NANOENGINEERED IMPLANTABLE DEVICES FOR CONTROLLED DRUG DELIVERY

DISSERTATION

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By

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ABSTRACT

Considerable advances have been made in the field of drug delivery technology over the last three decades, resulting in many breakthroughs in clinical medicine. However, important classes of drugs have yet to benefit from these technological successes. The creation of drug delivery devices that are capable of delivering therapeutic agents that cannot be delivered by any other means or that have diminishment of therapeutic efficacy when given by other means of administration is a challenge in this area of research, while at the same time the financial interest because of the continuously growing drug delivery market cannot be ignored. One of the major requirements for an implantable drug delivery device is controlled release of therapeutic agents, especially biological molecules, as a continuous delivery over an extended period of time. The goal here is to achieve a continuous drug release profile consistent with zero-order kinetics where the concentration of drug in blood remains constant throughout the delivery period. Another significant challenge in drug delivery is to engineer a delivery system that can deliver drug in a manipulated non-zero order fashion such as pulsatile or ramp or some other pattern.

The goal of this research is to deliver technological innovations to address these requirements. Silicon was chosen as a carrier vehicle and nanochannel delivery systems (nDS) of progressively increasing degrees of functionality were conceived. The
fundamental embodiment of the first device, nDS1, employs high-precision nanoengineered clefts to yield the long-term zero-order release of therapeutic agents. This device was designed and fabricated targeting four nanochannel sizes. These were 20 nm, 40 nm, 60 nm and 100 nm. The achieved nanochannel heights measured by Atomic Force Microscope (AFM) were 18 nm, 43 nm, 70 nm, and 108 nm, respectively. Glucose diffusion through a nominal 100 nm channel for a period of 15 days, through a nominal 60 nm channel for a period of 5 days and interferon-alpha (IFN-α) release through a nominal 100 nm channel for a period of 7 days showed a zero order release profile through this device. Further, it was proved that IFN-α preserves its functional activity after being released through this device. Next, the top substrate of the nDS1 device was replaced with a glass substrate (nDS1g) for improved bonding and a visual observation of fluid flow through the nanochannels of the device. Another implantable drug delivery system (nDS2) that is capable of being integrated with an external electronic circuit was designed and a fabrication process flow was developed. This device has integrated electrodes and the concept of drug delivery is based upon electrokinetic flow of molecules through the nanochannels of the device. This device can be connected to a pre-programmable circuit to achieve manipulable delivery, can be connected to a wireless circuit to achieve external control of delivery on demand, or can be connected with an implantable sensor through a feedback control circuit to achieve a contained system where the delivery can be triggered upon the requirement of the physiological system. These devices have potential to improve therapeutic efficacy, diminish potentially life-threatening side effects, improve patient compliance, minimize the intervention of healthcare personnel and reduce the duration of hospital stays.
To my parents:

Mrs. Prabha Sinha and Mr. Anand Mohan Sinha
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I have been accompanied, inspired and encouraged by numerous people who have helped me in immeasurable ways to not only complete this degree but also to amass many great and unforgettable memories, and I am delighted that now I have the opportunity to express my gratitude to all.

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CHAPTER 1

INTRODUCTION

1.1 Concept of Controlled Drug Delivery - A Perspective

Drug Delivery Systems can be defined as mechanisms to introduce therapeutic agents into the body. Chewing leaves and roots of medical plants and inhalation of soot from the burning of medical substances in the earliest times are examples of drug delivery. However, these primitive approaches of delivering drugs lacked a very basic need in drug delivery; that is consistency and uniformity (a required drug dose). This led to the development of different drug delivery methods in the later part of the eighteenth century and early nineteenth century. Those methods included pills, syrups, capsules, tablets, elixirs, solutions, extracts, emulsions, suspension, cachets, troches, lozenges, nebulizers, and many other ‘traditional’ delivery mechanisms. Many of these delivery mechanisms use drugs derived from plant extracts.

The modern era of the development of medicine started with the discovery of vaccines in 1885 and techniques for purification of drugs from plant sources in the late nineteenth century, followed by the introduction of penicillin after its discovery in 1929, and a subsequent era of prolific drug discovery. The development and production of many pharmaceuticals involves the genetic modification of microorganisms to transform them into drug-producing factories. Examples are recombinant
DNA, human insulin, interferon (for the treatment of acquired immunodeficiency syndrome (AIDS) related Kaposi’s sarcoma, Hairy cell leukemia, Hepatitis B &C, etc.), interleukin-2 (Renal cell and other carcinomas), erythropoietin (for the treatment of anemia associated with chronic renal failure/AIDS/anti-retroviral agents, chemotherapy-associated anemia in nonmyloid malignancy patient), and tissue plasminogen activator [1]. It is now possible to produce oligonucleotide, peptide, and protein drugs in large quantities, while gene therapies also appear to be clinically feasible. Each of these therapeutic agents, by virtue of size, stability, or the need for targeting, requires a specialized drug delivery system [2]. While the conventional drug delivery forms are simple oral, topical, inhaled or injections, more sophisticated delivery systems need to take into account pharmacokinetic principles, specific drug characteristics and variability of response from one person to another and within the same person under different conditions.

The efficacy of many therapeutic agents depends on their action on target macromolecules located either within or on the surface of particular cells types. Many drugs interact with enzymes or other macromolecules that are shared by a large number of cell types, while most often a drug exerts its action on one cell type for the desired therapeutic effect. Certain hormones, for example, interact with receptor mechanisms that are present in only one or a few cell types. An ideal gene delivery system should allow the gene to find its target cell, penetrate the cell membrane, and enter into the nucleus. Further, genes should not be released until they find their target and one has to decide whether to release the genes only once or repeatedly through a predetermined way [2]. Thus, the therapeutic efficacy of a drug can be improved and toxic effects can be reduced by augmenting the amount and persistence of drugs
in the vicinity of the target cells, while reducing the drug exposure to the nontarget cells. This is the basic rationale behind controlled drug delivery. A controlled drug delivery system requires simultaneous consideration of several factors, such as the drug property, route of administration, nature of delivery vehicle, mechanism of drug release, ability of targeting, and biocompatibility. It is not easy to achieve all these in one system because of extensive independency of these factors (Figure 1.1). Further, reliability and reproducibility of any drug delivery system is the most important factor while designing such a system. The emphasis here is on the need for precision of control and to minimize any contribution to intra- and intersubject variability associated with the drug delivery system. There are many different approaches for controlled drug delivery applications. They are summarized in the next section [3].
1.2 Different Approach for Controlled Drug Delivery

1. **Localized drug delivery:** In many cases, it would be desirable to deliver drug at a specific site inside the body to a particular diseased tissue or organ. This kind of regional therapy mechanism would reduce systemic toxicity and achieve peak drug level directly at the target site. A few examples of drugs that require this kind of therapy are anticancer drugs, anti-fertility agents, and anti-inflammatory steroids. These drugs have many severe unintended side effects in addition to their therapeutic effects.

2. **Targeted drug delivery:** The best controlled mechanism would be delivery of drug exclusively to the targeted cells or cellular components. That means the development of a delivery mechanism which would equal or surpass the selectivity of naturally occurring effectors, such as peptide hormones. As in the case of hormone action, drug targeting would probably involve a ‘recognition’ event between the drug carrier mechanism and specific receptors at the cell surface. The most obvious candidates for the targetable drug carriers are cell-type specific immunoglobulins. The concept of targeted drug delivery is different than localized drug delivery. The latter simply implies localization of therapeutic agent at an organ or tissue site, while the former implies more subtle delivery to specific cell types.

3. **Sustained drug delivery (zero order release profile):** Injected or ingested drugs follow first-order kinetics, with initial high blood levels of the drug after initial administration, followed by an exponential fall in blood concentration.
Toxicity often occurs when blood levels peak, while efficacy of the drug diminishes as the drug levels fall below the therapeutic range. This profile is shown in Figure 1.2. This kind of drug kinetics is undesirable, especially in the case where the margin between toxicity and required therapeutic concentration levels is small. The importance of controlled-release drug delivery systems may be argued with reference to the goal of achieving a continuous drug release profile consistent with zero-order kinetics, wherein blood levels of drugs would remain constant throughout the delivery period. The therapeutic advantages of continuous-release drug delivery systems are thus significant, and encompass: In vivo predictability of release rates on the basis of in vitro data, minimized peak plasma levels and thereby reduced risk of toxic effects, predictable and extended duration of action, reduced inconvenience of frequent dosing and thereby improved patient compliance \[4, 5\].

The dashed line in Figure 1.3 illustrates the constant plasma concentration that is desired for many therapeutic agents. The controlled release aspect of sustained drug delivery systems pertain to a reliable and reproducible system whose rate of drug delivery is independent of the environment in which it is placed.

4. **Modulated drug delivery (non-zero order release profile):** A significant challenge in drug delivery is to create a delivery system that can achieve a manipulable non-zero order release profile. This could be pulsatile or ramp or some other pattern. In some cases it is also required that the release should be immediate. A pulsatile release profile within the therapeutic window is shown by the dotted line in Figure 1.3.
Figure 1.2: Plasma concentration versus time curve for intravenous drug administration showing first order kinetics.

Figure 1.3: Plasma concentration versus time curve for sustained release profile of zero order kinetics (- - -) and pulsatile release profile (...).
5. **Feedback controlled drug delivery:** The ideal drug delivery system is the feedback controlled drug delivery system that releases drug in response to a therapeutic marker. This can be classified into two classes: modulated device and triggered device. A modulated device involves the ability to monitor the chemical environment and changes drug delivery rate continuously in response to the specific external marker, while in a triggered device no drug release takes place until it is triggered by a marker.

These different approaches of drug delivery can have different routes of administration. Some of the most preferred routes are oral, pulmonary inhalation, transdermal, transmucosal and implantable systems.

### 1.3 Motivation

#### 1.3.1 Technological Advancement - A Step Towards Clinical Application

Although most controlled drug delivery systems are designed for transdermal, oral or injectable uses, implantable devices are very attractive for a number of classes of drugs, particularly those that cannot be delivered via the oral route or are irregularly absorbed via the gastrointestinal tract [6]. This replaces the repeated insertion of intravenous catheters. The basic idea behind this device is simple - the treatment of certain diseases that require the chronic administration of drug could benefit from the presence of implantable devices. These systems can also be used to deliver drug to the optimum physiological site. These systems are particularly suited for drug delivery requirements of different classes of drugs e.g. steroids, chemotherapeutics, antibiotics, analgesics and contraceptives, and some particular drugs such as insulin.
or heparin. Implantable systems are placed completely under the skin - usually in a convenient but inconspicuous location. Benefits include the reduction of side effect (drug delivery rate within the therapeutic window) caused by traditional techniques of administration, and better control. Ideally an implantable system will have a feedback controlled release mechanism and will be controlled by electronics with a long life power-source to achieve zero-order or manipulable non-zero order release profiles in a manner similar to a physiological release profile.

The focus of this research is on two major requirements of an implantable controlled drug delivery device:

1. One of the major requirements for implantable drug delivery devices is to allow controlled-release of therapeutic agents, especially biological molecules, continuously over an extended period of time. The goal here is to achieve a continuous drug release profile consistent with zero-order kinetics where the concentration of drug in blood remains constant throughout the delivery period. As mentioned earlier, the therapeutic advantages of continuous release of drug by implantable delivery devices are significant - minimized adverse reactions by reducing the peak levels, predictable and extended duration of action, reduced inconvenience of frequent dosing and thereby improved patient compliance.

2. Another requirement is to achieve a manipulable non-zero order release profile, such as pulsatile or any other pattern required for applications in therapeutic medicine. Vaccines and hormones are examples that require pulsatile delivery. Gonadotropin releasing hormone, for example, is most effective when delivered in a pulsatile manner to female patients undergoing treatment for infertility [7, 8].
A sequence of two implantable systems was developed to achieve the above mentioned goals. The first device, which addresses the first goal, is named nanochannel delivery system 1 (or nDS1), while the device that addresses the second goal is called nanochannel delivery system 2 (or nDS2).

1.3.2 The Economics of Drug Delivery Devices

The fact that drug delivery technology can bring both therapeutic and commercial value to health care products can not be neglected. Big pharmaceutical companies have recently started losing their market share to generic competitors after their patents expired, and therefore they have started recognizing the importance of drug delivery companies. Pharmaceutical companies are looking to extend their patents’ lifetimes by making strategic alliances with drug delivery technology companies - by presenting old drugs in new forms. Most of the drug delivery products therefore reach the market as a result of strategic alliance between drug delivery companies and pharmaceutical companies. Pharmaceutical companies provide the drug that may not be delivered efficaciously with a conventional delivery mechanism, while the drug delivery companies provide the cutting edge technology to administer the drug more effectively. The joint venture not only offers considerable advantages over the R&D efforts to bring new drug into the market as drug delivery systems provide means to reformulate existing products, but it also protects the drugs from erosion by generics in the case of patented drugs. As a result, drug delivery technology companies seem to enjoy a good return on their investments in the form of increased revenues and market share [9, 6].
The global drug delivery market grew between 1998 and 2002 with a compound annual growth rate (CAGR) of 13.7%, increasing from $39.6 billion to slightly over $66 billion. The market is expected to grow at a slightly lower CAGR of 11.6% between 2002 and 2007 corresponding to a market value of $114.3 billion by 2007. One of the contributing factors in this growth is the use of drug delivery systems as strategy to expand the shelf-life of products (particularly blockbusters), enabling pharmaceutical companies to sustain the revenue streams from their best-sellers.

The US market is the largest market for drug delivery systems in the world, having captured 47.9% of the global market’s revenue generation in 2002. This figure is forecast to fall to 41.9% by 2007 although the US market will retain its position as the leading market. The US market for drug delivery systems was worth $31.7 million in 2002, having experienced a CAGR of 12.6% during 1998-2002. Oral drug delivery systems had the largest market share, taking 47.7% of the total market share. Transmucosal, injectable and implantable systems together had 8.8% of the market share in 2002. The US market value for drug delivery systems is expected to grow at a rate of 8.5% annually reaching a value of $48 billion by 2007.

1.4 Organization of The Dissertation

The second chapter of this dissertation starts with a brief history of implantable devices followed by a detailed description of the uses of micro-electro-mechanical system (MEMS) for drug delivery applications that includes transdermal, oral, intravenous and implantable devices. It also provides a critical analysis of currently available implantable drug delivery systems. Chapter 3 focuses on the sacrificial oxide and has details about the growth and etching of silicon dioxide from the 'sacrificial
oxide’ perspective. This chapter also enlightens how sacrificial oxide has been used for
different applications. Chapter 4 talks about the criteria for electrode metal selection
for different applications and their fabrication techniques. Chapter 5 discusses the
research work that has been conducted as part of this program. Two devices were
developed for drug delivery application. One is to achieve long term release of ther-
apeutics, consistent with zero-order release kinetics, called nDS1. Later, a modified
version of this device was developed, and called nDS1g. The second device that is
called nDS2 has integrated electrodes, and is capable of being integrated with a circuit
of interest to achieve a desired flow profile. This chapter provides the detailed de-
scription of their design and fabrication steps. It also provides some characterization
results obtained for these devices. The fabrications steps are also summarized in the
appendices, however the details on fabrication are given in Chapter 5. Finally, Chap-
ter 6 provides a summary, conclusions derived from this work and recommendations
for future work that is required to bring these devices into clinical application.
A number of devices have been developed to achieve controlled drug delivery. These devices utilize different routes of administration and different materials for device fabrication. Typically each of these devices is targeted towards delivering one or a few therapeutics. The factors that need to be considered when designing a drug delivery device were outlined in Chapter 1 (Figure 1.1). This chapter starts with a brief history of implantable drug delivery devices. These include polymeric devices, osmotic pumps, micropumps and micro-electro-mechanical-systems (MEMS) based devices. Since the drug delivery devices developed in this research are based upon MEMS technology, a good understanding of MEMS fabrication technology is needed. Therefore section 2.2 provides a more in-depth description on the use of MEMS for different drug delivery devices. These include MEMS based implantable devices as well as transdermal, oral and injectable drug delivery devices. The chapter concludes with a critical analysis of implantable drug delivery devices.

2.1 A History of Implantable Drug Delivery Devices

The history of implantable devices goes back to May 1958 when the first implantable Cardiac Pacemaker was placed in an experimental animal [10]. Later that
year the first pacemaker was implanted in a human, however it operated for three hours and then failed [11]. The second unit operated for eight hours before failing, and the patient went unstimulated for three years before receiving a satisfactory implantable unit. The record shows that this patient was alive in 1991 and was using a pacemaker [12]. The development of an implantable pacemaker revolutionized the field of biomedical science and engineering over the last forty years providing many different implantable biomedical devices to the medical professionals for therapeutics and diagnostics. Today, implantable cardioverter/defibrillators, drug delivery systems, neurological stimulators, bone growth stimulators and other implantable devices make possible the treatment of a variety of diseases.

Extensive research has been done on implantable drug delivery devices over the last thirty years. Different technologies have been developed with many breakthroughs in clinical medicine. The first such device that saw extensive clinical use was reported in the 1970s [12, 13, 14, 15]. This system used a bellows-type pump activated by partially liquefied Freon. The Freon was reliquefied with each transcutaneous refill of the implantable device, and the administration was constant. Later extensive research started to develop more sophisticated devices that could offer better control and more clinical options. Another device was developed by Medtronic Company that has a peristaltic pump to deliver the drugs [16]. The device was controlled by electronics. Another system developed by MimiMed Technologies employs a solenoid pump, a reservoir and advanced electronic control [17]. The Infusaid Company developed an advanced programmable implantable pump that employed a bellows type pump and a solenoid valve set to control drug flow [18]. Other technologies developed to achieve this goal are summarized below.
2.1.1 Polymeric Implants

Polymers have been used extensively in controlled drug delivery systems. These can be classified as (1) Non-degradable polymeric reservoirs and matrices, and (2) Biodegradable polymeric devices. The first kind of polymeric devices are basically silicone elastomers. This kind of drug delivery system is based upon research conducted in the 1960s, when researchers recognized that certain dye molecules could penetrate through the walls of silicone tubing [19, 20, 21]. This lead to the development of reservoir based drug delivery systems, which consisted of hollow polymer tubes filled with a drug suspension. The drug is released by dissolution into the polymer and then diffusion through the walls of the polymeric device. The two most commonly used non-degradable polymers are silicone and poly(ethylene-co-vinyl acetate) (EVAc). The Norplant® 5-year contraceptive drug delivery system is based upon this technology [22]. Some of the implantable reservoir systems are simple cylindrical reservoirs surrounded by a polymeric membrane. The other variety in this first category is constructed of a solid matrix of non-degradable polymers. These systems are prepared by homogeneous dispersement of drug particles throughout the matrix [23]. Drug release occurs by diffusion through the polymer matrix, by leaching or by a combination of both [24]. The matrix may be composed of either a lipophilic or hydrophilic polymer depending on the properties of the drug and the rate of release desired. However, it is difficult to achieve constant rates of drug release with non-degradable matrix systems, e.g. the rate of release of carmustine from an EVAc matrix device drops continuously during incubation in buffered water [25]. Constant release can sometimes be achieved by making the matrix as a reservoir surrounded
by a shell of rate limiting polymeric membrane. In some cases, water soluble, cross-linked polymers can be used as matrices. Release is then activated by swelling of the polymer matrix after exposure to water [26]. One other kind is a magnetically controlled system where magnetic beads are dispersed within the matrix [23]. Drug is released by diffusion with concentration gradient. The addition of an external oscillating magnetic field alters the physical structure of the polymer, creating new channels, and thus leads to further drug release.

Biodegradable polymeric devices are formed by physically entrapping drug molecules into matrices or microspheres. These polymers dissolve when implanted (injected) and release drugs. Examples of biodegradable polymers are poly(lactide-co-glycolide) (PLGA), and poly(p-carboxyphenoxypropane-co-sebacic acid) (PCPP-SA) [21]. Some of the commercially available polymeric devices are Decapeptyl®, Lupron Depot® (microspheres) and Zoladex® (cylindrical implants) for prostate cancer and Gliadel® for recurrent malignant glioma. The half-life of therapeutics administered by microspheres is much longer than free drug injection. Polymers are also being investigated for treating brain tumors [27], and delivery of proteins and other macromolecules [28].

The above mentioned polymeric implants are utilized for sustained drug delivery. Methods have been developed to achieve controlled drug delivery profiles with implantable polymeric systems [29, 30]. These technologies include pre-programmed systems, as well as systems that are sensitive to (triggered or modulated by) modulated enzymatic or hydrolytic degradation, pH, magnetic fields, ultrasound, electric fields, temperature, light and mechanical stimulation. Researchers are also exploring the use of non-traditional MEMS fabrication techniques and materials that could be
used to form microwell or microreservoir based drug delivery devices. For example, microwells of varying sizes (as small as 3fL/well) have been fabricated by micromolding of poly(dimethylsiloxane) (PDMS) on a photoresist-coated silicon wafer that is photolithographically patterned [31].

2.1.2 Osmotic Pumps

Osmotic pumps are energy modulated devices [6]. These are usually capsular in shape. When the system is exposed to an aqueous environment such as that after subcutaneous implantation, water is drawn to the osmotically active agent through a semipermeable membrane, pressure is supplied to the collapsible drug reservoir and drug is released through an orifice with precise dimension. The delivery mechanism is dependent on the pressure created and is independent of drug properties. ALZET® pumps (only for investigational purpose at this time, not for humans) have been used in thousands of studies on the effects of controlled delivery of a wide range of experimental agents, including peptides, growth factors, cytokines, chemotherapeutic drugs, addictive drugs, hormones, steroids, and antibodies [32]. ALZA Corporation built the DUROS® implant based upon the foundation of the ALZET® osmotic pump, the system of choice for implant drug delivery in research laboratories around the world for more than 20 years. Viadur®, a once-yearly implant for the palliative treatment of advanced prostate cancer, is the first approved product to incorporate ALZA’s proprietary DUROS® implant technology. A single Viadur® implant continuously delivers precise levels of the peptide leuprolide for a period of one full year, providing an alternative to frequent leuprolide injections [32]. Although most of the osmotic pumps are designed for sustained release profile, research is being conducted
to modify this design for different patterns [6]. Further, a catheter has been attached
to the exit port of an implantable osmotic pump to achieve site specific drug delivery
at a location distant from site of implantation [33].

2.1.3 Micropumps

Micropumps have been actively investigated for drug delivery applications. Some
micropumps are nonmechanical and utilize electrohydrodynamic, electroosmotic, ul-
trasonic or thermocapillary forces [34]. However, most of the micropumps are me-
chanical, composed of mechanically moving membranes. A number of mechanical
micropumps have been developed using various mechanisms, including piezoelectric
[35], electrostatic [36], thermopneumatic [37], electromagnetic [38], bimetallic [39],
shape memory alloy (SMA) [40], ionic conducting polymer films (ICPF) [41] and sur-
face tension driven actuators [34]. One example is the silicon piezoelectric micropump
based on silicon bulk micromachining, silicon pyrex anodic bonding and piezoelectric
actuation [35]. This can be used for applications requiring low (typically 1 µl/min),
precisely controlled flow rate. The whole system includes the refillable reservoir, con-
trol and telemetry electronics and battery. This can be implanted in the abdomen
and a catheter can be brought to the specific site the drug needs to be delivered to.
The SynchroMed® pump is an implantable, programmable, battery-powered device
commercially available from Medtronics [42].

