Electrical and Electronics Engineering

EE-517

Bio-Nano-Chip Design

EPFL

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Bio-Nano-Chip Design

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

Q1

Which Master Program are you following?

A. Electrical Engineering
B. Microengineering
C. Robotics
D. Life Science
E. Chemical Engineering
F. Material Science
G. Mechanical Engineering
H. Others

Q2

How did you get aware of this course?

A. By a generic list of optional courses
B. By the specific list of options of my minor/specialization
C. By a professor who suggested me
D. By another student who suggested me

Q3

Why did you choose this course?

A. For basic knowledge with generic interest
B. For a specific interest
C. I heard that’s a good course
D. I heard that’s an easy course
E. I need credits any way

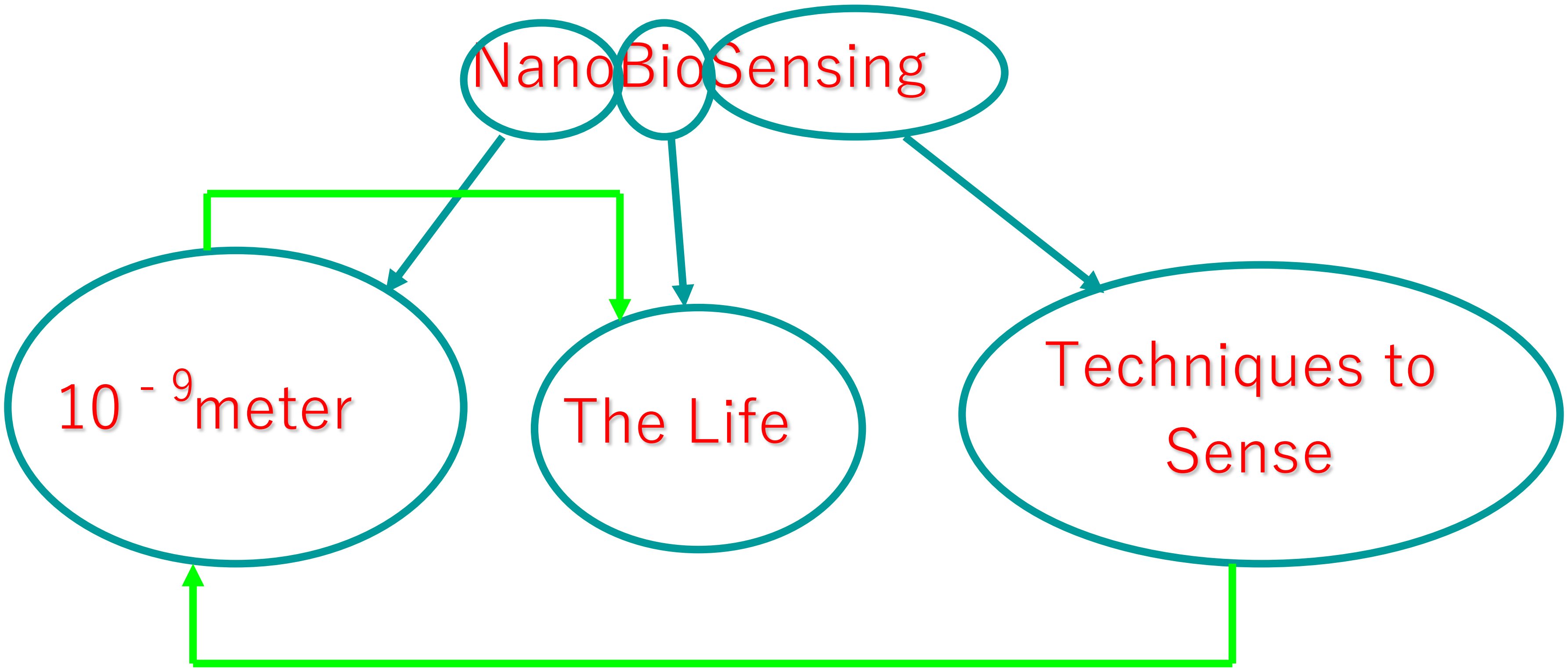
What's about The Course?

Nano-Bio-Sensing and Bio/CMOS interfaces

Technology

Nano-Bio-Technology

What's about Nano-Bio-Sensing?



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

AFFYMETRIX

The Motivation

- 100.000 $ (machinery)
- 1.000 $ the single µ-array

Labeled

Label-Free

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

Bayer HealthCare

The Quicklab project by Siemens

Glucometer on iPhone

Next step: the future already begun

Glucose Personal Diagnostics on our Skin

Q4

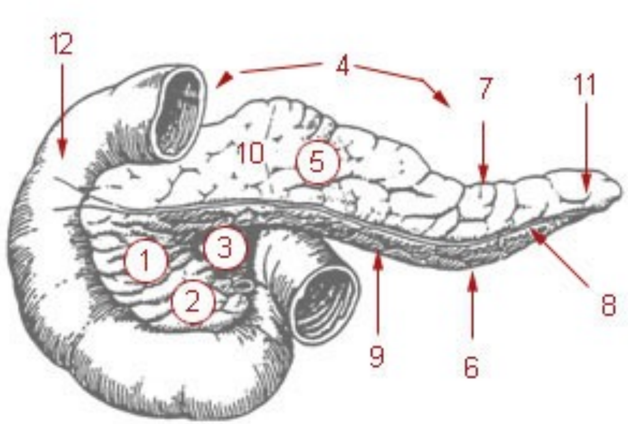
Does the pancreas just measure the glucose and produce insulin?

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 aceids
pH
Syrinic proteases
Glucose
Glycagone pancreatic
…….



OUT-put Signals

insulin
Lipase
Fospholipase A
Cholesterol estarase
Endopeptidase
Esopeptidase
Elastase
Ribonuclease
Enterochinase
…..

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)**

Bio-Markers may be simple molecules, proteins or genes

What else to sense?

Endogenous Metabolites	**Insulin (Diabetes)** **β-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

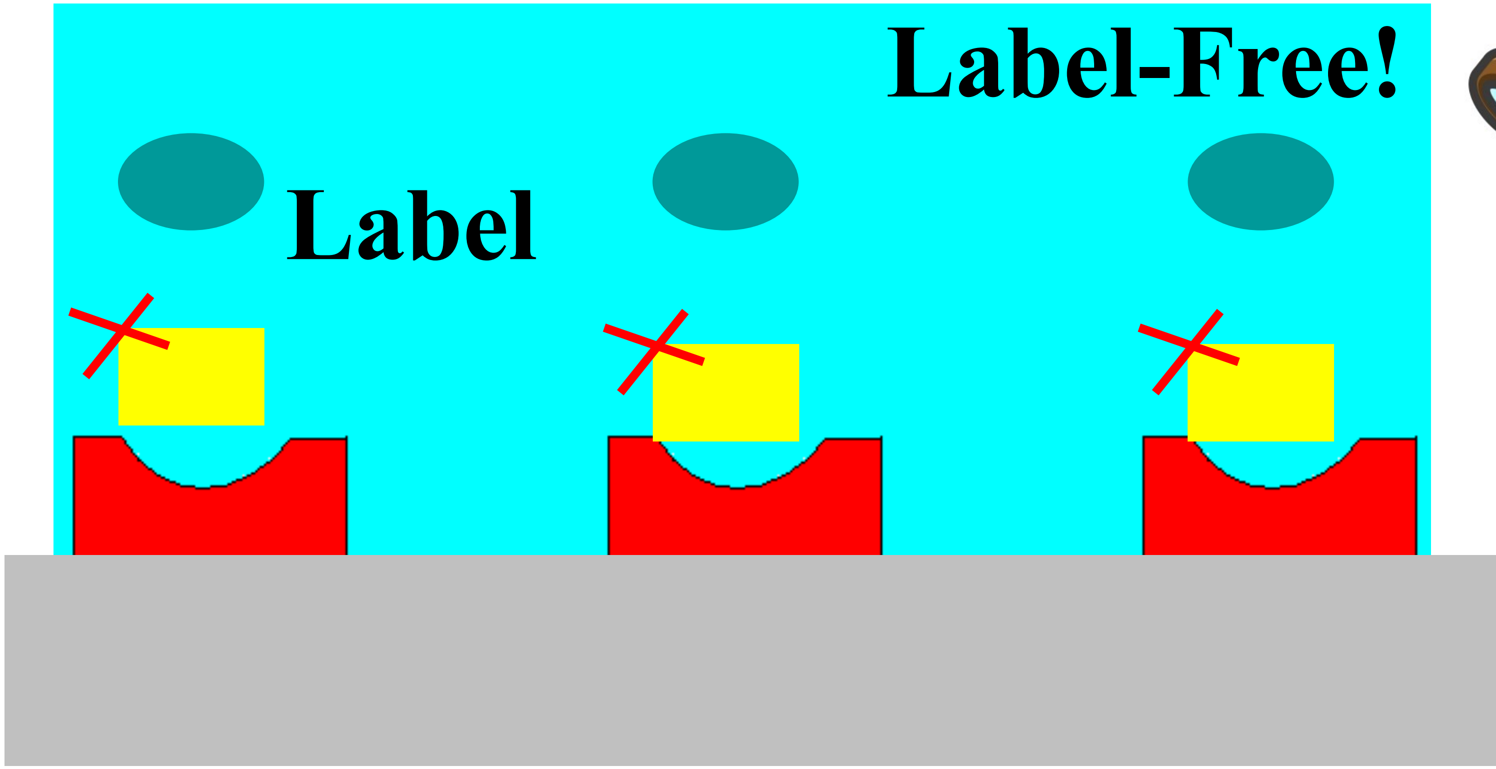
What to sense?

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?

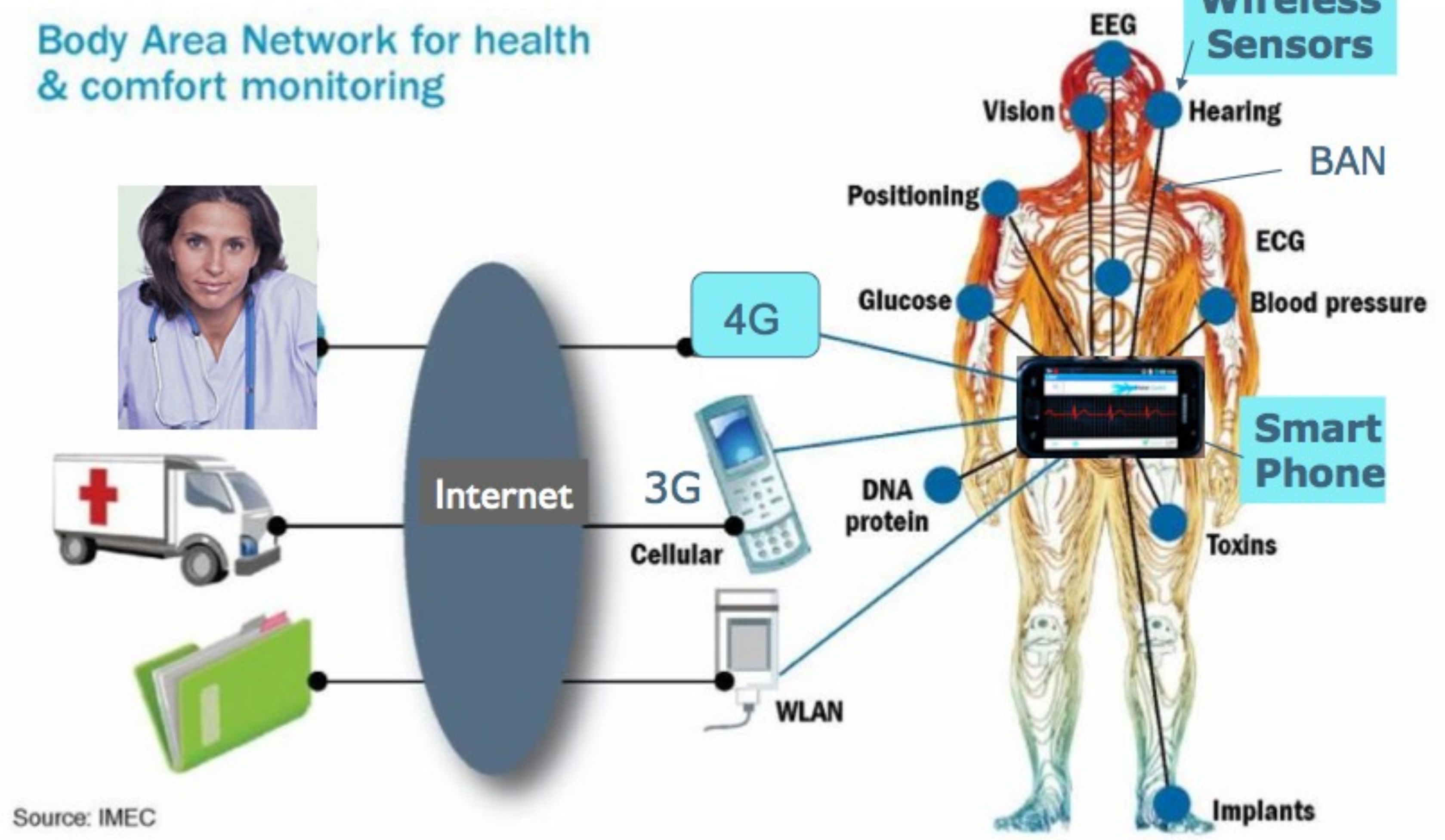
A. Yes, of course!
B. Yes, but it requires efforts
C. Yes, but requires little modifications
D. Yes, but depends by the applications
E. Not at all

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++



Courtesy, Hugo De Man (IMEC)

The Time' forecast on Human++

[TIME, February 2011]

Chips under the skin?

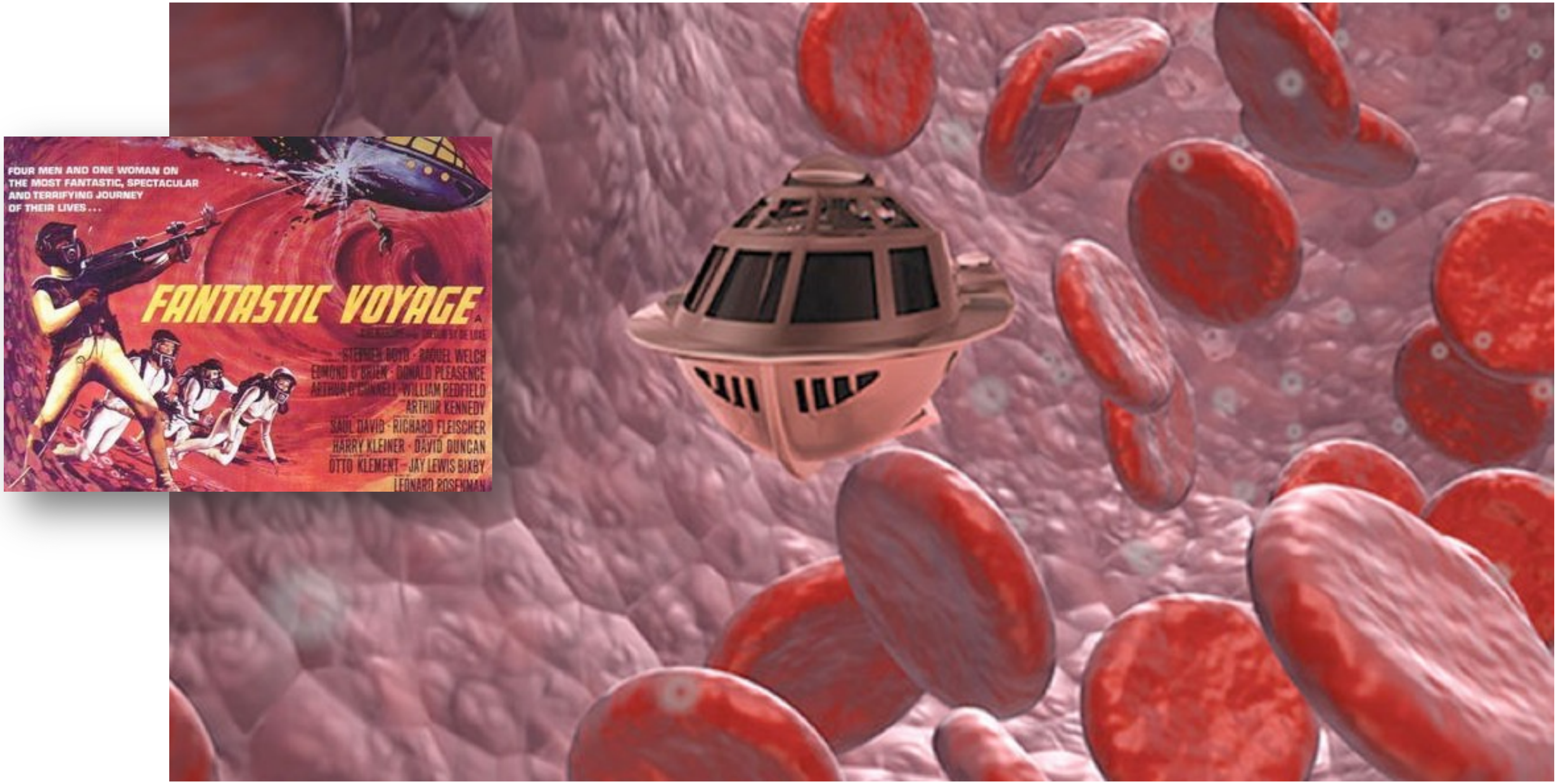
Under the skin: how insertable microchips could unlock the future

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

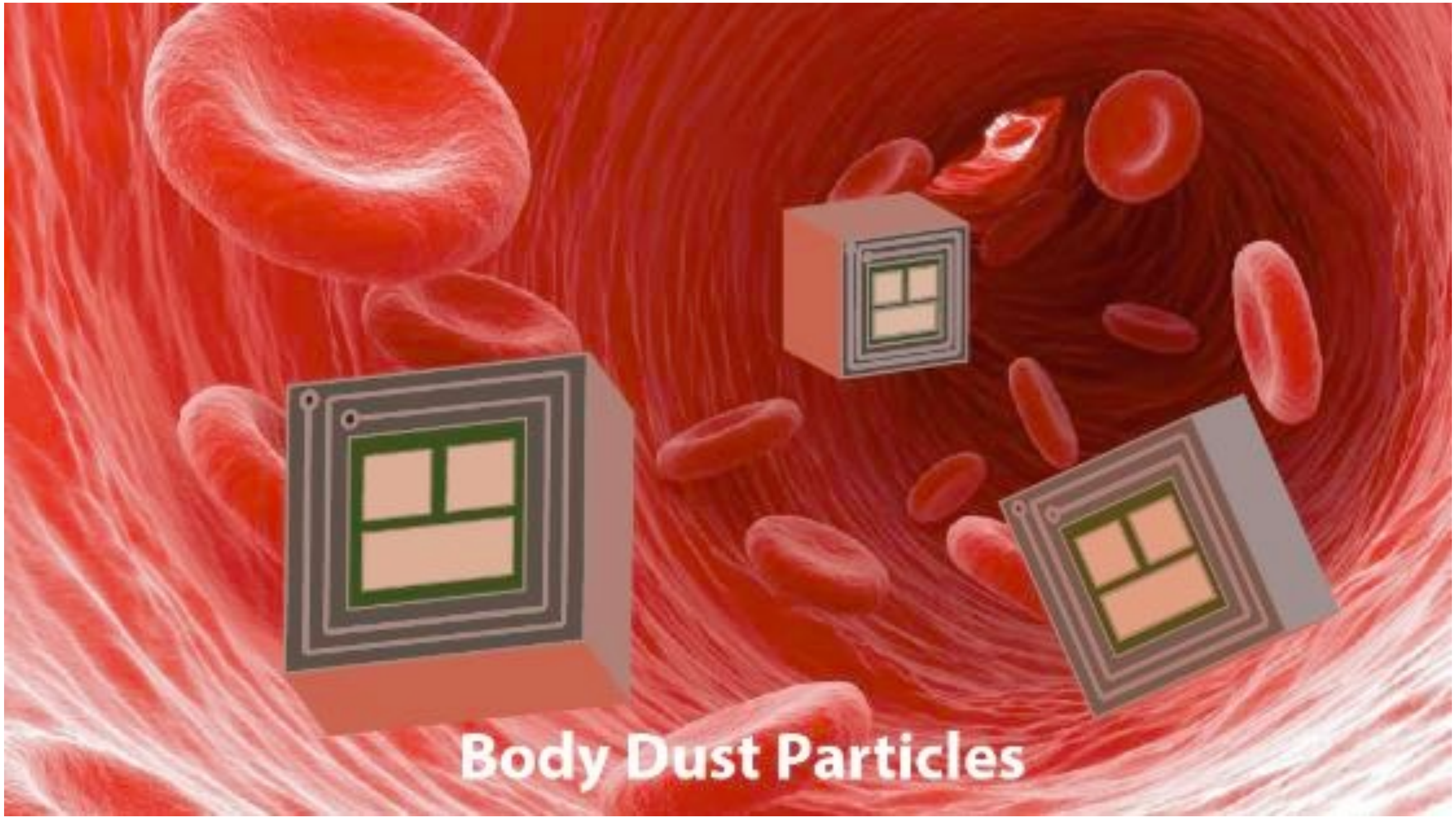
[The Guardian, October 2017]

How small Chips under the skin?



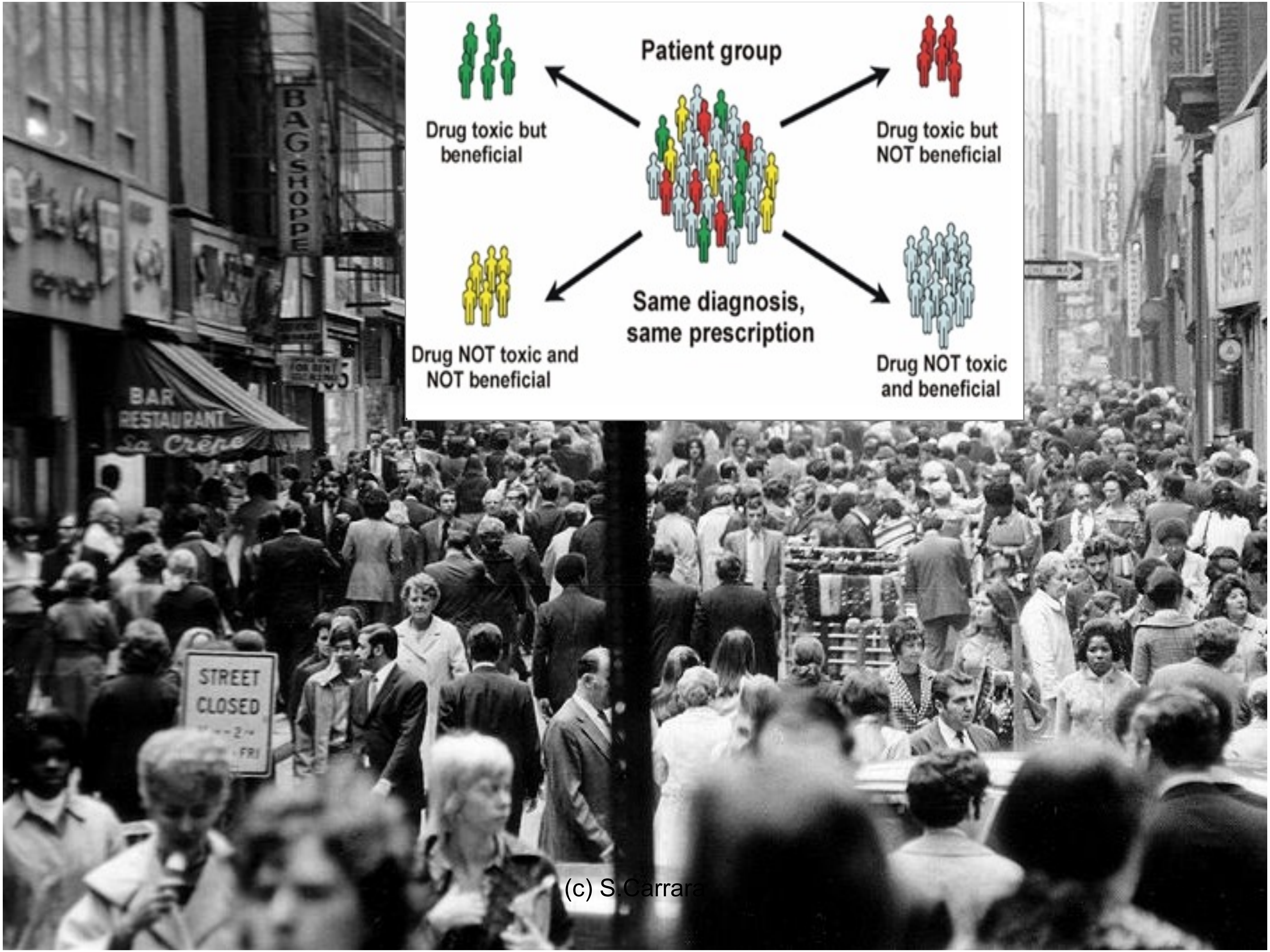
[1966 Sci. Fi. movie titled “Fantastic Voyage”]

Body Dust: Drinkable CMOS Bioelectronics

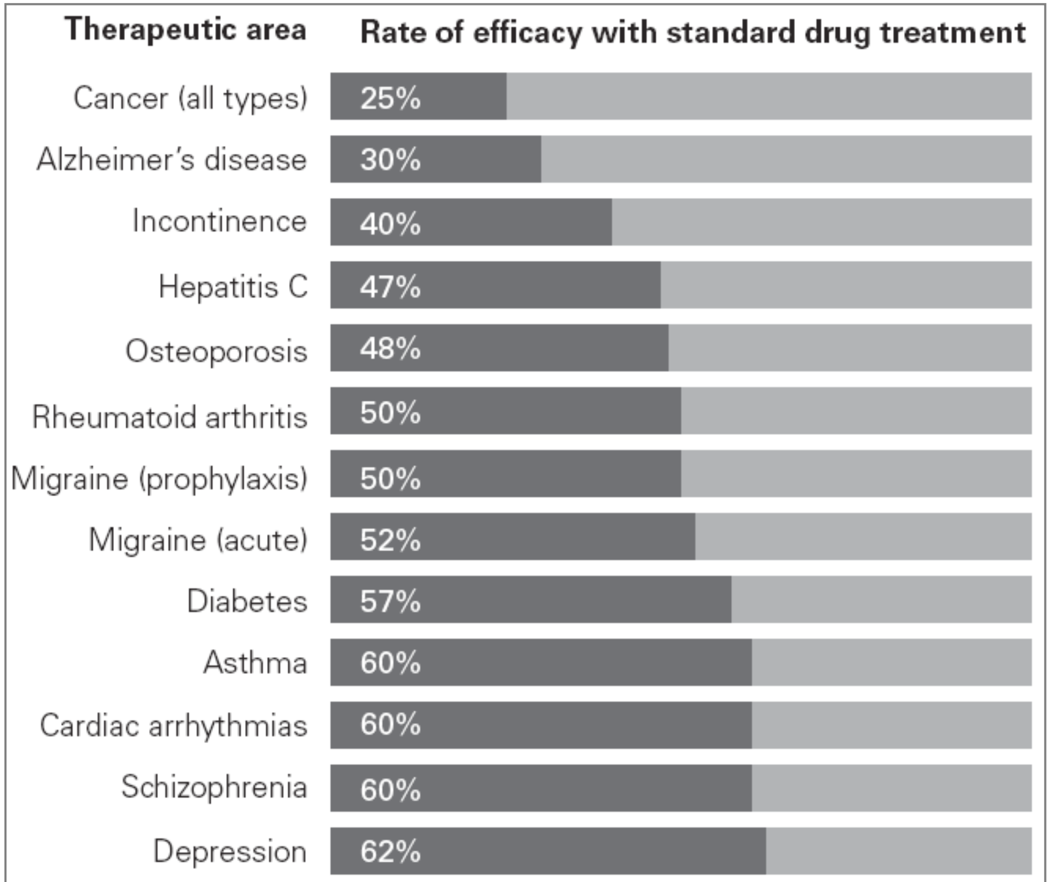


Tracking cancer-cell developing "drinkable" electronic sensors

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


Patient group
Drug toxic but
beneficial
Drug toxic but
NOT beneficial
Drug NOT toxic and
NOT beneficial
Same diagnosis,
same prescription
Drug NOT toxic
and beneficial
BAG SHOPPE
BAR
RESTAURANT
La Crêpe
STREET
CLOSED

Low efficacy of used compounds



For depression, the data apply specifically to the drug class known as selective serotonin reuptake inhibitors.

