

Measurement of Electrophysiological Signals In Vitro Using High-Performance Organic Electrochemical Transistors

James E. Tyrrell, Martyn G. Boutelle, and Alasdair J. Campbell*

Biological environments use ions in charge transport for information transmission. The properties of mixed electronic and ionic conductivity in organic materials make them ideal candidates to transduce physiological information into electronically processable signals. A device proven to be highly successful in measuring such information is the organic electrochemical transistor (OECT). Previous electrophysiological measurements performed using OECTs show superior signal-to-noise ratios than electrodes at low frequencies. Subsequent development has significantly improved critical performance parameters such as transconductance and response time. Here, interdigitated-electrode OECTs are fabricated on flexible substrates, with one such state-of-the-art device achieving a peak transconductance of 139 mS with a 138 μ s response time. The devices are implemented into an array with interconnects suitable for micro-electrocorticographic application and eight architecture variations are compared. The two best-performing arrays are subject to the full electrophysiological spectrum using prerecorded signals. With frequency filtering, kHz-scale frequencies with 10 μ V-scale voltages are resolved. This is supported by a novel quantification of the noise, which compares the gate voltage input and drain current output. These results demonstrate that high-performance OECTs can resolve the full electrophysiological spectrum and suggest that superior signal-to-noise ratios could be achieved in high frequency measurements of multiunit activity.

1. Introduction

The measurement of neuronal signals has applications in brain-machine interfaces and diagnosing neurological disorders. Microelectrode arrays capture such activity by measuring the time-varying extracellular potential differences generated by ionic fluxes from the depolarizations of neurons. The activity of single neurons (SUA) has been resolved using spike-sorting algorithms of multiunit activity (MUA) from arrays placed on the surface of, or inserted into, the cortex.^[1,2] In recent years, an alternative method of measuring bioelectrical signals has been implemented through the use of organic electrochemical transistors (OECTs).^[3–8] The OECT is typically a three-terminal device in which an ionic flux across an organic active layer causes a variation in current between two surrounding electrodes, known as the source and drain. The ionic fluxes are generated by the gate electrode, situated in an electrolyte. For electrocorticographic measurements, this is analogous to the changes in the extracellular ionic concentrations of cerebrospinal fluid that are associated with

neuronal action potentials. The most commonly used organic layer for OECTs is poly(3,4-ethylenedioxythiophene):polystyrene sulfonate (PEDOT:PSS) due to its biocompatibility, high conductivity, film processability, low cost, low power operation and ambient stability.^[9–11] PEDOT is a hole-transporting conjugated polymer, and degenerative doping with PSS results in a p-type conducting polymer blend. When cations from the electrolyte enter the PEDOT:PSS volume, the PEDOT is de-doped, reducing the number of holes and so decreasing the current measured, as illustrated in **Figure 1a**. Therefore, for a change in gate-drain voltage, there is a change in drain current, giving an amplification defined as the transconductance, g_m . The OECT response time, τ , is determined by the time taken for ions to enter and leave the active layer and for the holes to traverse the length of the active layer.^[12] To measure bioelectrical signals such as MUA, the variations in extracellular ionic concentrations must result in measurable active layer de-doping. This requires sufficient amplification and temporal response of the OECT; however, there is a trade-off between such parameters as both are dependent on active layer thickness, d , as shown in **Figure 1b**.^[5,13]

The measurement of bioelectrical signals at a high spatial resolution sets a limit on the maximum device size. For example, Khodagholy et al. found that microelectrode arrays required a

J. E. Tyrrell, Prof. A. J. Campbell
Experimental Solid State Physics Group
Department of Physics
Imperial College London
Blackett Laboratory
South Kensington Campus, London SW7 2AZ, UK
E-mail: alasdair.campbell@imperial.ac.uk

J. E. Tyrrell, Prof. M. G. Boutelle
Centre for Neurotechnology
Imperial College London
South Kensington Campus, London SW7 2AZ, UK
Prof. M. G. Boutelle
Department of Bioengineering
Imperial College London
Bessemer Building
Exhibition Road, London SW7 2AZ, UK



The ORCID identification number(s) for the author(s) of this article can be found under <https://doi.org/10.1002/adfm.202007086>.

© 2020 The Authors. Published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

The copyright line for this article was changed on 25 September 2020 after original online publication.

DOI: 10.1002/adfm.202007086

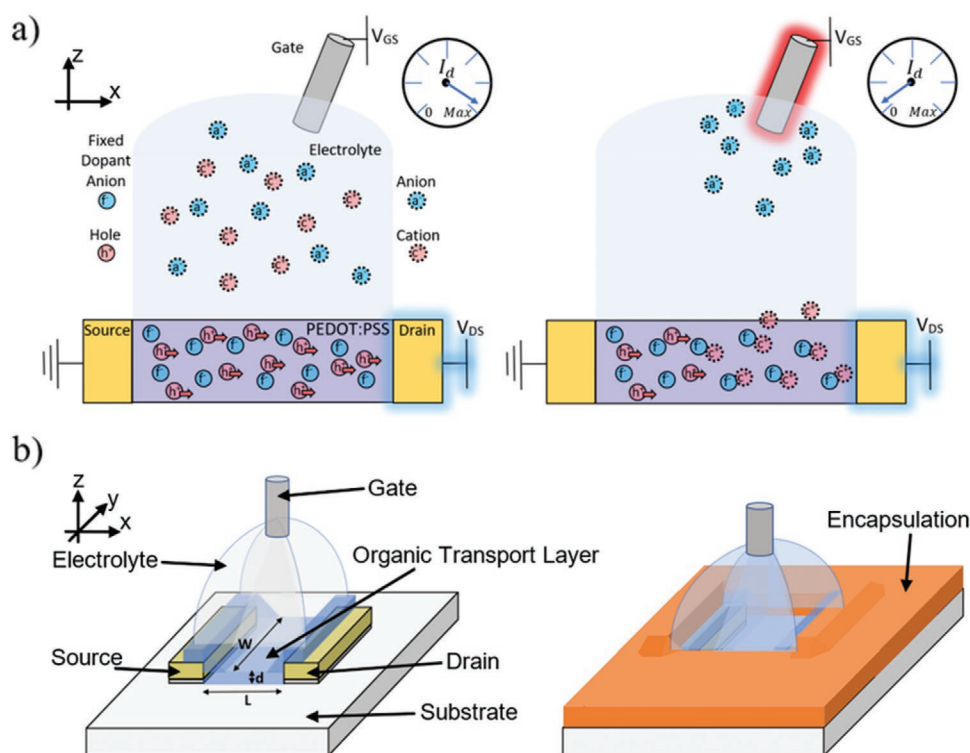


Figure 1. a) Mechanism of de-doping in a PEDOT:PSS-based OEET. The application of a sufficient gate-drain voltage results in the transport of the electrolyte cations into the PEDOT:PSS volume. Consequently, the cations compensate the dopant anions of the PSS, reducing the number of holes generated and thus decreasing the magnitude of the current as measured at the drain electrode. b) Structure of an organic electrochemical transistor with channel dimensions. The encapsulation is illustrated separately for clarity.

pitch of 30 μm and an electrode size of $10 \times 10 \mu\text{m}^2$ to determine SUA from MUA.^[1] Therefore, the transconductance, which is dependent on the fraction of active layer width to length, W/L , is limited if using a planar parallel-plate electrode geometry. Therefore, different electrode architectures are needed to maximize device performance. One such geometry is the vertical OEET, presented by Donahue et al. in 2018, where the electrodes were nonplanar. However, it was claimed that the parasitic capacitance, caused by excessive electrode overlap, limited the temporal response.^[14] An alternative electrode geometry which maintains the planar structure while maximizing W/L is the interdigitated electrode design. The style of interdigitation pattern investigated can be considered as interlocking source- and drain combs. Interdigitated-electrode OEETs were applied to measuring action potentials of cardiac cells, which have amplitudes on the mV scale.^[15,16]

Initial in vivo applications of OEETs in micro-electrocorticography (μECoG) yielded higher signal-to-noise ratios than microelectrodes of equivalent size for frequencies less than 200 Hz.^[4] Expanding this capability to include measurements at higher MUA frequencies is highly desirable. In this work, interdigitated-electrode, PEDOT:PSS-based, flexible OEETs were fabricated and characterized, resulting in devices with state-of-the-art peak transconductance values greater than 100 mS and response times approaching 100 μs . A set of 4×4 OEET arrays were then characterized and sampled whilst inputting pre-recorded electrophysiological signals. The entire bioelectric frequency-voltage range was investigated, and it was demonstrated that the OEETs had the capability to resolve all inputs.

