SUPPORTING INFORMATION

Quantum Capacitance as a Reagentless Molecular Sensing Element

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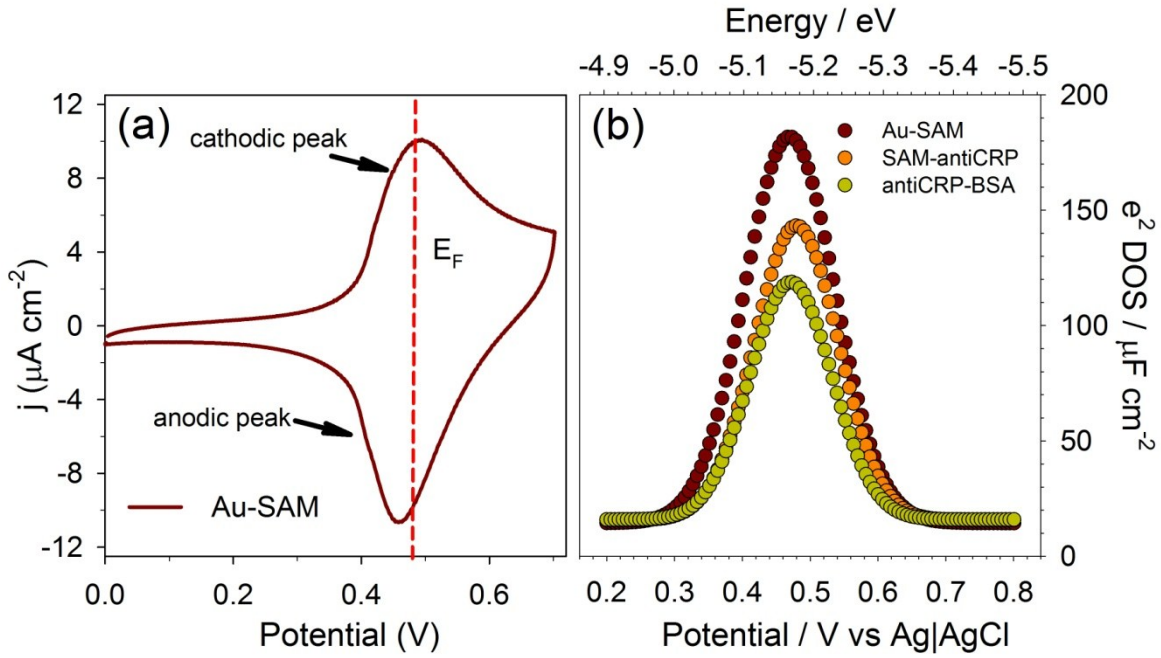
ESI-1 Experiment and methods detailed for Figure 2 and Figure 4

So prepared electrodes were immersed for 16 h in a mixed solution of 1.0 mmol L^{-1} 16-mercaptohexadecanoic acid (16MHDA) and 1.0 mmol L^{-1} 11-ferrocenyl-undecanethiol (11FcC) then washed using alcohol, water and dried under nitrogen. SAM carboxylate activation with 0.4 mol L^{-1} 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and 0.1 mol L^{-1} *N*-hydroxysuccinimide (NHS) in phosphate buffered solution (PBS, pH 7.4, 8 g L^{-1} NaCl, 0.2 g L^{-1} KH_2PO_4, 1.15 g L^{-1} $NaH_2PO_4 \cdot 12H_2O$, 0.2 g L^{-1} KCl, 0.2 g L^{-1} $NaNO_3$) for 30 min, was followed by immersion in 200 µL of 1 µmol L^{-1} of anti-CRP in PBS, for 1 h at 25 °C. To block unspecific sites, the anti-CRP functionalized electrodes were immersed in 200 µL of bovine serum albumin (BSA) 0.01% solution in PBS, for 1 h at 25 °C.

In calibrating, CRP aliquots (40 µL) were added to the interface across concentrations of 0.5 nM to 8.0 nM in PBS (pH 7.4). After 30 minutes of incubation, the electrode was rinsed with PBS and impedance-derived capacitance measurements were taken. The associated analytical curves carried out by dosing the receptive surface response (ranging from 0.5 nM to 8.0 nM) in PBS and appropriate negative controls (fetuin A).[1, 2] Figure 4 (in the main text) shows the results for these experiments.

