EPFL

Master in Electrical and Electronics Engineering

EE-517: Bio-Nano-Chip Design

Lecture #14

Review by Exam Simulation

Master in Electrical and Electronics Engineering

EE-517: Bio-Nano-Chip Design

Subject of the week	Chapter' paragraphs*
Introduction to Bio-Nano-Chip design, and Conductive Solutions	§1.1-1.5, §2.1-2.7, §2.14-15
Biological molecules: Proteins and DNA building blocks	§3.5-9, §4.13 and §4.17-18
Biological molecules interactions (DNA, Antibodies, Oxidases and Cytochromes)	§4.4-17 and §4.19-23
Biosensors Principle with DNA, Antibodies, and Enzymes	§6.1-4 and §8.2
Biosensors Principle by Redox reactions and Faradaic processes	§8.4-8
Nanotechnology for molecular assembly on chip' surfaces (absorption models)	§5.1
Nanotechnology for checking molecular assembly on chip' surfaces (SPR+ AFM)	§5.2
Nanotechnology to prevent electron transfer	§6.3-7
Nanotechnology to enhance electron transfer in redox reactions	§8.4-8, and 8.3 and 8.9
Chip design for electrochemical sensing: basic configurations and equivalent circuits	§9.1-9.2
Amperometric biosensing in constant-bias (Current-to-Voltage & FTCC Methods)	§9.1.2 and 9.3-5
Amperometric biosensing in voltage-scan (VDCM & DDSM Methods)	§10.3-5
Label-free capacitance detection (CBCM & FTCM Methods)	§7.2-6
Review for final exam	

Bio

Nano

CMOS

Simulation of

textbook : Sandro Carrara, Bio/CMOS interfaces and Co-Design, Springer publisher, New York, 2013

Considered Scenario similar to Abbot technology for glucose

Simulated Exam: Considered Scenario

We need to realize a wearable biosensing system to detect the lactate (a small organic human metabolite) and the potassium (one of the main intracellular ions) as released on the skin and, then, measurable in the sweat during sports competitions and training exercises. We plan to realize the amperometric detection for the lactate by using a biosensors based on the Lactate Oxidase, while we plan to realize the potentiometric detection for the potassium by using a polymeric ion-selective membrane deposited onto an electrode. In the case of the potassium, we plan a kind of potentiometric detection similar to the one sometimes proposed for measuring the pH with deposition of Iridium Oxide. To improve the Electron Transfer, we may consider incorporating Multi-Walled Carbon Nanotubes (MWCNT) when suitably required. Having this in mind, please, solve the following exercises and answer the related questions.

Simulated Exam: Considered Scenario

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Clicker test

Do we can incorporate the Lactate Oxidases as well as the ion-selective membrane in the same working electrode for two different sensory aims?

A. Yes, sure!
B. Yes, if we measure K^+ with Amperometry
C. No, we need three electrodes for lactate, lactate oxidase, K^+
D. No, we need two independent sensors

Clicker test

With the same sensing approach, may we plan the same amperometric detection method to sense both the lactate and the potassium?

A. Yes, sure!
B. Yes, if we measure lactated with Potentiometry
C. No, we need three electrodes for lactate, lactate oxidase, K^+
D. No, we need two independent sensors

Exercise 1

The selective sensor for the lactate is fabricated with the Lactate Oxidase, which has a molecular weight of 80 Kg/mol. The Oxidase is in powder. Stock solutions are required to dissolve the protein for preparing the sensory system. A stock solution is then prepared with a volume of 400 mL each, with proper solvents, by separately dissolving the Lactate Oxidase.

a) Calculate the molarity of a first stock solution if we dissolve 100 g of Lactate Oxidase in water.

Clicker test

How much is then the molarity of a stock solution if we dissolve 100 g of Lactate Oxidase (MW=80 Kg/mol) in 400 mL of water?

A. 0.13 mM
B. 1.13 mM
C. 3.13 mM
D. 5.13 mM

Given:
MW = *80* kg/mol
V = 400 ml
m = 100 g

Asked:
M = ?

$$M = \frac{n}{V} = \frac{\left(\frac{m}{MW}\right)}{V} = \frac{\left(\frac{100\ g}{80000\ g/mol}\right)}{400\ mL} = 3.13\ mM$$

Exercise 1

The selective sensor for the lactate is fabricated with the Lactate Oxidase, which has a molecular weight of 80 Kg/mol. The Oxidase is in powder. Stock solutions are required to dissolve the protein for preparing the sensory system. A stock solution is then prepared with a volume of 400 mL each, with proper solvents, by separately dissolving the Lactate Oxidase.

b) From the previously prepared stock solution, we want 2.5 mL of Lactate Oxidase solution with a final concentration of 0.1 mM. Which is the needed volume of the stock solution and how many mL of water must we add to obtain the final volume of 2.5 mL?

Clicker test

From a stock solution with M=3.13.mM, we want 2.5 mL of Lactate Oxidase solution with a final concentration of 0.1 mM. How much volume of the stock solution we need for for a final volume of 2.5 mL?

A. 8.000 mL
B. 0.800 mL
C. 0.080 mL
D. 0.008 mL

Given:
$C_1 = 3.13$ mM
$C_2 = 0.1$ mM
$V_2 = 2.5$ mL

Asked:

$V_1 = ?$

$$C_1 \times V_1 = C_2 \times V_2$$
$$(3.13\ mM) \times (V_1) = (0.1\ mM) \times (2.5\ mL)$$
$$V_1 = 0.08\ mL$$

Clicker test

From a stock solution with M=3.13.mM, we want 2.5 mL of Lactate Oxidase solution with a final concentration of 0.1 mM. How much water must we add for a final volume of 2.5 mL?

A. 2.42 mL
B. 2.24 mL
C. 0.24 mL
D. 0.02 mL

Given:
$C_1 = 3.13$ mM
$C_2 = 0.1$ mM
$V_2 = 2.5$ mL

Asked:

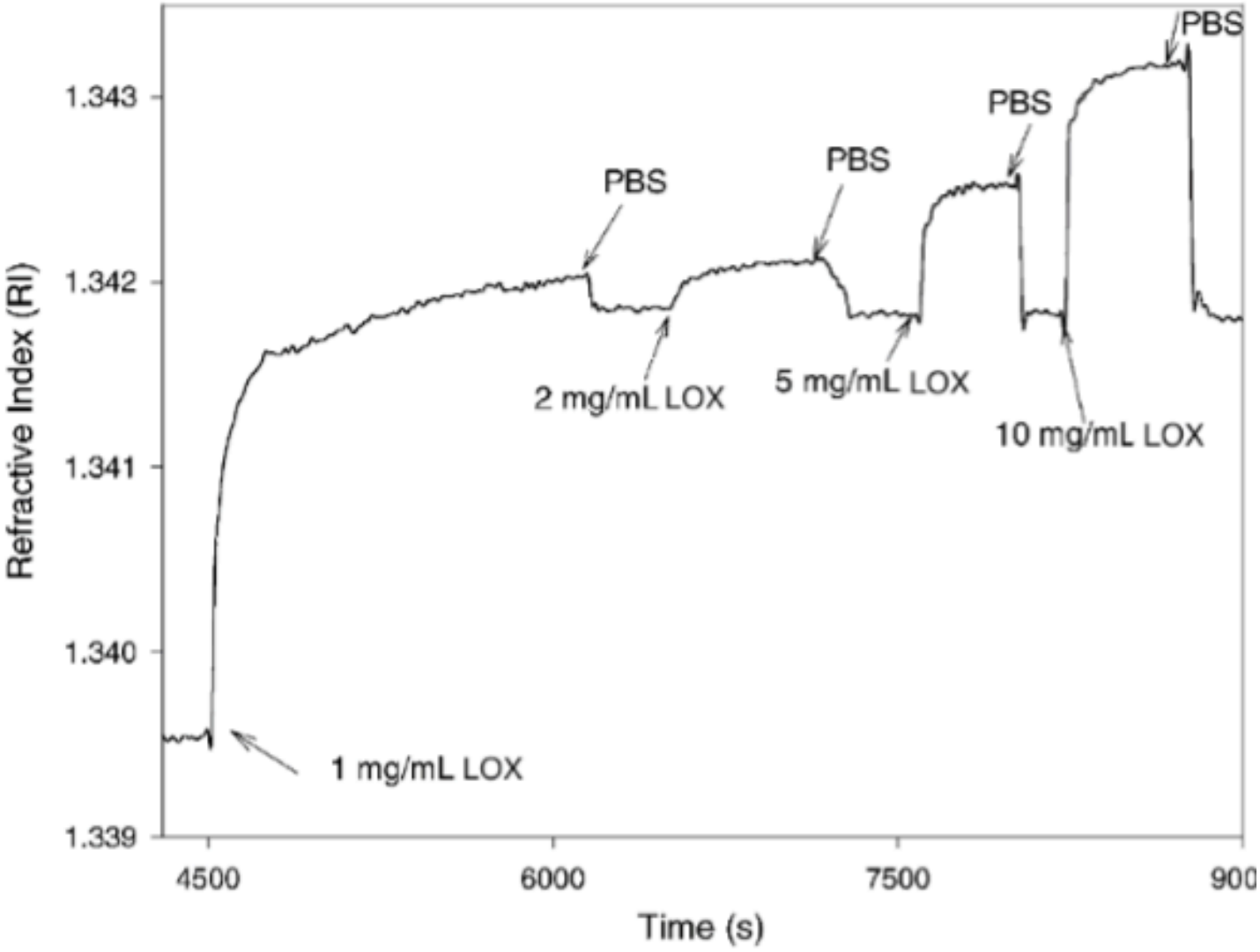
$V_1 = ?$
$V_{Buffer} = ?\ (2.5 - V_1) = ?$

$$C_1 \times V_1 = C_2 \times V_2$$
$$(3.13\ mM) \times (V_1) = (0.1\ mM) \times (2.5\ mL)$$
$$V_1 = 0.08\ mL$$
$$V_{Buffer} = (2.5 - 0.08) = 2.42\ mL$$

Exercise 2

As decided in the exercise # 1, we immobilize the Lactate Oxidase (LOX) onto the working electrode. Of course, the adsorption of the probe proteins might be different if we use different protein' solutions with different concentrations (here in mg/mL). Trying to improve the number of enzymes on the surface, different samples at different concentrations are then subsequently used on the same sensing surface, while SPR signals are acquired to check the functionalization process. After each single immobilization, the surface is always washed with a buffer solution (PBS). The SPR acquired data are reported in the next slide.

Exercise 2

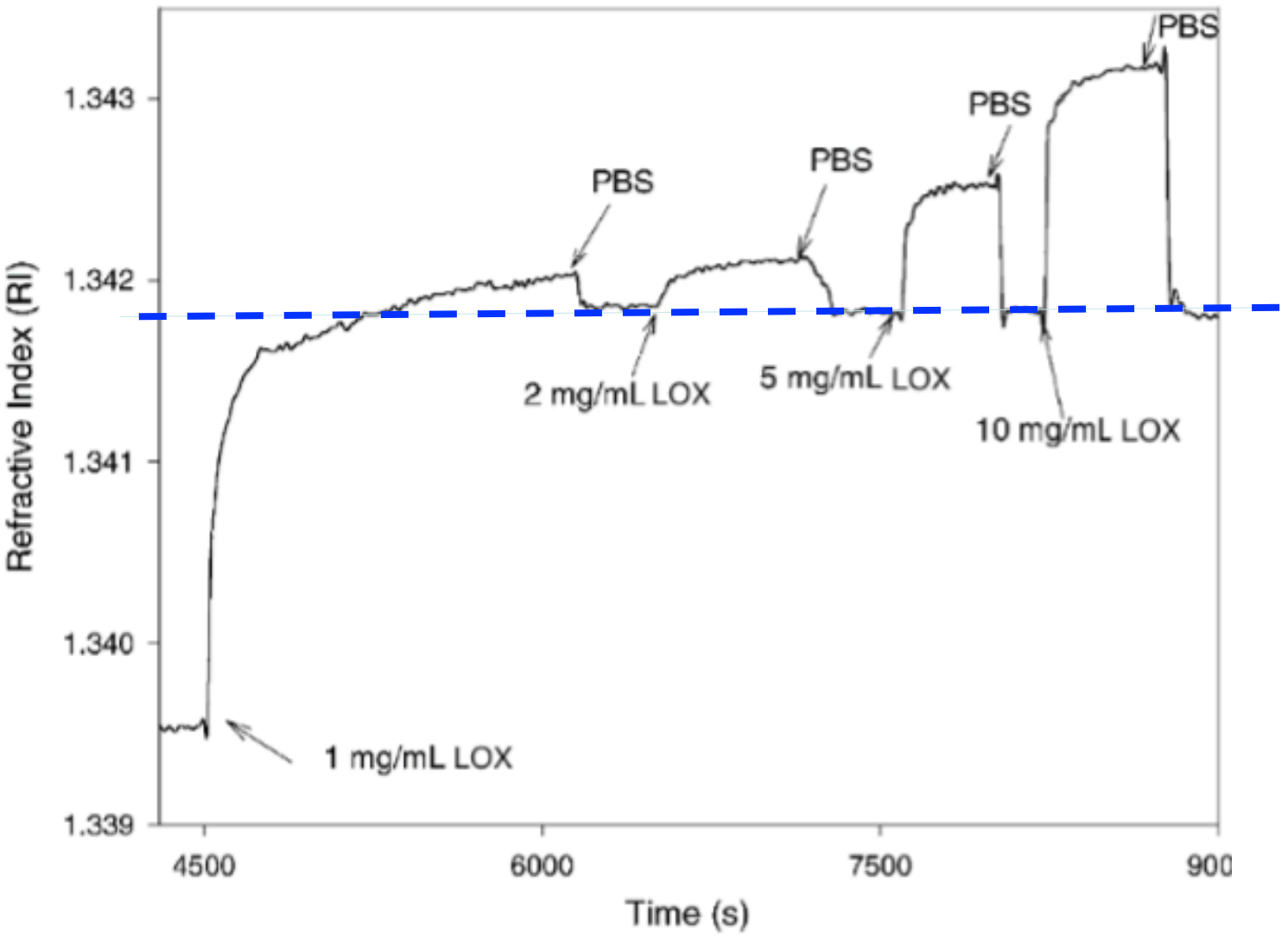

Refractive Index (RI)
1.343
1.342
1.341
1.340
1.339
4500
6000
7500
900
Time (s)
PBS
PBS
PBS
PBS
1 mg/mL LOX
2 mg/mL LOX
5 mg/mL LOX
10 mg/mL LOX

Clicker test

With respect these SPR data, there is any difference in functionalizing the working electrode with a subsequent sample of LOX at a concentration of 10 mg/mL?

A. No
B. Yes
C. Yes, but not statistically significant
D. May be
E. No, since any difference is not statistically significant

Exercise 2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1.343
1.342
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1.340
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4500
6000
7500
900
Time (s)
PBS
PBS
PBS
PBS
1 mg/mL LOX
2 mg/mL LOX
5 mg/mL LOX
10 mg/mL LOX

Exercise 2

b) Back to SPR data, and supposing now that each point of Refractive Index in the SPR signal (1 RI) corresponds to 1.47 ng of proteins successfully transferred onto the working electrode, compute the total amount of protein (in ng) remaining onto the working electrodes after bit-more- than 25 minutes from the first injection of the sample at the concentration of 1 mg/mL of LOX, as per the SPR data about reported above.

