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A DNA Hydrogel Gated Organic Field Effect Transistor

Justine Pallu¹, Meltem Avci-Adali², Peter Mackeben², Leila Mohammadnejad², Giorgio Mattana¹,
Vincent Noël¹, Benoît Piro^{1,*}

¹Univ. Paris Diderot, Sorbonne Paris Cité, ITODYS, UMR 7086 CNRS, 15 rue Jean-Antoine de Baïf,
75205 Paris Cedex 13, France

²Department of Thoracic and Cardiovascular Surgery, University Hospital Tübingen, Tübingen,
Germany

* Corresponding author: Benoît Piro. piro@univ-paris-diderot.fr

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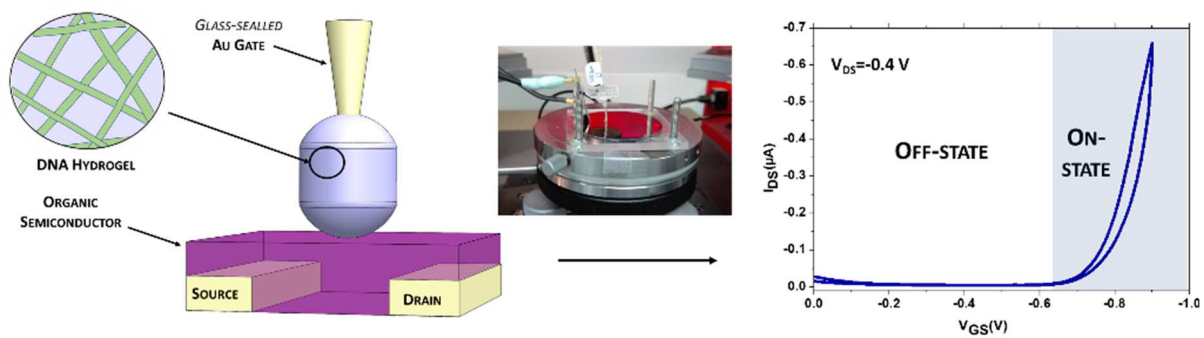
Highlights

- A surface-bound DNA hydrogel was prepared using an original combination of nucleotides isothermal amplification methods.
- The DNA hydrogel can gate an electrolyte-gate organic field effect transistor at ambient conditions.
- The transistor threshold voltage depends on the hydration ratio of the hydrogel.
- Transistor output characteristics can be used to transduce specific biorecognition events between an aptamer sequence constituting the gel and its target, here VEGF.

Abstract

In this work, we fabricated bulk DNA hydrogels that we grew onto the gold gate electrode of an electrolyte-gated organic field-effect transistor and we demonstrated that such a device kept the electrical characteristics which were expected from electrolyte-gated devices. We also demonstrated that the transistor can work without external electrolyte, as a solid-state hydrogel-gated device. As a first proof-of-concept, a vascular endothelial growth factor (VEGF)-specific DNA aptamer was incorporated into the DNA hydrogel and the dependence of the drain current of the transistor upon binding with the target VEGF was compared to the current response upon addition VEGF onto a similar hydrogel without aptamer. This is the first reported example of application of a bulk functional DNA hydrogel as solid-state electrolyte in an electrolyte-gated Organic Field-Effect Transistor (OFET).