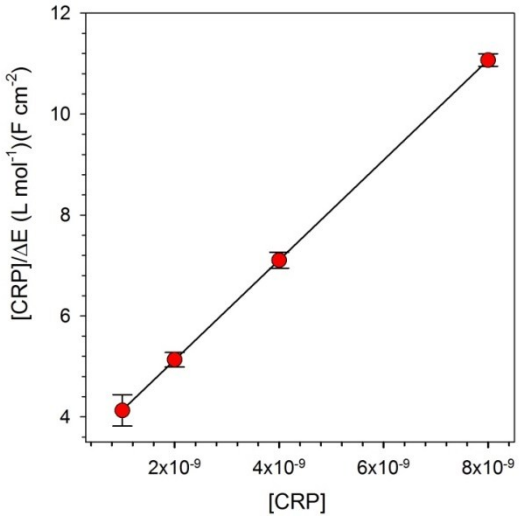
Cyclic voltammetry can be used to determine the surface potential corresponding to the Fermi energy of the junction (equilibrium conditions, that is, when the electrochemical potential equates to the electrochemical potential of electrons confined to the redox monolayer)[3] as shown in Figure ESI-1*a*, that corresponds to the redox potential.[4] Here the data is recorded at a scan rate of 0.1 V s^{-1} between +0.2 and +0.8 V *versus* Ag|AgCl as reference. The ratio between cathodic (i_{pc}) and anodic (i_{pa}) current peak was 0.97 with a potential different between peaks of 40 mV, indicating electrochemical reversibility. The cyclic voltammetry analysis, as expected[3, 5], coincides with the formal potential (Fermi energy) obtained as the maximum of the DOS curve. The Figure ESI-1*b* shows typical DOS changes for 16MHDA/11FcC mixed monolayers on gold during anti-CRP immobilization and subsequent interfacial blocking with BSA.



ESI-1. (a) Cyclic voltammetry analysis for 16MHDA/11FcC mixed monolayer. The formal potential was calculate as the average between the cathodic and anodic peaks resulting, in this case, in a value of 0.49 V *versus* Ag|AgCl reference electrode. (b) DOS changes as the electrodes are modified; 16-mercaptohexadecanoic acid + ferrocenethiol layer (Au-SAM), chemical modification with anti-CRP (SAM-antiCRP) receptive layer, and subsequently blocked with BSA 0.1% m/v (response labelled as antiCRP-BSA).

ESI-2 Determination of binding affinity constant

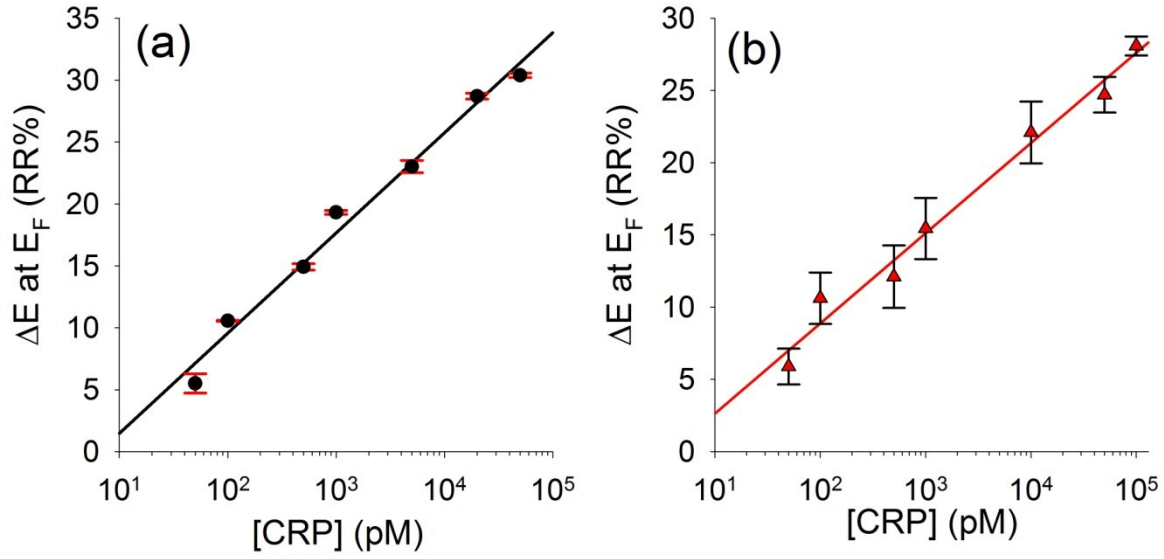
As show in experimental section of the main manuscript the linearized Langmuir isotherm can be constructed by plotting [CRP]/$^{\Delta E}$ *versus* [CRP]. This is shown in Figure ESI-2 (plotted here using data shown in Figure 4*b*). A ^{K_a} value of 3.2 ± 4 x 10^8 mol^{-1} L is obtained as the quotient between the angular ($^{1/\Delta E_m}$) and linear ($^{1/K_a \Delta E_m}$) coefficients.



