

**EPFL**

**Electrical and Electronics Engineering**

**EE-517**

# Bio-Nano-Chip Design

# EPFL

Electrical and Electronics Engineering

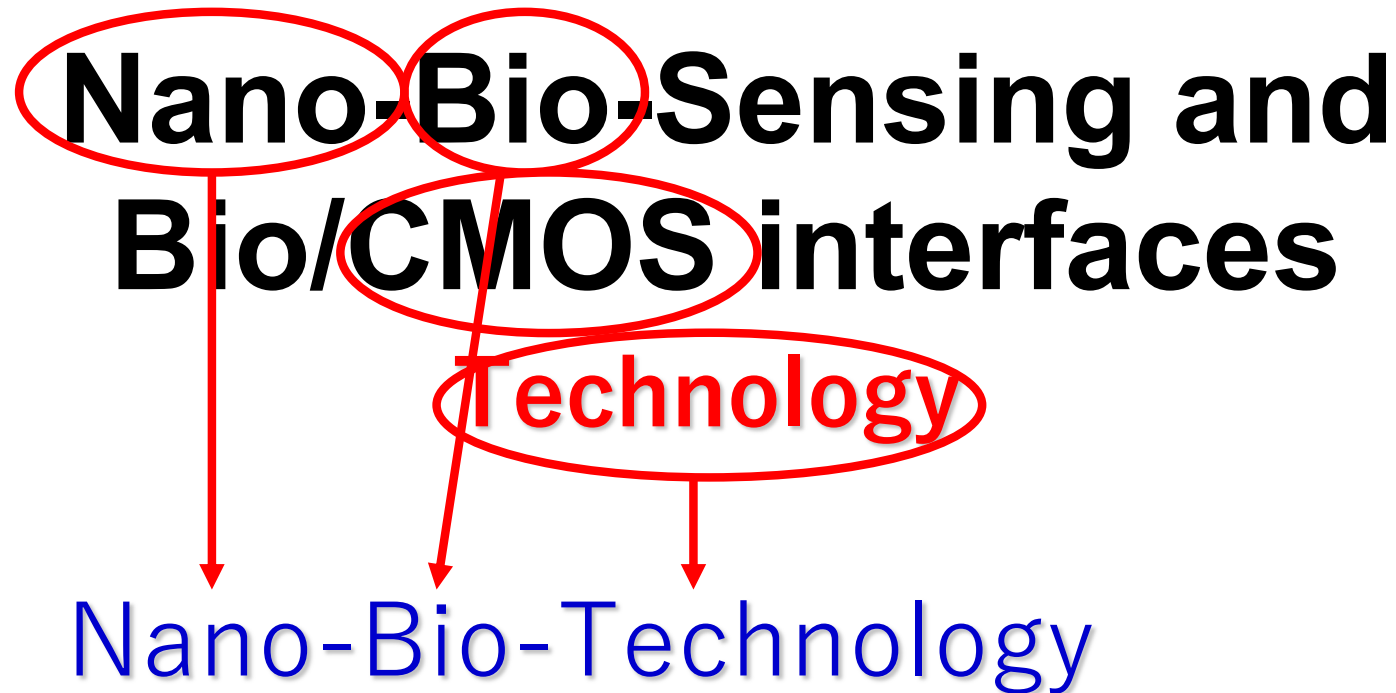
## EE-517

# Bio-Nano-Chip Design

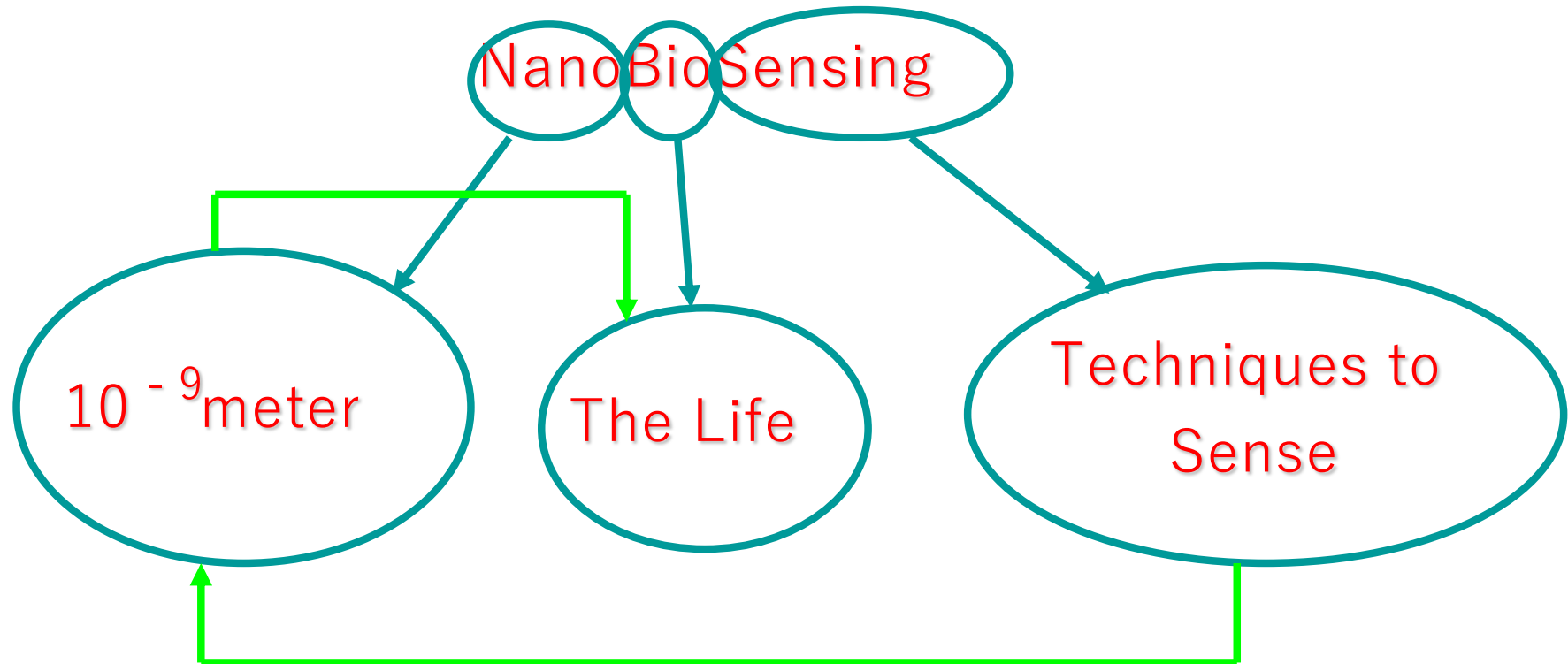
**1. LECTURES by videos  
(on SWITCHtube)**

**1. Q/A on Zoom  
(link by Moodle)**

What's about The Course?



# What's about Nano-Bio-Sensing?



That means “techniques at the nano-metric scale to sense information related to biological processes”

# The Motivation



- 100.000 \$ (machinery)
- 1.000 \$ the single  $\mu$ -array

Labeled



Label-Free

- 50 \$ (machinery)
- 0.05 \$ the single strip

# The Quicklab project by Siemens



# Glucometer on iPhone



# Next step: the future already begun

How to use the FreeStyle Libre System

1. **Apply sensor** with applicator
2. **Scan sensor** using FreeStyle Libre Reader
3. **Get reading** on the reader

FOR FULL INSTRUCTIONS  
[www.freestylelibre.co.uk](http://www.freestylelibre.co.uk) >

OVERVIEW  
**HOW TO USE**  
FIND OUT MORE

The infographic illustrates the three-step process of using the FreeStyle Libre System. It features a woman in a white t-shirt with a sensor on her upper arm, holding a black FreeStyle Libre Reader. The steps are: 1. Apply sensor with applicator, 2. Scan sensor using FreeStyle Libre Reader, and 3. Get reading on the reader. A navigation menu on the right includes 'OVERVIEW', 'HOW TO USE' (highlighted in yellow), and 'FIND OUT MORE'. A website link 'www.freestylelibre.co.uk' is provided for full instructions.

Glucose Personal Diagnostics on our Skin

(c) S.Carrara



Q4

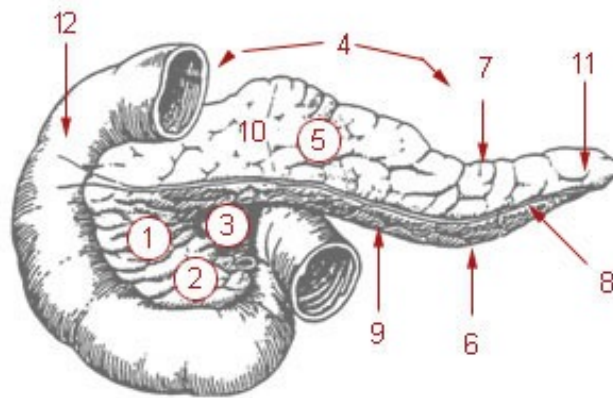
Does the pancreas just measure the glucose and produce insulin?

- A. Yes, nothing else
- B. Yes, that's the central organ for our glucose metabolism
- C. No, but that's one of its important functions
- D. No, but that's its most important functions
- E. Not at all

# The Pancreas Functions

## IN-put Signals

- Bile acids →
- pH →
- Syrinic proteases →
- Glucose →
- Glycagone pancreatic →
- .....



## OUT-put Signals

- insulin
- Lipase
- Fospholipase A
- Cholesterol esterase
- Endopeptidase
- Esopeptidase
- Elastase
- Ribonuclease
- Enterochinase
- .....

# What to sense?

<b>Simple Molecules</b>	<b>Glucose (Diabetes)</b> <b>Cholesterol (heart attack )</b>
<b>Proteins</b>	<b>AFP (Hepato Carcinoma)</b> <b>PSA (Prostate)</b>
<b>DNA sequences</b>	<b>PC-1 gene (prostate cancer)</b> <b>p53 gene (Hepato Carcinoma)</b>

**Bio-Markers may be simple molecules,  
proteins or genes**

# What else to sense?

**Endogenous  
Metabolites**

**Insulin (Diabetes)**

**$\beta$ -blockers (heart attack )**

**Anti-cancer  
compounds**

**Cyclophosphamide (Breast Cancer)**

**Docetaxel (Prostate Cancer)**

**Anesthetics**

**Propofol (surgery)**

**Midazolam (surgery)**

Endogenous and Exogenous Metabolites  
are usually simple molecules

# What to sense?

Simple  
Molecules

Glucose (Diabetes)

Cholesterol (heart attack )



Proteins

AFP (Hepato Carcinoma)

PSA (Prostate)

DNA  
sequences

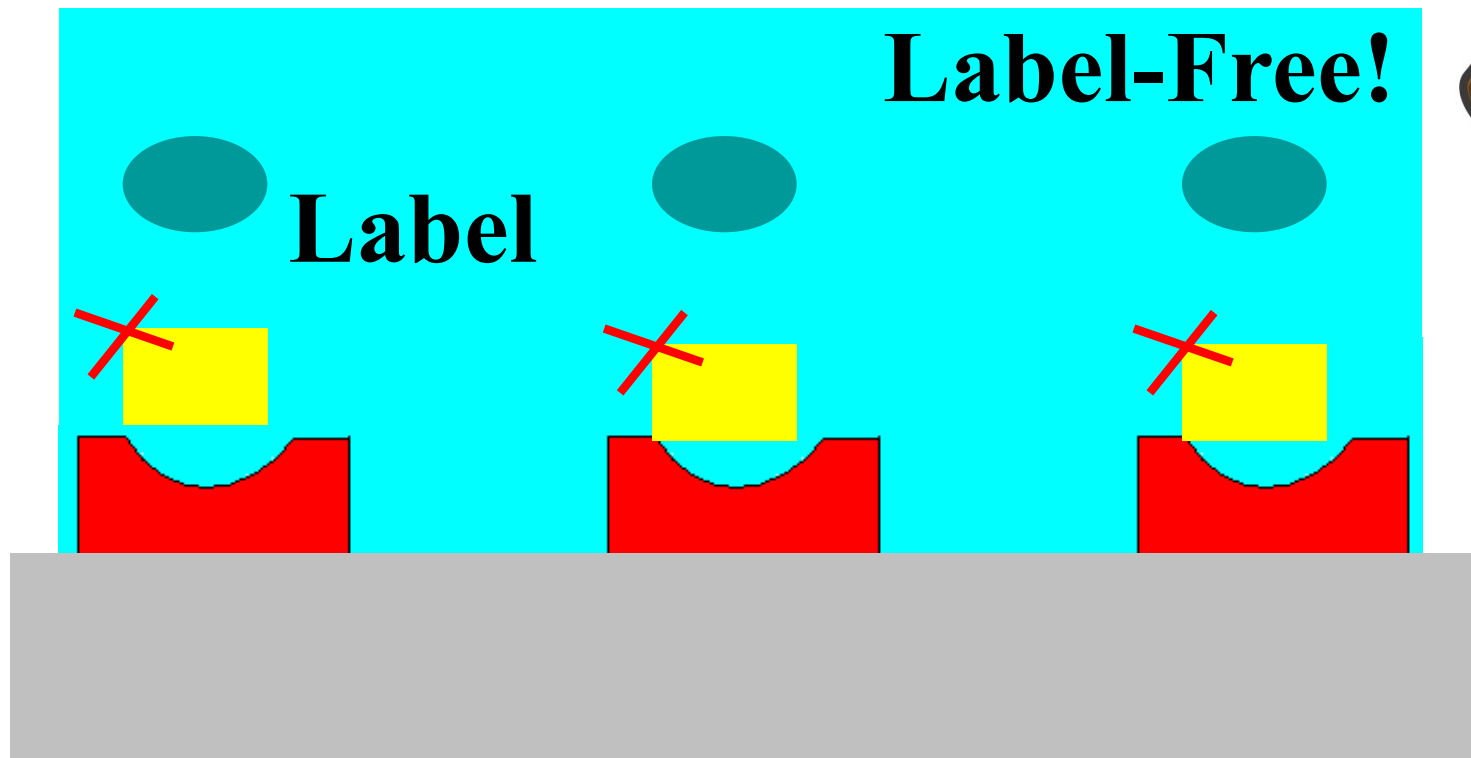
PC-1 gene (prostate cancer)

p53 gene (Hepato Carcinoma)

How to  
detect Bio-  
Markers?

Bio-Markers may be simple molecules,  
proteins or genes

# Measuring Bio-Markers



The Measure of Bio-markers may be performed in a labeled manner or in label-free mode



Q5

Do we can measure any other molecule like we do for glucose?

- A. Yes, of course!
- B. Yes, but it requires efforts
- C. Yes, but requires little modifications
- D. Yes, but depends by the applications
- E. Not at all



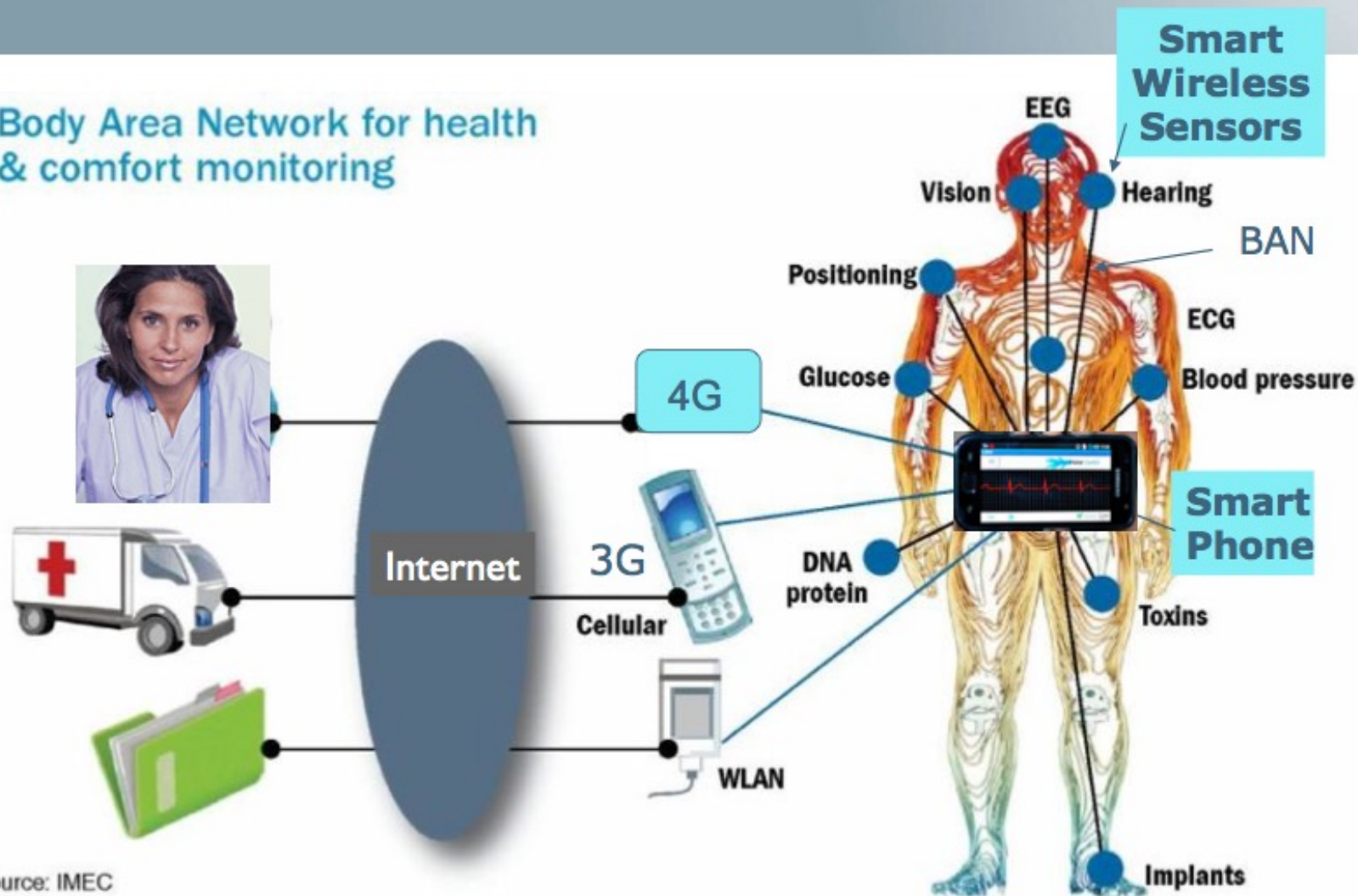
Q6

# Why we do not measure directly the insulin?

- A. Since an insulin sensor doesn't exist
- B. Since an insulin sensor does exist but it's too expensive
- C. Since an insulin sensor does exist but it's not enough sensitive
- D. Since an insulin sensor does exist but it's not commercially available
- E. Since that's not useful

# Fully-Connected Human++

Body Area Network for health & comfort monitoring



Source: IMEC

Courtesy, Hugo De Man (IMEC)

# The Time' forecast on Human++



[TIME, February 2011]

# Chips under the skin?



## Under the skin: how insertable microchips could unlock the future

Volunteers in Melbourne have had microchips inserted for three months, designed to unlock doors and carry out other tasks. Will they really be any use?

THEGUARDIAN.COM

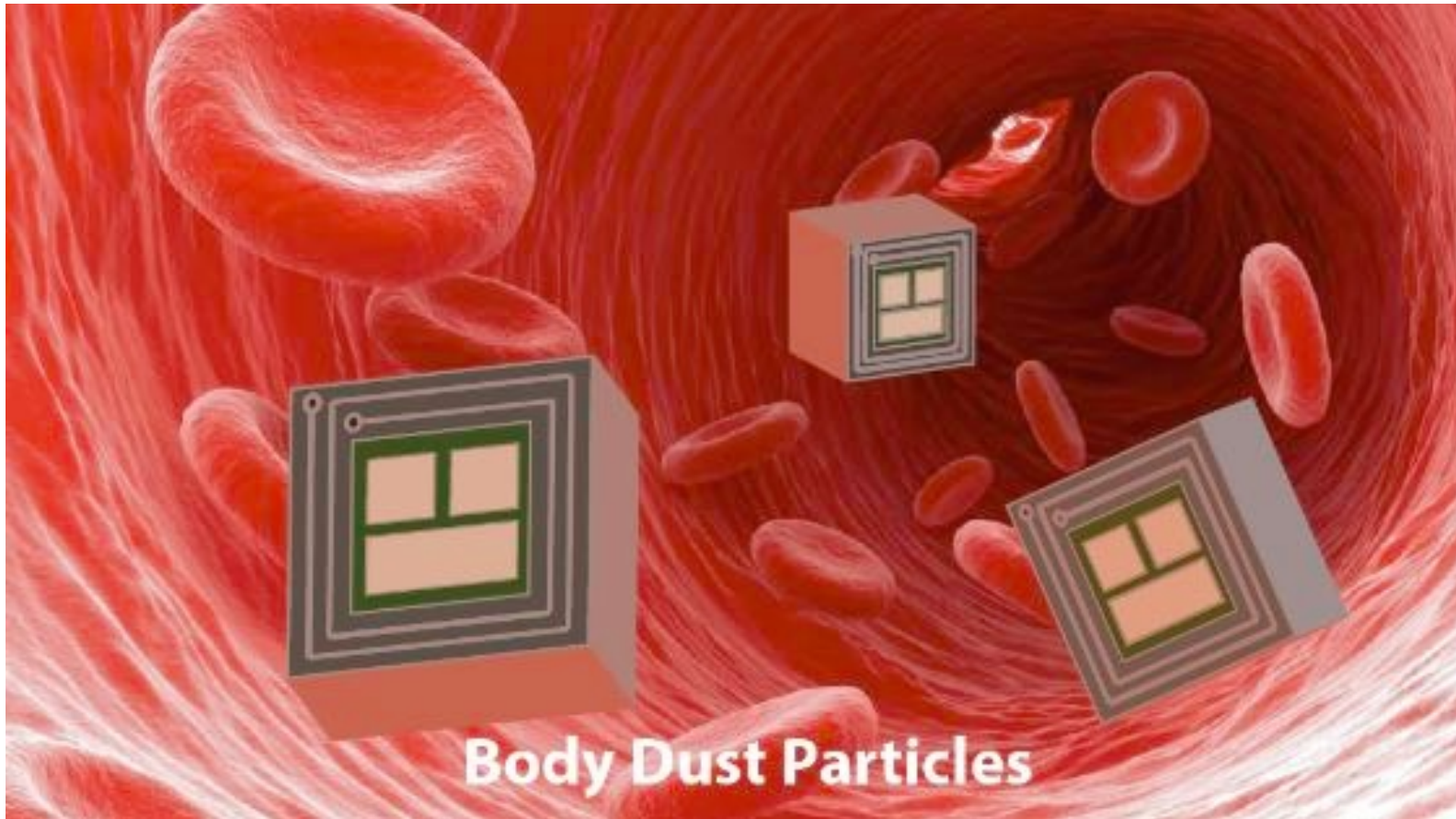
[The Guardian, October 2017]

# How small Chips under the skin?



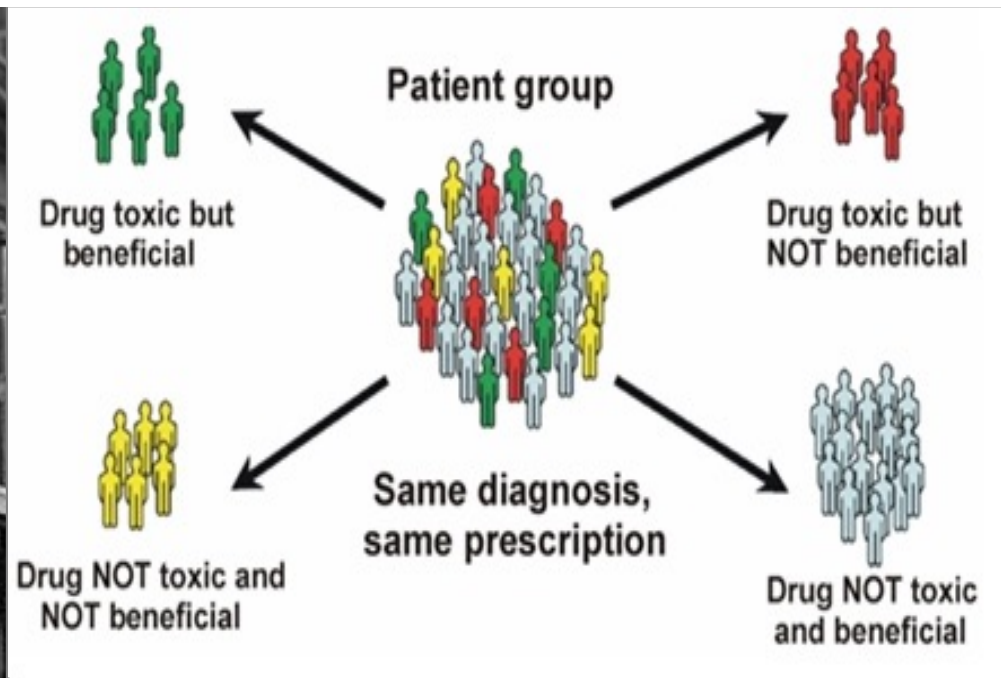
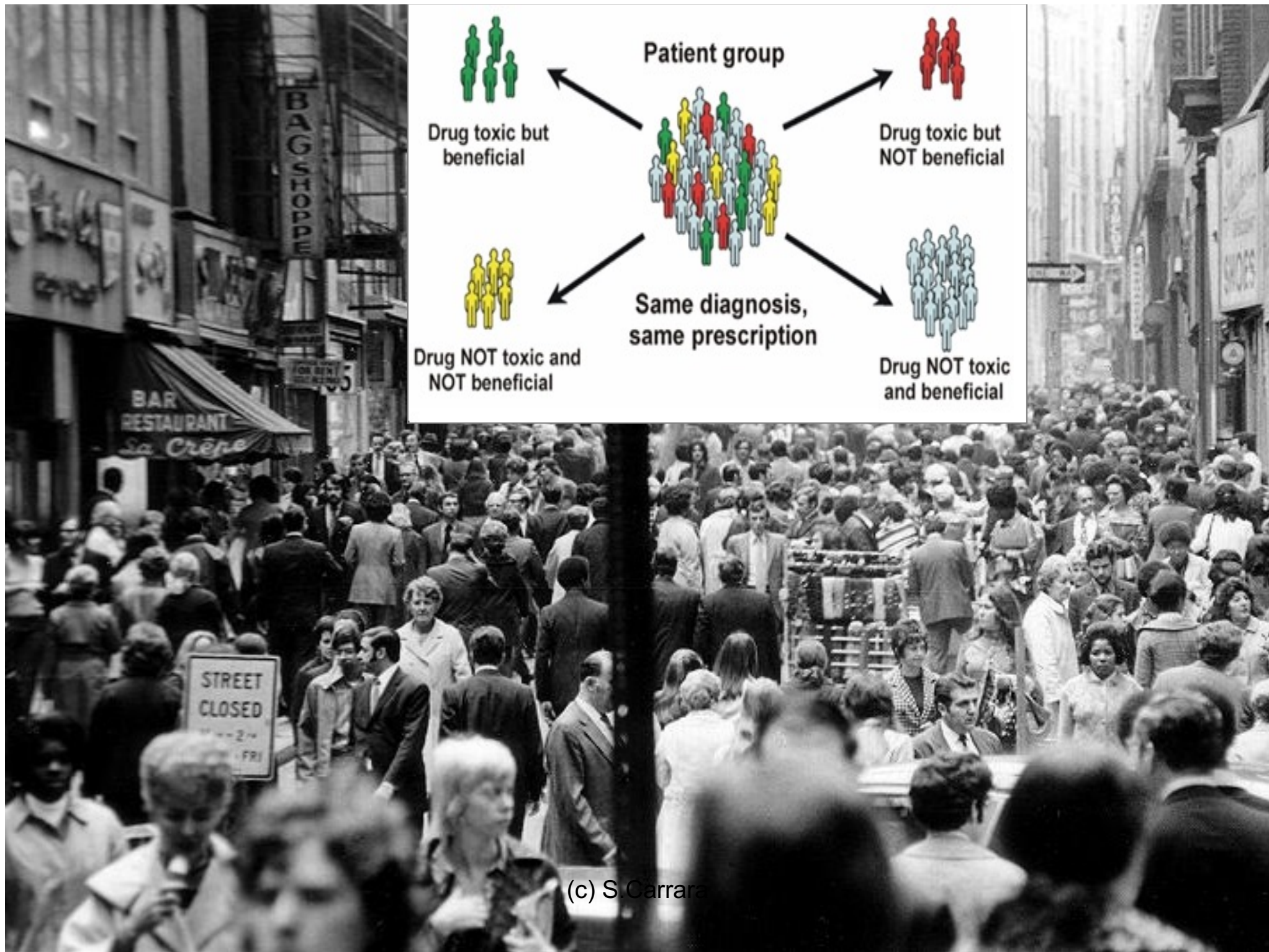
[1966 Sci. Fi. movie titled "Fantastic Voyage"]

