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Materials for microfabricated implantable devices: a review

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The application of microfabrication to the development of biomedical implants has produced a new generation of miniaturized technology for assisting treatment and research. Microfabricated implantable devices (μID) are an increasingly important tool, and the development of new μIDs is a rapidly growing field that requires new microtechnologies able to safely and accurately function *in vivo*. Here, we present a review of μID research that examines the critical role of material choice in design and fabrication. Materials commonly used for μID production are identified and presented along with their relevant physical properties and a survey of the state-of-the-art in μID development. The consequence of material choice as it pertains to microfabrication and biocompatibility is discussed in detail with a particular focus on the divide between hard, rigid materials and soft, pliable polymers.

1. Introduction

Biomedical devices intended for *in vivo* implantation, whether diagnostic or therapeutic, face familiar challenges of

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size, power consumption, biocompatibility and efficacy. Engineering devices with micron-scale precision enables significant reduction in footprint, encumbrance and power demand, and an accompanying increase in device complexity and often capability. By adapting semiconductor micromachining processes to the field of biomedical implants, researchers have opened broad new avenues of research and promulgated a generation of new implantable technologies, so-called microfabricated implantable devices (μID). Examples are numerous and include physiological sensors, biochemical sensors, neural prostheses, cochlear prostheses, drug delivery devices, ocular implants, and vascular stents. For the researcher, μIDs present an elegant solution for problems requiring targeted manipulation or observation of living tissue; for the patient, μIDs present an option for minimally invasive point-of-care treatment. For the engineer, however, μIDs present a series of interconnected design challenges; device structure and fabrication method are constrained by material choice, which must satisfy desired physical properties as well as required hermeticity and biocompatibility.

As the body of research on μID development grows, designs increasingly take advantage of a greater variety of materials, and numerous reports describe implants fabricated from unconventional materials, including polymers and biopolymers (*e.g.* polymethylmethacrylate, polyethylene glycol, chitosan), synthetic materials and synthetic composites (*e.g.* hydrogels, poly(*N*-isopropylacrylamide)), and nanostructured materials (*e.g.* nanoparticles, nanowires, graphene). The nature of an expanding field such as this precludes the compilation of an exhaustive list of all materials under investigation. However, for implantable devices the path from preliminary work to translation is long and perilous, and material composition is often a major determinant. Government regulations governing approval for medical devices are stringent and often inconsistent between countries, and the requisite testing to ensure compliance can be laborious and costly.[1] Many materials which are successful in *in vitro* experiments may encounter unforeseen complications when implanted, including unexpected immune responses or slow but appreciable degradation. For μIDs, these issues can be magnified; the extremely thin layers of materials common in micro-devices may degrade at rates too slow to accurately measure, but that nonetheless lead to device failure within patient lifetime, and even minor immune response can be sufficient to isolate a micron-sized device and prevent proper operation.

This review will discuss the role of material choice in the design and fabrication of μIDs, with a primary focus on a small group of well-vetted materials that dominates the literature and has therefore played a critical role in establishing the history of the field. For ease of analysis, we have broadly characterized those surveyed as either 'hard' or 'soft', the former comprising high Young's moduli materials such as silicon, glass, metals and ceramics and the latter comprising low Young's moduli polymers including polydimethylsiloxane (PDMS), polyimide, poly(chloro-*p*-xylylene) (Parylene C), and biodegradable polymers. For engineers embarking on the design and development of a new device, choice of material may be the first and most critical decision; material properties dictate available fabrication and packaging methods, device performance and chemical compatibility, and, for μIDs specifically, material choice strongly influences interaction between the device and host. This review will explore how material choice influences and, at times, limits design and fabrication of μIDs, and will describe the advantages and challenges of working with different materials, with a focus on the differences in approaches for soft and hard devices. We will begin with an overview of the physical and chemical properties of commonly employed materials and the available microfabrication methods and tools. A survey of μIDs described in the established literature, categorized by material composition, follows, with a focus on how material selection influenced device design and operation. Finally, we present a discussion of current challenges affecting use of different materials in μID development.

2. Material considerations

2.1 Biocompatibility

The requirement of biocompatibility, that the material be both safe to an implanted host and able to function in *in vivo* conditions, represents perhaps the strictest prerequisite on materials for μIDs.[2] Williams formalized the definition as "the ability of a material to perform with an appropriate host response in a specific situation",[3] acknowledging varying requirements on materials in separate sites and applications. Biocompatibility is a more significant concern for implants intended for chronic use, but even for acute applications, exposed material must satisfy demands of both patient safety and device efficacy. Materials are tested for toxicity and carcinogenicity, as well as any leached or degradation products, and to determine the degradation, corrosion and dissolution profile at the ambient temperature, pressure and salinity typical of the *in vivo* environment. Host response is strongly influenced not only by the chemical composition of the implant material, but also surface morphology, crystallinity, and surface energy, and bulk mechanical properties such as elastic constants and shape (see section 2.2).[4] For a more detailed discussion of material biocompatibility, the reader is referred to reviews by Williams.[4,5]

Biocompatibility requirements exclude many materials common in microfabrication and microelectromechanical systems (MEMS) for μIDs; many metals corrode quickly in *in vivo* environments[6] while polymers with low melting or softening temperatures, or high solubility in water, fail mechanically. For μIDs intended for chronic implantation, there are considerations of water and gas intrusion,[7] fatigue failure,[8] and failure due to immune response.[9–11] Scar formation and other foreign body reactions present a significant obstacle to long-term implantation,[9,11] and are a common failure mode for otherwise successful μIDs. Common strategies to countering (or limiting) the immune response include careful design and implant placement, minimizing size to

reduce tissue damage, biomolecular coatings,[12,13] and pharmaceutical approaches;[14–16] however, choice of material remains critical.[17]

Common examples of materials considered biocompatible and used in μIDs include: cobalt-chromium, iridium, titanium, platinum, nitinol, certain glasses, PDMS, Parylene C, polymethylmethacrylate (PMMA) and polyimide.[1,7,18,19] Silicon, polysilicon, SU-8 polymer, SiO_2, Si_3N_4, and SiC have been tested by Kotzar *et al.* under regulatory guidelines (FDA ISO 10-993), and minimal biocompatibility issues were reported for all but SU-8.[20] Subsequent tests of implanted devices likewise suggest silicon to be a viable material for μIDs,[9,21] however such data falls short of what is needed for regulatory approval. Extensive data on histopathology for cortical implants specifically was compiled by Stensaas and Stensaas,[22] and organizes materials as non-reactive (*e.g.* aluminum, ceramic alumina, gold, platinum and certain productions of polyethylene and Teflon), reactive (*e.g.* SiO_2, nichrome, TiO_2) and toxic (*e.g.* Silastic RTV silicone, silver, iron and copper).

Due to concerns of electrochemical corrosion, biofouling and irritation, micromachined devices are frequently encapsulated in conformal polymers, bonded to glass, or enclosed in biocompatible metal casings.[23] Encapsulation is a common approach even for devices comprising exclusively biocompatible materials, as an insulating or hermetic seal is often required to prevent water and soluble ions from damaging or shorting electrical connections. Material choice for encapsulants must satisfy not only conditions of biocompatibility, but also desired low permeability, ease of deposition, and conformality.