ESI-2. Linearized Langmuir isotherm with a correlation coefficient (R-squared) of 0.999.

ESI-3 Experiment and methods detailed for Figure 6

In Figure 6*a* glassy carbon electrode (GCE) interfaces were utilized; these were mechanically polished with 1.0 μm, 0.3 μm and 0.05 μm alumina slurries and then sonicated in H_2O and ethanol successively for 5 s. They were subsequently modified with electrochemically reduced graphene oxide (ERGO) thus; 20 μL of GO suspension in water (10 μg mL^{-1}) was added onto the surface of cleaned GCE and allowed to dry to form GO film. The GCE/GO was immersed into an aqueous electrolyte of 0.05 M PBS, and then scanning for 20 consecutive cycles at a scan rate of 100 mV s^{-1} from 0 to −2.0 V (*versus* Ag|AgCl reference electrode).[6] Remaining carboxylate activation was carried out by immersion in EDC/NHS solution for 30 min followed by the immobilization of the anti-CRP antibody (Ab-CRP), by incubation in 200μL at concentration of 100 nM of the Ab-CRP for 1 hour. Prior to activated ester deactivation by immersion in ethanolamine 1 M for 5 minutes. The responsiveness of this GCE/ERGO/Ab-CRP to its target was evaluated against CRP concentration ranging from 50 pM to 5 x 10^4 pM. The measurements were carried out using PBS as electrolyte. The results are presented in the Figure 6*a* in the main text. In the case of measurements conducted in Figure 6*b* and 6*c*, made in redox-composite chemically modified micro-fabricated electrodes, we first assured the correct translation of the measurement made in disk-electrodes to those made in micro-fabricated. In so doing, polycrystalline electrode of METROHM (2.0 mm diameter) were polished and chemically modified with an optimized redox-composite optimized (with controlled thickness kept at 9-10 nm by ellipsometry). The chemical modification consisted of the following steps: first self-assembled monolayers were generated by immersing freshly cleaned gold-disk in an ethanolic (HPLC grade) solution of 2.0 mM of 11-ferrocenyl-undecanethiol (11-FcC) for 16 h. Subsequently, the 11-FcC modified electrodes were rinsed with absolute ethanol and dried in a flow of nitrogen gas before incubation in aqueous solutions of 2 mg/mL graphene oxide (GO) overnight at room temperature in a glove box. The modified gold-disks were placed in a reaction tube sealed with rubber septum stoppers before removal from the glove box. Then 25 mL of a degassed solution of 7.5 mmol of CBMA dissolved in H_2O/methanol solvent (1:1 volume ratio) was transferred to the tube using a syringe and kept under agitation (using a magnetic stirrer) with nitrogen protection by 8 h. After the formation of the redox-composite the modified gold-disks were removed and rinsed with H_2O/methanol, H_2O and then dried with N_2 flow. The carboxylate groups (presents in both GO and CBMA) were activated by 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC)(0.4 M) and N-Hydroxysuccinimide (NHS) (0.1 M) for 40 min, followed by incubation in 1 μM CRP antibody PBS solution overnight at 4 °C. Finally, the CRP recruiting interface (Au/11-FcC/GO/CBMA/Ab-CRP) were immersed in 1 M ethanolamine (pH of 8.5) for 5 minutes to deactivate any unreacted activated carboxylic groups and washed with PBS prior to measurements. Each step of the fabrication of receptor interface was characterized by cyclic voltammetry and impedance-derived capacitance analysis (the measurements were conducted in a supporting electrolyte of 20 mM $TBAClO_4$ following the procedures indicated in ESI-1, ESI-3 and experimental section of the main text). The formal potential of this interface was found as 0.45 V *versus* Ag|AgCl reference electrode. This receptive surface was tested against CRP at concentrations ranging from 50 pM to 5 x 10^4 pM in PBS (R-squared of 0.980) (Fig. ESI-3*a*). The sensitivity was 8.6 % $conc.^{-1}$ with LoD of 21.6 ± 5.2 pM (with the errors corresponding to average of three assays made at the same electrode).