# Body Dust: Drinkable CMOS Bioelectronics



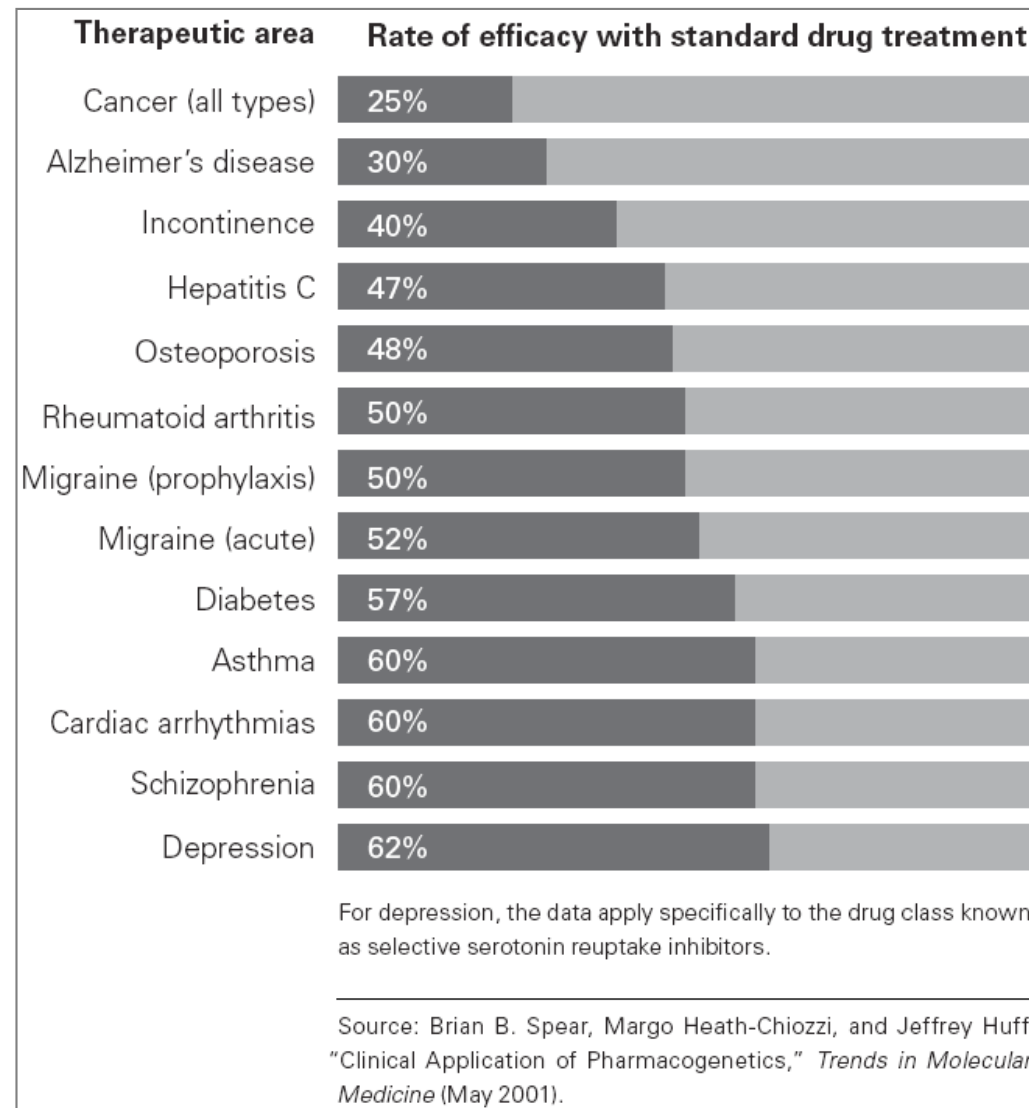
Tracking cancer-cell developing “drinkable” electronic sensors

<https://actu.epfl.ch/news/tracking-cancer-cell-development-with-drinkable-el/>



(c) S. Carrara

# Low efficacy of used compounds



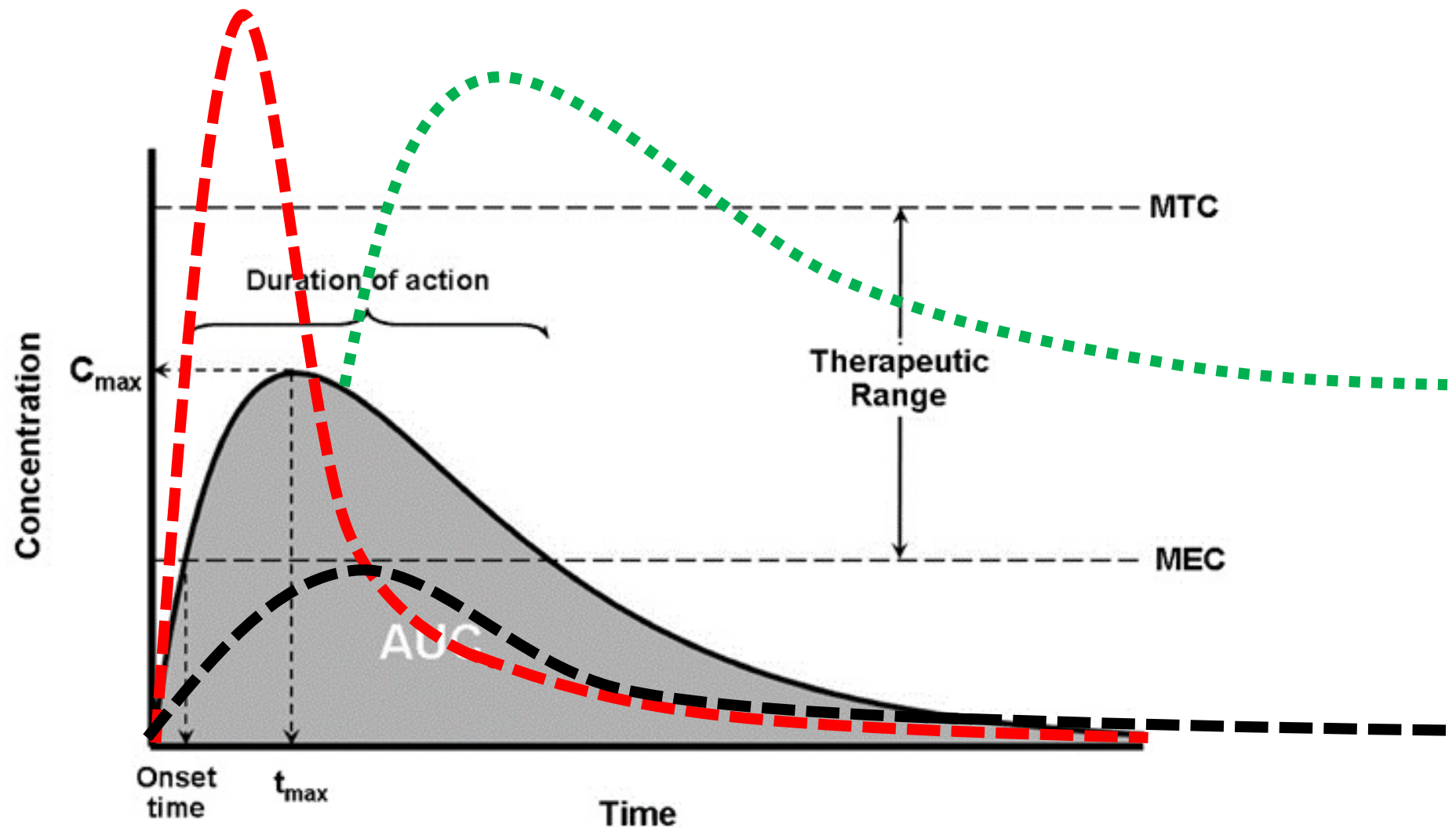


Q7

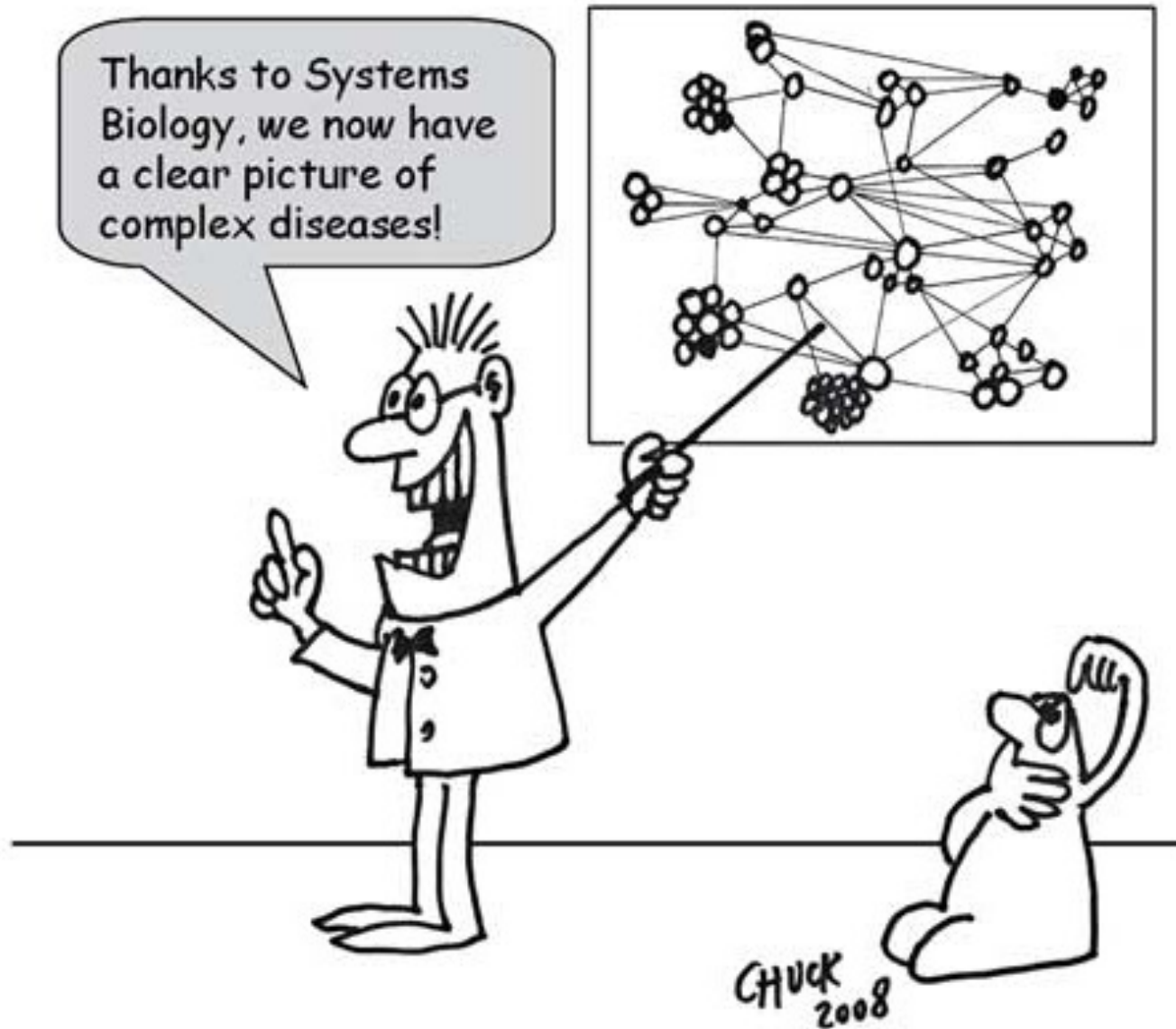
# Why different outputs from same kind of patients?

- A. Since therapy effect is random
- B. Since patient's response to therapy is random
- C. Since therapy effect depends on dose
- D. Since therapy effect depends on patient
- E. No reasons

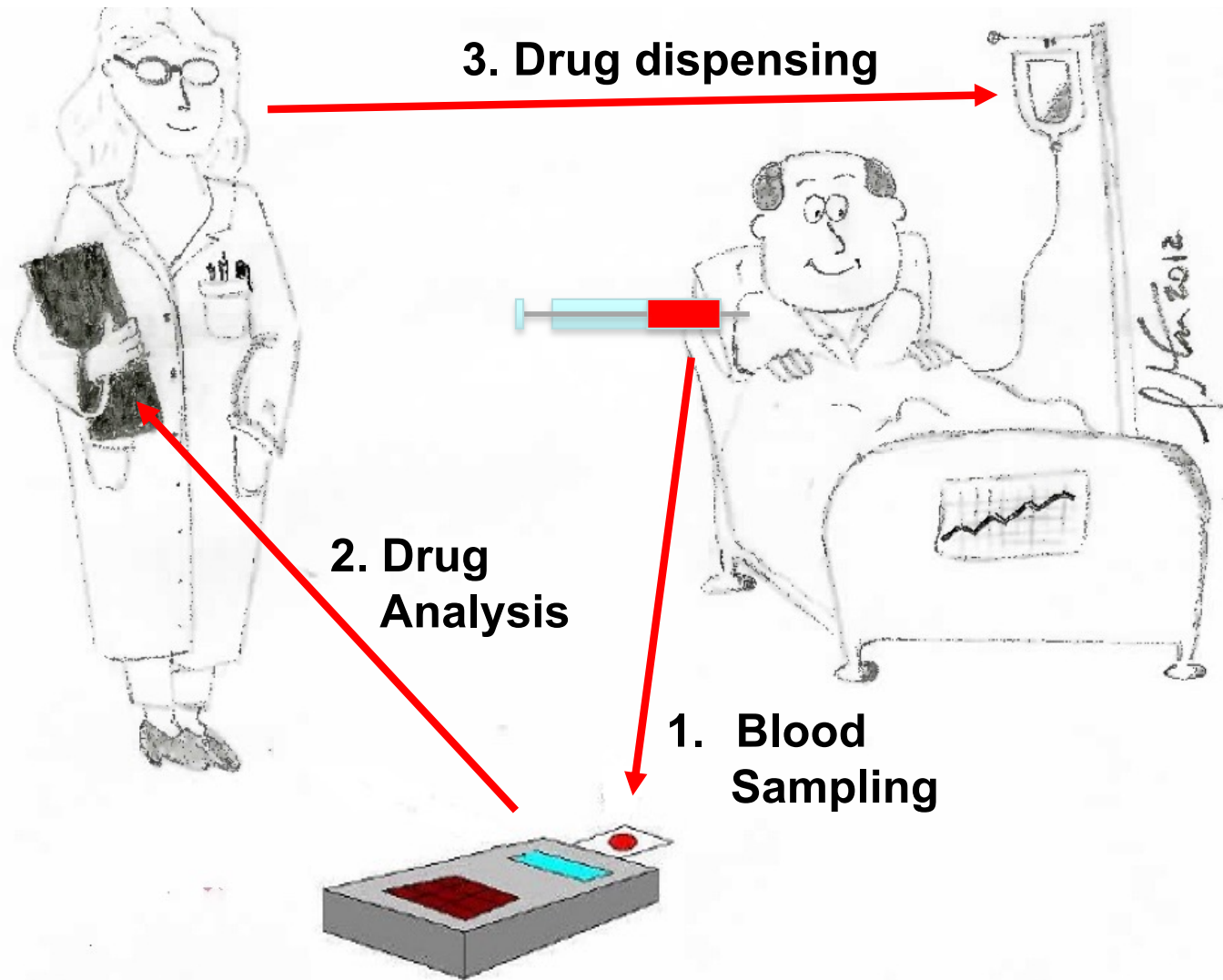
# Personalized Therapy: the right dose in the right moment!



# System Biology is not enough



# Personalized Therapy

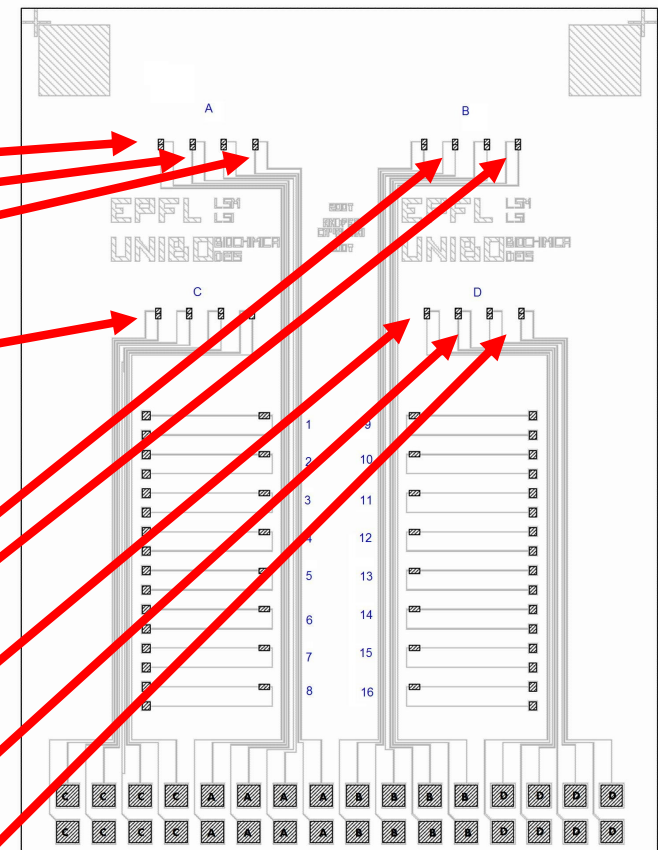


Drugs injection based on patient's pharmacokinetics

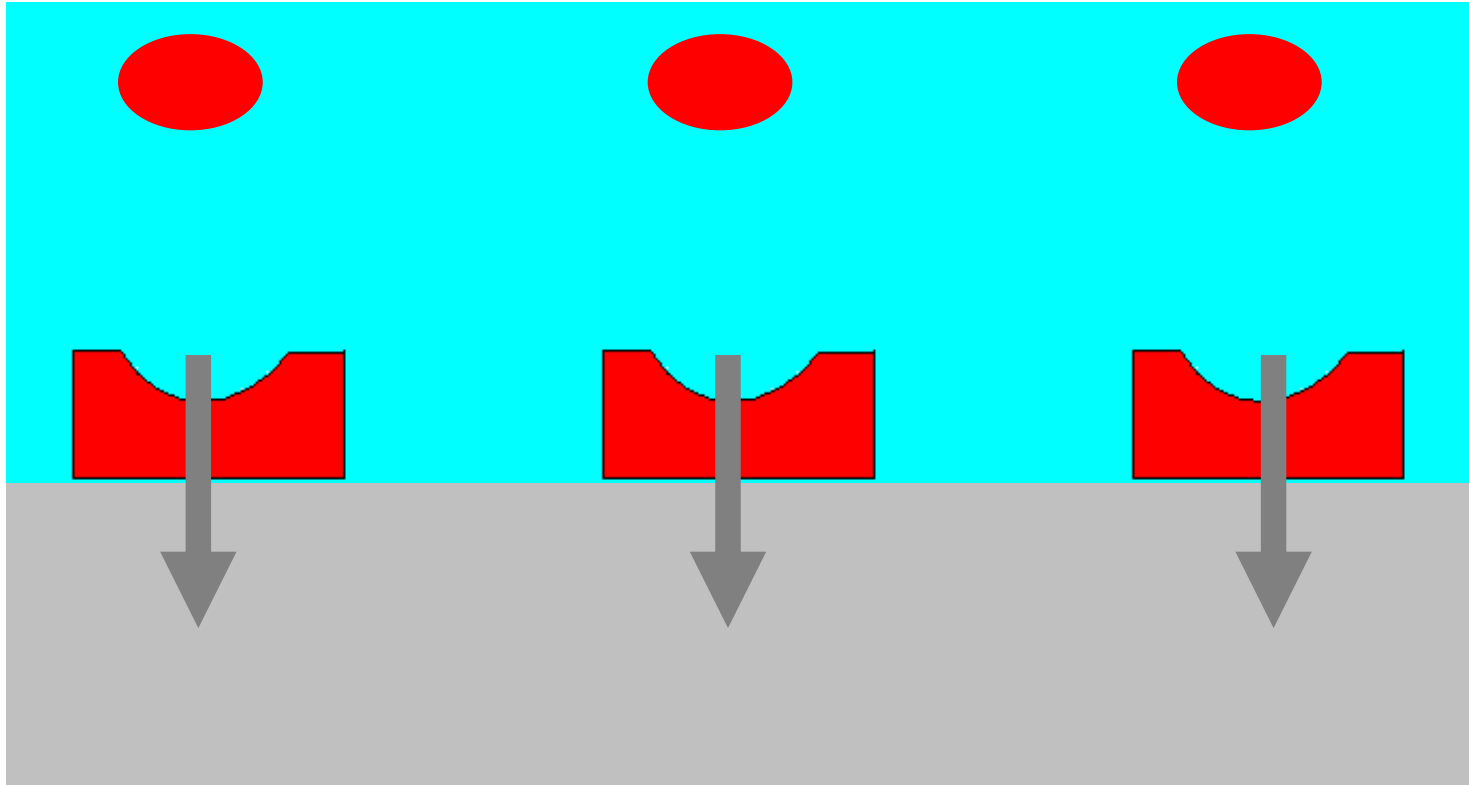
# The need for new Bio/CMOS systems

## TARGETS

Endogenous metabolites	Exogenous metabolites
Glucose	
Lactate	
Glutamate	
Cholesterol	
	Benzphetamine
	Dextromethorphan
	Cyclophosphamide
	Flurbiprofen
	Naproxen

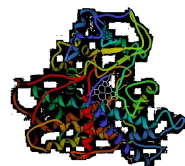


# CMOS/Sample interface



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

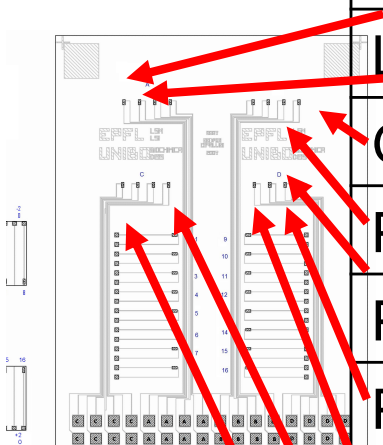
# Applications in Personalized Therapy



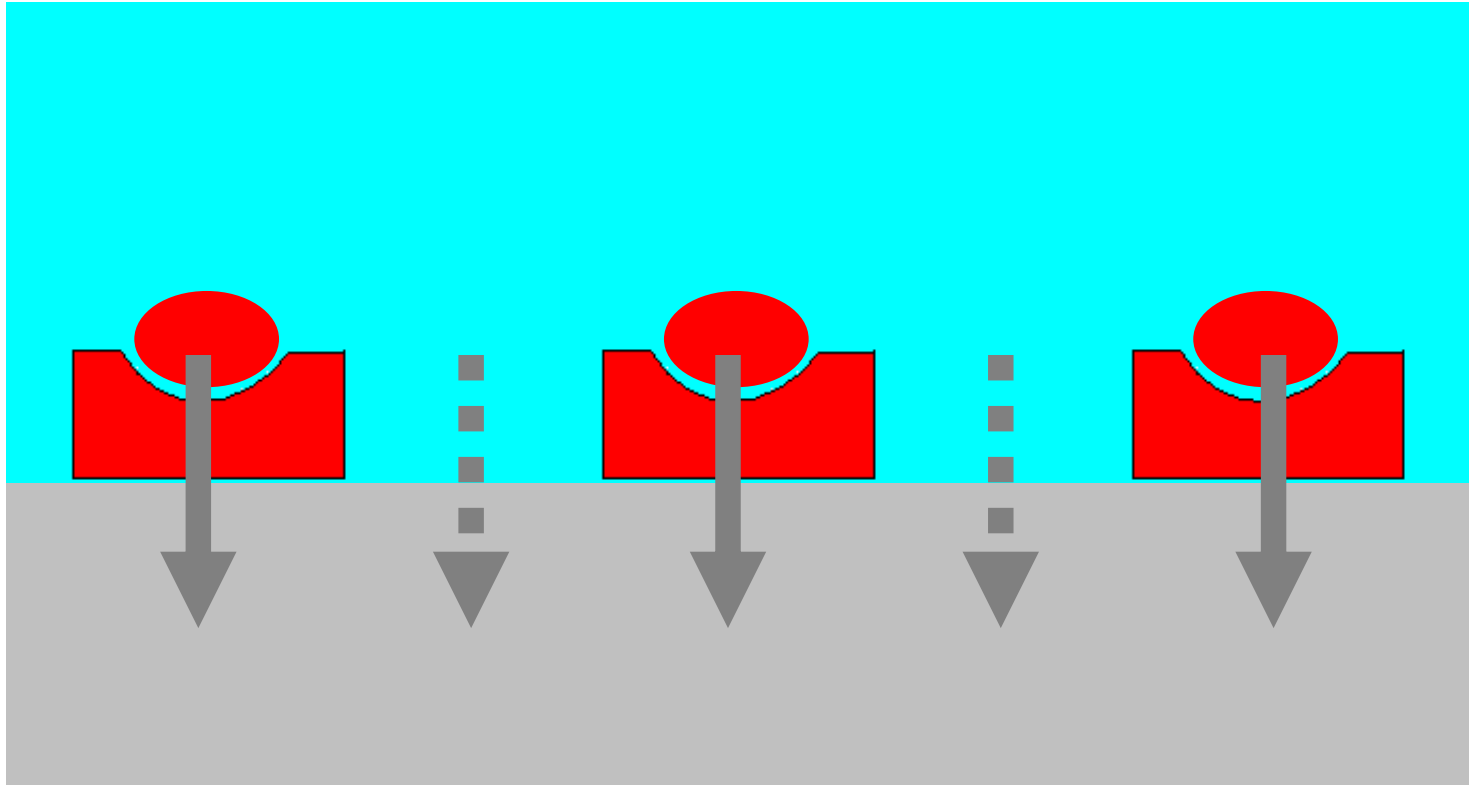
## TARGETS



Probe Enzymes	Endogenous metabolites	Exogenous metabolites
Glucose Oxidase	Glucose	
Lactate Oxidase	Lactate	
Glutamate Oxidase	Glutamate	
P450 11A1	Cholesterol	
P450 2B4		Benzphetamine
P450 3A4		Dextrometorphane
P450 3A4		Cyclophocphamide
P450 2C9		Flurbiprofene
P450 2C9		Naproxene



