Ceramic Packaging in Neural Implants

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Abstract

The lifetime of neural implants is strongly dependent on packaging due to the aqueous and biochemically aggressive nature of the body. Over the last decade, there has been a drive towards neuromodulatory implants which are wireless and approaching millimeter-scales with increasing electrode count. A so-far unrealized goal for these new types of devices is an in-vivo lifetime comparable to a sizable fraction of a healthy patient's lifetime (>10-20 years). Existing, approved medical implants commonly encapsulate components in metal enclosures (e.g. titanium) with brazed ceramic inserts for electrode feedthrough. It is unclear how amenable the traditional approach is to the simultaneous goals of miniaturization, increased channel count, and wireless communication. Ceramic materials have also played a significant role in traditional medical implants due to their dielectric properties, corrosion resistance, biocompatibility, and high strength, but are not as commonly used for housing materials due to their brittleness and the difficulty they present in creating complex housing geometries. However, thin film technology has opened new opportunities for ceramics processing. Thin films derived largely from the semiconductor industry can be deposited and patterned in new ways, have conductivities which can be altered during manufacturing to provide conductors as well as insulators, and can be used to fabricate flexible substrates. In this review, we give an overview of packaging for neural implants, with an emphasis on how ceramic materials have been utilized in medical device packaging, as well as how ceramic thin film micromachining and processing may be further developed to create truly reliable, miniaturized, neural implants

1. Introduction

As is well known, the ability to interface with nervous tissue has great therapeutic potential, promising to treat a wide range of conditions ranging from motor dysfunction (Parkinsonian tremor, tetraplegia, Meige syndrome, etc.), psychiatric disorders (depression, OCD, etc.) (Chen, et al., 2017, Sun & Morrell, 2014), and peripheral nerve applications (Tracey, 2002, Borovikova, et al., 2000, Bosch & Groen, 2000, Slavin, et al., 2006) among others. Additionally, bidirectional communication with the nervous system allows for continuous monitoring and modulation of the nervous system, such that preventative actions can be taken to slow or even halt the progression of neuropathies (Famm, et al., 2013, Rouse, et al., 2011, Poon, 2014). Commercial efforts to deploy these types of interventions through the use of active implantable medical devices (AIMDs) is growing rapidly; an oft-cited estimate shows that the neuromodulation device industry was valued at 8.4 billion dollars in 2018 and is expected to grow to 13.3 billion dollars by 2022 (Cavuoto, 2018).

1.1 New and Existing Challenges in clinical neural implant packaging

The majority of neuromodulation devices rely on metal electrodes. Most of the electrochemical action occurs at the electrode-tissue interface; electrical current injected by the device changes the chemical potential of the local environment of a nerve, modulating the activity of nerve targets to achieve some therapeutic effect. These electrodes can also be used to detect extracellular changes in chemical potential, which can be used as a proxy for neuronal or peripheral nerve activity. A typical neural implant consists of: 1) microelectronics which assist in recording neural signals from or transmitting stimulation waveforms to metal electrodes; 2) the metal electrodes which interface and make contact with tissue; 3) insulated, conductive leads which connect the electrodes to the microelectronics; and 4) a battery, antenna coil, wires and/or other means to provide power to the implant. Depending on the application, emerging implants may need to interface with hundreds or thousands of electrode channels (Cha, et al., 1992, Lovell, et al., 2005, Buzsáki, 2004, Viventi, et al., 2011, Chang, 2015, Chung, et al., 2019). For most applications, the implantation is expected to be performed once (i.e. no explantation is needed) and would remain functional for the patient's lifetime. Viewed from the perspective of implant mechanical design and

material choices, both the tissue reaction to the implant (biotic) and the implant's response to the tissue environment (abiotic) must be considered to achieve a long lifetime in-vivo (Fig. 1). Percutaneous connections can serve as routes for infection, so ideally all four components of the neural implant are fully implanted within the body.

Once the device is implanted, the body mounts an immune response against the device. This has been well-studied and covered by numerous reviews (Kozai, et al., 2015, Polikov, et al., 2005, Potter, et al., 2012, Szarowski, et al., 2003). A hallmark event of the immune response to implanted foreign body is gliosis in the central nervous system (Wellman, et al., 2019, Seymour & Kipke, 2007, Lind, et al., 2013, Turner, et al., 1999) and fibrosis in the peripheral nervous system (Romero, et al., 2001, Grill & Mortimer, 2000, Christensen, et al., 2014). While fibrosis can occasionally be useful to stabilize implants, the presence of scar tissue in both the central nervous system and peripheral nervous system reduces the efficacy of implanted devices by walling off healthy tissue from the electrodes (Fig. 1a,b). However, smaller implants have been found to have reduce scar tissue encapsulation around the device (Seymour & Kipke, 2007). Furthermore, large implants require more invasive surgeries and can also result in discomfort for the patient, or worse, skin erosion (Peña, et al., 2008). Thus, miniaturizing implants is highly desirable to increase the efficacy of chronic implants.

