# Non invasive microwave dielectric spectroscopy for biological characterization and healthcare applications : Importance of a differential approach

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https://www.laas.fr/public/en/mh2f



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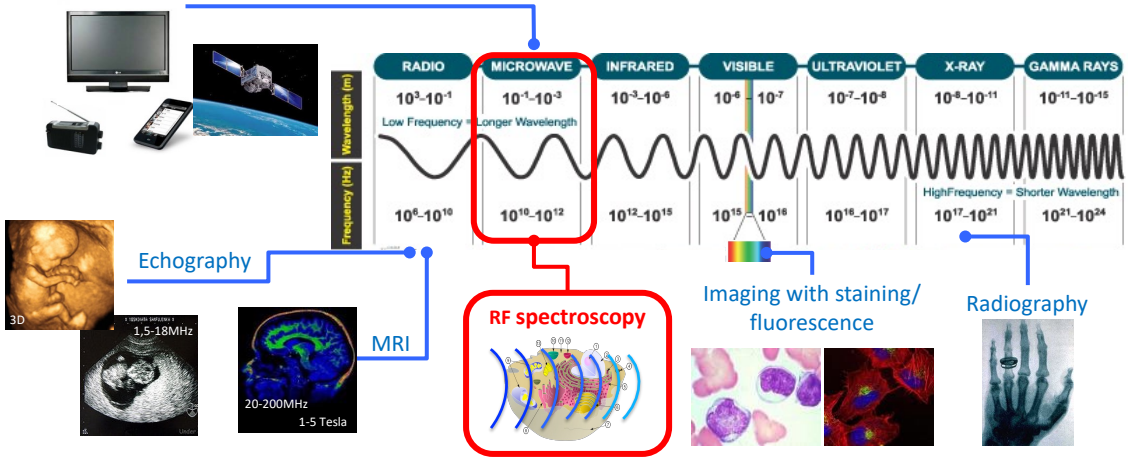
## *Microwaving* the living matter for sensing




***What about dielectrically analyzing the living in the microwave range?***



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# Classical characterization methods of cells and tissues analysis

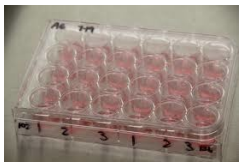
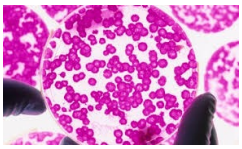
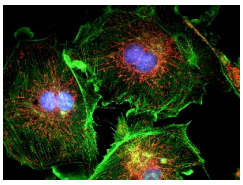
- Optics
- Laser detection
- Flow cytometry

→ Reference techniques ✓

**However…**

- > Invasive and toxic for cells
- > Destructive
- > Time consuming
- > Costly

✗

→ ***Interest in non invasive and label-free bio-analysis***



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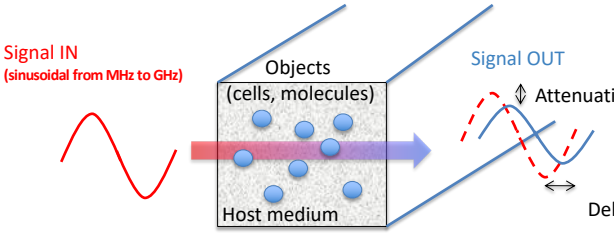
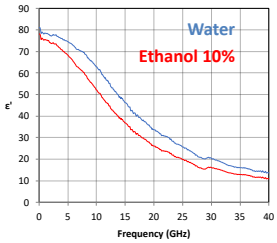
# Microwave dielectric spectroscopy readouts




Attenuation : $\varepsilon'' = \frac{\Delta\varepsilon}{1+\left(f/f_r\right)^2} \cdot \frac{f}{f_r}$

Delay : $\varepsilon' = \varepsilon_\infty + \frac{\Delta\varepsilon}{1+\left(f/f_r\right)^2}$

- ➢ Both ε' and ε" are readouts of
  - *Scanning frequency,*
  - *Dipolar moment,*
  - *Size of the objects (volume fraction)*
  - *Viscosity*
- ➢ Modification of the molecular network structure
  - →Change of the microwave dielectric response