Clicker test

Back to SPR data, if each point of Refractive Index corresponds to 1.47 ng, compute the total amount of protein (in ng) onto the WE after bit-more than 25 minutes from the first injection

A. 3.4 pg
B. 0.34 ng
C. 1.97 µg
D. 0.19 mg

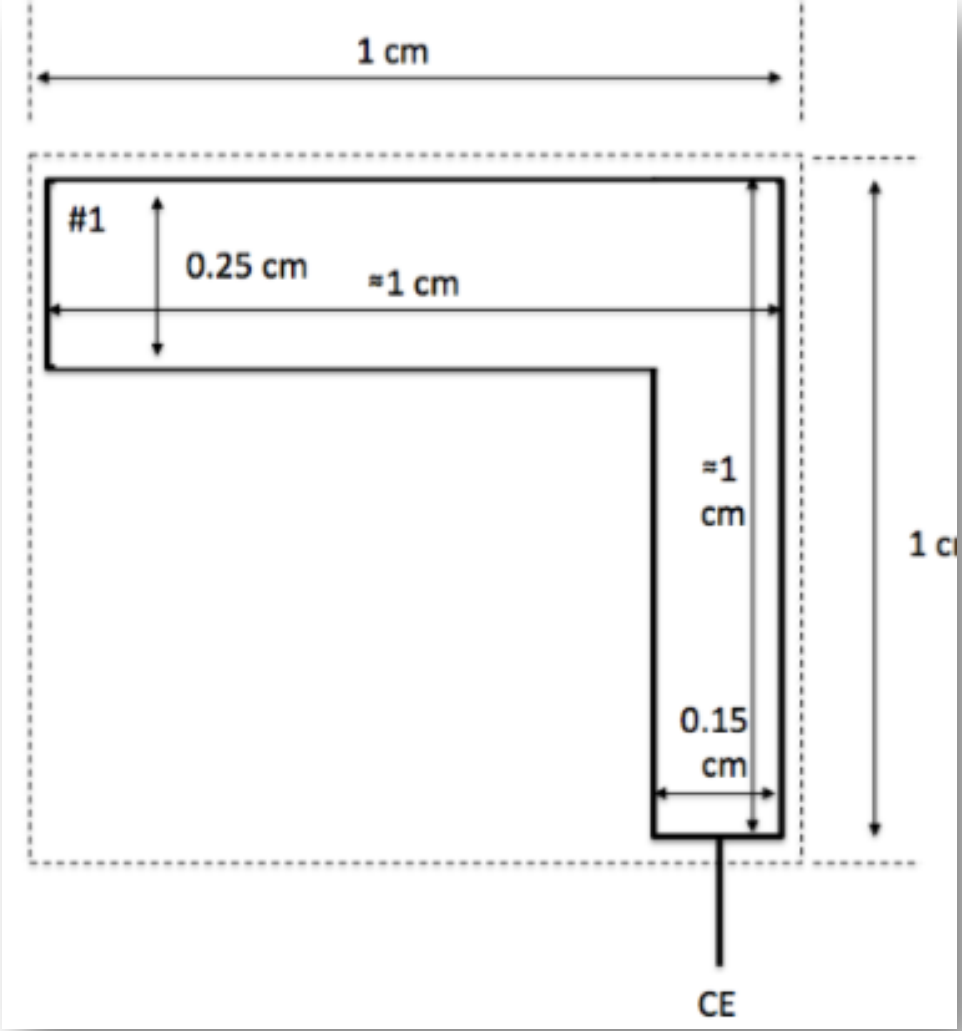
Amount LOX = Delta-RU x 1.47 ng ≈ (1.3418-1.3395) x 1.47 ng = 0.0034 ng = 3.4 pg

Exercise 3

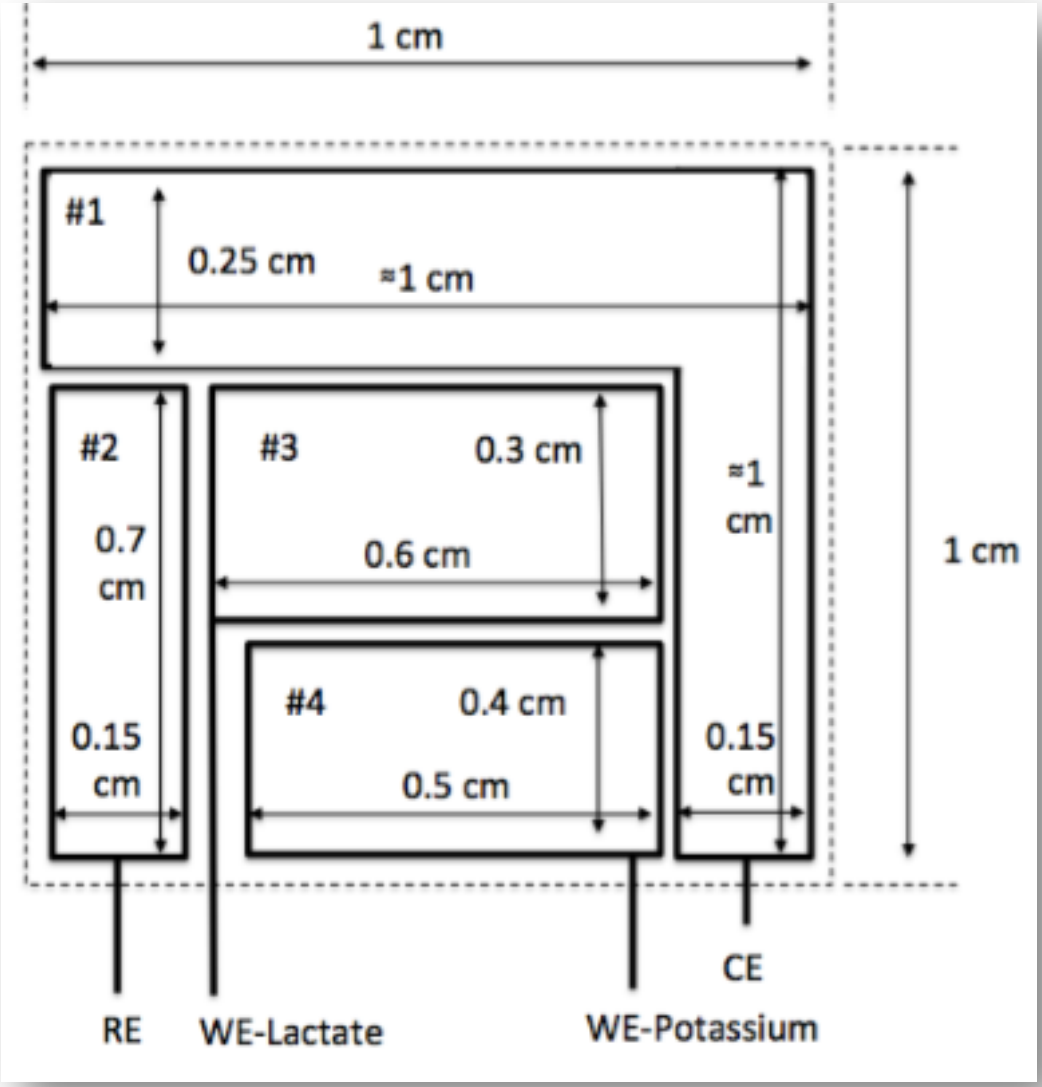
To realize the bio/CMOS interface of the planned wearable biosensing system, we need now to design the electrodes geometry of the sensing interface. System specifications require filling a maximum of surface area up to 1 cm^2. The electrodes' geometry needs to maximize the detection sensitivity as well as to minimize the risk of saturation of the electronic frontend, if any.

a) Complete the drawn reported in the following slide with the electrodes geometry you want to realize, comment and justify your choices in the design layout (e.g., why you choose a certain the number of electrodes? Why their size? Which is the electrode for Lactate? Which is the electrode for Potassium?). Set a number for each electrode in your interface.

