EPFL

Electrical and Electronics Engineering

EE-517

Bio-Nano-Chip Design

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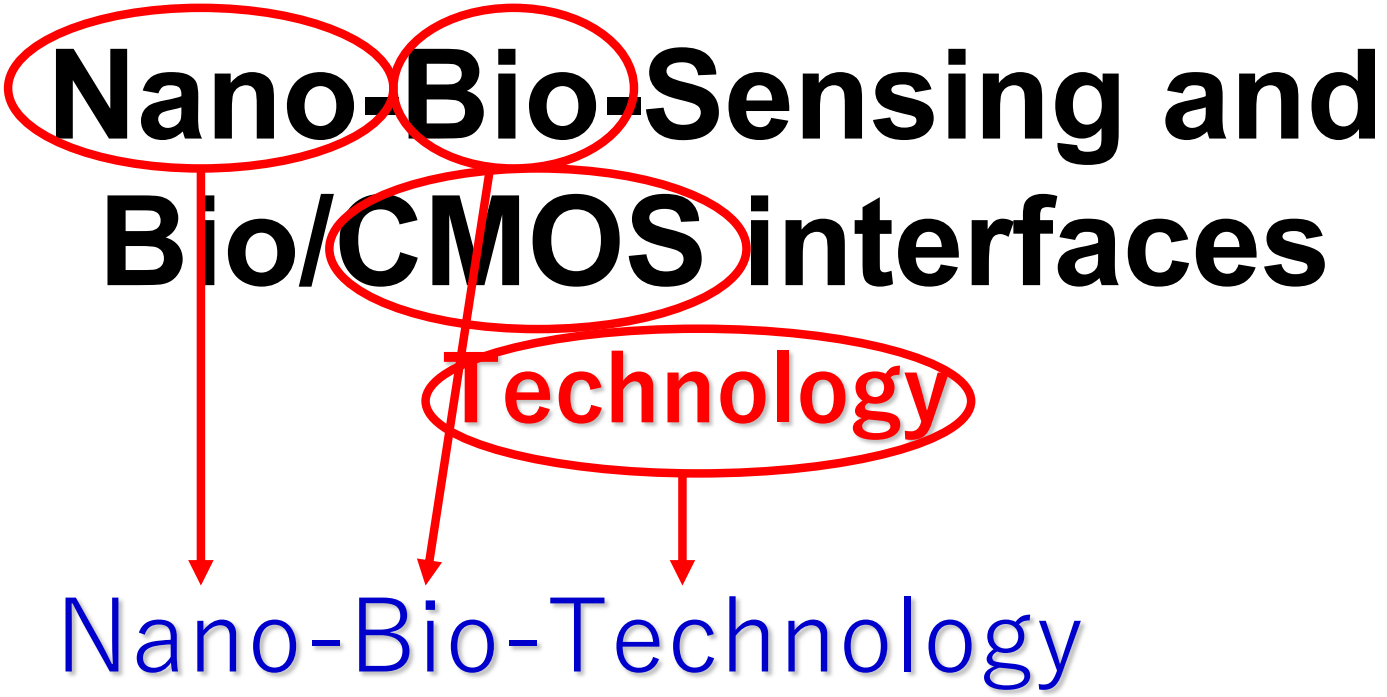
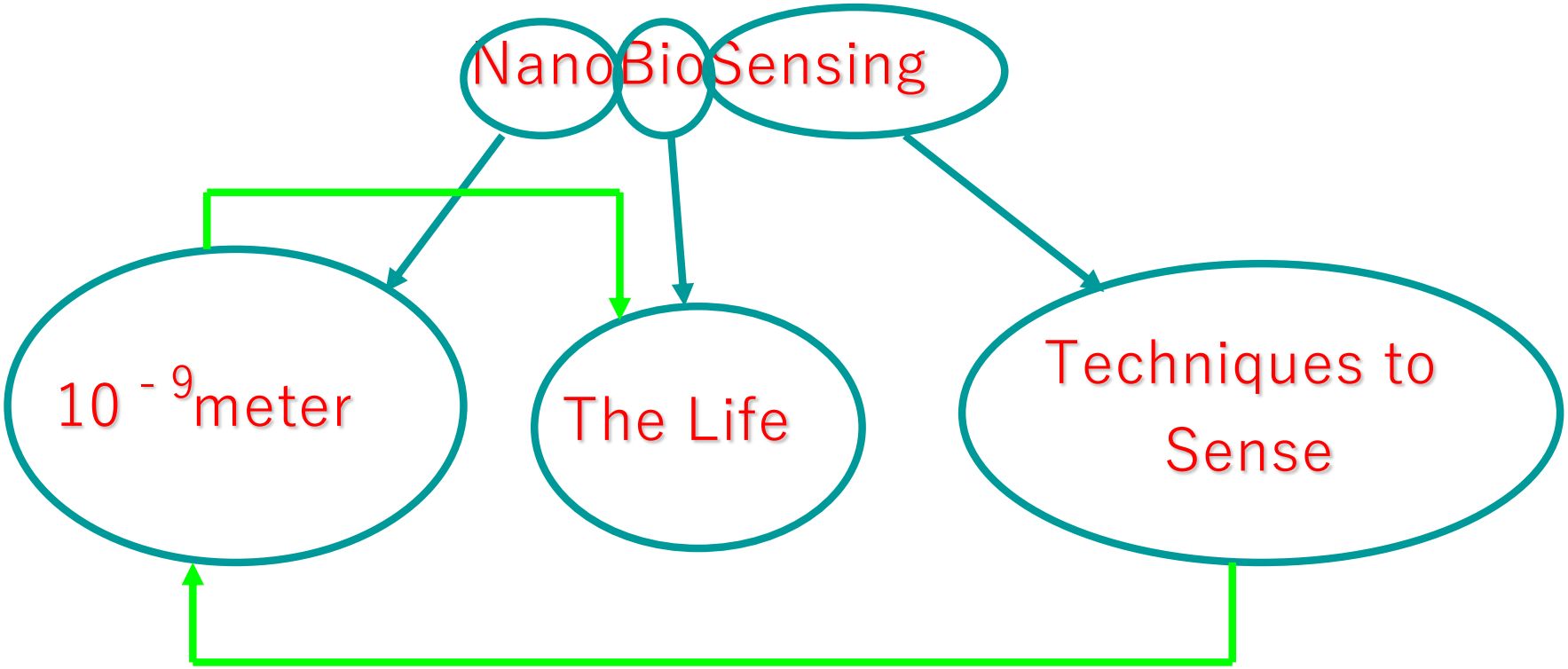
Bio-Nano-Chip Design

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 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

The Pancreas Functions

IN-put Signals

Bile aceids

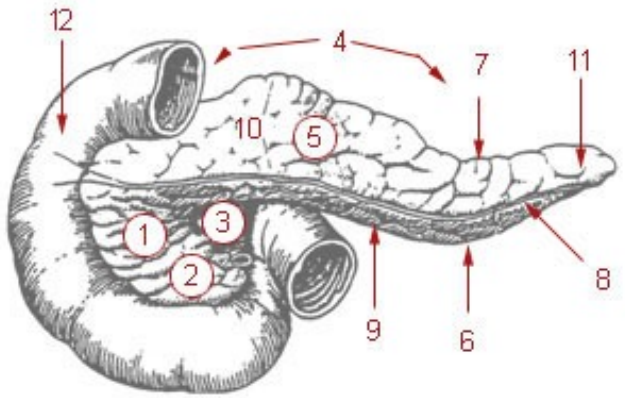
pH

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

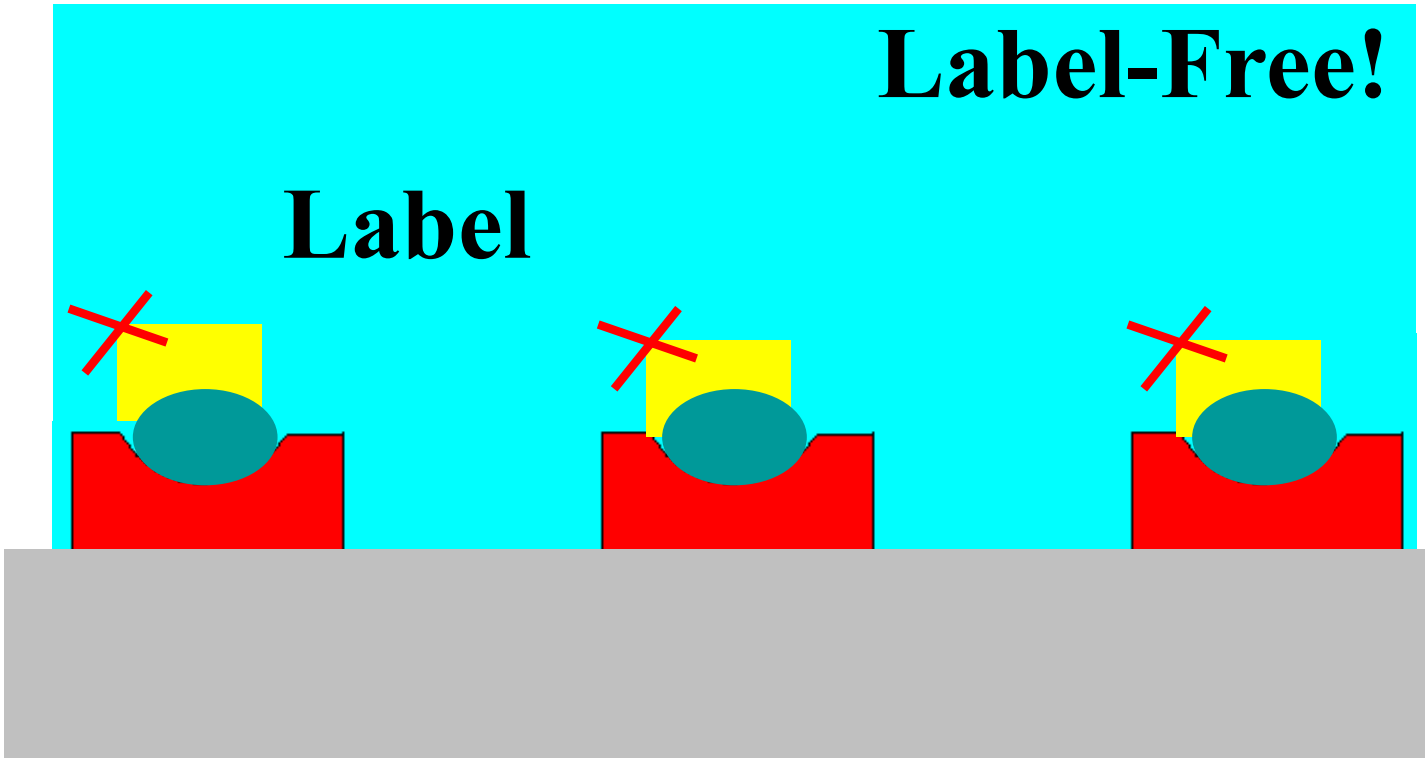
What to sense?

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?

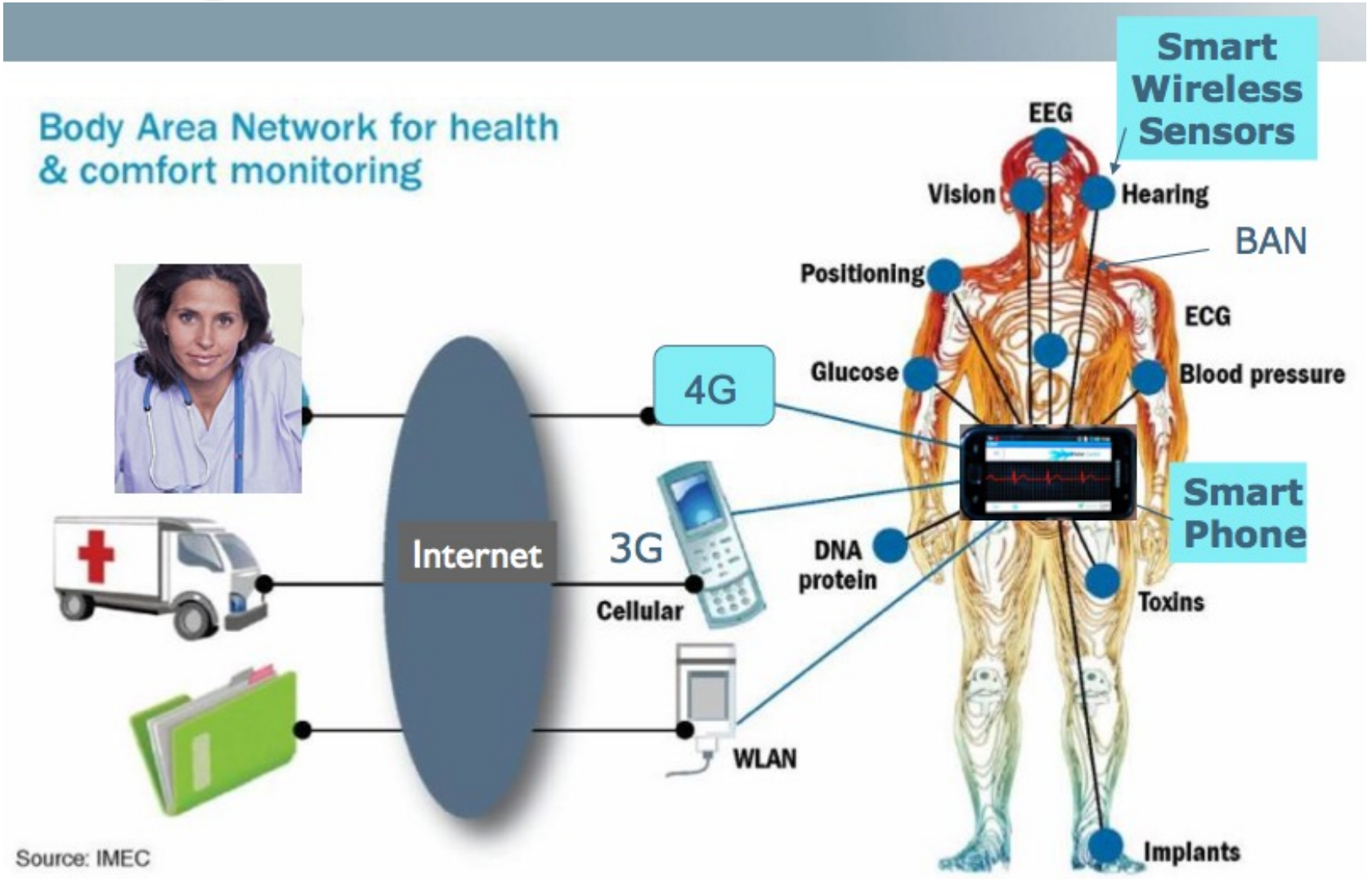
Bio-Markers may be simple molecules, proteins or genes

Measuring Bio-Markers



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

Fully-Connected Human++



Courtesy, Hugo De Man (IMEC)

The Time' forecast on Human++

[TIME, February 2011]

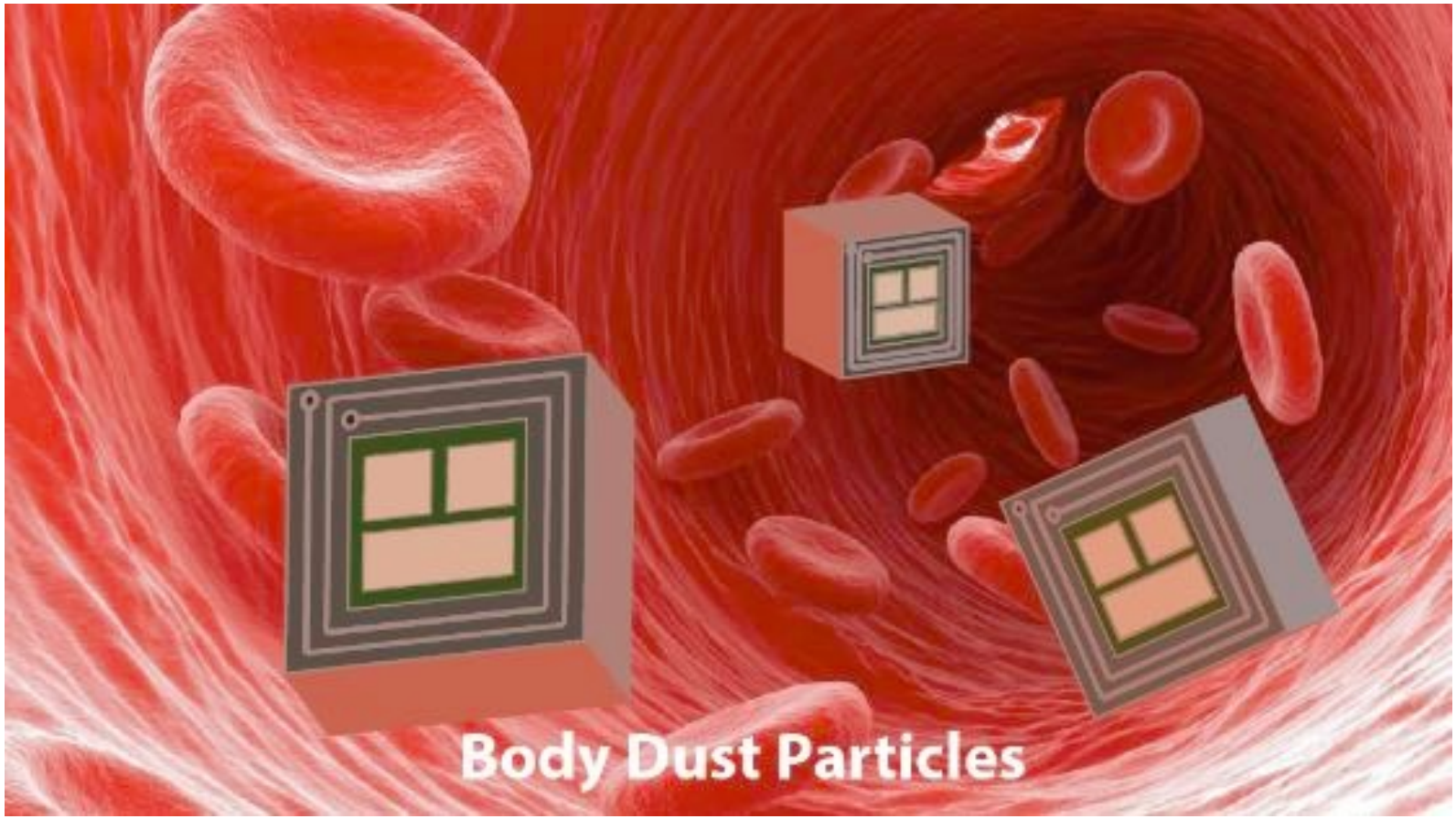
Chips under the skin?

[The Guardian, October 2017]

How small Chips under the skin?

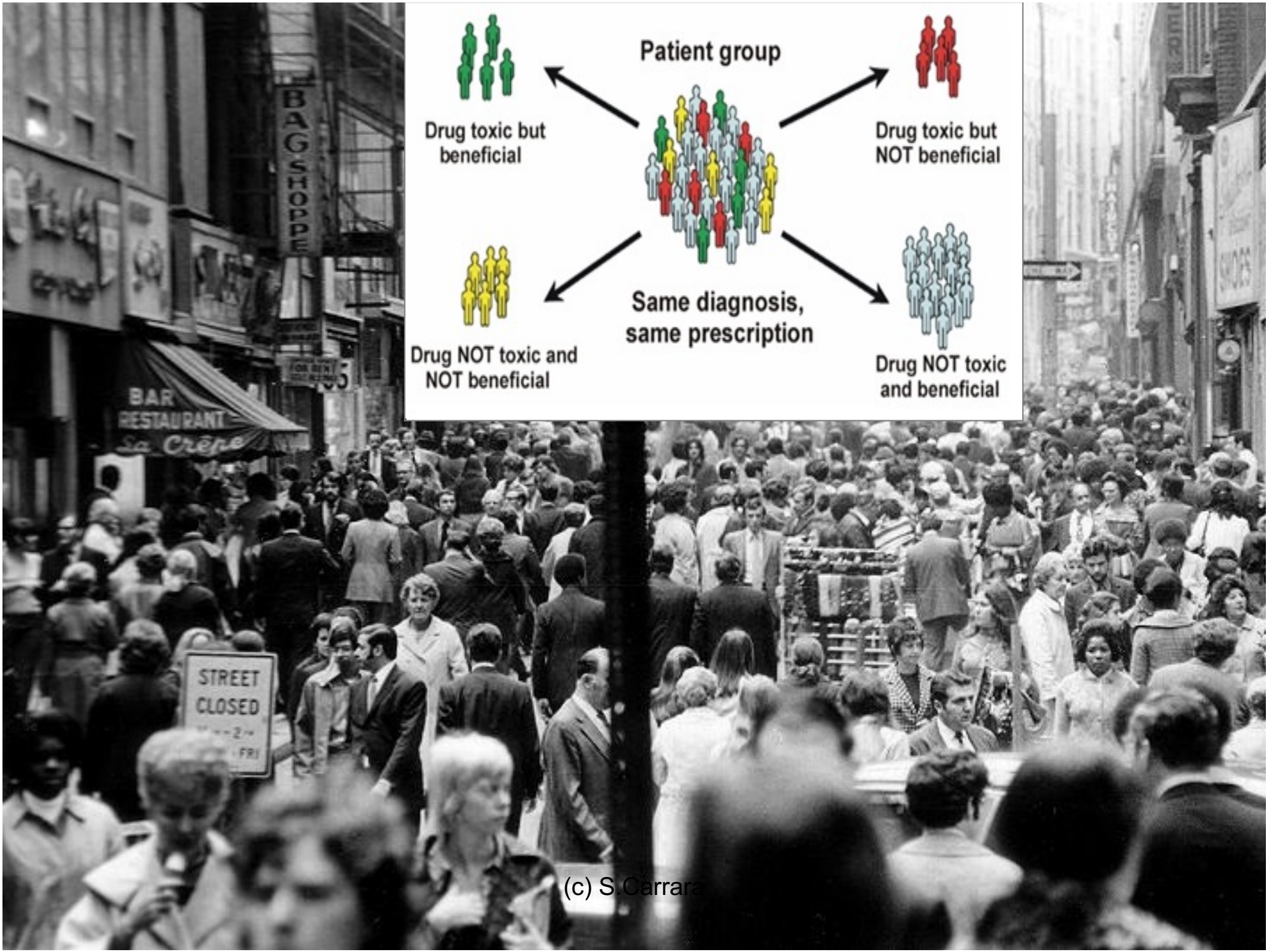
[1966 Sci. Fi. movie titled “Fantastic Voyage”]

Body Dust: Drinkable CMOS Bioelectronics

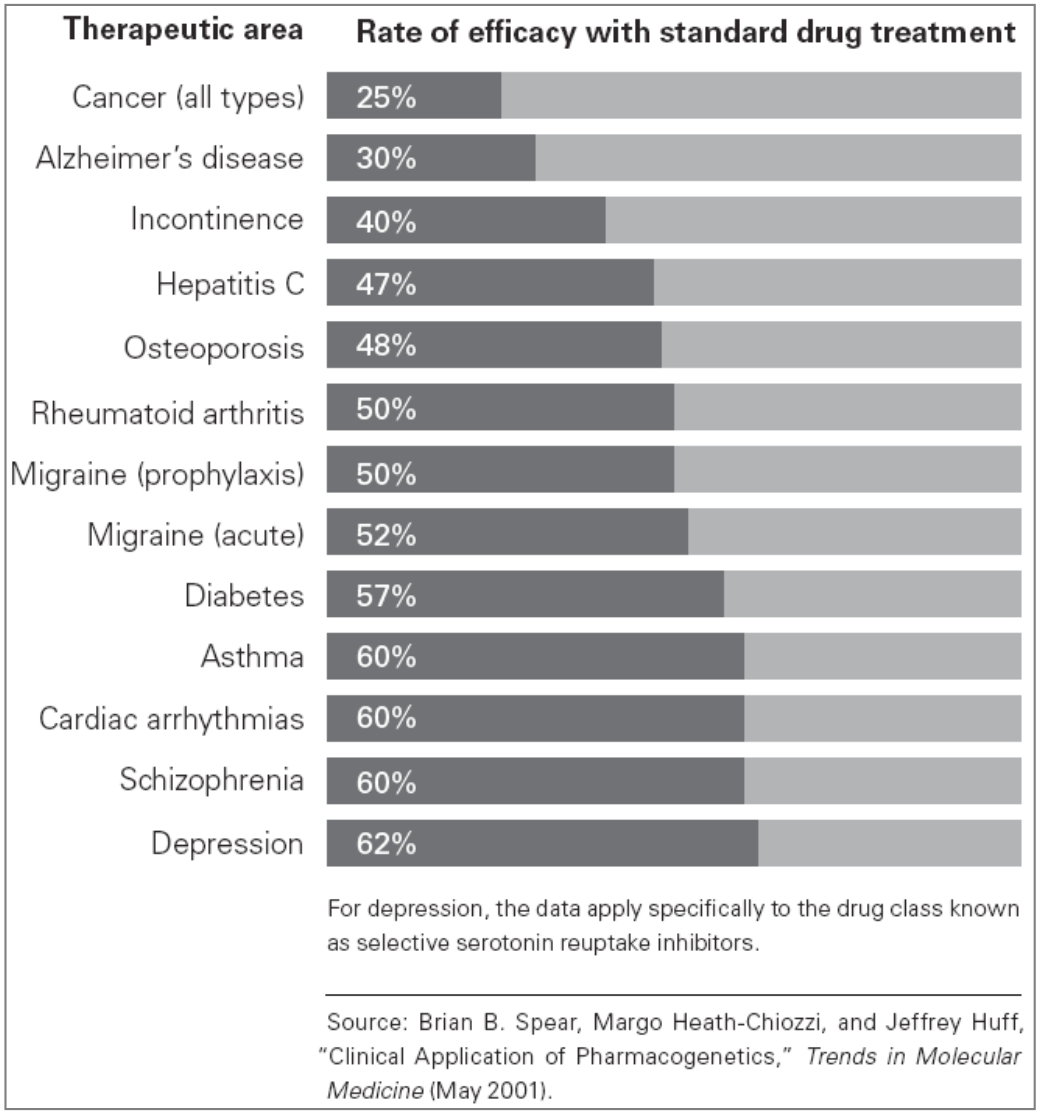


Tracking cancer-cell developing “drinkable” electronic sensors

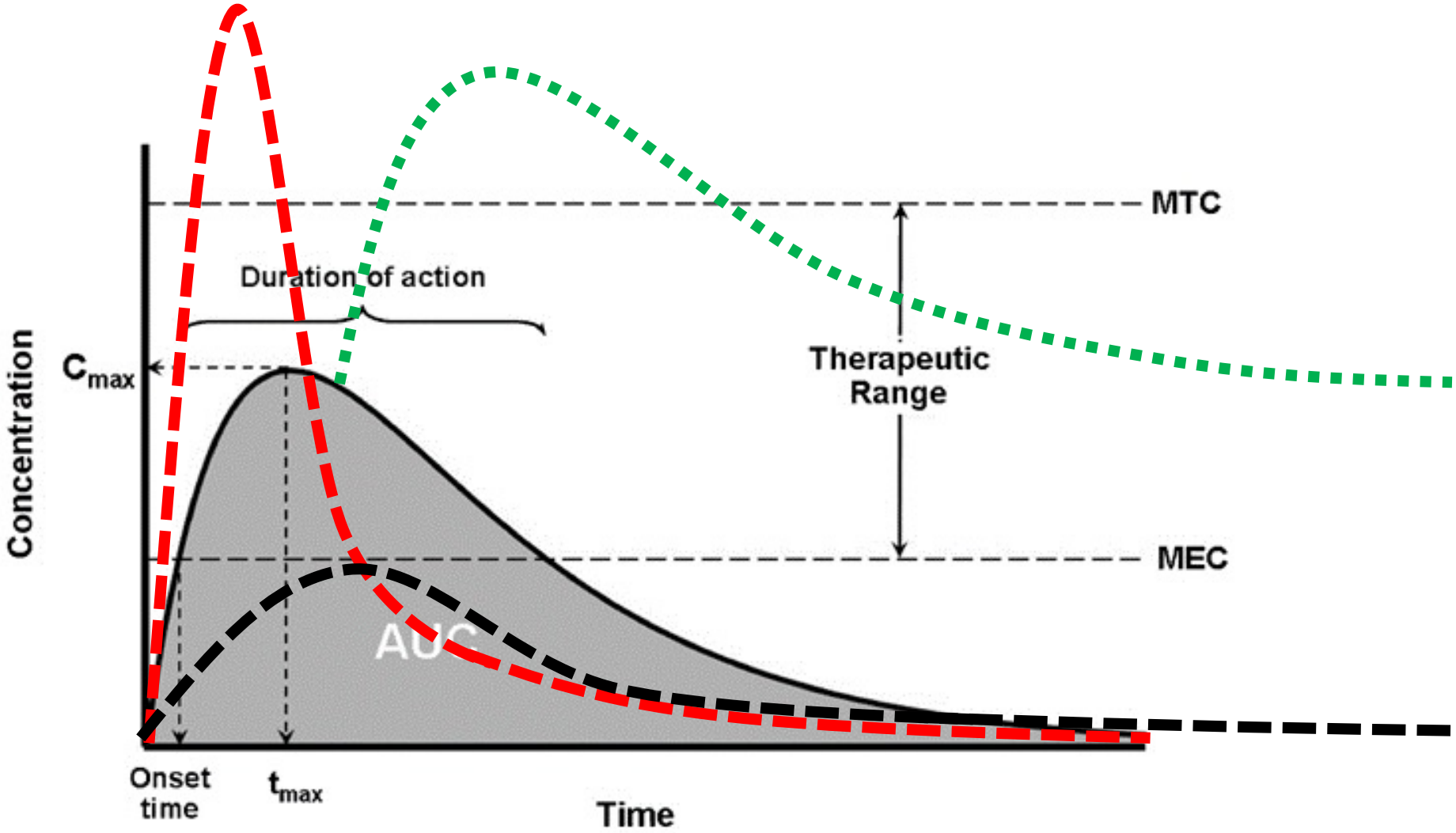
https://actu.epfl.ch/news/tracking-cancer-cell-development-with-drinkable-el/


