ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

Electrical and Electronics Engineering

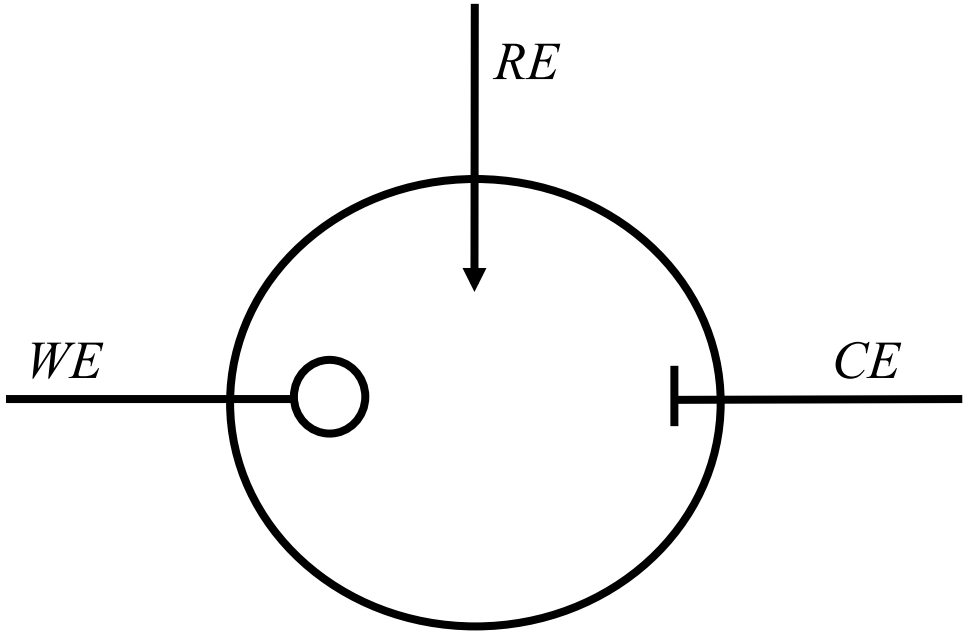
LSI
Integrated Systems Laboratory

EE-517

Bio-Nano-Chip Design

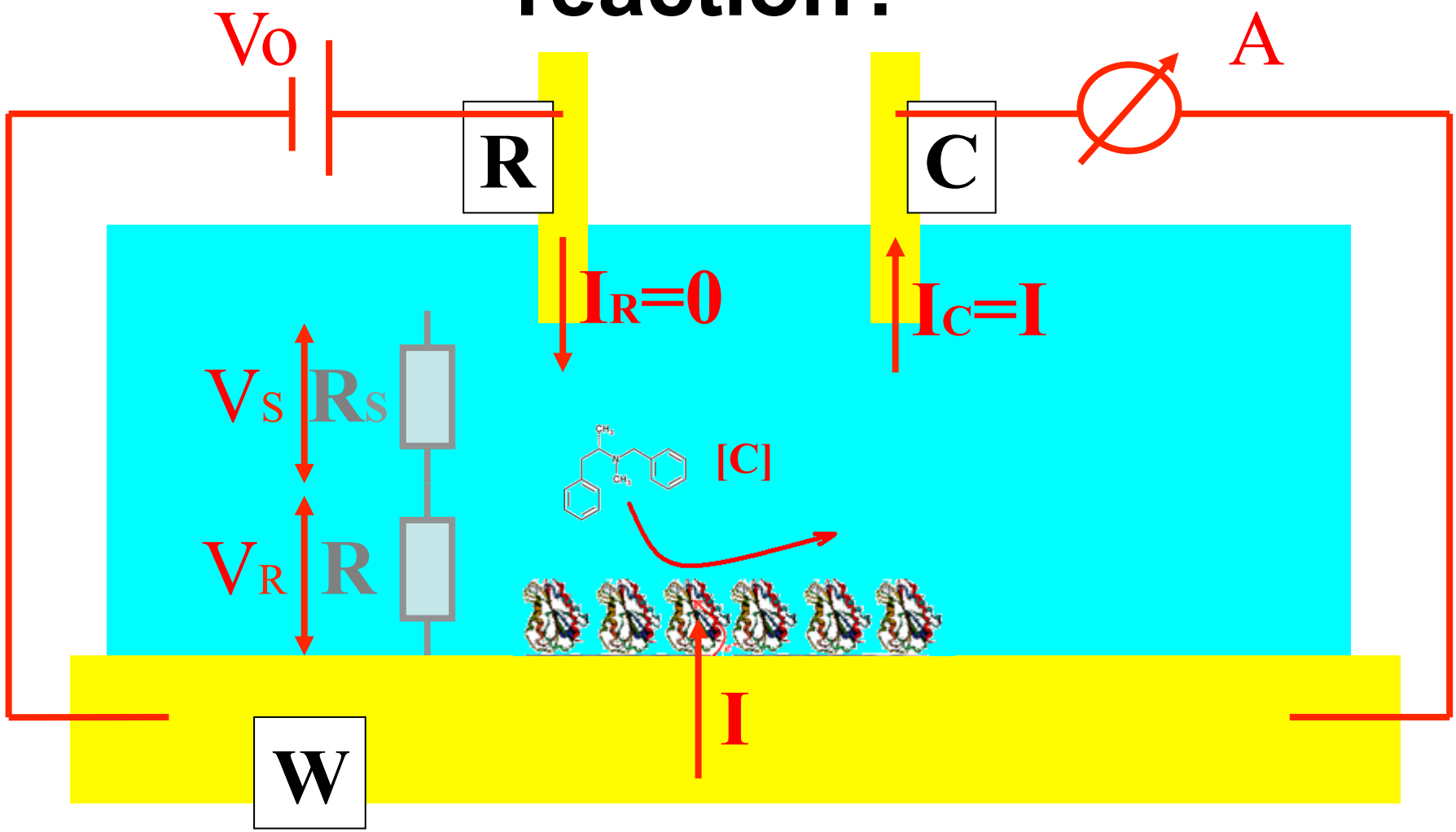
Glucometer on iPhone

The electrochemical Cell

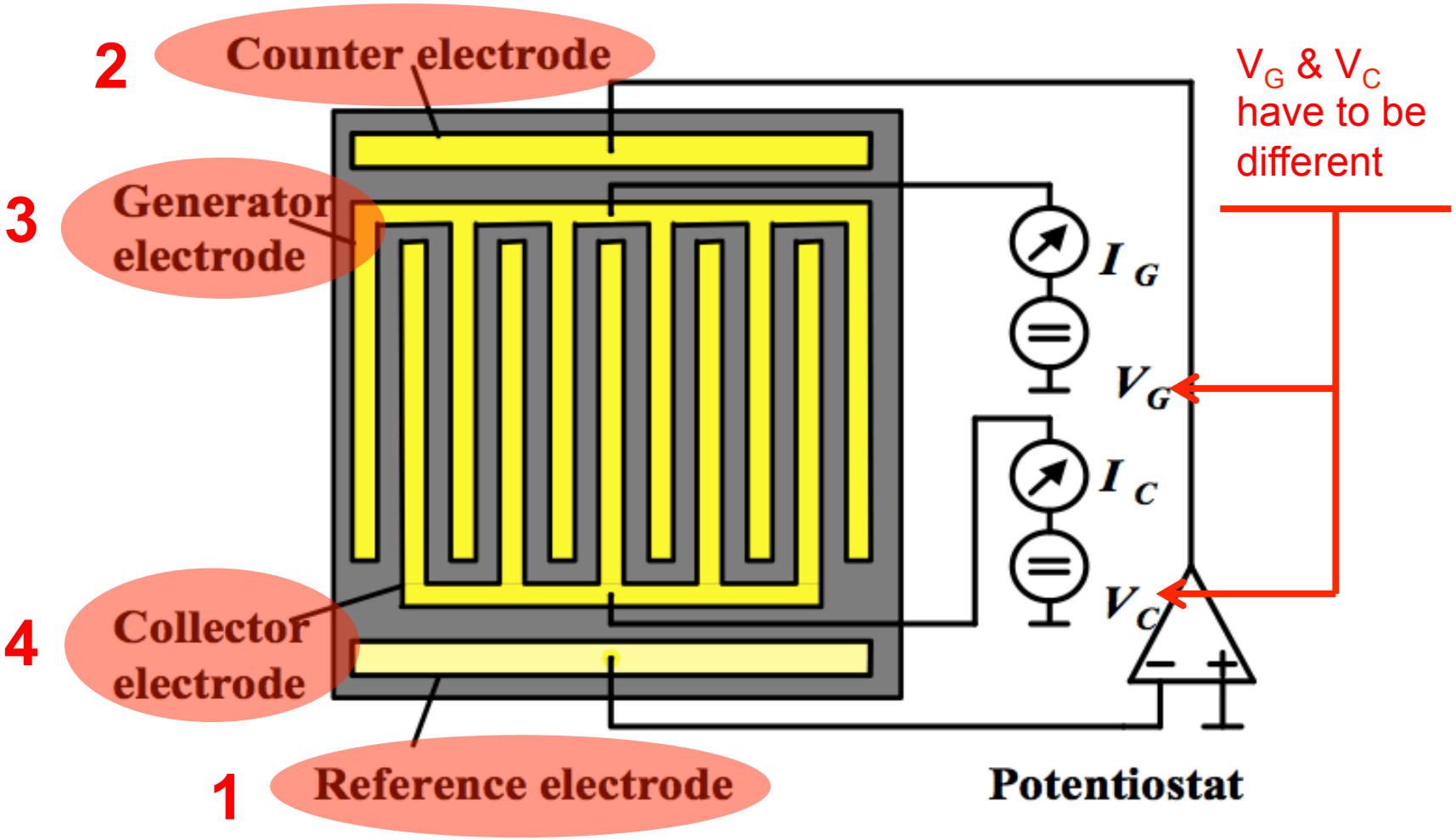


The typical electrochemical cell needs 3 electrodes: the working, the counter, and the reference

How to measure a redox reaction?