Graphical abstract



1. Introduction

Constant efforts have been made in the development of electronic-based point-of-care (POC) biosensors because they may be robust, possibly produced at low cost (e.g. printable), miniaturized and easy to interface with classical control electronics [1-4]. At the same time, organic electronics has proved to be particularly convenient for transducing and amplifying a recognition signal, such as in Organic Field-Effect Transistors (OFETs), which have been used in various formats (Ion-Sensitive OFETs, Enzyme-OFETs...), leading to extremely sensitive devices. Despite these benefits, FETs are still underused in the framework of POC. The main reason is the lack of versatile transduction schemes applicable to a large variety of targets. Indeed, in a conventional FET structure, the field effect is applied between two electrodes through a solid dielectric material, the dielectric constant of which driving the operating voltage of the transistor. Because the field effect is maximal within the dielectric material, the most sensitive part of the device sits within this layer. However, it is obviously pointless to functionalize the dielectric material in conventional FETs because no molecule can penetrate, diffuse and ultimately bind the specific probes therein. This is one of the reasons why the so-called Electrolyte-Gated Organic Field-Effect Transistor (EGOFET) is so attractive. In such devices, the capacitive coupling between the gate electrode and the organic semiconductor is made by an electrolyte instead of a conventional solid dielectric. Gate-source polarization causes the formation of an electric double layer (EDL) at the gate/electrolyte and organic semiconductor (OSC)/electrolyte interfaces. Consequently, mirror charges accumulate within the OSC and form a thin layer of carriers. The seminal works on EGOFETs were those from Bäcklund *et al.* [5], Panzer and Frisbie [6] or Crispin, Berggren and coworkers [7,8], who first reported these devices using solid electrolytes (polymer electrolytes or polyelectrolytes). Later, Kergoat *et al.* [9] demonstrated that solid electrolytes could be simply replaced by water. For biosensing applications, it has also been shown that EGOFETs are sensitive not only to changes at the OSC/electrolyte interface [10,11] but also to those occurring at the electrolyte/gate interface [12-14]. However, these devices cannot transduce molecular events occurring outside the EDLs, the thickness of which depends on the ionic concentration ($\lambda_D \approx 0.304/\sqrt{I}$, with λ_D in nm and I the ionic strength, in mol L⁻¹). In buffered media mimicking physiological conditions, λ_D is < 1 nm. This is an obvious drawback because most biomolecules, including oligonucleotides and DNA aptamers, have dimensions which exceed 1 nm. An approach to solve this problem is to use materials able to switch their overall 3D structure upon target binding. In that sense, hydrogels have attracted much attention due to their potentialities in a large range of applications such as biosensors, actuators and microelectromechanical systems [15,16]. For example, it has been shown that stimuli-responsive hydrogels (SRH) are able to change their 3D structure in response to external stimuli like pH, temperature, or ionic strength changes [17]. Capture molecules of interest can be inserted into these SRH by non-covalent or covalent interactions to obtain bio-functional hydrogels in which the ligand binding or the followed reaction (e.g., proton release by enzymes) could be

responsible for specific changes such as swelling of the hydrogel and changes in its dielectric constant [17,18]. Besides, seminal studies have already shown that DNA hydrogels (hydrogels crosslinked by complementary DNA sequences) were able to perform morphological structure changes after target binding. By using an aptamer as crosslinking component, the target binding leads to a large gel volume increase that can be transduced mainly by optical [19,20], but also by electrical methods [21].

In this work, we developed a pure DNA hydrogel grown onto a gold wire. We demonstrated that our transistors can be efficiently gated by this DNA hydrogel when put in-between the gate and the OSC, whether dipped into a liquid electrolyte or alone. As a first proof-of-concept, a vascular endothelial growth factor (VEGF)-specific DNA aptamer was incorporated into the DNA hydrogel and the dependence of the drain current of the transistor upon binding with the target VEGF was compared to the current response upon addition of VEGF on a DNA hydrogel that did not contain the specific aptamer.

2. Experimental

2.1. Materials and equipments

The fabrication procedures for the lithographed transistors and the gate microelectrodes are described in the Supplementary file (SI). Poly(N-alkyldiketopyrrolopyrrole dithienylthieno[3,2-b]thiophene) (DPP-DTT) was purchased from Ossila (England), with $M_w = 280 \pm 10$ kDa and $PDI = 3.8 \pm 0.1$. Phosphate buffer saline (PBS), dichlorobenzene 98%, chlorobenzene - anhydrous, 99.8%, isopropanol and all other reagents and solvents were purchased from Sigma Aldrich and used without further purification. Aqueous solutions were made with MilliQ water.