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
Crêpe
STREET CLOSED
FRI

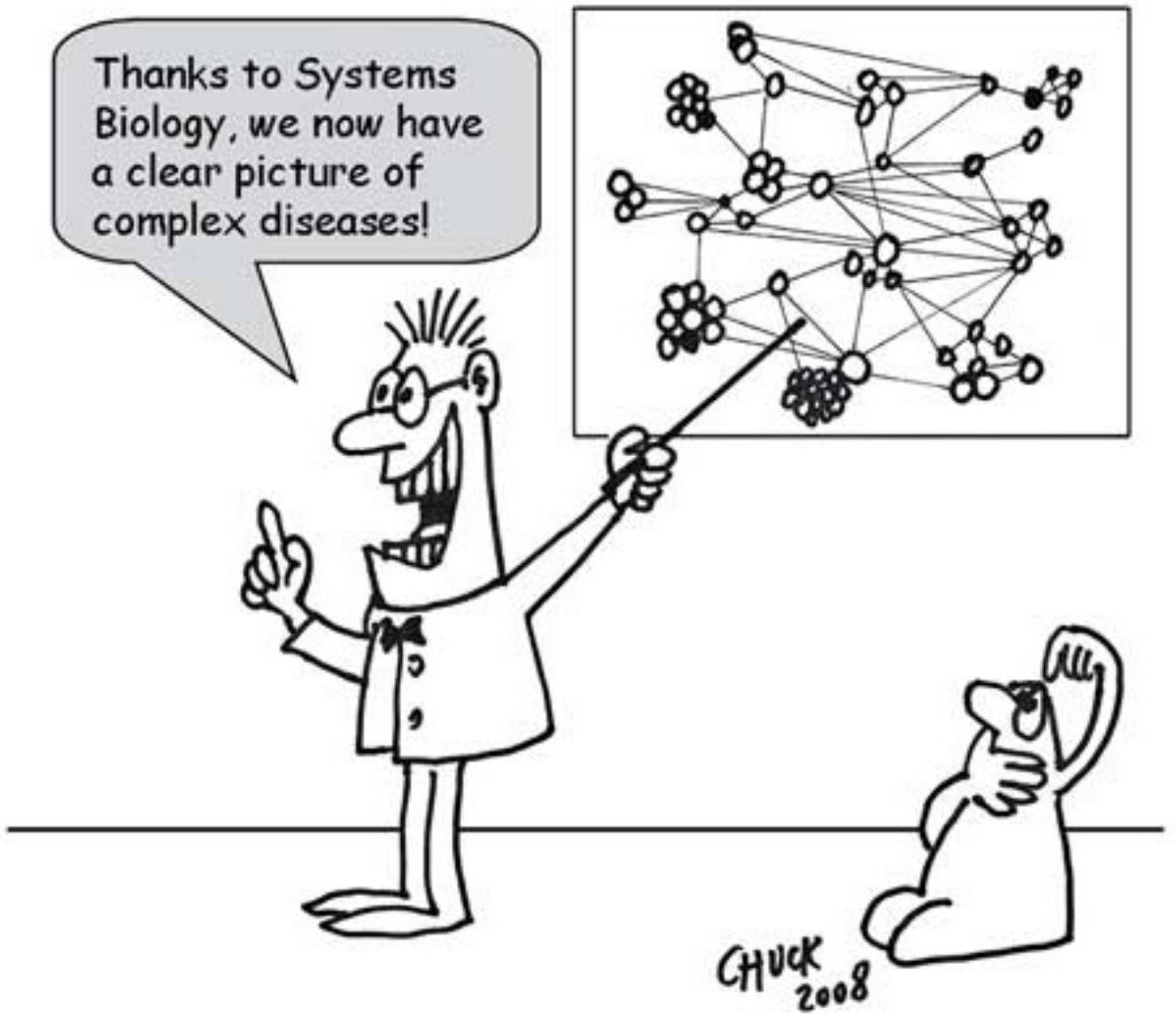
Low efficacy of used compounds



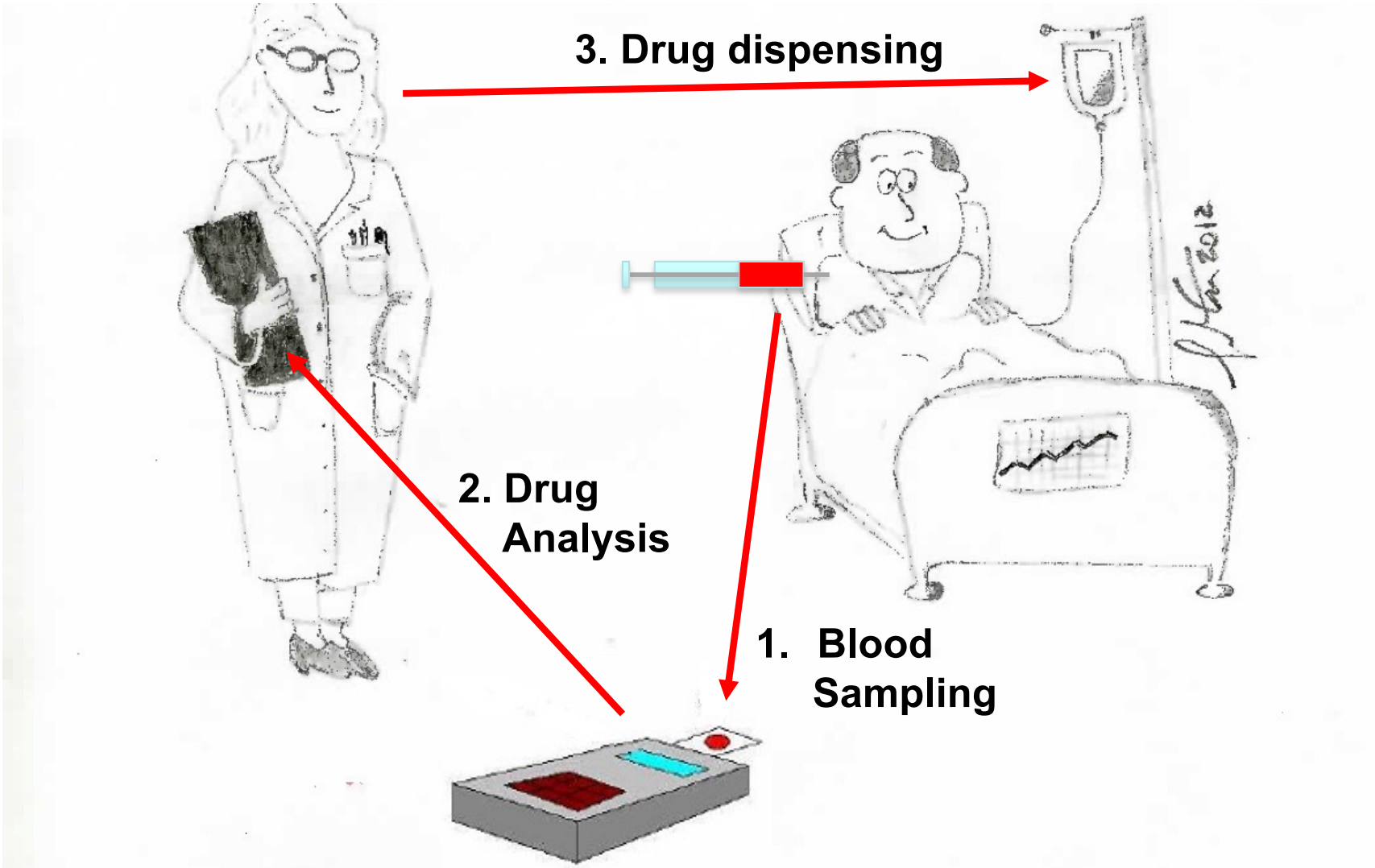
Personalized Therapy: the right dose in the right moment!



System Biology is not enough



Personalized Therapy

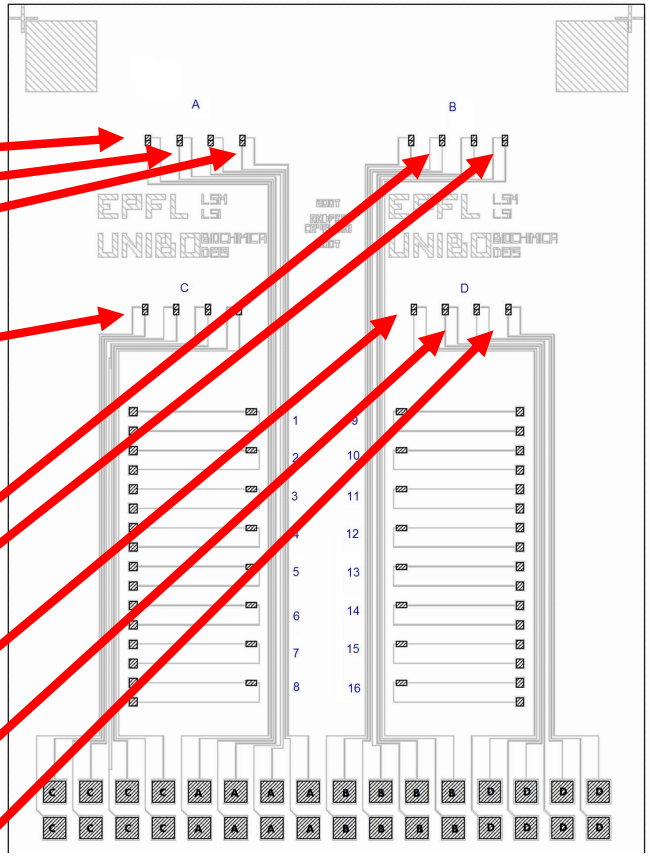


Drugs injection based on patient's pharmacokinetics

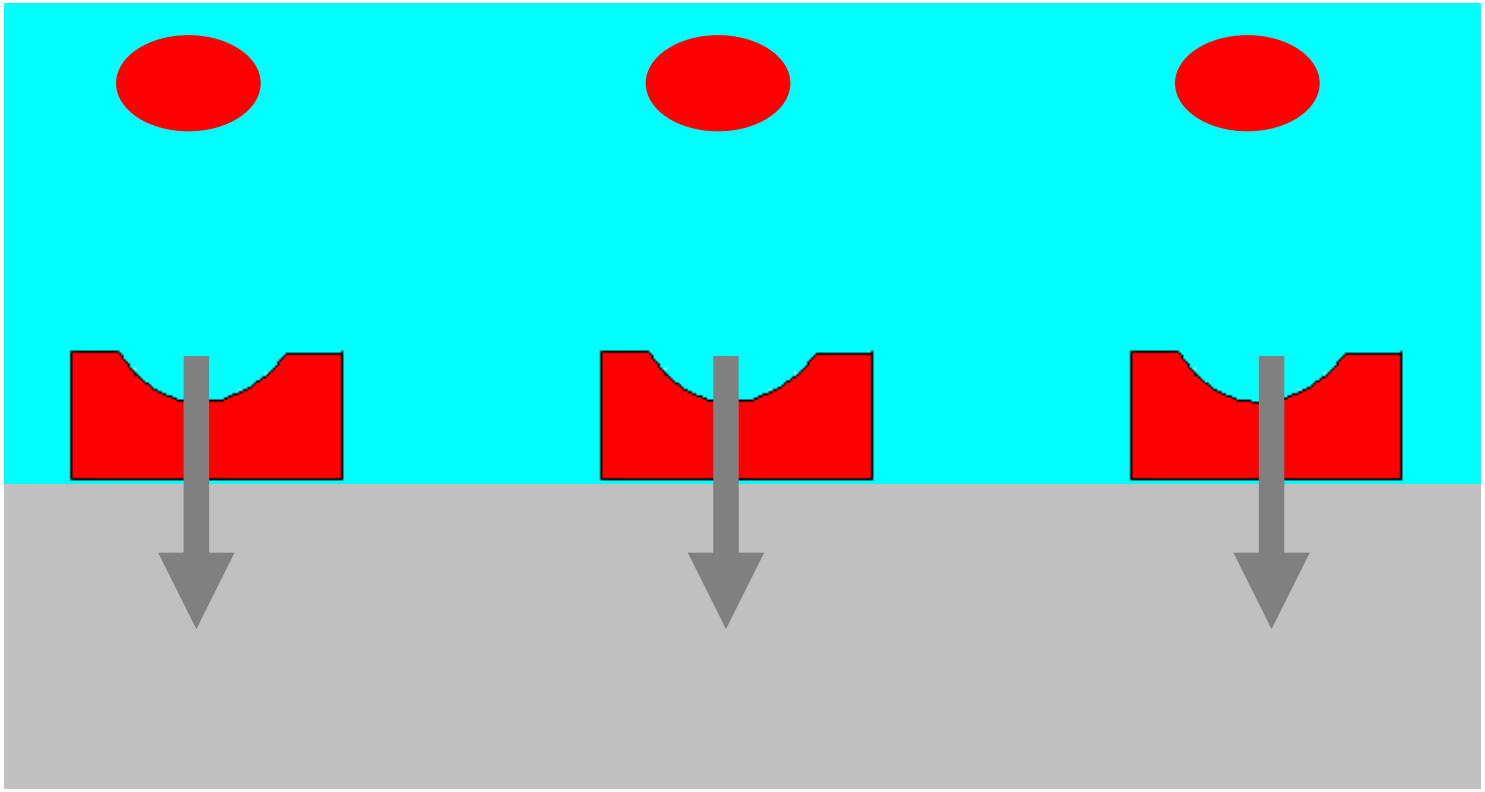
The need for new Bio/CMOS systems

TARGETS

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



CMOS/Sample interface

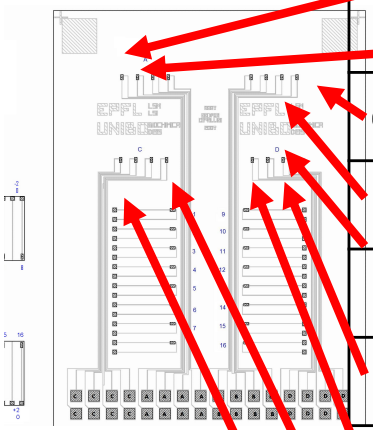


The interface between the CMOS circuit and the bio-sample needs to be deeply investigated and organized

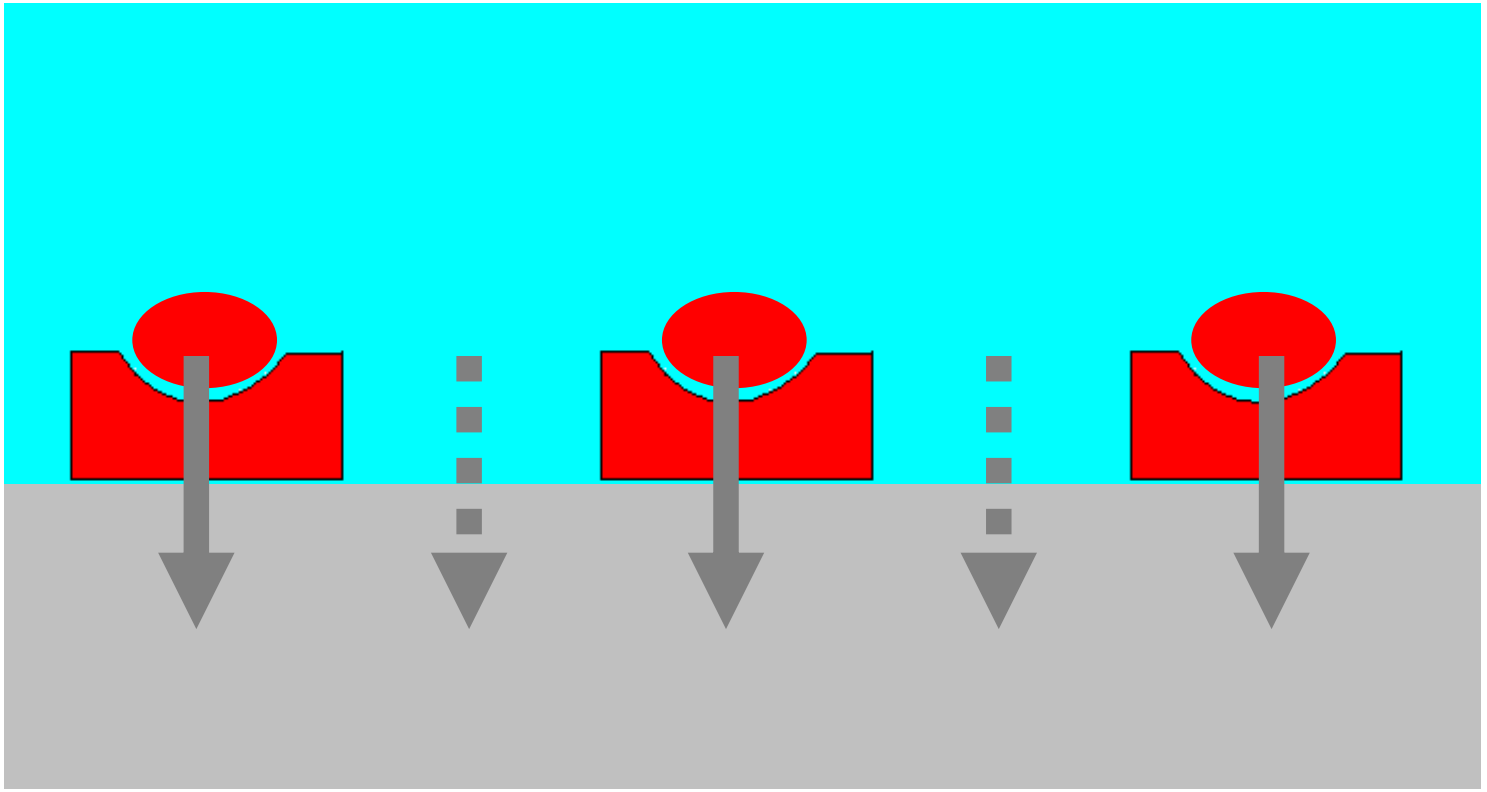
Applications in Personalized Therapy

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

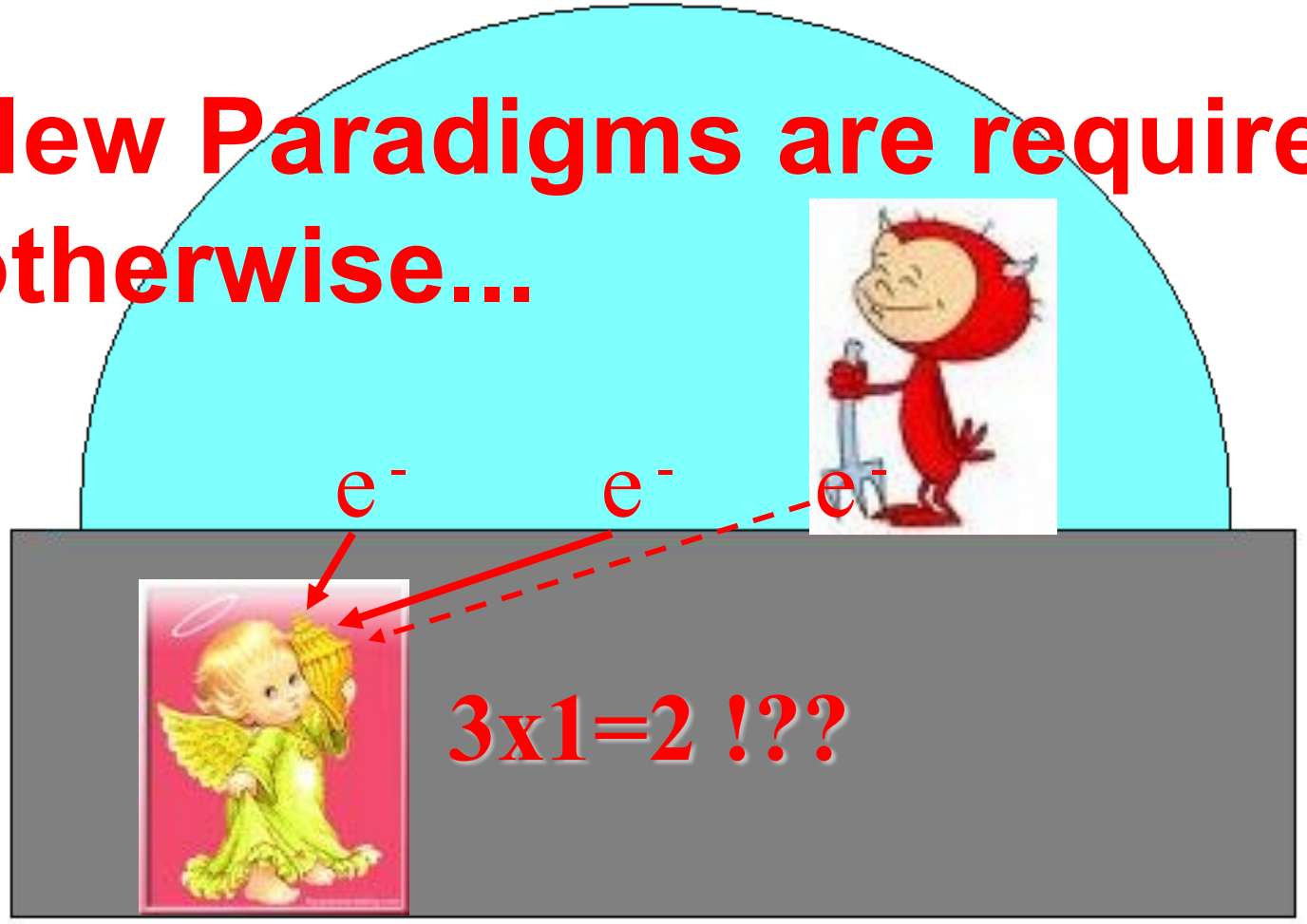


CMOS/Sample interface



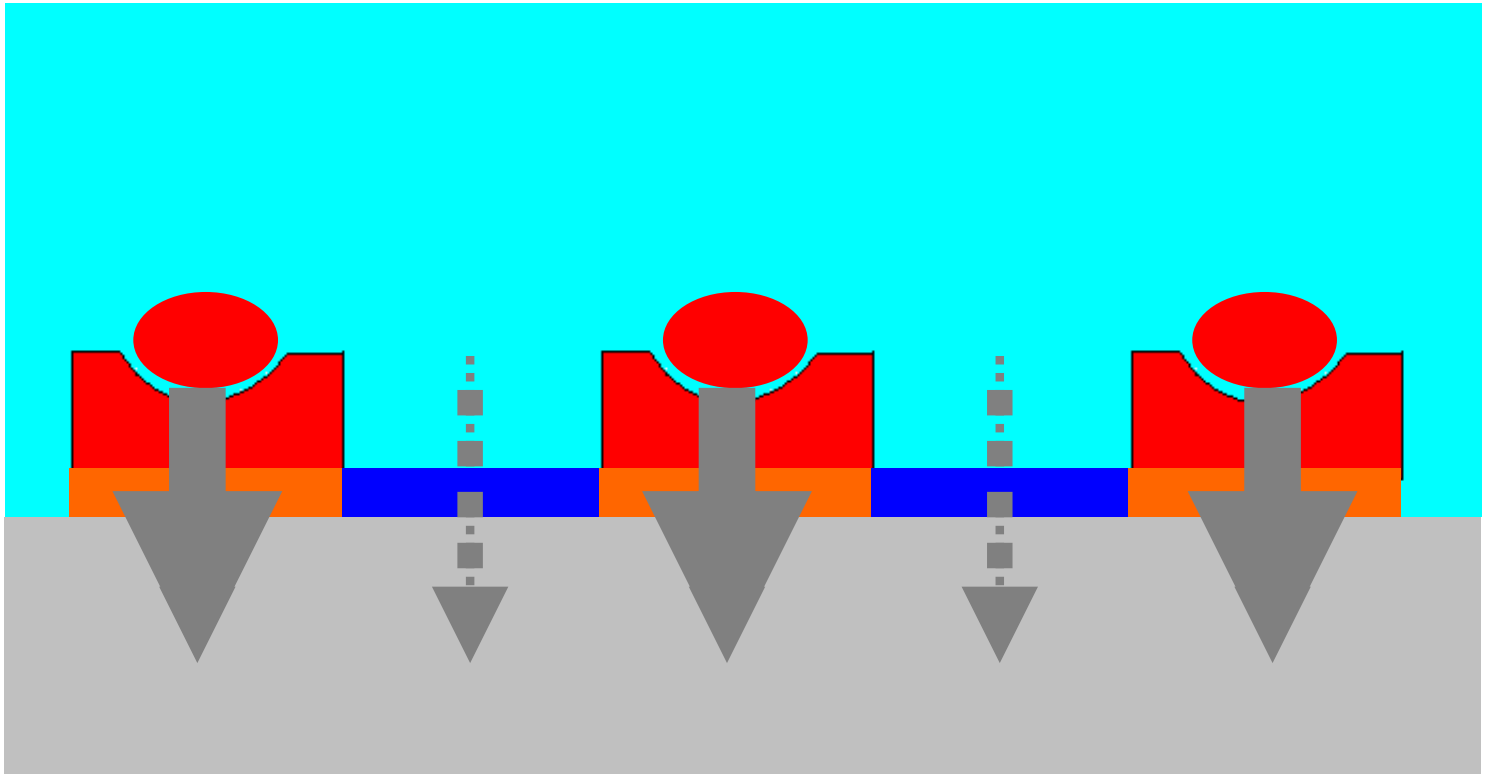
The interface between the CMOS circuit and the bio-sample needs to be deeply investigated and organized

New Paradigms are required otherwise...