2.2 Physical properties

As with any MEMS device, material selection must account for any necessary constraints on mechanical, electrical, thermal, optical and chemical properties, but there are often requirements of material properties unique to μIDs. For example, the elasticity or rigidity of a material, typically represented by the Young's modulus, must be considered to reduce mechanical mismatch between the device and surrounding tissue, an important criteria of minimizing tissue damage and foreign body response.[10,24,25] While mechanically compliant devices may better match the mechanical properties of soft tissue, high aspect ratio devices, such as micro-needles or probes, require sufficient compressive and tensile strength to survive insertion without mechanical buckling.[26] In general, common μID materials are considerably stiffer than tissue at most implantation sites, however the elastic moduli of both biological tissues and μID materials vary over several orders of magnitude (Fig. 1). A material selection that is 'too soft' for one site or application may be considered 'too hard' for another. Mechanical properties of materials can also influence critical feature dimensions, which can subsequently determine device shape and resulting biocompatibility. For example, Edel *et al.* determined that the sharpness of the tip of a microprobe could dramatically reduce the size of the neuron 'kill zone' surrounding implants.[27]

Thermal conductivity is of relevance for μIDs which may produce heating of surrounding tissue. Electrical conductivity and permeability to gas and water can determine whether a material requires encapsulation, or is suited as an encapsulant, while thermal stability (*e.g.* softening, melting and degradation temperatures) determines whether a material will survive *in vivo*. Other properties may only be relevant to particular devices, for example, optical transmissivity and optogenetic implants. Table 1 provides values from literature of important material properties for commonly chosen μID materials.

2.3 Fabrication technologies

Material choice determines the microfabrication tools and techniques available for μID production, and consequentially the minimum size and resolution and possible geometries

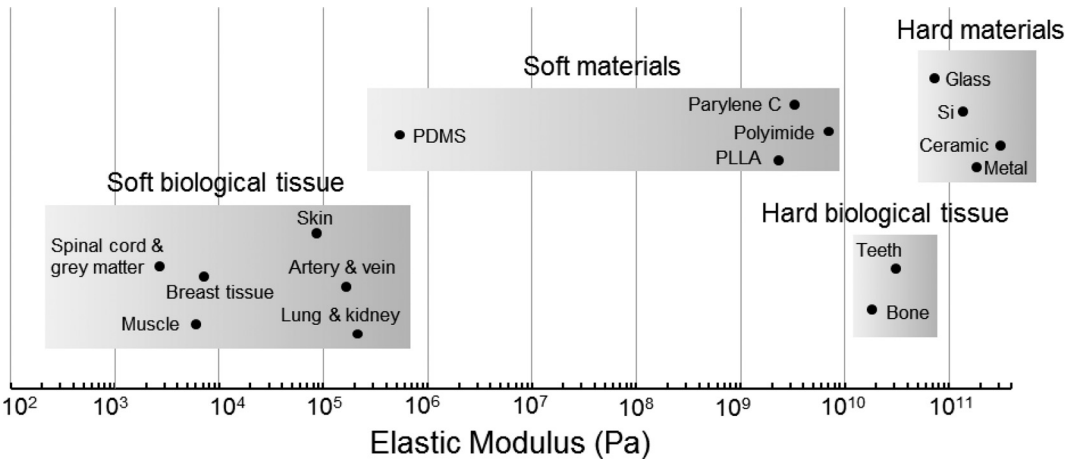

Fig. 1 Logarithmic plot of elastic (Young's) moduli for various biological tissues and common μID materials. Data points are representative values available in literature, shaded areas span full range of values for selected materials in referenced literature.[223–227,231,241–245]

Table 1 Material properties of silicon, glass, Parylene C, PDMS and polyimide, adapted from literature

		Silicon[a]	Glass	Parylene C[b]	PDMS	Polyimide
Young's modulus (MPa)		150 000	62 750[d] [ref. 223]	2760	0.360–0.870 [ref. 224]	2300–8500 [ref. 225–227]
Hardness		850 kg mm^{-2}	418[d] kg mm^{-2} [ref. 228]	80 (Rockwell B)	30–80 (Shore A) [ref. 226, 229]	50–99 (Rockwell E) [ref. 230]
Processing temperature limits (°C)	T_{melt}	1414	821[d] [ref. 223]–1700[e] [ref. 231]	290	—	—
	T_{glass}	—	—	90 [ref. 232]	—	325—410 [ref. 225–227]
	$T_{degredation}$	—	—	125 [ref. 233]	350 (oxidation) 750 (decomposition) [ref. 234]	510–620 [ref. 225–227]
Density (g cm^{-3})		2.329	2.23[d] [ref. 223]–2.27[e] [ref. 231]	1.289	0.970–1.11 [ref. 226, 229]	1.39–1.42 [ref. 226, 227]
Thermal conductivity[c] (W m^{-1} K^{-1})		156 [ref. 235]	1.15[d] [ref. 236]–1.4[e] [ref. 231]	0.084	0.168 (14.7 °C) 0.159 (50 °C) [ref. 226]	0.12 [ref. 226]
Electrical resistivity (Ω cm)		2.3 × 10^5 (intrinsic) [ref. 237]	10^{14d} [ref. 238] 10^{16e} [ref. 231]	8.8 × 10^{16}	2.4 × 10^{14}–1.5 × 10^{15} [ref. 226]	>10^{16} [ref. 227]
Dielectric constant		11.9	4.6[d] [ref. 223] 3.9[e] [ref. 231]	2.95–3.15	2.69–2.77 [ref. 226]	2.9–3.5 [ref. 227]
Gas permeability[c] (cm^3 mm m^{-2} day^{-1} atm^{-1})	N_2	—	—	0.4	1.8–2.6 × 104 [ref. 226, 239]	2.3 [ref. 226]
	CO_2	—	—	2.8	2.1–2.5 × 105 [ref. 226, 239]	17.3 [ref. 226]
	O_2	—	—	3.0	3.9–5.3 × 104 [ref. 226, 239]	9.6 [ref. 226]
	H_2	—	—	43.3	4.3–5.8 × 104 [ref. 226, 239]	96.3 [ref. 226]

[a] Values adapted from ref. 231 unless otherwise stated. [b] Values adapted from ref. 240 unless otherwise stated. [c] Values for 25 °C unless otherwise stated. [d] Values for Pyrex® borosilicate glass. [e] Values for SiO_2.

that can be produced during fabrication. Different methods, each with their limitations and idiosyncrasies, are available for depositing, etching and patterning different materials, therefore, material selection must be coincident with the initial design phase and accompany any discussions of critical dimensions as well as outlines for process flow.

The majority of μIDs are fabricated partially, or entirely, through use of standard cleanroom processing. This approach offers several advantages including compatibility with production of integrated circuitry, sub-micron precision in machining, and often batch-scale fabrication. Though many devices require manual packaging or final assembly before deployment, the parallelization of cleanroom processing enables large variable experimentation for academic research and low costs for commercial efforts. A key advantage of cleanroom processing is the large number of established protocols and equipment for microfabrication, developed over decades for the production of semiconductor and MEMS devices. At the same time, adherence and compatibility with established protocols may impose unnecessary limits on μID design. Common μID materials such as PDMS and other polymers may not be 'clean' enough for use in many facilities, while common cleanroom materials (*e.g.* silicon) have come to dominate the μID field because of their ubiquity among cleanroom microfabrication.