2. Results and Discussion

2.1. Fabrication and Device Structure

The substrate material was polyethylene terephthalate (PET), chosen for its flexibility and ability to support PEDOT:PSS without the addition of the crosslinker 3-glycidypropyltrimethoxysilane.^[17] The active layer consisted primarily of the biocompatible conducting polymer PEDOT:PSS, and was spin-coated to a 35 or 70 nm thickness. The thermally evaporated source and drain was comprised of a 200 or 300 nm gold layer with a 15 nm chromium adhesion layer. The spin-coated encapsulation layer was made of SU-8 with a 1 μm thickness. The SU-8 photoresist has also been shown to be suitable for at least short-term implantation.^[18] In device characterization and testing, Ringer's solution was used as the electrolyte and a silver/silver-chloride pellet electrode was used as the gate electrode.

The OEETs were fabricated with four different interdigitated-electrode patterns. There are 2 styles of interdigitation: "combs" and "spirals," as shown in **Figure 2**. The interdigitated electrodes were each patterned in two sizes, denoted "small" and "large," where the geometry dimensions are shown in **Table 1**. The resulting four electrode styles were patterned either with a 200 nm Au layer with 70 nm active layer thickness or 300 nm Au with 35 nm active layer. These combinations were chosen in order to vary the ratio between interconnect and channel resistance. As such, there were eight variations of device

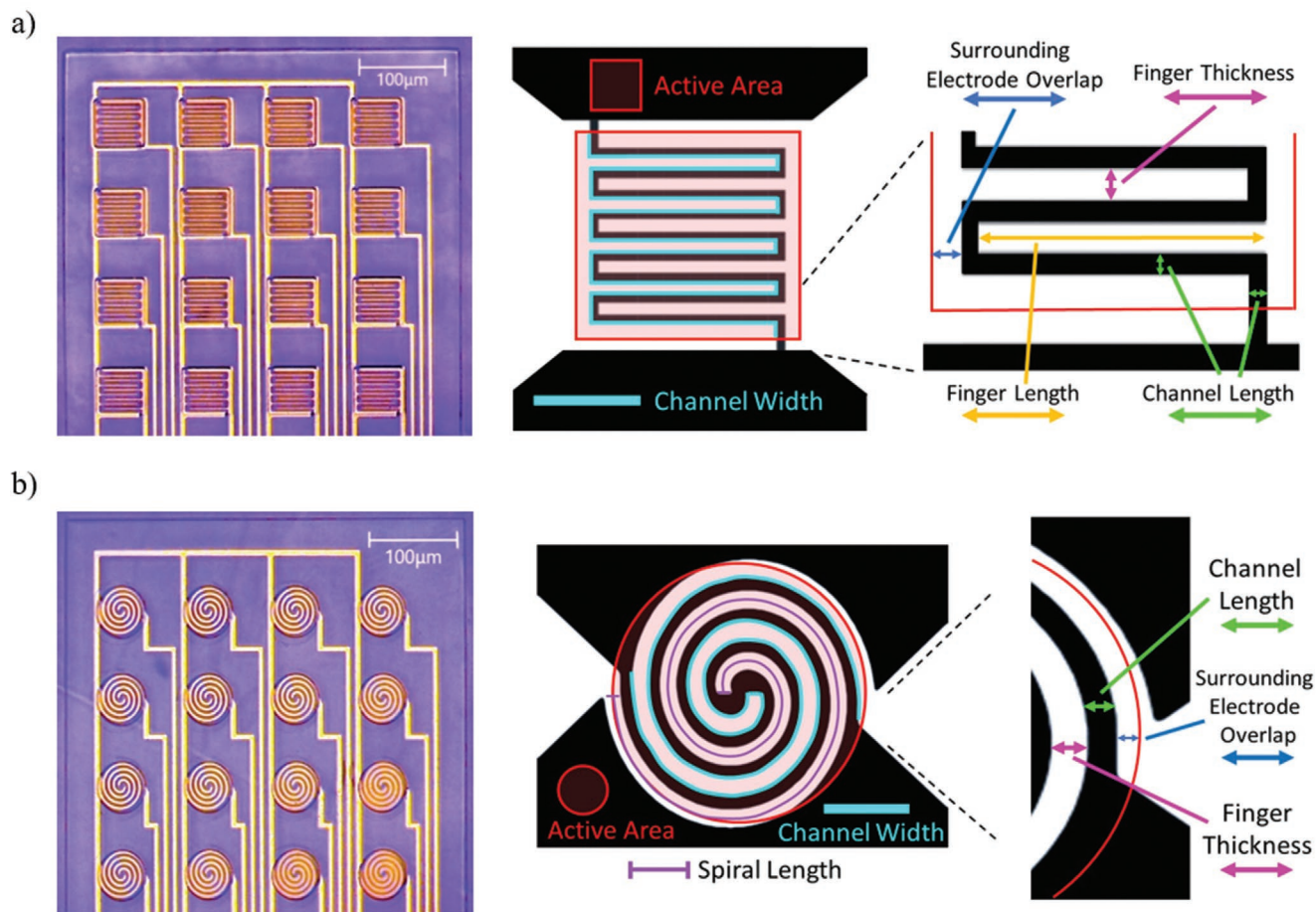


Figure 2. a) The geometry parameter of the “comb” interdigitation with microscope image of the small-comb array. b) Geometry of the “spiral” interdigitation with microscope image of the small-spiral array. Values of the geometry parameters are described in Table 1.

architecture in total. The interdigitated electrodes were connected to characterization equipment either through electrode pads or the array zero-insertion-force connectors. The array interconnect resistance was minimized whilst ensuring it was suitable for μ ECoG applications. The interconnects allowed an insertion of the array at depths comparable to the thickness of the human skull.^[19] A 3 mm width is also required for array insertion, which was chosen as it was smaller than the diameter

of small skull bore holes.^[20] The array output was made compatible with standard zero-insertion-force connectors, as shown in **Figure 3a**. To demonstrate the capability of the devices, the initial characterization presented is from a large comb-interdigitated, 70 nm thick active layer OECT with electrode pad connections, as shown in Figure 3b. The gate-drain potential difference was kept lower than the hydrolysis voltage for all characterizations.

Table 1. Geometry parameters of the four interdigitated electrode styles characterized. The parameters are illustrated in Figure 2.

Property	Small comb (SC)	Small spiral (SS)	Large comb (LC)	Large spiral (LS)
Active area [μm^2]	86×78	$\pi(40.5)^2$	180×168	$\pi(91)^2$
Surrounding electrode overlap [μm]	5	2.5	10	3
Device pitch [μm]	152	152	324	324
Channel length [μm]	4	4	8	8
Finger/turn number	5	2	6	3
Finger/spiral length [μm]	72	286	152	929
Finger/spiral thickness [μm]	4	5	6	6
W/L ratio	164.5	118.5	230	200

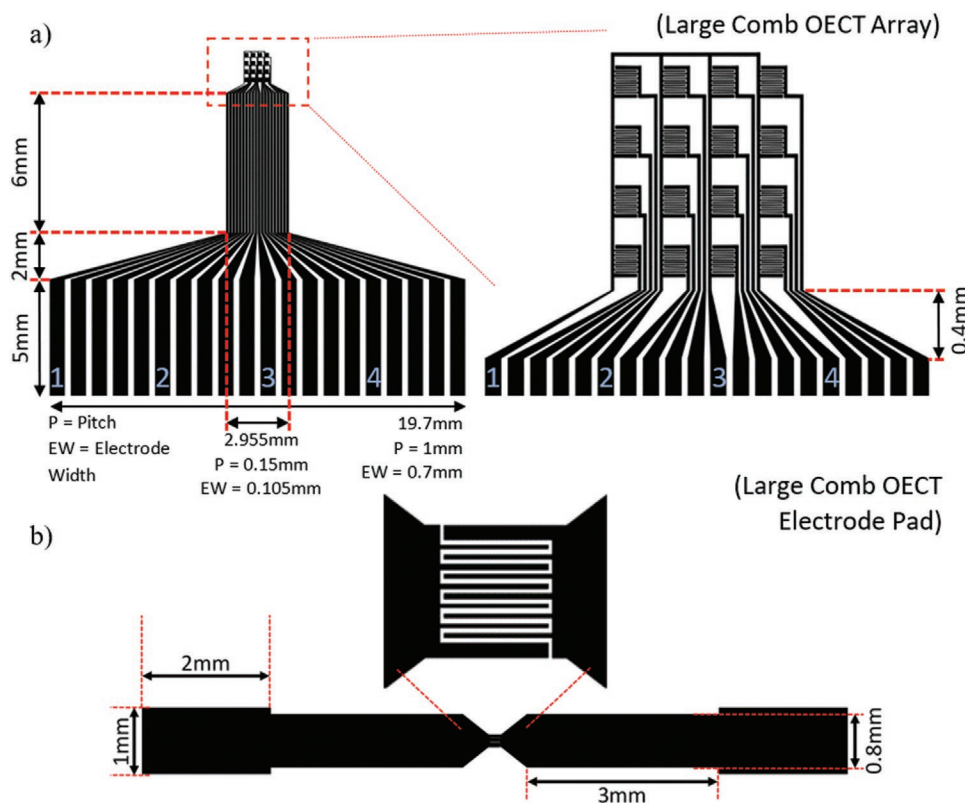


Figure 3. a) Interconnect design for 4×4 large-comb OEET arrays, tailored for μ ECoG application. The numbers on the connection wires identify the source electrode number. b) Electrode pad design, shown for the large-comb OEET array.

