Resveratrol-Loaded Polymer-Based Nanocomposite Probes for Neural Interfacing

BMNI Bio-inspired Materials for Neural Interfacing

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Department of Biomedical Engineering
A Joint Department of the CWRU Schools of Engineering and Medicine

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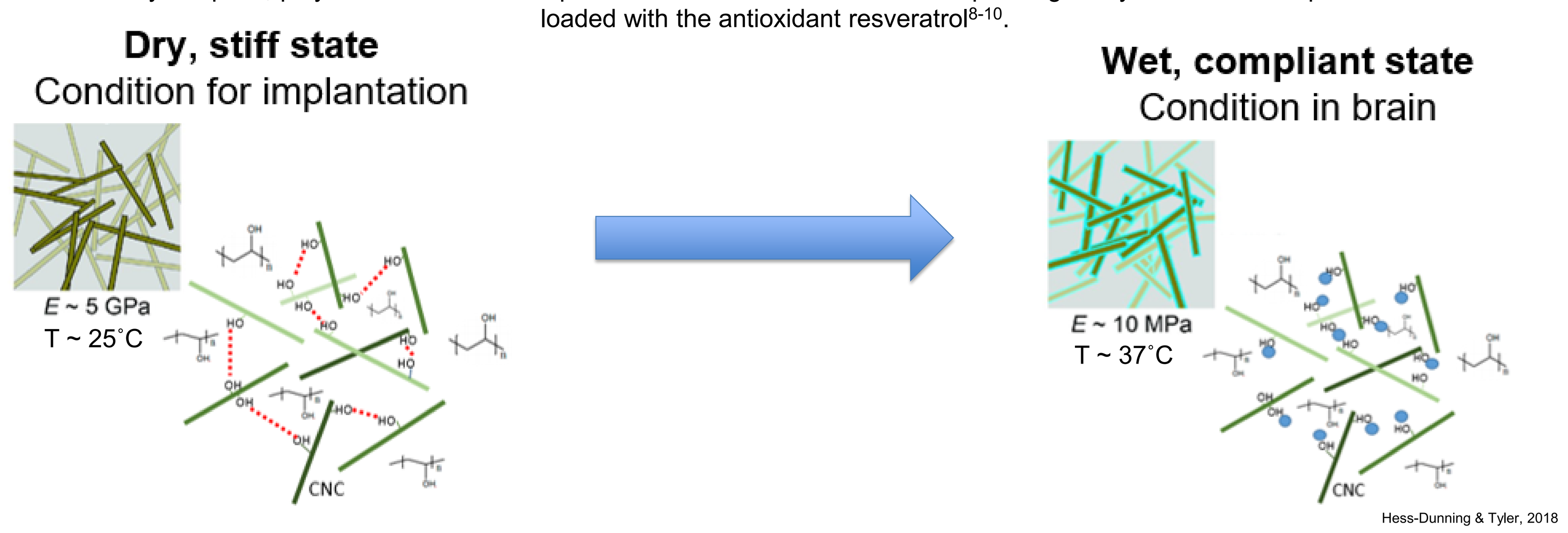
Significance

Intracortical microelectrodes are an important component of brain-computer interface (BCI) systems that are used in the restoration of motor and sensory function in neuromusculoskeletal rehabilitation, as well as in the treatment of neurodegenerative disorders[1,2]. However, they usually fail within weeks to months after implantation, resulting in reduced recording performance and therapeutic efficacy[3]. Failure is primarily associated with an increased neuroinflammatory response, with factors such as mechanical mismatch between the brain tissue and probe and the state of oxidative stress propagating neuroinflammation[4,5,6]. Previous studies in the lab have suggested that the use of mechanically-compliant materials and the administration of the antioxidant resveratrol lessened the neuroinflammatory response[7]. In this work, we refined material processing and microfabrication techniques to integrate recording electrodes on the resveratrol-loaded, polymer-based nanocomposite substrate. Additionally, we developed a resveratrol release profile after microfabrication using UV-Vis spectrophotometry to confirm that the drug was releasing from the material. Our results indicated that resveratrol was being released over a 72-hour period. Finally, we did a proof-of-concept pilot study to ensure these devices were functional and stable *in* vivo. The mechanically-adaptive functional devices were able to record single units over an 8-week period.