In parallel, the effect of the tissue environment on the implant material stack is also critical. The tissue environment is aqueous, saline, and both chemically rich and chemically aggressive. The immune response mounted by the body in response to an implant releases reactive oxidative species (ROS) which attack and degrade the implant (Fig. 1c) (Patrick, et al., 2011, Takmakov, et al., 2015). Corrosion of exposed metals is a major concern, with mitigation strategies heavily relying on material choices (Fig. 1d). Due to the saline environment of the tissue, galvanic corrosion between exposed metals can occur both in dissimilar metals and between identical metals in different environments (crevice corrosion) (Gilbert, et

al., 1993, Kennell & Evitts, 2009). Corrosion can also be exacerbated by electrical stimulation due to electrolysis, which reduces the pH around the implant (Donaldson & Sayer, 1981, James, et al., 2016).

The consequence of these abiotic failure modes is eventual loss of hermeticity. This can result in moisture entering the packaging, shorting and corroding microelectronics. Simultaneously, non-biocompatible materials from the packaged microelectronics may leach into tissue, causing cell death and/or exacerbating the foreign body response (Vanhoestenbergh & Donaldson, 2013). Additionally, the packaging must be a good molecular barrier beyond water vapor since diffusion of mobile ions such as Na^+ , K^+ , and Cl^- into the integrated circuits within the housing can cause premature failure of the implant (Song, et al., 2017).

Putting the aforementioned requirements together, the ideal implant is capable of high channel counts while being extremely miniaturized, wireless, biocompatible, biostable, and ultimately hermetic for timescales commensurate with a patient's lifetime. The technology limitation is not in the microelectronics or the interface, as many miniaturized devices with hundreds of channels have been demonstrated (Zhou, et al., 2019, Jun, et al., 2017, Raducanu, et al., 2017, Viventi, et al., 2011, Stevenson & Kording, 2011), but rather in the packaging of the implant components.

1.2 Packaging Materials for Medical Implants

Previous iterations of AIMDs have generally relied on polymeric potting (i.e. insulation and mechanical protection) or metal housings. For example, the original pacemakers were encapsulated in thick epoxy before titanium housing became the standard housing for implants (although the leads between internal pulse generators and their electrodes are still potted in silicone). Many researchers have long seen the choice between polymeric encapsulation and metal housing as equivalent to using a conformal material vs the manufacturing of an impermeable envelope (Donaldson, 1976). Unfortunately, while polymer encapsulation materials (including silicone, parylene, polyimide, and epoxy) have the advantage of being highly conformal, inexpensive, and easy to apply, polymeric materials are not good long lifetime materials due to their relatively high water vapor permeabilities (Traeger, 1977). This is often circumvented for

larger implants by increasing polymer thickness to many millimeters (or more) but it is not a viable strategy for very thin layers in miniaturized devices. In addition, the ROS species discussed earlier are well-known to participate in the breakdown of polymer coatings. For example, parylene is known to crack after months of implantation in the body (Barrese, et al., 2013, Takmakov, et al., 2015). Additionally, polymers such as parylene and liquid crystal polymers will undergo material property changes at high temperatures, which prevents the use of steam autoclaves, which generally operate at 120 °C. While ethylene oxide (EtO) sterilization can be used at much lower temperatures, the permeability of polymeric potting materials can allow both EtO and moisture to be stored in the material bulk and a degassing step is required (Stieglitz, 2010).

Due to their very low water vapor permeabilities, metals have been the industry standard for housing implantable microelectronics. In particular, titanium has been the material of choice for AIMD housings due to the formation of a stable and inert oxide passivation layer (Bowman & Meindl, 1986). While titanium housings have been an excellent workhorse during the past 50+ years, they have some limitations. For example, metals alone cannot be used in packaging, as the electrical feedthroughs which connect the electrodes to the microelectronics must be electrically isolated from each other. More conspicuously, the use of metal-only housings generally precludes the ability to efficiently transfer energy wirelessly using electromagnetics without undue heating of the package caused by eddy currents.

In contrast to metals, ceramic materials not only have low water vapor permeabilities, are transparent to RF, can be rendered optically transparent, and, recently, have been shown to be amenable to ultrasonic power transfer (Gutierrez, et al., 2017). Many ceramics are also chemically inert, biocompatible, electrically insulating, and harder and stronger than most metals (Piconi & Maccauro, 1999, Vlasov & Karabanova, 1993). Due to these favorable properties, ceramics have had a long history as implant materials both alone and in conjunction with titanium housing. As implants become more ubiquitous and

continue to shrink, ceramics will play an increasingly important role in the development of active implantable medical devices.

