EUROPEAN MICROWAVE WEEK

JAARBEURS UTRECHT THE NETHERLANDS

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THE ART OF MICROWAVES

EUMW2020

Radio Frequency sensors & lab-on-chip technologies: news opportunities for biomedical diagnosis

WF-02 Recent Advances in Topologies, Technologies and Practical Realizations of Microwave Sensors

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Introduction

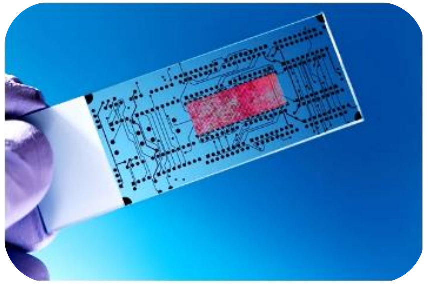
- Objectives of the SUMCASTEC Project
- Motivation
- Cell dielectric spectroscopy as a new analysis approach in the microwave spectrum
- Toward New generation of lab on chip with imbedded CMOS electronics?
- Sensing system based on Injection Lock Oscillator architecture
- Measurement and few ppm sensing capability demonstration
- Conclusion

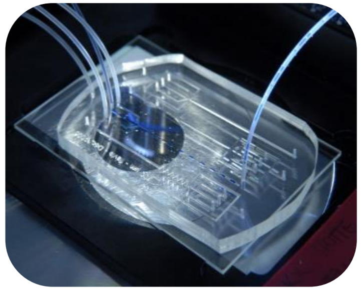
The SUMCASTEC project

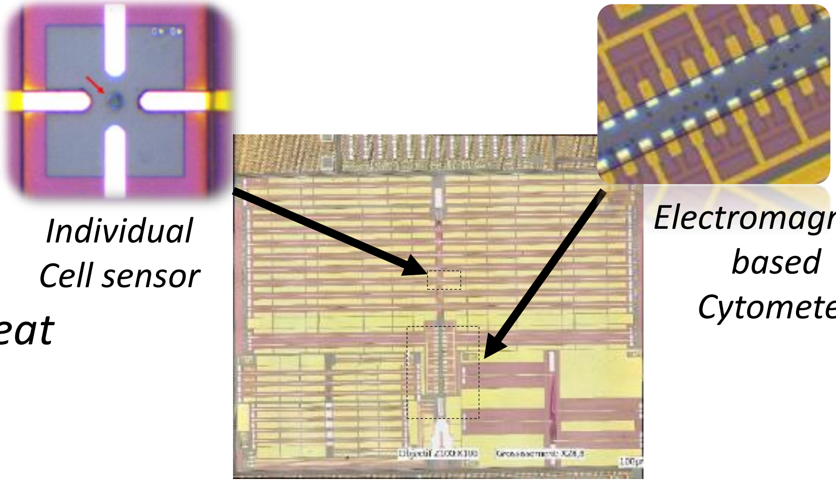
Sumcastec H2020 FET program supported by EU commission

New Generation of Microwave Lab-on-Chip for **Cancerous Stem Cells** Neutralization using Electromagnetic Waves Stimulation

Concept: *Exploit the non-thermal effects of* ***EM radiations*** *on living organizes to* ***sense*** *and* ***stimulate*** *specifically targeted biological cells*







Individual Cell sensor

Electromagnetic based Cytometer

Prototype of microfluidic sensing platform on CMOS chip

Methodology: *Take benefit of*

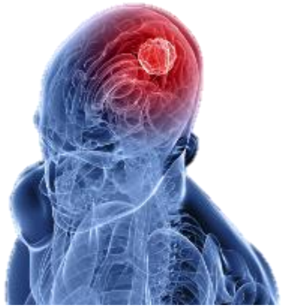
- *-**Microsystem technologies** to individually treat cells on a dedicated Lab-on-Chip (LOC)*
- -***CMOS technology*** to implement required microwave sources, sensors, applicators and detectors on the same chip

