Imaging circuit activity in the rat brain with fast neural EIT and depth arrays

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Abstract—Few techniques are specialized for neuroscience at the "mesoscopic" level of neural circuits. Fast neural electrical impedance tomography (fnEIT) is a novel imaging technique that offers affordability, portability, and high spatial (~100 μm) and temporal (~1 ms) resolution. fnEIT with depth arrays offers the opportunity to study the dynamics of circuits in the brains of animal models.

However, current depth array geometries are not optimized for this imaging modality. They feature small, closely packed electrodes with high impedance that do not provide sufficient SNR for high resolution EIT image reconstruction. They also have a highly limited range. It is necessary to develop depth arrays suitable for fnEIT and evaluate their performance in a representative setting for circuit neuroscience.

In this study, we optimized the geometry of depth arrays for fnEIT, and then investigated the prospects of imaging thalamocortical circuit activity in the rat brain. Optimization was consistent with the hypothesis that small, closely spaced electrodes were not suitable for fnEIT. *In vivo* experiments with the optimized geometry then showed that fnEIT can image thalamocortical circuit activity at a high enough resolution to see the activity propagating from specific thalamic nuclei to specific regions of the somatosensory cortex. This bodes well for fnEIT's potential as a technique for circuit neuroscience.

Keywords—electrical impedance tomography, brain imaging, neural circuits, depth probe

I. Introduction

Fast neural electrical impedance tomography (fnEIT) is an emerging neural imaging technique that offers high spatial (~100 μm) and temporal resolution (~1 ms), portability and affordability[1]. fnEIT has the potential to image neural circuit activity at a higher spatial resolution than LFP[2], while providing accurate image reconstruction thanks to its unique inverse solution[3].

fnEIT has been used successfully to image evoked somatosensory activity in the cortex of the rat[4]. However, imaging deep subcortical activity with epicortical arrays has proven challenging. Increasingly, neuroscientists are choosing to use depth arrays (such as NeuroPixels) to image activity in the deeper regions of the brain[5].

However, standard depth array geometries feature small electrodes (on the order of 10 μm) clustered in a highly localized region of the brain. This kind of geometry is not optimal for fnEIT since it suffers from high impedance (>100 kΩ) and limited imaging range, as well as being more suited for imaging microscopic activity than circuit activity[2][5].

The **purpose** of this study was to answer two main questions: **(1)** what is the optimal depth array geometry for fnEIT in the rat brain?, and **(2)** can fnEIT image evoked somatosensory activity in the thalamus and cortex with a high enough resolution to localize activity to the expected cortical subregions and thalamic nuclei?

II. Methods

A. Experimental Design

This study consisted of two parts: *in silico* simulations to determine the optimal geometry for the depth array, and *in vivo* experiments to assess the array's capabilities for fnEIT. The paradigm of evoked somatosensory activity (thalamocortical loop) was used, as this is a well-characterized circuit in the rat brain that also exhibits a pattern of activity allowing for easy repetition and averaging.

B. Optimisation Study

MATLAB and COMSOL Multiphysics were used to generate finite-element meshes of 1000 candidate geometries. These geometries were generated by logarithmically varying several key parameters (shank width, electrode height, electrode number, shank spacing, inter-electrode spacing) between realistic limits. Candidates with impossible geometries were eliminated, leaving 766 to be considered.

Candidates were evaluated by simulating EIT. Each was placed in a 1 cm cube of "brain tissue" at a uniform baseline conductivity of 0.3 Sm^{-1}. Neural activity was simulated by placing 50 and 200 μm diameter spherical perturbations of 0.4% conductivity change vs. background.

Candidates were assessed via an objective function. This function attempted to maximize the number of measurements above the noise and the signal-to-noise ratio (SNR) while minimizing the shank width and the number of shanks per unit volume (to minimize tissue damage).