2. Classical ceramic packaging methods

Currently, the major application of ceramics in AIMDs is in hermetic feedthroughs, which provide pathways for electrical signals to be routed into and out of the implant housing. The development of the alumina-titanium feedthrough for the cardiac pacemaker significantly increased the longevity of AIMDs from months to years and the hermetic alumina-titanium paradigm has been a mainstay of the AIMD industry ever since (Ruys, 2018). Ceramics have also been used to improve wireless transmission in titanium housings, acting as windows with some degree of RF transparency (Borton, et al., 2013, Bjune, et al., 2015). As a clinical example, the Axonics sacral nerve stimulator utilizes a hybrid titanium-ceramic package for the implantable pulse generator (IPG) which allows for high efficiency electromagnetic coupling (Elterman, 2018). This unique construction allows for an extremely small charging coil, enabling the Axonics IPG to be as small as 5 cm³. In contrast, other IPGs housed solely in titanium are on the order of tens of cm³. While completely ceramic housings have been explored, particularly in cochlear implants in which wireless communication is essential, the brittleness of ceramic has been a reliability concern. In cochlear implants, all-alumina housing was explored by Cochlear Ltd, MED-EL, and Neurolec, but due to the large amount of exposed area, the housings were vulnerable to failure due to mechanical impact (Fig. 2a) (Stöver & Lenarz, 2009). Similarly, the first generation BION microstimulator used a glass housing to enhance RF transparency, but found that the housing was prone to fracture after repeated bending stress due to muscle contraction (Fig. 2b) (Loeb, et al., 2007). Careful mechanical design was able to improve the strength of the BION glass housing; subsequent versions of the implant utilized a ceramic housing with a 7x improvement in bending strength (Kane, et al., 2011). Arguably, the reason glass worked at all for the BION was the small size and relatively thick glass walls. For larger implants, titanium housings remain the preferred solution. Thus, while ceramics may not comprise the majority of modern implant packages, they

are an essential component. To this end, whether the ceramic part acts as a communication window, substrate, or feedthrough, it must be shaped and then joined to the rest of the implant.

2.1 Forming of ceramic packaging components

Conventionally, ceramic parts are created from powder, which is consolidated and shaped into a “green body”, then fired to densify the final part (Fig. 3). Shaping of the green body can be done in a variety of ways but is dominated by “wet-forming” and “dry-forming” methods. In wet-forming methods, the ceramic powder is added to a liquid medium to form a slurry in which binders and plasticizers can be added. This slurry can then be poured into a mold (injection molding) to form a complex shape; tapecast into a sheet for green machining; or slipcast to form a hollow shape; among other methods (Yeong, et al., 2013). In dry-forming methods, the ceramic powder is simply pressed to form the desired shape using methods like uniaxial die pressing or cold isostatic pressing (Ruys, 2018). When forming ceramics, the major concern is avoiding structural defects, such as cracks. These cracks tend to occur during drying processes, such as the drying step needed to remove organic binders and solvents from ceramic slurries. Dry-forming does reduce the risk of cracking, but particle packing homogeneity and shape complexity are worse than for wet-forming methods. Injection molding allows for complex parts with high precision and have been used to form the “comb” style alumina feedthroughs used in cochlear implants (Fig. 4b). However, injection molding can be limited; particularly complex geometries may result in short shots (incomplete filling of the mold) or knit-lines (improper mixing of the slurry from multiple injection points resulting in stress-lines) (Christian & Kenis, 2007). The main method of forming ceramic substrates, particularly for electronics, has been tape-casting; this method can create ceramic substrates with sub-mm thickness (Tummala, 1991). With this method, a ceramic slurry is doctor-bladed across a surface with a controlled velocity and height to achieve a green sheet with a target thickness. This sheet can then be machined and fired to form the final substrate. 3D printed ceramics are also a promising new technology, allowing for very rapid and cheap manufacturing since they do not require tooling. However, in its current state, 3D printing cannot achieve the same thin substrates as tapecasting; additionally, dimensional

accuracy, surface finish and high porosity remain issues (Travitzky, et al., 2014). As in many material domains, the prospect of being able to rapidly and cheaply manufacture ceramic parts with high geometric complexity is accelerating the development of 3D printed ceramics; with improvements, additive manufacturing may soon replace techniques like injection molding and cold isostatic pressing (Chen, et al., 2019).

2.2 Joining and metallization of ceramics

Once the ceramic part is formed, it must be hermetically joined to the housing material to form feedthroughs, windows or seals. In a feedthrough, one or more metal pins are also joined to the ceramic body to create conductive paths between the outside and the inside of the package; the ceramic body is then joined to the metal housing of the implant (Fig. 4a). The most common method of joining ceramic is brazing, in which two materials are joined with a filler material at a temperature exceeding 450 °C (differentiating it from soldering, which occurs at lower temperatures). Brazing fillers can be either passive or active. In an active braze alloy, the paste generally contains an active element such as Ti or Zr which promotes the adhesion and wetting of the ceramic material (Apollo, et al., 2016). As such, brazing with active braze alloys (ABA) generally requires a vacuum furnace, capable of pumping down to at least 10^{-5} torr. ABAs are widely used hermetic joining of feedthroughs and housing sealing. A classic example is the Ti-Cu-Ni brazing alloy used in alumina-titanium bonding process; the Ti content promotes wetting of the braze alloy on the alumina, and endows the joint with high biocompatibility and corrosion resistance. Partially because of objections to the cytotoxicity of copper, copper-free braze alloys have been explored. Ti-Ni brazes have been shown to hermetically seal zirconia-to-titanium (Jiang, et al., 2005) and pure Ni itself was found to be able to hermetically seal the same materials because the titanium from the part was able to diffuse into the nickel to form a eutectic alloy (Jiang & Zhou, 2009). Both gold and silver ABAs have been utilized to hermetically seal polycrystalline diamond (PCD) packages; the high gold content of the gold-ABA arguably promotes biocompatibility (Lichter, et al., 2015). In the last example, it was found

that the gold-ABA did not wet the PCD well, but the silver-ABA could be used as an intermediate layer, with the silver layer not exposed to the tissue environment after encapsulation by the gold layer.

