Anagha Navale*, Ioana-Georgiana Vasilaș, Paul Čvančara, Thomas Stieglitz

Molecular and Optical Degradation Pathways in Polyimide Substrates: An Accelerated Aging Study for Implantable Devices

https://doi.org/10.1515/cdbme-2025-0217

Abstract: Microelectrode arrays (MEAs), a widely used class of neural implants, are susceptible to *in vivo* degradation despite using biocompatible materials like polyimide (PI). While PI has been extensively studied for its biostability, the role of oxidative stress, particularly from hydrogen peroxide (H_2O_2), a reactive oxygen species (ROS) released during foreign body reactions (FBR), remains underexplored. This study investigates the effects of *in vivo* environments, with a particular focus on H_2O_2 exposure, on the PI layer of MEAs. Scanning Electron Microscopy (SEM) and Time of Flight-Secondary Ion Mass Spectroscopy (ToF-SIMS) are used to study the structural and molecular changes, respectively. The findings indicate that reactive accelerated aging (RAA) mimicking *in vivo* conditions do not alter PI at the molecular level. Surface modifications, primarily due to oxidative degradation, were observed; however, the underlying material remained intact, confirming PI's durability for long-term implantable devices.

Keywords: neural implants, microelectrode arrays, polyimide, hydrogen peroxide, oxidative degradation, reactive accelerated aging, surface analysis (SEM, ToF-SIMS)

***Corresponding author: Anagha Navale:** Laboratory for Biomedical Microtechnology, Department of Microsystems Engineering, Engineering – IMTEK, IMBIT // NeuroProbes, BrainLinks-BrainTools Center, University of Freiburg, Georges-Koehler-Allee 201, 79110 Freiburg, Germany, E-mail: navaleanagha26@gmail.com

Ioana-Georgiana Vasilas, Paul Čvančara, Thomas Stieglitz: Laboratory for Biomedical Microtechnology, Department of Microsystems Engineering – IMTEK, IMBIT // NeuroProbes, BrainLinks-BrainTools Center, University of Freiburg, Georges-Koehler-Allee 201, 79110 Freiburg, Germany

Thomas Stieglitz is also with the Bernstein Center Freiburg, Univerity of Freiburg, Hansastr. 9 a, 79104 Freiburg, Germany

1 Introduction

Implantable neural interfaces have seen significant advancements with the rise of medical and neurotechnology fields, evolving from tools for restoring sensory or motor function to applications in brain mapping and neuronal restoration. However, their long-term stability still remains a critical challenge [1, 2].

Chronic (≥30 days) neural implants are exposed to complex biological environments that elicit immune responses such as release of ROS, glial scarring, and inflammation, leading to implant material degradation and tissue damage. These effects impair signal quality, device performance, and safety, limiting clinical longevity [2].

Reported structural and functional damage, including altered impedance and reduced accuracy in neural signal detection or recording may arise from multiple sources: the initial immune response triggered by the implant (FBR and ROS), mechanical stress or trauma during explantation, or chemical interactions with fixation agents used during tissue preservation [3, 4].

Thin-film polyimide (PI) is commonly used in neural probes for its flexibility, chemical stability, and biocompatibility, often serving as a substrate or insulation layer [3]. However, their long-term stability under oxidative stress, particularly in the presence of ROS like H_2O_2, needs further investigation.

This study investigates the degradation behavior of polyimide (PI) under conditions simulating chronic in vivo environments. An *in vitro* accelerated aging approach using H_2O_2 and phosphate-buffered saline (PBS) was employed to mimic oxidative stress, simulating one and twelve months of implantation. SEM aids detecting surface abnormalities, while ToF-SIMS revealed molecular-level degradation, offering insights beyond conventional surface analyses. By analyzing changes in the PI surface and structure post-aging, this research aims to identify damage mechanisms and contribute to the development of more robust neural implants for long-term clinical and research applications.

2 Materials and methods

2.1 Experimental procedure

The PI type used in this study is BPDA-PPD, chosen for its low water absorption and high resistance to hydrolytic degradation. Owing to these properties, it has been previously employed in neural implant applications [3]. PI films (5 mm × 5 mm, 5 µm thick) were obtained by spin-coating the PI on silicon wafers, laser-cut (LUMERA/COHERENT Rapid 10), peeled, and stored for further use.