Alternate micromachining methods include direct laser milling or writing, which has been utilized in metal and polymers.[28–32] Typical processes have resolutions between 10 and 100 μm for fabricating features, while surface morphology can be altered at the nanometer scale using laser exposure.[33] Direct writing requires serial processing, which can increase cost and inter-device variation, but allows for rapid prototyping and may remove the need for cleanroom facilities. Of the solid freeform fabrication methods, only stereolithography offers sufficient resolution to build microfabricated structures,[34] and there is limited work detailing the biocompatibility of the specialized resins required.[35,36] Other research utilizes *ad hoc* fabrication techniques, for example the Anikeeva group has produced optrode neural implants using a repurposed optical fiber-pulling tower.[37,38] Such approaches often yield excitingly novel devices, but the fabrication methods are rarely generalizable beyond the original application. In any case, choice of material will largely narrow the available microfabrication methods, as amenability to microfabrication is a key consideration when selecting materials for production of μIDs. Below, we delineate some of the most common methods available for micromachining of biocompatible μID materials.

Several methods for depositing thin films of metals, including those common biocompatible choices listed above, are ubiquitous in microfabrication facilities. Evaporation, using electron-beam or heated coils, and sputtering offer batch-scale deposition of metal films up to hundreds of nanometers thick, with single nanometer precision.[2] Such films can be patterned using lithographic shadow masks, with resolution limited by the lithography procedure and surface roughness of the targeted substrate. Thicker metal structures (up to several mm) can be deposited through

electroplating, however this requires electrically conductive substrates and can result in rough surfaces or other defects.[2] Materials such as silicon, silicon nitride, silicon dioxide, and some polymers (*e.g.* Parylene), can be deposited conformally by way of chemical vapor deposition (CVD).[2,39] Though numerous different incarnations of the process exist, most require high temperatures and low pressures and all require an available chemical precursor. CVD processes offer a high dynamic range of thickness, from monolayers to tens of microns, high uniformity and excellent conformality, but may not be compatible with all substrates or materials, and are not amenable to shadow masking.[39] Polymeric materials such as PDMS and polyimide can be deposited in wet processes, or cast from solvents or uncured states.[40] Spin-coating offers highly uniform, but non-conformal, coverage of substrates at thicknesses ranging from single to hundreds of microns. Greater conformality can be afforded by casting directly from an uncured state, but uniformity is sacrificed.[40]

For those materials not easily patterned during deposition, the availability of useful etching techniques is critical. A large variety of tested techniques exist for silicon etching, including isotropic and anisotropic wet etchants, isotropic gas etchants, isotropic plasma etchants, and deep reactive ion etches (DRIE), many with high selectivity and etch rates, facilitating surface and bulk micromachining for MEMS fabrication. However, for other materials common in μID development, options are often limited. Glass can be etched isotropically by HF and anisotropically with DRIE processes using SF_6 or C_4F_8,[41–43] but etch rates for the latter are considerably slower than those achievable with silicon. Polyimide and Parylene are typically patterned with reactive ion etches (RIE) and oxygen containing plasmas,[44–49] as wet etching, in most cases, is not feasible.[46,50] Typical masking materials (*i.e.* photoresists) etch at similar rates, unfortunately with selectivity as low as 1 : 1 and thereby limiting etch depth.[47] DRIE of Parylene can be achieved with cycles of SF_6 and O_2 plasma followed by C_4F_8, but reported aspect ratios are poor compared to silicon DRIE.[51] PDMS is notoriously difficult to etch, due to its high chemical inertness. Dry etching methods exist that use reactive ion or microwave generated plasmas of CF_4 and O_2 mixtures,[52,53] however many of these methods suffer from slow etch rates and poor aspect ratios, and often yield rough surfaces.

Few MEMS or μIDs comprise a single homogeneous material, as such compatibility with other materials and material processing, strength of inter-material adhesion and availability of bonding methods is a chief concern. For materials requiring a biocompatible or hermetic seal for chronic implantation, but are nonetheless commonly used in μIDs (*e.g.* silicon), adhesion strength and durability with encapsulants is critical. For silicon μIDs, several reports have described adhesion with conformal coatings of silicone rubbers,[54,55] Parylene,[55–59] and polyimide,[60] as well as methods for creating long-lasting hermetically sealed devices with anodic bonding to glass.[59,61,62] An excellent comparative analysis by Treager of encapsulant efficacy against moisture intrusion highlights the superiority of metals and glasses over organic adhesives and silicones.[63] A thorough review specific to silicon μID encapsulation has been compiled by Wasikiewicz and Roohpour.[55] For polymeric materials adhesion strength and surface area has been noted to improve with plasma exposure or the use of adhesion promotors such as silane A-174.[56] Inter-material bonding and compatibility is also important for hybrid devices, where multiple materials serve structural purposes beyond encapsulation; these material interfaces include glass-silicon,[64–67] glass-Parylene,[68] silicon-polyimide,[69] and silicon-Parylene.[70] Reliability of inter-material bonding is also critical for packaging and assembly of microfabricated components. For a detailed description of established methods for micropackaging and microassembly of μIDs the reader is directed to texts by Schuettler and Stieglitz,[71] and Inmann and Hodgins.[72]

3. 'Hard' materials for microfabricated implantable devices

'Hard' materials, representing those non-polymeric materials with high Young's moduli ($>10^4$ MPa), high hardness ($>10^2$ kg mm^{-2}), high working temperatures (>500 °C), and effectively zero gas or liquid permeability, include silicon, glass, ceramics, and metals, the most common materials used in MEMS production and historically the first materials used for producing μIDs. As early as 1970, researchers were adapting semiconductor manufacturing processes to create simple implantable electrodes for recording neural activity.[73] Following the onset of MEMS research and development, silicon micromachining was used to produce the first μID pressure sensors,[74,75] drug delivery devices,[76,77] and neural electrode arrays.[78,79] Glass and metal structures became commonly used in conjunction with silicon μIDs, providing biocompatible or hermetic encapsulation, or serving as mechanical or electrical components. More recently microfabricated devices comprising only glass or metal structures have grown in popularity, owing to new fabrication methods such as glass reflow,[80] and laser milling.[29] Due to widespread familiarity with silicon micromachining, and the importance of compatibility with CMOS processing and integrated circuitry (IC), silicon remains the most common choice of material for μID fabrication. Hard materials, in general, are favored for their mechanical strength, large thermal budget, and impermeability to liquid intrusion.

Hard μIDs are typically produced by way of bulk and/or surface micromachining of preformed substrates. Bulk micromachining typically relies upon chemical etchants or physical machining methods to produce mechanically robust, high aspect-ratio three-dimensional structures for implantable MEMS, while surface micromachining methods include UV and electron-beam lithography, thin-film deposition (*e.g.* CVD, sputtering and evaporation of metals, dielectrics and polymers), oxide growth, and dopant implantation, with applications for patterning planar devices such as electrodes or circuit components. Through combinations of these

methods, an impressive number of hard μIDs have been developed and tested: electrochemical and optical probes for stimulating and recording neural activity, drug delivery devices, physical, chemical and electrical sensors, and prostheses. This section will review microfabrication approaches for a popular subset of hard substrates, namely silicon, glasses, ceramics and metals, as they pertain to the development of μIDs, and examine the challenges of using such materials.

