Organic bio-electronic sensors for ultra-sensitive chiral differential detection

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“A. Moro”
outlook

① developing and applying new methods for early diagnostics / PoC

② printable bio-electronic field-effect transistors

③ detections down to fM, chiral differential detection with an ESF > 6

④ Odorant Binding and anti-C Reactive Protein as cases of study
printable electronics

- Portable sensor
  - T. Sekitani et al.

- Epidermal electronic system
  - W.-H. Yeo et al.

- Imperceptible tactile sensor
  - W.-H. Yeo et al.

- Bending down to r=100 μm

- Smart diapers alert parents, detect disease

- Wereable sensors

- E-test strip
minority report – Steven Spielberg (2002)
SAMSUNG Flexible AM OLED

https://www.youtube.com/watch?v=-k6r2HQY9Ws

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point-of-care biosensors

No sample pretreatment

Neonatal care unit

Rapid Results

Ambulance & rescue

Real Time Monitoring

Patient’s home

Early diagnosis

Police checkpoint

Reduce the frequency of hospital visits

POC devices

Reduce the medical costs

Doctor’s office

Emergency room

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sensing arrays: this is the way to go

Affymax DNA chip

Label-free
Low cost, low power, disposable electronic sensing system
Implemented on flex substrate (plastic, fabric, paper)

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OFET BIO-electronic vs.

optical and electrochemical method

**PROS**
- Easy miniaturization
- CMOS compatible (no reference electrode)
  - Label-free
- Low cost (printing fab on plastic, fabric, paper)

**CONS**
- Totally novel approach
- New production paradigms
- Critical is the control of the interfaces

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the search for quantitative stick testing

Schematic drawing of the RenaStick dipstick showing advantages and disadvantages of point-of-care testing in the setting of acute kidney injury. www.nature.com 2014

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printed circuits on paper

electronic OFET bio-sensors @UNIBA


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impact of a binding event on electronic properties

- impacts on OSC or gate metal electrochemical potential → $V_T$ changes
- impacts on the OSC transport properties → $\mu_{FET}$ changes
- Impacts on the gating system capacitance → $C_i$ changes

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Ion Selective FET (ISFET) like bio-sensor

\[ \sqrt{I_{DS}} = \sqrt{\frac{W}{2L} \mu_{FET} C_i \cdot (V_G - V_T)} \]

\[ \mu_{FET} = \text{cost} \]

\[ C_i = \text{cost} \]

\[ \frac{\Delta I}{I} = \frac{2 \Delta V_T}{(V_G - V_T)} \]

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GAS & Ion-Selective FET (ISFET)


\[ \Delta \text{def} + \Delta \text{shift} \]

\[ \varepsilon \]

\[ V_{DS} \]

\[ V_{TO} \]

\[ \text{pH2} \rightarrow \text{pH10} \]

Structure: SnO₂/Al/SiO₂/Si Gate ISFET

Sensitivity: 55.7(mV/pH)
Condition: Constant Current
SnO₂ formed by Sputtering
\( V_0 = 0.2 \text{V}, T = 25^\circ \text{C} \)

\[ \text{Transconductance (uA/\text{V})} \]

\[ \text{Drain Current (uA)} \]

\[ \text{SHIFT (mV)} \]

\[ \text{HYDROGEN PRESSURE (Torr)} \]

\[ I. \text{ Lundström et al. / Sensors and Actuators B 121 (2007) 247–262} \]
electronic OFET bio-sensors


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Interfacial electronic effects in functional biolayers integrated into organic field-effect transistors
Tailoring Functional Interlayers in Organic Field-Effect Transistor Biosensors

Maria Magliulo, Kyriaki Manoli, Eleonora Macchia, Gerardo Palazzo, and Luisa Torsi*
electronic OFET bio-sensors


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how Electrolyte Gated OFETs work

H. Klauk, *Organic electronics II: More materials and applications*; Wiley-VCH
S. H. Kim, K. Hong, W. Xie, K. H. Lee, S. Zhang, T. P. Lodge, C. D. Frisbie,