2.2. Characterization

The OEET characteristics for the OEET with the large comb interdigitated pattern, a 70 nm active layer and electrode pad connections, as illustrated in Figure 3b, is shown in Figure 4. The output and transfer characteristics show that the devices operate in p-type depletion mode. The output characteristics show clear linear and saturation regimes. For all electrode patterns, no short-channel effects were observed. The transfer characteristics gave a peak extrinsic transconductance of 139 mS for a drain-source potential difference of -0.6 V. To achieve this value with an active layer thickness less than 100 nm redefines state-of-the-art for OEET characteristics. The turn-off voltage was greater than the hydrolysis level, being identified at a gate-drain potential difference of ≈ 1.5 V. The shift in characteristics from hysteresis was minimal.

To characterize the response time, a step waveform voltage was applied at the gate with $V_{DS} = -0.6$ V. At the step, an exponential was fit to the data and the time required for the best-fit function to reach 90% of its final steady-state value was calculated, giving a value of 138 μ s for this device. With a peak transconductance of 139 mS, the transconductance/response time fraction was 1000 S s^{-1} . These devices have higher transconductance values compared to previously fabricated interdigitated-electrode OEETs, planar OEETs of the same geometry, and vertical OEETs.^[14,16] The transconductance-frequency relationship was also determined. A sine wave of varying frequency with a peak-to-peak voltage of 400 mV was used

at the gate with $V_{DS} = -0.6$ V. The transconductance was found to remain substantial at 10 kHz, with a value of over 15 mS. The cutoff frequency, the frequency at which the transconductance decreased by 29%, occurred at over 1.3 kHz.

The devices need to maintain performance over extended time periods to be viable for brain-machine interfaces. To measure stability, the device was subject to a series of gate pulses. An OEET was immersed in Ringers solution over a period of 8 weeks and the device was tested for stability five times throughout this period. The stability characterization was performed using a drain voltage of $V_{DS} = -0.6$ V and a square wave gate voltage input of 1 Hz frequency with an amplitude varying between $V_{GS} = 0$ V and $V_{GS} = 0.25$ V. Over the 1000 s (and thus 1000 cycles of the gate input function), the change in transconductance was determined (see Figure S1, Supporting Information). During each test, the transconductance reduced by 1.62% on average. However, between the first and final test 8 weeks later, the average transconductance had increased by 115%. This showed that the active layer was still present and had maintained its high performance throughout the testing. The increase may have been due to additional swelling of the active layer in the Ringers solution, resulting in an increase in thickness of the PEDOT:PSS.

2.3. Array Comparison

As predicted by Bernardis and Malliaras, the conductance showed proportionality to the peak transconductance, as

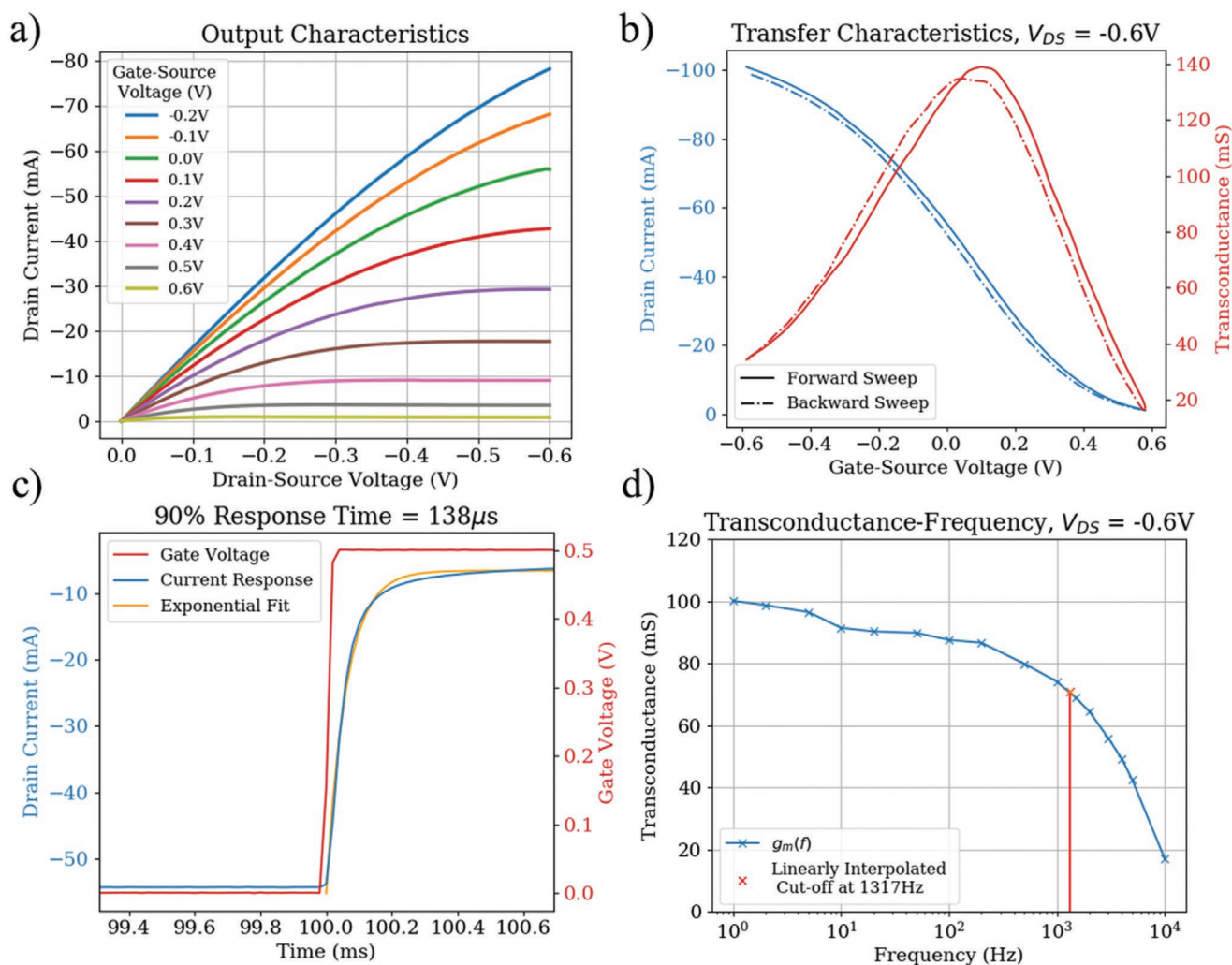


Figure 4. OECT characteristics for the large comb OECT electrode pad with a 70 nm active layer. a) Output characteristics shown for $V_{DS} < 0$. b) Transfer characteristics showing transconductance and hysteresis for $V_{DS} = -0.6$ V. c) Response time characteristics for $V_{DS} = -0.6$ V showing gate voltage, drain current response and an exponential best-fit. d) Transconductance-frequency characteristics for $V_{DS} = -0.6$ V showing how the transconductance varied with frequency of sinusoidal gate input.

shown in Figure 5a.^[12] The comparison of the array interconnect design relative to the pad interconnect design, as shown in Figure 3, shows that interconnect resistance is much greater for the array design. For the case of the 200 nm interconnects with the 70 nm active layer, the device resistance could not be separated between that of the channel and the interconnects. This motivated the fabrication of the 300 nm interconnects with the 35 nm active layer. As such, the ratio of interconnect to channel resistance was varied, and it was found that the device was not so significantly limited by interconnect resistance (see Figure S2, Supporting Information). With the greater resistance imposed by the μ ECOG array design, the peak transconductance values of the OECT arrays remained primarily above 10 mS, as shown in Figure 5b, which still places them within state-of-the-art. With the electrode pad devices achieving values greater than 100 mS, it was evident that the implementation of an interconnect design which adheres to physiological requirements significantly decreases device transconductance. This shows that considerations of an optimal interconnect design

are needed to maximize device performance for electrophysiological applications.