3.1 Silicon

Though best known for its semiconducting properties, silicon is commonly used in μID production as a mechanical material or bulk substrate due to the ease with which it can be micromachined with high resolution and repeatability. Several μIDs produced through silicon micromachining are presented in Fig. 2. Wet etching of bulk silicon through lithographically patterned mask layers provides a low-cost, batch scalable method for fabricating a variety of desired structures on a micrometer size scale. Examples of such structures include simple cavities. Several variations of wireless μID pressure sensors comprise silicon cavities vacuum sealed by silicon–silicon fusion bonding or silicon-glass anodic bonding.[65,66,75,81–85] The design, adapted for biomedical use by Bäcklund *et al.* in 1990,[75] consists of a vacuum sealed cavity enclosed on at least one side by a thin membrane; deflections in the membrane due to changes in physiological pressure are measured capacitively[65,66,75,81–84] or piezoelectrically.[85] The design is robust and versatile, facilitates simple integration of planar metal coils for wireless monitoring, and was successfully employed for monitoring intraocular[75,83] and cardiovascular pressures.[82,84,85]

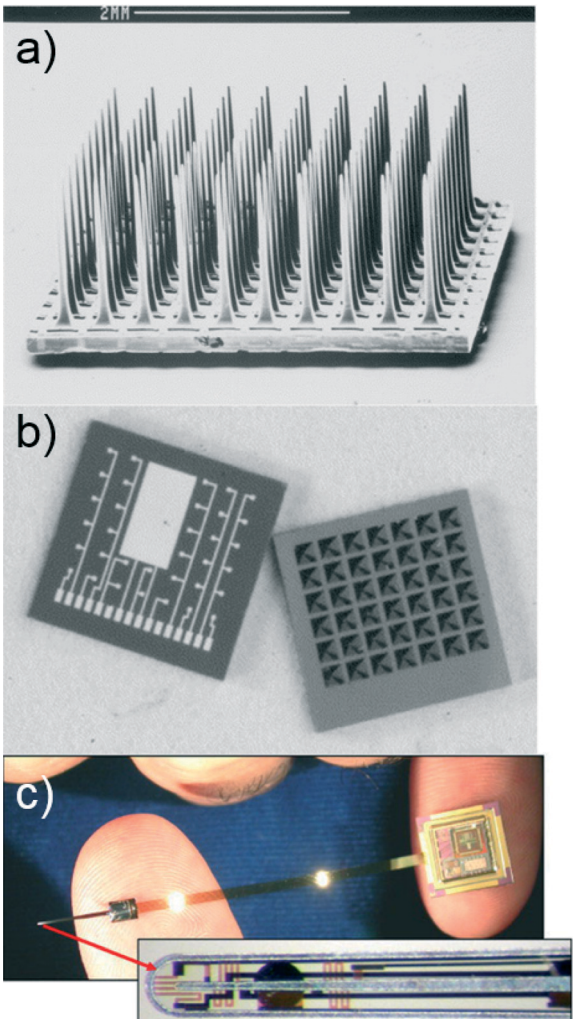

Fig. 2 Examples of microfabricated implantable devices machined from silicon. (a) Intracortical recording electrode array: reprinted from ref. 91 © Elsevier 1998. (b) KOH etched silicon drug release microchip: reprinted from ref. 9 © Elsevier 2003. (c) Cochlear prosthesis stimulating electrode (inset) connected to application specific integrated circuit: reprinted from ref. 94 © Elsevier 2008.

A similar fabrication approach was used to produce reservoir cavities for implantable drug delivery/release devices.[9,77,86–89] Santini *et al.* used KOH, an anisotropic etchant, to create implantable arrays of square pyramidal microreservoirs sealed with individually addressed membranes that could be electrochemically dissolved for controlled, *in vivo* release of therapeutics such as polypetides.[77,89] Elman *et al.* used similar KOH etched reservoirs with release driven by electro-thermal destruction of the sealing silicon nitride membrane; the design has shown success in intracranial delivery of chemotherapeutics in rodent models.[86,87] These designs allow for large numbers of individually addressable, low-volume reservoirs in a solid-state device, though the reliance on concentration based diffusion makes controlling dosing rate difficult.

Micromachining of silicon is also used to fabricate high-aspect ratio shanks, as a structure for penetrating neural probes. μID neural probes comprise long and thin support structures patterned with conductive electrodes for electrochemical recording and/or stimulation of brain tissue or peripheral nerves. There has been considerable work on silicon neural probes and neural probe arrays, with the devices known as the 'Utah array' and 'Michigan array' being the most successful. The 'Utah array', an intracortical microelectrode array composed of metal-tipped silicon needles, is fabricated by isotropically etching mechanically-cut silicon columns in a series of acid baths (5% HF, 95% HNO_3).[79,90,91] This process tapers the columns into thin needles with sharp tips, enabling penetration into the neural cortex. The 'Michigan array' consists of electrode coated microprobes fabricated from stacked layers of boron doped silicon, SiO_2, Si_3N_4, and patterned metal traces, released from a silicon wafer by etching away the undoped silicon with ethylenediamine-pyrocatechol.[78,92] This is a versatile method that enables fabrication of very thin devices; in one report, the approach was adapted to produce a flexible electrode array for a cochlear prosthesis.[93,94] These methods provide for batch-scale, parallel fabrication of high-aspect ratio structures, with precisely controlled shank dimensions and electrode impedances and placement. The selection of silicon enables the fabrication of

sharp probes that easily penetrate brain tissue, and eases connection to ancillary electronics.

In addition to wet etchants, dry silicon etchants, including isotropic XeF_2 gas, ionized plasma, and highly anisotropic DRIE methods (*e.g.* Bosch processes), offer controlled micromachining with high selectivity for many masking materials.[95,96] Dry micromachining of silicon avoids issues inherent to wet fabrication such as stiction, and DRIE enables improved control of etch profile, however these processes frequently require serial processing and expensive instruments. These techniques are increasingly used to produce high-aspect ratio silicon structures with sharp features for MEMS devices, which includes several examples of μIDs such as microelectrode shanks for neural recording[97,98] and implantable micromechanical pumps for drug delivery.[99]

In addition to its role as a support substrate or mechanical material in MEMS devices, silicon is the dominant choice of semiconductor for fabrication of application specific integrated circuitry (ASIC) for μID controls. Use of silicon ICs in biomedical implants predates the development of implantable MEMS by some years, and examples include conventionally fabricated devices such as pacemakers, neuro- and muscular-stimulators, and middle ear and cochlear auditory prostheses.[100] Inclusion of silicon ASICs in μIDs has become a critical component of powered devices, particularly those for chronic implantation requiring circuitry for wireless communication and battery charging, in addition to control and data logging. A more thorough discussion of IC technology in implants, and biotelemetry in particular, can be found in reviews by Ko *et al.*[100] and Receveur *et al.*[101] ASICs and transducers are frequently fabricated separately then packaged together, and as such choice of other materials for μID fabrication does not preclude use of silicon controls. However, direct integration of control circuitry is possible with silicon μIDs, and offers reduced device profiles.[102,103]

3.2 Glass

Glasses, including borosilicate glasses such as Pyrex, quartz, thermally grown or deposited SiO_2, and silicon oxynitride, are frequently used for sealing or encapsulating silicon μIDs due to their high impermeability, chemical inertness, and biocompatibility. In addition, glasses and oxides are excellent electrical insulators, which is desirable for wirelessly interrogated μIDs that require electrical insulation of microfabricated transmission coils or antennae. Biostability, however, can range greatly depending on specific composition and even deposition method,[104] and several glasses have high dissolution rates in saline. Dissolution rates *in vivo* have been measured as low as 0.33 nm per day for CVD silicon nitride, and as high as 3.5 nm per day for CVD silicon oxide.[105] In tests of subretinal implants, a TEOS oxide (tetra-ethylorthosilicate) layer 0.5 μm thick dissolved entirely, leading to corrosion of the underlying silicon device, following one year of implantation.[106] Evidently the formation of pinhole-free, low-defect layers is necessary for oxide insulated devices intended for chronic implantation. Alternatively, glass encapsulation may make use of considerably thicker layers; accelerated age testing on Pyrex-sealed silicon devices by the Najafi group extrapolated lifetimes of greater than 100 years.[107,108]