Material Properties

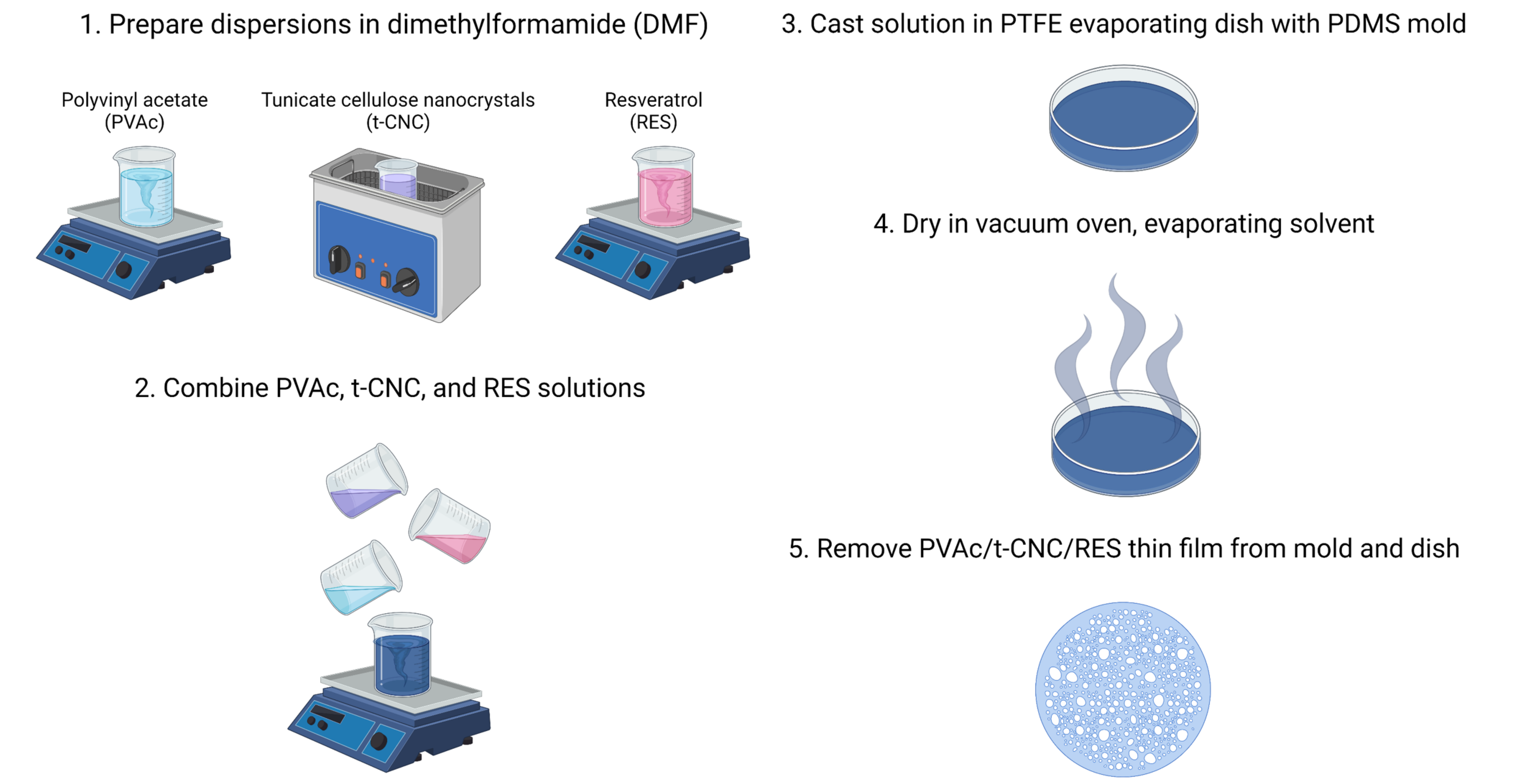
Material: Polyvinyl acetate with tunicate cellulose nanocrystals (PVAc/t-CNC)

Mechanically-adaptive, polymer-based nanocomposite with two mechanical states depending on hydration and temperature that can be loaded with the antioxidant resveratrol[8-10].