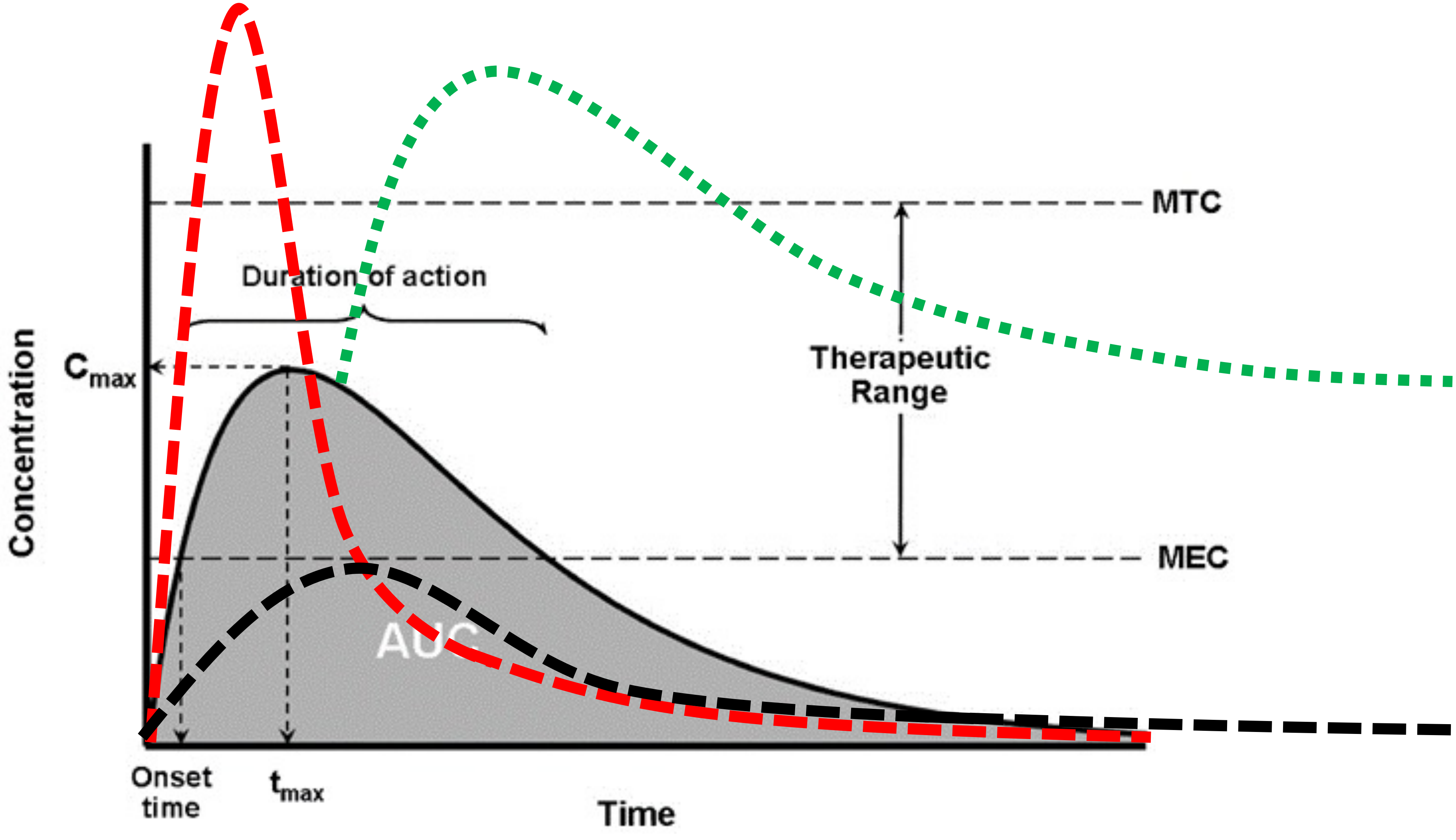
Source: Brian B. Spear, Margo Heath-Chiozzi, and Jeffrey Huff, "Clinical Application of Pharmacogenetics," *Trends in Molecular Medicine* (May 2001).

Q7

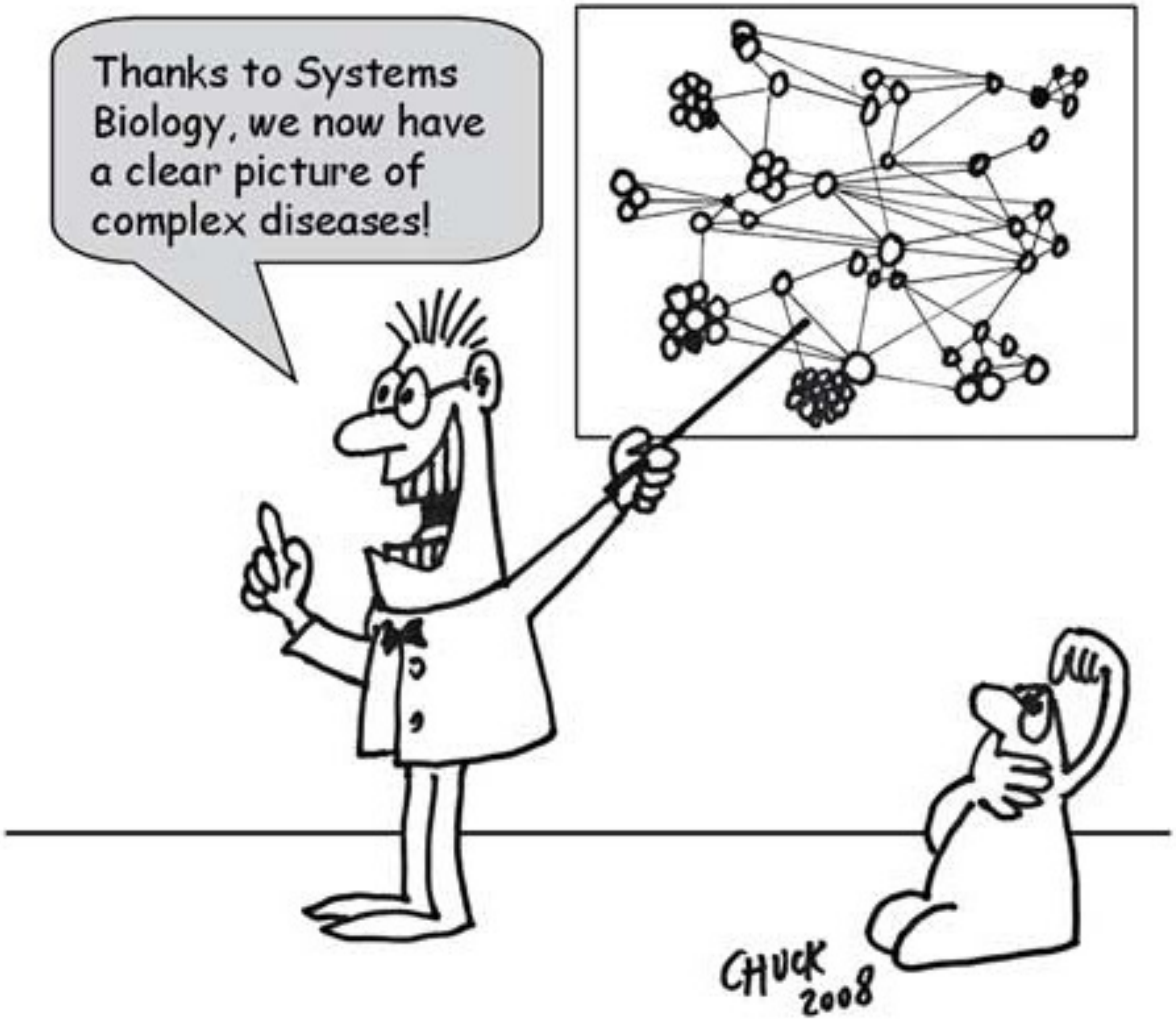
Why different outputs from same kind of patients?

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

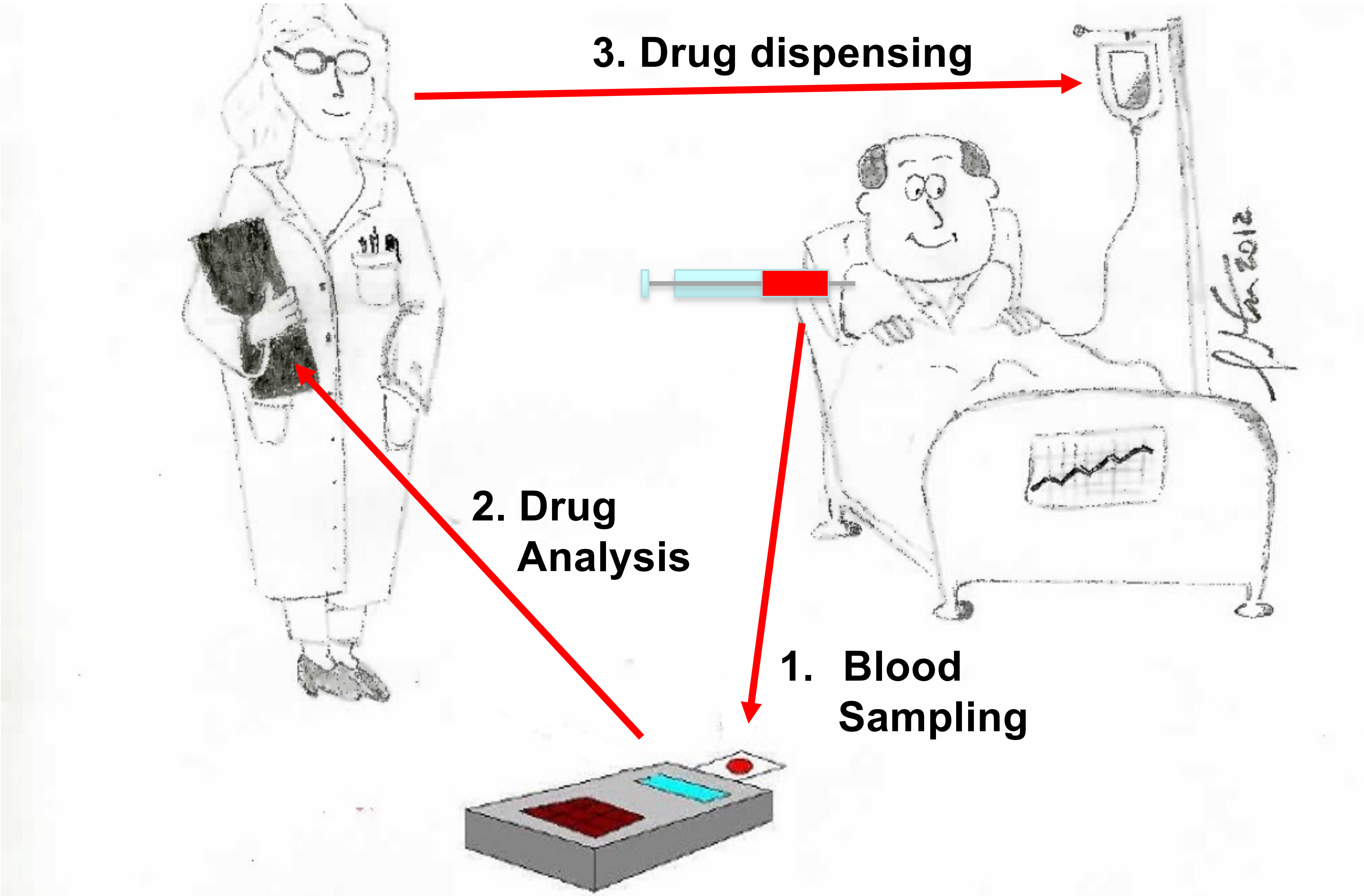
Personalized Therapy: the right dose in the right moment!



System Biology is not enough



Personalized Therapy

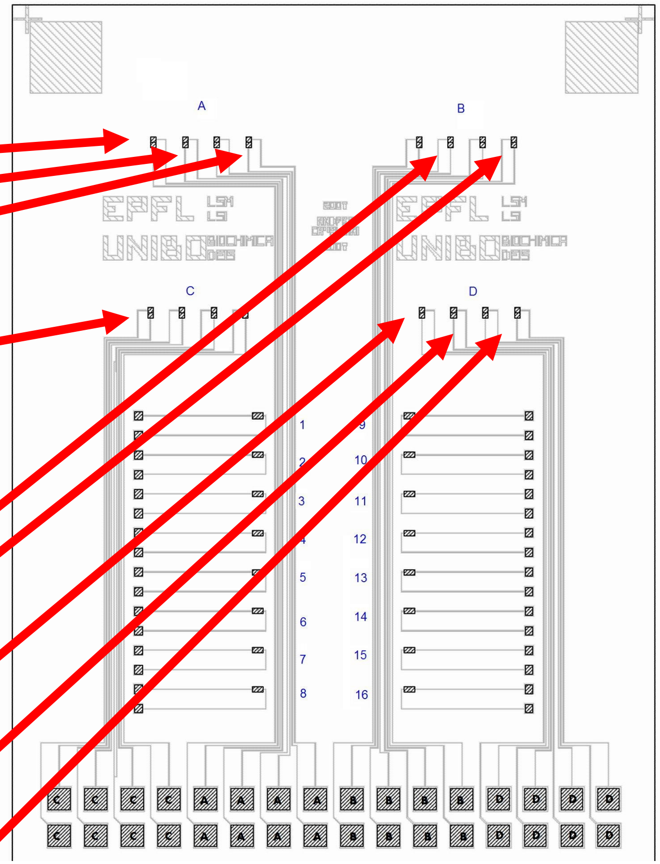


Drugs injection based on patient's pharmacokinetics

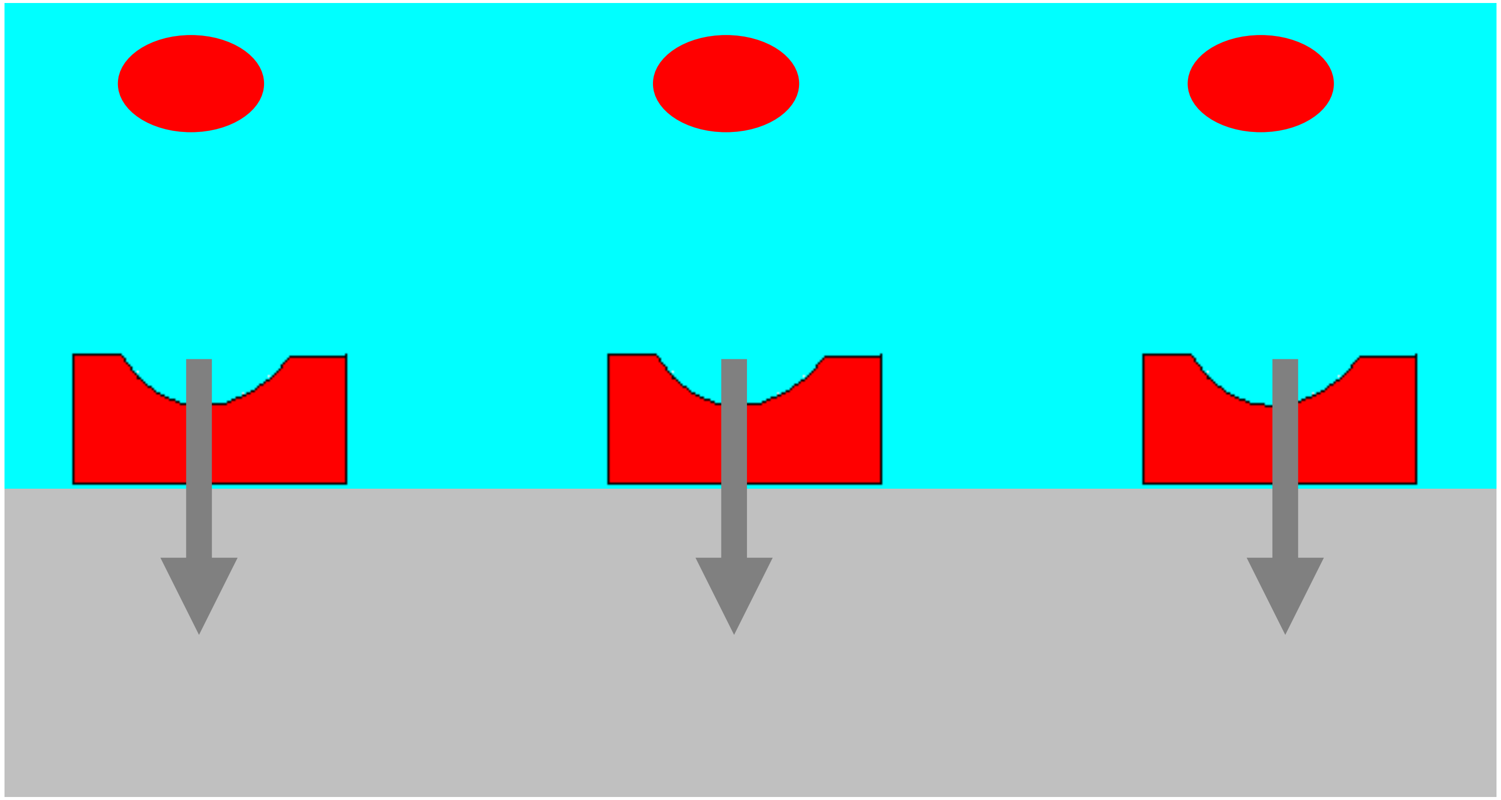
The need for new Bio/CMOS systems

TARGETS

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

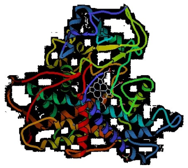


CMOS/Sample interface

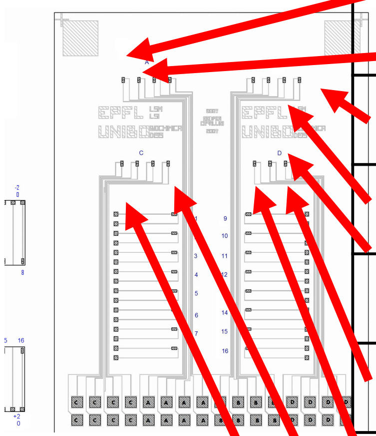


The interface between the CMOS circuit and the bio-sample needs to be deeply investigated and organized