Motivation: Handling pathology with high recurrence

Need for new therapeutic strategies dedicated to poor outcome diseases

Ex: Meduloblastoma , Glioblastoma:

- *Tumor with high recurrence*
- *Strong resistance to existing treatments*
- *Highly heterogeneous brain tumors*



Resulting efficiency from standard therapies is very low

- *Poor patient survival rate*
- *Frequent relapse*

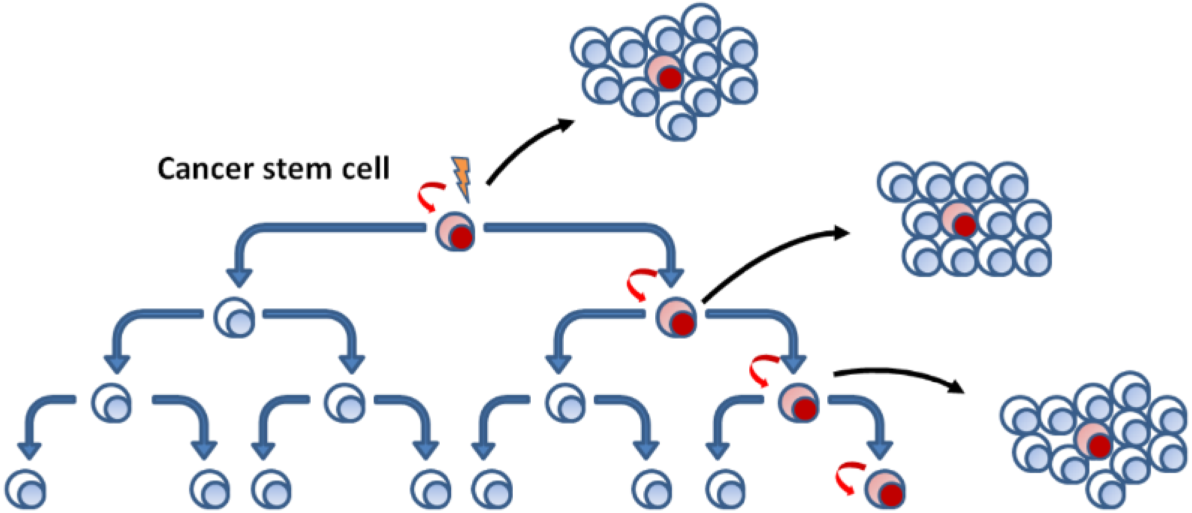
Role of some hidden tumor-initiating cells ?

How fight them more efficiently?
How many are they?
Where are they?

Cancerous Stem Cells

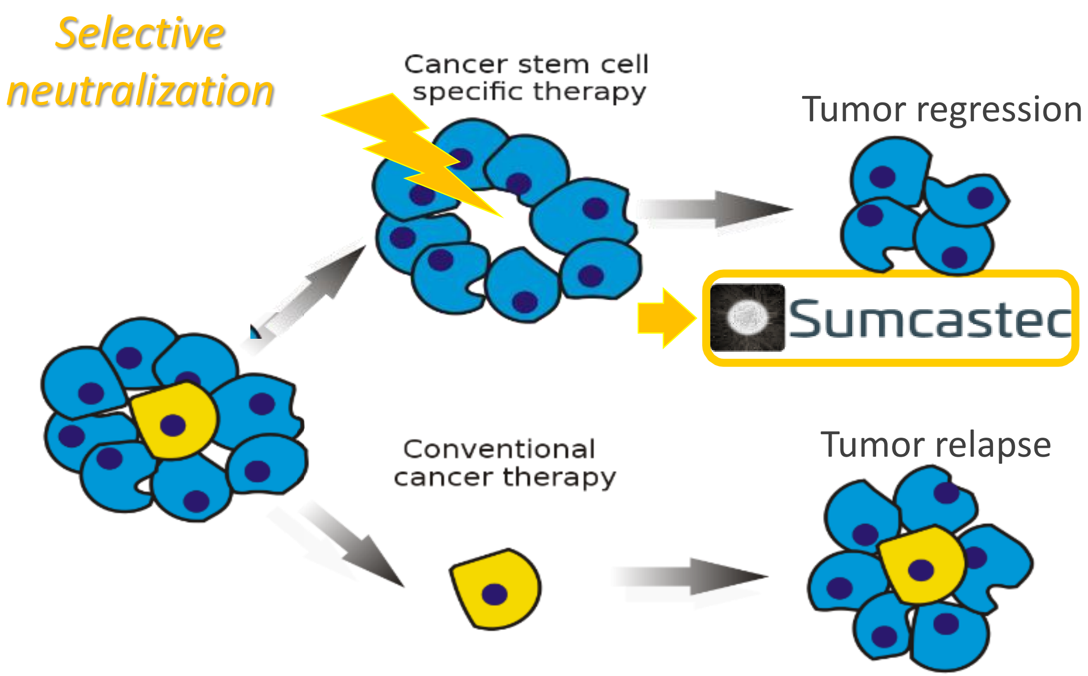
Tumorigenic cells with ability to give rise to all tumor cell types:

- with self-renewal capabilities
- differentiation into multiple cell types (progenitors…)
- hypothesized to be the main cause of relapse and metastasis



New therapies targeting CSCs

Quiescent properties -> Resistant to conventional chemo and ionizing treatments :

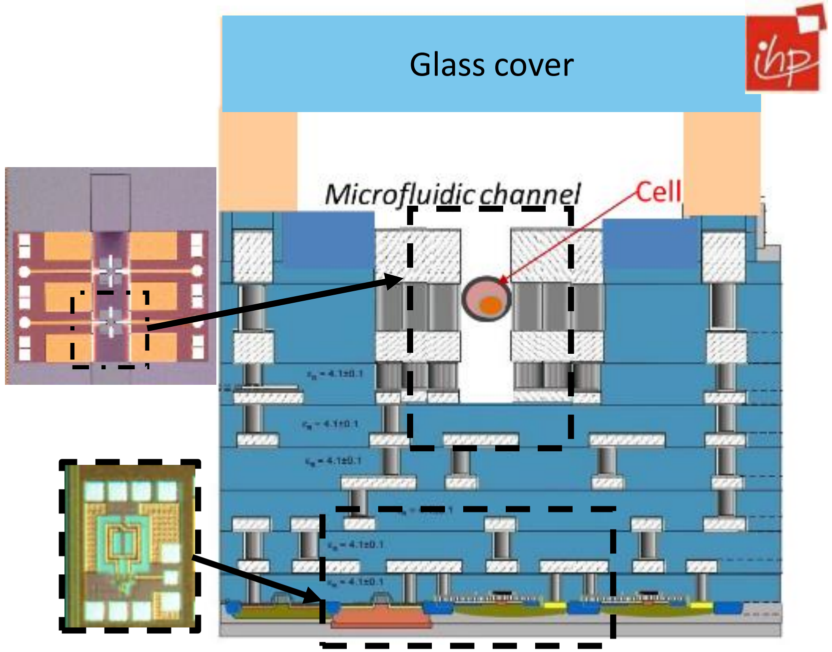


Why CMOS technology?

Advantages of BiCMOS technology:

✓ Complete system integration with several electronic functions on the same chip

▶ ***Mature technology able to quickly address a large market***

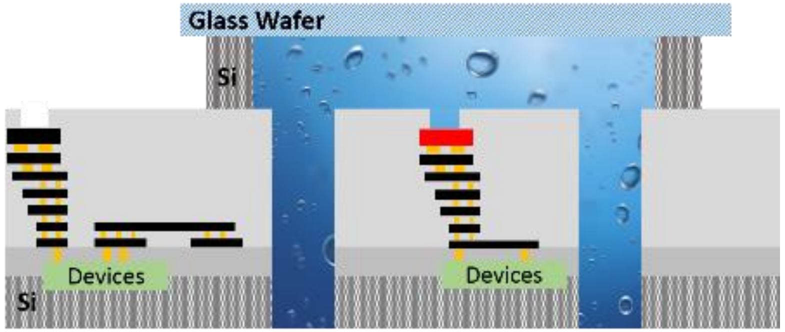


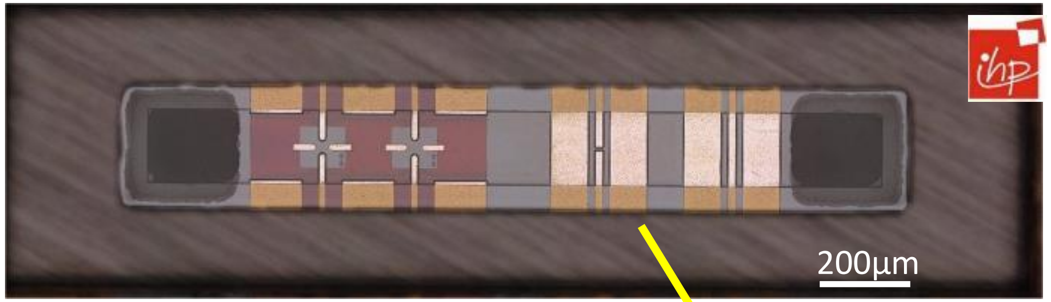
Why CMOS technology?

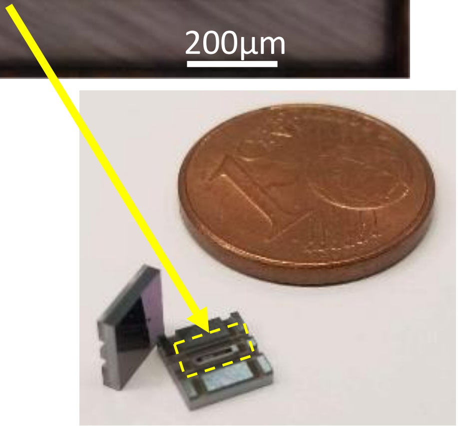
Advantages of BiCMOS technology:

- ✓ Complete system integration with several electronic functions on the same chip
- ✓ Miniaturization of the complete device and Lab-On-Chip compatible

▶ ***Full and monolithic integration of microfluidic***

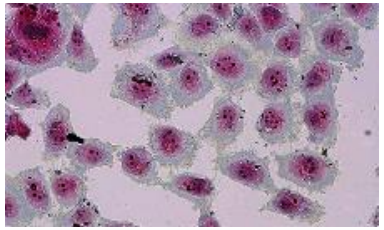




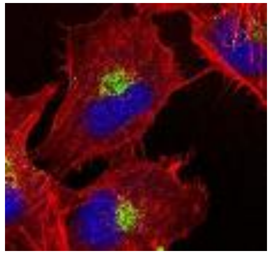


How biologists study CSC's currently?

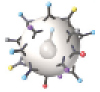
Optical microscopy



Staining

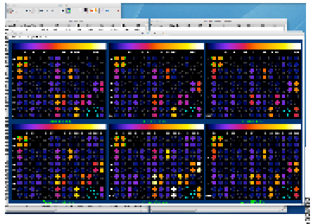


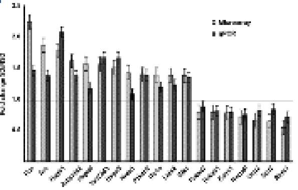
Fluorescence labeling



Flow cytometry

QPCR & Protein Array analysis





Main difficulties :

- *CSC's are rare and require amplification of population*
- *Specific* immunostaining markers are lacking

Stemness lineament are accessed using *generic markers* of normal stem cells:

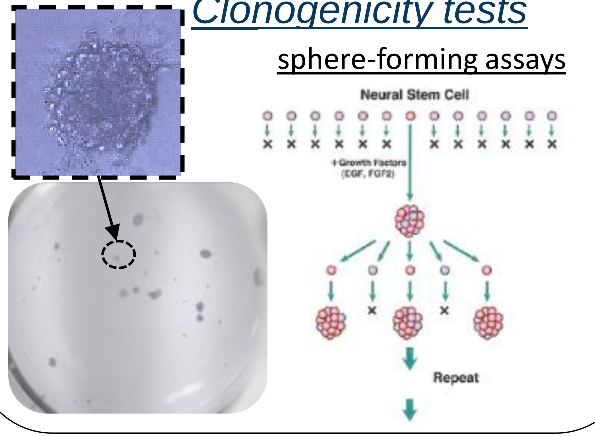
- *Undifferentiation & Anti proliferation markers* :Nanog, Sox2, OCT4, CD133…
- *Cross coupling* of makers gives evidence but without *100% absolute certainty*

Functional tests allow to identify CSC

Functional tests prove ability to renew a tumor mass

Clonogenicity tests

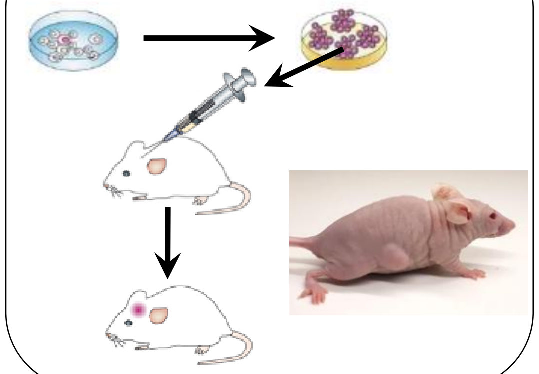
sphere-forming assays



But….
long (~20-40 days), costly and complex tests to implement

-> Never used in clinic..

Tumorigenicity tests

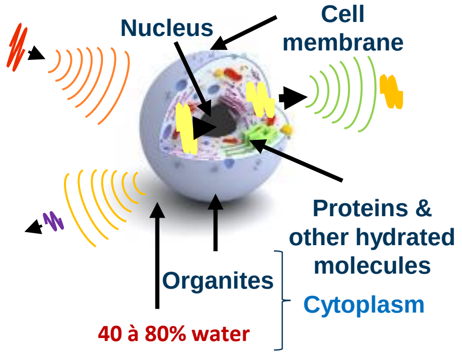


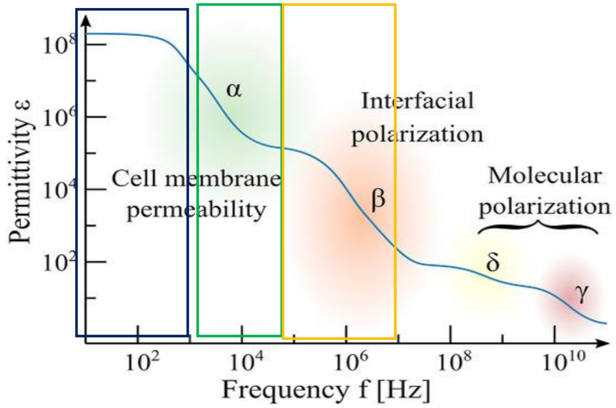
Interest to develop others approaches investigating intracellular specificities

What about using EM field to identify CSC's?

Depending the frequency EM field could interact with different cell constituents

- Low frequency -> Cell shape/ morphology/size influence
  - Mid frequency -> Plasma Membrane specificities
    - High frequency -> Intracellular content properties