Though glass is compatible with many lithographic and surface patterning techniques, bulk micromachining of glass is considerably more arduous compared with silicon. Etching techniques for glasses include wet etching, dry etching, and DRIE as well as physical ablation methods such as sandblasting, however, in general, these approaches lack the requisite combination of scalability, high resolution, and/or high etch rates for ease of fabrication. As such, there are limited though notable examples of glass μIDs. A cooperative effort by Allen and CardioMEMS™ produced a passive, implantable pressure sensor for chronic arterial monitoring, fabricated by sealing an LC resonator within a glass etched cavity.[109] The approach was similar to silicon designs described above; HF was used to isotopically etch a recessed cavity in glass. Then after electrodepositing a planar metal inductor coil, the cavity was hermetically sealed by a glass plate supporting a corresponding coil. Haque *et al.* departed from this approach and developed a novel glass reflow process for fabricating an intraocular pressure sensor.[80] The process involves creating a silicon mold using a DRIE Bosch process, anodically bonding the etched silicon to a Pyrex wafer, and then heating the Pyrex such that the glass reflows into the etched features. The silicon is then etched away, leaving behind a smooth, homogeneous glass structure with high resolution features. Using this method, Haque *et al.* fabricated a glass μID housing an antennae, battery, ASIC, and the capacitive diaphragm pressure sensor for chronic monitoring of intraocular pressure.[80]

A characteristic high optical transparency helped establish glass as the material of choice for commercial fiber optics and subsequently the material of choice for optical μID research. The use of fiber optics in endoscopic surgery has increased familiarity with the technology among medical professionals, motivating the development of all-glass pressure and temperature sensors fabricated on fiber tips. Such devices rely on micromachined Fabry–Perot cavities or Bragg gratings to create sensitive transducers for *in vivo* conditions. Increasingly, the field of optogenetics utilizes μIDs comprising glass fibers or waveguides for exciting light-sensitive proteins or detecting fluorescence in neural research. Following initial efforts relying on unmodified commercial fibers,[110–112] the development of micromachined glass optical probes offered spatially focused stimulation easily paired with silicon electrode probes. Zhang *et al.* used HF to taper an optical fiber to a sharp point, and gold deposition to create an optical aperture of approximately 1 μm.[113] The 'optrode' (Fig. 3a) was manually integrated with a commercial silicon neural probe array to create a combined optical and electrical probe for simultaneous excitation and monitoring of the light sensitive *channelrhodopsin* protein.[113] Subsequent efforts adapted this approach for other optogenetic circuits and animal models, as well as devices with multiple optrodes.[114–116]

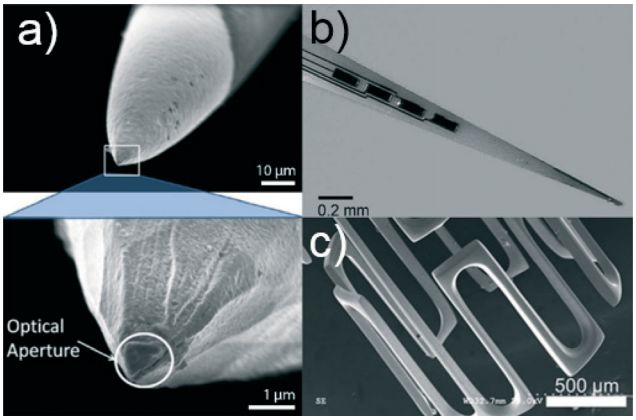

Fig. 3 Examples of microfabricated implantable devices machined from glass, ceramic, and metal. (a) Glass fiber 'optrode' for optical neural stimulation: reprinted from ref. 113 © IOP Publishing 2009. (b) Ceramic shank electrode for electrochemical sensing of L-glutamate: reprinted from ref. 126 © Elsevier 2002. (c) Arterial stent fabricated from stainless steel with electro-discharge machining: reprinted from ref. 133 © Springer 2011.

Abaya *et al.* recently presented an alternative fabrication method that used a combination of wet etching and mechanical dicing to create an optrode array from a single quartz substrate.[117] Other glass μIDs for optogenetic research use lithographic patterning to create embedded microfabricated waveguides; Wu *et al.* presented a method for creating optical waveguides comprising an oxynitride core clad in SiO_2.[118] Such designs offer greater integration with lithographically patterned electrodes, but require more complex fabrication.

3.3 Ceramic

Owing to a lack of suitable etching and micro-patterning methods, there are few examples of ceramic μIDs despite the successful use of the material in medical implants such as hip prostheses.[119] Ceramic packaging of microfabricated devices has been adopted for implants, as new techniques allow for a high density of electrical feed-throughs while maintaining impressively low permeability to water.[120–122] Similarly, low-temperature co-fired ceramics (LTCC) have found applications as the support substrate for multilayer implantable ASICs and antennae, particularly for devices requiring wireless telemetry.[123–125] The high dielectric constant of ceramic, and the ease with which low-profile, multilayer devices can be fabricated, have helped transition ceramic devices to *in vivo* applications.

Work from the Gerhardt group has demonstrated the suitability of ceramics as a μID substrate for more varied devices. Examples include electrochemical sensors for glutamate detection[126–128] and single neuron recording.[129] Typical devices consist of ceramic shanks, terminating in tips <5 μm wide, with micro-patterned platinum electrodes on one or both[128] sides (Fig. 3b). Advantages include high mechanical durability and biocompatibility, and a decrease in shunt capacitance compared to silicon electrodes as a result of the superior electrical insulation. Devices are fabricated by lithographically patterning metal electrodes and then individually carving each probe using a diamond blade.[130] Devices are finally released individually by mechanically dicing the substrate, underscoring the lack of methods for etching through thick ceramic substrates. This approach requires serial processing and may not be amenable to the production of many types of geometries; as such, there are still limited applications for ceramic μIDs.

3.4 Metal

Several metals have well established biocompatibility and a history of successful use in implanted medical devices, notably titanium and platinum, but also iridium, nitinol, some stainless steel variants, and other alloys. These metals exhibit excellent stability *in vivo* as well as excellent impermeability, and have long been the material of choice of hermetic seals around 'large' implants such as pacemakers. However, the need for wirelessly powered or wirelessly charged μIDs often precludes metal packaging, as opaqueness to electromagnetic radiation renders it unsuitable. Metals offer high mechanical strength and, unlike silicon, glass, or ceramics, low risk of brittle fracture, and therefore a lower risk of catastrophic mechanical failure. These features make metals an enticing choice of material for μIDs, though the characteristic high conductivity of most metals complicates the design of any device requiring surface patterned electronics. As such, use of metals for μID fabrication is typically reserved for applications requiring simple devices and robust structures, such as coronary stents. Laser milling of stainless steel is a common approach, but requires serial processing and provides limited resolution.[28,131] Electrical discharge machining (EDM) is an alternative method that offers improved resolution and the possibility of batch processing.[132] The technique involves generating electric spark discharge from microelectrodes to mill away material from a conductive substrates.[132] EDM has been successfully used to fabricate several stainless steel μIDs including novel variations on coronary stents[82,132,133] (Fig. 3c) and also blood vessel cuffs for *in vivo* flow measurements.[134,135] Fofonoff *et al.* demonstrated the use of EDM to produce a high density array of titanium microprobes for neural recording.[136] EDM fabricated titanium columns were etched with HCl to create a tapered tip only a few microns across, and then electroplated with platinum to provide a conductive surface. The probes were insulated with a conformal layer of Parylene and the insulation at the tips removed by laser ablation to create the recording electrode site. Arrays were mechanically robust with precise spacing, but the single electrode-site design limited applications.