The mean peak transconductance was consistently greater in the 70 nm devices than the 35 nm devices, even with a thinner interconnect layer significantly limiting the values. The active areas of the smaller patterns were $\approx 25\%$ of that of the larger patterns but provided transconductance values which were not significantly lower. The smaller pattern arrays also had $\approx 50\%$ smaller pitch values of 152 μm , thus would provide greater spatial resolution if applied to measuring bioelectric signals. The standard deviation in peak transconductance, as shown in Figure 5b, had contributions from variations in conductance which originated from the inherent array design and photolithographic patterning. The PEDOT:PSS active layer was patterned using photolithography, which has been shown to result in lower device variability than using the parylene-C peel-off method.^[21] Additional variations could have arisen from differences in the width of a Gaussian density-of-states describing the molecular disorder of PEDOT:PSS.^[22] However, such

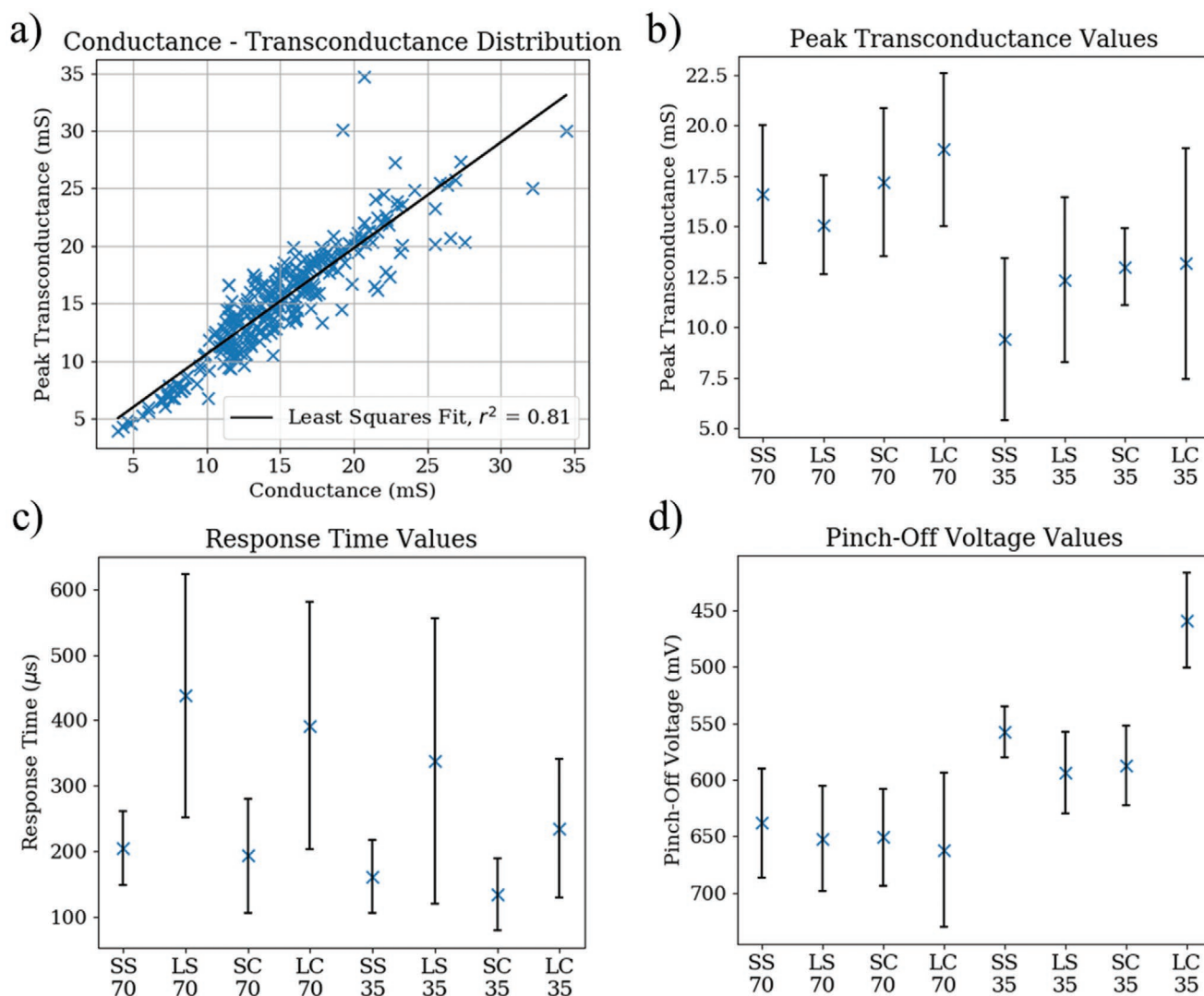


Figure 5. a) Distribution between conductance and peak transconductance values of the 8 OECT array variations with a linear fit using the least squares method giving an r^2 value of 0.81 (2 d.p.). Mean and standard deviation values of the eight array variations, where the labels 35 and 70 refer to 35 and 70 nm active layers, respectively, of the four electrode styles in Table 1, for b) peak transconductance, c) response time, d) pinch-off voltage.

variations were likely negligible for a given PEDOT:PSS thickness as the same conducting polymer solution was used in all device fabrications.

The response time characteristics show that there were contributions from the parasitic capacitance and the active layer thickness. With short channel lengths and high drain voltages, the device response time, τ , was limited by the ion transport time, which is dependent on the electrolyte resistance and the capacitance of the system.^[12] As a result, it is predicted that the response time dependence on channel dimensions scales as $\tau \sim d\sqrt{WL}$ (see Figure 1b).^[23] The parasitic contribution significantly increased the response time of the larger interdigitated patterns such that their capability to measure high-frequency bioelectric events was greatly reduced. However, the fastest devices were the 35 nm small comb electrode OECTs with a mean value of 134 μ s, thus showing suitability to temporally resolve the entire electrophysiological spectrum.

Analysis of the output characteristics revealed that devices with the 35 nm active layer had lower mean pinch-off voltages than the 70 nm devices, as shown in Figure 5d. This supported the prediction by Bernards et al. that pinch-off voltage decreases as active layer thickness decreases.^[12] The decrease implied that the devices began de-doping at smaller gate-drain potential differences, as illustrated in Figure S4 (Supporting Information). With the decrease in pinch-off voltage, a shift in the gate voltage at which the peak transconductance occurred, V_g^{peak} , was also observed (see Figure S3a in the Supporting Information). The additional decrease in pinch-off voltage for the 35 nm large comb-electrode devices was thought to originate from inter-array fabrication variation relative to the other 35 nm devices.

To compare the performance of all devices, the ratio of peak transconductance to response time was found. From this measure, the comb-electrode interdigitation provided superior performance when compared to the spiral-electrode interdigitation. Furthermore, the smaller interdigitated patterns

provided greater performance than their large counterparts (see Figure S3b in the Supporting Information). The two device types which provided the greatest ratios were the 35 and 70 nm small comb-electrode OECT arrays, with value of $\approx 100 \text{ S s}^{-1}$. Therefore, both arrays were used for bioelectric testing.

2.4. Testing Device Output for Prerecorded Electrophysiological Input

Prerecorded electrophysiological data were inputted into the gate electrode of the chosen OECT arrays and the drain current was sampled. The types of bioelectric signals tested were local field potentials (LFP), ECoG, spreading depolarizations, surface electromyography (EMG), and EMG fasciculations. Quantification on the devices' capability to reproduce the bioelectric inputs were made for the ECoG, spreading depolarization and EMG fasciculation recordings. Comparisons between the application of bandpass and notch filters were made in all analyses. First, the OECT recordings were compared to an equivalent, ideal OECT response using the residual sum of squares (RSS), and the effect of filter application was considered. In an analysis of the noise, the variation of the error between the recorded and ideal response with the change in gate voltage was examined. The relationship between the recorded transconductance values and the changes in gate voltage was then quantified. Finally, a Gaussian noise source was added to the ideal response and the resulting relationship between the transconductance and

the change in gate voltage was compared to that which was actually measured.

2.4.1. Device Response to Inputs

The prerecorded electrophysiological data were inputted through the gate electrode and the drain current was recorded with $V_{DS} = -0.6 \text{ V}$. The device responses for the 35 nm devices are shown in **Figure 6**. For each data type, a bandpass filter was applied to the gate input and drain output to investigate device efficacy in a desired frequency band. The low-pass, which acted at 5 kHz, was only applied if the frequency range exceeded 5 kHz, and the high-pass varied depending on input signal. A notch filter was then applied to only the drain output, which operated at 50 Hz and further odd harmonics. The effects of the bandpass and notch filters are illustrated in **Figure 7** for the ECoG and EMG fasciculation inputs, showing that the noise at 50 Hz noise and odd harmonics was significant. All filters were computationally applied after the data acquisition (see Supporting Information). All recordings were performed using approved wired instruments and were taken from raw anonymized data.