Helmholtz Stern Double layer

water self-ionization

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Polyelectrolytes in EGOFET

Plain Poly(acrylic acid) Gated Organic Field-Effect Transistors on a Flexible Substrate

Liviu M. Dumitru, Kyriaki Manoli, Maria Magliulo, Luigia Sabbatini, Gerardo Palazzo, and Luisa Torsi*

Department of Chemistry, “Aldo Moro” University, Via Orabona 4, Bari 70126, Italy

dx.doi.org/10.1021/am403008b | ACS Appl. Mater. Interfaces 2013, 5, 10819–10823
EGOFET - architectures

Devices channel length $L = 200 \, \mu m$
channel width $W = 4000 \, \mu m$
Substrates: polyimide (Kapton®)

L. Dumitru
New polyelectrolyte as gating material in OFETs

Calcium alginate fruit (blueberry) “caviar”

L. Dumitru

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Alginate capsules

Before gelation

Sol. of AA in H₂O(d)

Cold CaCl₂

Biopolymer “ball”

After gelation

5 min.

S D

10/10.000 µm

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**Electrical performance**

![Graph showing electrical performance](image)

<table>
<thead>
<tr>
<th>Capsule based OFET</th>
<th>Average ( \mu ) (( \text{cm}^2 \text{V}^{-1} \text{s}^{-1} )) ( (n=7) )</th>
<th>Best</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \mu )</td>
<td>( (1.7 \times 10^{-2} \pm 4 \times 10^{-3}) )</td>
<td>( 2.3 \times 10^{-2} )</td>
</tr>
<tr>
<td>( V_T ) (V)</td>
<td>( (-0.029 \pm 0.019) )</td>
<td>( -0.004 )</td>
</tr>
<tr>
<td>on/off</td>
<td>( (178 \pm 158) )</td>
<td>( 438 )</td>
</tr>
</tbody>
</table>
**Green Electronics**

Natural materials
or materials inspired by nature
in organic field-effect transistors

- **β-carotene** and **indigo** are natural p- and n-type organic semiconductors
- **sugar molecules** or **nucleobases**
- **hard gelatine** produced from collagen, or **caramelized glucose**
- **exotic substrate materials**

Hydrogen-Bonded Semiconducting Pigments for Air-Stable Field-Effect Transistors

Eric Daniel Głowacki,* Mihai Irimia-Vladu, Martin Kaltenbrunner, Jacek Gąsiorowski, Matthew S. White, Uwe Monkowius, Giuseppe Romanazzi, Gian Paolo Suranna, Piero Mastrorilli, Tsuyoshi Sekitani, Siegfried Bauer, Takao Someya, Luisa Torsi, and Niyazi Serdar Sarıçiftçi
From kitchen to lab: Curiosity driven research
**edible Gel di-electric**

Ion/Ioff = 983  
$\mu \text{ [cm}^2/\text{V.s]} = 5.6 \text{ E-1}$  
$V_t [V] = -0.53$  
Channel L/W: 10/10000  
$C = 5$ (taken as approximate value because for ion gels literature values are from 5 to 10)

Ion/Ioff = 302  
$\mu \text{ [cm}^2/\text{V.s]} = 5.7 \text{ E-2}$  
$V_t [V] = -0.74$  
Channel L/W: 5/10000

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how EGOFETs work

H. Klauk, *Organic electronics II: More materials and applications*; Wiley-VCH


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the capacity modulated device

\[ C_{CDL} \sim 10^{-2} \mu F/cm^2 \quad \text{and} \quad C_{BIO} \sim 10^{-1} \mu F/cm^2 \]

\[ C_{BIO} \ll C_{CDL} \]
electrolyte gated OFET (EGOFET) sensor

\[ \sqrt{I_{DS}} = \sqrt{\frac{W}{2L}} \mu_{FET} C_i \cdot (V_G - V_T) \]

\[ \mu_{FET} = \text{cost} \]

Top Gate OFET (TFT)

\[ \Delta I \over I = \frac{\Delta C_i}{C_i} - \frac{2 \Delta V_T}{(V_G - V_T)} \]

