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Human stress monitoring through an organic cotton-fiber biosensor†

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Selective detection of bioanalytes in physiological fluids, such as blood, sweat or saliva, by means of low-cost and non-invasive devices, is of crucial importance to improve diagnosis and prevention in healthcare. To be really useful in everyday life a sensing system needs to be handy, non-invasive, easy to read and possibly wearable. Only a sensor that satisfies these requirements could be eligible for applications in healthcare and physiological condition monitoring. Herein an organic electrochemical transistor has been investigated as a simple, low-cost and e-textile biosensor, fully integrated on a single cotton yarn. The biosensor has been used for real-time detection of adrenaline, selectively compared to the saline content in human physiological fluids. The sensing mechanism is based on the oxidation of adrenaline at the Pt-gate electrode surface, with the formation of adrenaline-quinone and adrenochrome. Two independent organic electrochemical transistors, characterized by different gate-electrode materials, detect saline and adrenaline concentrations, respectively, in real human sweat. Measurements performed in real-time mode show the complete independence of adrenaline detection from NaCl and, hence, guarantee the simultaneous monitoring of both concentrations. The oxidation of adrenaline has been studied by means of absorption spectroscopy in air, with either silver or platinum working electrodes. Our results confirm that the oxidation reaction driven by the Pt-electrode leads to the formation of adrenochrome, while with the Ag-electrode the oxidation is similar to the spontaneous one occurring in air. The cotton-based biosensor shows the possibility of monitoring human performances (hydration and stress) *in situ* and using a non-invasive approach, opening new unexplored opportunities in healthcare, fitness and work safety.

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Introduction

Performing continuous and selective detection of bioanalytes in physiological fluids, without invasive and complicated sampling-laboratory analysis, is an open challenge in prevention and diagnostics for healthcare applications. Hence, the idea to develop a wearable bio-sensing system, integrated in clothes, light, handy and non-invasive, could be an appealing solution. A wearable monitoring system offers several advantages, for example the prompt detection of molecules addressable to specific diseases or a critical physiological state, as well as the ability to perform an early preventive diagnosis of a large number of pathological conditions. Moreover, the continuous monitoring of physiological parameters, like glucose, lactate and saline concentration through a low cost, non-invasive device, allows an active control on patients' health and/or sport performances. Organic electrochemical transistors (OECTs) are

emerging as a feasible solution in biosensing applications thanks to their low cost, non-invasive and easy to read features.¹ So far OECTs have been applied as sensors for simple analytes such as hydrogen peroxide² and ions^{3,4} and with more complex bio-structures such as micelles,⁵ liposomes,⁶ DNA,⁷ and pigments.⁸ Extensive reviews about OECT bio-integration have been reported in the literature recently.^{1,9} In addition, OECTs can be easily integrated on cloths, realizing efficient e-textile organic devices. In recent times different approaches for the functionalization of cotton yarns (natural cellulose) have been used to realize conductive fibers,^{10–12} which have been applied as innovative textile-integrated sensing devices. Among the different strategies for the realization of an active layer, conductive polymeric materials,¹³ metal nanoparticles,^{10,14} or carbon nanotubes (CNTs)¹² have been successfully employed. The output characteristics of textile-OECT have been demonstrated for the first time using a gel electrolyte for ionic exchange.¹⁴ Successively cotton-OECT demonstrated to work in liquid solutions and they were applied for monitoring saline concentration in human sweat.¹⁵ Despite the high sensitivity and the very simple and handy structure, OECTs actually lack the required selectivity for the recognition of characteristic

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molecular species. Different approaches have been attempted to overcome this limitations, for example, a molecular membrane surrounding the active layer has been used to selectively detect potassium ions,¹³ or the lipid membrane allows discrimination between monovalent and divalent ions.¹⁶