In contrast, passive braze alloys do not contain reactive elements to promote wetting, which allows them to be used in low vacuum environments. Typically, these braze materials are noble metals such as gold or platinum (Siddiqui & Jones, 2014). Unfortunately, passive alloy joints are generally mechanically weaker and somewhat porous (Agathopoulos, et al., 2002, Correia, et al., 1998). Furthermore, the poor wetting of these alloys to ceramic materials requires a metal interlayer. This can be achieved through physical vapor deposition, chemical vapor deposition, screen printing, or other methods (Santella & Pak, 1993).

While hermetic brazed feedthroughs have had much success, they are limited in pin (conductor) density due to the risk of the ceramic cracking as the conductors are brought closer together (Kelly, et al., 2011). The density limit can be increased integrating metal parts or metal pastes with the ceramic green body and simultaneous firing, a method also known as co-firing (Schuettler & Stieglitz, 2013). Platinum is used for this due to its high melting temperature, low resistivity, and ability to form solid-state bonds with alumina (Allen & Borbidge, 1983, Guenther, et al., 2014). Solid Pt wires can be cofired with the ceramic, in which wires are placed between “loaves” of green sheet, compressed together, and fired (Fig. 4c) (Gill, et al., 2013). This method has been able to create 10 x 10 arrays of feedthroughs with pitches between 400 and 450 μm . When using metal pastes, slurries containing metal particles are screen printed into vias machined into the green body and sintered along with the ceramic (Fig. 4d) (Yang, et al., 2018, Green, et al., 2013). Afterwards, the ceramic substrate with metal vias can be metallized again to form interconnects. Substrates with ~1000 feedthroughs and pitches on the order of 40 μm have been demonstrated. To date, no other method has been able to provide such high feedthrough densities.

One drawback of brazing and co-firing is the high temperature required. During high temperature excursions, thermal expansion coefficient mismatches between different parts can result in cracking or

loss of hermeticity. Furthermore, due to the use of organic binders in metal paste feedthroughs, sintering of these pastes can result in void formation which also compromises the hermeticity of the via. Finally, where hermetic sealing of the housing is concerned, high temperature joining is often incompatible with the microelectronic components within the housing. Thus, low temperature methods of joining ceramic are highly desirable.

A relatively new method for low temperature feedthrough formation is to form extruded metal vias with stud bumping (Fig. 5) (Shah, et al., 2012, Langenmair, et al., 2018). In this method, vias are machined into a ceramic substrate and subsequently metallized. Gold bumps are placed over the vias using an ultrasonic ball bonder to alloy the gold with the via metallization, then coined. In this way, extremely dense hermetic feedthroughs in a ceramic substrate can be made at a low temperature, with a theoretical density up to 2500 feedthroughs/cm². While the feedthroughs themselves have been found to be hermetic, to date, substrates with over 100 feedthroughs have been found to be non-hermetic due to misalignment between the gold stud and the via. In published attempts, studs were manually bonded, which contributed to misalignment error. Further work illustrating that automation of the stud placement to improve alignment also improves hermeticity is needed to validate this technique.

Other approaches for sealing packages at low temperature have been explored. Schuettler et al. developed a 360-channel vision prosthetic on a ceramic substrate sealed to a metal cup with low temperature solder in a custom hermetic sealing chamber (Schuettler, et al., 2010, Schuettler, et al., 2010). While this method yielded devices with excellent hermeticity, the use of solder and the requirement of a solderable housing material left biocompatibility an open question. That work utilized a brass cup for solderability, as titanium is essentially impossible to solder (due to its surface oxide) but brass is cytotoxic as a copper-zinc alloy.

The standard practice for low temperature sealing of titanium housings remains laser welding (Xiansheng, et al., 2011, Gedopt & Delarbre, 2000). Laser welding allows for very localized deposition of

heat to melt and fuse materials together. This is advantageous for sealing housing without thermal damage to internal components. However, local heating is problematic for joining ceramics due to thermomechanical stresses generated by the large temperature gradient between the laser affected zone (LAZ) and the areas outside of it (Witte, et al., 2002). Early efforts to circumvent this issue have been to reduce the gradient by preheating the part prior to welding with an oven or a secondary laser (De Paris, et al., 1991, Riviere, et al., 1994, Exner & Nagel, 1999). Alternative methods to utilize laser welding include the use of a filler material such as glass frit to aid joining (Wu, et al., 2010); this enables a form of “laser brazing” proposed for hermetic vision prostheses as well as to seal the previously described PCD implants (Vanhoestenbergh, et al., 2008, Lichter, et al., 2015). More recently, ultrafast laser welding has been introduced as a method for crack-free ceramic joining without needing to preheat the parts (Penilla, et al., 2019, Watanabe, et al., 2006, Zimmermann, et al., 2013). An in-depth explanation behind the interaction between ultrashort laser pulses and matter can be found in both Miyamoto et al. and Penilla et al. (Miyamoto, et al., 2014, Penilla, et al., 2019). Briefly, ultrashort laser pulses stimulate non-linear absorption processes in material and can result in embedded molten pools within the bulk material. Because of the short pulse time, the material outside the molten pool remains its original temperature. The embedded molten pool then acts as an elastic body and thus does not generate thermomechanical stresses during cooling. Ultrafast laser welding for ceramic joining is a significant milestone for enabling all-ceramic housing and promises hermetic seals formed without heat-damage to the packaged components. Ultrafast laser welding does have material constraints, but careful engineering or tailoring of the ceramic microstructure can circumvent these issues (Penilla, et al., 2019).