Exercise 3



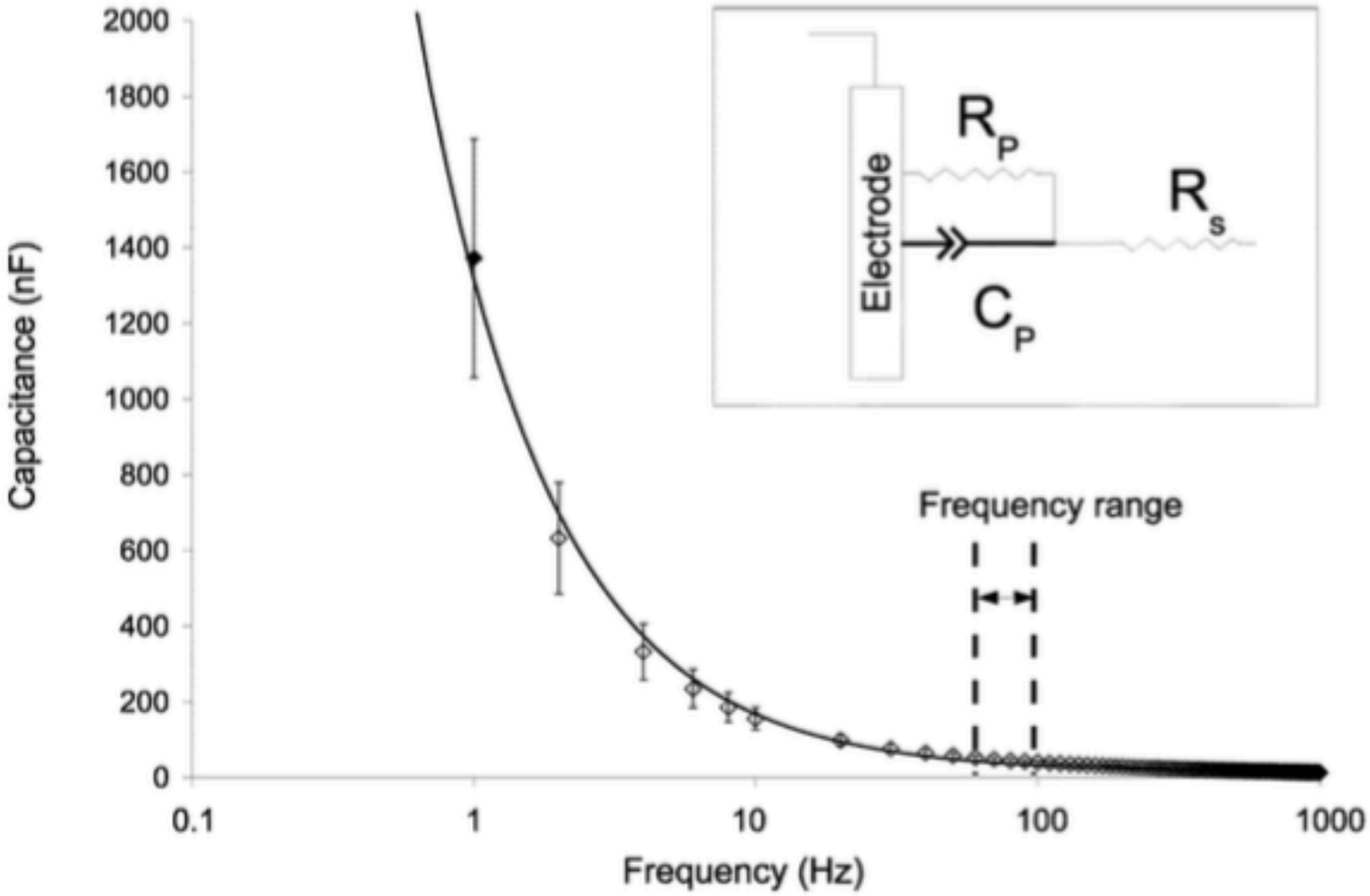
Solution: Exercise 3



Exercise 4

Let us consider now that the electrode you have designed for the detection of potassium in your previous drawing presents, before the deposition of the ion-selective membrane, the capacitive behavior in frequency as per the following slide.

Exercise 4


Capacitance (nF)
2000
1800
1600
1400
1200
1000
800
600
400
200
0
0.1
1
10
100
1000
Frequency (Hz)
Frequency range
Electrode
R_P
R_S
C_P

Clicker test

How much are the reactive and resistive components of its impedance at the frequency of 10Hz, by knowing that the phase (α) of its equivalent CPE behaviour has been measured to have the value of 0.8

A. 41 & 100 $k\Omega$

B.

C.

D.

Givens:

$\alpha = 0.8$

f = 10 Hz

$C_{CPE} = 160\text{x}10^{-9}$ F (read from the graph)

$$\omega = 2\pi f = 2\times 3.14\times 10\ rad/s = 62.8\ rad/s$$

$$C_P \cong C_{CPE}\times\alpha\times\omega^{1-\alpha}$$

$$C_P \cong (160\times10^{-9})\times(0.8)\times(62.8^{1-0.8}) = 293\times10^{-9}F = 0.3\ \mu F$$

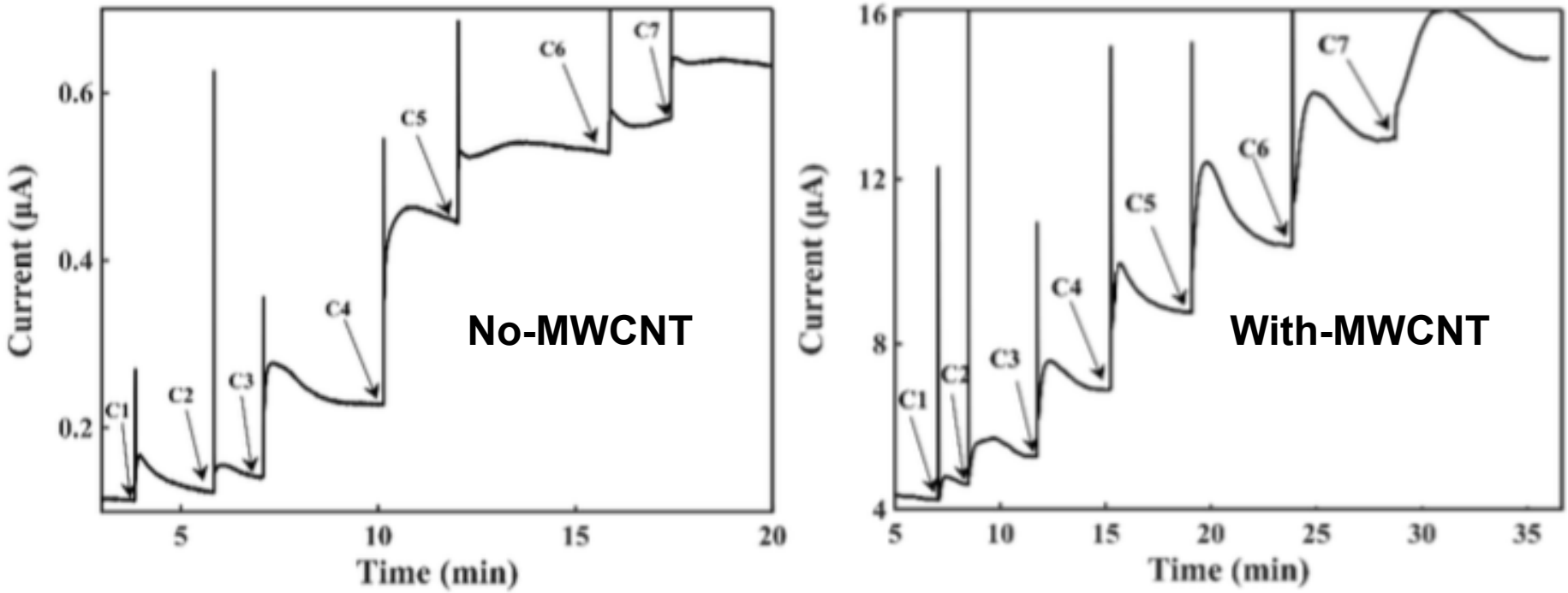
$$R_{CPE} \cong \frac{1}{\omega^{\alpha}C_P}\sqrt{(1-\alpha^2)} = \frac{1}{\omega^{\alpha}C_{CPE}\times\alpha\times\omega^{1-\alpha}}\sqrt{(1-\alpha^2)} = \frac{\sqrt{(1-\alpha^2)}}{C_{CPE}\times\alpha\times\omega} =$$

