Organic Electrochemical Transistors for Clinical Applications

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The ability of organic electrochemical transistors is explored to record human electrophysiological signals of clinical relevance. An organic electrochemical transistor (OECT) that shows a high (>1 mS) transconductance at zero applied gate voltage is used, necessitating only one power supply to bias the drain, while the gate circuit is driven by cutaneous electrical potentials. The OECT is successful in recording cardiac rhythm, eye movement, and brain activity of a human volunteer. These results pave the way for applications of OECTs as an amplifying transducer for human electrophysiology.

1. Introduction

Measuring the electrical activity of an organ, a tissue or even a single electrogenic cell is a common method to check its integrity and to better understand its function and dysfunction. When used for clinical applications, electrophysiology has two main purposes: The first is the monitoring of electrical activity of a vital organ such as the heart or the brain; the second is diagnosis, as a particular electrical behavior can be representative of a specific pathology. The nature of the recorded signals can be classified according to their frequency content. Most physiological signals of interest in clinical settings represent low-frequency phenomena (<100 Hz), which correspond to the synchrony of active cells, e.g., neurons and muscle cells. The most common synchronized electrophysiological activity is the cardiac cycle. It reflects the electrical activity of the heart, and enables the diagnosis of numerous dysfunctions.[1] Nervous system activity can also be recorded and, when interpreted correctly, could reflect limb movement.[2] Finally, in the field of neurophysiology, neural oscillations come from the synchronous activity of a large number of neurons in the brain[3,4] and are representative of specific cognitive functions such as perception,[5] motor control,[6] and memory.[7]

The quality of the recorded physiological information is highly dependent on the experimental setup. In the context of clinical applications, the vast majority of recordings are performed using Au or Ag/AgCl electrodes. The physical parameter that determines the quality of recordings is the impedance at the interface with the skin. A low impedance is desirable for high-quality recordings, and it can be achieved by increasing electrode area. As this, however, comes at the expense of spatial resolution,[8] numerous solutions have emerged to minimize impedance: These include the use of low impedance coatings, such as conducting polymers;[9–12] the incorporation of microfabricated tips at the electrode that ensure a good contact,[13–15] and the use of thin polymer substrates that render electrodes conformable.[16–18] Another approach involves the integration of pre-amplifiers near the electrodes. Such "active" electrodes minimize the impact of noise picked up by the cables leading to the amplifier. These systems, however, are more expensive than passive electrodes, which limits their broad use in the clinic.

The last few years there has been a great deal of interest in organic electrochemical transistors (OECTs) as transducers for signals of biological origin.[19] These devices combine ease of fabrication, compatibility with mechanically flexible substrates, facile miniaturization, stable operation in aqueous environments, and high transconductance, thereby constituting a low-cost and efficient means to transduce low amplitude signals of biological origin.[19–21] OECTs consist of a polymer channel, usually made of poly(3,4-ethylenedioxythiophene) doped with poly(styrene sulfonate) (PEDOT:PSS), which is in contact with an electrolyte.[22] Minute changes in the electrical potential at the interface between the electrolyte and the polymer film drive ions in and out of the channel and change its conductivity, thereby modulating the drain current. OECTs act as transconductance amplifiers and convert changes in electrical potential to changes in the drain current. This conversion amplifies the power of the signal by a factor determined by the transconductance.[23] OECTs were shown to exhibit record-high transconductance (in the mS range) among all transistor technologies,[23] and this motivated their use in in vivo electrophysiology. Recent work explored the ability of OECTs to record electrocorticograms in rats,[24] and electrocardiograms in