2.3 Hermeticity Testing

Ultimately, a package must protect the internal microelectronics from the body environment and prevent compounds from the microelectronics components from leaking into the body environment. Thus, after forming and joining, the package must be leak tested to ensure hermeticity. Hermeticity testing generally occurs in two phases – gross testing and fine testing. A gross leak is defined by the military

standard MIL-STD-883 as a package with a standard air equivalent leak rate greater than 10^{-5} atm-cc/sec (Greenhouse, 2000). A common gross-leak test is the *bubble test*, in which a detector liquid with a low boiling point is forced into the package by ‘bombing.’ Bombing is injection of the detector medium into the package by immersing the sealed package in the detector and pressurizing the fluid to drive it into the package. Post-bombing, the package is placed in an indicator liquid which has a much higher boiling temperature. The temperature of the indicator liquid is then raised above the boiling temperature of the detector liquid but below the boiling point of the indicator. This condition is maintained for at least 30 seconds. If bubbles are observed, the package is declared to be a “gross leaker”. Presuming the package passes the gross leak test, it is then tested for fine leaks. The current standard method of fine leak testing is to use helium (He) because of its small atomic size and rarity in the ambient environment. Two methods exist for helium leak testing: bombing and backfilling. In bombing, sealed packages are placed into a high pressure He environment, which drives He into the package. The bombed packages are then placed into a chamber with a mass spectrometer and the rate of helium leakage is measured. Alternatively, backfilling may be used in which packages are sealed in a helium environment and then transferred to a mass spectrometer to measure helium leakage. The leakage of He, of course, is not the same as the leakage of water vapor; to predict the water leakage rate, Graham’s Law of Effusion is used (Vanhoestenbergh & Donaldson, 2011):

$$L_{water} = \sqrt{\frac{M_{He}}{M_{water}}} L_{He}$$

Where L_{water} and L_{He} are the leak rates for water and helium and M_{He} and M_{water} are molar masses for helium and water. For reasons which will be explored in the next section, it is difficult to pin down a He leak rate that guarantees hermiticity.

3. MEMS-enabled miniaturization of ceramic packages

In the pursuit of highly miniaturized implants, techniques from microelectromechanical systems (MEMS) and other semiconductor processing methods continue to be employed to create devices with sub-millimeter dimensions and to further increase electrode density (Seymour, et al., 2017). While the previously mentioned work by Green et al. demonstrated feedthrough densities on the order of 1000/cm², it required a four-layer laminate structure, with each layer being roughly 200 µm thick (Green, et al., 2013). While the authors suggest that a two-layer structure is enough, this still results in a substrate at least 400 µm thick (not including the rest of the housing). Furthermore, the interconnects are structured using a laser machining process, which has a minimum line width of 20 µm. Microfabrication technology, however, can pattern sub-micron features on micron thick substrates and has a long history in the development of neural probes (Fig. 6) (Wise, 2005, Cheung, 2007). A representative, seminal, example is the technology developed at the University of Michigan. One of the early ‘Michigan Probes’ was only 20 µm wide, between 8 and 15 µm thick, between 1.5 and 3 mm long, and could support 10 channels (Fig. 6a) (Najafi, et al., 1985). This represents an electrode density of nearly 17000 channels/cm²! Modern neural probes have pushed this density even farther (Steinmetz, et al., 2018). The Neuropixel probe boasts 960 recording sites on a 1 cm long, 70 µm wide, and 20 µm thick silicon shank – an electrode density over 1 million channels/cm² (Fig. 6b) (Jun, et al., 2017).

3.1 The challenge of miniaturized packages

Although microfabrication is indisputably a favored manufacturing route to small implants and high densities, severe issues arise, not all of them obvious. For example, the decreasing volumes of microfabricated housings result in a higher likelihood of reaching dew point, resulting in moisture condensation. Thus, smaller packages must have higher hermeticity constraints than larger packages. The relationship between package volume and maximum leak rate can be expressed by (Guenther, et al., 2020):

$$L_{water} = -\frac{V}{t} \ln \left(1 - \frac{Q_{H_2O}}{P_{out,H_2O} - P_{in,H_2O}} \right)$$

Where Q_{H_2O} is the maximum allowed water partial pressure within the cavity, P_{out,H_2O} and P_{in,H_2O} are the initial partial pressures of water on the outside and inside of the housing respectively, V is the free-volume of the housing, and L_{water} is the maximum leak rate allowed to maintain hermeticity within a time period t . The maximum allowed water partial pressure is usually referenced to the MIL-STD-883 recommended value of 5000 PPM, which is derived from the Clausius-Claperyon relationship as the maximum permissible water vapor pressure before condensation occurs.