2.2 Generation of DNA hydrogel on gold wires

All DNA oligonucleotide sequences and procedures for rolling circle amplification (RCA) are given in Supplementary file. To attach the DNA hydrogel to gold wires, the surface was cleaned for 30 min with 100% ethanol. Subsequently, the gold surface was incubated in 5 mM Tris, 1 M NaClO₄, pH 7.4 with 230 μ M thiol-modified primer 3 for 2 h at room temperature (RT). The RCA mixture and 25 μ M of primer 2 with or without VEGF aptamer conjugation and thiol-modified primer 3 were added to the gold wires in a reaction tube. The multi-primed chain amplification (MCA) was performed for 20 h at 37°C.

2.3. Electrical characterizations

Gate electrodes were glass-sealed Au wires ($\varnothing = 1$ mm). For experiments performed in a liquid electrolyte, 15 μ L of PBS were put directly on the wafer over the semiconducting channel, without covering the electrical contacts, and the DNA hydrogel-modified gate was dipped into the PBS droplet. For experiments without liquid electrolyte, the DNA hydrogel supported on the Au gate was directly put in contact with the OSC. The electrical characteristics were recorded using a Keithley 4200 Semiconductor Characterization System. Output curves were acquired by sweeping the drain-

source voltage (V_{DS}) between 0 and -0.5 V while the gate-source voltage (V_{GS}) was kept at a constant value (-0.5, -0.6, -0.7, -0.8 and -0.9 V for each V_{DS} sweep). Transfer characteristics were acquired by keeping V_{DS} at a constant value (-0.4 V) and sweeping V_{GS} between + 0.2 and -0.9 V.

3. Results and discussion

3.1. Preparation of the hydrogel onto the Au gate electrode

Immobilization of the DNA hydrogel on the Au gate was done by introducing thiolated primers able to chemisorb on the Au gate surface. After incubation with thiolated primer 3, the gate was transferred into the RCA reaction mixture and the DNA gelation process was initiated by addition of primer 2 with or without VEGF aptamer and thiolated primer 3. This process led to the generation of a DNA hydrogel with a thickness of 1 mm on the Au wire, over a length of 2 mm (see **Fig. SI.1**).

3.2. DNA hydrogel without functionalization

3.2.1 DNA hydrogel without liquid electrolyte

First experiments were performed with a DNA hydrogel without specific binding properties, i.e. without the aptamer sequence added to its structure (MCA was performed with primer 2 only). The DNA hydrogel-modified gate was first swollen in PBS for a few minutes then dried with a flush of argon and placed directly onto the semiconductor channel, without surrounding electrolyte. Transfer and output curves of the DNA hydrogel-gated transistor are shown on **Fig. 1**. The output curves clearly show a field effect for $V_{GS} < -0.6$ V; the I_{ON}/I_{OFF} is 5×10^2 (off state at $V_{GS} = -0.4$ V, on state at $V_{GS} = -0.9$ V). From the plot of $\sqrt{I_D}$, we estimated the threshold voltage $V_{th} = -0.7$ V, shifted of ca. -400 mV compared to the reference system (bare Au gate, no hydrogel, PBS as electrolyte; see **Fig. SI.2**). **In this configuration, however, the hydrogel is stable for no more than a few minutes, then dries and shrinks, which hampers analytical applications.**

3.2.2. DNA hydrogel in liquid electrolyte

In this part of the work, experiments were performed with a drop of PBS deposited on the transistor, into which the hydrogel was placed, as it is depicted in the inset of **Fig. 1b**. In this configuration, the output curves clearly show a field effect for less negative V_{GS} than for the solid-state EGOFET described above, and the output curves present less hysteresis. The I_{ON}/I_{OFF} is also higher, reaching 10^3 (off state at $V_{GS} = -0.3$ V, on state at $V_{GS} = -0.9$ V). From the plot of $\sqrt{I_D}$, we can estimate the threshold voltage $V_{th} = -0.5$ V, **less negative of 200 mV** compared to the configuration without PBS.