ESI-3. The relative (%) linear response of $^{\Delta E}$, at the Fermi energy of the receptive interface made over an redox-composite, as a function of logarithm of concentration of CRP in PBS for (a) gold-disk electrodes (METROHM) wherein errors bar are standard deviations due to three measurements at the same electrode (LoD of 21.6 ± 5.2) and (b) gold-micro-fabricated electrodes (TRITEQ) with errors bar as the standard deviations across three different electrodes (LoD of 16.8 ± 1.2 pM). These results confirmed that surfaces prepared at gold-disk electrodes can be translated into micro-fabricated disposable electrodes.

To assure the proper translation of the receptive interface from gold-disk (Figure ESI-3*a*) to gold-micro-fabricated electrodes (Figure ESI-3*b*) the interfaces were tested in PBS following procedures discussed in the main text (see experimental section). Figures 6*b* and 6*c* are representative of observations subsequently made at gold micro-fabricated electrodes (TRITEQ, LtD, UK) that were rinsed with ethanol and then washed with water prior to electrochemical pre-treatment in 0.5 M H_2SO_4 using cyclic voltammetry (−0.2 to 1.6 V at a scan rate of 1 V s – up to 100 cycles) until a stable sharp peak (FWHM ~90 mV). More details are provided and discussed in the main text.

ESI-4 Equivalence to a Field-Effect Transistor and Equilibrium Binding Analysis

This section demonstrates that the quantum capacitive devices designed and introduced in the main text are analogous to a single contact FET format (short-circuited source and drain contacts) operating in an electrochemical environment.

Following the energetic schemes shown in Figure 1 (see legends), the difference of the potential between the electrode (a macroscopic electron reservoir) and that of the gate is defined as $dV_G = (V - V_r)/e = - d\mu/e$. The gate here is any modified layer (mesoscopic in character) in which electrochemical or quantum states are resolvable by an AC perturbation such that the potential in the bridge (or the channel of the FET), ^{V_c}, is dependent on the electron density in the channel, ^{N_c}, such as

$$V_c = V_G - eN_c/C_e, \qquad \text{(ESI-1)}$$

wherein $^{q_c = eN_c}$ is the charge in the bridge and $^{eN_c/C_e}$ is the potential of electrons in the bridge.

The capacitance in the gate can be thus written as

$$\frac{dq_c}{dV_G} = \frac{dq_c dV_c}{dV_c dV_G}, \qquad \text{(ESI-2)}$$

Now by applying the derivative of Eqn. (ESI-1) with respect to V_G it is attained that $dV_c/dV_G = 1 - [(1/C_e)(dq_c/dV_G)]$ and Eqn. (ESI-2) can be rewritten as

$$\frac{dq_c}{dV_G} = \frac{dq_c}{dV_c}\left(1 - \frac{1}{C_e}\frac{dq_c}{dV_G}\right). \qquad \text{(ESI-3)}$$

By assuming that dq_c/dV_G, the total capacitance, is the equivalent capacitance (of two series capacitance; the C_e and C_q) of the system, $C_{\bar{\mu}}$, and also by noting that dq_c/dV_c is the quantum capacitance, C_q, we obtain

$$\frac{1}{C_{\bar{\mu}}} = \frac{dV_G}{dq_c} = \left(\frac{C_q + C_e}{C_q C_e}\right) = \frac{1}{C_e} + \frac{1}{C_q}. \qquad \text{(ESI-4)}$$

The energy associated with this equivalent capacitance is $E = q^2/2C_{\bar{\mu}}$ as stated in Eqn. (1). Variations in this energy due to the occupancy of the states (in the gate or in the channel of the molecular films) associated with $C_{\bar{\mu}}$ are reported through derivatives of Eqn. (1) with respect to the (total) charge thus resulting in $dE/dq = q/C_{\bar{\mu}}$. For a single electron transfer reaction at a constant temperature and pressure $dE = dG = -edV_G = d\mu$; associated with the electrochemical potential difference between the electrons in the electrode and molecular films.

Alternatively, it can be noted that $1/C_{\bar{\mu}}$ is equivalent to dq/dV_G, wherein $qdV = \mu(N + dN) - \mu(dN) = d\mu$, for $dN = 1$ (that is a single electron charge change) and considering the negative elementary charge of the electron this becomes $-edV_G = d\mu$ which, when combined with $1/C_{\bar{\mu}} = dq/dV_G$ gives $e^2/C_{\bar{\mu}} = d\mu$.

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