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DOI: 10.1002/adhm.201400356

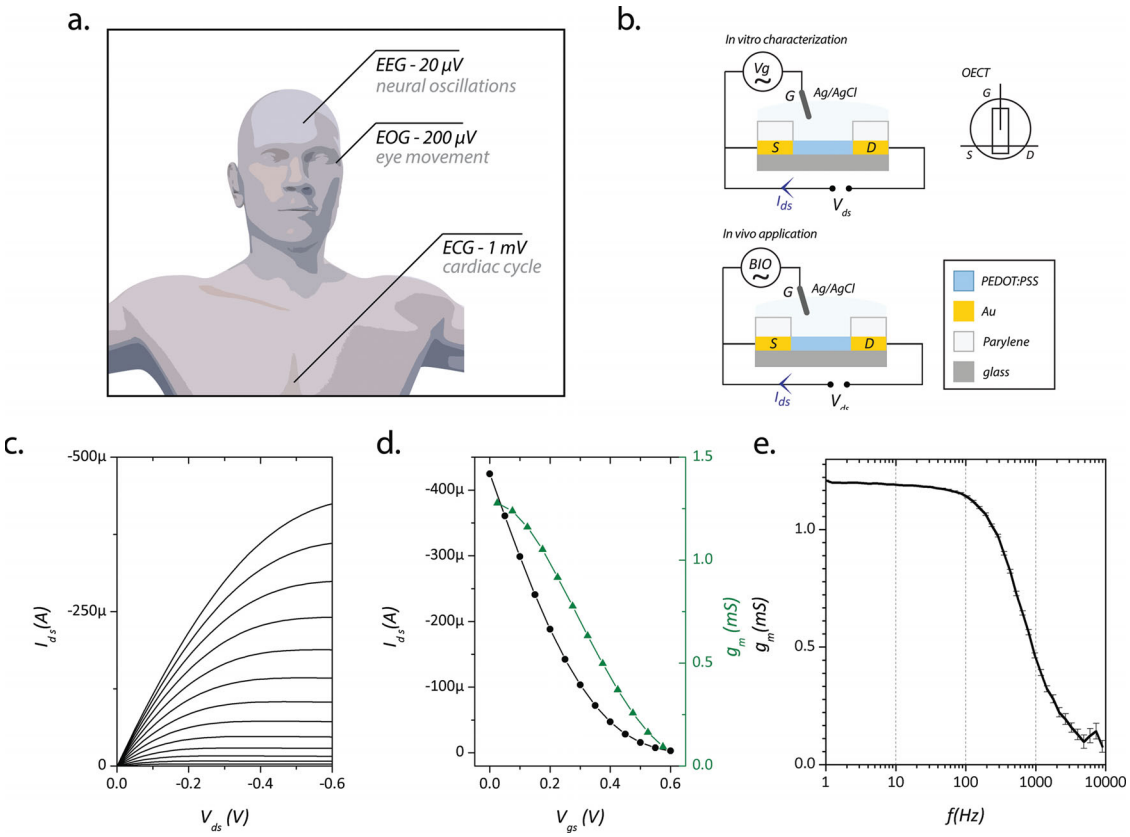

Figure 1. a) Cartoon showing the signal amplitude associated with different electrophysiological measurements, b) Schematic of an OECT and the wiring diagrams used in vitro (top) and in vivo (bottom), c) Output characteristics for V_{gs} varying from 0 (top curve) to +0.6 V (bottom curve) with a step of +0.05 V, d) Transfer curve for V_{ds} = –0.6 V, and the associated transconductance, e) Frequency dependence of the transconductance. The device was biased with V_{ds} = –0.6 V and V_{gs} = 0 V, and an additional 10 mV peak-to-peak gate voltage oscillation was applied to measure the small signal transconductance.

humans.[25] These results, coupled with the potential for low-cost fabrication, show that OECTs constitute a promising solution as amplifying transducers for electrophysiology and calls for a broader investigation of their capabilities to record electrical signals of relevance to the clinic.

2. Results and Discussion

In this work, we show that OECTs are able to measure a wide range of typical clinical physiological signals of a human volunteer. We first confirm that OECTs can monitor the cardiac cycle (electrocardiography, ECG), then use OECTs to track eye movement (electrooculography, EOG), and finally we measure a neurological rhythms (electroencephalography, EEG). As shown in **Figure 1**, these signals of range from a millivolt to tens of microvolts, a range that is representative of the majority of the noninvasive signals measured in the field of electrophysiology. EEG, in particular, represents a challenge, as it requires the ability to measure signals that are two orders of magnitude lower than the ones measured so far by OECTs.[24,25] We used an OECT that shows a high transconductance at zero gate voltage,[26] and after in vitro characterization, we wired the transistor as shown in Figure 1b, using electrical potentials of the human body to drive the gate circuit. The OECT had a PEDOT:PSS channel with length of 100 μm^2, width of 100 μm^2, and thickness of 140 nm, and a Ag/AgCl gate electrode. Its output curves, shown in Figure 1c, are typical for operation in the depletion mode. The transfer curve and corresponding transconductance for V_{ds} = –0.6 V are shown in Figure 1d. At zero gate voltage, the OECT shows a high transconductance of 1.3 mS. The frequency response of the transconductance was measured by applying V_{ds} = –0.6 V and using a small ac modulation at the gate, as shown in Figure 1b. The resulting bandwidth is shown to exceed 100 Hz (Figure 1e), and is therefore adequate for the applications pursued herein.

