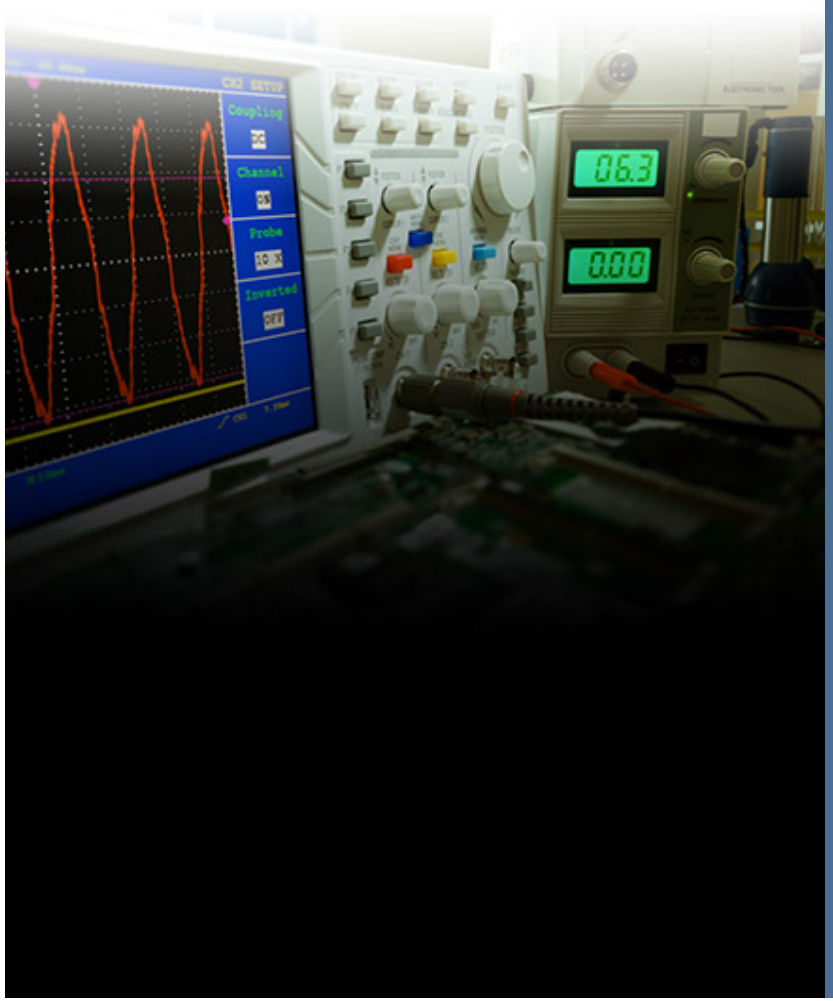
IEEE MTT-S WEBiNARS

YOUR EDUCATIONAL & PROFESSIONAL RESOURCE



Microwave Spectroscopy for non-Invasive Biological and Health Sensing

Presented by:

Katia Grenier

LAAS-CNRS, High Frequency and Fluidic Microwave Microsystems

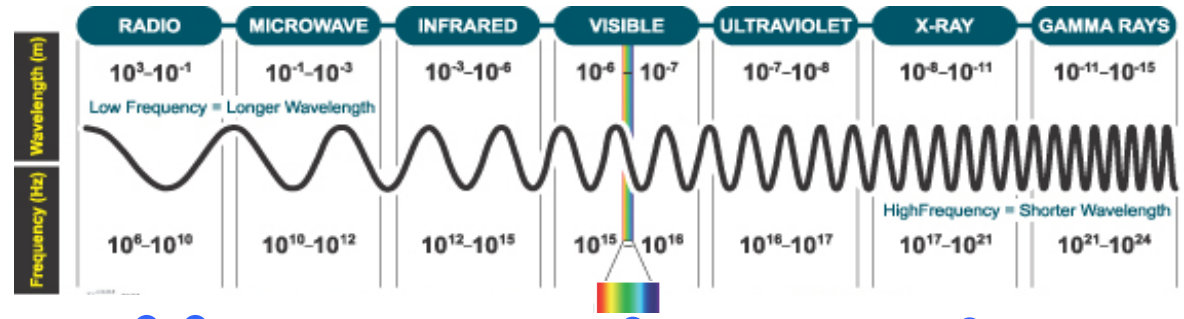
Microwave spectroscopy for non-invasive biological and health sensing

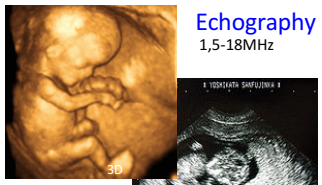
Katia Grenier

In collaboration with David Dubuc

LAAS-CNRS, France

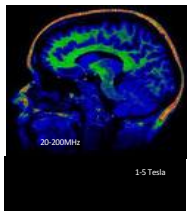
Waving the living matter
Imaging



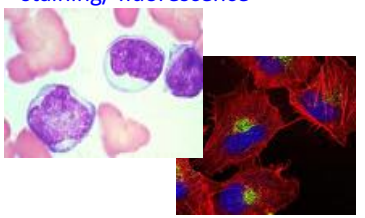


Echography
1,5-18MHz

MRI



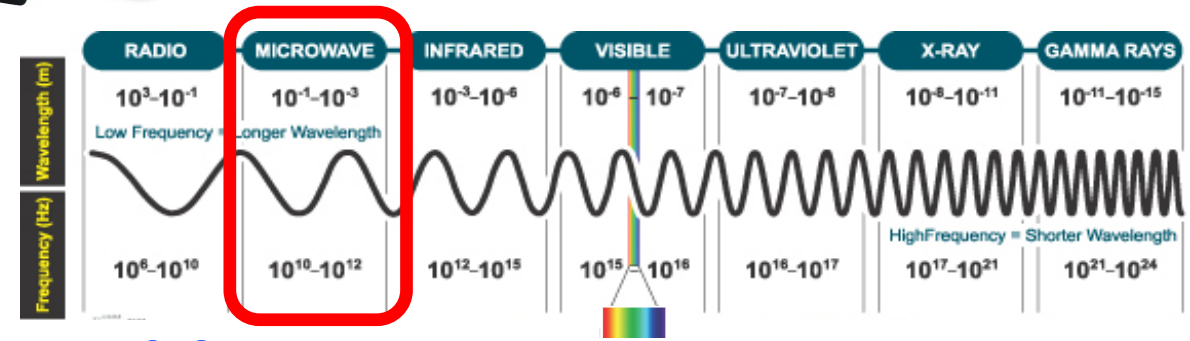
Imaging with staining/ fluorescence

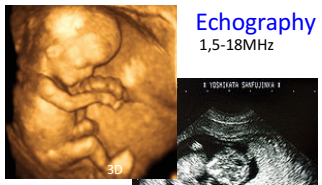


Radiography

Waving the living matter
Imaging

What about dielectrically analyzing cells in the microwave range?

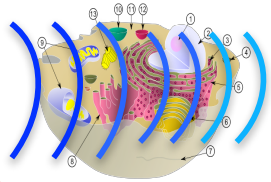




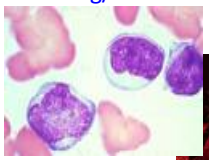
Echography
1,5-18MHz

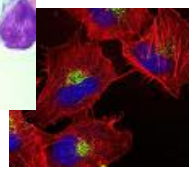
MRI

RF spectroscopy



Imaging with staining/ fluorescence





Radiography

Motivations

① Need of dielectric biomaterial characterization

➔ complex permittivity measurement

- Mainly done with organs and tissues up to GHz range
  (ex: *S. Gabriel et al., Phys. Med. Biol. 41, 1996)*,

  without often taking living heterogeneity into account
  (ex: strong heterogeneity demonstrated on 85 patient breast tissues due to disparity in adipose tissue content - - *Lazebnik et al, Phys. Med. Biol. 2007)*

- Lack of characterization and modeling at the cellular and molecular levels

➔ toward a permittivity library of biomaterials

Cells, DNAs, proteins, biomolecules, virus, bacteria…

IEEE

Motivations

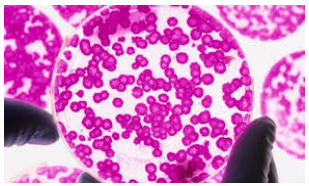
① Need of dielectric biomaterial characterization

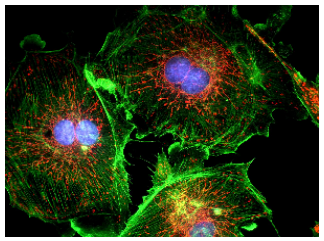
➔ complex permittivity measurement
➔ toward a permittivity library of biomaterials

② Cells analysis for biological and biomedical applications

Traditional techniques:

- Microscopy with stains or labels
- Laser detection
- Flow cytometry





➔ Invasive and toxic for cells
Destructive
Time consuming

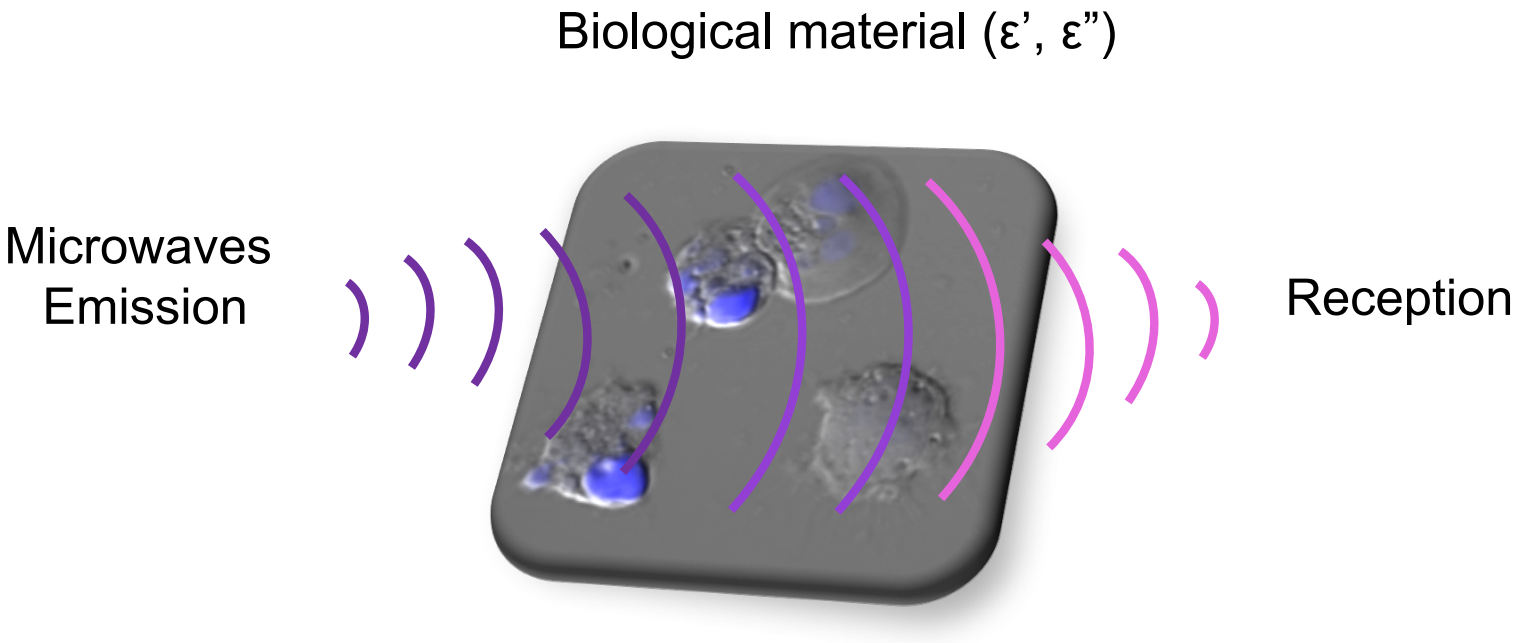
➔ **Interest in noninvasive bio-analysis**

Expected consequences on fundamental knowledge and therapy through:

- The diagnostic and prognostic of diseases – treatment efficiency
- Further understanding of biological processes and disease treatments

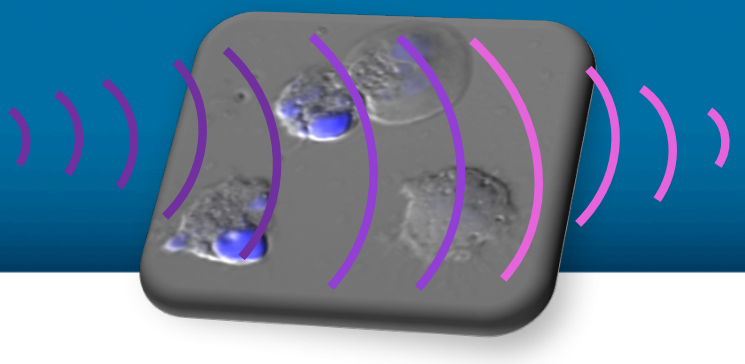
IEEE

Microwave spectroscopy



Characterization of a material with its **dielectric properties**

Pros & cons



Pros:

- *Dielectric spectroscopy*
  - Non destructive technique to probe various materials (solids, liquids, gaz)
  - No contact, no labeling
  - Non invasive for the cells
  - Volume interaction with realistic cellular environment (culture medium)
  - Fast and in quasi real time (millisec, even less)
  - "Specificity" of the *dielectric spectra*

- *Micro-nano technologies*
  - Compatible with cells size and low liquid volumes (µl, nl and below)