Spreading depolarizations can occur as a result of traumatic brain injury and represent the mass depolarization of cells.^[24] A prerecorded spreading depolarization was inputted into the gate electrode and the drain current response was sampled at 1 kHz. Both transistor types were able to measure the 10 mHz-scale, 20 mV depolarization. Using OECTs to measure

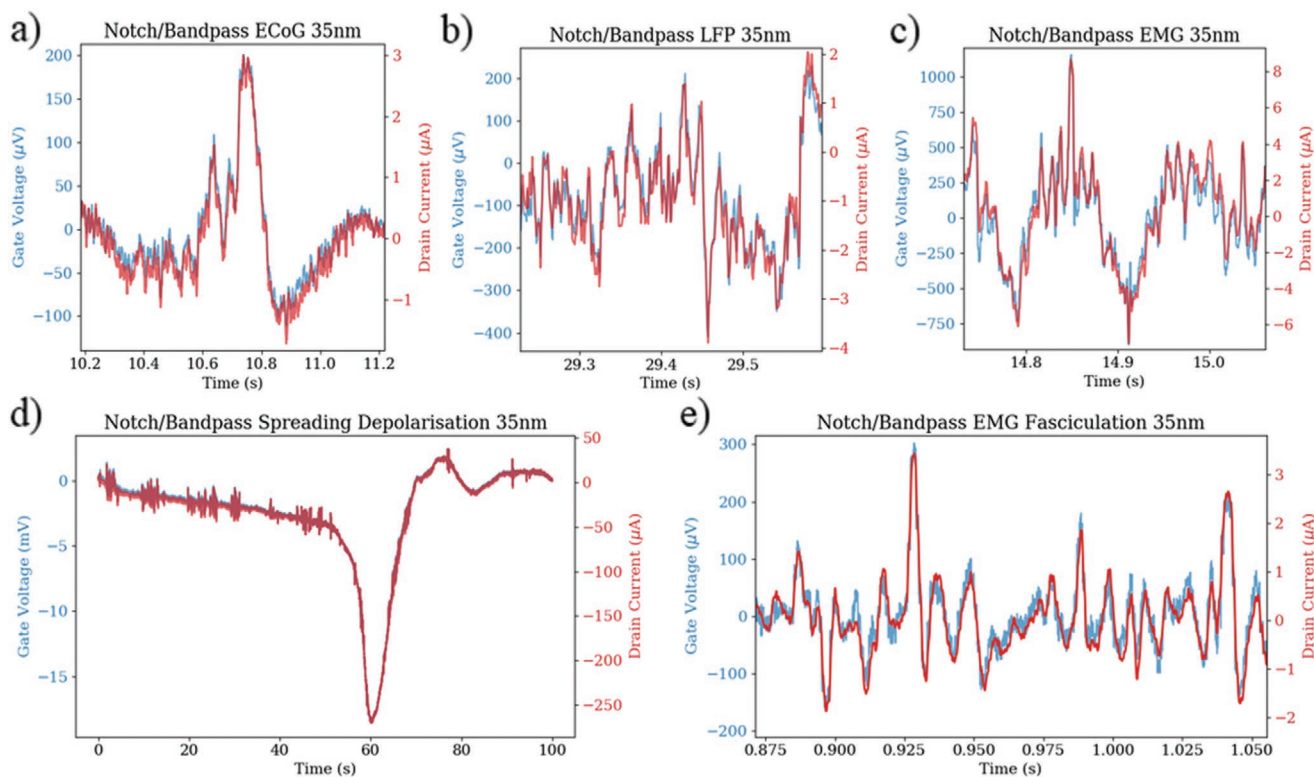


Figure 6. Bandpass-filtered gate voltage input and bandpass- and notch-filtered OECT current output for the electrophysiological recordings of a) ECoG, b) LFP, c) Surface EMG, d) spreading depolarization, e) EMG fasciculation.

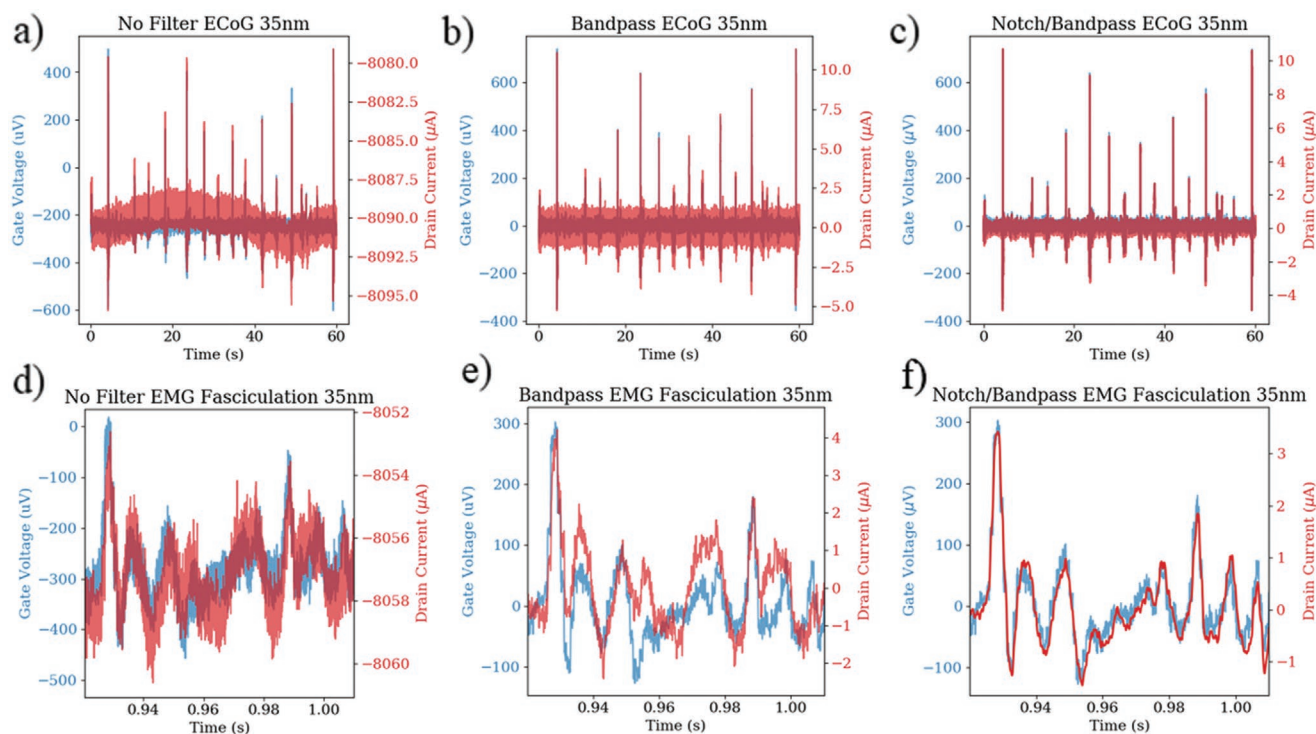


Figure 7. Gate voltage input and drain current output for the electrophysiological inputs of a) ECoG with no filter, b) ECoG with bandpass filter, c) ECoG with bandpass-filtered gate and bandpass- and notch-filtered drain current, d) EMG fasciculations with no filter, e) EMG fasciculations with bandpass filter, f) EMG fasciculations with bandpass-filtered gate and bandpass- and notch- filtered drain current.

such activity with their high SNRs may provide a new insight into their dynamics and guide intervention and treatment.

Low-frequency ECoG data and LFP recordings were sampled at 1.67 and 1 kHz, respectively. The frequency spectra showed that the primary recorded events had frequencies less than 200 Hz, which was expected of such signal types.^[25] The ECoG and LFP signals have voltage changes from 0.1 to 1 mV scale, and both 35 and 70 nm devices were able to reproduce the features of the ECoG and LFP inputs.

EMG is the measurement of electrical activity in muscle tissue. In surface EMG, measurements give voltage changes up to 10 mV with frequency components up to 150 Hz depending on the observed muscle.^[26] EMG measurements have extensive uses in rehabilitation such as their implementation in controlling robotic prostheses.^[27] Both 35 and 70 nm devices were successful in reproducing the EMG input.