The results presented in sections 3.2.1 and 3.2.2 demonstrate that a DNA hydrogel can be used successfully to gate an EGOFET. **The threshold voltage shift between transistor with and without liquid electrolyte, as well as the decrease in drain current is attributed to the fact that the gate capacitance is decreased in the absence of liquid. In PBS, the hydrogel is in its most swollen state, with massive penetration of water and ions inside its structure. This causes a higher dielectric**

permittivity (associated to a higher capacitance) compared with the case where the hydrogel, out of a liquid, is less swollen and therefore of lower capacitance.

The following section describes the utilization of such DNA-gated EGFETs for the recognition of a specific target.

[Insert Figure 1 here; single column]

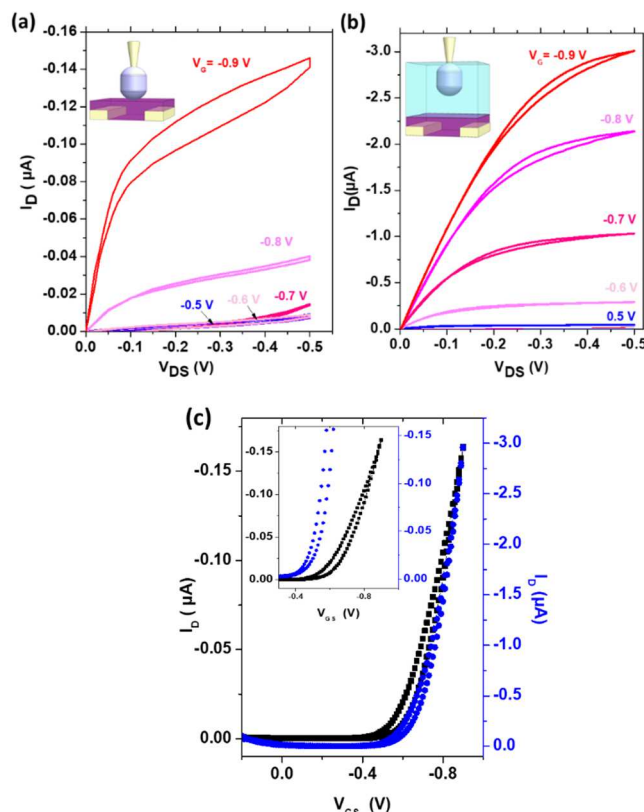


Figure 1. Output curves $I_D = f(V_{DS})$ acquired at V_{GS} from -0.5 V to -0.9 V for an Au gate modified by a DNA hydrogel (a) in standalone (air) and (b) in liquid electrolyte (PBS). Inset: Schematic view of the corresponding gate/hydrogel arrangement. (c) Transfer curves $I_D = f(V_{GS})$ obtained at $V_{DS} = -0.4$ V (■) for the hydrogel alone and (●) for the hydrogel dipped in PBS (inset: same y-scale for both curves). Gate electrode diameter = 1 mm; hydrogel thickness = 1 mm; hydrogel length = 2 mm.

3.3. Aptamer-containing DNA hydrogel in liquid electrolyte

The DNA hydrogel composition was modified by adding an aptamer sequence able to provide a recognition site for a specific target. This strategy has been reviewed in [22]. Therefore, the MCA was performed with primer 2 with covalently conjugated VEGF aptamer at its 5'-end. The presence of the VEGF aptamer and its accessibility was demonstrated using a FAM-labeled antidote (a