Applications in Personalized Therapy

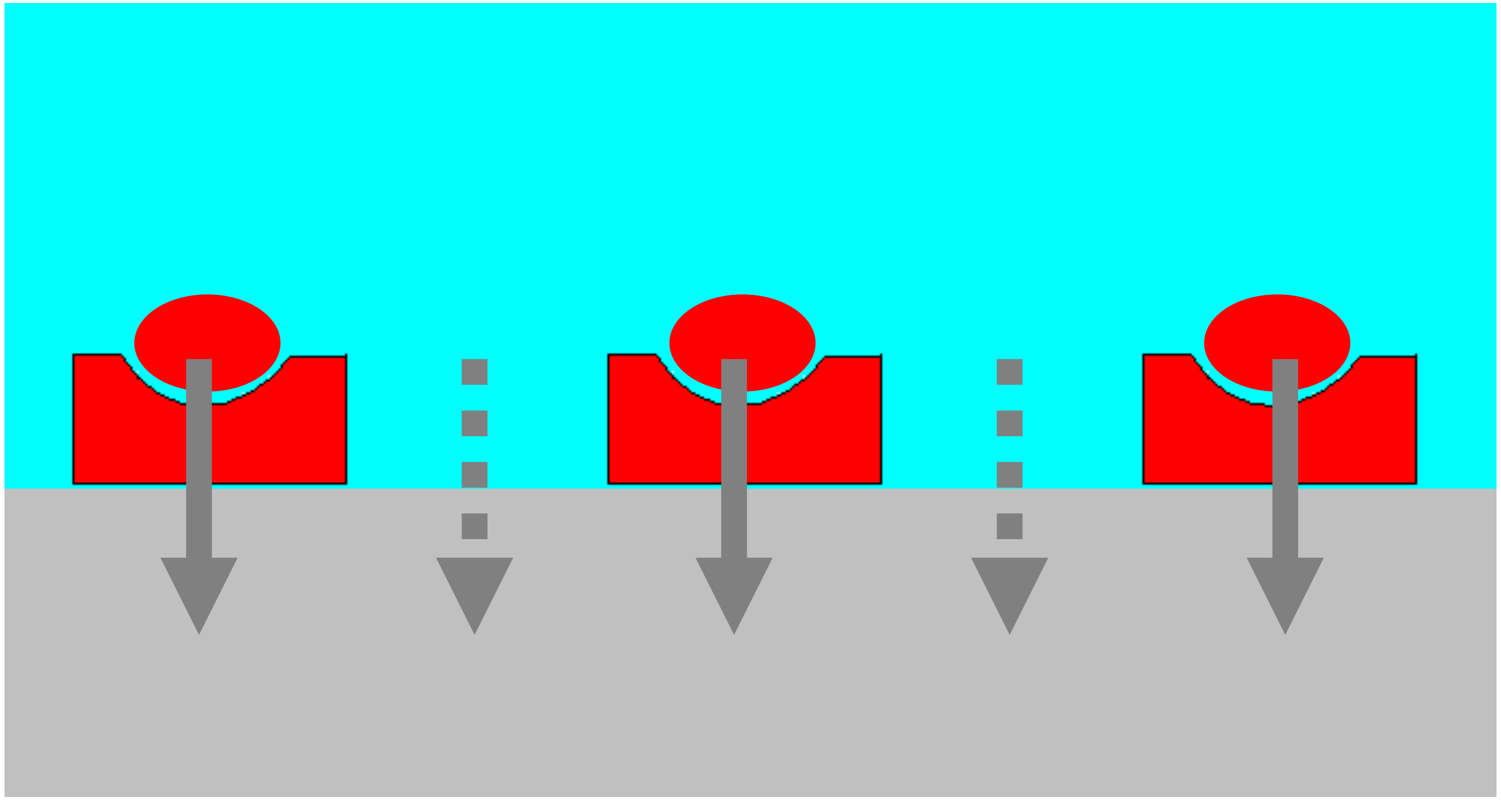


TARGETS



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



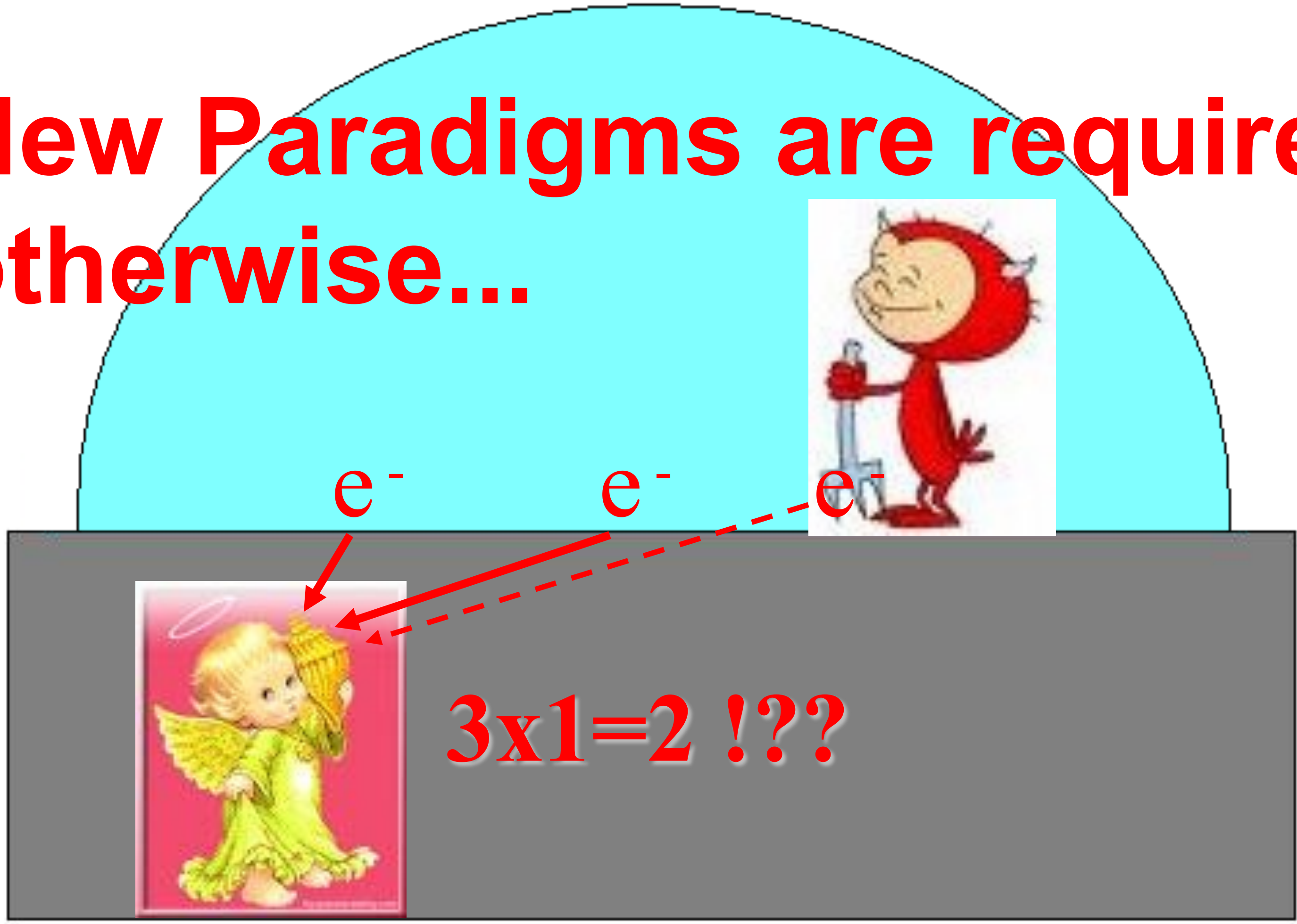
The interface between the CMOS circuit and the bio-sample needs to be deeply investigated and organized

Q8

Does present implantable CMOS chips allow metabolism monitoring?

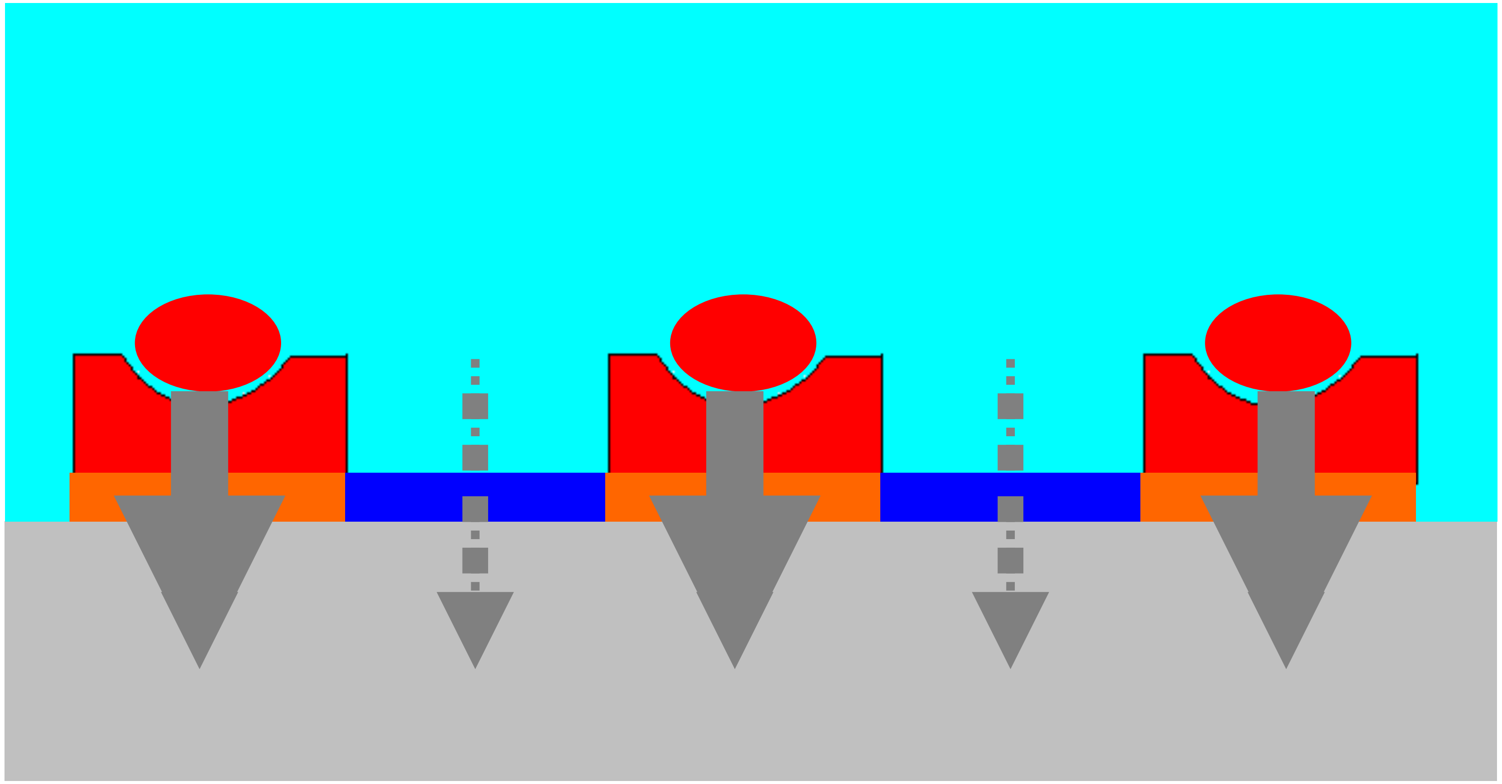
A. Not really
B. No if monitoring is non-related to glucose
C. No if monitoring is related to more metabolites
D. Yes, since they measure average parameters
E. Yes, that's easy to be done

New Paradigms are required otherwise...



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

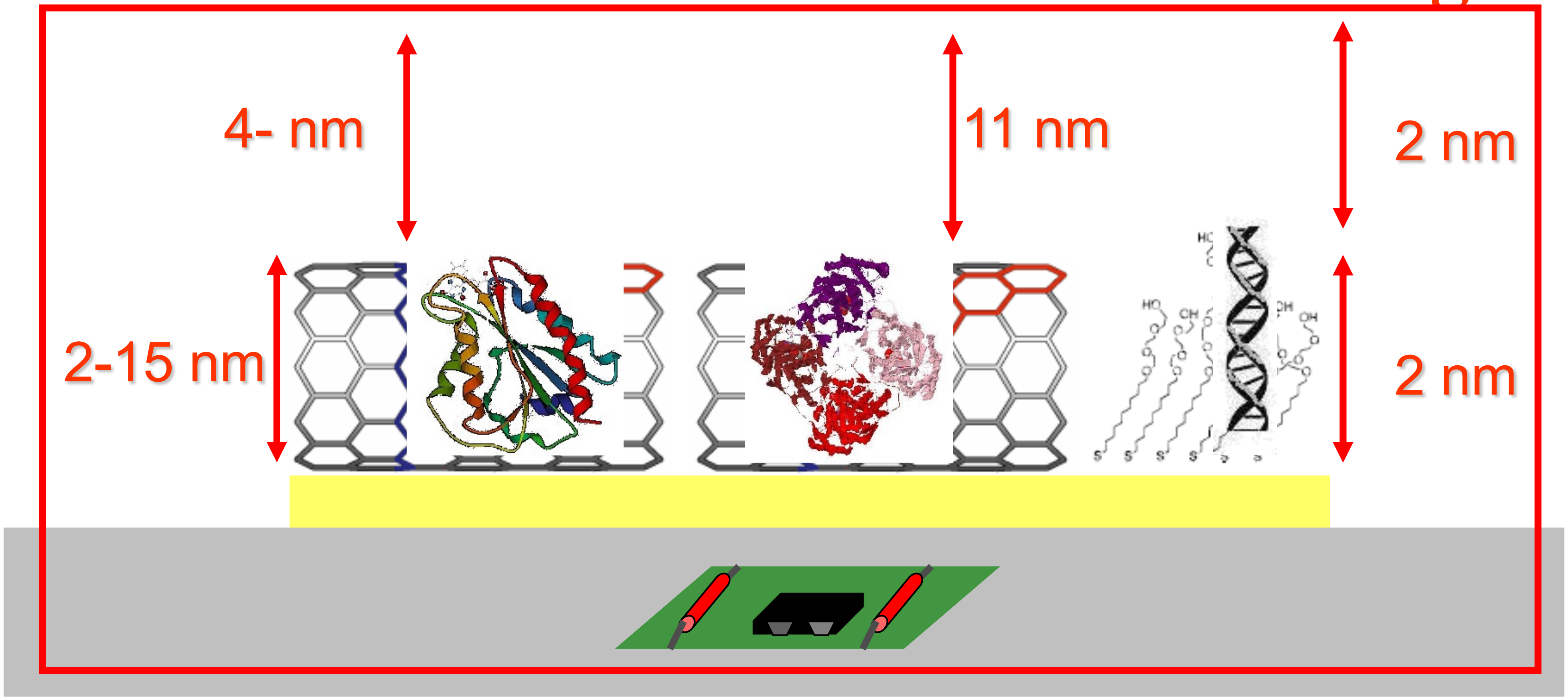
CMOS/Sample interface



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

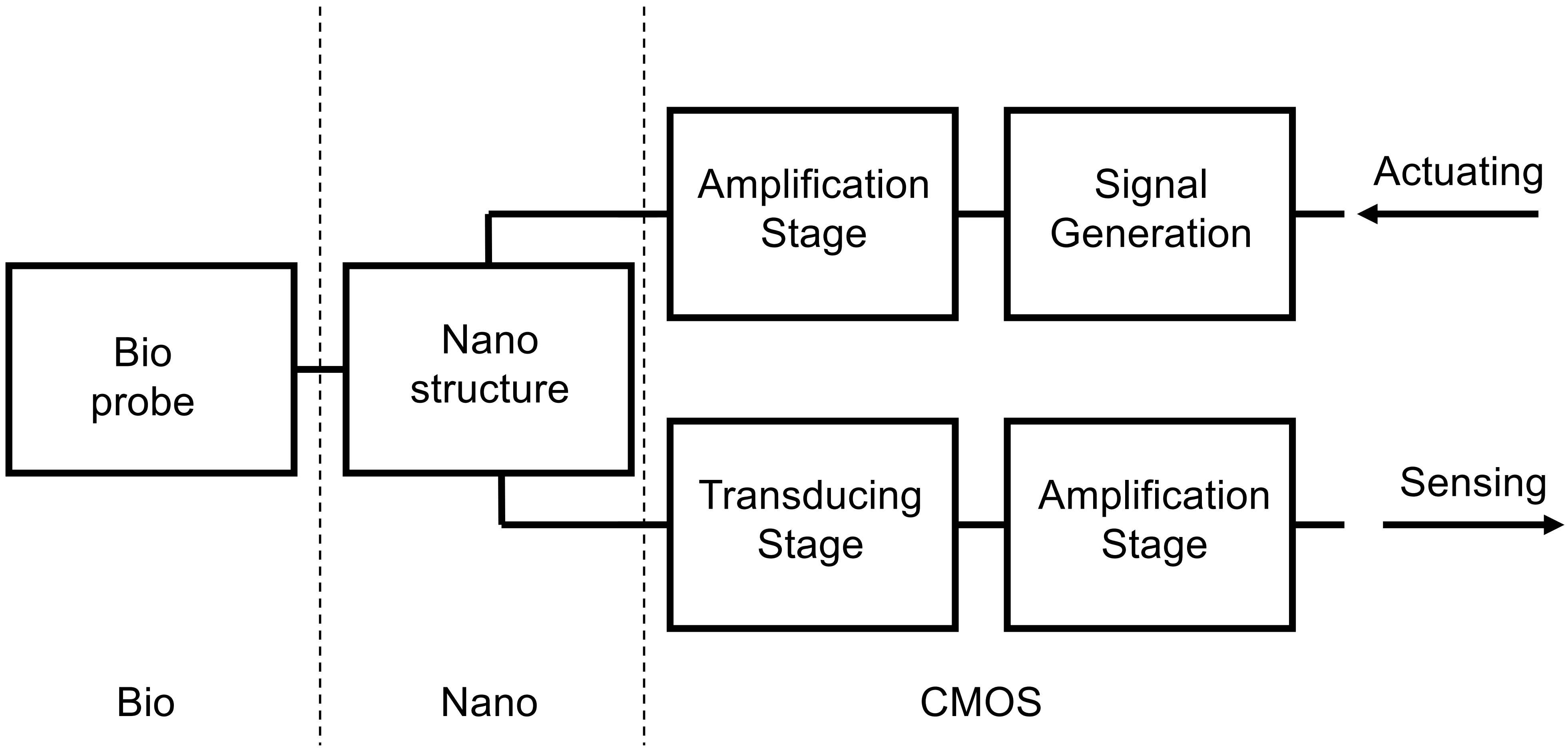
New Approach

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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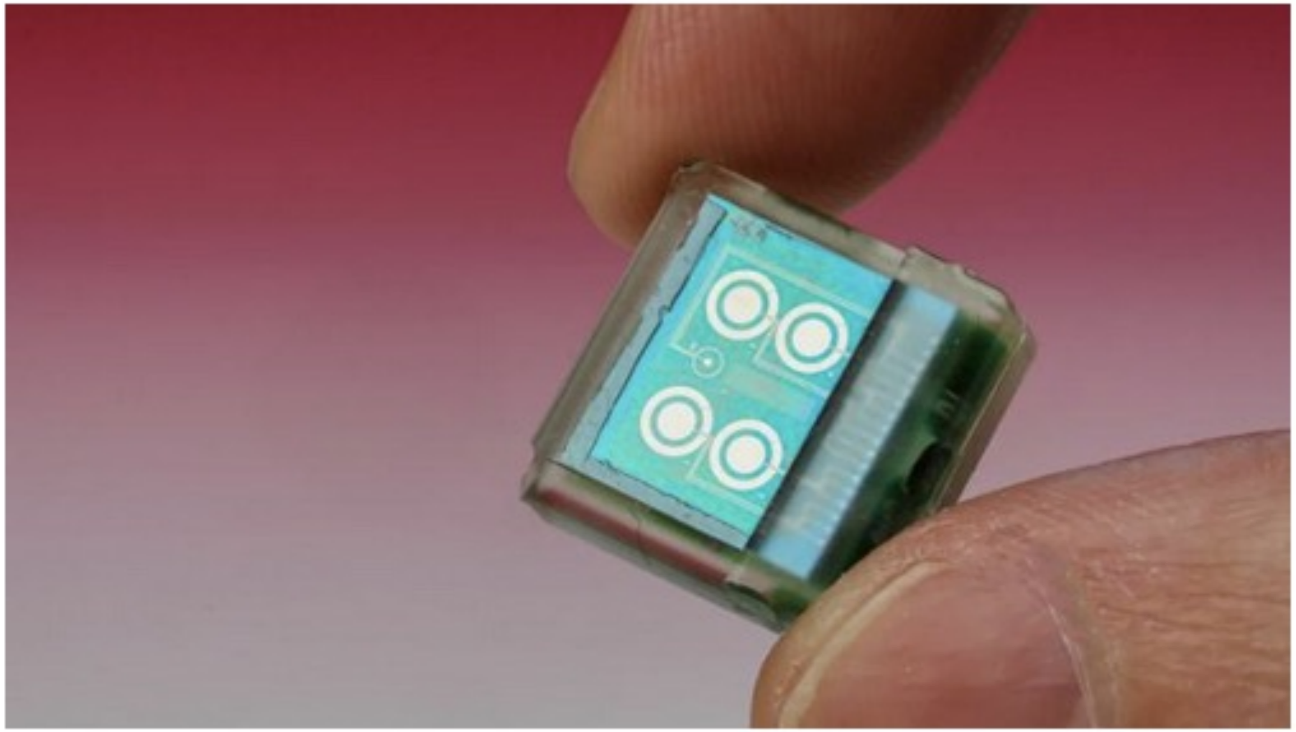
A subcutaneous biosensor chip to revolutionize tomorrow's medicine

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%

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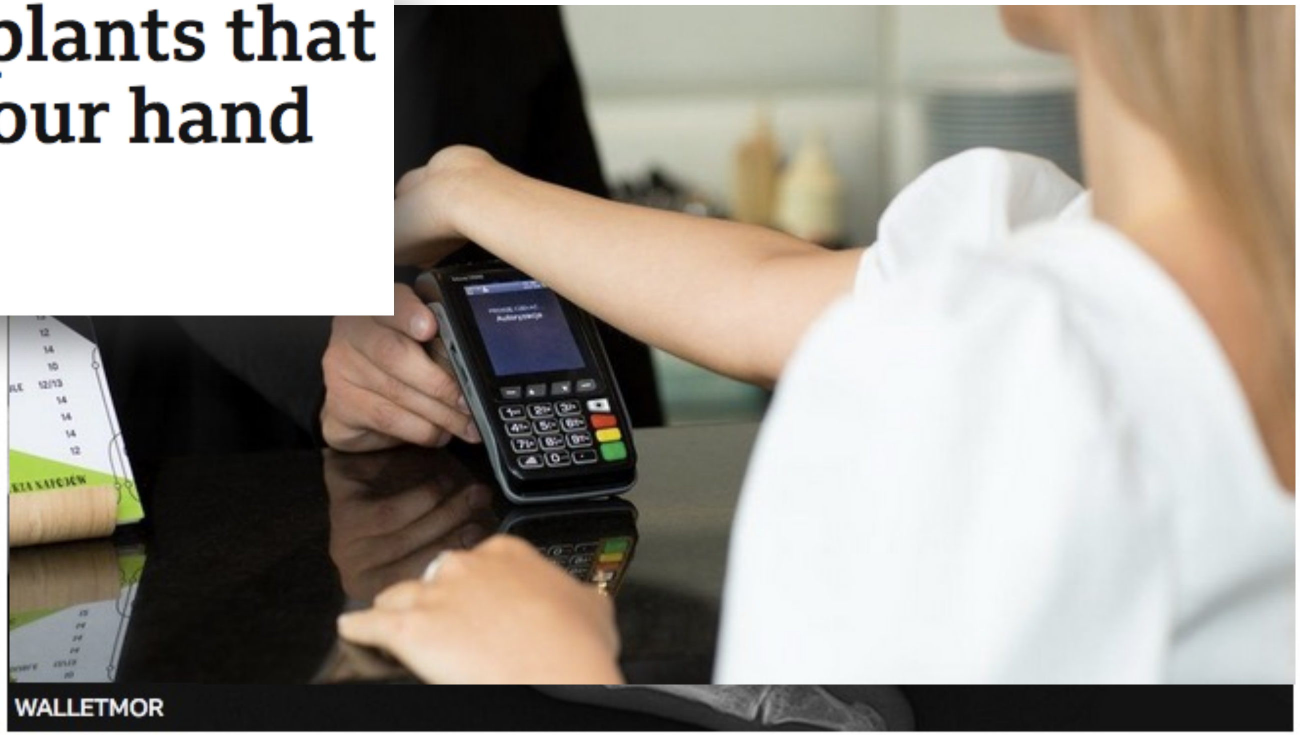
The microchip implants that let you pay with your hand

By Katherine Latham
Business reporter

April, 11th , 2022



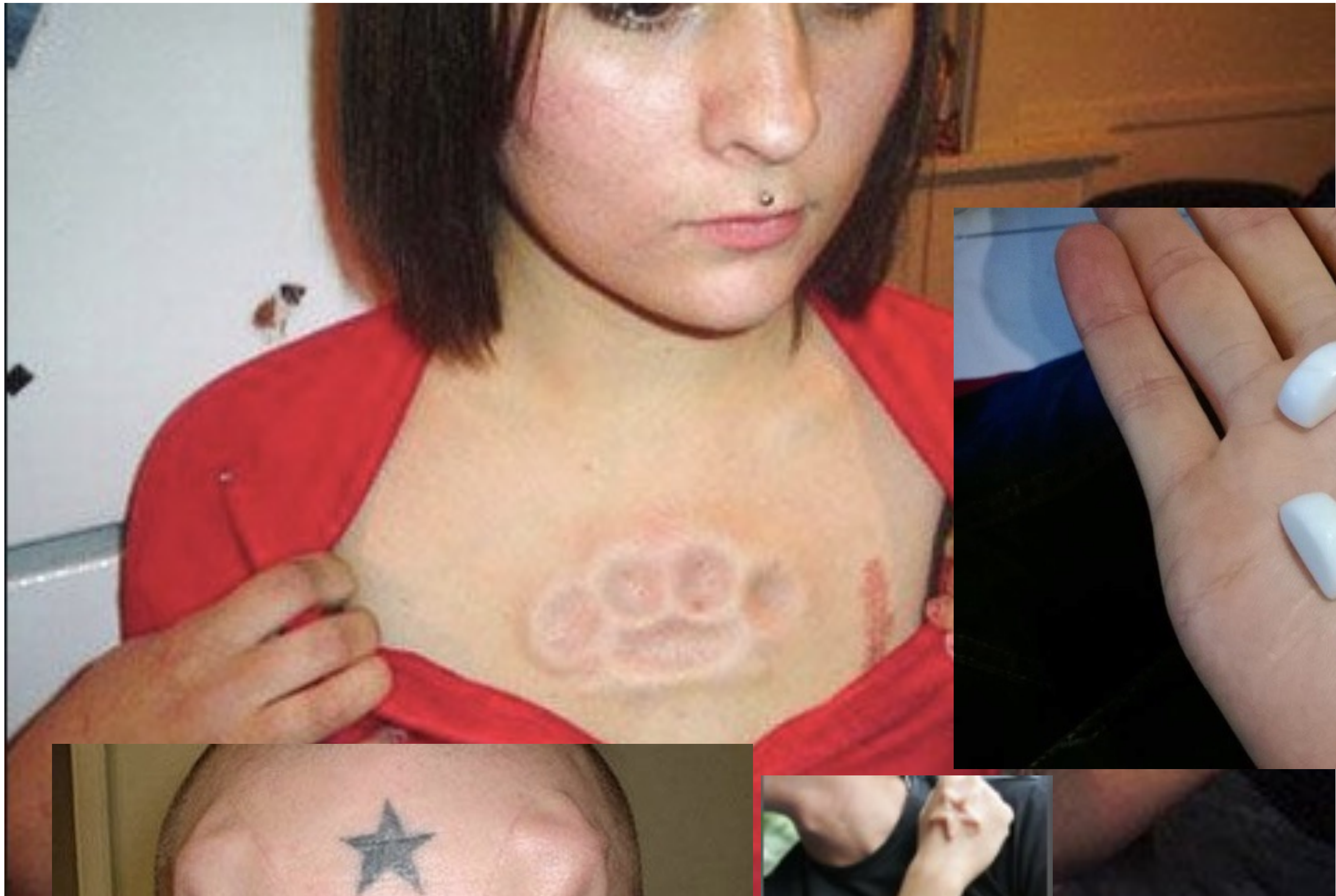
An x-ray showing a Walletmor implant, which are injected into a person's hand after a local anaesthetic

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.**

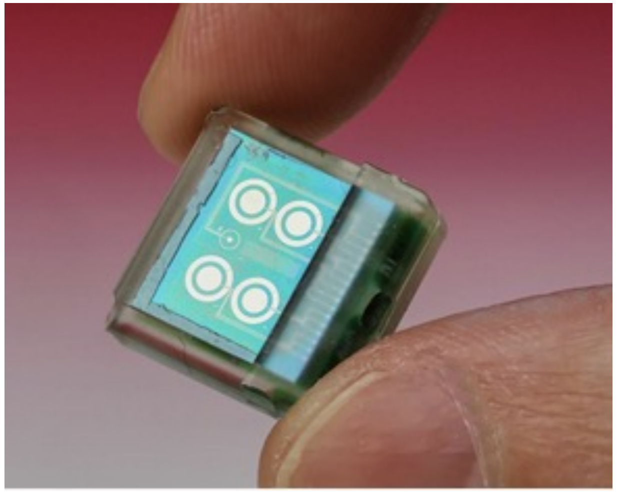
Chips under the skin?