The optimal candidate was fabricated by post-processing foundry wafers from TSMC. The wafers did not have an etch stop layer. The post-processing was done entirely at wafer-scale until the final packaging steps. The probes were thinned to ~65 μm to allow for tissue insertion while also preventing shank bowing due to residual stresses allowing strict electrode registry. The device consisted of a silicon mount with

aluminum tracks and gold electrodes. Each electrode was coated with a thin layer of PEDOT;pTS to improve contact impedance.

C. In Vivo fnEIT Imaging: Physiology & Preparation

Preliminary imaging data were collected in one adult Sprague-Dawley rat. The rat was placed under isoflurane anesthesia and its vital signs (ECG, temperature, respiratory rate, EEG) were continuously monitored to ensure good health. Saline was infused intraperitoneally to maintain internal fluid balance.

The scalp was incised with scissors and the right temporal muscle removed. A dental drill was then used to create a trapezoidal craniotomy window that exposed most of the right hemisphere. The dura was carefully removed with a dura hook. Artificial cerebrospinal fluid was applied throughout to prevent the cortex drying.

A 37 electrode epicortical array was placed on the cortex. This array had a 4 by 4 mm square aperture centered at 3 mm lateral and 1.5 mm posterior to bregma. The epicortical array was used to assess the health of the brain by confirming the presence of cortical somatosensory evoked potentials (SEPs).

SEPs were evoked by stimulating the contralateral forepaw with needle electrodes. Stimulation was delivered at 2 Hz with current at 2 mA and a pulse width of 300 μs, averaging for 1 minute with 500 ms epochs. Once the presence of EPs was confirmed, the depth array was inserted at the center of the aperture until the highest row of electrodes passed just beneath the cortical surface.

D. In Vivo fnEIT Imaging: Data Collection

SEPs were evoked continuously throughout EIT recording using the same parameters as in section C. Sinusoidal current of amplitude 20 μA and frequency 1475 Hz was injected with a Keithley 6221 current source (Keithley Instruments Ltd., Bracknell, UK) through a set of electrode pairs intended to homogenize current density in the region of interest.

Voltages were continuously measured at a sampling frequency of 100 kHz on all electrodes with a BrainVision actiCHAMP EEG amplifier (Brain Vision LLC, Cary, NC). All voltages were measured against a 10 mm diameter circular AgCl reference electrode implanted at the back of the head. There were 35 injection pairs injecting for 1 minute each, resulting in 35 minutes of total EIT recording.

E. In Vivo fnEIT Imaging: Data Processing

Data were processed using MATLAB. Data for each channel were chopped into 500 ms epochs around each forepaw stimulus. The data were filtered with a 5th order bandpass Butterworth filter with cut off frequencies 500 Hz either side of the injection frequency, demodulated using the Hilbert transform and then averaged across all epochs for each channel.

The averaged data were low-pass filtered with a 3rd order Butterworth filter at a cut off frequency of 200 Hz. Voltage changes were obtained by subtracting the baseline (a mean of the 250 ms period before stimulus) from each dataset. Changes with a baseline standard deviation of more than 1 μV were considered too noisy and excluded from the image reconstruction.
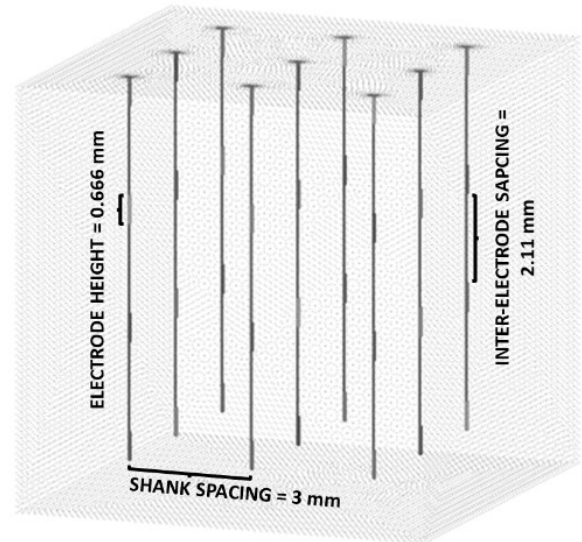