Subsequent work has led to multi-site metal neural probes by utilizing fabrication methods compatible with lithographic patterning. Motta *et al.* used electroplating to create nickel shanks with platinum recording electrodes insulated by silicon nitride.[137] However, devices required an additional gold encapsulation layer to prevent potentially dangerous leaching

of nickel ions into the brain. An alternative approach by McCarthy *et al.* takes advantage of recent advances in reactive ion etching of titanium[138] to bulk micromachine probes from lithographically patterned titanium substrates.[139,140]

3.5 Challenges of hard materials

The selection of hard materials incurs certain challenges, specific to μID applications, which must be taken into account during the design phase. Several such challenges relate to issues of biocompatibility. For example, the majority of the devices surveyed in this section require the addition of an encapsulating barrier material to provide electrical insulation, to shield the body from potentially harmful materials or to reduce protein adhesion and biofouling. Considerable work and literature has been dedicated to ameliorating this requirement, and numerous encapsulating methods and materials are available, including oxides, polyurethane, PDMS, Parylene and polyimide. Still, it remains a necessary additional step, and researchers must be cognizant of concerns including adhesion and conformality of the barrier layer, unwanted changes to electrical or electromagnetic properties, and additional processing steps needed to uncover critical features. Sharp edges or corners and hard surfaces intrinsic to hard materials are also of concern, as they can tear tissue during surgical placement or while implanted. Additionally, severe mismatch between the mechanical properties of such materials and the tissue at the targeted site is believed to induce trauma, resulting from micro-motion of the hard implant damaging surrounding tissue, and exacerbating the immune system's foreign-body response. Numerous reports, compiled in reviews by Polikov and Navarro,[10,141] describe efforts to reduce such damage through changes in design or electrode coating, but frequently, the stiff material composing the device is identified as the problem.[24,25,142] The high rigidity and stiffness of hard materials can also impede fabrication of devices requiring flexible or deformable components. For μIDs such as nerve 'cuffs', which require membranes with high mechanical compliance, hard materials are ill-suited.

4. 'Soft' materials for microfabricated implantable devices

Here we define 'soft' materials as those with low Young's moduli ($<10^4$ MPa) and low hardness ($<10^2$ kg mm^{-2}). Compared to silicon and glass these materials have lower thermal conductivity, lower density, and much greater mechanical compliance. Soft materials commonly used in biomedical implants include many plastics and rubbers, however this section will focus on those materials with a demonstrated amenability to microfabrication techniques and history of use in μID research, namely Parylene C, PDMS, and polyimide. Additional characteristics of such soft materials include constrained working temperatures (<350 °C), high chemical inertness, and susceptibility to gas and vapor intrusion. Notably, these materials have well-documented biocompatibility (many polymers are used in FDA approved medical implants), with negligible issues of cytotoxicity, corrosion or instability, and as such have been used for decades in conventional medical implants. Synthetic polymers and silicone rubbers, such as PDMS in particular, have long been a familiar choice for construction or coating of implantable catheters, shunts, fluidic valves, bladders, and cosmetic implants among others, due to ease of fabrication, low cost, and minimal foreign body response incurred by implantation.[143,144] Parylene and polyimide found early applications as insulating coatings for implantable electrodes,[145–148] and became increasingly common choices as biomedical encapsulation following studies confirming chronic biocompatibility.[149,150] μIDs utilizing soft materials became a topic of increasing focus in the 1990s, following the proliferation of polymer MEMS and spurred in part by the development of replica molding and soft lithographic techniques. "Free-film" devices, comprising soft material substrates, offer a combination of high biocompatibility, high flexibility, optical transparency, and electrical insulation that motivated continued research. Following improvements in deposition and patterning methods, numerous soft μIDs were developed, which to-date include flexible neural implants, retinal prosthetics, pressure sensors, and drug pumps. More recent efforts have focused on use of soft biodegradable materials, such as silk fibroin, and the first examples of fully biodegradable and bioresorbable μIDs have been demonstrated.[151]

4.1 Surface micromachining of polymers: Parylene, polyimide & PDMS

Fabrication of soft μIDs may entail surface micromachining of planar films or soft-lithographic molding to create three-dimensional or raised structures. The former entails depositing planar layers of polymers onto hard substrates (typically silicon wafers) using spin coating or CVD, and then using photolithography to pattern additional layers of metal, insulation and other materials. Several examples of devices fabricated in this manner are displayed in Fig. 4. This approach allows for production of very thin, flexible devices, frequently housing planar electrodes for electrochemical sensing or stimulation. The technique is well suited for the development of flexible neural interfaces; the combination of thin profile, robust electrical insulation, and greater mechanical compliance addresses several problems facing hard μID neural interfaces and conventional microwire probes. Numerous reports have described a range of devices fabricated using Parylene[152–159] or polyimide[69,160–172] films, and in some instances PDMS[173–177] and liquid crystal polymer.[178] The most common design archetype is a thin penetrating shank composed of a polymer-metal-polymer sandwich intended for implantation in the brain.[69,153–158,161–164,166–168,171,179] Typical fabrication relies on photolithography to pattern metal (frequently platinum) for electrodes and connective traces, and O_2 RIE for exposing the electrodes from insulation and

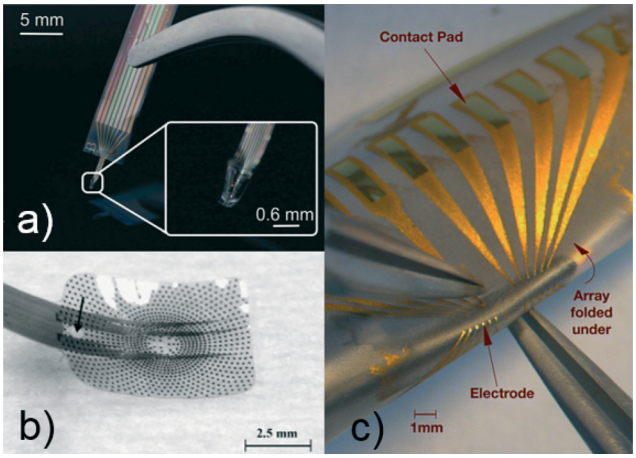

Fig. 4 Examples of flexible microfabricated implantable devices surface micromachined from soft polymers. (a) Neurotrophic sheath neural probe microfabricated from platinum and Parylene: reprinted from ref. 157 © RSC Publishing. (b) Curved retinal micro-electrode array with arrow denoting retinal tack hole: reprinted from ref. 184 © Elsevier 2008. (c) PDMS multi-electrode array for stimulation of spinal cord, shown here wrapped around 2 mm diameter wire: reprinted from ref. 177 © Springer 2007.

defining the shape of the probes. Several reports describe hybrid devices incorporating polymer substrates with sections of silicon[69,156,179] or silicon nitride,[171] or thin sheets of metal,[163] to increase mechanical strength without sacrificing flexibility.