complementary sequence to the aptamer) (**Fig. SI.3A**). DNA hydrogels with immobilized VEGF aptamers demonstrated significantly increased VEGF binding compared to the DNA hydrogels without VEGF aptamer (**Fig. SI.3B**): after incubation with VEGF, approximately 175 ± 22 pg VEGF were bound to a 50 μ L DNA hydrogel (whose weight is about 50 mg). See Sections 1.4 and 1.5 of the Supporting Materials for details. It is expected that the molecular recognition cause a thorough reorganization of the hydrogel, and therefore a change in its overall capacitance, which should generate a change in the electrical characteristics of the transistor. For the aptamer-containing hydrogel, we measured strictly no difference in electrical characteristics compared to the aptamer-free hydrogel (results not shown). Using a gate modified with a VEGF aptamer-containing hydrogel, we recorded the drain current vs time upon addition of VEGF at a concentration of ca. 2.5 pg μ L⁻¹ in the electrolyte surrounding the hydrogel. These measurements were also performed with a gate modified with a pure DNA hydrogel, as a negative control. The results are presented in **Fig. 2**. No significant current change was observed upon addition of VEGF to the DNA hydrogel, which did not contain the VEGF aptamer (curve a; 5% change in amplitude, attributed to the normal drift of the device). In contrast, the addition of VEGF to the aptamer-containing hydrogel led to a significant current change (curve b, ca. $30 \pm 5\%$ change in amplitude: $n = 20$). The

[Insert Figure 2 here; single column]

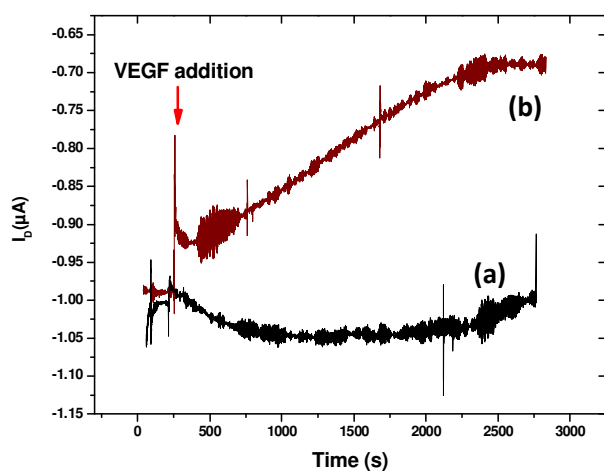


Figure 2. Variation of the drain current $I_D = f(t)$, for addition of 40 pg VEGF in the electrolyte surrounding the hydrogel, for (a) a hydrogel without aptamer, and (b) a VEGF aptamer-containing hydrogel. $V_{GS} = -0.50$ V and $V_{DS} = -0.40$ V. Gate diameter = 1 mm. Hydrogel thickness = 1 mm; Hydrogel length = 2 mm. The liquid electrolyte was contained into a PDMS well of 200 μ L which strongly reduced its evaporation during the experiment. $n = 20$ hydrogel-modified gates were studied. 75% presented similar characteristics, as shown, while 25% shortly detached (partially or totally) from the gate.

The long response time (several tens of minutes) is attributed to the diffusion time of VEGF into the 1 mm hydrogel. Current change upon VEGF binding could be due to change in the total hydrogel capacitance **as well** as a shift of transistor threshold voltage. A new approach of growing ultra-thin DNA hydrogels directly from the gate electrode is being currently developed and will permit deciphering the transduction mechanism. The corresponding results will be presented in a forthcoming paper.

4. Conclusion

The fully original result that we demonstrated in this short communication is that it is possible to use a DNA hydrogel to gate an EGOFET, with or without a surrounding liquid electrolyte. More easily than for conventional polyelectrolytes, a molecular recognition moiety can be added within this DNA hydrogel, in the form of an aptamer sequence, which paves the way for a large variety of targets due to the infinite possibilities offered by aptamers. **We are designing an experiment to be able to measure the gate capacitance as a function of time, with or without aptamer, with or without VEGF, in order to decipher which factor is responsible for the transduction; we plan to describe the results in a forthcoming full-length publication.**

Despite the advantages brought by this approach, the slow target diffusion within the hydrogel hampers practical applications. We are now developing approaches to grow ultra-thin SRH layers, able to quickly switch their morphology in the presence of traces of a given target, as we reported recently using surface-initiated atom transfer radical polymerization (*SI-ATRP*) [23], where the initiator is covalently immobilized on the electrode surface and the SHG is grown from it.

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Conflicts of Interest. The authors declare no conflict of interest. The funders had no role in the design of the study, in the collection, analyses, or interpretation of data, in the writing of the manuscript or in the decision to publish the results.

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