In this paper we present the selective detection of adrenaline with respect to the saline content in human physiological fluids. Adrenaline is a functional neurotransmitter, playing a central role in many instinctive responses, especially under stress situations and strongly physical conditions. Timely sensing of abnormal adrenaline concentration could be a fingerprint of a pathological situation, like panic or heart attack, or could identify a typical *flight, fight and fright* response. Moreover it could be used to monitor athletes, where the control of physiological performances during competition and training is required. The adrenaline sensing in a complex fluid (human sweat) is herein reported for the first time using OECTs, enabling real-time monitoring of human physiological parameters. To detect adrenaline in an independent way with respect to the saline content, an innovative system of two OECTs completely integrated in cotton fibers has been proposed. The sensing mechanism of adrenaline relies on the oxidation process at the platinum metal gate, leading to the formation of different intermediates and eventually adrenochrome. To make a step further towards real on-field applications, we applied the device to the study of real human sweat: measurements have been recorded in real-time using human sweat as an electrolyte and monitored the OECT sensing upon injection of adrenaline during acquisition, showing the complete independence of adrenaline sensing with respect to salt sensing. This innovative device is a useful tool for an *in situ* and *non-invasive* analysis of human performances (hydration and stress), finding applications in sports, healthcare and work safety.

Different analytical methods for the detection of adrenaline in human physiological fluids like blood, sweat¹⁷ or saliva¹⁸ have been approached, including liquid chromatography (LC),¹⁹ spectrophotometry,²⁰ fluorimetry,^{21,22} capillary electrophoresis (CE),^{23,24} amperometric,²⁵ chemiluminescence (CL)^{26,27} and electrochemiluminescence²⁸ detection. Nevertheless, despite all these methods being regarded as highly sensitive, they are also expensive, not portable and can perform off-line analysis only. The viability of methods and devices for fast and sensitive detection of adrenaline in biological fluids is, on the other hand, desirable for daily screening and preventive diagnosis. So a wearable and highly sensitive device sensor could be also more appealing and readily applicable to patients or sports men.

Experimental

Device fabrication

The OECT device on cotton (hereafter referred to as the cotton-OECT) has been fabricated on a cotton fiber (the yarn) by a simple soaking process, as reported in ref. 15: the yarn was immersed into an aqueous solution of PEDOT:PSS (CleviosPH500, Starck GmbH) for 5 min, followed by baking on a hot plate at 150 °C for 3 hours. The PEDOT:PSS solution was previously modified with addition of ethylene glycol (20%) and

dodecyl benzene sulfonic acid (DBSA) surfactant (12%) in order to increase electrical conductivity and decrease solubility in water.^{14,29,30} The process did not change significantly the flexibility of the cotton yarn (see ESI†). The measured electrical resistance of the as-prepared yarn was 430 Ohm over a linear length of 1 cm; this value allows the use of voltages in the mV range. Fig. 1a shows a FE-SEM image of a thin layer of PEDOT:PSS surrounding the cotton yarn. The layer appears uniformly distributed in the nanometer scale with an estimated thickness of about 50 nm; few layer borders could be seen on the side of the yarn. A drop of about 200 µL of the electrolyte solution is placed on the yarn between the source and drain contacts, allowing the liquid to reach the gate electrode. The channel of the cotton-OECT is defined by the overlapping of the liquid electrolyte with the polymer, as evidenced by the darker area on the cotton fiber reported in Fig. 1b. After processing with PEDOT:PSS, the yarn still maintains its flexibility and can

