Prototype: Closed-Loop Multifunctional Neural Probe for Chemical Neuromodulation in Epilepsy

Abstract

This prototype is a multifunctional multishank neural probe designed for closed-loop chemical neuromodulation to treat epilepsy. Inspired by conventional electrophoretic drug delivery, neural probes, and the RNS neurostimulation system, the device integrates both sensing and localized drug delivery within a fully implantable architecture. The device enables real-time recording, detection, and on-demand drug delivery of GABA+, a key inhibitory transmitter, into target brain regions. The device consists of three major functional components: a sensing module (located at the probe tip), a signal processing chain (localized under the electrodes), and an actuation module (a tinyML microcontroller at the probe base that controls drug release). This approach differs significantly from standard electrical stimulation systems, offering a chemical-based alternative with closed-loop drug delivery capability. Most existing neural probes are open-loop and serve only as recording tools without therapeutic output. This device uniquely integrates sensing, processing, and actuation in a miniature, long-term, implantable form.

Introduction

Systemic drug treatments often fail to effectively treat neurological disorders due to side effects and poor targeting. This has led to the development of localized drug delivery methods that focus treatment directly on the affected brain regions, reducing unwanted side effects. However, some promising approaches—such as optogenetic and designer receptors exclusively activated by designer drugs (DREADDs)—face safety concerns due to their reliance on viral vectors [1] [2]. Others, such as direct injection or pressure-driven delivery, can cause complications such as clogging or swelling at the injection site due to increased pressure [3].

In this work, I show that electrophoretic drug delivery can avoid these issues, allowing for precise, on-demand drug release. Epilepsy is a model condition for this device because seizures occur intermittently, as a system that activates only when needed—like during the early stages of seizure activity—offers a more targeted and safer alternative to constant systemic treatment.

Neural Sensing and Recording

The probe is constructed from silicon, with an upper insulation of parlylene c in which the gold signal traces for the iridium electrodes, along with their individual signal-processing systems, are etched. [4] Recording electrodes at the tip of the shank record local field potentials (LFPs), continuously monitoring neural activity in the hippocampal CA1, CA2, or CA3 regions—common seizure foci [5] [6].

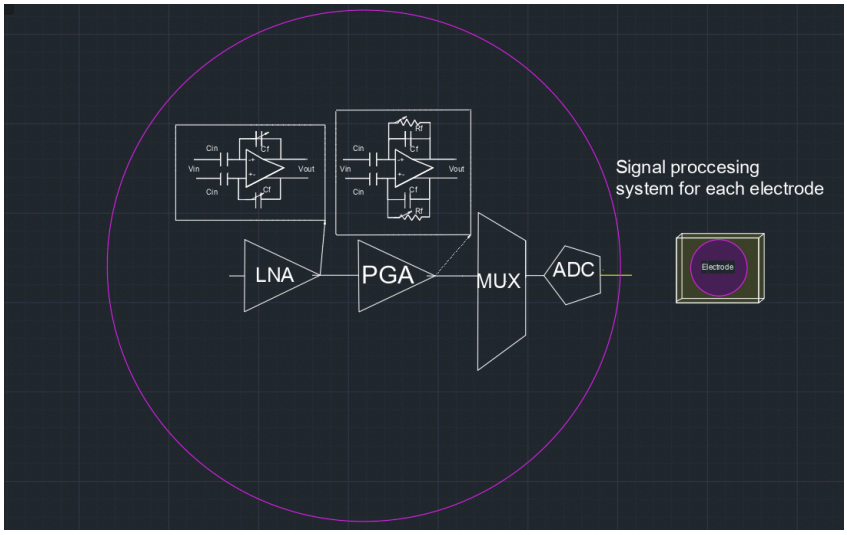

Figure 1: Signal Processing System under each electrode

Each recording electrode is integrated with a localized signal conditioning circuit: starts with a low-noise amplifier (LNA) with high input impedance to amplify weak neural signals while minimizing electrode noise, to programmable gain amplifier (PGA) for dynamic range matching, to a multiplexer (MUX) that selectively routes signals from multiple channels, and to a single analog-to-digital converter (ADC). Each ADC digitizes the signal and transmits it over signal lines to a shared FPGA at the probe base. [7] [8]

TinyML Model

To implement real-time seizure detection and trigger responsive drug release, this prototype will use a TinyML algorithm to predict seizures. The TinyML model was developed with the use of the TUH EEG dataset and GitHub repository for "Real-Time Seizure Detection using EEG: A Comprehensive Comparison of Recent Approaches under a Realistic Setting". The machine learning model was then optimized for TinyML application. The google colab is linked here:https://colab.research.google.com/drive/13JqGUmJUZwmur2Nz1PKpS0JYbvfj0PT9?usp=sharing.