A large number of other implantable drug delivery devices have been developed in
the last decade utilizing the silicon microfabrication technology that was developed
in the Integrated Circuits industry. These are discussed in section 2.2.4.
2.2 MEMS for Drug Delivery

Since the invention of silicon microfabrication technology in the early 1960s, the integrated circuit (IC) has changed our world. During the last 40 years, the semiconductor industry has become the fastest growing industry in our history. From a modest beginning, that allowed a few transistors on a chip, we have reached integration levels of tens of millions of components in a square cm of silicon. The minimum feature size on silicon is reducing and thus the number of devices per square cm is increasing. In 1965 Gordon Moore [43], co-founder of Intel, made the observation that the number of transistors per square inch on integrated circuits was doubling every year. Moore predicted that this trend would continue for the foreseeable future. In subsequent years, the pace slowed down a bit, but data density has doubled approximately every 18 months, and this is the current definition of Moore’s Law.

This silicon fabrication technology was later extended to machining mechanical microdevices - that are now called microelectromechanical systems (MEMS). The pioneer work was done by Nathanson et al. in 1965 when they demonstrated the first micromachined structure by fabricating a free standing gold beam electrode used in a resonant gate transistor [44]. By the late 1970s, there was an immense interest in silicon as a mechanical material [45, 46]. During the 1980s and 1990s, many MEMS devices were fabricated, e.g. micromotors [47, 48, 49], deformable mirrors [50, 51], accelerometers [52, 53, 54, 55, 56], and comb-drive actuators [57].

In recent years, this fabrication technology has been extensively used for the development of microfluidic devices for biological and biochemical applications (these are called ‘bio-MEMS’) [58, 59]. Further, the integration of microfluidic devices and integrated circuits over the last decade has revolutionized chemical and biological
analysis systems, and has opened the possibility of fabricating devices with increased functionality and complexity for these applications [60, 61, 62]. These tiny devices hold promise for precision surgery with micrometer control, rapid screening of common diseases and genetic predispositions, and autonomous therapeutic management of allergies, pain and neurodegenerative diseases [4]. The development of retinal implants to treat blindness [63], neural implants for stimulation and recording from the central nervous system [64], and microneedles for painless vaccination [65] are examples in which MEMS technology has been used. With microfabrication technology it is also possible to produce novel drug delivery modalities with capabilities not present in the current systems. A variety of microfabricated devices such as microparticles, microneedles, microchips, nanoporous membranes, and micropumps, have been developed in recent years for drug delivery applications [66, 67, 68, 69]. This section reviews various microfabricated devices. These have been categorized and described next as microfabricated devices for transdermal, oral, intravenous and implantable drug delivery devices.

2.2.1 Microneedles for Transdermal Drug Deliver

Transdermal drug delivery is a favored way of drug delivery since it avoids any degradation of molecules in the gastrointestinal tract and first-pass effects of the liver, both of which are associated with oral drug delivery, and eliminates the pain associated with intravenous injection [70, 71, 72, 73, 74]. However, the major barrier for transdermal delivery is the stratum corneum, the outermost dead layer of the skin. In human, it is 10-20 μm thick. A number of different approaches have been studied with two common goals: first to disrupt the stratum corneum structure in order to
create “holes” big enough for molecules to pass through and the second goal is to develop microneedles that are long enough to provide transport pathways across the stratum corneum and short enough so that they do not reach nerves found in deeper tissues.

MEMS technology has provided an attractive approach to transdermal drug delivery. The development of microneedles for transdermal drug delivery enhances the poor permeability of the skin by creating microscale conduits for transport across the stratum corneum [74, 67]. Needles of micron dimensions can pierce into the skin surface to create holes large enough for molecules to enter, but small enough to avoid pain or significant damage. Although the microneedles concept was proposed in the 1970s [75], it was not demonstrated experimentally until the 1990s [76]. Since then, many different kinds of microneedles have been fabricated in several materials, such as silicon, glass and metal. Further these microneedles can be fabricated in-plane, where the needle lumen (flow channel) is parallel to the substrate surface, or out-of-plane, where the lumen is normal to the substrate. Some of these are described next.

Lin and Pisano [77] fabricated microneedles in silicon (Figure 2.1). The primary structural material of these microneedles was silicon nitride, forming the top, and a bulk micromachined boron doped silicon base defined by etching the substrate in ethylene-diamine pyrocatechol (EDP). This layer of silicon varied in thickness from about 50 µm at the shank to 12 µm near the tip providing good structural strength. The lumen was defined by a sacrificial layer of phosphorous doped glass. These microneedles were 1-6 mm in length with lumens 9 µm high and 30-50 µm wide. The proximal ends of the microstructures had integrated polycrystalline silicon heater strips. The heater could generate bubbles, which were useful in pumping fluid down
the lumen. The authors suggested that electrodes could also be patterned along the length of the needle, by a slight process modification, for the measurement of neural activity.

Another microneedle, made out of polysilicon by a molding process, was reported by Talbot and Pisano [78] (Figure 2.2). The two halves of the mold are produced by bulk micromachining of silicon wafers followed by deposition of a 2 µm phosphosilicate glass (PSG) release layer. The two halves were temporarily bonded together under nitrogen ambient at 1000°C. After bonding, a 3 µm layer of amorphous silicon
was deposited by LPCVD through access holes in the top mold wafer. The mold, along with the deposited film, was then annealed at 1000°C. Deposition and annealing steps were repeated until the desired thickness of 12-18 µm was obtained. Plasma etching was used to remove the polysilicon coating the funnel-shaped access holes in the top mold layer. The devices were released from the mold by etching in concentrated hydrofluoric acid which selectively attacks the PSG. The mold could be used repeatedly by redepositing PSG, the release layer, in order to minimize the cost. The resulting polysilicon microneedles were 1-7 mm long, with 110-200 µm rectangular cross-section and sub-micrometer tip radii.

Brazzle et al. [79, 80, 81] and Papautsky et al. [82] fabricated metal microneedles using a micromolding process. The fabrication process of the microneedles developed by Papautsky is shown in Figure 2.3. A P+ etch stop layer was formed and backside anisotropic etching in KOH was performed to define a thin membrane. The lower wall of the microneedles consisted of deposited and patterned metal layers. A thick layer (5-50 µm) of positive photoresist was then spin coated and lithographically patterned on the top of the lower metal walls. The dimensions of this sacrificial layer precisely defined the cross section of the lumen. After sputter deposition of a Pd seed layer, the thick metal structure walls and top of the microneedles were formed by electrodeposition. The sacrificial photoresist was removed with acetone and the P+ membrane was etched away in an SF₆ plasma, resulting in a one dimensional array of hollow microneedles released from the substrate.

An out of plane array of microneedles was fabricated by Stoeber and Liepmann [83, 84]. The fabrication process is summarized in Figure 2.4. A double side polished
Figure 2.2: Microneedles fabricated from a polysilicon molding process using two silicon wafers [78].
Figure 2.3: Fabrication process of a hollow in-plane microneedles [82].
wafer was oxidized. The lumen was etched through the wafer by plasma etching following a mask patterned at the backside. A silicon nitride film was then deposited across the backside and into the etched holes. Needle locations were photolithographically defined on the top surface on the wafer. The microneedle shaft was created by isotropic etching of silicon. The isotropic etching forms a microneedle with a gradually increasing diameter along the shaft. By displacing the circular pattern for isotropic etching from the center of the lumen, a pointed needle shape was obtained. These microneedles were 200 $\mu$m tall, with a base diameter of 425 $\mu$m tapering to a 40 $\mu$m lumen. Individual needles were 750 $\mu$m apart. Injection was demonstrated by delivering fluid under the skin of a chicken thigh at a depth of approximately 100 $\mu$m.

Figure 2.4: Out of plane array of microneedles. [Left] Fabrication steps, [Right] Symmetric and asymmetric needles [84].
Figure 2.5: [Left] Scanning electron micrograph of microneedles made by reactive ion etching technique. [Right] Microneedle tips inserted across epidermis. The underside of the epidermis is shown, indicating that the microneedles penetrated across the tissue and that the tips were not damaged. Arrows indicate some of the microneedle tips [85].

Solid microneedles with no lumen were demonstrated by Henry et al. (Figure 2.5) [74, 85]. A chrome mask was deposited on a silicon wafers and patterned into dots that have a diameter approximately equal to that of the base of the desired needles. A deep reactive ion etch was performed. Etching proceeded until the mask fell off from undercutting. The region protected by chromium remained and eventually became the microneedles. The tapering of the microneedles was controlled by adjusting the degree of anisotropy in the etch process. The resulting microneedles were 150 µm tall, and could be fabricated in dense arrays.

Gardeniers et al. [86] fabricated out of plane microneedles that employed reactive ion etching from both the sides on a (100) oriented silicon wafer (Figure 2.6). A hole (feature a in Figure 2.6) which becomes the lumen and a slot (feature b) that defines the position of the needles tip and needle sidewalls were etched at the top surface. These structures were aligned to the crystallographic planes of silicon
Figure 2.6: Out of plane microneedles fabricated that employed reactive ion etching from both the side of (100) silicon. [Left] Fabrication steps, [Right] A micrograph showing microneedle [86].

so that anisotropic etching performed later produces the slanted structure. The connecting lumen (feature c) was etched from the back side. The substrate, including the sidewalls of the etched features were coated with chemically vapor deposited silicon nitride. The nitride was removed from the top surface of the wafer and which was then etched in KOH. The etch left a structure defined by a (111) planes in the areas where the nitride slot walls were concave, but where the mask was convex, the etch found all of the fast etching planes. The nitride mask was stripped at the end of the process.

Microneedles have also been developed for gene delivery. One such structure was fabricated by Dizon et al., which they call ‘Microprobes’ [87]. This structure was
fabricated in a dense array using a silicon bulk micromachining technique (Figure 2.7). The microprobes were approximately 80 µm high topped by a wedge shaped tip with a radius of curvature less than 0.1 µm. The facets of the microstructure was fabricated utilizing fast etching (411) planes, produced by convex-corner undercutting in an anisotropic etching solution, and a square mask. These microprobes can be coated with genes and pressed into cells or tissues. The sharp tips penetrate into cells and affect the transport of genetic material. Successful expression of foreign genes using this technique has been demonstrated in the nematode Caenorhabditis elegans [88], tobacco leafs [89] and mammalian cells [90].

Mikszta et al. [65] used silicon micromachining technology for DNA and vaccine delivery to the epidermis. Figure 2.8 shows the microstructure, which they call microenhancer arrays (MEAs), that was fabricated by isotropic chemical etching of silicon wafers.

On the whole, existing microneedle-based drug delivery devices offer several advantages such as the ability to inject drugs directly through the stratum corneum at reproducible and accurate depth of penetration, minimal pain, and on-board ability to probe or sample the same device. Nevertheless, local irritation and low mechanical stability are some of the potential drawbacks that demand further investigation for alternate fabrication techniques and materials. Furthermore, improved fluid flow models that determine the most effective structural, fluidic, and biological design considerations for a given delivery application continue to be required.
Figure 2.7: Solid silicon microprobe for gene delivery [87].
2.2.2 Microparticles for Oral Drug Delivery

The oral route is a preferred method of drug delivery because of its ease of administration and better patient compliance. However, oral delivery of peptides and proteins has remained an illusive goal to the date. The two main reasons why it is currently impossible are: 1) destruction or inactivation due to enzymatic action, and the acidity of the upper gastrointestinal (GI) tract, and 2) the physiological permeation barrier, opposing penetration of large biological molecules through the intestinal walls [69]. These are mucosal layers and the tight junctions connecting intestinal epithelial cells, which restrict the possible passageways to be transcellular, thus exposing the diffusing biomolecule to enzymatic degradation. This method of
drug delivery, therefore, leads to unacceptably low oral bioavailability. As a consequence, various approaches based on the use of protective coatings [91], targeted delivery [92], permeation enhancers [93], protease inhibitors [94], and bioadhesive agents [95, 96, 97] have been explored in recent years. While all these methods have been shown to increase the oral bioavailability of drug molecules, none of these offer a complete solution for adequate and safe oral delivery of peptides and proteins.

Microfabrication technology may address the shortcomings of the current oral drug delivery systems by combining the aforesaid approaches in a single drug delivery platform. Fabrication of microparticles of silicon and silicon dioxide has been conceptualized and demonstrated to achieve this [98, 99, 100]. Unlike other spherical drug delivery particles, microfabricated devices may be designed to be flat, thin, and disc-shaped to maximize contact area with the intestinal lining and minimize the side areas exposed to the constant flow of liquids through the intestines [101]. The size of the particles (within thickness of 1-50 Å and diameters of 1 to 100s of microns) can be selected to have good contact with the undulations of the intestinal wall and large enough to avoid endocytosis of the entire particle. Permeation enhancers such as bile salts and metal chelating agents can be added to loosen the tight junctions of the intestinal epithelium. Aprotinin, or other enzyme inhibitors, can also be added to protect the macromolecule from intestinal degradation. In addition, one can selectively attach bioadhesive agents onto the device surface using relatively simple surface chemical modification strategies. By replacing the specific markers attached to the microparticles, specific cell types and tissues can be targeted for therapy as well as imaging. This would allow a high concentration of drug to be locally delivered while keeping the systemic concentration at a low level. Finally, these devices can
have multiple reservoirs of the desired size to contain not just one, but many drugs/biomolecules of interest [102].

iMEDD Inc., in collaboration with Ferrari, et al. [102] has developed OralMEDDS (Oral Micro-Engineered Delivery Devices), a novel porous silicon particle that can be used as an oral drug-delivery vehicle. The microparticle dimensions ranged from 150 × 150 × 25 (µm) to 240 × 240 × 25 (µm) with a pore size distribution of 20-100 nm (Figure 2.9). Once prepared, the particles could be loaded with a liquid drug formulation through simple capillary action. Interstitial air is removed by vacuum aspiration, and the formulation is dried completely using vacuum drying or freeze-drying. OralMEDDS particles have been designed to target intestinal epithelial cells, adhere to the apical cell surface, and deliver a drug formulation containing a permeation enhancer that would open the local tight junctions of the paracellular transport pathway. The absorption of macromolecules and hydrophilic drugs, which are unable to undergo transcellular transport across lipid membranes, is largely restricted to this paracellular route. Therefore, the intestinal absorption of orally administered water-soluble drugs can be greatly enhanced through the utilization of OralMEDDs particles.

Micromachined silicon dioxide and PMMA microparticles designed by Desai and coworkers [104, 68] can be best described as microparticles with reservoirs (Figure 2.10 and 2.11). These microparticles are adaptable for use as a bioadhesive controlled release oral drug delivery system. Silicon dioxide microparticles were created by growing a thermal oxide under wet conditions followed by Low-pressure chemical vapor deposition to deposit a sacrificial layer of poly-crystalline silicon [104]. Next, a layer of low temperature silicon dioxide (LTO) was deposited to form the device
Figure 2.9: Scanning electron microscopy images of a porous silicon particle: [Top] demonstrating the thickness, [Bottom] demonstrating the pore size distribution of \( \sim 20\text{-}100 \text{ nm} \) [103].
layer. Positive lithography was carried out to define the shape of the device reservoir. A reactive ion etch (RIE) with SF$_6$ and O$_2$ was used to fabricate the actual reservoir in the LTO device layer and any remaining photoresist was then removed in negative photoresist remover. Negative lithography was carried out to define the device bodies. Reservoir features on the mask were aligned to the photomask features using front side alignment. The unmasked area of the LTO layer was etched using RIE and the remaining photoresist was removed. These microdevices were then released into KOH solution by etching the sacrificial polysilicon layer. The particles were uniform and semi-transparent due to their polycrystalline nature. Later, a lectin-biotin-avidin complex suited for binding these microparticles to the intestinal mucosa was developed. The Caco-2 cell line was used to examine the bioadhesive properties of microparticles in vitro. Bioadhesive silicon dioxide microparticles demonstrated greater adherence to Caco-2 cells as compared to unmodified particles.

Poly(methyl methacrylate)(PMMA) particles were fabricated by spin casting PMMA (device layer) onto a clean silicon wafer [68]. The process flow of the device fabrication is shown in Figure 2.12. Positive lithography was carried out to define the device bodies followed by reactive ion etching to carve the devices. Then a second mask positive photolithography was carried out to carve the device reservoir. The dimensions of the reservoir can be altered by changing the masked area and their depth can be modified by changing the time and/or flow rate of gases in the RIE. By creating smaller reservoirs, a series of multiple reservoirs can be etched into the particles to create separate reservoirs for a combination of drugs or permeation enhancers. Since the PMMA is adherent to the surface of silicon by linkage to the native
oxide layer, the wafer was soaked in basic solution to break this bonding and immediately release the particles. Bioadhesive properties were introduced to microfabricated poly(methyl methacrylate) (PMMA) microdevices by attachment of lectins, a group of proteins capable of specifically targeting cells in the gastrointestinal tract. In this process, the PMMA microdevices were chemically modified by aminolysis to yield amine-terminated surfaces. Avidin molecules were covalently bound to the surface of the particles using a hydroxysuccinimide catalyzed carbodiimide reagent and then incubated in an aqueous solution of biotinylated lectin. The bioadhesive characteristics of lectin-modified microdevices were successfully demonstrated in vitro.
Figure 2.11: [Top] 50 micron particles with 25 micron reservoirs. [Bottom] AFM image of the particles (25 m reservoir, 50 m particles) [104].
Figure 2.12: Process flow of PMMA microdevices with reservoir for oral drug delivery. (A) Silicon wafers, (B) Device layer PMMA, (C) Spin cast photoresist, (D) Define device bodies, (E) Develop photoresist, (F) Carve device bodies, (G) Define device reservoir - positive photolithography, (H) Carve device reservoir, (I) Remove photoresist [68].
2.2.3 Microparticles for Intravenous Drug Delivery

The same microfabrication technology that has been used quite extensively for the fabrication of particles for oral drug delivery can be employed to develop precisely sized and shaped microparticles with high specific targeting abilities for intravenous (IV) delivery, especially for the treatment of diseases where oral and transdermal delivery are not effective. As an example, systemic chemotherapy using cytotoxic treatment is the only treatment available for many patients with advanced metastatic cancer. While many tumors respond to initial courses of chemotherapy, after multiple courses and drugs, cancer cells become resistant to further therapy. In addition, growth of metastatic tumors is supported by factors, secreted by tumor cells themselves, that cause angiogenic leaky vessels to grow. One strategy for preventing or treating metastatic tumors is to intervene in the process of angiogenesis by destroying the blood vessels that supply tumor cells rather than the tumor cells themselves [105]. In such cases, precisely sized and shaped microparticles especially designed for intravenous (IV) delivery of cytotoxic biomolecules/drugs to the microvasculature of tumors can be employed. These are described next.

Nonporous Microparticles:

The first generation of nonporous (solid) microparticles of silicon and silicon dioxide suitable for intravenous drug delivery [98, 99], were rectangular shaped with a thickness of 0.9 μm, and varied from 1 to 3 μm in length and width (Figure 2.13). These microparticles were treated with amino- and mercaptosilanes, followed by coupling to human antibody (IgG) using the heterobifunctional crosslinker succinimidyl 4-(N-maleimidolmethyl)-cyclohexane-1-carboxylate, to
Figure 2.13: Scanning-electron micrographs of microparticles. Left panel top view dimensions are $2.2 \times 2.1$ (± 0.1) mm for the larger particles, and $1.2 \times 1.1$ (± 0.05) mm for the smaller ones. Right panel shows tilted view of larger microparticles [98].

demonstrate their capability towards specific attachment of bioadhesive agents.

These solid microparticles and their next generations are currently being explored for drug delivery and bioimaging applications [106].

Nanoporous Microparticles:

More recently, porous silicon has begun to receive significant attention for biomedical usage. Nano- and microparticulates of this material have immense potential to be clinically and diagnostically significant both in and ex vivo [107, 108]. Li et al. [109] have demonstrated the incorporation, characterization, and release of cis-platin (cis-diammine dichloroplatinum(II)), carbo-platin [cis-diammine (cyclobutane-1, 1-dicarboxylato] platinum(II)), and Pt(en)Cl$_2$ (ethylenediamminedichloro platinum(II)) within layers of calcium phosphate on porous Si/Si substrates for the purpose of bone cancer treatment.
Superior control over particle dimensions, pore size, pore shape, and loading capacity is critical for microparticles for intravenous drug delivery [106, 110]. iMEDD Inc. has developed nanoporous microparticles (called IV-MEDDS or NK-MEDDS, where NK denotes the fact that the particles mimic Natural Killer cells) to treat systemically accessible solid tumors, specifically the multiple lesion sites associated with metastatic disease [69]. The approach here is to kill the circulatory accessible endothelial cells that support the existing tumor capillaries using micromachined asymmetrical particles, i.e. the top face of the particle contains a pore loaded with cytotoxic drugs, which is plugged with an erodible gelatinous material and layered with chemically grafted ligand (including growth factors such as FGF, EGF and VEGF to bind endothelial or tumor cell receptors or folate and tumor-targeting RGD peptides to bind $\alpha_v\beta_3$ integrins with high affinity) for targeting and protection. Designed to mimic the behavior of NK cells, a potent cytolytic agent such as bee venom-derived melittin can be plugged with a material designed to erode in 1-48 hours. After injection, the particles circulate within the blood stream for several minutes to several hours. After that particles that are still freely circulating are removed from the body by the body’s immune system. Bound particles should release their contents in the vicinity of the tumors and cause lysis and death of the target endothelial cells. Melittin peptides released by particles elsewhere in the body and not bound to the endothelial target, are inactivated by binding to albumin and thus are not toxic to normal cells [69].

Based on the above-mentioned concept, Cohen et al. [110] prepared micron-sized particles with nanometer-sized pores out of porous silicon and porous silicon dioxide. The fabrication steps are shown in Figure 2.14, 2.15 and 2.16. The particles were
fabricated with precise shapes and sizes. The size and thickness of these particles could be altered by changing the dimensions of the photolithography mask, the anodization time, and the electropolishing time. The porous silicon dioxide particles were 4.7 µm squares with a thickness of 1.0 µm. The porosity of silicon dioxide particles was 52.5%. In order to determine the safe particle size and concentration for intravenous drug delivery, a safety study was performed using solid silicon particles with various shapes (squares and circles) and varying sizes (2 µm, 5 µm, and 10 µm). Results indicated that at concentrations of \(1 \times 10^7\) particles per mouse, particles of size 2 and 5 µm safely circulate throughout the vasculature. No mice survived for any length of time when they were injected with 10 µm particles. Work is underway to demonstrate the coupling of EGF to porous dioxide particles that will allow for the particles to bind to the cells that express EGF receptors [110].