Fasciculations are the electrical events associated with muscle twitches, and their recordings are important in the diagnosis of motor neuron diseases such as amyotrophic lateral sclerosis (ALS). Fasciculations are associated with the discharges of motor units and have voltage and frequency characteristics similar to MUA. Their recorded amplitudes are on the scale of 100 – 300 μ V and show a full potential cycle within 10 ms.^[28] The devices successfully reproduced the features of the EMG fasciculations. Gate electrode changes with magnitudes of 50 μ V and durations of 5 ms were resolvable in the OECT drain current. This capability was seen in both 35 and 70 nm devices. Cortical neurons share the same voltage and frequency characteristics, suggesting they would be resolvable by the OECTs.

A comparison of Fourier transforms of the electrophysiological inputs and outputs was performed. It was found that the

OECTs were capable of transducing frequencies from 10 mHz to approaching an upper limit of 10 kHz (see Figure S5 in the Supporting Information). Both 35 and 70 nm devices showed such capability, which was expected because their response time values were not significantly different. Therefore, both device types were suitable for the measurement of the full bioelectric spectrum.

2.4.2. Noise Analysis

Traditional methods of determining noise in a transistor require a constant gate-source voltage while sampling the drain current. For OECTs, the resulting power spectral density has previously revealed a dominant contribution from $1/f$ noise, considered to originate from charge fluctuations local to the active layer.^[29] Analysis of the noise level is crucial in determining the feasibility of applying the devices to the different frequency–voltage regions within electrophysiology. Furthermore, considerations of frequency filtering can help to optimize future experimental methods in the analysis of bioelectric readout. In this novel analysis, three quantifications of noise are presented from the comparison between the time-varying electrophysiological voltage gate input and the drain current output. For each input signal, the effects of applying bandpass and notch filters are examined. In each case, the noise quantified the gate voltage input, which corresponded to the fluctuations found in the drain current output. The resulting noise values shared resemblance to gate voltage V_{RMS} noise values as they were found to increase when considering a greater frequency range of the bioelectric input (see Figure S10 in the Supporting Information).^[30]

The ideal OECT response is a linear amplification of the gate voltage input to a drain current output through the transconductance. The OECT transconductance for the measured data, g_m , was found and used to determine the ideal response. The residual sum-of-squares (RSS) between the recorded and ideal response was calculated for the unfiltered data, bandpass-filtered and notch-filtered data. It was found that the bandpass- and notch-filters both decreased the RSS value (see Table S2 in the Supporting Information). It was expected that the application of the bandpass filter would decrease the RSS value because the current drift and high-frequency noise contributions would be reduced. The notch filter was applied only to the drain current and consistently reduced the RSS value. Therefore, the notch-filtered drain current gave an improved representation of the ideal behavior, implying the noise powers at those frequencies were significant.

There were three quantifications of noise found by comparing the input gate voltage and output drain current. First, an error in the drain current was defined as the difference between the change in recorded and ideal current response.

The relationship between error and gate voltage change, δV_G , was found, as illustrated in Figure 8a. For all neural inputs, there was a linear decrease with an addition of an approximate Gaussian distribution of error. In placing the data points into bins, as shown in Figure 8b, the mean values quantified the linear component and the standard deviation parameterized the Gaussian spread. The linearity described the error quantity introduced per unit of δV_G . For small δV_G , it was shown, based on the definition of the error, that the linear component was approximately equivalent to the transconductance used in the ideal response. This relation was confirmed in analyzing the comparison between the notch- and bandpass-filtered responses and the ideal response. In addition, for small δV_G , the standard deviation, σ , of the Gaussian distributions remained constant and so was used to quantify the drain current noise (see Table S3 in the Supporting Information). Approximately 95% of the errors were contained within 4σ and so the equivalent gate voltage noise was found through the transconductance (see Table S4 in the Supporting Information). The error of the 35 and 70 nm devices were consistently on the same scale and

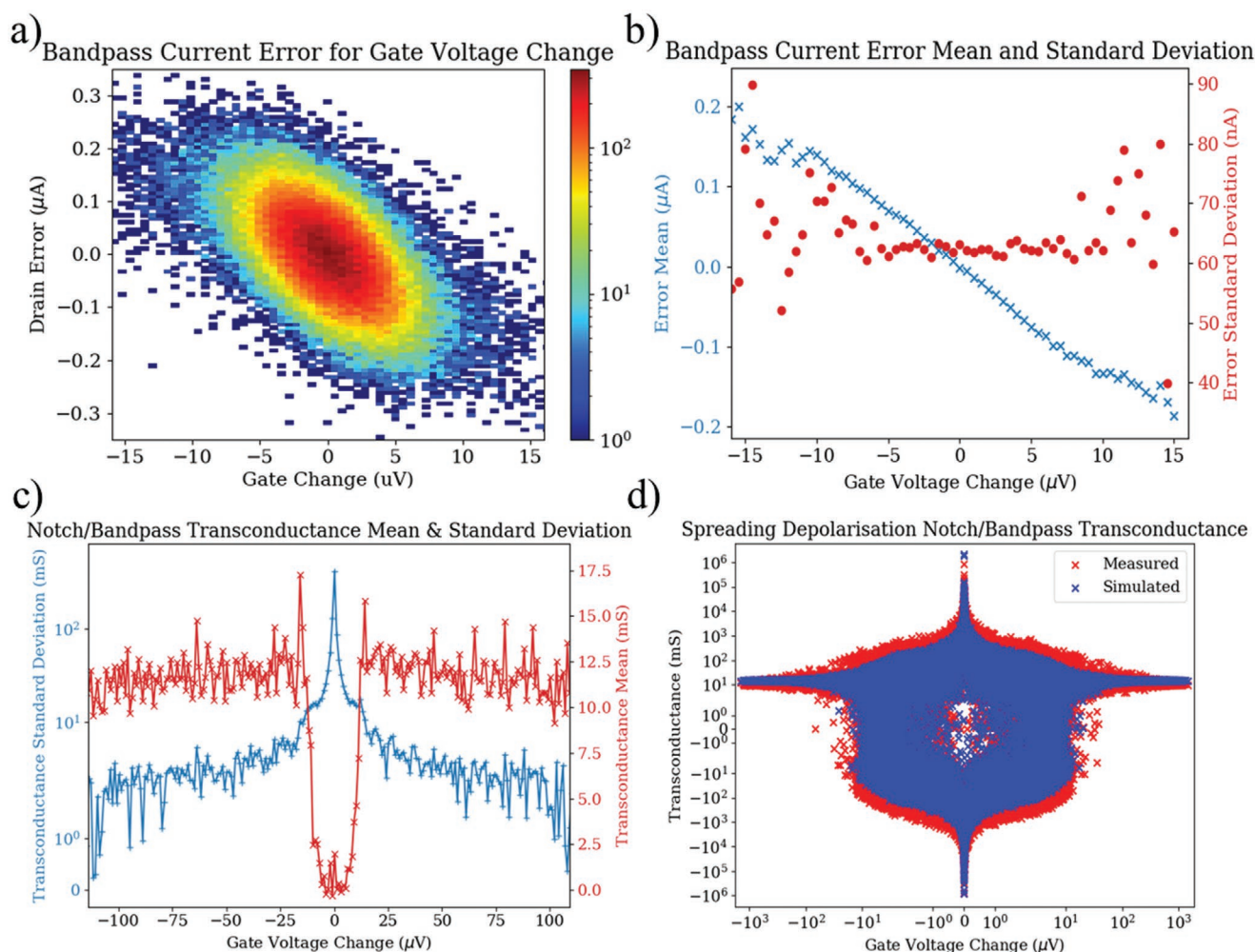


Figure 8. a) 2D histogram of drain current error with gate voltage change for the 35 nm EMG fasciculation response with bandpass filter, b) mean and standard deviation of binned data represented in Figure 8a, c) mean and standard deviation of transconductance values placed into gate voltage change bins for the 35 nm spreading depolarization response with bandpass- and notch-filters, where the binning has been applied to the “measured” data presented in Figure 8d, d) measured and simulated transconductance-gate voltage change relationships.

the noise values reduced with filter application. Approximately, for the notch- and bandpass-filtered data, the ECoG noise value was 20 μV , the depolarization value was 30 μV and the fasciculation value was 2 μV .

Second, for each measured datapoint there was a change in gate voltage and drain current. Therefore, the transconductance value for each gate voltage change, δV_G , was found. The transconductance values were placed into 0.5 μV bins of δV_G and the standard deviation, σ , of each bin was calculated, as shown in Figure 8c. Using the initially determined device transconductance, g_m , the δV_G of smallest magnitude for which $g_m - 3\sigma(\delta V_G) > 0$ was identified. This represented the change in gate voltage at which the transconductance remained positive 95% of the time. The 35 and 70 nm devices gave δV_G values on the same scale and reduced with filter application (results in Table S5, Supporting Information). Approximately, for the notch- and bandpass- filtered data, the ECoG δV_G value was 15 μV , the depolarization value was 20 μV and the fasciculation value was 2 μV .