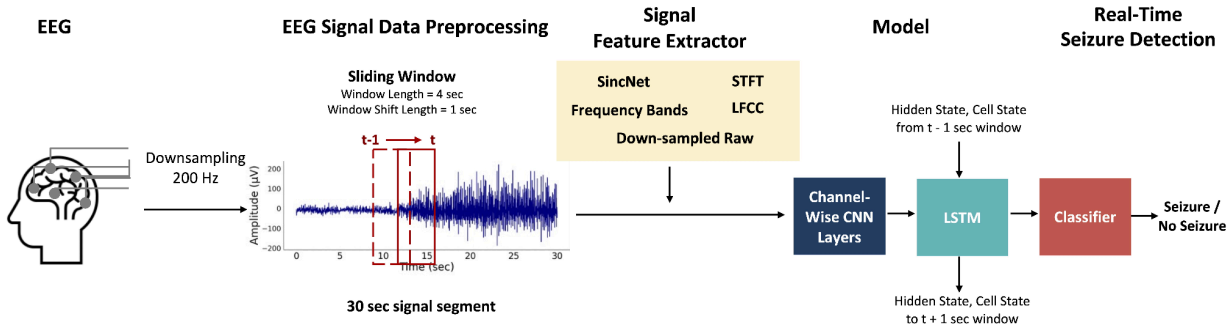

Figure 2: Overview of seizure detection pipeline used to train and validate the tinyML model, adapted from GitHub repository [https://github.com/AITRICS/EEG_real_time_seizure_detection/blob/master/README.md]

The TinyML model can be deployed onto an Altera FPGA using the Nios V soft-core processor [9]. The process begins with designing the FPGA hardware system in the Quarus Prime development environment, where the Nios V processor is instantiated, adding necessary peripherals (PWM module), and generating the hardware bitstream for programming the FPGA. Then, the integration of TensorFlow Lite for Microcontrollers (TFLite Micro) into the Nios V software environment can be performed by creating a static TFLite library. This involves cloning the TFLite Micro repository, using the create_tflm_tree.py script to generate a project tree, and customizing the system timing function to interface properly with the hardware. Compiler flags can be adjusted for memory efficiency and optimization, and the application code can be built using the Ashling RiscFree IDE via common line tools.

To test the integration, I used the TFlite "Hello World" example—a sine wave regression model—to validate inference capability on the FPGA. Once the setup successfully prints "ALL TESTS PASSED," the dummy model can be replaced with a trained seizure detection model. The system can then be deployed to classify EEG signals on-chip, using real-time input to drive a PWM output through a low-pass RC filter and sending it to the gold electrode, thereby activating the electrophoretic drug delivery mechanism. This entire pipeline enables an efficient, low-power, and fully implantable closed-loop neuromodulation system designed specifically for epilepsy management [10].

Microcontroller Stimulation

The microfluidic ion pump's gold electrode is actuated by a DC voltage derived from a PWM signal that is filtered through a cascaded two-stage RC low-pass filter network. The cutoff frequency of the second stage. Calculated to be approximately 15.9 Hz, governs the filter's bandwidth, dictating the trade-off between output voltage ripple and transit response time. Importantly, the DC output voltage magnitude is determined by the PWM duty cycle multiplied by the PWM's peak amplitude; for a 5 V PWM signal, a 20% duty cycle corresponds to a steady-state output voltage of approximately 1 V after filtering. This configuration ensures that the output voltage is sufficiently smooth to prevent electrical artifacts while maintaining the temporal resolution necessary for responsive drug delivery. The selected cutoff frequency enables the system to achieve a response time on the order of tens of milliseconds, which is crucial for the timely modulation of ion pump activity in closed-loop neurostimulation [11][12].