We first demonstrate the application of OECTs in electrocardiography, which corresponds to the signal with the largest amplitude among the ones considered here. Although ECG recordings with OECT were demonstrated recently on the forearm of a human volunteer,[25] here we measure ECG in the standard configuration used in the clinic. The measurement configuration, shown in **Figure 2**, consisted of two identical OECTs making four contacts to the body. The first OECT measured the voltage difference between electrodes placed at the left and right arms, while the second one measures the voltage difference between the left leg and left arm. This is the standard two main limb lead configuration,[27] however, the setup can be

Adv. Healthcare Mater. 2014,
DOI: 10.1002/adhm.201400356

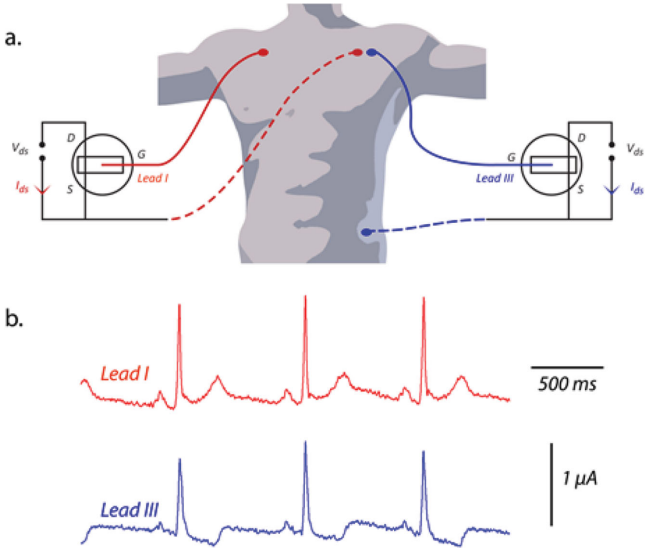

Figure 2. a) Wiring configuration of the OECT for spontaneous ECG recordings, and b) spontaneous heart activity measured on a human volunteer.

extended in a straightforward way to the full "12-lead" system for diagnosis purposes.[28] Representative recordings of the drain current of the two OECTs are shown in Figure 2b. The temporal coincidence of the peaks in the traces recorded by the two OECTs confirms the biological origin of the recorded activity. The recorded traces correspond to the expected electrical activity of a human heart: The main peak, called the QRS complex, reflects the depolarization of the ventricles. It has a peak-to-peak amplitude of the order of a mV, and a duration around 100 ms. The P and T waves correspond to normal atrial depolarization and repolarization of the ventricles, respectively. They are usually around 200 μV in peak-to-peak amplitude with a duration around 80 and 160 ms, respectively. These peaks are well resolved with the OECT, with the QRS complex corresponding to an easily readable change of 1 μA in the drain current, demonstrating the potential of this device for measurements at a clinical setting.

The second application we investigated is electrooculography. There is significant interest in this technique as it can be used for measuring eyeball movement with high sensitivity. The applications are numerous, including use in marketing studies and in the detection of drowsiness or sleepiness stages.[29,30] EOG is also used for eye tracking[31] and has applications in research on the visual system,[32] in psychiatry,[33] and in cognitive linguistics.[34] We investigated the suitability of OECTs for this application by measuring both horizontal and vertical eyeball movements. We used two OECTs, wired as shown in **Figure 3**, to simultaneously track both the horizontal (blue traces) and vertical (red traces) movements of the eyes of a human volunteer. The volunteer looked straight in front of him at a specific marker, and was then asked to move his eyes into extreme positions. Figure 3b,c shows the recorded signal, in the case of horizontal and vertical eye movement, respectively. The baseline corresponds to the eyes looking at the central position. The amplitude of the recorded signal is larger on the channel following the movement direction: The blue trace, following