This relationship between hermeticity (measured in He leak rate), housing free-volume, and moisture content is plotted in Fig. 7, which shows the water vapor partial pressure in PPM of a package of a given size and He leak-rate after 10 years. The manufacturing consequence of this phenomenon is that the maximum allowed leak rate for such small packages becomes too low to be detected by most He leak rate detectors currently employed, which are typically limited to 10^{-11} atm-cm³/s. Some methods have been used to try to improve the detection floor, such as cumulative helium leak detection (CHLD). In CHLD, a specialized cryo-pump is used which is capable of pumping out all other gases besides He from the test chamber, resulting in a higher detection sensitivity. However, Guenther et al. found several problems with this method when applied to microscale packages: outgassing of He from rubber o-rings created significant background noise, and the manufacturer's requirement of having a test-chamber volume to sample-cavity volume ratio of less than 100 was very difficult without major modifications of the commercially available CHLD instruments (Guenther, et al., 2020).

3.2 MEMS-enabled ceramic neural implants

Due to the difficulty of leak testing miniaturized housings, it follows that a potential path towards long-lasting hermetic implants is to conformally coat devices with packaging material, resulting in zero free-volume within the packaging. Thin film deposition techniques such as chemical vapor deposition (CVD) and atomic layer deposition (ALD) can result in highly conformal coatings to encapsulate implants. These thin films can be on the order of microns to sub-microns thick, which means that the packaging of the device will not add a significant amount of volume to the device. Furthermore, the ability to deposit a film

over the microelectronics obviates the need for separate joining processes to seal housings. This is advantageous not only for miniaturization, but also in wireless transmission, where even the small amount of metal in the braze alloy can detune an antenna. Many ceramics can be deposited in this way and have been used as encapsulation materials. Again harkening back to the classic Michigan probe, the conductors on the probe were encapsulated by a bilayer of CVD silicon nitride (SiN) and silicon dioxide (SiO₂) (Najafi, et al., 1985). Xie et al. demonstrated the use of ALD alumina (Al₂O₃) in combination with parylene as a hermetic bilayer, projecting a lifetime beyond 5 years at 37 °C (Xie, et al., 2013). Weiland et al. showed that 5 µm thick diamond-like carbon thin films were effective moisture and ion-barriers, showing only a single pinhole over a 1000 mm² area and less than 1% change in electrical properties of an encapsulated integrated circuit (IC) (Weiland, et al., 2013).

The work done by Weiland et al. demonstrates another benefit of thin-film deposition technology: low temperature deposition. The high temperatures required for ceramic sintering and brazing for sealing housing are often incompatible with CMOS technology. However, thin-film deposition can often be done at much lower temperatures, with additional energy introduced to the system with plasma rather than heat. Amorphous silicon carbide (a-SiC) for example has been pursued as a coating for neural implants due to its biocompatibility and chemical inertness and can be deposited at temperatures lower than 400 °C through the use of plasma-enhanced CVD (PECVD) (Cogan, et al., 2003, Hsu, et al., 2007). Lei et al. demonstrated the use of PECVD a-SiC deposited at 350 °C as a dielectric coating for retinal implants in which 240 nm. SiC coated retinal prostheses were implanted in rats for up to 1 year, showing significantly less degradation than only SiN coated prostheses (Lei, et al., 2016). ALD hafnium oxide (HfO₂) coatings have also been explored. Jeong et al. deposited alternating layers of 10 nm thick HfO₂ and SiO₂ at 250 °C to form a 100 nm thick coating over an RF communication IC. The encapsulated ICs were demonstrated to work while submerged in 87 °C saline for over 180 days, suggesting much longer lifetimes at physiological temperatures (Jeong, et al., 2019).

Another major benefit of thin film ceramic coatings is low flexural rigidity which is a property that bulk ceramic does not have and limits its use as a housing material. As an example, microns-thick silicon carbide can be fabricated into compliant high channel count microelectrocorticography (ECoG) arrays flexible enough to be wrapped entirely around the sciatic nerve of a rat (Fig. 8a) (Diaz-Botia, et al., 2017). Similarly, methods for transferring sub-micron thick SiO₂ layers over flexible electronics have been developed (Fang, et al., 2016). By laminating thermally-grown SiO₂, Fang et al. demonstrated a 0.95 cm x 1.15 cm, 900-nm thick, 396 channel, capacitive sensor for electrophysiological measurement, which was flexible enough to fit to the curvature of cardiac tissue (Fig. 8b, d) (Fang, et al., 2017). That work has been extended to SiN, SiC, and HfO₂ (Fig. 8c) (Song, et al., 2018, Song, et al., 2017, Phan, et al., 2019).

At these thicknesses, however, degradation mechanisms such as hydrolysis begin to have non-negligible etch rates. For example, ALD Al₂O₃ is known to dissolve in water, hence the need to protect Al₂O₃ layers with CVD parylene or ALD titania (Abdulagatov, et al., 2011, Kim, et al., 2014). Furthermore, the material itself is not the only deciding factor for long-term stability of a thin film. The deposition method and parameters are critical to control film quality, bond-composition, morphology, among other physical properties. For example, thermal oxide films were shown by Fang et al. to have a dissolution rate in physiological conditions of roughly 0.04 nm/day, whereas a previous study by Maloney et al. showed a dissolution rate of 3.5 nm/day for PECVD silicon dioxide (Fang, et al., 2016, Maloney, et al., 2005). Similarly, Hsu et al. found that PECVD a-SiC films deposited at temperatures lower than 200 °C with low hydrogen dilution and high silane-to-methane precursor flow were dramatically less stable than a-SiC films deposited at higher temperatures in silane-starved conditions, which showed nearly no degradation in saline soak tests (Hsu, et al., 2007). Hermeticity testing of thin films is always essential; even small process variations can result in significant changes in film stability.