Finally, in finding that the errors were approximately Gaussian distributed, a device response was modelled as the summation of the ideal response and a Gaussian noise source of zero mean and standard deviation, σ_{model} . The noise source was added to the gate input so the equivalent gate-input noise could be determined. The resulting response was subject to the transconductance analysis as previously described, allowing the comparison of the modelled transconductance to that which was recorded, as illustrated in Figure 8d. The σ_{model} of the modeled response which best replicated the standard deviations of the δV_G bins of the recorded response was identified. Again, the 35 and 70 nm devices gave σ_{model} values on the same scale and reduced with filter application (results in Table S6, Supporting Information). Approximately, for the notch- and bandpass- filtered data, the ECoG $4\sigma_{\text{model}}$ value was 14 μV , the depolarization value was 22 μV and the fasciculation value was 2 μV . It was found that the Gaussian noise source accurately represented the transconductance variance at small δV_G and accurately reproduced the recorded transconductance distribution.

The three methods of quantifying noise gave approximately the same value. The lower noise values of the EMG fasciculation data can be attributed to the frequency filters acting over a greater frequency range (see Figure S10 in the Supporting Information). Achieving noise values on the μV -scale while recording kHz-scale features allowed an accurate resolution of the bioelectric inputs. It is noted that the device responses were limited by that of the electrophysiological recordings. In instances where the devices measure electrical activity through the direct measurement of ionic fluctuations in physiological electrolytes, such as μECoG in cerebrospinal fluid, it is expected that there would be greater signal-to-noise ratios than the equipment used to record the inputs in this experiment.^[4] This would be equivalent to having greater gate voltage inputs but the same level of noise. Therefore, in measuring the gate voltage signals obtained by more limited mechanisms, it is highly expected that the interdigitated-electrode OECT devices, arranged as presented here, would be capable of resolving the full electrophysiological spectrum if applied in vivo.

3. Conclusion

A range of OECT devices were fabricated with the aim to maximize performance in the electrophysiological spectrum. Interdigitated electrodes and active layers of varying sizes were characterized and compared. The OECTs were organized into 4×4 grids with interconnect lines and connections that were suitably sized for the placement of the arrays onto the surface of the human cortex with electrical connection external to the skull.

The capability of the interdigitated OECT style was illustrated. A state-of-the-art device was fabricated with a 100 mS-scale peak transconductance and a 100 μs -scale response time. Multiple devices presented characteristics on this scale, showing that the fabrication method consistently allowed for high-performance devices.

The implementation of the interdigitated OECTs into the designed array structures also showed exceptional characteristics. In particular, the small comb 35 nm active layer thickness devices had response times on the 100 μs scale and transconductance values on the 10 mS scale. These performance parameters were ideally suited to electrophysiological applications where the highest frequency events approach 10 kHz. The 35 and 70 nm active layer small-comb devices were chosen for testing their capability to resolve electrophysiological signals. The OECT arrays have showed capability to resolve bioelectrical activity ranging from spreading depolarizations to EMG fasciculations. Such activity has ranged in voltage scales from 10 mV to 10 μV and in frequency scales from 10 mHz to up to 10 kHz. This was supported by the three quantifications of noise, which suggested that the noise level was equivalent to 2–20 μV , depending on frequency filters and sampling frequency. Both devices tested provided similar values of noise over the three measures, which was expected because the devices had similar transconductance and response time characteristics.

4. Experimental Section

Fabrication: To fabricate the OECTs, a 125 μm thick PET substrate (Melinex Polyester Film) was first cleaned by immersion and agitation in acetone for 10 min and then repeated in isopropanol (IPA) for 10 min. The metallic layers were then evaporated using a BOC Edwards Auto 306. The chromium (15 nm) was first evaporated and then the gold (200 or 300 nm). The substrates were then again cleaned by sonication in acetone for 10 min and then in IPA for 10 min. To help facilitate film processing and finish the cleaning procedure, the substrates were subject to an Emitech K1050X oxygen plasma asher (40 W) for 3 min. To pattern the electrodes, the positive photoresist Microposit S1805 was spin-coated at 2000 rpm for 30 s and baked on a hotplate at 115°C for 75 s. The sample was then exposed to 365 nm UV light from a Karl Suss MJB-3 mask aligner (16.3 mW cm^{-2}) for 10 s. To develop the photoresist, the sample was immersed without agitation in Megaposit MF-26a developer for 6 s and immediately immersed with light agitation in de-ionized (DI) water until any photoresist residue was removed. The sample was then baked on a hotplate at 115 °C for 3 min. The undesired gold and chromium areas were removed using etchant. The sample was initially immersed in gold etchant for 60 s and washed in DI water. It was then immersed in chromium etchant for 10 s and washed in DI water. To remove the photoresist, the sample was immersed in acetone without agitation for 5 min.

To pattern the negative-photoresist encapsulation, an SU-8 formulation of 20% solids was first made by using a solution of SU-8

2005 (44%) and SU-8 2000 (56%). The sample was then cleaned by sonication in acetone for 10 minutes and then in IPA for 10 min, followed by oxygen plasma ashing (40 W) for 3 min. The SU-8 formulation was then spin-coated at 1000 rpm for 30 s, giving a 1 μm thick layer. The sample was baked on a hotplate at 90 °C for 75 s and exposed to 365 nm UV light (16.3 mW cm⁻²) for 10 s. The substrate then had a postexposure bake on a hotplate of 110 °C for 4 min. To develop the SU-8 encapsulation, propylene glycol monomethyl ether acetate (Sigma Aldrich) was deposited through micropipette during a dynamic spin-coating cycle. The spin cycle had two cycles and the developer was deposited after the first stage had begun. The first stage had a spin speed of 500 rpm for 5 s and the second stage had a speed of 7000 rpm for 3 s. The first stage distributed the developer across the sample and the second stage removed it from the sample. The sample was then dried using a nitrogen gun to remove any excess developer. The sample was then baked on a hotplate at 120 °C for 20 min.

To pattern the organic active layer, a PEDOT:PSS solution was first produced. This solution consisted of Heraeus Clevios PH1000 PEDOT:PSS (91.7%), ethylene glycol (8%) and dodecyl-benzene-sulfonic acid (0.3%), and was sonicated for 20 min to ensure sufficient mixing. The sample was initially cleaned by subjecting it to an oxygen plasma asher (40 W) for 3 min. The PEDOT:PSS solution was then spin-coated at 3000 rpm (giving a 70 nm layer) or 12 000 rpm (giving a 35 nm layer) for 30 s. The sample was then baked on a hotplate at 100 °C for 100 s. To pattern the active layer, a negative photoresist designed to be compatible with organic semiconductors, known as OSCoR 4001 by Orthogonal Inc., was spin-coated at 3000 rpm for 30 s and baked on a hotplate at 100 °C for 120 s. The sample was then exposed to 365 nm UV light (16.3 mW cm⁻²) for 6 s and had a postexposure bake on a hotplate at 100 °C for 120 s. To develop the photoresist, a double-puddle technique was employed. A developer, known as developer 100 by Orthogonal Inc., was deposited onto the sample and left to react for 45 s. The sample was then spun at 5000 rpm for 5 s to remove the developer and blown dry using nitrogen to remove excess developer. This process was typically repeated for a total of two developer depositions. To remove the undesired areas of PEDOT:PSS, the sample was subject to the oxygen plasma asher (50 W) for 4 min. The photoresist was then stripped from the sample by its sonication for 5 min in a stripper known as stripper 903 by Orthogonal Inc. The sample was baked on a hotplate at 150 °C for 75 min. Finally, the sample was immersed in DI water for 15 min, causing the active layer to swell and the removal of low-molecular-weight compounds.

The solution used for the electrolyte was standard, unbuffered Ringer's solution by VWR. This contained sodium chloride (147 mmol), potassium chloride (4 mmol), and calcium chloride (3 mmol) in endotoxin free water. The electrolyte was deposited onto the sample over the active area through pipette. The chosen gate electrode was an Ag/Ag-Cl pellet electrode by VWR of diameter and thickness of 2 mm. The gate electrode was inserted into the electrolyte and positioned above the active area.