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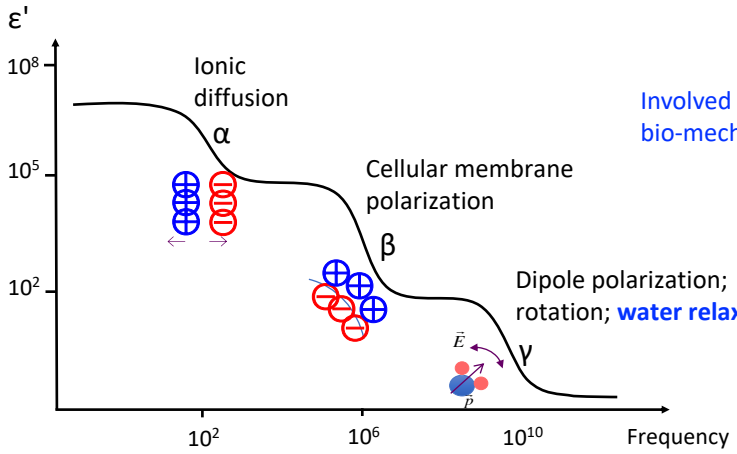
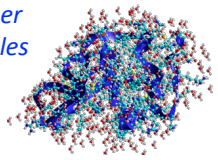
# Electromagnetic wave interaction with the living

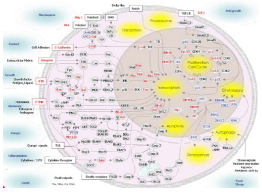
*Water: abundant constituent of the living*




*Affinity with other molecules/particles*



Involved in many bio-mechanisms



*H. Schwan, 1985*



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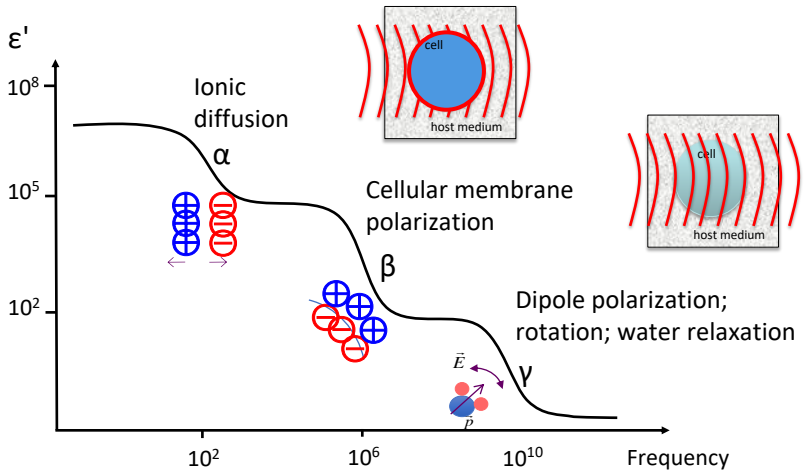


*H. Schwan, 1985*



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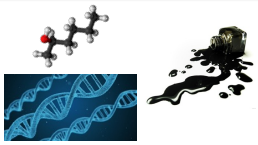
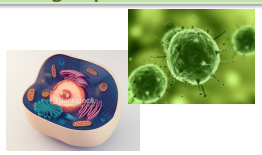
# Multi scales

***Different sample scales***

1-Biomolecules, ions, particles → 2- Cells in their culture medium and biological processes → 3- Animal, Human

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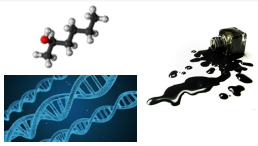
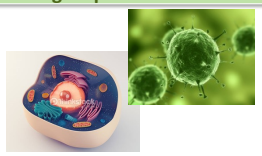
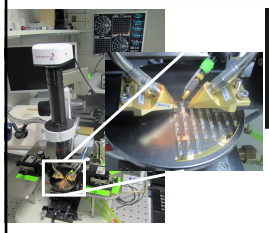
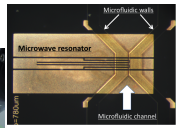
# Multi scales // multi sensing solutions

1-Biomolecules, ions, particles → 2- Cells in their culture medium and biological processes → 3- Animal, Human

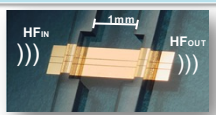




***Different sensors and test setups solutions***

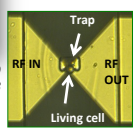
**In transmission** • **Narrowband** • **Broadband** **In reflection**


