Master in Electrical and Electronics Engineering

EE-517: Bio-Nano-Chip Design

Lecture #8

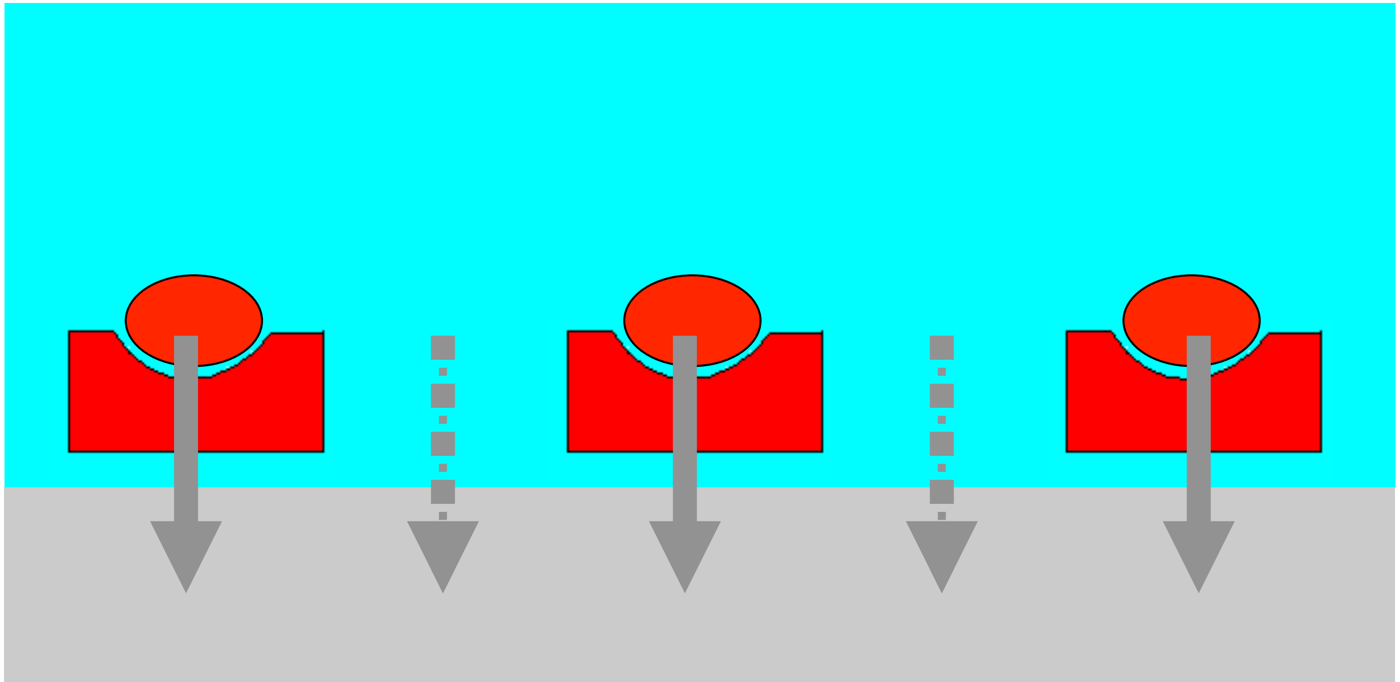
Nanotechnology to prevent Electron Transfer

Lecture Outline

(Book Bio/CMOS: Chapter' paragraphs §6.3-8)

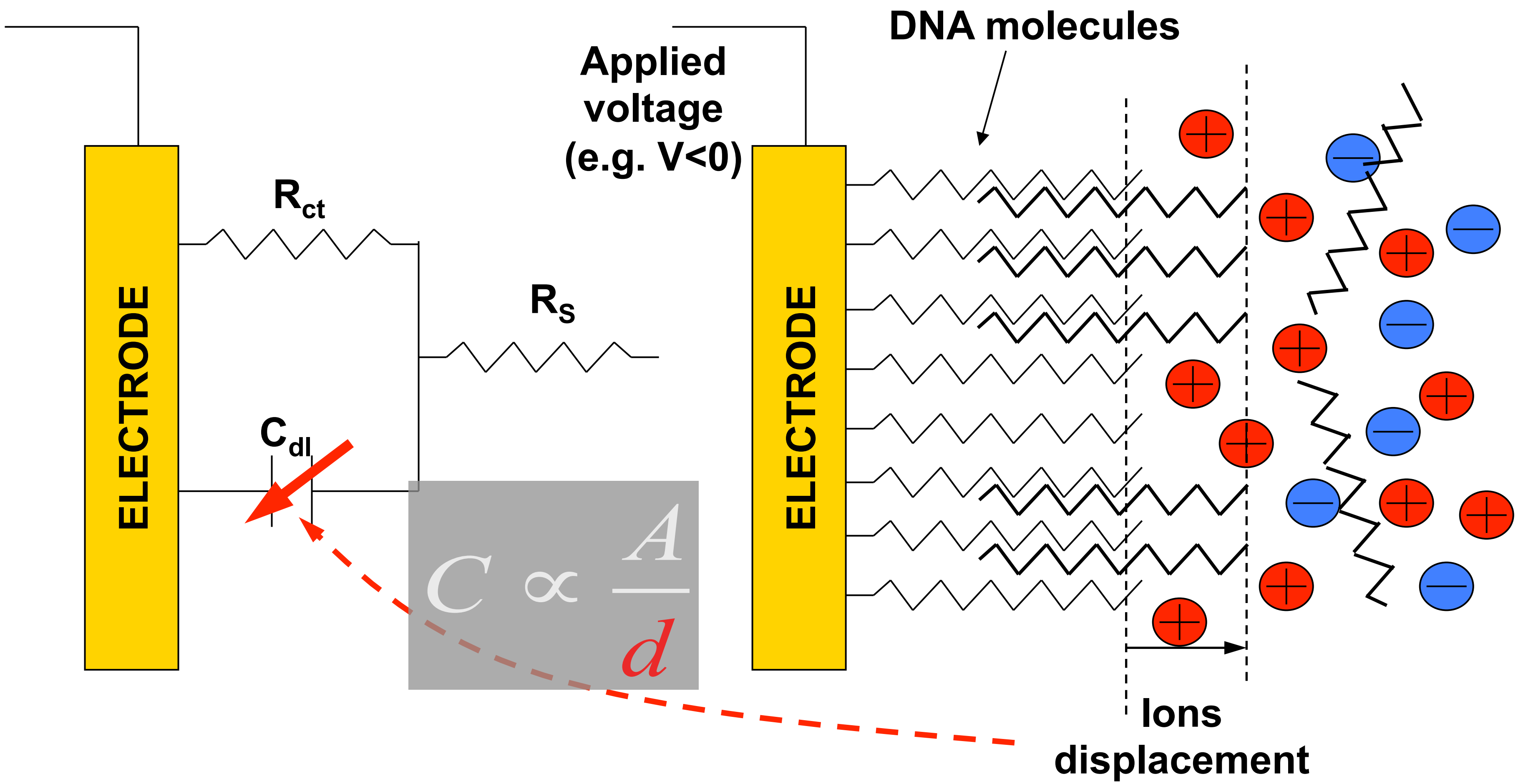
- Electrical behavior of DNA at the interface
- Nanoscale properties of DNA films
- Blocking agents
- Precursor films
- Electrical behavior of Antibodies

CMOS/Sample interface



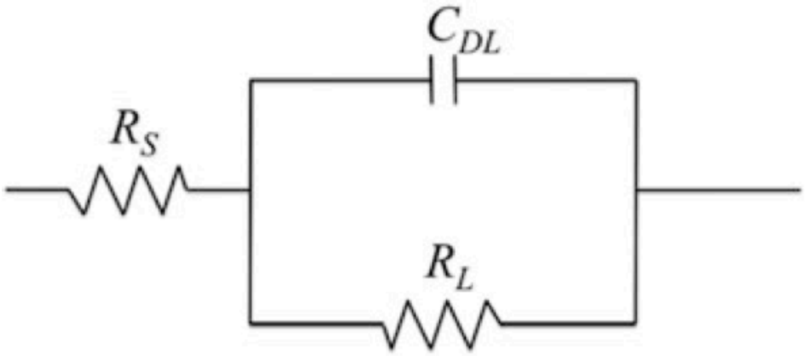
The interface between the CMOS circuit and the bio-sample needs to be deeply investigated and organized

The Capacitance DNA Detection



Unlabeled ssDNA may be detected with capacitance measurements as due to charge displacement

Randle Model



$$C_{DL} = \varepsilon_{DNA}\varepsilon_o \frac{A}{d}$$

$$Z_{//} = \frac{R_L}{j\omega C_{DL} R_L + 1}$$

$$I_{non-F} = \frac{V_{ref}}{Z} = \frac{1 + j\omega C_{DL} R_L}{R_L} V_{ref}$$

Equivalent circuits of DNA Bio/CMOS interface

Recall: Frequency behavior of a bare gold surface

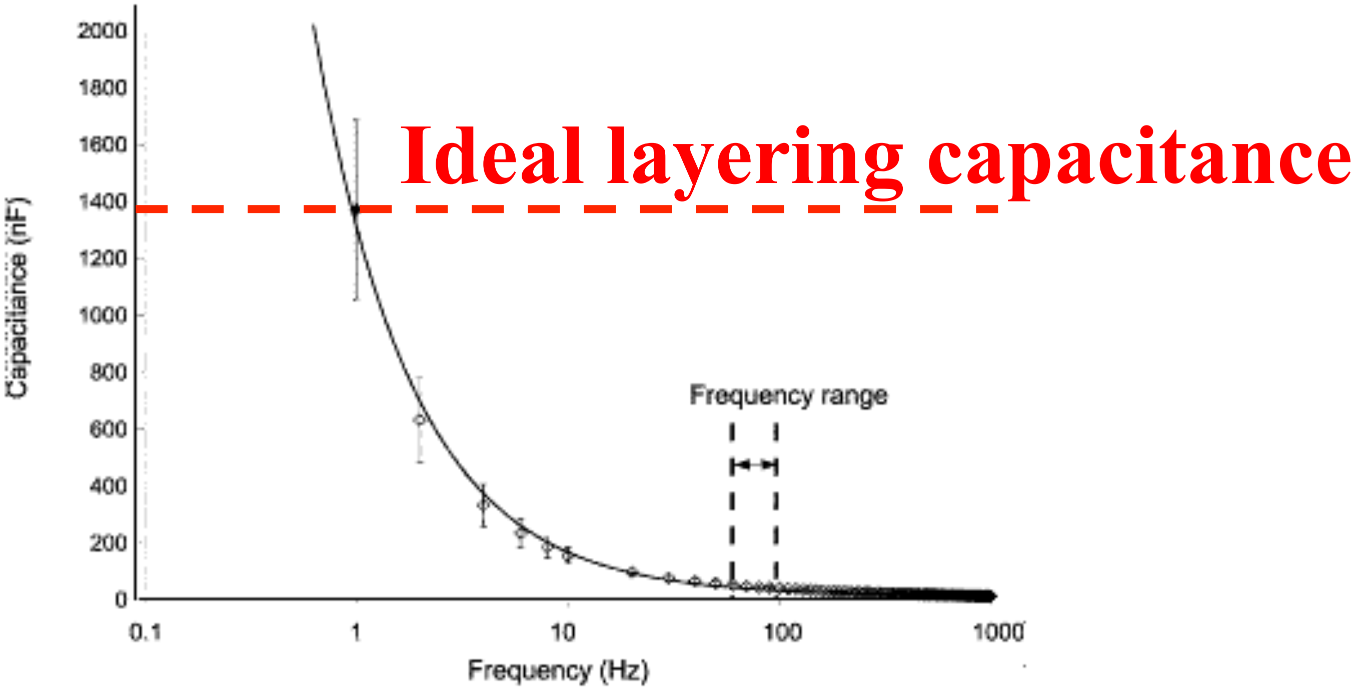
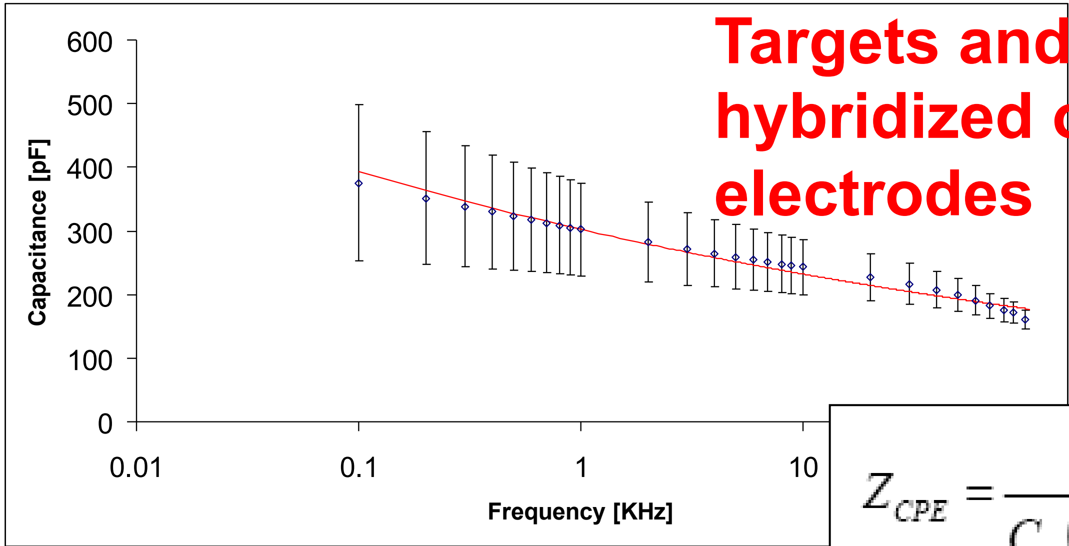


Fig. 9. Measured capacitance versus charge/discharge frequency on clean gold electrodes. The continuous line shows the fitting.