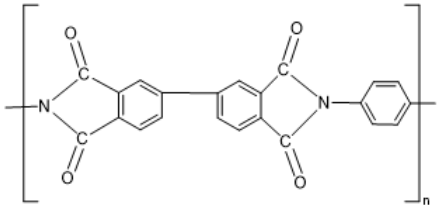

Figure 1: Chemical structure of BPDA-PPD monomer [3].

In this study, accelerated aging was simulated using two separate media: 30% (≈8.82 M) H_2O_2 (Carl Roth GmbH + Co.KG, Germany) and 0.01 M PBS (Sigma–Aldrich Chemie GmbH, Germany). H_2O_2 was used for the first month to mimic the oxidative stress caused by ROS, which cannot be replicated by PBS alone. The H_2O_2 was changed every day manually in order to maintain a steady concentration throughout the aging duration. This was followed by aging in PBS, which better represents the ionic environment of body fluids. Elevated H_2O_2 concentrations were chosen to model adverse conditions beyond physiological levels, as ROS play a critical role in material degradation and immune responses, such as microglial activation, observed *in vivo* between two and 16 weeks post-implantation [5]. An accelerated aging factor (*Q10*) of two was chosen based on the simplified Arrhenius equation (see Equation 1) [6]. Here, *tp* is the projected aging time to be calculated, *ta* is the *in vivo* implantation duration, *Ta* is the ambient temperature, and *Tp* is the accelerated temperature.

$$t_p = t_a \, Q_{10}^{(Ta-Tp)/10°C} \quad (1)$$

RAA was performed at 60°C for a period of seven days and 80 days, mimicking one and twelve months of *in vivo* implantation durations. For each condition shown in Table 1, 10 samples (n=10) were characterized. Before undergoing surface examination, samples were rinsed with deionized water (DI), patted dry with clean-room towels, and then dried in an incubator for two hours at 60°C to obtain moisture-free samples.

Table 1: Aging conditions for PI samples.

	Condition Parameters	Nomenclature
1-month aging	PI + H_2O_2 30%	C1
12-months aging	PI + H_2O_2 30% + PBS	C2

2.2 Surface characterization techniques

2.2.1 Visual characterization

Scanning Electron Microscopy (SEM), equipped with a focused ion beam (FIB, Gallium (Ga) source), was used to visually characterize the PI samples (Helios 5 CX (Thermo Fisher Scientific Inc., Waltham, Massachusetts, USA) was used for SEM. Prior to the characterization, samples were coated with a 5 nm Tungsten (W) layer and mounted on a sample holder with silver-based conductive glue (Acheson Silver DAG 1415, Plano GmbH, Wetzlar, Germany) to prevent charge buildup during microscopy.

2.2.2 Molecular characterization

The surface properties of materials are often different from the bulk properties. ToF-SIMS (Tofwerk, Thun, Switzerland) was used for an accurate and reliable characterization of the surface at a molecular level, considering its high sensitivity to the slightest modifications. This is a semi-quantitative method, where the high-energy primary FIB is focused on the surface of the sample, which causes the ejection of various ions, radicals, and neutrals, which are detected by the detector to plot a mass spectrum of both the masses and their abundance [7].

The TOF-SIMS is integrated into the Helios 5 CX FIB-SEM microscope with a Ga FIB, termed as the primary ion source. The parameters for mass extraction that have been used are listed in Table 2.

Table 2: Parameters used in ToF-SIMS measurements.

Component	Operating Conditions
Voltage	30 kV
Current	80 pA
Analysis area	30 µm x 30 µm
Number of frames	50
Dwell time	10 µsec

3 Results

3.1 Visual characterization

When compared to pristine PI, the SEM pictures of the sample from condition C1, which used solely H_2O_2 as the aging medium, revealed the presence of white spots on the surface. Samples from condition C2, aged first in H_2O_2 and then in PBS, showed similar but marginally thicker white spots, with no major differences in surface alteration.

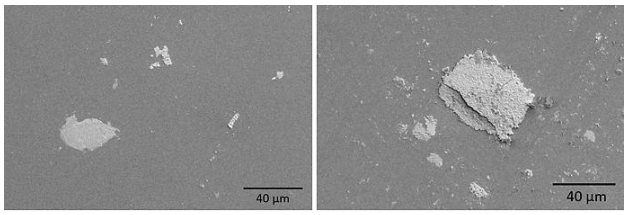

Figure 2: SEM images from sample from condition C1 with aging in H_2O_2 for one month (left) and condition C2 with twelve months aging in H_2O_2 followed by PBS (right).