# CMOS/Sample interface



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

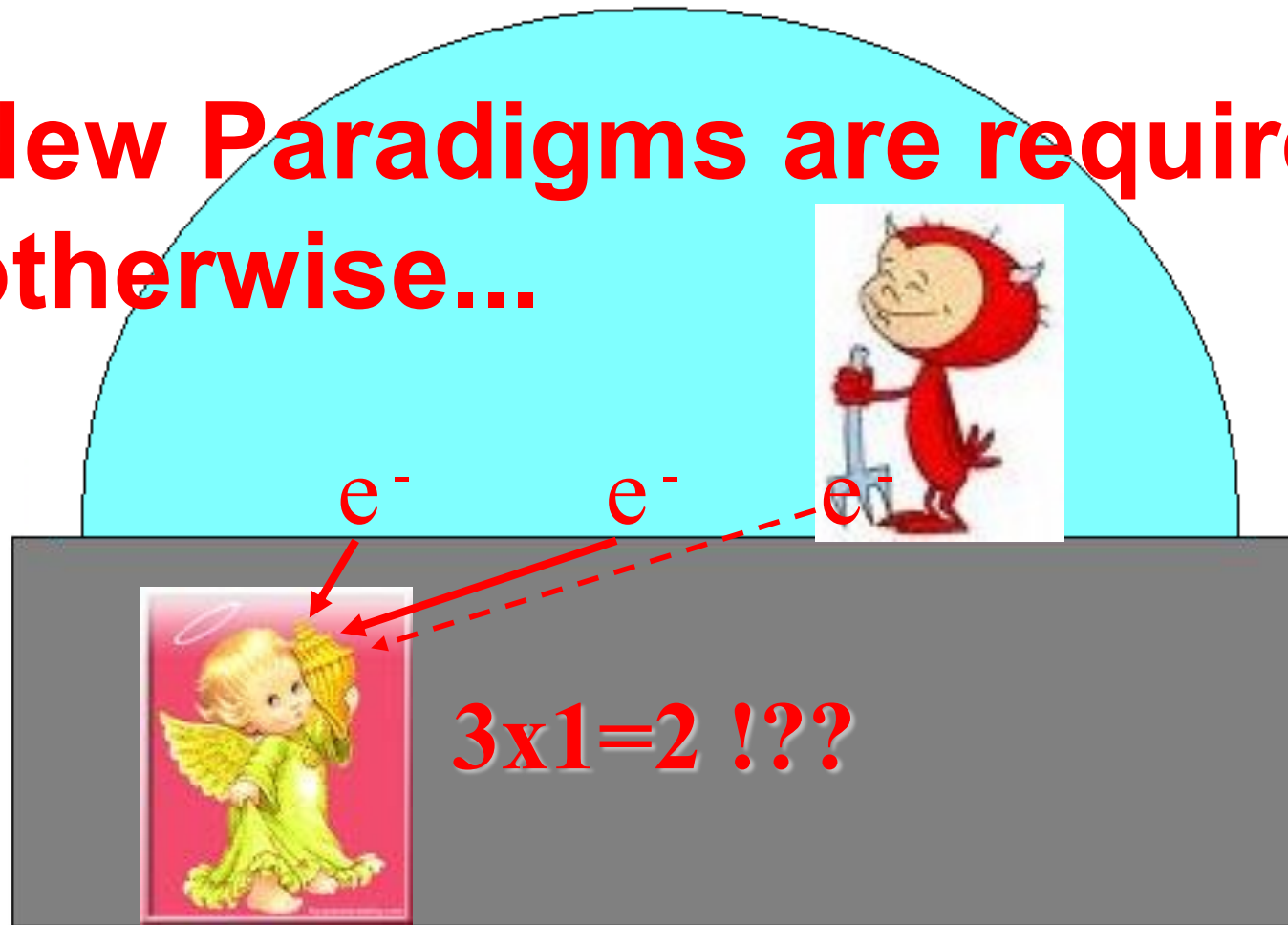


Q8

# Does present implantable CMOS chips allow metabolism monitoring?

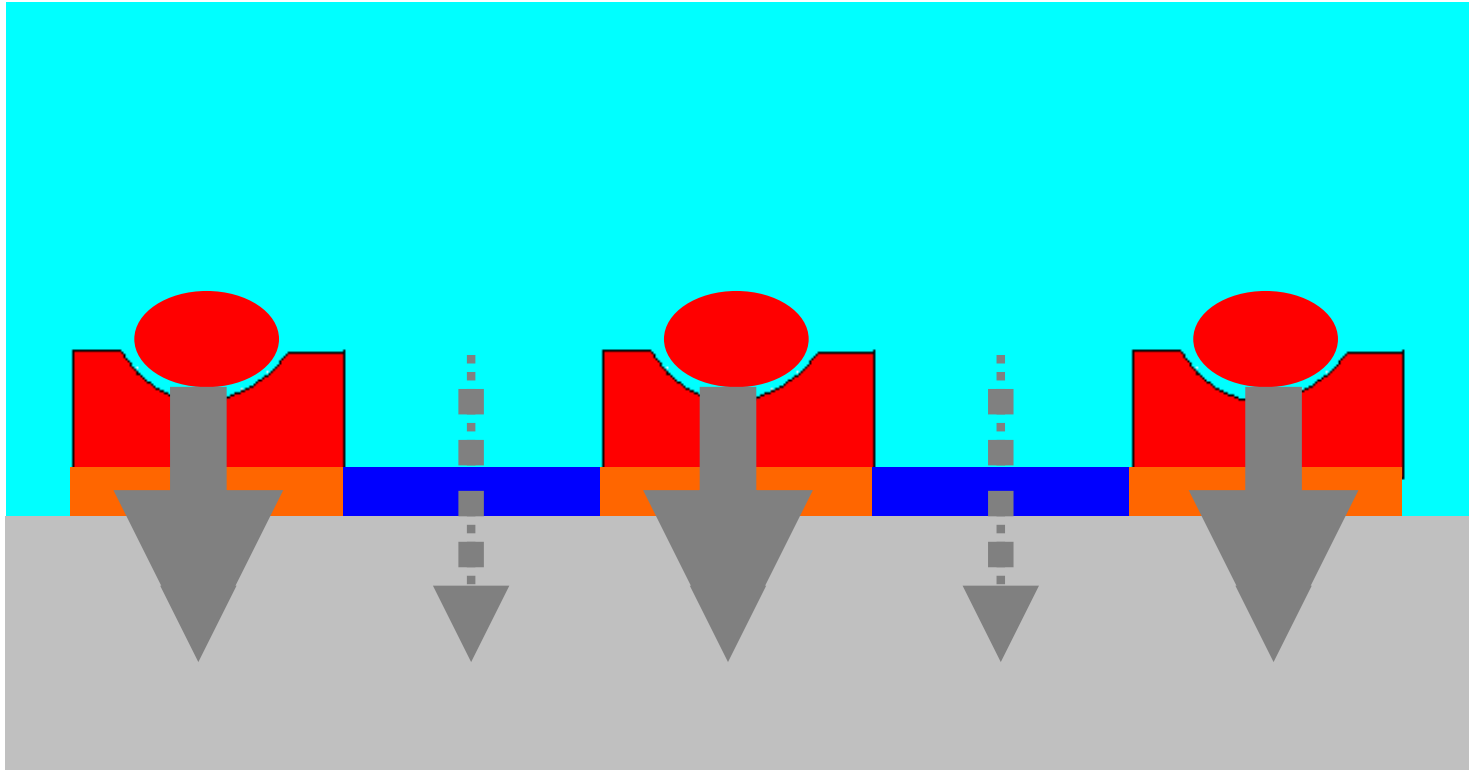
- A. Not really
- B. No if monitoring is non-related to glucose
- C. No if monitoring is related to more metabolites
- D. Yes, since they measure average parameters
- E. Yes, that's easy to be done

**New Paradigms are required  
otherwise...**



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

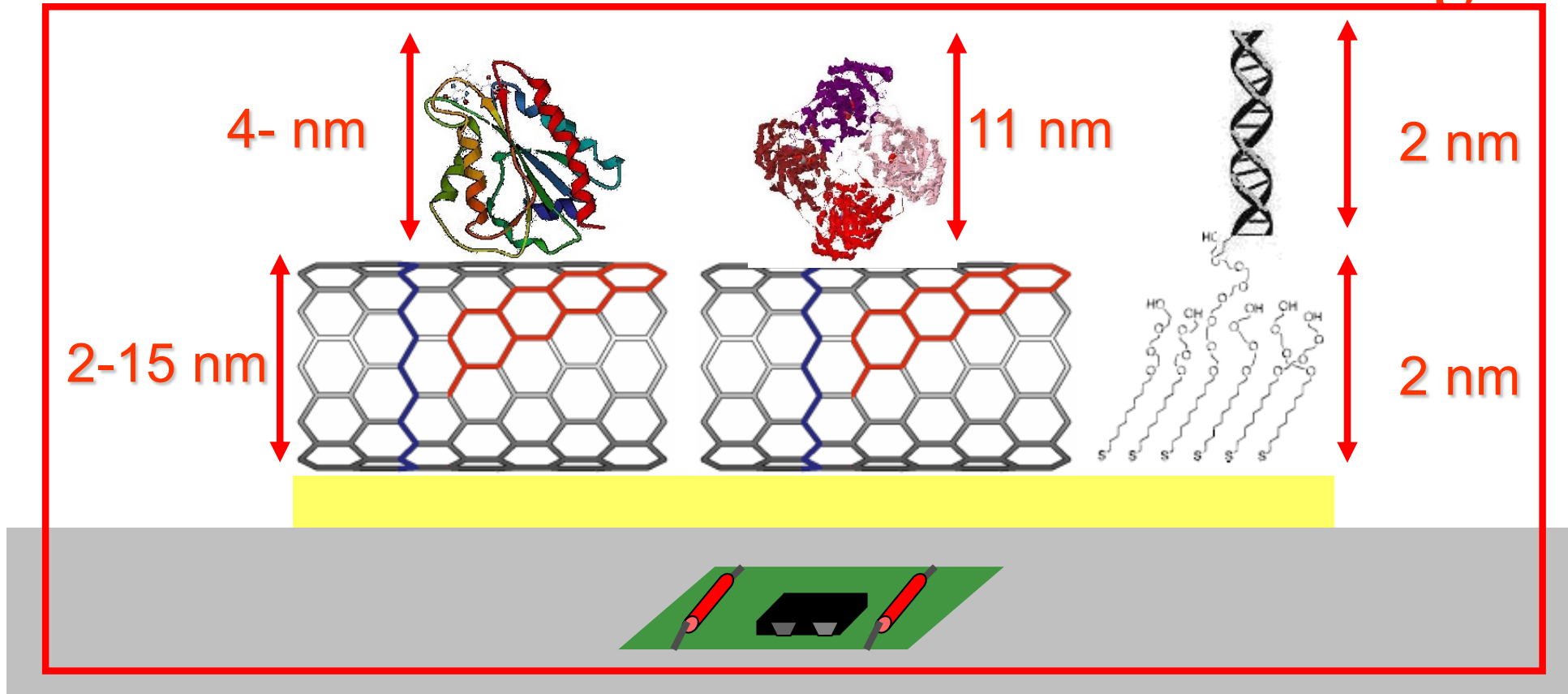
# CMOS/Sample interface



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

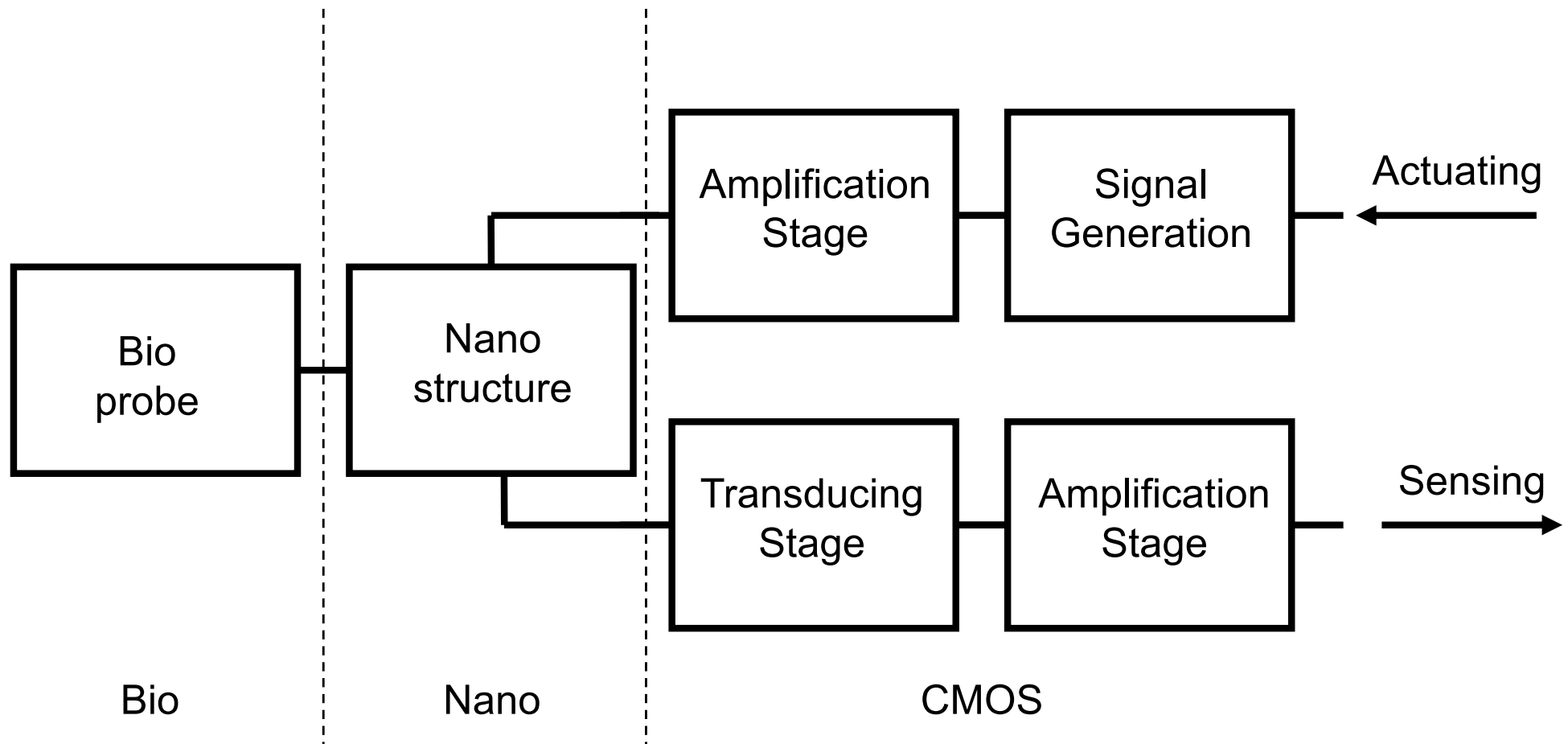
# New Approach

## Bio/Nano/CMOS Co-Design!



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

# Design of the all interfaces



## The Bio/Nano/CMOS interface

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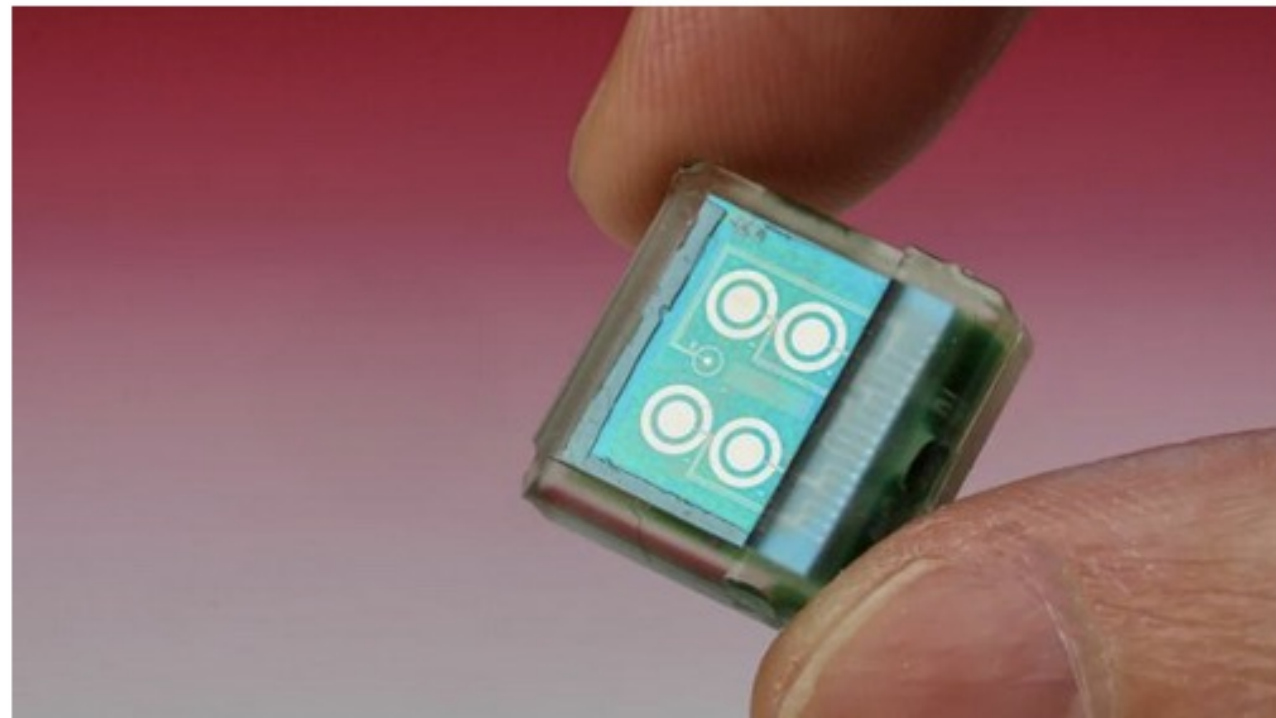
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# A subcutaneous biosensor chip to revolutionize tomorrow's medicine

May 29, 2015 9:26 AM  
[Relaxnews](#)





Q9

Does future implantable CMOS metabolism-monitors will ever been accepted by everyone?

- A. Not really
- B. No if there is not a life threat
- C. No if monitoring is not-related to more metabolites
- D. Yes, but easier by young generations
- E. Yes, that's easy to be accepted
- F. > 50%

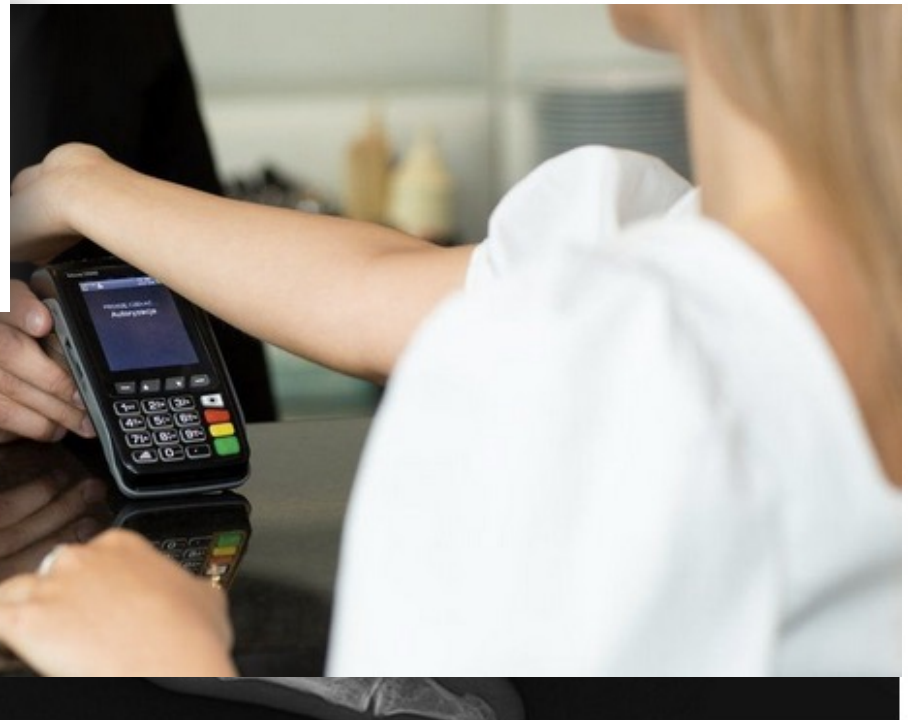
# NEWS

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## The microchip implants that let you pay with your hand

By Katherine Latham  
Business reporter

🕒 April, 11th, 2022

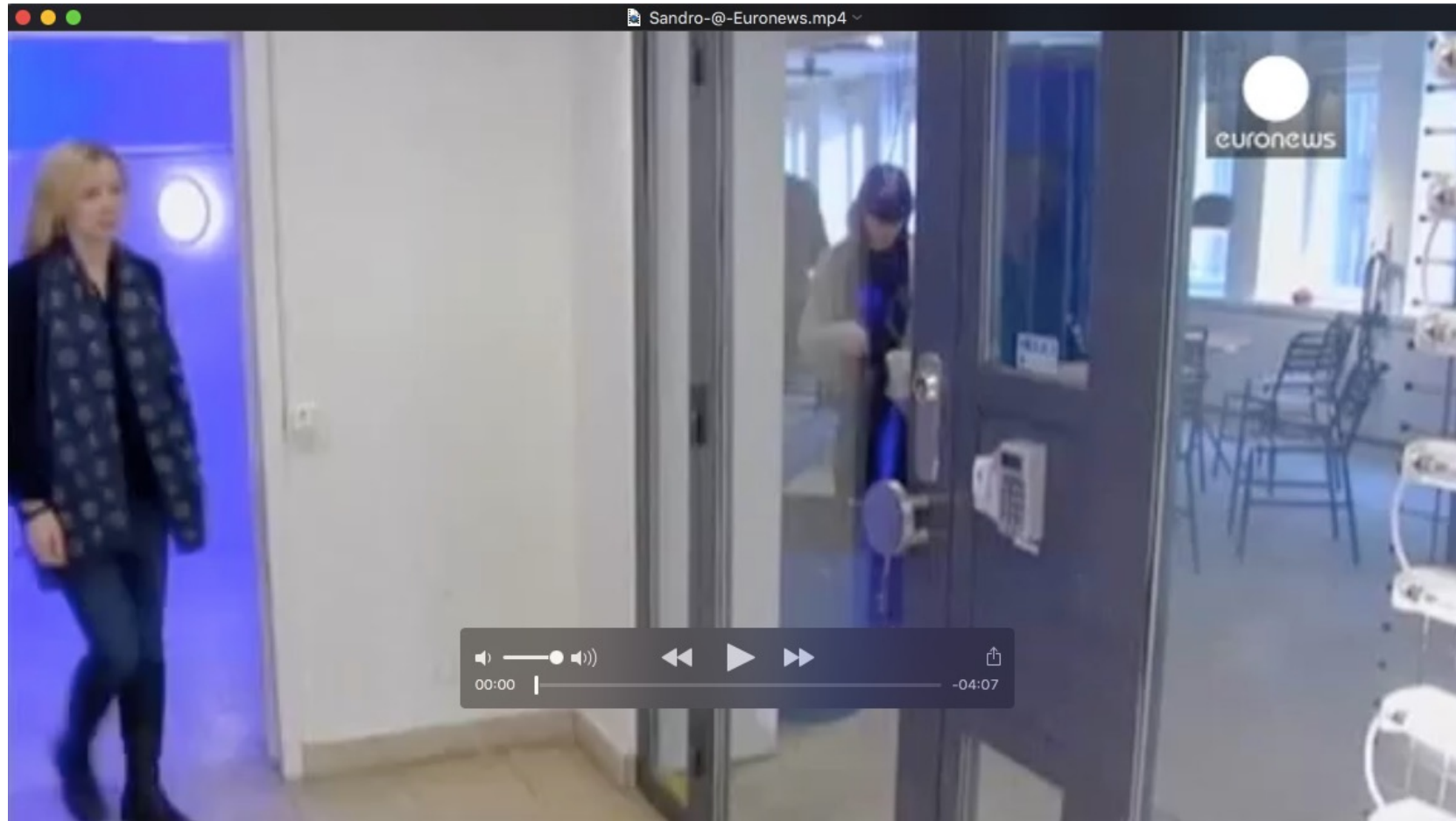


WALLETMOR

An x-ray showing a Walletmor implant, which are injected into a person's hand after a local anaesthetic

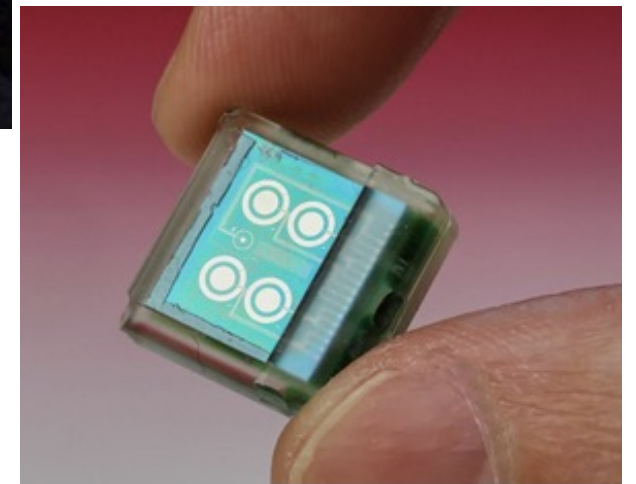
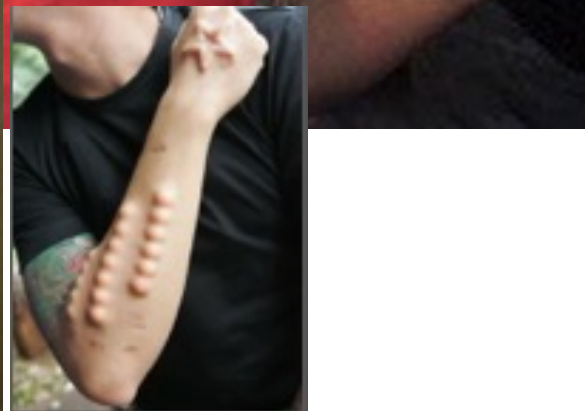
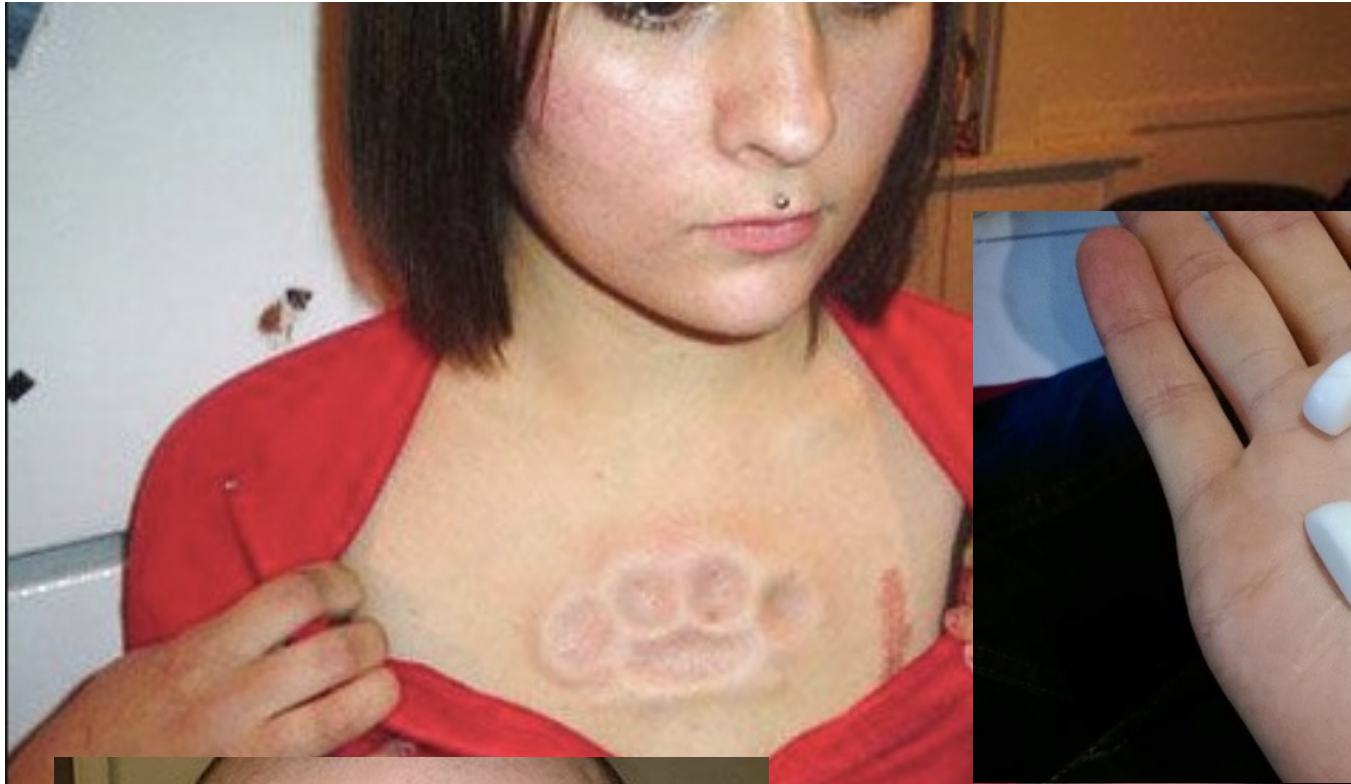
For many of us, the idea of having such a chip implanted in our body is an appalling one, but a 2021 survey of more than 4,000 people across the UK and the European Union found that 51% would consider it.

# Chips under the skin?



[EuroNews, June 2015]

# Under the skin for body sculpting

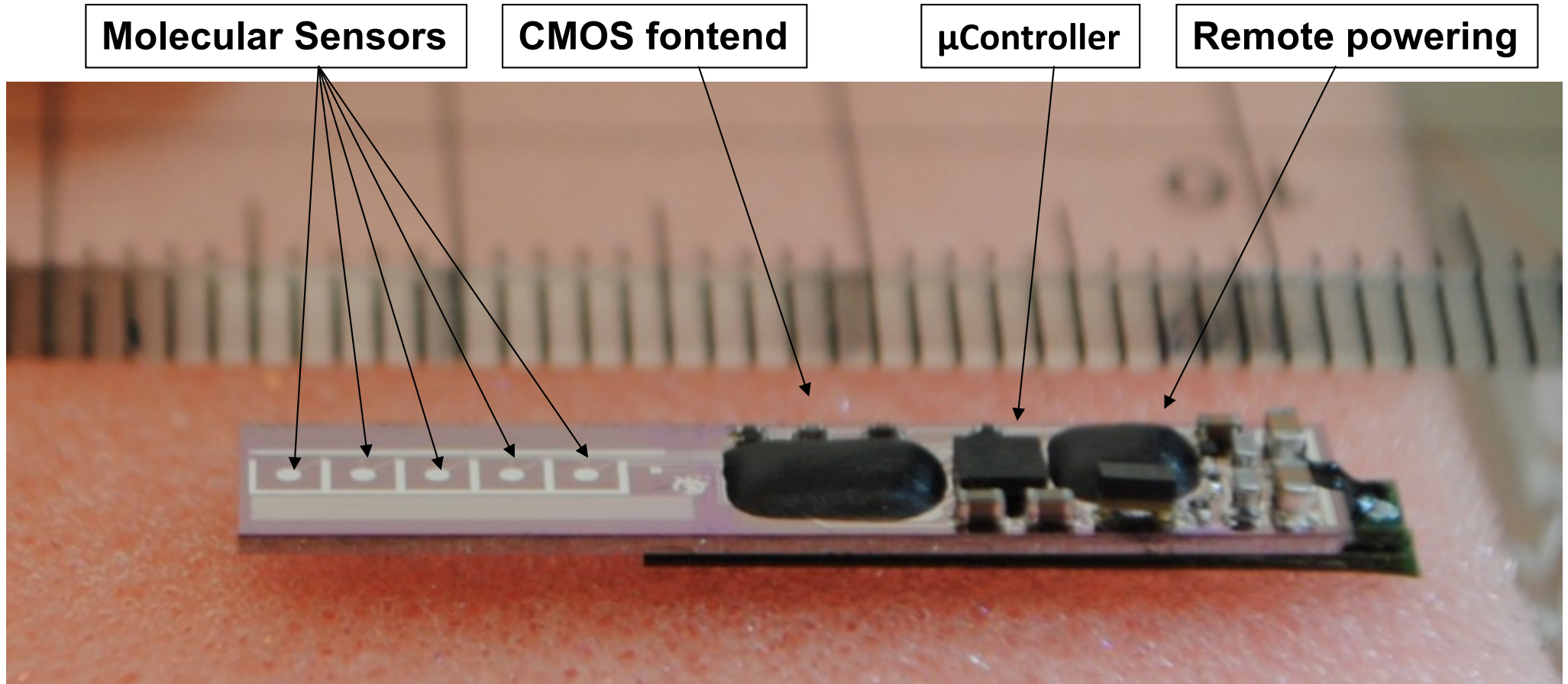


(c) S.Carrara

# Enhancing human being



# Size and Shape to be injectable as a Needle?



The IC has been fabricated in UMC 0.18 technology and interfaced to the passive multi-panel platform

# ECG monitoring by Medtronic



Mark Phelps by Medtronic, and the Reveal LINQ™ system



Q10

May we built a CMOS interface working with all kind of biosensors?