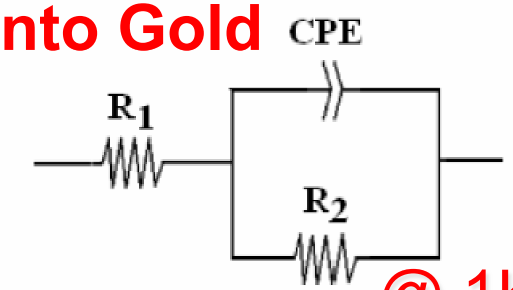
STAGNI *et al.*: FULLY ELECTRONIC LABEL-FREE DNA SENSOR CHIP IEEE SENSORS JOURNAL, VOL. 7, NO. 4, APRIL 2007

The equivalent capacitance of Helmholtz ion planes on bare electrodes is frequency-dependent

Recall: Frequency behavior of DNA surfaces



Targets and probes hybridized onto Gold electrodes



@ 1KHz

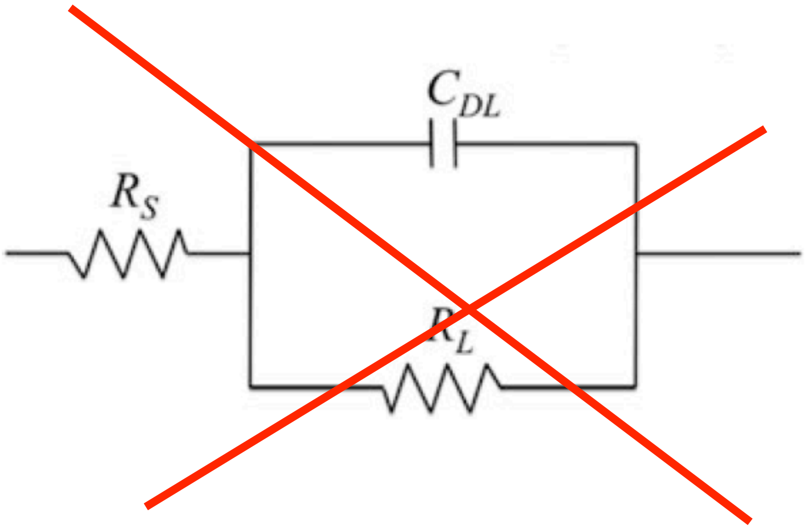
$$Z_{CPE} = \frac{1}{C_p (j\omega)^{\alpha}} \cong \frac{1}{\omega^{\alpha} C_p}\sqrt{1-\alpha^2} - j\frac{1}{\omega^{\alpha} C_p}\alpha$$

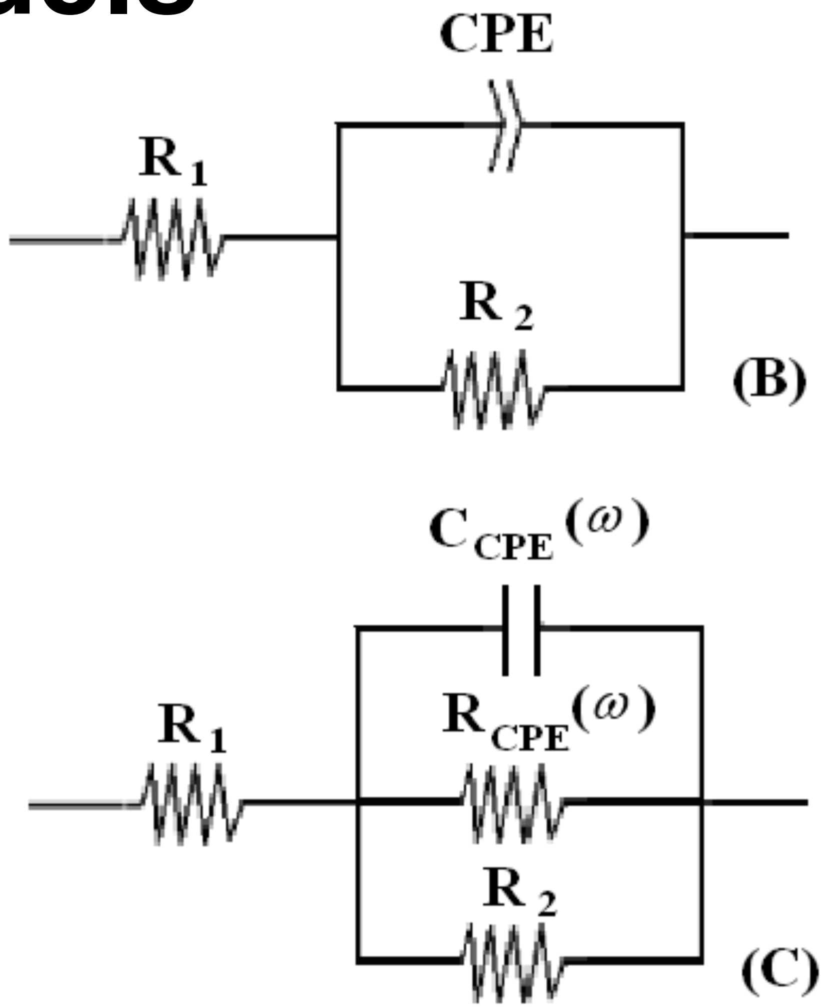
CPE parameters	Bare electrode	DNA Probes	DNA Target
R(GΩ)	45	177	177
X(GΩ)	123	837	970

S.Carrara et al., Sensors and Transducer Journal 76 (2007) 969-977

Charge transfer pathways through the DNA layer affect the ideal Capacitance behavior of the interface with the solution sample

Interface models





Equivalent circuits of DNA Bio/CMOS interface

CPE element

$$Z_{CPE} = \frac{1}{C_p(j\omega)^{\alpha}} = \frac{\cos\left(\frac{\pi}{2}\alpha\right)}{C_p\omega^{\alpha}} - j\frac{\sin\left(\frac{\pi}{2}\alpha\right)}{C_p\omega^{\alpha}}$$

$$Z_{CPE} \cong \frac{1}{\omega^{\alpha}C_p}\sqrt{1-\alpha^2} + \frac{1}{j\omega^{\alpha}C_p}\alpha.$$

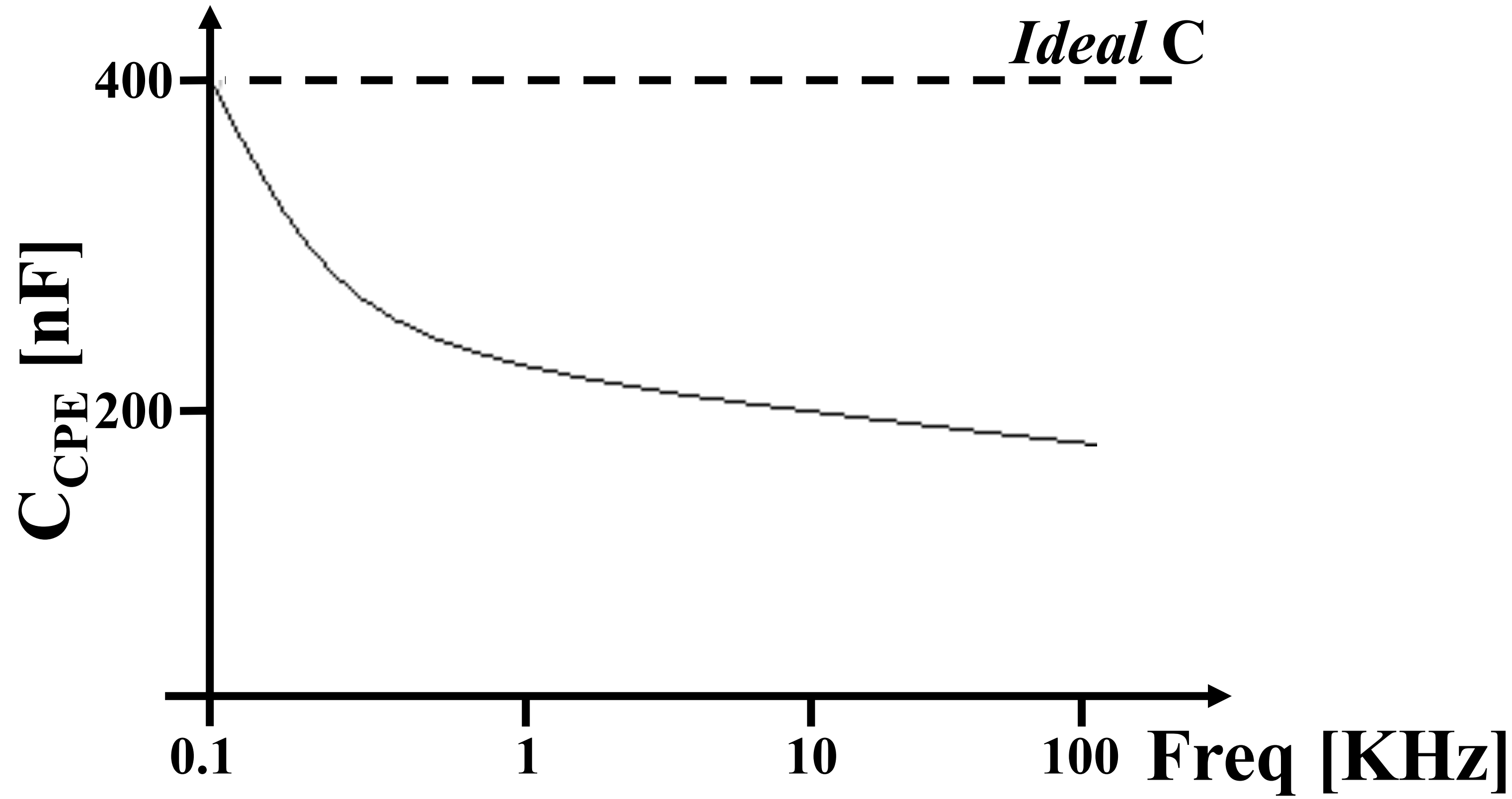
CPE element

$$Z_{CPE}\begin{cases} R_{CPE} \cong \frac{1}{\omega^{\alpha} C_p}\sqrt{1-\alpha^2} \\ X_{CPE} \cong \frac{-1}{\omega^{\alpha} C_p}\alpha \end{cases}$$

$$|X_{CPE}| \cong \frac{1}{\omega^{\alpha} C_p}\alpha = \frac{1}{\omega^{\alpha-1}\omega\, C_p}\alpha = \frac{1}{\omega\left(\frac{C_p}{\alpha\,\omega^{1-\alpha}}\right)}$$

$$C_{CPE} \cong \frac{C_p}{\alpha\,\omega^{1-\alpha}}$$

Equivalent Capacitance vs frequency



The problem of time instability

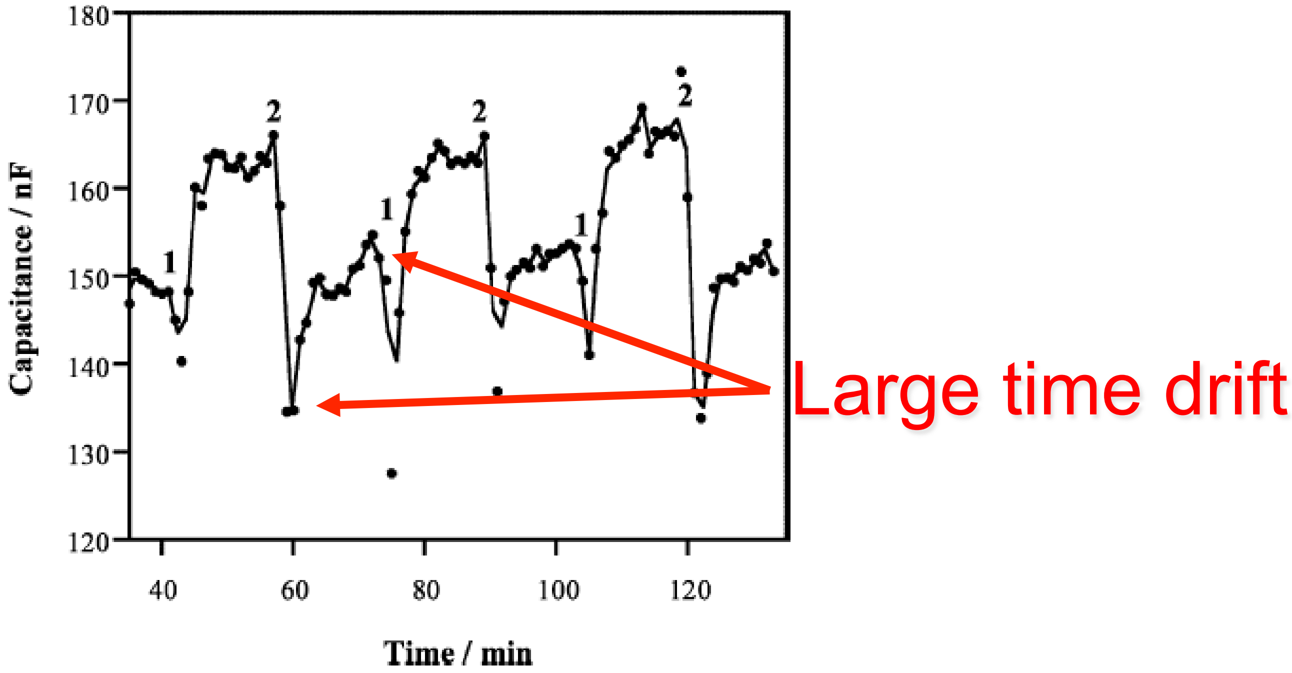
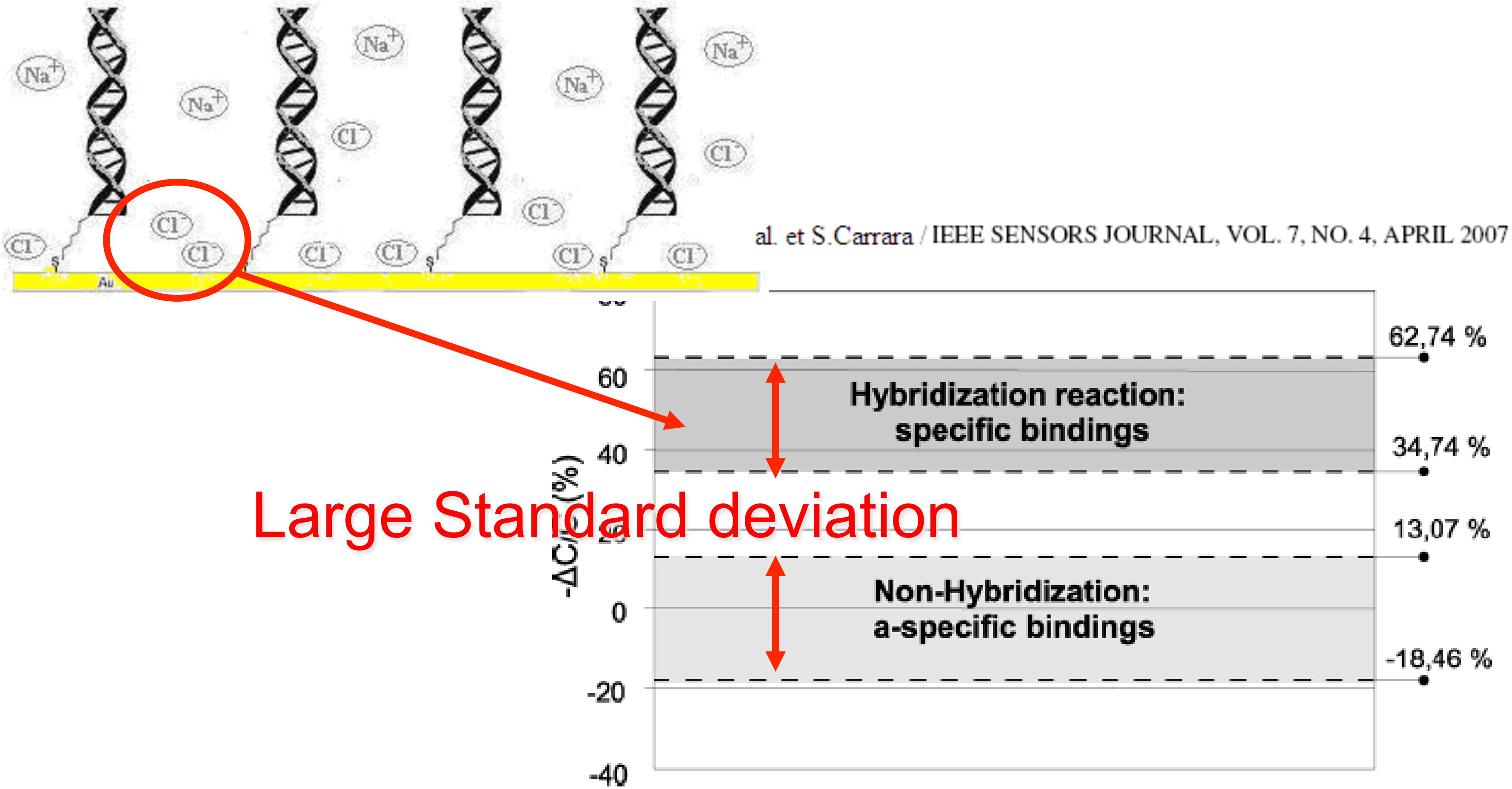


Fig. 7. Regeneration of the EC20 modified electrode with (1) 1 mM EDTA after injections of (2) 100 μM Zn^{2+}. Other experimental conditions are as in Fig. 5.