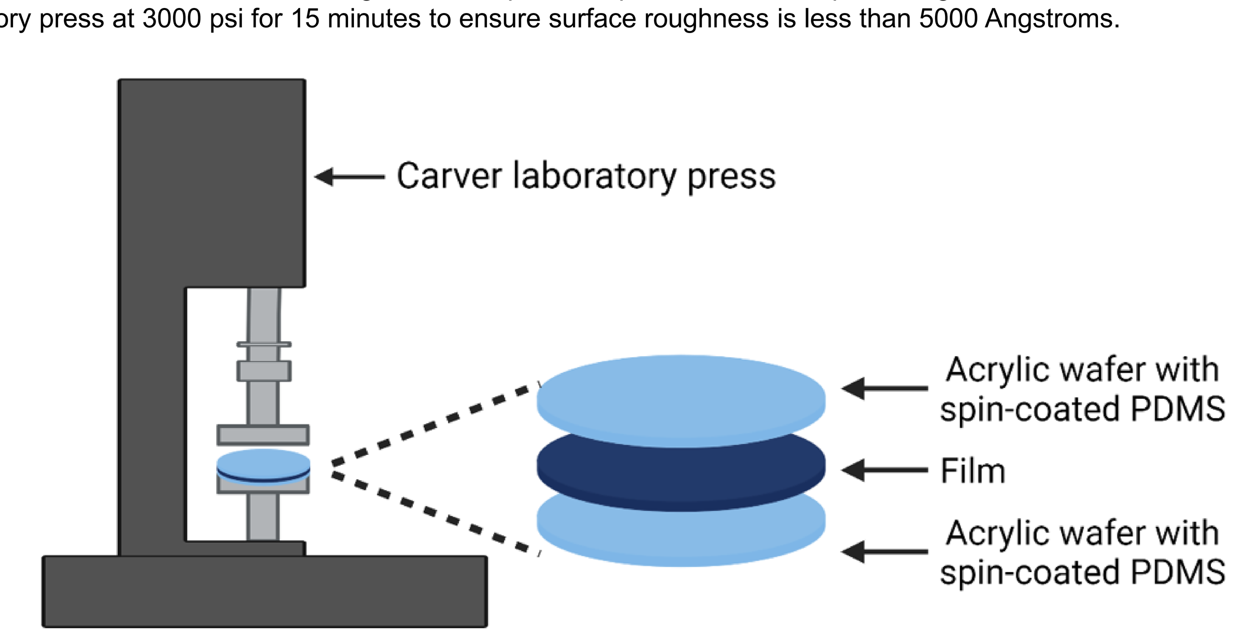


Material Processing

Resveratrol-loaded, polymer-based nanocomposite thin film substrates are developed by dispersing the materials in an organic solvent, casting the dispersion, and then evaporating the solvent.