3.2 Molecular characterization

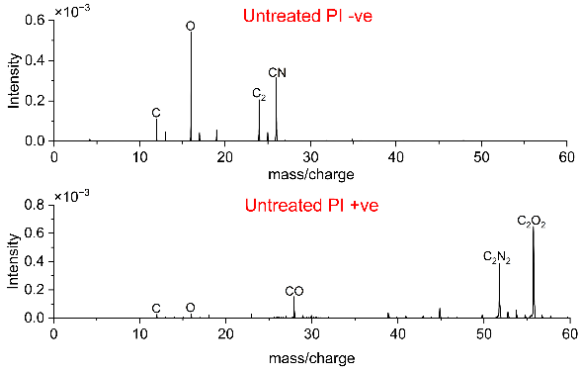

Figure 3: ToF-SIMS spectra, -ve ion mode (top) and +ve ion mode (bottom) for the untreated reference PI sample (n=1).

Samples from conditions C1 and C2 were analysed in the positive (+ve) and the negative (-ve) ion mode using ToF-SIMS. Characteristic peaks from the PI backbone were detected in both the +ve and the -ve ion modes. Mass spectra for the untreated pristine PI were used as a reference to compare the aged PI mass spectra (Figure 3). The +ve spectra showed peaks representing molecules like CO, C_2N_2, and C_2O_2, while the -ve spectra showed peaks for fragments C_2- and CN-. These fragments reflect typical breakdown products under high-energy ion bombardment and correspond to the molecular structure of PI.

In Figure 4, oxygen (O) was represented in the -ve ion spectra as a strong peak in the samples from condition C1 at mass/charge = 16. This peak accounts for the oxidative reaction facilitated by H_2O_2. The +ve ion spectra, however, shows multiple intense peaks with a new, prominent peak at mass/charge = 40, representing the fragment C_2NH_2. H_2O_2 can oxidize the nitrogen (N) in imide groups (−CO−N−CO−) of PI, potentially forming N-oxide derivatives.

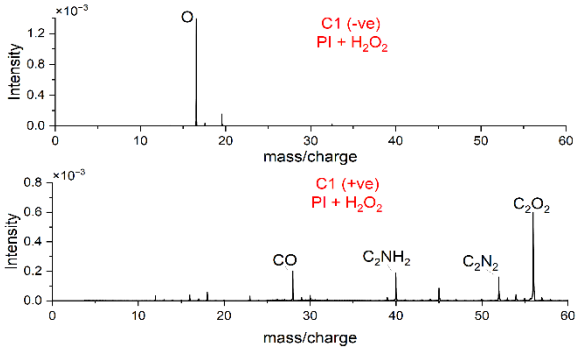

Figure 4: ToF-SIMS spectra, -ve (top) and +ve ion mode (bottom) for samples from condition C1 involving aging of PI for one month in H_2O_2 (n=1).

This oxidative process may also cause chain scission, leading to the formation of carboxylic acid (−COOH) and amino ($-NH_2$) groups [8]. This detected molecule, C_2NH_2 reflects the oxidative reaction of PI and H_2O_2. These modified regions are more susceptible to bond cleavage under high-energy ion bombardment during ToF-SIMS analysis, resulting in enhanced chain scission at these locations and the observed fragments.

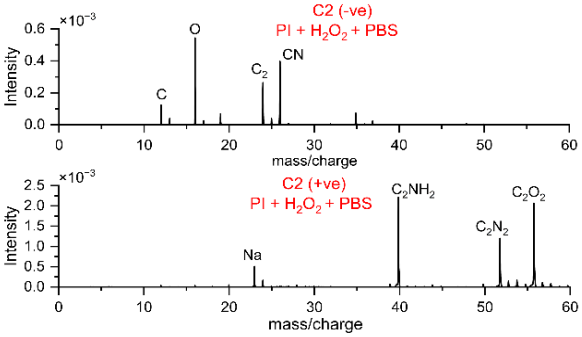

Figure 5: ToF-SIMS spectra, -ve (top) and +ve ion mode (bottom) for samples from condition C2 involving aging of PI for twelve months in H_2O_2 followed by PBS (n=1).