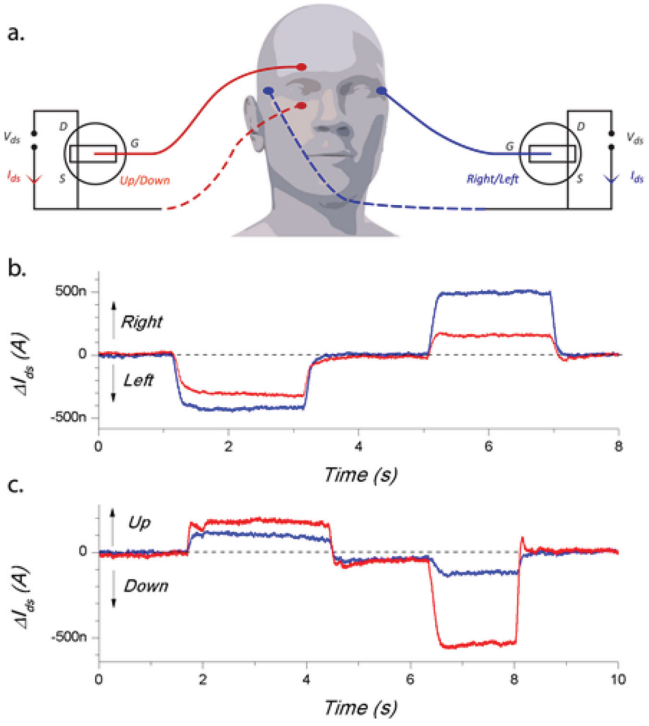

Figure 3. a) Wiring configuration chosen for the EOG measurement, b) recording of electrical activity during left/right eyeball movements, c) recording of electrical activity during up/down eyeball movements. Both up/down (red) and left/right (blue) activities are measured.

horizontal eye movements is larger in Figure 3b than in Figure 3c, and vice versa for the red trace. In the case of the horizontal eye movements, the signal presents an equal amplitude change around the baseline when the eyes move to extreme left and extreme right positions. This symmetry is lost in the case of the up/down eyeball movement, which is expected due to the presence of the supraorbital ridge that limits the movement of the eyeball in the up direction. These recordings, which show drain current changes in the range of hundreds of nA, confirm that the OECT can be used to monitor eye movement. It should be noted that diagonal or unusual movements of the eyeballs could also be tracked by analyzing the horizontal and vertical components of the movement registered on the two transistors.

An additional use of EOG is to detect drowsiness, which is extracted from the amplitude, frequency, and duration of spontaneous blinking.[29,30] We measured the blinking pattern of an awake human volunteer, and compared it to the pattern corresponding to the intentional closing of the eye (Figure S1, Supporting Information). The OECT was able to record both of these signals, showing a larger amplitude in the vertical direction, which corresponds to the direction of eyelid movement. The blinking pattern shows a rise time around 100 ms whereas response time was about three times longer when the eye was closed intentionally. OECTs, therefore, can accurately resolve eye blinking and are suitable for applications in the detection of drowsiness.

The last clinical diagnostic technique we investigated is electroencephalography. The synchronized activity of large numbers of cortical neurons in EEG is called a rhythm. Depending