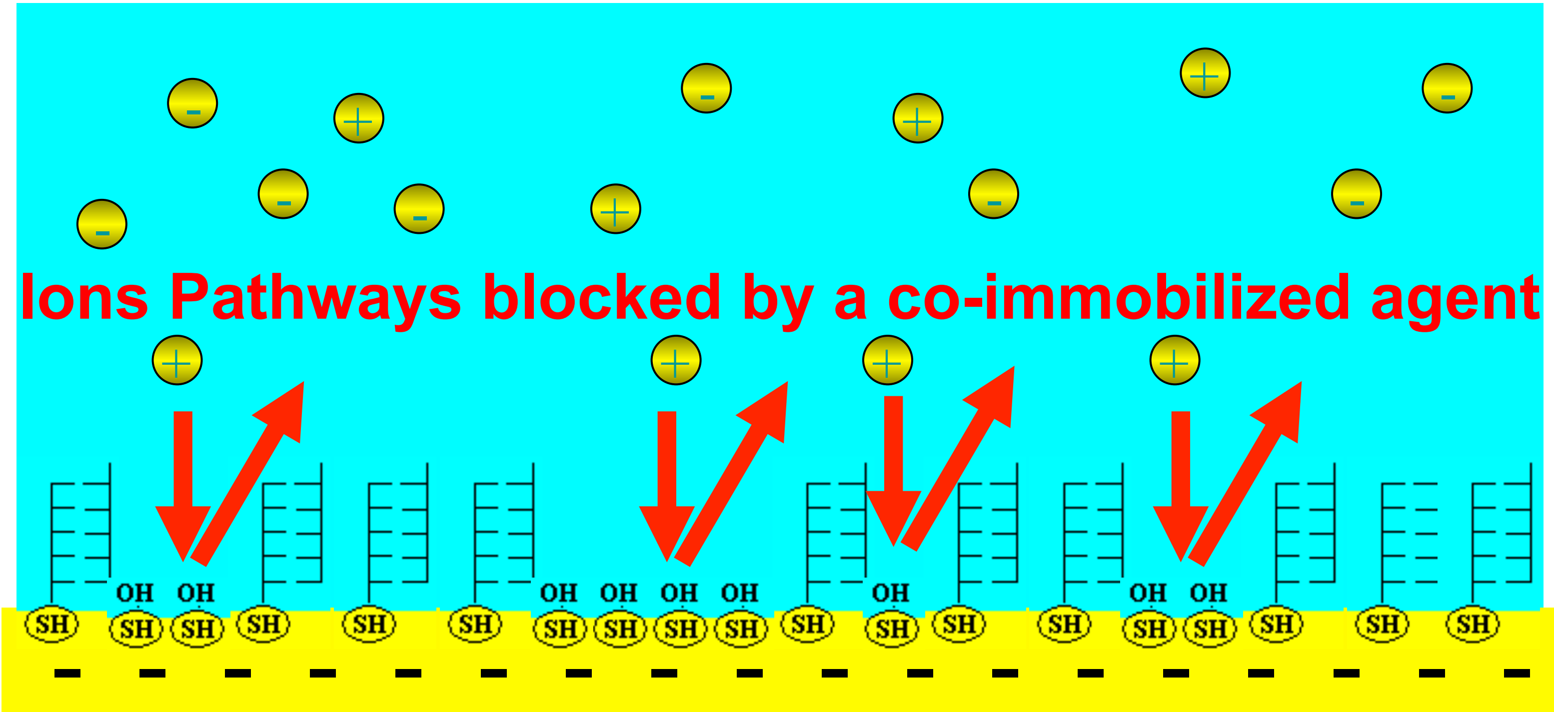
Heavy metal ion capacitance detection by using phytochelatine as probe molecule

Nano-aperture in the probes film



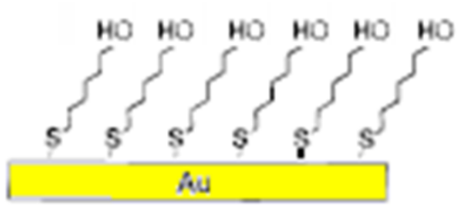
Solution ions in free contact with electrodes surface results in very large standard deviations

Nano-aperture blocked in the probes film

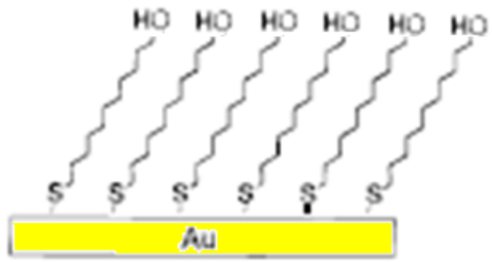


Ion Pathways blocked at the nanoscale

Blocking Agents



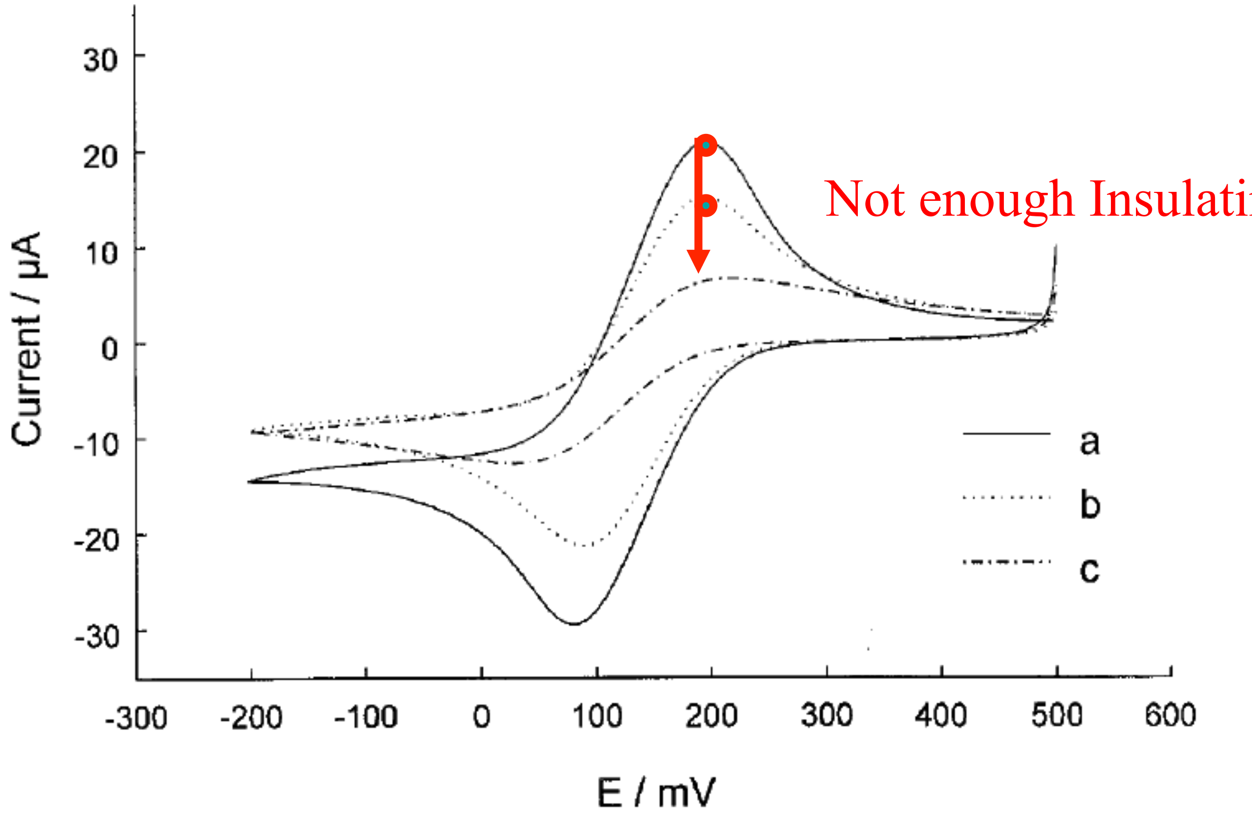
Mercapto-Hexanol



Mercapto-Undecanoic Acid

Increased stability by using mercapto-hexanol or longer thiols

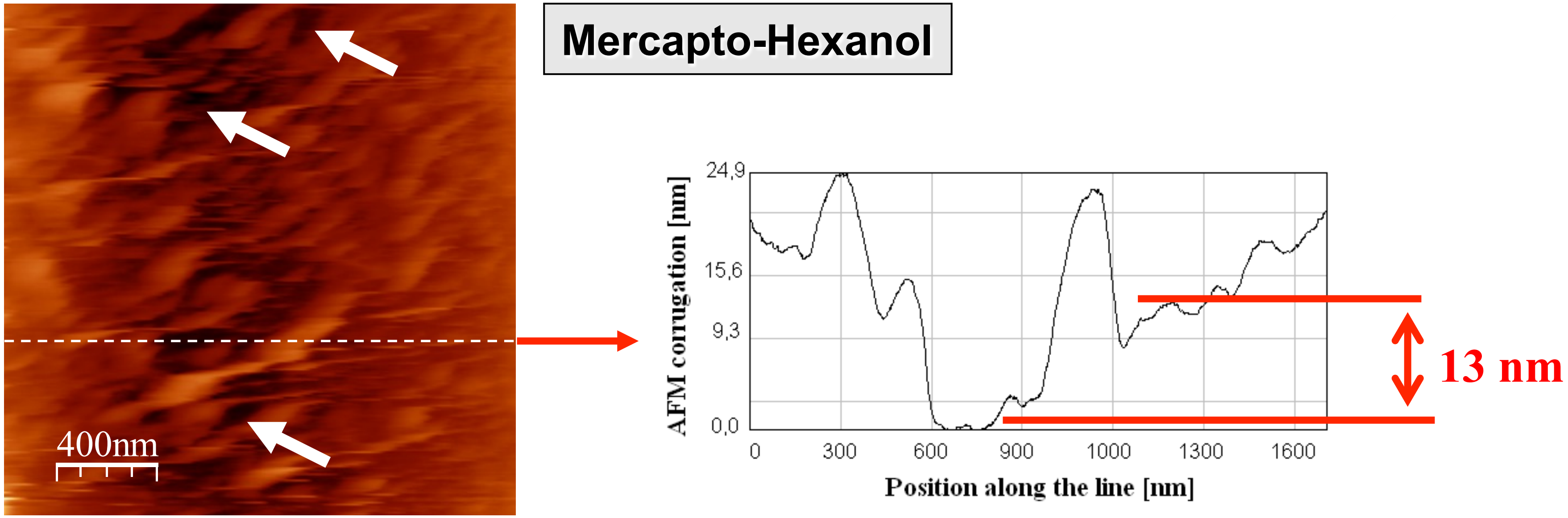
Improved insulating behavior



C. Berggren et al. Electroanalysis **1999**, 11, No. 3

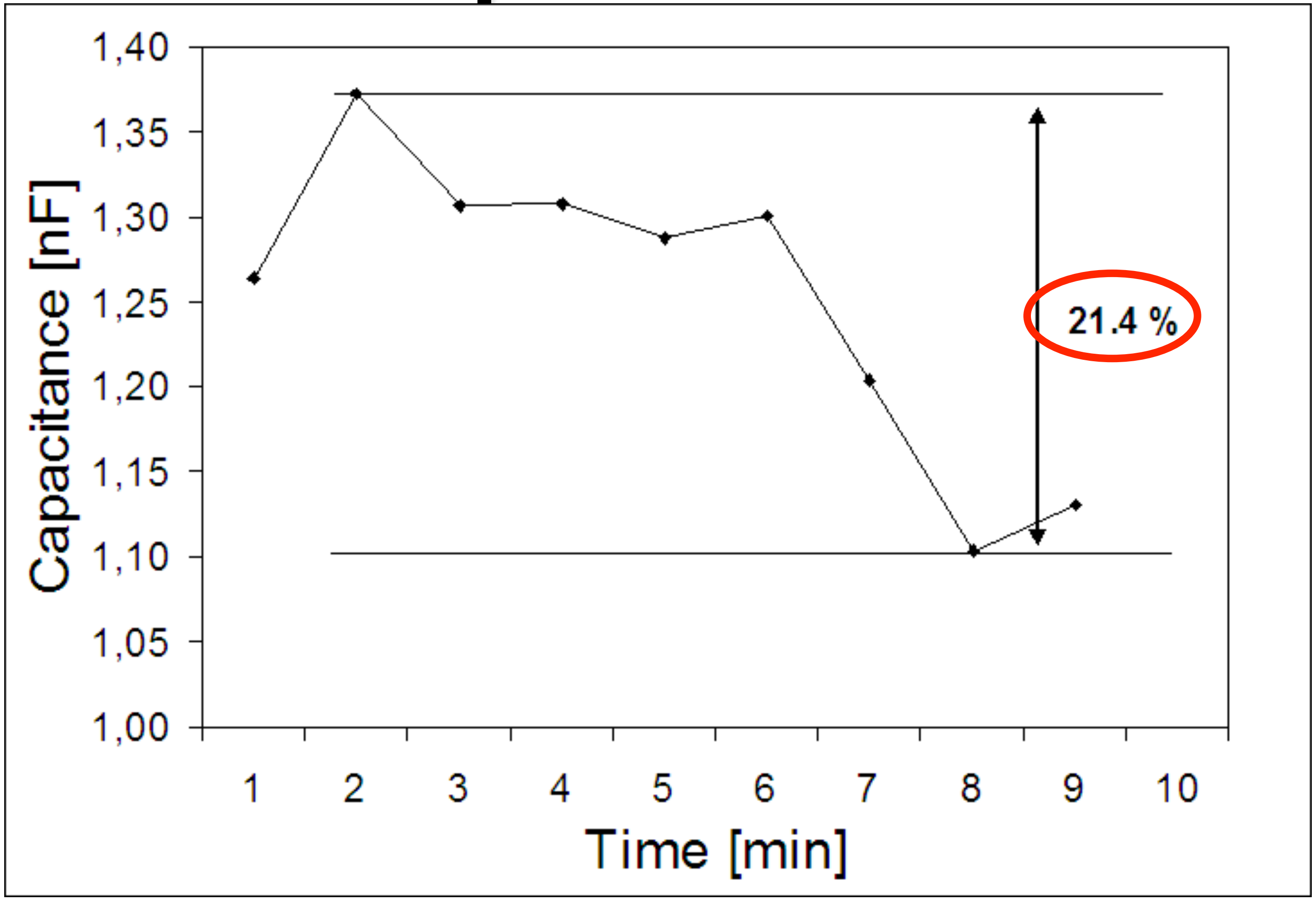
Redox reaction of K3Fe(CN)6 on gold electrode (a),
ss-DNA onto gold (b) and ss-DNA + 1-dodecanethiol onto gold (c)

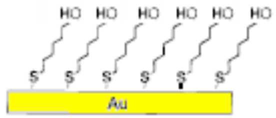
Nano-scale Apertures



Monolayers of ssDNA with blocking agents still present deep groves crossing the film

Capacitance Instability

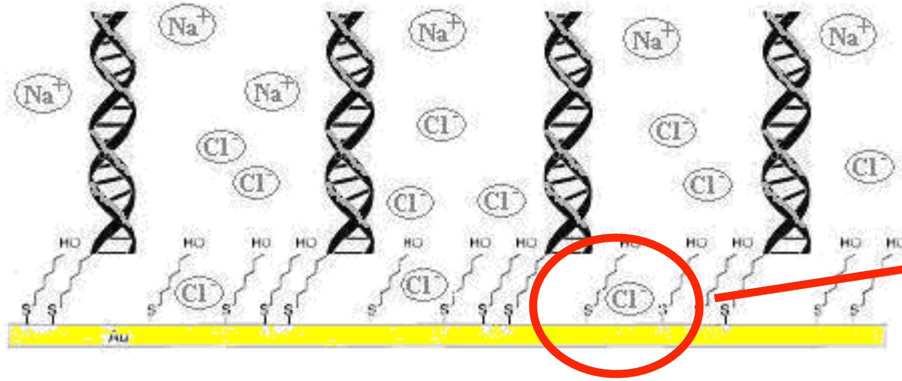


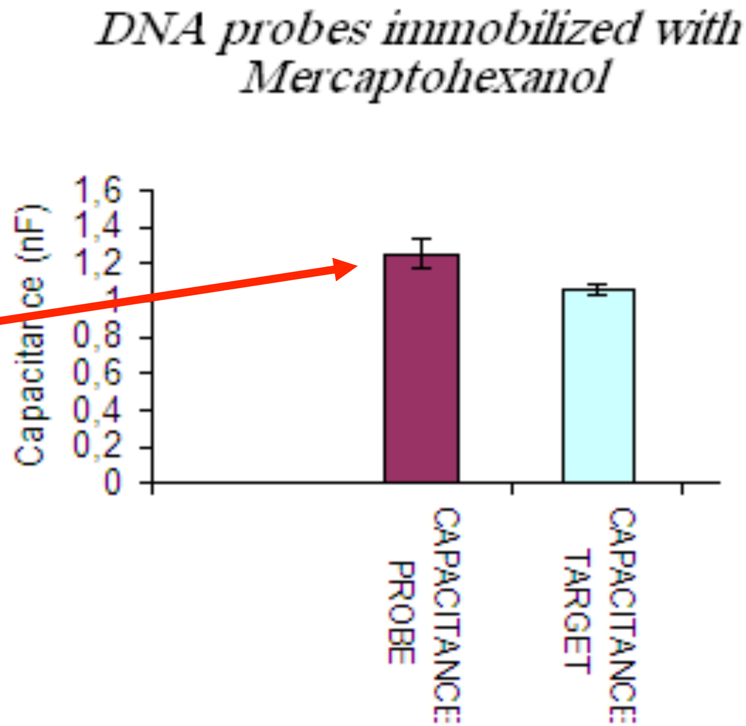


Mercapto-Hexanol

Mercapto-Hexanol is not enough as blocking agent

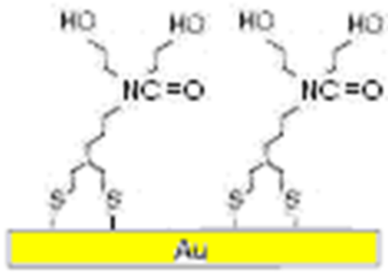
Mercapto-Hexanol partially block



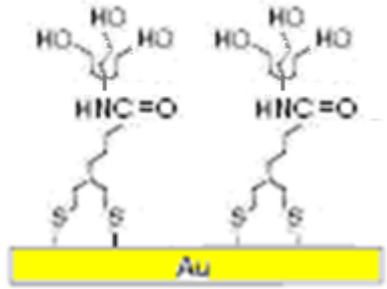


The presence of mercapto-hexanol partially prevent the solution ions in free contact with electrodes and results in a reduction of the standard deviations

