	4.141	1.096
n-butyl acetate	15.8	3.7	6.3	4.979	1.318
n-hexane	14.9	0	0	9.826	2.600
n-methyl formamide	17.4	18.8	15.9	17.763	4.700
octadecene	16.4	0	0	8.083	2.139
oleic acid	16	2.8	6.2	4.784	1.266
o-xylene	17.8	3.1	5.7	1.535	0.406
propylene glycol	16.8	10.4	21.3	16.963	4.489
quinoline	20.5	5.6	5.7	4.669	1.235
styrene	18.6	1	4.1	3.779	1.000
tetrahydrofuran	16.8	5.7	8	3.932	1.040
tetrahydronaphthalene	19.6	2	2.9	4.552	1.205
tetrahydrothiophene	18.6	6.7	6	2.476	0.655
toluene	18	1.4	2	4.772	1.263
valeraldehyde	15.7	9.4	5.8	7.188	1.902
water	15.5	16	42.3	38.781	10.262

Source: By the author