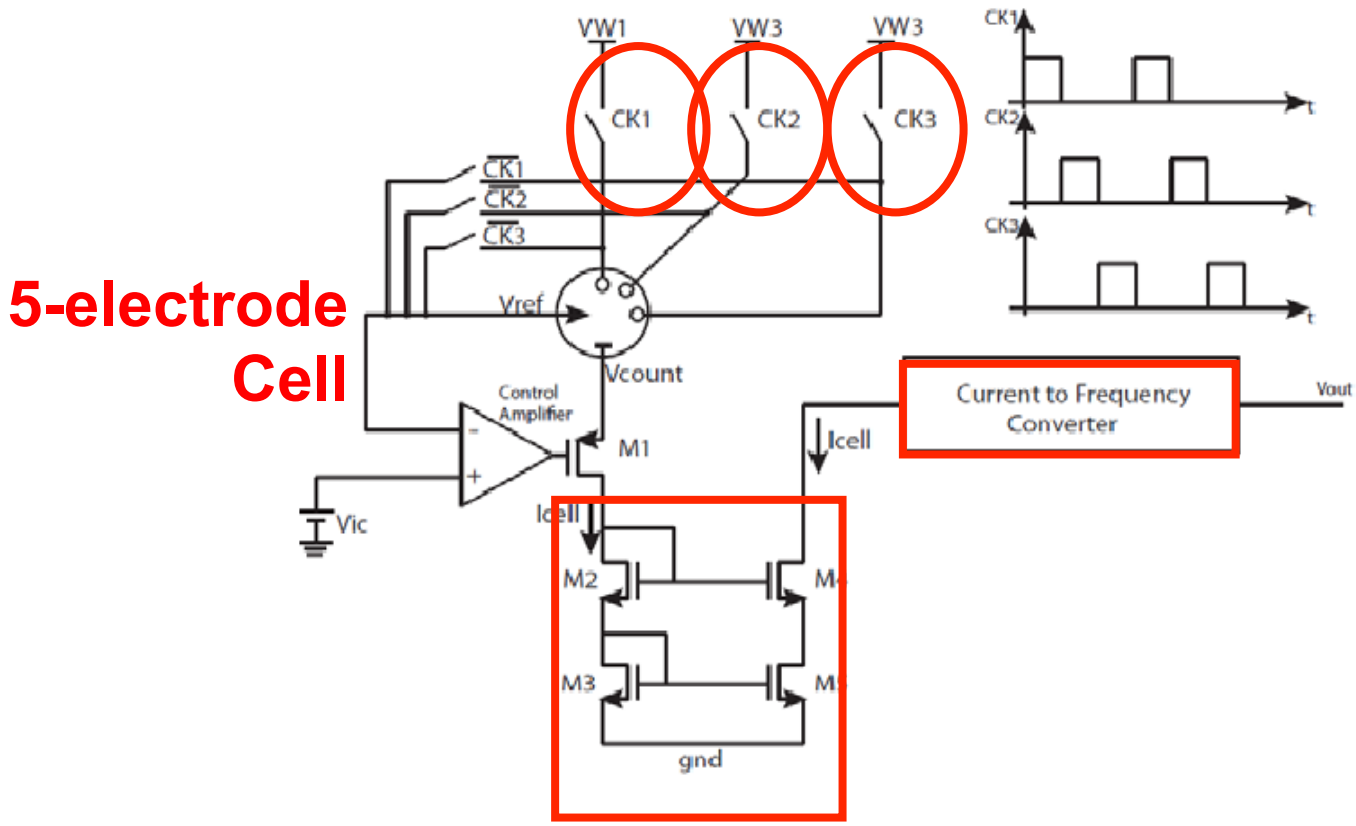
The 4e Electrochemical Cell



A 4-electrode Electrochemical Cell is here required

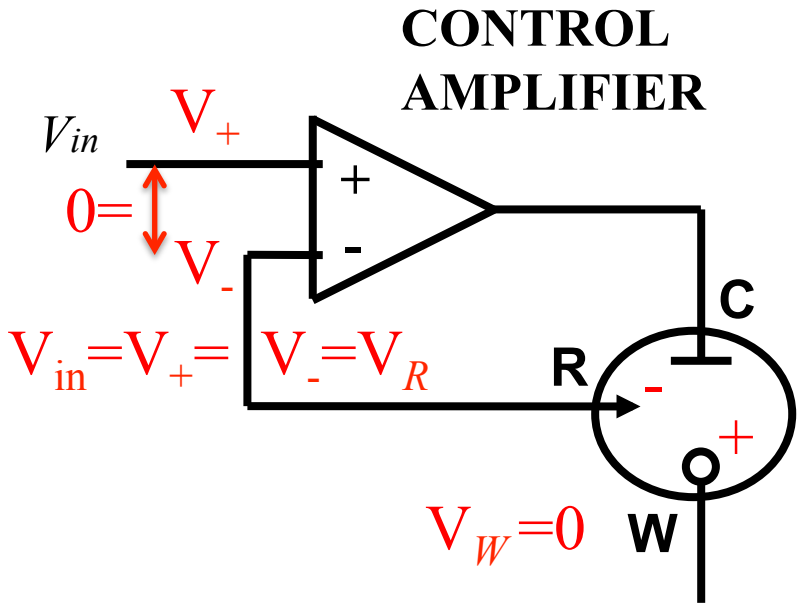
Multiplexing several workings

5-electrode Cell



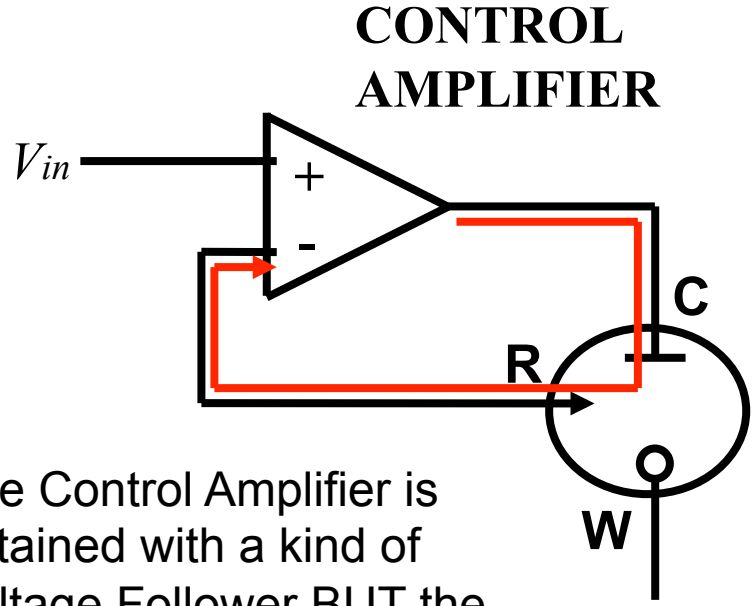
Different working electrodes are multiplexed to a common current-to-frequency converter

Control Amplifier @ RE



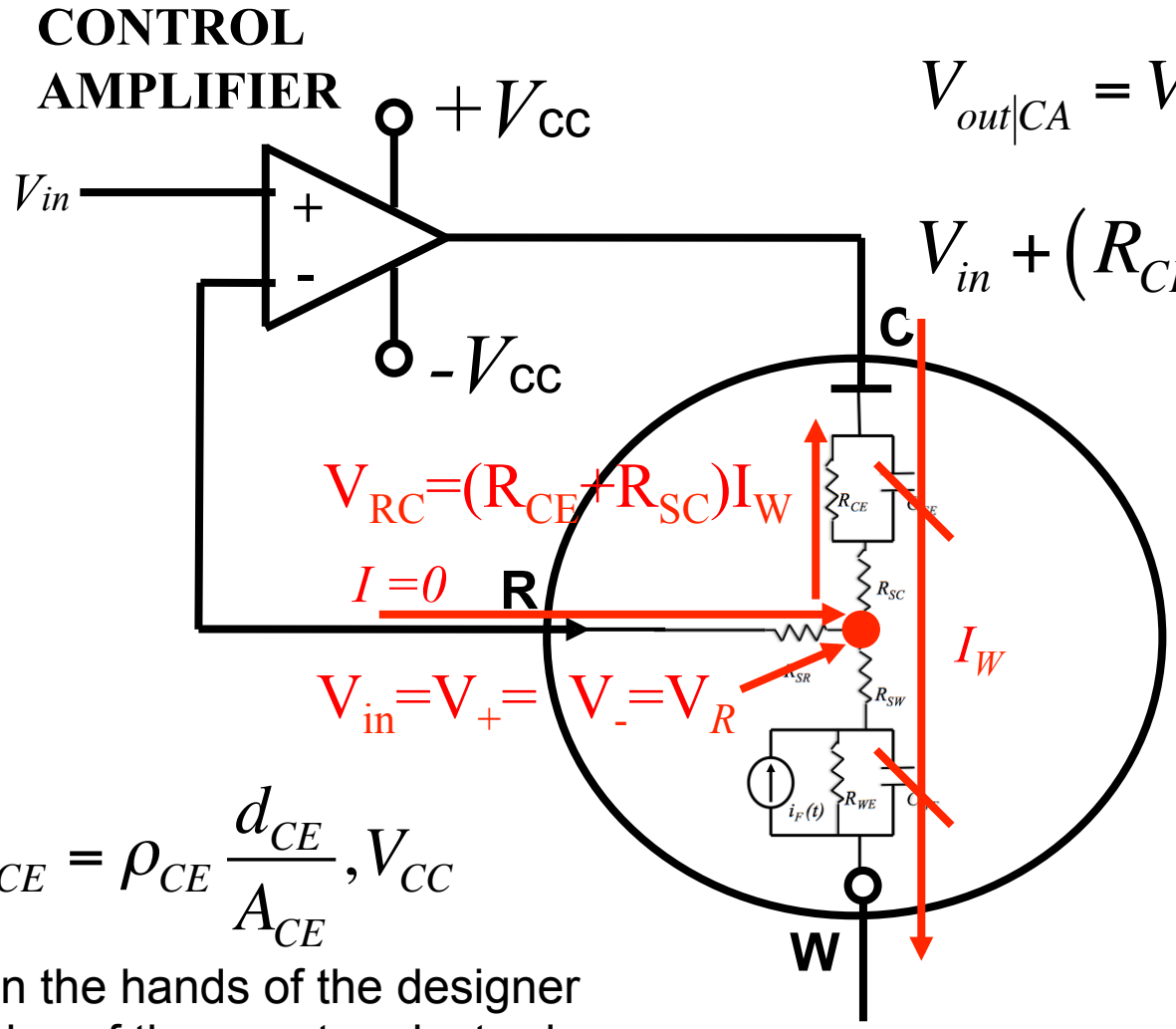
$$V_{in} = V_R = - V_{WR}$$

Risk of Saturation



1. The Control Amplifier is obtained with a kind of Voltage Follower BUT the Cell is inserted in its feedback loop
2. Thus, the Voltage Follower might saturate if the design (both Cell & Follower) are not co-designed properly

Risk of Saturation



$$V_{out|CA} = V_{in} + \left(R_{CE} + R_{SC}\right) I_W$$

$$V_{in} + \left(R_{CE} + R_{SC}\right) I_W > V_{CC}$$

The Control Amplifier is then in SATURATION!

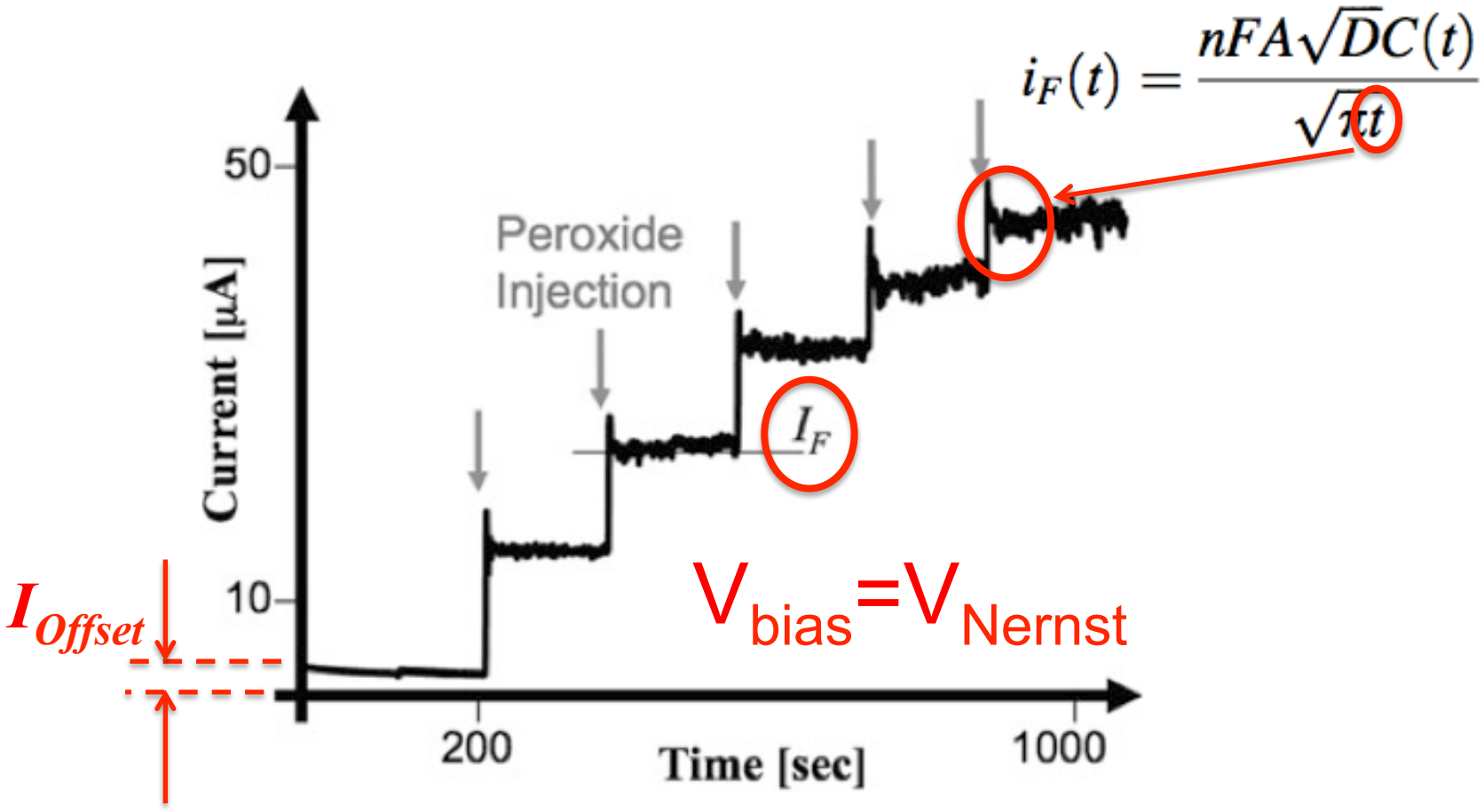
$$V_{in}, R_{SC}, I_W$$

Typically depend on the application (kind of redox we are monitoring)

$$R_{CE} = \rho_{CE} \frac{d_{CE}}{A_{CE}}, V_{CC}$$

Are on the hands of the designer (the size of the counter electrode and/or the circuit powering)