Characterization: To characterize the OECTs, the source and drain electrodes were connected to a Keysight B2902a precision source/measure unit. The gate electrode was also connected to the B2902a in all characterizations except that of transconductance-frequency, where it was connected to a Keysight 33210a waveform generator. In all characterizations, the source electrode was grounded and the Quick-IV measurement software, available from Keysight, was used. To measure conductance, the drain-source potential was swept from -0.1 to 0.1 V and the drain current was measured. To measure output characteristics, a gate-source potential difference was applied from -0.2 V to 0.6 V in 0.1 V steps and the drain-source potential was swept from 0.6 V to -0.6 V for each step during which drain current was measured. To measure transfer characteristics, the drain-source potential was kept constant at -0.6 V and drain current was measured. The gate-source potential was swept from -0.6 to 0.6 V and gate current was also measured. To measure response time, the drain-source potential was kept constant at -0.6 V and a voltage step was applied to the gate from 0 to 0.5 V. The drain current and gate voltage were sampled. To measure stability,

the drain-source potential was kept constant at -0.6 V and a square-wave of 1 Hz frequency varying from 0 to 0.25 V was applied to the gate. The drain current and gate voltage were again sampled. To measure the transconductance-frequency, the drain-source potential was kept constant at -0.6 V and was sampled. A sinusoid varying from -0.2 to 0.2 V was applied to the gate for frequencies ranging from 1 Hz to 10 kHz. The OECT parameter values were extracted from the measurements using custom python code.

Bioelectric Testing: To test the ability of the OECTs to respond to bioelectric input signals, the gate electrode was connected to a Keysight 33220a waveform generator. As the minimum voltage output of the waveform generator was 20 mV, voltage attenuators were used to decrease the output voltage by up to a factor of 1000. The B2902a sampled the output of the waveform generator and the drain current response of the OECT. The underlying data supporting this publication can be requested at datainquiryEXSS@imperial.ac.uk.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Acknowledgements

This work was supported by the UK Engineering and Physical Sciences Research Council (EPSRC) [grant number EP/L016737/1] for the Imperial College London Centre for Doctoral Training in Neurotechnology. The authors thank Konstantinos Petkos and Prof. Emmanuel Drakakis for providing the Keysight 33220a waveform generator with the prerecorded electrophysiological signals.

Conflict of Interest

The authors declare no conflict of interest.

Keywords

bioelectronics, electrophysiology, interdigitated electrode arrays, organic electrochemical transistors, plastic electronics

Received: August 20, 2020
Published online: September 24, 2020

- [1] D. Khodagholy, J. N. Gelinas, T. Thesen, W. Doyle, O. Devinsky, G. G. Malliaras, G. Buzsáki, *Nat. Neurosci.* **2015**, *18*, 310.
- [2] J. J. Jun, N. A. Steinmetz, J. H. Siegle, D. J. Denman, M. Bauza, B. Barbarits, A. K. Lee, C. A. Anastassiou, A. Andrei, Ç. Aydın, M. Barbic, T. J. Blanche, V. Bonin, J. Couto, B. Dutta, S. L. Gratiy, D. A. Gutnisky, M. Häusser, B. Karsh, P. Ledochowitsch, C. M. Lopez, C. Mitelut, S. Musa, M. Okun, M. Pachitariu, J. Putzeys, P. D. Rich, C. Rossant, W.-L. Sun, K. Svoboda, M. Carandini, K. D. Harris, C. Koch, J. O'Keefe, T. D. Harris, *Nature* **2017**, *551*, 232.
- [3] P. Leleux, J. Rivnay, T. Lonjaret, J.-M. Badier, C. Benar, T. Herve, P. Chauvel, G. G. Malliaras, *Adv. Healthcare Mater.* **2015**, *4*, 142.
- [4] D. Khodagholy, T. Doublet, P. Quilichini, M. Gurfinkel, P. Leleux, A. Ghestem, E. Ismailova, T. Hervé, S. Sanaur, C. Bernard, G. G. Malliaras, *Nat. Commun.* **2013**, *4*, 1575.

- [5] J. Rivnay, P. Leleux, M. Ferro, M. Sessolo, A. Williamson, D. A. Koutsouras, D. Khodagholy, M. Ramuz, X. Strakosas, R. M. Owens, C. Benar, J.-M. Badier, C. Bernard, G. G. Malliaras, *Sci. Adv.* **2015**, *1*, e1400251.
- [6] A. Campana, T. Cramer, D. T. Simon, M. Berggren, F. Biscarini, *Adv. Mater.* **2014**, *26*, 3874.
- [7] W. Lee, D. Kim, J. Rivnay, N. Matsuhisa, T. Lonjaret, T. Yokota, H. Yawo, M. Sekino, G. G. Malliaras, T. Someya, *Adv. Mater.* **2016**, *28*, 9722.
- [8] G. D. Spyropoulos, J. N. Gelinas, D. Khodagholy, *Sci. Adv.* **2019**, *5*, eaau7378.
- [9] D. Khodagholy, J. Rivnay, M. Sessolo, M. Gurfinkel, P. Leleux, L. H. Jimison, E. Stavrinidou, T. Herve, S. Sanaur, R. M. Owens, G. G. Malliaras, *Nat. Commun.* **2013**, *4*, 2133.
- [10] S. Střiteský, A. Marková, J. Víteček, E. Šafaříková, M. Hrabal, L. Kubáč, L. Kubala, M. Weiter, M. Vala, *J. Biomed. Mater. Res., Part A* **2018**, *106*, 1121.
- [11] R. M. Owens, G. G. Malliaras, *MRS Bull.* **2010**, *35*, 449.
- [12] D. A. Bernards, G. G. Malliaras, *Adv. Funct. Mater.* **2007**, *17*, 3538.
- [13] J. T. Friedlein, S. E. Shaheen, G. G. Malliaras, R. R. McLeod, *Adv. Electron. Mater.* **2015**, *1*, 1500189.
- [14] M. J. Donahue, A. Williamson, X. Strakosas, J. T. Friedlein, R. R. McLeod, H. Gleskova, G. G. Malliaras, *Adv. Mater.* **2018**, *30*, 1705031.
- [15] F. Hempel, J. K.-Y. Law, T. C. Nguyen, W. Munief, X. Lu, V. Pachauri, A. Susloparova, X. T. Vu, S. Ingebrandt, *Biosens. Bioelectron.* **2017**, *93*, 132.
- [16] Y. Liang, F. Brings, V. Maybeck, S. Ingebrandt, B. Wolfrum, A. Pich, A. Offenhäusser, D. Mayer, *Adv. Funct. Mater.* **2019**, *29*, 1902085.
- [17] S. Zhang, E. Hubis, C. Girard, P. Kumar, J. Defranco, F. Cicoira, *J. Mater. Chem. C* **2016**, *4*, 1382.
- [18] K. V. Nemani, K. L. Moodie, J. B. Brennick, A. Su, B. Gimi, *Mater. Sci. Eng., C* **2013**, *33*, 4453.
- [19] E. M. Lillie, J. E. Urban, A. A. Weaver, A. K. Powers, J. D. Stitzel, *J. Anat.* **2015**, *226*, 73.
- [20] J. Sharim, P. Pezeshkian, A. Desalles, N. Pouratian, *Neuromodulation* **2015**, *18*, 574.
- [21] M. Braendlein, A. M. Pappa, M. Ferro, A. Lopresti, C. Acquaviva, E. Mamessier, G. G. Malliaras, R. M. Owens, *Adv. Mater.* **2017**, *29*, 1605744.
- [22] J. T. Friedlein, J. Rivnay, D. H. Dunlap, I. McCulloch, S. E. Shaheen, R. R. McLeod, G. G. Malliaras, *Appl. Phys. Lett.* **2017**, *111*, 023301.
- [23] J. T. Friedlein, R. R. McLeod, J. Rivnay, *Org. Electron.* **2018**, *63*, 398.
- [24] M. L. Rogers, C. L. Leong, S. A. Gowers, I. C. Samper, S. L. Jewell, A. Khan, L. McCarthy, C. Pahl, C. M. Talias, D. C. Walsh, A. J. Strong, M. G. Boutelle, *J. Cereb. Blood Flow Metab.* **2017**, *37*, 1883.
- [25] G. Buzsáki, C. A. Anastassiou, C. Koch, *Nat. Rev. Neurosci.* **2012**, *13*, 407.
- [26] M. B. I. Reaz, M. S. Hussain, F. Mohd-Yasin, *Biol. Proced. Online* **2006**, *8*, 11.
- [27] P. Geethanjali, *Med. Devices* **2016**, *9*, 247.
- [28] K. R. Mills, *Brain* **2010**, *133*, 3458.
- [29] R. L. Stoop, K. Thodkar, M. Sessolo, H. J. Bolink, C. Schönenberger, M. Calame, *Phys. Rev. Appl.* **2017**, *7*, 014009.
- [30] A. G. Polyavas, V. F. Curto, N. Schaefer, A. B. Calia, A. Guimera-Brunet, J. A. Garrido, G. G. Malliaras, *Flexible Printed Electron.* **2019**, *4*, 044003.