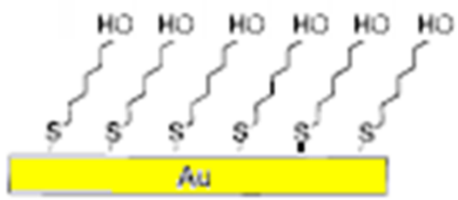
More Effective Blocking Agents



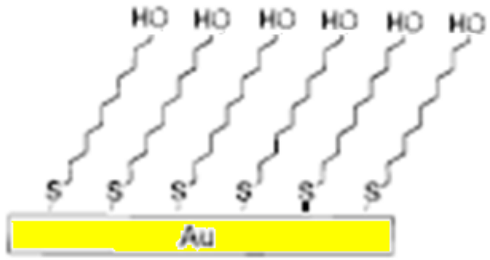
Lipa-DEA



Lipa-Tris



Mercapto-Hexanol

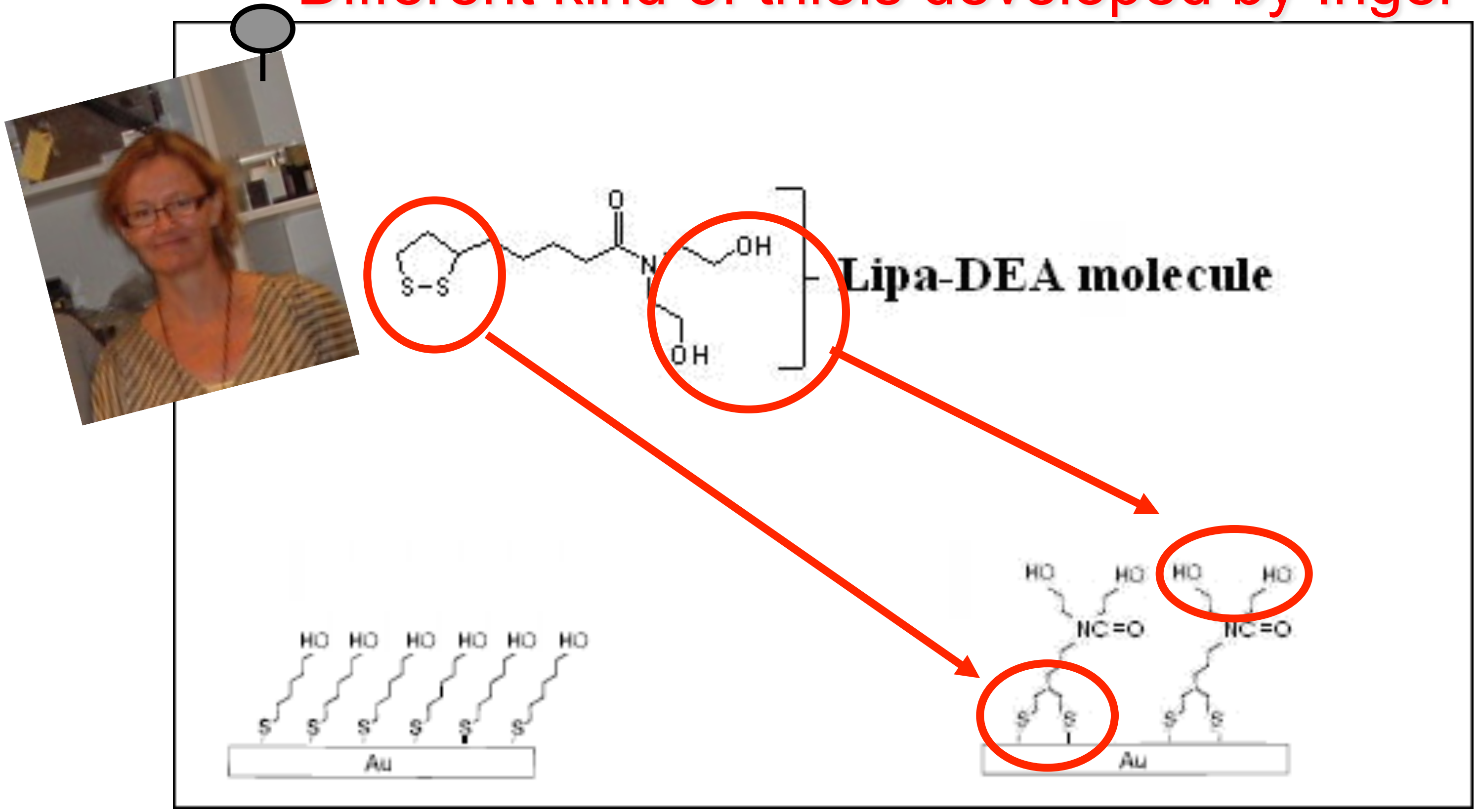


Mercapto-Undecanoic Acid

Increased stability by using Lipa-DEA as blocking agent

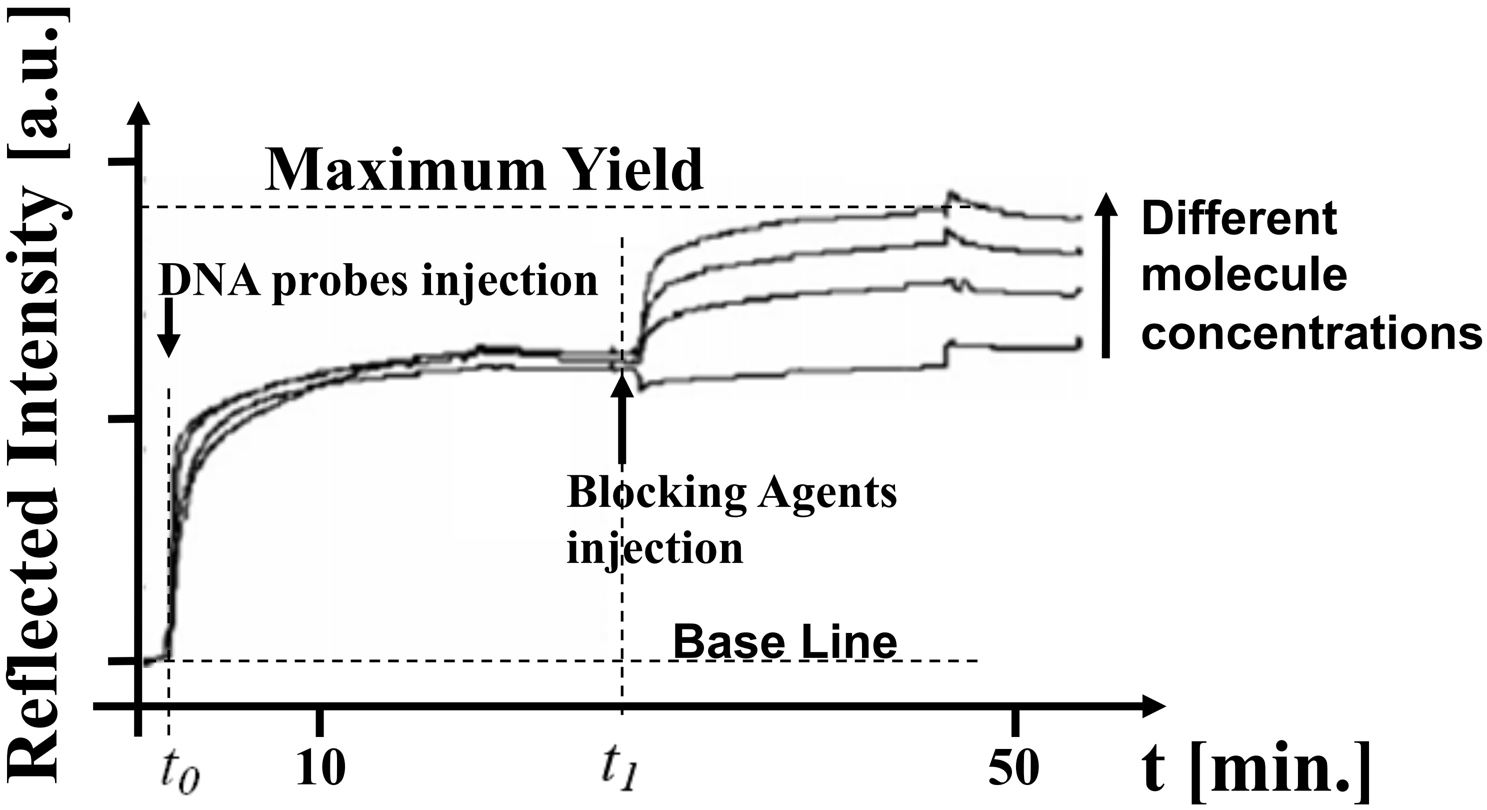
Lipa-DEA blockers

Different kind of thiols developed by Inger Vikholm



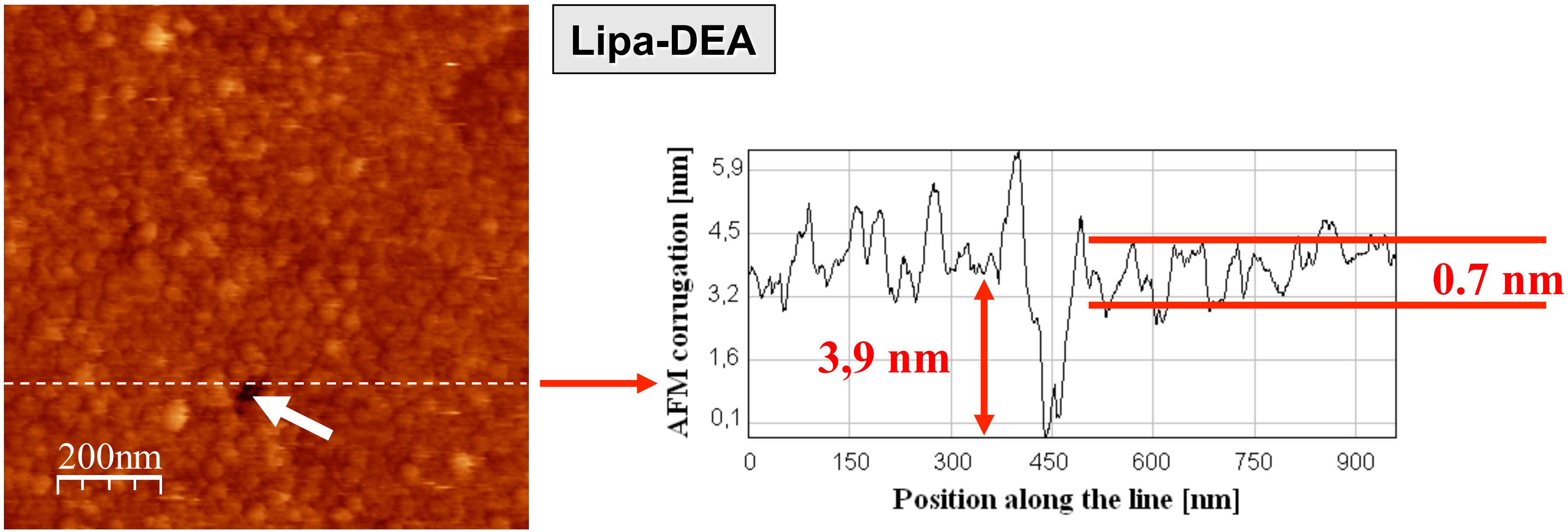
N,N-bis(2-hydroxyethyl)-α-lipoamide (Lipa-DEA) may be used as more efficient blocking agents

SPR on successive deposition of Blocking Agents



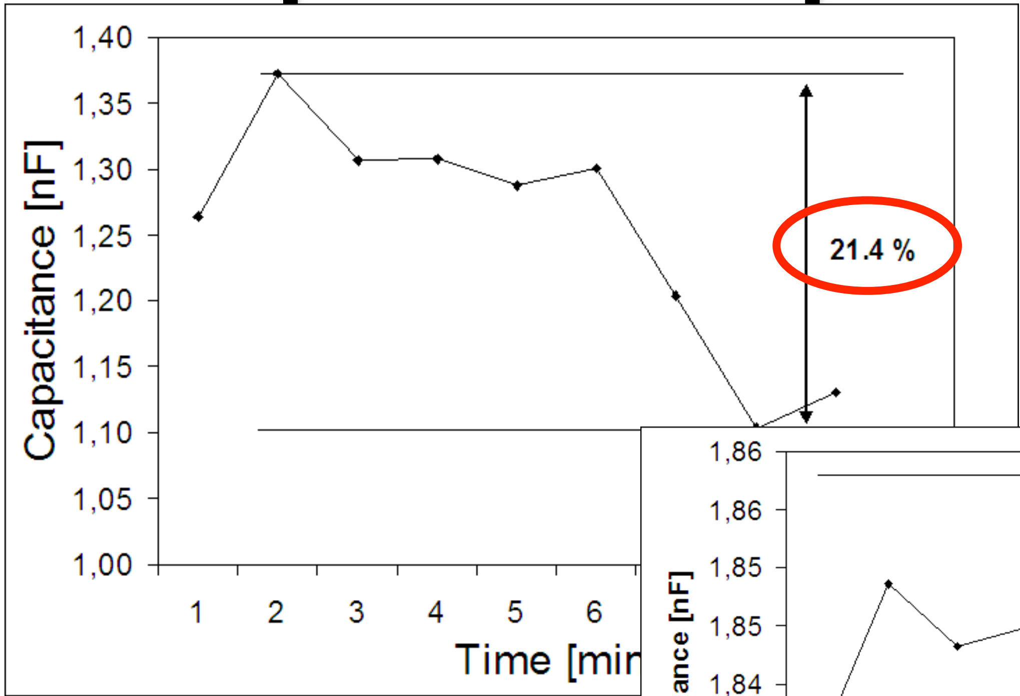
I. Vikholm-Lundin et al. / Biosensors and Bioelectronics 22 (2007) 1323–1329