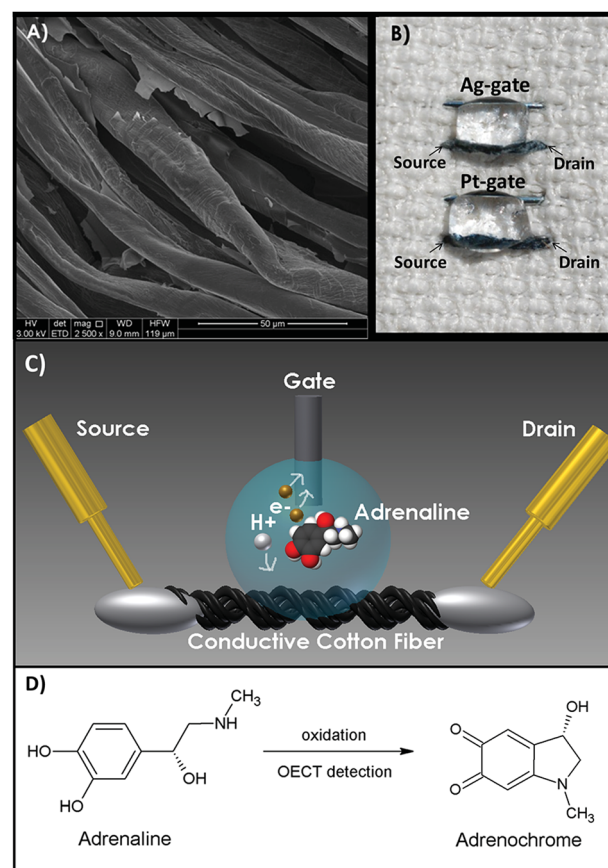


Fig. 1 (a) Field emission SEM image of the cotton wire functionalized with PEDOT:PSS. Treats are uniformly covered. The PEDOT:PSS film thickness is randomly highlighted by some fringes at the treat borders; (b) the cotton-OECT, directly integrated on cloth. On the top is shown an OECT device with an Ag-gate, while at the bottom the same device with a Pt-gate is shown. A drop of liquid electrolyte is placed in contact with the thread and the gate, the overlapping between the liquid electrolyte and the PEDOT:PSS wire defines the OECT channel. (c) Schematic of the cotton-OECT device with a Pt gate and an adrenaline molecule in its sensing process. (d) Adrenaline oxidation and adrenochrome formation simplified reaction.

be easily integrated on cloth. In this respect, it is important to note that the output characteristics are not altered by bending. This property is very important for real e-textile applications, for example in the case of integration of the device in shirts used in fitness or daily routines.

To realize a cotton-OECT sensor with selective sensing capability, two OECTs were integrated on the same fabric patch, very close to each other but working independently. The devices are shown side by side in Fig. 1b, one with a silver (Ag) wire as the gate electrode and the other with a platinum (Pt) wire. As previously described the black yarn at the bottom side of each device is the cotton fiber coated with the PEDOT:PSS polymer. The two cotton-OECTs can detect simultaneously and independently different kinds of analytes; in particular the Ag cotton-OECT is sensitive to ions,^{3,4} while the Pt-OECT is capable of reacting with an adrenaline molecule. Electric measurements were performed contemporary on both devices, taking the electrolyte from the same common batch. In order to monitor the oxidation process of adrenaline at the Pt-gate electrode surface, spectroscopic investigations were also performed: absorption spectra (Jasco V-530 spectrophotometer in the 250–650 nm range with a 1 nm step) were recorded as a function of time to better understand the role of OECT detection in the oxidation rate of adrenaline. A 1 mM adrenaline solution in 0.1 M NaCl was used for monitoring the adrenochrome evolution, considering both the spontaneous adrenaline oxidation, as well as during OECT operation.

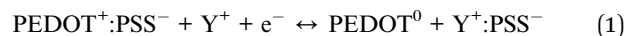
Device characterization

Fig. 1c shows a schematic view of the cotton-OECT electrical circuit and the sensing mechanism involved in the detection of adrenaline: adrenaline undergoes electro-oxidation to adrenaline-quinone and to adrenochrome at the surface of the Pt-gate electrode (Fig. 1d); as a consequence a faradaic current flowing in the source-gate circuit is generated and hydrogen protons are released in the solution.⁸ The OECT response depends on the potential drops occurring at the gate/electrolyte and electrolyte/polymer interfaces. Under the OECT faradaic regime of operation^{3,31} the potential drop at the electrolyte/gate interface decreases and the effective gate voltage ($V_{gs}^{eff} = V_g + V_{g,drop}$) increases, the latter forcing H^+ cations to move toward the polymer surface and de-dope PEDOT:PSS. The sensing mechanism is similar to the OECT-based sensor for hydrogen peroxide,³² dopamine³³ or melanin pigment reported recently,⁸ meaning that catecholamine molecules, like adrenaline, are suitable to be studied by OECT technology.

The output curves were acquired by sweeping V_{ds} between 0 and -0.5 V with steps of 0.1 V, at fixed V_{gs} values between 0 and 0.5 V (V_{gs} steps of 0.1 V). Transfer characteristics of OECTs were acquired by measuring I_{ds} vs. time, fixing V_{ds} at -0.2 V and pulsing V_{gs} between 0 V and 0.5 V with 0.1 V steps. They have been expressed as current modulation $\Delta I_{ds}/I_{ds,0}$ vs. V_{gs} , $V_{ds} = -0.2$ V.

