Microfabrication Technologies for Neural Drug Delivery

by

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Jury

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ABSTRACT

Keywords: Polyimide, Neural Probe, microfabrication, bonding

Throughout this thesis, different methods and techniques were employed in order to fabricate flexible polyimide microfluidic devices. This devices constituted by one reservoir and one microchannel with several outlets are to perform a local delivery by diffusion of a drug that will interact with the tissue in its proximity. This neural probe could have a significant impact on biomedical applications: if associated to the microelectrodes technology, neural probes for recording and stimulation of electric activity of the brain could incorporate a release of anti-inflammatory drug and prevent one of the major problems in the MEMS area: device failure due to tissue response during and after implantation. Special concern was given to the polymeric material properties and behaviour for a better understanding of the bonding step required to create the microfluidic channels. A successful bonding led to closed channels and reservoirs and well manufactured devices. After packaging, the devices were loaded with nanoparticles for in vitro and an anti-inflammatory drug for in vivo tests. The in vitro tests showed good results regarding the functionality of the neural probes. The neural probes were then implanted in a rodent’s brain to comprove its efficacity. The immunohistological results were not conclusive and unfortunately there was no time to obtain further results that would be extremely useful in order to evaluate the performance of this neural probe in reducing the inflammatory response.
RESUMO

Palavras-chave: Polimida, sonda cerebral, microfabricação. “bonding”

Ao longo desta tese, várias técnicas e métodos foram utilizados para fabricar microdispositivos flexíveis em polimida para manipulação de fluidos. Estes dispositivos constituídos por um reservatório e um microcanal com várias aberturas, vão ser utilizados para libertação local por difusão, de medicamentos que vão interagir com os tecidos na sua proximidade. Esta sonda cerebral pode ter um impacto significativo nas aplicações biomédicas: se associada à tecnologia dos microeletródos, as sondas cerebrais para registo e estimulação da actividade eléctrica do cérebro, podem vir a incorporar um mecanismo de libertação de um medicamento anti-inflamatório, prevenindo assim um dos maiores problemas na área dos MEMS: falha de dispositivos devido à resposta dos tecidos durante e após a implantação.

Foi dada especial atenção às propriedades assim como o comportamento dos materiais poliméricos, para uma melhor compreensão do processo de “bonding” utilizado para a criação dos canais microfluídicos. Graças ao sucesso deste processo, foram obtidos canais e reservatórios devidamente selados e dispositivos correctamente fabricados.

Após a fase de “packaging”, os dispositivos foram enchidos com nanopartículas para os testes in vitro e medicamento anti-inflamatório para os testes in vivo. Os testes in vitro demonstraram bons resultados relativamente à funcionalidade das sondas cerebrais. Estas foram de seguida implantadas no cérebro de um rato para comprovar a sua eficácia. Os resultados immunhistológicos não foram conclusivos e infelizmente não houve tempo para obter mais resultados que seriam extremamente úteis na avaliação da performance das sondas cerebrais em bloquear a resposta inflamatória.
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**LIST OF ABBREVIATIONS**

Al - Aluminium  
BioMEMS - biomedical microelectromechanical Systems  
BPDA-PDA - Biphenylene Dianhydride, p-Phenylenediamine  
CAD - computer aided design  
CIF - Common Intermediate Format  
CMI - Centre for MicroNanoTechnology  
Cr - Chrome  
DAPI - 4’,6-diamidino-2-phenylindone  
DC - Direct current  
EPFL - École Polytechnique Fédérale de Lausanne  
GDSII - Graphic data system II  
GFAP - Glial fibrillary acidic protein  
h - hour  
HDMS - Hexamethydisilazane  
Iba 1 - Ionized Calcium-Binding Adapter Molecule 1  
ICP - Inductively Coupled Plasma  
LMIS4 - Laboratoire de Microsystèmes 4  
LOC - Lab-on chip  
MEMS - Microelectromechanical Systems  
mg - milligram  
min - minutes  
MIT - Massachusetts Institute of Technology  
mm - millimetre  
mTAS - micro Total Analysis Systems  
nm - nanometre  
NMP - N-methyl pyrrolidone  
PAA - poly(amic acid)  
PDMS - polydimethylsiloxane  
PET - polyethylene terephthalate or polyester  
PI - Polyimide  
PMMA - polymethylmethacrylate  
PR - Photoresist  
Pt - Platinum  
QDR - Quick Dump Rinse  
RF - Radio frequency  
rpm - rotations per minute
SEM - Scanning Electron Microscopy
secs - seconds
SiO₂ - Silicon oxide
Ti - Titanium
UC - Ultra clean
µL - microLitre
µm - micrometer
UV - Ultra-Violet
W - Tungsten

B - concentration of drug bound and internalized
C - Concentration of a given substance
C₀ - initial concentration
Cₘₐₓ - concentration at the infinite
Dₜ - diffusion coefficient
D - adapted diffusion constant
J - particle flux
k - Boltzmann constant
Kᵦᵦ - binding constant
Kₑl - elimination constant
K - adapted elimination constant
Re(C) - rate of drug elimination
t - time
T - temperature
x - distance
xₜ - Diffusion distance of a particle
tₜ - diffusion time
1. Introduction

This master project is based on previous and current work done regarding polymeric neural probes and microelectrodes in the LMIS4 at the EPFL, Switzerland. This thesis mainly concerns the techniques of microfabrication for biomedical applications and also approaches related areas as device design, implant packaging and in vivo and in vitro validation.

1.1 Background

Microelectromechanical systems (MEMS) technologies as well as the microfluidics area have become increasingly important nowadays as they are very promising for applications on the biomedical domain, namely disease diagnostic, molecular biology and chemistry.

These technologies are based on microfabrication technologies which have arise from the manufacturing techniques on the semiconductor sector and are greatly influenced by its advances. Microfabricated devices which range from several micrometers to the millimetre scale are characterized by their very small size, batch production and the elevated degree of control during the manufacture process.

Great progress can be made with this technology and not only scientifically or medically but also economically. The use of this type of devices broadens many areas as manipulation of biomolecules, LOC technology, mTAS, drug delivery or even the combination of some of these areas. Microelectrodes for example, are a large area of research and are widespread used on the biomedical domain. Microelectrodes have been implanted in the nervous tissue to stimulate and record neural activity and can mimic neural function lost due to trauma or disease. Some of the applications of implanted microelectrodes include Movement disorders and Parkinson disease, pain treatment, epilepsy, and even cochlear and retinal implants.

1.2 Motivation

Microelectrodes can be fabricated from a number of different materials such as silicon, glass or polymers being silicon the most used. Silicon-based microelectrodes are rigid structures which can lead to problems on in-vivo applications due to silicon’s brittleness. Therefore polymers have been extensively used as an alternative since they are flexible and have other advantages that will be described later.
Rigid probes often induce tissue damage due to its movement. When using polymer-based probes there is reduced damage in the insertion due to its flexibility although this step is also more difficult to achieve. Polymer-based probes also comply better with brain tissue motion [16]. Nonetheless one of the limitations brought by silicon use on microelectrodes still persists when using flexible polymeric probes. This is device failure. The device failure is due to the inflammatory tissue reaction following implantation and during device implantation which leads to degradation of the electrodes and spoils the stimulation and recording characteristics of the device (fig. 1.1).

Fig. 1.1 Inflammatory response of the tissues surrounding a foreign structure. Astrocytes are represented in red while microglia is in green. Courtesy of A. Mercanzini.

The response of a tissue to a device is not solely based on its materials but also to its process steps and chemicals, shape, type of insertion etc. Nevertheless no matter how compatible and non-invasive these parameters are there will always be a natural tendency for proteins and cells to adsorb to foreign structures. This will in turn, trigger the inflammatory response.

Astrocytes and microglia which are the primary support cells of the brain and spinal cord and a type of glial cell, divide to make new cells that migrate to the implantation site which is the site of injury, surrounding it. These cells cover the probe, forming a glial scar, encapsulating the probe and isolating it from the neural tissue.

In the inflammatory process, there is first an acute inflammatory response to a harmful stimuli followed in time by a chronic inflammatory response. The acute inflammation is characterized by an infiltration of the tissues by plasma and leukocytes and happens parallel to inflammatory mediators cascade systems.

The fibrosis which leads to encapsulation of the probe occurs normally over long-term implantation, during the chronic response (fig. 1.2).

The chronic inflammatory response is not only an active inflammatory response but also, tissue destruction and repairing. The chronic response which is characterized by the presence of macrophages and fibroblasts is normally caused by persistent acute inflammation.
So, in spite of all the advances made in the bioMEMS industry, unless this problem is solved, the use of neural probes will be limited.

The inflammatory response surrounding implantable probes has been proved to be controlled through local release of dexamethasone, an anti-inflammatory agent, at the site of implantation [33, 34].

Would the dexamethasone be released via a neural probe itself, then the inflammatory response could be controlled directly on the surroundings of the probe leading to a longer life span of the probe.

1.3 The project: Structure and objectives

This project aims to create a flexible polyimide microfluidic device by microfabrication methods at the Microsystems Laboratory at the EPFL.

This device incorporates a reservoir and a tip with a micro-channel with several outlets (fig. 1.3).

This device will hold and deliver a liquid anti-inflammatory drug to the site of implantation. This neural drug delivery device will deliver a solution of Dexamethasone, which as it has been mentioned above controls the inflammatory response.
The device will be implanted in the brain of a rat. The validation of the device will be performed in vivo by verifying the efficacy of the drug delivery therapy by immunohistological techniques.

Therefore, the ultimate goal of this thesis is to demonstrate the disruption of the anti-inflammatory response on the use of a polymeric neural probe with anti-inflammatory drug delivery function. If it succeeds to meet its objectives, the neural probe will be used in the future as the base structure for creating microelectrodes with an integrated reservoir and microchannel for drug delivery by diffusion mechanisms.
2. Design

2.1 Introduction and features

This device was designed as a probe-type device to incorporate one reservoir with a long tip for insertion into the brain. This tip has one buried microchannel with several outlets. The number of outlets was decided subsequently to calculations since these can only exist in the extremity of the tip. The outlets are on both sides of the substrate so that both sides can have fluidic interfaces.

The integration of valves or other type of pressure or pumping mechanism was discarded since it could further complicate the device in terms of manufacturing, functioning and validation. The diffusion approach was then chosen as a more suitable and practical solution for this type of problem.

Pillars were created inside the reservoir area for support so that the cover layer wouldn’t come into contact with the bottom. On this first prototype, two columns with three pillars each were created, making a total of six pillars.

The corners of the reservoir as well as the tip were made round for a less angular device.

2.2 Parameters: Dimensions/Capacity

The structures were designed in order to get approximately 1µL Volume over the neural probe. Mainly the reservoir is accounted for desired volume since the microchannels, pillars and openings are too small. The dimensions were obtained following calculations.

2.2.1 Calculations

Since the height is the most limited dimension in the fabrication process and once it is also one of the most important parameters for the design of the device, the lateral dimensions were calculated subsequently depending on the first one. Nonetheless, these dimensions still remain with a certain degree of freedom over the fabrication process.

The height of both the channel and the reservoir were selected in order for the top layer not to collapse over minimal applied pressure but also so that it was acceptable for the microfabrication procedure.
The cover layer thickness was thoroughly studied in order to prevent collapsing. The estimated value for the thickness of the top layer suffered some modifications throughout the fabrication processes due to material specifications, procedure and problems encountered in machine utilisation due to excessive tension over wafers.