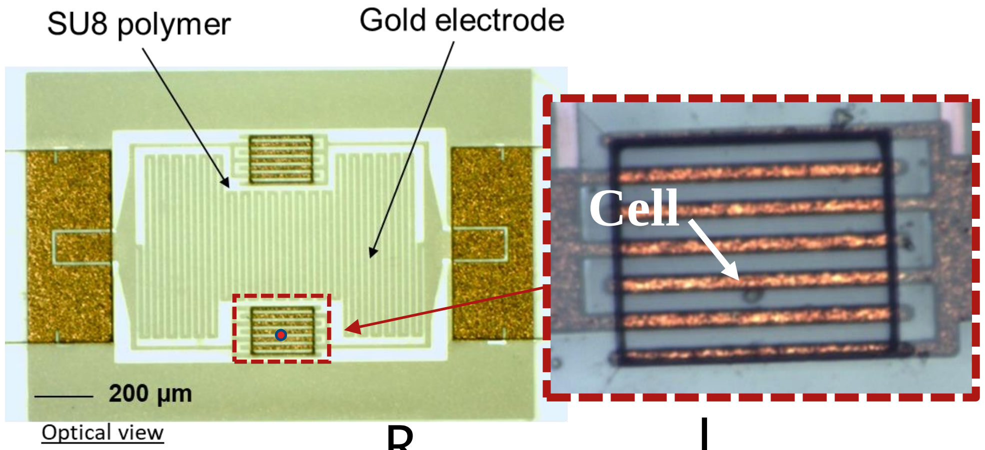
Own cell dielectric properties = **A signature** *that can be specific*

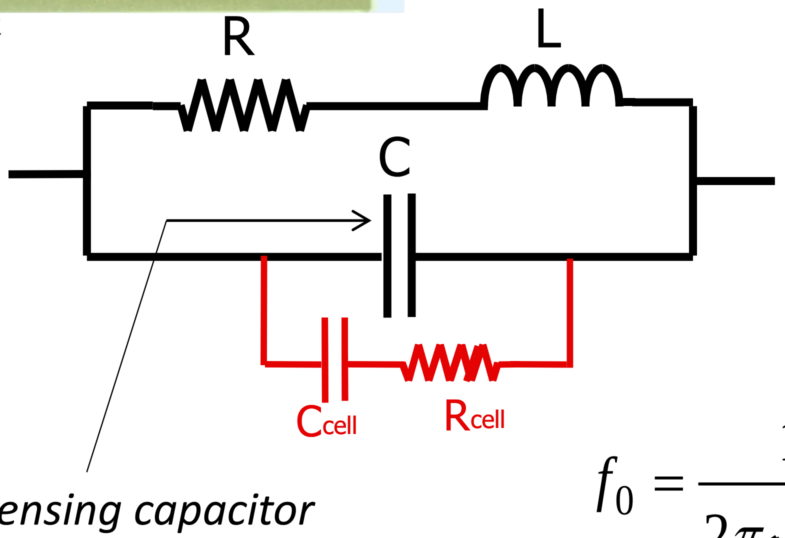
High frequency signal well suitable to access to cell interior properties and measure specificities

Dielectric spectroscopy allows **non destructive** & **label free** characterization

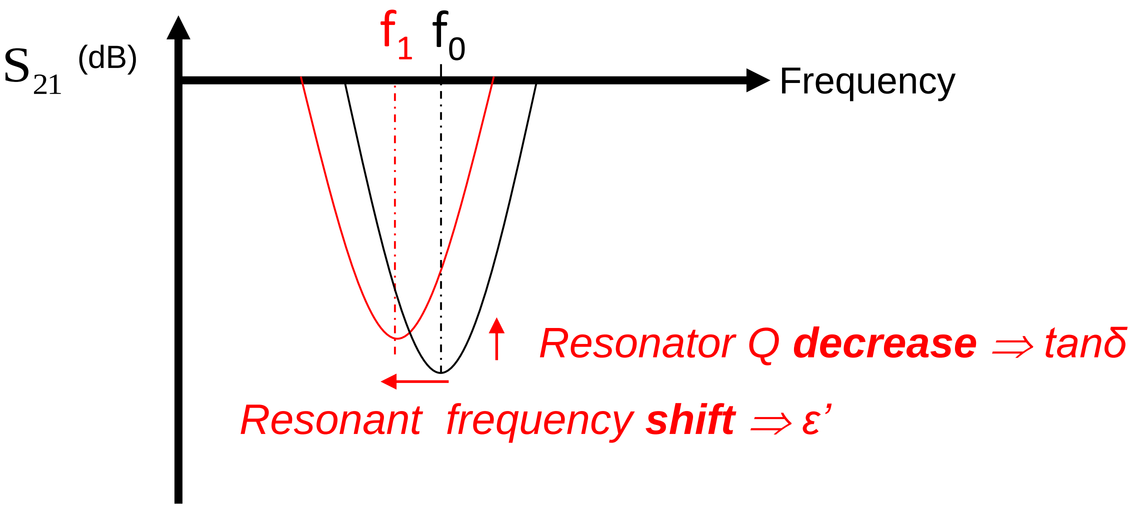
Resonant RF-sensors can be good sensor candidates