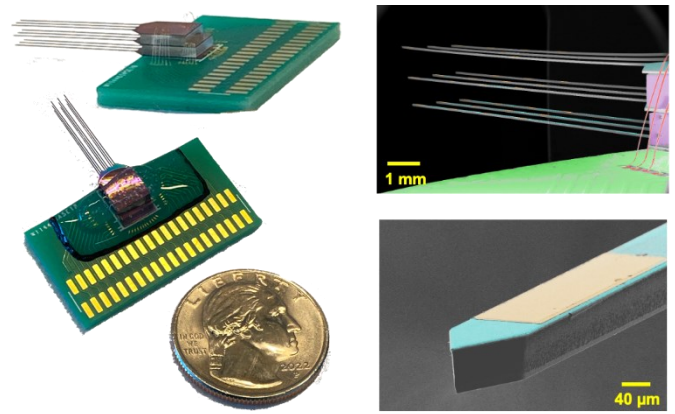Fig. 1: Geometry of the optimal candidate according to our objective function

Fig. 2: Manufactured depth array for fnEIT

F. In Vivo fnEIT Imaging: Image Reconstruction

The Jacobian (sensitivity) matrix and simulated boundary voltages were obtained for a 9 million element mesh of the shanks in a 1 cm cube of brain tissue with a uniform background conductivity of 0.3 Sm^{-1}. The same protocol was used as in section D. The forward problem was solved with the bespoke software PEITS (parallel EIT solver).

Images were reconstructed by solving the inverse problem on a hexahedral mesh with 125000 elements. The Jacobian was inverted and multiplied by the measured voltages to obtain the conductivity changes in the brain tissue. The inverse solution was regularized via zeroth order Tikonov regularization, generalized cross-validation, and noise-based correction.

Images were converted to VTK format and assessed visually in ParaView. Images were thresholded to only show changes with a magnitude above 50% of the maximum change. Conductivity changes were sampled every 1 ms from 10 ms before stimulus to 50 ms after stimulus, generating a sequence of 61 images for each reconstruction. The images were aligned with a realistic rat brain mesh to assess the location of the changes in the brain.

III. RESULTS

A. Optimisation of Array Geometry

The objective function suggested that candidates with a small number of large, widely spaced electrodes were more suitable for fnEIT than candidates with many small, closely spaced electrodes. The higher the level of simulated background noise, the more such candidates were favored.

The optimal candidate (Fig. 1) had 9 shanks, each with 4 electrodes giving 36 electrodes in the total. The electrodes had a height of approx. 0.7 mm, a spacing along the shank of 2 mm and a spacing between shanks of 3 mm. The shank width was 0.01 mm.

Adjustments had to be made to this design in light of manufacturing constraints (Fig. 2). The shank width was increased to 120 μm to prevent failure during insertion. The shank spacing had to be reduced to 1 mm due to limitations in wire-bonding. The electrode height was reduced to 0.5 mm to create the required space for other components.

These changes reduced the array's overall coverage and potentially increased the risk of tissue damage during insertion. Nonetheless, since the overall geometry of the electrode array in the contained region remained similar (in terms of electrode size and spacing), it was not expected that these changes would negatively impact SNR in the main regions of interest.

B. Somatosensory Evoked Potentials

The epicortical array recorded EPs of amplitude up to 150 μV and peak latency 15 ms. The location was consistent with the expected location for forepaw activity and of a size that indicated good brain health.

The depth array recorded EPs on two channels, and these had a similar latency and duration to the epicortical EPs. These depth EPs had an amplitude of 250 and 150 μV respectively. They were seen on the two highest electrodes on the lateral-most shank of the array's middle layer.