Both the channel and the reservoir were designed to have heights of 30 µm leading to a height of 36 µm for the bottom layer for both the reservoir part and the tip part, due to polyimide layers deposition parameters. The top layer was designed to have a thickness of 22 µm but this value underwent further modifications as mentioned above (fig. 2.1).

Fig. 2.1 First prototype of the neural probe. Dimensions are according to the first assumptions.

The interior reservoir area was calculated to be approximately 33 µm² (1 µL = 1 µm³, Area =1/0.030) and so the reservoir was assigned to have a width of 5 mm and a length of 6.6 mm.

The channel dimensions were adjusted to two different sizes. The width of the channels is of 50 or 100 µm but the length is maintained at 2mm. Only the section area was varied in order to assess fluidic resistance and ultimate performance of the probe.

The exterior dimensions were calculated subsequently to the interior ones. The exterior part of the reservoir was designed to have dimensions of 7mmx5.4 mm in order to maintain 200 µm thick walls all around the reservoir. Each pillar inside the reservoir has a diameter of 500 µm (fig. 2.2).
The tip length was of 2mm plus the extremity part which measures approximately 75/150 µm depending on the total width of the tip (fig. 2.3). The total tip width varies between 150 and 300 µm with 50/100 µm walls lateral to the channel (fig. 2.4).

The outlets were positioned closer to the tip for better fluidic connections. The channel outlets have a circular form and diameters of either 50 µm or 100 µm. The space between the outlets is of 50 µm and the number of outlets was designed to be of four (fig. 2.4).
All this values come form the first assumption that only the volume of the reservoir (~1 µm³) is taken into consideration for capacity calculation. The Volume of the channel is only of 0.009/0.017 µm³ and the four openings 0.00056/0.0024 µm³ while the pillars take up a space of 0.03534 µm³. We can therefore assume that this other values can be neglected.

All these values were maintained throughout the project except for the total height of the device, which as it has been said before underwent changes due to the bonding procedure and choice of materials. The final designed height of the device is 102 µm instead of 90.

These dimensions were also used for microfluidic calculations regarding drug diffusion.

2.3 Software layout

The design of the devices was made using layout software – Clewin. This software was used also for creating the masks that are used in the photolithography process (fig. 2.5). There are two types of devices on the masks with different dimensions. Some of them have thicker tips with thicker channels and wider outlets while some have thinner channels and tips and smaller outlets. These two types of devices were created in order to evaluate the different performances of thicker/thinner channels and wider or smaller outlets on the fluid diffusion and on the tissue interaction.
The bottom mask consists of the reservoir with pillars as well as the microfluidic channel (fig. 2.6). It was created with extra channels surrounding the devices so that later in the bonding process solvent gases could escape.

Fig. 2.6 bottom mask containing extra channels surrounding the microfluidic devices.
The top mask has the final devices shape with four holes over the tips (fig. 2.7).
Both masks contained alignment marks so that structures can be aligned later.

Fig. 2.7 Top mask containing probes in two different sizes.
3. Microfluidics: fluid delivery to tissue

3.1 Introduction

The neural probe device designed on the previous step is intended to establish a continuous fluidic interface with the biological tissue surrounding it. The fluid delivered by the probe is bound to interact with the cell communication in that precise zone. This device achieves a localized drug delivery affecting only the tissue in its proximity.

Since oral medication doesn’t cross the blood-brain barrier, intracerebral drugs have to be delivered in situ. This probe provides an alternative for syringes or needles which do not provide a sustained nor a controlled release. Microfabrication also allows this device to be explored for further applications because it can be combined with other type of systems as is the case of a drug delivery and recording probe.

Due to the microdimensions of the device, some factors have to be taken into consideration for an analysis of the fluidic delivery mechanisms of the probe. Microfluidics is the area that studies miniaturized devices for handling flows of picolitre/microlitre quantities of fluids. When dealing with microscale dimensions, the behaviour of fluid is influenced by different types of forces than at the normal scale. Mechanisms such as diffusion, fluidic resistance, laminar flow are dominant. In this device the volume of liquid inside the reservoir is released by diffusion. Diffusion is the process, by which a concentrated group of particles in a volume will, by Brownian motion, spread out over time so that the average concentration of particles throughout the volume is constant [1]. The mass transfer process is passive and slow and the pressure range at which this device functions is then low.

To characterize this process some equations can be used:

Fick’s Law particle Flux:

\[ J = -D_c \frac{\partial C}{\partial x} \]  (1)

Where \( D_c \) is the diffusion coefficient and \( C \) is the concentration of the particles

Fick’s second law:

\[ \frac{\partial C}{\partial t} = D_c \nabla^2 C \]  (2)

which at 1 dimension is

\[ \frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2} \]  (3)
Diffusion distance of a particle at one dimension over time:

\[ x_D = \sqrt{2D_c t} \quad (4) \]

Time required for a diffusion over a given distance:

\[ t_D = \frac{x^2}{2D_c} \quad (5) \]

3.2 Dexamethasone

Dexamethasone loaded Nanoparticules were first considered for the drug delivery into the cerebral tissues but since these were not stable, water soluble dexamethasone was used instead. Dexamethasone is an anti-inflammatory and immunosuppressant drug belonging to the steroid hormones class with a molecular weight of 392.461g/mol [55].

For the calculations regarding diffusion and fluidics, a diffusion constant was found for dexamethasone in the brain. This data was obtained from experiences described in some the articles by Y. Moussy et al. [25, 26] where they compared measured concentration profiles and the mathematical model with good agreement. They determined the diffusion coefficient subcutaneous \( 4.11 \pm 1.77 \times 10^{-10} \text{ m}^2/\text{s} \) and compared it to the diffusion coefficient in the brain \( 2.0 \times 10^{-10} \text{ m}^2/\text{s} \) [26]. The elimination constant for the brain is \( k = 1.19 \times 10^{-5} \text{ s}^{-1} \) [26].

We should be using the diffusion constant for water soluble dexamethasone but since this is relatively recent there is no data on that matter. Even before these articles about dexamethasone analysis only the diffusion constant of dexamethasone in water was accounted for \( 6.82 \times 10^{-10} \text{ m}^2/\text{s} \) (l) estimated from the Stokes-Einstein equation.

Building a Mathematical model even with approximate data, already can give us some idea of the behaviour of the drug delivery by the device.

The works by Y. Moussy et al also showed that Dexamethasone is of extreme importance in controlling the inflammatory response at the site of implantation.

3.3 Release calculations: diffusion mechanism

The diffusion mechanism in the human body follows an equation somewhat different of Fick second law. This equation must take into account chemical reactions that occur during mass transfer. The diffusion equation is then:
\[
\frac{\partial C}{\partial t} = D_c \frac{\partial^2 C}{\partial x^2} + \text{Re}(C) - \frac{\partial B}{\partial t} \tag{6}
\]

In this equation, \( C \) is the concentration of the drug in the tissues, \( D_c \) is the diffusion coefficient of the drug in the tissue, \( x \) is the distance at 1 dimension, and \( t \) is the time after implantation. This equation contains more two components that translate the rate of drug elimination on the tissues (\( \text{Re}(C) \)) and the concentration of drug bound and internalized (\( B \)).

On the general equation for transport in the brain, several assumptions are made:

\[
\text{Re}(C) = -K_{el} \times C \tag{7}
\]

which means first order elimination and

\[
\frac{\partial B}{\partial t} = K_{\text{bind}} \frac{\partial C}{\partial t} \tag{8}
\]

\( K_{el} \) is the elimination constant for the drug in the tissue.

This equation is only assumed for 1 dimension.

The resulting equation is:

\[
\frac{\partial C}{\partial t} = D_c \frac{\partial^2 C}{\partial x^2} - K_{el} \times C - K_{\text{bind}} \frac{\partial C}{\partial t} \tag{9}
\]

Which can be further simplified.

\[
(1 + K_{\text{bind}}) \frac{\partial C}{\partial t} = D_c \frac{\partial^2 C}{\partial x^2} - K_{el} \times C \tag{10}
\]

\[
\Leftrightarrow \frac{\partial C}{\partial t} = \frac{D_c}{(1 + K_{\text{bind}})} \frac{\partial^2 C}{\partial x^2} - \frac{K_{el}}{(1 + K_{\text{bind}})} \times C \tag{11}
\]

\[
\Rightarrow \frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2} - K \times C \tag{12}
\]

If \( \frac{\partial C}{\partial t} = 0 \), this equation would be reduced to a 1st order differential equation and no longer be a partial differential equation. This can only happen when the steady state is considered.

To solve this equation we must then considered it in two instants: inside the probe and outside the probe.
Inside the probe, we have a non permanent regime in which the flux is unsteady and the concentration varies with time ($\frac{\partial C}{\partial t} \neq 0$). Also, the elimination component of the equation can be discarded since this only occurs at the exterior of the probe.

$$\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2} \quad (13)$$

This equation must be solved with a new variable ($C(\varepsilon)$) since it is a partial differential equation:

$$\varepsilon = \frac{x}{\sqrt{4Dt}} \quad (14)$$

$$\Rightarrow \sqrt{4Dt} \times \varepsilon = x \quad (15)$$

$$\frac{\partial \varepsilon}{\partial x} = \frac{1}{\sqrt{4Dt}} \quad (16)$$

$$\frac{\partial \varepsilon}{\partial t} = \frac{x}{\sqrt{4D}} \times \left( \frac{1}{\sqrt{t}} \right) = \frac{x}{\sqrt{4D}} \times \frac{1}{\sqrt{t}} = \frac{1}{2t} \times \frac{x}{\sqrt{4Dt}} = -\frac{\varepsilon}{2t} \quad (17)$$

This way the new equation is:

$$\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2} \Rightarrow \frac{\partial C}{\partial t} \frac{\partial \varepsilon}{\partial t} = D \frac{\partial^2 C}{\partial \varepsilon^2} \left( \frac{\partial \varepsilon}{\partial x} \right)^2 \quad (18)$$

$$\Rightarrow -\frac{\varepsilon}{2t} \frac{\partial C}{\partial \varepsilon} = D \frac{\partial^2 C}{\partial \varepsilon^2} \times \left( \frac{1}{\sqrt{4Dt}} \right)^2 \quad (19)$$

$$-\frac{\varepsilon}{2t} \frac{\partial C}{\partial \varepsilon} = D \left( \frac{1}{\sqrt{4Dt}} \right)^2 \frac{\partial^2 C}{\partial \varepsilon^2} \quad (20)$$

$$\Rightarrow -\frac{\varepsilon}{2} \frac{\partial C}{\partial \varepsilon} = \frac{1}{4} \frac{\partial^2 C}{\partial \varepsilon^2} \quad (21)$$

$$\Rightarrow -2 \frac{\varepsilon}{\partial \varepsilon} = \frac{\partial^2 C}{\partial \varepsilon^2} \quad (22)$$

so

$$0 = \frac{\partial^2 C}{\partial \varepsilon^2} + 2 \varepsilon \frac{\partial C}{\partial \varepsilon} \quad (23)$$

Which can be compared to a differential equation of the type $ac''+bc'+dc=0$, where $a=1$, $b= 2\varepsilon$ and $d=0$. To achieve this variable replacement the diffusion constant was considered independent of time, place and concentration.
The solution of this equation corresponds to the mathematical model of the diffusion of dexamethasone in the brain.