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

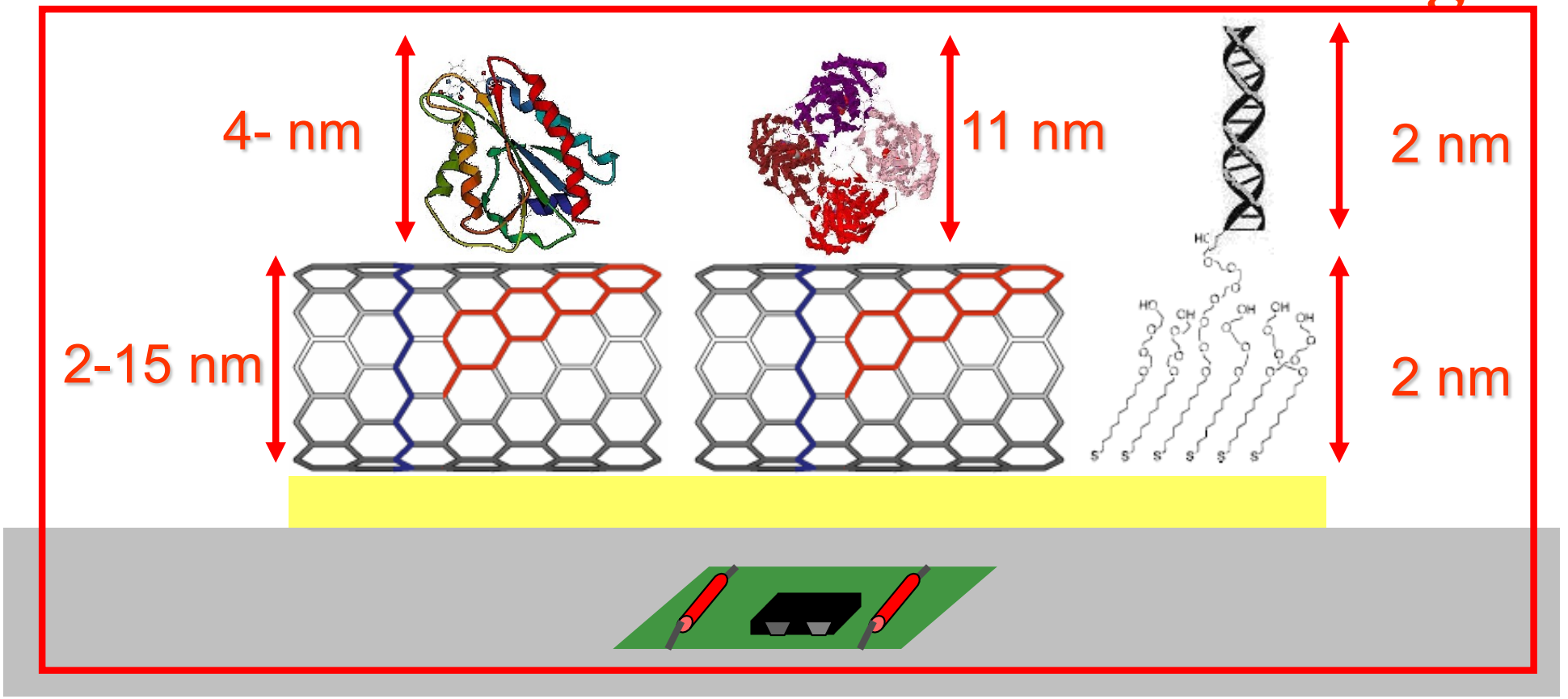
CMOS/Sample interface



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

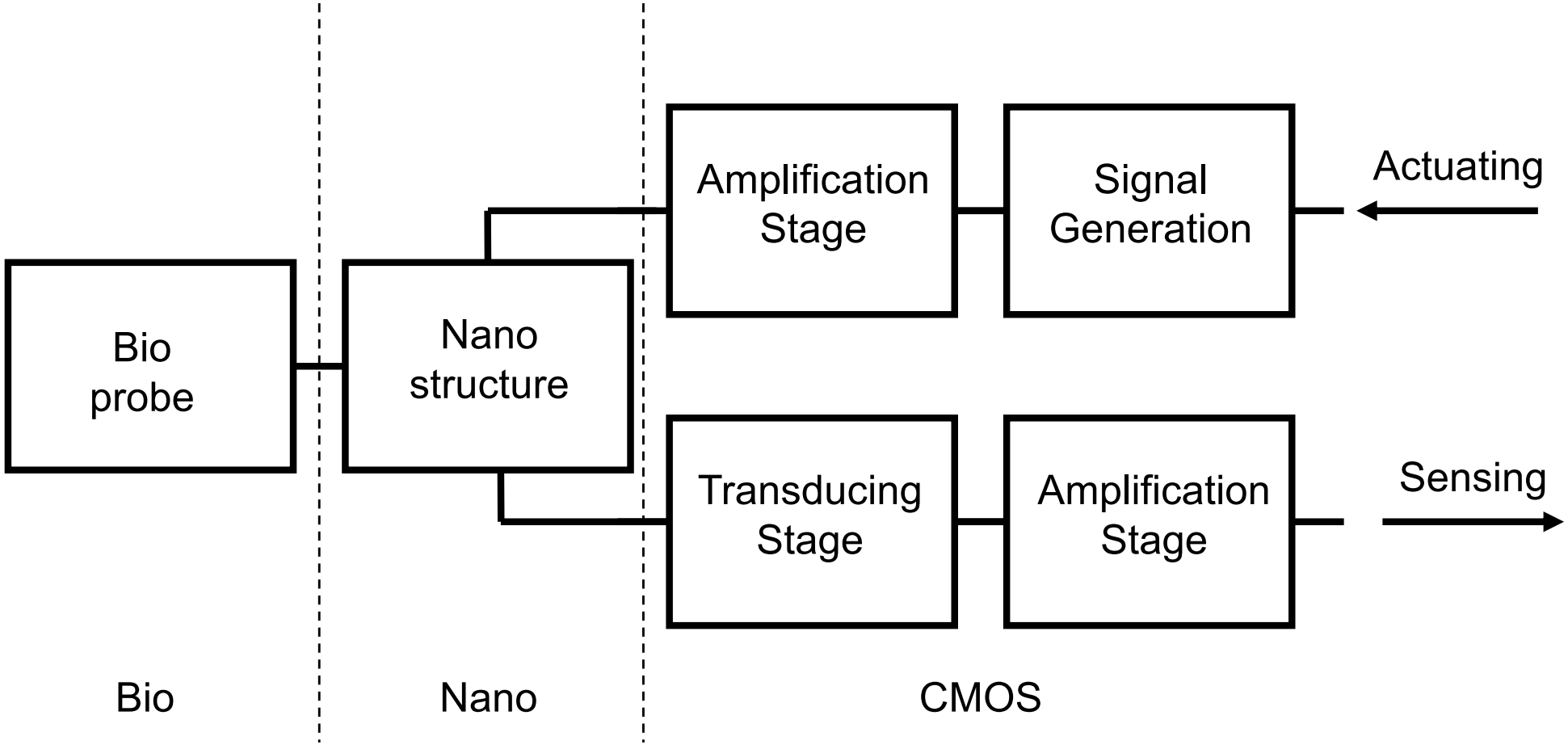
New Approach

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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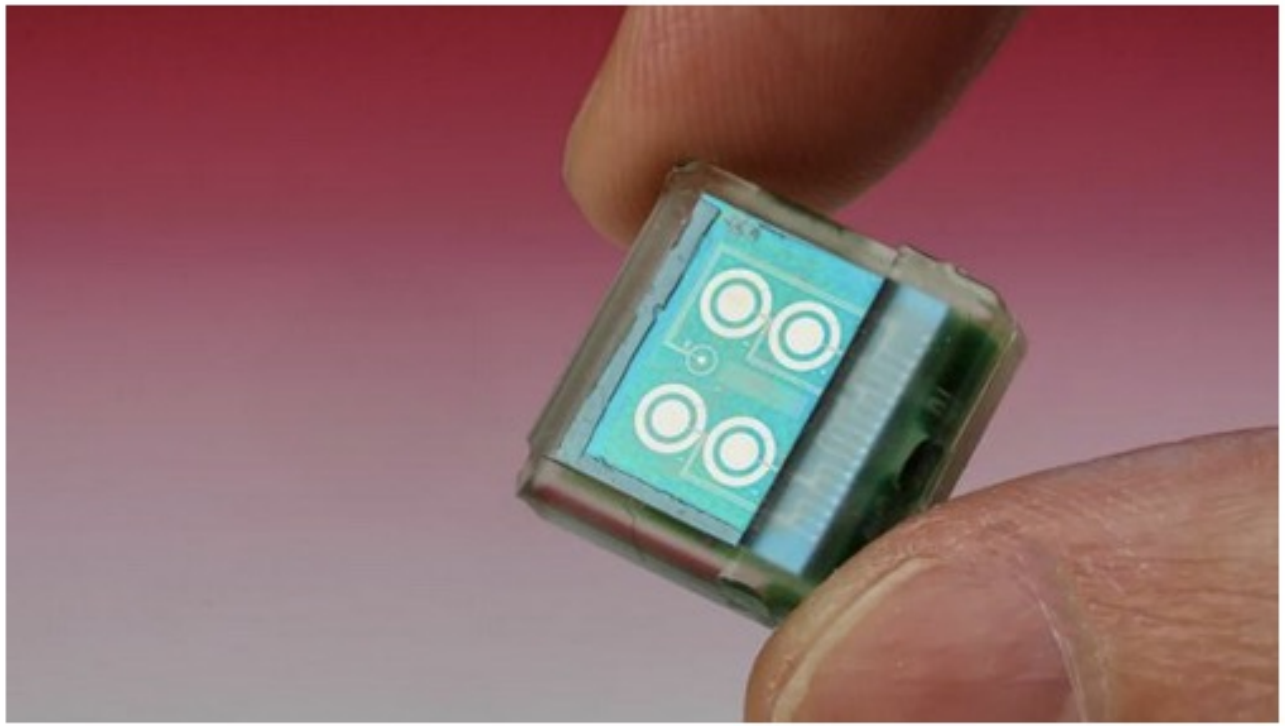
A subcutaneous biosensor chip to revolutionize tomorrow's medicine

May 29, 2015 9:26 AM
Relaxnews



The microchip implants that let you pay with your hand

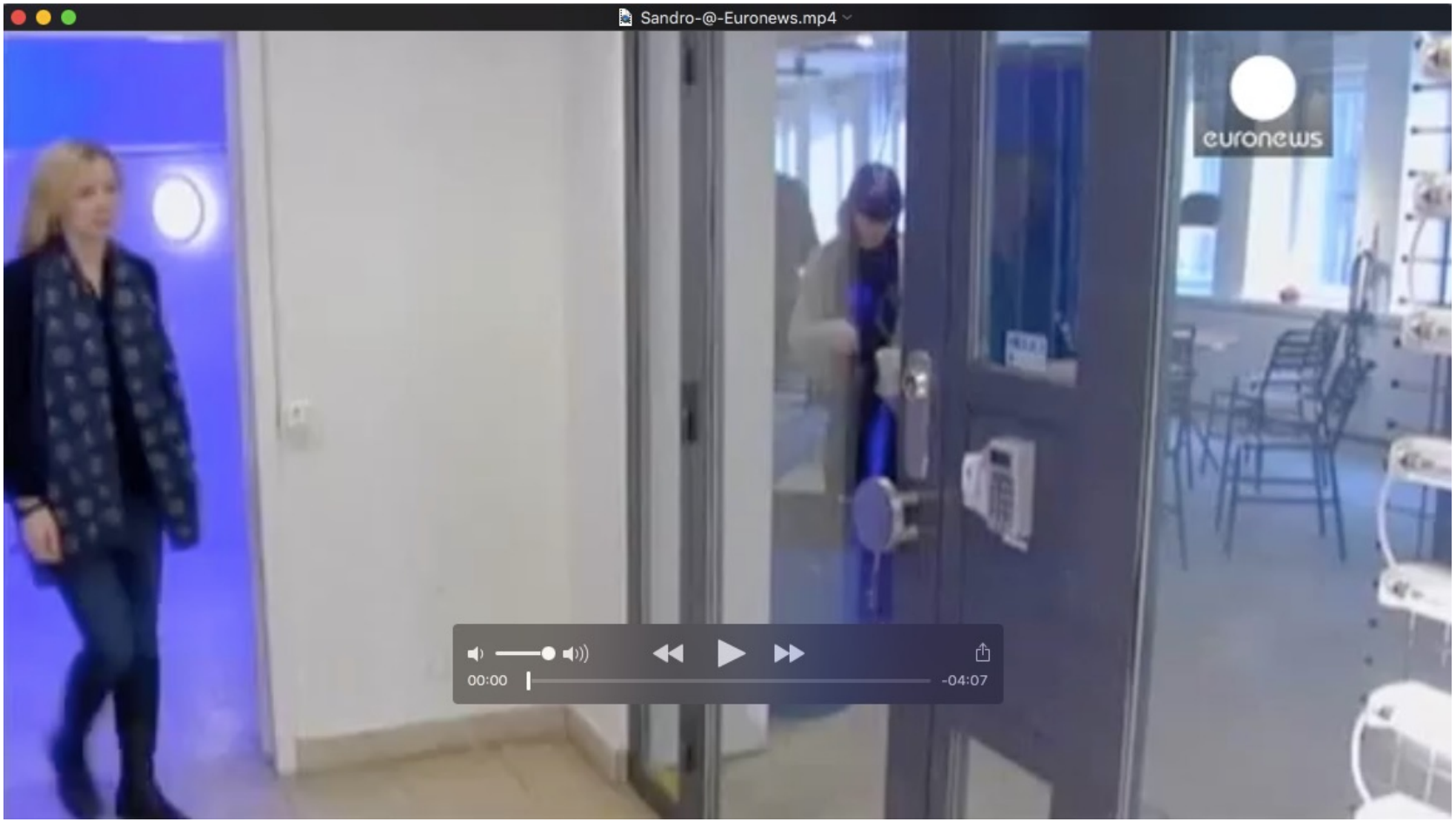
By Katherine Latham
Business reporter

April, 11th , 2022

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

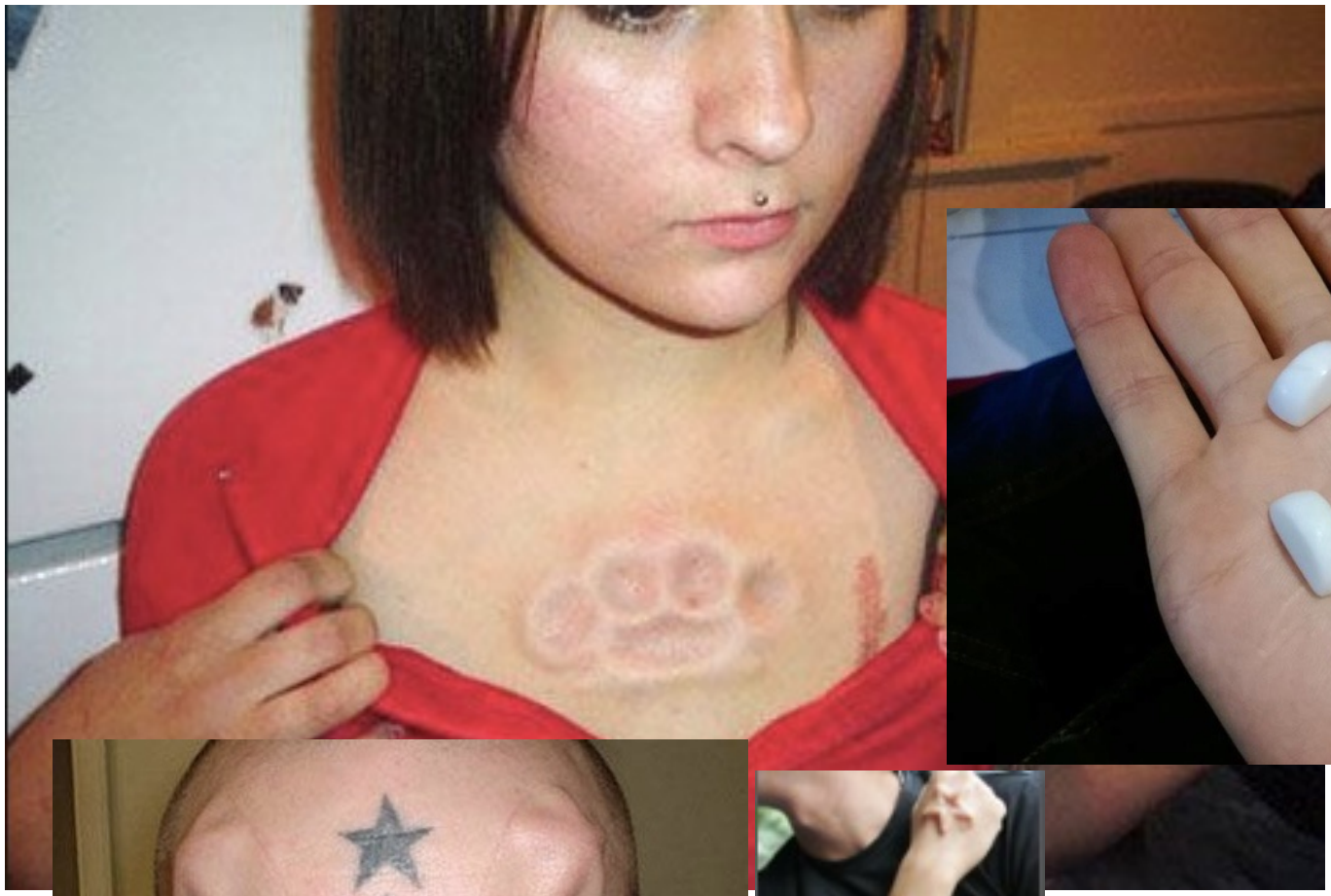
For many of us, the idea of having such a chip implanted in our body is an appalling one. **but a 2021 survey of more than 4,000 people across the UK and the European Union found that 51% would consider it.**

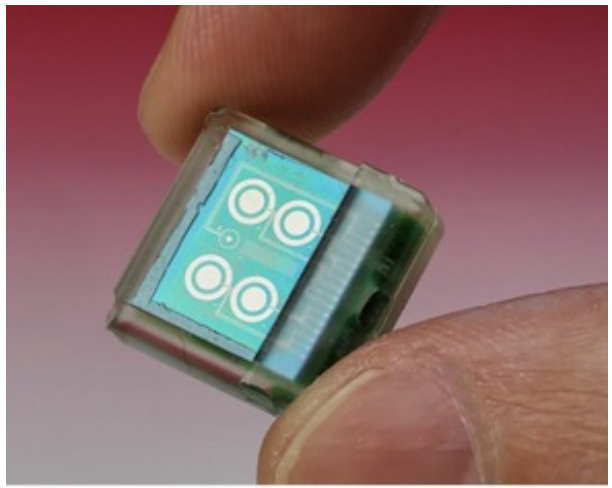
Chips under the skin?



[EuroNews, June 2015]