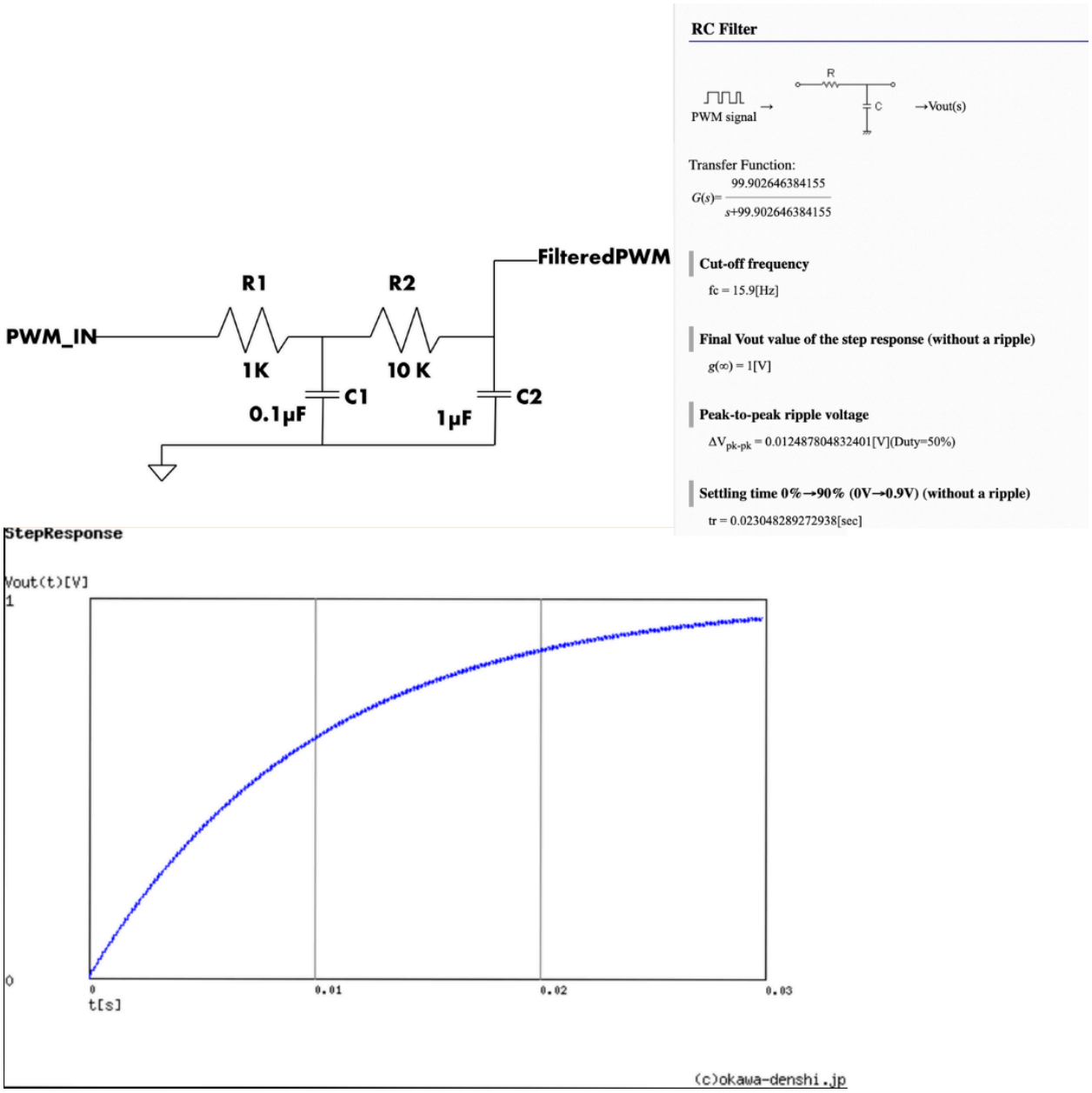

Figure 2: *Circuit diagram of an RC Low-pass filter used to convert a PWM signal into a smooth analog voltage for activating the µFIP. The circuit was designed using an online RC filter calculator. The transient analysis graph of the step response demonstrates signal smoothing and shows the system's settling time and peak voltage behavior.*

PWM switches a pin HIGH/LOW very fast. Duty cycle controls the average voltage. A low-pass RC filter smooths the PWM signal into a DC voltage that sends 1V to activate a gold electrode, which serves as the ion pump's electrical source [13]. This stimulates the microfluidic ion pump (µFIP) to release therapeutic agents. The ion flow is directed through a SU-8-based microfluidic channel to the probe tip, where PSS-based anion exchange membranes selectively allow cationic GABA+ to exit, allowing for only the ion without solvent, allowing for sizeable

drug delivery without the pressure increase [14]. The result is a targeted release of GABA+ to suppress abnormal neural activity. This forms a closed-loop system: neural activity is continuously monitored, abnormal signals are detected, and localized drug delivery is automatically triggered. The system repeats the cycle in real time, ensuring dynamic control over neuromodulation [15].