To solve this equation boundaries and initial conditions must be imposed:

\[ C = C_0 \quad \text{at} \quad t = 0 \quad \text{for} \quad 0 \leq x \leq x_0 \] (24)

the reservoir is filled at the beginning

\[ C = 0 \quad \text{at} \quad t = 0 \quad \text{for} \quad x_0 \leq x \] (25)

there is no drug outside the reservoir at the moment of implantation

\[ C = C_0 \quad \text{at} \quad t > 0 \quad \text{at} \quad x = 0 \] (26)

there is constant drug concentration at the bottom of the reservoir and

\[ \int_{x_0}^{\infty} Cdx = C_0 \quad \text{at} \quad t=0 \] (27)

These conditions can be translated into:

\[ \varepsilon = 0, \quad C(t) = C_0 \] (28)

And

\[ \varepsilon = \infty, \quad C(t) = 0 \] (29)

If we try to solve the equation then:

\[ 0 = \frac{\partial^2 C}{\partial \varepsilon^2} + 2\varepsilon \frac{\partial C}{\partial \varepsilon} \quad \Leftrightarrow \quad \frac{\partial^2 C}{\partial \varepsilon^2} = -2\varepsilon \frac{\partial C}{\partial \varepsilon} \] (30)

Integrating

\[ \frac{\partial C}{\partial \varepsilon} = a e^{-\varepsilon^2} = a e^{-\frac{x^2}{4Dt}} \] (31)

\[ \frac{\partial^2 C}{\partial \varepsilon^2} = a \left( -2\varepsilon e^{-\varepsilon^2} \right) = -2\varepsilon \frac{\partial C}{\partial \varepsilon} \] (32)

As seen in one microfluidic book [6], the 2nd integration can be solved like this:

\[ \int_{x_0}^{\infty} \frac{\partial C}{\partial \varepsilon} d\varepsilon = \int_0^\varepsilon ae^{-\varepsilon^2} d\varepsilon \] (33)

Leads to
\[
\frac{C(t) - C_0}{C_\infty - C_0} = \text{erf} (\varepsilon) = \frac{2}{\sqrt{\pi}} \int_0^\varepsilon e^{-u^2} \, du \quad (34)
\]

\[
C(t) - C_0 = -\frac{2}{\sqrt{\pi}} C_0 \int_0^\varepsilon e^{-u^2} \, du \quad (35)
\]

where \( a = -\frac{2}{\sqrt{\pi}} C_0 \)

\[
C(t) = C_0 - \frac{2C_0}{\sqrt{\pi}} \int_0^\varepsilon e^{-u^2} \, du \quad (36)
\]

The integral that appears in the equations is also known as function erf because this integral is not easily solved.

\[
\text{erf} (\varepsilon) = \frac{2}{\sqrt{\pi}} \int_0^\varepsilon e^{-t^2} \, dt \quad (37)
\]

It can be solved but with the use of summes:

\[
e^x = \sum_{n=0}^{\infty} \frac{x^n}{n!} \quad \text{(development } = 1 + \frac{x^2}{2!} + \frac{x^3}{3!} + \ldots + \frac{x^k}{k!}) \quad (38)
\]

\[
e^{-x^2} = \sum_{n=0}^{\infty} (-1)^n \frac{x^{2n}}{n!} \quad (39)
\]

\[
\int_0^\varepsilon e^{-u^2} \, du = \int_0^\varepsilon \sum_{n=0}^{\infty} (-1)^n \frac{u^{2n}}{n!} \, du = \sum_{n=0}^{\infty} \frac{(-1)^n}{n!} \int_0^\varepsilon u^{2n} \, du \quad (40)
\]

\[
\sum_{n=0}^{\infty} \frac{(-1)^n}{n!} \int_0^\varepsilon u^{2n} \, du = \sum_{n=0}^{\infty} \frac{(-1)^n}{n!} \left[ \frac{u^{2n+1}}{(2n+1)} \right]_0^\varepsilon = \sum_{n=0}^{\infty} \frac{(-1)^n}{n!} \frac{\varepsilon^{2n+1}}{(2n+1)} = \varepsilon - \frac{\varepsilon^3}{1 \times 3} + \frac{\varepsilon^5}{2 \times 5} + \ldots + (-1)^k \frac{\varepsilon^{2k+1}}{k!(2k+1)} \quad (41)
\]

So

\[
C(t) = C_0 - \frac{2C_0}{\sqrt{\pi}} \int_0^\varepsilon e^{-u^2} \, du \quad (42)
\]

\[
\Leftrightarrow C(t) - C_0 = -\frac{2}{\sqrt{\pi}} C_0 \sum_{n=0}^{\infty} \frac{(-1)^n}{n!} \frac{\varepsilon^{2n+1}}{(2n+1)} \quad (43)
\]

This leads to
\[
C(t) = C_0 - \frac{2}{\sqrt{\pi}} C_0 \sum_{n=0}^{\infty} \frac{(-1)^n}{n!(2n+1)} \left( \frac{x}{\sqrt{4Dt}} \right)^{2n+1} \quad (44)
\]
\[
C(t) = C_0 - \frac{2C_0}{\sqrt{\pi}} \left( \frac{x}{\sqrt{4Dt}} \right)^{3} + \frac{1}{5\times2} \left( \frac{x}{\sqrt{4Dt}} \right)^{5} - \frac{1}{7\times3!} \left( \frac{x}{\sqrt{4Dt}} \right)^{7} + \ldots \quad (45)
\]
\[
C(t) = C_0 - \frac{2C_0}{\sqrt{\pi}} \frac{x}{\sqrt{4Dt}} (1 - \frac{1}{3} \frac{x^2}{4Dt} + \frac{1}{10} \left( \frac{x^2}{4Dt} \right)^2) \quad (46)
\]

, if we neglect some fractions

Outside the probe we can assume that the concentration didn’t vary with time \( \frac{\partial C}{\partial t} = 0 \) and so assuming the steady state, the equation can be further simplified. However this model contemplates the elimination of the drugs that occurs in the tissues:

\[
0 = \frac{D}{(1 + K_{bind})} \frac{\partial^2 C}{\partial x^2} - \frac{K_{el}}{(1 + K_{bind})} \times C \quad (47)
\]
\[
\Leftrightarrow 0 = D_c \frac{\partial^2 C}{\partial x^2} - K_{el} \times C \quad (48)
\]
\[
\Leftrightarrow \frac{\partial^2 C}{\partial x^2} = \frac{K_{el}}{D_c} \times C \quad (49)
\]

The boundaries and initial conditions are different than before:

\[ C = 0 \quad \text{at} \quad t = 0; \quad x \geq 0 \quad (50) \]
, there is no drug in the tissues at the moment of implantation

\[ C = C_0 \quad \text{at} \quad t > 0; \quad x = 0 \quad (51) \]
, there is constant drug concentration at the interface and

\[ C = 0 \quad \text{at} \quad t > 0; \quad x \rightarrow \infty \quad (52) \]
, the drug is located in the proximity of the probe \( C_0 \) is the initial concentration).

The solution found to the equation with the conditions is:

\[ C = C_0 e^{-\frac{K_{el}x}{D_c}} \quad (53) \]
Since, the initial concentration is not available, nor the binding constant, and since the known diffusion constant is not exactly for the type of dexamethasone used one can only examine the equations with arbitrary constants.

The Evolution of the concentration is thought to be like on figure 3.1.

![Figure 3.1](image)

Fig. 3.1 Schematic drawing of the presumed evolution of the concentration inside and outside the probe. The overall curve for the concentration function of the distance is the sum of the two equations obtained for inside the reservoir and outside in the brain. $x_0$ is considered the initial boundary for the concentration outside the probe.

Nevertheless, an approximate time must be obtained to have some idea of in how much time will the reservoir be depleted.

A simple but not very approximate way to solve this problem is using the equations (4) and (5) for the length of the channel 2 cm (=20mm):

$$t \approx \frac{2^2}{2 \times 2.10^{-4}} \Rightarrow approx.2h47\ min\ (54)$$

For an approximate length of the entire probe at 1 dimension:

$$t \approx \frac{9^2}{2 \times 2.10^{-4}} \Rightarrow approx.2days8h\ (5)$$

Because we do not know the diffusion constant for the water soluble dexamethasone, no real conclusions can be taken from these results except that these are only approximate.

The dimensions chosen for the device can only be assessed after the experimental tests.
4. Microfabrication Material

For all the reasons explained previously on the motivation, the material used to microfabricate the neural probes is a polymer. Polymers are widely used to fabricate microfluidic devices. Examples of these are polyethylene terephthalate (PET), polymethylmethacrylate (PMMA), Polyimide, polydimethylsiloxane (PDMS) or SU-8.

The polymer chosen for this type of microfluidic application is polyimide which is very well known and commonly used in microfabrication and has outstanding characteristics excelling the other polymers. Because it has dielectric characteristics, it is extremely suitable as insulating material for microelectrode fabrication.

4.1 Polyimide

The polyimide components used during this project were mainly Polyimide PI 2611 (HD Microsystems) and Kapton foils of different thickness (fig. 4.1). Polyimide PI 2610 was also tried but did not have the characteristics needed for this type of application. Other materials and supports used during the manufacture process will be discussed later.

4.1 Polyimide: description of polyimide-based structures and chemistry

Polyimide is a polymer in which the subunits are imide groups (fig. 4.2). The polymer can be linear, aromatic depending on the monomers (fig.) and on the chain structure.
The imide group consists of 2 carbonyl groups (RR'C=O) (instead of 1: the amide case) bound to a primary amine (NR₃) or ammonia (NH₃). When an aromatic ring is attached to the cyclic imide group, the polymer is aromatic. The aromatic polyimides are the most used in the polymer industry for their stability over a wide range of temperatures which is mainly due to it polymeric stiffness.

Polyimides are formed normally in a procedure which involves two steps, consecutive in time which is known by the condensation route. The first part of the procedure involves the conversion of diamines (NR₂-NR₂) and dianhydrides molecules (R(C=O)-O-(C=O)R) into poly(amic acid) in a polar solvent.

The poly(amic acid) is sometimes called polyimide because being soluble it constitutes the liquid solution which is used to cast polyimide films although it is only the prepolymer. Polyimide is stored normally in the poly(amic acid) liquid form which is easier to handle but this should be avoided for long periods of time and only done at low temperatures since it can undergo chemical changes.

The solid polyimide is then only obtained in a second step by the conversion of the poly(amic acid). This conversion, which occurs by heating at elevated temperatures or by using chemical dehydrating agents is called cyclodehydration or imidisation because the cyclization of the molecules and formation of the polyimide happens with the loss of one water molecule.

An example of a polymer obtained via this route is the commercially well known Kapton (fig.4.3)
Beside condensation polymers there also exit addition and thermoplastic polyimides.

4.1.2 Characterization of Polyimide - important features

The structure of aromatic Polyimides enables them to be tremendously stable over a broad range of temperatures making them extremely appealing over the other existing polymers. Not only this characteristic but others as its reasonable cost and its minimal synthesis turned polyimide into the ultimate polymer commercially unmatched by no other.

Polyimide is known for its lack of properties variation when exposed to organic solvents or even dilute acids and elevated temperatures. Its extensive processability united with its biocompatibility contributes largely for his success as a biomaterial.

Although polyimide is considered highly flexible, it is mechanically tough due to good stress absorption. One extra advantage of this polymer is his low dielectric constant.