[EuroNews, June 2015]

Under the skin for body sculpting

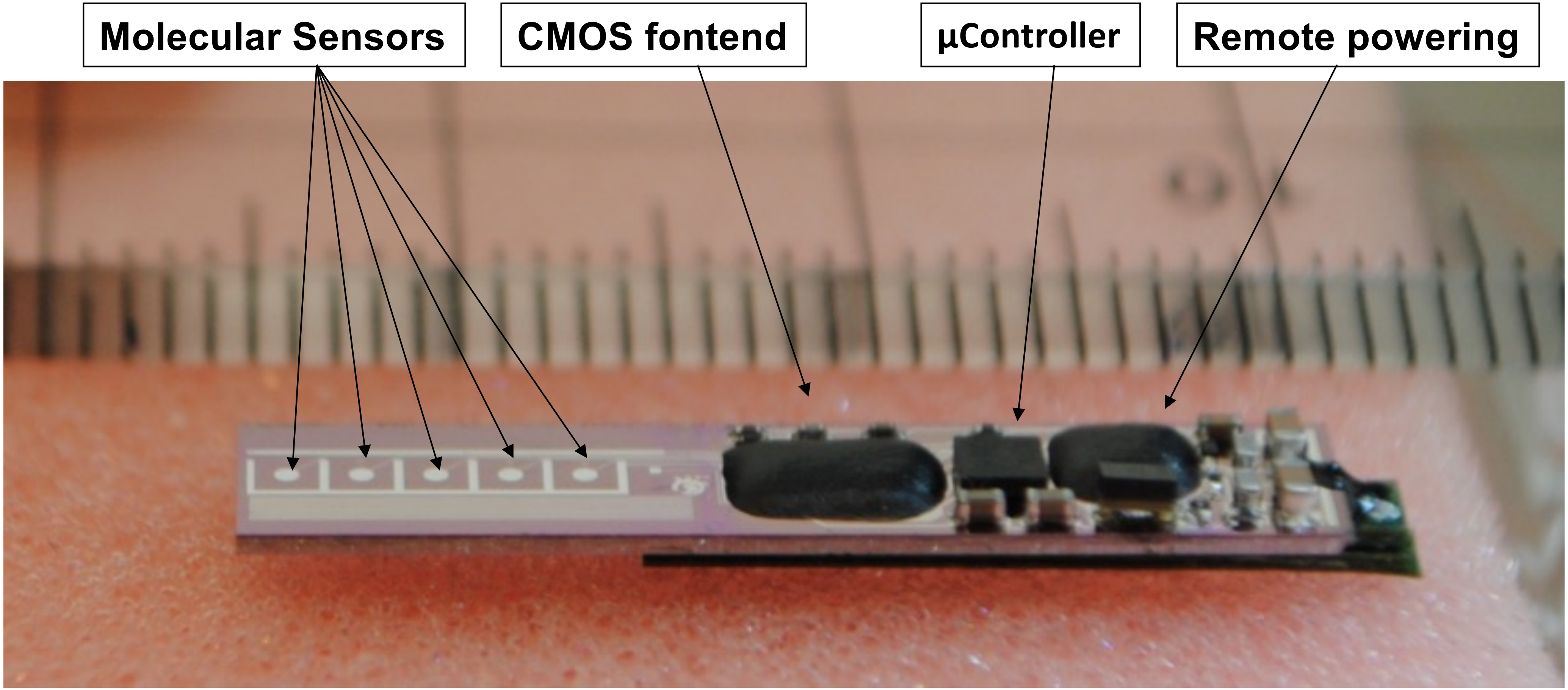


(c) S.Carrara



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^{TM} system

Q10

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

A. Some times, 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

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 **Bio**	§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 **Nano**	§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 **CMOS**	

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

EPFL

Master in Electrical and Electronics Engineering

EE-517: Bio-Nano-Chip Design

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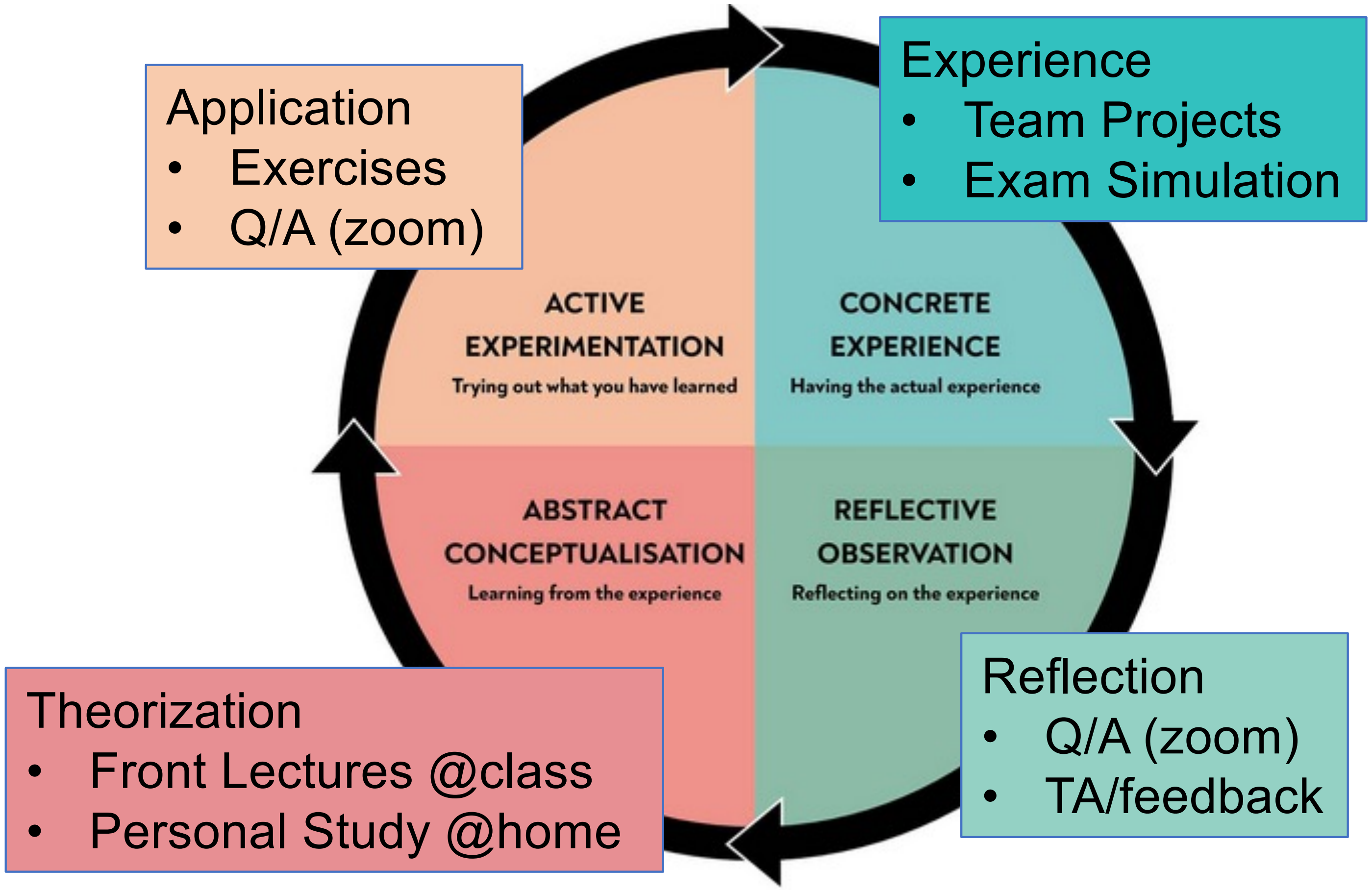
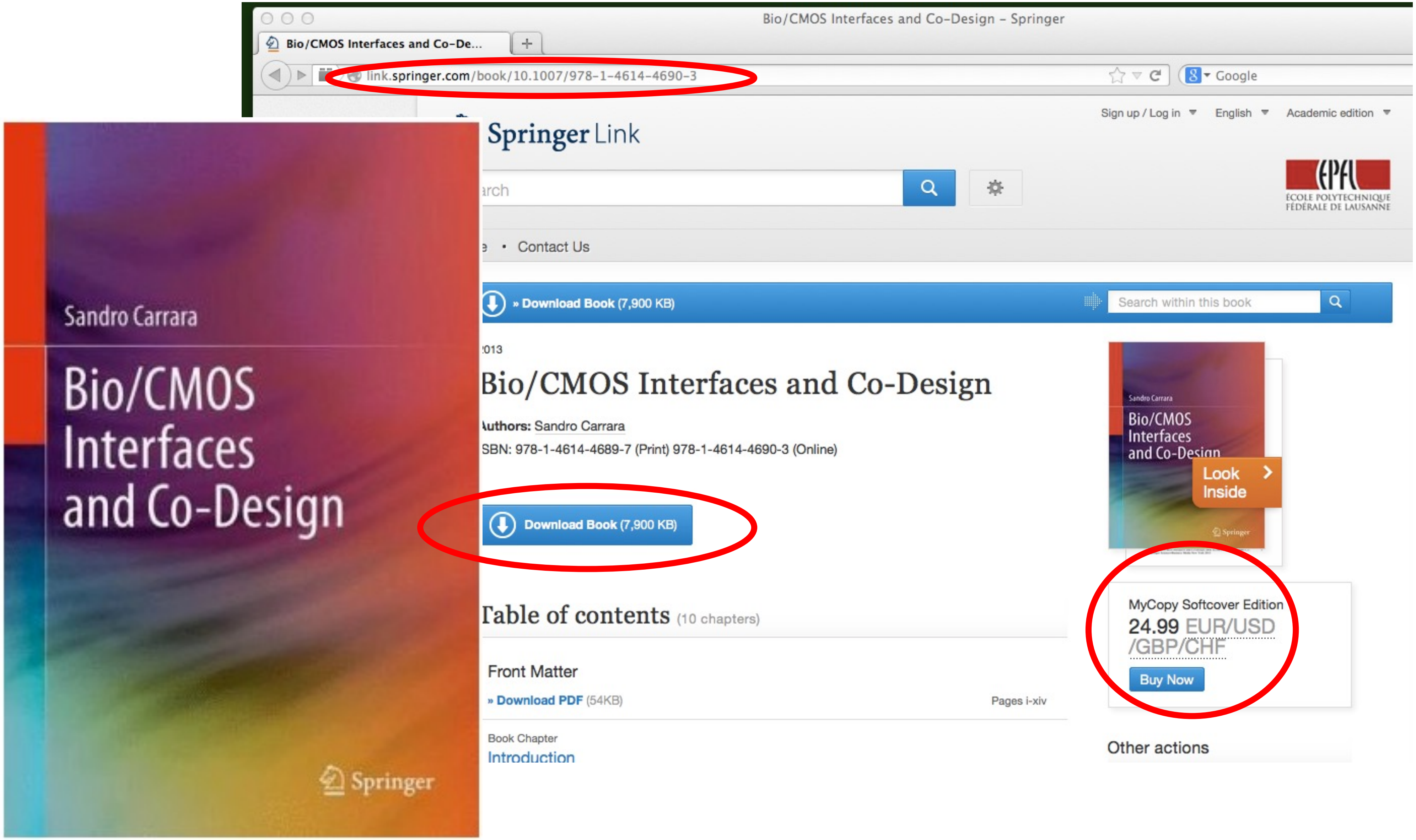
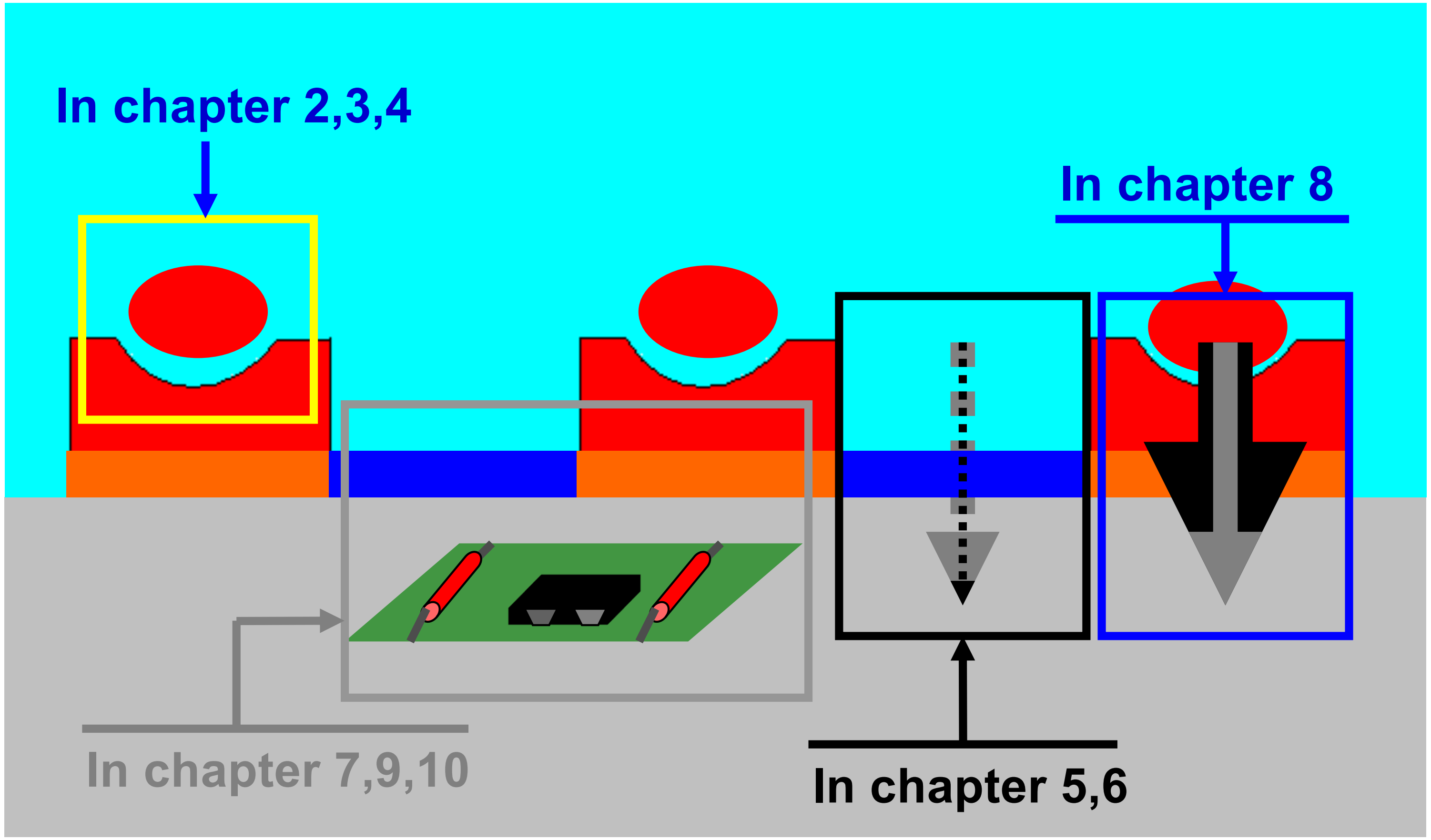


Kolb experimental learning cycle

The Course Textbook



Bio/CMOS interface book



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

Lecture #1

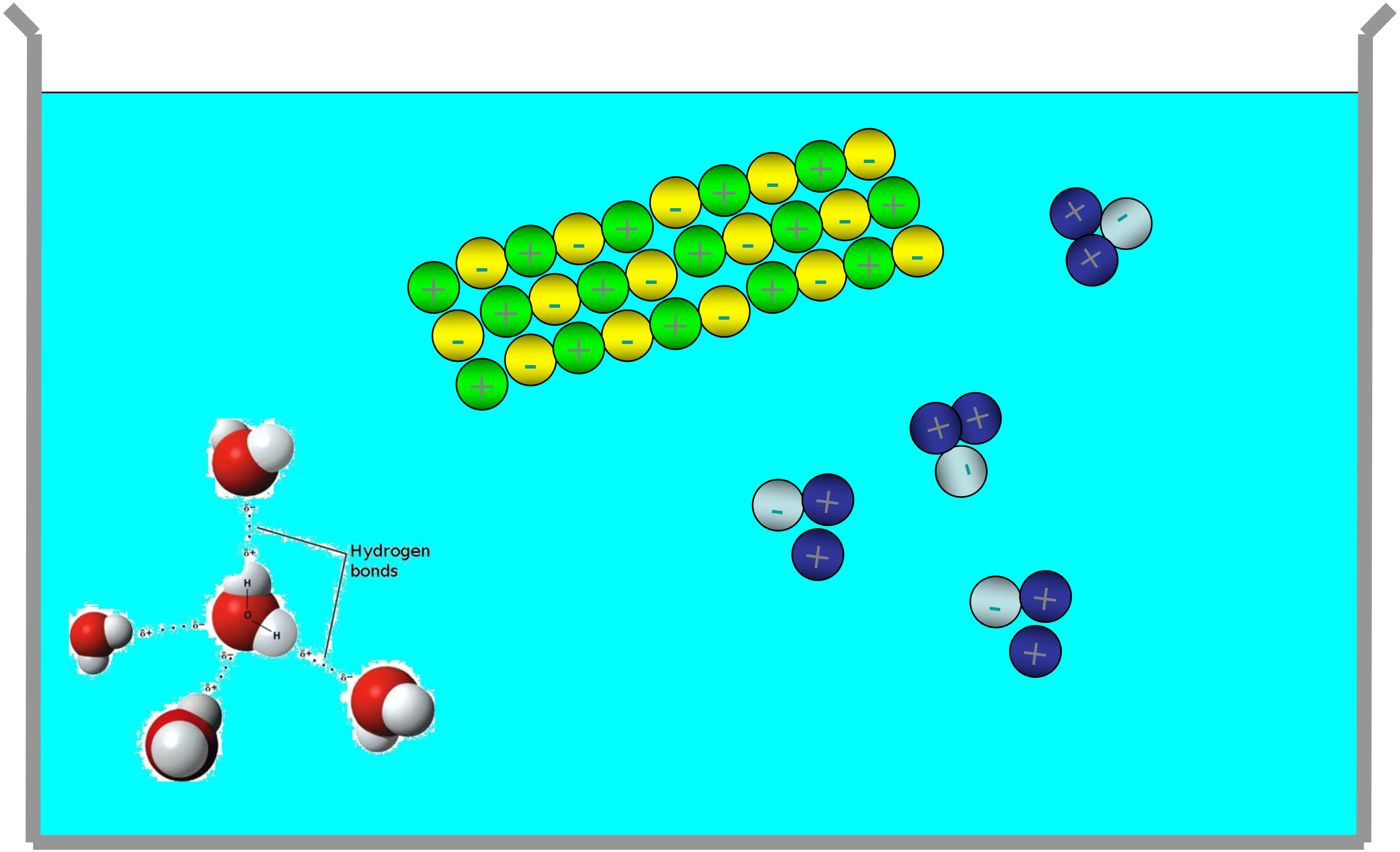
Conductive Solutions

Lecture Outline

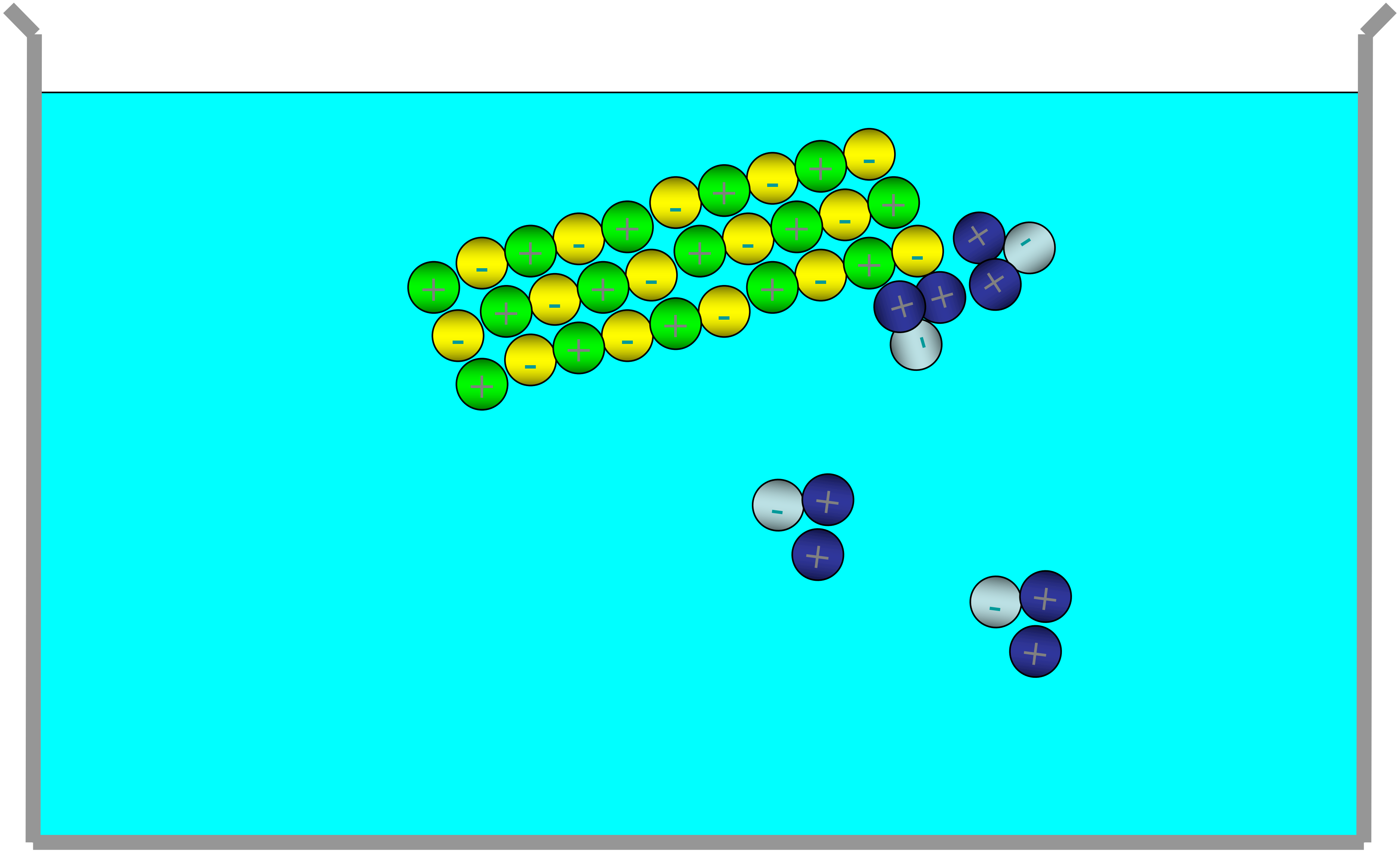
(Book Bio/CMOS: Chapter’ paragraphs § 2.1-2.7 and § 2.14-15)