*T. Chretiennot et al, IEEE TMTT 2013*

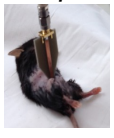



*K. Grenier et al, IEEE TMTT 2009*
*K. Grenier et al. IEEE TMTT 2013*
*G. Poiroux et al. IJBB 2020*

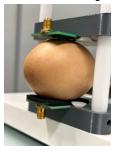



*A. Tamra et al. IEEE TMTT 2017*
*A. Tamra et al. IEEE IMBioC 202*
*A. Tamra et al IEEE TBME 2022*

***In hospital***



***In hatchery***



*K. Grenier et al, IEEE IMBioC 2017*
*F. Morfoisse et al. ATVB 2018*



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# Multi scales // multi sensing solutions

1-Biomolecules, ions, particles

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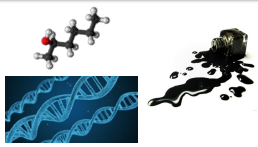
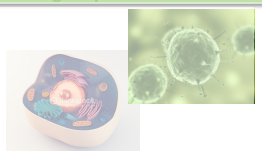
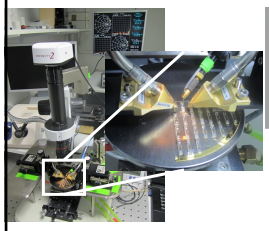
3- Animal, Human

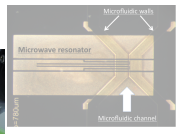




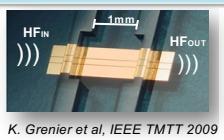
***Different sensors and test setups solutions***

**In transmission** • Narrowband • **Broadband** **In reflection**

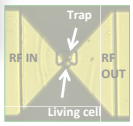




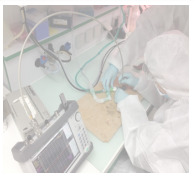

T. Chretiennot et al, IEEE TMTT 2013



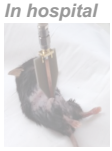

K. Grenier et al, IEEE TMTT 2009
K. Grenier et al. IEEE TMTT 2013
G. Poiroux et al. IJBB 2020




A. Tamra et al. IEEE TMTT 2017
A. Tamra et al. IEEE IMBioC 202
A. Tamra et al IEEE TBME 2022



*In hospital*



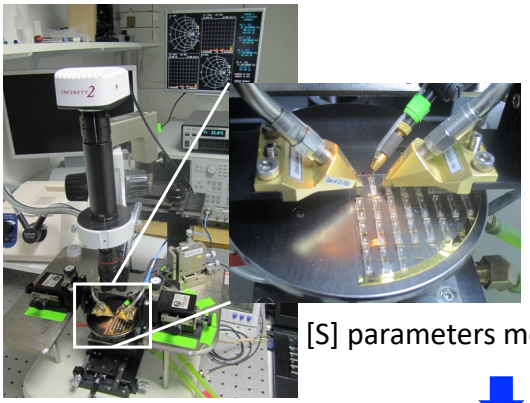
*In hatchery*

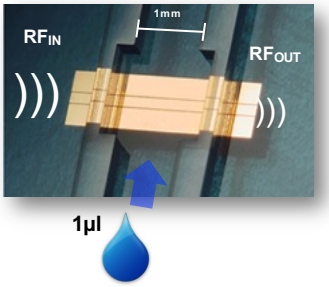
K. Grenier et al, IEEE IMBioC 2017
F. Morfoisse et al. ATVB 2018