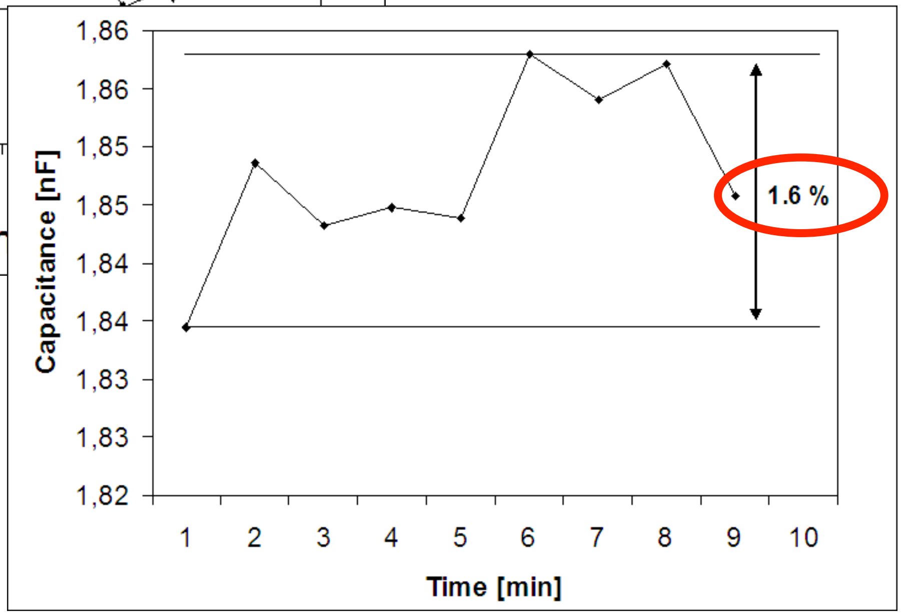
Nano-scale Apertures

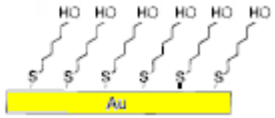


Monolayers of ssDNA with blocking agents still present deep groves crossing the film

Improved Capacitance Stability

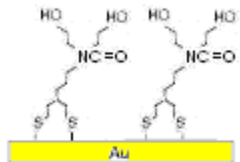






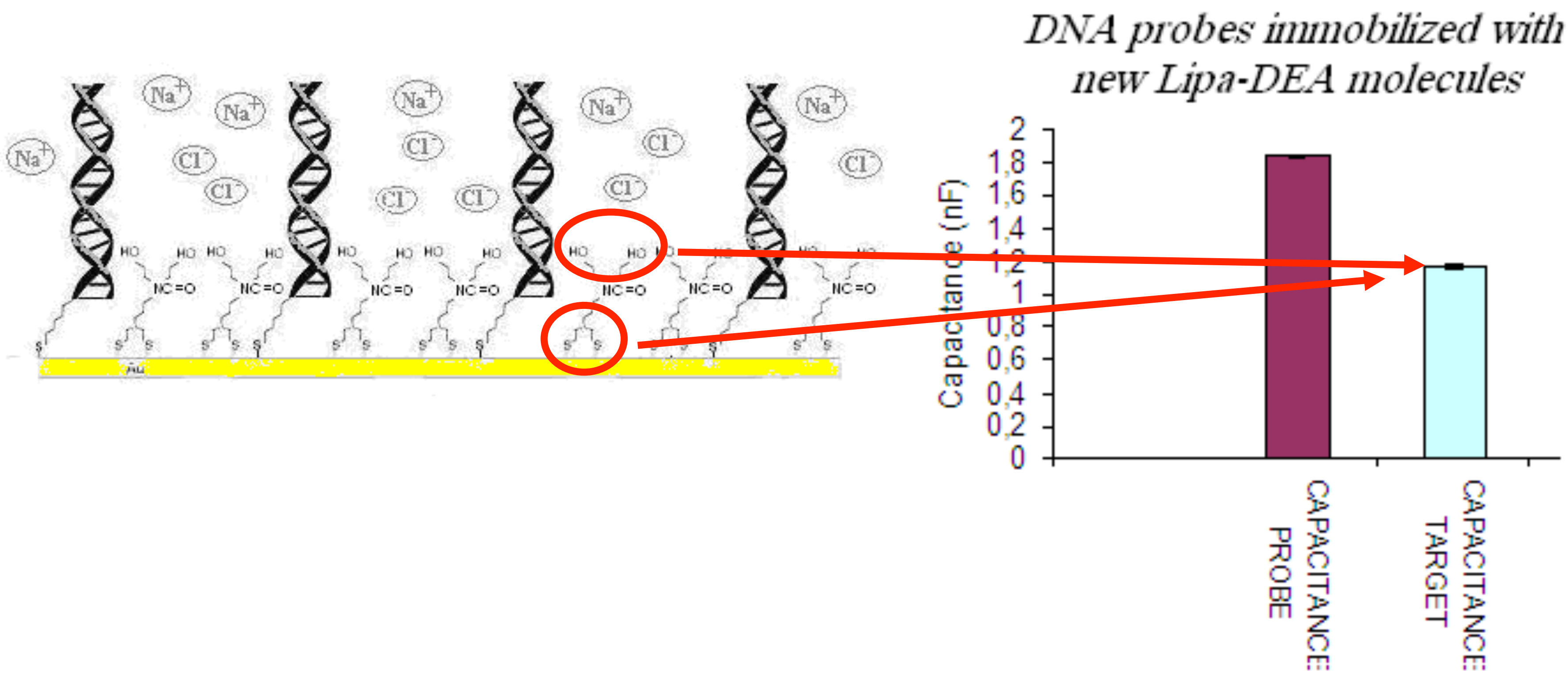
Mercapto-Hexanol

Lipa-DEA



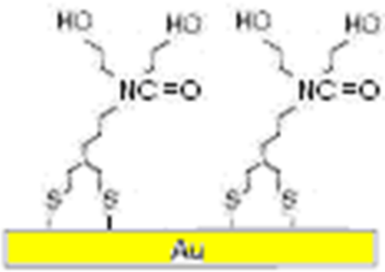
Increased stability by using Lipa-DEA as blocking agent

Lipa-DEA further improves

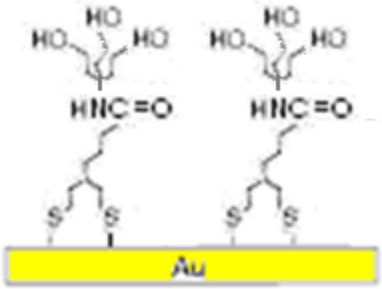


The presence of Lipa-DEA further prevent the solution ions in free contact with electrodes and results in a strong reduction of the standard deviations

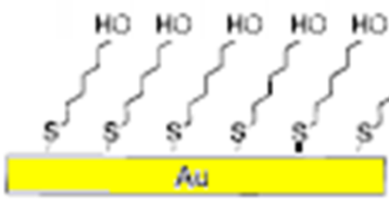
Precursors Monolayers



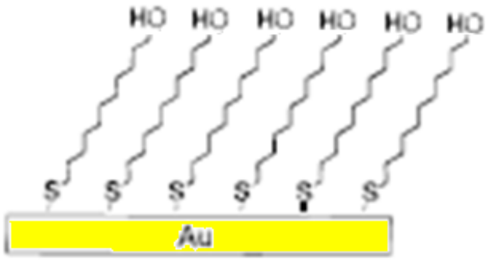
Lipa-DEA



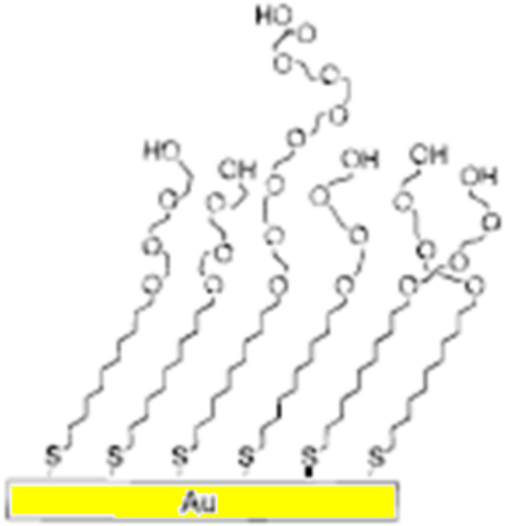
Lipa-Tris



Mercapto-Hexanol



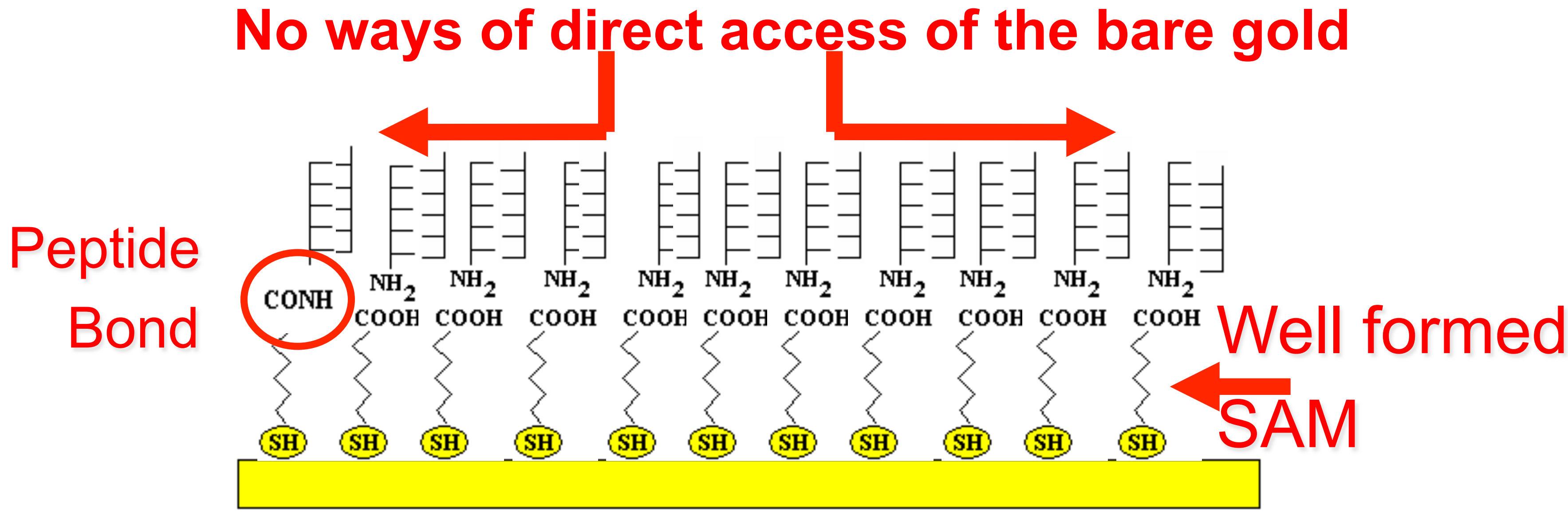
Mercapto-Undecanoic Acid



Ethylene-Glycol Thiols

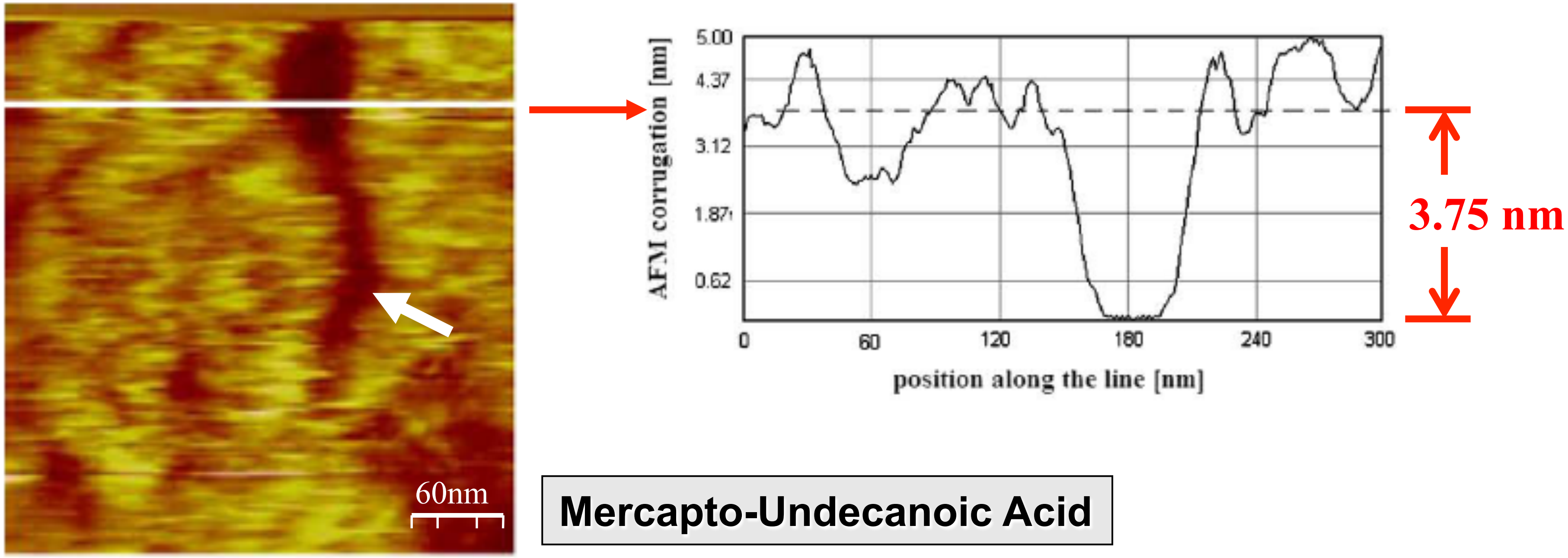
Increased stability by introducing precursors monolayers with Ethylene-Glycol function

Film precursors below probes



Highly packed thiols monolayer may be used to improve the DNA detection capability

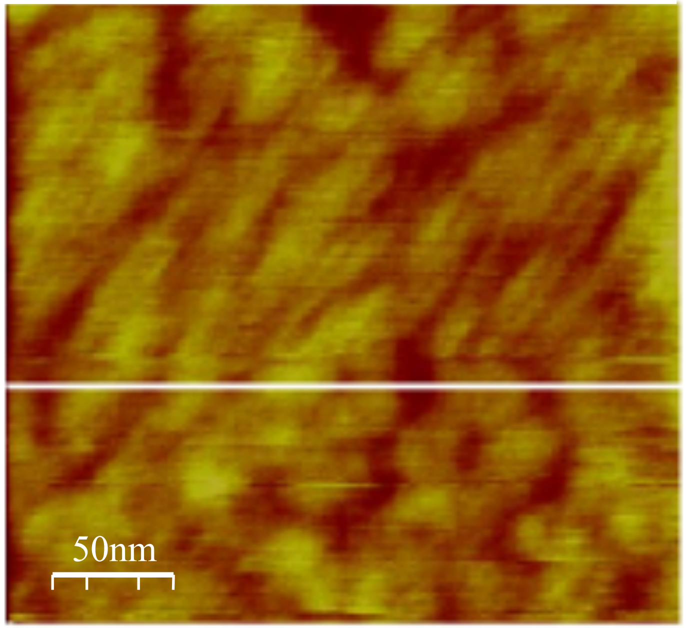
Nano-scale Apertures



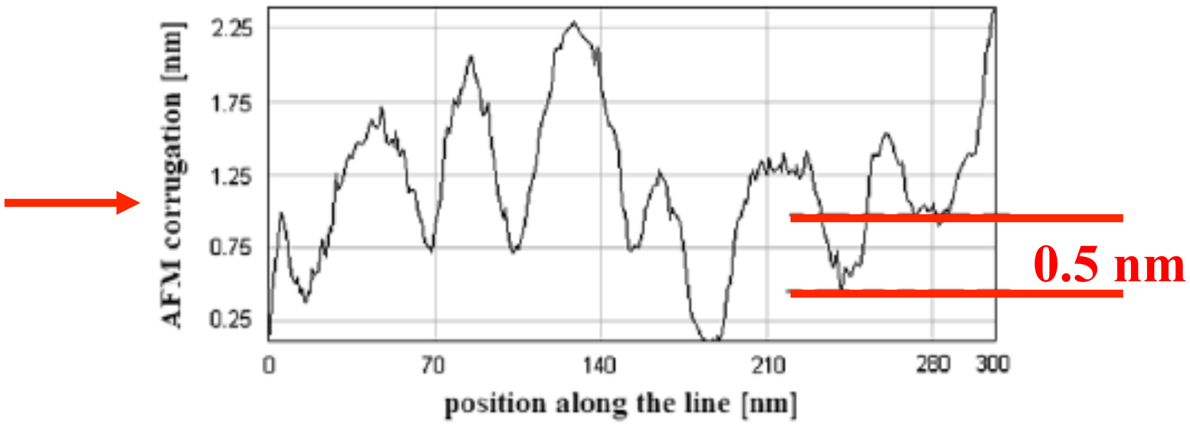
Mercapto-Undecanoic Acid

Monolayers of alkanethiols without ethylene-glycol chains still do present deep groves crossing the film