$$= \frac{\sqrt{(1-0.8^2)}}{293\times10^{-9}\times0.8\times62.8} = 40.8\times10^{-6}\times10^{+9} \approx 41\ k\Omega$$

$$X_{CPE} \cong \frac{\alpha}{\omega^{\alpha}C_P} = \frac{\alpha}{C_{CPE}\times\alpha\times\omega} = \frac{0.8}{160\times10^{-9}\times0.8\times62.8} = 99.6\times10^{-6}\times10^{+9} \approx 100\ k\Omega$$

Exercise 5

Consider now that some data have been acquired, as time-trends, on prototypes realized with the electrochemical interface you have designed to detect the lactate. The acquired data are here below reported.



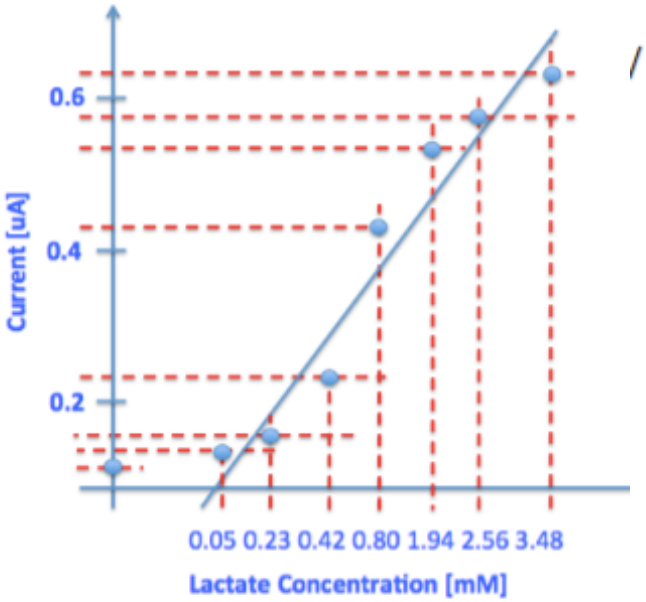
C1= 0.05 mM, C2= 0.23 mM, C3= 0.42 mM, C4= 0.80 mM, C5= 1.94 mM, C6= 2.56 mM, C7= 3.48 mM.

Clicker test

How much is the increase of the experimental sensitivity (in µA/mM) as due to the nano-structuration?

A. 10 times
B. 20 times
C. 30 times
D. 300 time

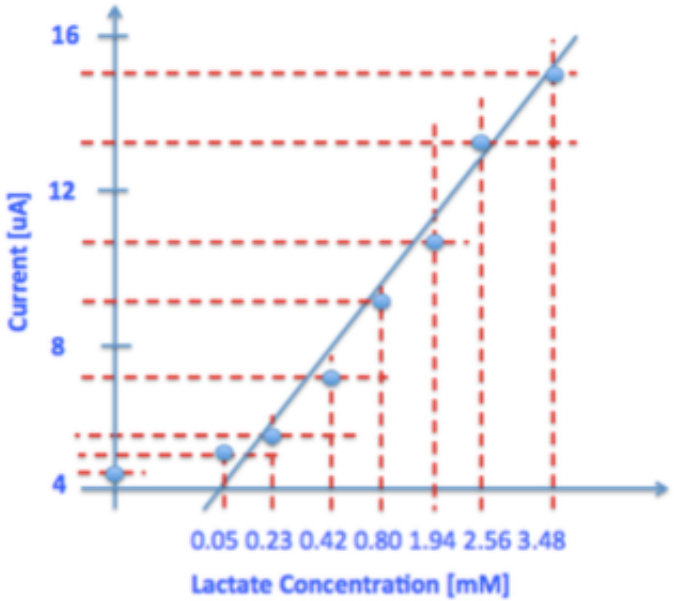
Calibration of lactate without MWCNT



Current = 0.11 µA for C1= 0.05 mM
Current = 0.64 µA for C7= 3.48 mM
S = ΔI/ΔC = (0.64-0.11)/(3.48-0.05)
S= 0.15 µA/mM

3.06/0.15 ≈ 20

Calibration of lactate with MWCNT



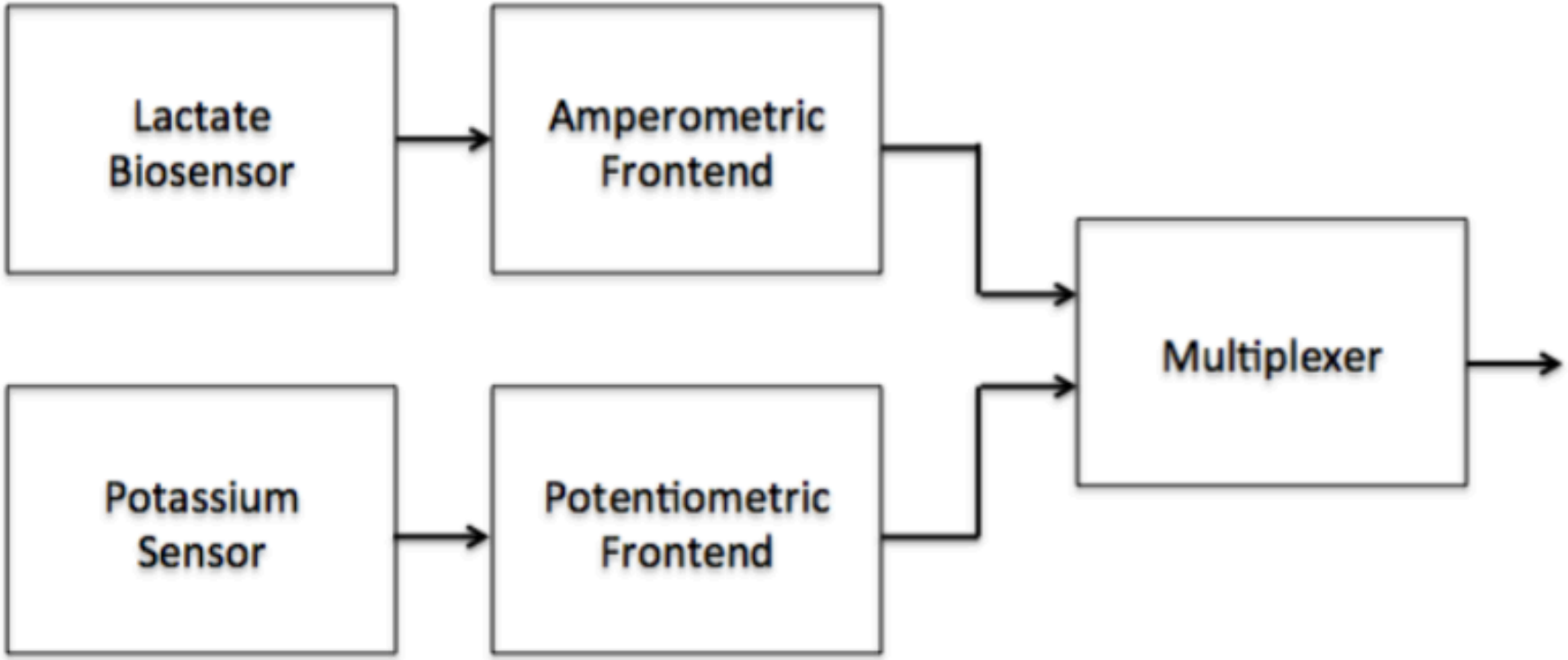
Current = 4.5 µA for C1= 0.05 mM
Current = 15.0 µA for C7= 3.48 mM
S = ΔI/ΔC = (15.0-4.5)/(3.48-0.05)
S= 3.06 µA/mM