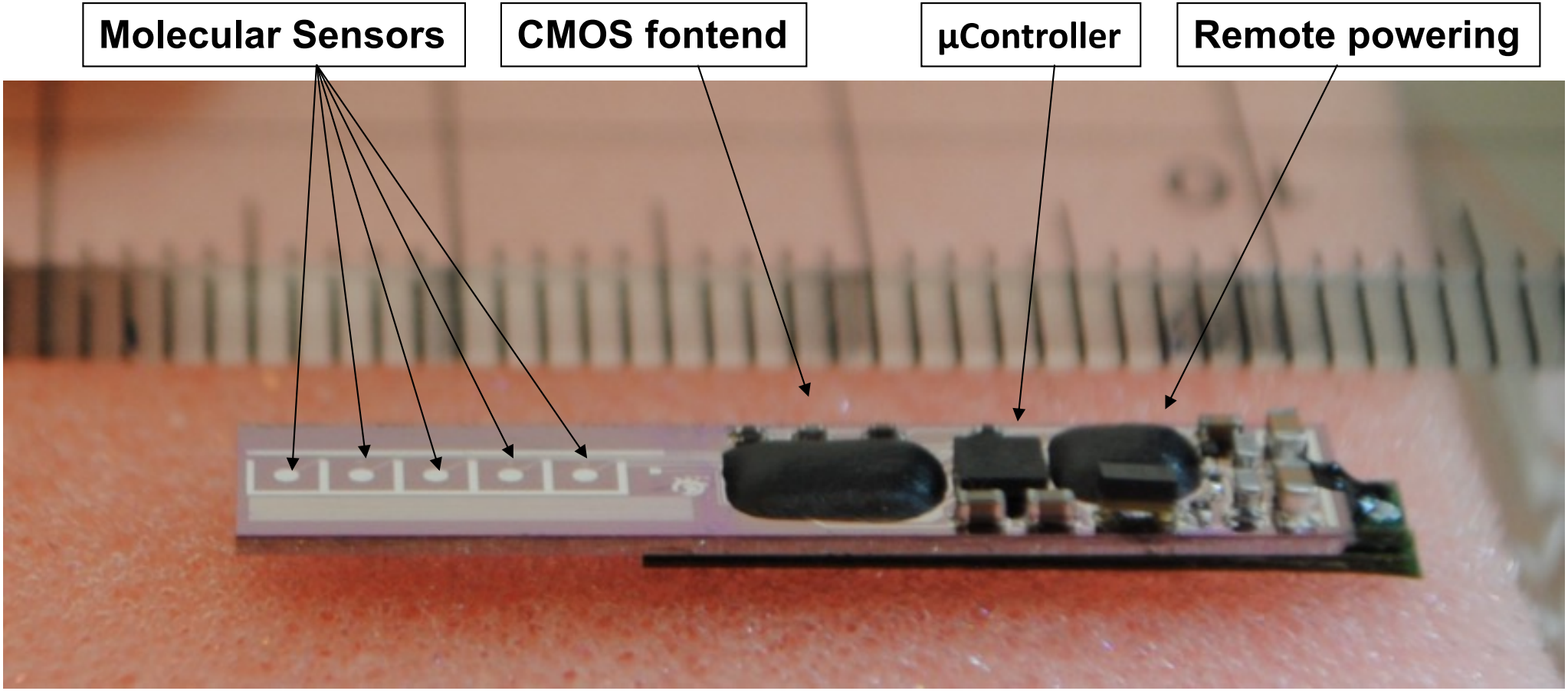
Under the skin for body sculpting





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

EPFL

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

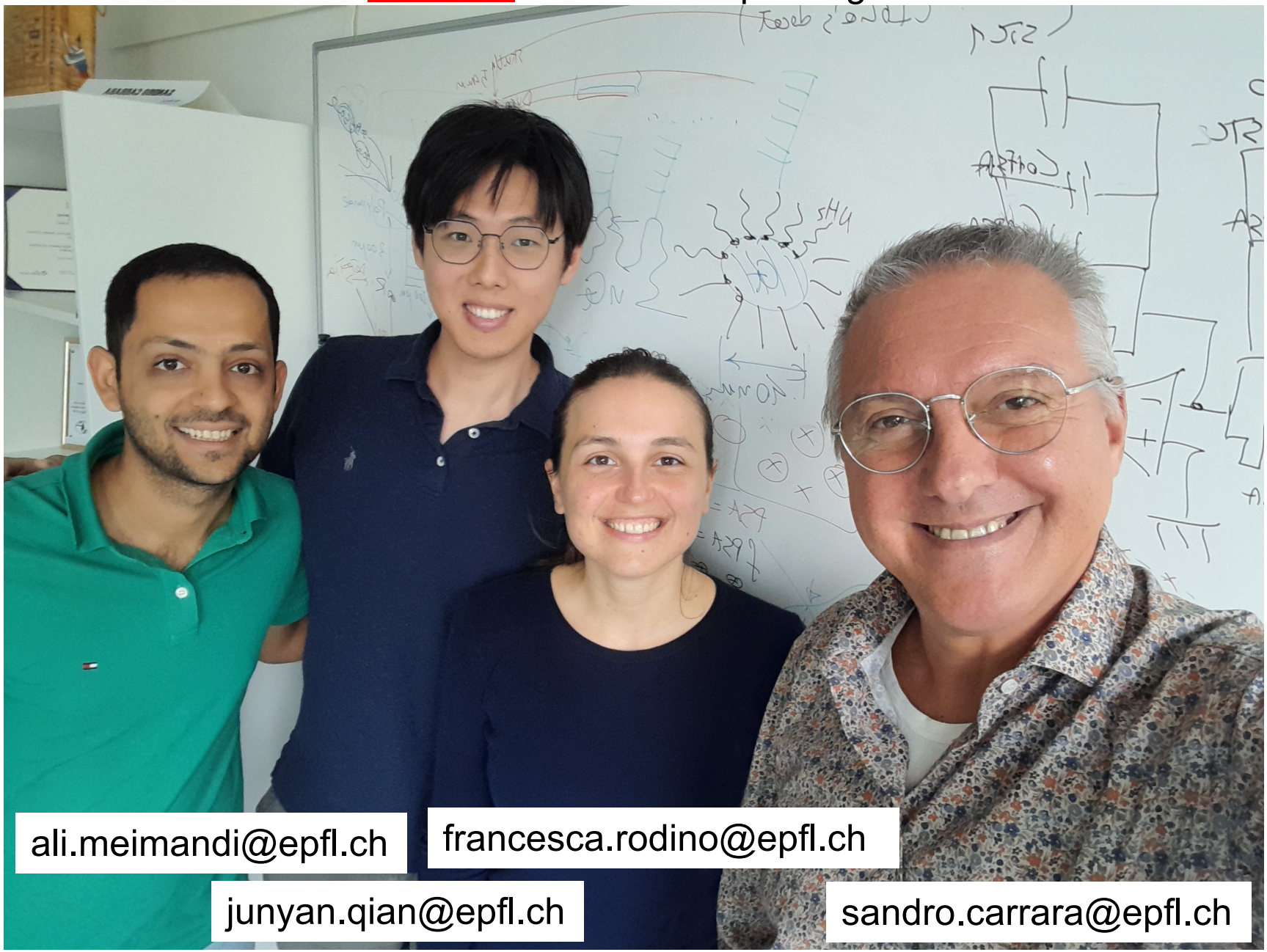
Nano

CMOS

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

Master in Electrical and Electronics Engineering

EE-517: Bio-Nano-Chip Design



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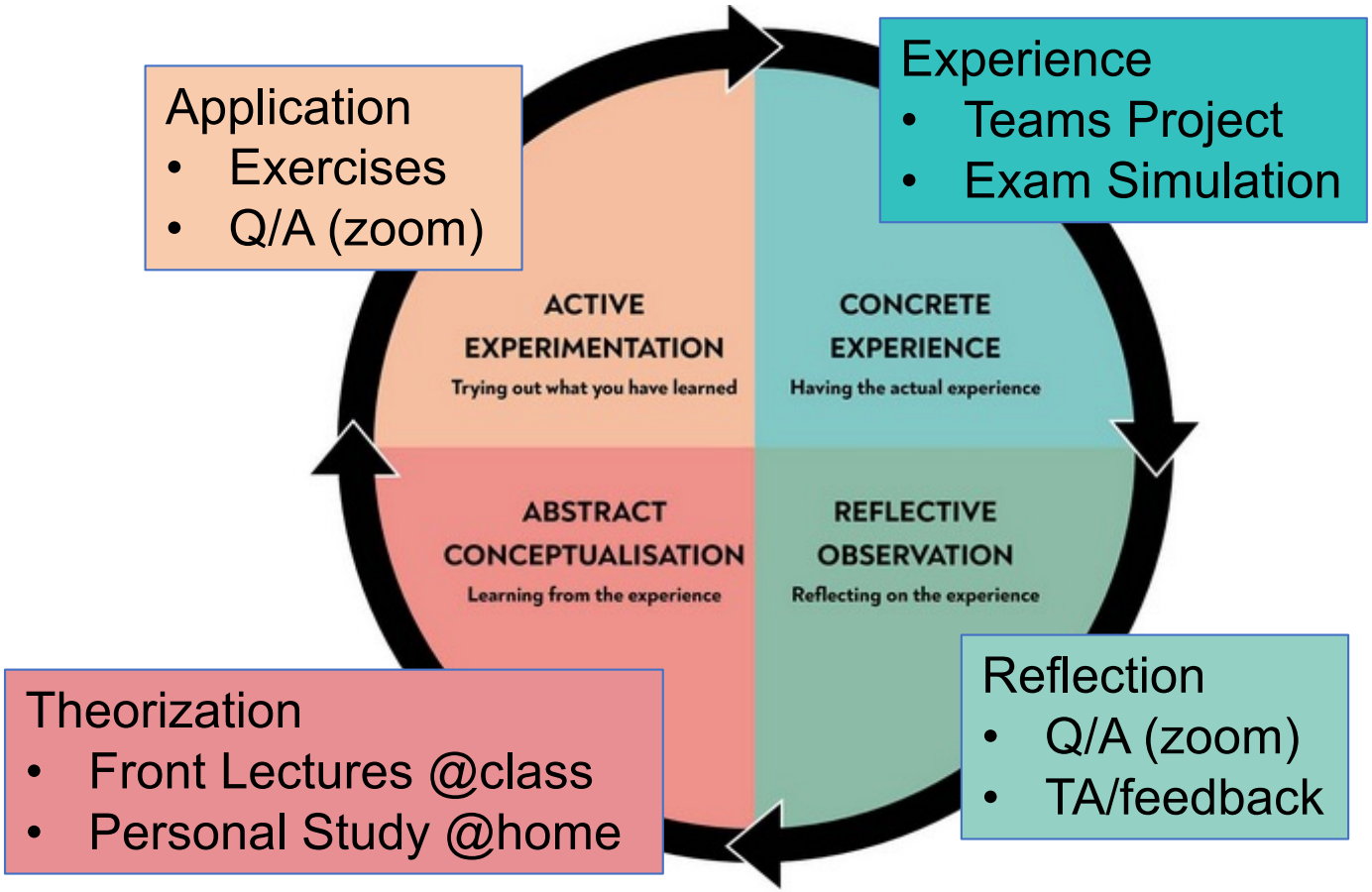
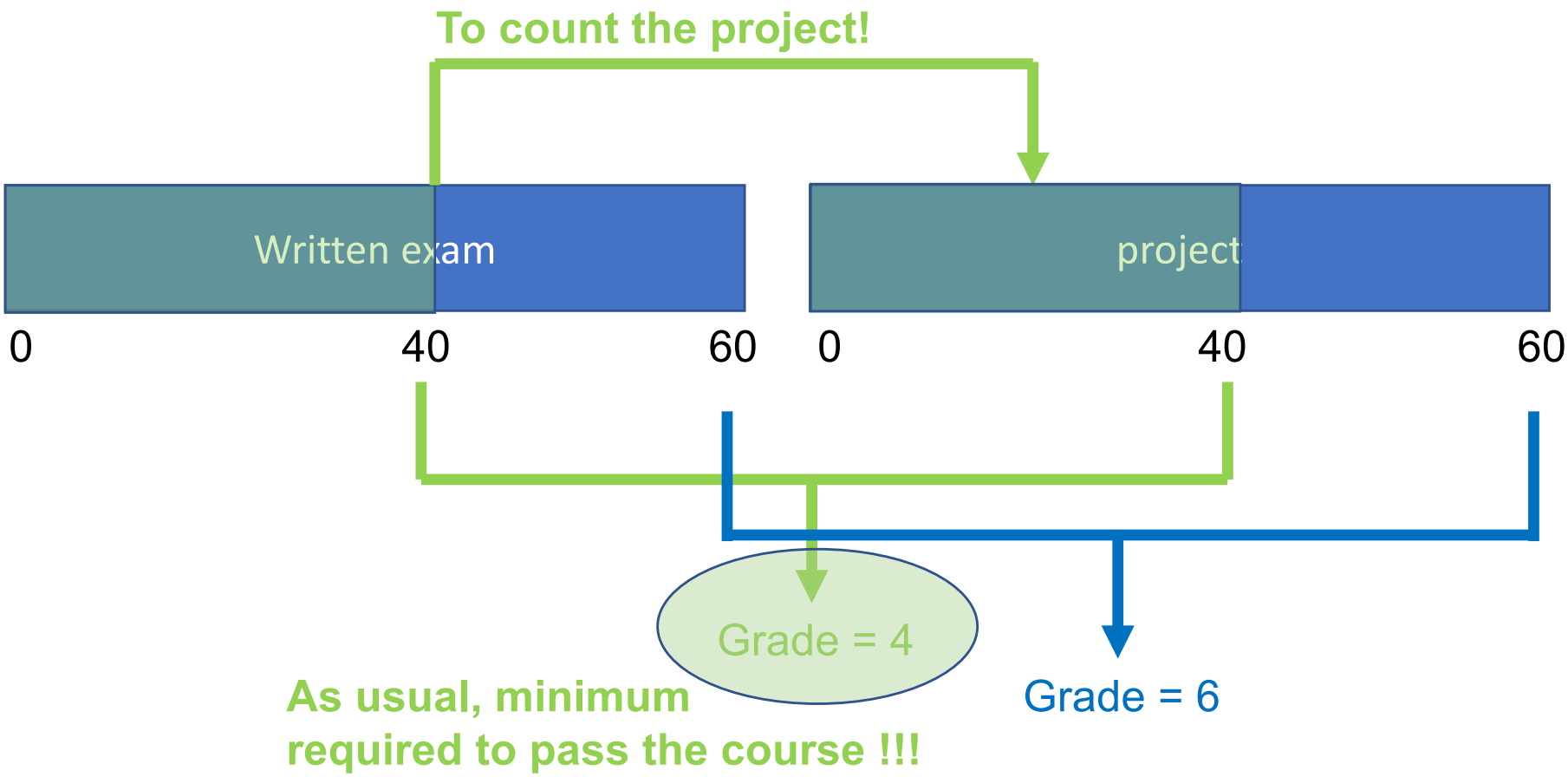


Kolb experimental learning cycle

- 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

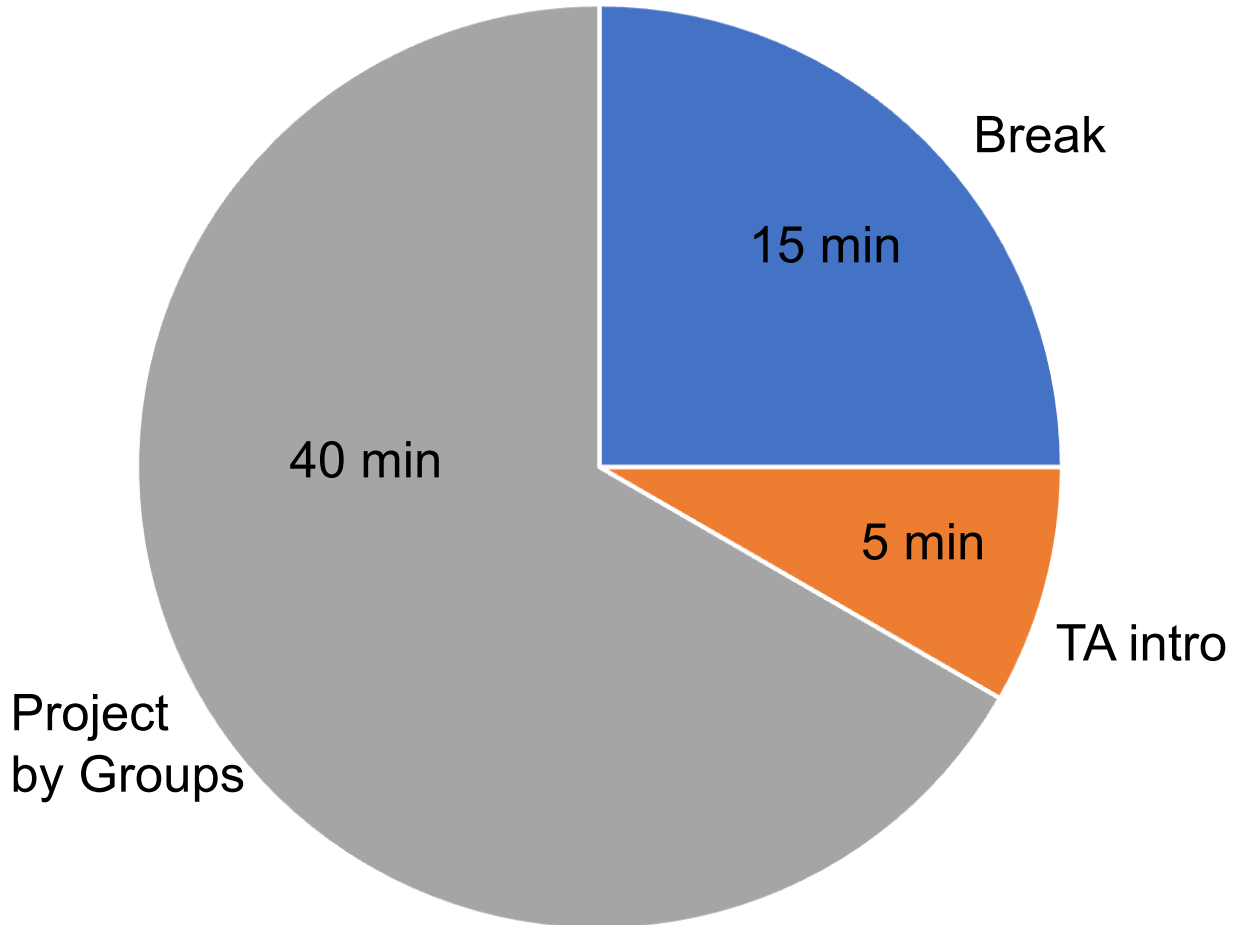


The Exam, the Project, and the Grade

Student Projects - Rules

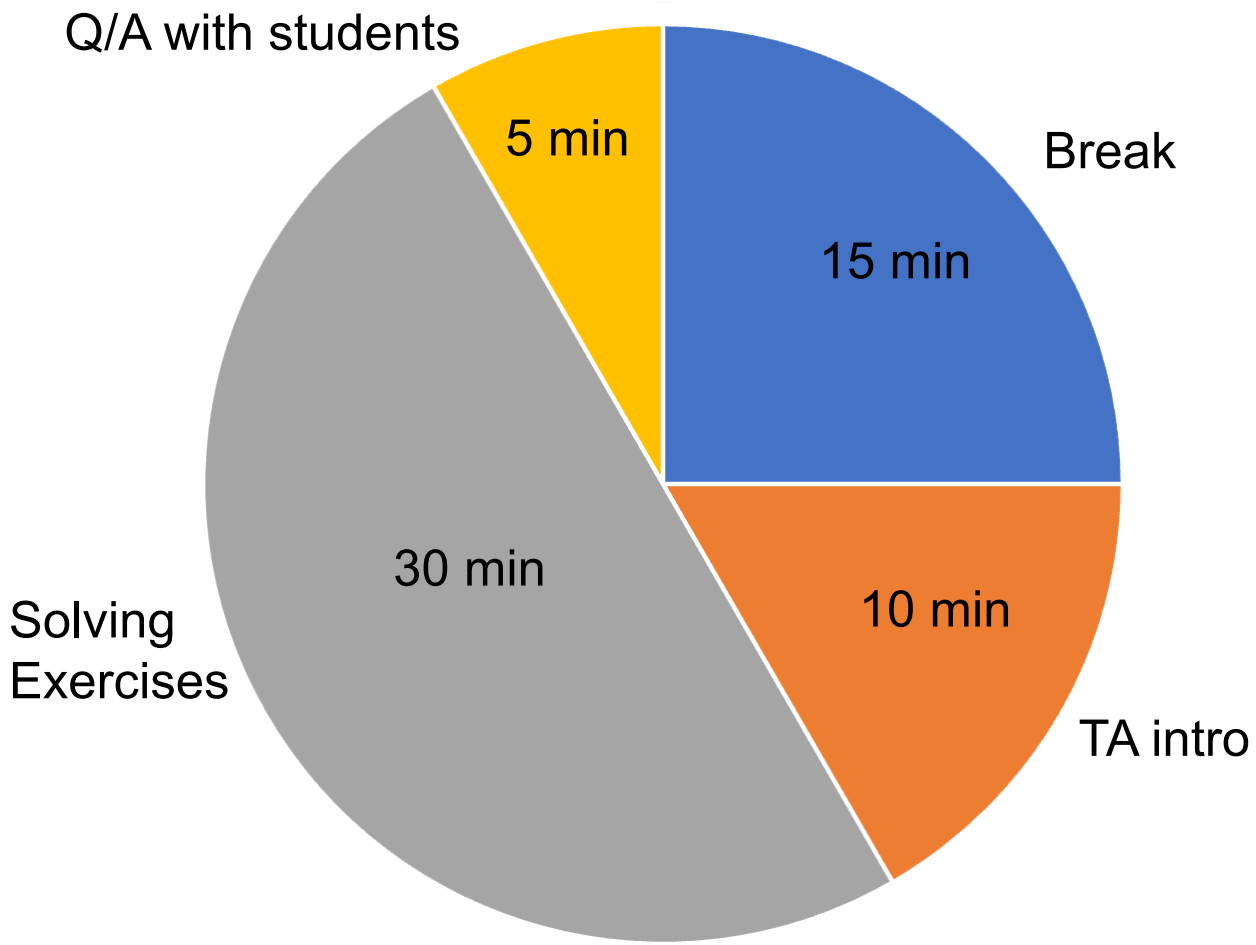
13. The **Project evaluation** is done based on the following aspects**:**
    a. **Individual proposal: 15 points (individual mark)**
    b. **Progressive report: 15 points (group mark)**
    c. **Final report: 15 points (group mark)**
    d. **Individual queries during the sessions: 15 points (individual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

EE-517: Bio-Nano-Chip Design



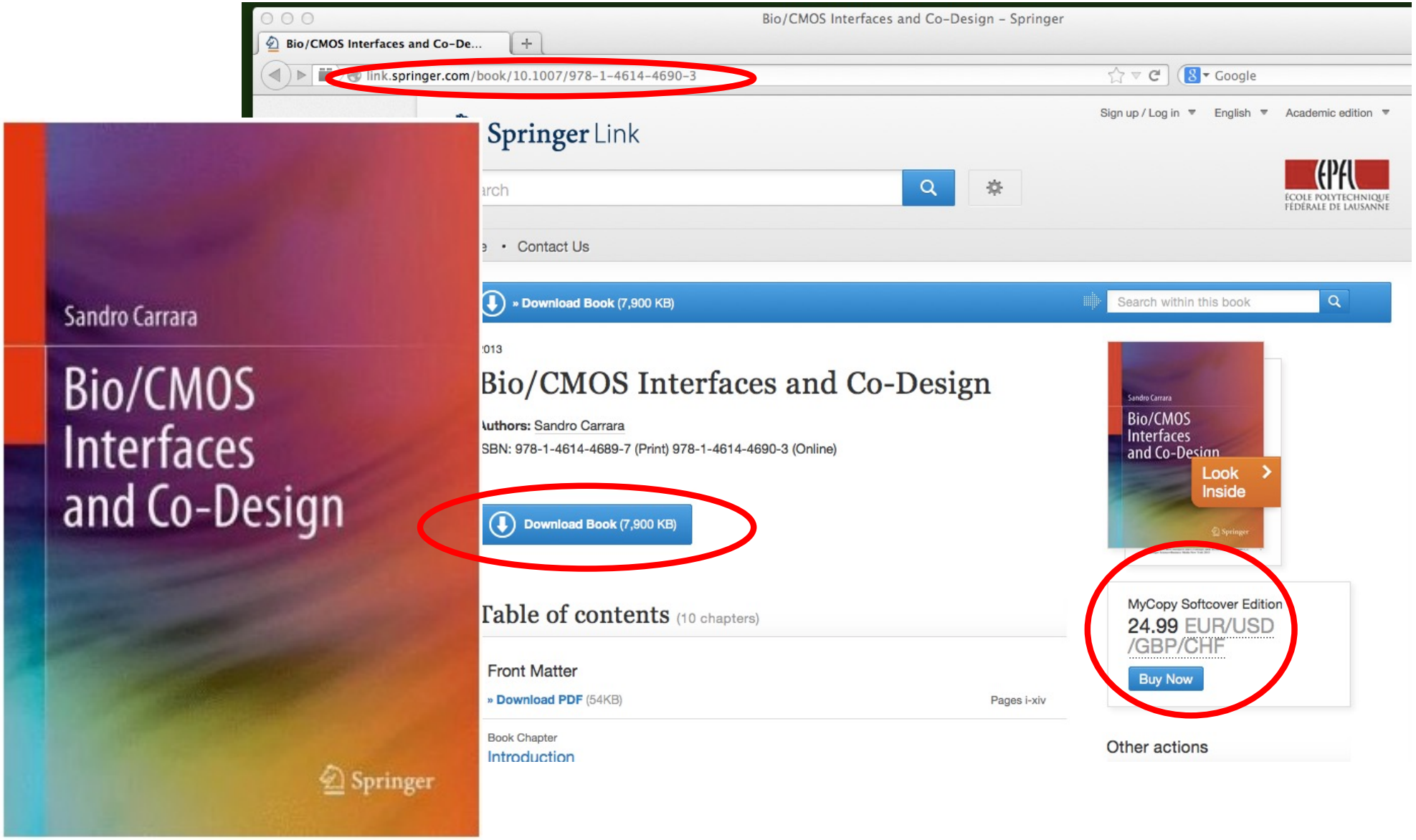
3rd hour every week

EE-517: Bio-Nano-Chip Design

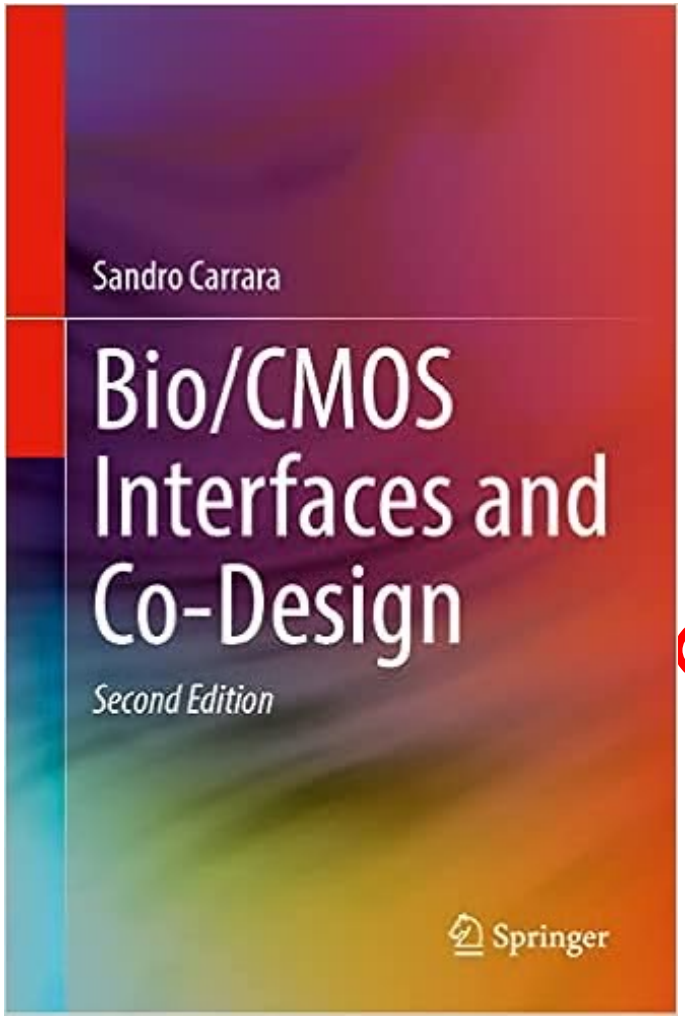


4th hour every week

The Course Textbook



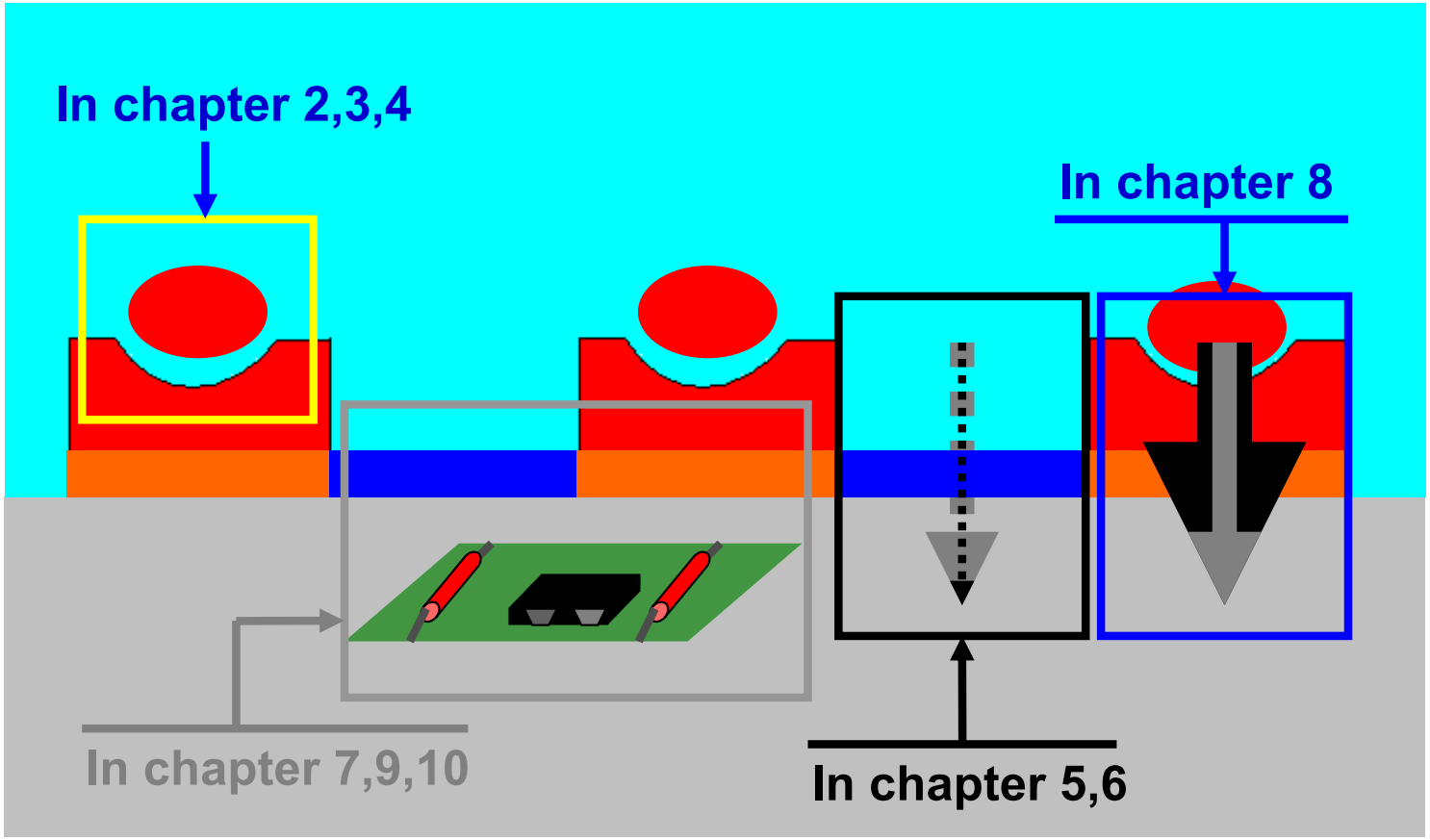
The Course Textbook: the 2nd Edition!



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.