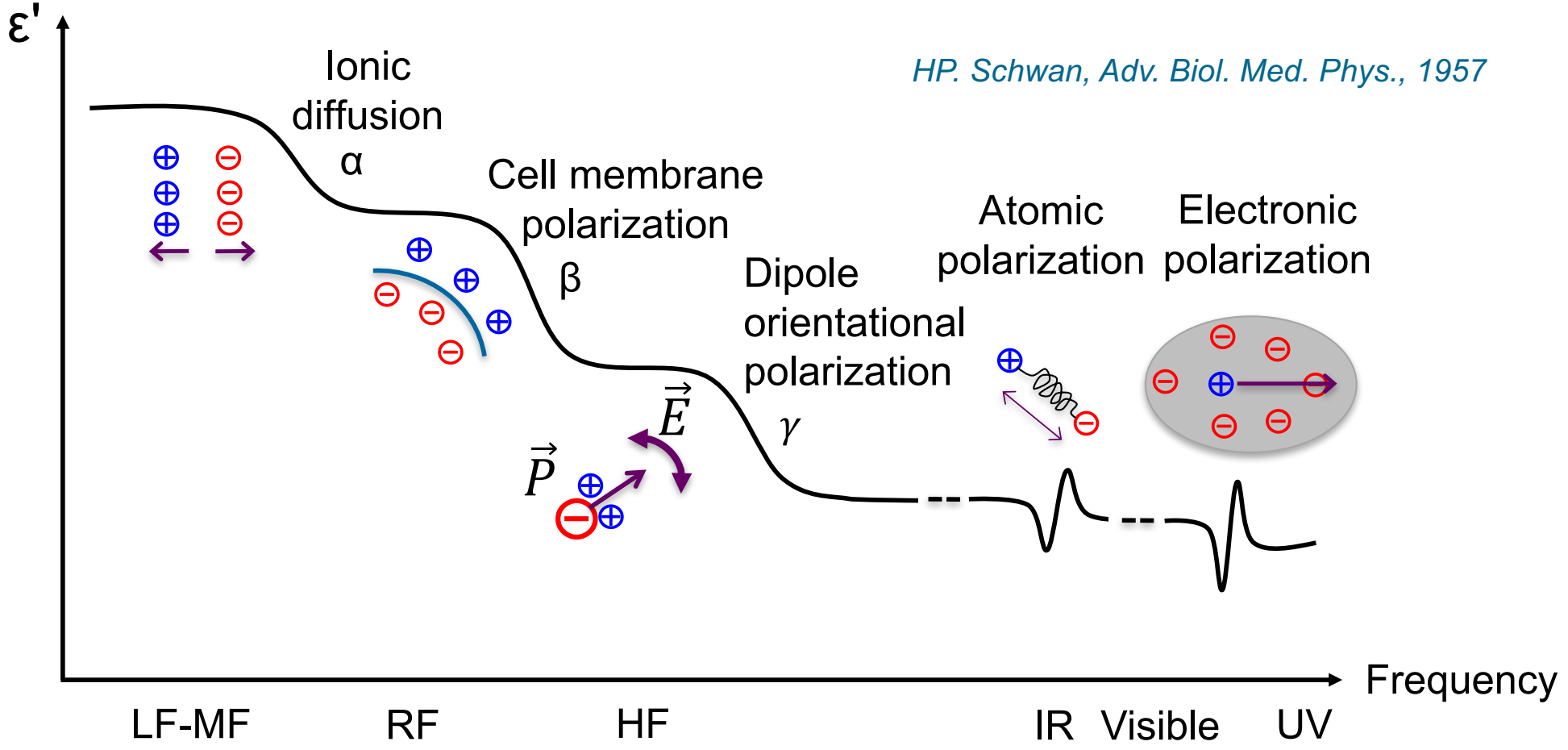
- *In the microwave and millimeterwave ranges*
  - INTRACELLULAR investigations

Cons:

- global measurement of cells
- Under development : capabilities and limitations have to be defined

IEEE

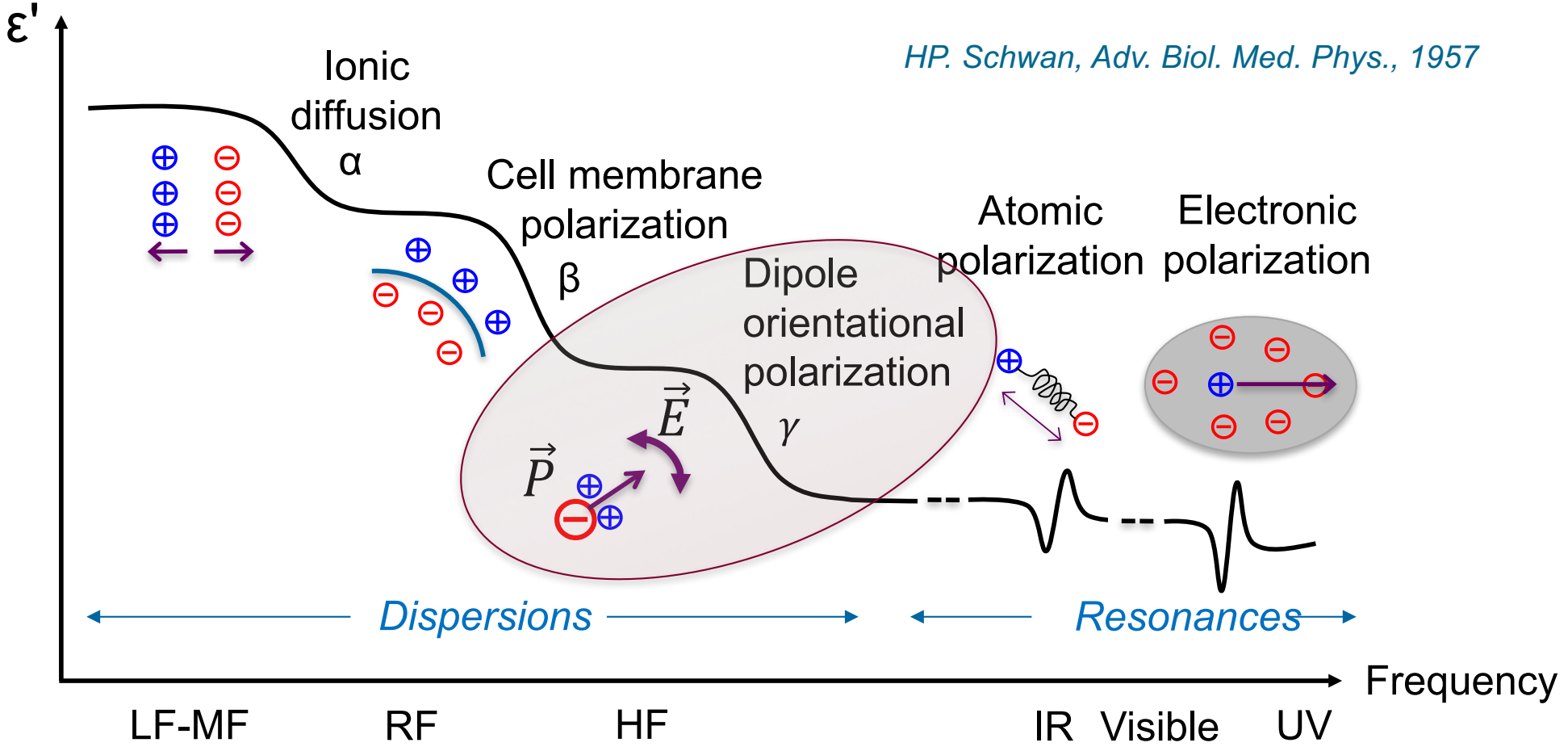
EM waves interaction with biomaterials



HP. Schwan, Adv. Biol. Med. Phys., 1957

- Biomaterials may be EM described with their ***dielectric properties***, which may be obtained from their measured complex relative permittivity
- Specific signature for each biological elements

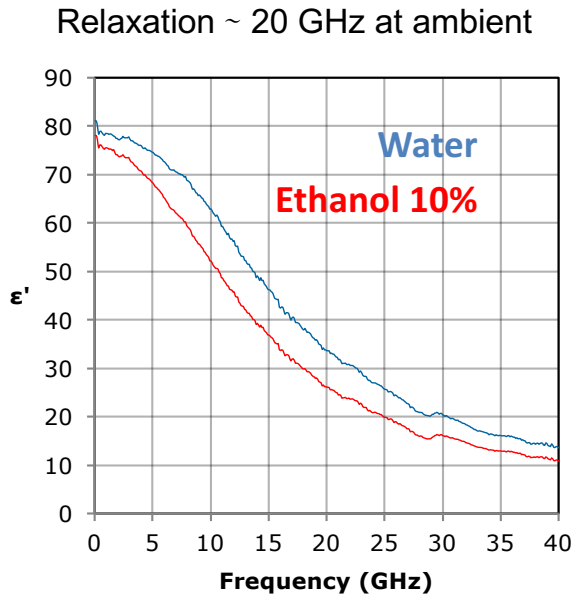
EM waves interaction with biomaterials



HP. Schwan, Adv. Biol. Med. Phys., 1957

❶ Water molecule, natural marker of microwave spectroscopy

- *Polar molecule with network structuration*
- *Affinity with other molecules/particles*
- *With a dielectric signature*

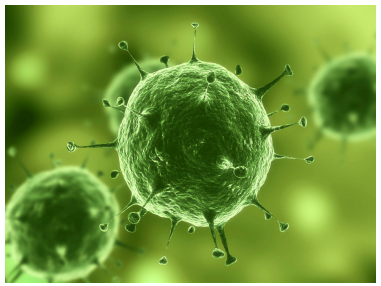


Modification of the molecular network

➜ Change of the microwave dielectric spectra

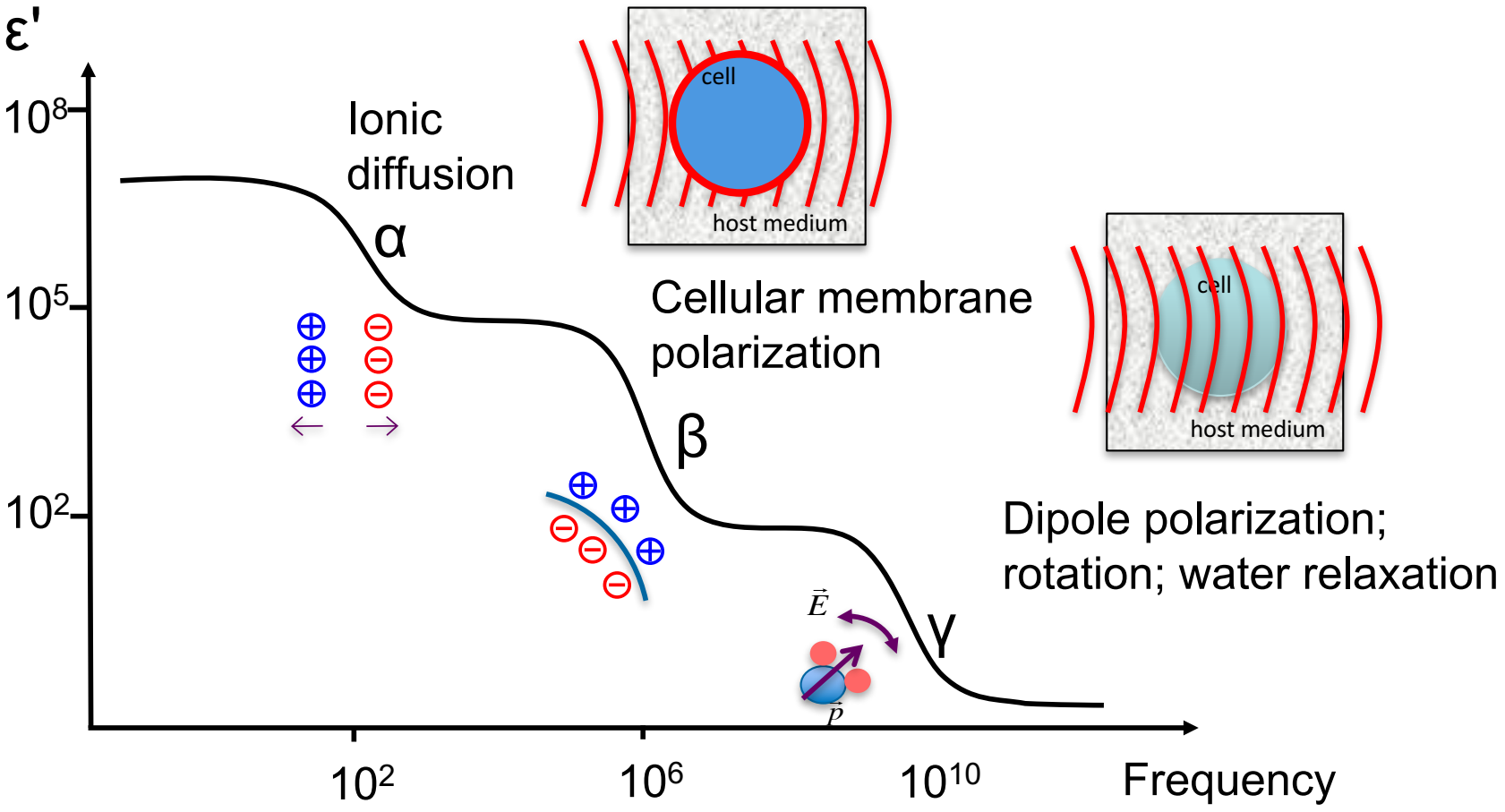
Water: abundant constituent of the living

Involved in many bio-mechanisms

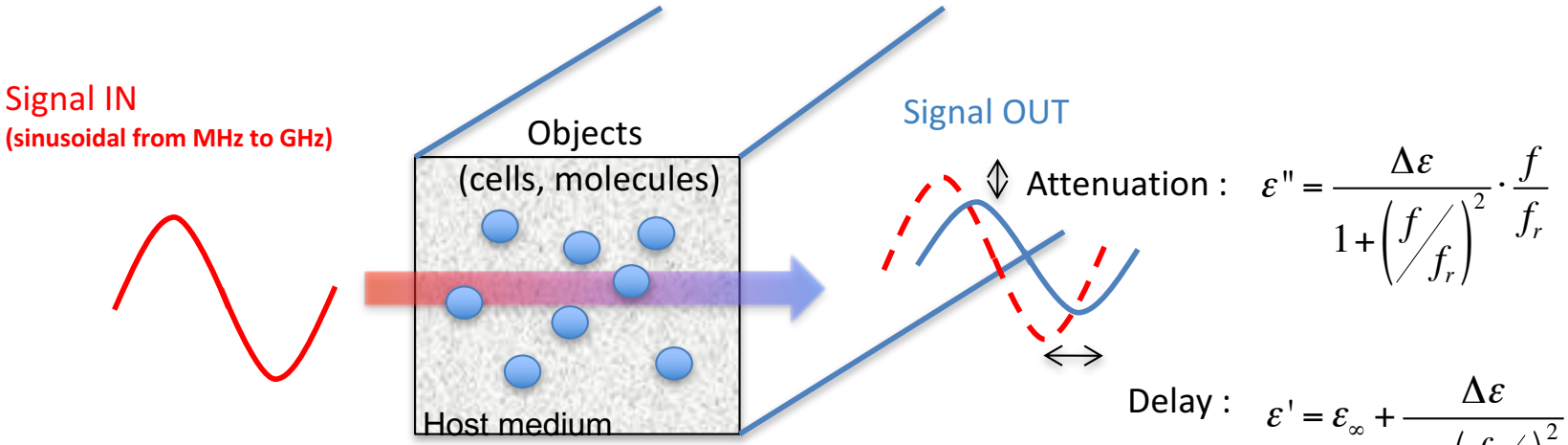


IEEE

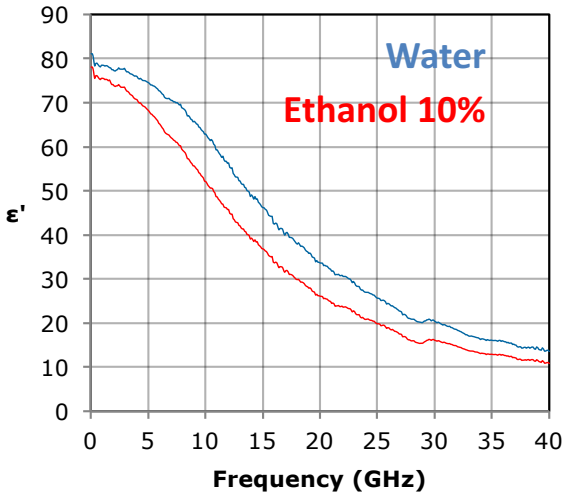
❷ Access to intracellular dielectric activity