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

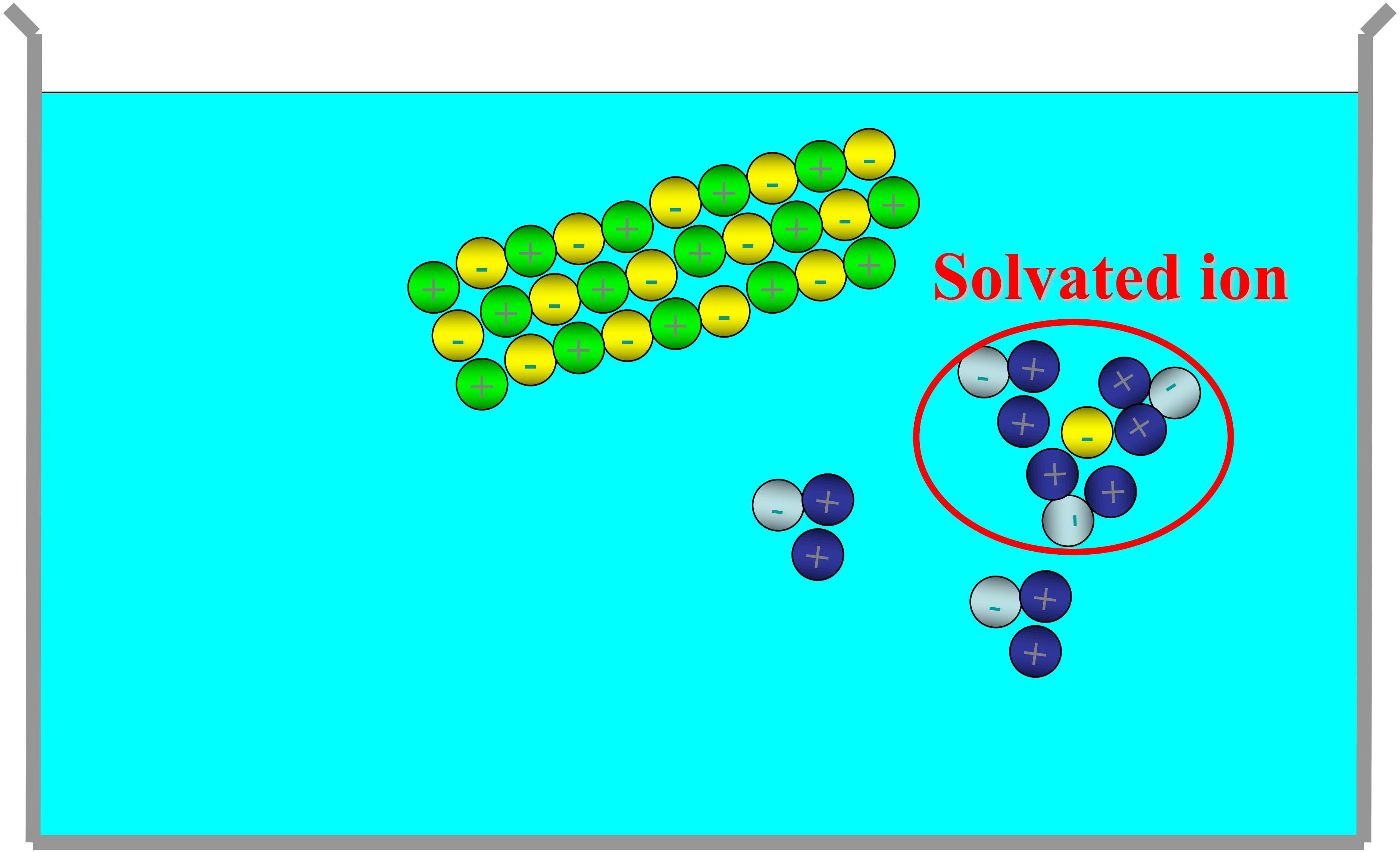
Liquid Solution: Ionic Solid in liquid



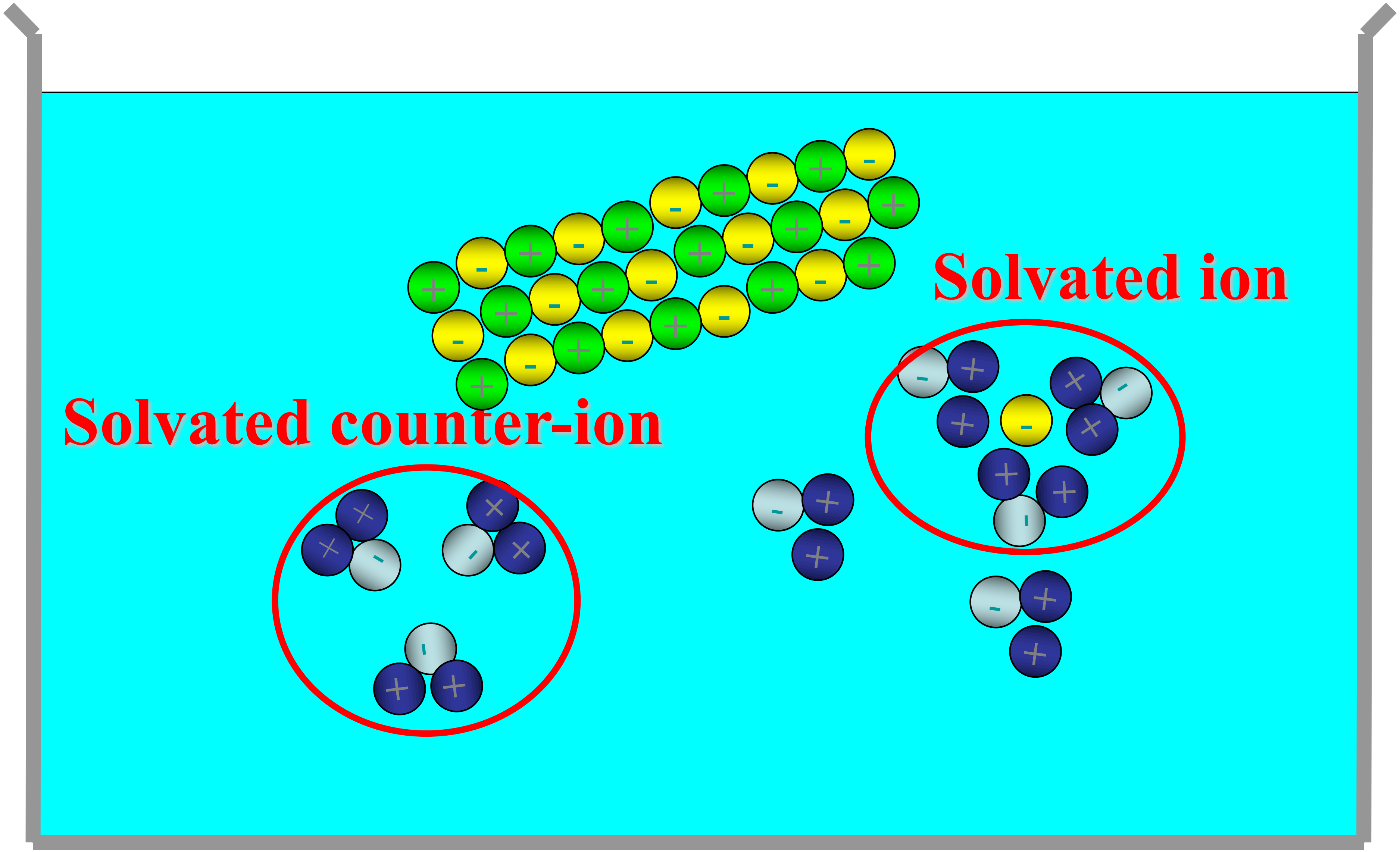
Liquid Solution: Ionic Solid in liquid



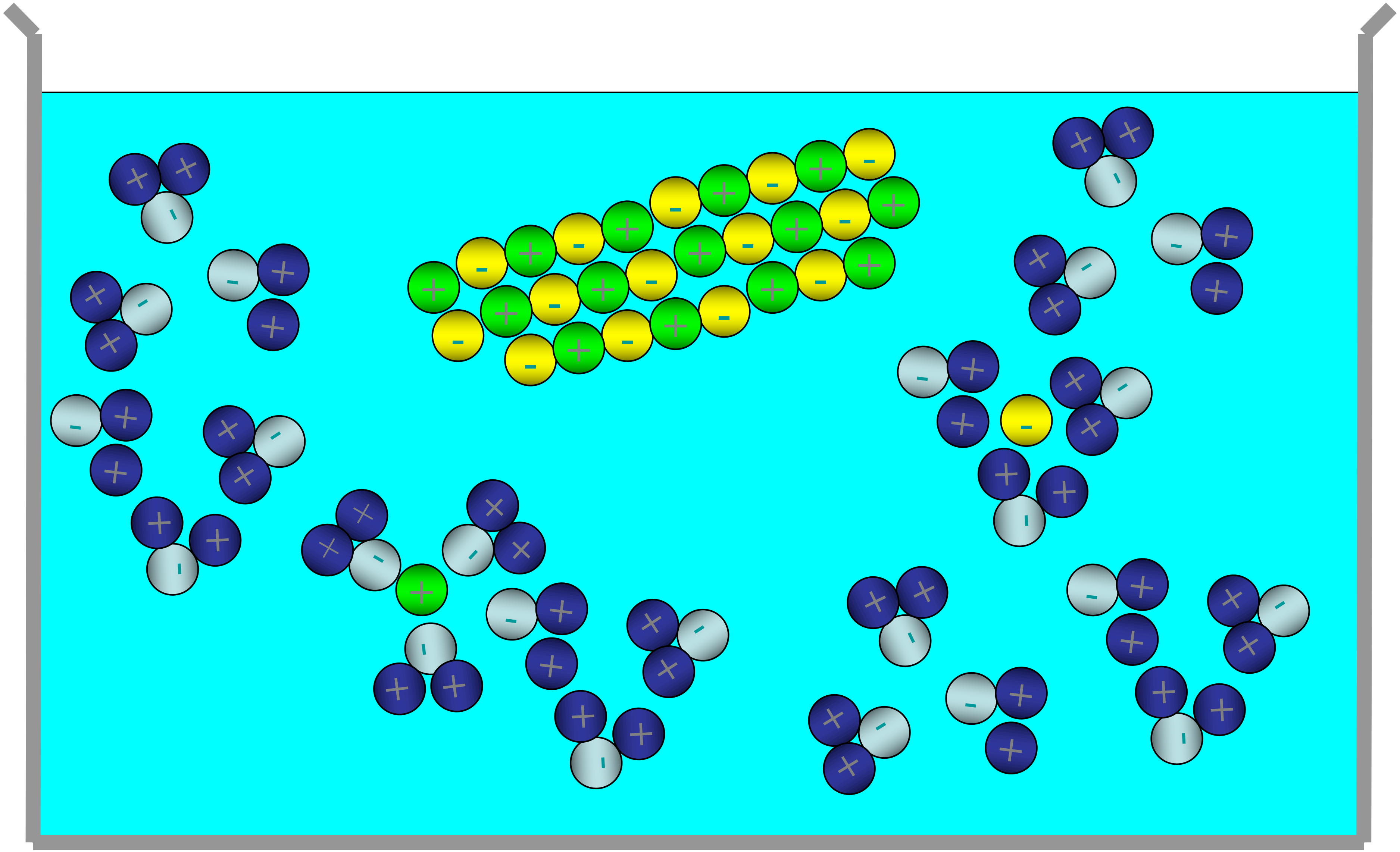
Liquid Solution: Ionic Solid in liquid



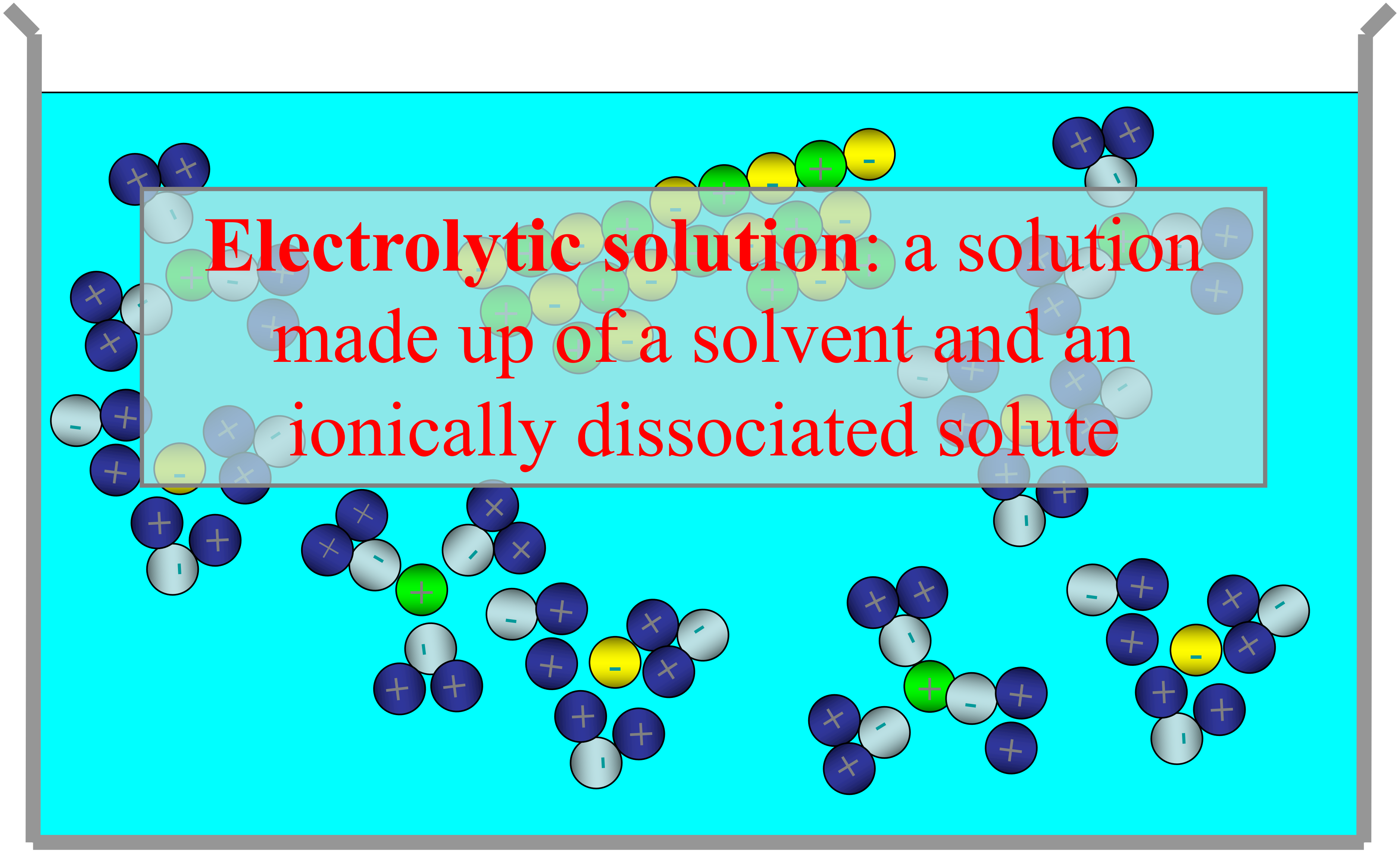
Liquid Solution: Ionic Solid in liquid



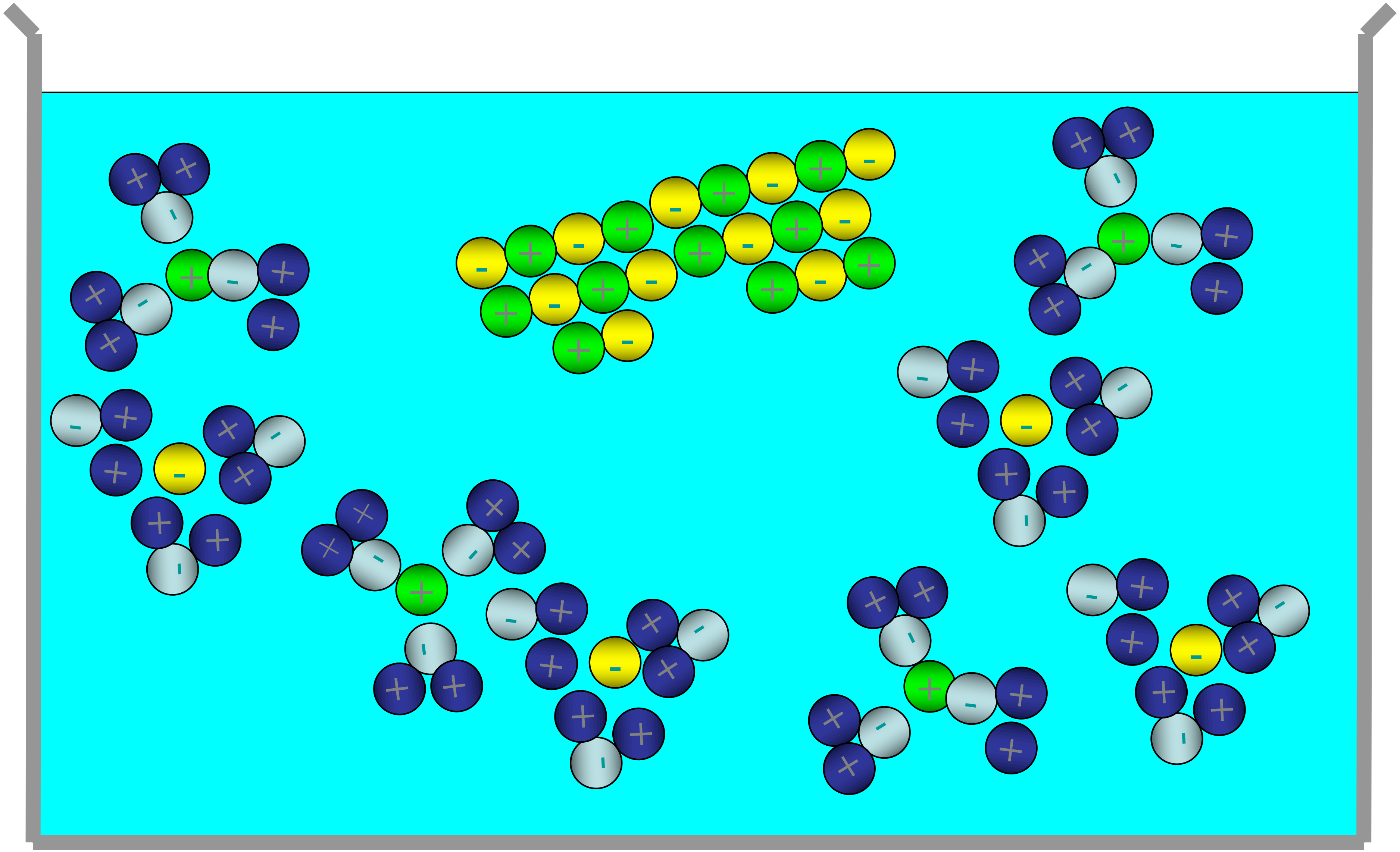
Liquid Solution: Ionic Solid in liquid



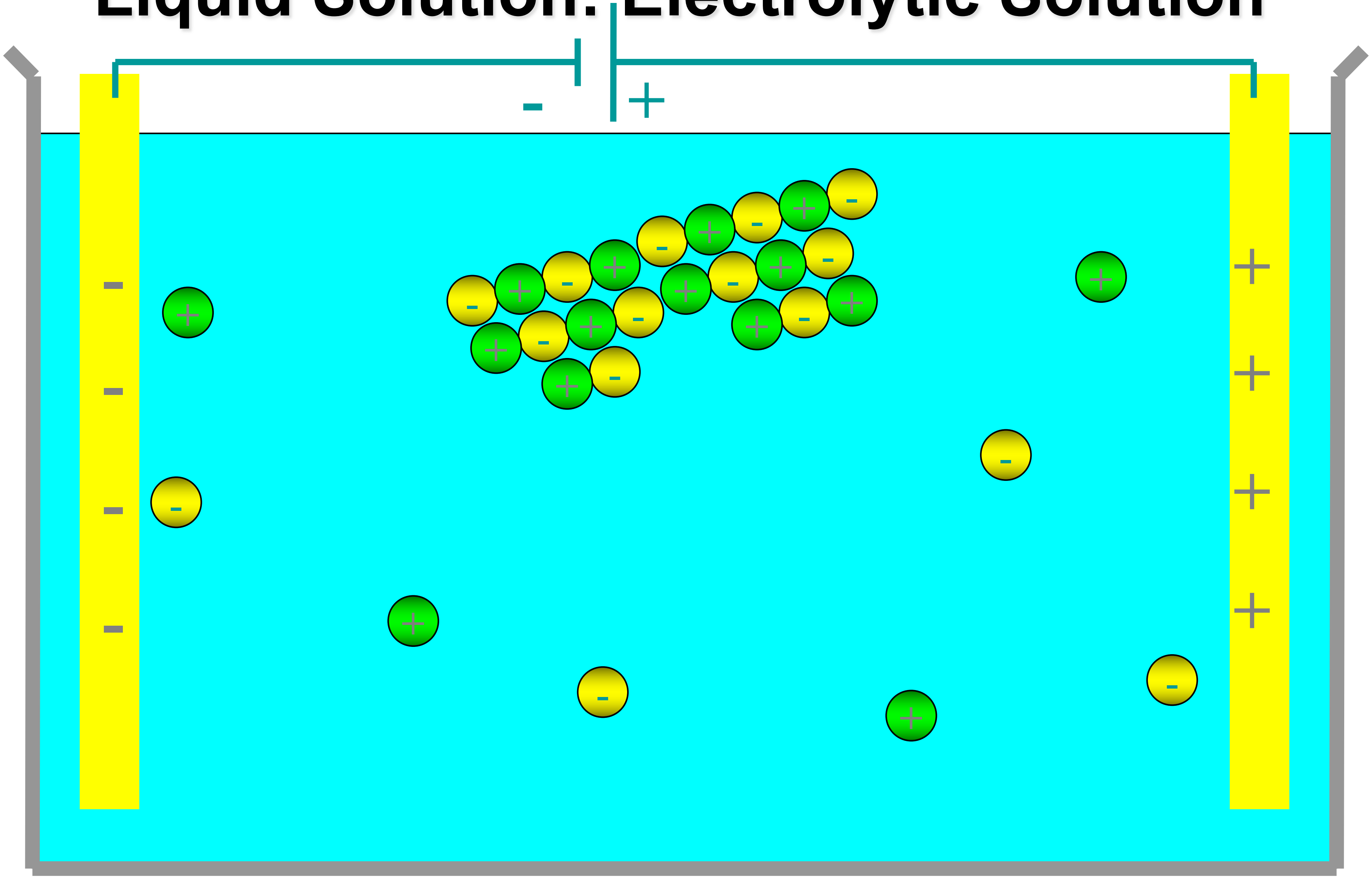
Liquid Solution: Ionic Solid in liquid



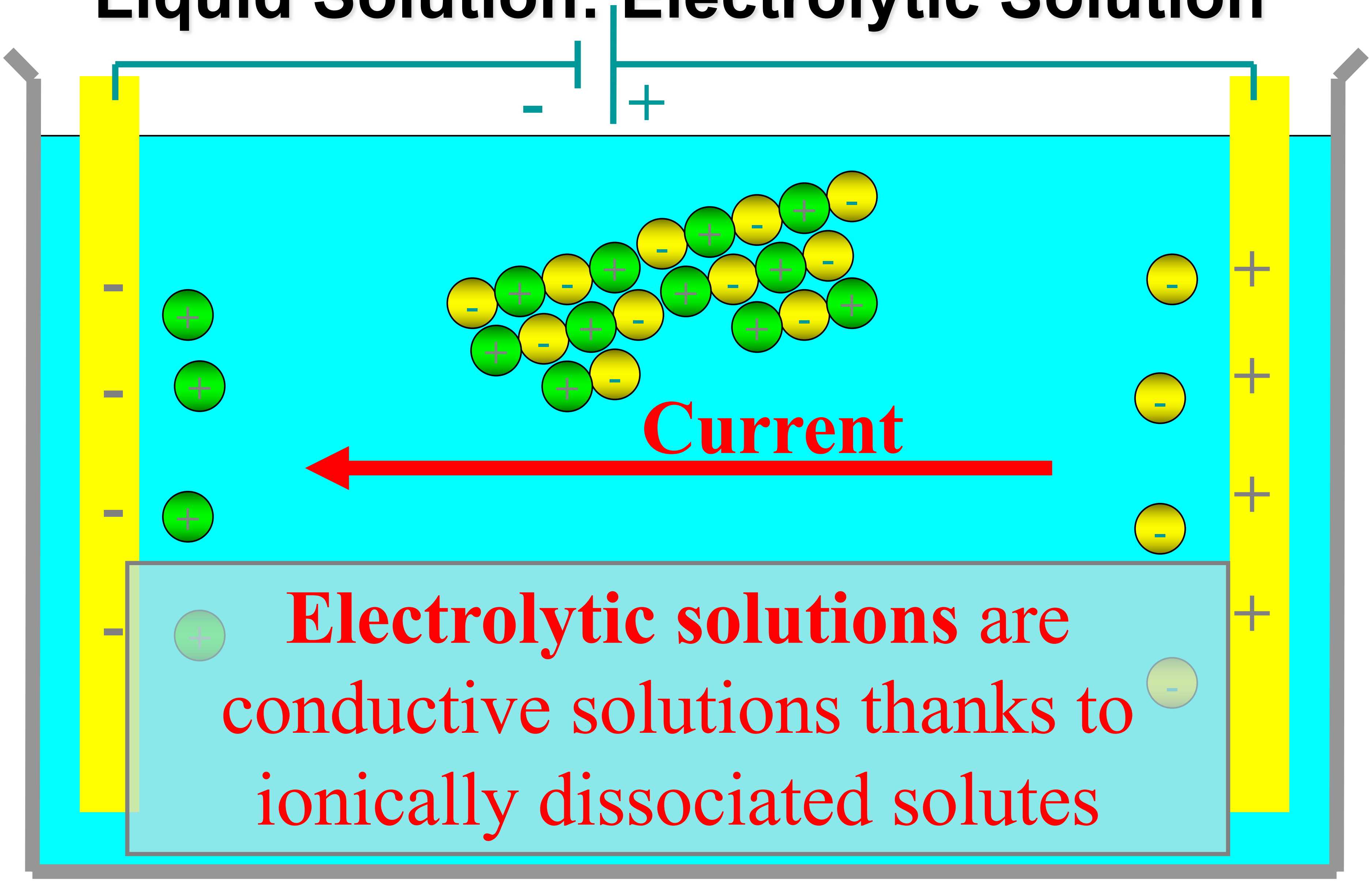
Liquid Solution: Electrolytic Solution



Liquid Solution: Electrolytic Solution



Liquid Solution: Electrolytic Solution



Electrolytic solutions are conductive solutions thanks to ionically dissociated solutes