2.2.4 MEMS for Implantable Drug Delivery Devices

Implantable devices are preferred for therapies that require many injections daily or weekly. The requirements and advantages of implantable drug delivery devices have been discussed in more detail in Chapter 1. These devices can either be implanted into the human body or placed under the skin, consequently reducing the risk of infection by eliminating the need for frequent injections. Most of the implantable microsystems are expected not to cause pain or tissue trauma owing to their small size and are often virtually invisible. The advances in microfabricated implantable drug delivery device have been reviewed next.
Figure 2.14: Fabrication details for porous silicon particles. (a) LPCVD silicon nitride deposition; (b) Photolithography; (c) dry etch silicon nitride; (d) piranha; (e) anodization of silicon; (f) electropolishing; and (g) particle release using a water-soluble tape [110].
Figure 2.15: Process flow of porous SiO$_2$ particle fabrication (a) aluminum deposition; (b) spun on mesoporous oxide (a solution of porous silicon dioxide) film; (c) baked mesoporous oxide film; (d) photolithography; (e) dry oxide etch; (f) particle release in piranha; (g) uncapped particles; and (h) particles capped with photoresist removed from the wafer with concentrated HCL [110].
Figure 2.16: (A) SEM images of released porous silicon particles: Top image shows the shape and size of the particles. Bottom image demonstrates pores in the size range of 20-100nm. (B) SEM images of mesoporous silicon oxide particles on wafer: (a) perpendicular view; (b) 45° view. (C) SEM images of released porous silicon dioxide particles; (D) SEM images of released porous silicon particles [110].
Microreservoirs

Silicon microfabrication technology has been used to develop drug delivery device consisting of an array of microreservoirs [111, 66, 112] (Figure 2.17). This device is currently being developed by MicroCHIPS, Inc., for use as external and implantable systems for the delivery of proteins, hormones, pain medications and other pharmaceutical compounds [113]. Each dosage is contained in a separate reservoir that is covered with a gold membrane. The membrane gets dissolved in the presence of chloride ions when anodic voltage is applied to the membrane of interest. This causes the membrane to weaken and rupture, allowing the drug within the reservoir to dissolve and diffuse into the surrounding tissues. This device allows the release of potent substance in a pulsatile manner. Each microreservoir can be individually filled, so multiple substances can be delivered from a single MEMS (Microelectromechanical systems) device. The open end of the reservoir is sealed after filling the reservoir with the therapeutics to be release using a thin adhesive plastic and water proof epoxy. Release of fluorescent dye and radiolabeled compounds has been demonstrated from these microreservoir devices in-vitro in saline solution and serum [66].

The release studies from this device demonstrated that the activation of each reservoir could be controlled individually, creating a possibility for achieving many complex release patterns. Varying amounts of chemical substances in solid, liquid or gel form could be released into solution in either a pulsatile manner, a continuous manner, or a combination of both, either sequentially or simultaneously from a single device. Such a device has additional potential advantages including small size, quick response times and low power consumption. In addition, all chemical substances to be released are stored in the reservoirs of the device itself, creating a possibility for the
Figure 2.17: A schematic of a silicon microchip for controlled release (a) cut away section showing anodes, cathodes, and reservoirs; (b) shape of an individual reservoir; (c) Photograph of a prototype microchip: the electrode-containing front side and the back side with openings for filling the reservoirs [12].
future development of autonomous devices. A microbattery, multiplexing circuitry and memory could be integrated directly onto the device, allowing the entire device to be mounted onto the tip of a small probe, implanted, swallowed, integrated with microfluidic components to develop a ‘laboratory-on-a-chip’, or incorporated into a standard electronic package, depending on the particular application. Proper selection of biocompatible device materials may result in the development of an autonomous, controlled-release implant or a highly controllable tablet for drug delivery applications [66].

**Nanoporous Silicon Membranes**

Silicon nanopore membranes were developed by Ferrari and coworkers for application as immunoisolating biocapsules, and for molecular filtration [114, 115, 116]. Immunoisolation, in this case, refers to the physical protection or separation of cells from immunological attack. These nanopore membranes were shown to be sufficiently permeable to oxygen, insulin and glucose, while at the same time, impermeable to larger proteins such as immunoglobulin G (IgG), which might lead to destruction of the cells transplanted inside the biocapsule [117]. Since the diffusion through these membranes is linear, they can also be used for sustained drug delivery. This is currently being developed by iMEDD, Inc. of Columbus, Ohio [69, 102]. Over the years, nanopore technology has undergone continued improvements. Nevertheless, the basic structure and fabrication protocol for the nanopores has remained the same. The membrane area is made of thin layers of polysilicon, silicon dioxide, and/or single crystalline silicon depending on the design employed. The strategy used to make nano-size pores was based on the use of a sacrificial oxide layer sandwiched between two structural layers, for the definition of the pore pathways. The first design of nanoporous
membranes consisted of a bilayer of polysilicon with L-shaped pore paths. The flow path of fluids and particles through the membrane is shown in (Figure 2.18A) [118]. As shown, fluid enters the pores through openings in the top polysilicon layer, travel laterally through the pores, make a 90° turn, and exit the pores through the bottom of the pore where both the top and bottom polysilicon layers lay on the etch stop layer). The fabrication process of this design is mentioned in Chapter 3 (Figure 3.6), where sacrificial oxide is discussed in more detail. While this design performed well for preventing the diffusion of the larger, unwanted immune system molecules, its L-shaped path slowed down and, in some cases, prevented the diffusion of the smaller molecules of interest. The pores in this design were fairly long, which led to the slow diffusion of the desired molecules. Also, because of the large area per pore, it was difficult to increase the pore density and thus the diffusion rate. The next design had an improvement in the production of short, straight, vertical pores through a single crystal base layer (Figure 2.18 B and C). This design had the advantage of direct flow paths [118]. The fabrication protocols are described in Chapter 3 (Figure 3.7). This direct path allows the smaller molecules of interest to diffuse much quicker through the membrane, while still size-separating the larger molecules. To further improve the reliability of the nanoporous membranes, several basic changes were made in the fabrication protocol from the previous membrane design to eliminate problems with the diffused etch stop layer [119]. This design also incorporated a shorter diffusion path length, based on the thicknesses of the two structural layers. The design of a new membrane fabrication protocol incorporated several desired improvements: a well defined etch stop layer, precise control of pore dimensions, and a lower stress
Figure 2.18: (A) Flow path through M1 filters, with lateral diffusion through the nanopores defined by sacrificial oxide. (B) Cross-section of M2 design showing direct flow path. Scanning electron micrographs of microfabricated membrane: (C) top view detail of M2 filter; (D) side view detail of M2 filter. [119].

state in the membrane. The new protocol also increased the exposed pore area of the membranes.

Nanopore membranes have been studied extensively for the use of drug delivery and the results are very encouraging. This is discussed next.

Zero-order kinetics through nanoporous membrane:

In-vitro release study of interferon through a 20-nm channel is given in Figure 2.19 [120]. The experimental results show a zero-order release profile (zero-order kinetics). It can be noticed that the zero-order kinetics does not follow Fick’s law. Fick’s laws are usually adequate to describe diffusion kinetics of solutes.
from a region of higher concentration to a region of lower concentration through a thin, semi-permeable membrane. But, when the size of the membrane-pores approaches that of the solute, an unexpected effect may occur, which deviates substantially from those predicted by Fick’s laws. Diffusion of molecules in microporous media such as zeolites has led to experimental evidence of such unusual phenomena as molecular traffic control and single file diffusion (SFD) [121, 122]. Theoretical treatments and simulations suggest that in the case of SFD, solute molecules of equal size cannot pass each other in pores which approximate the dimensions of the molecule itself, regardless of the influence of concentration gradient, and thus their initial rate of movement (or flux) is underestimated by Fick’s law [123, 124, 125, 126, 127].

The microfabricated nanopore channels are of molecular size in one dimension and therefore non-Fickian diffusion kinetics is observed. The observations are consistent with the diffusion reported for colloidal particles confined in closed one-dimensional channels of micrometer scale where particle self-diffusion is non-Fickian for long time periods and the distribution of particle displacements is a Gaussian function [122]. Zero-order flux is observed when a chamber filled with a solute is separated from a solute-free external medium by channels that are only several times wider than the hydrodynamic diameter of the individual molecules. The basic principle of diffusion as a mixing process with solutes free to undergo Brownian motion in three dimensions does not apply since in at least one dimension solute movement within the nanopore is physically constrained by the channel walls. Experimental observations of colloidal particles in a density matched fluid confined between two flat plates reveal that particle
Figure 2.19: In vitro interferon diffusion through nanopore membrane (20 nm pore size): experimental data (o), Fick's law prediction (-), model based simulation (–). [120]
diffusion becomes anisotropic near the interface; in this case leading to hindered diffusion as a consequence of constrained Brownian motion and hydrodynamic drag effects at distances close to the walls [128]. In the case of nano-porous membranes, it is not entirely certain that the ordering of solutes imposed by the nanopore geometry will be as strict as true cylindrical pores, nor that the sequence of particles passing through the nanopores under the influence of the concentration gradient will remain unchanged over the time required to travel the 4 μm length of the channel; particles could conceivably pass each other laterally. Whether a consequence of a SFD-like phenomenon or drag effects (or a combination of both), the nanopore membrane is rate-limiting and, if properly tuned, restricts solute diffusion to a point that flux rates across the membrane are entirely independent of concentration gradient and follow zero-order kinetics.

In order to achieve further insight on the mechanisms involved in nano-channel diffusion, a mathematical model is being developed. This will make it possible to simulate the diffusion experiments and fit the related data. A detailed description of such model is presented in reference [129].

**Biocompatibility of nanoporous membranes:**

In vivo membrane biocompatibility was evaluated using glucose as a model molecule [130]. Figure 2.20 shows the ratio of post explantation glucose diffusion rate compared to its initial value. There was no noticeable change in glucose diffusion rates pre- and post- implantation illustrating that the silicon membranes did not foul over a six-month implantation period. The membrane
was placed on a titanium capsule and the entire assembly was placed subcu-

taneously in mice. The assembly was removed after seven days and examined

visually. There was no visible evidence of tissue binding to the surface. Figure

2.21 shows a photograph of the implant site after thirty days of implantation.

As it can be seen, only a thin vascular capsule forms around the implant as

opposed to the avascular fibrous capsule. This minimal tissue response is sup-

posed to be responsible for the comparable pre- and post- implantation glucose

diffusion rates observed in this investigation.
Figure 2.21: Photograph of implantation site after thirty days in vivo. [130]

**Sandwich design filter**

Nanochannels fabricated between two directly bonded silicon wafers were also developed for the applications as immunoisolating biocapsules, and molecular filtration [131, 118, 132, 133, 134]. These devices possess high mechanical strength since the filtration occurs at the interface of two bonded silicon wafers instead of through a 1-10 μm-thick membrane (in the case of silicon nanopores membrane). Well-developed bulk microfabrication technology was used to fabricate these devices. With the use of a silicon dioxide sacrificial layer, pore sizes as small as 40 nm were fabricated with size variations less than 4%. It was already established in the case of silicon nanopore membranes that the diffusion of molecules though nanopores is constant,
and therefore the sandwich design filter can also be used for sustained drug delivery applications.

2.3 A Critical Analysis of Implantable Drug Delivery Devices

Despite considerable advances in the field of drug delivery technology that has brought many clinical products into the market, the major needs for drug delivery devices are still unmet and important classes of drugs have yet to benefit from these technological successes [4, 69, 135, 136]. Intravenous (IV) lines carry obvious contraindications in terms of patient inconvenience, discomfort, required hospital stay and adverse affects such as phlebitis, clotting, and infections. The central focus of any controlled drug delivery device is the ‘control’. This can only be achieved if [8, 112, 137, 138, 101, 139]

1. The dimensions of the device can be manufactured as accurately as possible,

2. The device can be produced with uniformity (reproducibility of the device),

3. The device is chemically and mechanically strong enough for implantable purposes,

4. The device is biocompatible, and

5. The rate of drug delivery should be independent of the environment where the device is placed.

Though there are many different routes of drug delivery (transdermal, oral, etc.) implantable devices are placed into the human body or placed under the skin, consequently reducing the risk of infection by eliminating the need for frequent injections.
Apart from a reduction in the number of injections, implantable drug delivery devices may offer other advantages such as, drug level in the blood level could be monitored precisely on-line and adapted to variation in physical activity; in some treatments such as chemotherapy, the device can be implanted at the place where the drug is needed.

Polymeric reservoir devices are difficult to fabricate [118, 140]. A mechanical defect in the reservoir, an event that is highly possible, can lead to dose dumping. Some of the therapeutic agents, e.g. protein, do not diffuse readily through any of the hydrophobic, biocompatible polymers that are commonly used for implantable reservoir devices, or they diffuse very slowly [140]. In the case of polymer matrix systems of delivery, it is difficult to achieve a constant release of drugs, and they need to be encapsulated by a shell of rate limiting polymeric membrane. This further adds to the complexity of the delivery system and the problems associated with the polymeric membranes persist. Degradable polymer implants exhibit an initial “burst effect” prior to sustained release and are typically not as efficient in controlling release rates of small molecules [141]. The polymeric implantable devices that are being developed for achieving pulsatile release are susceptible to interference from external environmental factors, e.g., temperature, light, magnetic field, ultrasound, etc.

Osmotic pumps lack the capabilities of on-board electronic integration for achieving higher levels of functionality (i.e. pre-programming and remote activation) and are limited with respect to the type of drug they can deliver. It is difficult to develop an effective dosage solution to deliver lipophilic compounds that have poor water solubility. These compounds need to be dissolved in neat co-solvent or in water-miscible co-solvents, and it was experimentally found that many of these co-solvents are not
compatible with the reservoir material of the pump [142]. Further, fully implantable pumps either for sustained release or for delivering drugs in a pre-programmed way are usually hampered by their size, cost, and ability to deliver only drugs in solution and limited stability of some drugs in solution at 37°C [66].

Most of the micropumps require either high operating voltages (piezoelectric and electrostatic actuations) or high operating powers (thermopneumatic, electromagnetic, and SMA actuations) [34]. Further, the moving component (valve) may lead to mechanical failure resulting in adverse effect on therapeutic treatment. It is suggested in the case of osmotic pumps and micropumps that a catheter can be attached to achieve site specific drug delivery at a location distant from site of implantation. However, implantable devices with percutaneous components such as ambulatory peritoneal dialysis catheters, intravenous catheters and orthopaedic implants are often associated with different failure modes. Infection, marsupialization, permigration, and avulsion are common occurrences [143, 144].

Silicon based devices solve most of these problems. Using well know silicon microfabrication technology these devices can be fabricated with high precision and reproducibility. The uniform pore size distribution in a device and reproducibility of the device may allow better control of drug release over traditional polymer based membrane systems. Silicon is also well known to be structurally insensitive to temperature, light, ultrasound, changes in pH, or molecules present in human body. Further silicon platform technology allows electronic integration.

Microreservoir devices can be used for pulsatile release; however it is difficult to achieve other manipulable patterns. Further, since the drug delivery is based on dumping the entire dose of one microreservoir at a time once the membrane covering
that microreservoir breaks, a sustained release cannot be achieved during the ‘release’ period of a pulse. This results in a first-order release kinetic as shown in Figure 1.3, resulting in initial high blood levels of the drug, followed by an exponential fall in blood concentration.

In the case of silicon nanopore membranes and sandwich design filters, sustained release is achieved by diffusion of molecules through tightly controlled pores that eliminates the need for any moving component and an external power supply. Silicon nanoporous membranes have also been extensively studied for drug delivery application and the results are very encouraging. However, silicon nanopore membranes are very thin (1-10 µm thick), and therefore are very fragile. When implanted inside the body, failure may occur if the body experiences an impulsive force; that may lead to dose dumping. Sandwich design approach addresses this problem. The nanochannels in the sandwich design filter were fabricated between two silicon substrates [145]. This device offers good control of channel size and pore distribution making it possible to control the release rate. Since the particles’ diffusion or the flow is between two directly bonded wafers (sandwich design approach - nanochannels between the two silicon substrates) the filter has more mechanical support and is thus structurally stronger. However, this filter has not been extensively investigated for drug delivery application. A linear diffusion through the nanochannels of this device would make it a suitable candidate for sustained drug delivery. Further, electronic integration with this device is possible, and an electroosmotic flow can be achieved. Electroosmotic flow would reduce the power and voltage requirement for this device as compared to micropumps [146], while electronic integration would allow this device to release therapeutic molecules in a manipulable non-zero order release profile. The degree
of integration that can be achieved on a single silicon substrate provides major ad-

c
vantages over other materials used for making drug delivery devices. The tightly
controlled dimensions, small feature size, and ability to integrate electronics to the
silicon platform may allow the use of potent drugs or molecules, such as hormones
and growth factors, in clinical applications.
CHAPTER 3

SACRIFICIAL OXIDE LAYER

3.1 Introduction

A very common method in silicon microfabrication is the use of a sacrificial layer. As the name suggests, a layer is created in surface or bulk micromachining in order to release different MEMS structures or in IC fabrication in order to improve the device performance, and is etched away later in the process. Sacrificial oxide is the key to the fabrication of nDS devices. The nanochannels of these devices are created using the sacrificial oxide technique, and this oxide defines the nanoscale dimension of the channel (that is the height of the channel). The delivery rate of the nDS1 device is completely dependent on the dimensions of the inbuilt nanochannel, while the delivery rate of nDS2 depends on the dimensions of the nanochannel as well as the current applied through the channel. Therefore, it is very important to understand the fabrication technology of the sacrificial layer.

Silicon dioxide ($\text{SiO}_2$) is usually chosen as a sacrificial oxide in such processes because of its common availability in IC processing and its compatibility with the elevated temperature during polycrystalline silicon (poly-Si) deposition and anneal. The oxide adheres well to the silicon surface and have stable and reproducible bulk
properties. The interface between Si and SiO₂ can be achieved with very few mechanical and electrical defects and is stable over time. Further, SiO₂ is chemically resistant to most of the chemicals used in silicon processing and yet can be easily patterned and selectively etched with specific chemical or dry plasma etches.

Accounting for its multiple uses, different varieties of oxides have been fabricated for use as sacrificial layers. Examples are: thermally grown oxide, CVD (chemical vapor deposition) oxide, PSG (phosphosilicate glass), SOI (silicon on insulator), and SOG (spin-on glass) [147]. The second section of this chapter describes the different fabrication technologies for silicon dioxide. Oxides fabricated by these different techniques have a slightly different composition and thus different etch rates. These oxides are usually etched in order to release or create a structure, and therefore good etch selectivity of oxide against the structure material (usually silicon) is required. Further, high solubility of etch products is required in order to avoid etch residues that may result in stiction. The third section reviews the different etching techniques and challenges encountered during etching. The last section reviews how sacrificial oxide has been used to fabricate different MEMS structures and ICs, followed by concluding remarks.

3.2 Silicon Dioxide Fabrication

When silicon is exposed to oxygen or ambient air at room temperature its surface immediately oxidizes forming a very thin layer of oxide of thickness 5-10 Å. The oxide growth then slows down and stops after a few hours with the oxide thickness of the order of 1-2 nm. This is called the ‘native oxide layer’ [148]. Both the growth rate and the final oxide thickness depend on the chemical residue from the previous cleaning
procedures. The sacrificial oxide layers are typically thicker than the native oxide, and are fabricated in a controlled way. Silicon dioxide fabrication can be divided into two categories: 1.) thermally grown oxide and 2.) deposited oxide. These fabrication technologies are described next.

3.2.1 Thermally Grown Oxide

Thermal oxidation of silicon can be achieved by heating the wafer to a high temperature, typically 850°C to 1200°C, in an atmosphere containing either pure oxygen (called dry oxidation) or water vapor (called wet oxidation). The chemical reaction occurring at the silicon surface for the case of dry oxidation is:

\[
\text{Si} + \text{O}_2 \rightarrow \text{SiO}_2
\]  

(3.1)

And for the case of wet oxidation it is:

\[
\text{Si} + 2\text{H}_2\text{O} \rightarrow \text{SiO}_2 + 2\text{H}_2
\]  

(3.2)

Silicon is consumed when oxide grows. The final oxide layer is approximately 54% above the original surface and 46% below the original surface [148]. A simple model was developed by Deal and Grove in the early 1960s to explain and predict oxidation kinetics [149, 150]. This model (also known as the linear parabolic model) assumes that an oxide of some thickness ‘\(x_i\)’ is already present on the silicon surface and the structure is one dimensional so that this model will only apply to oxide films grown on flat substrates. It also assumes that either equation 3.1 or equation 3.2 is taking place. Thus, this model cannot fully explain the oxidation of shaped surfaces or oxidation kinetics in mixed ambient or for very thin oxides.
In many cases, sacrificial oxides are thin films and are grown in dry conditions. This provides better control of oxide thickness. The initial oxidation is greatly enhanced by water vapor, and therefore generation of thin film oxides requires tight control of trace quantities of moisture. Quantities as low as 25 ppm of moisture in the supply gas can affect the oxide thickness [151]. The initial oxidation rate is also higher at higher temperatures, and therefore lower temperatures and reduced pressures are recommended [152].

Many models have been proposed to predict oxide growth rates in dry O\textsubscript{2} for thin oxides less than about 300 Å, each claiming an improvement over the Deal-Grove Model. In 1987, Reisman et al. [153] suggested a simple power law of the form:

\begin{align}
  x_o &= a(t + t_i)^b \\
  x_o &= a(t + (\frac{x_i}{a})^{1/b})^b
\end{align} \quad (3.3)

Where \( a \) and \( b \) are constants for a given set of process conditions and \( t_i \) is the time corresponding to the oxide thickness \( x_i \) at the beginning of the growth process.

Han and Helms [154] came up with another approach and suggested that a wide body of oxidation data, including the dry O\textsubscript{2} thin regime, could be modelled by an expression of the form:

\[
\frac{dx_o}{dt} = \frac{B_1}{2x_o + A_1} + \frac{B_2}{2x_o + A_2}
\] \quad (3.5)

Han and Helms found that by setting \( B_1/A_1 \) to infinity (i.e. \( A_1 = 0 \)) agreed well with the experiments. \( B_2/A_2 \) values for different silicon crystal planes are given in reference [154]. All of these rate constants were found to fit the Arrhenius expression.
Massoud [155, 156] presented another model for thin film oxide growth rate on undoped silicon that is given by

$$\frac{dh}{dt} = \frac{B}{2h + A} + C_1 e^{-(h/L_1)} + C_2 e^{-(h/L_2)}$$ (3.6)

Where $h$ is the oxide thickness, $A$ and $B$ are the linear and parabolic rate constants, and $C_1$, $C_2$, $L_1$ and $L_2$ are the characteristic constants and lengths respectively. This equation requires a limiting initial oxide thickness $h_i$ necessary to fit experimental data, and therefore an oxide thickness below $h_i$ cannot be computed using this model.

Many other models have been developed to explain the oxidation kinetics, all of them motivated by the shortcomings in the linear parabolic model. However, none of them have gained widespread acceptance. Most of the modelling efforts today use the Deal-Grove model as a starting model and then add or modify to it for the effect that is not considered or not modelled well.

### 3.2.2 Deposited Silicon Dioxide

A lot of oxide films today are deposited using LPCVD (low pressure chemical vapor deposition) or PECVD (plasma enhanced chemical vapor deposition) techniques [157]. Silane and oxygen are the most common source gases used for these CVD processes. The reaction that takes place is given below:

$$SiH_4 + O_2 \rightarrow SiO_2 + 2H_2$$ (3.7)

Deposition temperatures in LPCVD systems range from 300°C to 900°C. However, the low temperature deposition rate is usually quite low and the film quality may be
poor. High quality film may be deposited in the temperature range of 200°C to 350°C using PECVD.