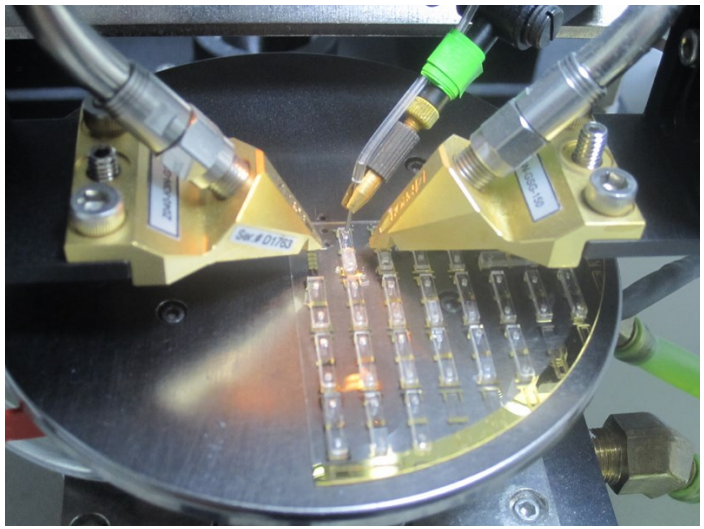
Dielectric readouts

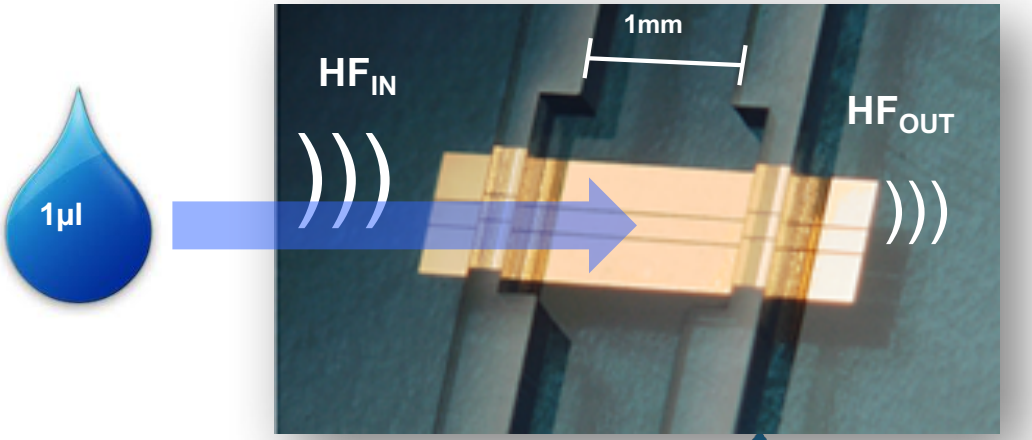


- both ε' and ε" are readouts of
  scanning frequency,
  dipolar moment, physical parameters (size of objects, viscosity), temperature



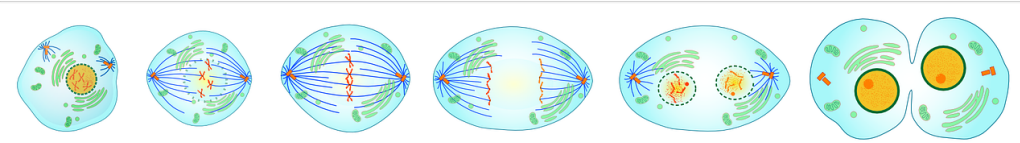
Microwave measurement setup



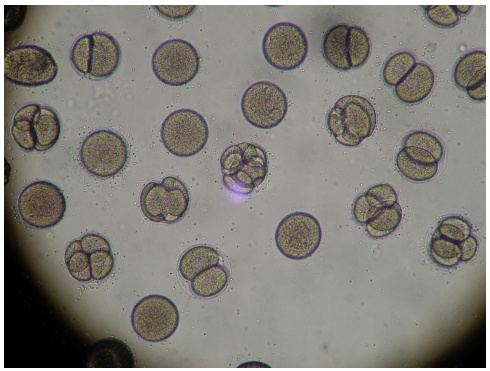


Which constraints induced by measuring living materials?

Living material is:



- constantly changing ; cell replication
- in a liquid environment rich in ions and nutrients, which is progressively consumed by the cells
- Heterogeneous
- May vary in temperature



All cells from the same cell line won't react and live exactly the same, but similarly

Strong measurements care have to be taken!

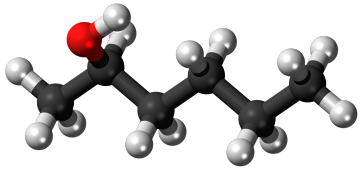
Repeatability is mandatory!

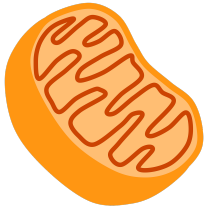
Biological complexity

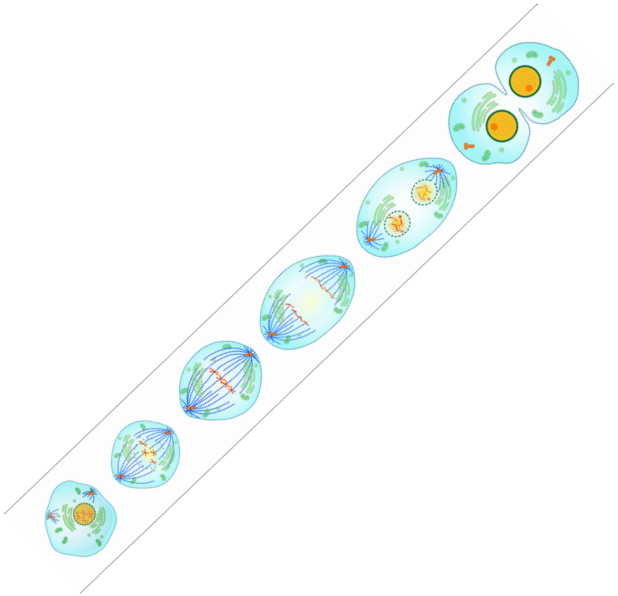
1-Biomolecules and supramolecular complexes

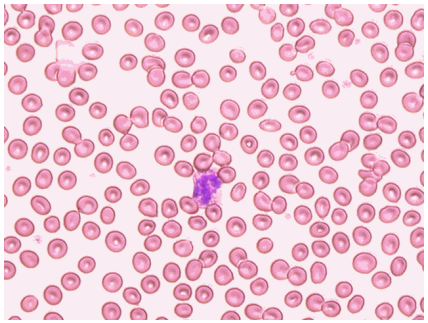
2-Live normal & cancer cells

3-Biological mechanisms





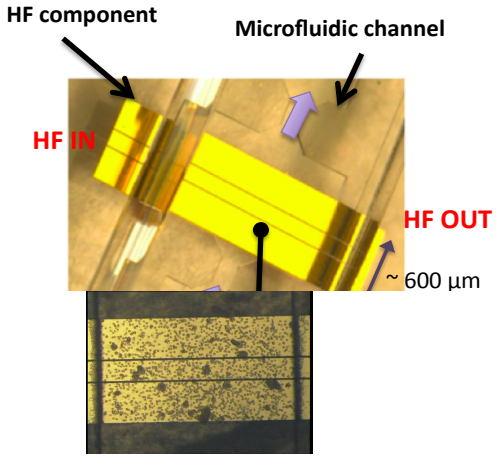




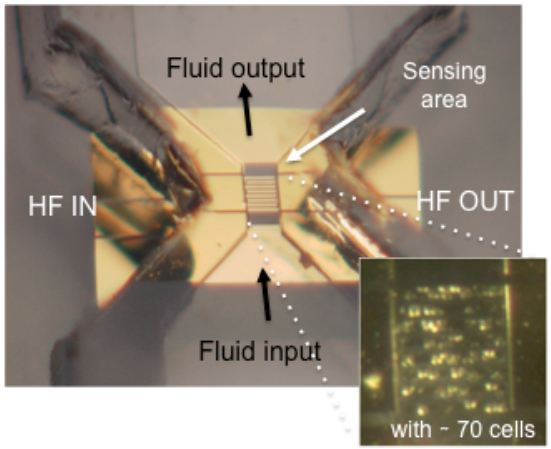
➢ Where microwave biosensing may be relevant?

IEEE

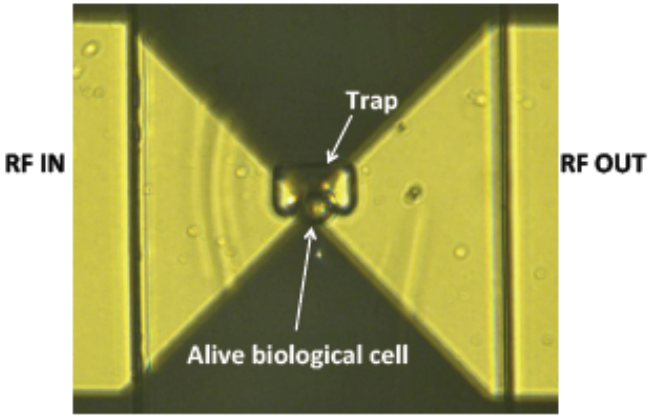
Microwave & Microfluidic biosensors



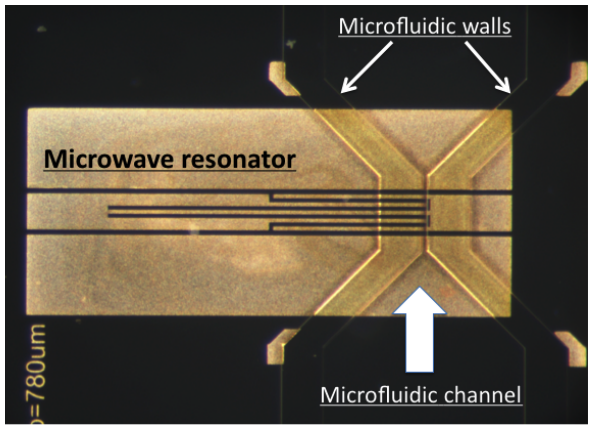
Grenier et. al., IEEE T-MTT 2009



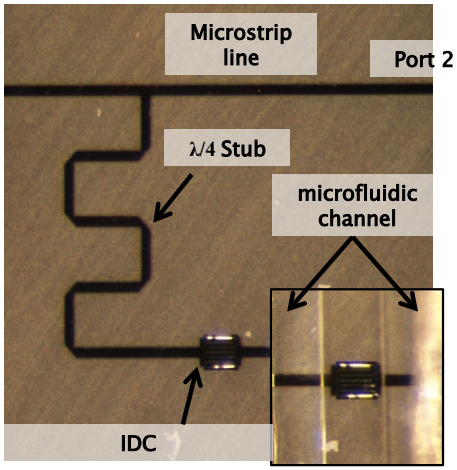
T. Chen et al, IEEE T-MTT Dec. 2012



T. Chen et al, IEEE IMS 2013



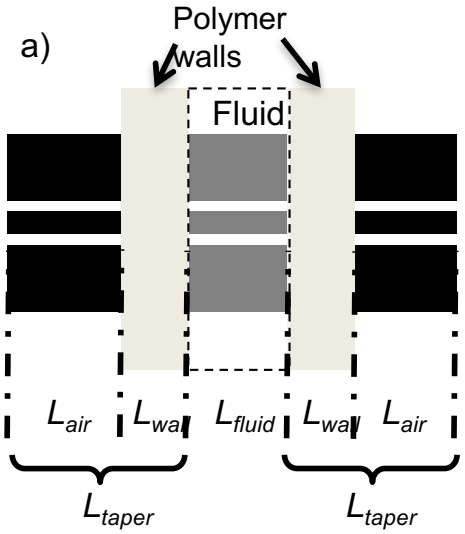
Chretiennot et al IEEE T-MTT-13 & EuMW 2013

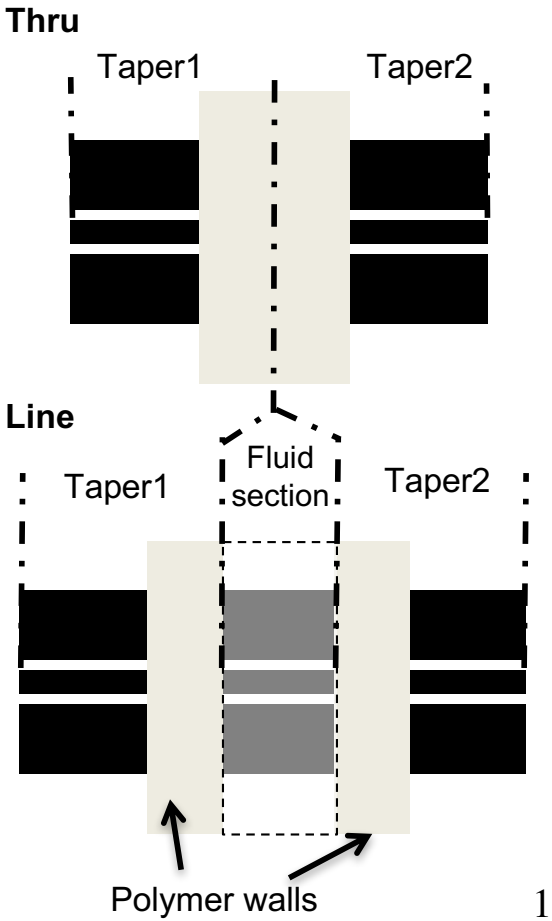


Chretiennot et al IEEE IMS2014

IEEE

De-embedding technique





$$T_{thru} = T_{taper1} \cdot T_{taper2}$$

$$T_{line} = T_{taper1} \cdot T_{fluid} \cdot T_{taper2}$$

$$T_{line} \cdot T_{thru}^{-1} = T_{taper1} \cdot T_{fluid} \cdot T_{taper1}^{-1}$$

$$Trace\left(T_{line} \cdot T_{thru}^{-1}\right) = Trace\left(T_{fluid}\right)$$

$$T_{fluid} = \begin{bmatrix} e^{-\gamma L_{fluid}} & 0 \\ 0 & e^{\gamma L_{fluid}} \end{bmatrix}$$

$$Tr\left(T_{fluid}\right) = 2 \cdot ch\left(\gamma \cdot L_{fluid}\right)$$

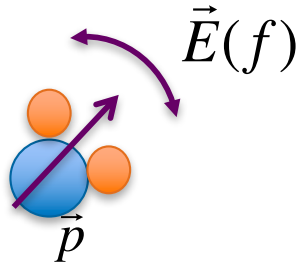
$$\gamma = \frac{1}{L_{fluid}} Argch\left(\frac{1}{2} \frac{S_{11}^{line} \cdot S_{22}^{thru} + S_{11}^{thru} \cdot S_{22}^{line} - \det\left[S^{thru}\right] - \det\left[S^{line}\right]}{S_{21}^{line} \cdot S_{12}^{thru}}\right)$$