His unique combination of features and properties are truly unbeatable making it suitable for a wide range of applications.
4.1.3 Applications of polyimide

In the semiconductors industry, Polyimide is used with several purposes. Polyimide films are intended to provide insulation while coatings are intended to absorb mechanical stress.

In microfabrication it can be applied as photoresist or resin for MEMS fabrication. Recently it is extremely requested for building devices for the field of biological interfaces, microelectrodes, probes, etc.

It is also found on flexible cables and even in the aerospace industry.

Polyimide is also commercialized as moulding powders, adhesives, fibbers and foams.

4.1.4 Material specification and Commercial status

Polyimides were first developed and commercialized by the DuPont Company. The most known product is Kapton® or Kapton™ which are polyimide films made from pyromellitic dianhydride and 4,4'-oxydianaline. Nowadays the DuPont Company merged resources and technology with Hitachi chemical resulting in HD Microsystems still providing PI products other than Kapton™. Pyralin® series of coatings are solutions of polyimide precursors poly(amic acids) (BPDA- PDA = Biphenylene Dianhydride, p-Phenylenediamine or PPD-BPDA) in a solvent of N-methyl-pyrollidone (NMP).

The coating used for this project was mostly PI 2611 due a greater degree of viscosity compared to PI 2610 which allows the obtention of thicker films. These coatings can be classified as or thermosetting resins and have good adhesion to metals and to themselves if uncured.

Kapton™ films are incredibly stable up to 400°C and also resist well to chemical environment and deformation. There are various types of Kapton™ films, being Kapton® HN the one used throughout this project. Kapton® HN (poly(4,4'-oxydiphenylene-pyromellitimide)) was used in the 100 HN standard size which is equivalent to a 25 µm thickness. Its properties are extremely appealing: good electrical properties; good mechanical properties and good thermal properties, it tends to shrink on its first exposure at high temperatures, but this shrinkage is only significant when temperatures are really elevated and for a long time). The shrinkage also happens with the liquid polyimide and will be better understood during the manufacturing process.
4.2 Supports and others

Silicon wafers were used as support for the polyimide structures. These wafers were used for materials deposition only (fig. 4.4). The wafers used had a size of 4 inches which corresponds to approximately 101.6 mm with a thickness of 525 µm. Glass wafer were also tried out but only for observation purposes since these lacked flats for orientation and the release method could not be applied.

![Fig. 4.4 Silicon wafer support and TiW/Al covered wafer with polyimide layers](image)

Besides polyimide Titanium, Tungsten and Aluminium metals were also deposited over the wafers for the release of the structures.

Teflon was used in the first bonding essays with kapton in order to separate it from the wafer but was no longer needed in the final procedure.

Mylar foils were used as an alternative to kapton in some essays regarding the bonding step, but were found not suited for the application. Mylar™ is a polyester film (PET) by DuPont and a thermoplastic polymer which can be used until 150°C-200°C. Above those temperatures it melts and can no longer be separated from the other materials.
5. Microfabrication: Machining and Techniques of Polyimide

Great part of the device manufacturing was done at the EPFL Centre for MicroNanoTechnology, the CMI. Learning about working in a clean room environment, microfabrication techniques and equipments, and handling of silicon wafers is essential for the procedure and was part of this project.

Microfabrication is the term used to describe the collection of technologies or processes for fabrication at the micrometer scale of electronic devices or MEMS (Microelectromechanical systems). Microfabrication is also known as micromachining and can be surface, creating structures on top of a substrate or bulk which produces structures inside a substrate. The fabrication of microdevices includes many processes, done in sequence and even repeatedly as for example Photolithography, Etching, film deposition, Wafer cleaning, etc.

5.1 Techniques

The techniques employed during this project mainly concerned polyimide but there was also some applied to metals so there will be a general introduction to several types of methods.

Every micromachining process which uses silicon wafers as mere substrates starts with deposition processes. These consist on depositing thin films of some kind of material onto a glass or metal substrate or over previously deposited layers, with thicknesses varying between some nanometers to a maximum of a hundred micrometers. These can be classified into two main categories: chemical deposition or physical deposition.

In chemical deposition, some type of solvent is deposited over a solid surface where it undergoes a chemical change turning into a solid layer. Spin coating is an example of chemical deposition. Here the solvent placed over the substrate is rotated at increasing speed by a spinner so that the fluid can be spread by centrifugal force until the desired thickness is obtained. The substrate is accelerated up to its desired rotation speed which determines as long with the viscosity of the solvent used, the thickness of the film; higher the speed, thinner the film. Spin coating is used mainly to deposit polymers as is the case of polyimide or photoresists and is normally followed by softbake and hardbake steps to remove excessive solvent and harden the layer. In the case of Polyimide, the coating that is applied over the wafers is a form of poly (amic acids) and only upon curing at temperatures between 200°C and 400°C will it convert to solid polyimide. This process can be used for building sequential layers in order to obtain greater thicknesses. Sometimes an adhesion promoter might be needed, but in the case of polyimide it tends to adhere well to metals and itself.

Physical deposition makes use of mechanical or thermodynamic means to obtain the same solid layer. Examples of physical deposition include Sputtering deposition which relies on a plasma (usually
Argon) to provoke the ejection of a few atoms at a time from a source material onto a substrate. Reactive sputtering mixes also a non-noble gas such as oxygen or nitrogen leading to the obtention of a thin film of oxide or nitride of the target material coated on a wafer. Silicon oxide thin films for example can be obtained by sputtering deposition.

Once films are deposited, they can be patterned by photolithography. Photolithography is a process used for selective removal of parts of a film. The process makes use of photosensitive material (photoresist) as it has the ability to change its properties upon light irradiation. The photoresist is normally applied by spin coating.

Usually, before photolithography can occur the wafer surface is treated in order to remove any moisture that may be present or even cleaned in order to remove possible contaminants. This can be done with a dehydration bake or an oxygen plasma step. Additionally an adhesion promoter such as HDMS (Hexamethyldisilazane) is applied in order to facilitate the adhesion of the photoresist to the top layer of the wafer.

The process starts with the exposure of the photosensitive material to a pattern of light (usually UV) thus transferring the pattern to the material. This is achieved by means of a mask which blocks part of the radiation transmitted to the photosensitive material. The photomask pattern is made of transparent areas and opaque chrome covered areas and originates from a computer file through a photolithographic process itself.

The irradiated material suffers changes in its physical properties differing from the unexposed material. Positive photoresist the most common type becomes less chemically robust when exposed while negative photoresist becomes more robust.

Chemical treatments afterwards allow a partial removal of the photosensible material, engraving the exposure pattern and providing a mask for the underlying substrate. This step is called development and makes use of a special solution to remove the photoresist (developer), which is delivered on a spinner. The PR mask provides protection for the underlying layers during the following etching steps in order to engrave the same pattern on those layers.

These etching steps are mainly used to remove the parts of the uppermost layer that are exposed. Once the photoresist is no longer needed to protect the underlying layers, it is removed, stripped in a special remover solution. Sometimes this step is not needed as the photoresist is automatically removed in the etching process when using plasma containing oxygen.

As briefly referred before, Etching is used in microfabrication for partial removal of the surface of the top layer surface on a wafer. Part of the layer surface is protected from the etching agent (etchant) by a "masking" material which resists the etching process. Photoresist patterned in photolithography is normally used for this purpose. Etching can be essentially of two types: wet or liquid-phase and dry or plasma-phase. On wet etching, the material is removed by dissolution when immersed in a chemical solution while on dry etching, material is removed by sputtering or dissolved by reactive ions or a vapor phase etchant. When using a plasma containing oxygen for etching, photoresist is also
removed. This is why, when etching polyimide, a hard mask of silicon oxide or metal is needed. Photoresist in only used for the etching this hard mask previously to the Pyralin etch. The depth of the erosion of the substrate is determined approximately by the etching rate and time. Normally this erosion is perfectly anisotropic so that it produces vertical sidewalls but it can also be isotropic so that the substrate is eroded equally in all directions.

Cleanliness in wafer fabrication is also known as surface preparation and is an important step in microfabrication. Although microfabrication is carried out in a clean room where air is filtered and parameters as temperature or humidity are under stringent control, there may always exist other types of contamination which can destroy the microfabricated devices. Active cleaning is then required to improve the surface conditions of the wafers and this can be done with specific solutions (isopropanol...) for this purpose, plasma oxygen treatments etc.

5.2 Equipment used in the clean room and parameters setting

Several equipments were used in order to microfabricate the neural probe devices. For a better understanding of the procedure and of the parameter settings, these will be presented. For the deposition processes and polymer bakes the following machines were used: Sawatec LMS200 Polymer Coater; Sawatec HP 401Z, Hotplate for Soft-bake; Hotplates; Hereaus T6060, Multipurpose Oven; Pfeiffer Vacuum Spider 600 – High Vacuum Sputtering cluster system 600 and Balzers BAS-450, Single chamber multi-target sputtering system. The photolithography steps were done using the EVG 150, coater and developer for positive resist and the Suss MA6 Double Side Mask Aligner. The etching was done on the STS Multiplex ICP, Plasma etcher – chlorine chemistry. The cleaning and Surface Preparation was done by means of the YES LPIII, HDMS primer oven and the Tepla 300, Microwave plasma stripper but sometimes also manually with proper chemical products. The Coillard Photolithography, Wet bench for resist develop and resist strip and the Coillard etching, Wet bench for oxide and metal etch were also used for cleaning despite its main function in this project being for etching in a mask manufacturing procedure. This procedure involved the use of the Heidelberg DWL200 Laser Writer/ lithography system and the Suss DV10 Mask and thick positive resist developer. This last equipment could also be used as an alternative in the development of the wafers. For visualization purposes the Nikon Optishot 200, optical microscope and the Zeiss LEO 1550, Scanning electron microscope were used.

Others equipments will be referred as although they were not considered in the final procedure, they were used in intermediate trials when other equipments failed or when trying out different approaches. These include the RiteTrack 88 Series, automatic coater track for positive resist and the RiteTrack 88 Series, automatic developer track for positive resist.
The equipments will now be introduced in order of utilization in the main procedure and auxiliary, alternative equipments as well as equipments used for mask manufacturing will be referred afterwards.

The Balzers BAS-450, Single chamber multi-target sputtering system (fig. 5.1a) is used for thin layers deposition over 100mm wafers. The material deposited can be metallic as is the case of aluminium, titanium and tungsten used during this process or insulator. There are two ways of depositing thin layers: DC sputtering (Direct current) for metallic layers and RF sputtering (Radio frequency) for dielectric layers. The gases used are Argon or Oxygen. The thickness of the film deposited depends on the energy used on the target.

![Balzers BAS-450 sputtering system](image1)

**Fig. 5.1a. Balzers BAS-450 sputtering system**

b. Sawatec LSM200 coater and HP401Z Hotplate. Courtesy of the CMI

The polyimide coating is done manually on the Sawatec LSM200, Polymer coater (fig 5.1b). The machine has an automatic dispensing system and a Microprocessor control for changing parameters and storing polyimide process recipes.

The process diagram used during this procedure can be seen on fig 5.2.