Drug Delivery Via Microfluidic Ion Pump (µFIP)

The µFIP is a modified organic electronic ion pump with an integrated U-shaped microfluidic channel made of SU-8 epoxy and sealed with a Parylene-C top layer. [1] At the tip, holes etched through the Parylene-C align with a PSS-based anion exchange membrane, forming the drug outlets. A gold electrode at the base of the fluidic channel functions as the ion pump source electrode [16]. It is activated by a PWM signal from the FPGA. Upon activation, GABA+ ions are electrophoretically pumped through the channel and released selectively through the outlet. This electrophoretic process is highly efficient, delivering $>10^{-3}$ nmol of GABA within seconds, rapidly increasing local concentrations above 10^{-5} M—enough to inhibit epileptiform activity [16] [17].

For epilepsy control, the probe can be implanted in the CA1, CA2, or CA3 regions of the hippocampus. However, physicians may customize implantation based on patient-specific epileptic zones using preoperative mapping. [6]

Discussion

Unlike conventional neural probes with external bases or wires, this device is designed for fully implanted operation, adapting the form factor of the NeuroPace RNS neurostimulator. Instead of delivering electrical stimulation directly to neurons, this system uses electrical signals to trigger chemical neuromodulation via the µFIP. The entire base , including the FPGA board, will be encapsulated in PDMS and implanted beneath the skull, mirroring the implantation strategy of clinical neurostimulators. [18] [19]

The following RNS system stimulation specifications serve as a reference point and provide a foundation for developing the device [14].

RNS® System Stimulation Specifications

Parameter	Specifications
Waveform	Current-controlled, symmetrical bi-phasic square wave
Montage	Any set of electrodes including the neurostimulator housing may be assigned to the anode or cathode
Amplitude	0-12 mA
Pulse Width	40-1000 microseconds per phase
Frequency	1-333 Hz
Burst Duration	10-60,000 milliseconds (PC Stim) 10-5,000 milliseconds (Responsive)
Number of Bursts	2 bursts; Burst 2 is delivered immediately after Burst 1; all parameters of Burst 2 may be different from Burst 1; Bursts 1 and 2 may be configured detection-specific
Adaptive Stimulation	Frequency may optionally be calculated as 6.25 to 200% of a pre-defined ECoG Half-Wave frequency
Synchronized Stimulation	Stimulation may optionally be synchronized to the phase (0-250 ms) and direction of a pre-defined ECoG Half-Wave

An onshape CAD model featuring the neural probe and base is featured here:https://cad.onshape.com/documents/16b0d1b2d2166942c21656f4/w/2c3c85c2cd17518b2f152709/e/708ba9b4b6724817589ca9e1?renderMode=0&uiState=689004640e57053fbab3d870

Conclusion

By integrating signal acquisition, embedded seizure detection, and on-demand GABA + delivery, the system represents a novel class of therapeutics for treating drug-resistant epilepsy. Future work will focus on in vivo validation and system miniaturization to enable clinical translation.

References:

1. Krook-Magnuson E., Armstrong C., Oijala M., Soltesz I., On-demand optogenetic control of spontaneous seizures in temporal lobe epilepsy. Nat. Commun. 4, 1376 (2013). https://doi.org/10.1038/ncomms2376
2. Dong S., Rogan S. C., Roth B. L., Directed molecular evolution of DREADDs: A generic approach to creating next-generation RASSLs. Nat. Protoc. 5, 561–573 (2010). https://doi.org/10.1038/nprot.2009.239