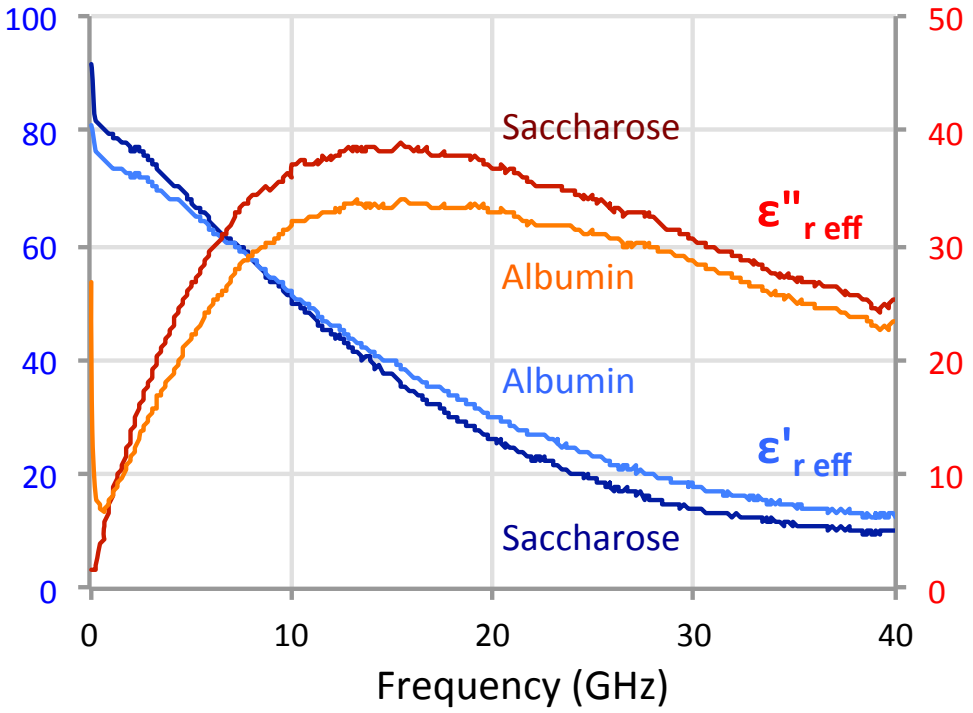
K. Grenier et al., IEEE T-MTT 2009

⇒ Complex permittivity extraction of the fluid under test

IEEE

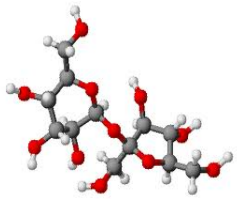
Molecules and dielectric spectroscopy





Albumine

Saccharose

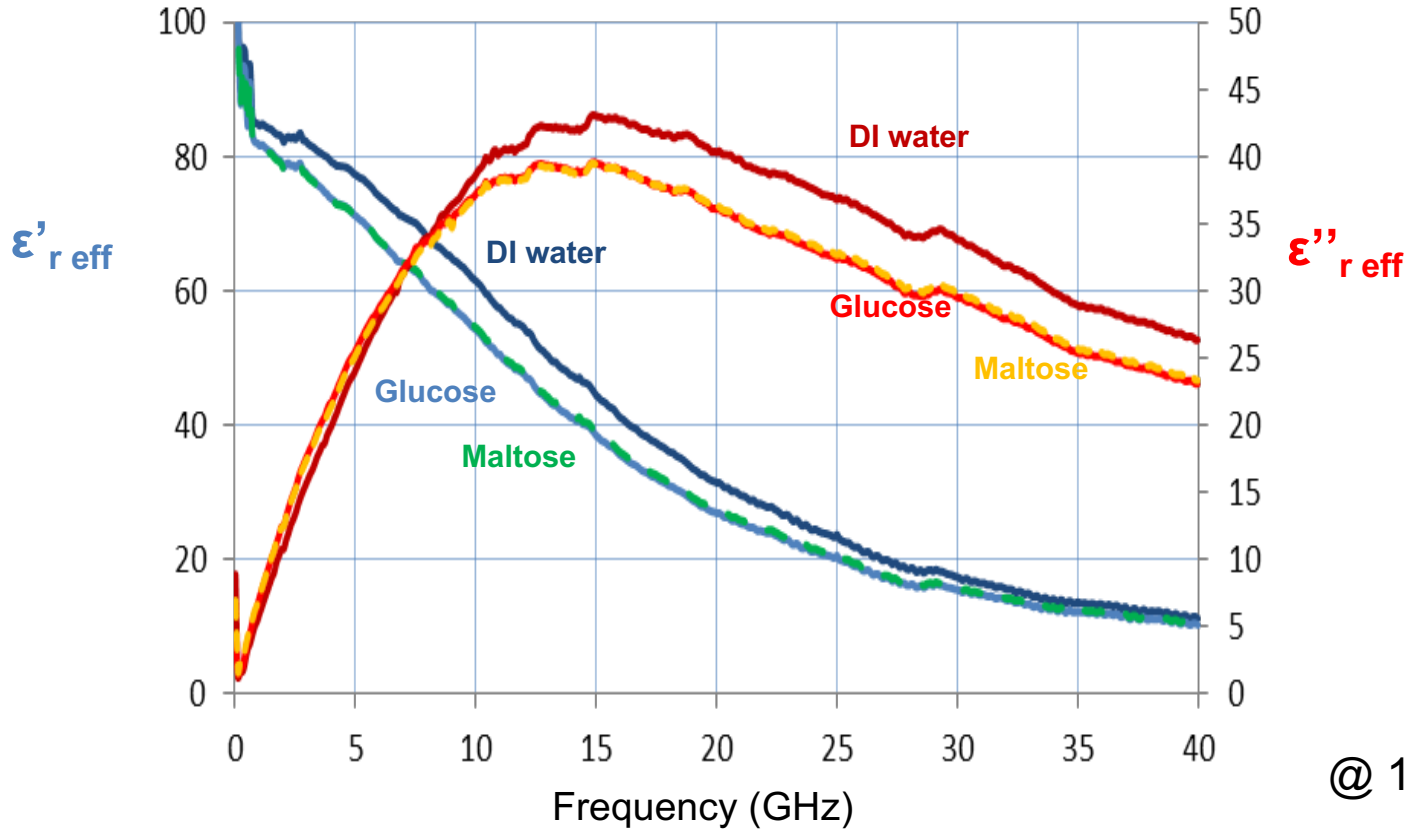


Protein concentration: 100 g/ml in aqueous solution

- Microwaves probes the molecules' *dipole reorientational* dynamics
- Specific molecular signature

Grenier et al., T-MTT 2013

Carbohydrates in aqueous solution

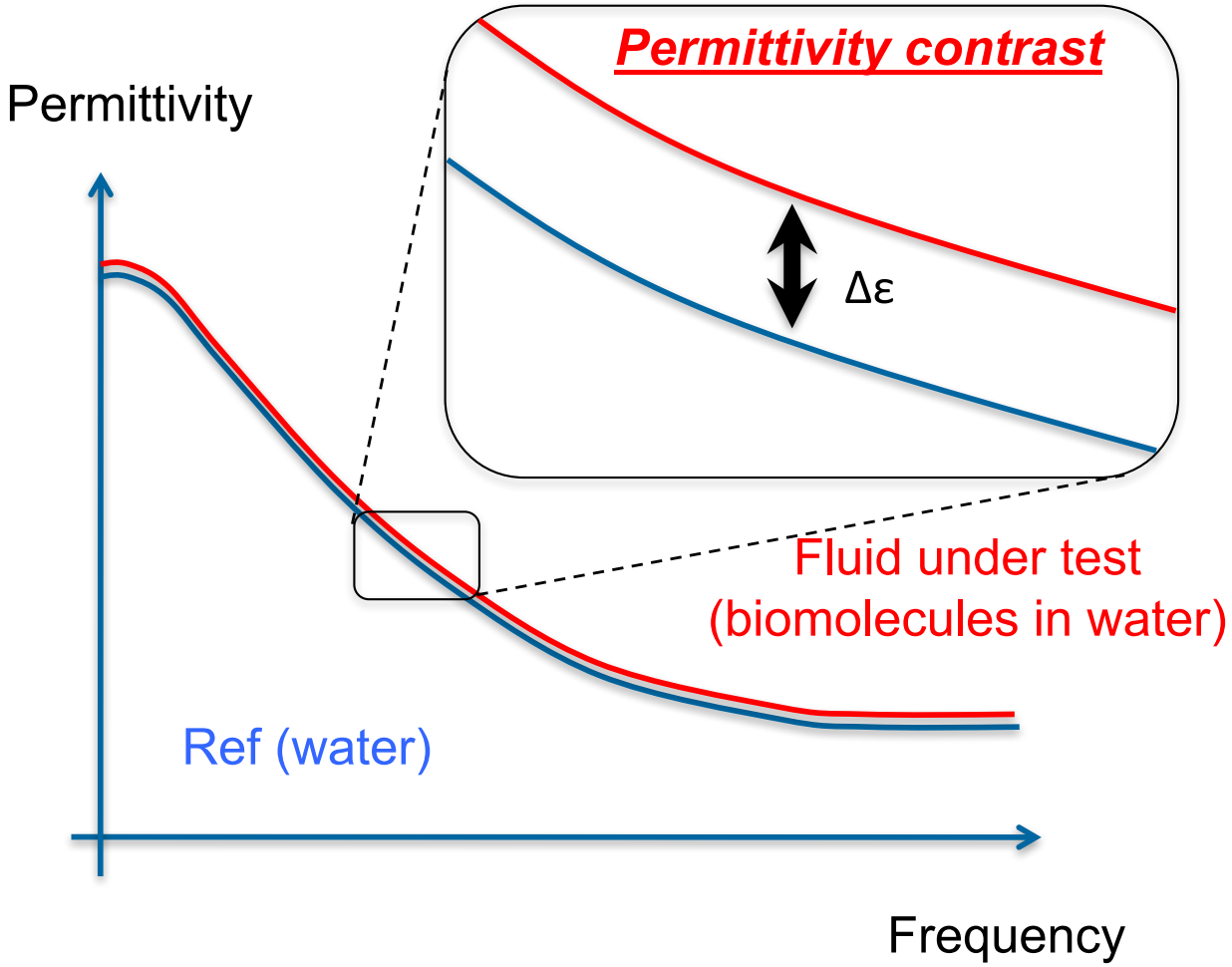


@ 100g/l

Very weak differences between carbohydrates signatures

⇒ Use of permittivity contrasts

Data processing approach



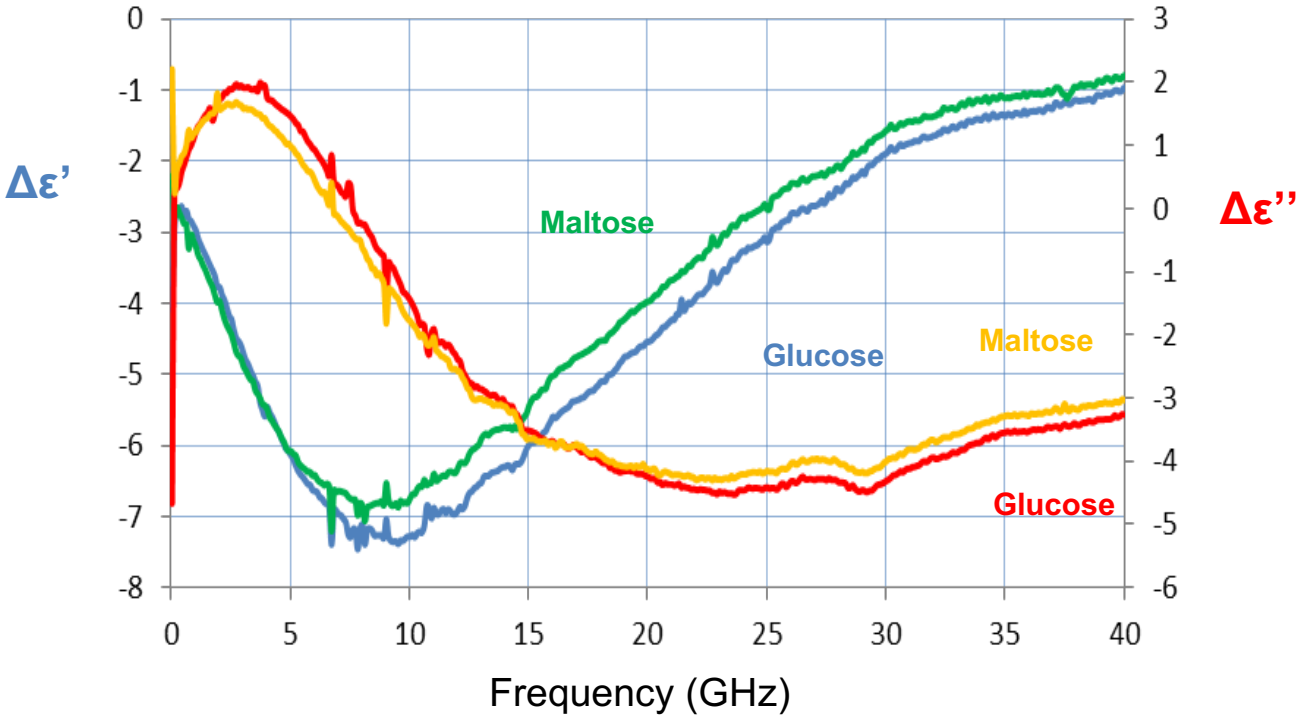
Large relaxation

Large ε variation
But small perturbation

Contrast evaluation
to compare similar fluids

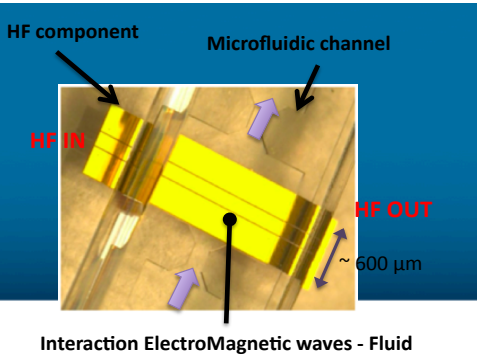
$\Delta\varepsilon = \varepsilon_{\text{fluid under test}} - \varepsilon_{\text{ref}}$