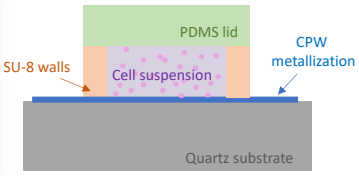




# Coplanar waveguide sensor for biomolecules in aqueous solution and cells suspensions analysis



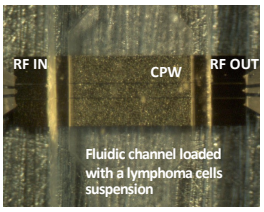



[S] parameters measurements

De-embedding

(ε', ε") vs frequency

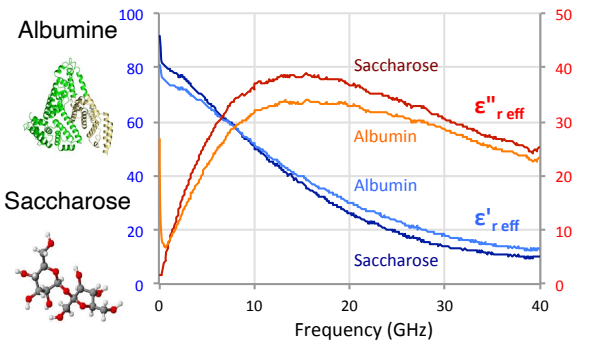



*More details in Grenier et al., IEEE T-MTT 2009*

# Molecules and dielectric spectroscopy

Concentration: 100 g/l
in aqueous solution

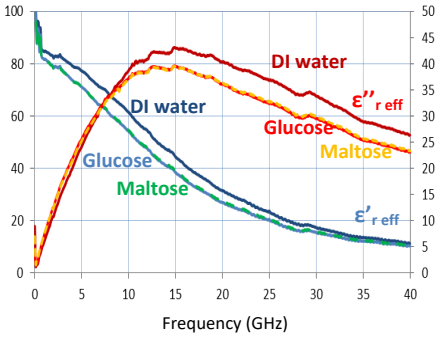
## Very different molecules

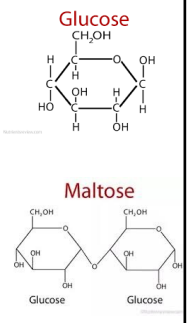



*K. Grenier et al., T-MTT 2013*

***Specific molecular dielectric response***

## Closer molecules: carbohydrates example




***Very weak differences between carbohydrates signatures***



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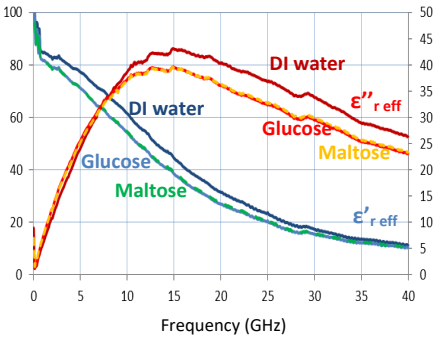
# Need to apply a differential approach for small ε perturbation

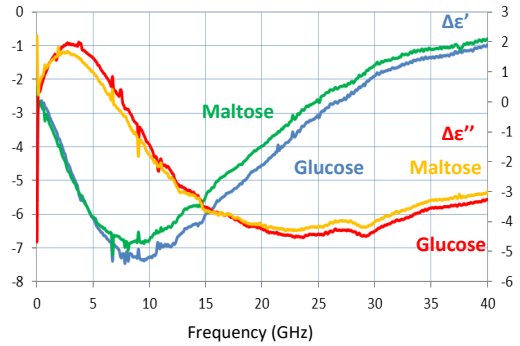
Concentration: 100 g/l
in aqueous solution

Here with permittivity
but it can be done on
any dielectric parameter




DI water

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




***Possible discrimination between these 2 carbohydrates***



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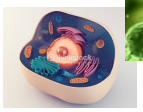
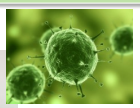
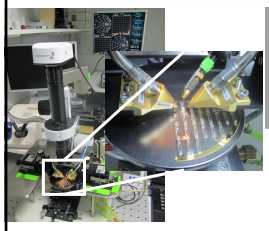
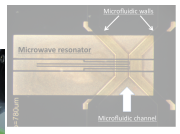
# Multi scales // multi sensing solutions

1-Biomolecules, ions, particles → 2- Cells in their culture medium and biological processes → 3- Animal, Human

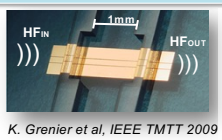




***Different sensors and test setups solutions***

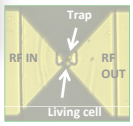
**In transmission** • Narrowband • **Broadband** **In reflection**

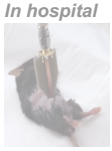

*T. Chretiennot et al, IEEE TMTT 2013*




*K. Grenier et al, IEEE TMTT 2009*
*K. Grenier et al. IEEE TMTT 2013*
*G. Poiroux et al. IJBB 2020*