Figure 5 representing samples from condition C2 also showed the presence of fragment C_2NH_2, resulting from the oxidation reactions by H_2O_2. Along with this, a high peak representing sodium (Na) at mass/charge = 23 was seen in the +ve ion spectrum. These peaks align with the characteristic ion composition of PBS, confirming surface interactions with the PBS solution. The -ve spectrum showed similar features to the untreated PI.

4 Discussion

SEM imaging of PI samples aged under both aging durations using RAA revealed consistent surface changes in the form of white patches confined to the surface. These surface features likely result from oxidative degradation of PI due to the high H_2O_2 concentration used, which far exceeds physiological levels (0.1 µM) and concentrations known to induce oxidative stress (~1 mM) [5, 9]. Additionally, these patches could be residues from the aging solutions. ToF-SIMS analysis of patches from H_2O_2-treated PI supported this, showing elevated oxygen levels due to oxidation. In samples treated further with PBS, additional elemental peaks indicated the presence of saline residues alongside oxidative effects, which was expected.

Similar trends in the mass spectra were observed across all samples from both conditions when analysed using ToF-SIMS. A new peak at m/Q = 40 (C_2NH_2) appeared in all treated PI samples (Figures 4 and 5), but was absent in the untreated PI, indicating its formation due to H_2O_2-induced oxidation. This suggests that oxidative degradation can result in the formation of amine groups, which may then fragment under the high-energy ion beam. Intense oxygen and sodium peaks further point to residues from PBS.

5 Conclusion

This study examined the impact of RAA on PI using SEM and ToF-SIMS, shedding light on the degradation mechanisms and challenges of PI in implantable applications under simulated conditions.

SEM imaging revealed surface changes, including white patches, primarily due to oxidative degradation, which were confined to the surface. These alterations did not affect the structural integrity of the underlying PI material.

ToF-SIMS analysis identified a new peak (C_2NH_2), suggesting oxidative degradation linked to molecular fragments formed from the high-energy ion beam. Variability in peak intensity and localized contamination highlight the method's sensitivity, indicating changes are from oxidation, contamination, and the ion beam rather than intrinsic molecular modifications in PI.

This research confirms that the PI layer remains intact despite exposure to adverse simulated *in vivo* conditions, suggesting that the degradation of neural probes is not attributable to this layer. However, delamination of the PI layer may facilitate fluids to seep into the neural implants, potentially contributing to the observed damage.

Author Statement

This work is part of BrainLinks-BrainTools, which was funded by the German Research Foundation (DFG, grant no. EXC 1086) and is currently funded by the Federal Ministry of Economics, Science and Arts of Baden-Württemberg within the sustainability program for projects of the excellence initiative II.

References

[1] C. Hassler, T. Boretius, and T. Stieglitz, Polymers for neural implants. J Polym Sci B Polym Phys. 2011;49:18–3.

[2] G. Kook, S. W. Lee, H. C. Lee, I.-J. Cho, and H. J. Lee. Neural Probes for Chronic Applications. Micromachines 2016;7.

[3] T. Stieglit, Hansjoerg Beutel, et al. Flexible, Polyimide-Based Neural Interfaces. Proceedings of the Seventh International Conference on Microelectronics for Neural, Fuzzy and Bio-Inspired Systems 1999;112–119.

[4] P. Takmakov, K. Ruda, K. Scott Phillips, I. S. Isayeva, V. Krauthamer, and C. G. Welle. Rapid evaluation of the durability of cortical neural implants using accelerated aging with reactive oxygen species. Journal of neural engineering 2015;1:26003

[5] George Charles McConnell. Chronic inflammation surrounding intra-cortical electrodes is correlated with a local neurodegenerative state 2008.

[6] D. W. L. Hukins, A. Mahomed, and S. N. Kukureka. Accelerated aging for testing polymeric biomaterials and medical devices. Medical engineering & physics 2008;30:1270–1274.

[7] D. J. Graham and L. J. Gamble. Back to the basics of time-of-flight secondary ion mass spectrometry data analysis of bio-related samples. II. Data processing and display. Biointerphases 2023;18.

[8] E. M. Christenson, J. M. Anderson, and A. Hiltner,. Oxidative mechanisms of poly(carbonate urethane) and poly(ether urethane) biodegradation: in vivo and in vitro correlations. Journal of biomedical materials research 2004;70:245–25.

[9] C. P. Constantin, M. Aflori, R. F. Damian, and R. D. Rusu. Biocompatibility of Polyimides: A Mini-Review. Materials (Basel, Switzerland) 2019;12.