Dielectric contrasts of carbohydrates

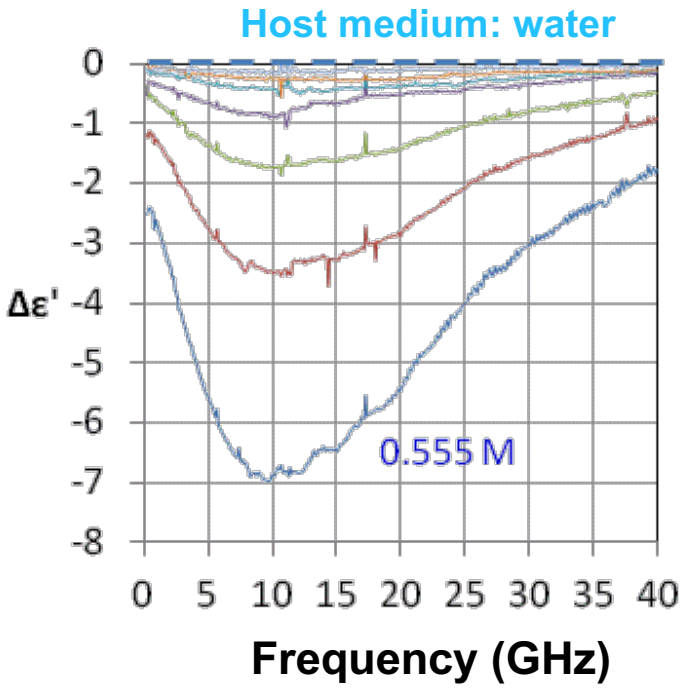


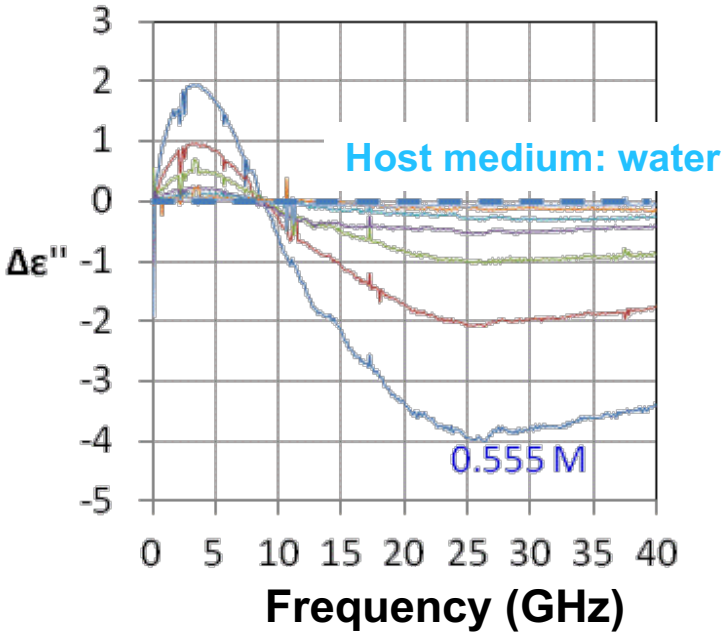
=> Possible discrimination between these 2 carbohydrates

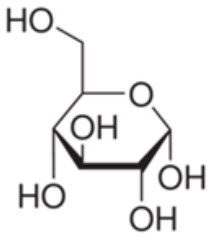
Sensitivity to molecular concentration



D-Glucose in DI water



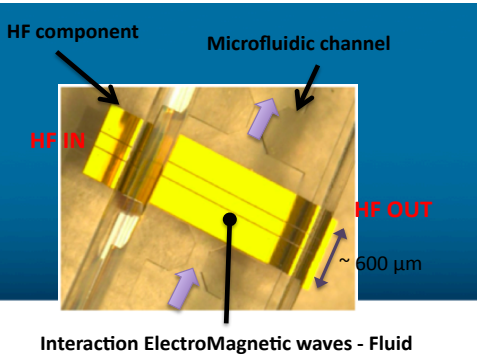




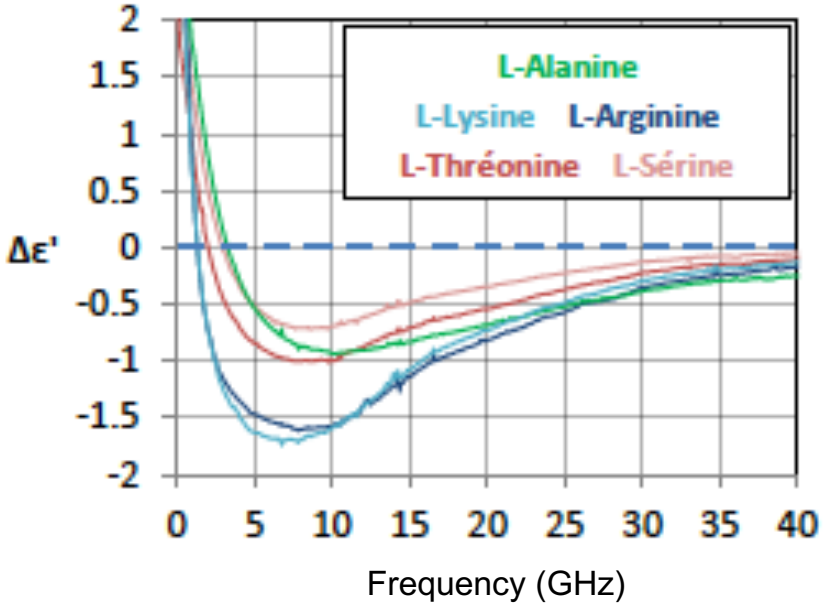
Molecular quantification

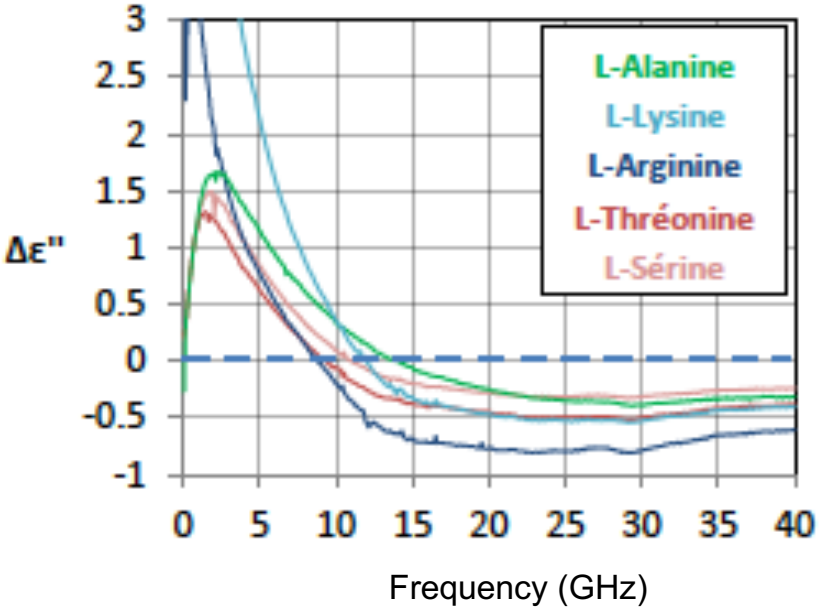
IEEE

Sensitivity to molecular types



Amino acids





[0.1M]

F. Artis et al., IEEE Biowireless,2015
K. Grenier et al., IEEE TMTT 2013

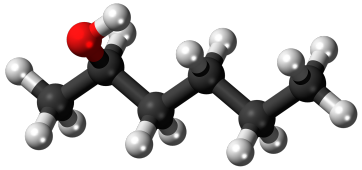
Molecular identification
Dielectric signatures - specificity

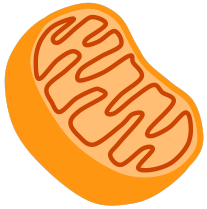
Biological complexity

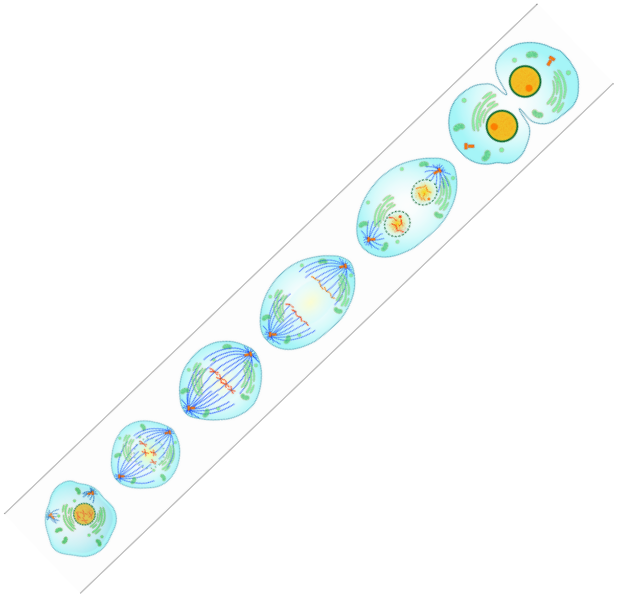
1-Biomolecules and supramolecular complexes

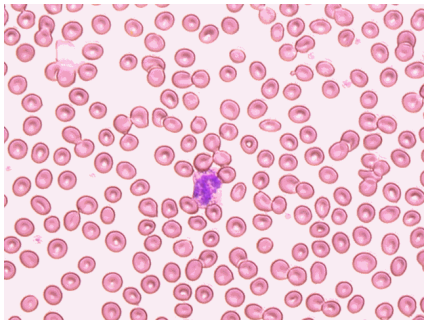
2-Live normal & cancer cells

3-Biological mechanisms



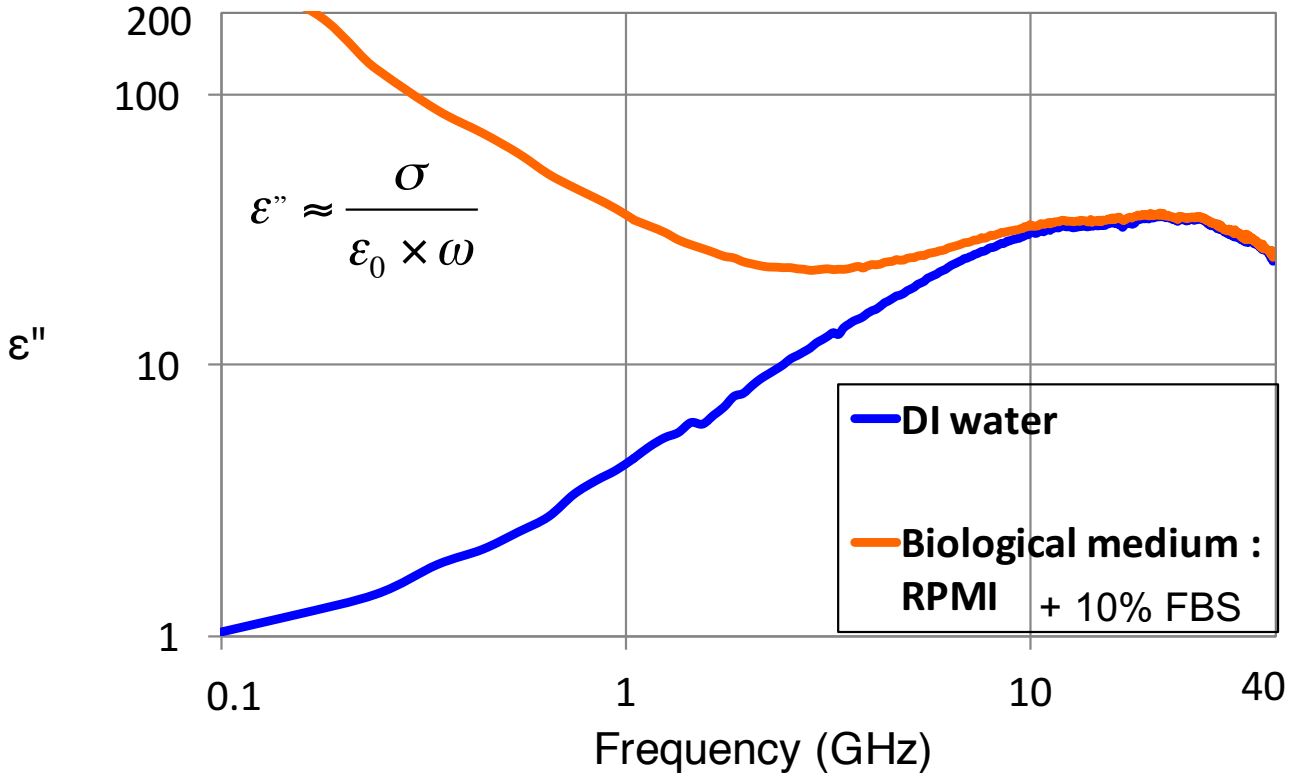




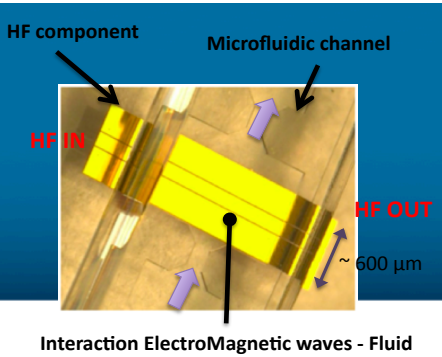


Direct measurement:
No specific preparation, label free, cells in their culture medium