*A. Tamra et al. IEEE TMTT 2017*
*A. Tamra et al. IEEE IMBioC 202*
*A. Tamra et al IEEE TBME 2022*

*In hospital*

*In hatchery*

*K. Grenier et al, IEEE IMBioC 2017*
*F. Morfoisse et al. ATVB 2018*



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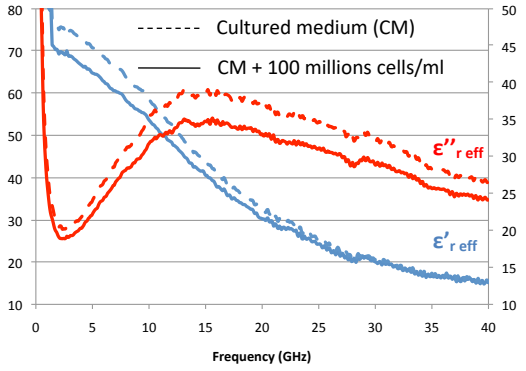
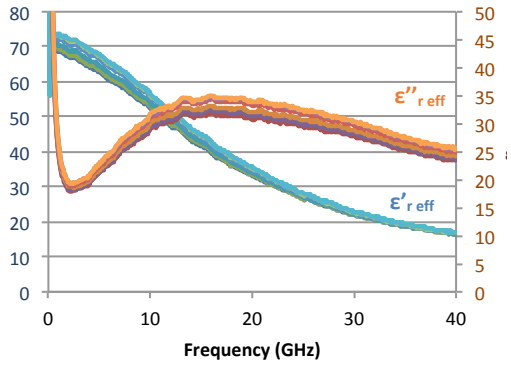
# Cells in suspension and dielectric spectroscopy

**RL lymphoma cells suspension comparison with medium**




***Easy to differentiate the two different situations***

**DOHH2 lymphoma cells suspensions different concentrations from 4, 8, 17, 35, 70, 108 millions cells/ml**




***Difficult to distinguish***



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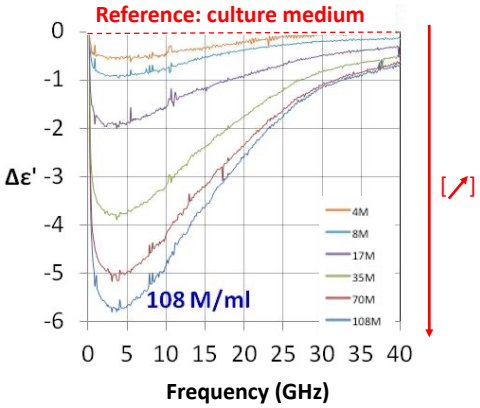
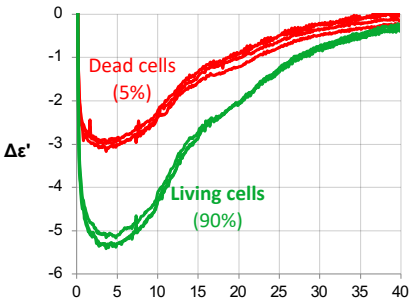
# Sensitivity to cell concentration with the differential approach

DOHH2 lymphoma in suspension




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

Sufficient sensitivity to identify pathological state in the case of the use of saponin on cells in suspension




*F. Artis et al., IEEE IMS 2014*



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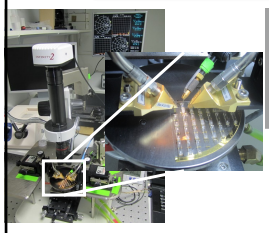
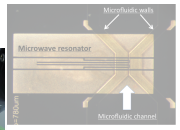
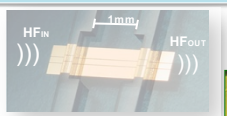
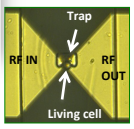





*T. Chretiennot et al, IEEE TMTT 2013*

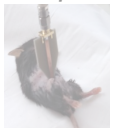



*K. Grenier et al, IEEE TMTT 2009*
*K. Grenier et al. IEEE TMTT 2013*
*G. Poiroux et al. IJBB 2020*