Absence of Nano-scale Apertures

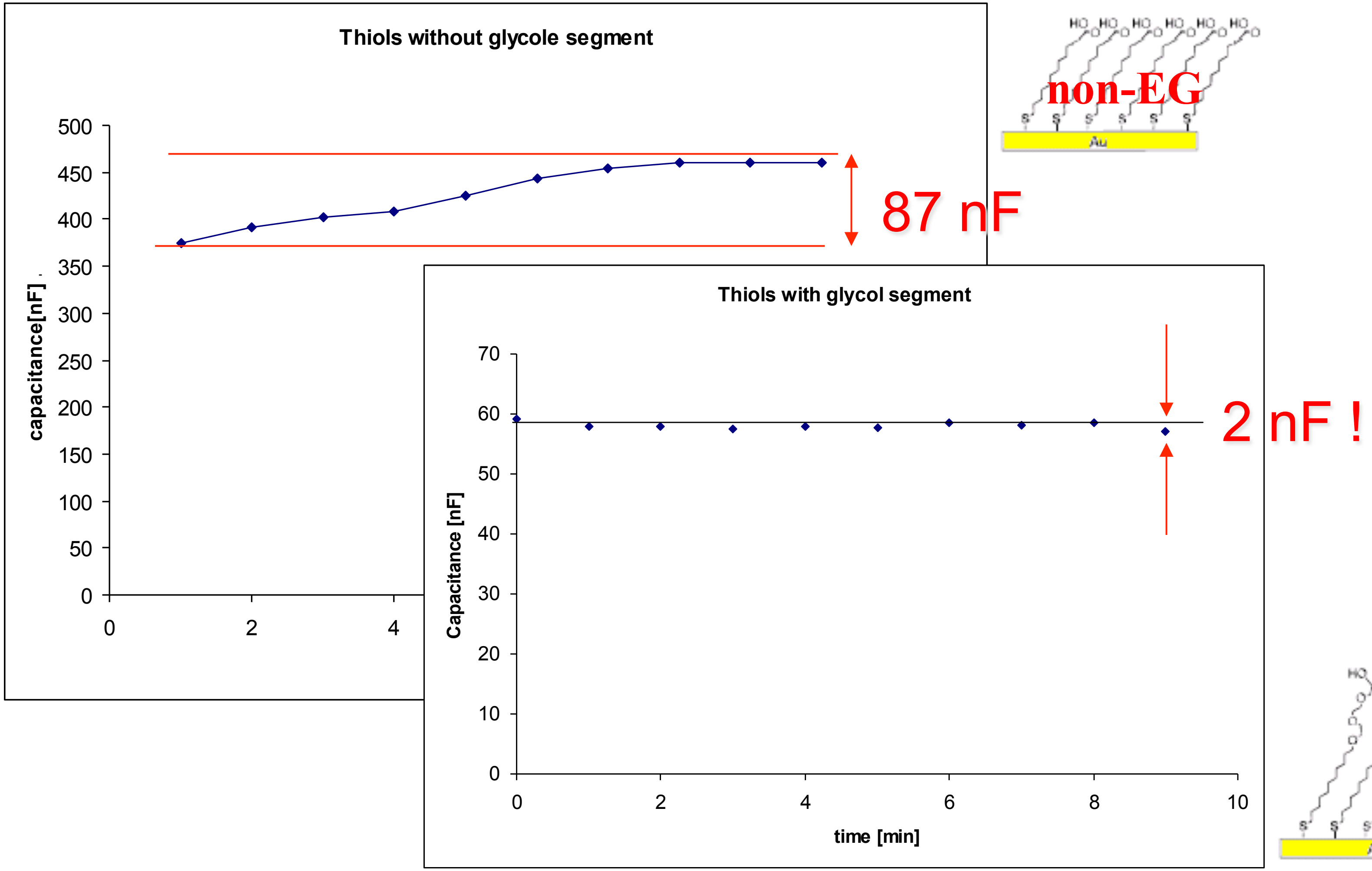


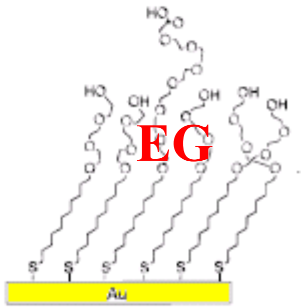
Ethylene-Glycol Film



Monolayers of alkanethiols with ethylene-glycol chains do not present deep groves crossing the film

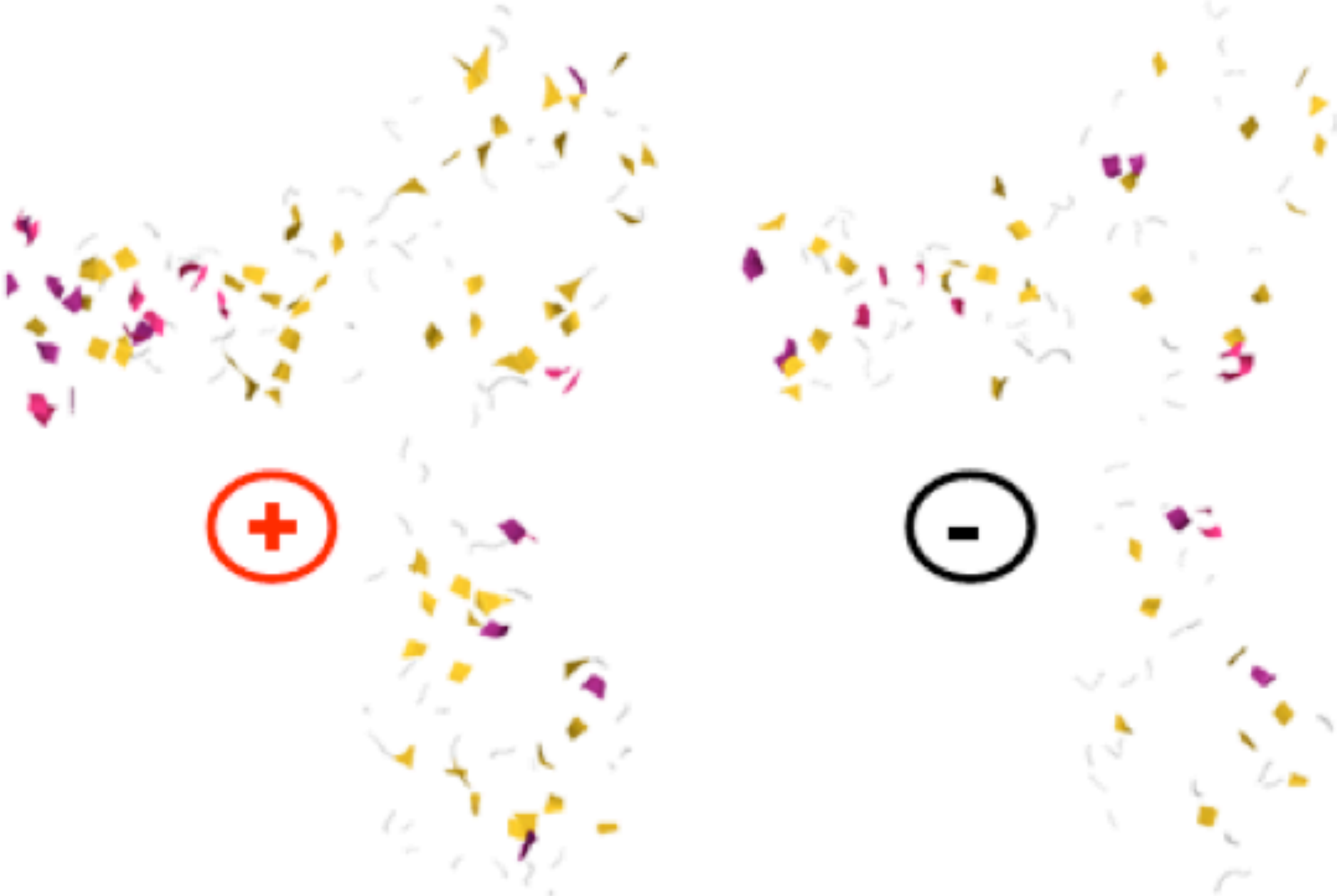
Improved Capacitance Stability





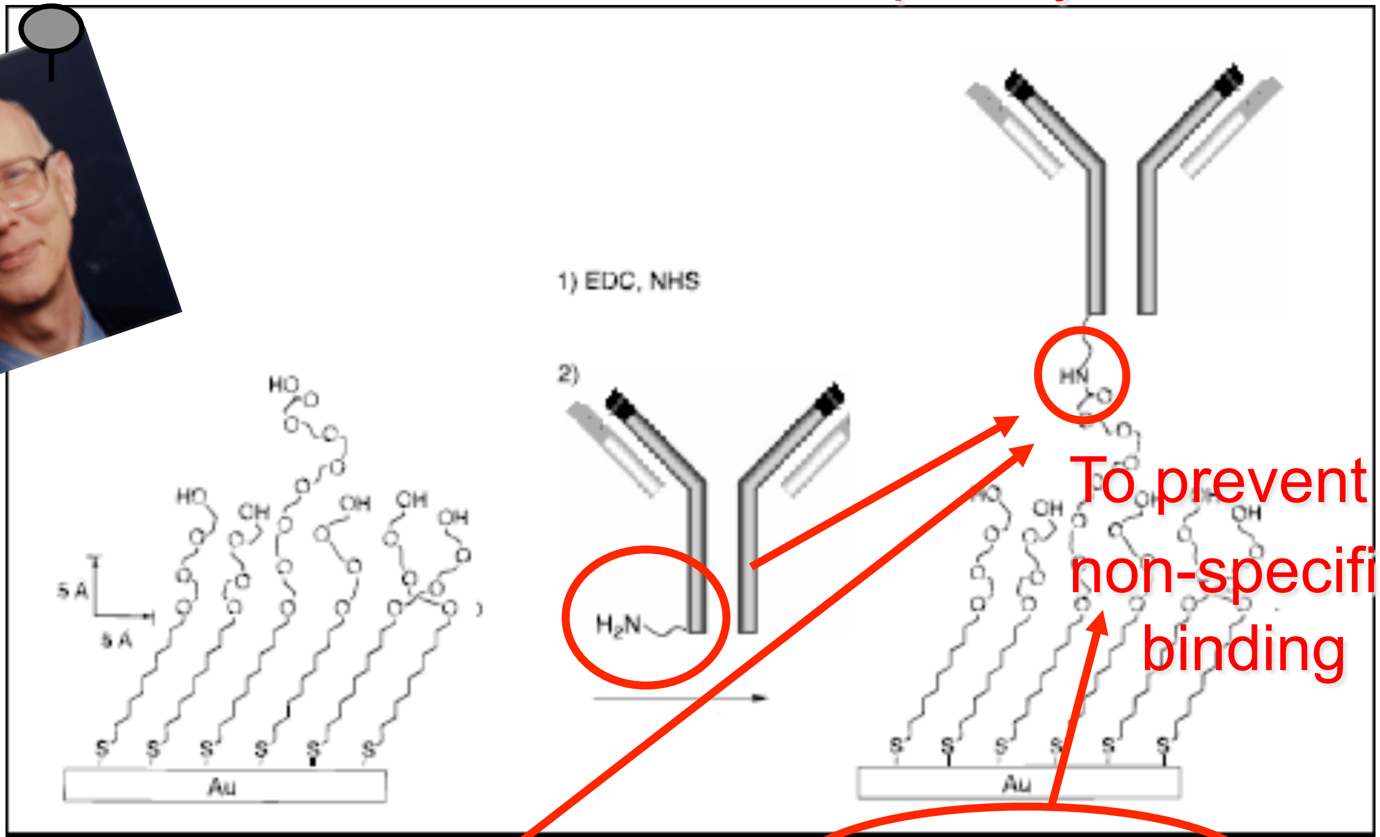
Increased stability by using Ethylene-Glycol thiols

Charges on an Antibody



Ethylene-Glycol Blockers

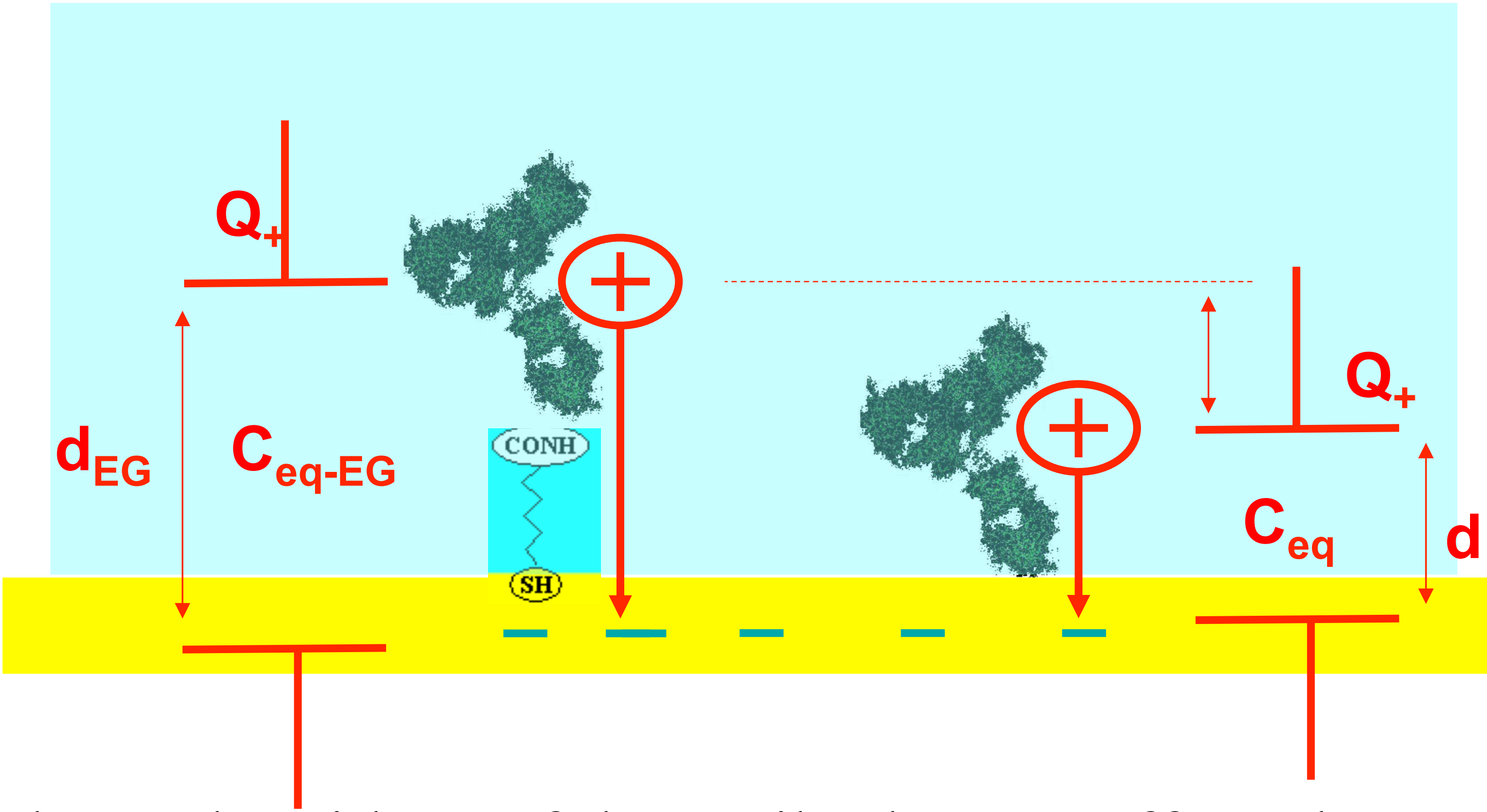
Different kind of thiols developed by G.M.Whitesides