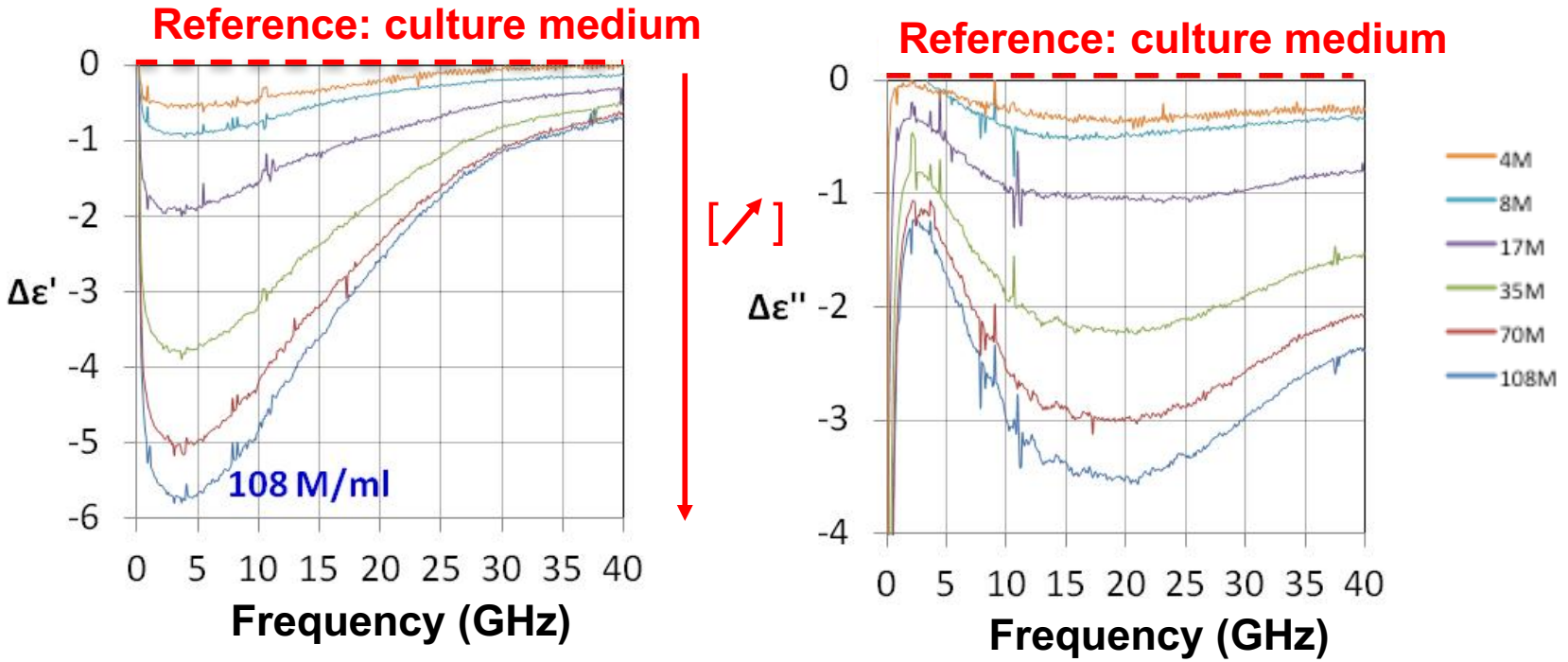
No screening with salt/ion content



Sensitivity to cell concentration



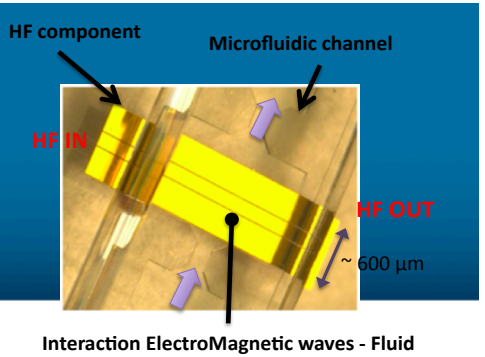
DOHH2 lymphoma
in suspension

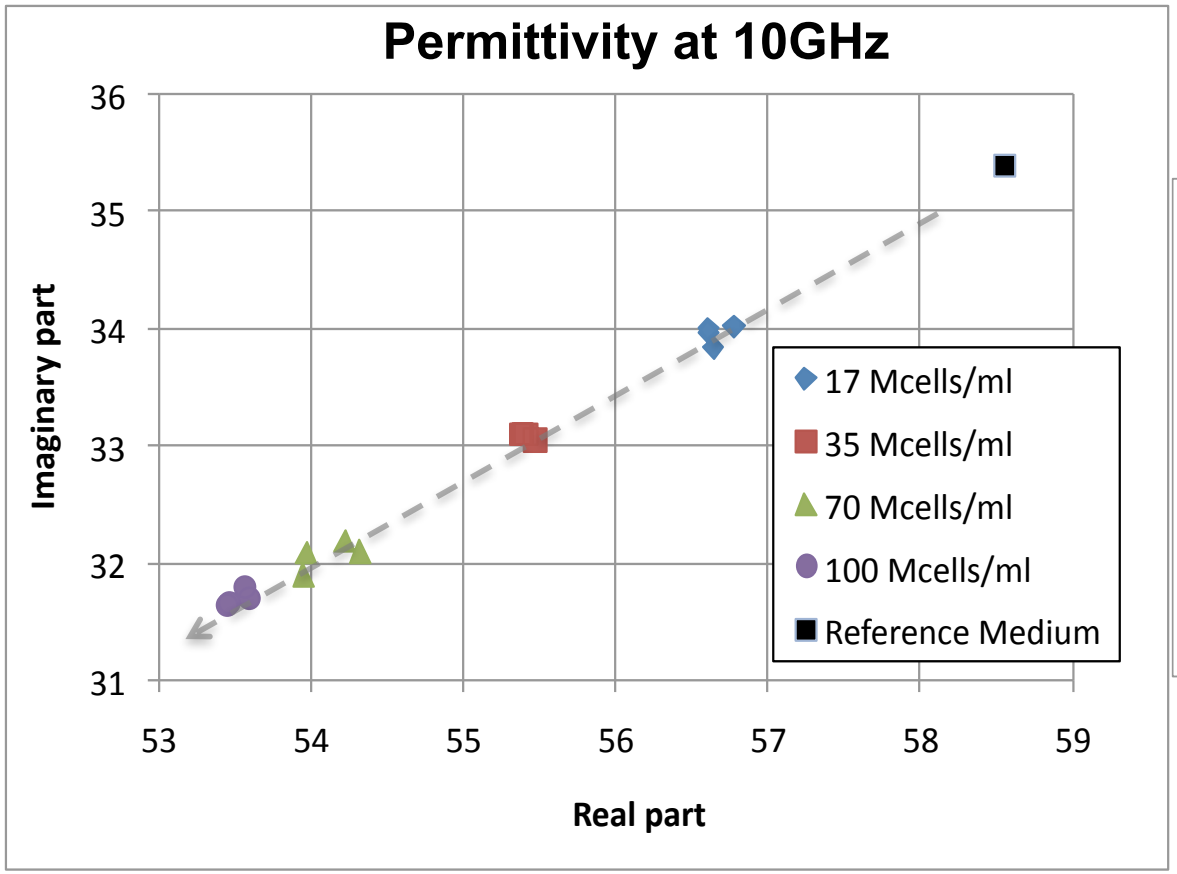


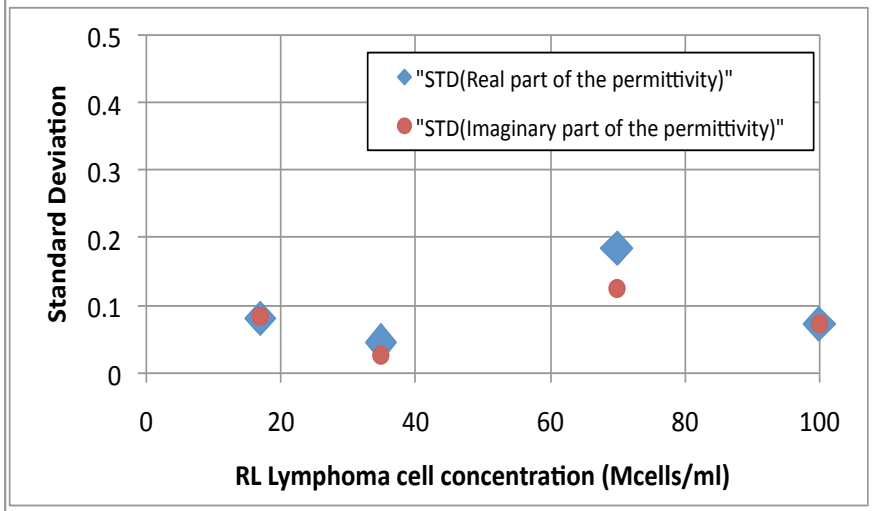
F. Artis et al., IEEE EuMW 2013
K. Grenier et al, IEEE Biowireless 2011

Cell quantification

Repeatability







F Artis et al., IEEE EuMC 2013

At low concentration -> standard deviation of the real part of the permittivity is < 0.1

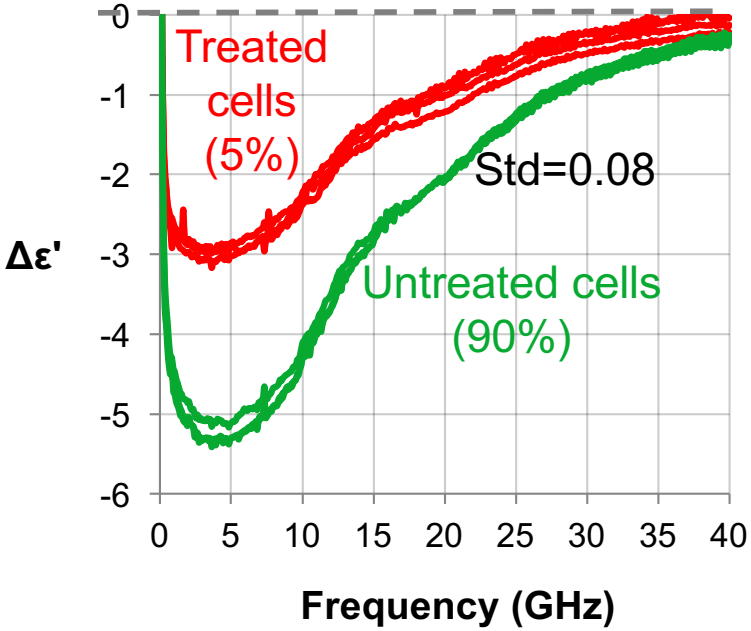
Cells quantification accuracy ≈ 1 Mcells/ml

Sensitivity to cellular permeabilization

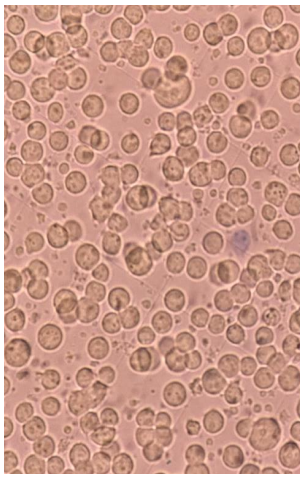
saponin

DOHH2 lymphoma
in suspension

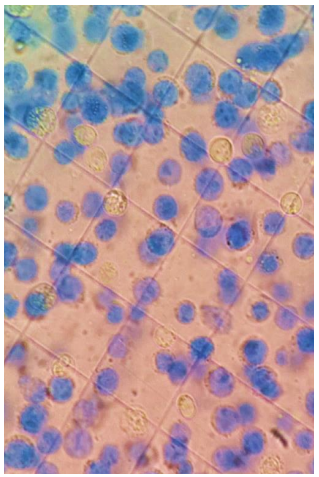
➜ Artificial cell death - Integrity of the cells kept (nucleus, mitochondria, endoplasmic reticulum and cytoskeleton intact)

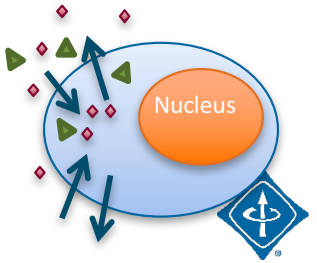


Untreated



Treated





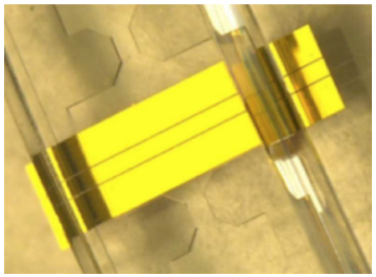
IEEE

F. Artis et al., IEEE IMS 2014

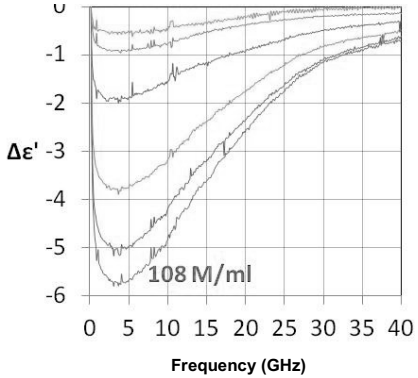
Microwave & Microfluidic biosensors

Scalable

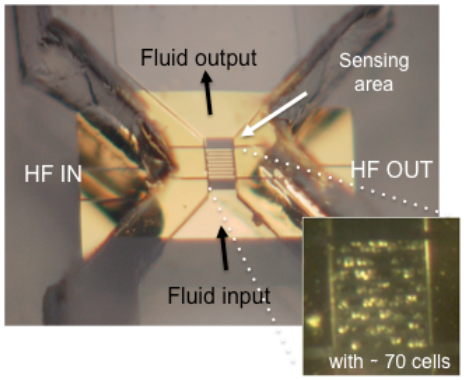
100 000 cells



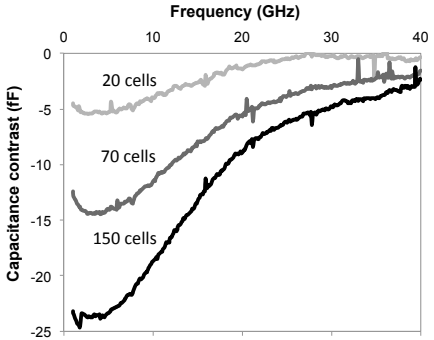
K. Grenier et al, IEEE TMTT 2009
F. Artis et al. EuMW 2013