Ionic Solution of HCl

Dissociation of Chloride Acid

$$2HCl + 2H_2O \rightarrow 2H_3O^+ + 2Cl^-$$

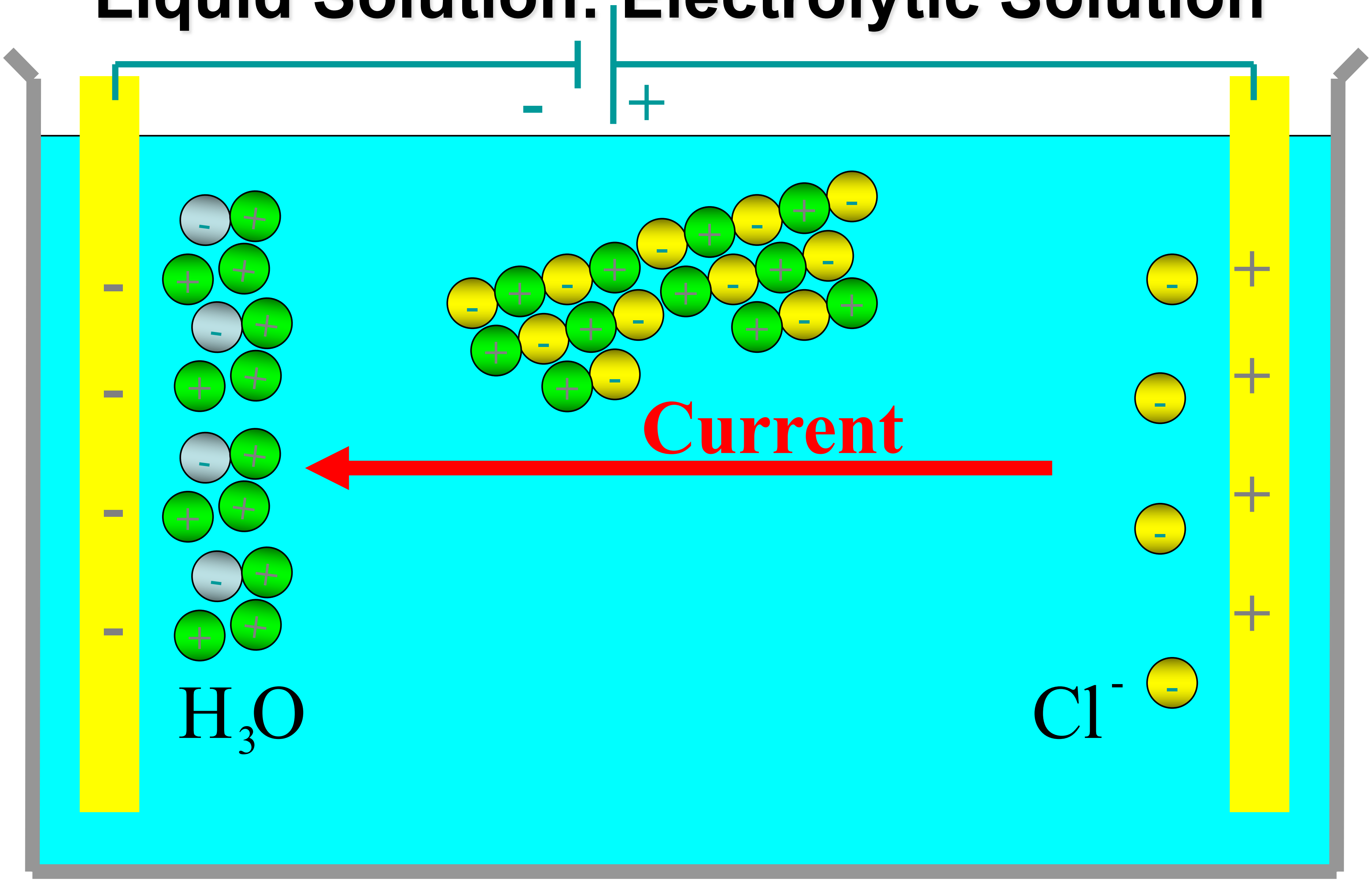
$$2H_3O^+ + 2e^- \rightarrow 2H_2O + H_2 \uparrow$$

– Electrode (Cathode)

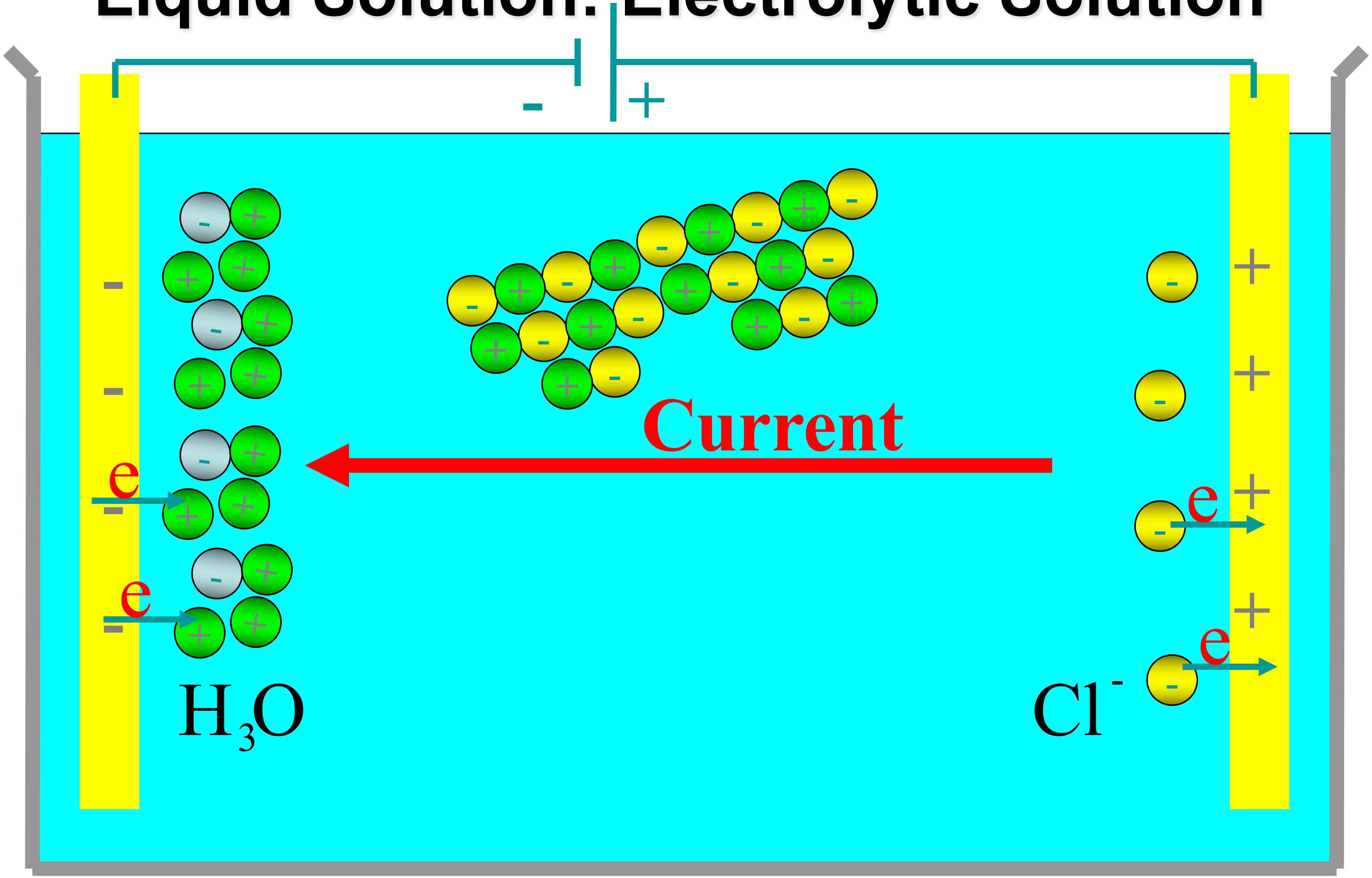
$$2Cl^- \rightarrow Cl_2 \uparrow + 2e^-$$

+ Electrode (Anode)