Sometimes other sources of O₂ are used, such as N₂O, NO, and CO₂. Silicon sources, other than silane have also been used. One such source is tetraethoxysilane or TEOS. It can form SiO₂ by decomposing via the reaction:

\[ Si(OC₂H₅)₄ → SiO₂ + \text{byproducts} \quad (3.8) \]

The decomposition of TEOS requires higher deposition temperatures, but results in improved step coverage.

When non-plasma, silane based deposition is done at temperature below 500°C, it is called low temperature oxide (LTO).

Depending upon the deposition method, large variations in density, chemical structure, stoichiometry, impurity content and dopant content are achieved. The requirements for electronic grade oxide and sacrificial oxide are usually different. For example, while long-term stability and chemical purity are the required conditions for dielectric layers, high etch rate and etch selectivity are the main requirements for the sacrificial oxide layer. Chemical impurities in a deposited layer can significantly change the etch rate, e.g. water uptake decrease the etch rate of phosphorous doped oxides [158]. Conformal step coverage of sacrificial oxide results in a well-defined step or height of the cavity in the released structure, while a planarizing sacrificial layer is desired for flat structures on top of steps in the topography. Conformal step coverage refers to uniform film coverage on both horizontal and vertical surfaces. Some requirements for sacrificial oxide and general considerations to achieve them are listed in Table 3.1.
Requirements for sacrificial oxide

<table>
<thead>
<tr>
<th>Requirements for sacrificial oxide</th>
<th>General consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etch selectivity against substrate and structural material</td>
<td>Proper choice of etchants</td>
</tr>
<tr>
<td>High etch rate</td>
<td>Proper choice of dopants, doping concentration and etchants</td>
</tr>
<tr>
<td>Large undercut</td>
<td>High diffusion coefficient of etchant required</td>
</tr>
<tr>
<td>High solubility of etch products in order to avoid etch residues</td>
<td>Appropriate rinse-dry methods</td>
</tr>
</tbody>
</table>
| Little shrinkage | • Densification and anneal steps  
  • Low stress oxide |
| Low thermal budget | Low temperature deposition, reflow, and anneal for maximum compatibility to implants and metallization |

Table 3.1: Requirements for sacrificial oxide and general considerations [147].
Deposited films are often doped with phosphorus or boron, or both in order to passivate or chemically stabilize the deposited oxide, lower the temperature of planarization reflow, and speed up the etching of the oxide. Depending upon the type of dopants these oxides are named as phosphosilicate glass (PSG), borosilicate glass (BSG) and borophosphosilicate glass (BPSG). LPCVD-BPSG has low reflow temperatures of 700-1000°C, and therefore can be used to overcome the problems of poor step coverage associated with LPCVD-LTO [147]. However, phosphorus content in excess of 6-8% results in a hygroscopic surface and can potentially cause phosphoric acid at the oxide surface. Boron of concentration in excess of 5% makes the surface hygroscopic and unstable [159].

### 3.2.3 Thermally Grown Oxide vs Deposited Oxide

Deposited SiO$_2$ does not consume silicon, and therefore can be deposited on any surface (metal, nitride, or others). In fact, deposition is the only option to obtain an oxide layer on top of an underlying film where silicon is not available from that underlying film for SiO$_2$ growth. Further, when it is not possible to process the wafer at high temperature, oxide is deposited, since some CVD processes can be used at lower temperature. However, deposited oxides are not used for thicknesses lower than 20 nm because control of the deposition process is not as good as the thermal oxidation process. When the control of oxide thickness is a major concern in thin film oxide, dry thermal oxidation is preferred over CVD oxide. Further, the interface between deposited oxide and silicon is not as good as in the case of thermally grown oxide. Deposited oxide/silicon interface is annealed to improve the interface.
properties. Depending upon the requirement of sacrificial oxide, a suitable process is chosen.

### 3.2.4 Silicon-On-Insulator (SOI) as Sacrificial Layer

In some cases silicon-on-insulator is used as a starting material and buried oxide is used as a sacrificial layer. An example of such a wafer is shown in Figure 3.1. Several approaches are used to fabricate these wafers. One such process is known as the SIMOX (separation by implanted oxygen) process. In this process, a large dose ($\sim 10^{18} \text{ cm}^{-2}$) of oxygen is implanted in a normal silicon wafer, followed by annealing. The silicon above the buried oxide is of reasonable crystal quality if the wafer is annealed properly, although the quality is generally not as good as the starting wafer. A second approach to achieve this kind of wafer is called BESOI (bonded and etch-back silicon-on-insulator). Two normal silicon wafers are oxidized first. After proper surface treatment, the two wafers are brought into contact with the two oxide surfaces facing each other. A good bonding is achieved after annealing. One of the two wafers is then etched or lapped away to leave the thin film of silicon on SiO$_2$. A combination of chemical mechanical polishing (CMP) and lapping is usually used for this purpose.

### 3.3 Sacrificial Oxide Etching

Sacrificial oxide is always etched away, sometimes during the process or mostly at the end of the process. A good etch selectivity is an important requirement for the sacrificial oxide etch. The etch rate depends upon many factors, such as doping material, doping concentration, oxide fabrication method and geometry of the sacrificial layer. Usually sacrificial oxides are buried layers and only small openings are
Figure 3.1: Silicon On Insulator (SOI) wafer technology.
available for the etchants to reach the surface being etched as well as for the etched products to come out of the cavity. In such case diffusion of etchants may become the rate limiting step. For these reasons, an understanding of etch kinetic is important.

3.3.1 Etch Mechanism

SiO$_2$ can be dissolved in bases such as alkaline hydroxides or carbonates, which are able to form an alkali silicate that is soluble in water. However, these alkaline solutions dissolve silicon too and therefore are usually not used with silicon micromachining. Common oxide etchants are hydrofluoric acid based compounds. Hydrofluoric species are able to break the strong Si-O bond because of the high electronegativity of the fluorine. The dissolution of SiO$_2$ in aqueous HF can be represented by the following equation:

$$SiO_2 + 6HF \rightleftharpoons 2H^+ + SiF_6^{2-} + 2H_2O$$ (3.9)

When diluted in water, HF dissociates into $H^+$, $F^-$ and various hydrofluoric species such as HF$^{2-}$ and (HF)$_2$.

When Buffered HF (BHF) is used to etch oxide, ammonium fluoride is dissociated as

$$NH_4F \rightleftharpoons NH_4^+ + F^-$$ (3.10)

The overall chemical reaction can be given as

$$SiO_2 + 4HF + 2NH_4F \rightleftharpoons 2NH_4^+ + SiF_6^{2-} + 2H_2O$$ (3.11)

$2NH_4^+$ and SiF$_6^{2-}$ can precipitate as (NH$_4$)$_2$SiF$_6$ due to its limited solubility [160].
Various models have been proposed to understand the role of HF, HF$^{2-}$ and (HF)$_2$ in the etch reaction and to calculate the etch rate dependence on concentration and temperature. The model introduced by Blumberg in 1959 [159] is given below:

$$J_{\text{react}} = k_0 (C_{HF})^n$$  \hfill (3.12)

Where, $k_0$ and $n$ are fitted to experimental data. $C_{HF}$ is the hydrofluoric acid concentration.

Many follow up models were developed to include HF$^{2-}$ and (HF)$_2$, but none can predict the etch rate over a large range of concentration and type of oxide. A good discussion on these models is given in reference [161]. A model incorporating second order effect of $C_{HF}$ was proposed in reference [162]. According to this model

$$J_{\text{react}} = k_1 (C_{HF}) + k_2 (C_{HF})^2$$ \hfill (3.13)

This uses vertical etch rate as well as underetch rate in sacrificial oxide channels to fit experimental parameters $k_1$ and $k_2$.

The etch rate dependence on temperature follows the Arrehenius law:

$$J = J_{\text{react}} \cdot \exp\left(-E_0/RT\right)$$ \hfill (3.14)

The activation energy $E_0$ was measured for various compositions of BHF for different oxides and is given in reference [163].

The sacrificial oxide etch rate is usually different than the regular oxide etch rate when the sacrificial oxide is not a top layer. In many cases the sacrificial oxide is a buried layer and there is a small opening that allows etchants to go to the oxide.
To model the etch kinetics of a buried sacrificial oxide, it is important to know how the etch-front proceeds in the cavity formed by extensive undercut. This is limited by the diffusion of reactive species to the etch front or by the diffusion of byproducts away from the etch front inside the cavity. The first order reaction kinetics is given by the Deal-Grove model [162, 164, 165]. The diffusion flux is proportional to the concentration difference of reacting species outside and inside of the cavity:

\[ J_{diff} = D \cdot (C_b - C_s)/\delta \]  

(3.15)

Where, \( C_b \) and \( C_s \) are the reactant concentrations in the bulk and at the oxide surface, respectively. \( D \) is the diffusion coefficient and \( \delta \) is the undercut distance. \( J_{diff} \) becomes equal to \( J_{react} \) at equilibrium when the etch rate is limited by the reactant exchange rate required for etching. However, because of different sacrificial oxide
structures in different MEMS devices, it is difficult to have a well defined model, and every different design needs to be considered differently. The sacrificial oxide grown in this research is a top layer, and therefore this is not a problem here.

### 3.3.2 Selectivity

Selectivity is another crucial issue in sacrificial oxide etch. Usually a critical device structures exists surrounding the sacrificial oxide layer, and poor selectivity damages that structure. The damage could be homogeneous chemical etching, local dissolution or corrosion because of the formation of local electrochemical cells. As mentioned earlier, alkaline etchants react with silicon and therefore are not good for releasing silicon MEMS structure from sacrificial oxides. HNO$_3$/HF is not suitable either, because HNO$_3$ oxidizes the silicon surface and the resulting oxide is dissolved in HF. Therefore, the etchant should be chosen very carefully considering the design requirements.

### 3.3.3 Stiction

The choice of oxide etchant is also important in order to prevent stiction. This effect has been addressed theoretically as well as experimentally [166, 167, 168, 169, 170, 171, 172]. A conventional wet etching may result in two kinds of stiction failure. The first is temporary deformation due to capillary forces between the micromachined superstructure and substrates during rinse-dry processes after the sacrificial oxide etch. Another failure is the permanent stiction of the deformed superstructure to the substrate due to the residue products from wet etching. For example, in the case of microactuators, very bad stiction occurs during operation [173, 174, 175, 176]. Small Si-H$_2$O contact angles at highly doped surfaces [174], native reoxidation of HF and
BHF etched surfaces [175], and smooth surfaces [177] enhance the probability of the occurrence of sticking. Consequently, sacrificial oxide etchants resulting in rough and hydrophobic surfaces are preferred. Various techniques have been developed to alleviate the stiction problem. The solutions include micromechanical temporary support [178], sublimation of final liquid by free dry or solidification dry [179, 180], removing the final liquid by supercritical method [170], or using low surface tension liquid [177, 169, 181]. Researchers have also etched sacrificial oxides using anhydrous HF and CH$_3$OH in gas phase to achieve dry release [171, 182]. Methanol of low vapor pressure was used here as a catalyst instead of water vapor to minimize residue products and avoid capillary forces.

Since, the sacrificial layer grown in this research is a top layer and does not define a structure on top of it, stiction is not a concern.

### 3.3.4 On-Chip Packaging

Another problem that is faced in sacrificial oxide etching is in the case of on-chip packaging of sealed cavities, robust membranes, and similar hollow structures. On-chip packaging is beneficial to many resonating devices, which frequently requires vacuum encapsulation of the device. In a conventional approach, the sacrificial oxide is removed by allowing the etchant (e.g. HF) to reach the sacrificial oxide surface through photolithographically defined holes, followed by the sealing of the etch access holes [183]. This causes long etching time, and extended exposure to the etchants raises concerns for material degradation [184]. Further, the sealing material on the surface of encapsulated device may affect the device properties. To overcome this problem a thin LPCVD deposited polysilicon was used as a shell material [185, 186, 187]. This
polysilicon was deposited under a special condition [188, 186, 187] such that it was permeable to HF based etchants. This allows the underlying sacrificial oxide to be removed directly through the polysilicon layer without making photolithographically defined access holes. A process to achieve a thick porous polysilicon shell layer that may be required in some application has also been reported [189]. A schematic of this approach is shown in Figure 3.3. The sacrificial oxide layer was etched by HF, which diffused through the pores of the polysilicon. The device was vacuum sealed by depositing PECVD low stress nitride at the end.

3.4 Application of Sacrificial Oxide in Devices

Sacrificial oxide has been used in IC fabrication as well in MEMS fabrication. This section reviews the use of sacrificial layers in fabrication of different devices.
3.4.1 Sacrificial Oxide for MEMS

In 1965, Nathanson et al. [44, 190, 191] first used a sacrificial oxide layer to fabricate resonant gate transistors consistent with silicon integrated circuit technology. They electroplated a gold beam electrode on top of a sacrificial layer. The sacrificial layer thickness determined the nominal beam-to-substrate distance. The sacrificial layer was etched at the end to release the beam electrode.

Howe and Muller [46] used sacrificial oxide to fabricate cantilever beams from polycrystalline silicon (polysilicon). The fabrication steps are shown in Figure 3.4. They etched holes in a sacrificial oxide layer fabricated on the silicon surface. Next, a polysilicon layer was deposited and plasma etched, leaving the desired cross-section to form a cantilever. Then the underlying sacrificial oxide was etched off in HF.
Kittilsland et al. [192] used sacrificial oxide to fabricate submicron particle filters in silicon. The fabrication steps are shown in Figure 3.5. A sacrificial silicon dioxide was grown on (100) n-type silicon substrate. The thickness of this oxide determined the membrane separation distance. A polysilicon layer of 1.5 \( \mu \text{m} \) was deposited on top of this oxide. A silicon dioxide layer was grown on top of the polysilicon layer to prevent damage during subsequent boron doping process [Figure 3.5(a)]. Holes in polysilicon and silicon dioxide were made using photolithography [Figure 3.5(b)]. Next, a high concentration of boron was diffused through the holes into the silicon [Figure 3.5(c)]. The wafer was then etched from the back side to create openings from the bottom. The heavily boron doped layer acted as an etch stop. The sacrificial oxide was then etched to form through holes in this structure [Figure 3.5(d)].
Chu et al. [152] used a sacrificial layer to fabricate silicon membrane nano-filters. These filters can also be used for immunoisolation. The filter channels were created by selective removal of sacrificial silicon dioxide sandwiched between silicon layers. They presented two sacrificial layer filter designs that can achieve pore sizes as low as 10 nm in size. Sacrificial oxides were grown selectively in both the designs and then etched later. The sacrificial oxide defined the pore size of the filter, and therefore control of oxide growth was important in both the cases. This was achieved by dry oxidation. Figure 3.6 shows the fabrication protocol of filter design 1. Hexagonal trenches were photolithographically defined and etched by plasma etching. These trenches were used to create support ridges. The wafers were then wet oxidized. This oxide served as an etch stop for final backside etching [Figure 3.6(a)]. LPCVD polysilicon was then deposited followed by an annealing step. This polysilicon was doped heavily with boron to improve selectivity during the long backside etch [Figure 3.6(b)]. Borosilicate glass (BSG) formed during this step was etched away from the top of the polysilicon surface. The wafer was then reoxidized and rectangular polysilicon holes were photolithographically defined and etched into the deposited p\(^+\) polysilicon for the exit channels [Figure 3.6(c)]. The wafer was cleaned and then oxidized. This oxide was removed in the final step to create the channels. This was achieved by dry oxidation at relatively low temperature (850\(^\circ\)C for 45 min gave a 20 nm channel in this case) [Figure 3.6(d)]. Figure 3.6(e) shows the anchor points defined by photolithography. A second polysilicon layer then deposited and heavily doped [Figure 3.6(f)]. This layer was anchored to the first polysilicon layer through the pre-defined anchor points. BSG was again removed from the top of this new polysilicon surface. Square holes were photolithographically defined and etched into
the second polysilicon layer to form entry pores [Figure 3.6(g)]. Finally, thermal oxide was grown and phosphosilicate glass (PSG) was deposited on both sides on the silicon wafer for protection from the final etch [Figure 3.6(h)]. A deep etched was performed from the backside of the wafer that stopped at the silicon dioxide interface [Figure 3.6(i)]. The sacrificial oxide was then etched in HF to open the pores.

The fabrication steps of the second design are shown in Figure 3.7. A silicon etch stop was created by heavy Boron diffusion on (100) silicon wafers. After the boron diffusion BSG was removed from the surface. Hexagonal trenches were photolithographically defined and plasma etched through the p⁺ doped silicon [Figure 3.7(a)]. A thin sacrificial oxide was grown on top of the etched silicon [Figure 3.7(b)] to define the channels. The same photolithographic mask was used to define anchor points by offsetting the alignment [Figure 3.7(c)]. The oxide in this region was then plasma etched. An updoped polysilicon was deposited on top of the etched thin oxide layer [Figure 3.7(d)]. The polysilicon was then p⁺ diffused and BSG was removed. Finally, the same mask was used with an offset to produce etch points [Figure 3.7(e)]. The wafer was then oxidised and LPCVD PSG was deposited for protection of the filter against the final deep etch [Figure 3.7(f)]. A deep etch was then performed from the back side of the wafer [Figure 3.7(g)]. The sacrificial oxide and PSG was then dissolved in HF to generate the pores for the filter [Figure 3.7(h)].

iMEDD Inc. [102] fabricated nanopores in silicon based on these sacrificial oxide technologies. Through holes in silicon in the range of 10-100 nm have been reported [102].

J. Tu and M. Ferrari developed microfabricated filters and immunoisolating capsules using a sacrificial layer [134]. They used sacrificial oxide to create nanochannels
Figure 3.6: Fabrication protocol of filter Design I by Chu et al. [152].
Figure 3.7: Fabrication protocol of filter Design II by Chu et al. [152].
in a sandwich structure. The oxides were grown by dry oxidation, and etched at the end of the process. The oxide growth consumed silicon and thus defined the nanochannels in the structure. Since the sacrificial oxide growth was the most important step in the filter fabrication, the oxide growth was controlled very accurately. The fabrication steps of this device have been discussed in chapter 2.

Devoe and Pisano [193] used sacrificial oxide to fabricate surface micromachined piezoelectric accelerometers. The cross-section of this device is shown in Figure 3.8. The fabrication protocols are summarized here. A passivation layer of silicon dioxide and low stress nitride was deposited on bare silicon, followed by 0.5 µm LPCVD phosphorous-doped polysilicon. The conductive polysilicon layer was patterned via reactive ion etching (RIE) to define electrical contacts to the bottom electrode of the accelerometer. Next, a 2.0 µm layer of phosphosilicate glass (PSG) was deposited by LPCVD that served as a sacrificial layer. This was patterned to define regions where the accelerometer structure was later anchored to the substrate. A second layer of 2.0 µm thick phosphorous doped polysilicon was deposited by LPCVD on top of the PSG and patterned by plasma etching to define the mechanical accelerometer structure. This layer also acted as lower electrode for the sensing film. A thin layer of stoichiometric silicon nitride was deposited followed by ZnO deposition. Finally, Pt was sputtered on top of the ZnO. The wafer was annealed and then the Pt, ZnO and Si$_3$N$_4$ layers were patterned in a single ion milling step. The devices were released by passivating the ZnO film with photoresist, immersing in BHF to remove the sacrificial PSG layer, and removing the photoresist by O$_2$ plasma ashing.

Pisano and co-workers have extensively used sacrificial oxide to fabricate different MEMS structure, e.g. silicon based microneedles [77], angular microactuators for
magnetic disk drives [194], polysilicon thin films containing through-pores measuring in the 10-50 nm diameter range [183, 186, 187], and different microfluidic devices for sampling and analysis of biological fluids [195].

Craighead and co-workers used sacrificial oxide to fabricate polycrystalline silicon and silicon nitride resonators for sensitive detection of bound mass of selected chemical and biological species [196]. These were nano-meter scale mass sensors with subattogram sensitivity. Figure 3.9 summarizes the fabrication steps of a resonating device. First a 2 µm thick silicon dioxide sacrificial layer was thermally grown [Figure 3.9(a)]. The device layer consisted of either low stress silicon nitride or amorphous silicon deposited using LPCVD. Photolithography with a gold lift-off was performed to define 10 µm gold octagons used for alignment in the subsequent steps. E-beam lithography (EBL) was used to define the body of the oscillator. Hard etch mask chromium was deposited and lifted off. The device layer was etched down to the sacrificial oxide by plasma etch and the remaining chromium was removed [Figure 3.9(b)]. A bilayer electron beam resist process was used to define the biomolecular
Figure 3.9: Fabrication steps of the resonating device. (a) 2 mm thermal oxidation and LPCVD deposition of the device layer. (b) Lithographically defining the oscillator. (c) Cr/Au deposition and defined via EBL, and lift-off. (d) Sacrificial oxide removal.

Tethering sites. The resist was patterned using EBL and developed with a placement accuracy of 10 nm. After patterning, Au/Cr was deposited and subsequently lifted off [Figure 3.9(c)]. The devices were finally released by etching the sacrificial oxide in HF [Figure 3.9(d)]. Stiction was reported for cantilever devices exceeding 20 µm in length with a thickness ranging between 160 and 250 nm.

Sacrificial silicon dioxide has been used to fabricate small metal cantilevers with integrated silicon tips to achieve high resonant frequency associated with low spring constant for use in atomic force microscopy (AFM) [197]. Figure 3.10 describes the
microfabrication process steps. The starting wafer was a (100)-oriented silicon-on-insulator (SOI) wafer. The thickness of the top silicon layer determined the height of the tip. The oxide layer served as an etch stop as well as sacrificial oxide. A pad oxide was grown followed by LPCVD nitride deposition to serve as a mask layer [Figure 3.10(a)]. The cantilever pattern was transferred into the mask at the bottom side of the wafer using photolithography. Next, a crystallographic deep etch was performed into the silicon substrate using the nitride as a hard mask [Figure 3.10(b)]. A small circular pattern at the top side of the wafer was then defined photolithographically to form a tip. This was aligned with the structure at the back side. This circular pattern was at the end of the cantilever. Mask layers, underlying silicon and buried oxide were then etched [Figure 3.10(c)]. Next, the silicon layer of the cantilever was etched until the oxide layer was reached leaving behind a sacrificial oxide [Figure 3.10(d)]. The silicon tip was then sharpened using crystallographic KOH etching [Figure 3.10(e)]. Metallization was carried out by sputter deposition on the backside of the wafer, and then the cantilever was released by dissolving the sacrificial oxide in an RIE process [Figure 3.10(f)].