The current values were determined from current transient measurements considering the quasi-steady state current level. The application of V_{ds} induces a drift of the holes along the PEDOT:PSS channel, generating a drain-source current (I_{ds}).

Upon application of a positive gate voltage (V_{gs}), cations (Y^+) from the electrolyte enter the PEDOT:PSS channel causing its de-doping according to the eqn (1):³⁴



In the “de-doping process”³⁵ a decrease of the module of drain current $|I_{ds}|$ (less holes available for conduction) is induced as a consequence of cation incorporation into the PEDOT:PSS backbone and reduction of the oxidized PEDOT⁺ to PEDOT⁰. This process is reversible and when V_{gs} is switched off ($V_{gs} = 0$ V), ions diffuse from PEDOT:PSS to the electrolyte, increasing the number of conducting holes and, consequently, $|I_{ds}|$. Such a process is referred to as “doping”.³⁶

Results and discussion

Fig. 2 shows the basic output characteristics (I_{ds} vs. V_{ds} , at different gate voltages, V_{gs}) of the cotton-OECT device with the Pt-gate electrode measured in 0.1 M NaCl.

Transfer characteristics of OECTs are shown in Fig. 3a for adrenaline diluted in 0.1 M NaCl at 1×10^{-3} M and 1×10^{-9} M concentrations. The transfer curves of the cotton-OECT with a Pt-gate electrode and characterized with two concentrations of adrenaline (1×10^{-3} M and 1×10^{-9} M) shift to a lower gate voltage (overall shift > 300 mV) for a higher concentration of adrenaline (1×10^{-3} M). This indicates that the effective gate voltage (V_g^{eff}) is increased due to the electro-oxidation of adrenaline at the Pt gate electrode surface.

The source-gate current (I_{gs}) was acquired simultaneously during transfer measurements because the gate current analysis provides information about electron transfer reaction occurring at the gate electrode, as well as operational mode of the OECT.³ The catechol-type structures belonging to the reduced state of adrenaline undergoes oxidation at the gate electrode providing electrons to the I_{gs} current of the gate circuit.

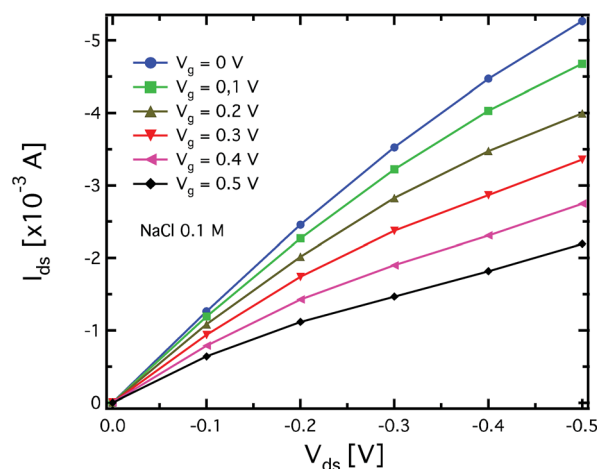


Fig. 2 Output characteristics of the cotton-OECT based on PEDOT:PSS realized with 0.1 M NaCl.

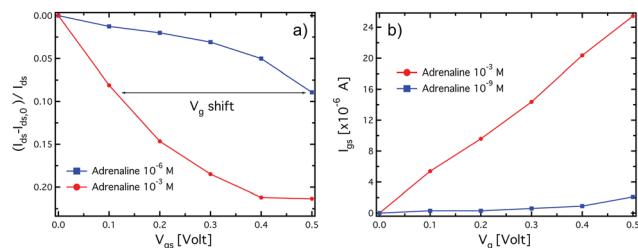


Fig. 3 (a) Transfer curves of the cotton OEET with a Pt gate at two different concentrations of adrenaline in 0.1 M NaCl, a clear voltage shift is observed. (b) Gate current for two concentrations of adrenaline in 0.1 M NaCl (1×10^{-3} and 1×10^{-9} M) the expected gate current increases for the higher concentration of adrenaline, probing the presence of electron transfer occurring at the gate electrode surface.