![Polyimide coating process diagram](image2)

**Fig. 5.2 Polyimide coating process diagram. Table with the Duration and speed of each segment of the process curb.**

<table>
<thead>
<tr>
<th>Segment</th>
<th>Segment Time [s]</th>
<th>Process Time [s]</th>
<th>Speed at end of segment [rpm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.0</td>
<td>5.0</td>
<td>500</td>
</tr>
<tr>
<td>2</td>
<td>5.0</td>
<td>10.0</td>
<td>500</td>
</tr>
<tr>
<td>3</td>
<td>5.0</td>
<td>15.0</td>
<td>1400</td>
</tr>
<tr>
<td>4</td>
<td>10.0</td>
<td>45.0</td>
<td>1400</td>
</tr>
<tr>
<td>5</td>
<td>10.0</td>
<td>55.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

The first speed is to spread the polymer and then it is increased to set the desired thickness. 1400 rpm corresponds to approximately 11µm of PI2611 (see Annexe 1). This rotation speed is maintained when the polyimide is spun directly onto the wafer or over the other polyimide layers. Normally, when
several layers are required the velocity of the upward platform must be adjusted so that the same layer thickness is obtained. Here no adjustments where made because the values did not have a significant difference.

Sawatec HP 401-Z is a hotplate used for softbake but a set of different hotplates were used instead for this step of the process. The set of hotplates consists of 2 large area hotplates at constant temperature and 1 cooling plate. The first hotplate is set at 75ºC for stabilising the polyimide film and the second one is set at 105ºC for evaporating the first solvents.

Once the PI layers are completely softbaked, they are ready for a more complete baking that can only occur on a Nitrogen atmosphere oven. The Nitrogen inert atmosphere must be used, otherwise the polyimide might burn. The hardbake step is done in the Hereaus T6060 multipurpose oven (fig. 5.3a). The baking curve is defined by defining the time and temperature of each step. The entire program takes about 5h30 minutes. Nitrogen is automatically turned on after 200ºC and again off later. Once the program is finished, the oven takes approximately one and a half hour to cool down. Further processing of the PI covered layers as oxide deposition or etching require that the Polyimide is fully cured; otherwise problems will occur as it is seen later.

The Silicon oxide is deposited on the Pfeiffer Vacuum Spider 600 - High vacuum sputter cluster system (fig. 5.3b). This machine deposits metallic or insulator thin layers over wafers using a technique called sputtering which was already seen on the Balzers BAS-450 sputtering system. However this equipment has a different system which allows a quicker deposition process. The deposition of oxide or nitrites occurs in the presence of oxygen with a metallic target and is considered reactive sputtering. For a given layer thickness the sputtering time has to be calculated for a sputtering speed of 42.50 nm/min.

Once the silicon oxide is deposited, the process can proceed to the photolithography step but previous surface treatment must occur.
The YES LPIII HMDS primer oven, is used for priming of the Silicon oxide to enhance adhesion of polymer such as the positive photoresist used in this process. The priming agent used is Hexamethyldisilazane (H.M.D.S.) in vapour phase at a temperature of 150 °C, with an exposure time of 5 minutes. The process carried in the oven removes the moisture that is chemically bound to the surface so the silane/substrate bond isn’t impaired. Then, when HDMS is applied, a superior bond is formed that is stable even after exposure to atmospheric moisture. This process dramatically improves the application of HMDS as a surface priming treatment.

The EVG 150 coater and developer system for positive resist is used for deposition, coating and baking of photoresist as well as for the development step later (fig.5.4a and 5.4b). The photoresist used is the AZ9260 with a thickness of 5 µm.

![Fig. 5.4a Spinner on the EVG coater and developer system b. EVG 150 c. Süss MA6.](image)

Courtesy of the CMI

For the photoresist engravement, the Süss MA6, Double side mask aligner is used (fig. 5.4c). This mask aligner is a UV exposition equipment which enables a quick transfer of motifs from a chrome mask to a photosensible material covered substrate (PR). The key operation of this type of equipment is that it allows the relative alignment of the motifs on the chrome mask over pre-existent structured motifs on the substrate.

The results obtained depend on the defaults provoked by dust and on the carefulness associated with the substrate preparation. A short delay of 5 minutes between the coating and the exposure as well as a 10 minutes delay between the exposure and the development is advised.

The mask aligner is used with a 5x5” Mask and a 100mm wafer. The wafers are exposed twice for 9.5 seconds.

Once the photoresist is photostructured the underlying layers are removed by dry etching. The STS Multiplex ICP, plasma etcher-chlorine chemistry (fig. 5.5) is used to etch a large range of materials with high density plasma: insulators as is the case of silicon oxide, silicon, metals and alloys as for example Platinum or Titanium, and even polyimide. The polyimide etching is in the presence of oxygen also leading to photoresist removal while on this procedure. Both oxide etch (for SiO₂) and pyralin etch (for polyimide) are carried at room temperature. The silicon oxide etch occurs at an etch rate of 0.25 µm/min. Since the photoresist mask has a selectivity of about 1:1 which is rather poor, the photoresist thickness must be a bit higher than the one of the oxide. In this procedure silicon oxide
films will vary from 0.5 µm to 2.2 µm so a photoresist thickness of at least 4 µm is needed; for the AZ9260 photoresist, the ideal thickness required is 5 µm. There should always exist an over etch time to ensure that the oxide layer is totally removed over the polyimide zones to etch. For 0.5 µm of oxide an etching time superior to 2 minutes is advised.

The pyralin etch is performed at an etch rate of about 1 µm/min. Silicon oxide being a hard mask has a selectivity of about 50:1 which means that in order to etch 50 µm of polyimide there should exist at least 1 µm of silicon oxide to protect the underlying layer from being all etched away.

On the first pyralin etch a depth of approximate 30 µm which corresponds to etching for 30 minutes was done with an oxide mask of 500 nm. If we consider a selectivity of 50:1, it means that a layer of 600 nm should have been used instead, but the selectivity is only approximate and is expected to be superior to the one declared.

The second etch which is a total etch was done with varying polyimide thicknesses so the oxide layer also varied. The final values were 2.2 µm of oxide for 110 µm polyimide thickness.

The first oxide etch of the final etch had a duration superior to 10 minutes so it had to be done in segments in order to avoid the resist to heat up and burn.

5.2.1 Mask making and other procedures

In order for the photographic steps to occur during the microfabrication procedure, masks had to be created. The creation of the masks is done using a photolithographic process itself.

In the first part of this process the Heidelberg DWL200 Laser Writer/lithography system is used (fig.5.6a). This machine is a fast to medium speed tool to write on g, h-line photoresist, in order to create masks.

Mask layout is made using specialized CAD tools that generate multilayer drawings for a complete set of mask level. Clewin was used as the layout editors but there were other softwares as L-edit, AutoCAD, etc. The mask designs should be in a standard layout format: CIF or GDSII.
Before using the machine, the mask designs have to be converted using a conversion software which translates CIF or GDSII formats into the internal DWL200 data format (LIC).

The material used for the mask creation is the Cr-blank mask which consists of a fused quartz substrate covered with a layer of chrome.

In the machine, there is a beam of electrons which exposes the pattern defined in the data file. This beam travels over the surface of the Cr-blank mask in a scan manner. In the areas of the mask where the photoresist is exposed, the photoresist can be removed followed by the chrome by chemical etching and this will leave a transparent area for the light to cross through.

![Fig. 5.6a. Heidelberg DWL200 b. Suss DV10c. Coillard wet benches. Courtesy of the CMI](image)

The photoresist removal of the masks was done in the Süss DV10 mask and thick positive developer (fig. 5.6b). It is a machine for treatment of photosensitive resists which uses Puddle development over the substrate with oscillating movements while on reaction periods. Recipes also include purge steps as well as rinsing and drying of the substrate. It can be used for 5 inches chrome blank nanofilms as well as for 4 inches wafers.

This machine is used after the laser writer in the mask fabrication process and precedes the coillard wet benches.

It is also as an alternative to the EVG 150 developer for developing AZ9260 5 µm or for Ritetrack 88 automatic developer for developing AZ92XX 4 µm among other recipes.

The coillard wet benches (fig. 5.6c) are used in the mask fabrication process but also for resist strip in case of a bad deposition on wafers or even just to clean wafers. Their utilisation requires special care and protection. The user must wear a facial protection, chemical gloves with long sleeves and an apron.

The baskets are used for putting the wafers inside the baths. Special baskets are provided for masks. The remover 1165 baths on the coillard photolithography wet bench for resist develop and resist strip, are used for positive photoresist stripping. The following procedure must be carried out: First the basket is placed in the “OLD” bath for a minimum of 5 minutes. Then it is placed for the same amount of time on the “NEW” bath. Once the remover baths are finished the basket is placed on the QDR. QDR means Quick Dump Rinse and is used for a quick rinsing of the wafers or mask. The final rinsing is done on the UC Ultra clean step. Finally the wafers are dried one by on the BLE spinner (fig 5.7).
The chrome etch bath on the coillard etching wet bench for oxide and metal etch, is used for chrome etching on the mask fabrication process. This bath carries a wet attack of the chrome on the masks as well as chrome oxide. The following procedure must be carried out:

First the basket is placed in the chrome etch bath for approximately 1min50sec. The end of the chrome attack is determined visually. Then it is placed on the QDR followed by the UC. Once this is done, the photolithography wet bench must be used to remove the photoresist and this is done in a similar way as described before. This time the baskets are place in each remover bath for minimum 10 minutes. The masks are to be dried manually using the azote pistol. (fig. 5.7)

During the procedure and once it was finished, microscopes were used for evaluation of the structures.

The Nikon optishot 200, optical microscopes (fig. 5.8) used for wafer observation suffered adaptations for this purpose.

The Zeiss LEO 1550 Scanning electron microscope (fig. 5.8) can be used for observation of many types of samples including 4 inch wafers or cut pieces. The maximal resolution can attain 1nm, while the zooming capacity ranges from 50x to 900’000x.

Fig 5.7 Procedure in the coillard photolithography wet bench and the coillard etching wet bench. Courtesy of the CMI.

Fig 5.8 Nikon optishot 200 and Zeiss LEO 1550 SEM. Courtesy of the CMI
A pre-treatment is an optional step before the polyimide deposition or even to activate the polyimide surface before metal deposition. This can be done with the Tepla 300, Microwave plasma stripper. This equipment uses a high frequency plasma for applications such as surface cleaning and treatment before procedures, photoresist stripping after development etc.

![Fig 5.9a. RiteTrack 88 series b. Süss RC8 coater](image)

Throughout this procedure alternative equipment was tried out (fig 5.9). The RiteTrack 88 series automatic coater for positive resist uses an automatic track for coating photoresist. This equipment did not contain recipes for the AZ9260 so the AZ92XX was used as an alternative but the outcome was a little bit different. The AZ92XX is made by diluting the AZ9260. The recipe of the AZ92XX 4 µm which allows backside removal was used. The steps of spin-coating on a coater, baking on a hotplate and cooling on a chill plate succeed after each other automatically. The RiteTrack 88 series automatic developer for positive resist uses an automatic track for developing photoresist and consists of several units, using a developer and a hotplate for softbake as well as a chill plate for cooling down wafers at the end.

Switching to the AZ92XX lead to some changes in the exposure parameters on the MA6 mask aligner. The time of exposition was decreased to 2 exposures of 6.5 sec each (see Annex 2).

During some experimental trials with thick Polyimide covered wafers problems occurred because these were too curved for the vacuum to work either on the EVG or the RiteTrack. Because these wafers were not accepted on both machines, the Süss RC8 Negative Resist coater had to be used as an alternative on the first wafers where this problem occurred. In the end this problem was solved by reducing the polyimide thickness and therefore avoiding overstressed wafers.