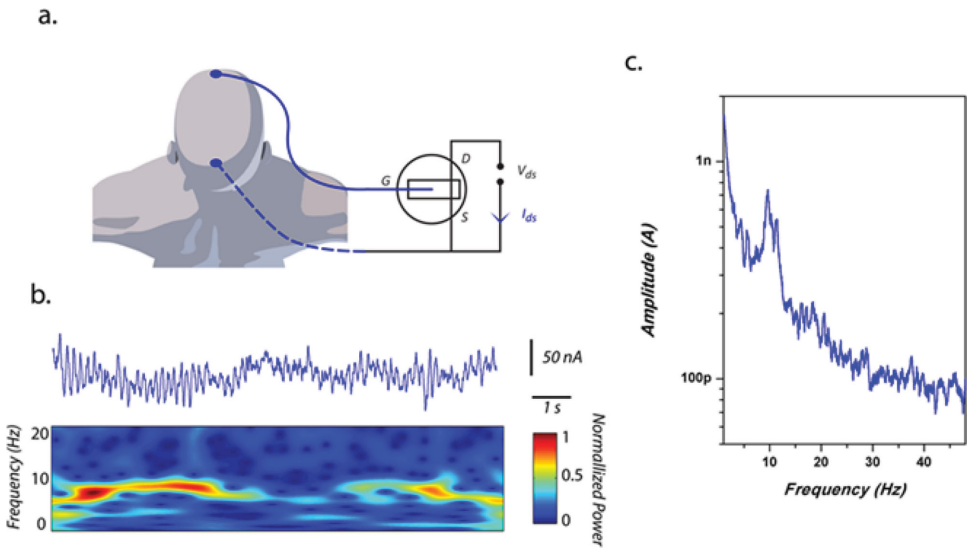

Figure 4. a) Wiring configuration used for the EEG measurement, b) Recording of spontaneous brain activity (top) showing the alpha rhythm, and associated time-frequency spectrogram (bottom), c) Fourier analysis of a 3 min recording.

on their frequency content and amplitude, they are indicative of global conditions like awareness or are linked to cognitive functions such as information transfer, perception, motor control, and memory.[4] The most common one is called the alpha rhythm and corresponds to a 8–12 Hz neural oscillation with an amplitude usually below 50 μV when measured on the scalp of adults subjects. We measured this rhythm on an awake human volunteer using the recording configuration shown in **Figure 4**. A sample extracted from a recording is shown in Figure 4b (top), demonstrating that spontaneous brain activity induces drain current changes of the order of tens of nA. The corresponding time–frequency analysis (bottom) reveals frequency components corresponding to the alpha rhythm, as expected regarding the behavior of the subject during the measurement.[35] The high quality of the signal can be seen in Figure 4c, which displays the fast Fourier transform of a 3 min recording: A clear peak corresponding to the alpha rhythm is well resolved over the $1/f$ background activity of the brain. This confirms that OECT provides sufficient resolution to successfully capture brain oscillations.

The data presented above show that organic electrochemical transistors can record a large variety of electrophysiological signals of relevance to the clinic. A rigorous comparison with other recording devices/configurations is very difficult, given the diversity in equipment and measurement protocols used in clinical settings. The signals recorded here, however, were of adequate quality to make these devices clinically relevant. These signals range over two orders of magnitude in their amplitudes, with spontaneous brain activity being the most challenging to measure and corresponding to a ≈100 times lower signal amplitude than measured before with an OECT. The temporal resolution of OECTs was also found to be adequate for these applications, which correspond to phenomena occurring below 100 Hz. OECTs are relatively new devices, and their operation, which involves volumetric changes in the doping of a polymer field, is significantly different from that of traditional field-effect devices. As a result, their mechanism of operation is not fully understood and their limits of performance have not yet been adequately explored. OECTs offering a transconductance in the mS range, such as the one used here, can lead to amplification in the power of a signal exceeding 50 dB.[26] Tuning the dimensions of the channel can help trade off some bandwidth for higher gain,[23] though the exact scaling of these parameters on geometry is not yet elucidated. Moreover, these devices can be easily miniaturized in microarrays,[36] and integrated with thin substrates that are highly conformable.[24] Such arrays could be placed directly on the skin using commercial gels for cutaneous electrodes,[25] or even ionic liquid gels that do not dry and enable long-term recordings.[37] OECTs, therefore, represent a very attractive proposition as amplifying transducers that can be produced at a low cost and offer high resolution recordings. Future work should focus on exploring the ultimate spatial resolution of OECTs (in the context of a particular application), by means of tuning device dimensions and investigating the gain versus bandwidth trade-off. Such an exploration would also pave the way for applications in neuroprosthetics, where high-quality recordings are needed to drive artificial limbs and exoskeletons.

3. Conclusions

In conclusion, we explored the ability of organic electrochemical transistors to record human electrophysiological signals of clinical relevance. We used an OECT that shows a high (>1 mS) transconductance at zero applied gate voltage, which necessitated only one power supply to bias the drain, while the gate circuit was driven by cutaneous electrical potentials. The OECT was successful in recording cardiac rhythm, eye movement, and brain activity of a human volunteer. These results pave the way for applications of OECTs as an amplifying transducer for human electrophysiology.