Fig. 3b shows the trend of the gate current (I_{gs} vs. V_{gs}), acquired in the 0 to 0.5 V V_{gs} range, in the presence of adrenaline at two different concentrations (1×10^{-3} M and 1×10^{-9} M). I_{gs} in the presence of adrenaline 10^{-9} M is almost constant through all the V_{gs} range, while in the presence of 10^{-3} M adrenaline, gate current, as expected, is clearly higher for all the V_{gs} ranges. This indicates that the OEET operates in faradic mode^{3,31} and that a redox reaction occurs at the gate electrode surface. The analysis of I_{gs} suggests the possibility of OEET technology to be used as a tool for monitoring redox states of molecules.⁸

In Fig. 4 real-time acquisition of the drain-current I_{ds} as a function of time is reported. The plots show the different sensing capabilities of the device to adrenaline with the Ag- and Pt-gate electrodes. Measurements have been realized using real human sweat as the electrolyte bath and injecting a 10 μ L droplet of adrenaline in it at a fixed time.

In Fig. 4a I_{ds} has been measured with an Ag-gate electrode ($V_{ds} = -0.2$ V, $V_{gs} = +0.4$ V): two successive injections of 10 μ L droplets of adrenaline solution, at 550 s and 580 s, were done without any evident variation in the I_{ds} current. In Fig. 4b I_{ds} has been measured by the same procedure, but with the use of a Pt-gate electrode, resulting in an evident decrease of $|I_{ds}|$ (y-axis is negative in the figure).

The sensor reacts almost instantaneously (less than 1 s) upon the liquid injection, with a relative change in the current signal (I_{ds}) of about 200% with respect to the base signal. Real-time measurements are intuitive and provide clear evidence that the reaction at the electrode is completely different for the Ag or Pt gate electrodes. In a similar way, it has been demonstrated in previous publications^{3,37} that it is possible to detect the injection of a droplet containing NaCl salt in real-sweat with the Ag-gate electrode, while no signal change occurs with a Pt-gate. The combination of these two complementary results allows us to selectively detect a rush of adrenaline in a saline solution, like human sweat, without confusing it with a change in saline concentration, because they are detected independently by the two different electrodes.

In Fig. 5 the current modulation of I_{ds} (here expressed as $(I_{ds} - I_{ds,0})/I_{ds,0}$) is reported as a function of adrenaline concentration. Adrenaline has been diluted in 0.1 M NaCl and

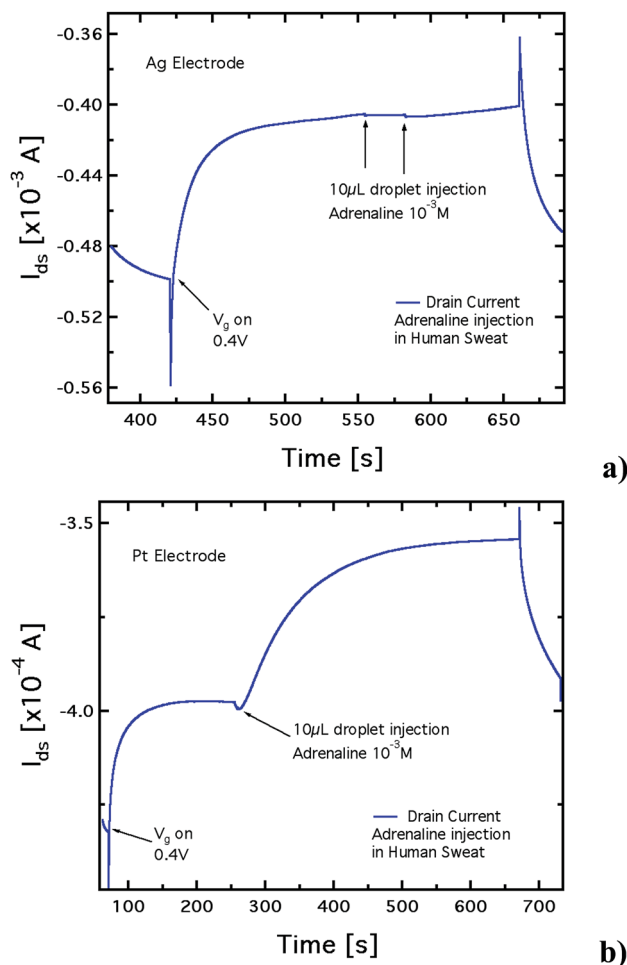


Fig. 4 Measurements of adrenaline in human sweat, the plots represent the cotton-OEET drain current (I_{ds}) vs. time. Upon *in situ* addition of adrenaline solution as evidenced by the black arrows in the graph, the OEET response is negligible using an Ag-gate (a) while it is readily measurable using the Pt-gate electrode (b).