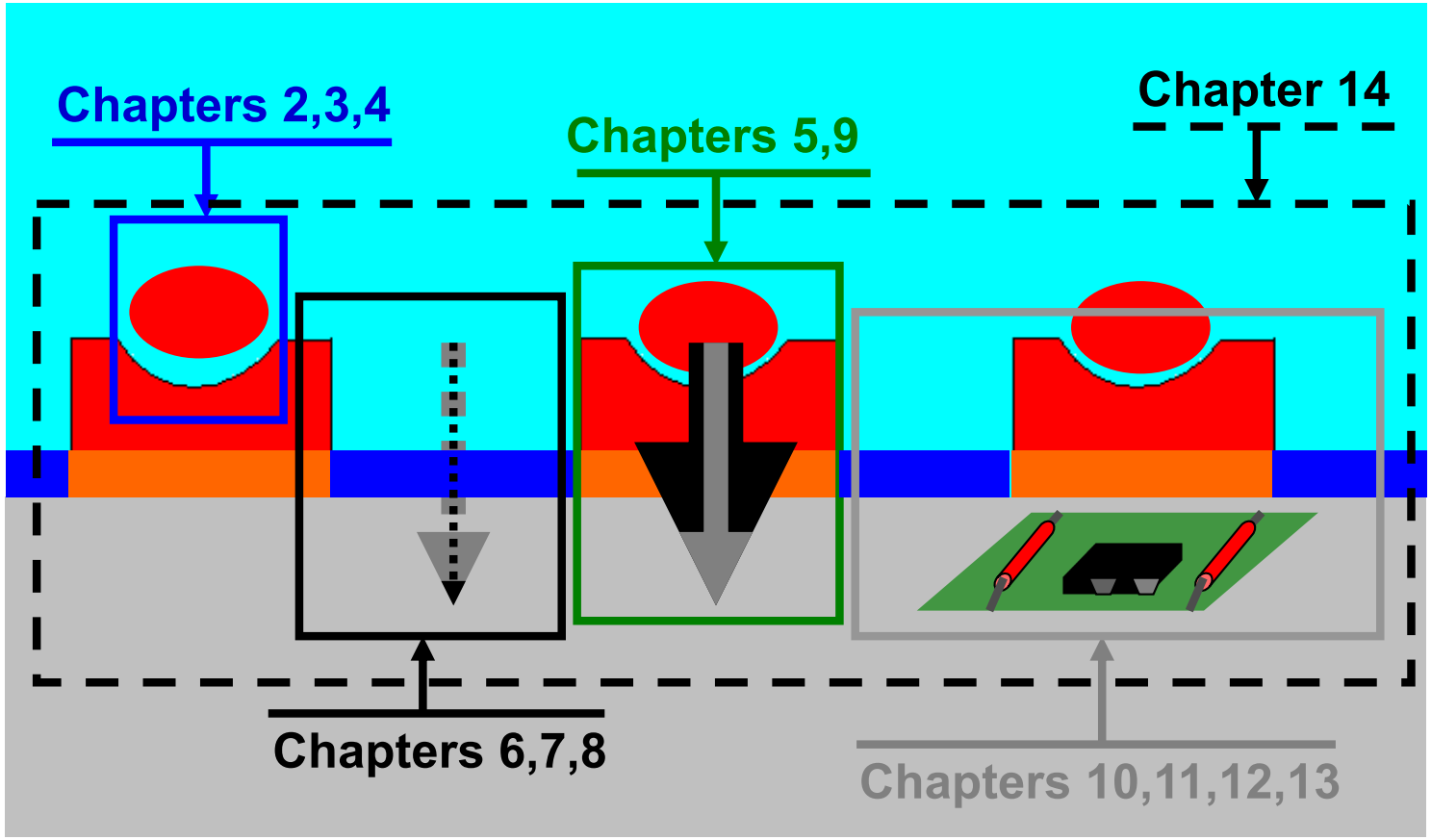
https://link.springer.com/book/10.1007/978-3-031-31832-0

Bio/CMOS interface book (1st Edition)



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

Bio/CMOS interface book (2nd Edition)



Lecture #1

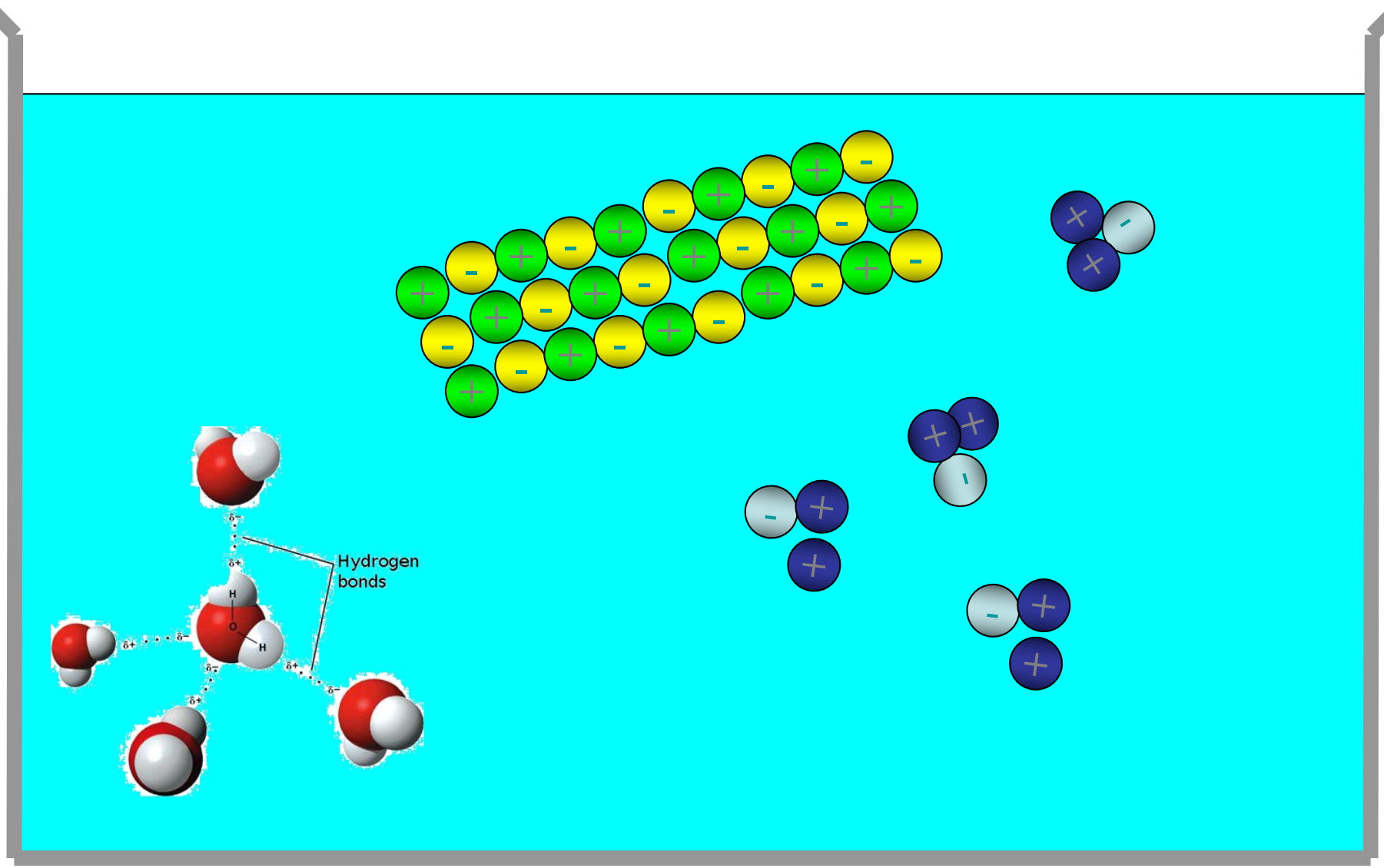
Conductive Solutions

Lecture Outline

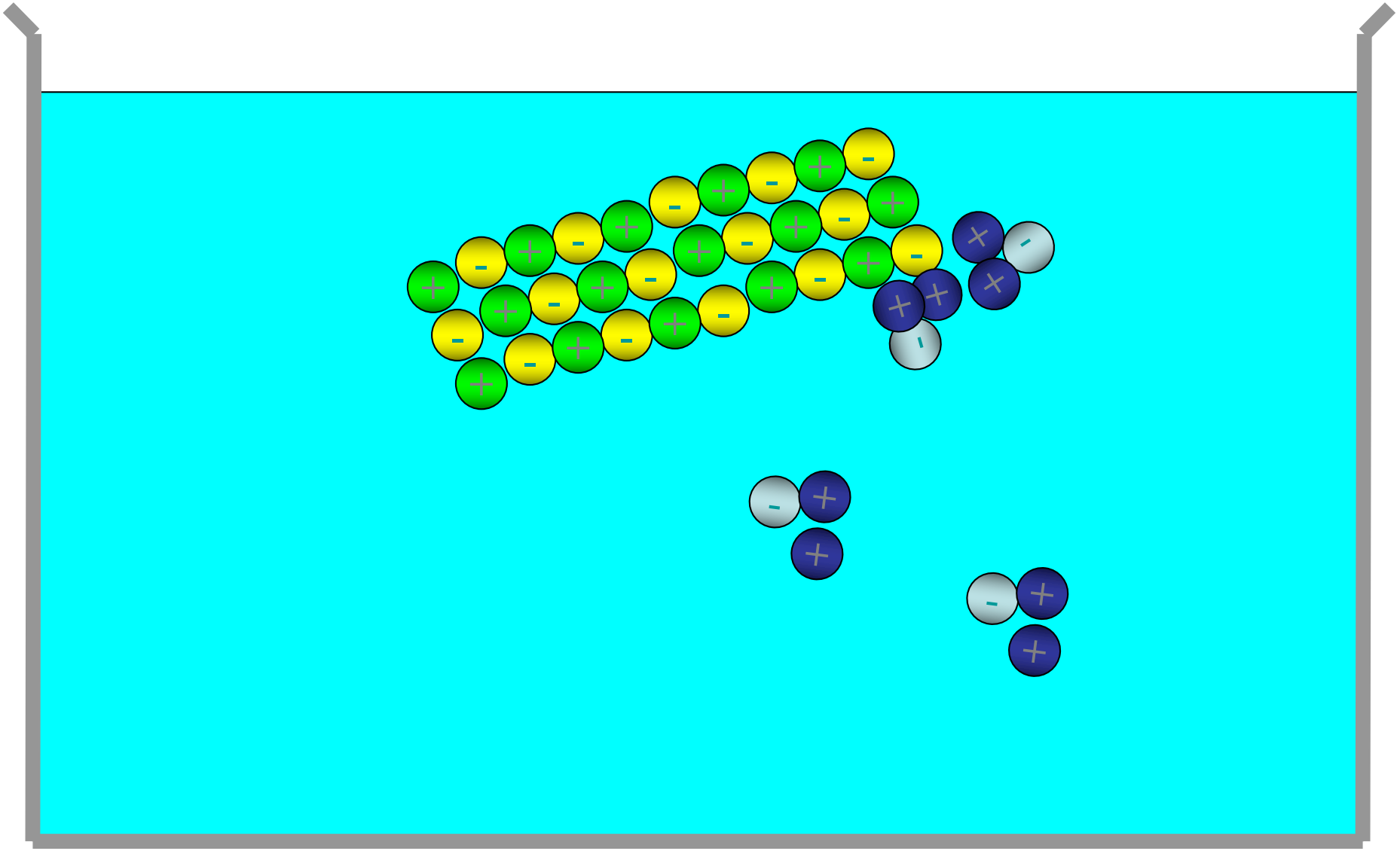
(Book Bio/CMOS: Chapter' paragraphs § 2.1-2.7 and § 2.14-15)