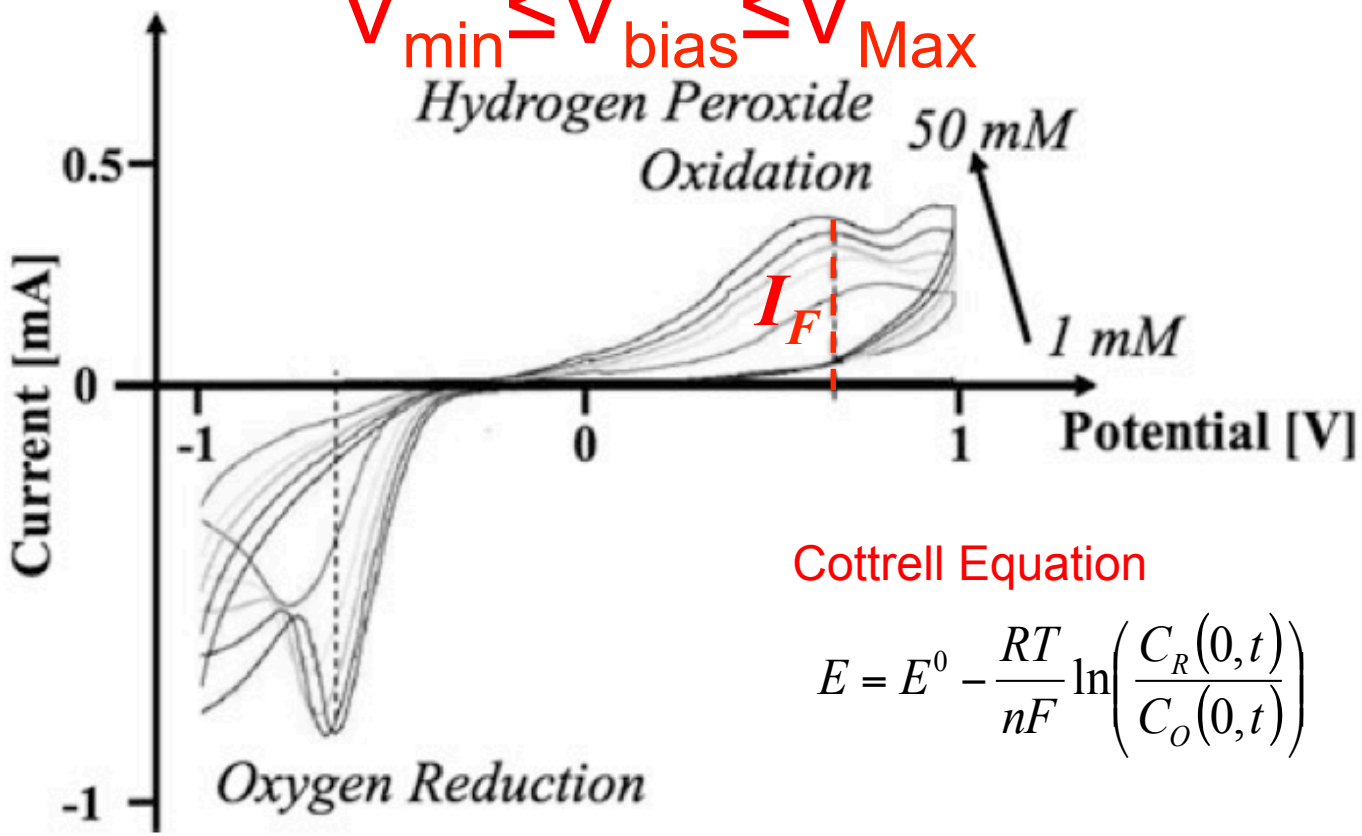
Faradaic Current @ Fixed Bias



Typical curve in chronoamperometry

Faradaic Current in Voltage Scan

$V_{min} \leq V_{bias} \leq V_{Max}$

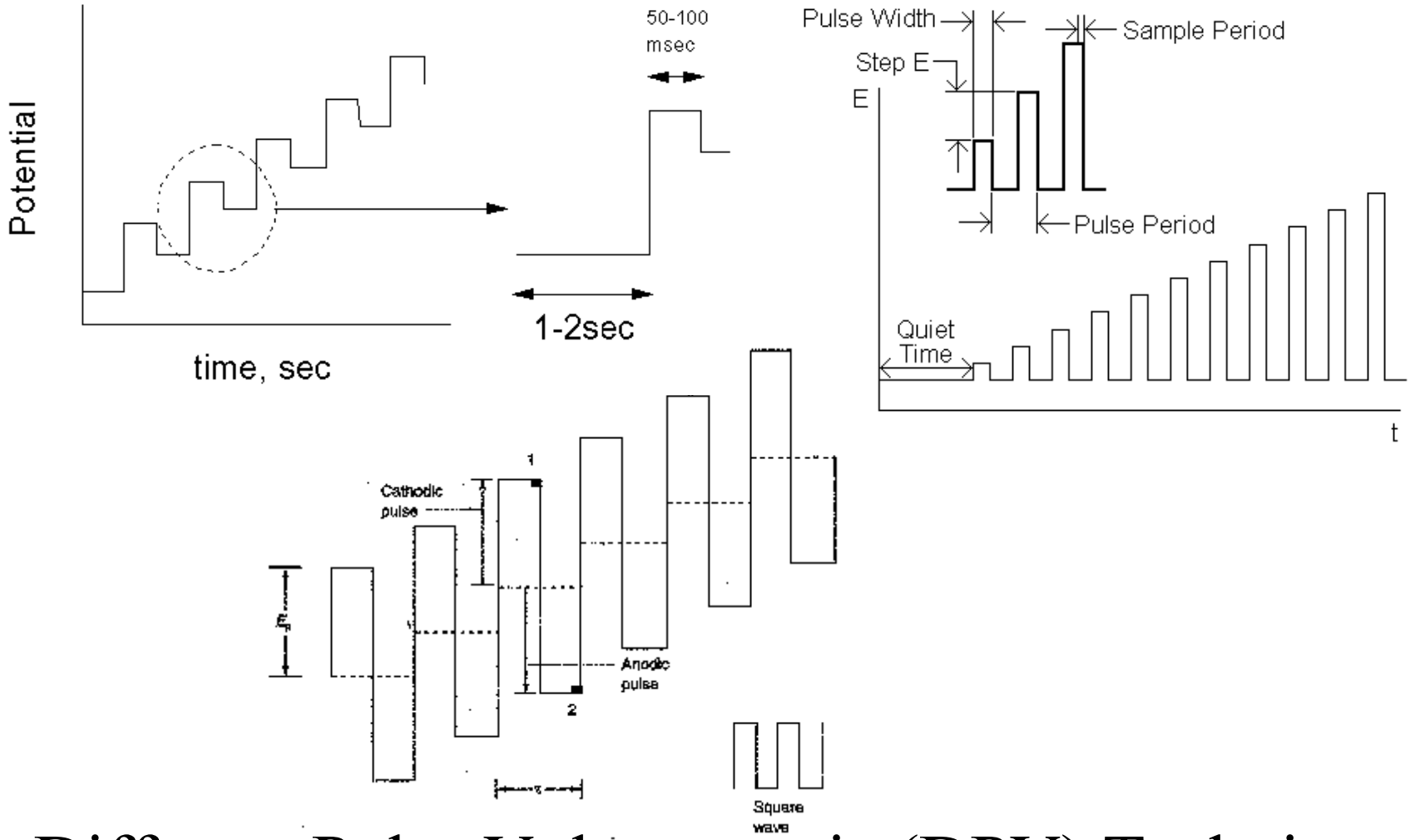


Cottrell Equation

$$E = E^0 - \frac{RT}{nF} \ln\left(\frac{C_R(0,t)}{C_O(0,t)}\right)$$

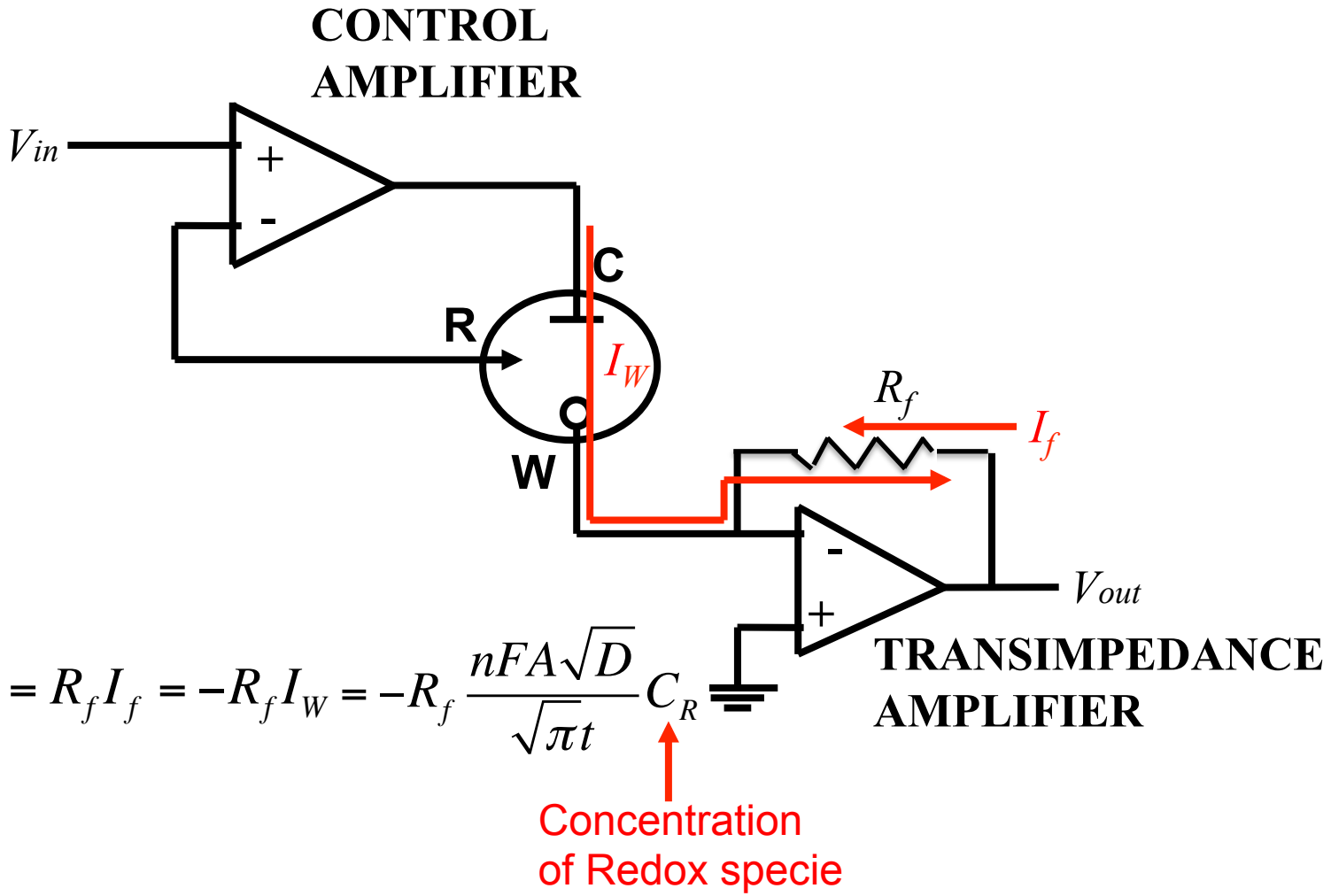
O+ reduction and H_2O_2 oxidation observed in Cyclic Voltammetry (CV)