An example of micromachined polysilicon actuator is given in reference [182] that uses sacrificial oxide. A dry etch process using HF gas was used to etch the sacrificial oxide and release the structure in order to avoid process induced stiction. LPCVD TEOS oxide was used here as a sacrificial layer.
Figure 3.10: Fabrication steps for microfabrication of Si tip integrated metal cantilevers [197].
3.4.2 Sacrificial Oxide in ICs

Via holes are used in microelectronic industry to connect different metal layers in integrated circuit. Through-wafer via holes make it possible to realize three-dimensional structure by electrically connecting both sides of a wafer and manufacture microelectronic or micromechanical components within the bulk of the wafer, such as three-dimensional inductors [198]. In some applications, it is necessary to cover the via hole with a thin electrically conductive membrane, e.g. a seed layer for electroplating through the wafer via holes or as an anode in microhollow cathode discharge [199, 200]. In these cases, it is important to achieve electrical isolation between the via holes and adjacent structure. It has been suggested that the sacrificial oxide can be used to achieve electrically isolated via structure covered by a thin conductive membrane [201]. The silicon dioxide sacrificial layer is used to cover the via structure during high-temperature steps and is removed at the end of the process after the membrane material has been deposited over the sacrificial oxide. This allows using any membrane material since the membrane material is deposited at the end of the process. A schematic of the process steps is shown in Figure 3.11.

3.5 Summary

Sacrificial oxide is a common method in silicon microfabrication technology. This layer is created in order to release different MEMS structure or in integrated circuits in order to improve the device performance. This layer is etched away later in the process. SiO₂ is used as a sacrificial layer because of its availability in silicon microfabrication processes and etch selectivity against silicon. It has stable and
Figure 3.11: A schematic diagram of the fabrication steps of electrically isolated via hole from the adjacent structure. (a) The wafer is patterned (b) Etching down to the oxide layer (c) Thermal oxidation (d) Final membrane deposition onto the wafer and removal of the oxide layer above membrane by dry etching [201].
reproducible properties, and is compatible with high temperature during polycrystalline silicon deposition. Different varieties of oxides are used as sacrificial oxide. They can be thermally grown or CVD deposited. Thin oxides are usually grown in dry ambient condition (pure oxygen). Wet oxidation (water vapor) is used for thick oxide. Silicon is consumed when oxide is grown. Deal-Grove model explains and predicts the oxidation kinetic. However, this model does not fully explain the oxidation of shaped surface oxidation kinetics in mixed ambient or growth of very thin oxide. Many models have been developed to predict the oxidation behavior for thin oxides, all motivated by improvement over the Deal-Grove model, but none has gained widespread acceptance. Most of the models today use the Deal-Grove model as a beginning equation and then add to or modify it. Silicon dioxides are also deposited using CVD techniques. Deposition usually occurs at lower temperature than growth, and an oxide film can be deposited on top of surfaces where silicon is not available for oxide growth. Silane and oxygen are the common gas sources used for CVD deposition. Tetraethoxysilane (TEOS) can also be used as a source of silicon for oxide deposition. Silicon-on-insulator is also used as a starting material, with the buried oxide as a sacrificial oxide. These fabricated oxides are etched away sometimes during the process. In many cases, the sacrificial oxide is a buried layer, where a small opening allows the etchants to reach the oxide surface as well as allows the etch products to come out of the cavity. Therefore, modelling the etch kinetics of every design needs to be considered differently. The etchants used in sacrificial oxide etching should have high selectivity against the device structure material, typically silicon. Some hydrofluoric acid based solutions are good for sacrificial oxide etching. Wet etching may result in failure due to the permanent stiction of the device
structure to the substrate due to the residue products from wet etching. Various techniques have been developed to alleviate this problem. One is using anhydrous HF and CH$_3$OH in gas phase to achieve dry release of the device structure. Applications of sacrificial oxide include MEMS as well as IC fabrication. A few examples are: micromotors, sensors, actuators and accelerometers as well as immunoisolating biocapsules, drug delivery devices, microneedles and DNA electrophoretic devices. A silicon dioxide sacrificial layer is used in IC fabrication in order to capture defects in the silicon surface before gate oxide growth.
4.1 Introduction

The nDS2 device requires integration of electrodes. By applying voltage across these electrodes the drug dose can be controlled, and by connecting these electrodes to an external pre-programmable circuit, a manipulable drug delivery can be achieved. Therefore, it is important to understand the strategy of electrode positioning, choice of electrode material and choice of substrate material. Microfluidic and Lab-on-Chip systems developed in the last decade present a variety of strategies for the development of electrodes used for the electrokinetic transport of fluids, solutes, biological cells and particles [60, 61, 62]. Many of such devices that utilize electrically driven flow for liquid phase analysis such as capillary electrophoresis (CE) [202, 203], electrophor- matography [204], capillary gel electrophoresis for DNA restriction and digestion and subsequent size-based separation [205, 206, 207], and DNA sequencing [208] have been successfully realized in a microchip. All these microchips have a number of structures fabricated in silicon or glass substrates, micro/nanochannels and strategically placed electrodes to drive fluid through these channels. These integrated structures combine chemical and biological reactions such as sample preparation, separation and
detection on a single microchip device to perform complex assays. This integration increases the speed and information content of analysis and reduces sample volume. Many names have been given to such devices that include bio-chip, lab-on a chip or \(\mu\)TAS (micro- or miniaturized total analysis system). Substrate material, choice of electrode material, electrode placement, electrode fabrication and ease of connectivity with on-board or with an external electronics are important design considerations for such devices. The chapter reviews these design considerations in order to understand the fabrication and placement of electrode in a substrate. It first reviews the choice of substrate materials and reasons for their selection, then it reviews the electrode materials used for such devices, followed by variety of strategies used for realization of these electrodes on chip. The paper ends with concluding remarks.

### 4.2 Selection of Substrate Material

Glass and silicon are the most commonly used substrates for microfluidic devices or lab-on-a-chip systems, primarily because there is a well developed microfabrication technology available. When fluid is driven through microchannels using electrokinetic forces, glass is favored because of its insulating properties. These glasses range from inexpensive glass to high quality quartz \([208, 209]\). Silicon is not best for making such devices because of its semiconducting properties. However, silicon is widely used as substrate because the crystallographic characteristics of silicon can be exploited for the generation of 3-dimensional structures by micromachining and the semiconducting properties of silicon can be used for realization of integrated circuits on-board \([210, 211, 212]\). Further, there are many processes that can be used to create unique features on substrates are only compatible with silicon (e.g. sacrificial oxide) \([213]\).
Silicon can be used as a substrate with an insulating layer that can decouple electrodes from the semiconducting silicon. Stoichiometric silicon nitride (SiN₄) [58], silicon-rich nitride (SiRN) [214] and silicon oxide [215] have been used as insulating materials. The thickness of nitride is usually kept below 0.25 µm to limit built-in stress.

In some applications where flexible disposable systems are required polymers such as polymide, polycarbonate, and polyester are good alternatives [216, 217, 218].

Glass was chosen as a substrate for electrode integration in this research primarily because of its insulating properties and availability of a well known glass microfabrication technology. Further glass can be bonded with silicon using anodic bonding and the thermal expansion coefficient of pyrex 7740 glass is comparable to silicon.

### 4.3 Selection of Electrode Material

A working electrode in an electrochemical system must act as a source or sink of electrons for exchange with molecules in the interfacial region (the solution adjacent to the electrode surface), and must be an electrical conductor. It must also be biocompatible and electrochemically inert over a potential range of interest [219]. Further, it should be possible to fabricate the electrodes in a substrate of choice - the glass substrate in this case.

Thin film electrodes that are used in most of the lab-on-chip systems have electrochemical properties comparable to their bulk counterparts. However, due to their limited thickness, their surfaces can not be mechanically polished. These electrodes are therefore disposable. Mechanical polishing is required if material adsorbs to the surface of a working electrode that degrades the current response.
Nobel metals such as Pt, Ag, Au, Pd and Ir have been used most widely as electrode metals [220]. These require an intermediate layer to improve their adhesion to the substrate, i.e., Si₃N₄ or SiO₂ layer (an insulating layer on silicon). Ti or Ta are the most frequently used adhesion promoters, and are deposited prior to the deposition of noble metals. Typical thicknesses of the adhesion layers and noble metal electrodes layers are of the order of 0.05 μm and 0.15 μm respectively [220]. These electrode metals are deposited using evaporation or sputtering techniques [221].

Carbon has also been used as an electrode; however it is more difficult to adapt carbon to thin film technology. Bulk resistivity, good adhesion to the substrate surface and crystallographic morphology must be controlled to achieve good electrochemical properties. Well adhering carbon thin film with good electrode properties can either be obtained by high temperature pyrolysis [222, 223] or by sputtering process in a DC or RF deposition mode [224, 225].

Mathies et al. [62] have used Pt working and counter electrodes, and an Ag/AgCl reference electrode for capillary electrophoresis chips with integrated electrochemical detection. The Pt electrodes were deposited by RF sputtering (2600 Å thick with 200 Å Ti adhesion layer). Glass was used as a substrate here.

Chromium has also been used as an adhesion promoter in the case of platinum electrodes. Bashir et al. [215] deposited 600 Å thick films of chromium as an adhesion layer, followed by 800 Å RF sputtered platinum. The sheet resistance of the metal electrode was 2.1 Ω/square. After Pt was deposited and patterned, a 600 Å thick SiO₂ insulating layer was deposited using plasma enhanced chemical vapor deposition (PECVD). A window was etched (dry/wet) in this insulating layer to expose active
the Pt electrode surface, while keeping the Cr covered so that it does not interact with the solution flowing through the channels.

These noble metal electrodes are widely used in lab-on-a-chip system, however Pt is used most commonly as an implantable electrode, mostly in the case of neural stimulation [226, 227, 228]. Pt is chosen as an electrode because it is well known to be tolerated by the body and it survives in this corrosive environment [229, 230, 231, 232]. Small platinum coils have also been implanted in the veins of brain for the treatment of intracranial aneurysms because of their high stability, non toxicity and non solubility [230, 233].

Platinum was chosen as the electrode material for nDS2 because it is a good electrical conductor, is nontoxic, is electrochemically stable, has been used as an implantable electrode and can also be integrated with silicon and glass substrates.

4.4 Electrode Fabrication and Placement on Substrate

The electrode metals are usually evaporated or sputtered onto the substrates. The most important process in thin film electrode fabrication is metal patterning. This is achieved by photolithography accompanied by chemical etching (subtractive process) or lift-off (additive process) [234]. A process flow for making thin film electrode by subtractive and additive processes are shown in Figure 4.1. In chemical etching, a metal layer is first deposited. Electrode areas are photolithographically defined and then wet or dry etching is performed to remove the metal from unwanted areas. Photoresist is usually spin-cast, but it can be sprayed-coated on the side-walls and at the bottom of etched grooves to obtain a uniform layer [235]. Lift-off has been used to pattern noble metals for which no etch process is compatible with photoresist
Figure 4.1: Process flow for making thin film electrodes patterns by (a) chemical etching, and (b) lift-off [234].
masking. Examples are Pt, Ir or Pd [58, 220, 234]. In the case of lift-off, electrode areas are photolithographically defined, followed by electrode metal deposition. By dissolving the underlying photoresist in an appropriate solvent, unwanted metallic parts are lifted off, leaving the desired pattern on the surface. A high aspect ratio of photoresist and thin film electrode is required for a successful pattern transfer. Vertical separation must be sufficient to prevent the metal deposition from becoming a continuous film. Pretreatment of photoresist has been suggested to form overhangs in order to achieve better lift-off. This process involves soaking a prebaked photoresist in an aromatic solvent (e.g. chlorobenzene) before or after the exposure to UV-light [236]. This overhang gives discontinuity between the metal layer deposited on the photoresist and that on the underlying layer or substrate, resulting in better defined electrode edge as shown in Figure 4.2. An alternative to this is to use a two-layer resist structure. Different materials are used for these two layers. A difference
in development rate after exposure causes an undercut in the bottom layer that ultimately forms an overhang in the top resist. This is important for small inter-electrode spacing when a short circuit may result because of uncleaned electrode edges. Positive photoresists are used more frequently since they dissolve in acetone easily. Even a carbon film can be patterned using plasma etching [237] or lift-off [223].

In most cases a top passivation layer is deposited on the top of these electrodes. It may consist of Si₃N₄ or SiO₂ deposited at low temperature. The suggested deposition methods are low pressure chemical vapor deposition (LPCVD) or plasma enhanced chemical vapor deposition (PECVD) processes. PECVD is used when high temperature processes cannot be used as in the case of glass substrates (the annealing point of pyrex 7740 glass is 560°C and the softening point is 821°C). The top passivation layer is then photolithographically patterned to expose the active surface of electrodes and the bonding pads.

4.5 Summary

Glass is most widely used as a substrate for microfluidic devices because of its insulating properties. Silicon is used in many cases to exploit its crystallographic properties or when integration of electronics on-board is desired. In case of silicon, an insulating layer is used between conducting electrodes and semiconducting silicon to avoid current leakage. The common choice of material for thin film electrodes is Pt in devices where fluids are electrokinetically driven through the micro or nanochannels and there is a possibility of electrode tissue interaction. Ti has been used as an adhesion promoter in the case of Pt electrodes. Cr has also been used as an adhesion
promoter in some cases, however in those cases the Cr layer was well covered so that it does not interact with the solution. Carbon has also been used as an electrode in some cases. These electrodes are deposited by evaporation or sputtering methods. Lift-off is the most commonly used fabrication technique for electrodes on substrate where metal etching is not possible.
Nanochannel delivery systems or nDS devices were conceptualized to achieve controlled implantable drug delivery. In the series of nDS devices, the first device nDS1 is a passive device. This can be used for continuous drug delivery for a long period of time. An improved version of this device was later designed and named nDS1g. This device has a transparent top surface that allows visual inspection of fluid flow through the nanochannels. Further, a new and unique device was designed and a fabrication process flow was developed to integrate electrodes with the nanochannel system, named nDS2. This is capable of achieving manipulable drug delivery. The integrated electrodes in the nDS2 device allow electrokinetic flow through the nanochannels. The flow rate through the nanochannels can be controlled by controlling the current between the electrodes. The design of this device is a ‘universal’ design and it in fact can be used as an nDS1 device if no voltage is applied. Further, the way this device has been designed, it can be connected to a variety of integrated circuits without changing the design, which opens up a number of possibilities. Some of these are:
1. The device can be connected to a programmable circuit that can be pre-programmed before implantation. An example could be: Deliver 2 µ-gram of therapeutics in 5 minutes after every 10 hours for 3 months. This configuration can be named as nDS2.

2. The device can be connected to a wireless device and implanted in the body. The remote control outside can trigger the delivery. This could be beneficial for pain relief mediation. This configuration can be named nDS3.

3. The device can be connected to a biological sensor through a feedback control circuit. The sensor can sense and can cause the circuit to trigger the release of drug. This configuration can be named as nDS4.

The design and fabrication details of nDS1, nDS1g and nDS2 devices are described in this chapter. The fabrication steps are also listed in Appendices A, B and C, however this chapter provides the details of device fabrication. Devices nDS1 and nDS1g were designed, fabricated and characterized, while nDS2 design were conceptualized and fabrication details were worked out in this research. While describing the fabrication details of these devices, many process recipes are referred to. These recipes are given in detail in section 5.5 at the end of the chapter. The experimental characterization results on nDS1 and nDS1g are also included in this chapter.

5.1 nDS1

5.1.1 Device Design

nDS1 devices are fabricated using two silicon substrates [213]. The silicon substrates are micromachined and then bonded together. The nanochannels are formed
between the two bonded silicon wafers. A schematic three dimensional view of the 
device is shown in Figure 5.1 and Figure 5.2 shows a cross sectional view of the device.
The overall device dimensions were chosen to be 4 mm × 3 mm × 1 mm. The 1 mm
thickness comes from bonding two 0.5 mm thick silicon wafers, while the other dimen-
sions were kept according to the packaging requirements (discussed in section 5.4).
The top substrate has an entry port that is etched all the way through the wafer, and
aligns with the entry flow chamber on the bottom substrate. The entry port opening
at the bottom side of the wafer, which is in contact with the entry flow chamber, is
200 µm × 3mm. The bottom substrate contains the rest of the features. A top view
of the bottom substrate is drawn in Figure 5.3. Figure 5.4 shows the key dimensions
of different features in the bottom substrate. The bottom substrate includes anchor
regions along the edges (500 µm) and anchor points (6 µm) at many places between
the nanochannels, where the top substrate is bonded to the bottom substrate. The
anchor regions and anchor points keep the nanochannels from closing from stiction
or due to mechanical forces such as bending. Interdigitated input and output fingers
(each 6 µm wide)open into the edges of the entry and exit flow chambers (each 200
µm wide), respectively, with the nanochannels connecting between them. The drug
being delivered comes to the entry flow chamber in the bottom substrate through
the entry port in the top substrate, passes to the input fingers, diffuses through the
nanochannels to the output fingers and then to the exit flow chamber. The exit port
that is aligned to the exit flow chamber in the bottom substrate provides a means
for the drug to leave the device. The spacer region at the tip of the fingers closes
the fingers so that all drugs must flow through the nanochannels. The interdigitated
design of several fingers with many nanochannels connecting them increases the drug
flux. The nanochannel height defines the delivery rate limit. The effective porosity of the device depends upon the number, length, and width of the nanochannels, the width and periodicity of the anchor points, and the channel height. The flow rate for different molecules through different nanochannel sizes can be established and nanochannel size can be optimized for a desired flow of a particular molecule.

The concept of nanochannel fabrication is based upon selectively growing oxide while consuming silicon during growth, and then etching the oxide layer (called sacrificial oxide, discussed in detail in chapter 3). The nanochannel depth is defined as:

\[ d = 0.46 \times t_{\text{ox}} \]  

(5.1)

Dry oxidation with a well-controlled temperature and time allows precise control of the nanochannel’s height. The fabrication details and characterization results are described in the next three sections.
Figure 5.2: A cross-sectional view of nDS1 device.

Figure 5.3: A top view of the bottom substrate of nDS1 device.
Figure 5.4: A top view of the bottom substrate of nDS1 device showing the key dimensions.
5.1.2 Device Fabrication

The silicon wafers used for nDS1 fabrication had the following specifications:

- Double side polished with two SEMI-standard flats
- Type(Dopant): P-type (boron doped)
- Orientation: $<100>$ single crystal
- Diameter: 4”
- Thickness: 500-550 μm
- Resistivity: 1-10 Ω-cm

The overall fabrication process can be divided into three major steps: (1) Bottom substrate processing, (2) Top substrate processing and (3) Wafer bonding.

**Bottom Substrate Processing**

The silicon wafers were cleaned by dipping for 10 minutes in piranha bath (recipe C3). The first step was the fabrication of the entry flow chamber, exit flow chamber, input fingers and output fingers. 0.5 μm thick oxide was used as a mask layer to etch these features into the silicon substrate. This oxide was grown by wet oxidation at 1100°C for 38 minutes.

The oxide thickness measured by ellipsometry was 0.48 μm. Precise control of this oxide thickness is not required, since it is used only as a mask layer. However it is important to know the thickness, as this oxide needs to be etched in the next step.

The entry flow chamber, exit flow chamber, input fingers and output fingers were photolithographically defined (recipe P1) using mask 1. A schematic diagram of mask 1 showing all the dimensions is shown in Figure 5.5. The white regions in the mask
represents these features. It is important to note that each finger width is 6 µm, and
the region between the two fingers, where the nanochannels would be placed later,
is 5 µm. The mask oxide was etched by RIE (reactive ion etching) in the defined
areas using a He + CHF₃ + CF₄ plasma (recipe R1). The wafers were etched for 1
minute to achieve etch through the oxide mask. Photoresist was then stripped off in
piranha (recipe C3) by dipping the wafers for 10 minutes. The step in the oxide mask
measured by profilometry was 0.49-0.50 µm. The above mentioned features (entry
flow chamber, exit flow chamber, input fingers and output fingers) were then etched
into the silicon using 45wt% KOH:H₂O solution heated at 70°C (recipe Chem1). The
characterized etch rate under these conditions was 0.47 µm/min. The wafers were
dipped in the prepared KOH solution for 4 minutes 15 seconds to achieve 2 µm deep
features in silicon. The mask oxide was then stripped in 7:1 BHF solution (recipe
Chem2) by dipping the wafers in the bath for 18 minutes before proceeding to the
next step. Other HF solutions can also be used for stripping this oxide, since the
HF etch of oxide is selective against etching silicon. The etch depth was verified by
profilometry and was found to be 1.95 to 2.0 µm. This 2 µm deep etch can also be
achieved by RIE. RIE will give vertical side walls. A scanning electron microscope
(SEM) micrograph of the end of an etched finger is shown in Figure 5.6. The image
was taken at ×6k magnification. A sloped side wall can be seen in this micrograph.
Silicon etching in KOH depends upon the orientation of the crystal. It etches faster
in the [100] direction than in the [111] direction, because the (111) planes are most
closely packed and etch more slowly [157]. The silicon wafer chosen here has < 100 >
orientation, and therefore an etch angle of 54.7° from the surface is achieved because
the {111} planes intersect the {100} surface at a 54.7° angle. A schematic diagram of
three different cross-sections of the bottom substrate at this step is shown in Figure 5.7.

Nanochannels were defined and fabricated in the next step. The sacrificial oxide for the nanochannels was grown thermally in a dry oxygen ambient with $\pm 10\%$ uniformity across the wafers as characterized in the University of California (UC) Berkeley cleanroom. The most common mask against such a local oxidation process is silicon nitride, which was used here. A pad oxide was first grown thermally by dry oxidation at 1000°C for 28 minutes.

The oxide thickness measured by ellipsometry was 23 nm. The pad oxide reduces the stress between the silicon and silicon nitride layers and therefore enhances the
Figure 5.6: A micrograph showing etched fingers and sloped walls that appears because of crystallographic selective nature of KOH etching. The image was taken at ×6k magnification.

Figure 5.7: A cross-sectional view of the bottom substrate after mask 1 process at different cross-sections.
Figure 5.8: A schematic diagram of mask 2 overlayed on mask 1 for the bottom substrate fabrication of nDS1. The blue regions were defined by mask 1. White regions are the features on mask 2.

adhesion of nitride to silicon. A low stress LPCVD (low pressure chemical vapor deposition) nitride was then deposited using dichlorosilane (DCS) and NH$_3$ (100DCS/25NH$_3$/140mTorr/835°C) (recipe D1). A low stress nitride is preferred as a mask for deep silicon etch (using KOH) to avoid breaking the wafers. The deposited nitride thickness was $\sim$100 nm. To measure the nitride thickness, a dummy silicon wafer was kept in the LPCVD furnace along with the device wafers, and the nitride thickness was measured using a NanoSpec® (NANOMetrics, Inc. [238]).