When using the Suss RC8 coater for depositing the AZ9260 parameters like rotation time and speed had to be adjusted. In the EVG equipment (as well as in the RiteTrack) the rotation speed is already defined in each available recipe. We only have to choose the photoresist thickness that we intend to spin and the speed is defined automatically by the machine. If we access the recipes we can see that the speed for 5 µm in the Evg is 6800 rpm (see Annex 2).

Since the maximum speed of the RC8 coater is 4500 rpm the thickness of the AZ9260 layer has to be modified and a new speed calculated. In the EVG the closest recipe to the 5 µm recipe is the 8 µm which uses a rotation speed of 2800 rpm (see Annex 2).
In the EVG the rotation speed for a given thickness is given by a graph (fig. 5.10) which characterizes the deposition of photoresist on silicon oxide. If we use that graph we can obtain the rotation speed for any desired thickness other than 5 µm and 8 µm. A chart is given by the CMI for this calculations and this information can be cross-checked in the Clariant AG AZseries specifications sheet (see Annexe 2).

Fig. 5.10 Spin curve for the AZ9260. Courtesy of the CMI

A velocity of 4000 rpm during 1min30 was tried out for an approximate thickness of 7 µm. A rotation speed of 3500 rpm was also tried out to increase a little bit further the photoresist thickness which happens with decreasing speed.

The softbake step of the photoresist has to be done in an oven, since here the Polyimide layer is too thick for the heat of a hotplate to be sufficient. The duration and temperature of the oven had to be adjusted.

Switching the thickness of the AZ9260 lead to some changes in the exposure parameters in the MA6. The new exposure time was 28 seconds divide in two exposures (14 seconds each) according to the data available by the CMI (see Annexe 2). This information comes from tests from the MA150 mask aligner but can be applied to the MA6 mask aligner since the lamp power is approximate the same.
5.3 Main Procedure

Microfabrication Procedure

Utilization of a Silicon Substrate: <100>, 4", 525 µm, single side, p type, 0.1-100 Ωcm.
Silicon wafers provided by the CMI.

1. SACRIFICIAL LAYER DEPOSITION
Deposition of a 500nm Titanium/Tungsten layer (W:Ti 10%) and a 100nm Aluminium layer.
Machine employed: Balzers BAS-450, Single chamber multi-target sputtering system (Z4).

2. POLYIMIDE LAYERS DEPOSITION
6 layers of Polyimide PI 2611 were deposited and spin coated using the Sawatec LMS200 Polymer Coater (Z1). Each layer had approximately 11 µm and was deposited and spin-coated at a speed of 1400 rpm followed by softbake. The total thickness of the polyimide layers is though to be of approximately 66 µm.

The softbake step was done on the hotplates (Z1) and consisted of 3 to 4 minutes at a temperature of 75°C followed by minimum 4 minutes at 105°C. First layers of polyimide were left at 105°C for 8 minutes, but increasing layers required further time for the softbake step to be completed as well as some temperature increase for later layers. The softbake was verified by analysing the edges of the wafer, and then the wafers were cooled down for 30 seconds.

After that, wafers had to be hardbaked in the Hereaus T6060, Multipurpose Oven (Z2). The baking curve consists of several steps: a ramp from 55°C to 200°C which lasts 1h30, a step at 200°C for 1h30, a ramp again from 200°C to 300°C for 2h, and finally a step at 300°C for 1h. The Wafers were then progressively cooled down. Nitrogen was used for the curing process of the polyimide and was turned on automatically after 200°C. The total baking process is approximately 7 hours.
3. **OXIDE DEPOSITION**

Silicon oxide ($\text{SiO}_2$) was deposited in the Pfeiffer Vacuum Spider 600 – High Vacuum Sputtering cluster system 600 (Z4). The deposition time was of 12 minutes at room temperature for a thickness of 500 nm.

4. **PHOTOLITHOGRAPHY**

The YES LPIII, HDMS primer oven (Z1) was used right before photolithography in for priming of the silicon oxide to enhance Photoresist adhesion.

The EVG 150, coater for positive resist (Z6) was used for deposition and spin-coating of the photoresist (AZ9260 5 µm).

The PR coated wafers were then exposed twice to UV light in the Süß MA6 Double Side Mask Aligner (Z6) with the microchannel mask for 9.5 seconds, with a waiting time of 20 seconds.

After the photostructuring of the photoresist, the development was processed on the EVG 150, developer for positive resist (Z6).

5. **OXIDE “DRY“ ETCHING**

The exposed layer of silicon oxide was removed by etching between 4 min. and 4.30 min. on the STS Multiplex ICP, Plasma etcher, (CF$_4$) exposing the polyimide.

6. **PARTIAL PYRALIN ETCHING**

The polyimide layer was then partially etched in the same machine for 30min30secs Since the etching speed is of approximately 1 µm/min, the polyimide was etched for approximately 30 µm deep.
7. OXIDE “DRY” ETCHING

The remaining oxide was then etched in the same way leaving the polyimide engraved. There was no need to remove the photoresist since it was etched away during the previous step.

The first part of the procedure is then finished with the polyimide covered wafer structured with the microchannels and the reservoir.

For the bonding step, the wafer has to be removed from the clean room. This process occurs outside, in the microtechniques laboratory.

8. BONDING

One layer of polyimide PI2611 was spinned on a Kapton foil over a silicon wafer (with a water droplet), followed by softbake and turned over on the patterned wafer prepared on the previous steps. The thickness of the spinned layer was again of 11 µm.

The wafers were then put in a nitrogen oven inside electrodes plates for layer transfer with specific pressure and heat conditions.

Since this was the most important step in the process it will be further explained in another section.

Once the reservoirs and the channels were correctly sealed, the wafer returned to the clean room for the second part of the procedure. Special attention was given to the cleaning of the wafer since it had been exposed to a non totally controlled environment.

9. SECOND OXIDE DEPOSITION

The second deposition of Silicon oxide (SiO$_2$) is also carried in the Pfeiffer Vacuum Spider 600 – High Vacuum Sputtering cluster system 600 (Z4). A thicker layer of silicon oxide is deposited this time. The deposition time is of 52 minutes at room temperature for a thickness of 2.2 µm.

10. PHOTOLITHOGRAPHY
The YES LPIII, HDMS primer oven (Z1) is used again right before photolithography which is carried as described previously. The probe structure mask is used this time in the MA6 Double Side Mask Aligner (Z6) for photostructuring.

11. OXIDE “DRY” ETCHING

The exposed layer of silicon oxide is removed by etching but this time it is done in 6 steps of 2min30 which correspond to the total etching type between 12-15minutes.

12. PYRALIN ETCHING

The exposed polyimide layer is completely etched through to the Aluminium, on the STS Multiplex ICP, Plasma etcher. Since the etching speed is of approximately 1 µm/min, and the polyimide total thickness is thought to be of about 102 µm deep, the etching time is calculated to be of approximately 1hour and 45minutes. The etch is stopped visually when the aluminium layer is totally exposed.

13. OXIDE “DRY” ETCHING

The remaining oxide is then etched for 6 minutes leaving the structures on the aluminium layer. Most of the silicon oxide layer was removed during the pyralin etch. Nonetheless this step should be carried out, just in case. There is no need again to remove the photoresist.

14. FINAL SUPPORT WAFER REMOVAL

The Release of the structures is carried on the LMIS4 Sacrificial Release Tank as it will be explained after. Microdevices when detached float in solution and must be retrieved for rinsing and drying.
5.4 Procedures outside clean room: Bonding and separation

Two of the steps of the microfabrication procedure occurred outside the clean room: the bonding step and the final support wafer removal. These steps required the use of some other microfabrication techniques as well as specific equipment.

Throughout this process there has been a special attention to the technology development regarding the bonding step. Several possibilities were considered; several trials were effectuated in order to achieve a successful bonding which was made difficult due to the biotolerability condition over the materials used.

The bonding of microfluidic components of polyimide devices and film lamination were tried out in the LMIS4 hot press, spinner and nitrogen oven (fig. 5.11).

![Equipment for bonding trials](image1.png)

**Fig. 5.11** Equipment from the LMIS4 used for the bonding trials: hot press, spinner and nitrogen oven.

The final solution to seal the open reservoirs and channels was done by film lamination. For this, one layer of polyimide PI2611 was spinned on a Kapton foil over a silicon wafer (with a water droplet) using the spinner on LMIS4 lab. It was then softbaked on a hotplate and turned over on the patterned wafer prepared on the previous steps. The wafers were then put in the LMIS4 nitrogen oven inside the electrodes plates (fig. 5.12).

![Electrodes plates and nitrogen oven](image2.png)

**Fig. 5.12** Electrodes plates and nitrogen oven used in the bonding process.
The Electrodes plates are used for compressing and heating the wafers. Layer transfer requires specific pressure and heat conditions.

The nitrogen oven was programmed with the Temperature curve on fig. 5.13 obtained after several iterations of the experimental data. The heating process lasts for approximately 7 hours and 40 minutes plus some more hours for cooling down.

![Baking Curve](image)

**Fig 5.13:** Temperature curve used for the bonding process: t1: 3h - T1: 200°C; t2: 2h - T2: 200°C; t3: 1h40 - T3: 350°C; t4: 1h - T4: 350°C; t5: ? h - T5=0°C; N2 turned on after 200°C – after 5h.

A successful bonding leads to closed channels and reservoirs.

The support wafer removal was achieved by anodic dissolution of sacrificial aluminum. The final release of the polyimide structures was carried on the LMIS4 Sacrificial Release Tank (fig 5.14).

The Wafers were immersed in a sodium chloride solution (~2% NaCl) with Pt counter electrode. Constant positive potential is applied to the aluminium layer (0.1-0.8 V) by a laboratory constant-voltage. The time required for the liberation depends among other factors on the salt concentration and the voltage applied but corresponds normally to a maximum of 72h.

![Images](image)

**Fig 5.14a.** Final wafer b. sacrificial release tank c. released devices

Microdevices when detached float in the solution and must be retrieved for rinsing and drying.
5.4.1 Bonding: Layer transfer and sealing techniques

The fabrication of microchannels is normally done by sacrificial layer methods or more commonly by bonding techniques which require the microfabrication of open channels on a substrate and a top layer for sealing by a specific bonding procedure. This bonding procedure is also called adhesive bonding since materials are made to adhere to each others. Regarding polymers, the bonding process is normally chemical because it is done by formation of molecular bonds and entangling of the molecules.

During microfabrication procedures polyimide is normally processed in the liquid form to cast films or form coatings unless one is dealing directly with commercialized films or sheets or other type of material. The chemical reactions of the curing process can then be used for establishing the bonding or adhesion between layers. This way, polyimide in the precursor form can be used as an adhesive to unite the bottom and top polyimide layers of the devices. The sealing occurs when the ensemble is cured, because thermal imidisation allows interdiffusion across the interfaces as well as cross-linking between different molecules hardening the polyimide. If pressure is applied during the curing process, the layer transfer also occurs by lamination.

5.4.1.1 Adhesion of Polyimide

As users are constantly faced with the conversion of the PAA into solid polyimide, one should understand better what happens at the molecular level when variables change. The curing process of polymers is a complex process which still requires extensive research. During cure cycles, several mechanisms can occur.

With the increase of temperature, imidisation occurs at the same time as solvent starts evaporating. The residual solvent loss occurs at 150°C-200°C as can be observed from the experimental data summarized on fig.5.15. Therefore, cyclisation should start to decrease from there on due to the lack of mobility.

![Graphical representation of the weight loss of the polyimide](image)

Fig. 5.15 Graphical representation of the weight loss of the polyimide when exposed to a curing cycle.