To prevent non-specific binding

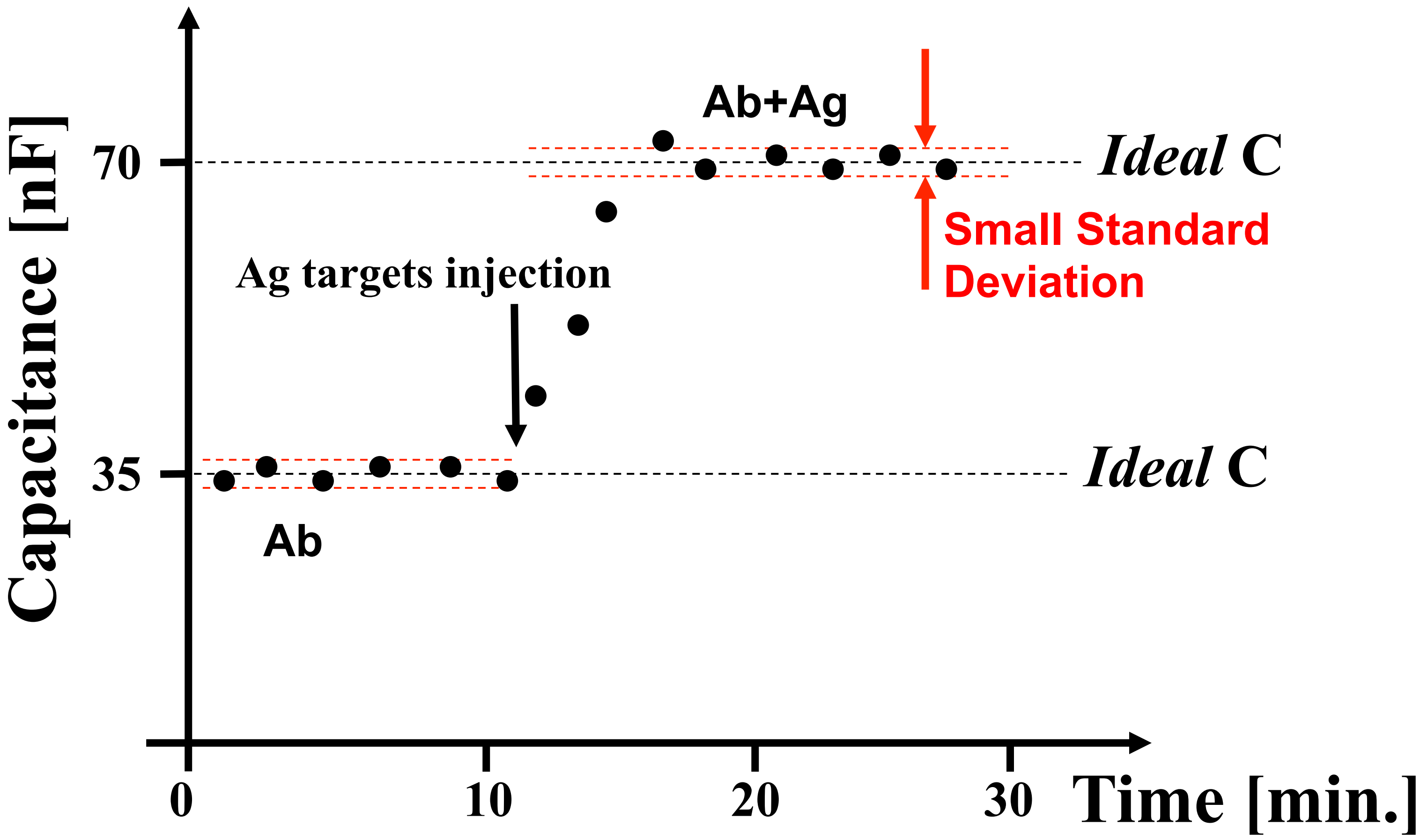
Covalently linked by using Ethylene-Glycol carboxyl terminated alkyl Thiols

Capacitive detection

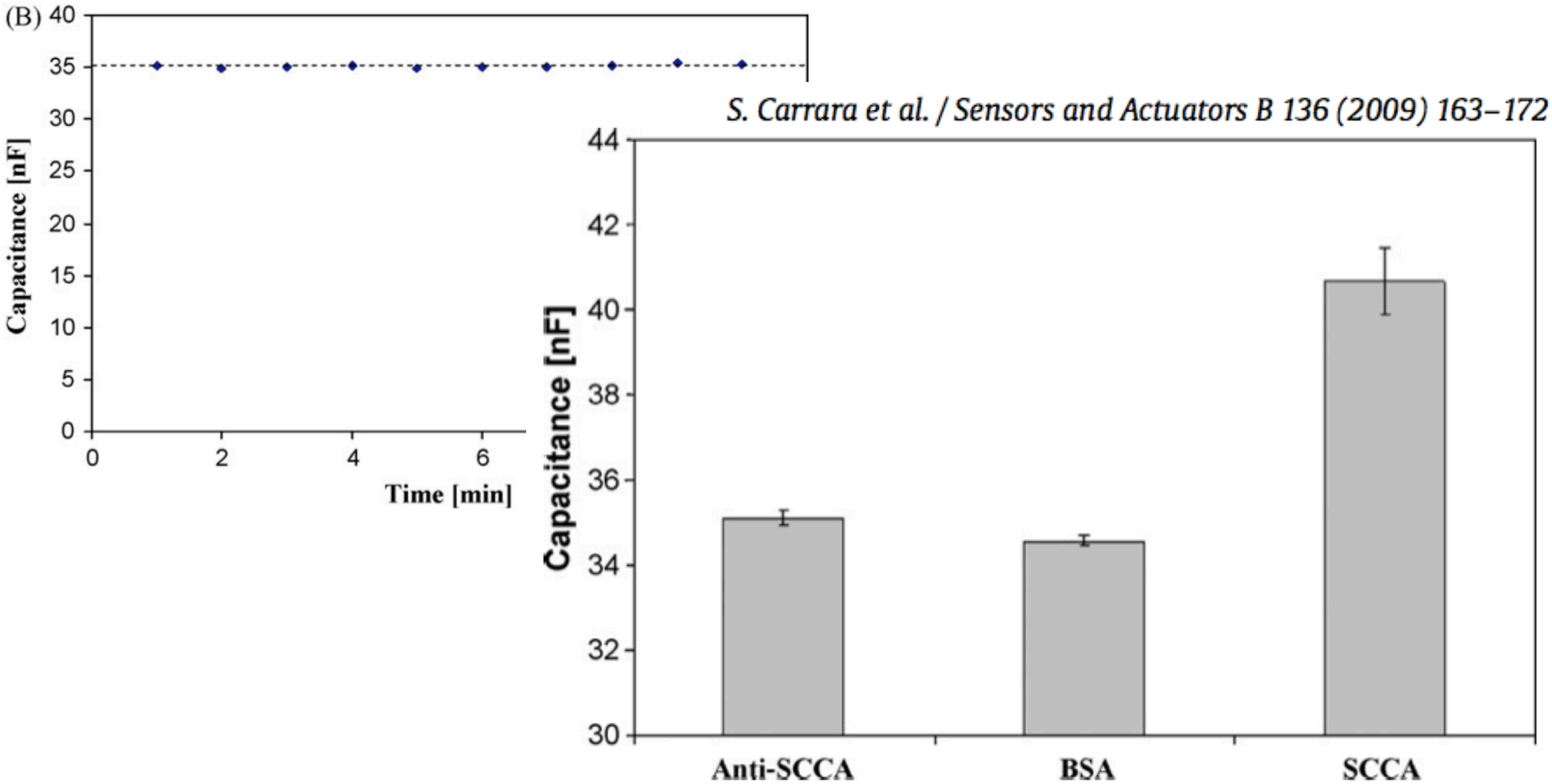


Charged residues of the antibody may affect charge carriers in the electrode

Reduced scattered-data



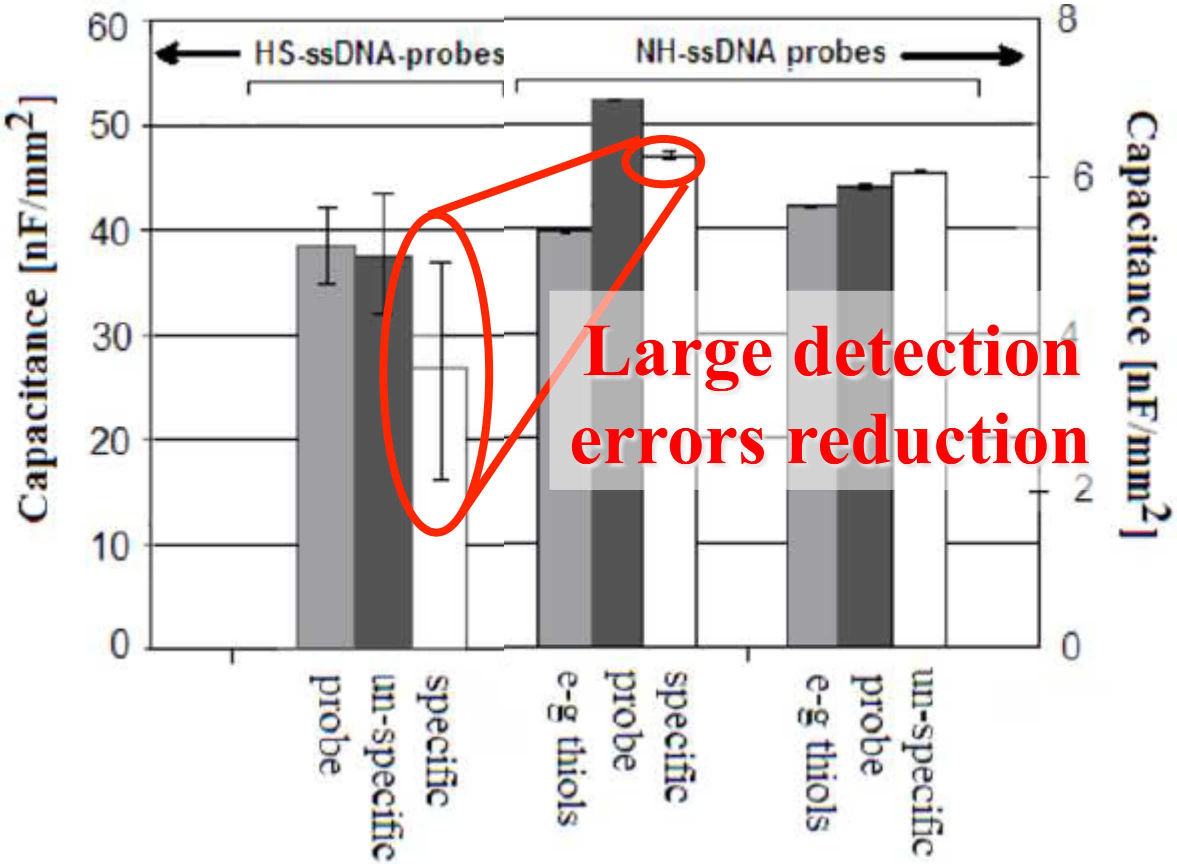
Cancer Marker Capacitance Detection



Highly reproducible Capacitance detection of the cancer-marker protein SCCA by immobilizing the antibodies onto EG-Thiols precursors

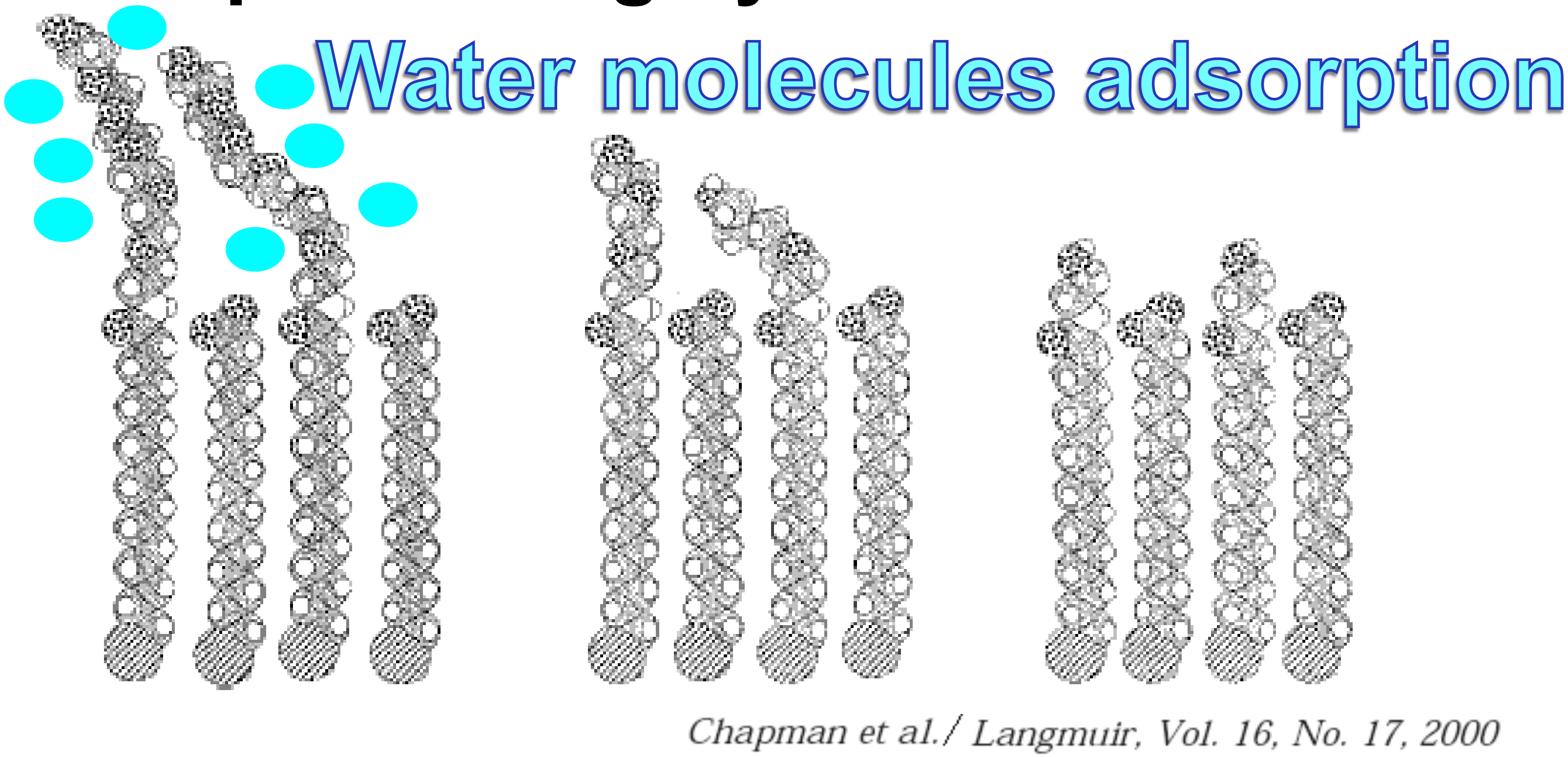
Capacitance detection of DNA

S. Carrara et al. / Biosensors and Bioelectronics 24 (2009) 3425–3429



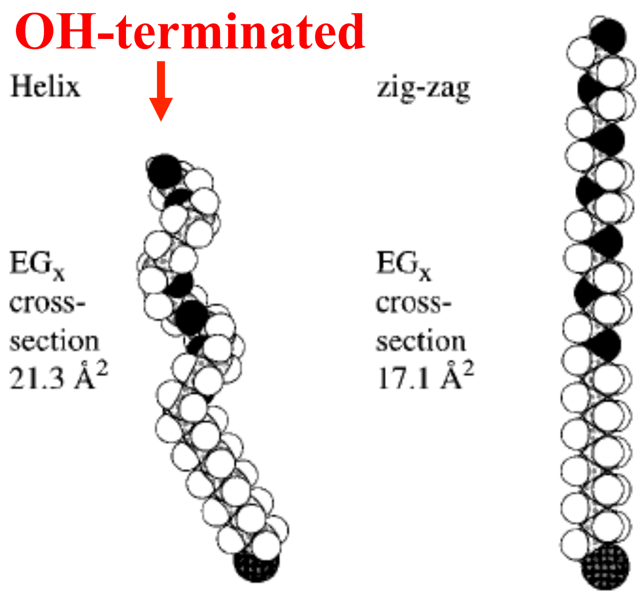
Highly –reproducible DNA detection based on ss-DNA-SH terminated directly immobilized onto gold and ss-DNA-NH2 terminated immobilized onto EG-Thiols

Why it works so well to close nano-apertures? Space filling by EG thiols



Space filling molecular model illustration of EG-thiols film presenting a 1:1 mixture of -CON(CH2CH2O)*n*H (*n*) 1, 3, or 6) and O2H/CO2- groups.