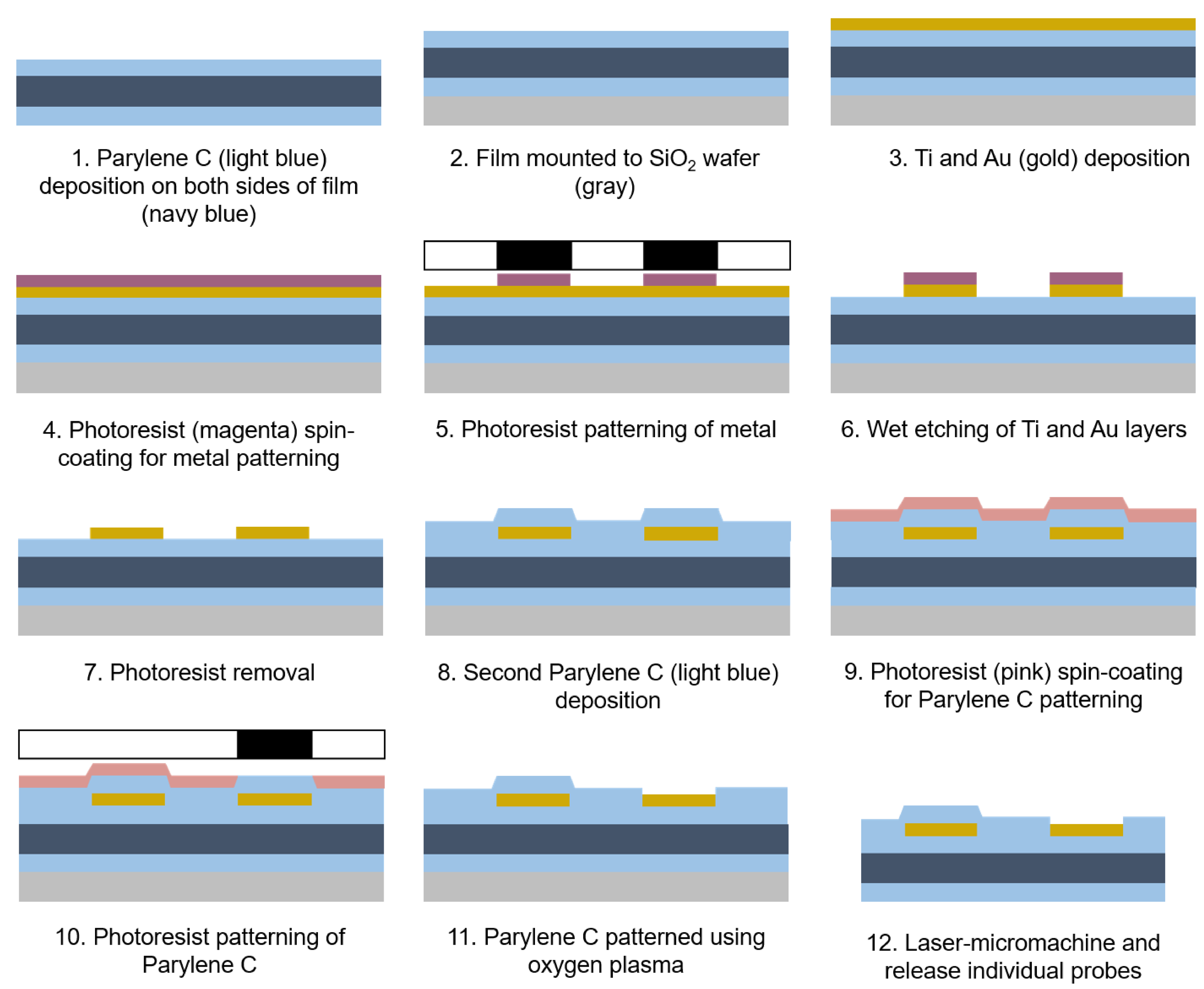


After casting, films have inherent surface roughness that prevents precise electrode patterning on the substrate. The film is pressed in a Carver laboratory press at 3000 psi for 15 minutes to ensure surface roughness is less than 5000 Angstroms.