- A. Sometimes, not always
- B. No if the CMOS is not in contact with the hosting body
- C. Might be but that's not easier to be done
- D. Yes, since we need biological functions
- E. Not at all

### EE-517: Bio-Nano-Chip Design

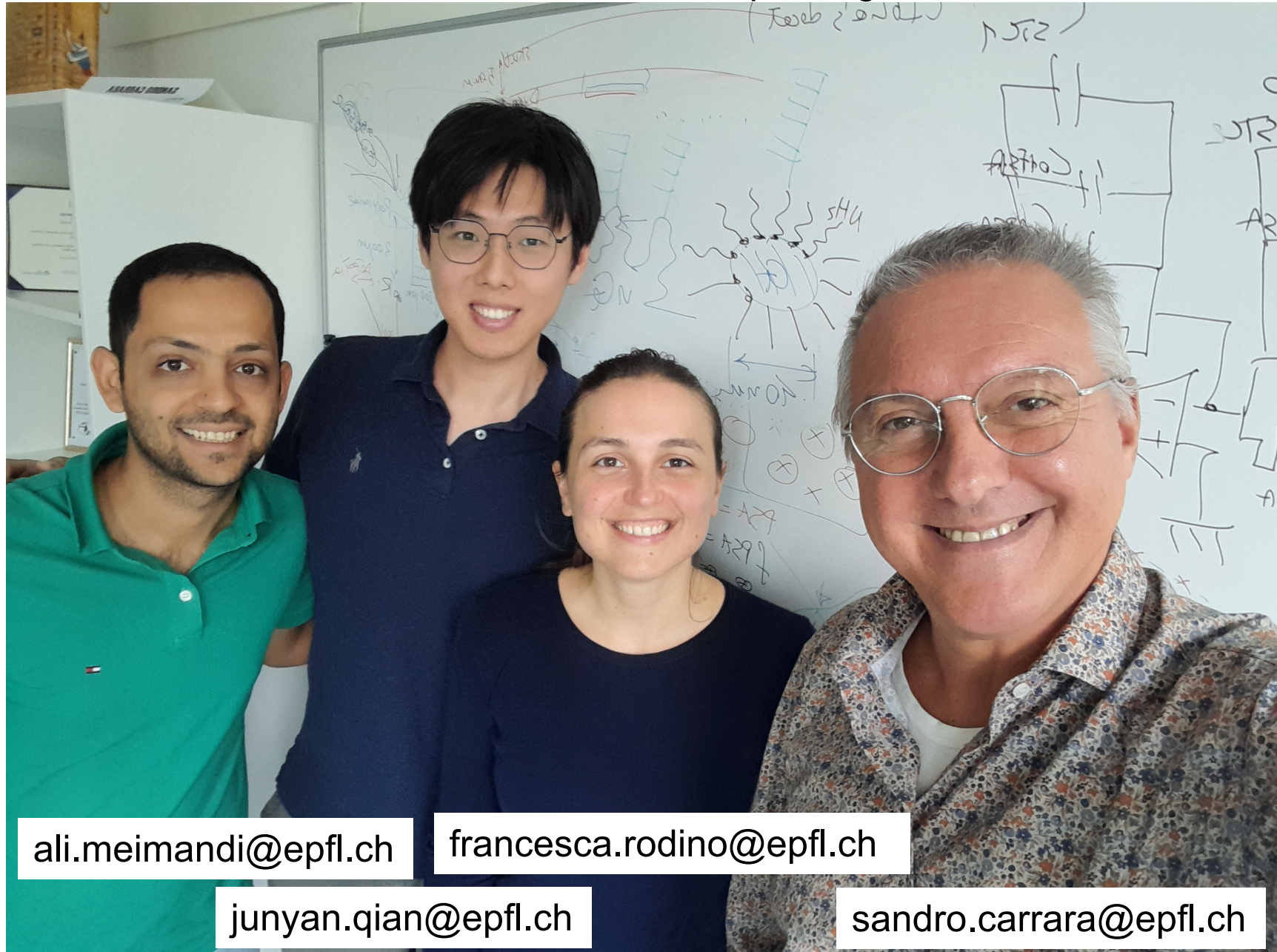
Subject of the week	Chapter' paragraphs*
Introduction to Bio-Nano-Chip design, and Conductive Solutions	§1.1-1.5, §2.1-2.7, §2.14-15
Biological molecules: Proteins and DNA building blocks	§3.5-9, §4.13 and §4.17-18
Biological molecules interactions (DNA, Antibodies, Oxidases and Cytochromes)	§4.4-17 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 & FTCCM Methods)	§7.2-6
Review for final exam	

**Bio**

**Nano**

**CMOS**

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

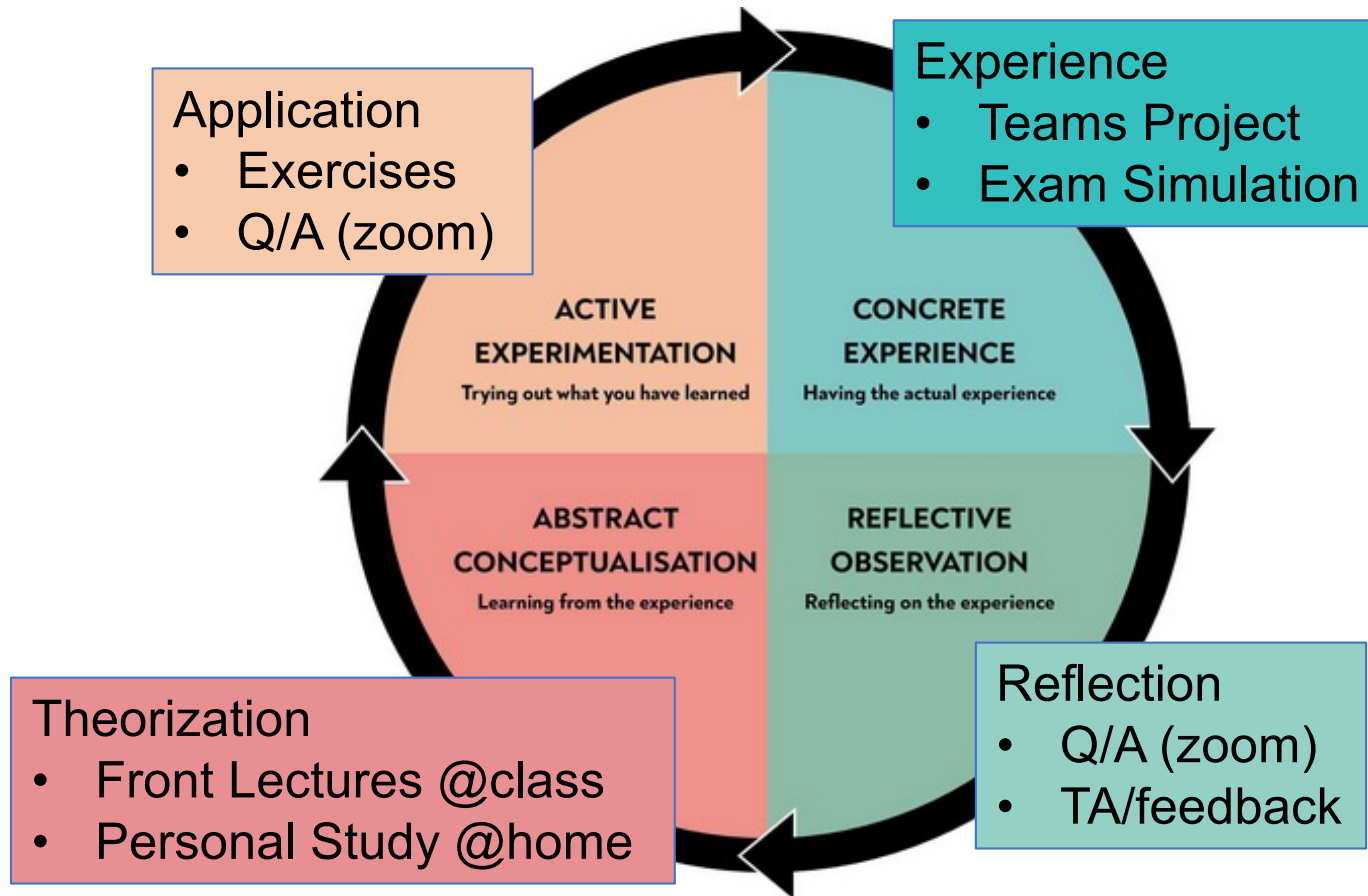


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[junyan.qian@epfl.ch](mailto:junyan.qian@epfl.ch)

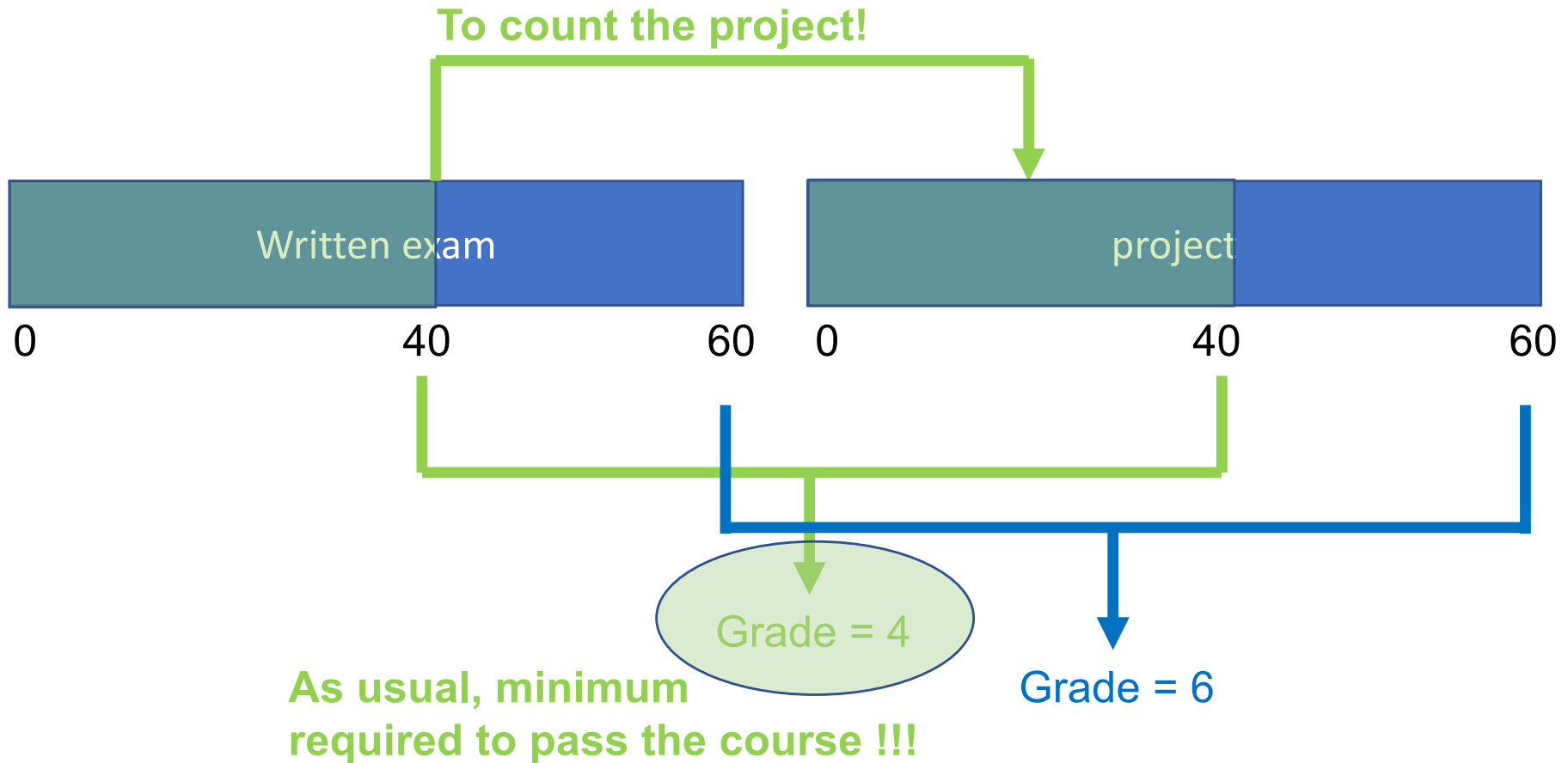
[sandro.carrara@epfl.ch](mailto:sandro.carrara@epfl.ch)



Kolb experimental learning cycle

- The project is **mandatory**.
- Project and written exam count for 60 points each
- **Obtaining 40 points out of 60 in the written exam is mandatory for the project to count.**
- **The final grade is obtained by cumulating points by the written exam and by the project.**
- **The grade is maximum 6**, as usual, obtained by compressing the 120 max points to 6 max grade.

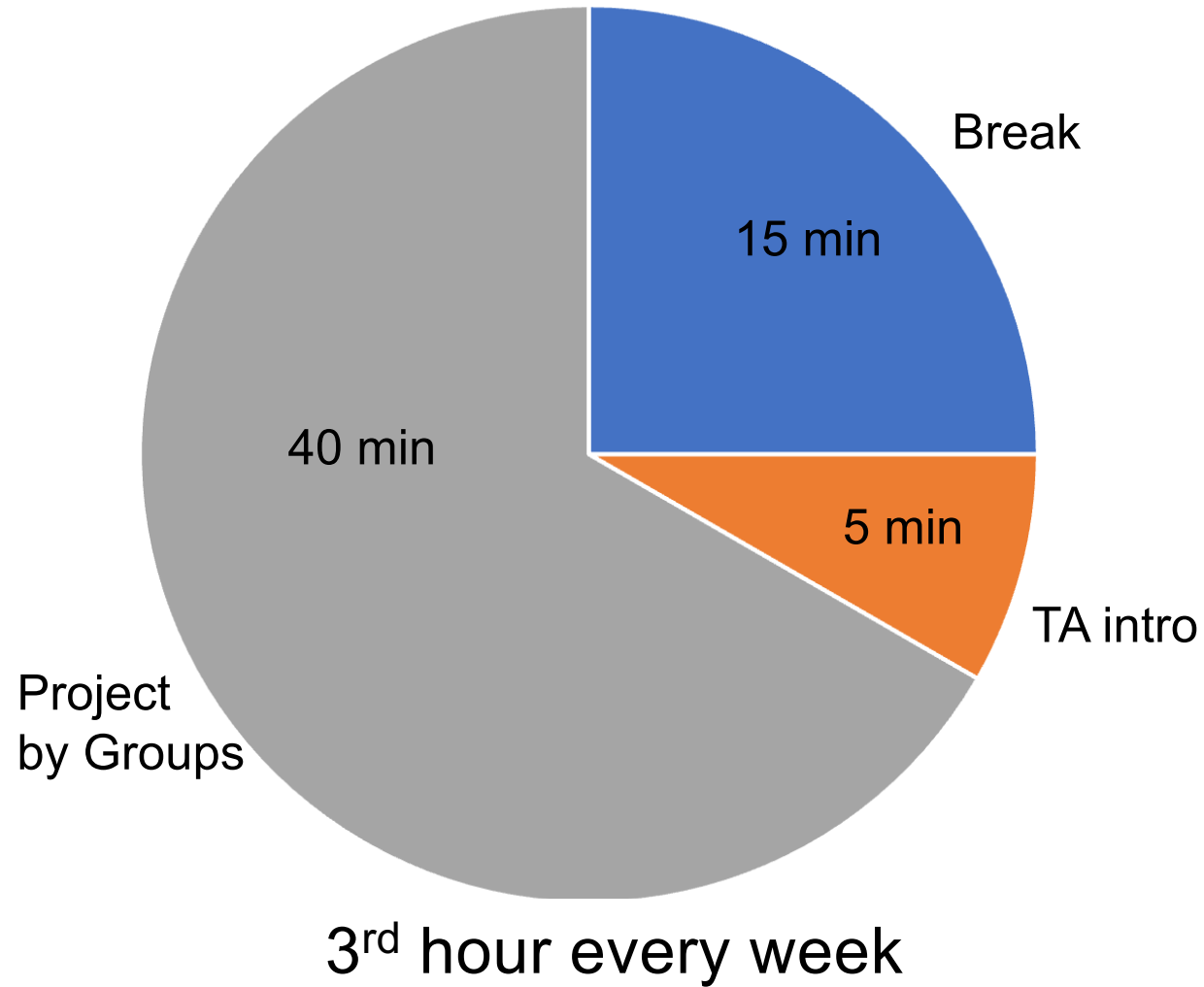
The Exam, the Project, and the Grade

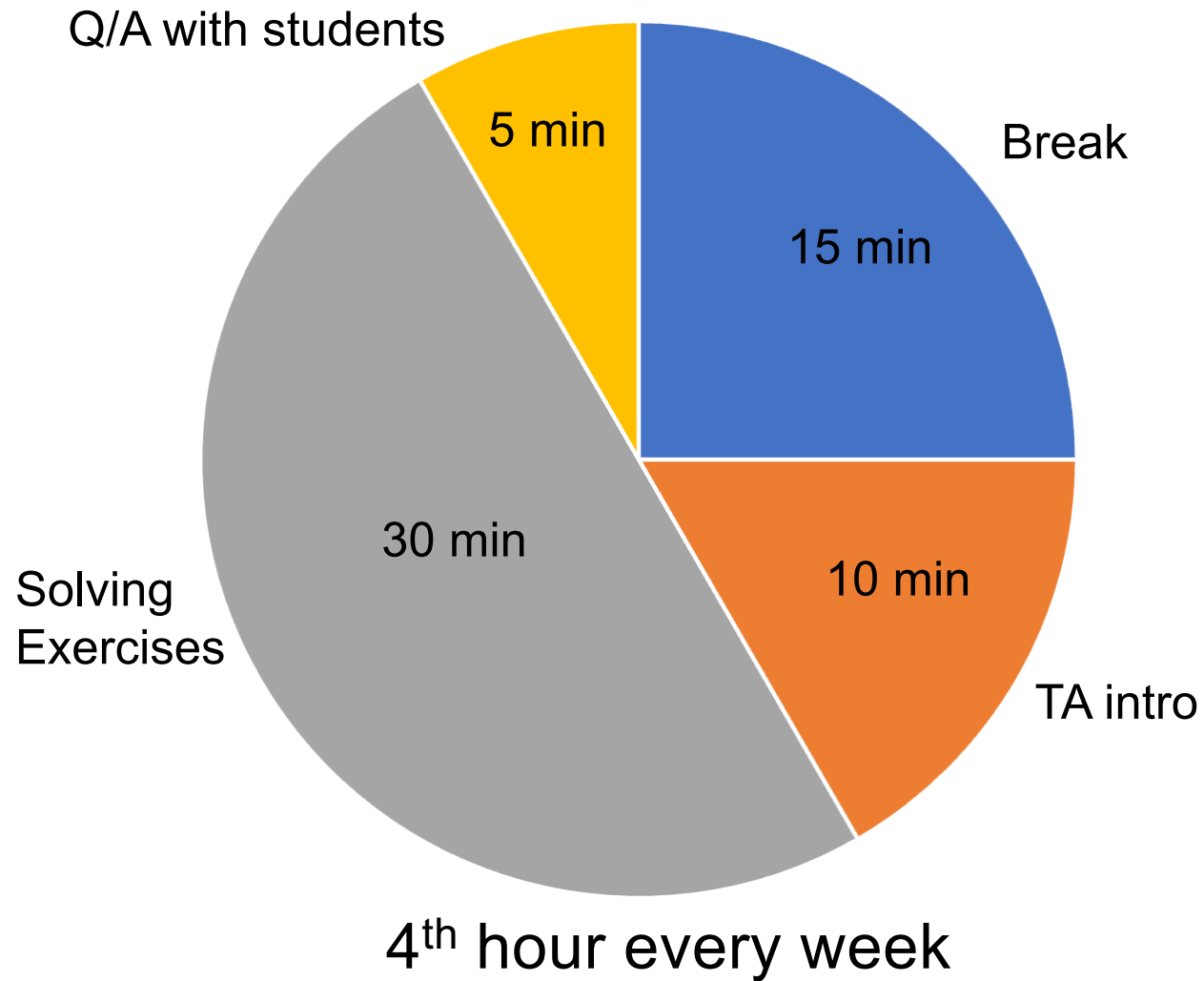


## The Exam, the Project, and the Grade

## Student Projects - Rules

13. The **Project evaluation** is done based on the following aspects:
- a. **Individual proposal: 15 points (individual mark)**
  - b. **Progressive report: 15 points (group mark)**
  - c. **Final report: 15 points (group mark)**
  - d. **Individual queries during the sessions: 15 points (individual mark)**





# The Course Textbook

Bio/CMOS Interfaces and Co-Design - Springer

link.springer.com/book/10.1007/978-1-4614-4690-3

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Sandro Carrara

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Authors: Sandro Carrara

SBN: 978-1-4614-4689-7 (Print) 978-1-4614-4690-3 (Online)

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Book Chapter

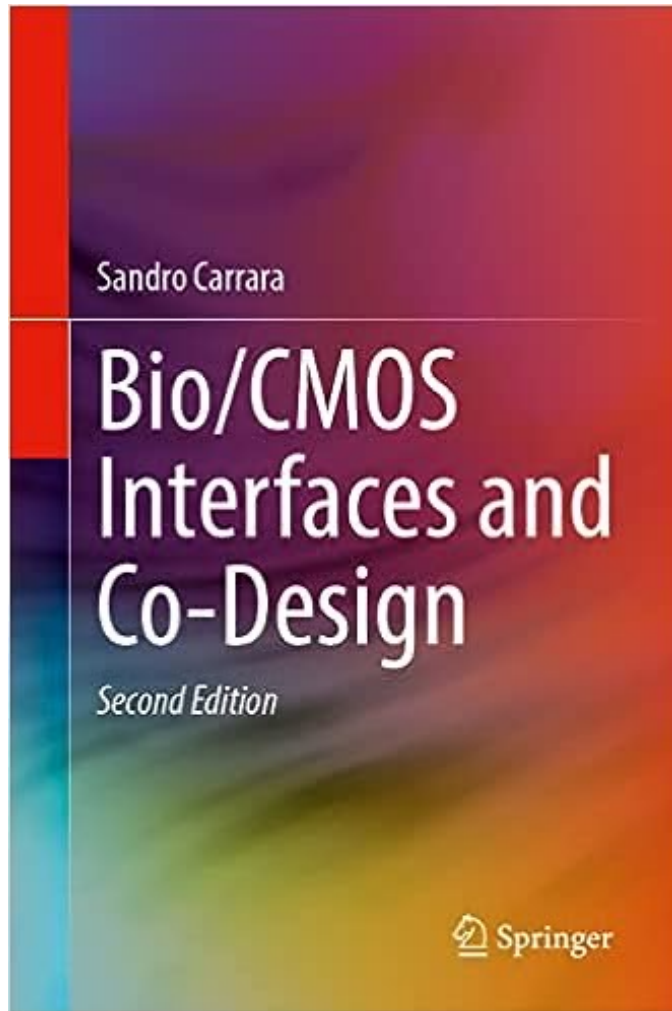
Introduction

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# The Course Textbook: the 2<sup>nd</sup> Edition!

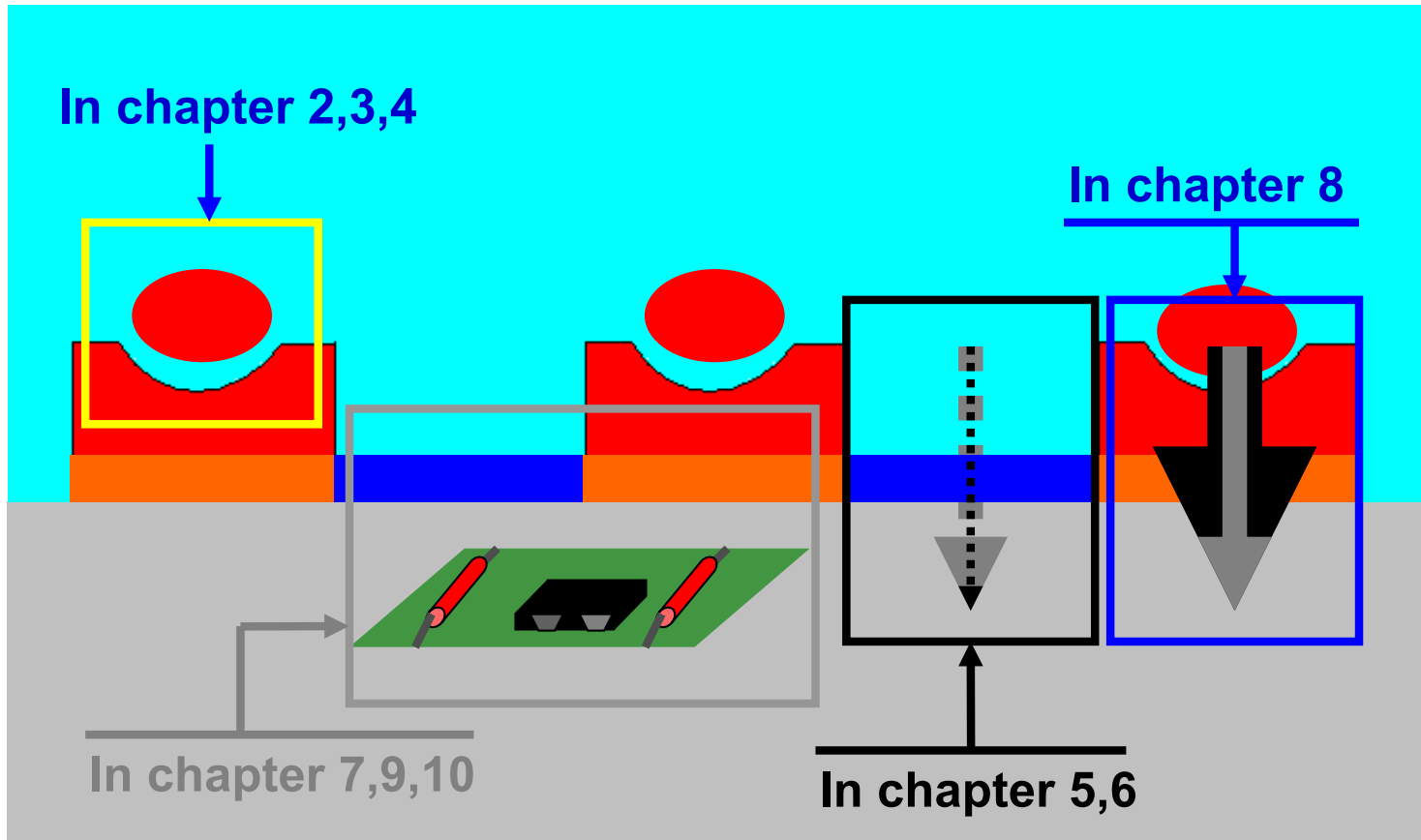


This textbook demonstrates new paradigms for the interface between CMOS circuits and the biological world. A deep theoretical description of such an interface is defined and discussed, while various real applications are demonstrated by also discussing several analog CMOS circuits. Electrochemical techniques are proposed in detail to learn how to design integrated biosensors. Biological materials are described to provide devices selectivity. Nanoscale materials are discussed to provide device sensitivity. CMOS circuits are analyzed to provide real applications. Extensive examples with solutions are provided, as well as exercises at the end of each chapter.