0.01 M NaCl to show the independence of the detection of adrenaline from the NaCl concentration. These values fall in the physiological range of saline concentration in human sweat, *i.e.* 30–60 mmol.

The OEET response has been measured at increasing concentrations of adrenaline, ranging from 10^{-9} M to 10^{-3} M. In Fig. 5a the current modulation, acquired at $V_{gs} = +0.3$ V by using the Ag-gate electrode, is reported for the two NaCl solutions. The curves do not show any dependence on adrenaline concentration, being constant within the experimental errors.

Radically different behavior is observed when a Pt-gate electrode is employed (Fig. 5b). The modulation with the Pt-gate is constant down to a 10^{-6} M adrenaline concentration and then increases monotonically for higher values. It is worth noting that the increase in modulation is proportional to the adrenaline concentration. The dynamic sensing range at $V_{gs} = +0.3$ V is between 1×10^{-6} M and 1×10^{-3} M, with a signal about 2 times larger. The different concentrations of salt do not affect the sensing properties of the OEET sensor, and probe the

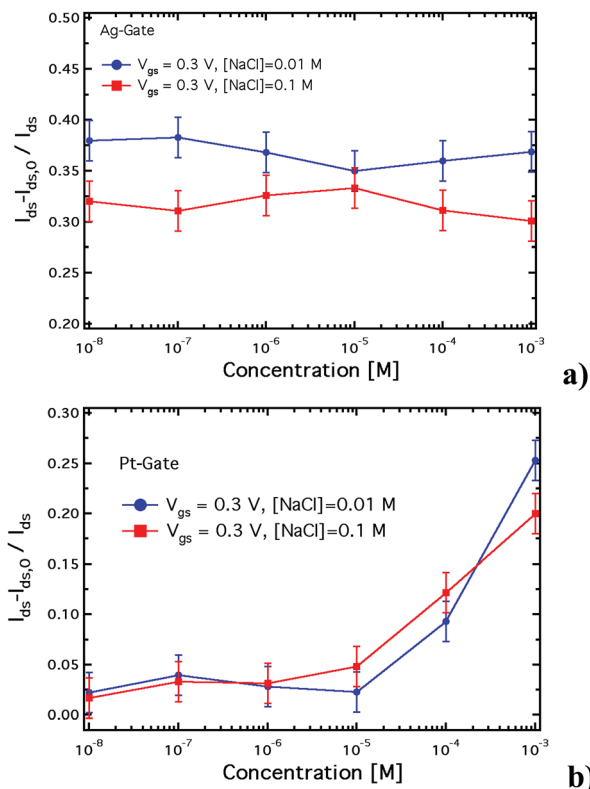


Fig. 5 Plots of the normalized transistor response at different concentrations of adrenaline from 10^{-8} to 10^{-3} M, with an Ag-gate electrode (a) and a Pt-gate electrode (b) at two different NaCl concentrations (10^{-1} and 10^{-2} M).

independence of the adrenaline sensing with respect to NaCl sensing.

We have previously reported¹⁵ that a cotton-OECT may measure the saline content of real human sweat. In that case the sensing mechanism relied on the redox reaction occurring at the Ag-gate electrode surface. In the case of adrenaline, instead, the sensing mechanism is due to the oxidation of adrenaline at the Pt-gate surface, which makes the cotton-OECT device work under a faradaic operation regime.³³

To further investigate the oxidation of adrenaline induced in the OECT with respect to self-oxidation in air, absorption spectroscopy has been performed, using a dedicate experimental setup. Adrenaline undergoes self-oxidation resulting in the formation of adrenaline-quinone and then adrenochrome,^{38–40} through an oxidation pathway that produces different intermediates (adrenaline semi-quinone/quinone, leucochrome, and leucochrome quinone).⁴¹ The exact determination of these intermediates is not trivial^{42–45} and is beyond the scope of this work; nevertheless according to UV-Vis analysis reported in Fig. 6, we have found meaningful differences between adrenaline self-oxidation in air (Fig. 6a) and the corresponding oxidation during OECT sensing (Fig. 6c).