Water Adsorption in thin films

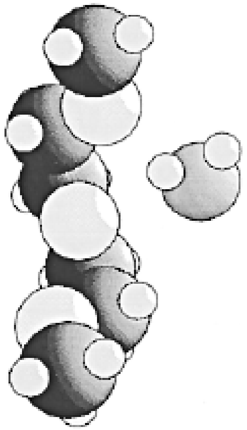


Harder et al. / *J. Phys. Chem. B, Vol. 102, No. 2, 1998*

Infrared spectroscopy demonstrates that ethylene-glycol chains in the methoxy-terminated monolayer are mainly in great disorder, while the hydroxyl-terminated monolayer chains are in a crystalline helical phase (Harder et al 1998)

Molecular conformations driven by terminal groups in EG-thiols

Water Adsorption in thin films



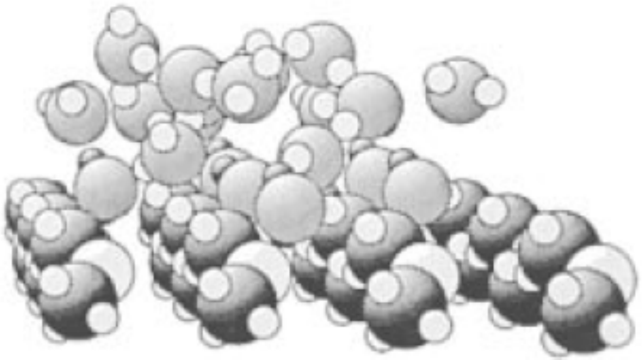
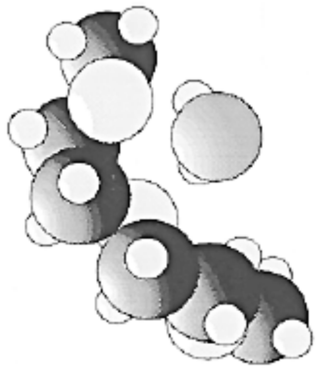


Figure 7. 20 water molecules form three adsorption layers on a hexagonal cluster of a helical OEG film with lattice constant 5 Å consisting of 3 × 4 helical OEG strands.

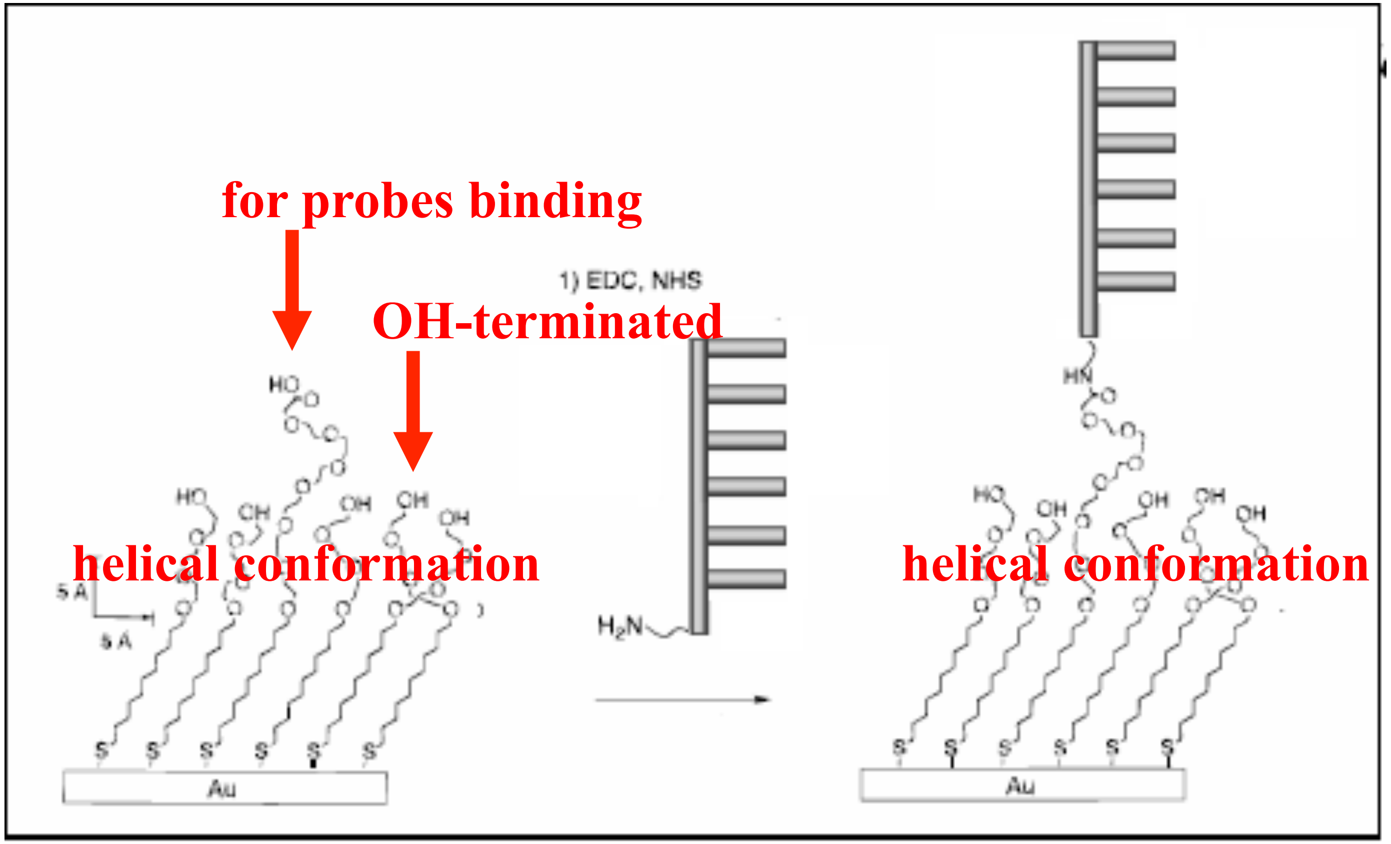


Wang et al. / *J. Phys. Chem. B, Vol. 101, No. 47, 1997*

We conclude the following: OEG in its helical conformation, but not in its "all-trans" form, is amphiphilic with respect to water. The stability of the water interface with helical OEG prevents proteins and other molecules from adsorbing irreversibly on the OEG surface.

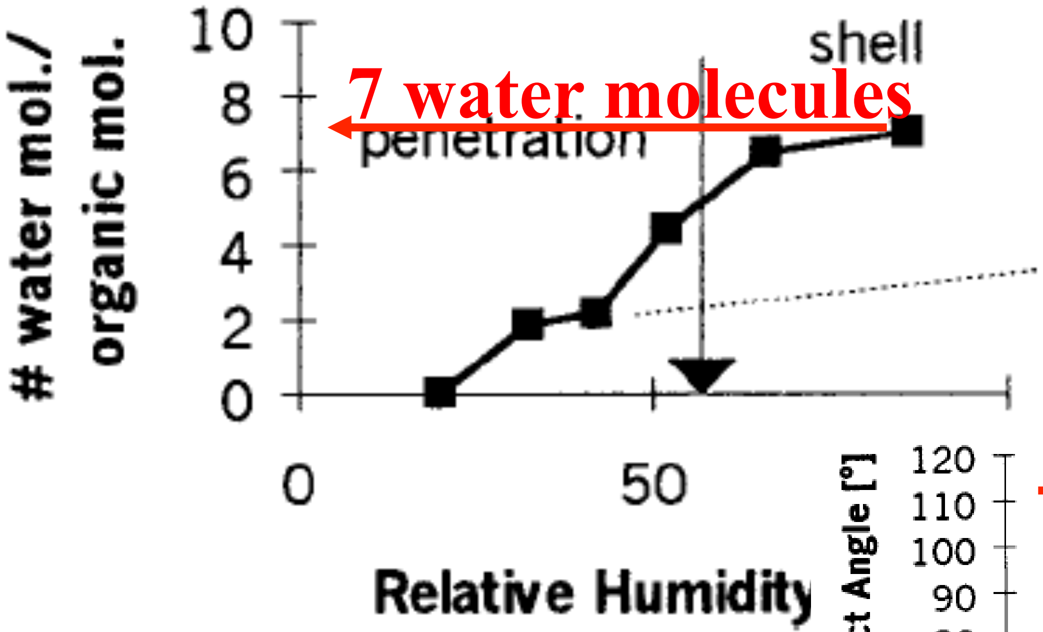
Water adsorption and Molecular conformation in EG-thiols Film

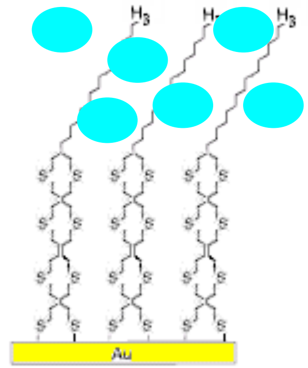
Water Adsorption in thin films

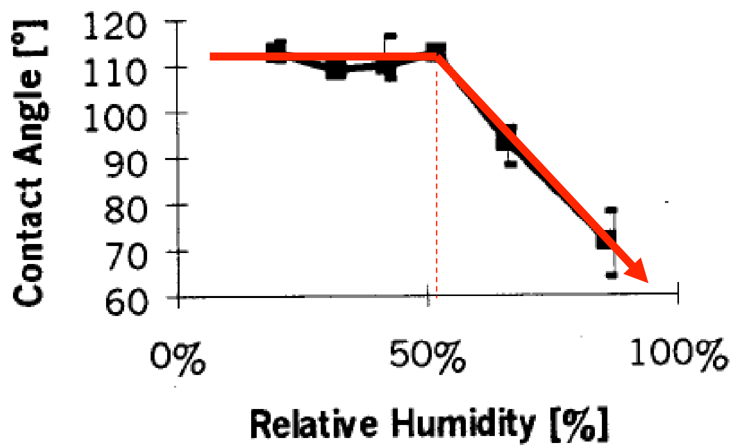


Covalently linked by using three-glycol carboxyl terminated alkyl Thiols

Water Adsorption in thin films



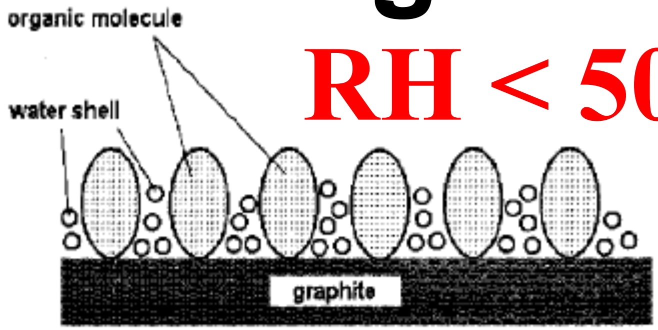




Film Water adsorption on alkyl thiol film chains

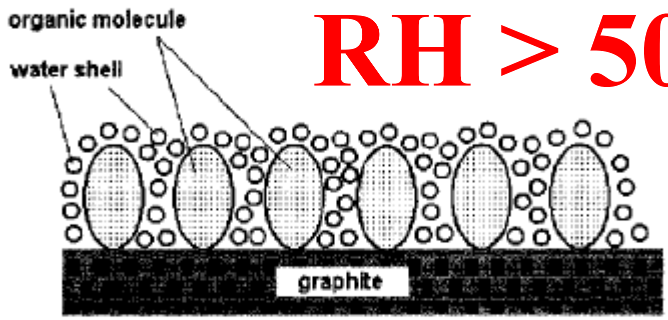
Water in Organic Films

RH < 50%



(A)

RH > 50%

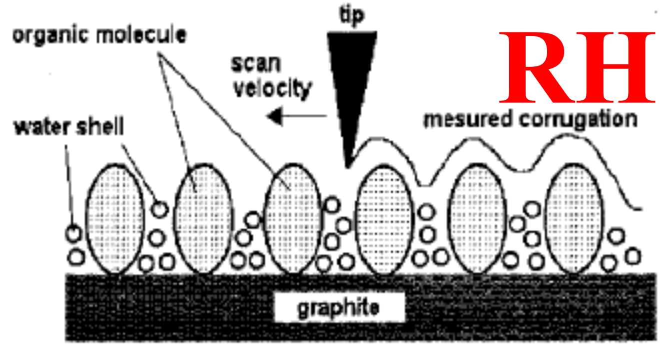


(B)

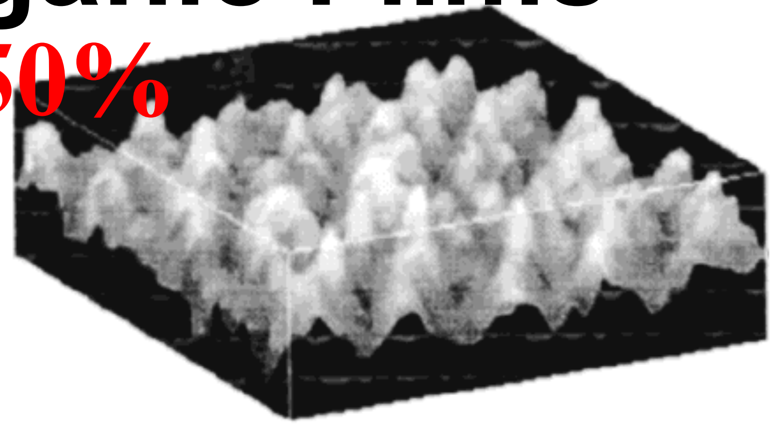
Water molecule are stored in the intra-molecular space in the thin film

Water in Organic Films

RH < 50%

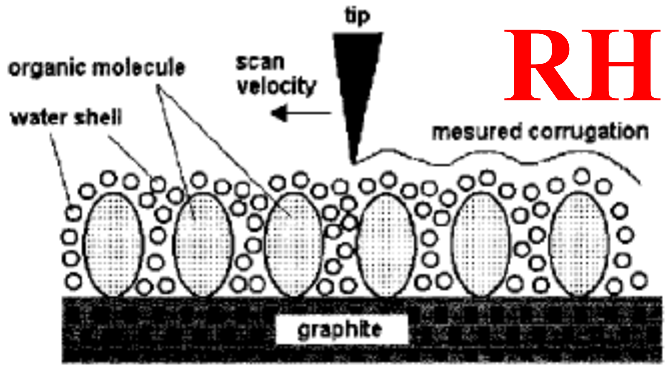


(A)

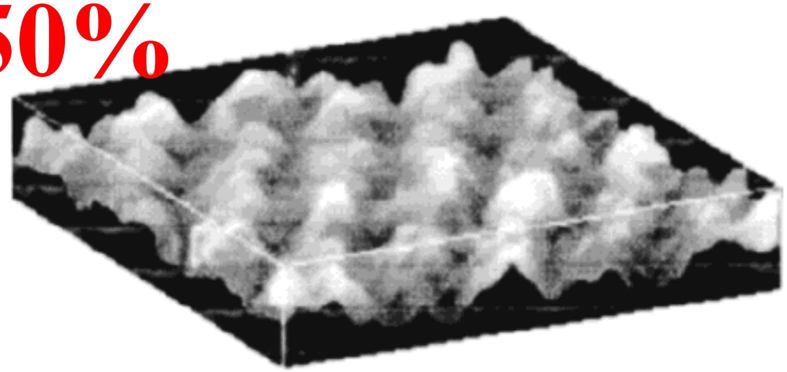


(A)

RH > 50%



(B)



(B)

STM imaging showed water molecule stored in the intra-molecular space in the thin film

Water Adsorption in thin films

Mass change	# of water molecules/EG-molecules
0,14 ng/mm^2	16

The estimated mass changing correspond to 16 water molecules each ethylene-glycol alkanethiol. Up to 7 water molecules for each organic molecules may be fund in dried alkyl chains film (Carrara et al. 2000). The other water molecules are strongly coordinated by ethylene-glycol chains in our film

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QCM measurements on dried EG-thiols film conditioned with water buffer