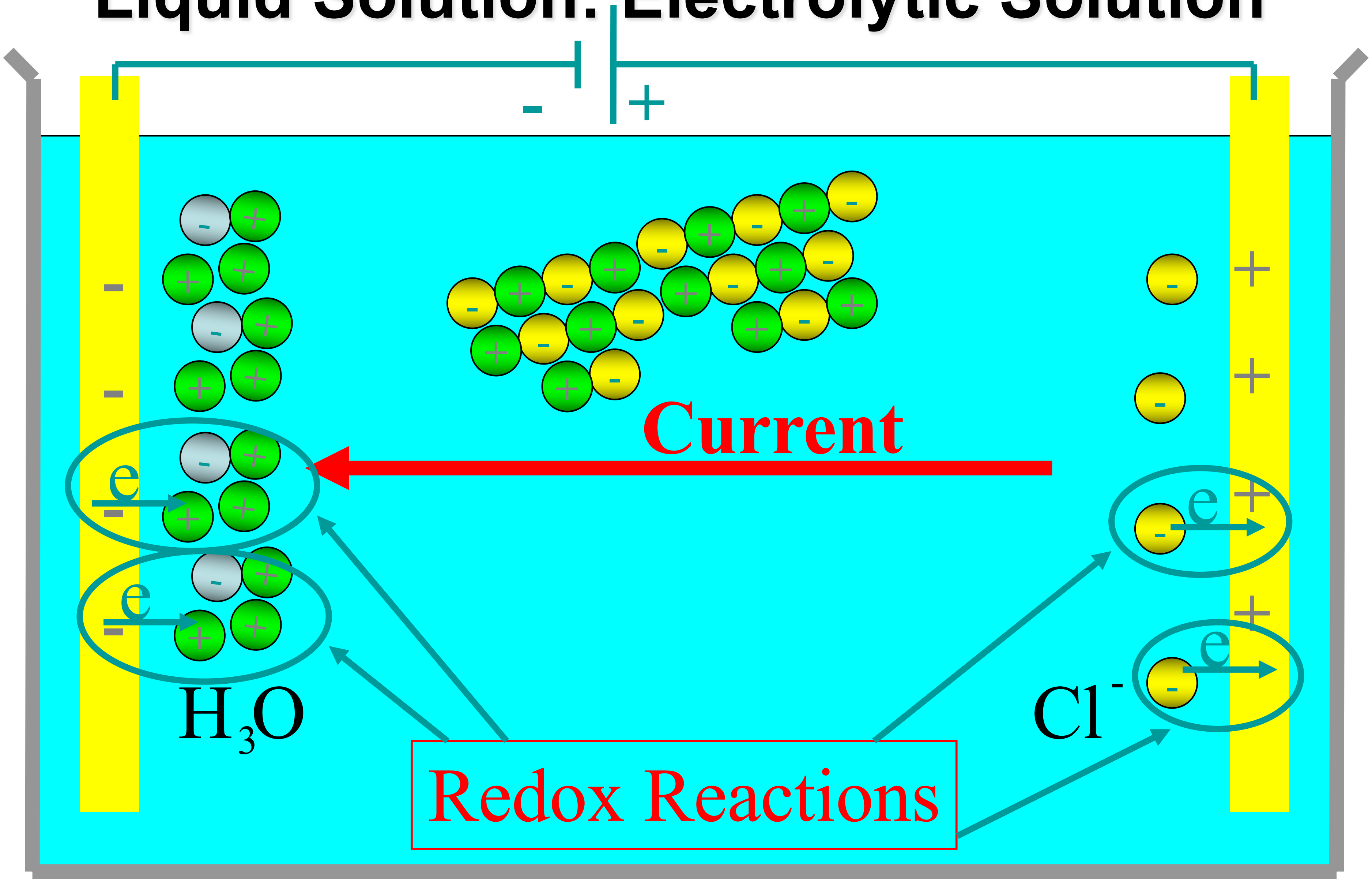
Liquid Solution: Electrolytic Solution



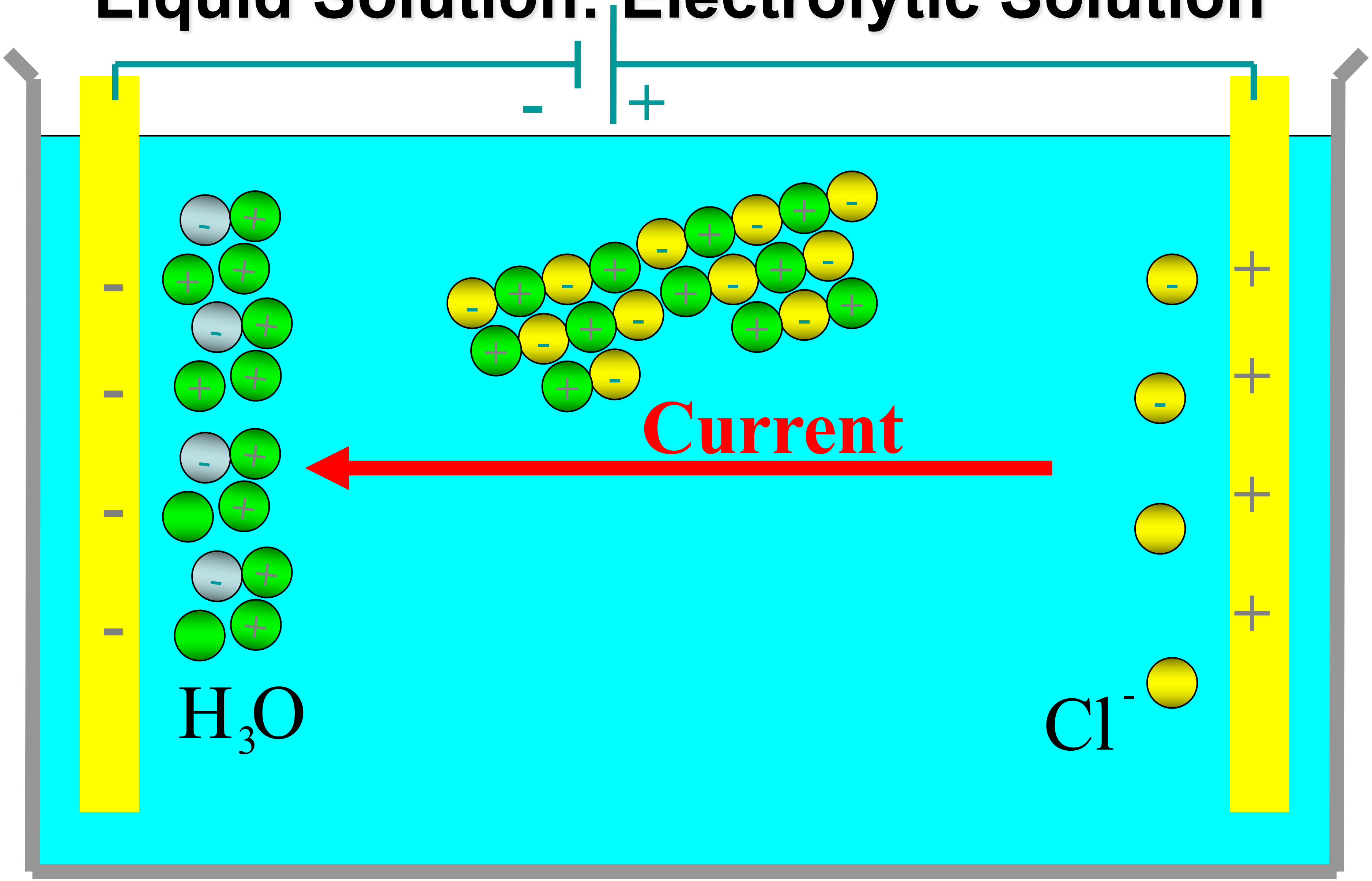
Liquid Solution: Electrolytic Solution



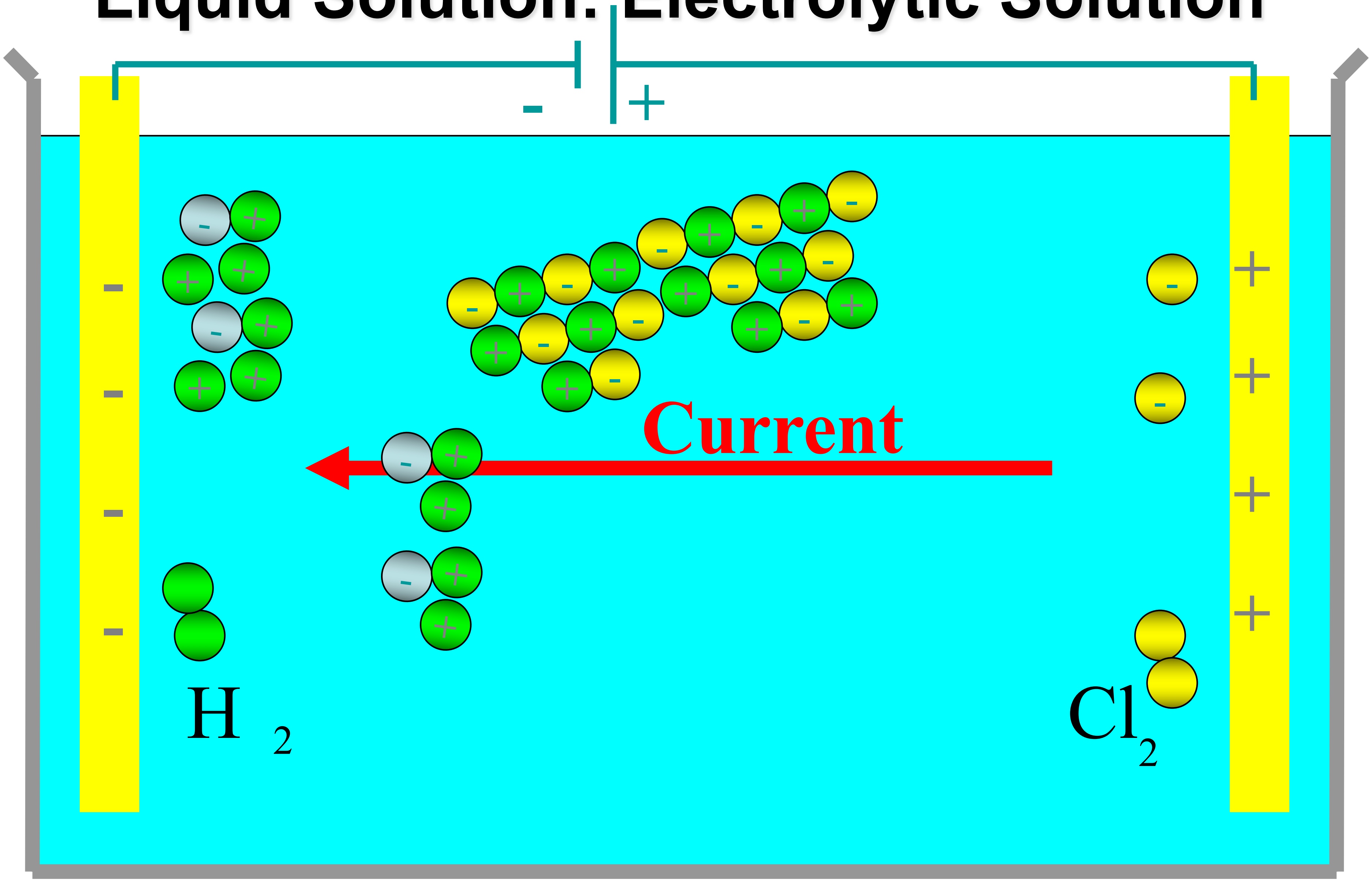
Liquid Solution: Electrolytic Solution



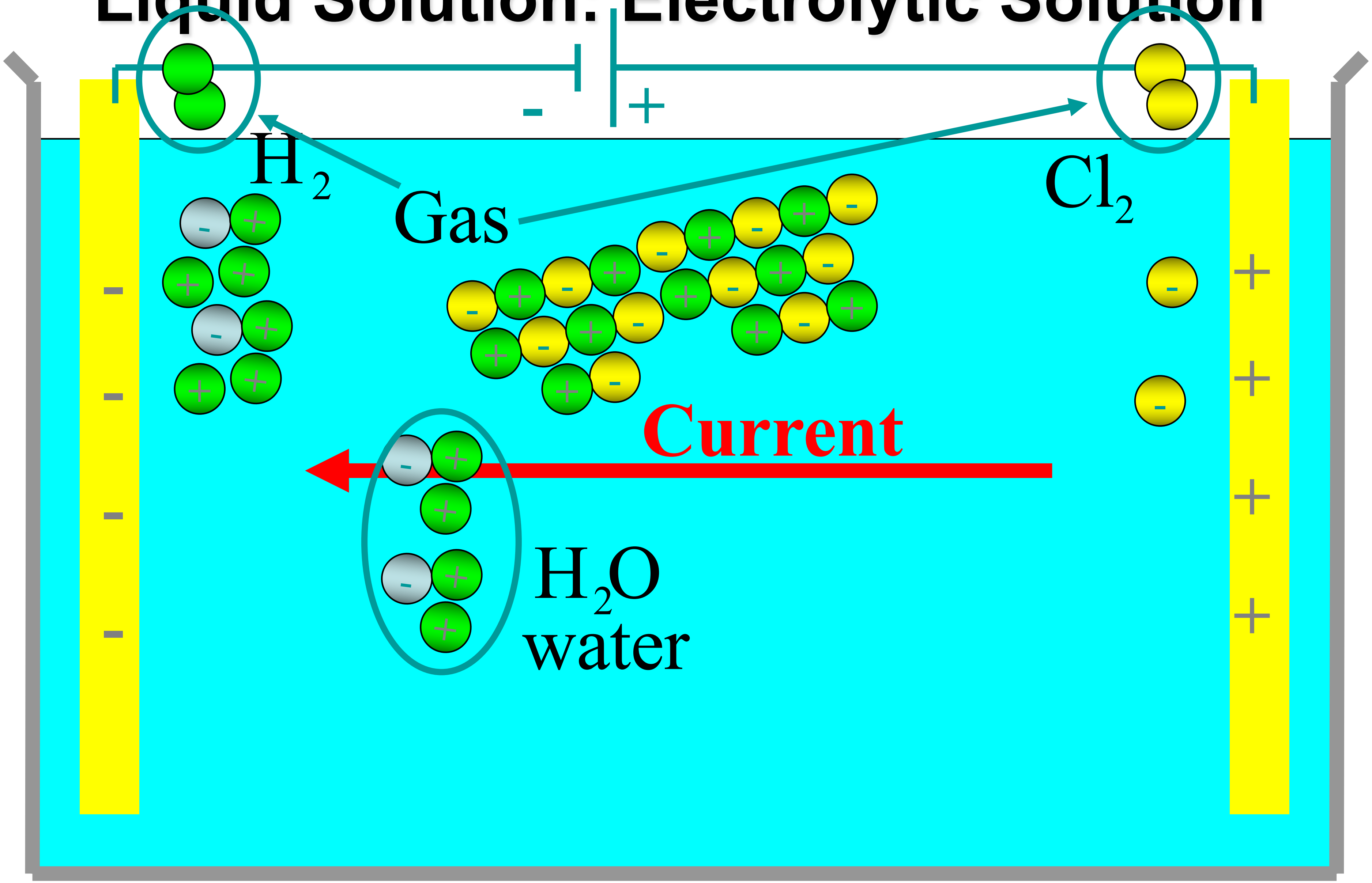
Liquid Solution: Electrolytic Solution



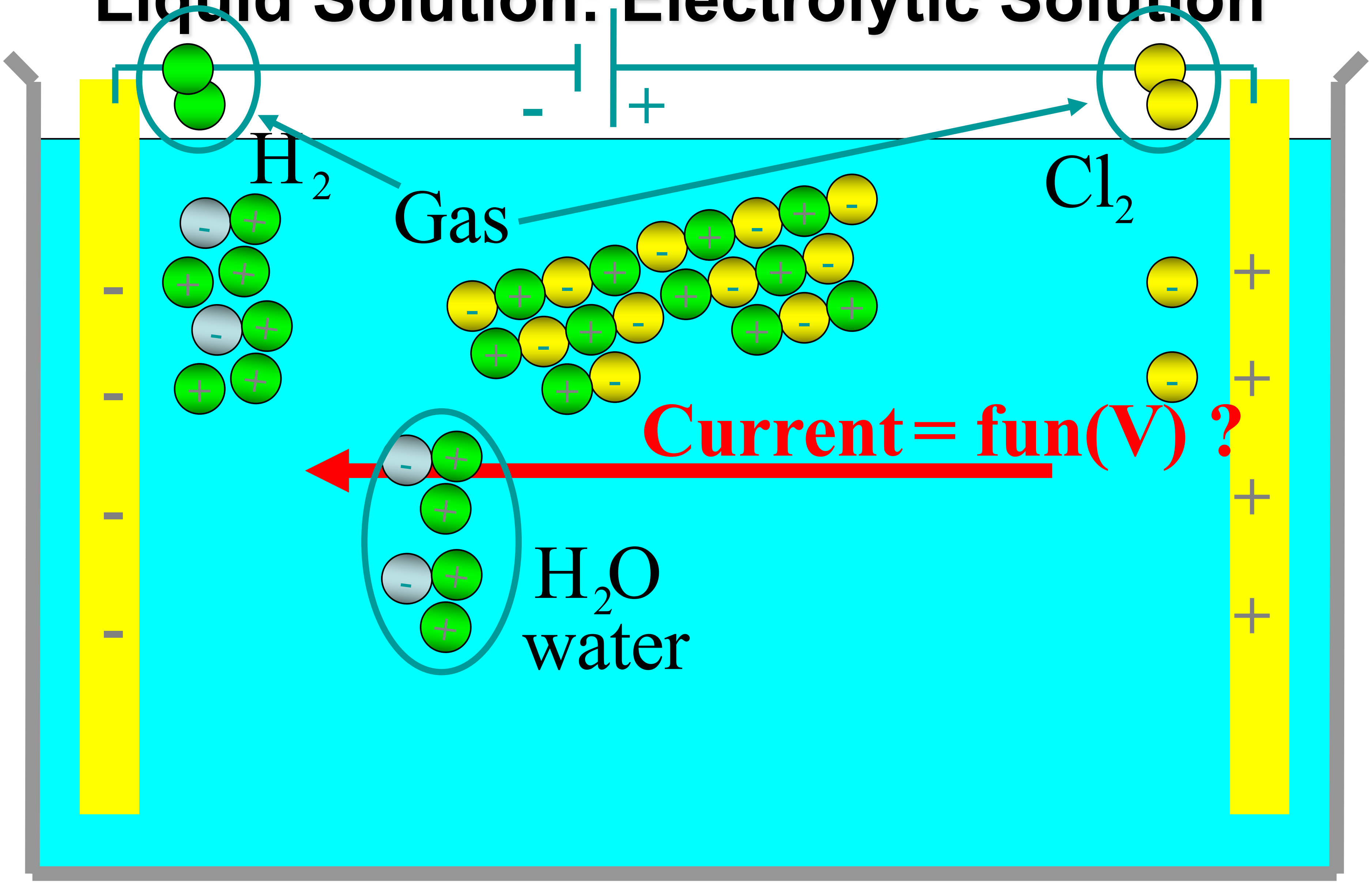
Liquid Solution: Electrolytic Solution



Liquid Solution: Electrolytic Solution



Liquid Solution: Electrolytic Solution

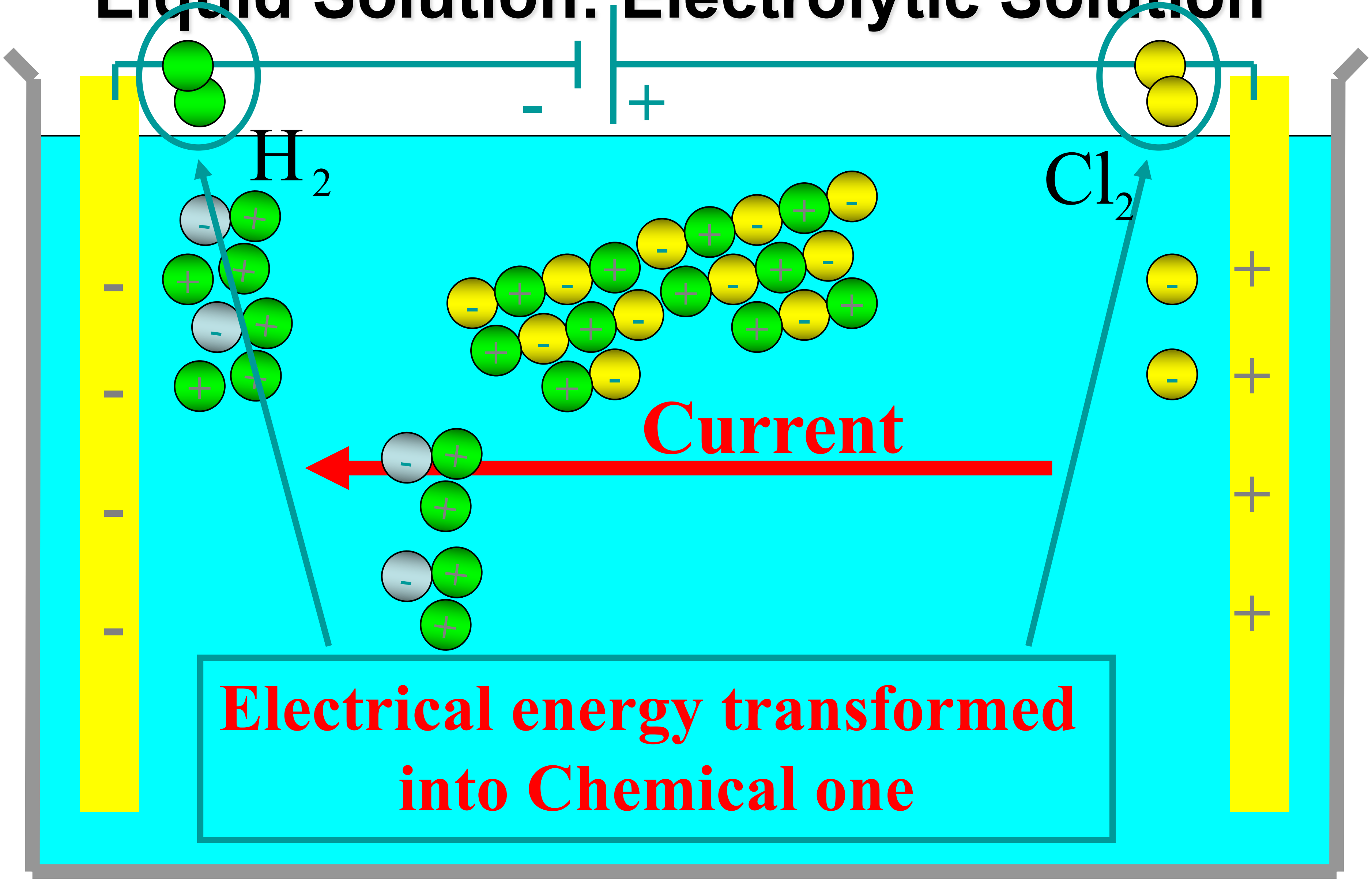


Q11

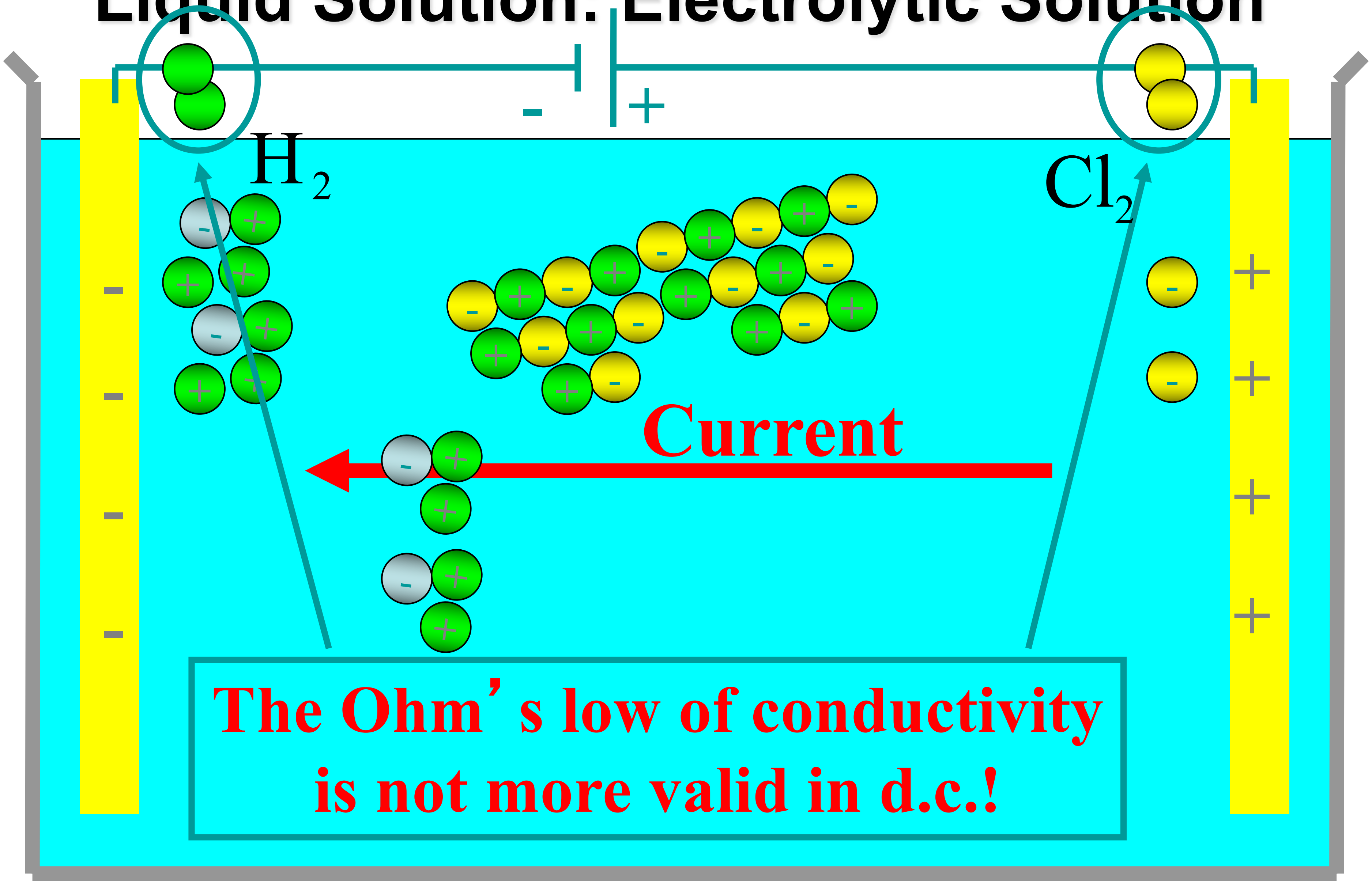
Does the Ohm law is still valid in electrolytic solutions?

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!

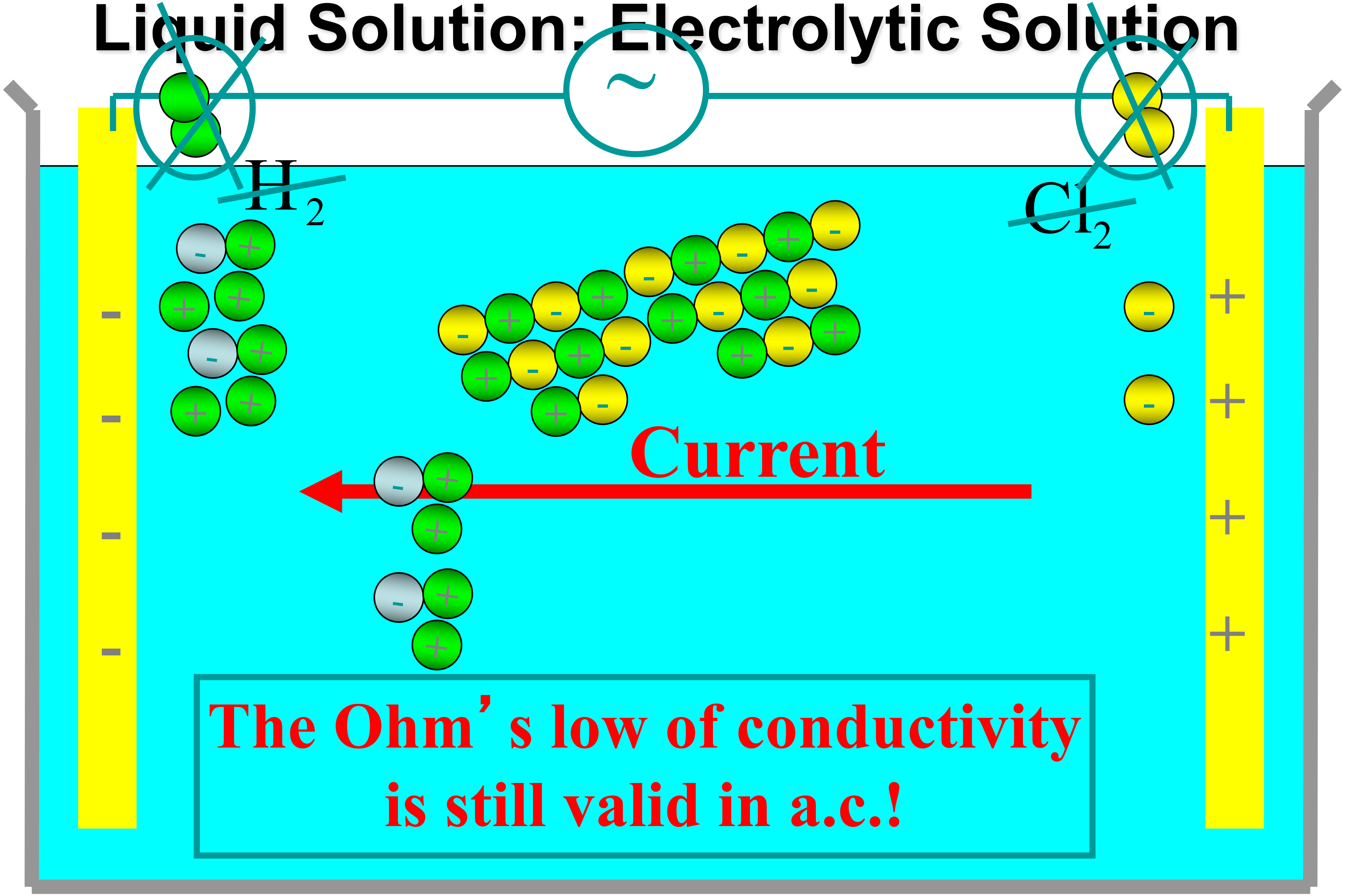
Liquid Solution: Electrolytic Solution



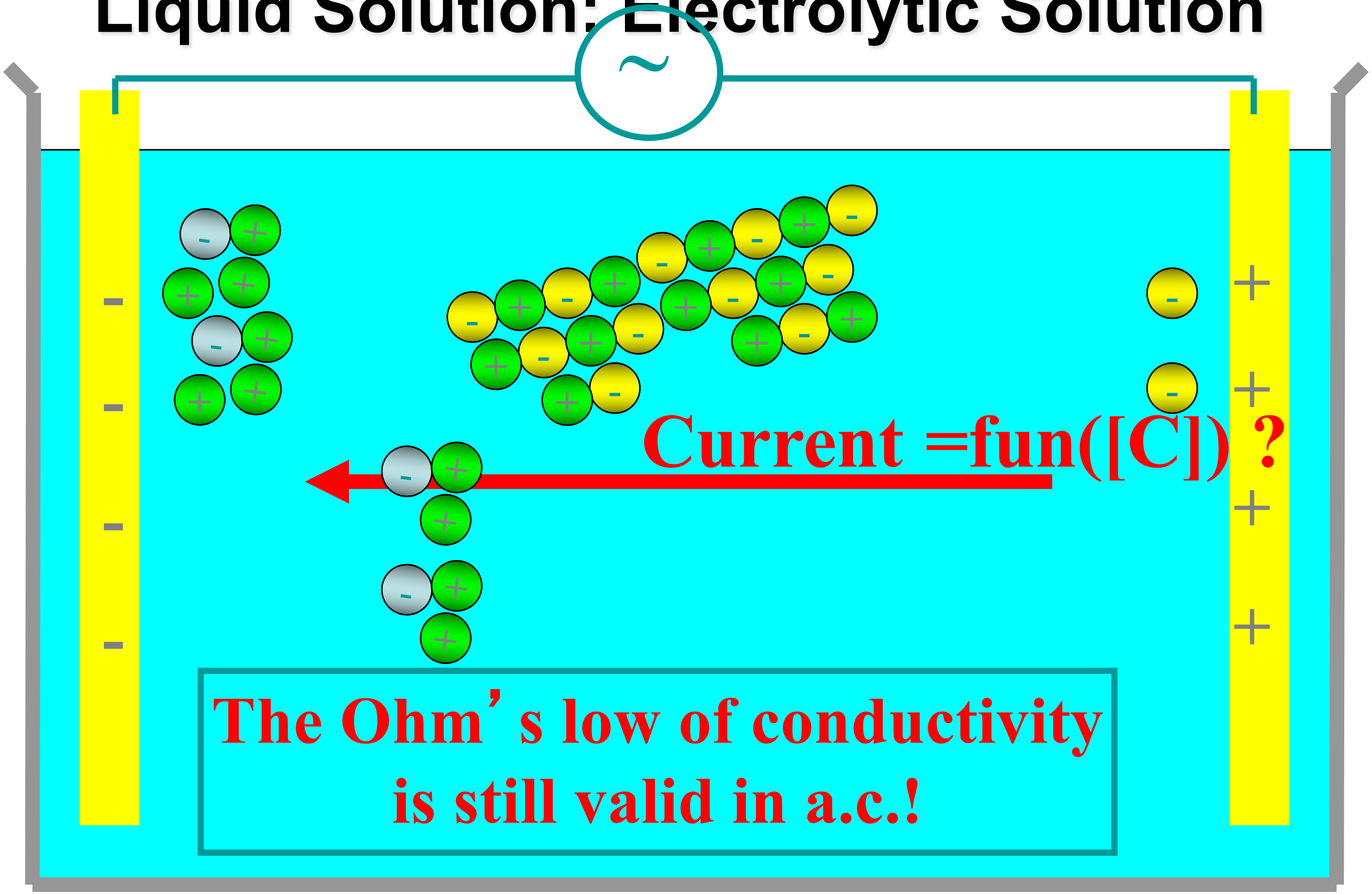
Liquid Solution: Electrolytic Solution



Liquid Solution: Electrolytic Solution



Liquid Solution: Electrolytic Solution



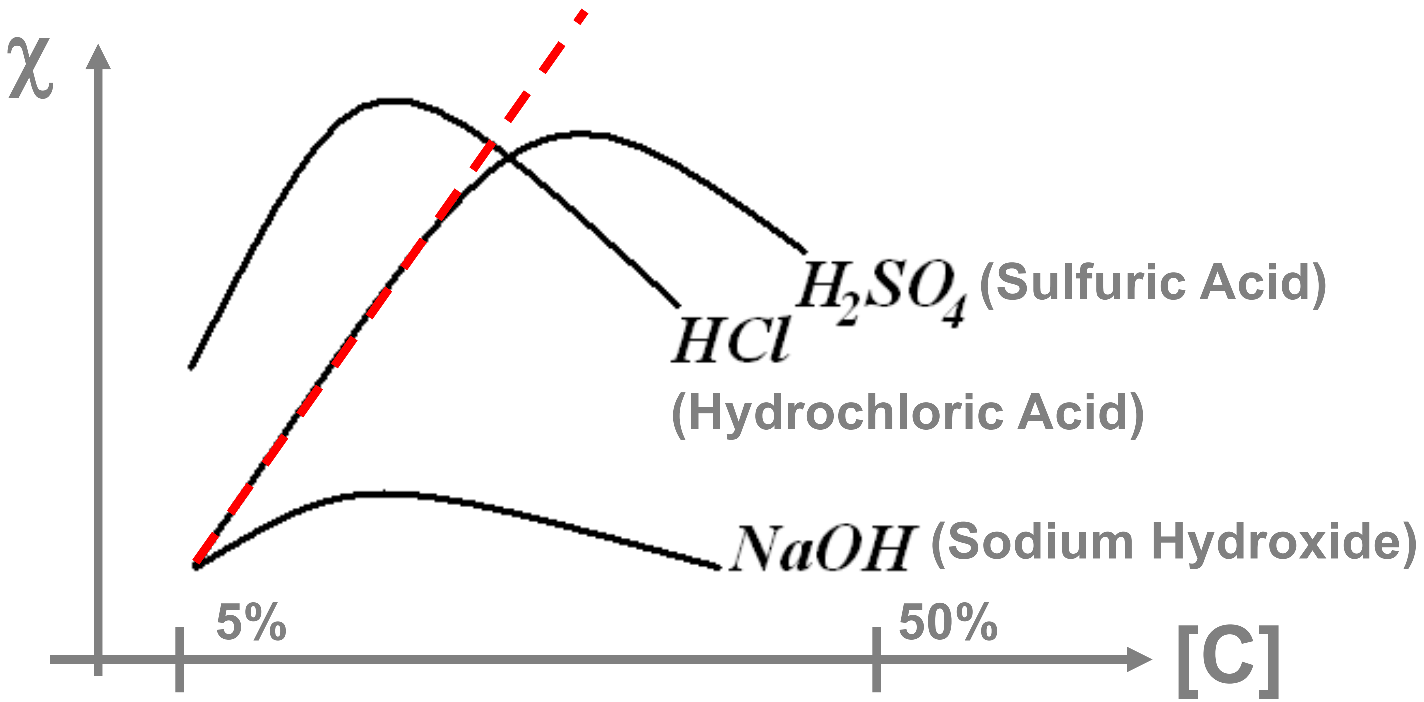
Q12

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

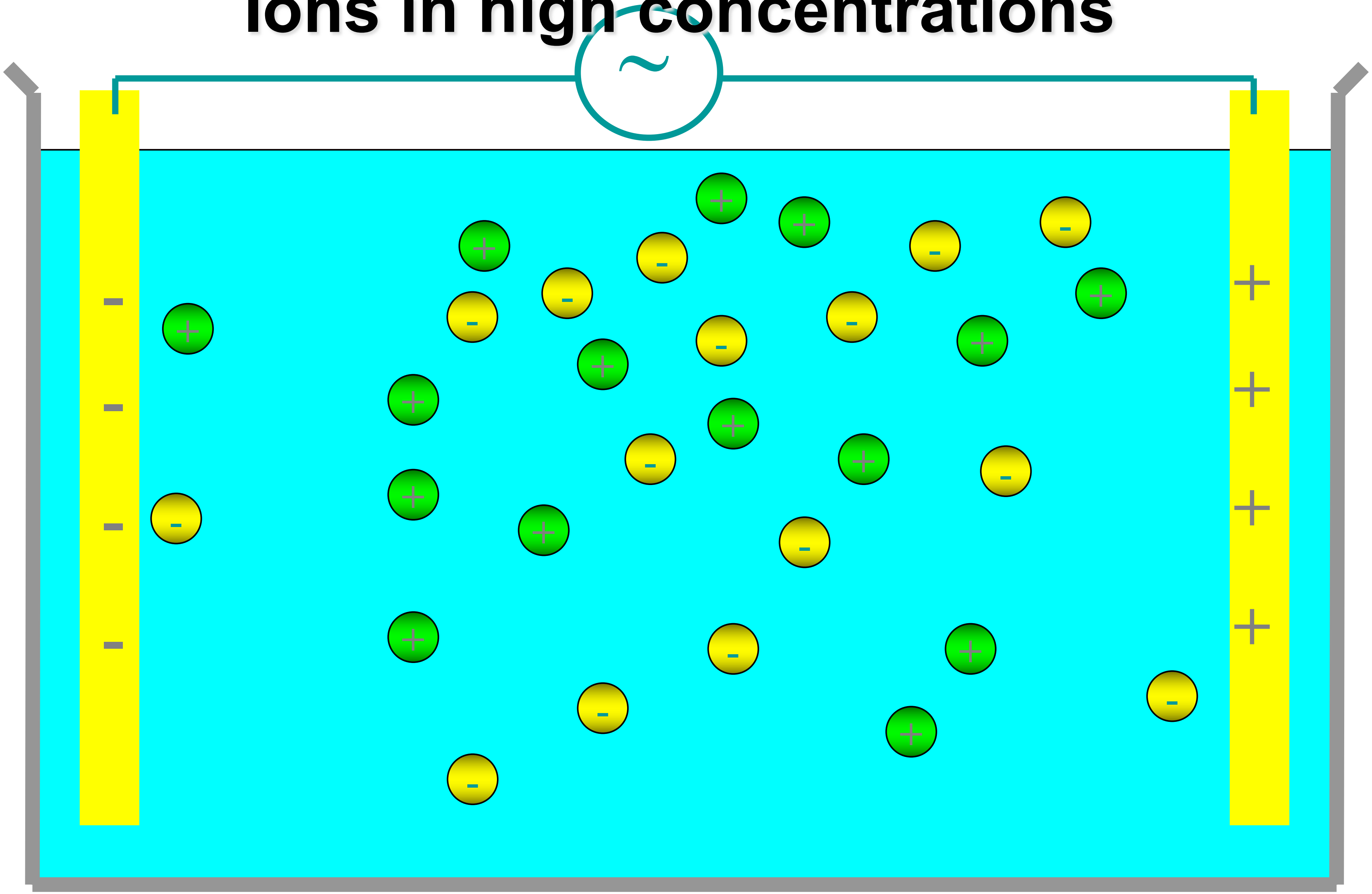


Q13

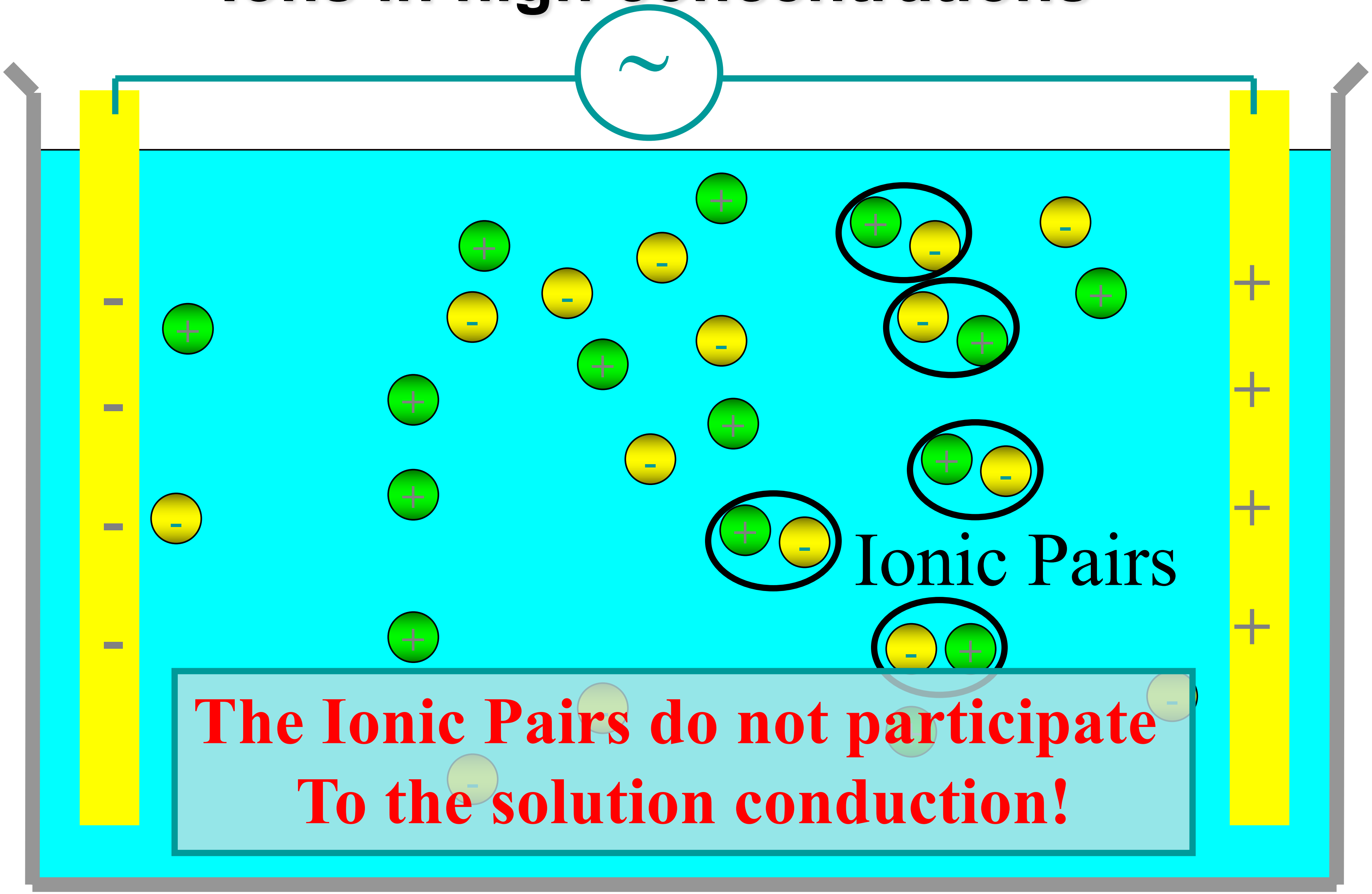
Why the conductivity goes down for higher solution' concentrations?