Exercise 6

We need now to design the electronic circuit that can serve as CMOS frontend to detect the lactate and potassium in human sweat on the skin. System specifications require using the minimum number of transistors in order to minimize both chip area and power consumption, while maintaining a sufficiently good performance of the sensors' readout. This CMOS frontend is required to perform amperometric measurements for the lactate while providing the measures of the open-circuit-potential for the potassium.

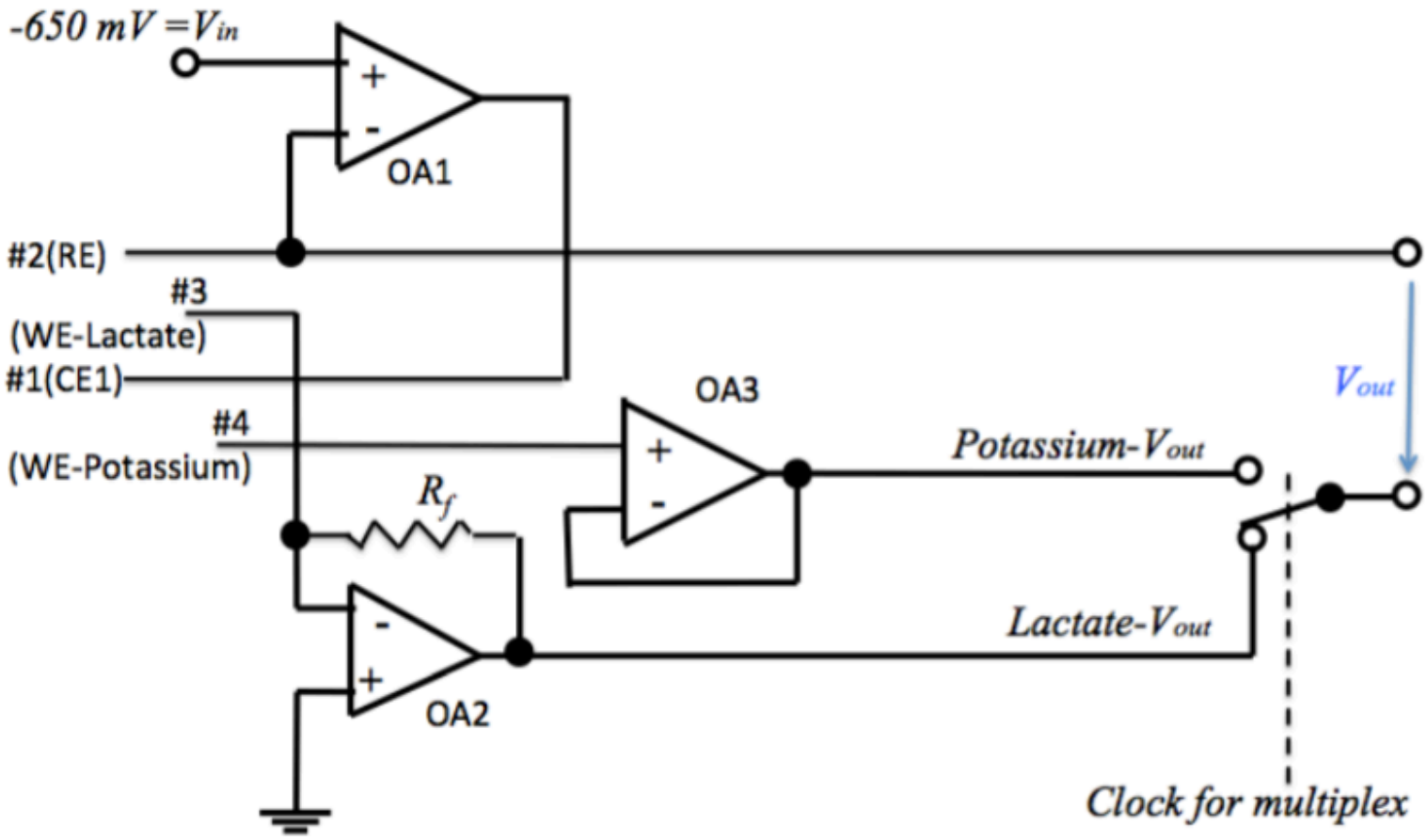
Exercise 6

a) Starting from the sensors you have foreseen in your sensing system, draw here the block diagram of the frontend system you plan to realize for driving all your sensors and acquiring data from them about lactate and potassium.