Alternative geometries have been developed for interfacing with peripheral nerves, and include sieve electrodes[170] and curved devices for use as nerve 'cuffs'.[159,172,174–177] Nerve cuffs consist of a micromachined polymer film patterned with electrodes, which wraps around a peripheral nerve, providing contact for electrical recording or stimulation. These devices exploit the flexibility of polymer μIDs to create geometries not feasible with rigid substrates. Surface micromachined polyimide[172,180] and Parylene[159] nerve cuffs have been demonstrated for sciatic nerves, but PDMS[174–177] is a more common choice. Fabrication of PDMS devices often involves use of photo-patternable PDMS to expose the electrode sites.[174,175] The use of RIE to etch away an insulating PDMS has also been demonstrated, but requires prohibitively long etch times.[177] The ability to form micro-patterned curved surfaces is a notable advantage of soft μIDs; examples of other implantable technologies fabricated in this manner include cochlear electrodes,[181,182] retinal prostheses[183–185] and catheter compatible flow sensors.[186]

4.2 PDMS soft-lithography

For μIDs requiring non-planar structures such as cavities, actuators or fluidics, poor availability of chemical etchants with high etch rates and high selectivity for soft polymers preclude the use of bulk micromachining. Physical machining methods such as laser ablation are available, but, in general, these methods offer poor resolution and control, and require serial processing. Instead, a mold of the structure can be produced from thick photoresist or etched silicon, and the geometry transferred to a soft polymer using soft-lithography, micro-molding, or embossing. Typically, the desired material is cast over the hard mold, in the form of an uncured elastomer precursor or deposited by CVD, and then either the underlying structure is dissolved chemically or the device is peeled off mechanically. This technique is a low cost approach for creating devices requiring high-aspect, three-dimensional geometries from soft materials.

Soft lithography with PDMS was first developed to pattern microfluidic channels. Typical fabrication is conducted by first patterning a design in thick photoresist (frequently SU-8), then casting and curing PDMS elastomer over the mold. The cured PDMS containing a negative imprint of the pattern is physically peeled off the mold releasing the device. In work by Lin *et al.*, a PDMS microfluidic manometer was fabricated in this manner for powerless sensing of intraocular pressure.[187] The device consists of a PDMS microfluidic channel connected to a reservoir of green dye sealed under a deformable PDMS membrane, and operates by transducing changes in pressure into changes in the length of dye-filled portion of the channel. Other PDMS μID pressure sensors rely on strain gauges[188] or contain LC resonators in hermetically sealed cavities, reminiscent of devices fabricated in silicon.[189] In these efforts, the use of soft lithographic molding replaced chemical bulk micromachining, simplifying fabrication and yielding pliable PDMS μIDs that did not require additional encapsulation.

Similarly, the soft lithography method has been adapted to fabricating implantable drug delivery devices relying on PDMS fluidic reservoirs. In one design variation, a hollow PDMS reservoir is integrated with a fluidic cannula (Fig. 5a);[190–192] the reservoir can be filled and refilled by way of a standard syringe owing to the self-resealing ability of the elastic PDMS. Electrolysis, driven by integrated electrodes, can be used to electrochemically control drug delivery by generating bubbles that expel drug out of the cannula.[190,191] Huang *et al.* developed an electrolysis-driven reservoir array, fabricated with PDMS soft lithography and developed for single use *in vivo* drug delivery.[193] PDMS reservoirs, containing drug aliquots, were integrated with electrodes and IC control, and sealed with a membrane that burst upon application of electrolysis. Other designs rely on passive drug release; Chen *et al.* sealed drug-filled PDMS microreservoirs with a nanohydrogel membrane that became permeable when the surrounding environment reached a certain level of acidity.[194] Here, PDMS was chosen both for its biocompatibility and its ability to bond with the poly(*N*-isopropylacrylamide-co-MAA) membrane.

4.3 Parylene micro-molding

Raised and 3D-structures can be fabricated in Parylene using an analogous micro-molding technique; typically a mold of patterned sacrificial polymer (*e.g.* photoresist, polyethylene

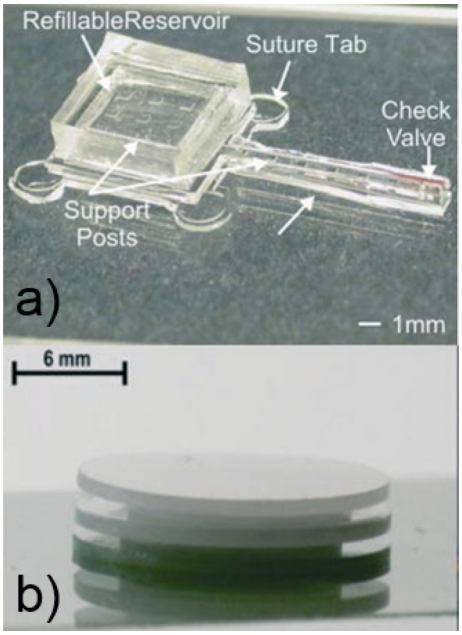

Fig. 5 Examples of microfabricated implantable devices fabricated with micro-molded polymers. (a) Refillable drug delivery device for chronic implantation, fabricated through PDMS soft-lithography: reprinted from ref. 192 © RSC Publishing 2008. (b) Microfabricated bellows cast from Parylene C onto a polyethylene glycol mold: reprinted from ref. 201 © Springer 2012.

glycol) or etched silicon is prepared, and then coated conformally with Parylene by way of CVD. Following dissolution of the mold or removal of the Parylene by peeling, the geometry is retained in the Parylene substrate. This technique allows for the fabrication of Parylene cavities, channels, reservoirs as well as more complex shapes with high-aspect ratios, without relying on deep chemical or plasma etching. Examples of μIDs fabricated in this approach include several variations of intraocular pressure sensors,[195–197] including a micro-molded Bourbon tube design[197] and Parylene variants on LC resonator cavities,[195,196] and electrochemical pressure sensors designed for monitoring hydrocephalus shunt performance.[198,199] A Parylene actuator for an implantable, micro-scale drug pump using a combination of soft lithography and Parylene micro-molding was developed.[68,200,201] The fabrication approach for the bellows requires a PDMS mold that is used to cast stacked disks of polyethylene glycol (PEG), which are subsequently coated in a thin film of Parylene (Fig. 5b). Dissolving the PEG in water leaves microfabricated Parylene bellows, which are installed in a fluidic reservoir on-top of electrolysis electrodes. Generation of bubbles actuates the bellows, which displaces the liquid in the reservoir, allowing for precise, targeted delivery *in vivo*.