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…

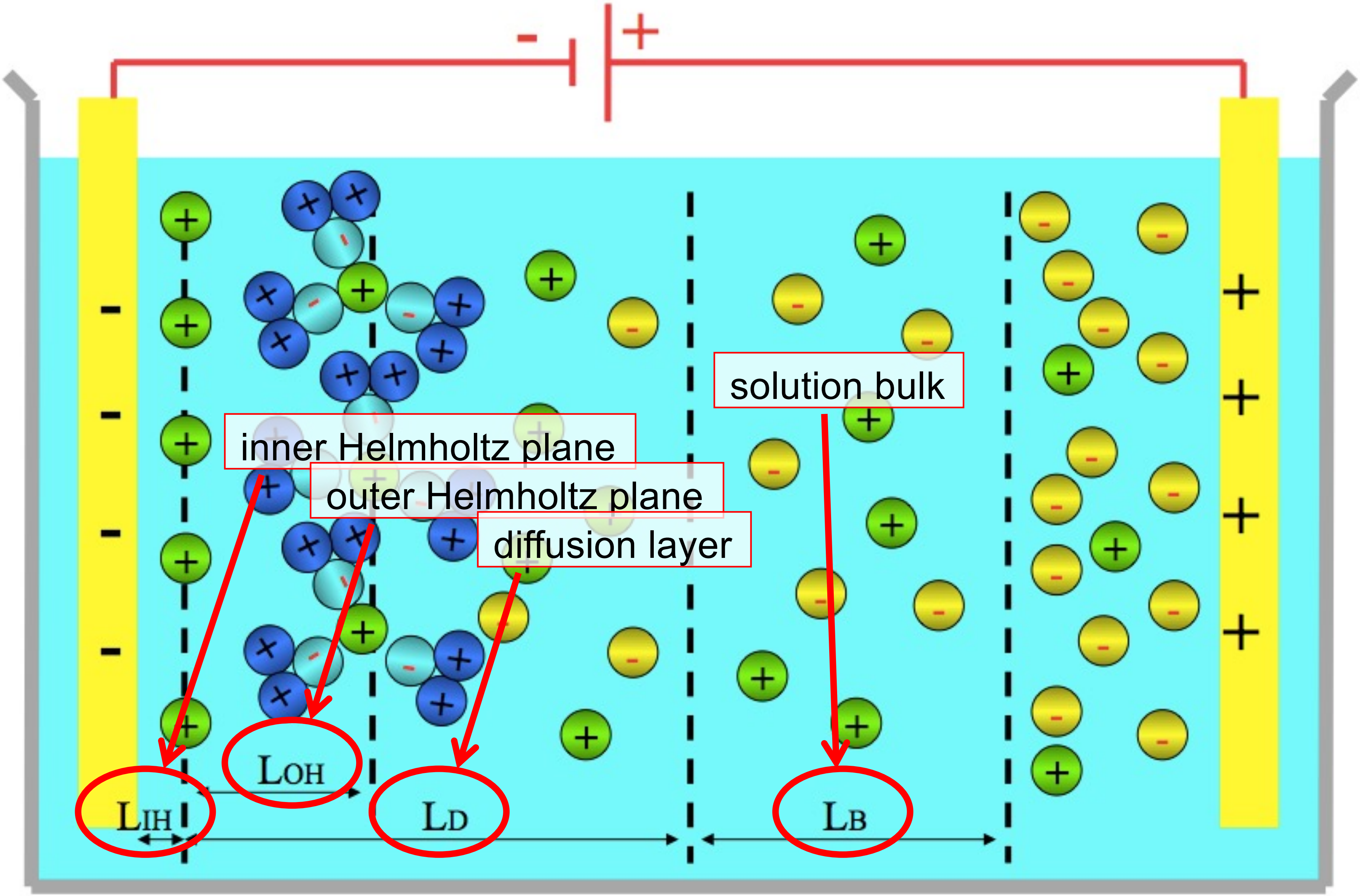
Ions in high concentrations



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

$$\nabla^2 \phi = -\frac{\rho_e}{\kappa \varepsilon_0}$$ Close to electrodes

For perturbation away from equilibrium at finite temperature

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

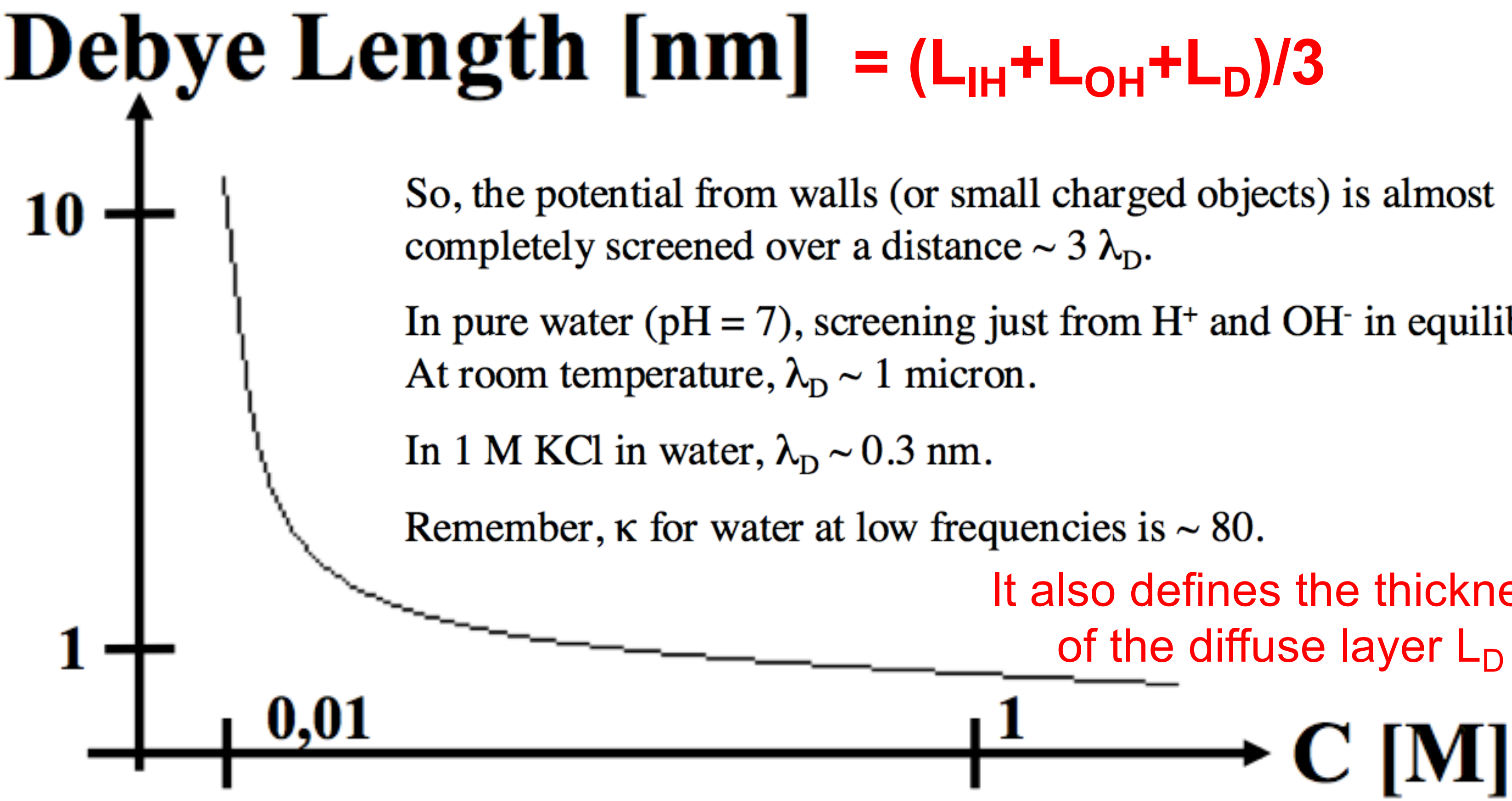
Debye Length

$$\nabla^2 \hat{\phi} = -\frac{1}{\kappa \varepsilon_0} \sum_i z_i e n_{i0} \exp\left(-\frac{z_i e \hat{\phi}}{k_B T} \right) \approx -\frac{1}{\kappa \varepsilon_0} \sum_i z_i e n_{i0} + \frac{e^2}{\kappa \varepsilon_0 k_B T} \sum_i z_i^2 n_{i0} \hat{\phi} \equiv \frac{1}{\lambda_D^2} \hat{\phi}$$

~ 0 for equilibrium neutrality

$$\lambda_D \equiv \left(\frac{e^2}{\kappa \varepsilon_0 k_B T} \sum_i z_i^2 n_{i0} \right)^{-1/2}$$

Debye Length



= $(L_{IH}+L_{OH}+L_D)/3$

So, the potential from walls (or small charged objects) is almost completely screened over a distance ~ 3 λ_D.

In pure water (pH = 7), screening just from H^+ and OH^- in equilibrium. At room temperature, λ_D ~ 1 micron.

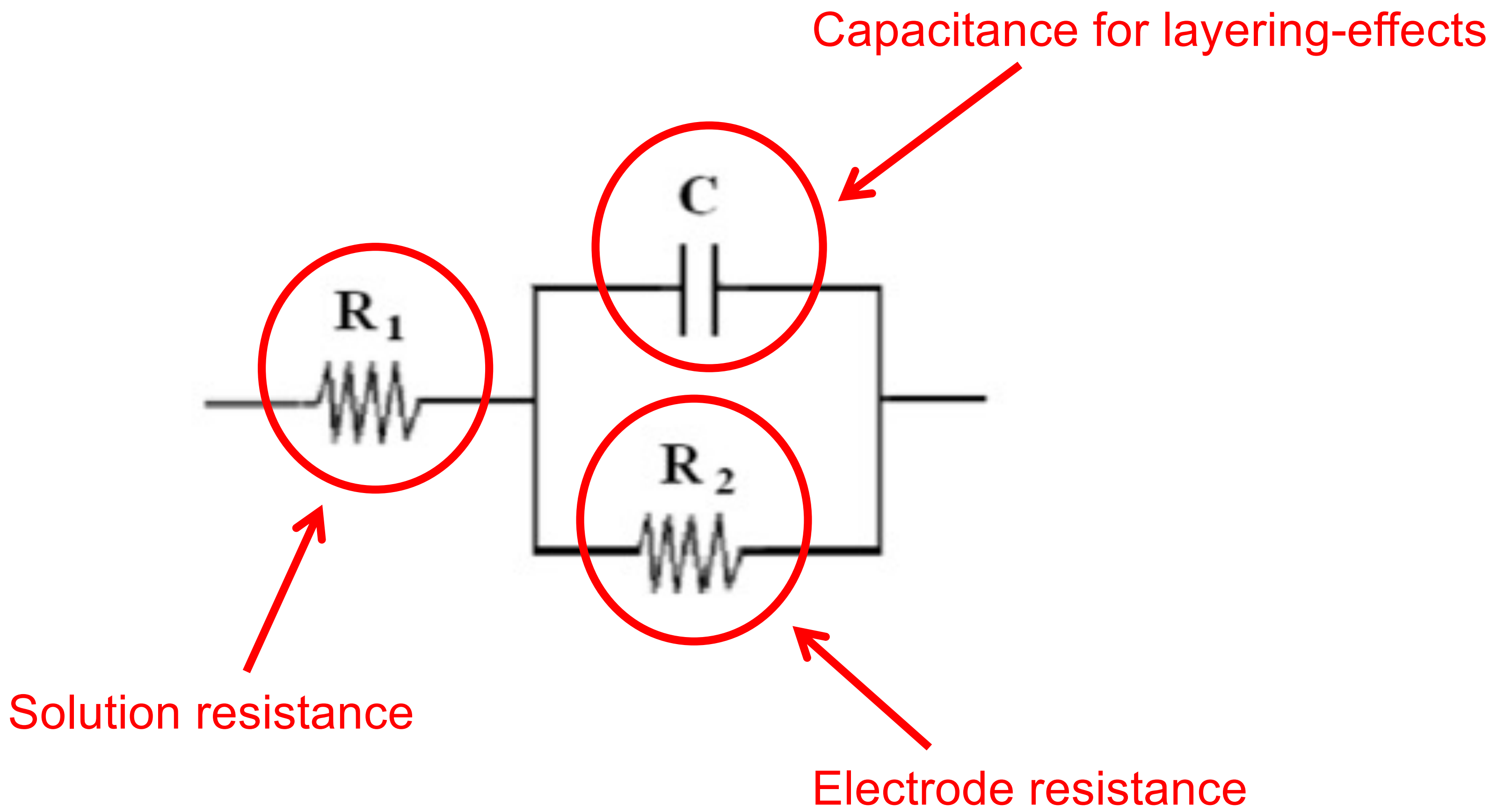
In 1 M KCl in water, λ_D ~ 0.3 nm.

Remember, κ for water at low frequencies is ~ 80.

It also defines the thickness of the diffuse layer L_D

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

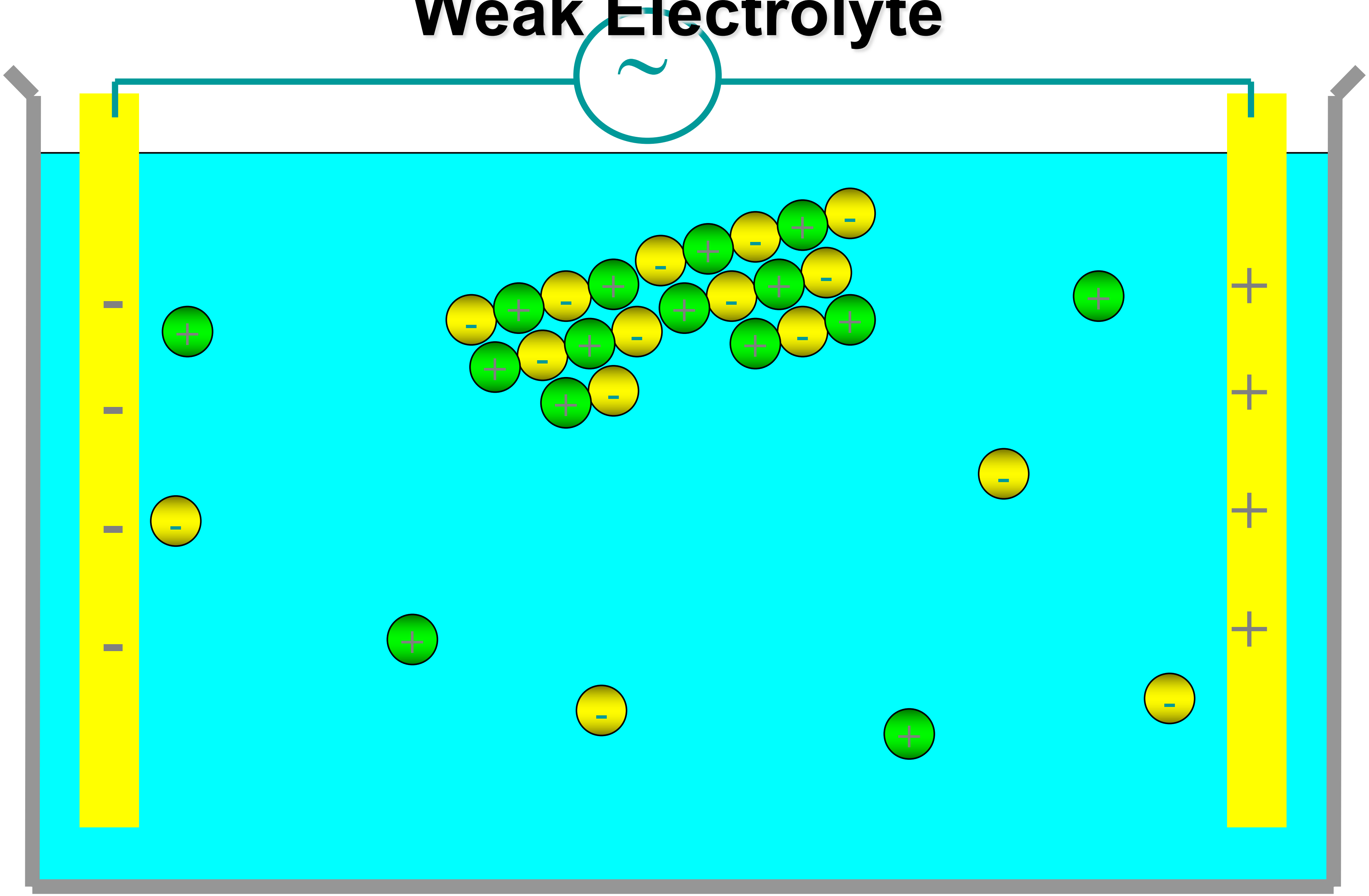
Equivalent Circuit with Layering effects



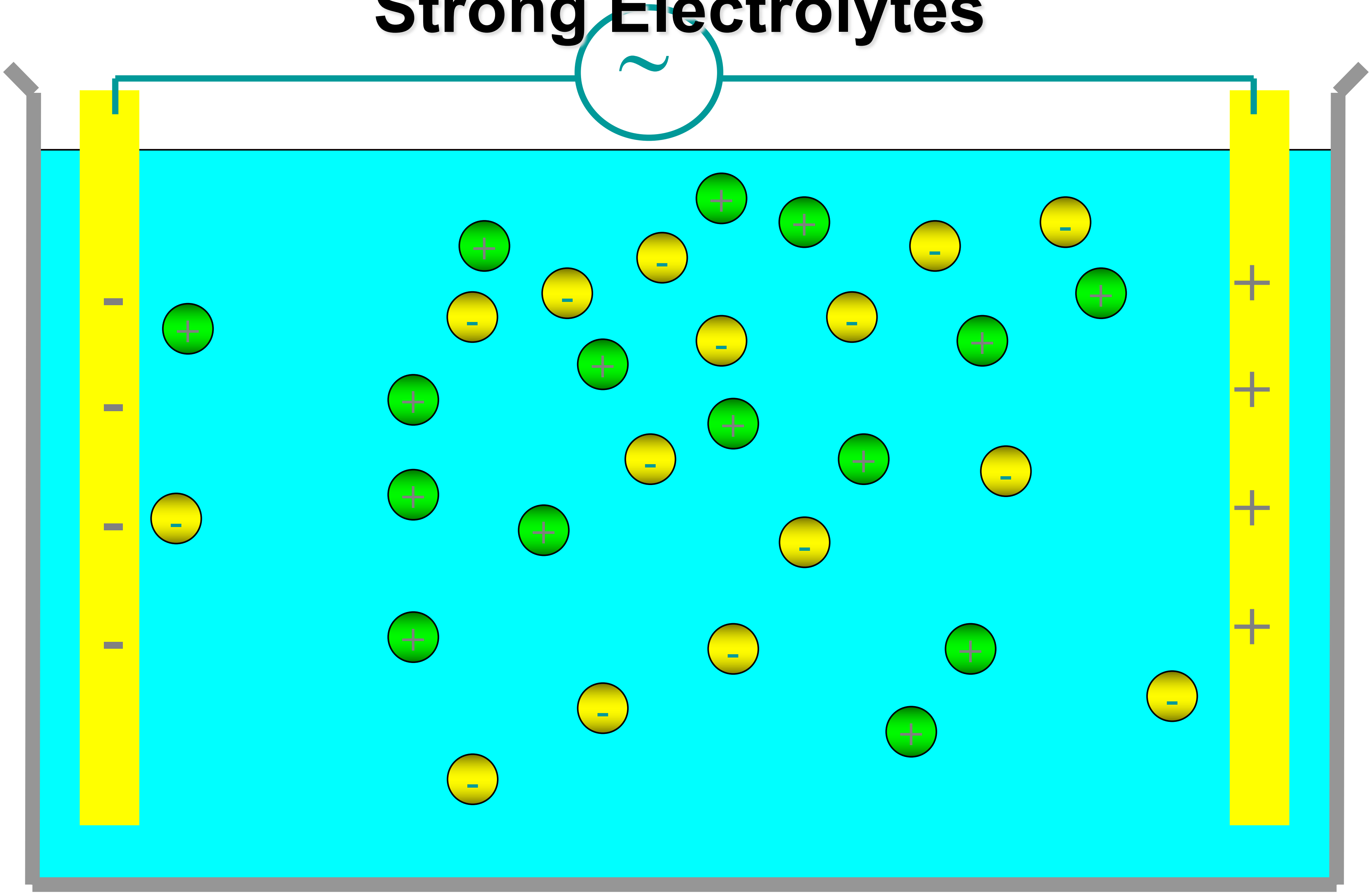
Kind of Electrolytes

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

Weak Electrolyte



Strong Electrolytes



Hard and weak Electrolytes

Dissociation of the Sodium Chloride

$$NaCl + H_2O \rightarrow Na^+ + Cl^- + H_2O$$

Dissociation of Hydrogen Cyanide

$$HCN + H_2O \underset{\rightarrow}{\longleftarrow} H_3O^+ + CN^-$$

α = **Dissociation Degree**

Equilibrium Constant

$$AB + H_2O \xleftrightarrow{\alpha} A^+ + B^- + H_2O$$

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

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

$$CH_3COOH + 2H_2O \rightarrow CH_3COO^- + H^+ + 2H_2O$$

Acid

The Sodium Hydroxide

$$NaOH + H_2O \rightarrow Na^+ + OH^- + H_2O$$

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

$$2H_2O \leftrightarrow H_3O^+ + OH^-$$

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

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

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

$$[H_3O^+] > 10^{-7}\,M \rightarrow Acid\ Solution$$
$$[H_3O^+] = 10^{-7}\,M \rightarrow Neutral\ Solution$$
$$[H_3O^+] < 10^{-7}\,M \rightarrow Basic\ Solution$$

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