3. .Löscher W., Klitgaard H., Twyman R. E., Schmidt D., New avenues for anti-epileptic drug discovery and development. Nat. Rev. Drug Discov. 12, 757–776 (2013). https://doi.org/10.1038/nrd4126
4. Malekoshoaraie, M. H., Wu, B., Krahe, D. D., Ahmed, Z., Pupa, S., Jain, V., Cui, X. T., & Chamanzar, M. (2024). Fully flexible implantable neural probes for electrophysiology recording and controlled neurochemical modulation. *Microsystems & nanoengineering*, *10*, 91. https://doi.org/10.1038/s41378-024-00685-6
5. Lee, H. J., Son, Y., Kim, J., Lee, C. J., Yoon, E. S., & Cho, I. J. (2015). A multichannel neural probe with embedded microfluidic channels for simultaneous in vivo neural recording and drug delivery. *Lab on a chip*, *15*(6), 1590–1597. https://doi.org/10.1039/c4lc01321b
6. Shin, H., Son, Y., Chae, U., Kim, J., Choi, N., Lee, H. J., Woo, J., Cho, Y., Yang, S. H., Lee, C. J., & Cho, I. J. (2019). Multifunctional multi-shank neural probe for investigating and modulating long-range neural circuits in vivo. *Nature communications*, *10*(1), 3777. https://doi.org/10.1038/s41467-019-11628-5
7. Raducanu, B. C., Yazicioglu, R. F., Lopez, C. M., Ballini, M., Putzeys, J., Wang, S., Andrei, A., Rochus, V., Welkenhuysen, M., Helleputte, N. V., Musa, S., Puers, R., Kloosterman, F., Hoof, C. V., Fiáth, R., Ulbert, I., & Mitra, S. (2017). Time Multiplexed Active Neural Probe with 1356 Parallel Recording Sites. *Sensors (Basel, Switzerland)*, *17*(10), 2388. https://doi.org/10.3390/s17102388
8. Ranjandish, R., & Schmid, A. (2020). A Review of Microelectronic Systems and Circuit Techniques for Electrical Neural Recording Aimed at Closed-Loop Epilepsy Control. *Sensors (Basel, Switzerland)*, *20*(19), 5716. https://doi.org/10.3390/s20195716
9. Altman, M. B., Wan, W., Hosseini, A. S., Arabi Nowdeh, S., & Alizadeh, M. (2024). Machine learning algorithms for FPGA Implementation in biomedical engineering applications: A review. *Heliyon*, *10*(4), e26652. https://doi.org/10.1016/j.heliyon.2024.e26652
10. Deploying tinyML* on Altera® FPGAs White Paper. (2024). Retrieved July 28, 2025, from Intel website: https://www.intel.com/content/www/us/en/content-details/833277/deploying-tinyml-on-altera-fpgas-white-paper.html

11. Keim, R. (2016, April 11). Low-Pass Filter a PWM Signal into an Analog Voltage - Technical Articles. Retrieved from www.allaboutcircuits.com website: https://www.allaboutcircuits.com/technical-articles/low-pass-filter-a-pwm-signal-into-an-analog-voltage/
12. *TB3250 Using PWM to Generate an Analog Output*. (n.d.). Retrieved from https://ww1.microchip.com/downloads/en/Appnotes/90003250A.pdf
13. Uguz, I., Proctor, C. M., Curto, V. F., Pappa, A. M., Donahue, M. J., Ferro, M., Owens, R. M., Khodagholy, D., Inal, S., & Malliaras, G. G. (2017). A Microfluidic Ion Pump for In Vivo Drug Delivery. *Advanced materials (Deerfield Beach, Fla.)*, *29*(27), 10.1002/adma.201701217. https://doi.org/10.1002/adma.201701217
14. Riahi, R., Tamayol, A., Shaegh, S. A. M., Ghaemmaghami, A., Dokmeci, M. R., & Khademshosseini, A. (2015). Microfluidics for Advanced Drug Delivery Systems. *Current opinion in chemical engineering*, *7*, 101–112. https://doi.org/10.1016/j.coche.2014.12.001
15. Proctor, C. M., Slézia, A., Kaszas, A., Ghestem, A., Del Agua, I., Pappa, A. M., Bernard, C., Williamson, A., & Malliaras, G. G. (2018). Electrophoretic drug delivery for seizure control. *Science advances*, *4*(8), eaau1291. https://doi.org/10.1126/sciadv.aau1291
16. Proctor, C. M., Uguz, I., Slezia, A., Curto, V., Inal, S., Williamson, A., & Malliaras, G. G. (2019). An Electrocorticography Device with an Integrated Microfluidic Ion Pump for Simultaneous Neural Recording and Electrophoretic Drug Delivery In Vivo. *Advanced biosystems*, *3*(2), e1800270. https://doi.org/10.1002/adbi.201800270
17. Skarpaas, T. L., Jarosiewicz, B., & Morrell, M. J. (2019). Brain-responsive neurostimulation for epilepsy (RNS® System). *Epilepsy research*, *153*, 68–70. https://doi.org/10.1016/j.eplepsyres.2019.02.003
18. Jarosiewicz, B., & Morrell, M. (2021). The RNS System: brain-responsive neurostimulation for the treatment of epilepsy. *Expert review of medical devices*, *18*(2), 129–138. https://doi.org/10.1080/17434440.2019.1683445
19. NeuroPace, Inc. (n.d.). *The NeuroPace® RNS® System for responsive neurostimulation* [Company materials]. Exhibit C. Retrieved from https://www.neuropace.com/

GitHUb Repository:

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