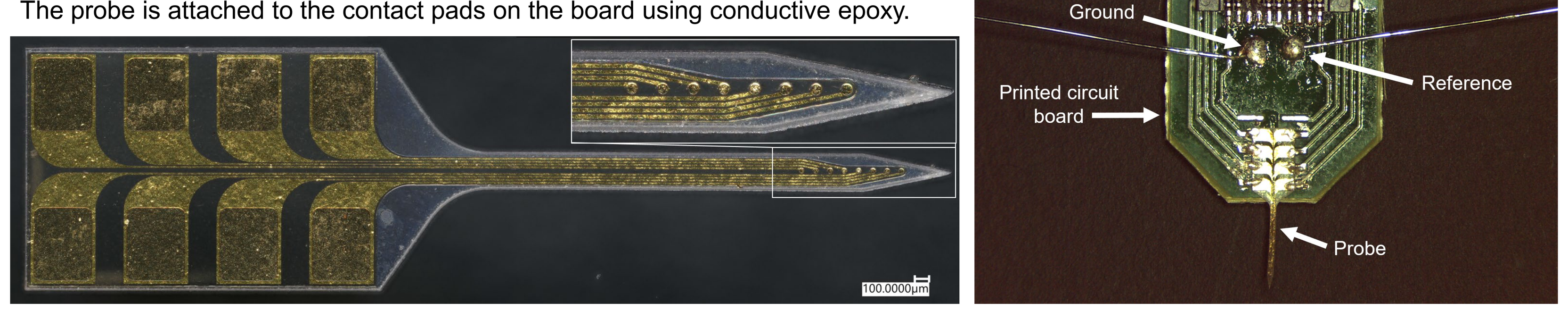
Electrode Fabrication

A unique microfabrication process was used to integrate functional recording electrodes on the resveratrol-loaded, polymer-based nanocomposite substrate[10]. Colors corresponding to layers are denoted in parentheses.



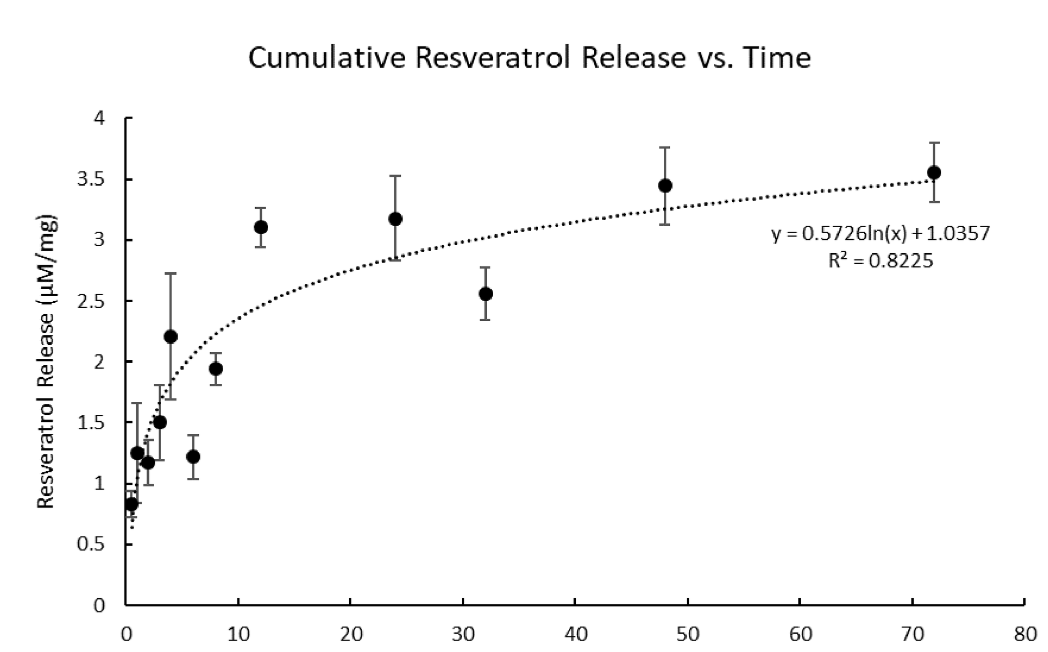
Device Packaging

The image below shows a resveratrol-loaded nanocomposite probe with functional electrodes. The inset displays the recording contacts. The probe is then attached to the custom-made electronic package, consisting of a printed circuit board with a Hirose connector, a reference wire, and a ground wire soldered onto the board. The probe is attached to the contact pads on the board using conductive epoxy.