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charged species $\rightarrow$ stronger long-range coulomb interactions 
(10-100 kJ/mol) $\rightarrow$ electrochemical potential $\rightarrow$ ISFET

neutral species (or species carrying a dipole moment) $\rightarrow$ weaker short-range interactions such as the dipole-dipole or the dispersive ones 
(2 kJ/mol) $\rightarrow$ chemical potential $\rightarrow$ capacity modulated FET


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Odorant Binding Proteins  EGOFET sensor

Mulla, M.Y. et al. Nature Communications, 2015, 6, 6010

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pOBP is a monomer of 157 amino acid residues (molecular mass of *ca.* 19 kDa) with a height of 38.04 Å and a base of 25.70 Å x 26.40 Å.
Odorant Binding Proteins

Artist: Emily Harrington. Copyright: All rights reserved

Shuttle odorant molecules
Odorant clearance mechanism

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vertebrate odorant system
why odorant binding proteins?

- OBPs are present in high concentrations of mM range in mammalian nose and insects antennae
- Soluble proteins, can be expressed in bacterial systems at low-cost
- Highly stable – in ambient/hot conditions
  - Binds reversibly to odorants

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pig Odorant Binding Proteins (pOGBP)

The protein is characterized by a hydrophobic β-barrel cavity,

Differently from other OBPs such as the bovine one, pOGBP b-barrel cavity is devoid of naturally occurring bound ligand

It bears a negative charge

No study on chiral interactions; carvone enantiomers

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chiral ligand molecules

R(-)-Carvone  S(+)‐Carvone

Caraway smell  Spearmint Smell

hydrophobic volatile, neutral small molecules are perceived as spearmint or caraway flavours with human threshold for detections of 30 and 420 nM

dipole moment of 3.2-3.6 D associated with the ketone group

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The binding process

Ligand (L) + Protein (P) ⇌ Complex P-L

\[ K_D = [L] \text{ @ half occupied protein sites} \]
competitive fluorescent binding assay

\[ K_{\text{sol}}^{(+)} = 0.50 \pm 0.01 \ \mu M \text{ and } K_{\text{sol}}^{(-)} = 1.22 \pm 0.05 \ \mu M \]

2-phenylethanol is shown to bind very weakly to pOBPs (\( K_D \text{ ca. } 40 \ \text{mM} \))

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OBP in a water gated OFET sensor

Mulla, M.Y. et al. *Nature Communications*, 2015, 6, 6010
Cinzia Di Franco - CNR - Bari
Maria Vittoria Santacroce and Gaetano Scamarcio - University of Bari

Mulla, M.Y. et al. *Nature Communications*, 2015, 6, 6010

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Electrochemical pOBP SAM characterization

\[ B = 1 - \left( \frac{I_{0}^{\text{Fun}}}{I_{0}^{\text{Au}}} \right) \]

Where, \( I_{0}^{\text{Fun}} \) and \( I_{0}^{\text{Au}} \) are the oxidative peak currents obtained from the CV curves for functionalized electrode (3MPA alone and 3MPA-pOBP) and the bare Au electrode respectively.

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XPS pO BP SAM characterization

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bare gold electrode

Dr. Nicoletta Di Taranto

pO BP-SAM functionalized gold electrode confirming presence of (a) carbon 1s, (b) sulfur 2p, (c) oxygen 1s and (d) Nitrogen.

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$V_T = -0.01 \pm 0.06 \text{ V}, \text{ on/off current ratio of } 150 \pm 110 \text{ and } 
\mu_{\text{FET}} = 1.1 \pm 0.2 \times 10^{-1} \text{ cm}^2/\text{Vs}.$
Sensing of tine neutral species with WGOFETs

- Sensitivity of pOBP WGOFT exposed to (S)-(+)-carvone
- pOBP-SAM
  - 100 pM
  - 500 pM
  - 1 nM
  - 5 nM

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dose-curves with WGOFETs

$$\Delta I/I$$

-0.6
-0.4
-0.2
0.0

[S]-(+)-carvone
(R)-(-)-carvone
2-phenylethanol

[ligand] (pM)