Faradaic Current in Voltage Scan

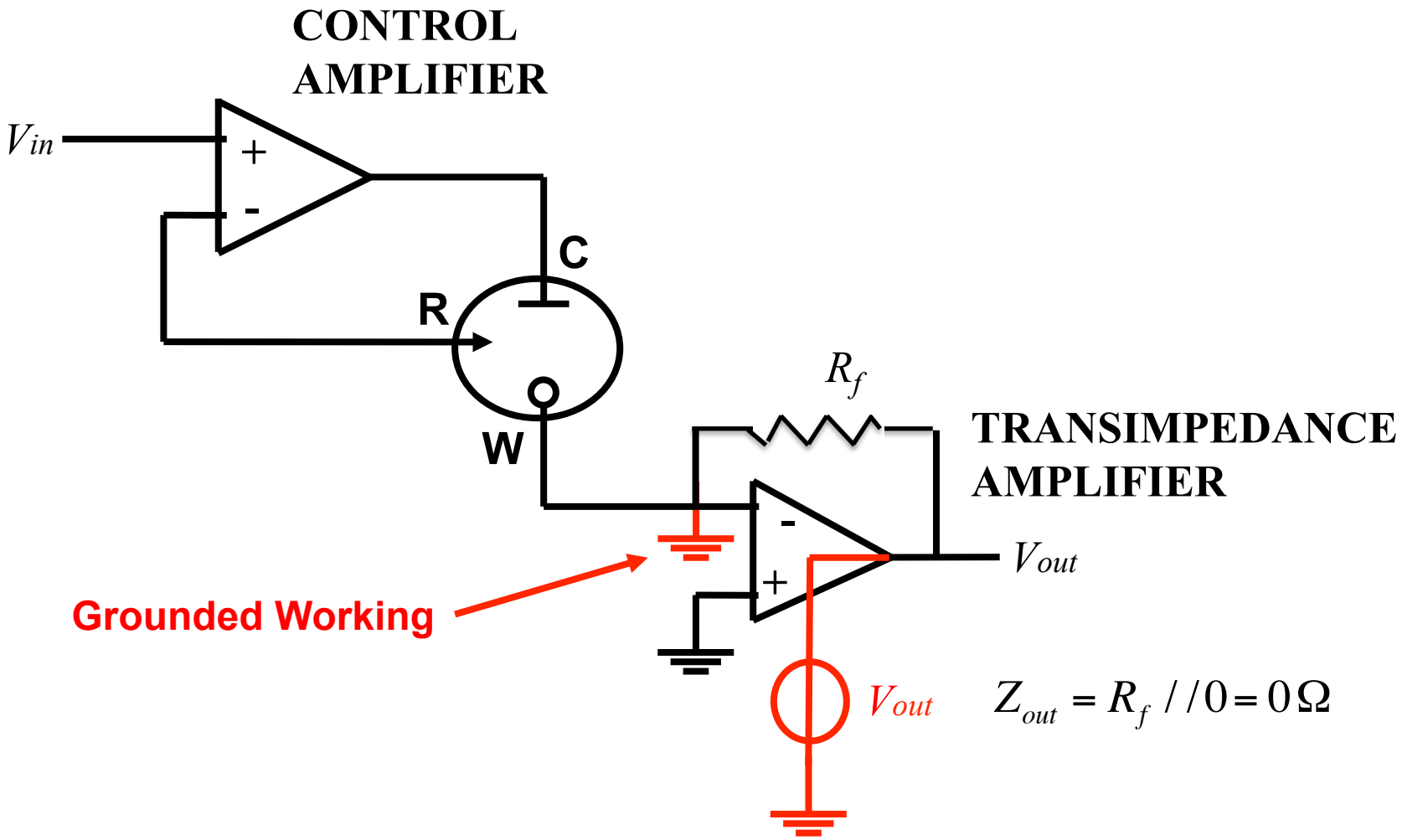


Different Pulse Voltammetric (DPV) Techniques

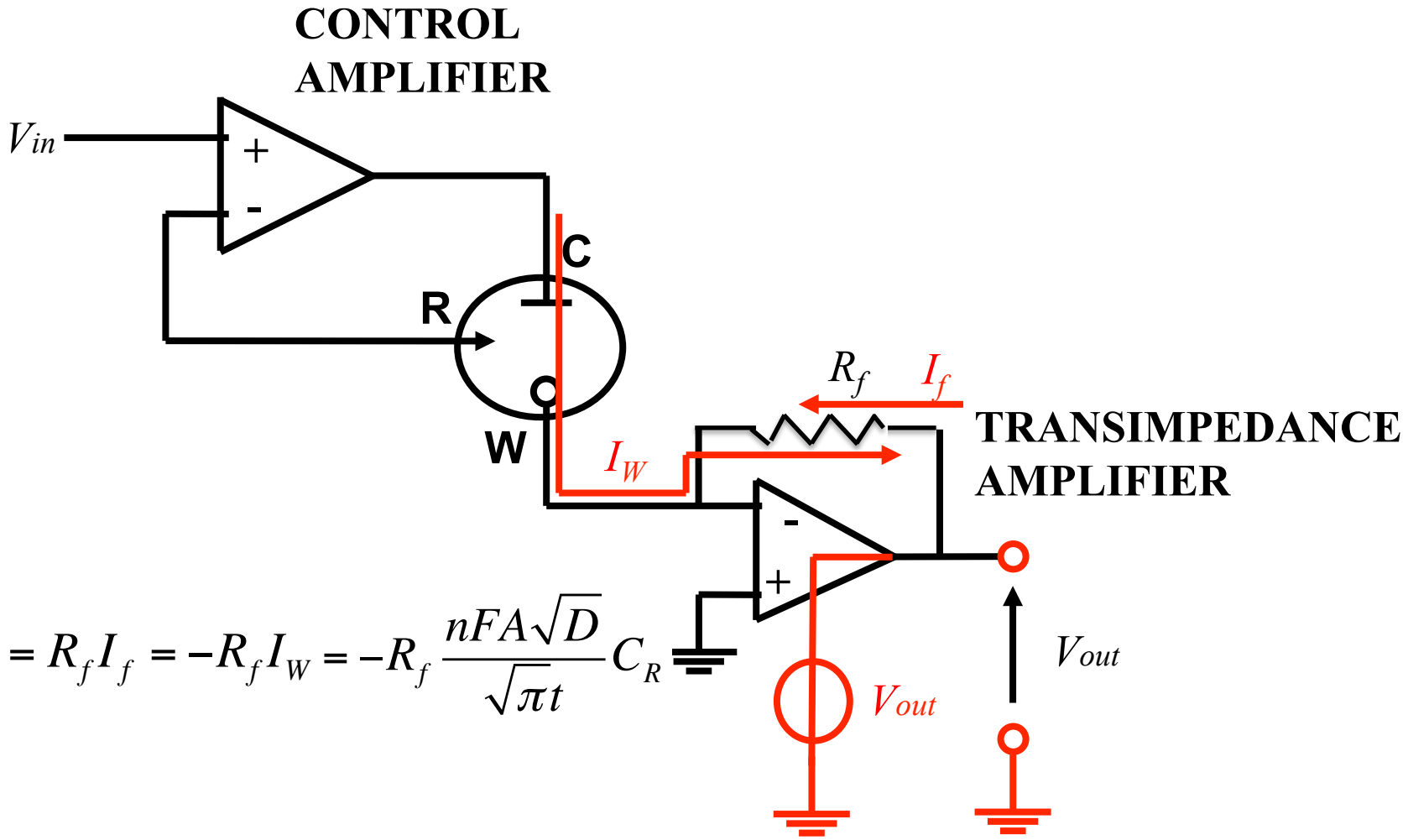
Transimpedance Amplifier @ WE



Grounded Working

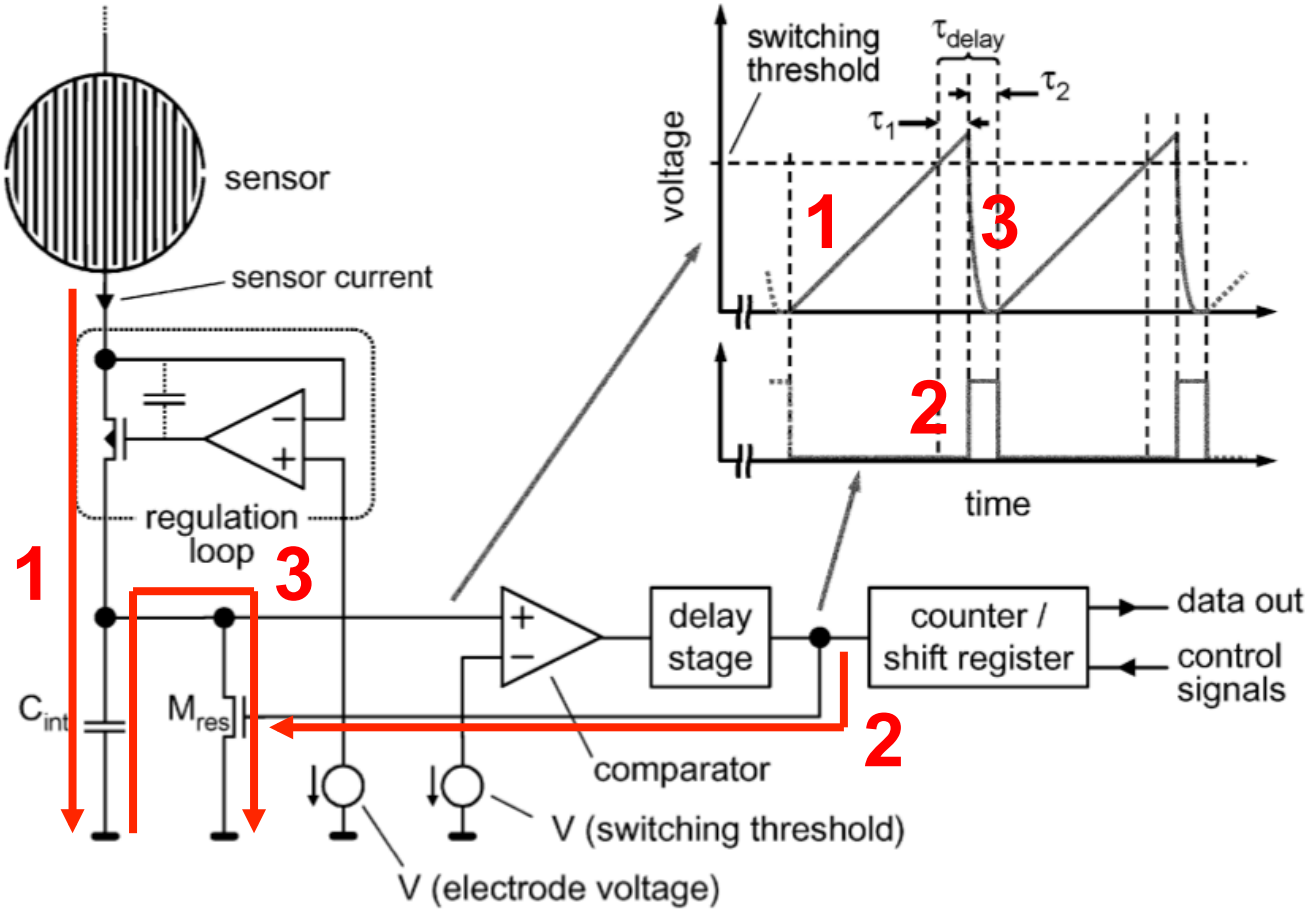


Current-to-Voltage Conversion



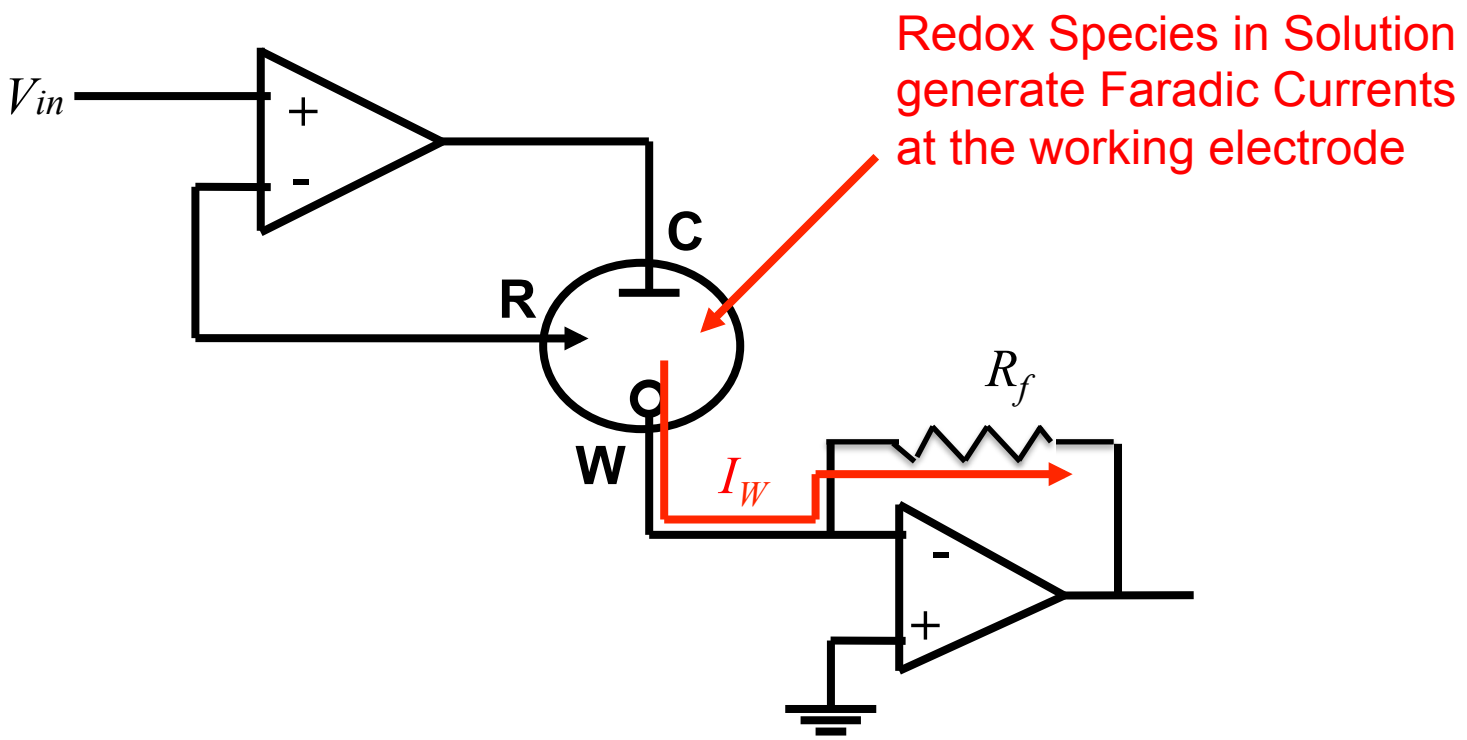
$$V_{out} = R_f I_f = -R_f I_W = -R_f \frac{nFA\sqrt{D}}{\sqrt{\pi t}} C_R$$

Time-based Potentiostats



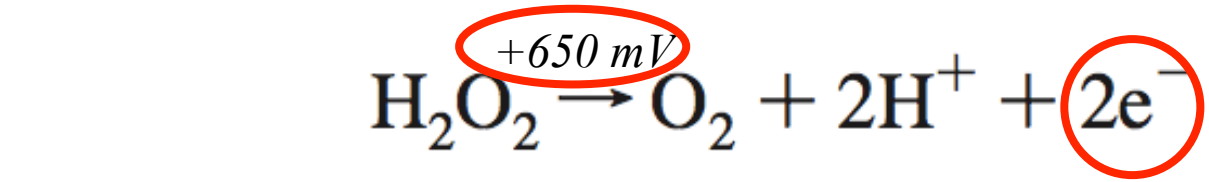
Current-to-Frequency Conversion in reading a Faradaic current

Inside the Cell: Faradaic Currents

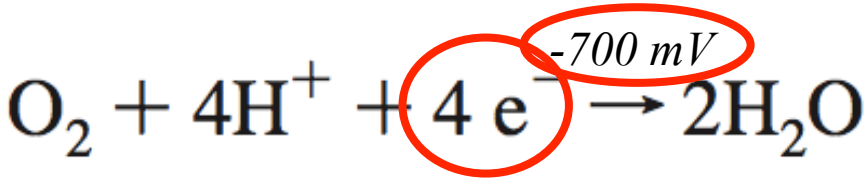


Direct Redox

The hydrogen peroxide provides two possible redox reactions.
An oxidation:



And a reduction (of the oxygen):



Redox mediated by oxidases

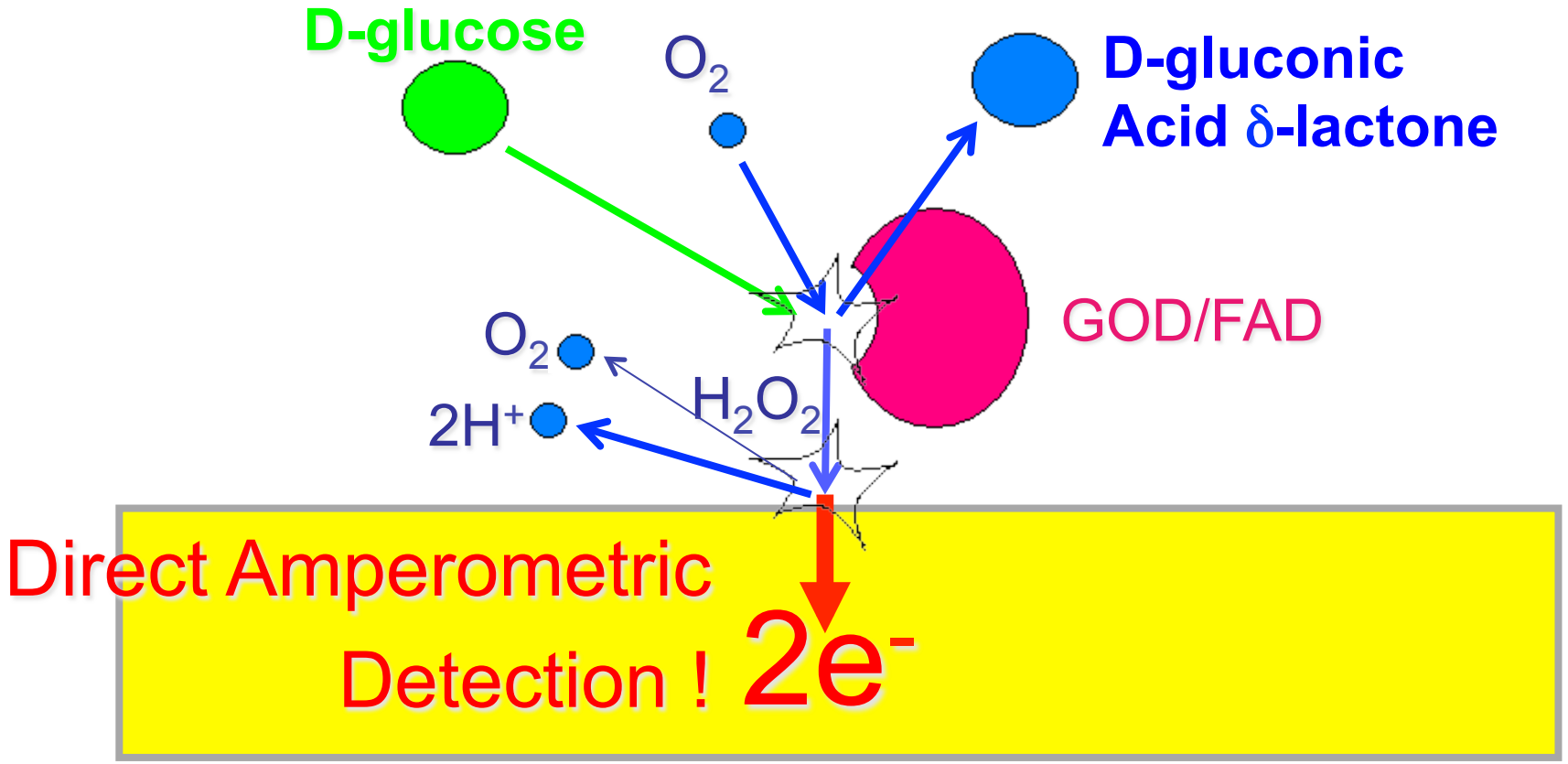
The typical redox involving an oxidase is as follows:

$$XOD/FAD + X \rightarrow XOD/FADH_2 + X_p$$

The FAD (Flavin Adenine Dinucleotide) is a functional part of the protein that gains a hydrogen molecule after the reaction. Therefore, the oxidase is not yet ready for another transformation because the FAD has gained the H_2. To return to its initial state, the enzyme needs to release that hydrogen molecule:

$$XOD/FADH_2 + O_2 \longrightarrow XOD/FAD + H_2O_2$$

Oxidases based detection



Redox mediated by P450

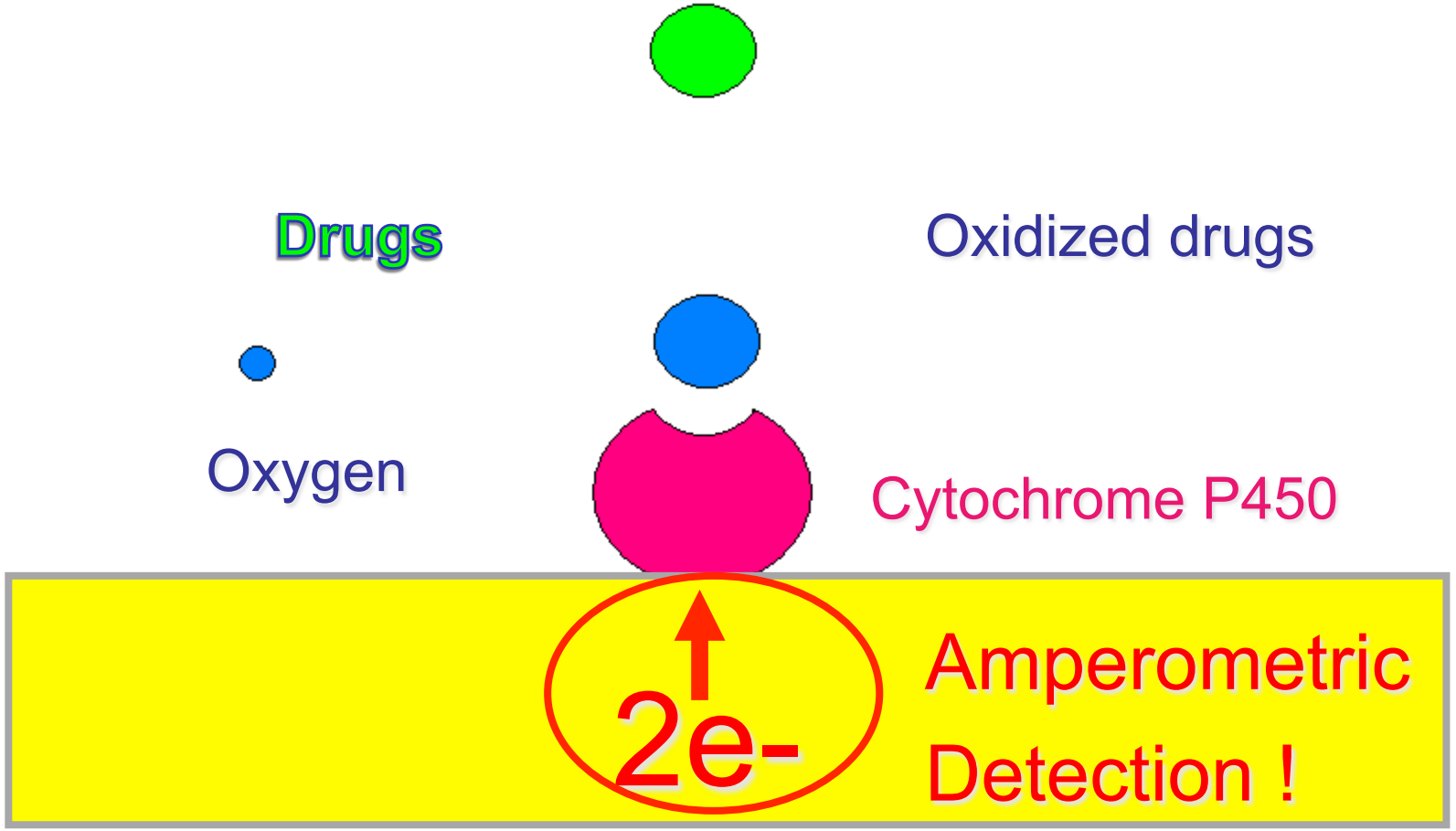
The typical redox involving a cytochrome P450 is as follows:

$$RH + O_2 + NADPH + H^+ \xrightarrow{P450} ROH + NADP^+ + H_2O$$

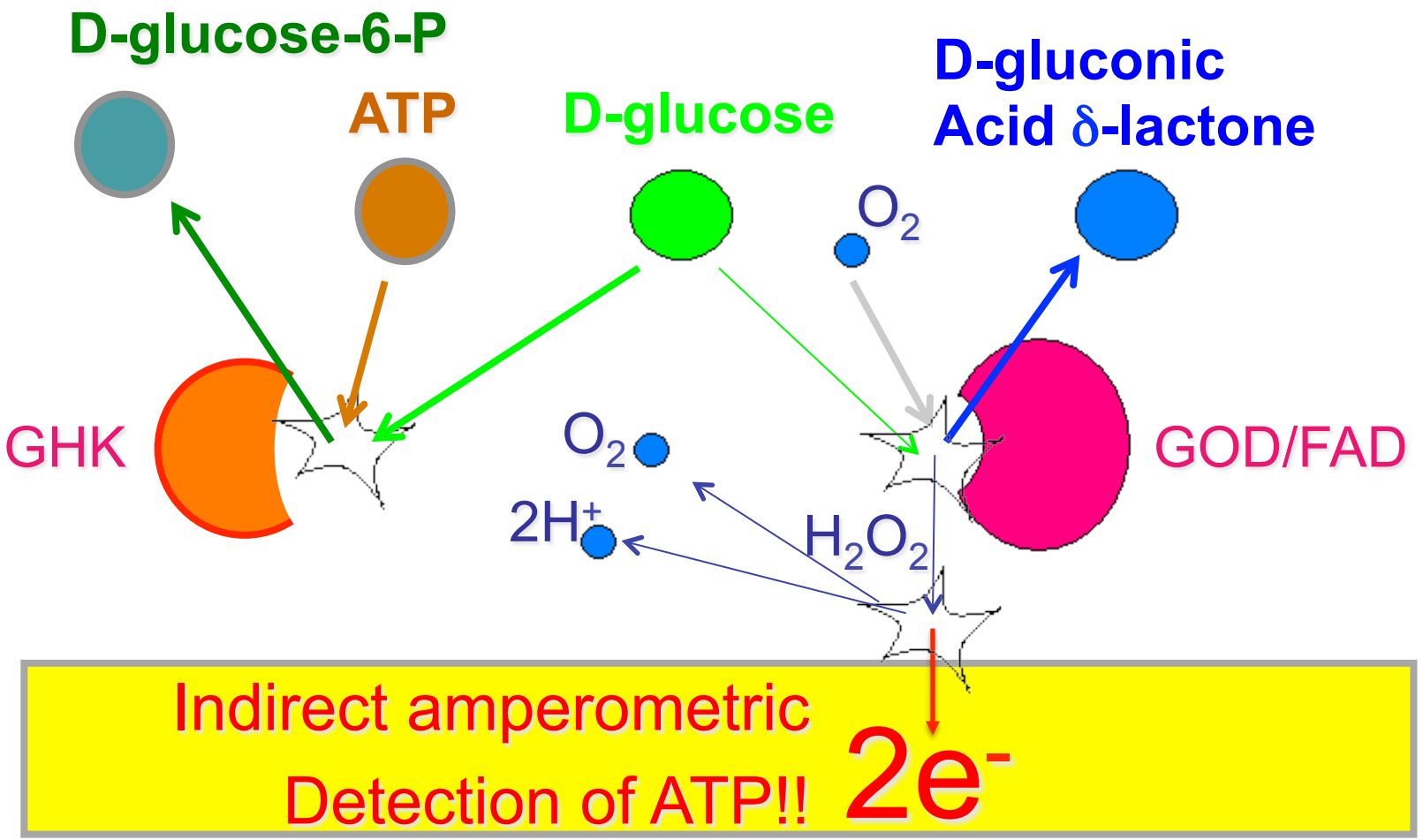
The coenzyme NADPH is mainly providing the need for two electrons required by the drug transformation. Without NADPH, the reaction occurs in water solution using hydrogen ions by water but need two extra electrons:

$$RH + O_2 + 2H^+ + 2e^- \xrightarrow{P450} ROH + H_2O$$

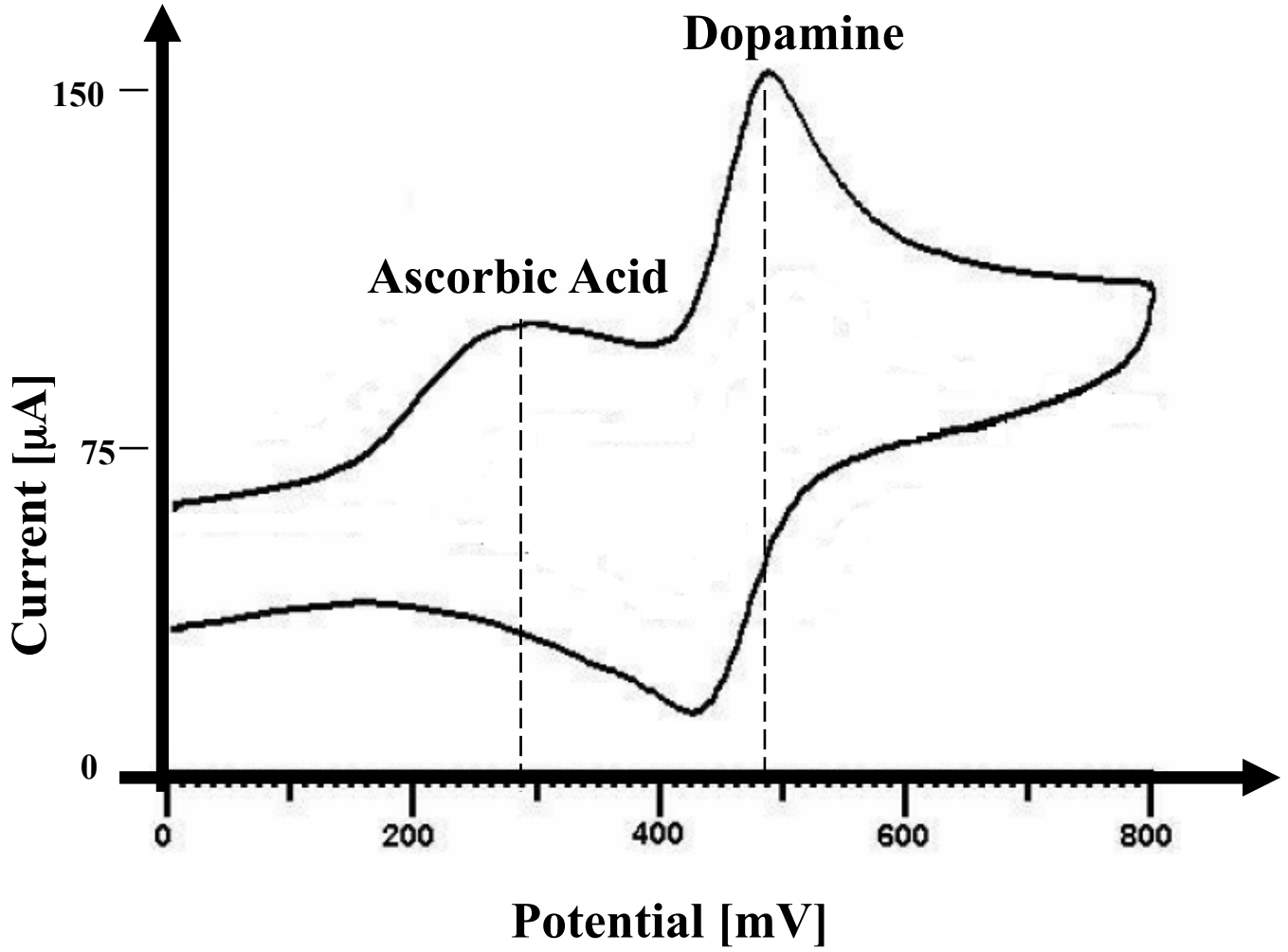
P450-based Detection



Indirect Detection: e.g., the ATP

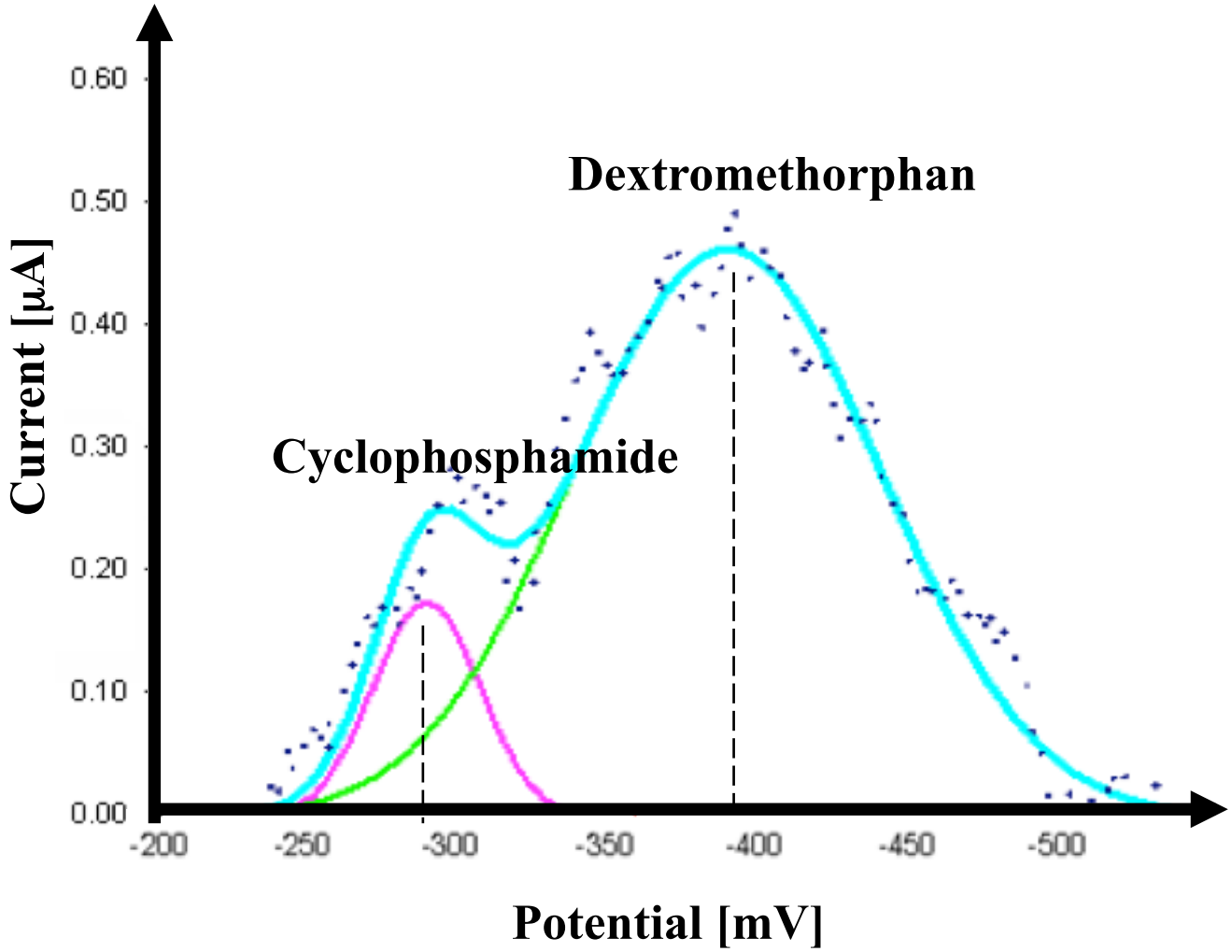


Endogenous Metabolites in voltage-scan



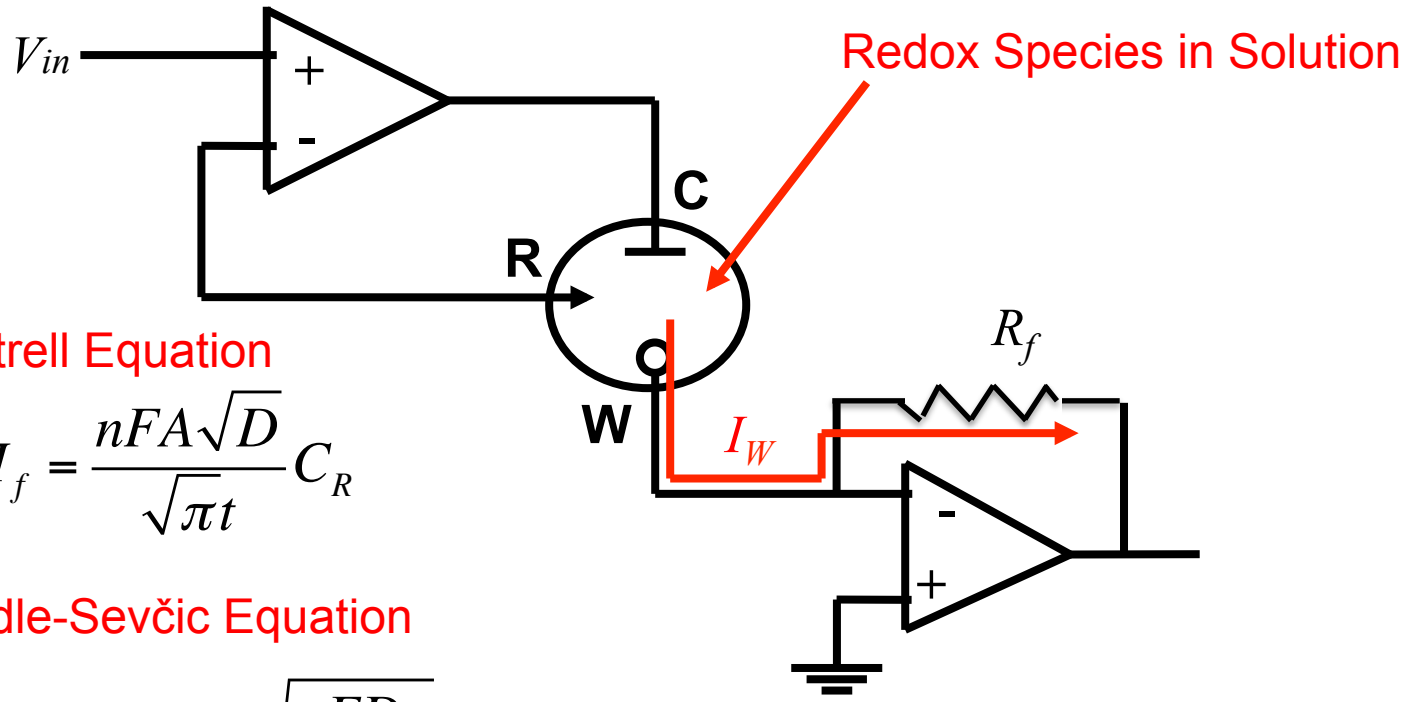
The use of carbon nanotubes shift the peaks potential

Exogenous Metabolites in voltage-scan



Two separate peaks as detected by a P450 3A4

Inside the Cell: Faradaic Currents



Cottrell Equation

$$I_f = \frac{nFA\sqrt{D}}{\sqrt{\pi t}} C_R$$

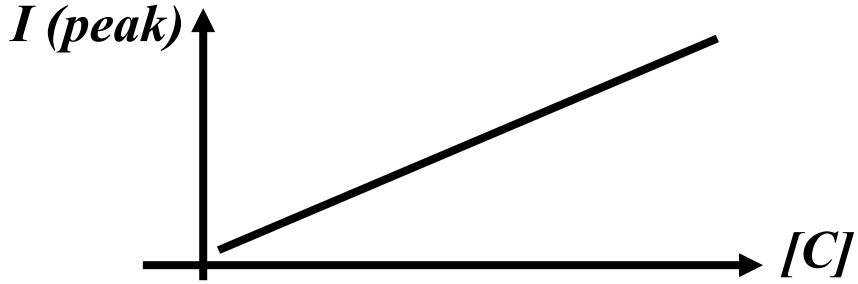
Randle-Sevčic Equation

$$I_f \propto nFAD\sqrt{\frac{nFDv}{RT}} C_R$$

Detection Principle

- Sensitivity: definition

$$i(t) = nFAD\sqrt{\frac{nFDv}{RT}}C(0,t)$$

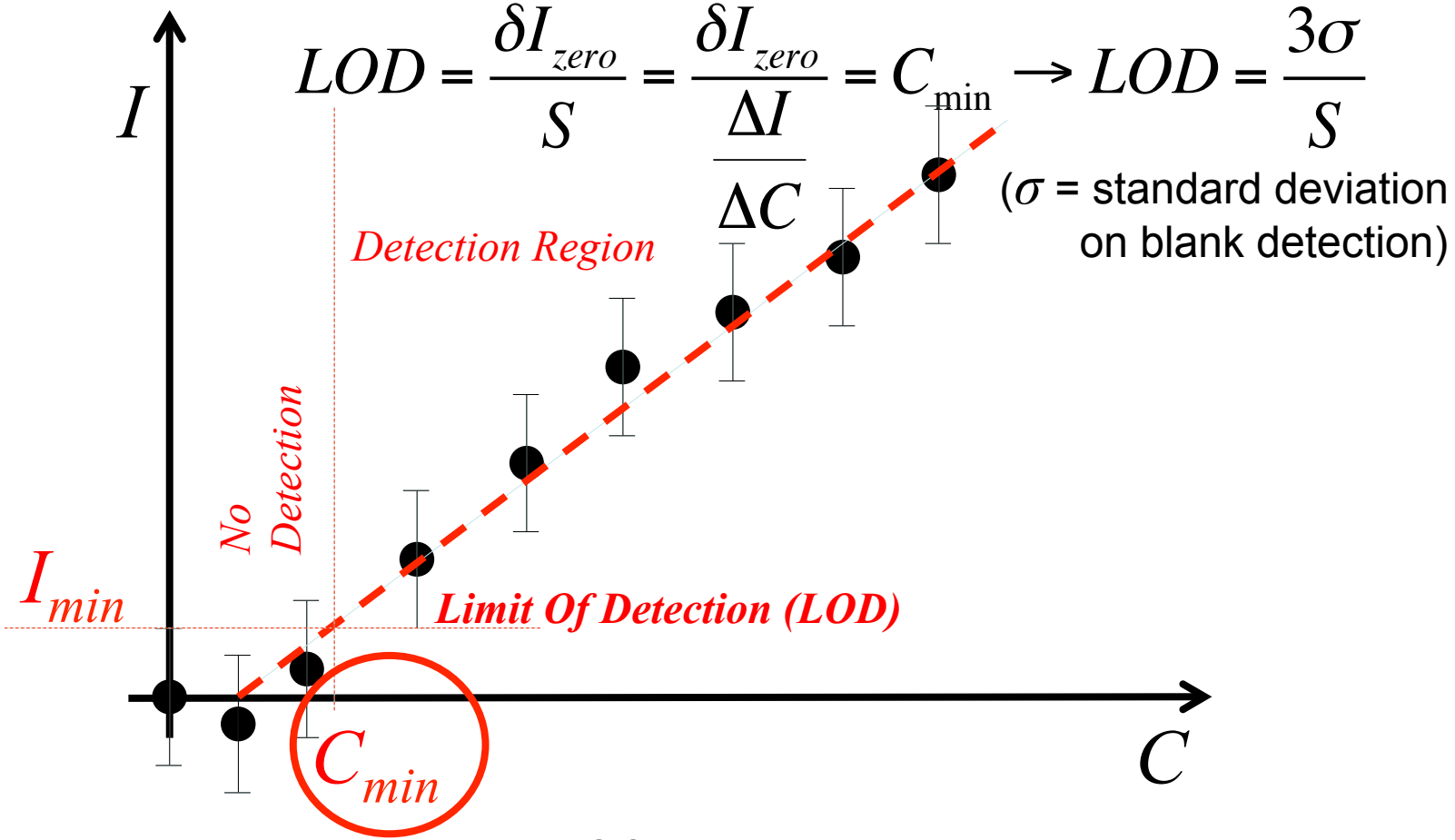


$$\Delta i = nFAD\sqrt{\frac{nFDv}{RT}}\Delta C \rightarrow \frac{\Delta i}{\Delta C} \equiv S$$

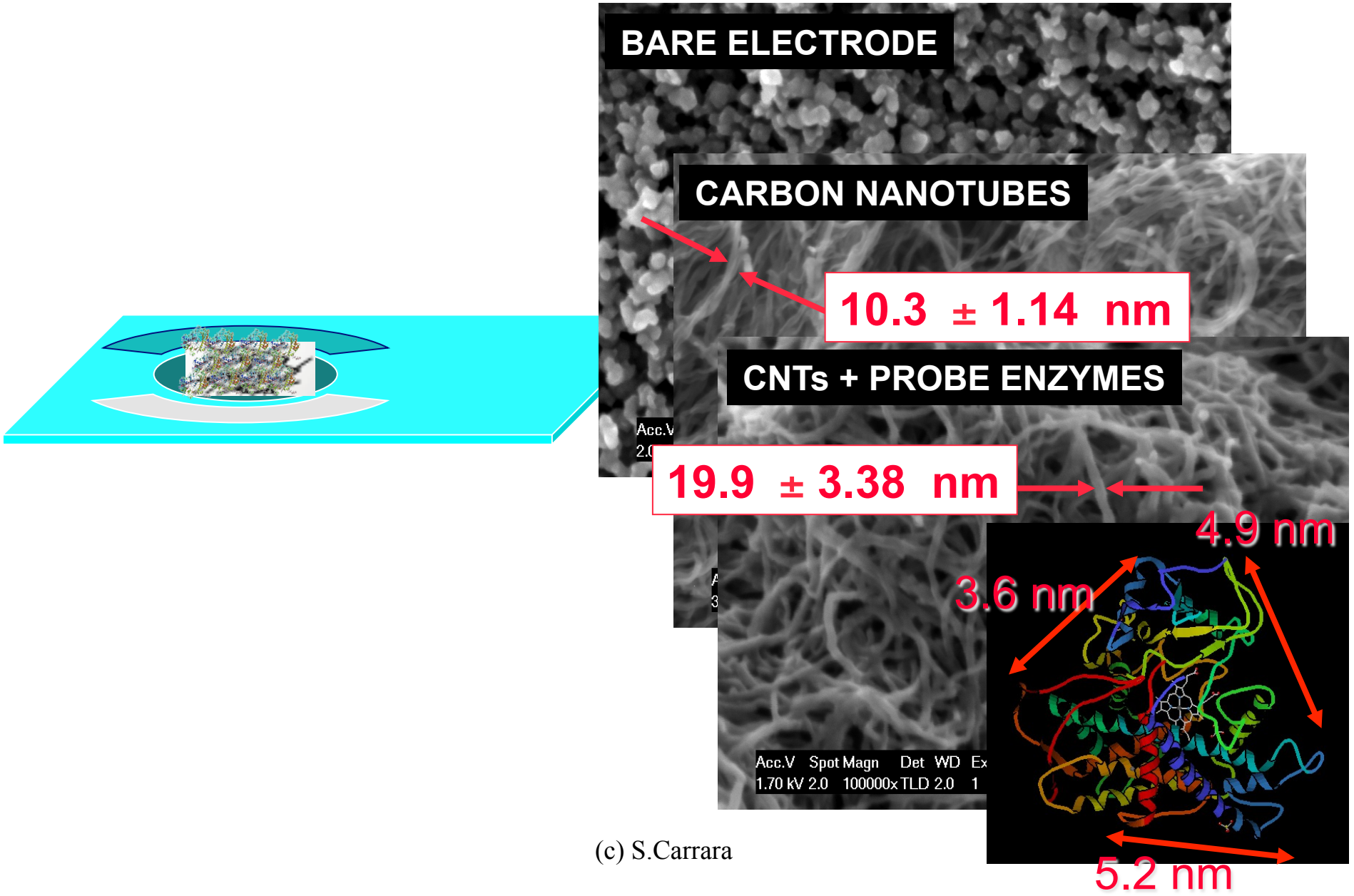
Detection Sensitivity!