Several instances of Parylene based implantable electrodes combine micro-molding with surface micromachining, to create implantable electrochemical probes with non-planar features. Examples include flexible electrode probes with microfluidic channels,[158] 'sheath' electrodes[153] and hemispherical electrodes[202] that incorporate raised structures to delivery neurotrophic agents and improve recording impedances. Wang *et al.* developed Parylene based electrode arrays for retinal prosthesis, using micro-molding onto etched silicon structures to create impressively sharp but flexible probes.[203,204] The technique has also been used to create ancillary structures for silicon neural probes, such as an IC 'pocket' integrated onto a silicon probe array.[205]

4.4 Biodegradable materials

Biomedical implants composed in part or entirely of biodegradable materials confer several advantages, including mitigation of the host's foreign-body response, reduction in size of implant following implantation, dissolution of temporary structures needed only during insertion, and often obviation of need for explant surgery. The success of biodegradable polymers in time-release drug delivery capsules and dissolvable sutures has motivated recent work exploring biodegradable materials for μID fabrication. Several reports on μID neural probes have described the use of biodegradable polymers such as PEG,[157,206] chitosan,[207] and silk[208,209] as temporary stiffening agents to assist in implantation, however, there have been only a few reports describing the use of biodegradable materials as the primary substrate in microfabricated implants (Fig. 6). Notable exceptions include work by Grayson *et al.* on the development of a biodegradable drug-delivery array;[210] the device consists of micro-reservoirs embedded in comparatively slow degrading poly(L-lactic acid) (PLLA), preloaded with different compounds and sealed with the fast degrading poly(lactic-co-glycolic acid) (PLGA). Fabrication entailed compression molding of a PLLA preform with a machined aluminum die. Fig. 6a shows an example of a PLLA preform after the hot embossing process, showing the regularity, but limited resolution, of such fabrication. A similar fabrication method has been used to produce implantable RLC resonators from biodegradable polymers (Fig. 6b), embedded with conductive polypyrrole nanoparticles, for producing powered, biodegradable μIDs.[211,212] Recently, Petersen *et al.* demonstrated a hot embossing method using an etched silicon stamp to produce PLLA drug release devices with significantly improved resolution over traditional compression molding techniques.[213] Similar examples of biodegradable devices include bio-resorbable coronary stents, fabricated from preforms of PLLA and other polymers using direct laser milling (Fig. 6d).[214,215] However, as with compression molding, this approach is compatible with a limited subset of μID designs.

Biodegradable silk membranes offer an enticing alternative. Recent efforts have developed a host of tools for microfabrication on biodegradable silk including methods for contact printing, soft-lithographic patterning and metal deposition.[216] Several reports outline adapting these methods to produce biodegradable silk MEMS as optical[217] and electronic[218] implantable devices. Fully functional, wirelessly powered and successfully implanted devices have been

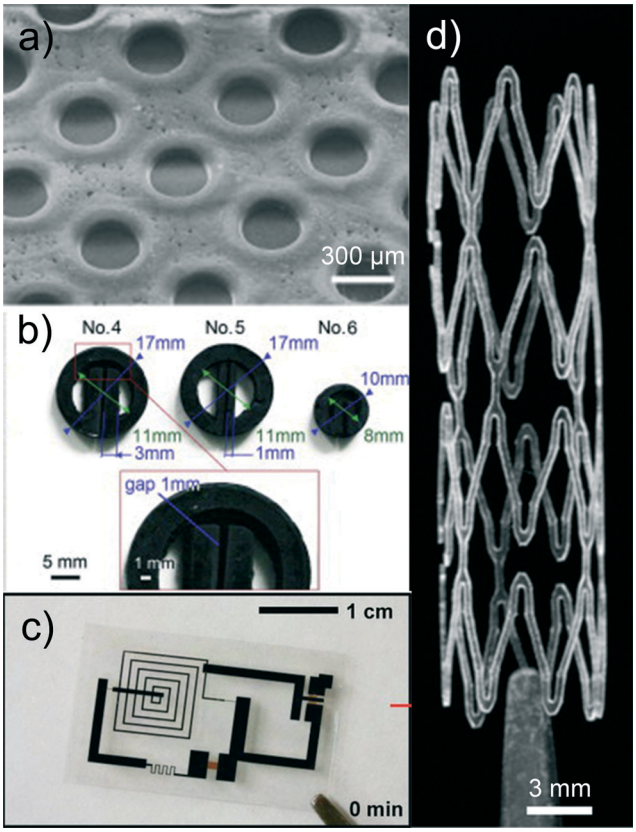

Fig. 6 Examples of microfabricated implantable devices built from biodegradable materials. (a) Microfabricated holes in a PLLA preform embedded using a hot embossing technique: reprinted from ref. 213 © Elsevier 2015. (b) RLC resonators fabricated from poly(ε-caprolactone)-polypyrrole using a hot embossing technique: reprinted from ref. 211 © Elsevier 2013. (c) Dissolvable electronics microfabricated from Mg/MgO and silk fibroin: reprinted from ref. 218 © AAAS. (d) Laser machined stent fabricated from biodegradable PLLA: reprinted from ref. 215 © Elsevier 2014.

developed from silk fibroin substrates patterned with conductive magnesium coils and resistive heaters (Fig. 6c).[219,220] Though use of biodegradable materials necessarily places significant restrictions on fabrication efforts, these nascent efforts show that many devices may still be realizable using resorbable materials.

4.5 Challenges of soft materials

Challenges confronting the development of soft μIDs include obstacles to both fabrication and operation. There are extensive, though often surmountable, limitations in the tools and methods available for microfabrication of the materials discussed here. Slow etch rates and poor selectivity to photoresist masks restrict the types of structures that can be etched in soft materials, and make release of thick-film devices difficult. There are few options for anisotropic etching or DRIE. Photo-patternable variants of polyimide and PDMS are often introduced as an alternative method for surface micromachining, but the biocompatibility of these materials is not well understood. Due to the limited thermal budgets of polymeric materials, many are not compatible with high temperature processing steps, including some bake steps, bonding methods, and CVD steps. Low working temperatures may also prevent use of solder connections, requiring the use of zero-insertion force connections or conductive epoxy for electrical connection. Those materials focused on in this section all suffer from some degree of gas and vapor permeability. This can create problems such as bubbles of intruded gas forming during fabrication, and can also promote delamination of device structural layers after implantation. The latter presents a critical issue for soft μIDs intended for chronic use, as the inevitable intrusion of water vapor can lead to electrical shorts and catastrophic failures.

Low Young's moduli, though often desirable, can create problems during implantation. Soft material neural shanks, for example, frequently require a stiffening agent or tool to assist in insertion,[221,222] which can complicate implantation surgery. For some applications, such as inertial sensing, stiffer materials may be preferred or even required, and many applications ultimately require batteries and ICs built from hard materials, undercutting the advantage of a soft μID approach.

5. Conclusion and outlook

Given the diverse array of μID devices and applications, material choice will always be dependent on the requirements of any specific problem. Chief consideration must be that of biocompatibility, ensuring both that implanted materials do not harm the body and that material resilience is such that *in vivo* conditions do not prevent proper function of the device, and such issues will always be dependent on questions of device placement, operation, and desired duration. For devices intended for mass commercialization, cost of material and ease of batch scale fabrication may determine material selection, while for small-batch devices intended as research material choice may be determined by specific device design, or the availability of suitable microfabrication tools. The trend towards μIDs comprising soft materials is likely to continue as on-going research yields more microfabrication techniques developed specifically for soft polymers. However, given the ubiquity of silicon fabrication facilities, the need for semiconductor based ICs, and applications requiring mechanically hard or stiff substrates, hard devices, and silicon in particular, are likely to remain the most common choice for the near future. A large number of materials, new and old, with potential uses in μIDs were not discussed here, and continuing research is likely to produce even more in following years. Given such increasing options researchers should remain cognizant of the available materials and their capabilities to best inform design of new and improved μIDs.

Conflict of interest disclosure

E. Meng has a significant financial interest in Fluid Synchrony LLC.

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