The nanochannel regions were then defined photolithographically (recipe P2) using mask 2. A different photolithography recipe was used here because this process was
done at UC Berkeley. Recipe P1 would have also worked for this step. A schematic
diagram of mask 2 overlayed to mask 1 is shown in Figure 5.8. The dark blue region
is mask 1, and white regions are the nanochannel regions in mask 2. The region
between the two nanochannels in the bottom substrate is an anchor point where
the top substrate bonds to the bottom substrate. There are seven nanochannels
per ridge (in between the two fingers). Each nanochannel is 166 µm wide and is
separated by an anchor point of width 6 µm. The nanochannel’s lengths are 6 µm
and align with the 5 µm ridge defined between two fingers by mask 1. There was 1
µm alignment tolerance (0.5 µm each side) included in this direction in mask 2. This
is very important in order to connect the input fingers to the output fingers through
the nanochannels. The nitride layer was etched by RIE in the defined areas using He
+ SF₆ plasma (recipe R2). This etch was controlled so that the underlying pad oxide
is not completely etched, so that the underlying silicon is not exposed. This is very
important in order to achieve good control of the nanochannel height. The wafers
were etched for approximately 1 minute to remove the 100 nm nitride. An automatic
endpoint detection technique mentioned in recipe R2 was used to achieve this, rather
than a simple timed etch. The etch depth was verified by profilometry. The etched
regions were also verified by NanoSpec® for the thickness of the remaining pad
oxide, which was found to be about 100-150 Å on different wafers. Subsequently, the
underlying pad oxide was selectively (against silicon) etched by dipping the wafers in
25:1 BHF (recipe Chem2) for 2 minutes. The predicted etch rate of dry oxide in 25:1
BHF is 95 Å/min. The overetch was included to ensure that all oxide was etched
away and that the silicon surface was exposed. A schematic of the cross-section of
the device after the pad oxide etch is shown in Figure 5.9. Once the silicon surface
was exposed in the nanochannel regions, a thermal oxide was grown to the desired thickness. This oxide growth consumes silicon and thus defines the nanochannels size as described by equation 5.1. Four nanochannels heights were targeted. These were 20 nm, 40 nm, 60 nm and 100 nm. The corresponding oxide thickness, and time and temperature for these oxide growths in dry oxygen ambient are summarized in Table 5.1. The purpose was to demonstrate the fabrication of nanochannels and therefore the time and temperature for dry oxide growth was determined based upon the linear parabolic model [149], and were not optimized for the specific apparatus used. The oxide growth chart for the linear parabolic model for dry oxidation of (100) silicon is shown in Figure 5.10. Table 5.1 also shows the measured oxide thickness values under the respective conditions. The growth conditions can be optimized to achieve more accurate oxide thickness. A schematic diagram of three different cross-sections of the device after sacrificial oxide growth is shown in Figure 5.11.

The final photolithography step for the bottom wafer processing was for the exit port that was deep etched from the bottom side of this wafer. The exit port aligns

<table>
<thead>
<tr>
<th>Targeted nanochannel size (nm)</th>
<th>Corresponding oxide thickness (Å)</th>
<th>Oxide growth temperature (°C)</th>
<th>Oxide growth time (hr:min)</th>
<th>Measured oxide thickness (Å)</th>
<th>Corresponding nanochannel size (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>435</td>
<td>950</td>
<td>2:17</td>
<td>460</td>
<td>21</td>
</tr>
<tr>
<td>40</td>
<td>870</td>
<td>1050</td>
<td>1:12</td>
<td>900</td>
<td>41</td>
</tr>
<tr>
<td>60</td>
<td>1304</td>
<td>1050</td>
<td>2:30</td>
<td>1560</td>
<td>71</td>
</tr>
<tr>
<td>100</td>
<td>2174</td>
<td>1050</td>
<td>5:20</td>
<td>2350</td>
<td>108</td>
</tr>
</tbody>
</table>

Table 5.1: Oxide growth table for nDS1.
to the exit flow chamber. Another layer of low stress LPCVD nitride was deposited (recipe D1). The deposited nitride thickness was \( \sim 220 \text{ nm} \). This nitride was thicker so as to protect the oxide in the nanochannel regions from being etched during the subsequent deep silicon etch process. Backside photolithography (recipe P1, using mask 3) was then performed to define the region of the exit port. A schematic of this mask with dimensions is shown in Figure 5.12. The white region in the figure is the exit port region. The dimensions of the clear region of the mask was made larger considering the crystallographically selective nature of the KOH etch and 500 \( \mu \text{m} \) thick wafer, so that it matches with the 200 \( \mu \text{m} \times 3 \text{ mm} \) exit flow chamber on the other side of the wafer. The mask nitride and underlying pad oxide were etched in the defined area using an He + SF\(_6\) plasma (recipe R2). The total thickness of the
Figure 5.10: Oxide growth chart under dry oxidation conditions for (100) silicon based upon the linear-parabolic model after [149, 150].
nitride mask was (100 nm + 220 nm =) 320 nm, deposited in two earlier steps. A tightly controlled etch of nitride is not critical here because the silicon underneath will be etched all the way through in the subsequent step. Thus this etch was performed until the silicon surface was exposed. This was a timed etch for 3 minutes and 20 seconds (including overetch). A deep etch was then performed in 45wt% KOH:H₂O solution heated at 80°C (recipe Chem1). The silicon etch rate at this temperature was 0.65 µm/min. The predicted etch time was ~ 13 hours. The wafers were taken out of the bath after 6 hours, cleaned in QDR (recipe C1) and SRD (recipe C2) and rotated by 180° in the cassette to help achieve uniform etching. The wafers were dipped in KOH bath again for the remaining etch period. However, the end point of the deep etch was observed by looking at the wafers. Deep etch all the way through.
Figure 5.12: A schematic diagram of mask 3 for the bottom substrate fabrication of nDS1.
the wafers was visible to the naked eye. A schematic diagram of the device after this step is shown in Figure 5.13. The mask layer nitride, underlying pad oxide, and the sacrificial oxide in nanochannel region were stripped afterwards in 49% HF solution (recipe Chem2). Three cross-sectional views of the bottom substrate after complete fabrication are shown in Figure 5.14.

**Top Substrate Fabrication**

2 µm deep dicing alleys were first etched on the top surface of the top silicon substrate. A 0.5 µm thick oxide mask was used for this step. The oxide was grown in H₂O ambient as described earlier. The following process sequence was followed to create this:

1. Dicing alley regions were photolithographically defined (recipe P1),

2. The oxide mask was etched by RIE in a He + CHF₃ + CF₄ plasma (recipe R1) for 1 minute,
3. The silicon was etched in 45 wt% KOH heated at 70°C (recipe Chem1) for 2 minutes, and

4. The oxide mask was stripped in 7:1 BHF (recipe Chem2) by dipping the wafers in the bath for 18 minutes.

The dicing saw would be aligned to these alleys while dicing the completed devices at the end of the process.

The entry port was fabricated in the top substrate using a deep etch completely through the silicon wafer. Silicon nitride was used as the mask for this deep etch. A pad oxide of 22 nm thickness was first grown by dry thermal oxidation at 1000°C for 28 minutes, and then low stress LPCVD nitride (recipe D1) of thickness ~ 320 nm was deposited. The entry port region was photolithographically defined (recipe P1) in the
Figure 5.15: A cross-sectional view of the top substrate after deep silicon etch.

Figure 5.16: A cross-sectional view of the top substrate after entry port fabrication.

mask nitride using mask 3. The defined regions in the mask nitride and the underlying pad oxide were etched using a He + SF$_6$ plasma (recipe R2). This was a timed etch for 3 minutes and 20 seconds (including overetch) to expose the underlying silicon surface. The deep etch in silicon was performed in 45wt% KOH:H$_2$O solution heated at 80°C (recipe Chem1) as described for the bottom substrate deep etch process. A cross-section of the top substrate at this step is shown in Figure 5.15. The mask layer nitride and pad oxide were stripped afterwards in 49% HF (recipe Chem3) as shown in Figure 5.16.
Wafer Bonding

A silicon-silicon fusion bonding technique was used to bond the top and bottom substrates together. Both wafers were cleaned in a piranha bath (recipe C3) to remove any organic contamination. The wafers were then dipped in 25:1 HF solution for 10 minutes to ensure there was no residual nitride or oxide left on the silicon surface from earlier processes. The wafers were again dipped into a fresh piranha solution to grow a new layer of native oxide. Alignment of the top and bottom substrates were first attempted using a Karl-Suss mask aligner/wafer bonder, but the entry port and exit ports that are etch all the way through the wafers interfered with the vacuum used to hold the wafers. To overcome this problem, dicing tape was placed on the wafer to cover the holes in the wafer, while keeping small openings in the dicing tape to expose the alignment marks. A pre-bonding was achieved on the Karl-Suss aligner/bonder, but the pre-bonded wafers were stuck to the bonding chuck after the pre-bonding. While taking the pre-bonded wafers out of the chuck, the pre-bonding was lost. Many attempts were made, but this happened every time. Then manual alignment under a microscope was attempted. The two wafers were aligned under microscope at a 100x microscope objective so that the entry port in the top wafer aligns to the entry flow chamber in the bottom wafer. After the alignment, the pre-bonding was achieved by applying a slight pressure with fingers on the wafers starting from the center and dragging fingers away from the center while maintaining the applied pressure. A good pre-bonding was achieved. The wafers could not be separated without pushing tweezers in between the wafers. The wafers were annealed in nitrogen ambient at 1050°C for 4 hours to strengthen the bond. A schematic cross-section of bonded wafers is shown in Figure 5.17. There were 19 × 16 devices separated from each
other by a 250 $\mu$m dicing alley on each wafer. The bonded wafers were then diced into separate devices.

![Figure 5.17: A cross-sectional view of the bonded device.](image)

### 5.1.3 Device Characterization

Figure 5.18 shows an IR (infrared) image of the bonded wafers, illustrating entry port, exit port and the features in between the two. It is not possible to resolve all the features at this magnification; however these features include input finger, output finger, nanochannels and the anchor points. Figure 5.19 is an SEM image of the top surface of the bottom substrate, showing the fingers, the nanochannel regions and the spacer region. The nanochannels are between two fingers (input finger and output finger), and each finger is blocked by a spacer region at the end. Another SEM
Figure 5.18: Infra-Red (IR) image of a bonded nDS1 device wafer. This is an undiced wafer that has many devices on it. One device and its features are marked.

micrograph in Figure 5.20 shows anchor points, and nanochannel and finger regions. The SEM micrograph in Figure 5.21 shows anchor points at a higher magnification.

AFM (Atomic force microscope) images were taken to demonstrate the fabricated structure in the bottom silicon substrate and also to measure the step heights between the anchor point and the nanochannel region. These step heights define the nanoscale dimension of the nanochannel after bonding with the top substrate. Figure 5.22 shows a three-dimensional image of a fabricated device. It shows input/output fingers, anchor points and nanochannel regions. Figure 5.23 shows a three-dimensional image of the step height for a nominally 100 nm channel. The AFM measurement shows
Figure 5.19: Micrograph showing fingers, nanochannel regions and spacer region in the bottom substrate. The image was taken at ×1k magnification.

Figure 5.20: Micrograph showing fingers, nanochannel regions and anchor points in the bottom substrate. The image was taken at ×1.2k magnification.
a 108 nm step height. Figure 5.24 and 5.25 shows a step height measurement and a three-dimensional image of the step height for a nominally 60 nm channel. The AFM measurement shows a 70 nm step height. This device was targeted for 60 nm, but a 70 nm channel height was achieved because the time and temperature for oxide growth were not optimized. Once again, a very controlled thickness can be achieved with an optimized time and temperature. Figure 5.26 and 5.27 show a step height measurement and a three-dimensional image of the step height for a nominally 20 nm channel. The AFM measurement shows an 18 nm step height.

5.1.4 Glucose and Interferon-alpha Diffusion

Diffusion characteristics of molecules through the completely fabricated nanochannel delivery systems were investigated using glucose as the model molecule [239]. The diffusion chamber was mounted on the tray of a plate shaker. The experiments were
Figure 5.22: AFM image showing three-dimensional view of a fabricated nDS1 bottom substrate.

performed by applying 11 ml of a phosphate buffered saline (PBS) solution, containing 0.02% of sodium azide, to the basolateral side of the diffusion chamber, and 0.22 ml of glucose solution (330 mg/mL) on the top of it. An 8-mm diameter stainless steel sphere was placed into the basolateral side of the well and the plates were shaken at ~ 120 rpm in order to make the solution homogeneous throughout the diffusion experiments. Samples were withdrawn at different time intervals and analyzed for the presence of glucose using Glucose-SL assay (Diagnostic Chemicals Limited, Connecticut, USA). Figure 5.28 shows the experimental set up.

Figure 5.29 shows the release profile of glucose through a 70 nm channel device over a 5 day period and Figure 5.30 shows the release profile of glucose through a 100 nm channel device over a 15 day period. The figures include total glucose released and
Figure 5.23: AFM image showing a three-dimensional view of a fabricated 108 nm step in the bottom substrate of a nDS1 device.
Figure 5.24: Step height measurement of a 70 nm step height using AFM.

Figure 5.25: AFM image showing three-dimensional view of a fabricated 70 nm step in the bottom substrate of nDS1 device.
Figure 5.26: Step height measurement of a nominally 20 nm step height using AFM. The measurement shows the step height to be 18 nm.
Figure 5.27: AFM image showing a three-dimensional view of a nominally 20 nm step in the bottom substrate of a nDS1 device. Measurement shows the step height to be 18 nm.
Figure 5.28: Costar transwell plate setup. Digital photograph demonstrating one well of the Costar 6-well plate, containing a diffusion chamber fitted with a 100 nm nDS device [239].
glucose released per day over the period investigated. A zero order release profile was achieved within the experimental error (over three devices), allowing for maintenance of drug delivery through the nanochannels in a therapeutic window.

Release of Interferon-alpha (IFN-α) was studied through a 100 nm channel device [239]. IFN-α is commonly used in the treatment of malignant melanoma, both as an adjuvant to surgical resection and in the setting of advanced disease. nDS1 may significantly improve the administration of IFN-α. An experimental setup similar to the glucose diffusion experiment was designed for IFN-α release through 100 nm channels. The diffusion chambers were mounted on the tray of a plate shaker. The chambers were filled with 10 mL of a phosphate buffered saline (PBS) solution containing 0.2% sodium azide on the basolateral side, and 0.22 mL of interferon solution (19 g/mL, or $5.94 \times 10^{11} \mu M$) on the donor side. An 8-mm diameter sphere was
placed into the basolateral side of the well as described earlier. Plates were shaken at 120 rpm. Samples were withdrawn at different time intervals and analyzed for the presence of interferon using a commercially available ELISA kit (R & D Systems, Inc., Minneapolis, MN). Figure 5.31 shows IFN-α release for 7 days through the 100 nm nDS1 device. The functional activity of diffused IFN-α through the nanopores of nDS1 device was verified (Figure 5.32) as discussed in reference [239].

5.2 nDS1g

nDS1g is a second generation of the nDS1 device. The top substrate in nDS1g is glass (glass type: Pyrex 7740). The top glass substrate offers the following advantages over a silicon top substrate:
Figure 5.31: IFN-α release profile through a 100 nm channel over a period of 7 days [239].
Figure 5.32: IFN-α diffused through 100 nDS1 showing functional activity [239].
1. Pyrex 7740 and silicon have similar thermal expansion coefficients and therefore a good bond can be achieved between the two. Glass-silicon anodic bonding is stronger than silicon-silicon fusion bonding. This gives a higher yield.

2. The transparent glass top substrate allows visual inspection of fluid flow through the nanochannels. This may facilitate laboratory research on flow characteristics through the nanochannels.

Device Fabrication

The glass wafer had the following specifications:

Glass type: Pyrex 7740
Double side polished with two SEMI-standard flats
Diameter: 100 mm ± 0.5 mm
Thickness: 0.525 mm ± 0.025 mm
Surface finish: 4-8 Å

An exit port was ultrasonically drilled through the glass wafer (done at Sensorprep Services, Inc. [240]). The bottom substrate fabrication was the same as for the nDS1 bottom substrate. Figure 5.33 shows a schematic of the nDS1g device.

Wafer Bonding

To bond the silicon bottom substrate and glass top substrate together, the two wafers were aligned under a microscope so that the entry port in the top wafer aligned to the entry flow chamber in the bottom wafer, and then clamped together. The two wafers were bonded under the anodic bonding conditions given in recipe B1.
5.2.1 Device Characterization

Figure 5.34 shows a photo micrograph of a bonded nDS1g device. Anchor points, input/output fingers, and nanochannels can be seen through the glass top substrate. In order to see the wetting through the nanochannels Iso-propyl-alcohol (IPA) was flowed through the 100 nm channel and the fluid front was photographed (Figure 5.35).

5.3 nDS2

The nDS2 device was conceptualized to achieve a manipulable release profile of drug delivery. An electrode was integrated into this device. An applied current across the electrodes controls the electrokinetic flow of molecules of interest through this device. These electrodes can be connected to an external circuit that can be a pre-programmable circuit, a wireless circuit or a feedback control circuit for a biological
Figure 5.34: A picture of a fabricated nDS1g device showing anchor points, input/output fingers, and nanochannels. These features can be seen through the glass top substrate.

Figure 5.35: A fluid front showing Iso-propyl-alcohol (IPA) flow through a nDS1g device. The color shadow in the nanochannels is the moving fluid front.
sensor. The design and fabrication details of this device are discussed in the next two sections.

5.3.1 Device Design

A schematic diagram of an nDS2 device is shown in Figure 5.36. The devices are made up of a silicon substrate and a glass substrate. The bottom substrate is a silicon substrate that has many similar features to the nDS1 device, while the top substrate is a glass substrate. In addition to the advantages mentioned in section 5.2 of having a top glass substrate, the insulating properties of the glass substrate is an added advantage in nDS2. Electrodes are integrated in the top glass substrate, and the insulating properties of glass prevents any short-circuit between the two electrodes. Both of the substrates are micromachined and then bonded together. As with nDS1 and nDS1g the nanochannels exist between the two bonded wafer surfaces. A top view of the device is shown in Figure 5.37. Locations of three cross sections are marked as A, B and C in this figure. Cross-sectional views at these locations are shown in Figure 5.38 and other figures in this sections of the dissertation. Cross-section A shows the internal features including entry/exit flow chambers, input/output fingers, nanochannels, anchor points, anchor regions and spacer regions. Cross-section B shows the glass seal around the electrodes to prevent fluid leaking from the entry/exit flow chambers to the contact pad regions. Cross-section C shows the bonding pad regions. The top substrate has electrode contact chambers that are fabricated to expose the electrodes to the fluid. These chambers are aligned with the entry and exit flow chambers on the bottom silicon substrate. The top glass substrate also has an entry port that is etched all the way through the
wafer, and aligns with one of the electrode contact chambers. The bottom substrate contains the rest of the features. This includes anchor regions along the edges and anchor points at many places between the nanochannels, where the top substrate is bonded to the bottom substrate. Interdigitated input and output fingers open into the edges of the entry and exit flow chambers, respectively, with the nanochannels connecting between them. The drug being delivered comes to the entry flow chamber in the bottom substrate through the entry port in the top substrate, passes to the input fingers, driven through the nanochannels to the output fingers and then to the exit flow chamber. The exit port that is aligned to the exit flow chamber in the bottom substrate provides a means for the drug to leave the device. The spacer region at the tip of the fingers closes the fingers so that all drugs must flow through the nanochannels. The interdigitated design of several fingers with many nanochannels connecting them increases the drug flux. The nanochannel height and applied current between the electrodes define the delivery rate. Dry oxidation with a well-controlled temperature and time is used to achieve precise control of the nanochannel’s height similar to the case of nDS1. The overall device dimensions were chosen to be 5.5 mm × 3 mm × 1 mm. The 3 mm dimension was kept the same as nDS1 to fit in the titanium capsule described in section 5.4, but the other dimension was increased from 4 mm to 5.5 mm to incorporate the bonding pad areas. The 1 mm height is determined by the thickness of the two bonded wafers. The fabrication details of the device are described next.
Figure 5.36: A schematic 3-dimensional view of nDS2 device.

Figure 5.37: A top view of nDS2 device. There are three cross-section locations marked as A, B and C in this figure. Cross-sectional views at these locations are shown in other figures in this section of the dissertation.
Figure 5.38: Cross-sectional views of the nDS2 device at the locations defined in Figure 5.37.
5.3.2 Device Fabrication

The fabrication steps are divided into three sections: (1) Bottom substrate processing, (2) Top substrate processing and (3) Wafer bonding.

**Bottom Substrate Processing**

Most of the nDS2 bottom substrate fabrication steps were similar to those for the nDS1 bottom substrate fabrication. A few changes were made to accommodate the new device design and process availability. These have been outlined while describing the fabrication details.

The silicon wafers were cleaned by dipping the wafers for 10 minutes in piranha bath (recipe C3). The first step was the fabrication of the entry flow chamber, exit flow chamber, input fingers and output fingers. A 0.5 µm thick oxide layer was used as a mask layer. This oxide was grown by wet oxidation at 1100°C for 38 minutes.

The oxide thickness measured by ellipsometry was 0.48 µm. Precise control of this oxide thickness is not required for the same reason mentioned in the case of nDS1.

The entry flow chamber, exit flow chamber, input fingers and output fingers were photolithographically defined (recipe P1) using mask 1. The schematic of mask 1 is shown in Figure 5.39. This mask is similar to mask 1 of nDS1 except for the dimensions. Some of these modifications were made from the experience of using the nDS1 device, while other were to accommodate the new design. The anchor regions along the edges were made 750 µm. This is 250 µm more than for the nDS1 device. This dimension was increased to provide more space for putting glue while packaging the device. The spacer layer was decreased from 250 µm to 150 µm. This features serves as a blockage wall for the fluid from leaking from the fingers to the
entry/exit flow chambers, and therefore 150 \( \mu m \) wide spacer region should serve the purpose. The finger width was increased from 6 \( \mu m \) to 8 \( \mu m \) to improve wetting. The nanochannel length was kept 5 \( \mu m \), same as in the case of nDS1. This is one of the most critical dimensions of the device (The other critical dimension is the height of the nanochannel). The entry/exit flow chambers were made 325 \( \mu m \) wide to match with the electrode contact chambers in the top substrate that had to be at least this wide in order to achieve ultrasonic drilling to make the entry port. The bonding pad regions (1 mm) and sealing area (~0.8 mm) are shown together in the figure.
Following the photolithography, the mask oxide was etched in the defined areas by RIE using a He + CHF$_3$ + CF$_4$ plasma (recipe R1). The wafers were etched for 1 minute to achieve a 0.48 µm deep etch in the oxide mask. Photoresist was later stripped in piranha (recipe C3) by dipping the wafers for 10 minutes. The step in the oxide mask measured by profilometry was 0.49-0.50 µm. The above mentioned features (entry flow chamber, exit flow chamber, input fingers and output fingers) were then etched into the silicon using 45wt% KOH:H$_2$O solution heated at 70°C (recipe Chem1). The wafers were dipped in the prepared KOH solution for 4 minutes 15 seconds to achieve 2 µm deep features in the silicon. The mask oxide was then stripped in 7:1 BHF solution (recipe Chem2) by dipping the wafers in the bath for 18 minutes before proceeding to the next step. The etch depth in silicon was verified by profilometry and it was found to be 1.95-2.0 µm.

Nanochannels were defined and fabricated in the next step. The sacrificial oxide for the nanochannels was grown thermally in a dry oxygen ambient. A stoichiometric silicon nitride mask was used for this local oxidation process. A pad oxide of 62 nm thickness was first grown thermally by dry oxidation. A thicker pad oxide than for nDS1 was used here because the silicon nitride was etched later in the process using a plasma reactor that did not have automatic end point detection, requiring a timed etch. Therefore, a thick pad oxide was needed to avoid etching into the underlying silicon. The pad oxide was grown thermally by dry oxidation at 950°C for 3 hours 20 minutes.