Detection Principle

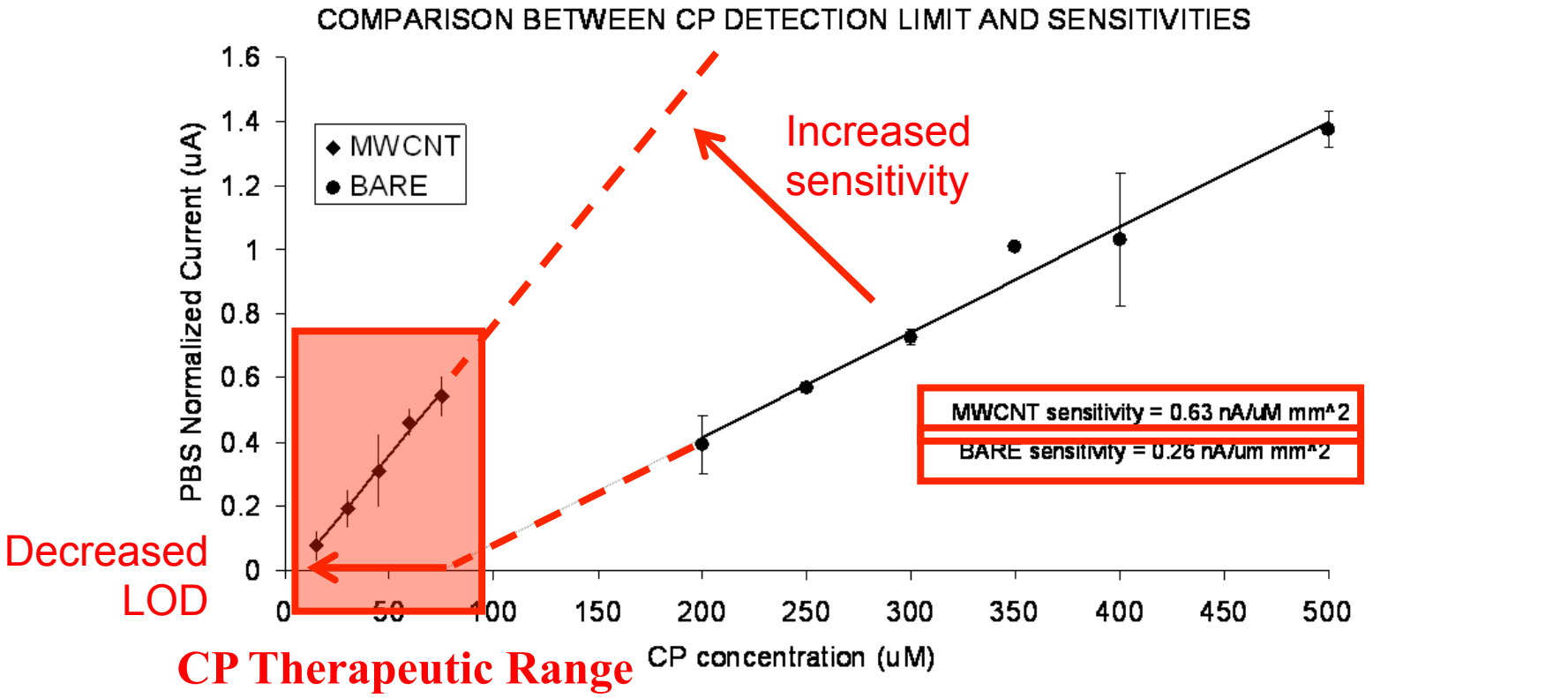
- Detection Limit: a graphic interpretation



Nano-Bio-Sensors integration



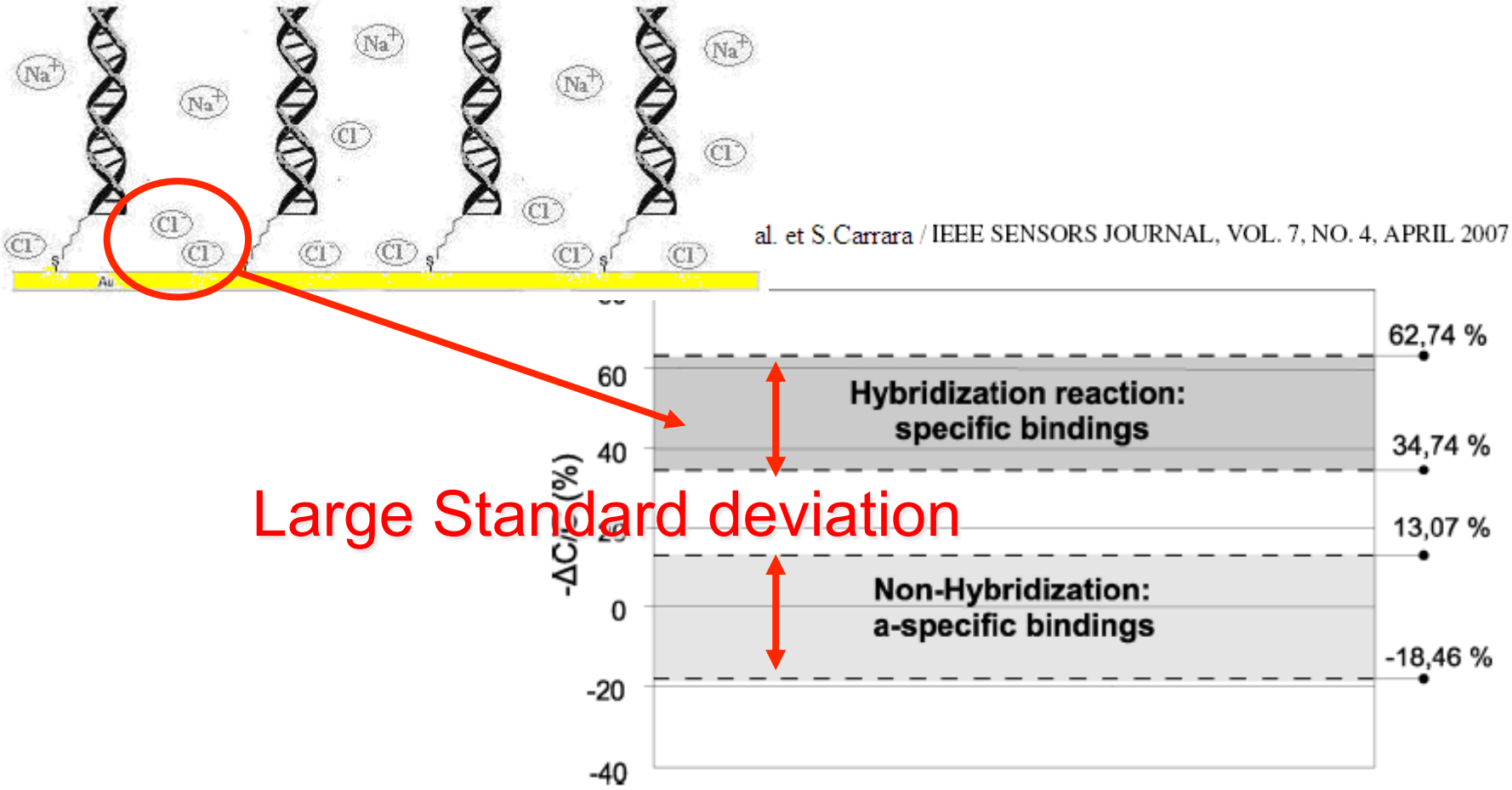
Randles-Sevçik effect on P450 3A4



S. Carrara et al. / Biosensors and Bioelectronics 26 (2011) 3914–3919

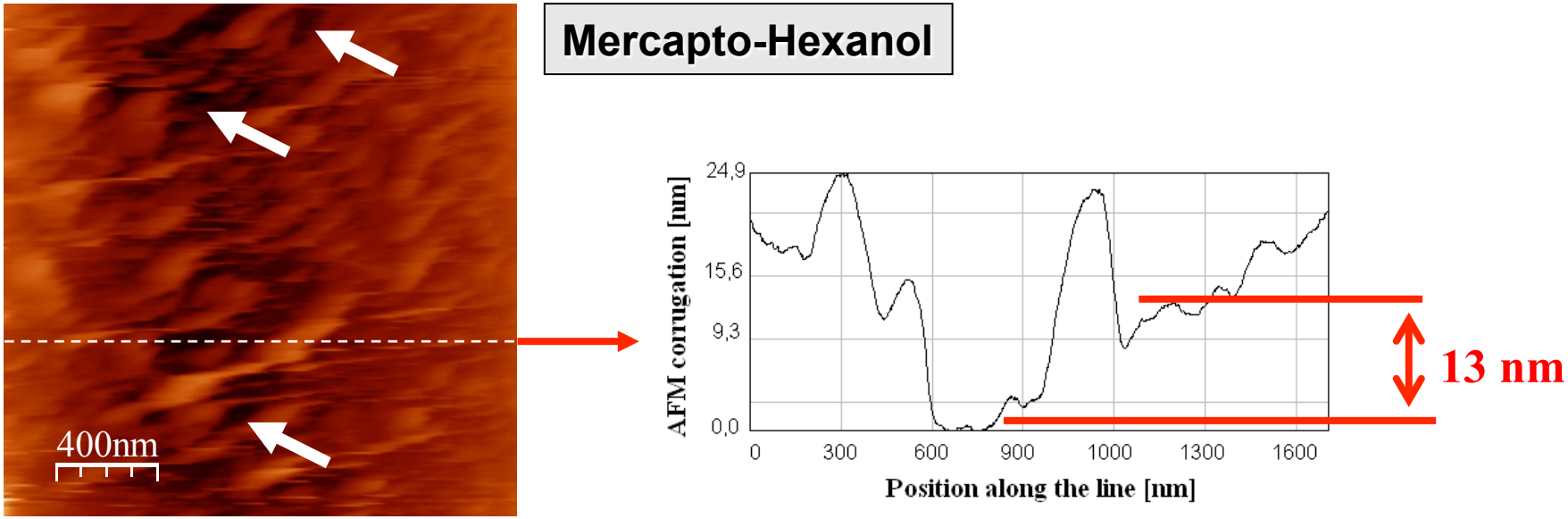
Cyclophosphamide (CP), an anti-cancer agent, is detected by P450 3A4 in its therapeutic range

Nano-aperture in the probes film



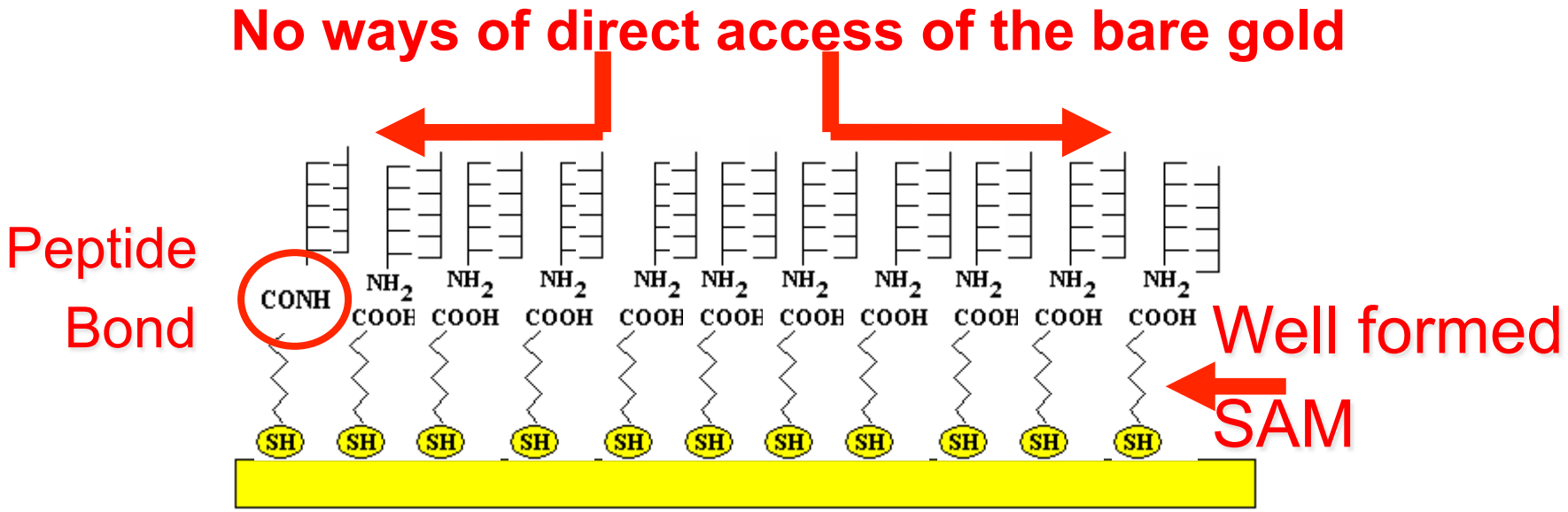
Solution ions in free contact with electrodes surface results in very large standard deviations