(c) S.Carrara

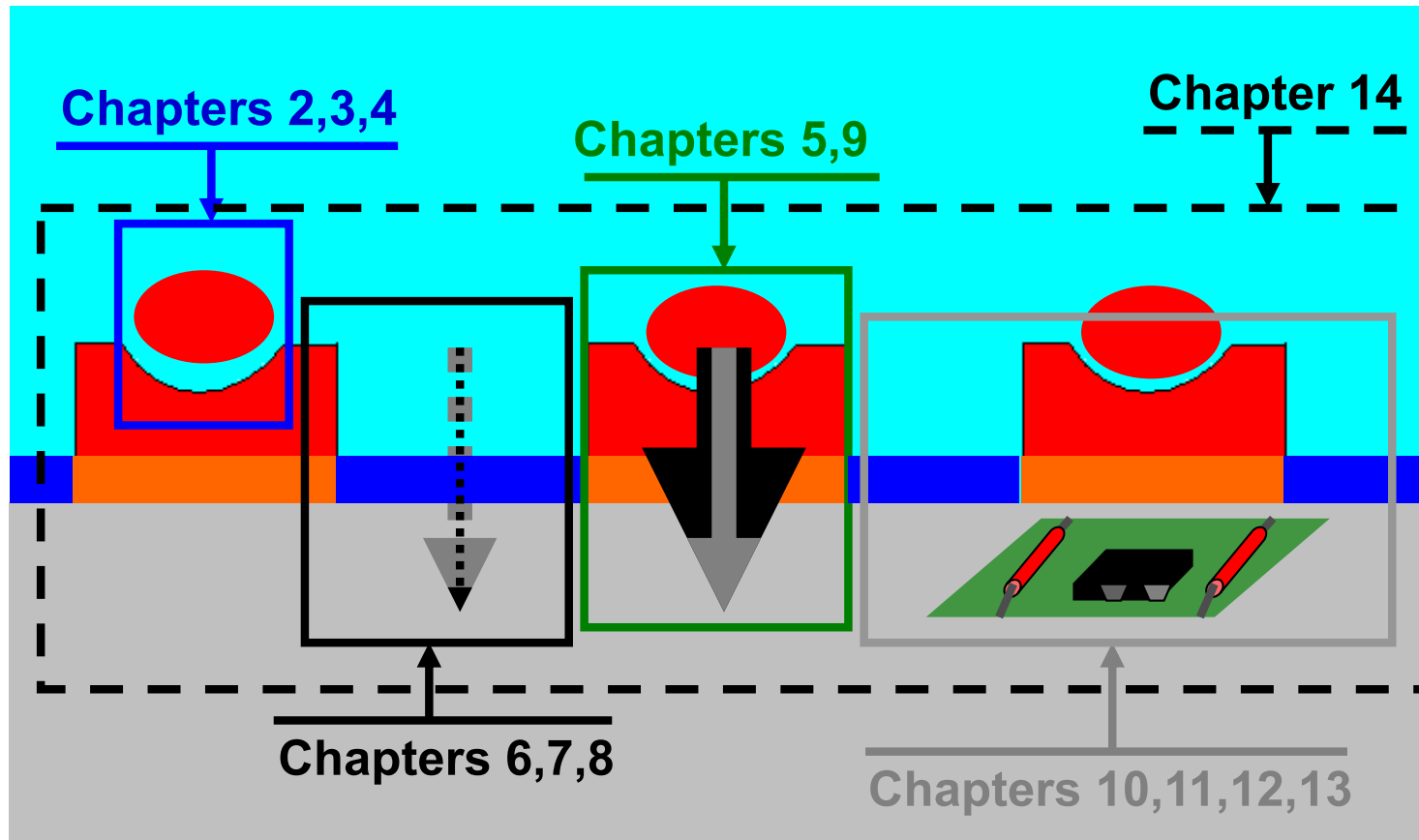
<https://link.springer.com/book/10.1007/978-3-031-31832-0>

# Bio/CMOS interface book (1<sup>st</sup> Edition)



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

# Bio/CMOS interface book (2<sup>nd</sup> Edition)





**Master in Electrical and Electronics Engineering**

**EE-517: Bio-Nano-Chip Design**

# **Lecture #1**

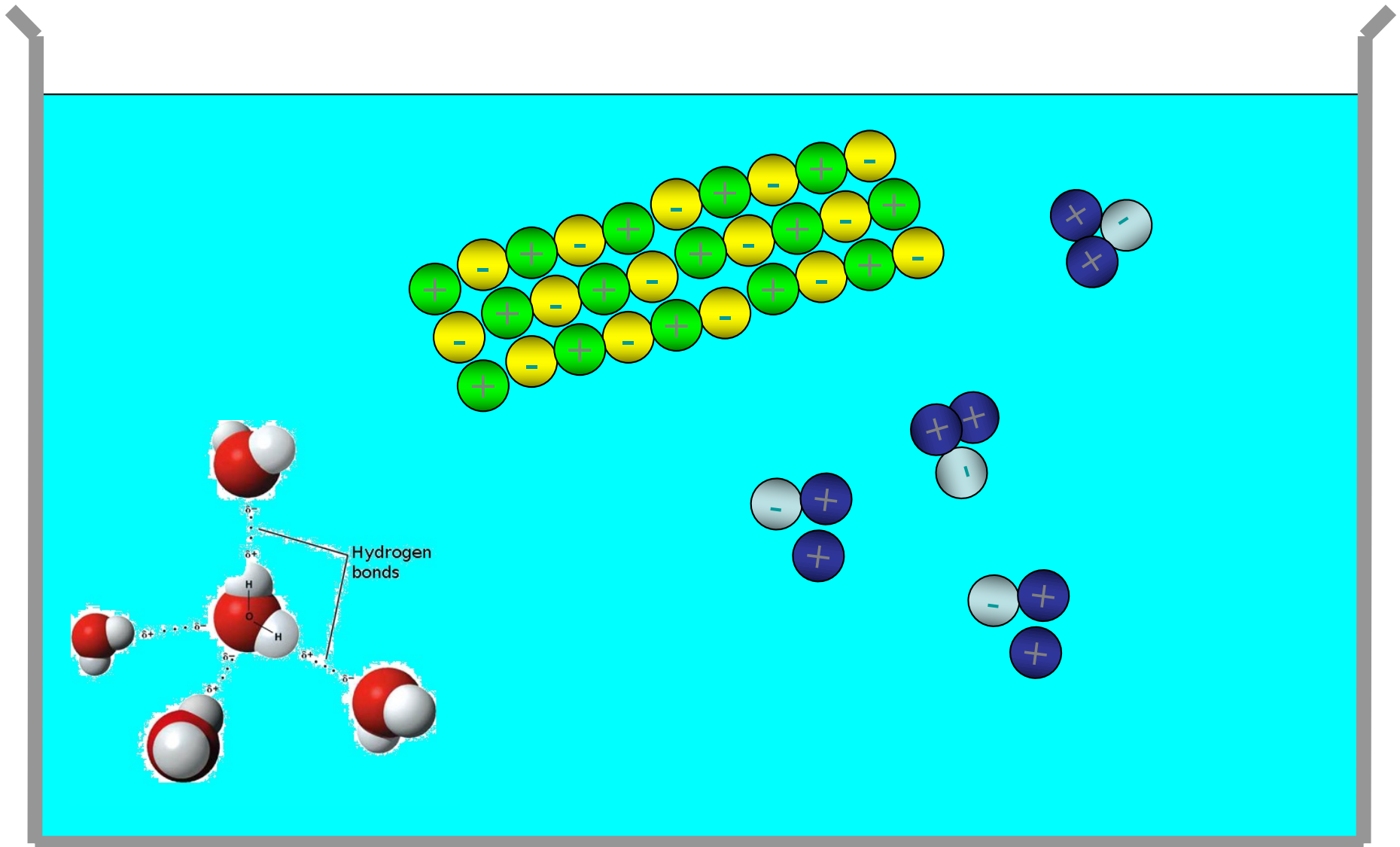
# **Conductive Solutions**

# Lecture Outline

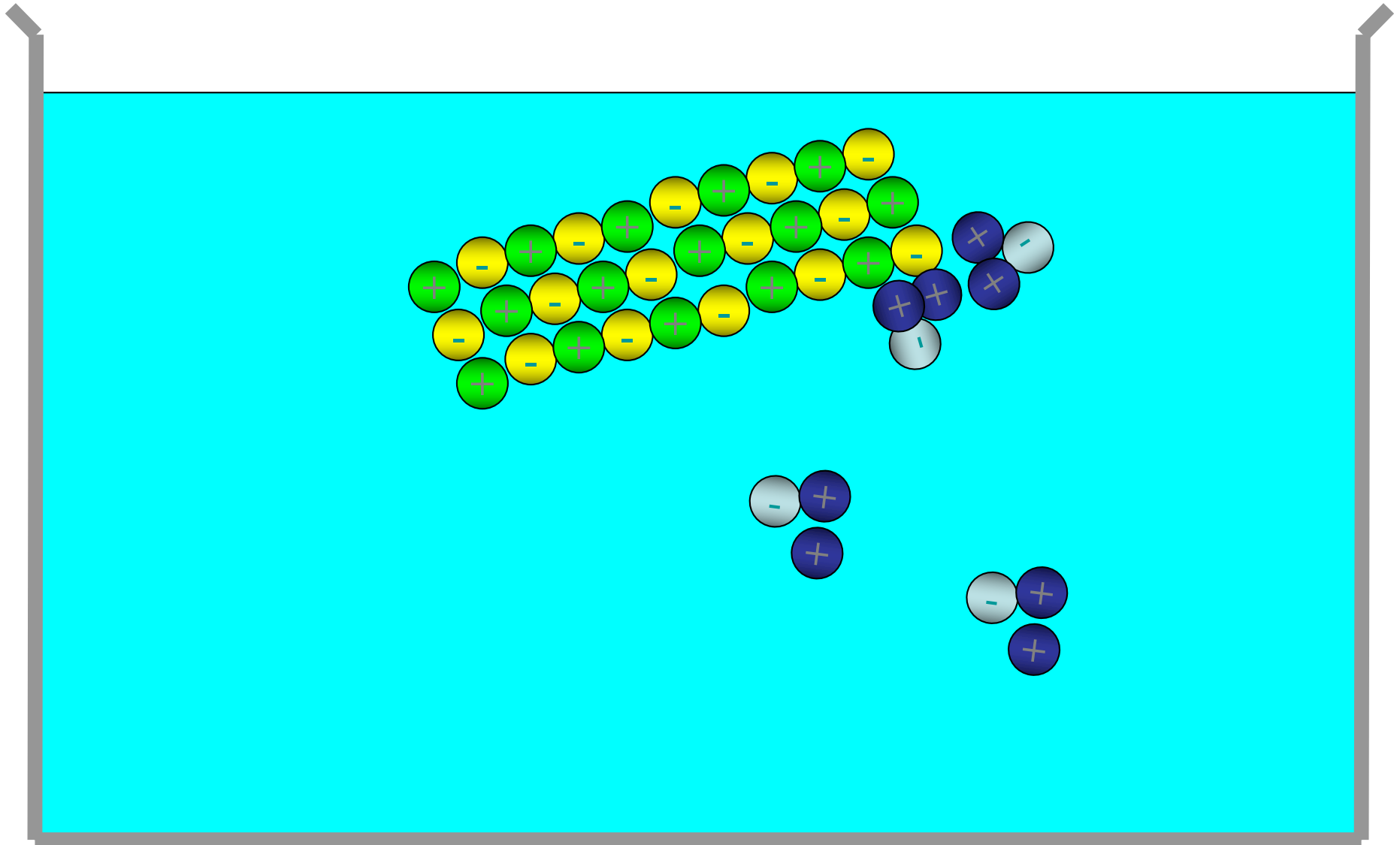
(Book Bio/CMOS: Chapter' paragraphs § 2.1-2.7 and § 2.14-15)

- Solutions of ionic solutes
- Solutions of electrolytes
- Conductive Solutions
- Helmholtz planes
- Redox reactions
- pH

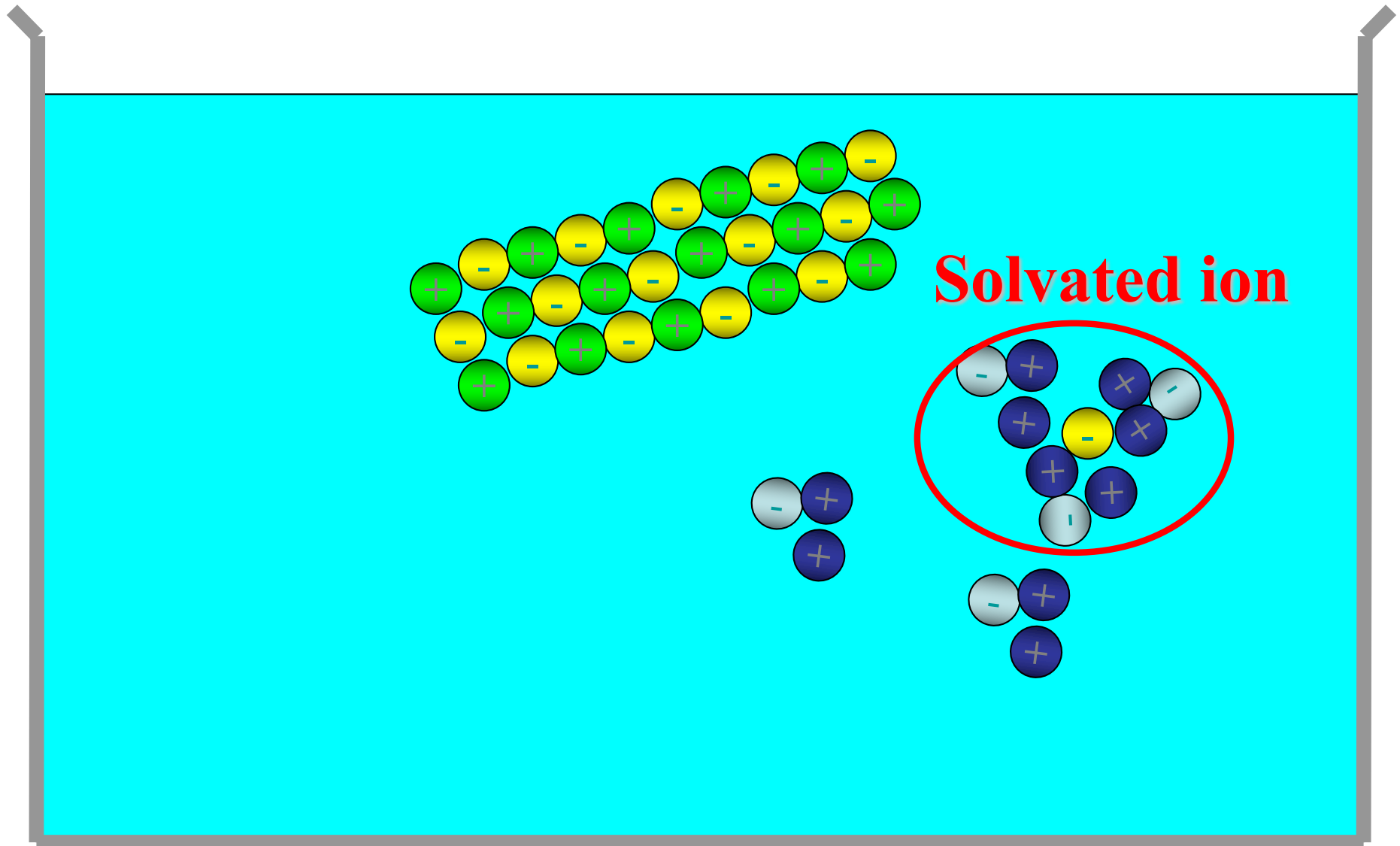
# Liquid Solution: Ionic Solid in liquid



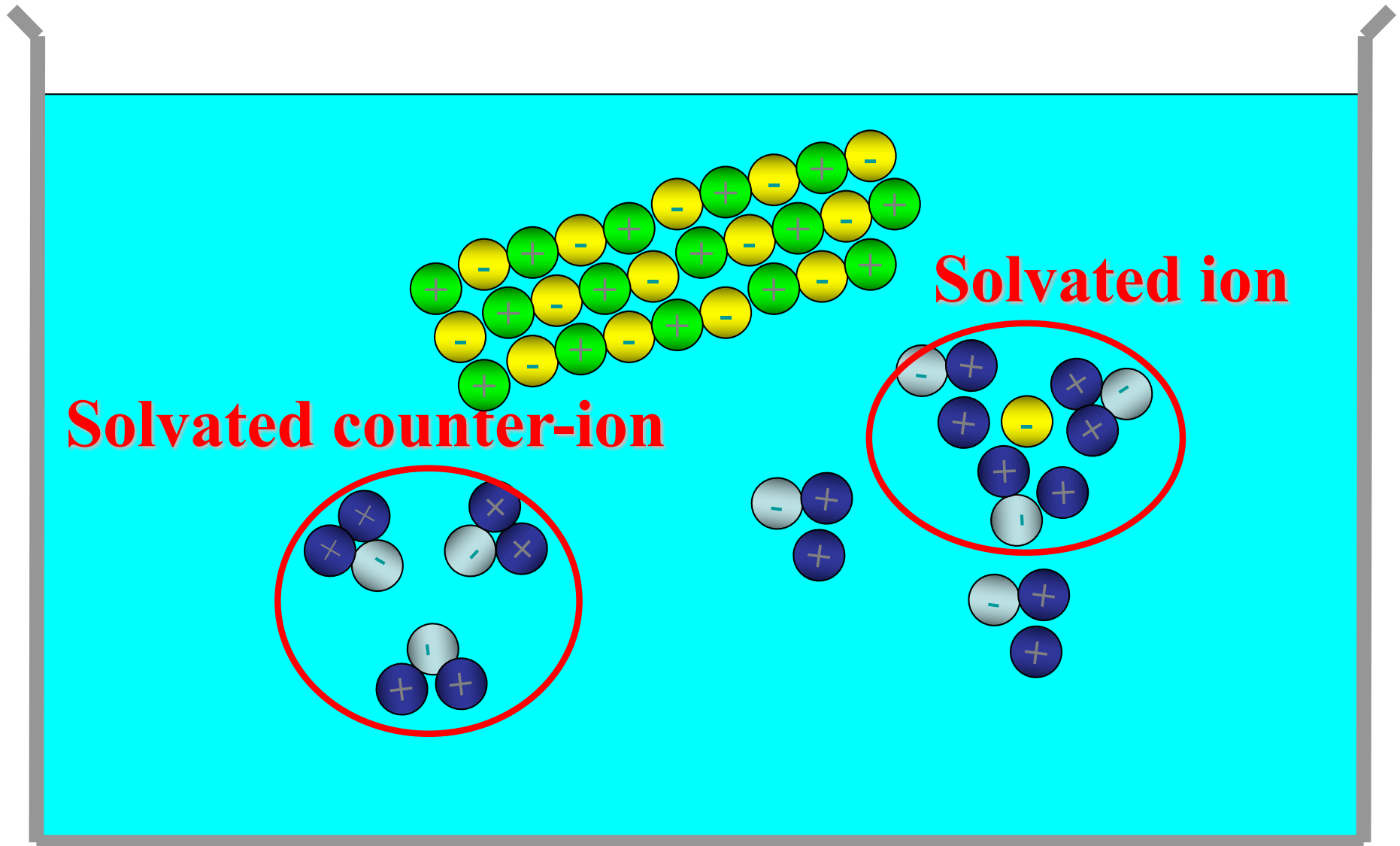
# Liquid Solution: Ionic Solid in liquid



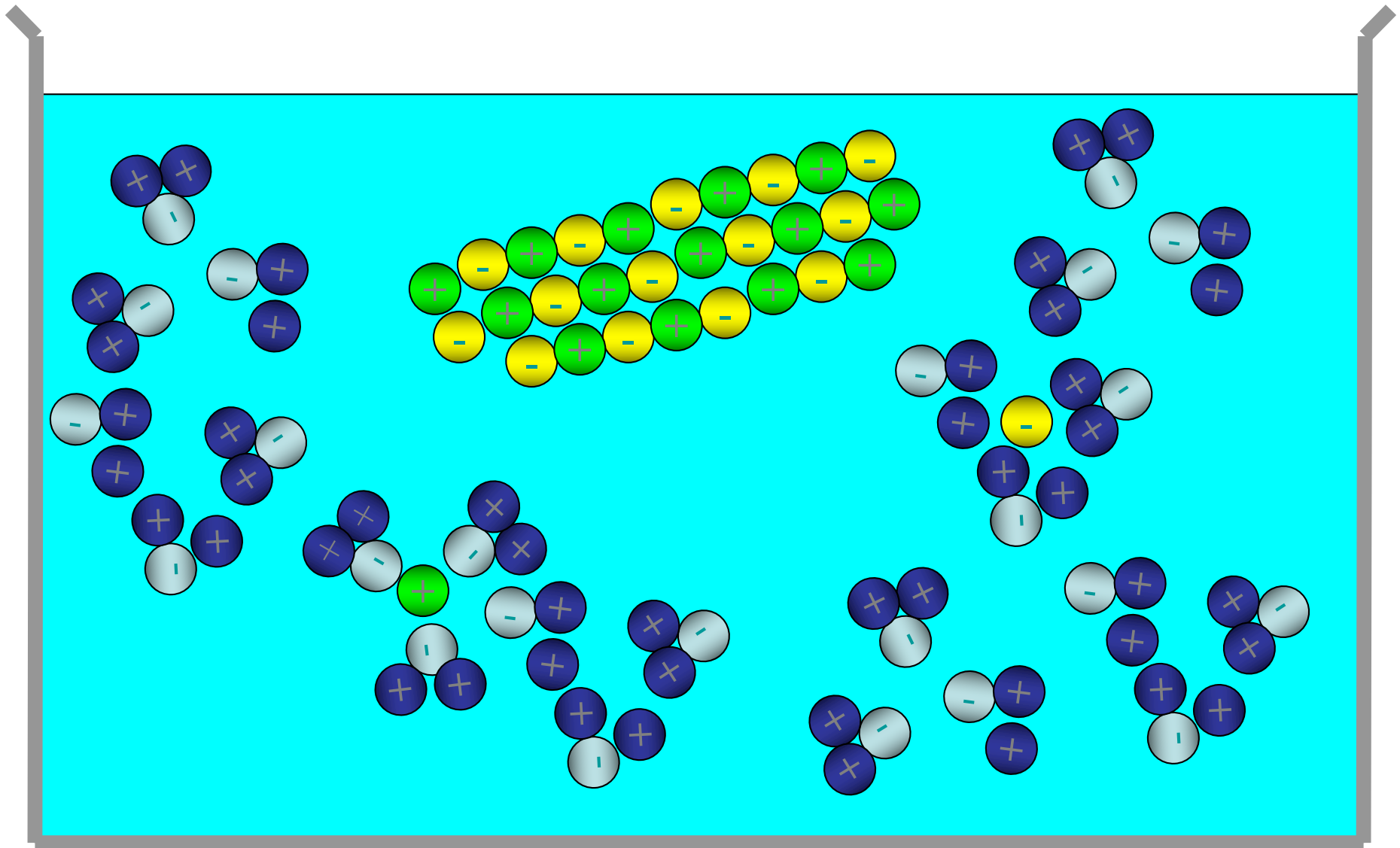
# Liquid Solution: Ionic Solid in liquid



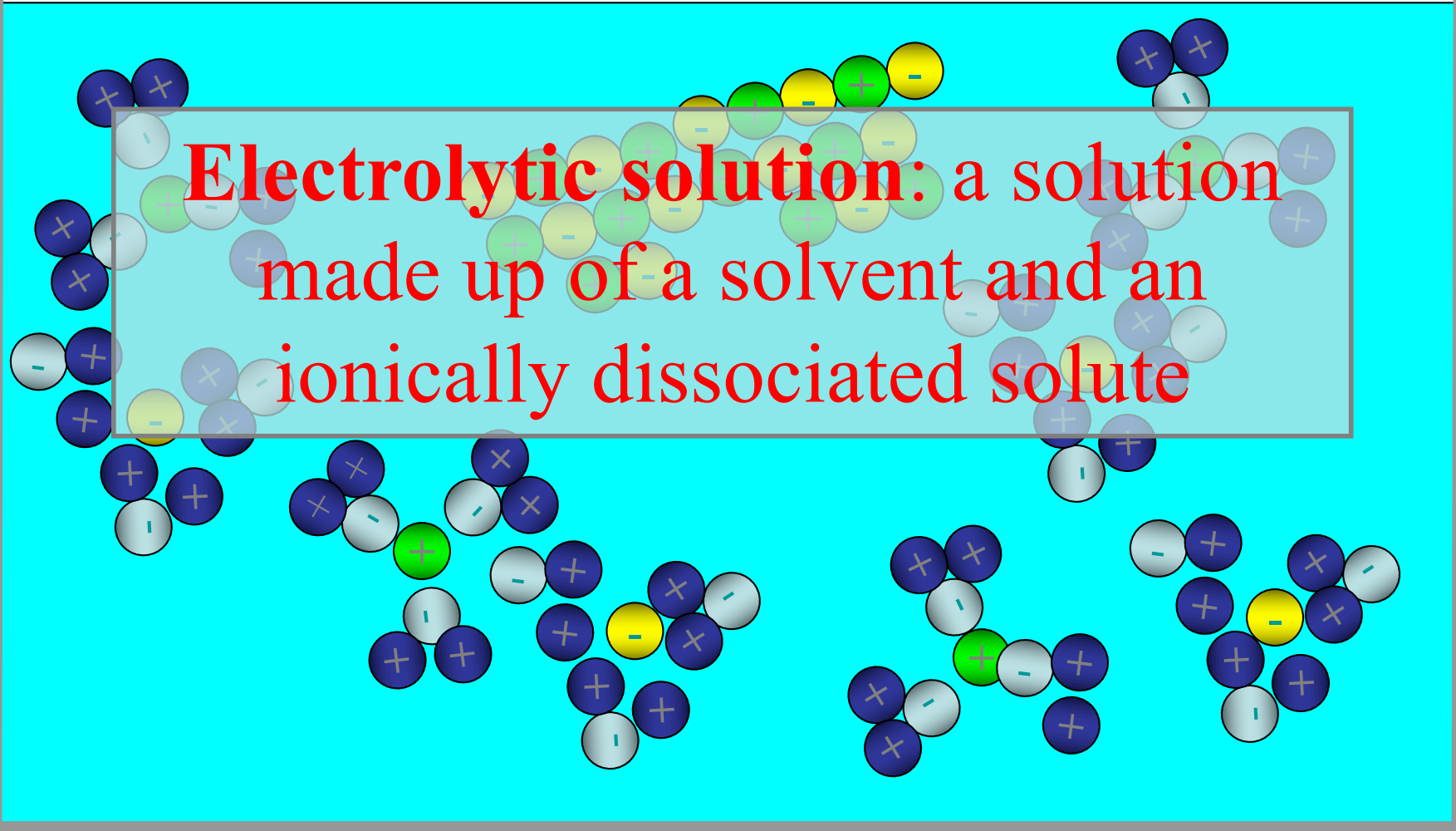
# Liquid Solution: Ionic Solid in liquid



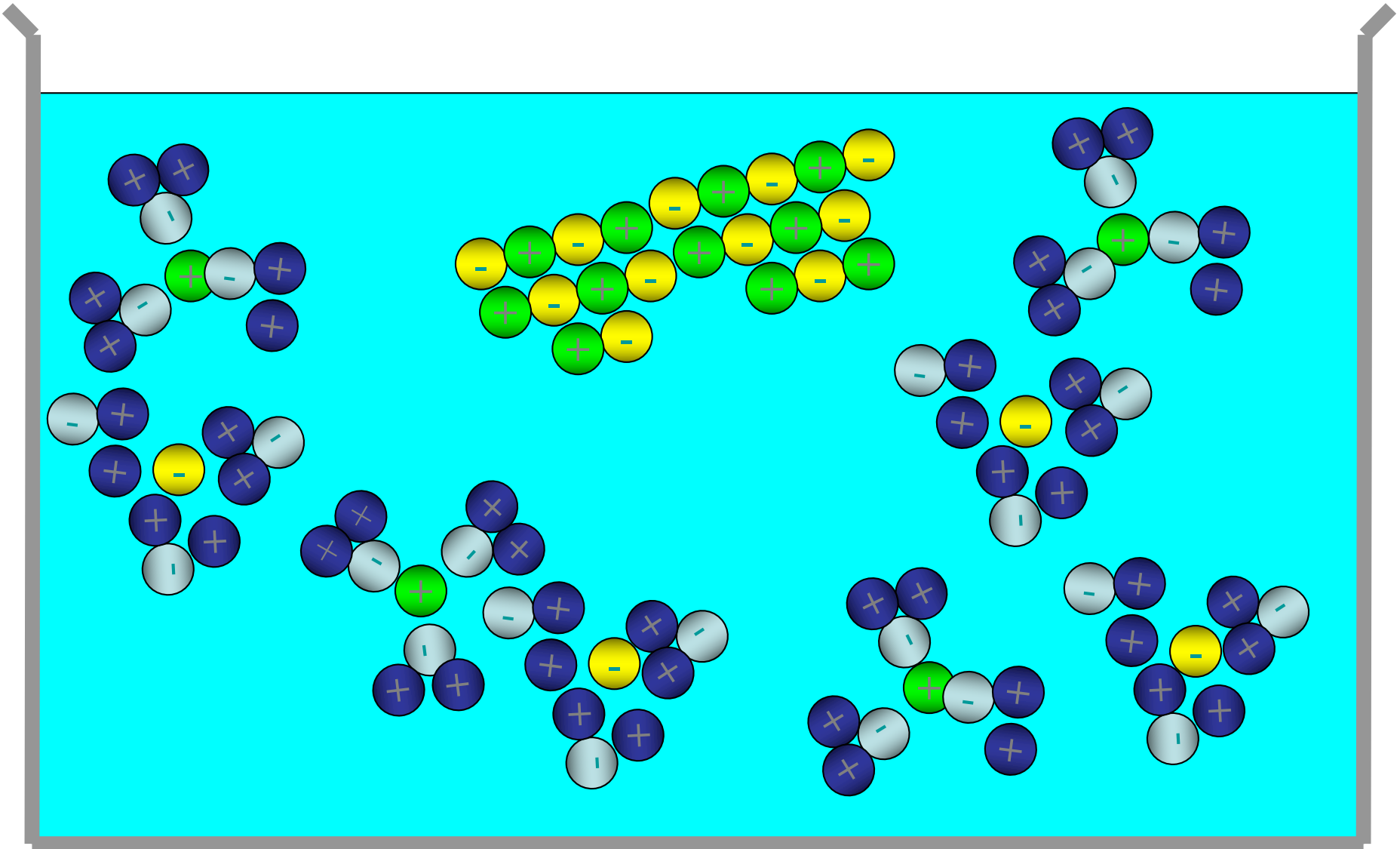
# Liquid Solution: Ionic Solid in liquid