The oxide thickness measured by ellipsometry was 62-65 nm. A stoichiometric nitride (recipe D2) on top of the pad oxide was deposited as a mask. A stoichiometric nitride was used here, not a low stress LPCVD nitride, because a low stress nitride
was not needed, as the subsequent deep silicon etch is performed using plasma etch in place of the KOH etch. However, a low stress nitride could also be used for this process. The deposited nitride thickness was $\sim 200$ nm. To measure the nitride thickness, a dummy silicon wafer was kept in the LPCVD furnace along with the device wafers, and the nitride thickness was measured by NanoSpec®.

Next, the nanochannel regions were photolithographically defined (recipe P1) using mask 2. The schematic view of this mask looks like mask 2 of nDS1 (Figure 5.8), but the nanochannel regions are 54 $\mu$m wide and are separated by an anchor point of width 8 $\mu$m. Comparing to the nDS1 device, more anchor points were presented and the nanochannel widths were made shorter to provide more area for bonding with the top substrate. The length of the nanochannel area was made 7 $\mu$m. This included 2 $\mu$m of alignment tolerance (actual nanochannel length is 5 $\mu$m) to facilitate mask 2 alignment with mask 1. This is a critical feature and must connect the entry and exit fingers. The nitride layer was etched in the defined areas by RIE using He + SF$_6$ plasma (recipe R3). This etch was timed so that the underlying pad oxide did not get completely etched to prevent exposing the underlying silicon surface. This was very important in order to achieve good control of the nanochannel height. The etch rate of stoichiometric nitride was 200 nm/minute. The wafers were etched for 1 minutes 15 seconds (included 15 seconds of over etch time) to etch 200 nm nitride. The thickness of underlying pad oxide was measured by NanoSpec® in the big rectangle in the alignment marks region. This was 400-500 Å. Subsequently, the remaining pad oxide was selectively (against silicon) etched by dipping the wafers in 7:1 BHF (recipe Chem2) for 45 seconds. The characterized etch rate of dry oxide in 7:1 BHF was 750 Å/min. The over etch was included to ensure that all oxide was
Table 5.2: Oxide growth table for nDS2. The oxide thickness uniformity across the wafer was ±15%.

etched away and that the silicon surface was exposed. Once the silicon surface was exposed in the nanochannel regions, a thermal oxide was grown to the desired thickness according to equation 5.1. This oxide growth consumes silicon and thus defines the nanochannels size. Three nanochannels heights were targeted. These were 20 nm, 60 nm and 100 nm. The corresponding oxide thickness, time and temperature for these oxide growths in dry atmospheric condition, and measured oxide thickness on a characterization wafer are summarized in Table 5.2.

Rest of the bottom substrate fabrication is in progress. It is described next how to achieve this:

The final photolithography step for the bottom wafer processing is for the exit port and contact pad region that is etched from the bottom side of this wafer by deep reactive ion etching (DRIE). A schematic of the mask is show in Figure 5.40. The exit port aligns to the exit flow chamber and contact pad region exposes the area of the electrode contact pads. The mask layer nitride, underlying pad oxide, and the
sacrificial oxide in nanochannel region are stripped afterwards in 49% HF solution. This completes the fabrication of the bottom substrate.

**Top Substrate Processing**

The top substrate in nDS2 is a glass substrate (pyrex 7740) on which the electrodes, electrode contact chambers and entry port are fabricated.

The first feature that was fabricated in glass was the wells for the electrodes. Wells for the electrodes were etched into the glass wafers deeper than the thickness
of the metal electrode. Oxide was deposited after metal deposition to bury the metal electrode underneath the oxide. This was done in order to achieve good bonding between silicon and glass, and to avoid metal electrode/silicon contact that may cause a shunt current path between the two electrodes. The deposited oxide also blocks any open path between the entry flow/exit flow chambers and the contact pad regions (cross-section B in Figure 5.37), and consequently prevents any leakage of fluid.

To fabricate this structure, the glass wafers were first cleaned in piranha solution (recipe C3). The well regions were photolithographically defined (recipe P1) using mask 1. A schematic of mask 1 is shown in Figure 5.41. The key dimensions are show in this figure. The mask is extended by 50 $\mu$m into the dicing alley region (black region in the figure). The reason for this extension is explained later when discussing the mask 2 design. These regions were etched by RIE in a He + CHF$_3$ + CF$_4$ plasma (recipe R4). Please note that this plasma etch recipe is different than the oxide etch recipe used earlier. The applied power and the chemical composition of the gases are different. This recipe was used to improve the glass/photoresistivity selectivity. This recipe etches SP 1813 photoresist at a rate of 0.2 $\mu$m/min, while the characterized glass etch rate is $\sim 1100$ Å/min. Recipe P1 coats photoresist of thickness $\sim 1.3$ $\mu$m.

Therefore, etching glass with recipe R4 for 4 minute 15 seconds should give an etch depth of $\sim 0.5$ $\mu$m in glass and should etch away $\sim 0.85$ $\mu$m of photoresist. The glass wafers were etched for 4 minutes 15 seconds, and then the photoresist was stripped in a piranha solution (recipe C3). The etch depth measured using AFM was 0.45-0.50 $\mu$m. AFM was used to measure the etch depth because the profilometer was out of order. Otherwise a profilometer could be used for this depth measurement.
schematic cross-sectional view of three sections of the device at this step is shown in Figure 5.42.

Next, the metal electrode were placed in these wells using a lift-off technique. A second photolithography step (recipe P1) was carried out to define the metal regions. Mask 2 was used for this purpose and was aligned with the alignment marks created during the mask 1 process. A schematic diagram of mask 2 overlayed on mask 1 is shown in Figure 5.43. The dark blue region is the mask 1 region, while the white ares are the clear region on mask 2. It can be seen that mask 2 had similar features to mask 1, but the features were 100 µm smaller (50 µm from each side) in each of the x and y directions. Such a large gap was given so that a conformal oxide deposition could be achieved filling the gaps between the electrode edges and the well walls, and to prevent the formation of voids. This also prevented metal deposition on the side walls of the etched well regions and/or avoided any metal deposition on the top surface of the glass wafer in case of any misalignment between mask 2 and mask 1. The 50 µm smaller mask 2 also ensured that the metal is not deposited in the dicing alleys. Please note that in this photoliphtography step, the wafers were not hard baked so that the photoresist could be removed easily during the lift-off process. Mask 2 opened up the regions where the electrode had to be deposited, while all other regions were still coated with photoresist.

Titanium (Ti 0.05 µm)/ Platinum (Pt 0.15 µm) was used for the electrodes. Electron-beam (e-beam) metal evaporation was used to deposit the metals on the entire wafer surface. Figure 5.44 shows a schematic cross-sectional view at this step. After metal deposition, the wafers were dipped in positive photoresist remover heated at 50°C. The photoresist remover was first heated in a beaker on a hot plate. Wafers
Figure 5.41: A schematic view of mask 1 for nDS2 top substrate fabrication.
Figure 5.42: A cross-sectional view of three sections of nDS2 after mask 1 process.
Figure 5.43: A schematic view of mask 2 overlayed to mask 1 for nDS2 top substrate fabrication. The dark blue region is mask 1 region, while the white areas are the clear region.
were transferred into the beaker, and then the beaker was transferred into the ultrasonic bath. Metal from unwanted regions was lifted-off along with the photoresist as shown in Figure 5.45. Figure 5.46, 5.47 and 5.48 show microscopic images of the edges of the deposited metal using 5x, 50x and 100x microscope objectives respectively.

Next, a 1 µm thick oxide was deposited on this wafer. This was done through MEMS Exchange [241]. A PECVD (plasma enhanced chemical vapor deposition) process was used to deposit oxide at 200°C. The 50 µm spacing between the electrode metal and the walls of the etched well regions (from mask 1) is wide enough for deposited oxide to fill conformally and to avoid any void formation.
Figure 5.45: A cross-sectional view of three sections of nDS2 after lift-off.
Figure 5.46: Microscopic image of the deposited electrode after lift-off. The picture was taken using a 5x microscope objective and shows the metal inside the well etched into the glass.

Figure 5.47: Microscopic image of the deposited electrode after lift-off. The picture was taken using a 50x microscope objective and shows the metal inside the well etched into the glass.
PECVD oxide deposition leaves the glass surface unlevelled. It was flattened by a chemical mechanical polishing (CMP) step. CMP of deposited oxide was accomplished until the original glass surface was reached. The flat surface is required to achieve glass-silicon anodic bonding. The theory of anodic bonding is to apply a large voltage potential across the glass-wafer complex to generate an electric field that drives Na+ ions in a glass wafer away from the interface region. Thus an Na+ depletion zone is formed and leaves oxygen molecules at the interface. Oxygen molecules diffuse into silicon to form a layer of amorphous SiO$_2$. Thus a glass-silicon bonding is achieved. The CMP was done through MEMS Exchange. A timed CMP was done to achieve this. A schematic cross-section of the device after CMP is shown in Figure 5.49.
Figure 5.49: A cross-sectional view of three sections of nDS2 device after chemical mechanical polishing (CMP).
The rest of the top substrate fabrication is in progress. It is described next how to achieve this:

Dicing allyes are fabricated next on this wafer at the back side of the wafer so that the devices can be separated from the wafers at the end. Back side photolithography (recipe P1) is carried out using dicing alley mask. RIE (recipe R4) of glass is done to make 2 μm deep dicing alleys. The photoresist is then stripped off in piranha.

The next step is the fabrication of electrode contact chambers and contact pads at the front side of the wafer. Photolithography (recipe modified P1) is carried out using mask 3. The spin speed in recipe P1 is changed to 2000 rpm to get thicker photoresist. A schematic view of mask 3 overlayed to the mask 2 (electrode region) is shown in Figure 5.50. The dark blue region is mask 2 region (electrodes), while the white areas are the clear regions of mask 3. The goal of this etch is to expose metal side walls in the electrode contact chambers and to expose the metal for the contact pads. An overlap of 25 μm in the electrode contact chamber over the metal electrode was designed in mask 3 to assure metal exposure in the electrode contact chambers. The contact pad regions were made 20 μm smaller in each side with respect to the metal to limit etching to only the regions directly over the metal bond pads. The width of the electrode contact chamber was designed to match with the entry flow chamber. Further, the etch depth of the electrode contact chambers should be more than the depth etched during the mask 1 process to ensure the metal exposure. Metal exposure in this region is very important for establishing an electrokinetic flow in the device. The photolithographically defined regions are etch by RIE in a He + CHF₃ + CF₄ plasma (recipe R4). The wafers are etched for 4 minutes 15 seconds during mask 1 step, therefore the electrode contact chambers are etched for 5 minutes using recipe
Figure 5.50: A schematic view of mask 3 overlayed to mask 2 for nDS2 top substrate fabrication. The white regions are the clear region of mask 3 and the blue regions are the electrodes.

R4. The photoresist may not survive for 5 minutes, that is why a thicker photoresist is spin cast here by reducing the spin speed in recipe P1 to 200 rpm. A cross-section of the top substrate at this step is shown in Figure 5.51.

The last step is the fabrication of the exit port all the way through the wafer from the back side of the glass wafer. This is done using ultrasonic drilling (at Sensorprep Services, Inc) similar to that used for nDS1g. A schematic view of the wafers at this step is shown in Figure 5.52.

**Wafer Bonding**

The two wafers (silicon bottom substrate and glass top substrate) are bonded together so that the two electrode contact chambers are aligned with the entry/exit
Figure 5.51: A cross-sectional view of three sections of the nDS2 device after the mask 3 process.
Figure 5.52: A cross-sectional view of three sections of the nDS2 device after entry port is ultrasonically drilled into the wafer.
flow chambers and the entry port is aligned with the entry flow chamber. The bonding is achieved by the anodic bonding method (recipe B1).

5.4 Packaging of nDS Devices

In practice, the nDS devices are mounted on a carrier that is placed in a cylindrical titanium capsule (encasement) for the purpose of implantation in the body. This implant assembly was obtained from Manufacturing Technical Solutions (Carroll, OH). Figure 5.53 shows a drawing of the implant fitted with an nDS device and Figure 5.54 is a photograph of a prototype implant illustrating its size relative to the USA one cent coin. The nDS device is affixed over a small-bore opening within a cylindrical methacrylate insert carrier using general purpose silicone adhesive followed by 3 hours cure at 55°C. This carrier is fitted with two rubber O-rings at the ends. The completed carrier is inserted into the titanium capsule until the device region is fully aligned under the grate opening in the titanium capsule. The carrier divides the volume inside the capsule into two chambers, with the only connection between the chambers being by flow through the nanochannel device. The drug is contained in the chamber below the carrier and nDS device. The chamber above the nDS device is open to the body via the grate opening of the titanium cylinder, of size comparable to the nanochannel device. Methacrylate end caps containing re-sealable rubber septa are used to seal the ends of the titanium capsule using silicone adhesive followed by 3 hours cure at 55°C. For filling the drug in the capsule, the implant was oriented vertically and a 27 gauge luer-lock needle was inserted into the upper septa for use as an air vent. The liquid suspension was slowly injected into the implant via the lower septa until all the air within the implant was removed, as indicated by the presence
of liquid exuding from the upper needle. The needles were removed under gentle liquid injection pressure to avoid any concomitant influx of air upon withdrawal. The implants were rinsed by immersion in appropriate buffer prior to either placement into a testing vessel or surgical implantation. The small size of the capsule allows for relatively simple subcutaneous insertion in the arm or abdomen. Titanium alloy as an implantable capsule is currently being used in the DUROS® implant (Alza Corporation) that is an osmotic pump based drug delivery device.

5.5 Process Recipes

The different process recipes mentioned during the fabrication details of the nDS devices are discussed below. The recipe also mentions the location the process was performed. This includes the MicroMD clean-room, The Ohio State University, Columbus, OH (OSU). Other locations are University of California, Berkeley (UCB) and Case Western Reserve University (CWRU), Cleveland, OH.
Recipe C1: Quick Dump Rinse (QDR)

Location: OSU, UCB

This is a DI water station programmed to rinse wafers to an acceptable water resistivity level (>10 Mega Ohm-cm), and to get rid of excess etchant, and/or contaminant. Therefore, it is very important to make sure the cassette and wafers go through the full QDR cycles, as any remaining acid etchant can easily ruin the subsequent SRD machine and/or contaminate other equipment in the lab, particularly the furnaces. This station is set-up for two cycles. In each cycle wafers are initially showered with DI water followed by two DI fill-dump operations.

Recipe C2: Spin Rinse Dryer (SRD)

Location: OSU, UCB
Wafers are rinsed in DI water followed by two spin dry cycles. The cassette of wafers is put in SRD after QRD operation. A typical set-up of cycle times is:

1. DI water spin/rinse: 120 sec

2. Dry time 1 (high speed dry at 1800 rpm): 160 sec

3. Dry time 2 (low speed dry at 500 rpm): 180 sec

A short duration, high speed dry cycle followed by a longer duration, low speed dry cycle, is found to produce best result.

**Recipe C3: Piranha Clean**

Location: OSU, UCB

Piranha is made by adding 100 ml of hydrogen peroxide to 6000 mL of sulfuric acid bath. The hydrogen peroxide is added just before immersing every batch of wafers. After cleaning the wafers in piranha, they must be rinsed in the QDR station and dried in SRD.

**Recipe D1: Low Stress LPCVD Nitride Deposition**

Location: UCB

Furnace manufacturer: Tystar Corporation

Definition:

- Low stress nitride (LSN): This is a silicon rich nitride, which has tensile film stress around 300 MPa or lower.
1. Dichlorosilane (SiH₂Cl₂) (DCS): Used as a source of silicon. Decomposition of DCS supplies silicon for the LSN film.

2. Ammonia (NH₃): Used as a source of nitrogen in the nitride process. NH₃ is also used in the post deposition step to neutralize HCl, which is a byproduct of DCS decomposition.

Deposition conditions:

- Gases: 100 sccm DCS/25 sccm NH₃
- Pressure: 140mTorr
- Temperature: 835°C

Deposition rate: 40 Å/min ± 10%

Uniformity: Within Wafer <15%; Wafer to Wafer <25%

**Recipe D2: Stoichiometric Nitride Deposition**

Location: Case Western Reserve University, Cleveland, OH

Definition:

- Stoichiometric (Standard) Nitride: This is chemically balanced silicon nitride (Si₃N₄) that usually has tensile film stress over 1000 MPa.

Gases used:

1. Dichlorosilane/DCS (SiH₂Cl₂): Used as a source of silicon. Decomposition of DCS supplies silicon for the nitride film.
2. Ammonia (NH\textsubscript{3}): Used as a source of nitrogen in the nitride process. NH\textsubscript{3} is also used in the post deposition step to neutralize HCl, which is a byproduct of DCS decomposition.

Deposition condition:

- Gases: 25DCS/75NH\textsubscript{3}
- Pressure: 300 mTorr
- Temperature: 800°C

**Recipe R1: RIE of SiO\textsubscript{2}**

Location: OSU

Manufacturer: Lam Research Corporation

Definitions:

- **RIE**: An etching technique that uses the neutral radical gas atoms/molecules as well as ion species, generated by plasma, as the etchants to remove the thin film material on a substrate or the substrate itself. The electrically neutral species are the chemical components of RIE, while the ionic species are responsible for anisotropic etching. A thorough description of RIE process can be found in reference [157].

- Entries in the COMPL field in the program controlling the etcher specify how a particular step gets completed. There are five entries that can be chosen:
  
  - **TIME**: The step will complete after the time entered in the WAIT field. The process then advances to the next step.
– **STABILITY OR TIME**: The step will complete and the process advances to the next step when all the parameters in the step reach their set points within the time limit entered in the MAX field.

– **TIME & ENDPT**: The step will prompt the machine to move to the next step when the Automatic Endpoint Detection conditions are met or after the time entered in the WAIT field is elapsed.

– **OVERETCH**: The step will complete after the percentage, entered in the % field, of time of the previous etch step.

– **RECIPE**: This signifies the end of the recipe. All parameters in this step and after are ignored.

The recipe used in the Lam etcher for oxide etching is given in Table 5.3.

<table>
<thead>
<tr>
<th>Purpose→</th>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
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Table 5.3: Recipe for SiO₂ etch.
Etch rate of oxide = 500 Å/min

Recipe R2: RIE of Nitride

Location: UCB

Manufacturer: Lam Research Corporation

Definitions:

Automatic Endpoint Detector: An optical device that traces the light emitted by the etch byproduct in the plasma. It can be programmed to end the etch process at a specified condition. This etcher uses Channel A (405 nm) to monitor the amount of SiN species in the plasma.

Setting up Automatic Endpoint Detection:

- A 15 seconds delay time was set-up. The automatic endpoint detector disregards any signal in this first period of the etch step because the plasma was just started and is still stabilizing.

- 5 seconds Normalize time was used. The automatic endpoint detector collects and averages the tracer signal from the plasma in this second period of the etch step. The averaged (normalized) signal strength is used as the base for endpoint triggering.

- End-point was set to trigger at 95% of the normalized value. When the tracer signal reaches 95%, the end point is triggered, the etch step completes and the process advances to the next step.
Table 5.4: Recipe for nitride etch.

The recipe used in the Lam etcher for nitride etching is given in Table 5.5.

Etch rate: 1000 Å/min ± 10%

Etch uniformity: Within Wafer < 10%; Wafer to Wafer < 10%

**Recipe R3: RIE for Nitride and Pad oxide at OSU**

Location: OSU

Manufacturer: Lam Research Corporation

The recipe used in the Lam etcher for stoichiometric nitride and pad oxide etching is given in Table 5.5.
Table 5.5: Recipe for stoichiometric nitride etch used at OSU.

Etch rate of stoichiometric nitride = 200 nm/min

This does not have automatic end point detection.

**Recipe R4: RIE of SiO$_2$ Used for Pyrex 7740**

Location: OSU

Manufacturer: Lam Research Corporation

The recipe used in the Lam etcher for Pyrex 7740 etching is given in Table 5.6.

Etch rate of pyrex 7740 = 1100 Å/min

**Recipe Chem1: Wet Chemical Etch of Silicon using KOH**

Chemical: 45 wt% KOH

Manufacturer: J T Baker
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<th>Step 2</th>
<th>Step 3</th>
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<td>1:00</td>
<td>Etch time</td>
<td>00:10</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.6: Recipe for SiO₂ used for pyrex 7740 etch.

This chemical was heated at the desired temperature in a continuously agitated bath. Figure 5.55 shows how the KOH etch rate for (100) silicon varies with concentration and temperature. The in-lab characterized etch rates at different temperature are:

- 0.47 µm/min at 70°C
- 0.65 µm/min at 80°C

A KOH etch was always followed by QDR and SRD steps.

**Recipe Chem2: Wet chemical etch of thermally grown SiO₂**

Manufacturer: J T Baker

The in-lab characterized etch rates for different concentrations of HF and buffered HF (BHF) are:
Figure 5.55: Si (100) etch rate in KOH with concentration and temperature [242, 243].

- Chemical: 49 wt% HF - (room temperature) $\sim 20$ kÅ/min
- Chemical: 5:1 BHF - (room temperature) $\sim 1000$ Å/min
- Chemical: 7:1 BHF - (room temperature) $\sim 750$ Å/min
- Chemical: 10:1 BHF - (room temperature) $\sim 230$ Å/min
- Chemical: 25:1 BHF - (room temperature) $\sim 100$ Å/min

For critical processes, the etch rate need to be characterized every time a chemical etch process is used, unless a fresh batch of chemical is being used.