Nano-scale Apertures



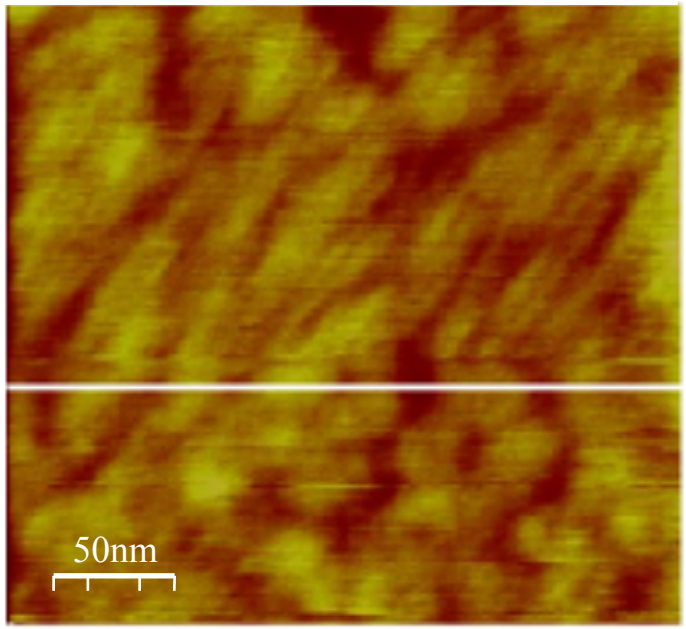
Monolayer of ssDNA with blocking agents still present deep groves crossing the film

Film precursors below probes

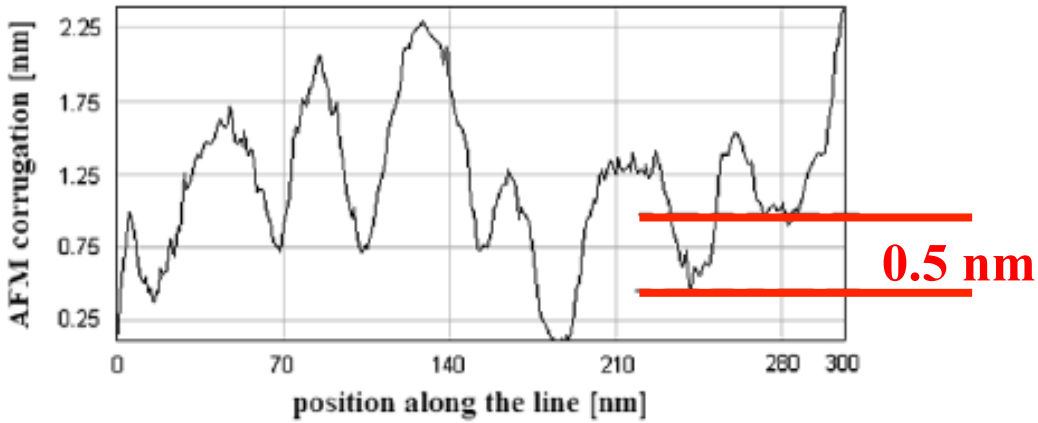


Highly packed thiols monolayer may be used to improve the DNA detection capability

Absence of Nano-scale Apertures

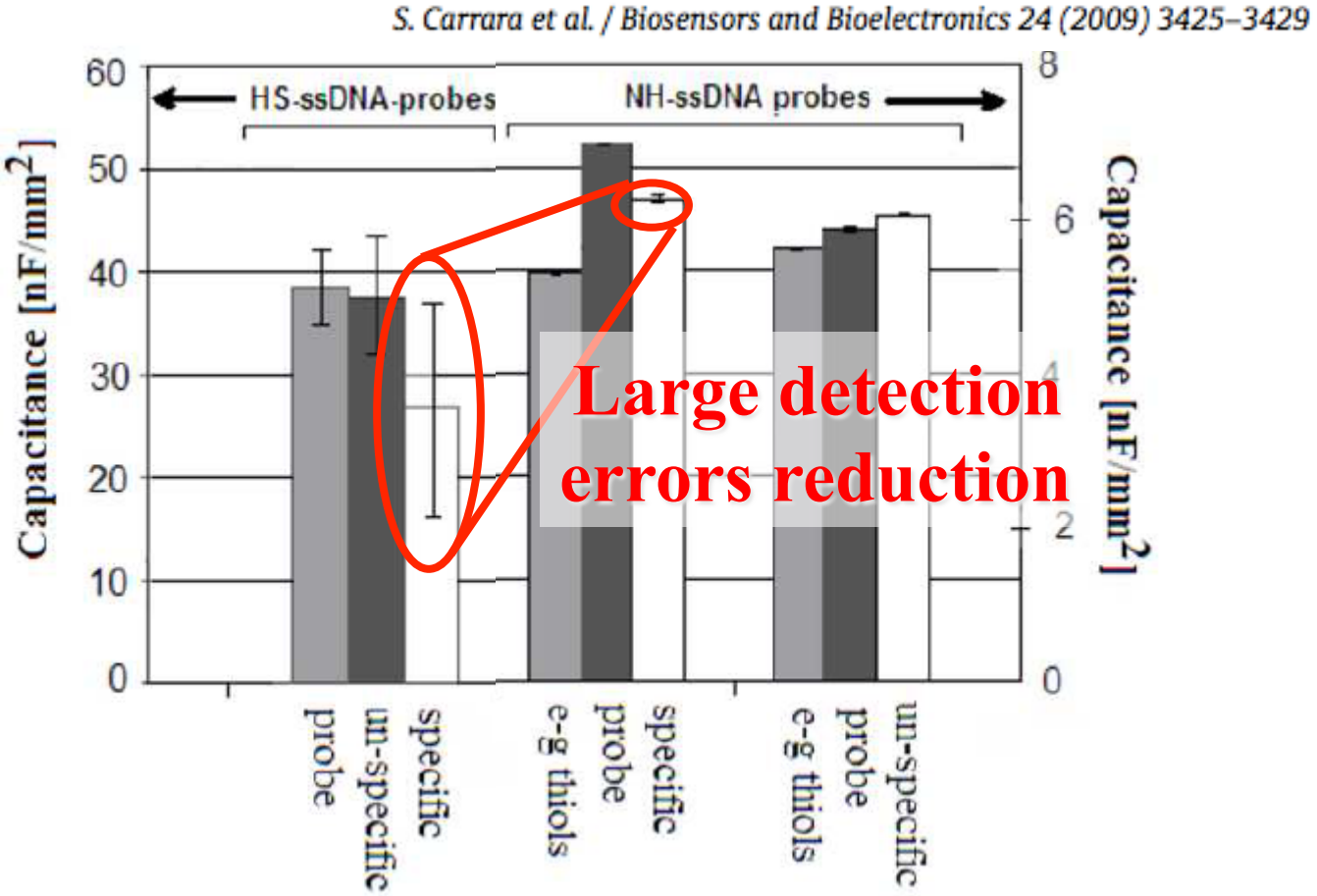


Ethylene-Glycol Film



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

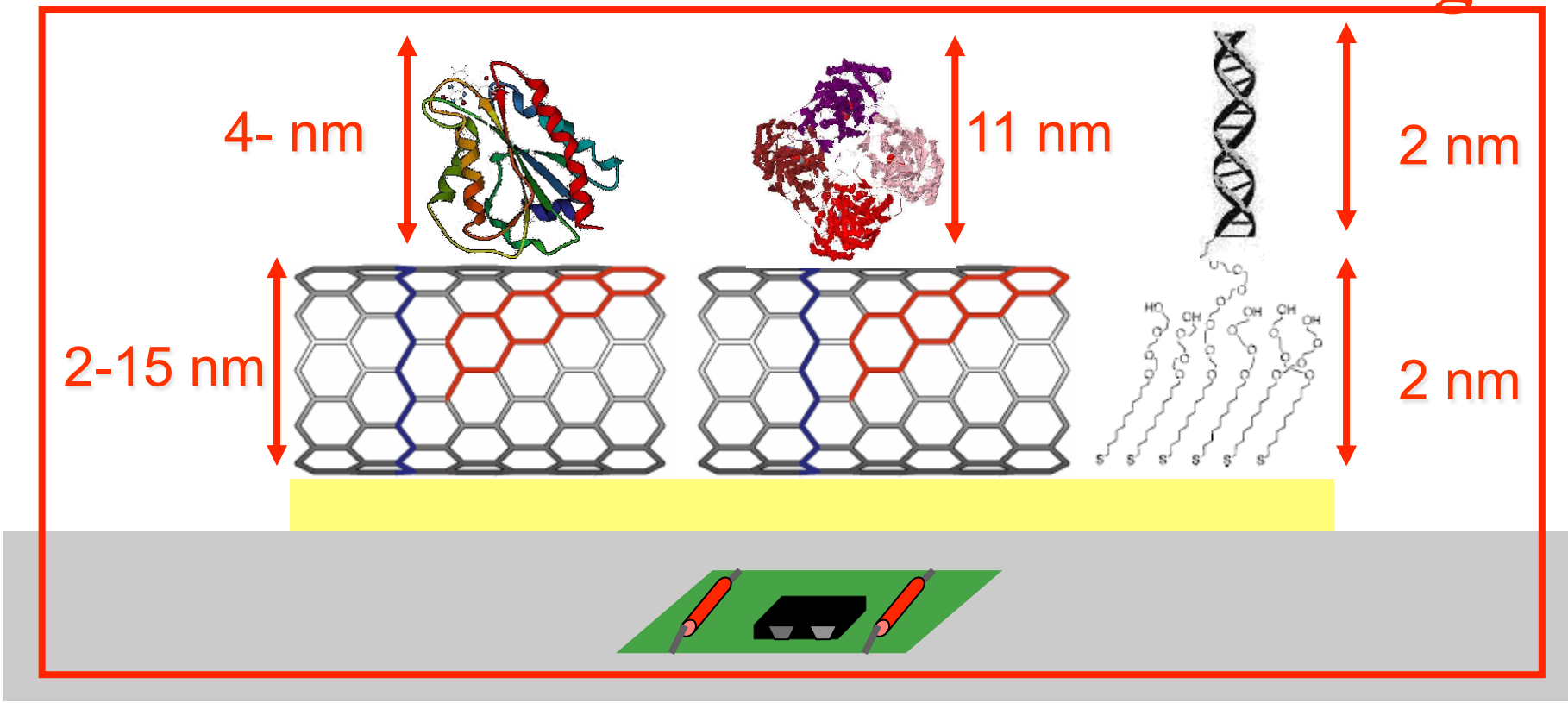
Capacitance detection of DNA



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

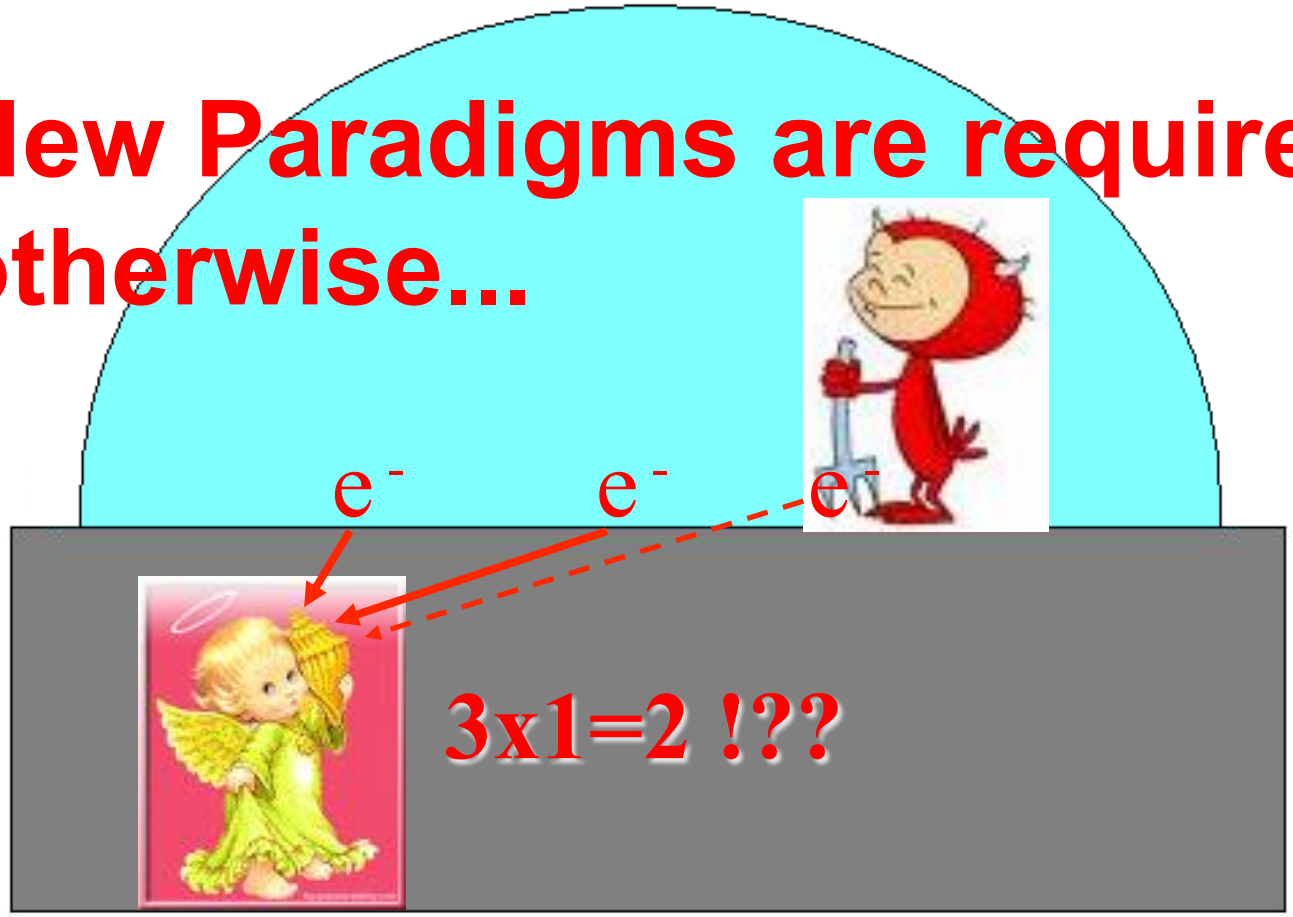
Aim of the course

Bio/Nano/CMOS Co-Design!



New paradigms for Nano-Bio-CMOS co-design are required to succeed in chip bio-sensing

New Paradigms are required otherwise...



Excellent CMOS technology is not sufficient if molecules are not doing their own job at the Bio/CMOS interface!