3.3 Quality testing for thin films

Several methods exist for leak testing thin films. He-leak testing can be performed but may be challenging due to the small sizes of the samples. One common method is to deposit the film-under-test

over a test material which is affected by moisture. For example, magnesium (Mg) is highly reactive when exposed to water, hydrolyzing rapidly; a simple method for leak test begins by depositing a thin film of the material to be tested over a square of Mg, then creating a channel over the film and filling the channel with solution (Fig. 9a) (Fang, et al., 2016, Song, et al., 2017, Phan, et al., 2019). Any pinholes in the film or impurities which can be etched away act as become leakage paths for water to ingress through the film and eventually cause the underlying Mg film to react. The film can be inspected periodically with a microscope for evidence of etching or reaction under the thin film under test. In this way, time to failure can also be recorded and different films can be compared. Optical methods can be unreliable, however; some defects may be too small to identify. A different set of methods rely on shifts in material dielectric properties due to moisture ingress. As an example, resonant inductor-capacitor circuits can be fabricated from thin films or discrete components, thin-film coated with the material to be tested, then placed in a humid environment. By appropriate design of the inductor and proper tuning of the resonant circuit, the resonator can be wirelessly interrogated and impedance spectra shifts caused by changes in the components, putatively caused by moisture ingress (Fig. 9b) (Yeon, et al., 2019).

Lastly, for materials acting as feedthrough or electrical insulators, any test should take into account that electrical potentials will exist across the encapsulation layer during operation. Electrical testing methods should apply these potentials during testing to accurately reproduce the implant environment. In leakage tests, this is usually done by applying a potential and measuring the resulting leakage current (Fig. 9c). Failure is determined when the leakage current rises above a set threshold current (Fang, et al., 2016, Diaz-Botia, et al., 2017, Haemmerli, et al., 2013).

4. Future Directions and Conclusion

There is no doubt that both bulk and thin-film ceramics will play a critical role in neural implants in contemporary and future devices. The use of alumina feedthroughs will remain an essential component of non-miniaturized AIMDs, as they currently are in cochlear implants, deep-brain-stimulation systems, and more. Microfabricated implants will also benefit from ceramic materials as the search for a thin-film

hermetic encapsulation material continues. In this final section, we will examine some unique directions for implants that ceramic materials can offer.

4.1 Silicon carbide for encapsulating neural implants

SiC has emerged as one of the main contenders for chronic hermetic encapsulation due to its chemical stability, biocompatibility, and molecular barrier properties. The silicon-carbon bond in SiC is extremely stable: silicon atoms are bound to carbon atoms throughout the material, giving SiC its high chemical resistance (Maboudian, et al., 2013). As a result, proper tuning of deposition parameters can result in SiC thin films that exhibit little-to-no hydrolysis in-vivo or in-vitro (Cogan, et al., 2003, Lei, et al., 2016, Hsu, et al., 2007, Phan, et al., 2019). Properly tuned films have also been demonstrated to be excellent molecular barriers. Diaz-Botia et al. showed that 100 nm of a-SiC outperformed 100 nm thermal-SiO₂ as a barrier to water vapor (Diaz-Botia, et al., 2016). Phan et al. showed that crystalline SiC exhibited very low ion diffusivity: after 12 weeks of soaking in 96 °C phosphate buffered saline (PBS), secondary ion mass spectroscopy revealed that by 100 nm through the film, no Na⁺ could be detected (Phan, et al., 2019). Additionally, the biocompatibility of SiC has been demonstrated both in-vivo and in-vitro (Cogan, et al., 2003, Sadow, et al., 2011, Frewin, et al., 2016). Cells cultured on SiC show better adhesion, proliferation, viability, and mitochondrial health than cells cultured on Si (Bonaventura, et al., 2019, Coletti, et al., 2007). SiC implants were also shown to have a decreased immune response compared to Si implants when utilized in-vivo. Frewin et al. found reduced microglia and macrophage activation attached to implanted SiC samples in rat tissue (Frewin, et al., 2011); Knaack et al. did not find significant differences between microglia and macrophage activation in a-SiC coated Si samples and uncoated Si samples, but did find reduced reactive astrocytes in a-SiC coated Si samples compared to the uncoated samples (Knaack, et al., 2016). Thus, while it is unclear if SiC is definitively more biocompatible than Si, it is evident that SiC is well tolerated by tissue and should be pursued as an encapsulation material. The Cogan group at the University of Texas at Dallas has demonstrated a-SiC encapsulated ultramicroelectrode planar arrays using and Utah

electrode arrays (Deku, et al., 2018, Joshi-Imre, et al., 2019). Furthermore, because SiC is a semiconductor, it can be doped to become electrically conducting. Applications of electrically conductive SiC will be explored in the next section.