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

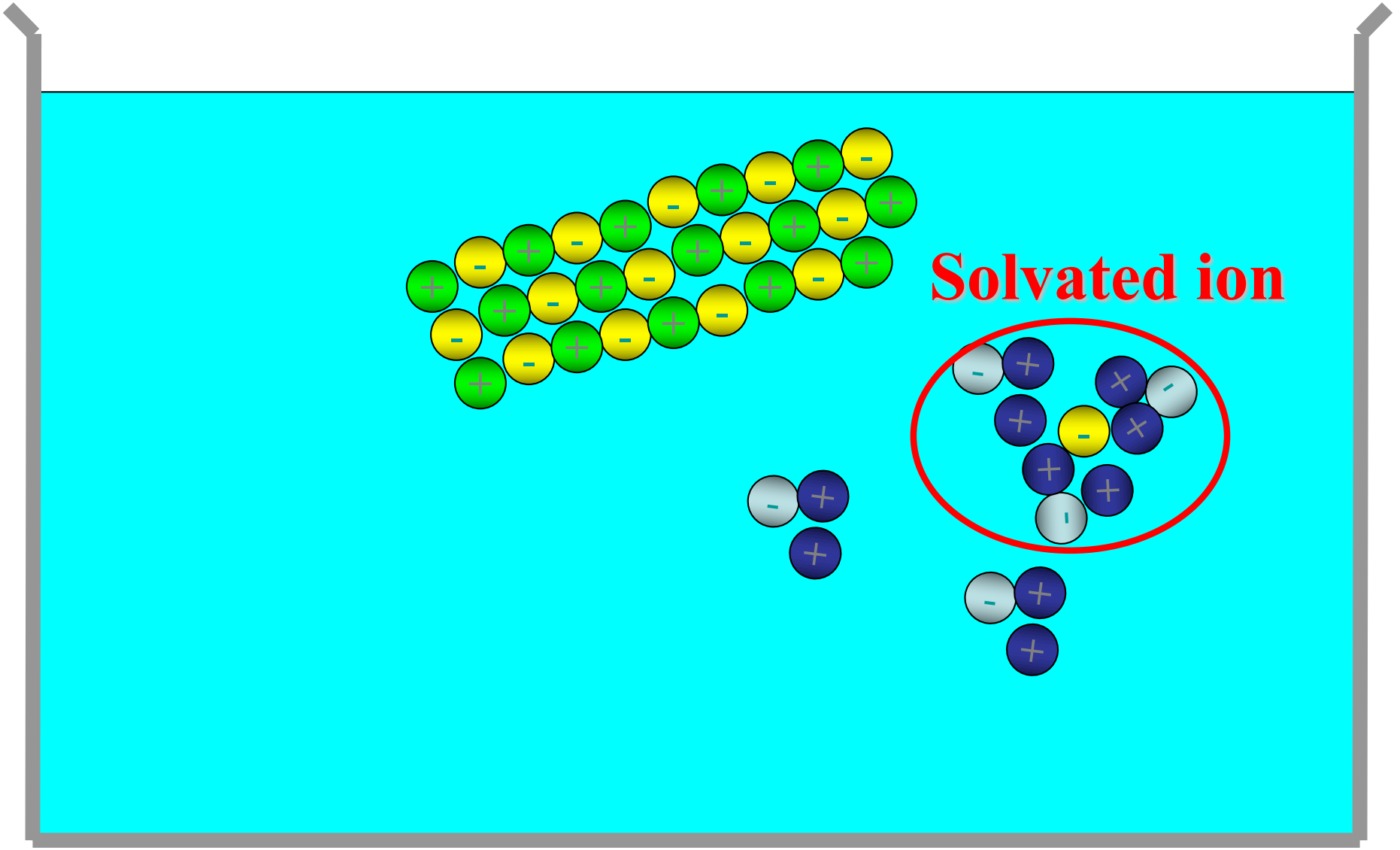
Liquid Solution: Ionic Solid in liquid



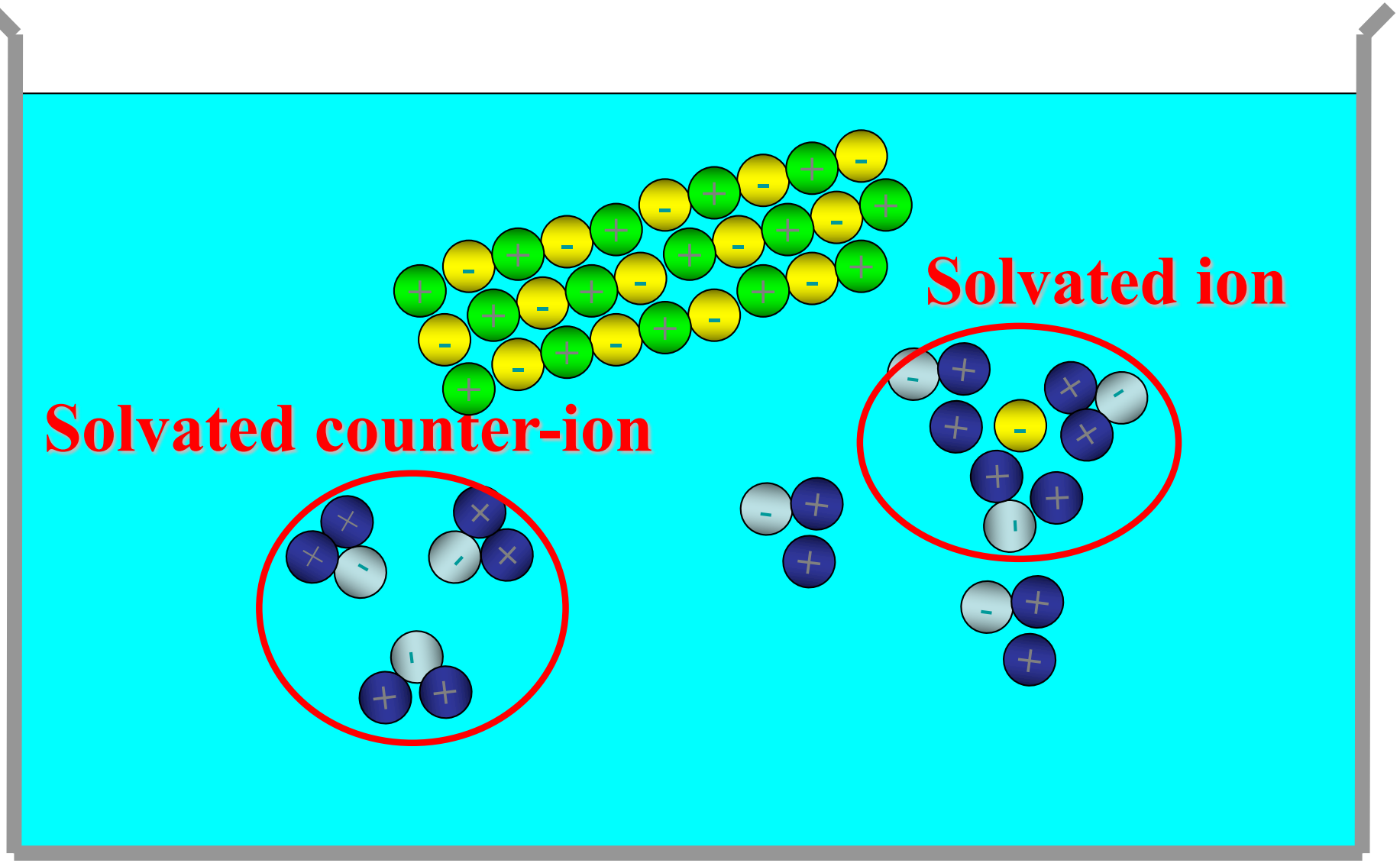
Liquid Solution: Ionic Solid in liquid



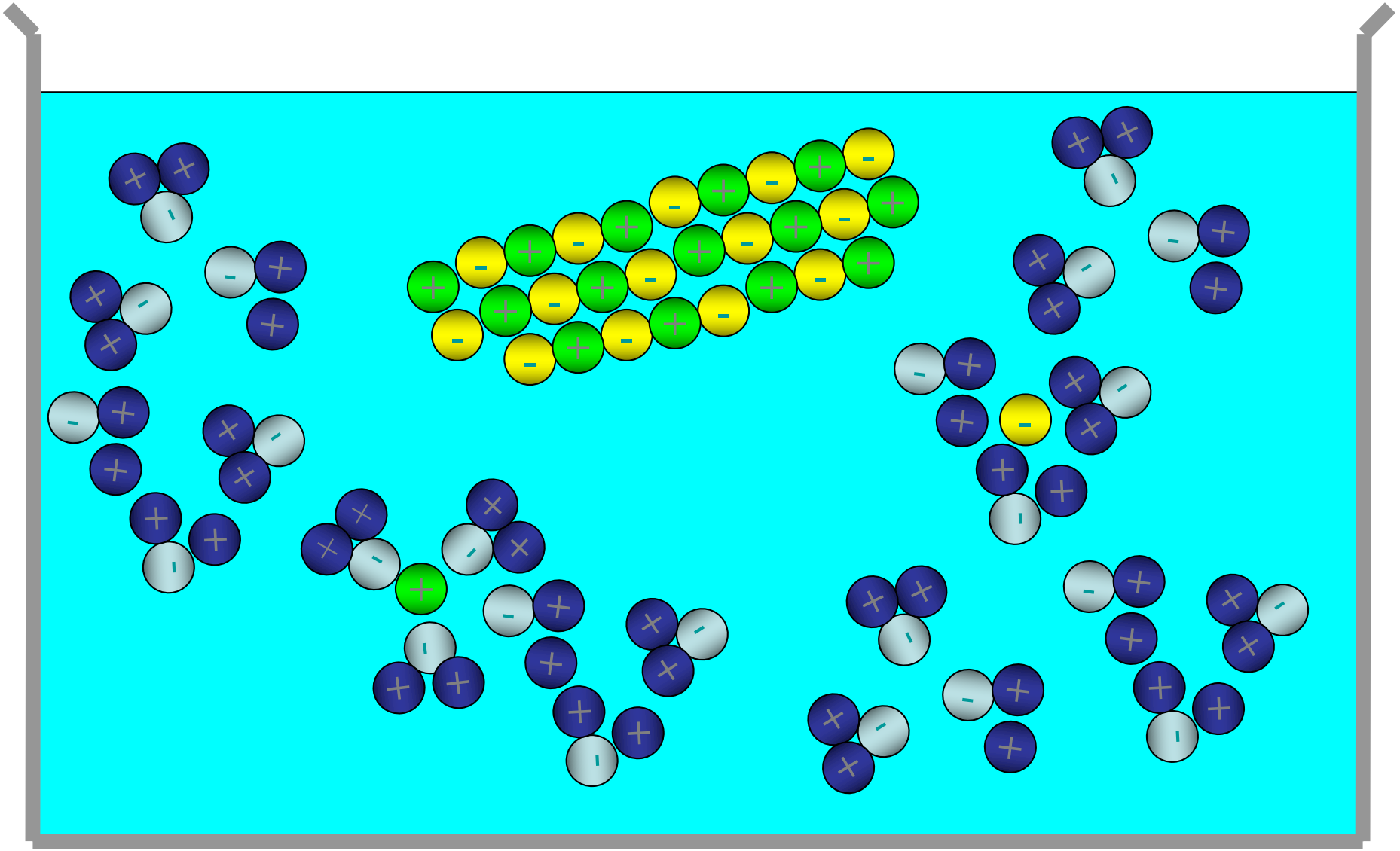
Liquid Solution: Ionic Solid in liquid



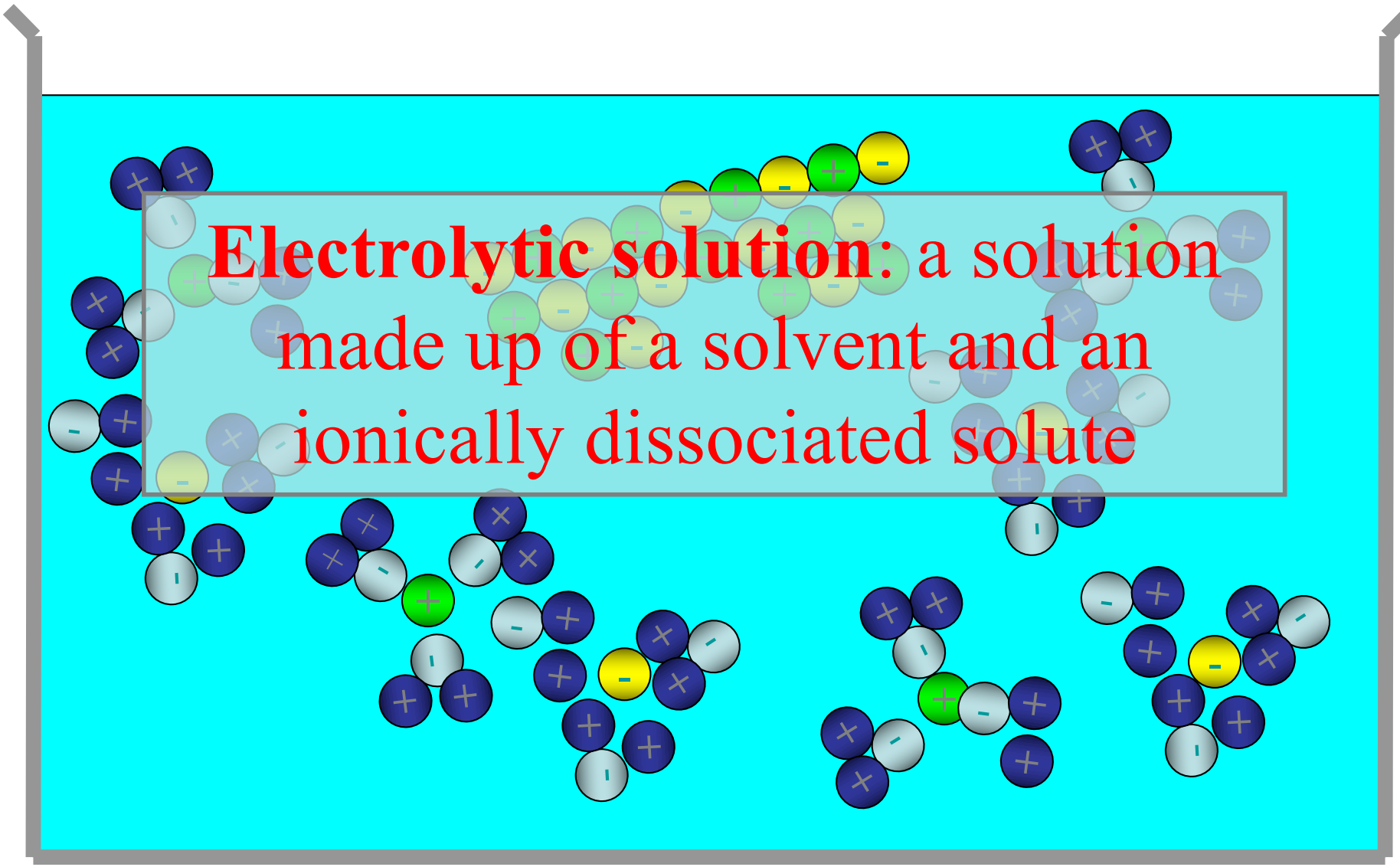
Liquid Solution: Ionic Solid in liquid



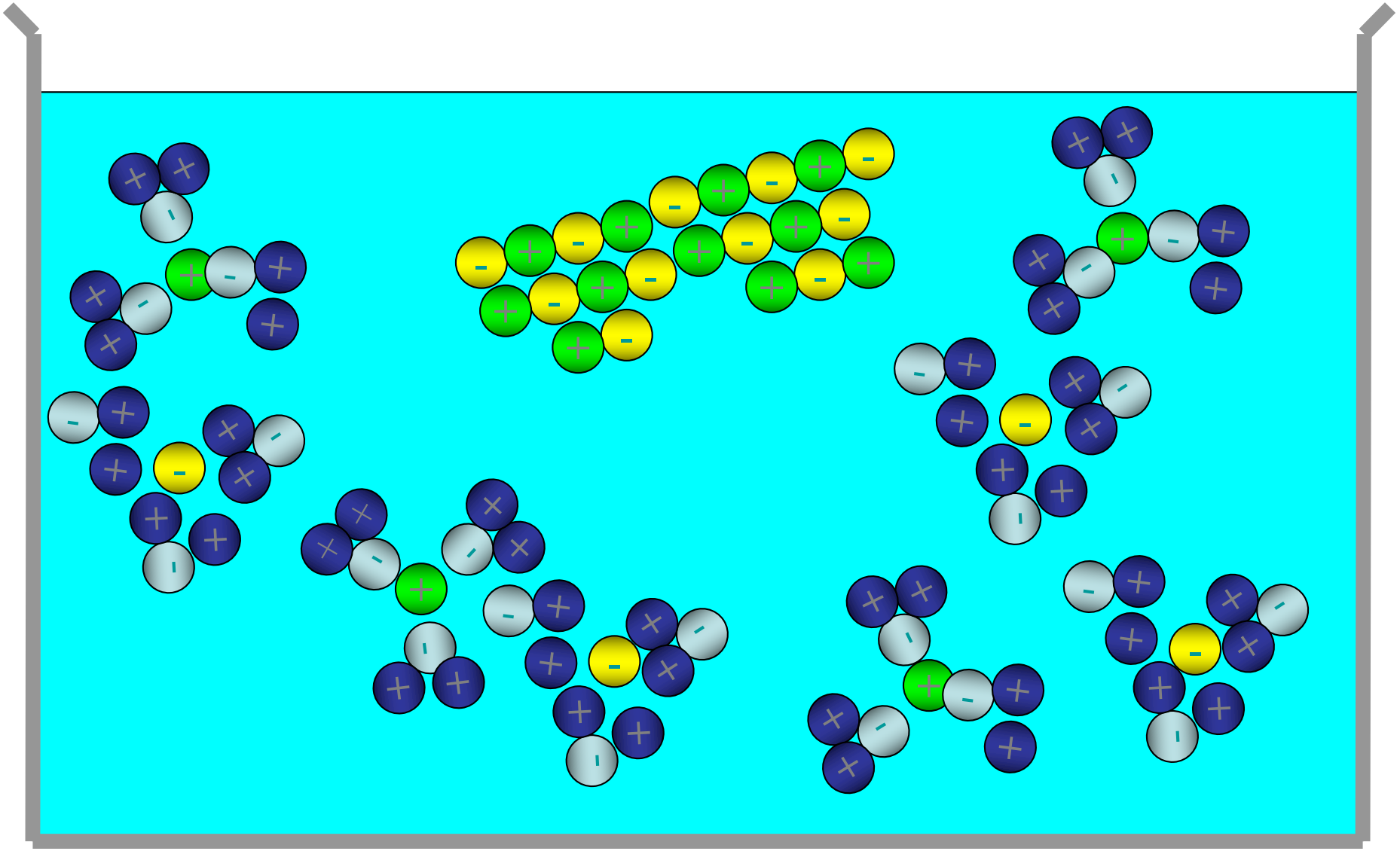
Liquid Solution: Ionic Solid in liquid



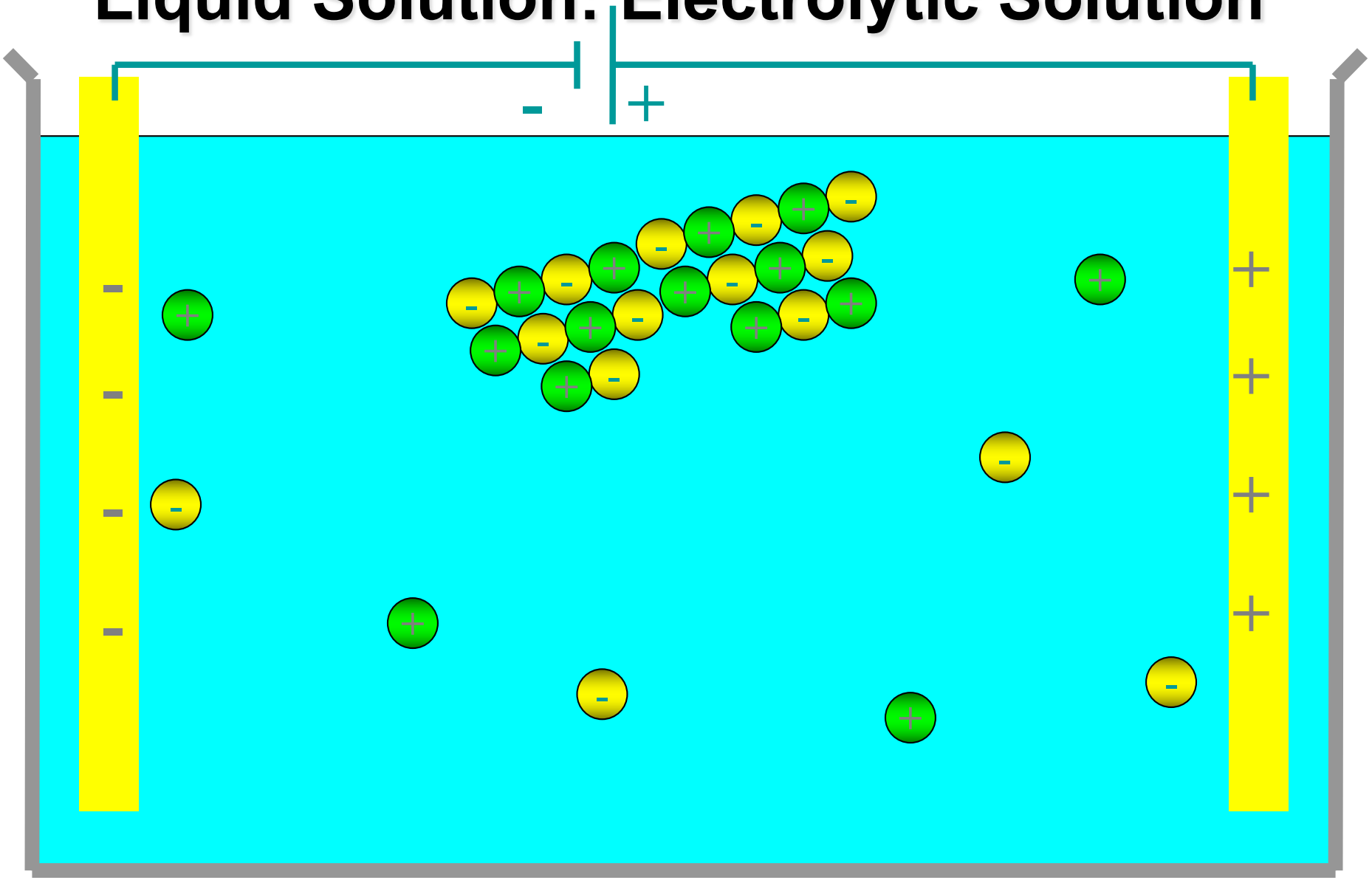
Liquid Solution: Ionic Solid in liquid



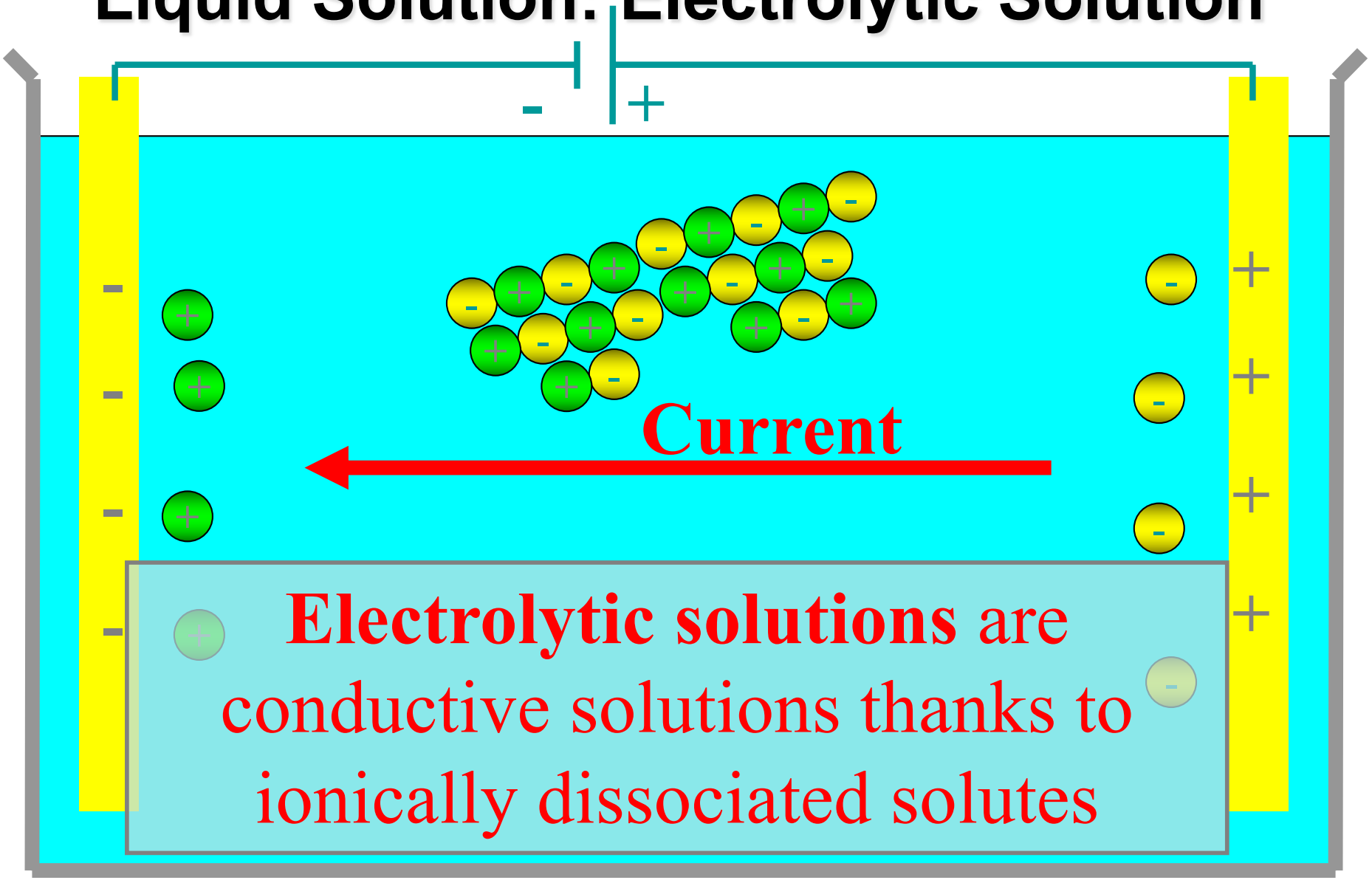
Liquid Solution: Electrolytic Solution



Liquid Solution: Electrolytic Solution



Liquid Solution: Electrolytic Solution



Ionic Solution of HCl

Dissociation of Chloride Acid

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

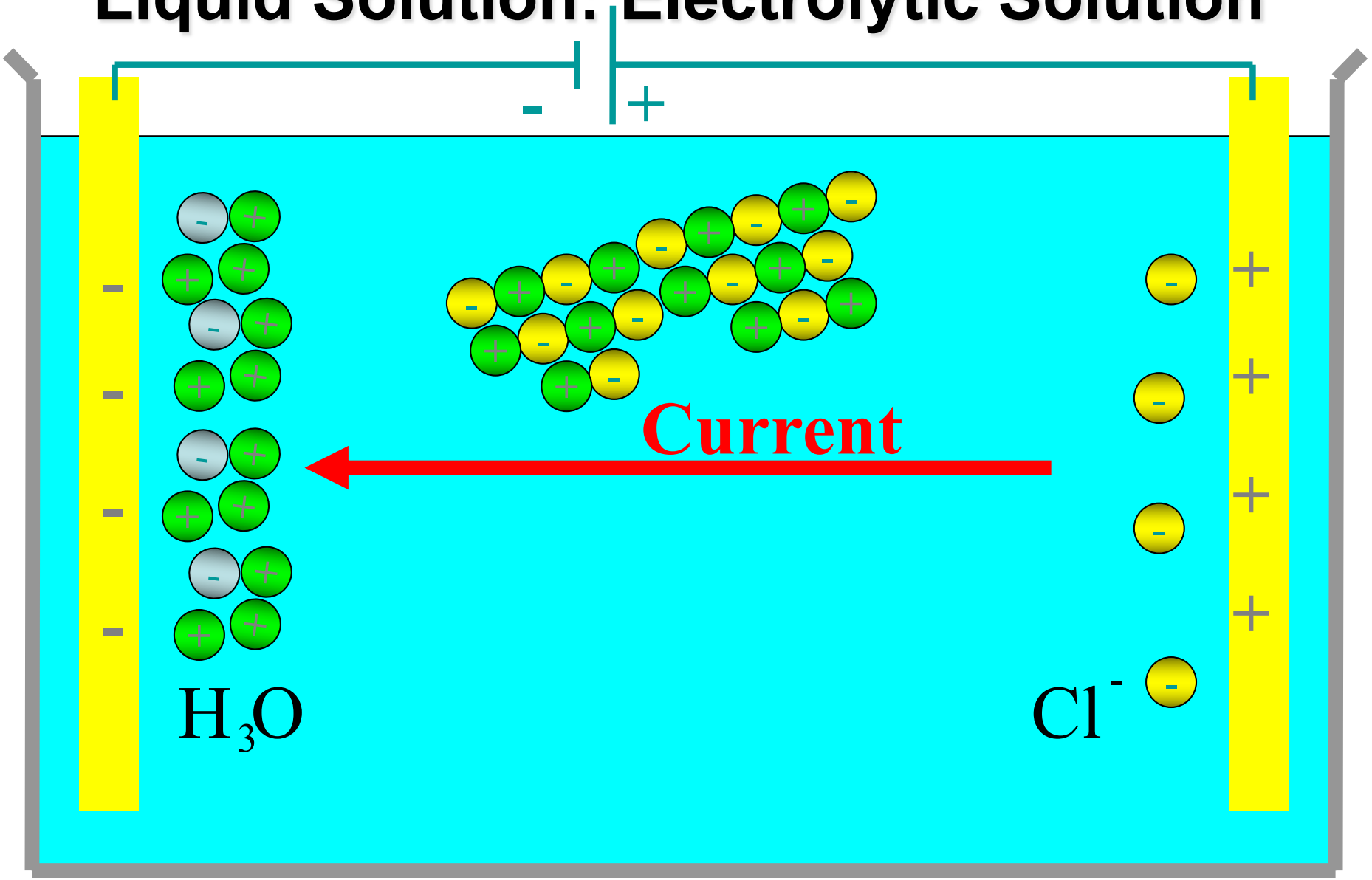
$$2H_3O^+ + 2e^- \rightarrow 2H_2O + H_2 \uparrow$$

– Electrode (Cathode)

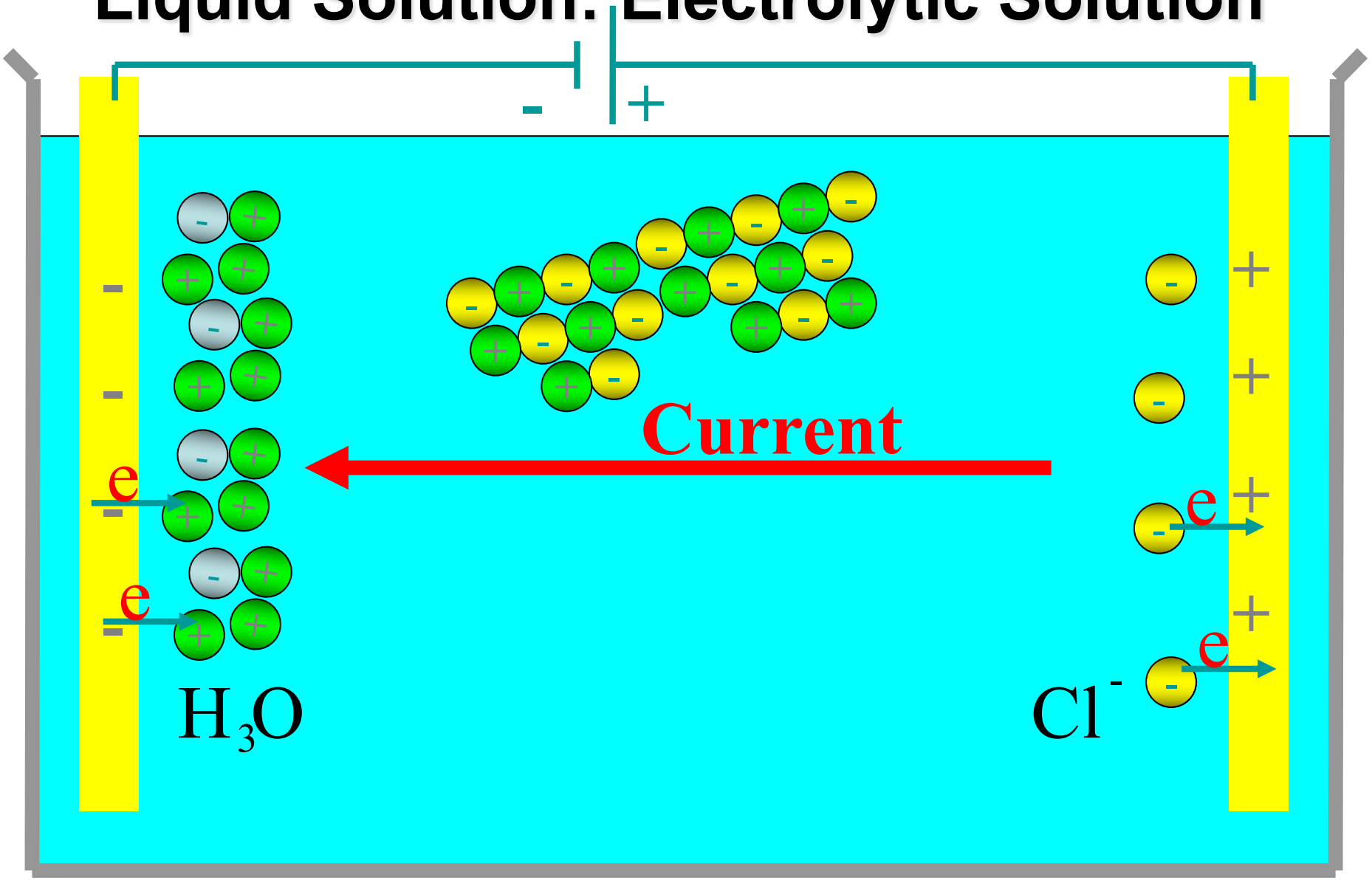
$$2Cl^- \rightarrow Cl_2 \uparrow + 2e^-$$

+ Electrode (Anode)