Adv. Healthcare Mater. **2014**,
DOI: 10.1002/adhm.201400356

4. Experimental Section

Device Fabrication: OECTs are fabricated photolithographically, as previously described.[10,26] Metal contacts and interconnects were patterned using Shipley 1813 photoresist, exposed with a SUSS MBJ4 contact aligner, and developed in MF-26 before thermal evaporation of Ti (5 nm)/Au (100 nm) and metal lift-off in acetone/IPA. Two 2 µm Parylene C layers (SCS Coating) were successively deposited with a SCS Labcoater 2, separated by an industrial cleaner (Micro-90) used as an anti-adhesive. 3-(trimethoxysilyl)propyl methacrylate (A-174 Silane) was used as an adhesion promoter for the first parylene layer. The final photolithographic patterning step was that of the PEDOT:PSS channel. AZ9260 photoresist was spun cast, exposed, and developed in AZ developer (AZ Electronic Materials). The unprotected layers of parylene were etched in an O_2 plasma for 15 min (Oxford 80 Plasmalab plus). The PEDOT:PSS formulation [20 mL of aqueous dispersion (Clevios PH-1000 from Heraeus Holding GmbH) mixed with ethylene glycol (5 mL), dodecyl benzene sulfonic acid (DBSA, 50 µL), and 1 wt% of (3-glycidyloxypropyl)trimethoxysilane (GOPS)] was spin-coated next. The sacrificial top Parylene C layer was mechanically peeled off to pattern the PEDOT:PSS channel. The completed devices were baked at 140 °C for 1 h, and then rinsed/soaked in DI water. Finally a glass ring was affixed using PDMS to confine the electrolyte over the channel.

OECT Electrical Characterization: All characterization was done with a solution of 100×10^{-3} M NaCl in DI water as the electrolyte and a Ag/AgCl wire (Warner Instruments) as the gate electrode. The measurements were performed using a National Instruments PXIe-1062Q system. The channel of the OECT was biased using one channel of a source-measurement unit NI PXIe-4145. The gate voltage was applied using a NI PXI-6289 modular instrument. Output and transfer curves were collected using the SMU channel used to apply the bias. For time response and bandwidth characterization of the OECT, one NI-PXI-4071 digital multimeter measured the drain current, and a channel of the NI PXI-6289 measured the gate voltage. The bandwidth measurements were performed by applying a sinusoidal modulation (10 mV peak-to-peak), $V_{ds} = -0.6$ V, and measuring the modulation in the drain current, and therefore g_m as a function of frequency. All the measurements were triggered through the built-in PXI architecture. The recorded signals were saved and analyzed using customized LabVIEW software.

In Vivo Recordings: All patients provided informed signed consent to participate in the study. Commercially available Ag/AgCl electrodes (Comepa Industries) were used to established contact between the skin and the appropriate terminals of the transistors. The measurements were performed using a National Instruments PXIe-1062Q system. In both cases, the channel of the OECT ($V_{ds} = -0.6$ V) was biased using one channel of a source-measurement unit NI PXIe-4145 and the recording of the drain current was made using the same SMU channel with a sampling rate of 1 kHz. All the measurements were triggered through the built-in PXI architecture. The acquisition system was controlled using customized LabVIEW software.

Post-acquisition Data Treatment: All recordings were digitally filtered using a 0.1 Hz high pass filter (in principle, an appropriate low pass filter could also be used to reject high frequency noise). The data were analyzed using custom-written tools in MATLAB (Mathworks). Spectral analysis was performed using fast Fourier transform of the EEG signal between 0.1 and 50 Hz. A Gabor wavelet time–frequency analysis was used to determine the frequency content of the recordings.

Supporting Information

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

Acknowledgements

This work was supported by the ANR, region PACA, and MicroVitae Technologies. J.R. was supported by a Marie Curie post-doctoral fellowship. The authors thank Valentin Moriceau for the artwork provided to conceive the figures.

Received: June 25, 2014
Published online:

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Adv. Healthcare Mater. **2014**,
DOI: 10.1002/adhm.201400356