The Neuropixels probe:
A CMOS based integrated microsystems platform for neuroscience and brain-computer interfaces

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Abstract— We review recent progress in neural probes for brain recording, with a focus on the Neuropixels platform. Historically the number of neurons’ recorded simultaneously, follows a Moore’s law like behavior, with numbers doubling every 6.7 years. Using traditional techniques of probe fabrication, continuing to scale up electrode densities is very challenging. We describe a custom CMOS process technology that enables electrode counts well beyond 1000 electrodes; with the aim to characterize large neural populations with single neuron spatial precision and millisecond timing resolution. This required integrating analog and digital circuitry with the electrode array, making it a standalone integrated electrophysiology recording system. Input referred noise and power per channel is 7.5 µV and <50 µW respectively to ensure tissue heating <1°C. This approach enables doubling the number of measured neurons every 12 months.

I. Introduction

To progress in neuroscience, there is a fundamental need to understand the sensory, motor and cognitive operations that involve the coordinated action of large neuronal populations in both deep and superficial areas across multiple brain regions [1]. A key tool and technique to study neuronal activity has been extracellular microelectrodes [2]. Until recently, however, the state-of-the-art of microelectrodes, was limited to probes capable of recording neural activity with excellent spatial and temporal (sub-millisecond) resolution, but from only a few dozen neurons per shank. In contrast, optical Ca2+ imaging[3] microscopy offers more surface (2D) coverage but offers limited depth access(<500µm). It also lacks the temporal resolution needed to reliably distinguish individual spikes and does not measure local field potentials.

To better understand the coordinated activity underlying brain computations, it is crucial to increase the number of single neurons that can be simultaneously recorded[2]. This requires large dense arrays of recording sites on a probe, ideally compatible with freely moving animals.

Advanced CMOS-based wafer scale integration provides a powerful technology to meet the diverse specifications and requirements needed to enable such large high density silicon microelectrodes arrays. Applying CMOS technology addresses the interconnectivity problem of integrating thousands of closely-spaced electrode based microsensors. It also improves the signal-to-noise characteristics, because, signal conditioning can be enabled on-chip close to the electrodes where very small signals (<7-10µV) are generated. Figure 3, shows the improvement in the slope of neural recording density since the adoption of Neuropixels probes based on integrated CMOS microsystem technology.

II. The Neuropixels Probe Platform

The Neuropixels platform is a custom implementation of a 200nm wafer scale 130nm CMOS silicon on insulator (SOI) technology with aluminum back-end of line (BEOL). A schematic cross section of a Neuropixels probe and an associated cross-section image is shown in Fig. 1. The platform provides:

- on-chip analog and digital circuitry (0.13µm node 5ML, 450K transistor/mm²), including 10 or 14 bit low power ADC’s to limit the per channel noise and power consumption to ~7.5µV and 25-50µW, limiting power dissipation such that the tissue heating is <1°C.
- micron sized titanium nitride (TiN)[4] bio-compatible electrodes, with areas from 25-150um², that are compatible with CMOS processing and feature low, uniform impedance (149 ± 6 kΩ, mean ± s.d., Fig. 2e).
- micro electromechanical systems modules to make shanks with small cross sectional area (50-75µm width, 20-25µm thickness and 10-50µm length).
- stress compensation layers limit the bending to ±100µm
- schematic layout design tools to realize variants in probe geometry for different animal models (Fig. 1, Inset 1.a-d)

III. Probe Design and Performance

Extracellular probes need to meet very specific performance targets to record large neuronal populations with single neuron precision. There are 9 major requirements that the Neuropixels platform is designed to meet. Two of the most critical relate to the geometry: (a) supporting thousands of dense recording sites to isolate many neurons across large regions of the brain[2]; and (b) a small cross-sectional area to minimize tissue damage and foreign body rejection. For example, in one instantiation of a Neuropixels probe[5] for rodent use, the platform enables 960-1280 electrodes on a single, 10-mm long, shank with 70 × 20-µm cross-section. This single shank is a large (10X) electrode count improvement over existing multi-shank silicon probes. This solution can be extended to multiple shanks for transverse coverage as indicated in a 5120 electrodes multi-shank implementation(Fig.1,Inset-1d). The 12×12-µm sites are arranged in a staggered pattern with 4 columns and 20-µm pitch. Additional key requirements enabled by the on chip low noise analogue amplifiers, multiplexers and digitizers on the probe base are: (c)user-programmable switches allow the recording channels to simultaneously address 384 of the 960-5120 total sites; (d)low noise read-out circuits; (e)resistance to crosstalk or other interference; (f)efficient data transmission.
This integration results in a probe of approximately 250mg in weight, which is small enough for chronic implants in mice (Fig. 2c). Figure 2-Inset1, shows the high level architecture of a particular rodent instantiation. In this version, we use 10-bit analogue-to-digital converters; to provide sufficient resolution for recording across a 0.5-10KHz frequency range. Each channel data are split into action potential (AP, 0.3–10 kHz) and local field potential (LFP, 0.5–1,000 Hz) bands – which have distinct neuroscience interpretations. These are separately amplified and digitized (AP, 30 kHz sampling; LFP, 2.5 kHz). This design and process co-integration, with low impedance TiN electrodes leads to uniform low noise ~5µV r.m.s.in the AP band; ~9µV r.m.s. in the LFP band (Fig.2d). The electrode composition fulfills two additional requirements: (g) long-term recording stability with uniform impedance (149 ± 6 kΩ, mean ± s.d., Fig. 2e); and (h) low-cost scalable fabrication with CMOS compatible materials. Last but not least (i) the platform must be modular to enable multiple variants of the probe for different animal models as shown in Fig 1-Inset 1. Although not strictly required, the platform can be further enhanced by adding new process modules that provide additional functionality such as integrated photonics for simultaneous electrophysiology and optogenetics experiments in deep structures [6].