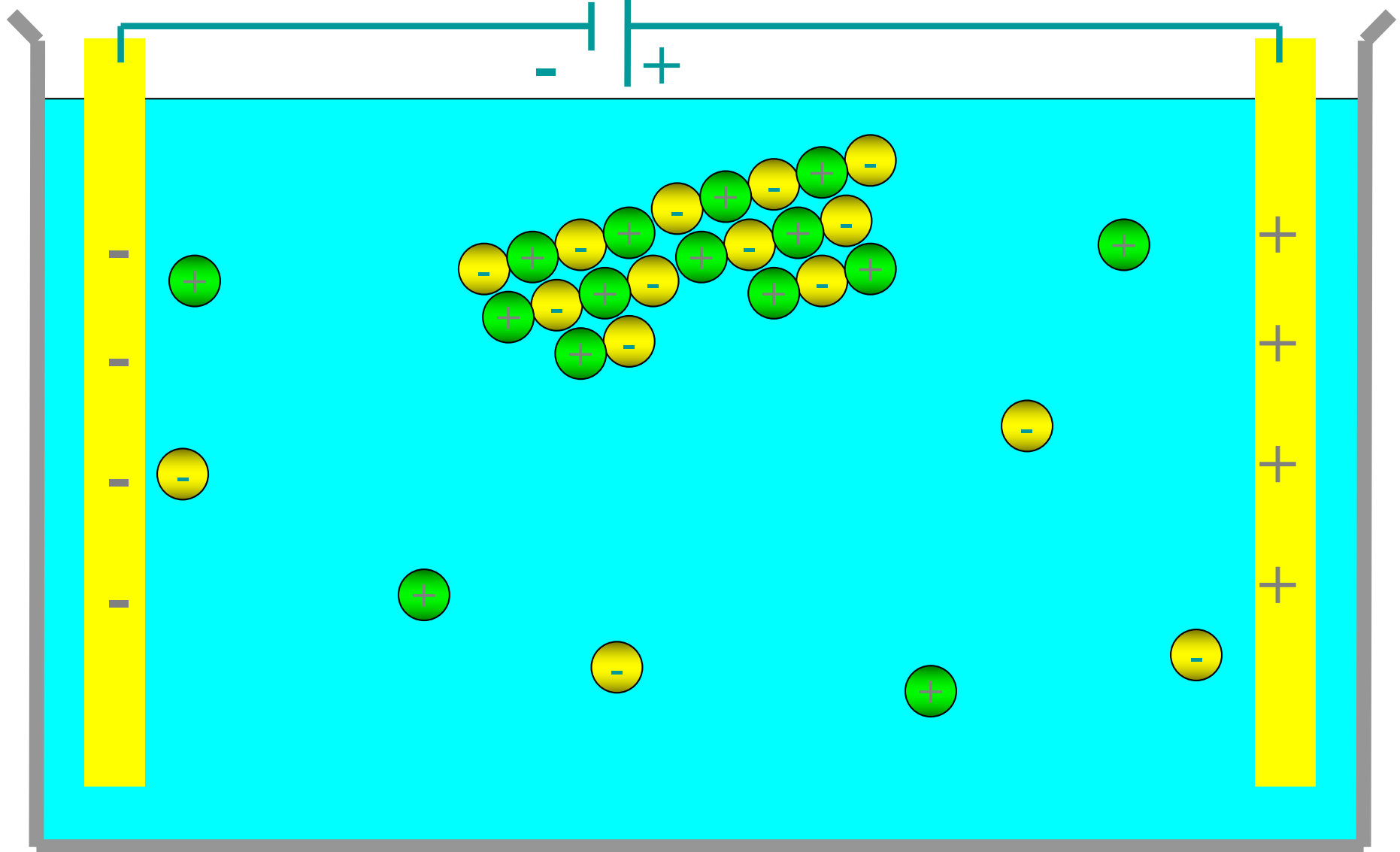
# Liquid Solution: Ionic Solid in liquid



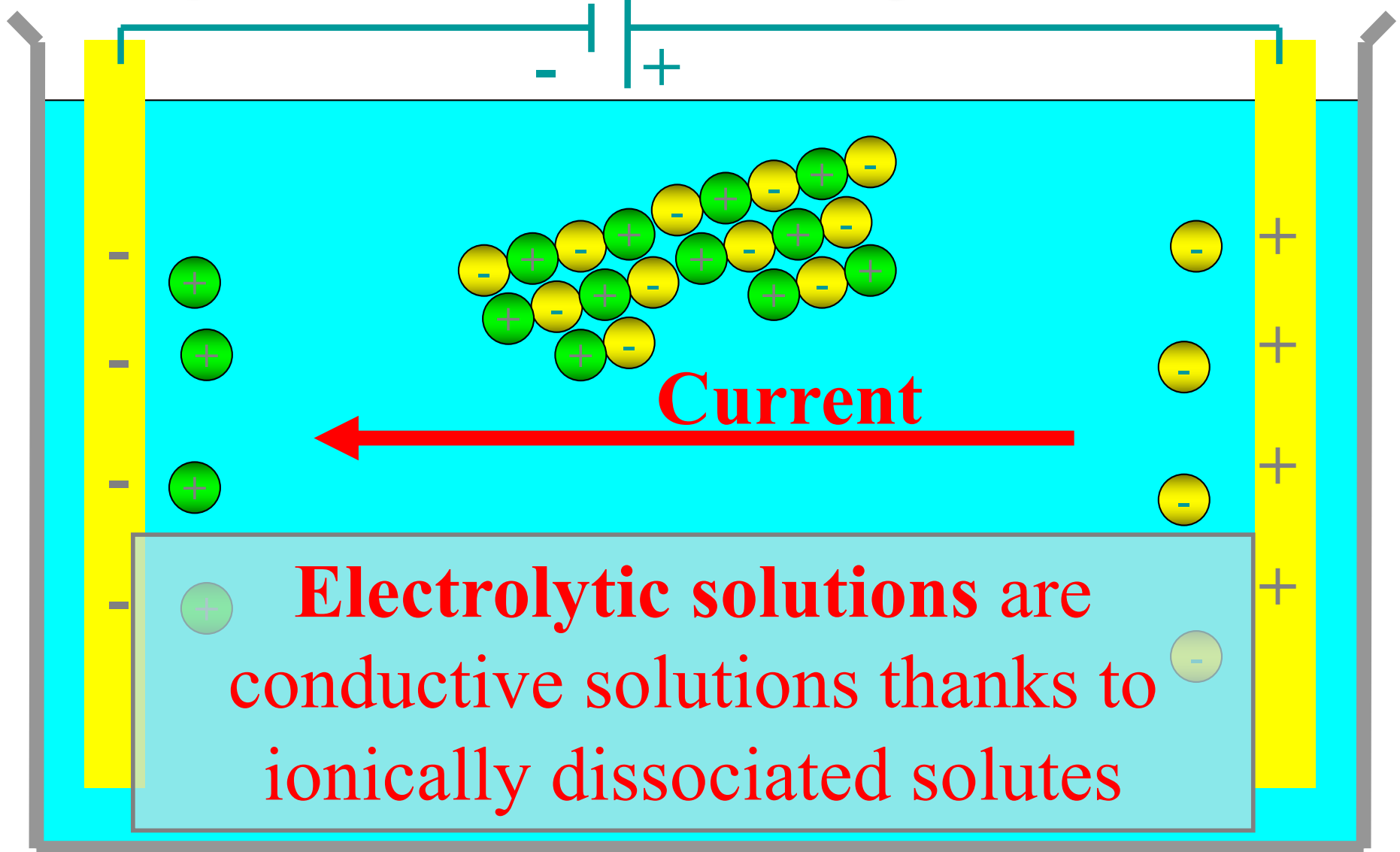
# Liquid Solution: Electrolytic Solution



# Liquid Solution: Electrolytic Solution



# Liquid Solution: Electrolytic Solution



# Ionic Solution of HCl

## Dissociation of Chloride Acid

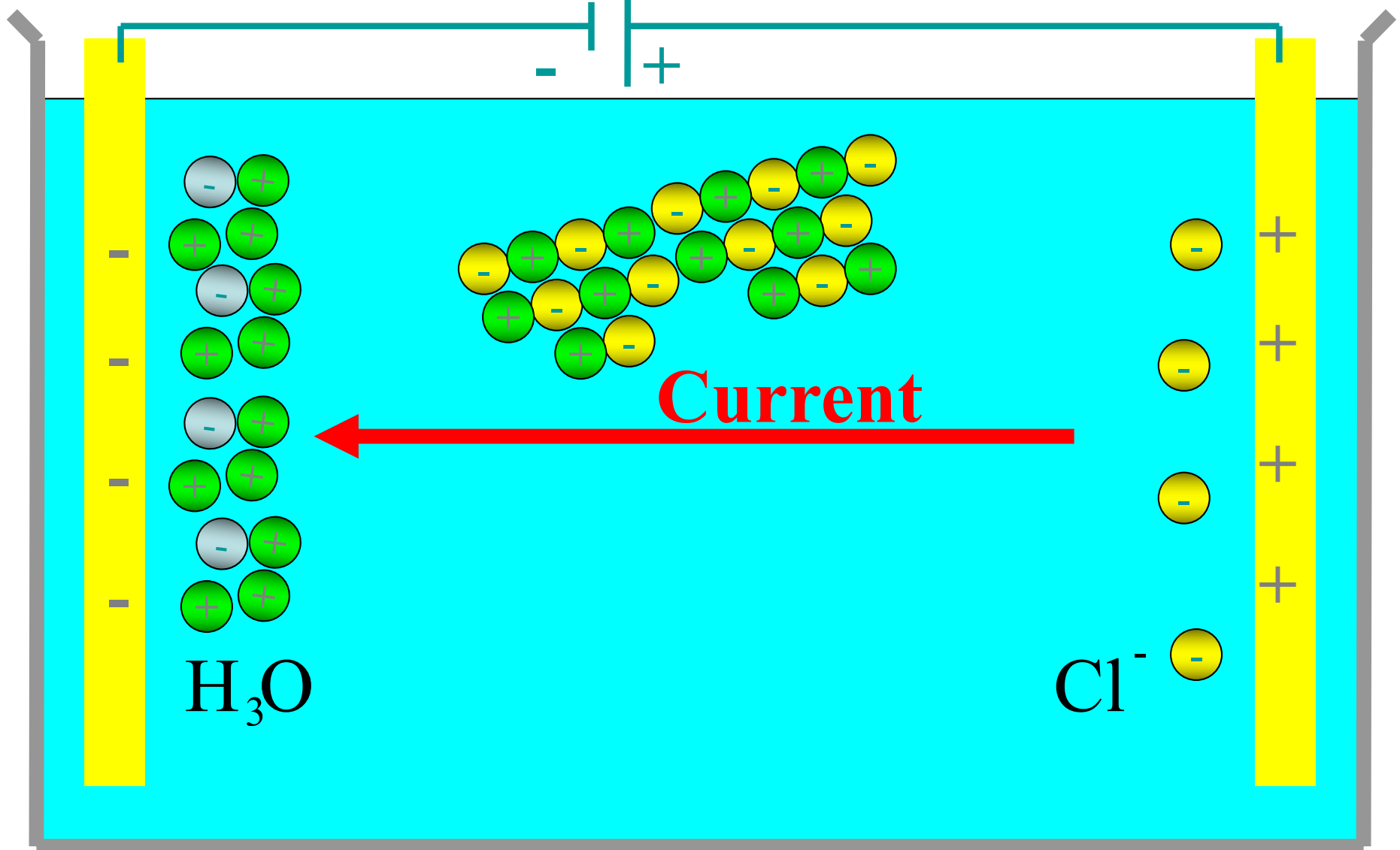


- **Electrode (Cathode)**

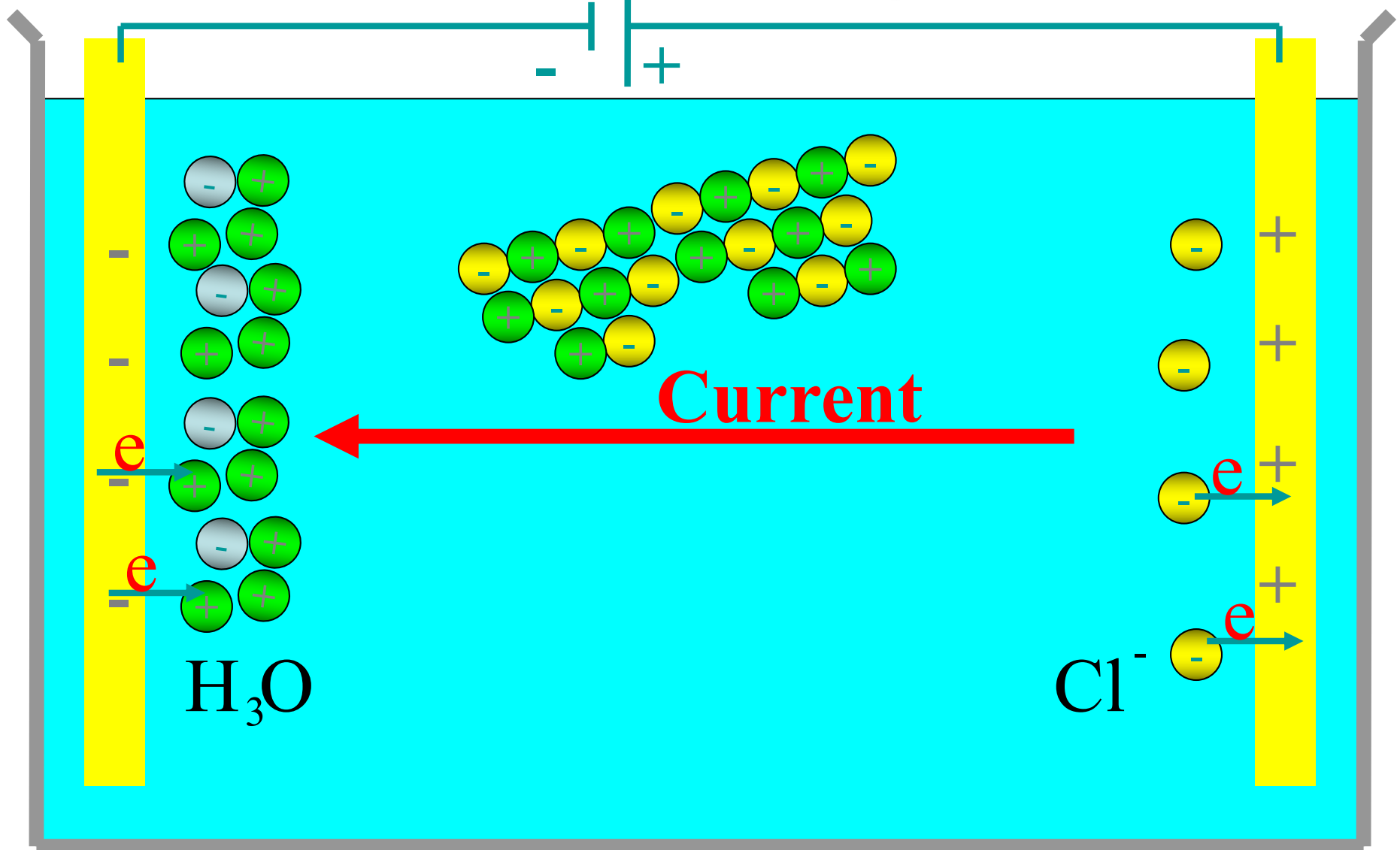


+ **Electrode (Anode)**

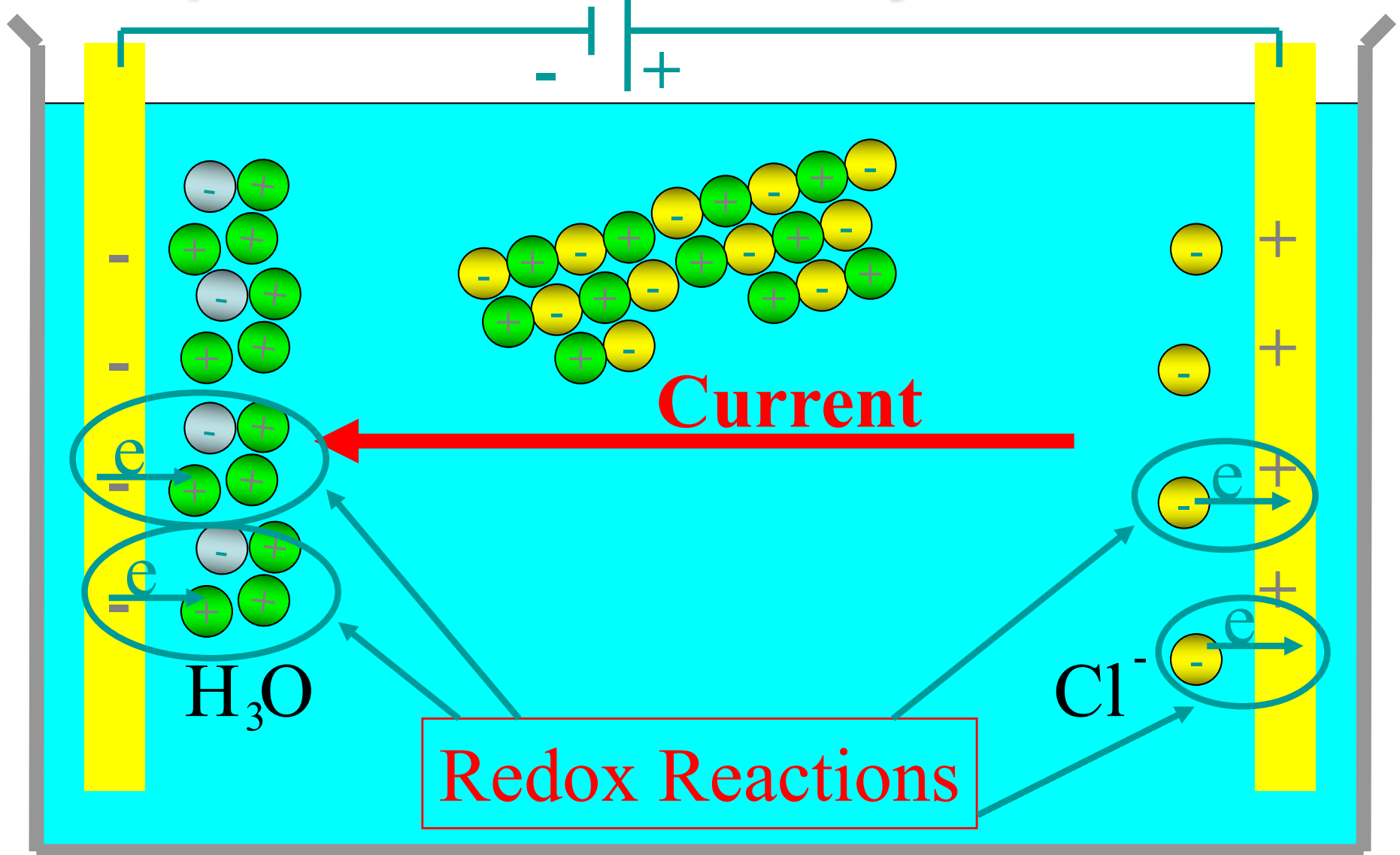
# Liquid Solution: Electrolytic Solution



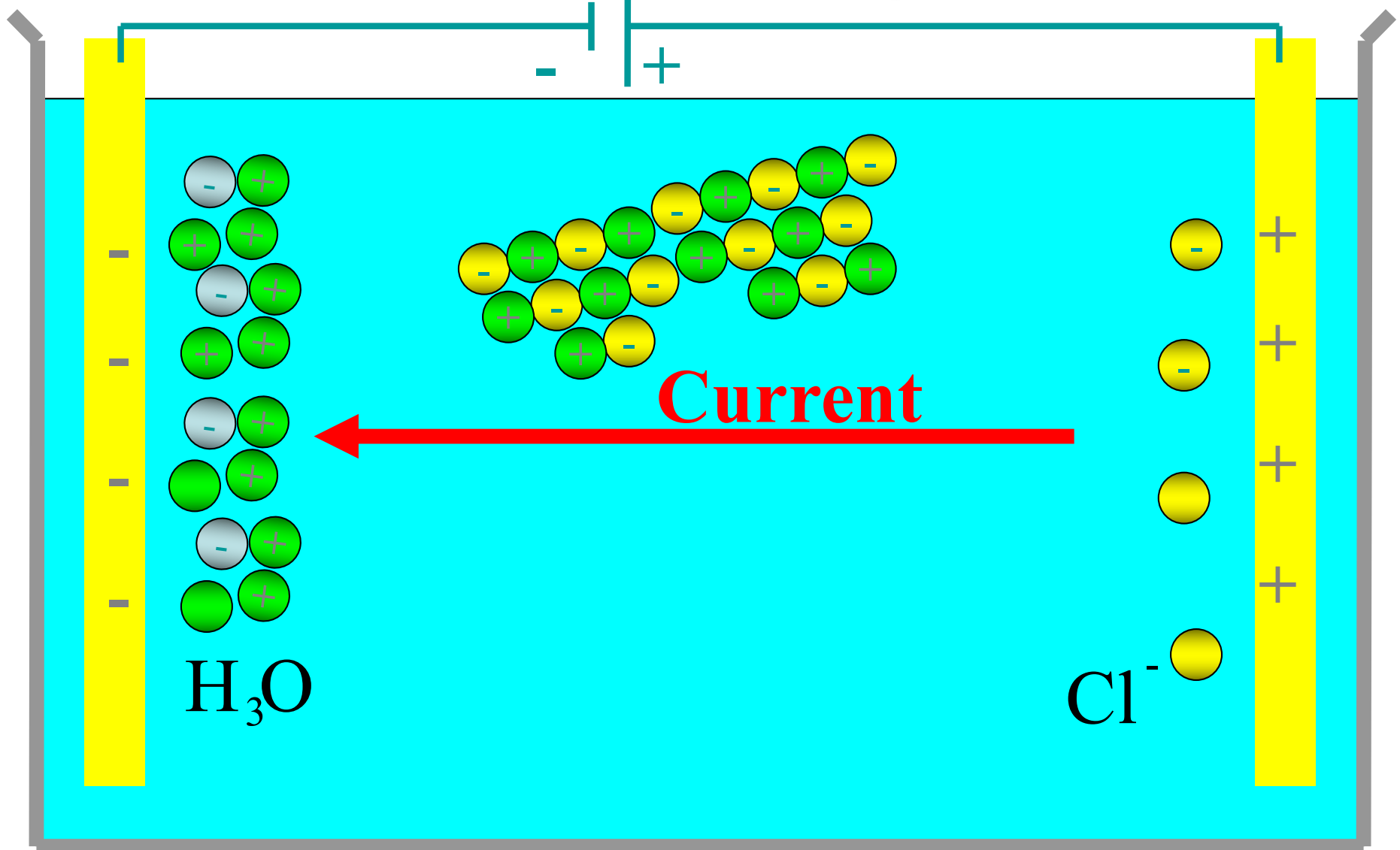
# Liquid Solution: Electrolytic Solution



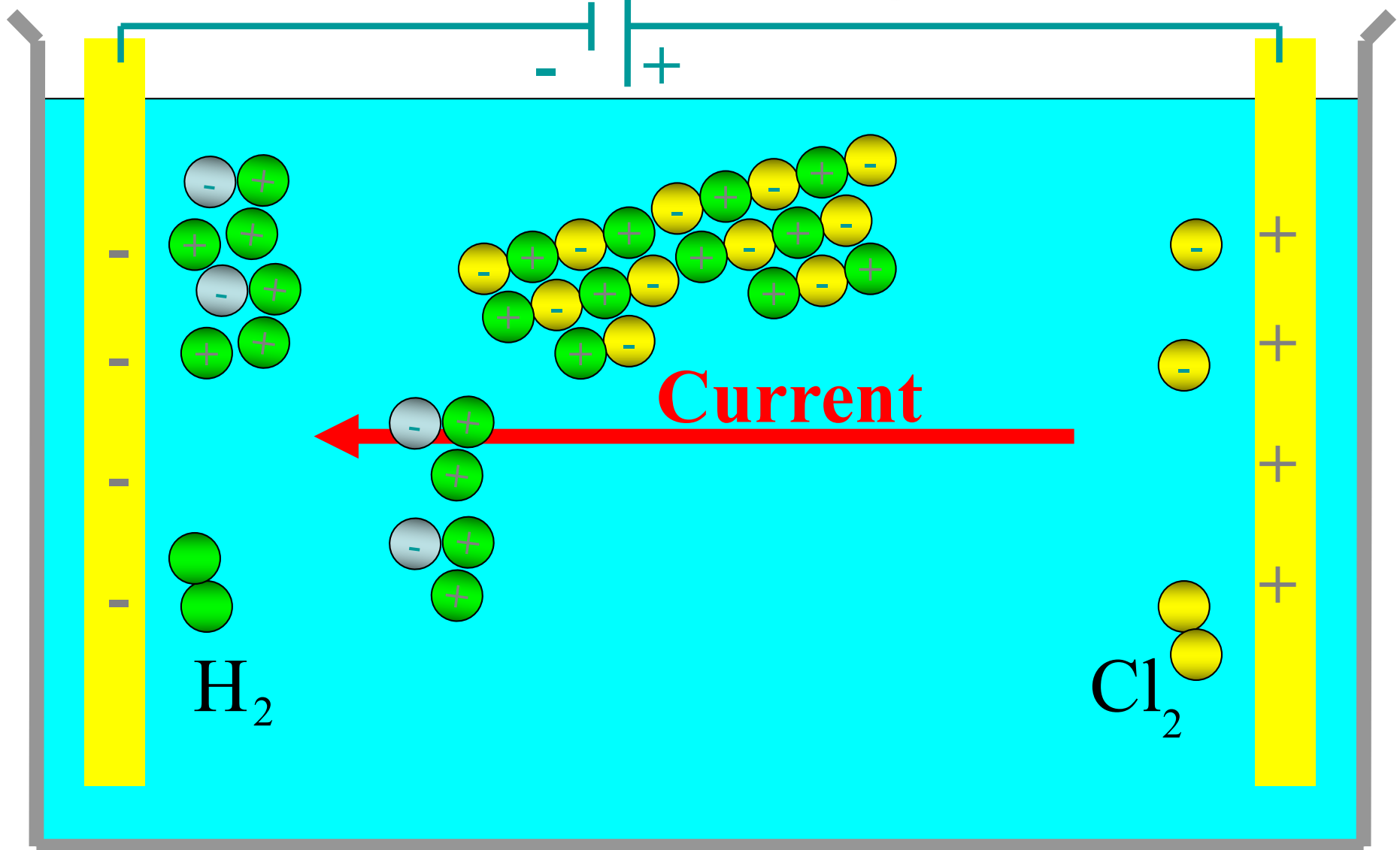
# Liquid Solution: Electrolytic Solution