Fig. 6c shows the simultaneous build up of the peak at 305 nm and of the broad band centered at 480 nm, which are the typical features of adrenochrome.^{40,41} The same features emerge to a far less extent during the self-oxidation in air (Fig. 6a) and

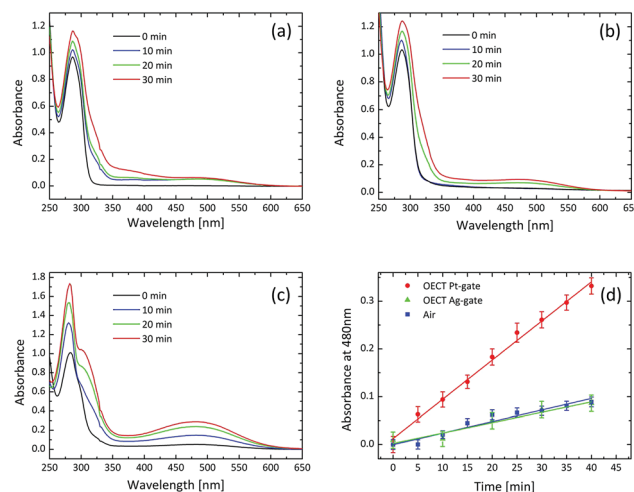


Fig. 6 Absorption spectra recorded at different times by monitoring the oxidation of adrenaline. (a) Adrenaline auto-oxidation in air. (b) Adrenaline oxidation during OECT measurement with an Ag gate. (c) Adrenaline oxidation during OECT measurement with a Pt-gate. (d) Evolution of the characteristic adrenochrome peak at 480 nm as a function of time.

during the oxidation induced by a working Ag-gate electrode in the OECT (Fig. 6b). Hence the oxidation induced by the Pt-gate completes faster and produces adrenochrome while the Ag-gate is similar to self-oxidation. No redox reactions take place at the Ag gate and the sensor response to adrenaline is almost negligible (Fig. 6a). In these cases, the characteristic peak at 305 nm is not visible, but a progressive shift of the absorption maximum at 290 nm towards the visible range is observed and can be addressed to the convolution of the characteristic adrenaline peak at 280 nm with a new one emerging at 295 nm, reported by Sun *et al.* in their study of adrenaline auto-oxidation.⁴⁶ Fig. 6d shows the evolution of adrenochrome as a function of time by monitoring the absorption maximum of the characteristic peak centered at 480 nm: interestingly no substantial difference is measured between self-oxidation and Ag-gate OECT, while platinum significantly increases the rate of adrenaline oxidation to adrenochrome.

Conclusions

In this work a simple, low cost, completely e-textile integrated biosensor for adrenaline sensing has been realized. The device is based on a cotton yarn functionalized with PEDOT:PSS and a Pt-wire used as the gate electrode. The detection mechanism is based on the oxidation of adrenaline at the Pt-gate electrode surface, with the formation of adrenaline-quinone and then adrenochrome. A setup with two independent cotton-OECTs with Pt-gate and Ag-gate electrodes gives the opportunity to detect independently saline concentration and adrenaline concentration in real human sweat. Real-time measurements show the complete independence of adrenaline sensing from NaCl sensing and the simultaneous monitoring of both the concentrations by means of the selective detection on the two

different electrodes. The oxidation of adrenaline has been also studied using absorption spectroscopy under different conditions: in air, and using either a silver or a platinum electrode. Our results confirm that adrenaline oxidation reaction is driven by the presence of a Pt electrode, which leads to faster and direct production of adrenochrome, while with an Ag electrode the oxidation process simply follows the spontaneous and slower oxidation of this molecule in air. The realized double-OECT biosensor could be used for an *in situ* and *non-invasive* analysis of human performances (hydration and stress) and find applications in sports, healthcare and work safety.

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