Our goal is to scale the Neuropixels technology, to enable recording of 50000-100000 neurons simultaneously using multiple probes in the same brain.

### III. IN VIVO MEASUREMENT DATA

Neuropixels probes have enabled electrophysiological measurements across multiple brain areas with an unprecedented level of detail. As an example, Fig 4, shows data from a probe inserted into the brain of an awake, head-fixed mouse[7]. Since the probes are able to record activity with the same spatial resolution along the entire shank, the data can be conveniently displayed as images with each site represented as a 'pixel'. Using these images, structural boundaries can be visualized using simple measures of neural activity, (Fig. 4a–c). From this recording, 206 putative individual neurons were isolated from the primary visual cortex, hippocampus, and lateral posterior nucleus of the thalamus (Fig 4c) using automated spike sorting methods with manual curation.

### IV. NEUROPIXELS FOR BRAIN COMPUTER INTERFACES (BCI)

Beyond basic research, new neurophysiology devices will also support medical interventions and become critical in brain-computer interfaces (BCIs), a broad class of technology that reads outs neural activity, processes it, and stimulates the brain [8]. BCIs are being investigated for restoring function, for people with paralysis by enabling them to control a computer cursor or robotic arm, or by re-animating paralyzed muscles or synthesizing speech. Further work has shown the value of BCIs in restoring the sense of touch and vision; epilepsy detection and intervention, and many other clinical indications.

Despite compelling demonstrations using ~8-200 recording and/or stimulating channels, BCIs are not yet ready for widespread medical use because much higher channel count recording is needed. Neuropixels probes are well-positioned to meet this translational need by providing a scalable platform for high-density recording. As an example, we’ve shown that a single 384-channel Neuropixels 1.0 probe can record more neurons in primate motor cortex, with characteristic tuning to movement direction, than the Utah array (Fig 5, [9]), which is the current gold standard for BCIs.

CMOS technology, provides a path to the miniaturization and chronic implantation, needed for most clinical applications. However, two important open questions are (1) device lifespan in the harsh environment of the brain, and (2) whether the health of the surrounding tissue will allow for long-term interfacing with the brain. To date, the longest recordings with Neuropixels in primates has been 160 days, but more data will be available, as Neuropixels become widely disseminated.

### V. CONCLUSION

Neuropixels probes enabled by a wafer scale integrated microsystem platform provide a >10X increase in the number of simultaneously recorded neurons obtained per shank. This increased recording capability is enabling many applications, such as the simultaneous recording of inputs and outputs of diverse brain regions, as well as studying the relationship of activity distributed across the brain and to an animal’s behavior. Recently a number of groups have been able to study the neural basis of behavior across more than 3000 neurons using such probes. There are also early indications the Neuropixels platform can enable, the type of functionality necessary to make clinically viable BCI’s a reality.

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## REFERENCES

Figure 1: Schematic Cross-section and Cross-section SEM Image of Neuropixels CMOS Probe platform and custom process modules in 130nm custom CMOS SOI process with Al BEOL.
Inset 1-Variants of Neuropixels probes: Inset 1a. Neuropixels 1.0-NHP for non-human primates with a 45mm long shank with 4560 electrodes, Inset 1b. Neuropixels-1.0 for large rodents with 10mm shank with 966 electrodes, Inset 1c. Neuropixels 2.0 single shank for small rodents with 1250 electrodes, Inset 1d. Neuropixels 2.0 multi-shank with 5120 electrodes on 4 shanks.

Figure 2: The Neuropixels probe: Inset 1: High-level architecture of the probe.
a. Illustration of probe tip, showing checkerboard site layout (dark squares). b. Scanning electron microscope image of probe tip. c. Probe packaging, including flex cable and headstage for bidirectional data transmission. d. Example of r.m.s. noise levels of the AP band in saline, for 384 sites (switchable option). Mean ± s.d. = 5.1 ± 0.6 µV. e. Typical site impedance in saline, for 384 sites, measured for each site with sinusoidal 1 nA injected currents at 1 kHz. Mean ± s.d. = 149 ± 6 kΩ.
Figure 3. Number of simultaneously recorded neurons as a function of time. [https://stevenson.lab.uconn.edu/scaling/ and Stevenson IH and Kording KP (2011) Nature Neuroscience, 14: 139-142.]

Figure 4. Recording from large neuronal populations with a single neuropixels probe in an awake head-fixed mouse. For the heat maps, each square represents a single site. a, r.m.s. amplitude of the AP band signal for 1-s intervals, averaged over 10 intervals. b, Firing rate measured from AP band crossings of a −50 µV threshold, in a 10-s interval. c, Distribution of putative single neuron locations (channel with peak amplitude), smoothed with a one-dimensional Gaussian filter (radius = 4.5 sites). d, Histological reconstruction of the probe track with 4′,6-diamidino-2-phenylindole (DAPI; blue) and Dil (red) staining. J J Jun et al. Nature 551, 232–236 (2017) doi:10.1038/nature24636

Figure 5. High density recording in non-human primates:
a) Non-CMOS based Utah array for chronic neural recordings with one electric channel per penetrating electrode b) Each channel on the Utah array is independent, sampling from a fixed depth in cortex. c) The Neuropixels probe enables high-density recordings via 960 electrodes spaced along the single10mm penetrating probe (384 selectable for simultaneous recording). d) Electrical signatures from numerous neurons in a single recording. Small signatures can be resolved as neurons, and information from all layers of cortex can be recorded simultaneously. e) Approximately 250-350 neurons can be recorded in a typical recording from the Neuropixels probe in primate motor cortex, enabling high performance BCI and scientific investigations.