Experiment performed with an initial mass of approximate 90 mg of polyimide.
With the increase of temperatures and lack of solvent, there is chain packaging and molecules start interacting with each other which leads to cross-linking around 300ºC. At elevated temperatures, polyimide tends to oxidize when exposed to air so normally during curing cycles, nitrogen atmosphere is used above 200ºC.

Depending on the heating cycle, temperatures used and specific duration of each step, the degree of imidisation can vary. Heating polyimide above 300ºC is advised for higher degrees of imidisation. Upon cure cycle adaptations, high bonding strengths can be obtained.

Due to the solvent removal, there are considerable changes in the polyimide structure and it tends to shrink. This also leads to changes in its physical properties.

5.4.2 Release and detachment of structures - Anodic metal dissolution

Once the microfabrication process is finished, structures have to be detached from their carrier support in order to be completely flexible and ready for implantation. For the release of the neural probe a technique based on anodic metal dissolution was used. This technique which was briefly described before was originally developed by S. Metz [19] and has been highly carried out in the LMIS4.

While other methods like wet chemical etching or solvent dissolution expose the structures to harsh chemicals, this method uses neutral salt solutions and does not damage the devices in any way. Compared to the traditional release methods, this process is a lot faster since it is not diffusion limited. Other advantages of this method include freedom in the choice of materials, and good incorporation of the sacrificial layers in the fabrication procedure.

In this method the substrate containing two metal layers is immersed in sodium chloride solution. When two metals of different electronegativity are in contact and exposed to an electrolyte they form an electrochemical cell also known as galvanic cell producing spontaneous redox reactions. This originates electron transfer between the two metals. From the two layers deposited in this procedure, the oxidation or loss of electrons occurs in the aluminium which is the less noble metal. The Aluminium which constitutes the anode in this electrochemical cell is selectively dissolved. When a Pt counter is immersed in the same electrolyte and a positive potential is applied between the Pt electrode and the aluminium layer, and additional driving force is supplied to the electron transfer increasing the current and the dissolution process.

While the aluminium is used as a sacrificial layer for the structures to be released, the titanium/tungsten layers ensures the electrical contact to avoid incomplete release.
5.5 Results

Before a final procedure was established, many trials had to be performed in order to optimize the different steps and to check the viability of some methods when applied to this process. Large part of the experiments regarded the bonding process and its outcome over the remaining stages. When these failed to work, special attention was directed to examining what went wrong and discovering the underlying causes. The numerous experiments lead to a greater degree of understanding towards the polyimide processability.

The heating press on the LMIS4 was used as a first approach for the first bonding experiment but without success due perhaps to the lack of nitrogen.

The Suss SB6, Vacuum Anodic bonder inside the clean room was considered as an alternative, but there was no need to use it. It was the LMIS4 nitrogen oven together with the microelectrodes plates that were used providing successful results.

These successful results obtained in the nitrogen oven were with unbaked PI coated wafers joined with kapton foils. An additional Teflon foil and wafer was added on top of this assembly so that once introduced between the microelectrodes plates, pressure could be exerted by the screw on top of the plates.

The same experiment was done with a half baked polyimide coated wafer but it failed to work. This wafer was already structured but there were some problems during the procedure. Since the Polyimide was only half-cured, there were still some remaining solvent which was pulled by the strong vacuum induced in oxide deposition.

The bonding process was done once again with an unbaked wafer. This time cuts were made by a scalpel throughout the wafer surface for the solvent to get out during the bonding process. Although the wafer had been kept in storage for to weeks, the bonding was successful (fig. 5.16).

Fig. 5.16 Polyimide covered wafer (PI 2611x2 not baked), bonded with a kapton foil.

From these experiments we can see that Kapton only seems to bond to unbaked polyimide.
Some attempts to seal the open reservoirs and channels were done by wafer/wafer bonding.
For this, 2 layers of polyimide PI2611 were spin-coated on a Ti/W Al coated wafer using the LMS200 Polymer Coater (Z1) and softbaked. No hardbake was done over these wafers. A patterned wafer prepared from the first part of the microfabrication procedure was joined together with the unbaked PI coated wafer, without aligning the flats. The wafers were then put in the LMIS4 nitrogen oven inside the microelectrodes plates in order to apply heat and pressure for bonding. A successful bonding led to closed channels and reservoirs.

![Fig. 5.17 Wafers manually separated after a bonding experiment: we can see that Polyimide was removed from one wafer and stayed attached to the other one, which shows a good bonding strength.](image1)

The problem in this method occurred in the detachment of one of the wafers so that the closed structures remained only in one support. Several wafer removal trials were done by the sacrificial dissolution of aluminium method but failed to work properly or took too much time and so this approach was abandoned.

![Fig. 5.18 Wafer release trials that didn’t work: some wafers were broken while manually trying to separate them while in others delamination occurred.](image2)

In one of the trials the aluminium layer was partially exposed by scratching off the polyimide layer on the wafer borders to be separated but no results were seen what so ever. On an other trial metal pieces were solded to the wafers so that electrodes could be better connected. After one week in the sacrificial release tank, wafers still had to be manually separated and the result was not that satisfactory. Nonetheless one wafer with enclosed channels entered the clean room for further processing.
The dissolution of the aluminium only occurs at the sacrificial material surface exposed to the electrolyte. Since the wafers were strongly bonded together and only a small area of aluminium was exposed, the odds are for this method not to be successful.

A Wafer was coated with 2 layers of Polyimide PI 2611 and structured. It was then bonded with an unbaked PI coated glass wafer.

The Structured wafer underwent the first part of the microfabrication procedure: PI coating and baking, Oxide deposition, Photolithography, oxide and pyralin etching and so had the microchannels and microreservoir engraved.

Some of the trials done on layer transfer in order to unite/seal layers failed to work.

On a first approach Polyimide (PI 2610) was spinned on a Kapton foil over a silicon wafer (with a water droplet) using the spinner on LMIS4 lab. It was then turned over the patterned wafer prepared from the first part of the microfabrication procedure and put in the LMIS4 nitrogen oven inside the microelectrodes plates in order to apply heat and pressure for the layer transfer.

Several experiments were done with changing variables. In one of the experiments the spinned polyimide was softbaked and in another it was unbaked. Surface treatment with Plasma oxygen was applied to the PI coated wafer to enhance the bonding step. No positive results were obtained whatsoever (fig. 5.20).

These attempts failed to work because the polyimide used was not viscous enough and the spinned layers were to thin for bonding purposes.
The same procedure was performed with PI2611. Two layers of PI2611 were spun over the kapton foil with softbake steps. This time bonding occurred and the procedure could continue. During the trials, parameters in the curing cycle were changed in order to optimize the bonding process.

Once there were some available sealed structures from the bonding process with layer transfer, the microfabrication procedure continued in the clean room.

Problems occurred in the photolithography step: the EVG 150 system and the RiteTrack 88 series machines wouldn’t take the wafers. Because of the overall thickness and weight of the wafers, these were subjected to too much tension which created problems on the vacuum and clamping mechanisms in the machines in the clean room.

The Süss Rc8 coater was used instead together with the oven for the softbake. The alignment was still done in the MA6 mask aligner with new parameters but there was some difficulty in aligning the wafer and the mask since the alignment marks were not that visible trough the thick polyimide. Upon several trials some satisfactory results were obtained.

Layer transfer over Mylar instead of kapton was also tried out but it failed to work because Mylar melted at the temperatures used in the bonding step. Mylar theoretically can be used till 150ºC which would bring the need of removing it during the bonding step. However peeling off Mylar does not give good results the majority of times. This approach was dropped.

Once the problems in the photolithography were overcome, the etching was done in the STS. Because of insufficient oxide layer protection the structures were etched away. The parameters were re-evaluated and new considerations were made. The etching process was tried once again with an increased oxide protective layer but clamping problems occurred damaging the wafer.
One essay was done with vacuum grease to glue a support wafer to avoid vibrations. Due to bad thermalisation, the photoresist was burned and the structures were etched away.

Even if the photolithography problem were overcome, problems still occurred afterwards. The only way to avoid this was to decrease the overall thickness of the polyimide by using thinner kapton foils.

The procedure was then carried out with special care on the oxide etch so that the resist wouldn't burn again.
5.6 Discussion

The devices built through this microfabrication procedure were observed using conventional microscopes as well as a scanning electron microscope. From the images obtained, we can see that their structure and characteristics are as projected (fig.5.21). However, the dimensions suffered some alterations due to the shrinkage of the polyimide upon cyclodehydration.

![Microscope images of the Devices obtained from the microfabrication procedure.](image)

The Alphastep spectrometer revealed a total height of 65 µm instead of the expected 102 µm. This was also confirmed upon visualization on the SEM (fig.5.22).

![Electronic microscope Image of the tip of one of the probes.](image)

Delamination was only observed in some structures and the bonding strength was assessed by trying to detach the kapton layer after the bonding process. Since high pressures are not needed in this device, no further tests were carried out to quantify the strength of the adhesion. Nevertheless, upon device packaging the enclosed structures will be protected from applied stresses.

The residual stress contained in the structures occurred due to mismatches in the thermal expansion coefficient of the different layers. This was rather accentuated for very thick structures which did not have a good processability in the clean room.

The overall procedure used in this project only allows Kapton foils of a certain thickness to be used but if this condition is respected the sealed channels and reservoirs can be easily photostructured.
6. Validation

6.1 Structures after completion – Packaging

Before the devices can be tested and implanted, they must go through a packaging step. This step is essential to provide a better physical and chemical protection and stability for the device while being handled during in vitro and in vivo tests.

Packaging can involve several processes depending on the required needs for the device. Since this device has no connection to external components, this step consists only in an encapsulation in a protective coating which will provide mechanic support in case of applied stresses. The packaging over these devices is done in two parts: when they are still attached to the support and once they have been released to complete the packaging over the backside.

The material used for such a purpose must also be biocompatible and so epoxy glue is a common choice. The transparent epoxy adhesive used was the commercial Araldite Crystal 5 minutes which is constituted by 2 reactants: the epoxy resin and a hardener. When mixed together, the epoxy resin curing process starts leading to a 5 minutes hardening. The epoxy resin is nothing less than a thermosetting polymer with an epoxy subunit.

The packaging was only done in the reservoir region so that the outlets remained open and the tip remained flexible to be introduced inside the brain. Only some of the devices were completely packed for testing.

6.2 Drug Loading of the device

Fluid loading was done by vacuum inducing. The tips of the probes were immersed in a colorant solution inside a glass chamber where vacuum was later induced (fig. 6.1a). There they remained for a couple of hours to assure that the solution got inside the probes entering by the outlets.

This was afterwards comproved by visual confirmation: the structures presented a somewhat red colour in the reservoir region which was due to the uptake of colorant solution (fig. 6.1b).
The same procedure of vacuum filling was used to load nanoparticles with fluorophores for the in vitro tests and dexamethasone for testing the inflammatory response in a rodent's brain. The devices were in a somewhat tilted position from the horizontal so that once the chamber was opened, and the devices were recovered, fluid remained inside the reservoir. The devices were manipulated with special care to preserve the drug inside till the moment of implantation. Dexamethasone loaded nanoparticles were not used because they failed to be stable in this procedure.

6.3 Characterization of release – in vitro

Fluorescence essays were performed in order to determine the functionality of the devices.