C. In Vivo EIT Imaging

Out of the 1260 independent voltage measurements (35 injection pairs * 36 electrodes), 50 showed a fast impedance change with an SNR of at least 2. The magnitude of the dZs ranged from 0.0015 to 0.15% of the standing potential with a mean of 0.03%. The SNR ranged from 2 to 20 with a mean of 5.

Changes were mostly seen on the central and medial shanks of the middle and posterior-most layers. Thalamic and cortical changes could be distinguished, with a peak latency of around 6 and 12 ms respectively. Both kinds of change had a duration of about 10 ms.

The image reconstruction showed two distinct active regions (Fig. 3). The first appeared 3 ms after stimulation (a.s.) and remained visible until 8 ms a.s.. It then returned at 22 ms a.s. and remained visible until 25 ms a.s. The second region appeared at 10 ms a.s. and remained visible until 15 ms a.s. It then returned at 22 ms a.s. and remained visible until 25 ms a.s..

The first active region was centered 2.5 mm posterior and 3 mm lateral to bregma at a depth of 5 mm below the cortical surface. It had a maximum diameter of 1.5 mm. The size, location and timing of this active region are all highly
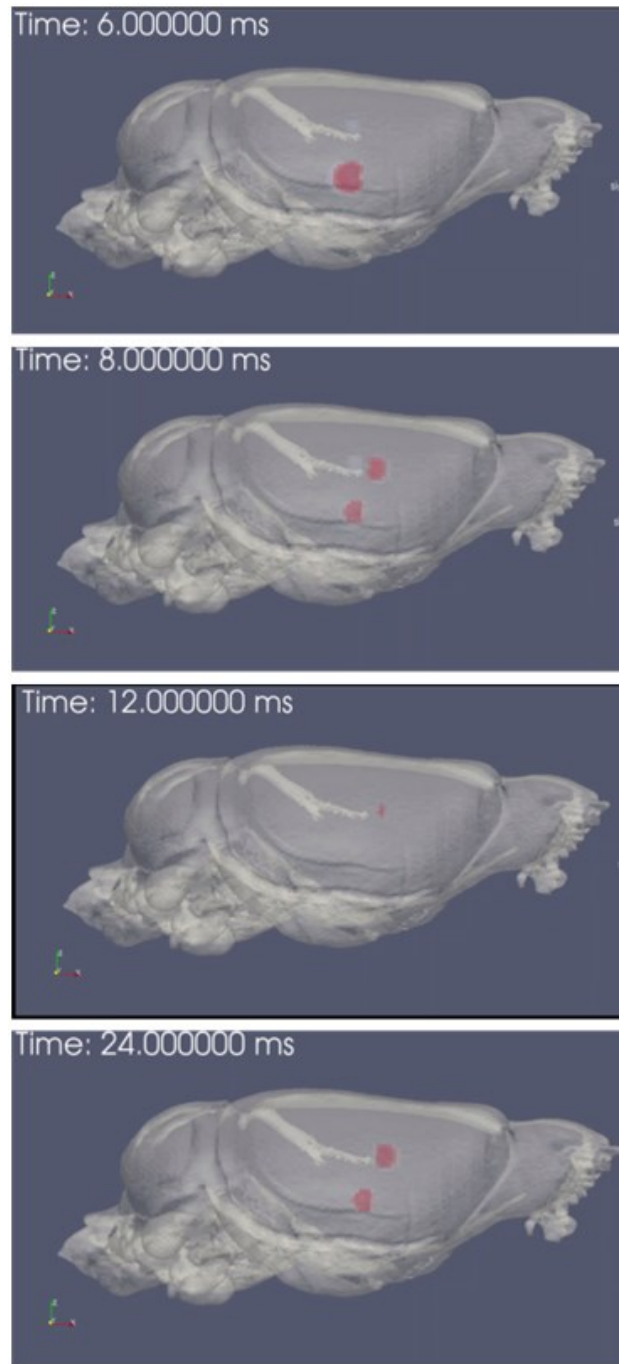

Fig. 3: EIT image reconstruction of activity in the rat brain following forepaw stimulation. Timestamp shown is time after stimulus. The brain is shown with the right hemisphere towards the viewer and the front of the brain on the right.

consistent with what is expected for the thalamic component of the thalamocortical loop.