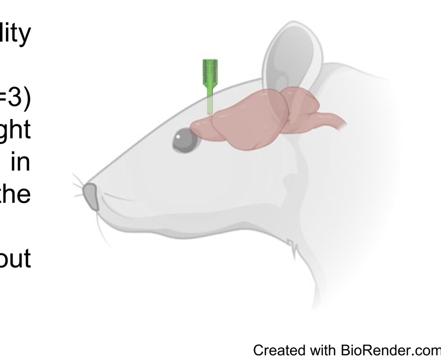
Resveratrol Release

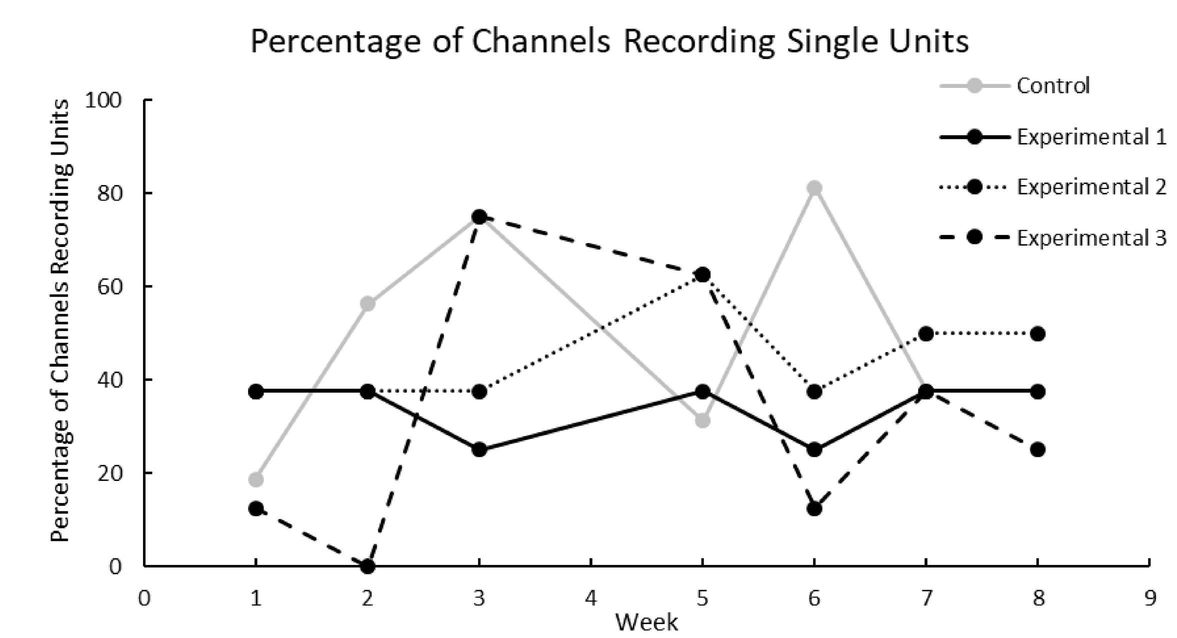
- Cut identical film pieces coated with Parylene C on both sides a using micromachining laser.
- Weighed film piece to determine theoretical resveratrol concentration.
- Immersed in 1X PBS incubation solution until designated time point (0.5-72 hours).
- At designated time point, used Nanodrop One to measure absorbance of incubation solution at 317 nm. 3 samples/timepoint, 3 measurements/sample.
- Concentration was correlated to absorbance using a calibration curve.
- Presented as concentration of resveratrol in incubation solution divided by weight of film piece.
- About 25% of resveratrol was released initially, with a slow release of remaining resveratrol over a 72-hour period, following an exponential release model.
- Error bars indicate standard error.