**Recipe Chem3: Wet Chemical Etch of Silicon Nitride**

Manufacturer: J T Baker

49 wt% HF at room temperature was used to etch silicon nitride (low stress nitride and stoichiometric nitride). The wafers were dipped in this chemical until all the nitride was stripped off. The end point was the hydrophobic nature of silicon surface.
Recipe P1: Positive Photolithography Using SP1813

Location: OSU

The photolithography process was carried out in the following steps:

1. HMDS Prime: 5 min vapor prime @ 150\degree

2. Spin/coat photoresist: SP1813 (I-Line)
   
   Acceleration: 2000 rpm/sec
   
   Spin Speed: 2925 rmp
   
   Time: 30 sec

   Thickness: \(~1.4\ \mu m\)

3. Soft bake: 115\degree C/60 seconds on hot plate

4. Expose:
   
   Manufacturer/Model: EV620
   
   500 W mercury arc lamp operating in constant intensity mode (365 nm)

   System’s intensity: 15 mW/cm\(^2\)

   Exposure time: 2.4 seconds

5. Develop:

   Developer: MF 320 Positive Resist Developer

   Develop time: 60 sec immersion

6. Hard bake: 115\degree C/30 minutes in oven
Recipe P2: Positive photolithography using OiR 10i photoresist

Location: UCB
Manufacturer/model: SVG8626 spin/bake wafer track

1. HMDS Prime: 5 min vapor prime @ 150°

2. Spin/coat photoresist: OiR 10i (I-Line)
   - Acceleration: 50,000 rpm/sec
   - Spin Speed: 4100 rpm
   - Time: 30 sec.
   - Thickness: ∼ 1.1 um

3. Soft bake: 90°C/60 seconds on hot plate

4. Expose:
   - Manufacturer/Model: Karl-Suss (MA6)
   - 100 W mercury arc lamp operating in constant intensity mode (365 nm)
   - System’s intensity: 25 mW/cm²
   - Exposure time: 2.4 seconds

5. Post exposure bake:
   - Manufacturer/Model: SVGDEV bake/develop wafer track
   - 120° for 30 seconds

6. Develop:
   - Developer: OPD 4262 Positive Resist Developer
   - Develop time: 60 sec spin on SVGDEV
7. Hard bake: 120°C for 30 minutes in oven

**Recipe B1: Silicon-Glass Anodic Bonding**

Location: Case Western Reserve University, Cleveland, OH

Bonding conditions:

- Temperature: 350°C
- Voltage: 600V
- Time: 2 min

**5.6 Summary**

A series of nanochannel devices were conceptualized for controlled drug delivery. These were collectively named nanochannel delivery systems or nDS. The basic device is made up of two silicon substrates that are micromachined and bonded together. It has in-built nano-channels that were fabricated using a sacrificial oxide technique. The first device in this series, nDS1 was a passive device. The design and the fabrication steps of this device were developed. Devices with nominal nanochannel sizes of 20 nm, 40 nm, 70 nm, and 100 nm were fabricated. The completed devices were measured to have nanochannel heights of 18 nm, 42 nm, 70 nm and 108 nm, respectively. The devices were studied for glucose and interferon-alpha (IFN-α) release in-vitro. The results suggest that a zero-order release profile can be achieved through the nanopores of this device. This is required for an implantable device that can be used to deliver drugs for a long period of time at a constant rate within a therapeutic window. Further, it was found that the functional activity of INF-α was preserved after release.
through a 100 nm device. nDS1 device was later modified and given the name nDS1g. This new device had glass (pyrex 7740) as a top substrate instead of silicon. The glass top substrate improves the bonding between the two substrates (silicon-glass anodic bonding as compare to silicon-silicon fusion bonding). Further, the transparent glass substrate allows visual inspection of fluid flow through the nanochannels that provides a better platform for nano-fluidic studies. The design and fabrication details of this device were presented in this chapter. The third device in the series of nanochannel delivery systems was nDS2. This device is made up of a glass (pyrex 7740) top substrate and a silicon bottom substrate. The nanochannels were fabricated in the bottom silicon substrate as in the case of nDS1, while electrodes were integrated in the top glass substrate. The purpose of this device is to achieve controlled flow through the nanochannels by applying electric field across the electrodes. This device can be connected to any external circuit. This could be pre-programmed circuit (nDS2), a wireless circuit (nDS3) or a sensor circuit (nDS4). Thus a manipulable, externally controlled or self-triggered device can be achieved. The design, fabrication process flow and the details of fabrications steps developed for this device were presented in this chapter.
6.1 Summary and Conclusions of the Research

Therapeutic efficacy of a drug is largely governed by the way it is delivered to the target. An ideal drug delivery system should be able to deploy medications to specifically targeted parts of the body through a medium that can control the drug’s administration by means of a physiological or chemical trigger. Considerable advances have been made in the field of drug delivery, however the major requirements of a drug delivery system for the newer therapeutics is still unmet. Conventional drug delivery techniques that rely on pills and injections are often not suitable for novel protein-based, DNA-based, and other therapeutic compounds produced by modern biotechnology. Therapeutic efficacies and potencies of many drugs are limited or otherwise reduced because of the partial degradation that occurs before they reach the desired target in the body. Once consumed, these time-release medications deliver treatment continuously without much control over the target site or rate of drug delivery. Furthermore, many of these drugs have a small concentration range for optimum therapeutic efficacy beyond which they can be impotent or even toxic. Thus, the
effectiveness of the therapy becomes largely dependent upon the frequency of administration and half-life of the drug. These requirements have necessitated exploring alternate approaches of drug delivery along with desired improvements in the existing drug delivery technologies. A key requirement to these therapies is the controlled delivery of therapeutics within the therapeutic window. The design of a controlled drug delivery system requires simultaneous consideration of several factors, such as the drug properties, route of administration, nature of delivery vehicle, mechanism of drug release, ability of targeting, and biocompatibility. It is not easy to achieve all these in one system because of extensive interdependency of these factors. A typical drug delivery device is designed considering a few of these factors in order to achieve a delivery system that is capable of delivering one or a few of the therapeutic agents.

The implantable route of delivery and silicon material was chosen in this research to achieve two major requirements of the therapeutic delivery. The first was the continuous release of therapeutic agents, especially biological molecules, over a long period of time (zero-order release kinetics). The second goal was to design a device that can be connected to a desired control circuit so that a manipulable delivery can be achieved. These replace the repeated insertion of intravenous catheters, and may deliver different classes of drug, eg. steroids, chemotherapeutics, antibiotics, analgesics and contraceptives, and some particular drugs such as insulin and heparin. Benefits include the reduction of side effect (drug delivery rate within the therapeutic window) caused by traditional administration techniques, and better control. Silicon was chosen as a device material since the fabrication technology of silicon is well known. Dimension control, uniformity and reproducibility, and high chemical and mechanical stability are a few of the advantages of using silicon. On the other
hand, polymeric devices are difficult to fabricate with high uniformity and precision, while degradable polymeric devices suffer from an initial “burst effect” prior to sustained release. Osmotic pumps and micropumps also suffer from drawbacks. Silicon nanopore membranes have shown a promising future in the area of drug delivery. Sustained release of glucose and interferon-alpha was reported through the tightly controlled nanopores. However, this device is very fragile and may not be useful as an implantable device.

Nanochannel delivery systems, or nDS, were conceptualized to achieve the above mentioned goals. The first device, nDS1, was design based upon a sandwich design filter that has nanochannels between two bonded silicon wafers. The basic concept of making these nanochannels is the sacrificial oxide technique, where silicon dioxide is grown in selective areas under dry conditions. The oxidation consumes silicon. This oxide is etched later in the process, and the step created by the oxide growth followed by etching defines the nanochannel height. A nano-size step was created this way in one of the wafers, which was then bonded with another silicon wafer. Thus, the gap between the two wafers became the nanochannels. This enhanced the mechanical strength of this device compared to the nanopore membranes where the nanochannels were made through a thin membrane in a single wafer. nDS1 devices were designed and fabricated targeting four nanochannel sizes. These were 20 nm, 40 nm, 60 nm and 100 nm. The purpose of this research was to demonstrate a successful fabrication of this device, and therefore the time and temperature of oxide growth was not optimized. The achieved nanochannel heights were 18 nm, 43 nm, 70 nm, and 108 nm. These heights were measure by atomic force microscope (AFM) before bonding the two wafers. Glucose diffusion through a nominal 100 nm channel for a
period of 15 days and through a nominal 60 nm channel for a period of 5 days, and interferon-alpha (IFN-\(\alpha\)) release through a nominal 100 nm channel for a period of 7 days showed a zero-order release profile. Further, it was demonstrated that IFN-\(\alpha\) preserves its functional activity after being released through this device.

Next, the top substrate of the nDS1 device was replaced with a glass (pyrex 7740) substrate. Glass-silicon anodic bonding results in higher bonding strength than silicon-silicon fusion bonding, and therefore a further improvement in mechanical strength was achieved. This device was named nDS1g. The glass top substrate also facilitates a visual inspection of the fluid flow through the nanochannels and thus provides a research platform for nanofluidic studies. The purpose of nDS1 and nDS1g was to achieve a zero-order release profile, and thus they can be used for continuous long term delivery of therapeutics.

Another device in the series of nDS was developed with a higher order of functionality (called nDS2). Electrodes were integrated in this structure. A major challenge in designing this structure was to bring the electrodes out in such a way that the circuit to be connected is isolated from the drug and body fluid. By applying an electric current across the electrodes, an electrokinetic fluid flow can be achieved through the nanochannels of the device, and thus the drug delivery through this device can be controlled by connecting this device to a control circuit. The design, process flow and fabrication details were developed for this device. This device has potential to achieve delivery of therapeutics in a manipulable fashion.

The key contributions of this research are outlined below:
1. The nDS1 device was designed and successfully fabricated. The bottom substrate fabrication was a three mask process while fabrication of the top substrate required two masks. Nanochannel of heights ranging from 18 nm to 108 nm were fabricated. Glucose diffusion and IFN-α release through the nDS1 device showed a zero-order release profile. Further, the IFN-α released through this device preserved its functional ability, and therefore this device is capable of delivering therapeutics at a constant rate over a long period of time.

2. The top substrate in the nDS1 device was replaced with a glass substrate and the new device, called nDS1g, was successfully fabricated. This device allows a visual inspection of device features and flow through the nanochannels. This device has the same characteristics as nDS1 in terms of release profile, but provides a higher mechanical strength compared to the nDS1 device because of the anodic bonding technique that was used to bond the two substrates of the nDS1g device. It may also provide a platform for nano-fluidics study.

3. The nDS2 device was designed, and a process flow and fabrication details were developed. Electrodes were integrated in the nDS2 structure to achieve electrokinetic flow through the nanochannels. Integrating electrodes at the device region, and achieving a good sealing between the device region and the contact pad was a major challenge in the design. This was important to achieve the electrokinetic flow through the nanochannels of the device with no leakage to the bonding pads. Further, the top glass substrate fabrication was a four mask process to integrate electrodes, which added complexity to the design and
fabrication of this device, and the bottom silicon substrate was a three mask process.

nDS2 is a universal design. If no current is applied to the electrodes, it will work as an nDS1 device. With applied current between the two electrodes, a manipulable release profile can be achieved. The design of the device makes it capable of being connected to a circuit of interest. This control circuit could be a pre-programmable circuit, a wireless circuit or a feedback control circuit connected between the nDS2 platform and a biological sensor.

6.2 Recommendations for Future Work

The ultimate goal of research on nDS is to develop implantable drug delivery devices to improve therapeutic efficacy. These devices should ultimately reach the clinic. The research in this dissertation provides a technological platform, and is the first few steps towards this goal. But, there is a lot more that needs to be done before these devices can be realized in practice. Further, considering the interdisciplinary nature of the work, researchers from different disciplines need to contribute to each-other’s work i.e. a collaborative synergy is required. These disciplines include silicon microfabrication, pharmacy, micro/nano-fluidics and medicine. Towards the end, a clinical-trial will be needed and the device will have to pass FDA (Food and Drug Administration) regulations. The mile-stones for a successful device realization and recommendations on how to achieve those are outlined below.

1. For nDS1 and nDS1g, more in-vitro and in-vivo characterization study is needed to understand the release profile. These could be glucose and drugs of interest.
Based upon these release studies, the nanochannel height in the device can be trimmed for a particular application.

2. Fabrication of nDS2 has been substantially completed, with the only remaining steps being formation of the exit port in the bottom substrate, entry port in the top substrate and anodic bonding. The completion of these steps was delayed by failure of needed process equipments and slow turn-around by vendors for CMP of the glass wafers. Once the fabrication is complete, the device needs to be characterized in-vitro. An experimental set-up needs to be designed for this characterization. The device can be mounted on a printed circuit board or can be glued on another glass wafer that has metal (maybe gold) deposited as two separate wires. The bonding pads of the device can be connected to these wires by a wire bonder. An electric current can be passed through these electrodes and release of ionic molecules can be studied. More in-depth thought is required to design an experimental set-up.

3. A nano-fluidic model is not well developed. Therefore, an in-vitro release study of drug molecules through different nanochannel sizes with different electrode biasing (in the case of nDS2) is important to develop a correlation between the molecule size, concentration, applied current and nanochannel size. This is important to achieve a ‘controlled’ drug delivery device.

4. Once an-vitro release model is established, an in-vivo study should be done and a correlation between an in-vitro and in-vivo release kinetic should be established. The performance of an ideal drug delivery device should be independent of the surrounding of the device. This means that the in-vitro delivery rate and in-vivo
delivery rate should be same and in-vivo delivery rate should be independent of
the location of the implantation site. This needs to be established, and if there
is a difference between the in-vitro and in-vivo release profile, the correlation
between the two needs to be known.

5. After the successful trial of these devices in animal models, the devices will
have to pass human trial, and get approval from the FDA regulatory board.
Since, the goal is not to develop a new drug, but instead to use established drug
delivered using this device, the device qualifies under 505(b) regulations.

6. Another requirement for all the nDS devices is to identify drugs that may be
delivered using these devices. Since these devices will be implanted in the body
for a long period of time, it is important to know the period of implantation, and
the drug stability for that period of time. A collaborative effort with medical
professionals and pharmacists is required for this.

7. These were the general considerations for a successful drug delivery device.
From the device fabrication point of view, packaging of the nDS2 device needs
to be completed. The way this device has been designed, the electrodes are
connected to the outer bonding pad areas that can be connected to a circuit of
interest. This could be a pre-programmable circuit or a wireless circuit or an
electronic implantable sensor. The desired circuit can be placed on the same
carrier that has the nDS2 device, and the two can be connected by wire bonding.
In fact, the nDS2 device may be connected to the circuit before loading these on
the carrier. These may be connected using wire bonding technique or flip-chip
technique. Figure 6.1 shows a suggested wire-bonded configuration loaded on
a carrier insert and the implant assembly for that. In the case of wire bonding technology, the control chip can be placed next to the nDS device and can be bonded to the contact pad of the nDS device. However, a wire bonded assembly may be fragile and can only be used for experimental purposes. A better approach for a large scale production may be flip-chip technology. In this case, a larger bonding pad will have to be fabricated, so that the chip can be flipped and directly attached on to the bonding pad on the nDS2 device. Figure 6.2 shows such a configuration loaded on a carrier insert and the implant assembly for that.
Figure 6.1: [Top] nDS2 and circuit loaded on the insert carrier and are connected by wire bonding. [Bottom] A complete implant assembly.
Figure 6.2: [Top] nDS2 and circuit loaded on the insert carrier and are attached using flip-chip technology. It shows an extended glass substrate and bonding pad where the chip (control circuit) is flipped and attached on top of it. [Bottom] A complete implant assembly.
APPENDIX A

nDS1 FABRICATION STEPS

The process step for nDS1 fabrication are mentioned below. Please look at section 5.1.2 for more details. Recipe details are given in section 5.5.

A. Bottom substrate processing:

1. Starting wafers: p-type, (100) Silicon
   Initial clean in piranha

2. Initial oxidation:
   Wet oxidation
   Target thickness = 0.5 µm (This thickness is not very critical, since this is used as a mask layer).

3. Photolithography
   Define entry-exit chamber, finger - Mask 1

4. RIE of oxide
   Etch depth = Oxide grown in step 2
   Gases = He+CHF₃+CF₄ (120 + 30 + 90 sccm)

5. Strip photoresist
6. Wet etching of silicon
   Chemical = KOH at 70°C
   Etch depth = 2 µm

7. Strip oxide
   Using 49% HF

8. Pad oxide growth
   Dry oxidation
   Target thickness = 20 nm (precise thickness is not required).

9. LPCVD nitride deposition
   Deposition conditions: 100DCS/25NH3/140mTorr/835°C
   Target thickness = 100 nm (precise thickness is not required).

10. Photolithography
    Define nano-channels - Mask 2
    Note: Very important to achieve good alignment.

11. RIE of nitride
    Etch depth = Deposited thickness in step 9
    Gases = He (50 sccm) + SF₆ (175 sccm)
    Note: End point detection was used here. The etch should be stopped in the pad oxide without reaching the silicon surface.

12. Wet etching of pad oxide
    BOE etch
    Etch depth = remaining pad oxide after RIE of nitride (The remaining pad
oxide thickness is measured by NanoSpec in the big rectangle in the alignment marks region).

Over etch is performed to assure that all the oxide is etched away.

13. Oxide growth

This is sacrificial oxide that defines the nanochannel height. This is grown by dry oxidation condition. A precise thickness is required here.

14. LPCVD nitride deposition

Deposition conditions: 100DCS/25NH3/140mTorr/835°C

Target thickness = 200 nm (precise thickness is not required).

15. Back side photolithography

Define exit port - Mask 3

16. RIE of nitride and remaining pad oxide

Gases = He (50 sccm) + SF₆ (175 sccm)

Target etch depth = total nitride deposited (steps 9 + 14) + pad oxide (step 8). Precise etch control is not required.

17. Deep silicon etch

Target etch depth ~ 500 µm

KOH etch at 80°C

Wafers are rotated by 180° at halftime of expected etch time to achieve uniform etching.

18. Strip nitride and oxide

Using 49% HF
**B. Top substrate processing**

19. Starting wafers: p-type, (100) Silicon

   Initial clean in piranha

20. Initial oxidation:

   Wet oxidation

   Target thickness = 0.5 µm (This thickness is not very critical, since this is used as a mask layer).

21. Photolithography

   Define Dicing alleys - Mask 4

22. RIE of oxide

   Etch depth = Oxide grown in step 20

   Gases = He+CHF$_3$+CF$_4$ (120 + 30 + 90 sccm)

23. Strip photoresist

24. Wet etching of silicon

   Chemical = KOH at 70°C

   Etch depth = 1 µm

25. Strip oxide

   Using 49% HF

26. Pad oxide growth:

   Dry oxidation

   Target thickness = 20 nm (precise thickness is not required).
27. LPCVD nitride deposition

Deposition conditions: 100DCS/25NH3/140mTorr/835°C

Target thickness = 300 nm (precise thickness is not required).

28. Photolithography

Define Entry port - Mask 3 (same as exit port mask)

29. RIE of nitride and pad oxide

Gases = He (50 sccm) + SF$_6$ (175 sccm)

Target etch depth = deposited nitride (step 27) + pad oxide(steps 26)

Precise control is not required.

30. Deep silicon etch

Target etch depth $\sim$ 500 $\mu$m

KOH etch at 80°C

Wafers are rotated by 180° at halftime of expected etch time to achieve uniform etching.

31. Strip nitride and pad oxide

Using 49% HF

C. Wafer bonding

Manually aligned under microscope.

Silicon-silicon fusion bonding.

Conditions: 1050 °C for 4 hrs in N$_2$ ambient
D. Wafer dicing

The device are separated by dicing the wafer at the dicing alleys.
APPENDIX B

nDS1g FABRICATION STEPS

The process step for nDS1g fabrication are mentioned below. Please look at section 5.2 for more details. Recipe details are given in section 5.5.

A. Bottom substrate processing:
This is same as nDS1 bottom substrate processing.

Top substrate processing:

1. Starting wafers: pyrex 7740
   Initial clean in piranha

2. Entry port fabrication
   Ultrasonically drilled at Sensor Prep Services Inc.
   (http://www.sensorprepservices.com)

C. Wafer bonding
Silicon-glass anodic bonding
Bonding conditions: 350°C/ 600V/ 2 min

D. Wafer dicing
The device are separated by dicing the wafer at the dicing alleys.
APPENDIX C

nDS2 FABRICATION STEPS

The process step for nDS2 fabrication are mentioned below. Please look at section 5.3.2 for more details. Recipe details are given in section 5.5.

A. Top substrate processing:

1. Starting wafers: pyrex 7740
   Initial clean in piranha

2. Photolithography
   Define wells for electrodes - Mask TS1

3. RIE of glass
   Etch depth = 0.5 μm
   Gases = He+CHF₃+CF₄ (120 + 40 + 45 sccm)

4. Strip photoresist

5. Photolithography
   Define metal electrode regions - Mask TS2
   Note: The photoresist is not hard baked.
6. Electrode fabrication
   
   E-beam deposition
   
   Ti (500 Å)/ Pt (1500 Å)

7. Lift-off photoresist
   
   Positive photoresist remover is used. NO piranha.

8. PECVD oxide deposition
   
   1 µm thick deposition at 200°C

9. Chemical mechanical polishing (CMP)
   
   Polish back to the pyrex surface

10. Back side photolithography
    
    Define dicing alleys - Mask TS3

11. RIE of glass
    
    Etch depth = 0.2 µm
    
    Gases = He+CHF₃+CF₄ (120 + 40 + 45 sccm)

12. Strip Photoresist

13. Photolithography at the front side of the wafer
    
    Define electrode contact chambers and contact pad regions - Mask TS4
    
    Spin speed in recipe P1 is changed to 2000 rpm to achieve thicker photoresist
    
    that is required for longer etch.

14. RIE of glass
    
    Etch depth = Should be > depth etched in step 3.
Gases = He+CHF$_3$+CF$_4$ (120 + 40 + 45 sccm)

Note: Add 30 to 45 sec in the etch time used in step 3.

15. Strip photoresist

16. Entry port fabrication from the back side of the wafer
   Ultrasonically drilled at Sensor Prep Services Inc.
   (http://www.sensorprepservices.com)

B. Bottom substrate processing:

17. Starting wafers: p-type, (100) Silicon
   Initial clean in piranha

18. Initial oxidation:
   Wet oxidation
   Target thickness = 0.5 μm (This thickness is not very critical, since this is used
   as a mask layer).

19. Photolithography
   Define entry-exit chamber, finger - Mask BS1

20. RIE of oxide
   Etch depth = Oxide grown in step 18
   Gases = He+CHF$_3$+CF$_4$ (120 + 30 + 90 sccm)

21. Strip photoresist
22. Wet etching of silicon
   Chemical = KOH at 70°C
   Etch depth = 2 µm

23. Strip oxide
   Using 49% HF

24. Pad oxide growth
   Dry oxidation
   Target thickness = 60 nm (precise thickness is not required).

25. Stoichiometric nitride deposition
   Deposition conditions: 25DCS/75NH3/300mTorr/800°C
   Target thickness = 200 nm (precise thickness is not required).

26. Photolithography
   Define nano-channels - Mask BS2
   Note: Very important to achieve good alignment.

27. RIE of nitride
   Etch depth = Deposited thickness in step 25
   Gases = He (50 sccm) + SF₆ (175 sccm)
   Note: The etch should be stopped in the pad oxide without reaching the silicon surface. A good characterization of nitride etch rate is important to achieve accurate timed etch, otherwise end point detection technique should be used.

28. Wet etching of pad oxide
   BOE etch
Etch depth = remaining pad oxide after RIE of nitride (The remaining pad oxide thickness is measured by NanoSpec in the big rectangle in the alignment marks region).

Over etch is performed to assure that all the oxide is etched away.

29. Oxide growth
   This is sacrificial oxide that defines the nanochannel height. This is grown by dry oxidation condition. A precise thickness is required here.

30. Back side photolithography
   Define exit port and contact pad region - Mask BS3

31. RIE of nitride and pad oxide
   Gases = He (50 sccm) + SF₆ (175 sccm)
   Target etch depth = nitride deposited in (steps 25) + pad oxide ( step 24) (Precise control is not required).

32. Strip Photoresist

33. Photolithography
   Define exit port and contact pad region - Mask BS3

34. Deep Reactive Ion Etch of Silicon (DRIE)
   Target etch depth ~ 500 µm

35. Strip nitride and oxide
   Using 49% HF
C. Wafer bonding

Silicon-glass anodic bonding

Bonding conditions: 350°C/ 600V/ 2 min

D. Wafer dicing

The device are separated by dicing the wafer at the dicing alleys.
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