*A. Tamra et al. IEEE TMTT 2017*
*A. Tamra et al. IEEE IMBioC 202*
*A. Tamra et al IEEE TBME 2022*

*In hospital*



*In hatchery*

*K. Grenier et al, IEEE IMBioC 2017*
*F. Morfoisse et al. ATVB 2018*



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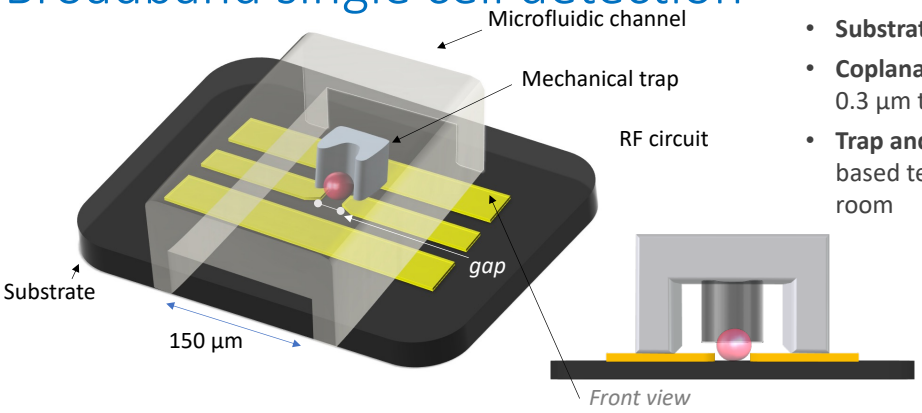
# Broadband single cell detection




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

[S] parameters measurements → ($\Delta C$, $\Delta G$) vs frequency

→ Because the precise cell size in unknown

De-embedding

*More details in Chen et al., IEEE T-MTT 2012*



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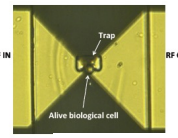
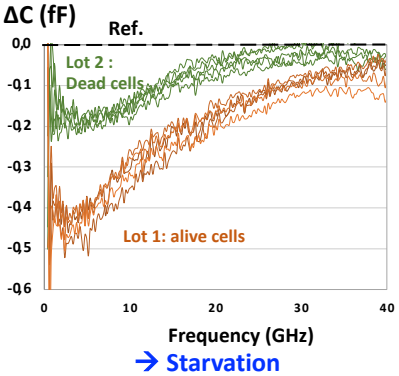
# Single cell and dielectric spectroscopy

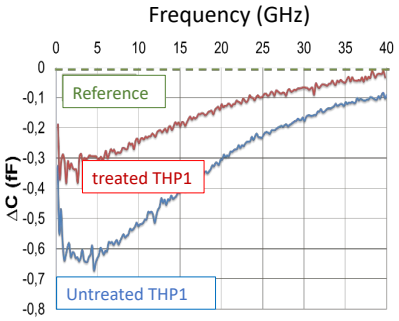



*Single THP1 cells in culture medium (RPMI+10%FVS)*

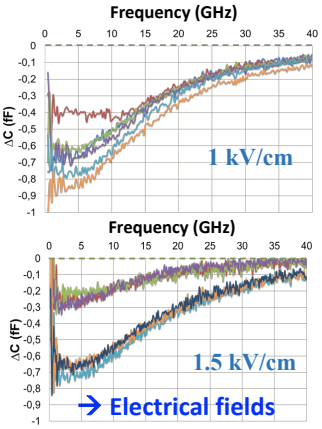
Differential approach allow to monitor cell state in different stress applied on the cell




→ **Starvation**




→ **Chemical agent (saponin)**




→ **Electrical fields**

*F. Artis et al., IEEE IMBioC 2019*

*A. Tamra et al., URSI-GASS 2021*
*A. Tamra et al., IEEE TBME 2022*



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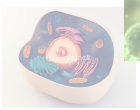
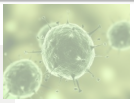
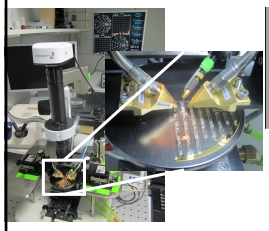
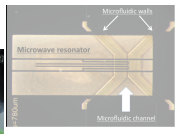
# Multi scales // multi sensing solutions