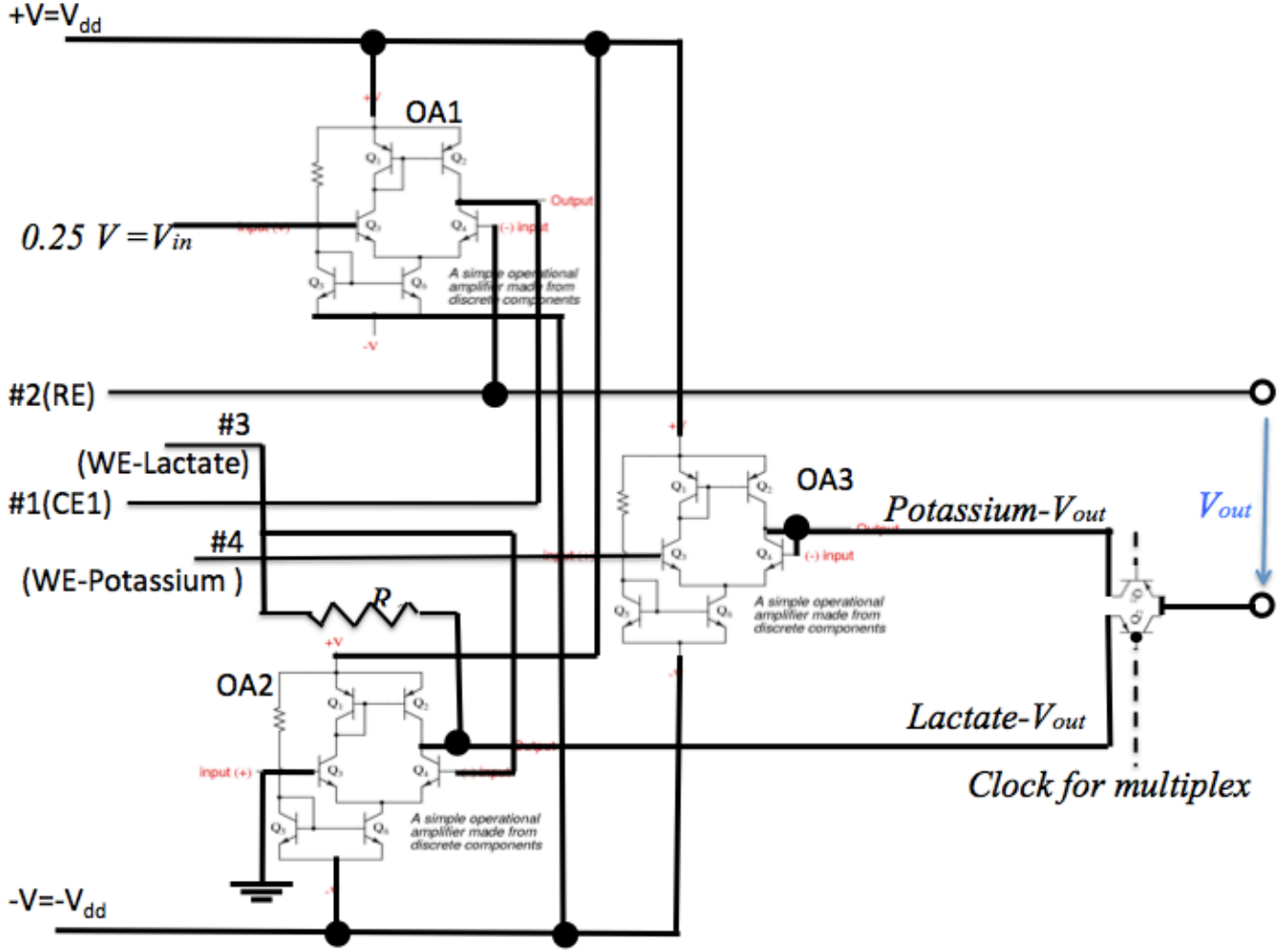
Exercise 6

b) Draw here the circuit of your frontend system at level of each Operational Amplifier. Please, minimize the number of used OpAmp.



Exercise 6

c) Draw now the circuit of your frontend system at level of each single transistor. Please, realize here with the minimum-possible-number of transistors.



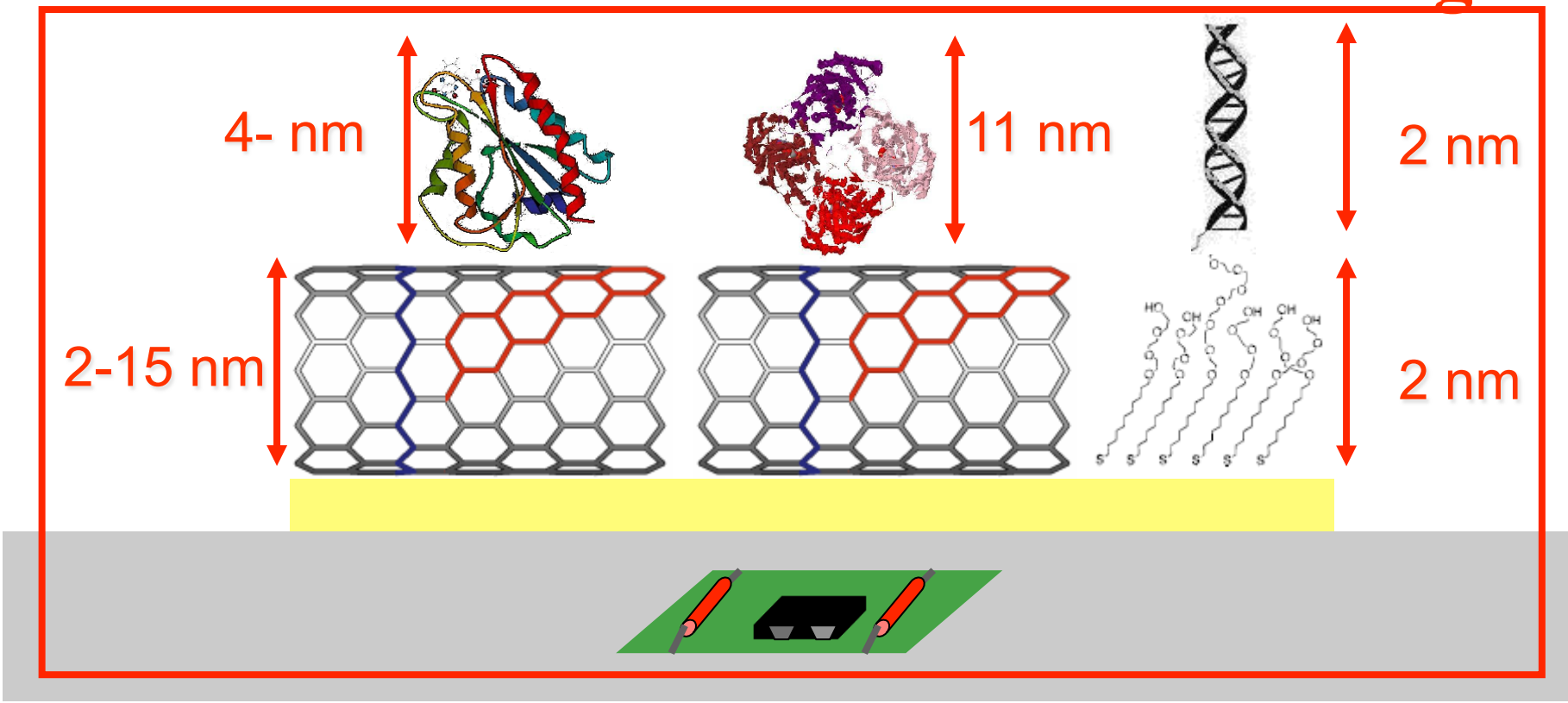
Clicker test

Do you think we need other sensors for calibrations on board of our wearable biosensing system?

A. No, neither lactate nor potassium sensors require any calibration
B. Yes, calibration for T of the skin
C. Yes, calibration for T-&-pH of the skin
D. Yes, more than calibrations for T-&-pH: several ions interferes with K^+