When dealing with polyimide-based microfluidic devices several problems can occur as is the case of channel clogging due to contamination or leakage due to debonding between the polyimide layers. This last problem is more bound to occur on sealing techniques like the one used during this project.

During the fluorescence test it was difficult to see inside the device because of the polyimide autofluorescence. If the reservoir was pressed, liquid could be seen going out by the tip holes showing the presence of liquid in the reservoir (fig 6.2). No leakage was observed throughout the device assuring no detached layers.
Fig. 6.2 Sequence of images taken during a fluorescence test. These images correspond to a partial area of the tip of the probe where the outlets could be observed. This images show the liquid filling the devices getting out by the outlets on the tip.

6.4 Experimental – implantation procedure in vivo

The devices were tested in vivo by insertion a mouse’s brain. This procedure was conducted by A. Mercanzini, the supervisor of this project, due to legal constraints that forbids non-authorized people to practice animal experiments.

All animal experiments were conducted in accordance with the guidelines of the local animal care authorities. Subjects were implanted in the primary motor cortex. Stereotaxic coordinates were set to +1.5 anterior, +2.5mm and -2.5mm lateral, toothbar was -3.3mm. An incision was made to expose the skull and four small circular craniotomies were performed. The holes were made using a 2mm diameter stainless steel drill with a mechanical stop at 0.80mm depth. This is deep enough to remove
the skull and pierce the dura mater. Local removal of the dura mater in this way improves the insertion of the device.

Two of the four craniotomies were used for mounting screws which serve to maintain the implants stable and in place for many weeks. The other two craniotomy holes are the regions of implantation.

The drug (water soluble dexamethasone 5mg/mL) loaded device was implanted in the right hemisphere. The control device containing phosphate buffered saline solution (0.01M – NaCl 0.138M, KCl 0.0027M, pH = 7.4 at 25 °C.) was implanted in the left hemisphere.

![Fig 6.3a.b.c Implantation of the device in a rodent’s brain](image)

The devices were slowly lowered into the primary motor cortex. The inserted devices were then fixed in place using dental acrylic which formed a large hard mass around the devices. The wound was sutured and a healing paste was applied. The animal was allowed to awaken and followed for signs of pain. 500mg of Dafalgan was administered in the water supply for the 4 days following implantation. The subject was sacrificed after 3 weeks implantation by fixing the brain in 4% paraformaldehyde.
7. Immunohistological Results

The immunohistological results were not conclusive since most part of the tissues to be analysed stayed attached to the device once these were removed. Brain slices were analysed using the different cell staining but the implantation site could not be retrieved.

General cells could be visualised in blue by UV exposure due to DAPI staining which is a fluorescent stain that binds to DNA in cells. Astrocytes can be identified in red when exposed, using GFAP antibodies. GFAP is a protein found in glial cells, as for example astrocytes and has increased expression in specific situations such as Astrocytic activation in inflammatory response of neural tissues. Microglial cells can be seen in green thanks to the use of anti-Iba1 antibodies. Iba1 is specifically expressed in microglia in the brain.

Further histological preparations must be carried out that allow cuts of the brain with the neural probe still inside it. Only then it would be possible to analyse thin slices of the brain and retrieving the implantation spot and analysing the surrounding zone.
8. Conclusion and parallel/future work

8.1 Parallel work

During the research and the development work for this thesis, there was a short collaboration with another project. This project involved the microfabrication of neurorecording and neurostimulation devices for collaborators at MIT and the Cochlear Technology Center, in Belgium. Prototypes of Cochlear Implants were micromachined with standard clean room techniques. These included Photolithographic processes for mask making, Polyimide deposition and oxide silicon deposition, photolithography and etching steps.

8.2 Future: Combining microfluidics and microelectrodes

Polyimide-based microelectrodes have been widely manufactured, namely on the Microtechnology laboratory at the EPFL. Example of these is the work by A. Mercanzini [16] who has reported on the fabrication, characterization and application of these devices for neural recording and stimulation. The technology involved in the manufacturing process of polyimide microelectrodes consists basically of metal layers buried in insulator layers of polyimide. Combining this technology with the previously exposed technology about microchannels fabrication is at reach and can bring significative advances by combining several functionalities in the same device. The outcome of such a fusion means the delivery of a drug associated with stimulation and recording in the precise same site.

If this was possible, microelectrodes could be preserved for longer periods by the delivery of an anti-inflammatory drug exactly in the surrounding zone. There is no reason to believe that this is unattainable. In fact the combination of microfluidic and microelectrodes technology has already been reported by several researchers as S. Metz [17] or P.J. Rousche [30], S. T. Retterer [29] and N. Ludvig [13].

8.3 Final conclusion

Throughout this thesis, different methods and techniques were employed in order to fabricate flexible devices for delivering drugs to cerebral tissue. Polyimide neural probes were manufactured by microfabrication techniques which allow a certain degree of freedom regarding the dimensions with the exception of the overall thickness. Special concern was given to the polymeric material properties and behaviour for a better understanding of the bonding step required to create the microfluidic channels. The majority of the resulting devices showed good adhesion and only few were delaminated. Characterization of the adhesion strength is still an existing problem to overcome in the
assessment of microstructures functionality. A qualitative evaluation of the devices suggested good stability for the type of application required in this project. Despite the good results obtained with this specific procedure, the layer transfer and the bonding step, which are performed outside of the clean room, demand a high level of manual operation as well as a great deal of time. The polyimide deposition and curing and the pyralin etching can also be quite time consuming. Although this process requires non-standard microfabrication procedures, it preserves biocompatibility, not only in the material used but also in the techniques employed. After running several in vitro tests, the devices were implanted in a rodent's brain to comprove its efficacy. Unfortunately there was no time to obtain further immunohistological results that would be extremely useful in order to evaluate the performance of this neural probe. As a normal research project, problems often occurred during the testing phase, delaying the project and not allowing certain subjects to be further addressed. The devices obtained with this fabrication process were built with a specific purpose but can be used for many other applications. This is especially true if this microfluidic functionality is combined with other technologies as for example microelectrodes.
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• [46] Clewin version 2.8 user’s manual, Feb. 2002
• [47] CMI - Center of MicroNanoTechnology: http://cmi.epfl.ch
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• [53] Department of Chemistry, University of Rochester : http://chem.chem.rochester.edu
• [54] Sawatec products : http://www.sawatec.com/
### Table 1: Spinning Speed for 11 µm Polyimide PI 2611. Courtesy of the CMI.

<table>
<thead>
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<th></th>
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<th></th>
</tr>
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<tr>
<td>11</td>
<td>1283,35755</td>
<td>11</td>
<td>1114,93488</td>
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</tbody>
</table>

![Graph showing the spin speed curve for Polyimide PI 2611.](image)

Fig. A1.1 Curve for determination of the layer thickness for Polyimide PI 2611 from the Spin speed. Courtesy of the CMI.
Fig A1.2 Curve for determination of the layer thickness for Polyimide PI 2611 over a polyimide layer from the Spin speed. Courtesy of the CMI.
Fig. A2.1 Spin curve for AZ Resists. Clariant AG AZseries specifications sheet

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
<th>Recipe name</th>
<th>Stations</th>
<th>Hotplates</th>
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<tbody>
<tr>
<td>Step1</td>
<td>SELECT WAFFERSIZE</td>
<td>4&quot;</td>
<td>1</td>
<td></td>
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<tr>
<td>Step2</td>
<td>LOAD FROM CASSETTE</td>
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<td>1</td>
<td></td>
</tr>
<tr>
<td>Step3</td>
<td>PREALIGN WAFER</td>
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<td></td>
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<td>Step4</td>
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<td>Step5</td>
<td>COOL WAFER</td>
<td>Cool_10s</td>
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<td>Step6</td>
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<td>Step7</td>
<td>COAT WAFER</td>
<td>AZ9260_5um, AZ9260_8um, AZ9260_14um, AZ9260_5um_NoEBR, AZ9260_8um_NoEBR, AZ9260_14um_NoEBR</td>
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<td>Step8</td>
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<td>Step9</td>
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<td>Step10</td>
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Table 2. Recipe for AZ9260 on the EVG 150 system. Courtesy of the CMI
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<tr>
<th>Step</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>SPINNER SPEED</td>
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<tr>
<td></td>
<td></td>
<td>Acceleration [rpm/s] 1000</td>
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<tr>
<td>2</td>
<td>DISPENSE</td>
<td>Dispense position CENTER</td>
</tr>
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<td></td>
<td></td>
<td>Material Cybor2</td>
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<td></td>
<td></td>
<td>Dispense volume [µl] 4000</td>
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<tr>
<td></td>
<td></td>
<td>Dispense rate [µl/s] 800</td>
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<td></td>
<td>Suckback volume [µl] 270</td>
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<td></td>
<td>Suckback rate [µl/s] 400</td>
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<td></td>
<td></td>
<td>Postdispense wait time [ms] 0</td>
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<td></td>
<td></td>
<td>Autodummy dispense Start Of Lot</td>
</tr>
<tr>
<td>3</td>
<td>SPINNER SPEED</td>
<td>Speed [rpm] 1500</td>
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<tr>
<td>4</td>
<td>SPINNER SPEED</td>
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<td>Acceleration [rpm/s] 4000</td>
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<tr>
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<tr>
<td>6</td>
<td>STOP SPINNER</td>
<td>Angle [°] 0</td>
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<td></td>
<td></td>
<td>Deceleration [rpm/s] 5000</td>
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<td>7</td>
<td>TIMER</td>
<td>Delay 00 min 15.0 sec</td>
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<td>8</td>
<td>SPINNER SPEED</td>
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<td></td>
<td></td>
<td>Acceleration [rpm/s] 1000</td>
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<td>Material BSR1</td>
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<td>Type ON</td>
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<td>10</td>
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<td>Material EBR1</td>
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<tr>
<td></td>
<td></td>
<td>Deceleration [rpm/s] 1000</td>
</tr>
</tbody>
</table>

| Table 3: Recipe for AZ9260 5 µm on the EVG 150 system. Courtesy of the CMI |
### Exposure parameters [mJ/cm²]

<table>
<thead>
<tr>
<th></th>
<th>2.0 µm thickness</th>
<th>3.0 µm thickness</th>
<th>4.0 µm thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best resolution @mJ/cm²</td>
<td>110</td>
<td>115</td>
<td>120</td>
</tr>
<tr>
<td>Contrast slope Gamma</td>
<td>3.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure Threshold (+3 Sigma)</td>
<td>112</td>
<td>117</td>
<td>121</td>
</tr>
<tr>
<td>Security threshold</td>
<td>125</td>
<td>130</td>
<td>135</td>
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</tbody>
</table>

Table 4: exposure parameters for the AZ92XX. Courtesy of the CMI

### Resist type and threshold doses [mJ/cm²] vs. Hg Power [mW/cm²]

<table>
<thead>
<tr>
<th>Resist type and threshold doses [mJ/cm²]</th>
<th>Hg Power [mW/cm²]</th>
<th>Exposure time [s]</th>
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<tbody>
<tr>
<td></td>
<td>Minimum</td>
<td>+33% safety</td>
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<tr>
<td>AZ9260 5µm</td>
<td>19</td>
<td>23</td>
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<td>AZ9260 8µm</td>
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<td>32</td>
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<tr>
<td>AZ9260 14µm</td>
<td>36</td>
<td>48</td>
</tr>
</tbody>
</table>

Table 5: Exposure time function of exposure doses and power of the Hg lamp – test performed on the MA150. Courtesy of the CMI