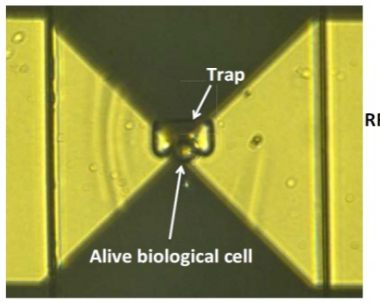
10 -100 cells



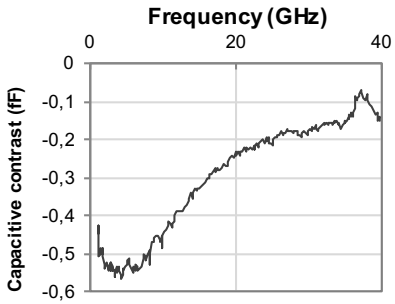
T. Chen et al. T-MTT Dec. 2012



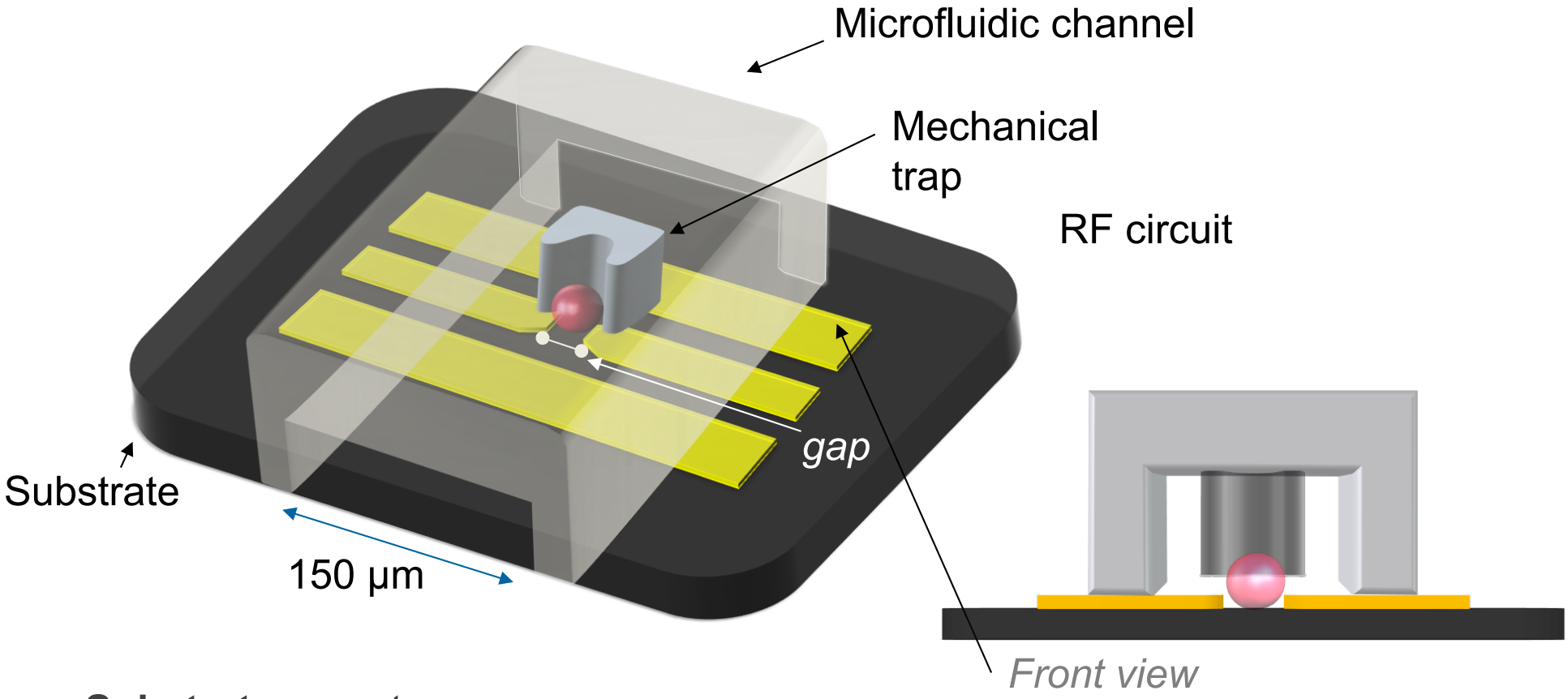
1 cell



T. Chen et al. IEEE IMS 2013
W. Chen et al. IEEE IMS 2015, EuMW 2015



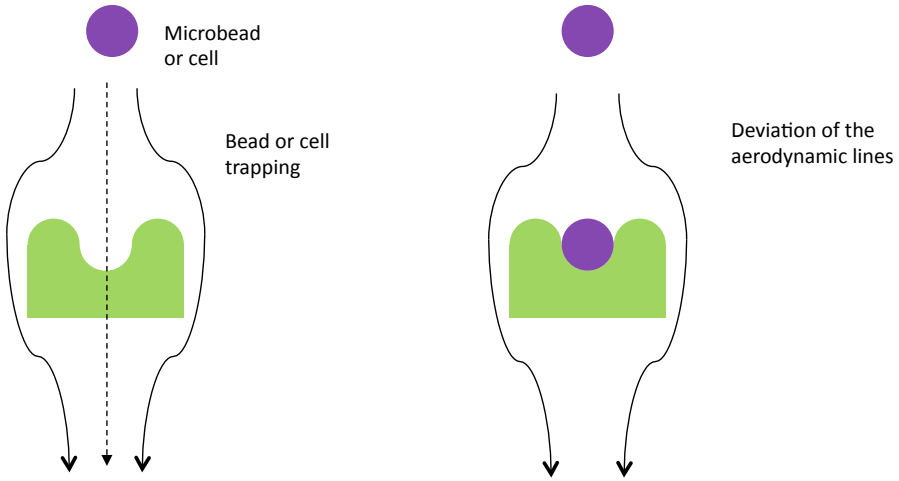
Broadband single cell detection



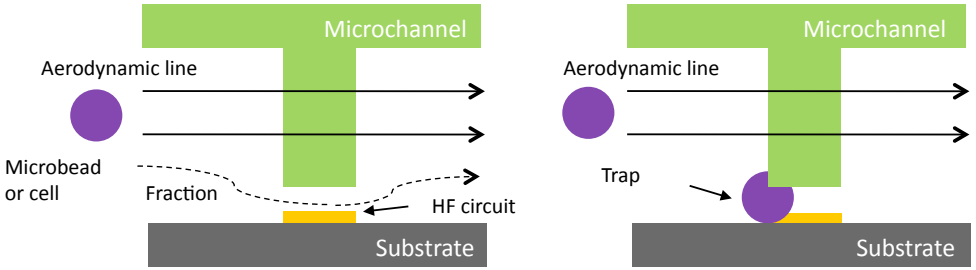
- **Substrate** : quartz
- **Coplanar waveguide**: gold layer of 0.3 µm thick, with a capacitive gap
- **Trap and fluidic channel**: polymer based technology

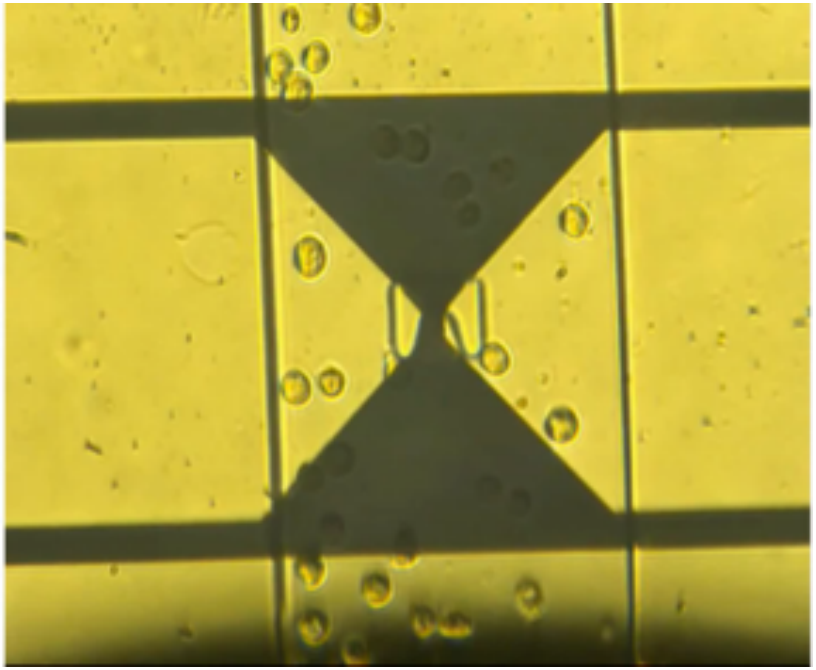
Single cell mechanical trapping

(a) Top views

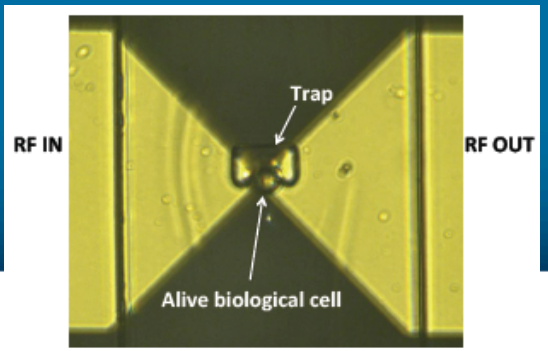


(b) Cross views



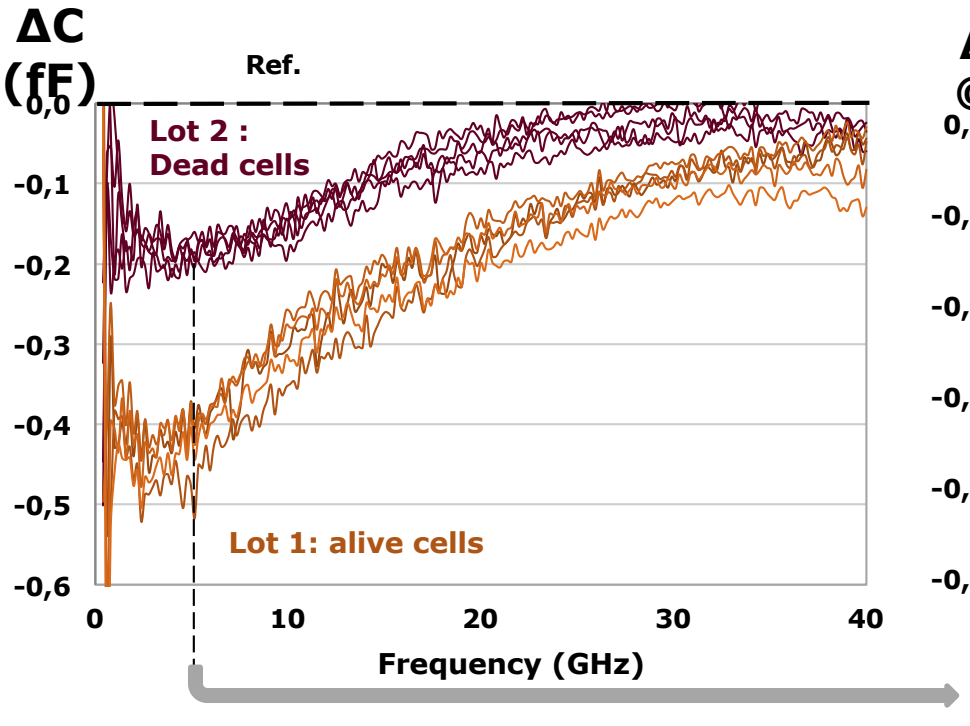


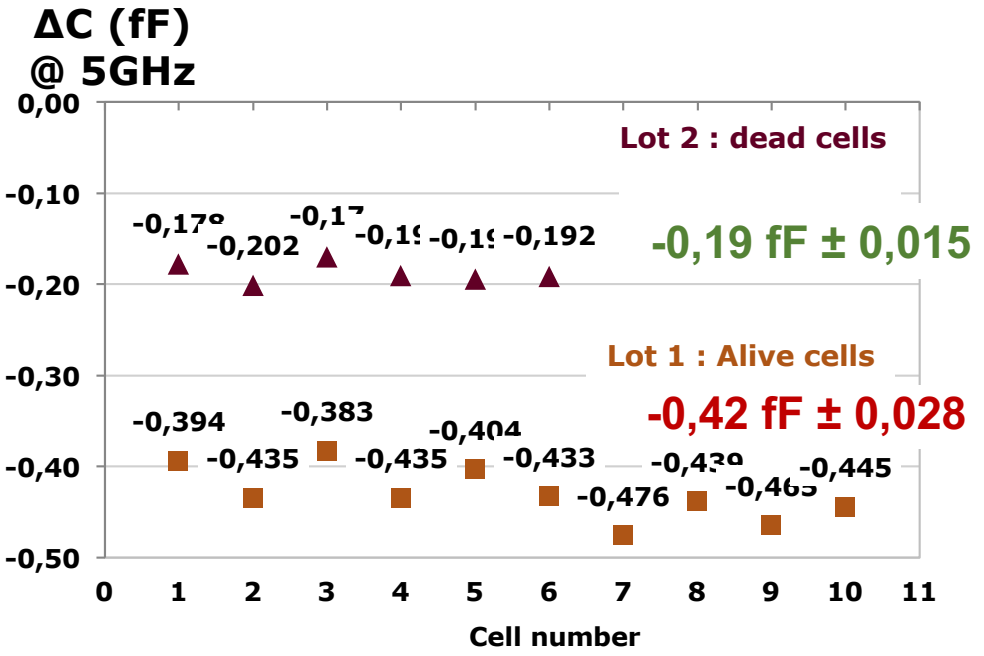
Sensitivity to cellular state



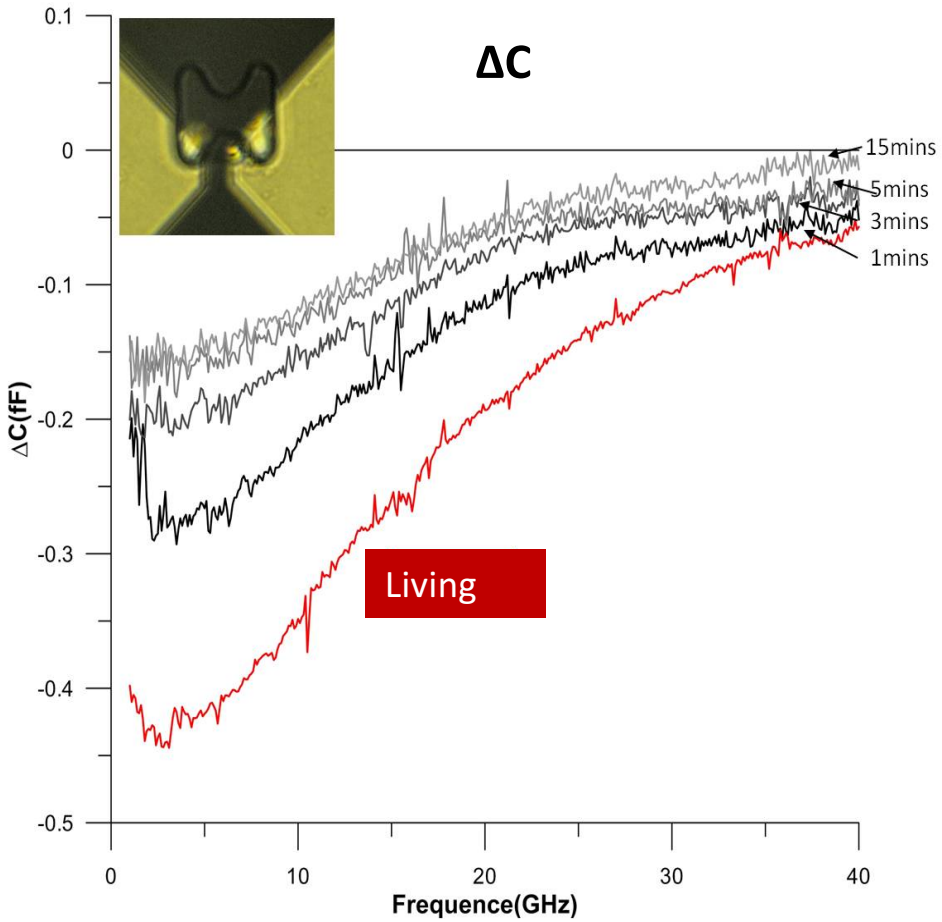
Cell death induced by starvation

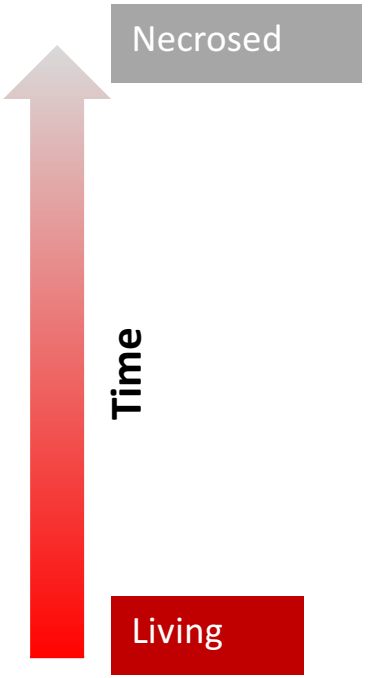
single THP1 cells in culture medium (RPMI+10%FVS)