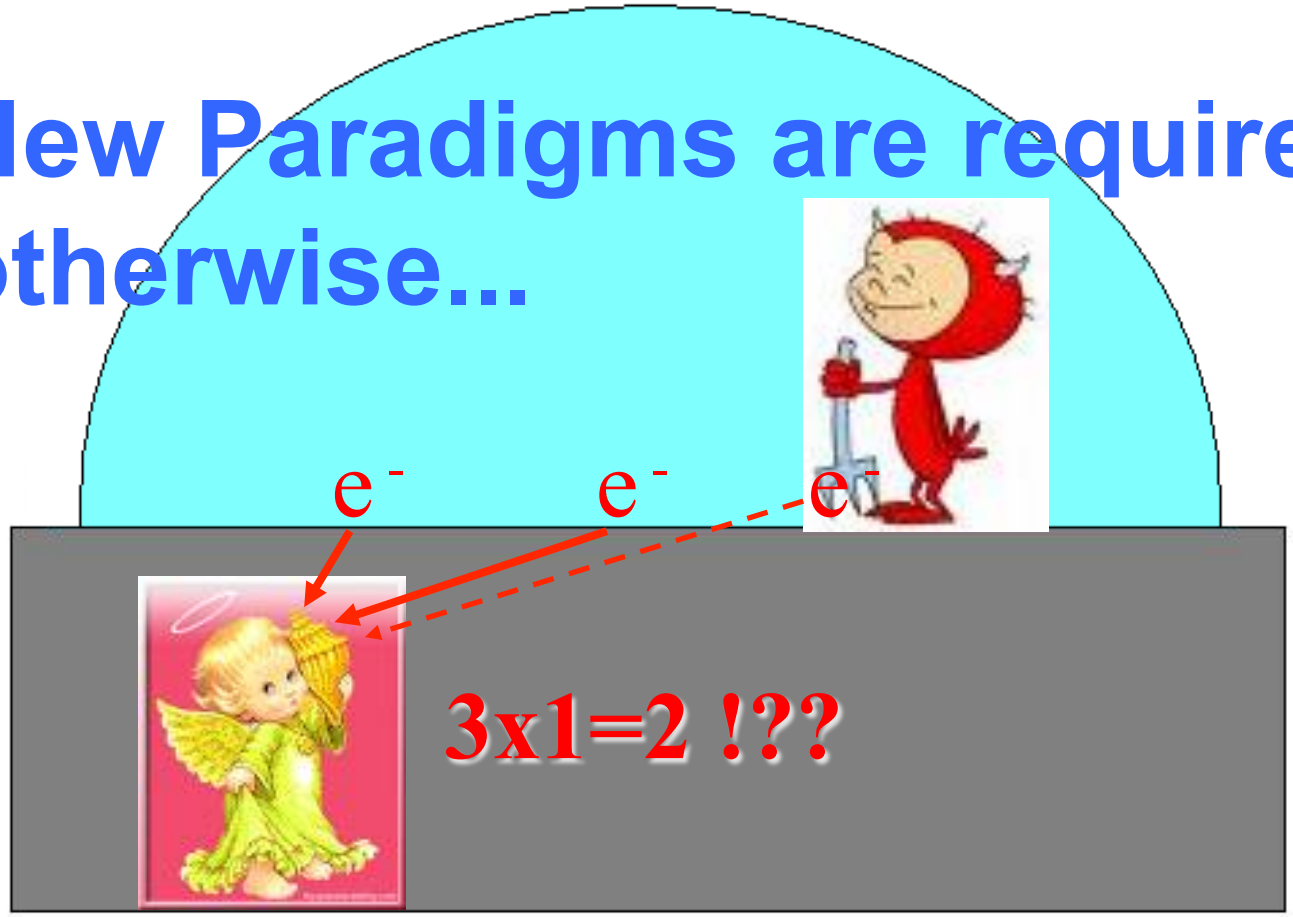
Take Home message by the course

Bio/Nano/CMOS Co-Design!



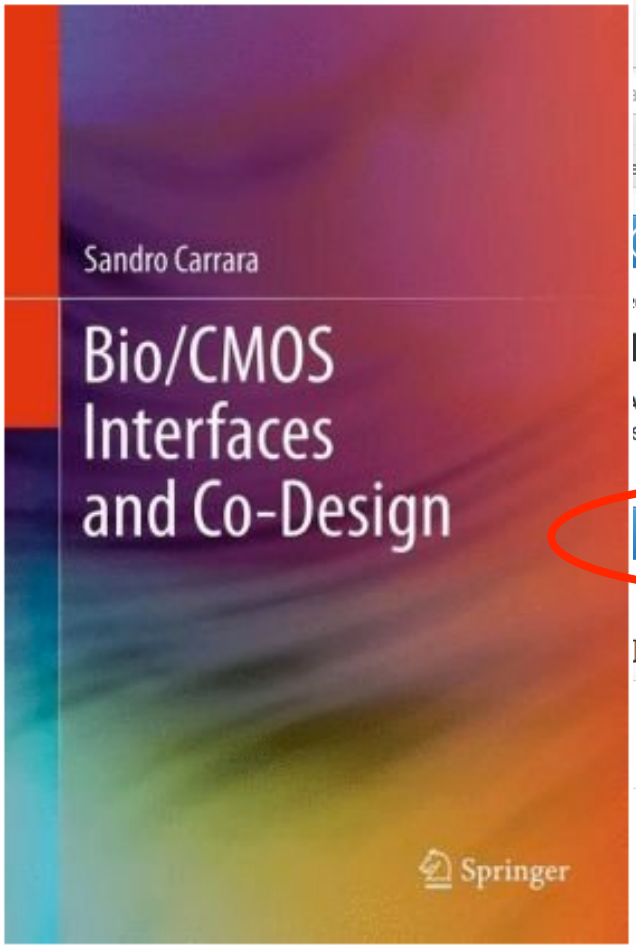
New paradigms for Nano-Bio-CMOS co-design are required to succeed in chip bio-sensing

New Paradigms are required otherwise...



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

The Course Textbook



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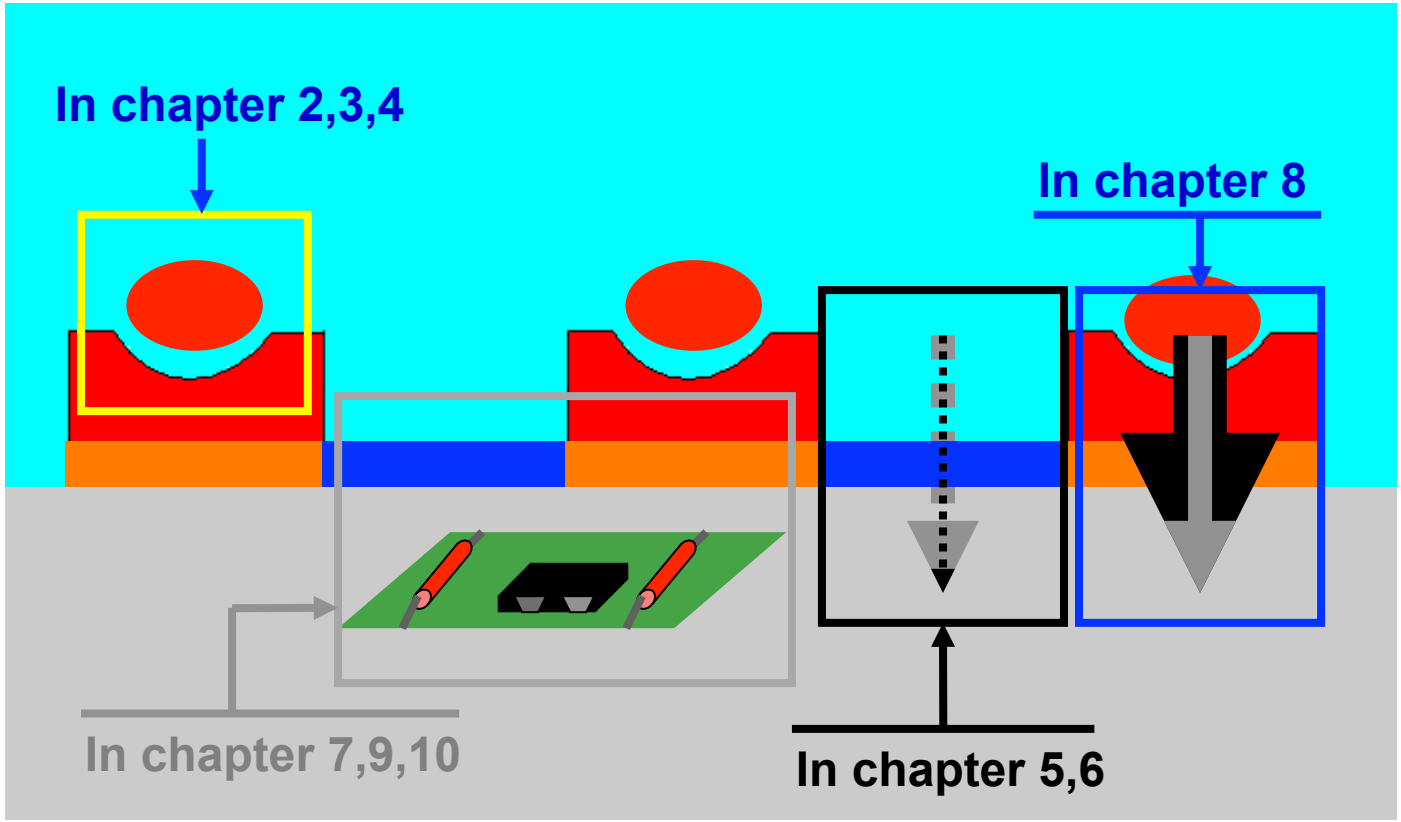
Bio/CMOS interface book



Introduction to Personal electronics, Distributed Diagnostics, and Bio/CMOS interfaces in Chapter 1