1-Biomolecules, ions, particles → 2- Cells in their culture medium and biological processes → 3- Animal, Human

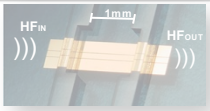




***Different sensors and test setups solutions***

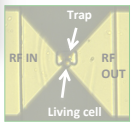
**In transmission** • Narrowband • **Broadband** **In reflection**

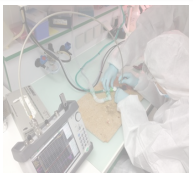

*T. Chretiennot et al, IEEE TMTT 2013*



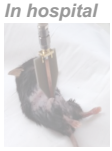

*K. Grenier et al, IEEE TMTT 2009*
*K. Grenier et al. IEEE TMTT 2013*
*G. Poiroux et al. IJBB 2020*




*A. Tamra et al. IEEE TMTT 2017*
*A. Tamra et al. IEEE IMBioC 202*
*A. Tamra et al IEEE TBME 2022*



*In hospital*



*In hatchery*

*K. Grenier et al, IEEE IMBioC 2017*
*F. Morfoisse et al. ATVB 2018*



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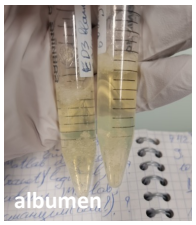
# The device used in extension to particular biological liquids

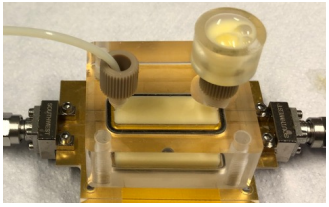
PPILOW

→ Study of egg constituents for quality assessment and early egg sexing


Fluids particularly sticky, viscous

Millifluidic sensor with appropriate RF measurement and cleaning protocols



S parameters measurements

*Y. Kozhemyakin et al., EuMW2022*



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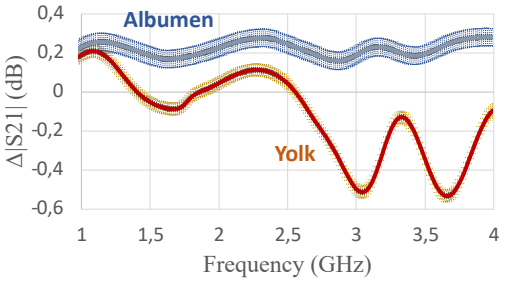
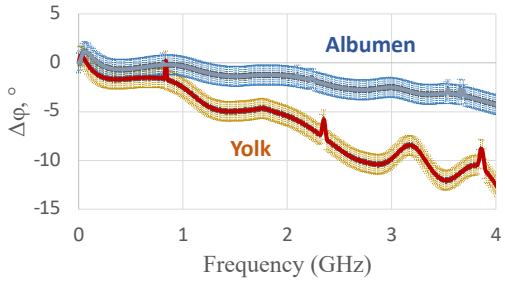
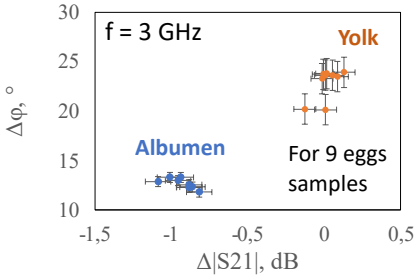
# Differential method on S parameters




- Reference liquid is DI water
- Measurement reproducible

Prove the feasibility to study complex biological fluid with the dielectric spectroscopy



# Importance of differential approach in microwave dielectric spectroscopy for biological characterization

- High sensitivity needed due to small variations to detect
- Interest demonstrated with various materials : Biomolecules in aqueous solutions, Cells in their culture medium (in suspension and at the single cell level), Complex liquids (eggs constituents for instance)

Perspectives:

- Applicative with new bioparameters: cells quantification, viability assessment + cell global state of cell and real time monitoring of biological processes
- Direct applications: helping in therapy decisions, **early diseases diagnostic**, enhancing treatment efficiency with **personalized medicine** (drugs screening on patient cells), with *in vitro* and also *in vivo*

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S. Réhault-Godberg. INRAE, Tours

And fundings from

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# Thank you for your attention!

**Any questions ?**