Real time monitoring of a cell death

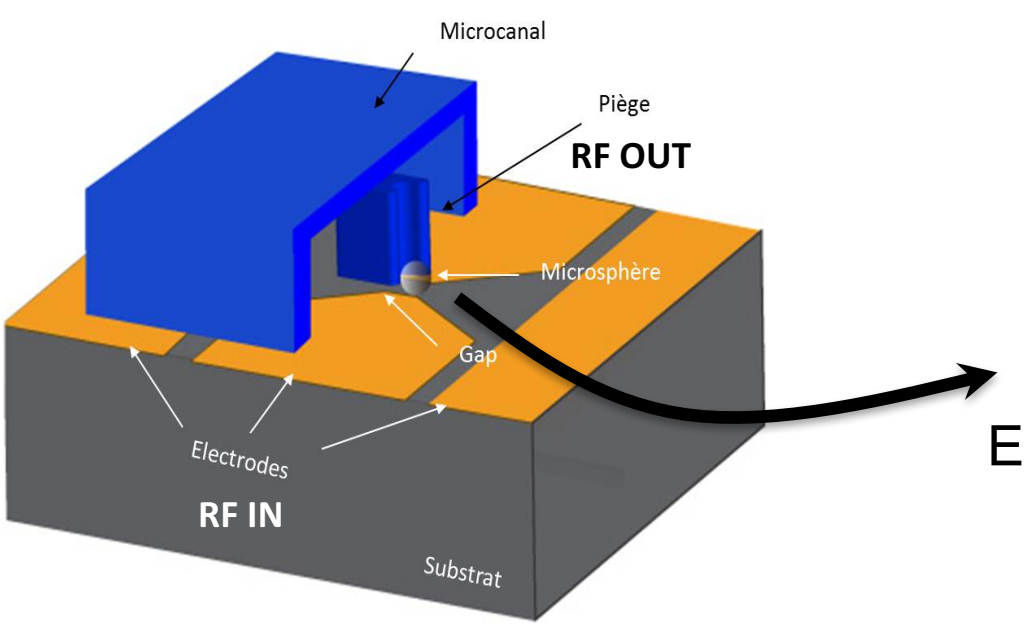


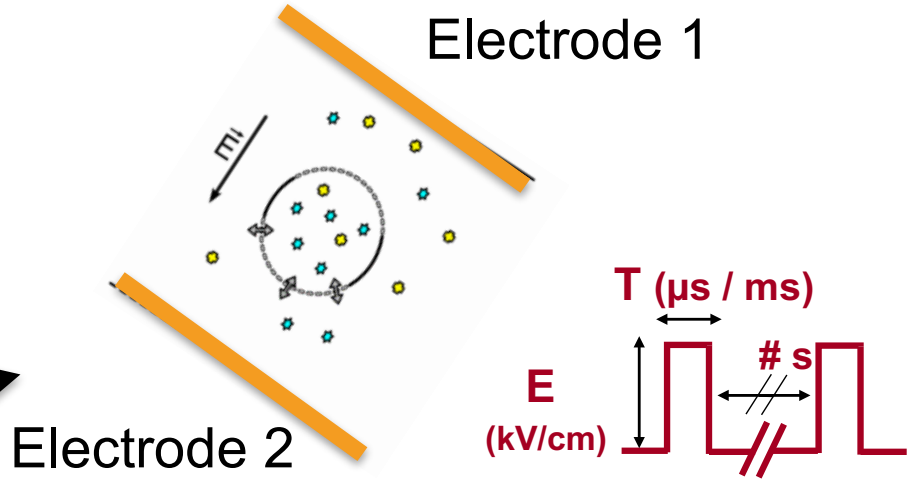


Culture medium +2% methanol

Monitoring of electro-permeabilization efficiency

Target: - Monitor stimulus effect with microwave spectroscopy





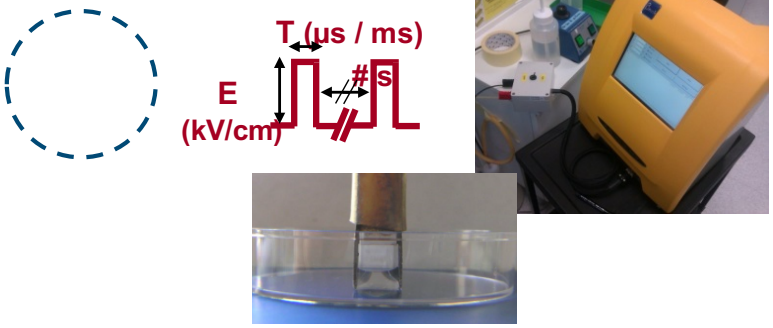
Cell permeabilization with electric fields application

Collaboration M.P. Rols team
PhD of Amar Tamra

Monitoring of electro-permeabilization

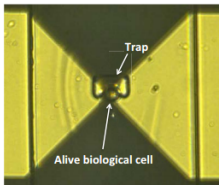
1/ Electroporation

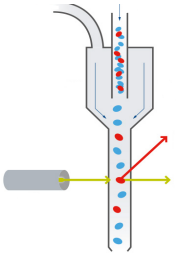
1,5 kV/cm, 100 µs, 1 Hz, n=8



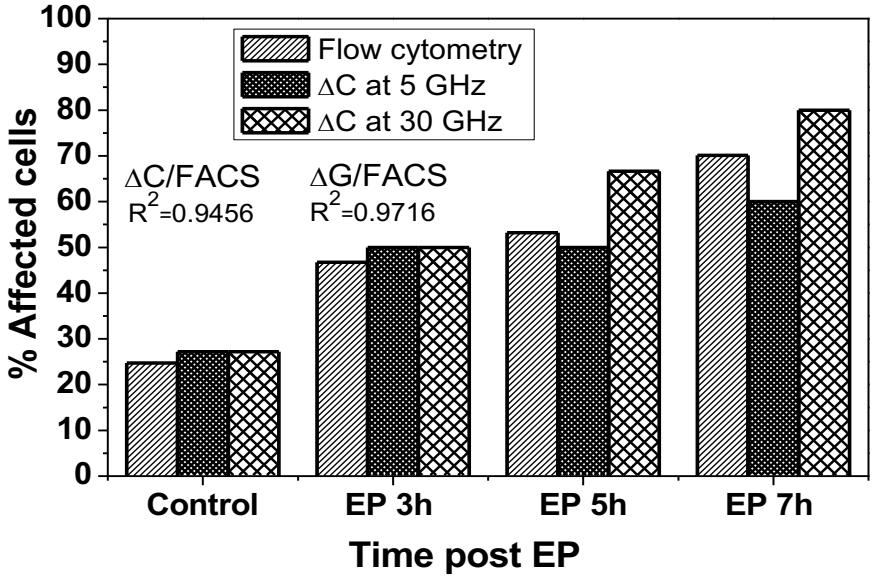
2/ Incubation

3/ RF and flow cytometry characterization





A. Tamra et al. IEEE IMS 2016



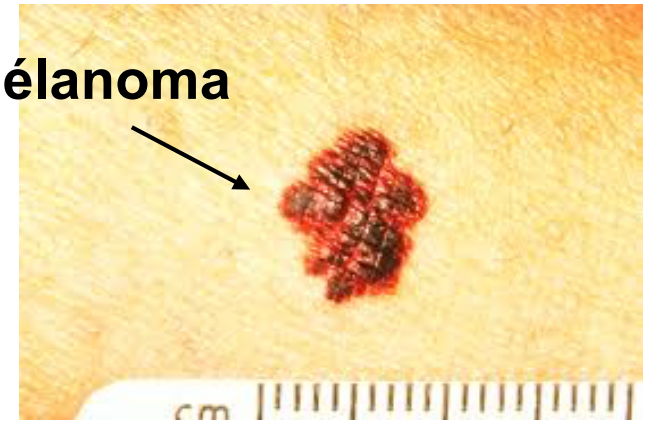
Good correlation between RF and flow cytometry results

➔ efficacy and robustness of the RF technique in depicting the kinetic effects of cell's electroporation

IEEE

Toward « in vivo » analysis

Skin cancer diagnosis



- Performed by trained dermatologists + optically-based microscopy
- Confirmation with biopsy

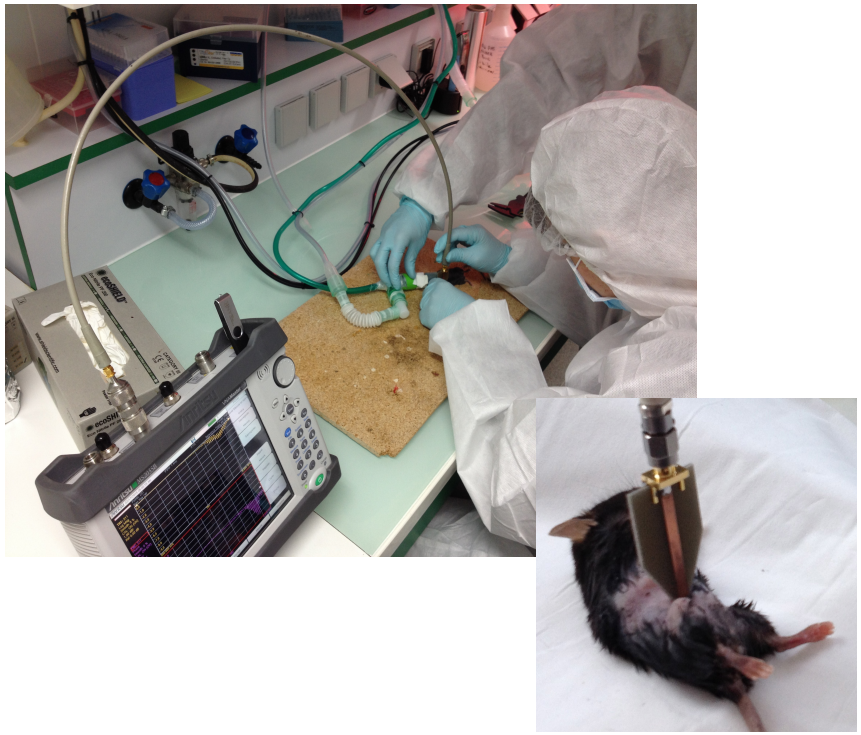
Early diagnosis proven to drastically increase the chance of recovery and survival

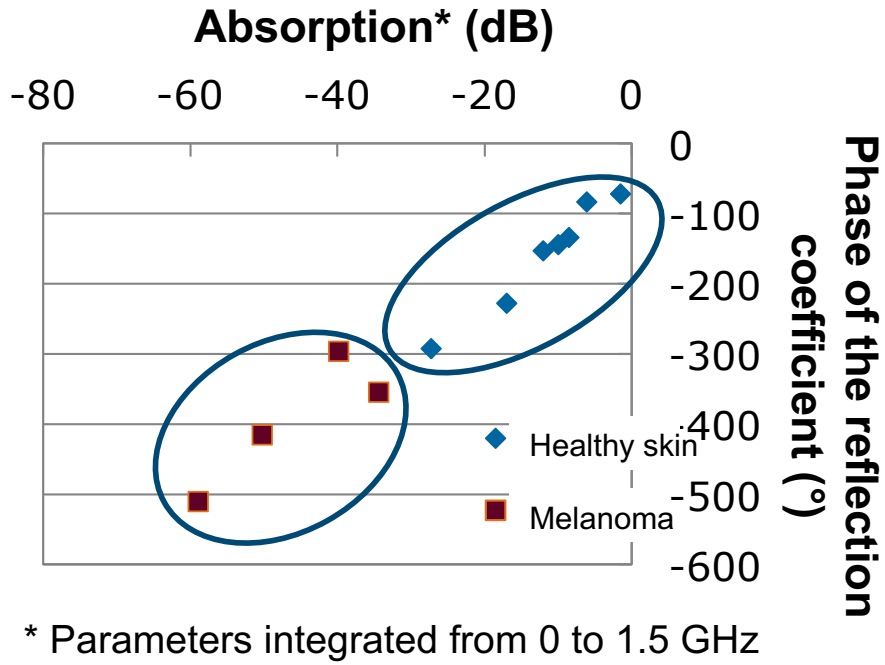
Needs:
- Bringing qualitative and quantitative physical parameters
- Providing **early** diagnostic
- **Non invasive** detection technique

IEEE

Toward « in vivo » analysis

Development of a low cost portable microwave test setup, compatible with sterile environment for « *in vivo* » measurements





* Parameters integrated from 0 to 1.5 GHz

K. Grenier et al., IEEE IMBioC 2017

➢ *2 distinct clouds with variability due to probe positioning*

➢ *Larger absorption and phase on the tumor area, which is in agreement with immuno-analysis*

Conclusions

- Interest in developing microwave dielectric spectroscopy for molecular and cellular analysis

  ➔ access to intracellular dielectric activity

- Microwave spectroscopy provides qualitative and quantitative new bioparameters: not only cells quantification and viability, but a global state of cell due to intracellular dielectric activity, real time monitoring of biological processes

- Opens new perspectives on fundamental biological knowledge and therapy, diseases diagnostic, personalized medicine notably (drugs screening on patient cells), with in vitro and also in vivo investigations, for ubiquitous healthcare

IEEE

Other complementary research trends

Microwave scanning microscopy

Complete analyzing system miniaturization

Implants

For further information

- IEEE publications and others;
  IEEE Microwave Mag. May 2015
- Conferences:
  - ✓ IEEE MTT-S: IMS and IMBioC
  - ✓ IEEE EMB-S
  - ✓ BDS

- Books:
  - ✓ *Dielectric relaxation in biological systems*, V. Raicu & Y. Feldman, Oxford Univ. Press
  - ✓ *Broadband dielectric spectroscopy*, F. Kremer & A. Schönhals, Springer
  - ✓ RF/Microwave interaction with biological tissues, A. Vander Vorst, A. Rosen, Y. Kotsuka, Wiley
  - ✓ Handbook of Biological effects of electromagnetic fields, C. Polk & E. Postow, CRC Press

IEEE

Thank you for your attention

IEEE MTT-S WEBINARS

YOUR EDUCATIONAL & PROFESSIONAL RESOURCE

Thank you for attending our webinar!

To obtain an IEEE PDH for this webinar, select the IEEE Continuing Education icon on the screen and fill out all the required information including the code: 2017MTTSWEB09MHS12DKG21