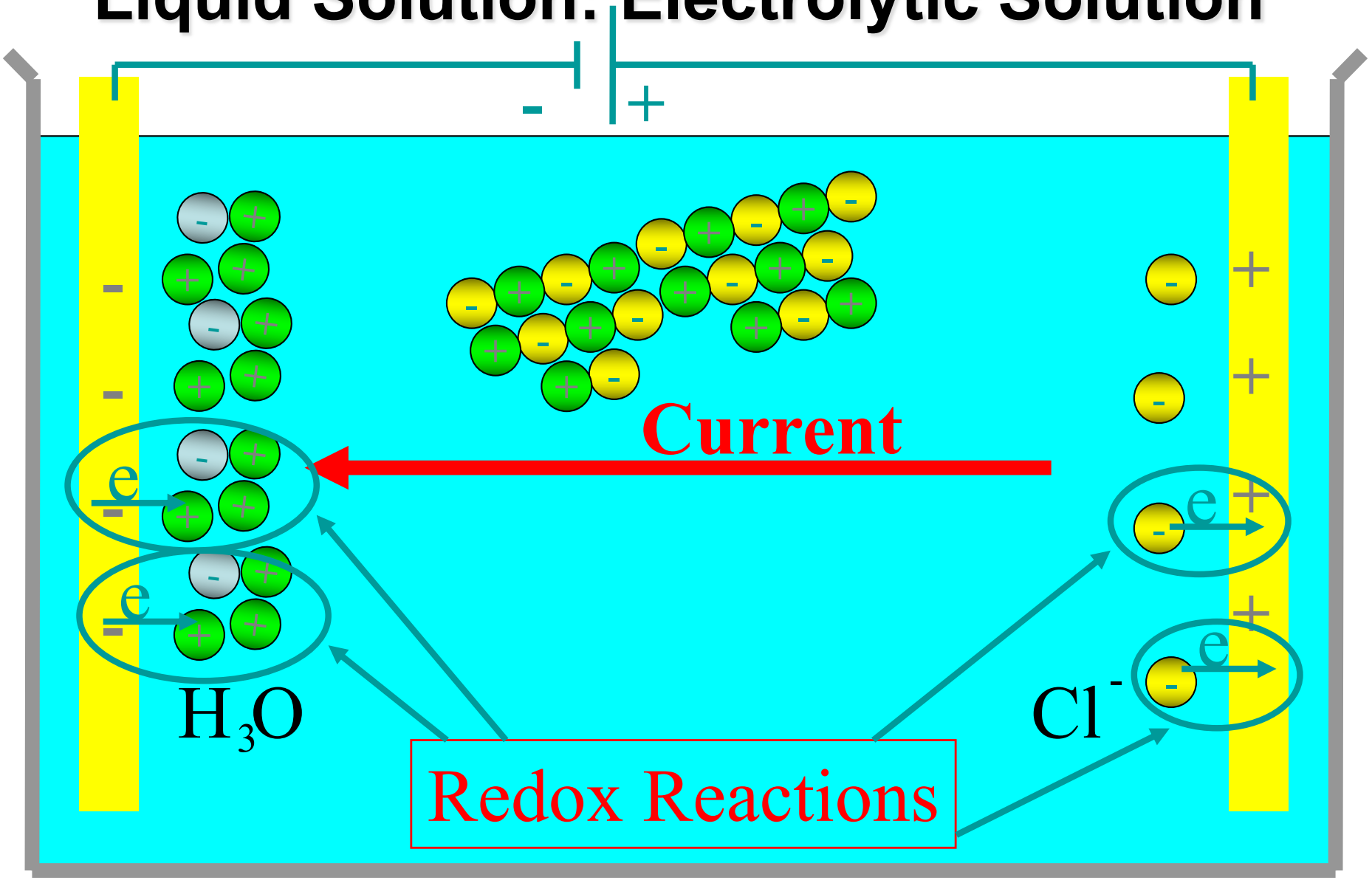
Liquid Solution: Electrolytic Solution



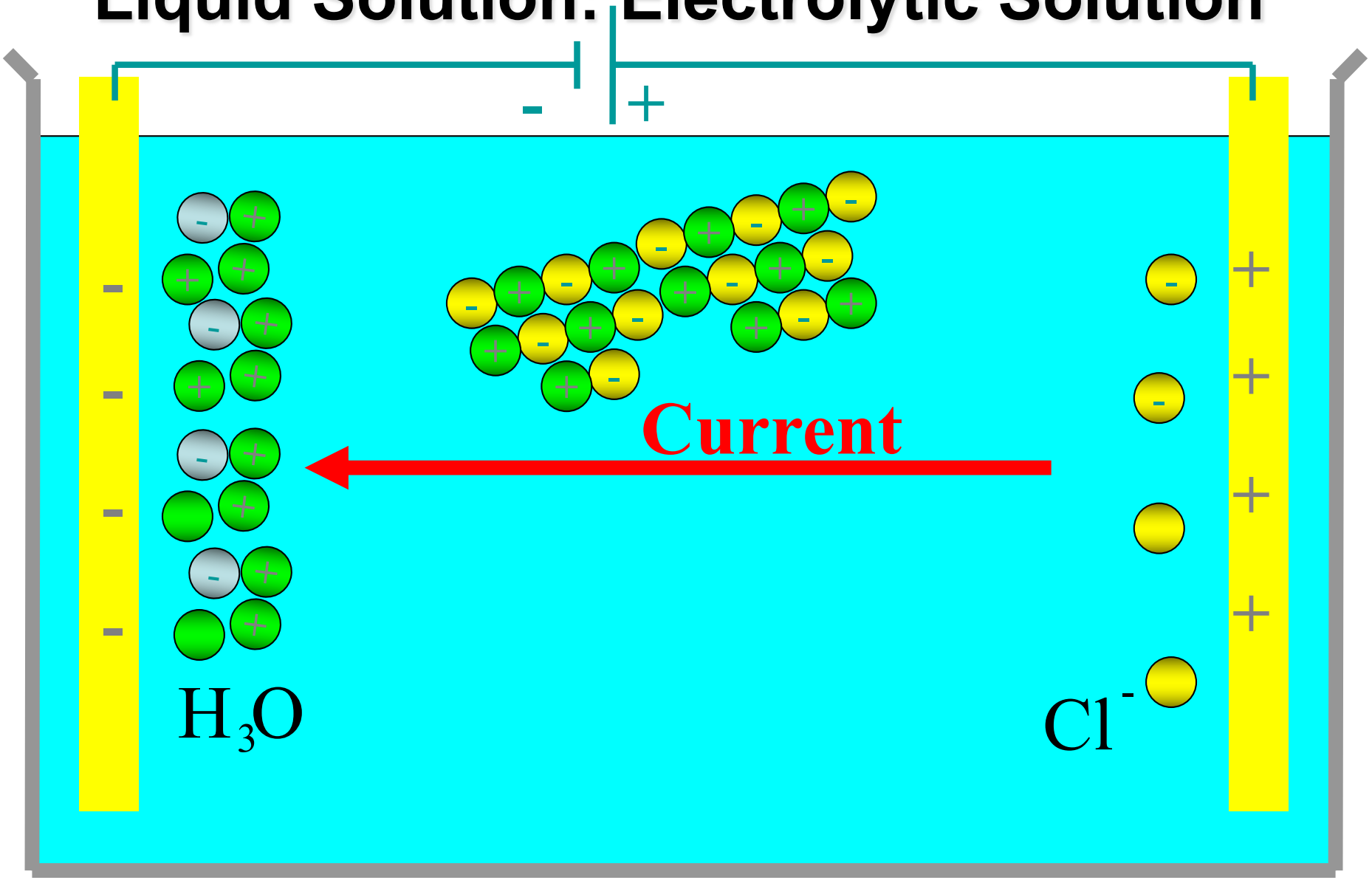
Liquid Solution: Electrolytic Solution



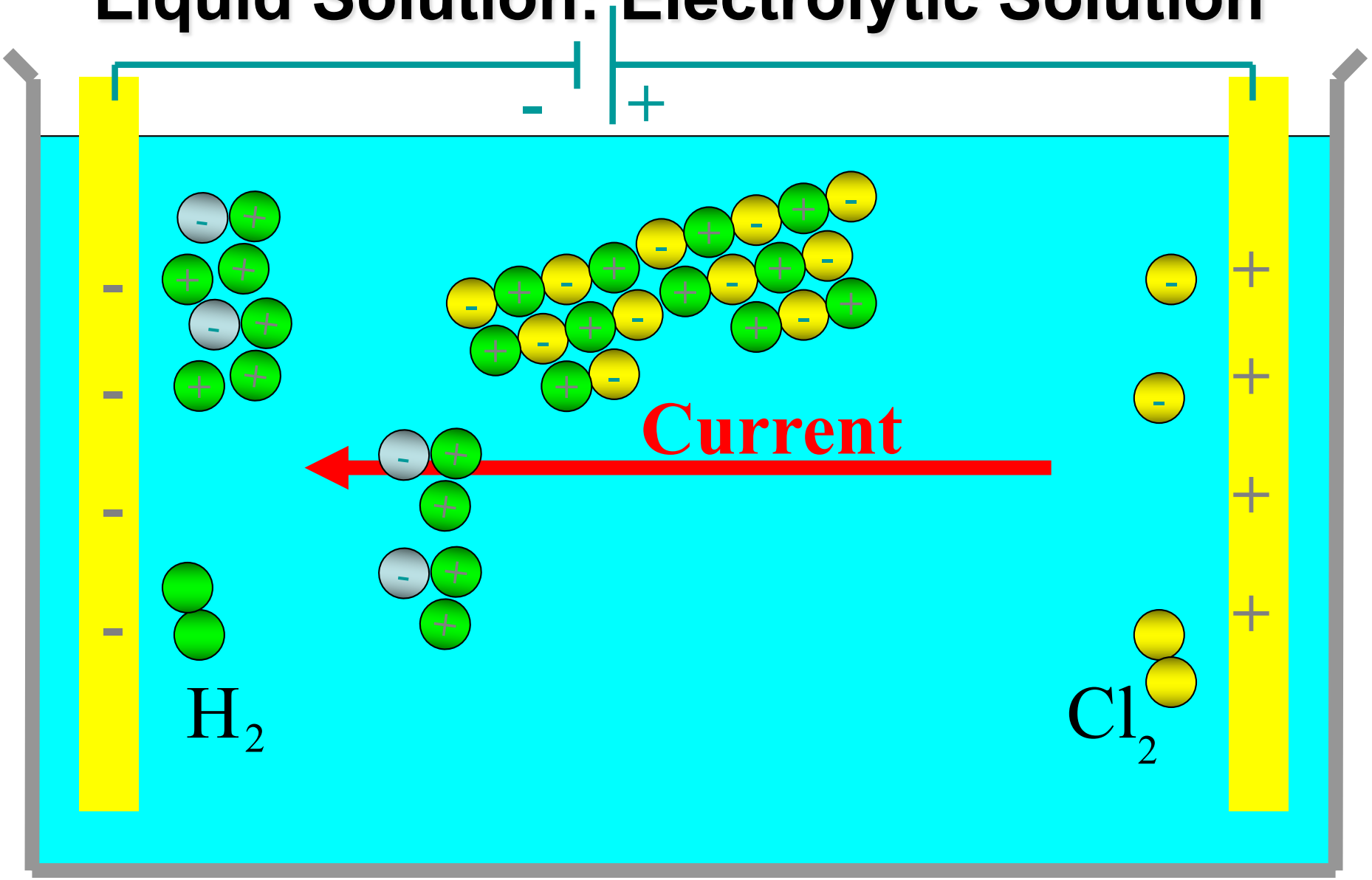
Liquid Solution: Electrolytic Solution



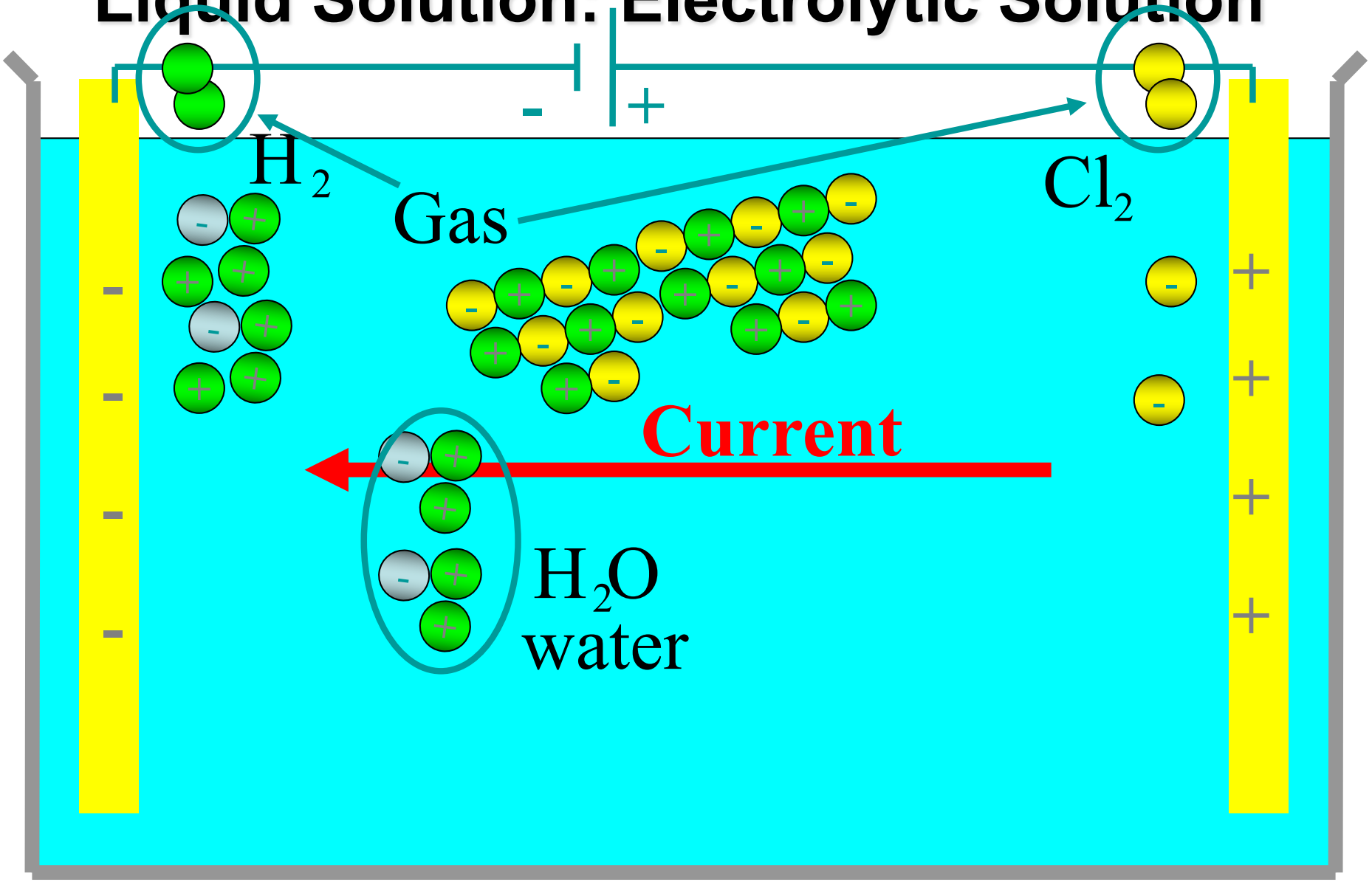
Liquid Solution: Electrolytic Solution



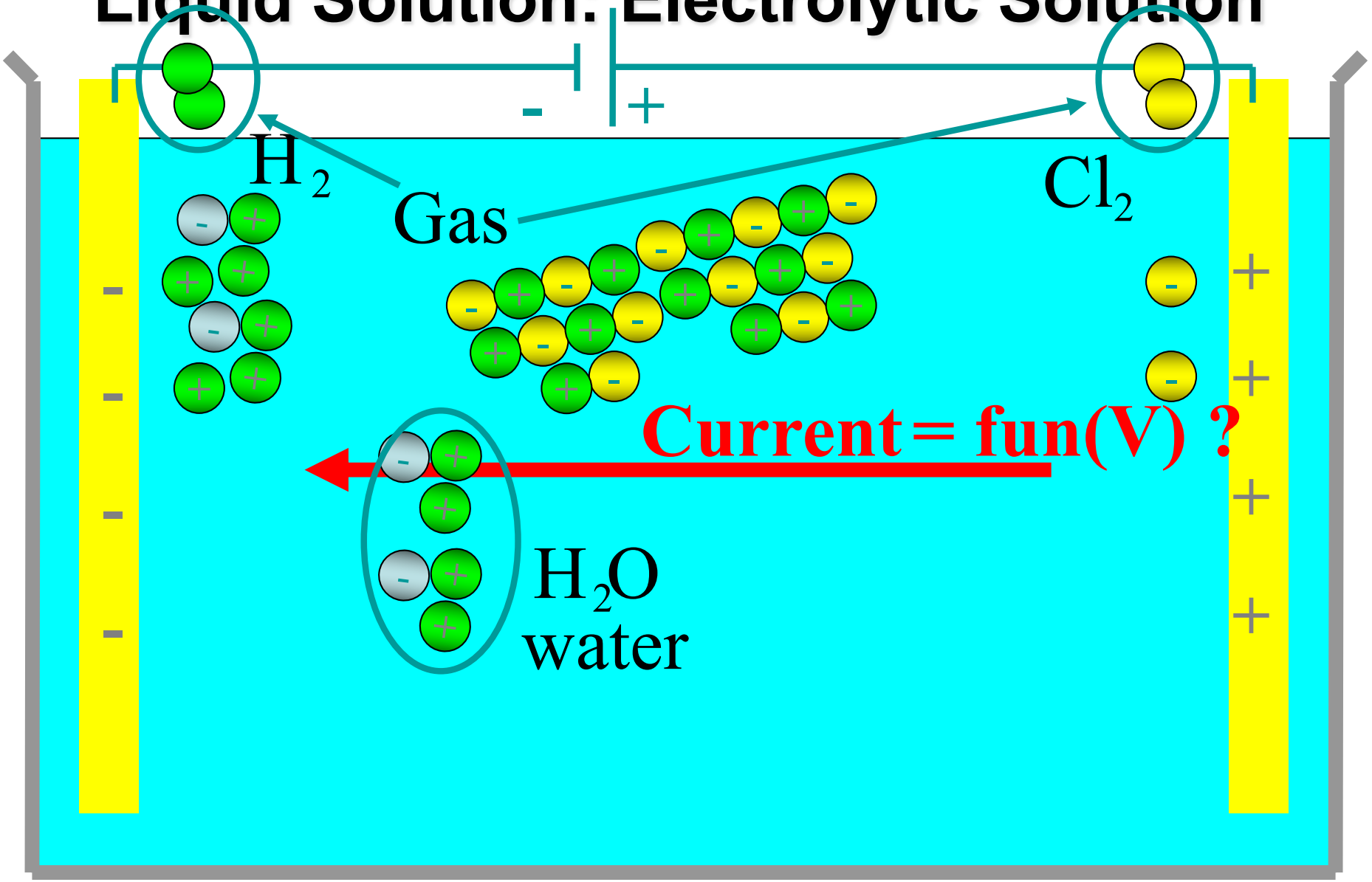
Liquid Solution: Electrolytic Solution



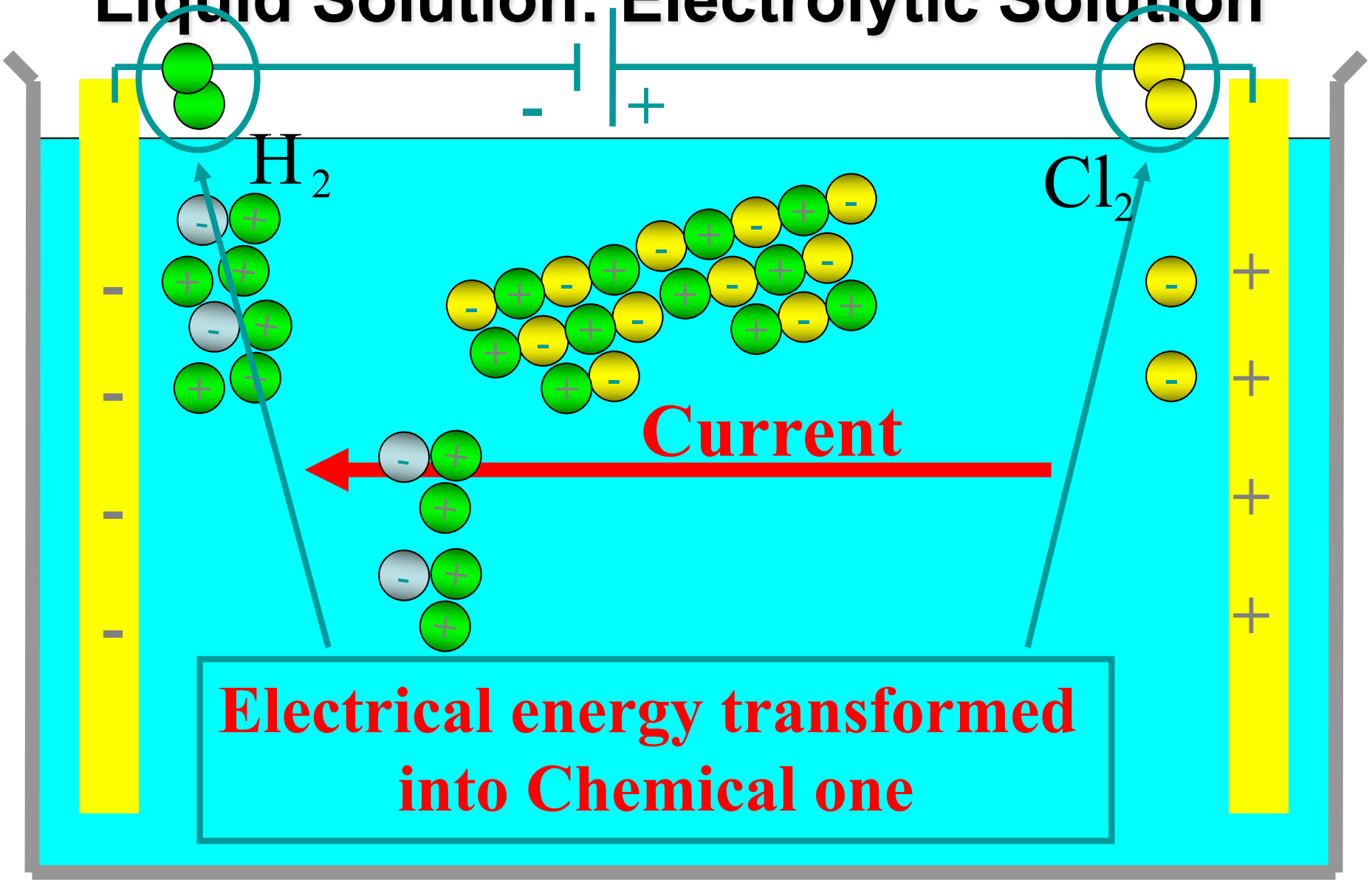
Liquid Solution: Electrolytic Solution



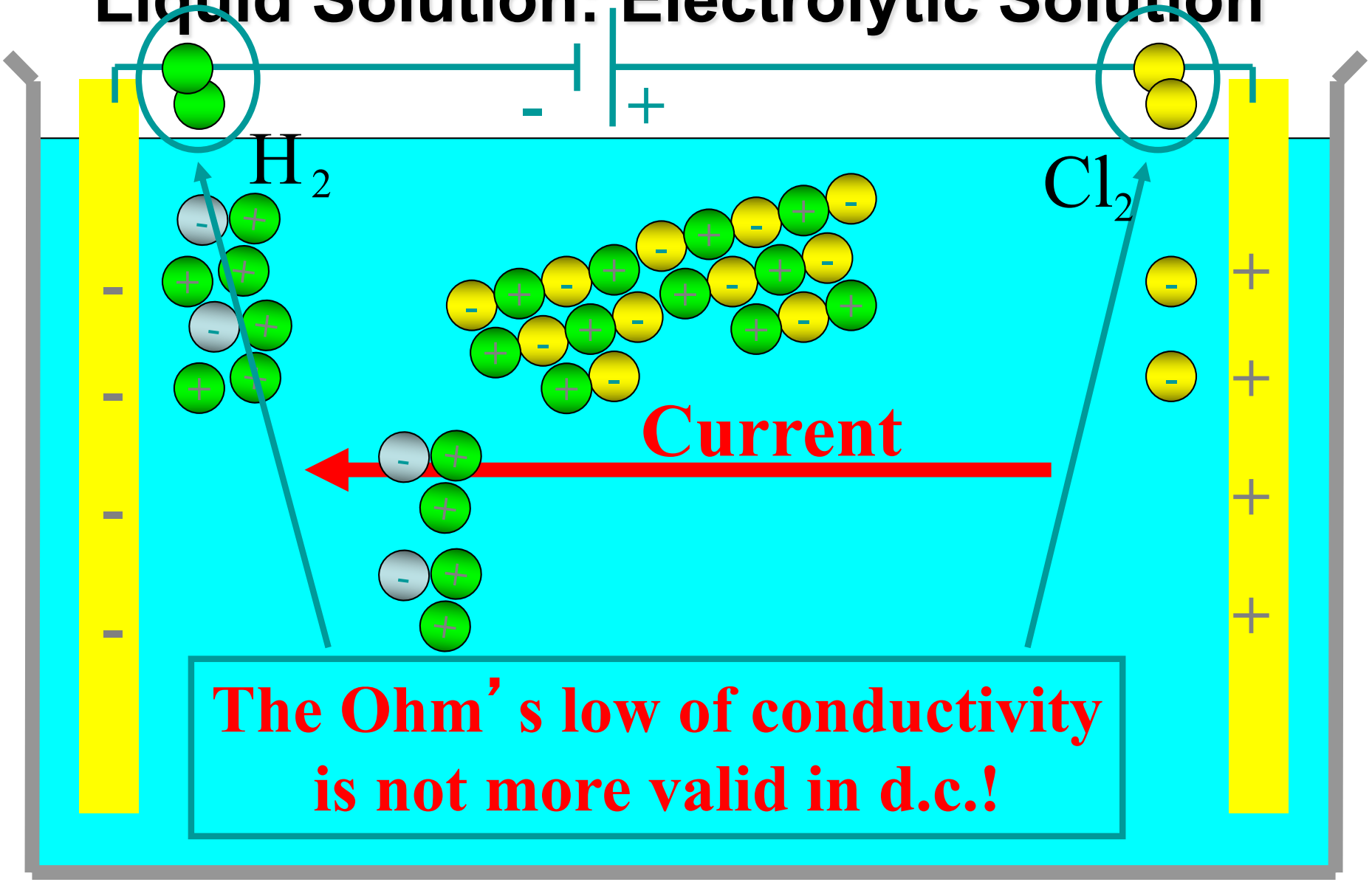
Liquid Solution: Electrolytic Solution



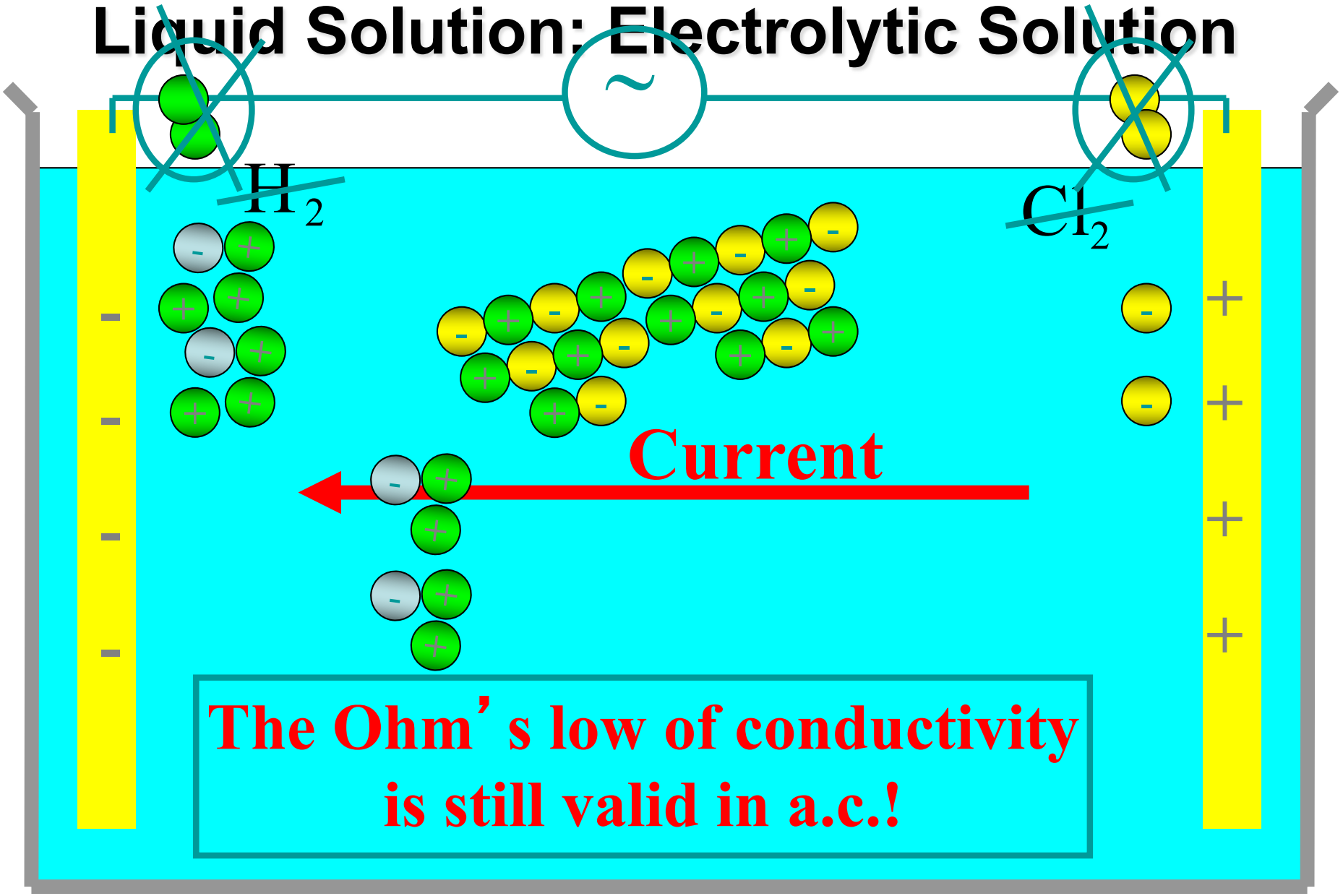
Liquid Solution: Electrolytic Solution



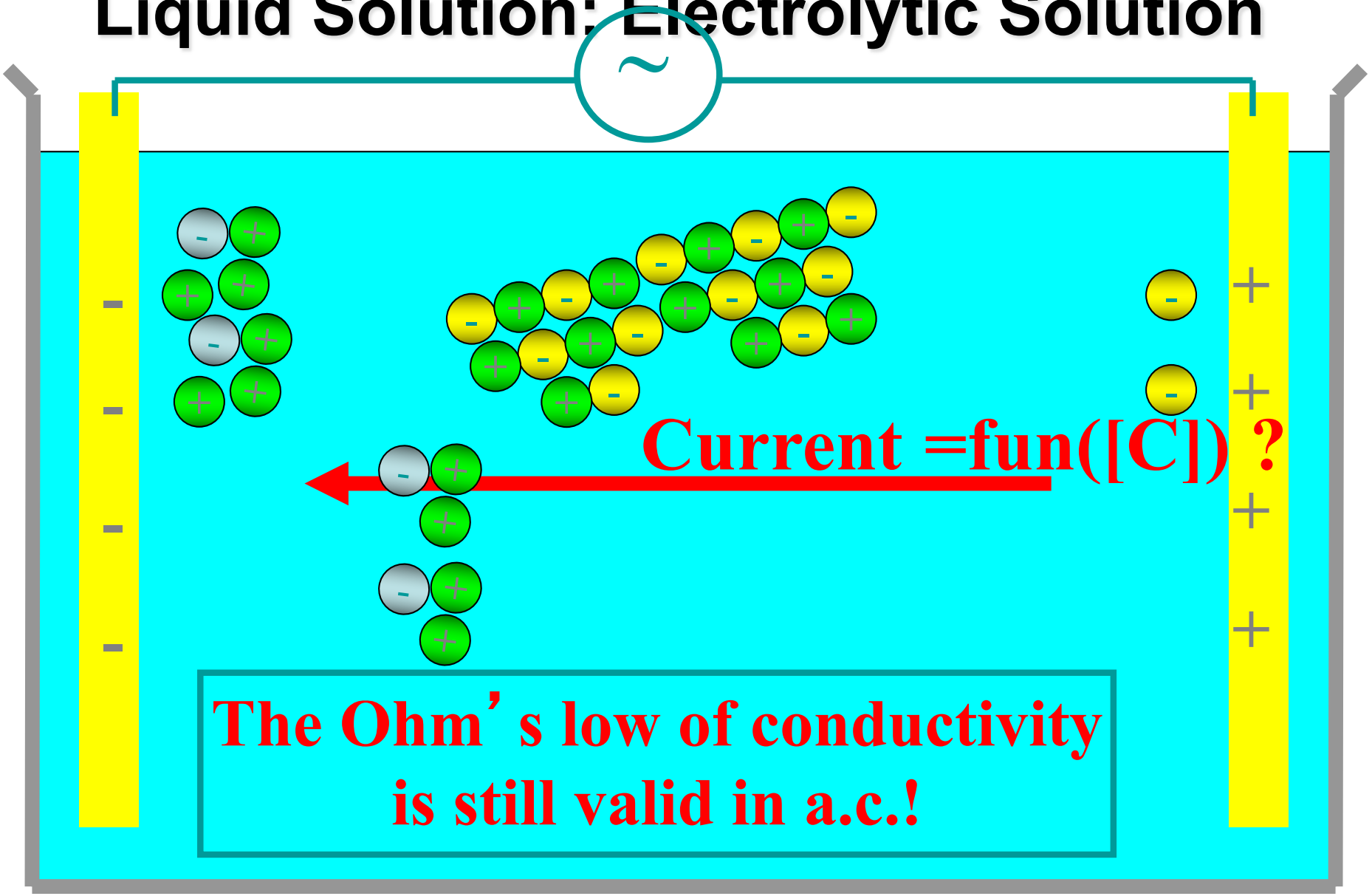
Liquid Solution: Electrolytic Solution



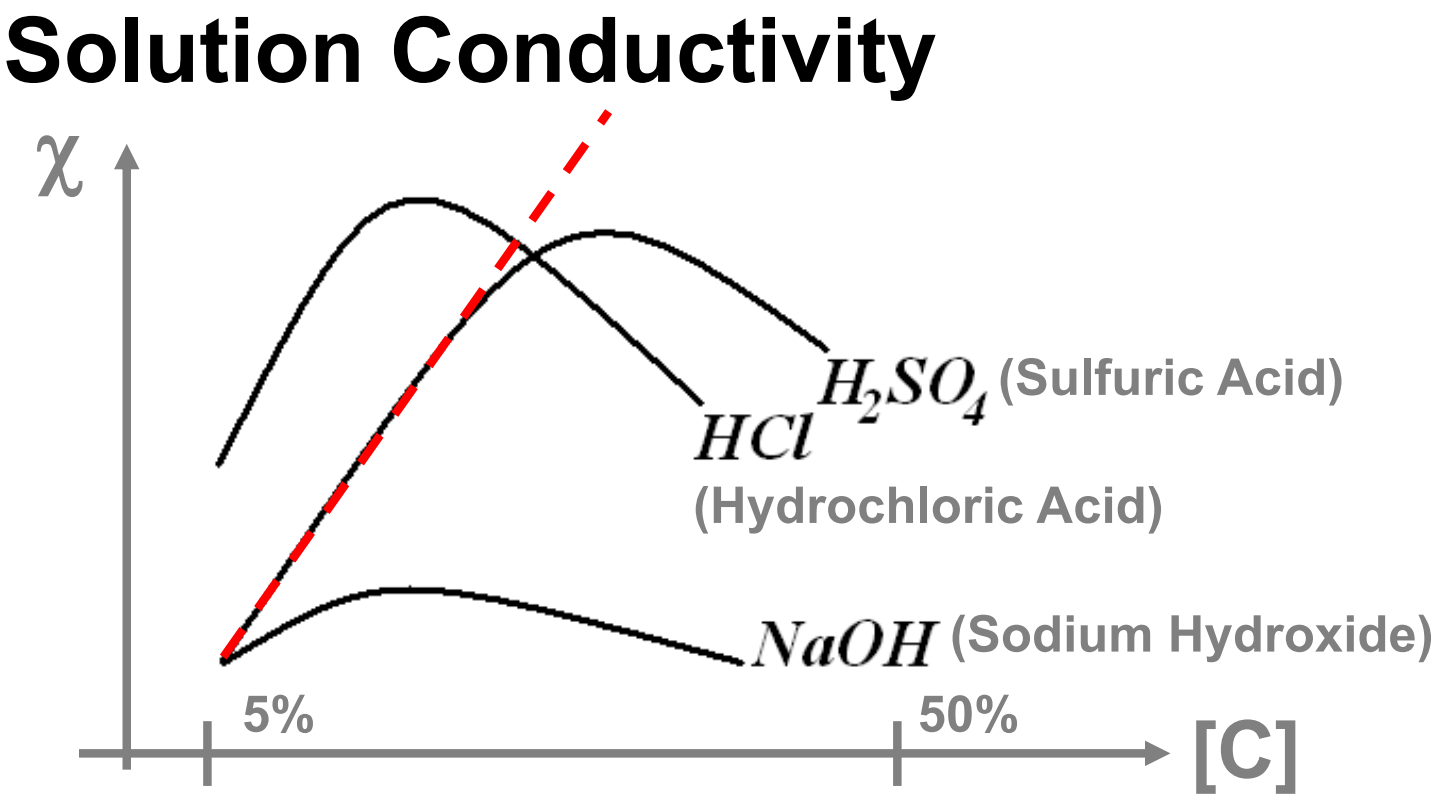
Liquid Solution: Electrolytic Solution



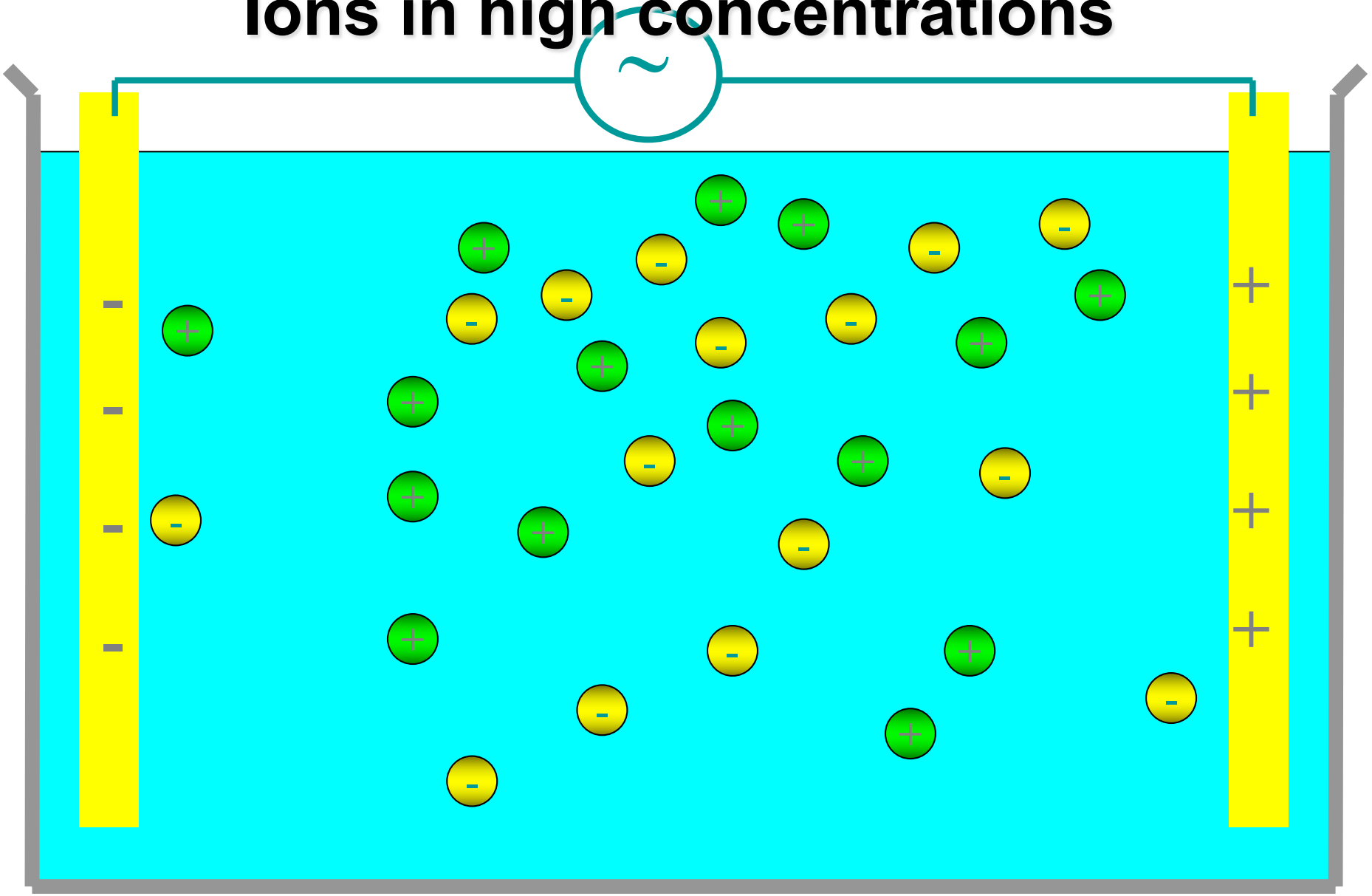
Liquid Solution: Electrolytic Solution



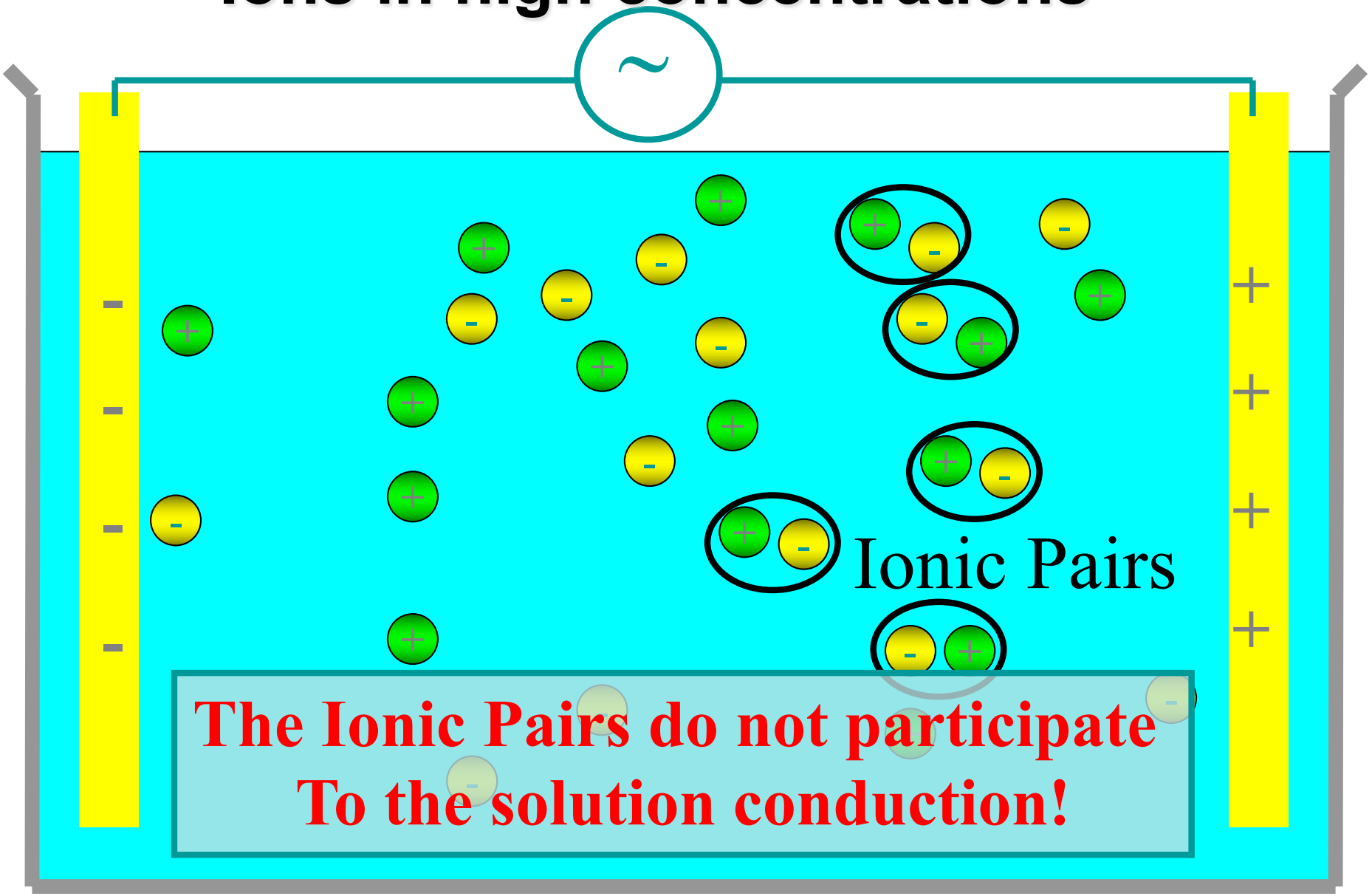
a.c. Conductivity in Ionic Solutions



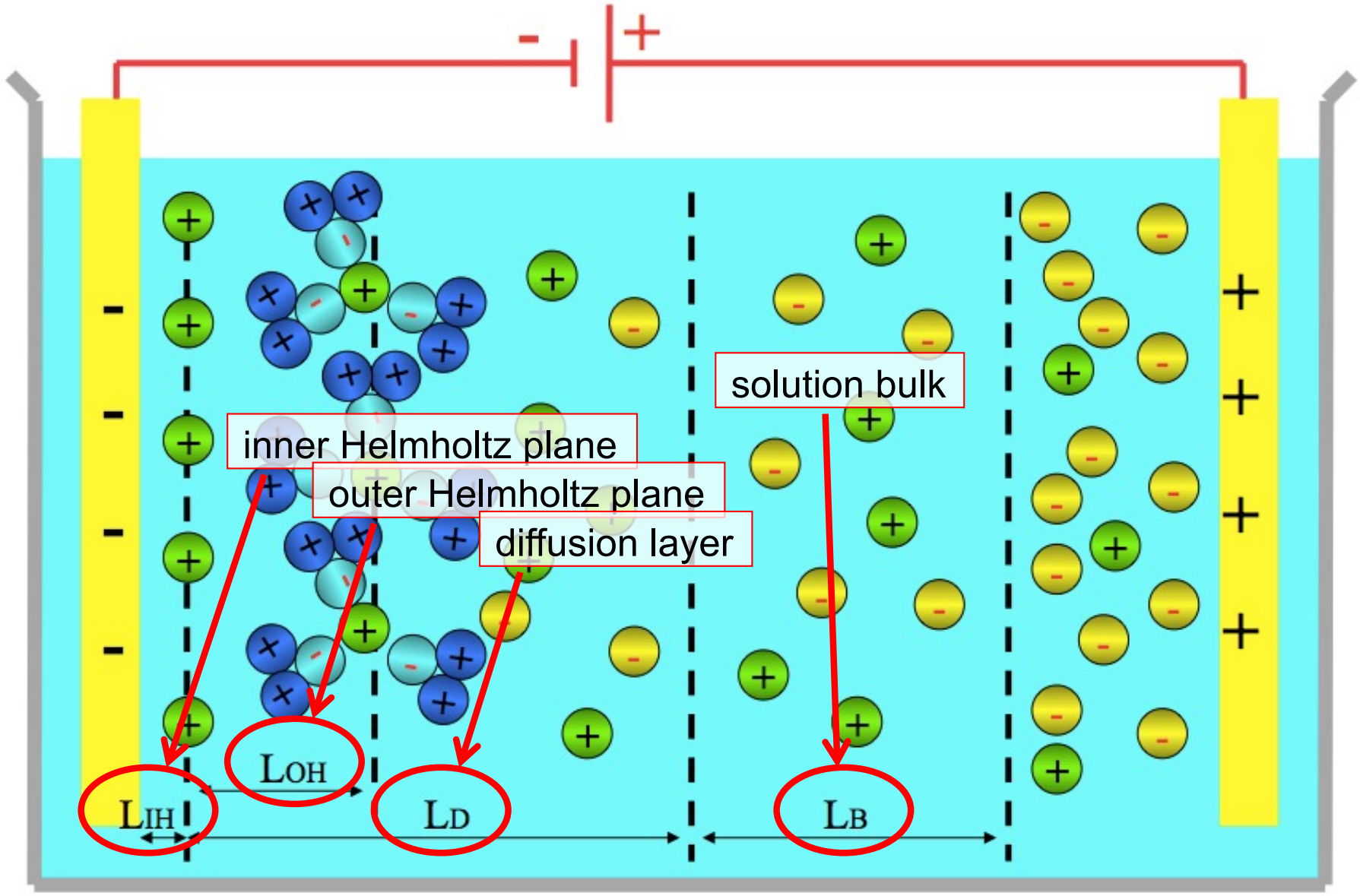
Ions in high concentrations



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

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