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the two enantiomers on the very same gate

Rinsing between each step

$I_{DS}$ ($\mu$A)

S-$(+)$-Carvone
R-$(−)$-Carvone

[ligand] (pM)

$10^0$  $10^1$  $10^2$  $10^3$  $10^4$  $10^5$  $10^6$
Decoupling capacitance and threshold voltage

\[ \frac{\Delta V_T}{V_G - V_T} \]

\[ \frac{\Delta C}{C} \]

\[ \sqrt{I_{DS}} \]

\[ V_{T0} \]

\[ V_T \]

\[ C_{i0} \]

\[ C_i \]

\[ [\text{ligand}] (\text{pM}) \]

\[ (S)-(+)\text{carvone} \]

\[ (R)-(-)\text{carvone} \]

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The response is dominated by capacitance

\[
\frac{\Delta I}{I} \approx \frac{\Delta C_i}{C_i}
\]

(S)-(+)carvone

[ligand] (pM)

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(S)-(+)carvone / pOBP complex

![Graph showing the response of (D)-(+)carvone and (S)-(+)carvone to different concentrations of carvone.](image)

- **LOD:** 50 pM
- **LOQ:** 150 pM

**Single-site Langmuir’s isotherm:**

\[
\frac{\Delta I}{I} = b_{\text{MAX}} \frac{[\text{carv}]}{K_{\text{FET}} + [\text{carv}]}
\]

- **\(K_{\text{FET}}^{(+)}\):** 0.81 ± 0.05 nM
- **\(\Delta I/I^{(+)}\):** as high as -60%; **LOD:** 50 pM
A sensitivity-enhanced field-effect chiral sensor

Figure 1: Bilayer OTFT chiral sensor structure. The transistor has a bottom-gate device structure that consists of a highly n-doped silicon wafer (resistivity 0.02–1 Ω cm⁻¹).
(R)-(-)-carvone / pOBP complex

Hill’s isotherm

\[ \frac{\Delta I}{I} = \frac{b_{MAX} [\text{carv}]^\alpha}{K_{FET} + [\text{carv}]^\alpha} \]

\( K_{FET}^{(-)} \) of 20 ± 20 nM

\( \Delta I/I^{(+)} \) of -17 % \( (\alpha = 0.5 \rightarrow \text{non-cooperative binding}) \)
enanthio-selectivity factor > 6

ESF = m+/m- = 6.3

markedly different levels of cooperativity and an exceptionally high ESF
The pOBP capacitance model

2.4% of the total surface of the protein exposed to the solvent (~7 nm²) it well accommodate a few water molecules.

R(-)-Carvone \[ C_{OBP} \approx C_w \]

S(+) - Carvone \[ C_{OBP} = C_p \]

high dielectric percolative path, “water channel”

G. Lattanzi

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dissociation constant for 2D receptors

\[ \Delta G^0 = RT \ln[K_D] \]

Surface segregated OBP

\[ \Delta G^\circ_{\text{FET}}^{(+)} = -(49.2 \pm 0.1) \text{ kJ/mol} \]
\[ \Delta G^\circ_{\text{FET}}^{(-)} = -(41 \pm 2) \text{ kJ/mol} \]

OBP in solution

\[ \Delta G^\circ_{\text{sol}}^{(+)} = -(36.00 \pm 0.05) \text{ kJ/mol} \]
\[ \Delta G^\circ_{\text{sol}}^{(-)} = -(33.0 \pm 0.1) \text{ kJ/mol} \]
the thermodynamic cycle

\[ \Delta G_{FET}^0 = \Delta G_{Sol}^0 + \Delta E_F + W \]

\[ \Delta E_F = (\bar{\mu}_e(P-L) - \bar{\mu}_e(P)) = -nF\Delta V_T \]

L = carvones  \quad P = \text{pOBP}  \quad e = \text{gate free-electrons}  \quad P-L=\text{complex}

binding surface work - surface tension

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Financial support
launching a new journal

Flexible and Printed Electronics™

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team & principal collaborations

Post-doc position in October will be launched.

Thanks