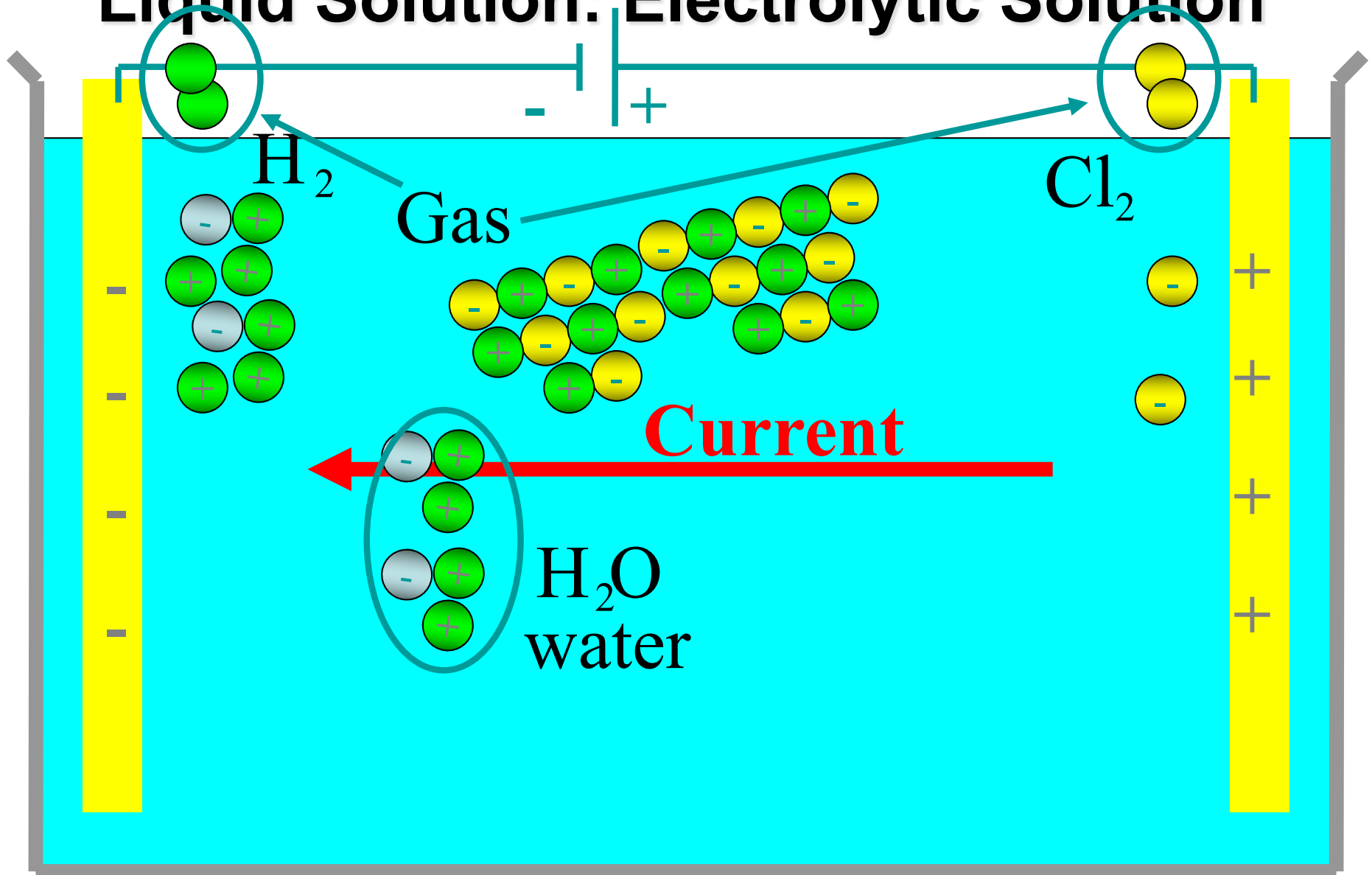
# Liquid Solution: Electrolytic Solution



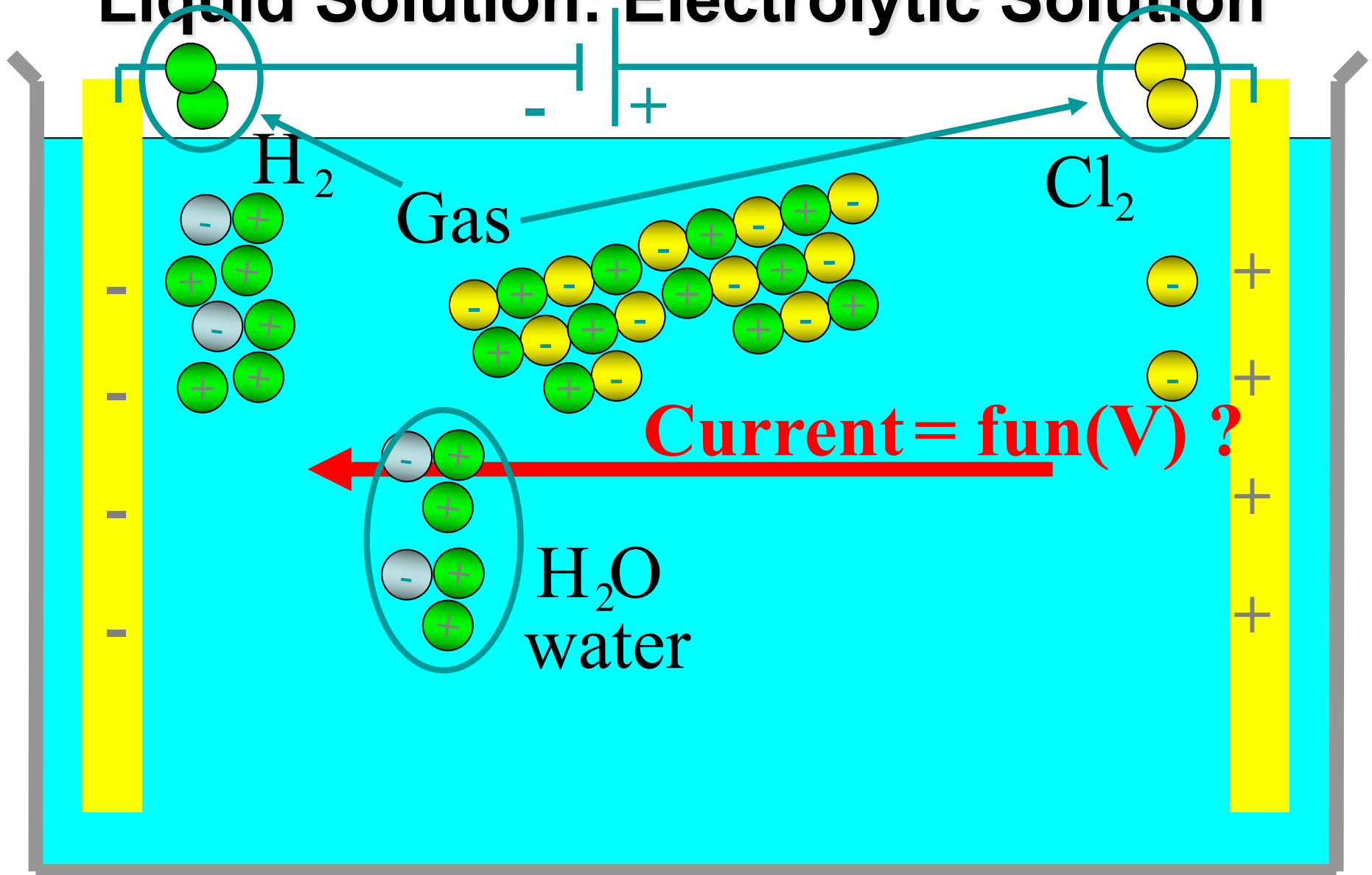
# Liquid Solution: Electrolytic Solution



# Liquid Solution: Electrolytic Solution



# Liquid Solution: Electrolytic Solution



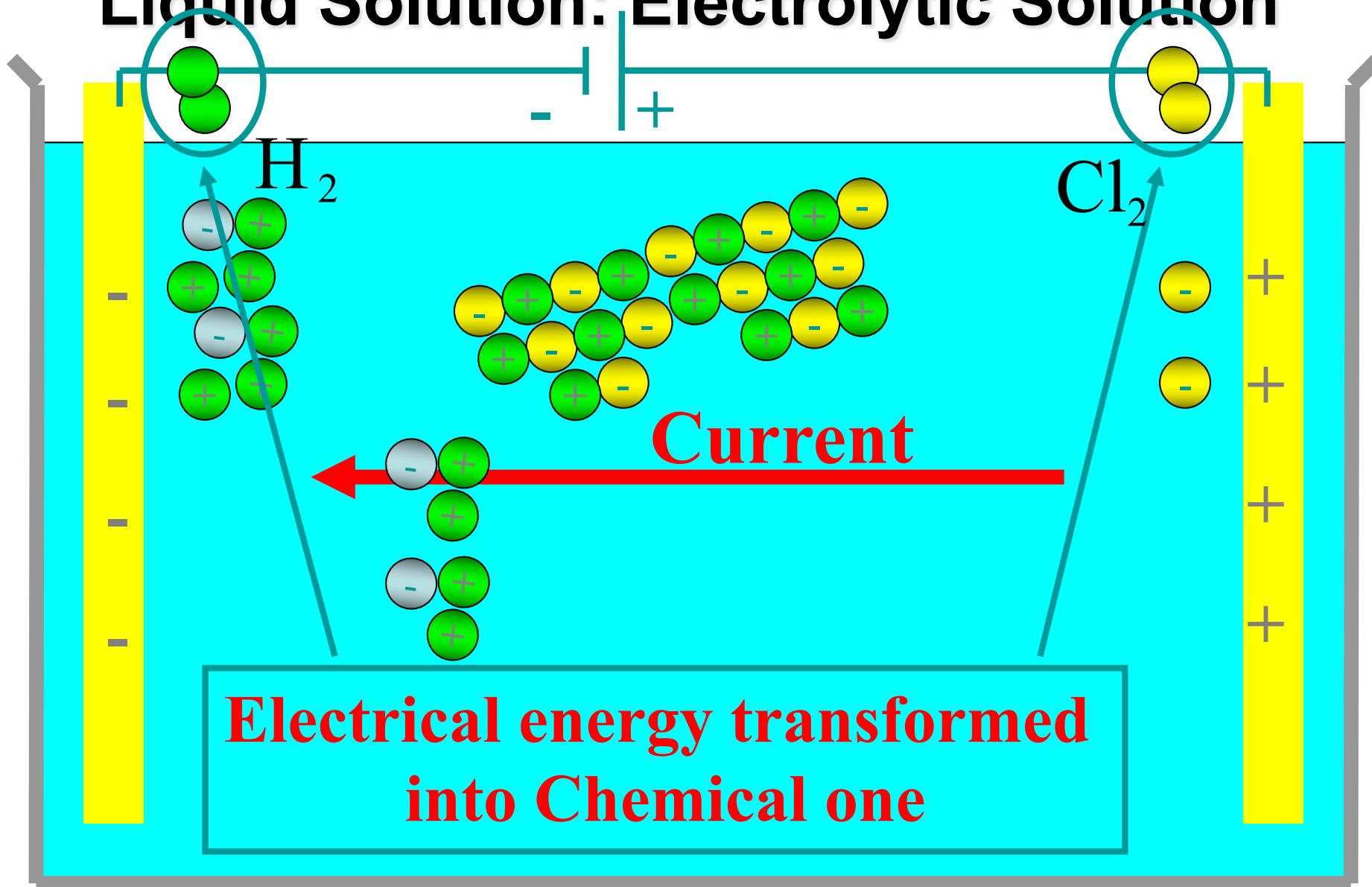


Q11

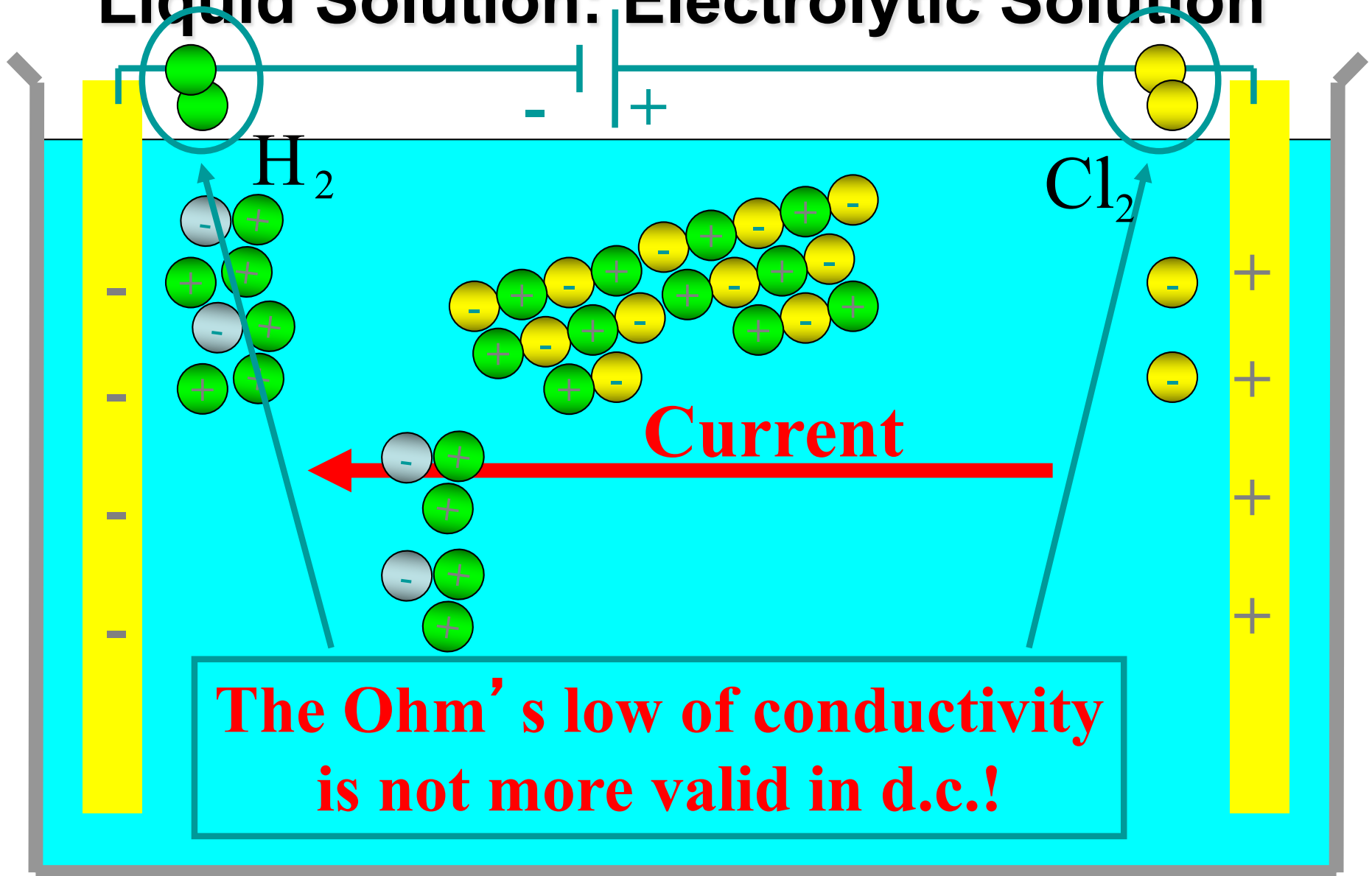
Does the Ohm law is still valid  
in electrolytic solutions?

- A. Yes, of course!
- B. It depends on kind of solution
- C. It depends on the concentration of the solution
- D. It depends on kind of current
- E. Not at all!

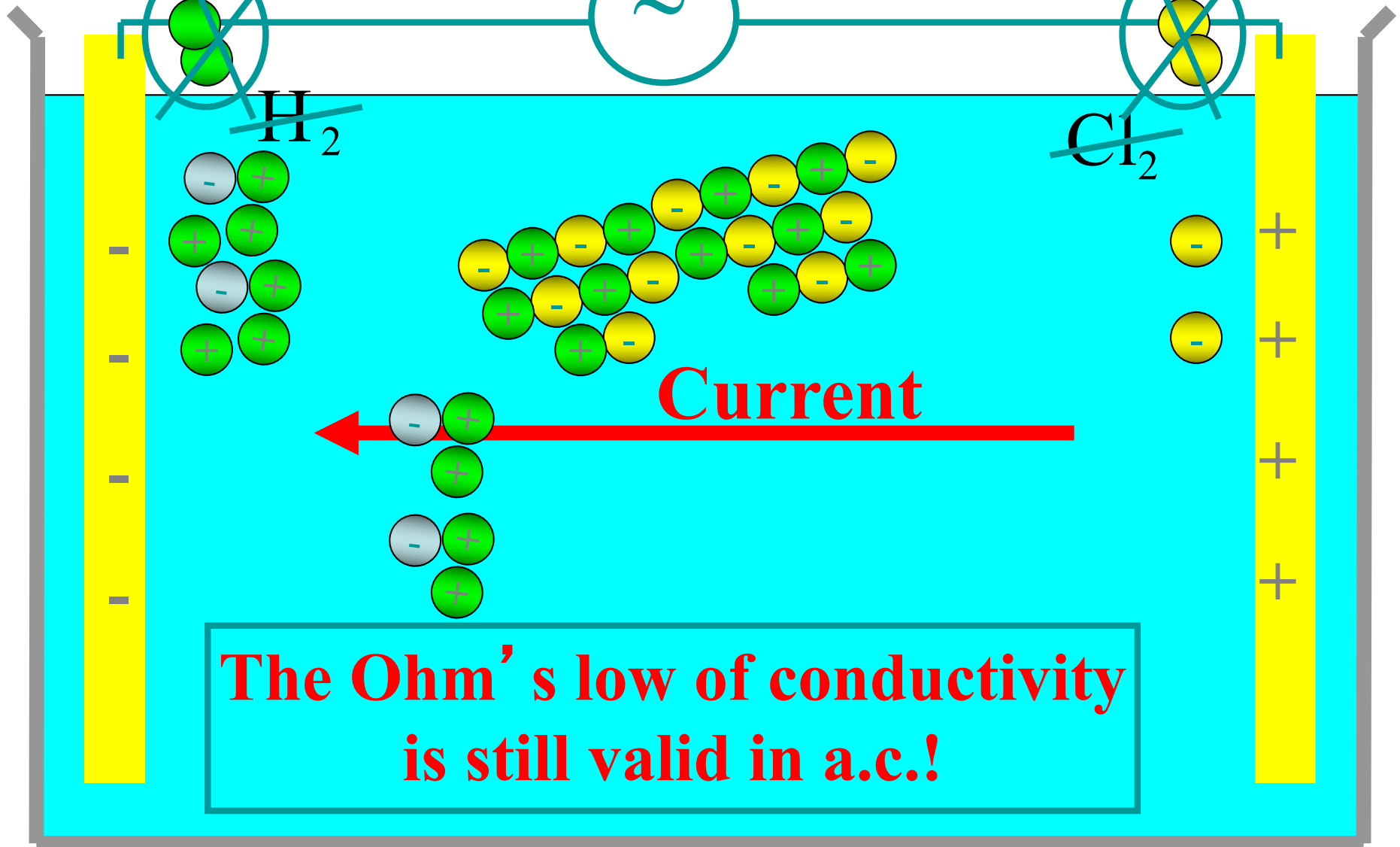
# Liquid Solution: Electrolytic Solution



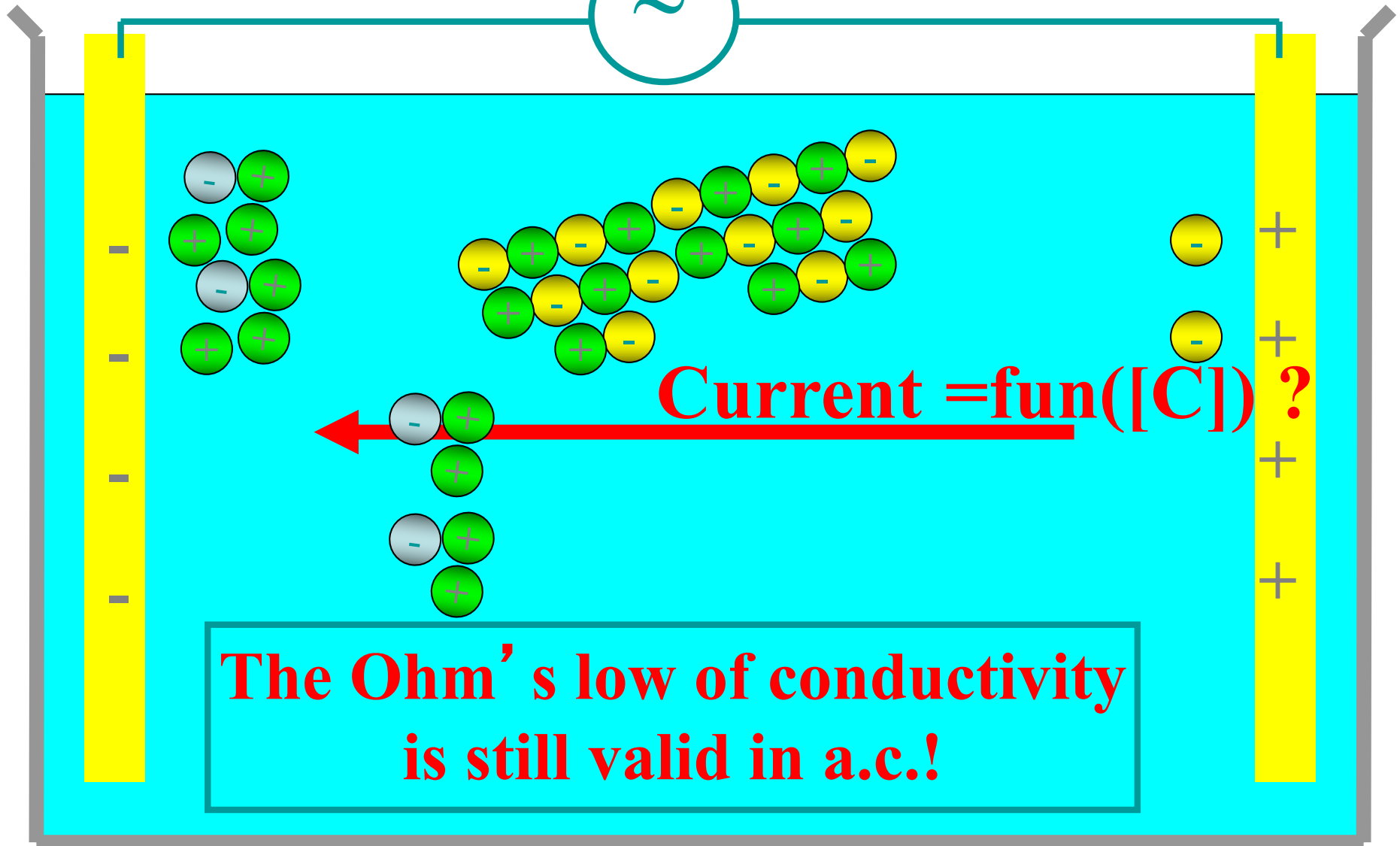
# Liquid Solution: Electrolytic Solution



# Liquid Solution: Electrolytic Solution



# Liquid Solution: Electrolytic Solution





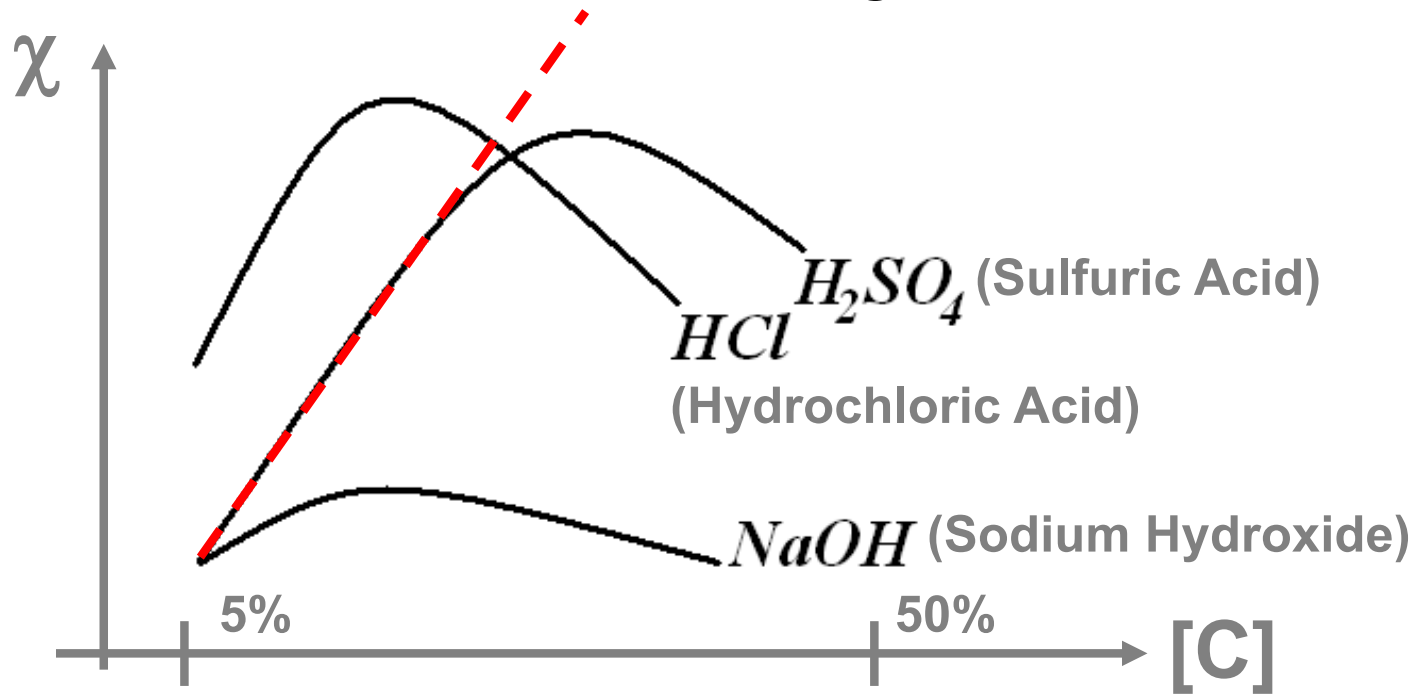
Q12

Does the conductivity is linear with the solution' concentration?

- A. Yes, of course!
- B. It depends on kind of solution
- C. It depends on the concentration of the solution
- D. It depends on kind of current
- E. Not at all!