In vivo pilot study

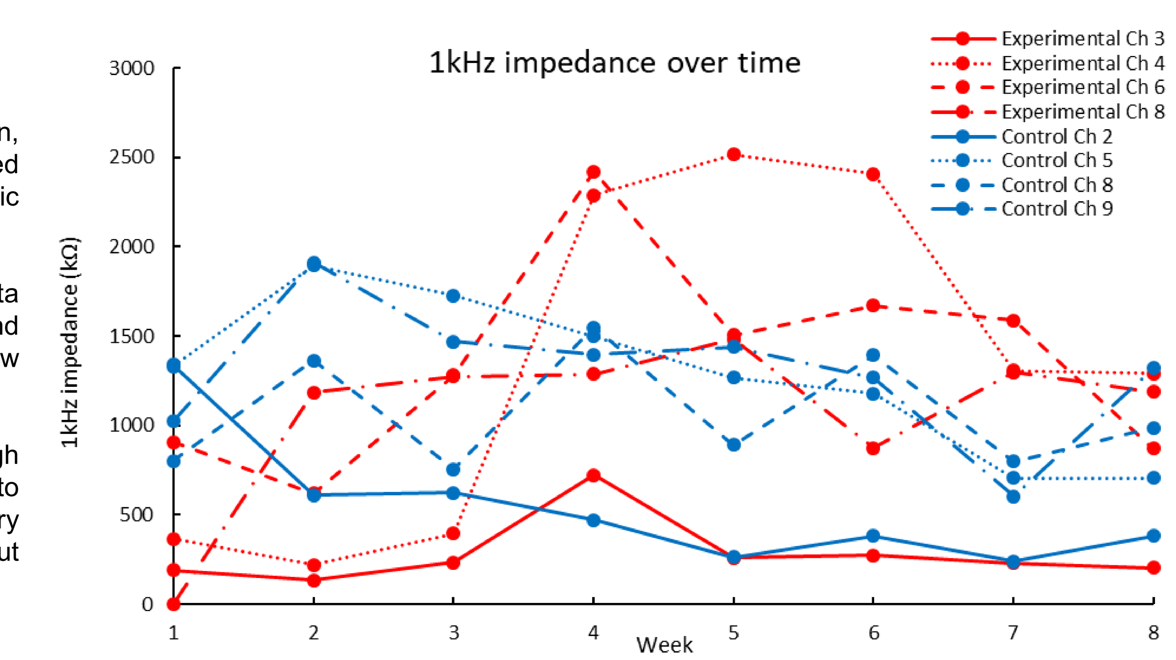
- A proof-of-concept *in vivo* pilot study was completed to evaluate device functionality and stability as well as compare performance metrics to control probes over a chronic period.
- Sprague-Dawley rats were implanted with polymer-based nanocomposite functional devices (n=3) and traditional silicon NeuroNexus devices (n=1) in the motor cortex. The image on the right shows the approximate location of the device implant. Additionally, 2 bone screws were placed in the skull in contact with the cerebrospinal fluid on the contralateral hemisphere to serve as the ground and reference for neural recording and impedance measurements.
- Neural recording sessions and impedance measurements were completed biweekly throughout the 8-week study to evaluate recording quality over time.





- Both control (silicon NeuroNexus) and experimental (polymer-based nanocomposite) groups showed variability in the percentage of single units recorded week-by-week.
- Percentage of units recorded stabilized around week 7-8, with about 30-50% channels recording in both groups.

- Impedance spectra were taken, with the 1kHz impedance isolated as this is the characteristic frequency of the action potential.
- Representative impedance data from 4 experimental channels and 4 control channels show variability.
- Although impedances were high throughout, we were able to record single units on every channel at least once throughout the 8-week period.



Conclusions

- A material formulation, casting, evaporation, and planarization method was used to create thin-film resveratrol-loaded, polymer-based nanocomposite substrates.
- Unique microfabrication techniques were refined to successfully integrate functional recording electrodes on the substrates.
- Resveratrol release was characterized and a profile was developed using UV-Vis spectrophotometry, indicating that about 25% of resveratrol is released initially, with the remaining amount releasing slowly over a 72-hour period.
- A proof-of-concept pilot study was completed and results showed that the polymer-based nanocomposite devices were functional and stable over an 8-week period.
- Future work will include studies to evaluate antioxidative activity of resveratrol released from the material. Additionally, a larger scale animal study with more control and experimental animals to characterize recording performance metrics and the neuroinflammatory response between the groups will be completed.

References

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Acknowledgements

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