4.2 Seamless ceramic interfaces

It is well known that many packaging failure modes occur at interfaces of dissimilar materials; though Joshi-Imre et al. demonstrated that a-SiC encapsulated Utah electrode arrays did not show evidence of dissolution or cracking in the encapsulation layer (in contrast to parylene), delamination of the a-SiC was one failure mode of the implanted arrays (Joshi-Imre, et al., 2019). Unfortunately, heterogeneous interfaces are unavoidable if feedthroughs are required. This failure point has been long recognized. For example, horizontal interconnects with vertical feedthroughs have been used to try to enhance hermiticity by increasing the length of the leakage path (Fig. 4b) (Guenther, et al., 2014). However, as conductor density increases within feedthroughs, ensuring hermiticity becomes more difficult as a single leak will result in a compromised device. Furthermore, miniaturization of devices will inevitably result in shorter leakage paths, increasing the risk of water vapor ingress.

Ceramic materials can provide a unique solution to this issue, in that some ceramics can be doped to vary the material from insulator to conductor. This raises the possibility that a feedthrough can be made of the same material, doped differently. Both penetrating and surface neural probes have been fabricated in all-SiC processes. Diaz-Botia et al.'s thin film SiC ECoGs utilized amorphous SiC as both the substrate and the encapsulation layer with n-SiC recording sites (Fig. 10a) and demonstrated electrical recordings of compound action potentials in the rat sciatic nerve (Diaz-Botia, et al., 2017). While complete device aging was not demonstrated in that work, the a-SiC thin film itself was aged in a benchtop reactive accelerated aging test and shown to be a superior encapsulation material to thermally grown SiO₂. The Sadow group at the University of Southern Florida has also been exploring all-SiC neural probes using crystalline SiC (Bernardin, et al., 2018, Beygi, et al., 2019). In that body of work, n-type crystalline SiC substrates were used and p-type crystalline SiC interconnects were created to form reverse-biased diodes

between interconnects for electrical isolation; a-SiC layer was used for encapsulation. While *in-vivo* results have not yet been demonstrated with these devices, the use of a homogenous material for all parts of the implant should greatly improve reliability.

Diamond is another ceramic material that can exist in both insulating and conductive forms as PCD and nitrogen-doped ultra nano-crystalline diamond (N-UNCD), respectively. Ganesan et al. have utilized this property to create all-diamond feedthrough arrays for retinal prostheses by starting with a PCD substrate and then growing N-UNCD electrodes on top of it (Fig. 10b) (Ganesan, et al., 2014, Stamp, et al., 2020). These feedthroughs have been demonstrated as hermetic and biocompatible. However, the chemical inertness of diamond makes it very difficult to etch, and laser machining was used to pattern both the PCD and the N-UNCD, making scalability difficult. Nevertheless, there is much promise in the general principle of seamless neural interfaces, enabled by ceramic materials.

4.3 Ceramics for Acoustics

Ceramics have been a major enabler of electromagnetic wireless power transfer but they also play an important role in ultrasonic power transfer. The use of ultrasound in medical implants has been gaining popularity due to the efficiency of ultrasonic propagation in tissue compared to electromagnetics (Seo, et al., 2015, Seo, et al., 2016, Piech, et al., 2017, Piech, et al., 2020, Ghanbary, et al., 2019, Vo, et al., 2020, Charthad, et al., 2018, Weber, et al., 2018, Chang, et al., 2017, Arbabian, et al., 2016, Charthad, et al., 2015, Sonmezoglu et al., 2020). Functional piezoelectric ceramics, such as lead-zirconate-titanate (PZT) and barium titanate (BaTiO_3), have been used extensively as power harvesting transducers to convert incoming mechanical energy to electrical energy thereby powering implant microelectronics. While the use of ultrasound allows for metallic housings (Shen & Maharbiz, 2019), engineered ceramics with nanoscale grain-size and low porosity have been shown to be good acoustic windows in non-active medical implants for ultrasound-based therapies (Gutierrez, et al., 2017). Thus, ceramic housings not only enable visible-to-RF EM transparency, but also can enable acoustic transparency.

4.4 Conclusion

Ceramic materials have great potential in the packaging of neural implants due to their biocompatibility, corrosion resistance, RF transparency, and tunable dielectric properties. Although bulk ceramic can be difficult to shape and can be prone to cracking, thin-film ceramics are not as susceptible to these issues. Metals and polymers will continue to have a central place in the packaging of neural probes but ceramics provide a complementary pathway to reliable, aggressively miniaturized, high electrode density, wireless AIMDs.

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Fig. 1. Failure modes of neural implants. a) Stain for glial fibrillary acidic protein (GFAP) in rats after explanting a penetrating neural probe left in the cortex for 12 weeks. The formation of a thick glial sheath around the implant site is clear, separating the implant from neurons (Turner, et al., 1999). b) Formation of a fibrotic capsule in the cat sciatic nerve after 5-6 weeks post implantation of a microelectrode array. The arrows indicate where the device was implanted (Christensen, et al., 2014). c) Cracks in the parylene encapsulation of a microelectrode array after 554-days post implantation in the cortex of a non-human primate (Barrese, et al., 2013). d) Corrosion in tungsten microwires after 87 days post-implantation in rat cortex. Inset shows the microwires prior to implantation. Roughening of the microwire surface, as well as delamination of the polyimide encapsulation can be seen (Patrick, et al., 2011).

Fig. 2. Mechanical failure of ceramic housings. a) Cracked alumina casing in a cochlear implant due to mechanical impact of the head (Stöver & Lenarz, 2009). b) Broken intramuscular microstimulators encased in glass housing due to bending stresses from muscle contractions (Loeb, et al., 2007).