# a.c. Conductivity in Ionic Solutions

## Solution Conductivity



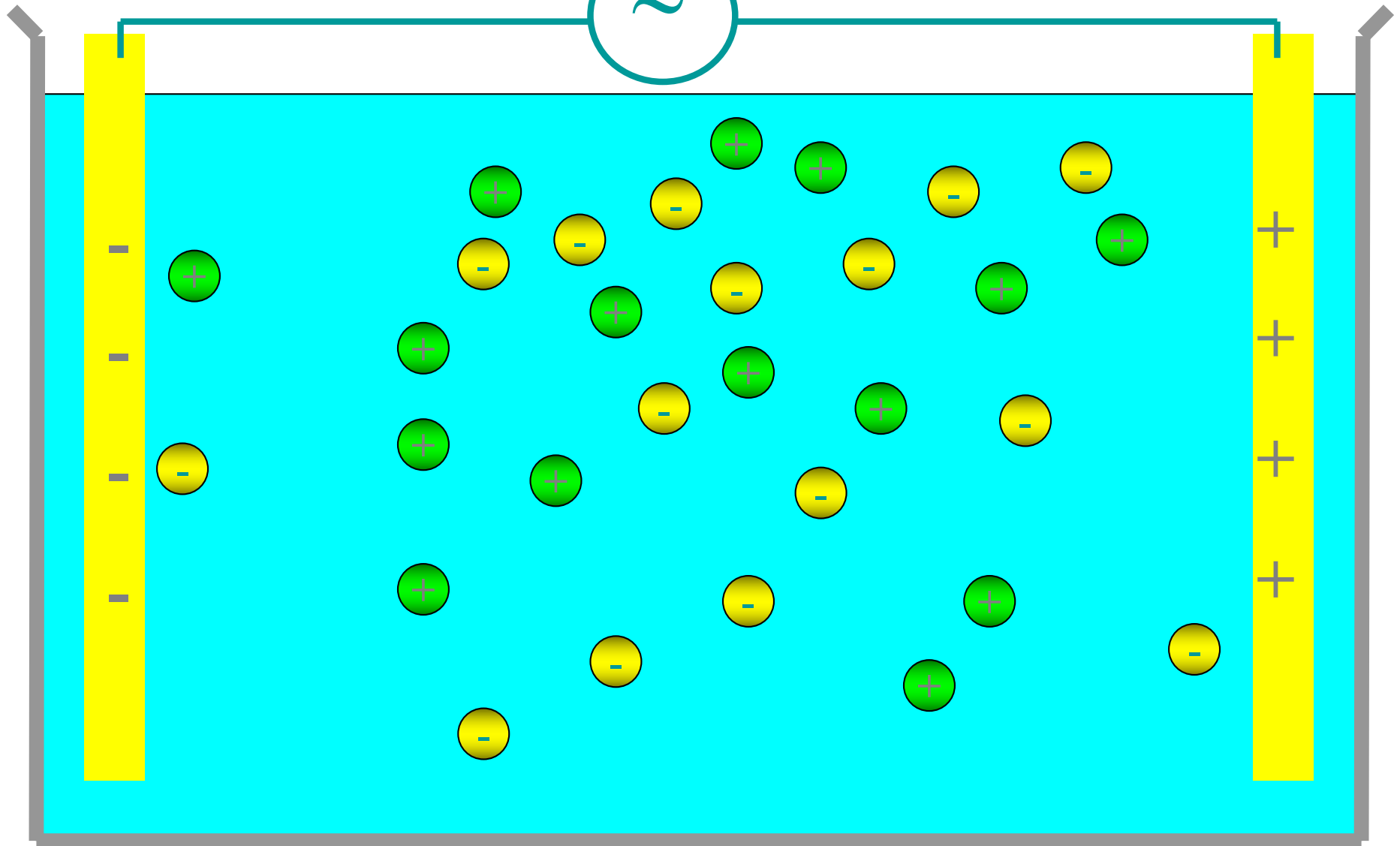


Q13

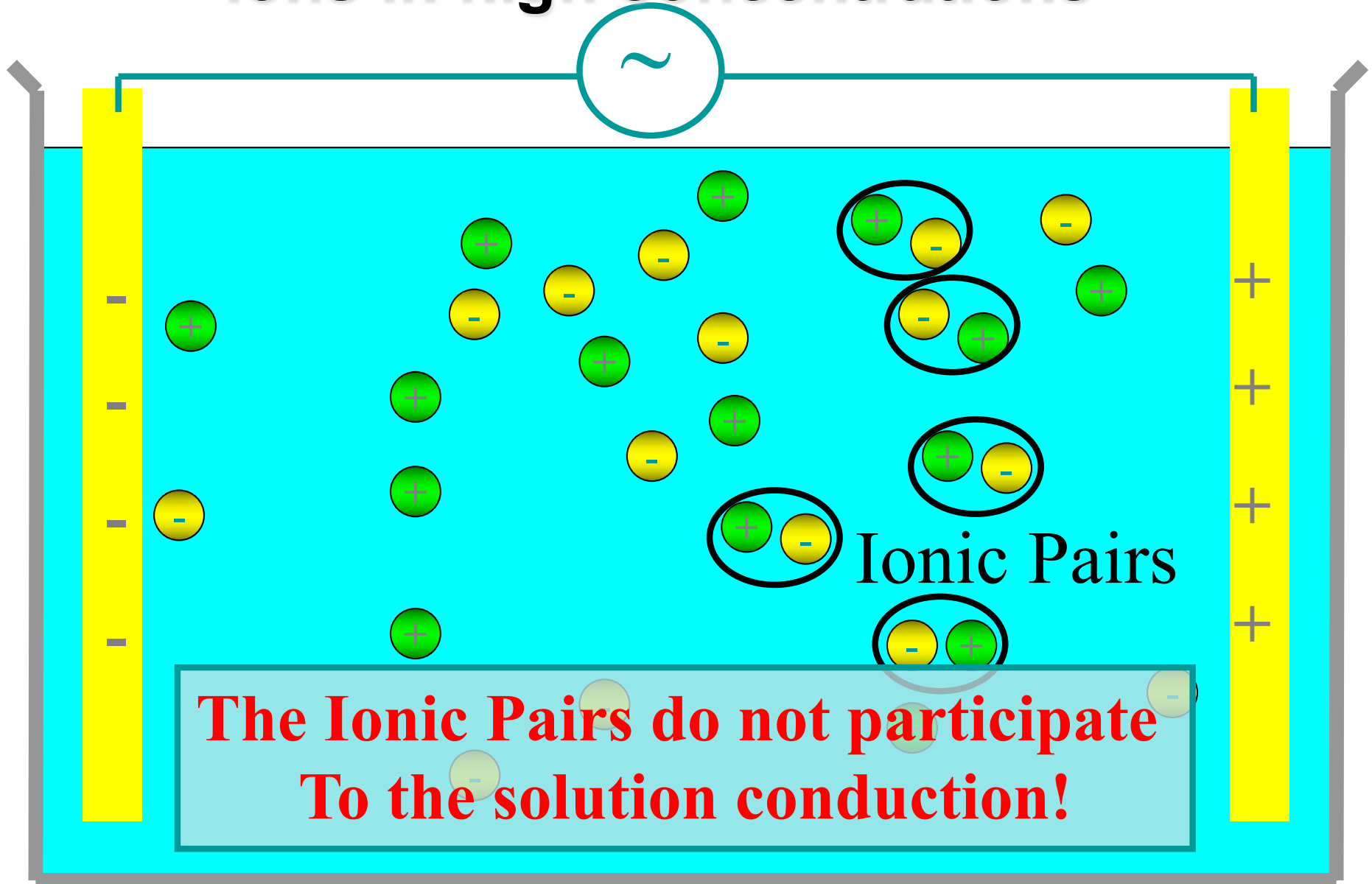
Why the conductivity goes down for higher solution' concentrations?

- A. Too much ions moving!
- B. Too faster ions' velocity
- C. Saturated number of ions available for the conductivity
- D. Less ions available for the conductivity
- E. No idea...

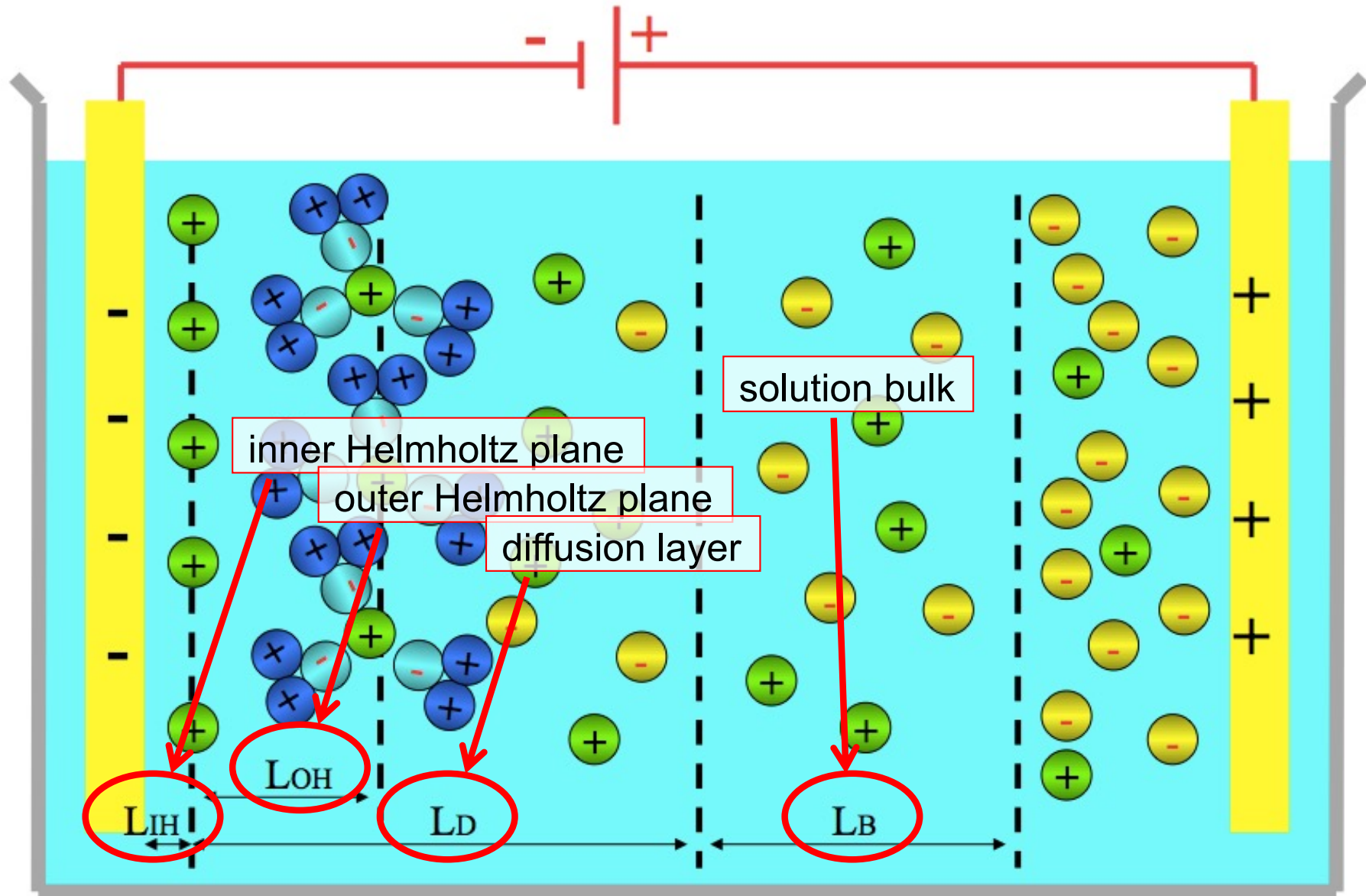
# Ions in high concentrations



# Ions in high concentrations



# Helmholtz Planes



# Debye Length

Charge density:  $\rho_e = \sum_i z_i e n_i$

$z_i$  = charge of species  $i$  (e.g. +2, -1, etc.)

$n_i$  = concentration of species  $i$  (number per volume)

$$\nabla^2 \phi = 0$$

In the bulk

$$\nabla^2 \phi = -\frac{\rho_e}{K\epsilon_0}$$

Close to electrodes

For perturbation away from equilibrium at finite temperature

$$\hat{\phi} \equiv \phi - \phi_0 \quad \rho_e = \sum_i z_i e n_{i0} \exp\left(-\frac{z_i e \hat{\phi}}{k_B T}\right)$$

# Debye Length

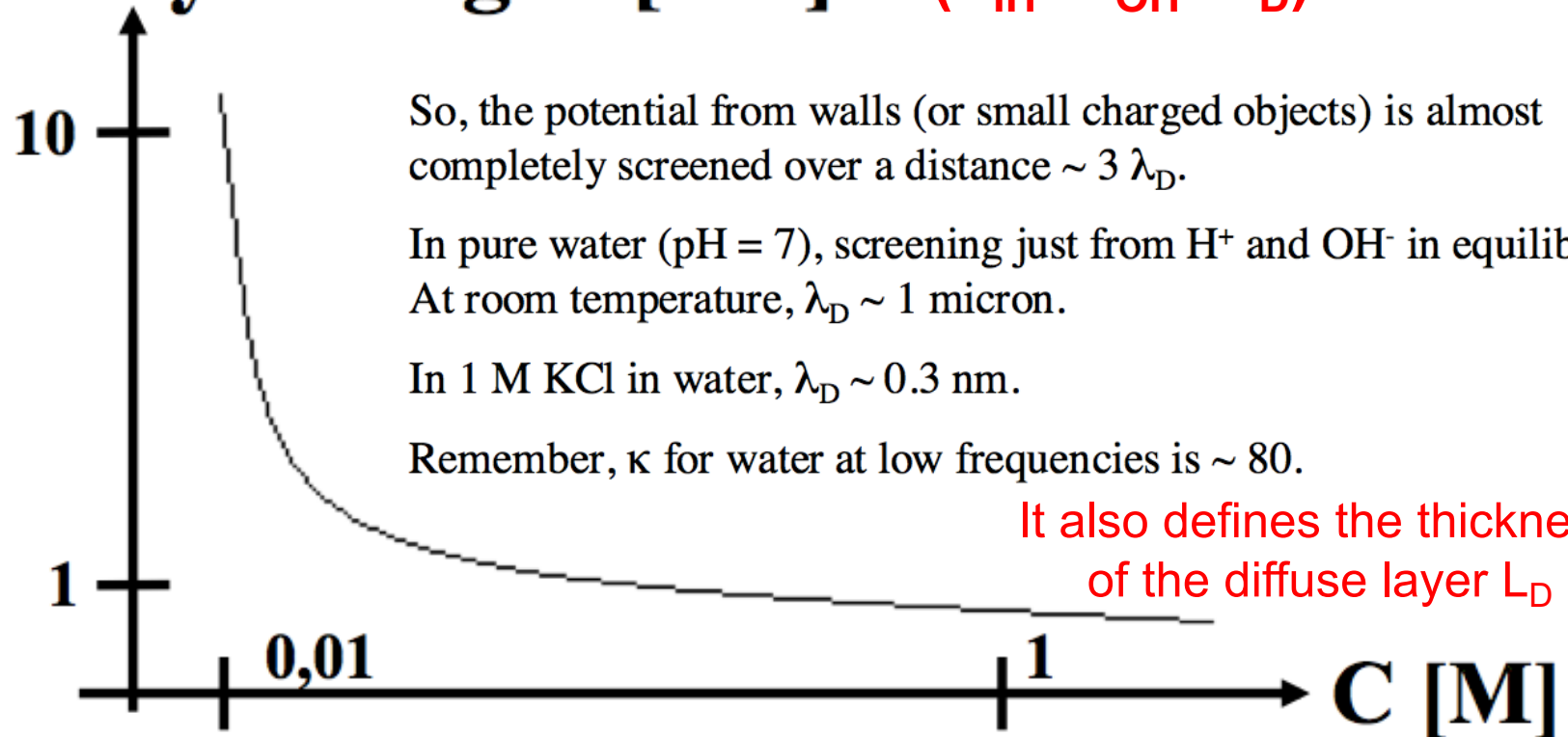
$$\nabla^2 \hat{\phi} = -\frac{1}{\kappa \epsilon_0} \sum_i z_i e n_{i0} \exp\left(-\frac{z_i e \hat{\phi}}{k_B T}\right) \approx -\frac{1}{\kappa \epsilon_0} \cancel{\sum_i z_i e n_{i0}} + \frac{e^2}{\kappa \epsilon_0 k_B T} \sum_i z_i^2 n_{i0} \hat{\phi} \equiv \frac{1}{\lambda_D^2} \hat{\phi}$$

*~ 0 for equilibrium neutrality*

$$\lambda_D \equiv \left( \frac{e^2}{\kappa \epsilon_0 k_B T} \sum_i z_i^2 n_{i0} \right)^{-1/2}$$

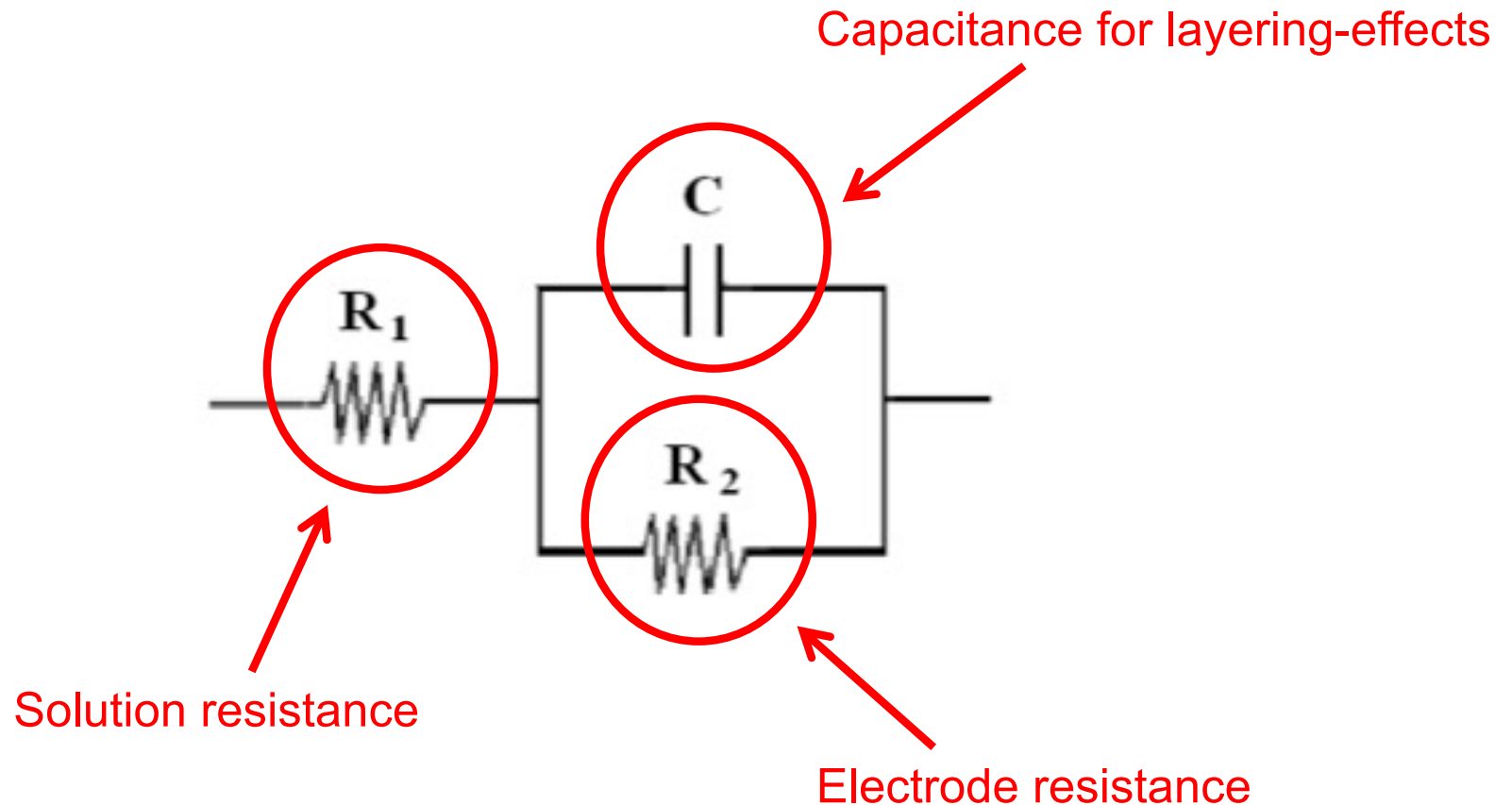
# Debye Length

$$\text{Debye Length [nm]} = (L_{\text{H}^+} + L_{\text{OH}^-} + L_{\text{D}}) / 3$$



The Debye Length is defined as the region of charge carrier's net electrostatic effect in solution

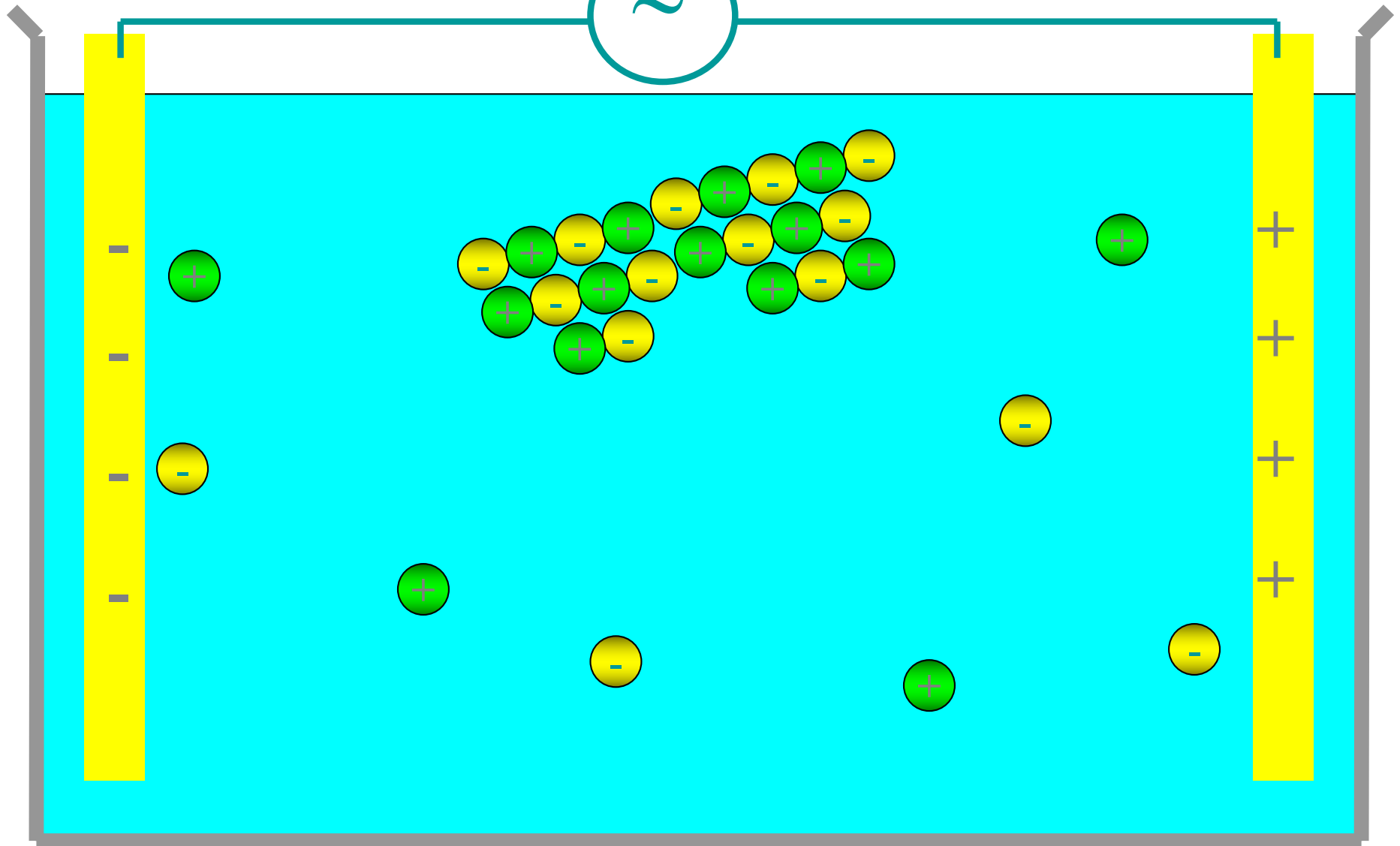
# Equivalent Circuit with Layering effects: Randles Model



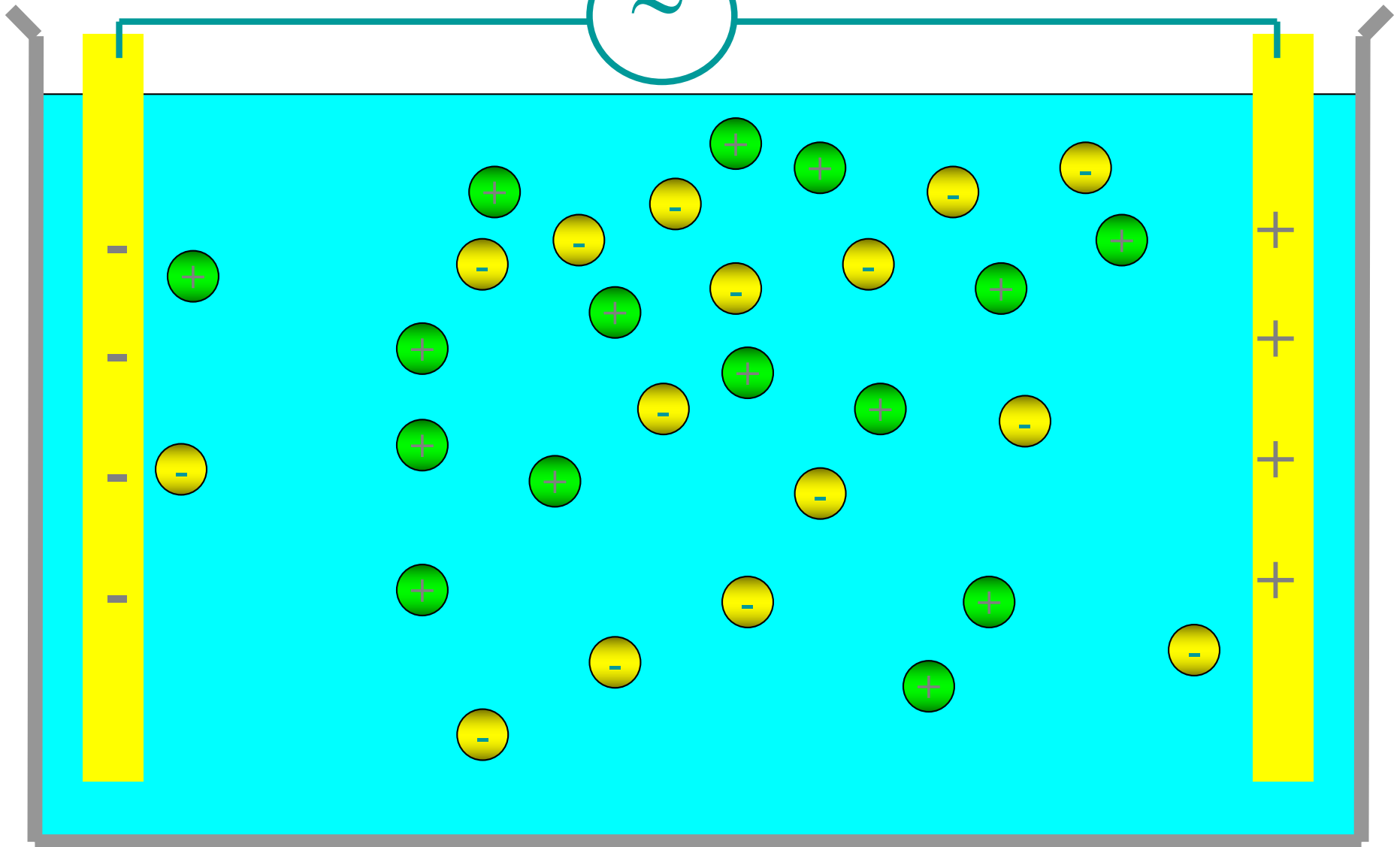
# Kind of Electrolytes

- **Strong Electrolytes**
- **Weak Electrolytes**

# Weak Electrolyte



# Strong Electrolytes

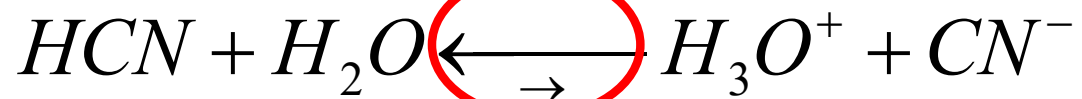


# Hard and weak Electrolytes

## Dissociation of the Sodium Chloride

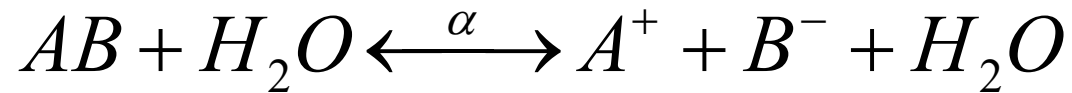


## Dissociation of Hydrogen Cyanide



$\alpha$  = Dissociation Degree

# Equilibrium Constant



$$K = \frac{[A^+][B^-]}{[AB]} = \frac{\alpha[AB]_0 \alpha[AB]_0}{(1-\alpha)[AB]_0} = \frac{\alpha^2}{1-\alpha} [AB]_0$$

**Actually true only for weak electrolytes  
in small concentration!**

# Kind of Electrolytes

- **Strong Electrolytes**

Salts

Strong Acids

Strong Bases

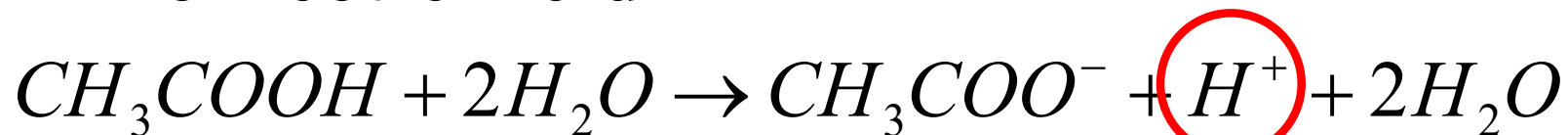
- **Weak Electrolytes**

Weak Acids

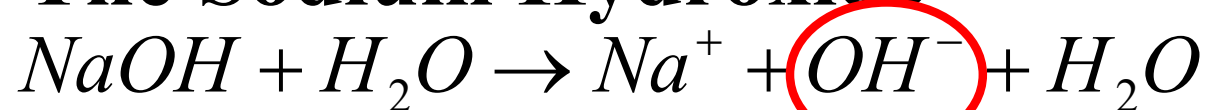
Weak Basis

# Acid or Basic Solutions

## The Acetic Acid



## The Sodium Hydroxide



Acid

Base

Arrhenius definition

(Not actually true but enough for our aims)



Q14

How much is  
the pH of pure water?

- A. 0
- B. Lower than 5
- C. 7
- D. Larger than 25
- E. infinite

# Water is neither a base nor an acid

## Water dissociation



$$K = \frac{[H_3O^+][OH^-]}{[H_2O]^2}$$

$$[H_2O] = 1 \rightarrow K_w = [H_3O^+][OH^-]$$

**Water Ionic product**

$$\Delta G^0 = -RT \ln K_w = \Delta G^0_{H_3O^+} + \Delta G^0_{OH^-} - 2\Delta G^0_{H_2O}$$

# Definition of pH

## Water dissociation

$$\Delta G^0 = -RT \ln K_w = \Delta G^0_{H_3O^+} + \Delta G^0_{OH^-} - 2\Delta G^0_{H_2O}$$

$$\ln K_w = -\frac{\Delta G^0_{H_3O^+} + \Delta G^0_{OH^-} - 2\Delta G^0_{H_2O}}{RT}$$

$$\ln K_w = -14$$

$$K_w = [H_3O^+][OH^-] = 10^{-14}$$

**pH=7, means “neutral pH”**


$$[H_3O^+] = [OH^-] = 10^{-7} M$$

# Acid, Neutral, or Basic Solutions

$[H_3O^+] > 10^{-7} M \rightarrow$  *Acid Solution*

$[H_3O^+] = 10^{-7} M \rightarrow$  *Neutral Solution*

$[H_3O^+] < 10^{-7} M \rightarrow$  *Basic Solution*

$$pH = \text{Log} \left( \frac{1}{[H_3O^+]} \right); \begin{cases} < 7 \rightarrow \textit{Acid Solution} \\ 7 \rightarrow \textit{Neutral Solution} \\ > 7 \rightarrow \textit{Basic Solution} \end{cases}$$