The second active region was centered 1.5 mm posterior and 4 mm lateral to bregma at a depth of 2.5 mm below the cortical surface. It had a maximum diameter of 1.4 mm. This location is consistent with cortical somatosensory evoked activity, although more lateral than expected for forepaw activity (centered 0.5 mm lateral to the lateral boundary of S1FL).

IV. DISCUSSION

This study has provided the first steps towards establishing fnEIT as a viable technique for investigating neural circuits with depth arrays. The geometrical optimization has provided valuable information about the design of depth arrays for brain imaging, The *in vivo* experiments show that fNEIT can image circuit activity with high spatial and temporal resolution. The total imageable tissue volume of 50 mm^3 is more than an order of magnitude greater than for previous probe geometries[2].

What is the optimal geometry for fnEIT in the rat brain?

Arrays with a small number of large, widely spaced electrodes achieve the best SNR for fnEIT in the rat brain. Such arrays are the most robust to an increase in background noise. This explains why previous fnEIT studies with more traditional depth array geometries struggled to achieve an imaging range of more 60 μm.

Manufacturing and insertion constraints necessitated changes to the geometry. These changes are unlikely to have significantly affected the SNR in the main regions of interest. Nonetheless, they highlight the difficulty of achieving large coverage and minimizing tissue damage while working with current depth array manufacturing capabilities.

Can fnEIT image evoked somatosensory activity in the thalamus and cortex with a high enough resolution to localize activity to the expected cortical subregions and thalamic nuclei?

Preliminary data suggest that fnEIT can indeed image activity in the thalamocortical loop at the required resolution. The temporal resolution was high enough (~1ms) to resolve all three components of the loop. Spatial resolution was high (~200 μm). Thalamic activity was localized with an error of ≤0.2 mm. Cortical activity had a localization error in the coronal plane of ≤0.5 mm.

Errors in the coronal localization are more likely a reflection of probe position than limitations in EIT reconstruction. The position of the epicortical array is subject to up to 0.5 mm of error due to variation during drilling and placement. As a result, the insertion site of the depth array is subject to an error of the same magnitude. This could be mitigated by greater precision during drilling.

Limitations & Future Work

Preliminary experiments with depth fnEIT have only produced one high resolution reconstruction of the thalamocortical loop. The biggest challenge with fnEIT remains the need to achieve sufficient SNR (≥3) on a wide range of channels. Impedance changes measured on the depth array are small (often less than 1 μV), requiring a background noise after averaging of less than 0.3 μV to achieve a high enough SNR for accurate image reconstruction.

Noise could be reduced by ensuring consistent and high-quality electrode coatings, adding on-probe CMOS circuitry, as well as by optimizing the grounding arrangements of the recording equipment. Signal size could be improved by further optimizing physiological protocols to maintain a high degree of brain health.

Insertion of depth arrays into neural tissue inevitably entails risk of traumatic brain injury and/ or hemorrhage. Attempts have been made to mitigate this risk, such as increasing smoothness of the array edges and optimizing the insertion protocol. Nonetheless, consistently avoiding damage to vasculature remains a challenge.

Future work will focus on improving the SNR as well as attempting to image activity with other somatosensory paradigms such as whisker and hind paw stimulation. Preliminary results suggest fnEIT can achieve sufficient spatial resolution to distinguish the activity of different stimulation paradigms.

While SNR remains a limiting factor, EIT continues to show increasing promise as a low cost, portable, high-resolution technique for the investigation of neural circuits in animal models.

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