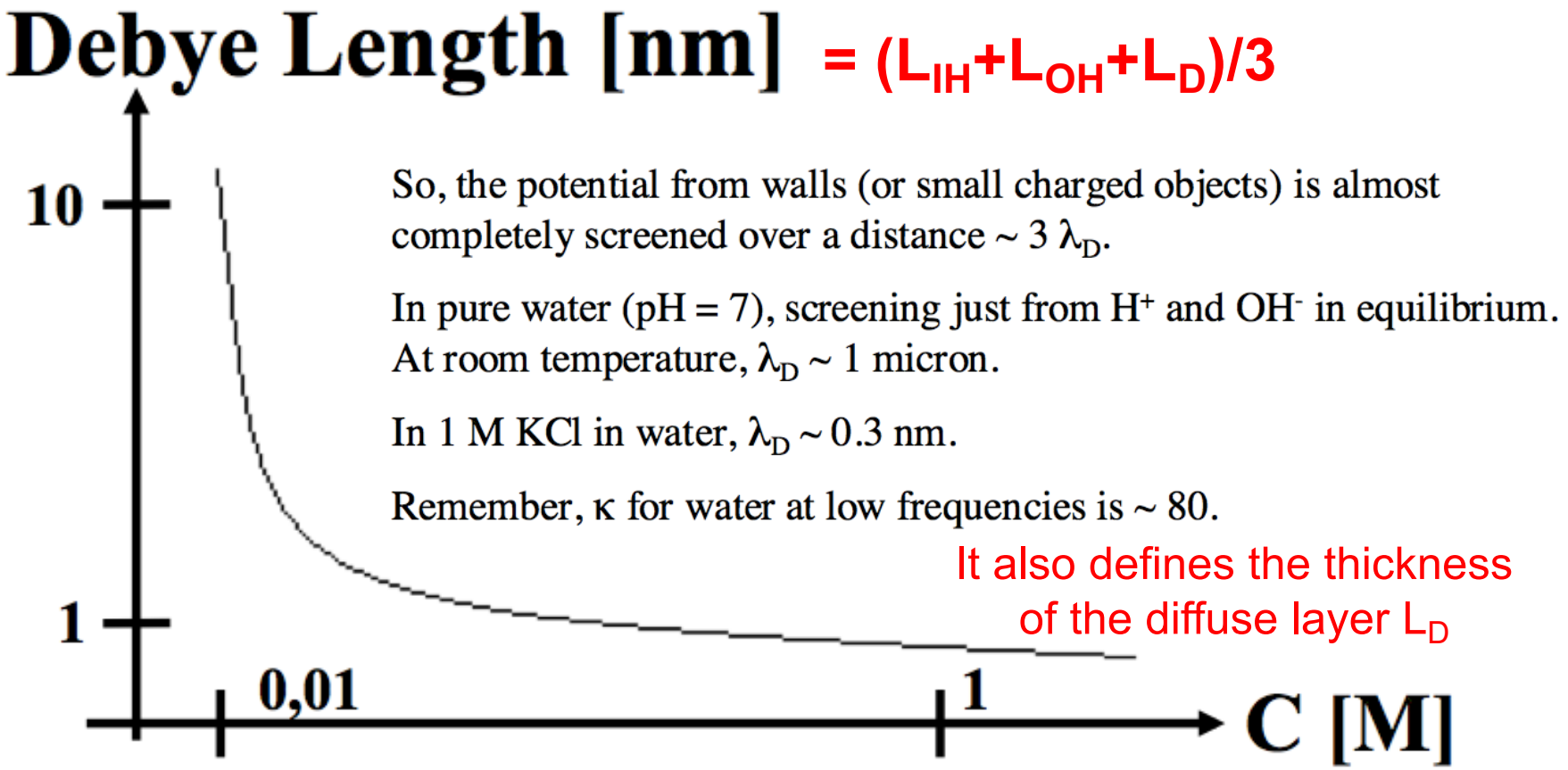
Debye Length

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

~ 0 for equilibrium neutrality

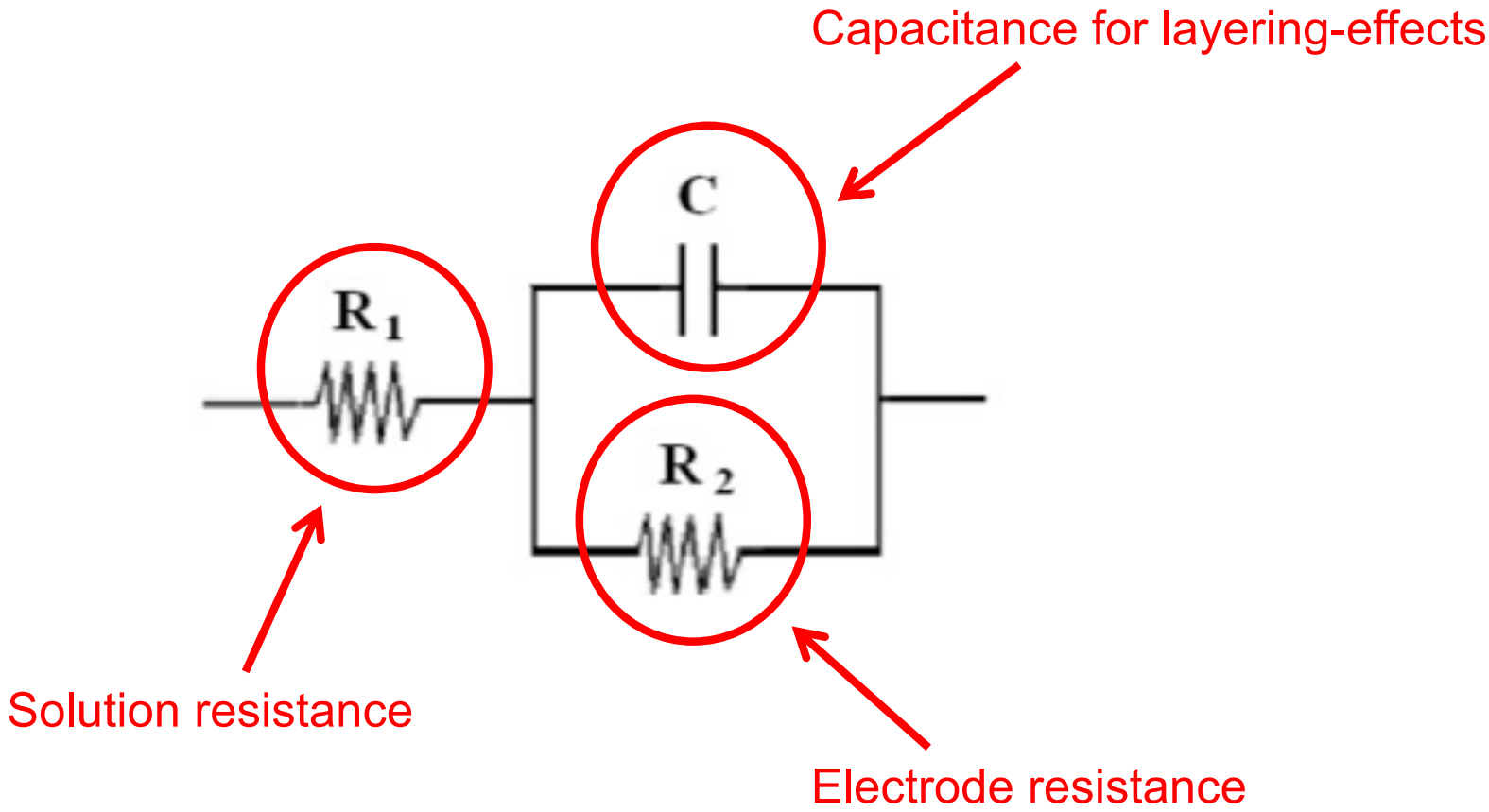
$$\lambda_D \equiv \left(\frac{e^2}{\kappa\varepsilon_0 k_B T}\sum_i z_i^2 n_{i0}\right)^{-1/2}$$

Debye Length



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

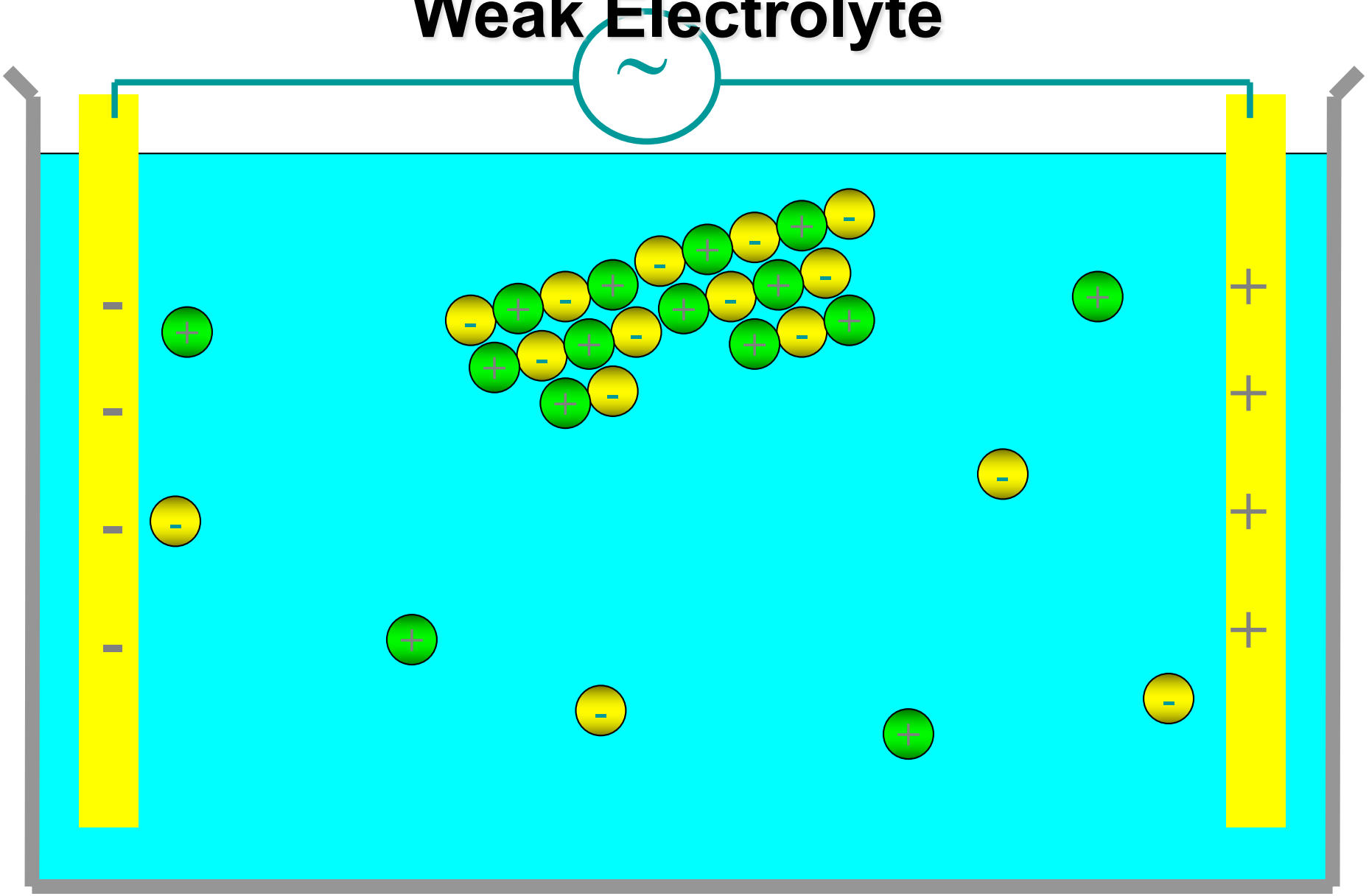
Equivalent Circuit with Layering effects: Randles Model



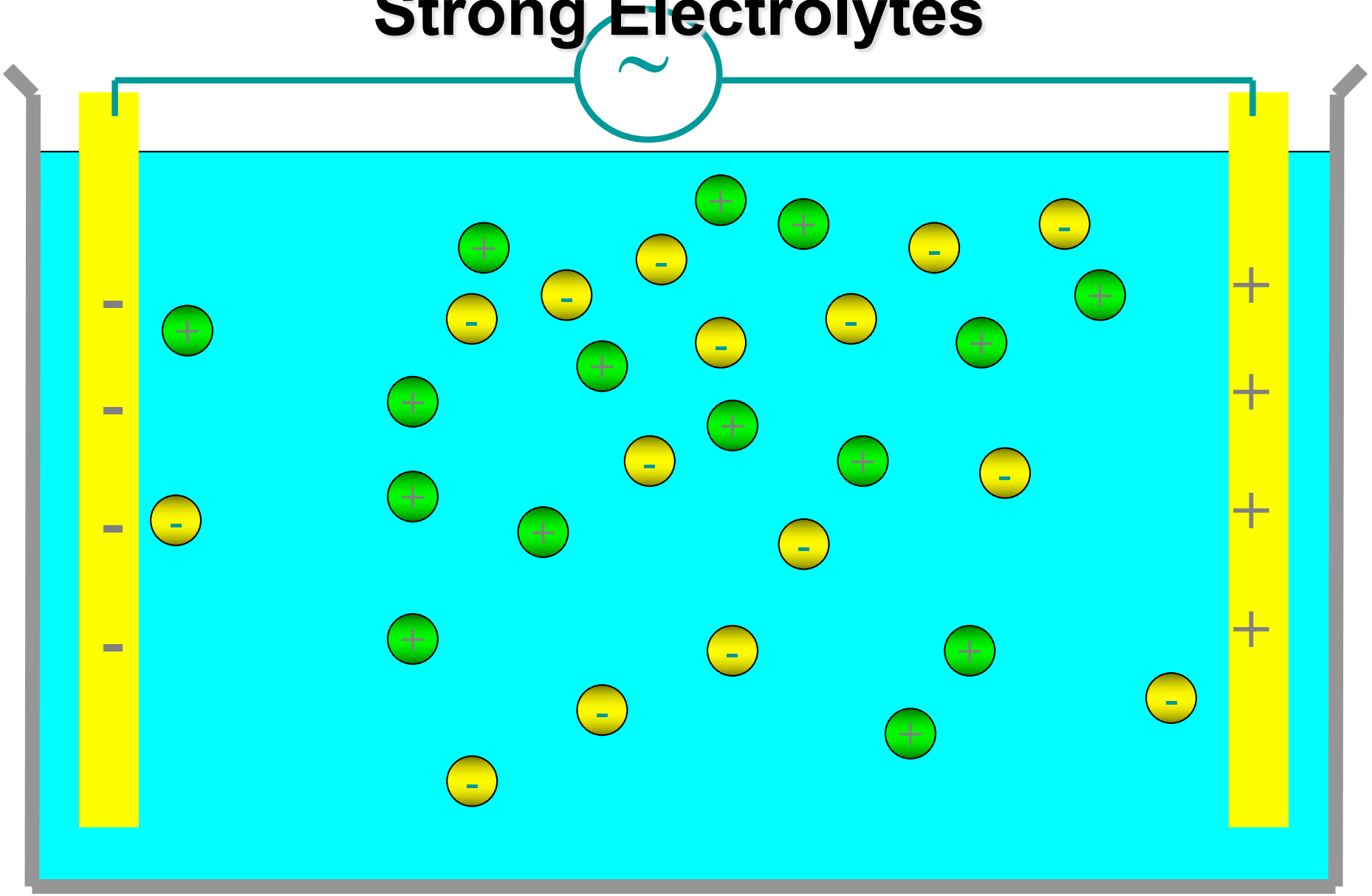
Kind of Electrolytes

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

Weak Electrolyte



Strong Electrolytes



Hard and weak Electrolytes

Dissociation of the Sodium Chloride

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

Dissociation of Hydrogen Cyanide

$$HCN + H_2O \rightleftharpoons H_3O^+ + CN^-$$

α = **Dissociation Degree**

Equilibrium Constant

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

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

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)

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

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

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