Targeting unique cell analysis requires superior sensing sensitivity



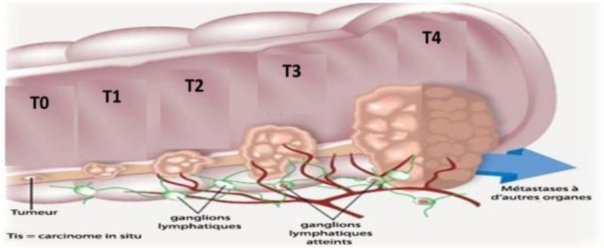


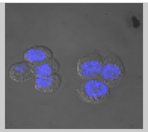
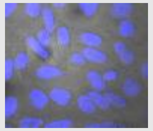
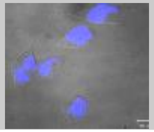
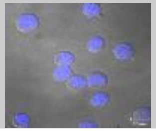
Is capacitive resonant sensors able to sense dielectric specificity?

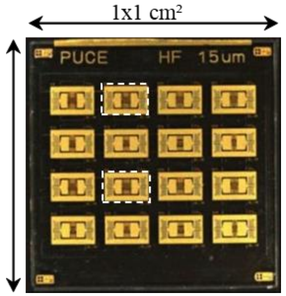


$$f_0 = \frac{1}{2\pi\sqrt{LC}} \Rightarrow f_1 = \frac{1}{2\pi\sqrt{L(C // C_{cell})}}$$

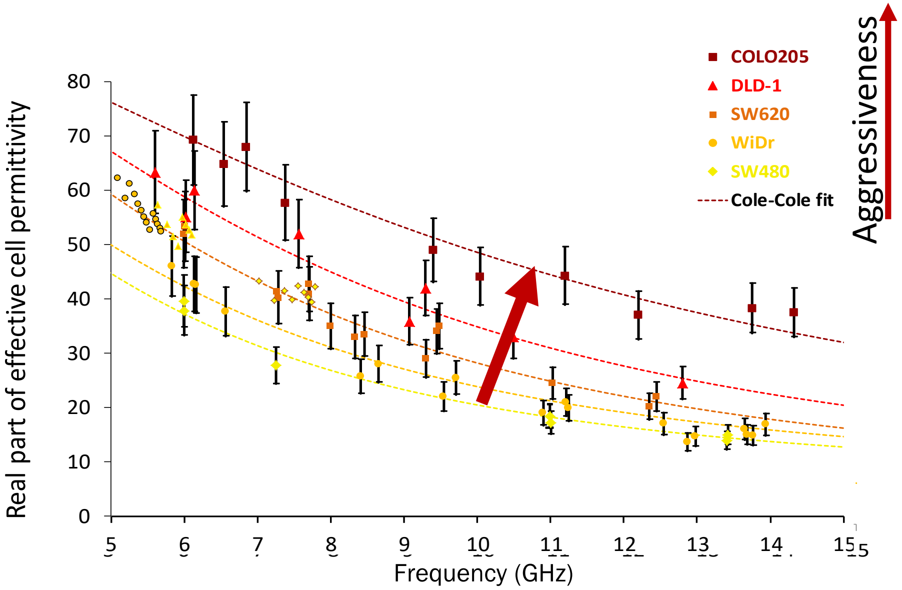
Discriminating cells with dielectric spectroscopy

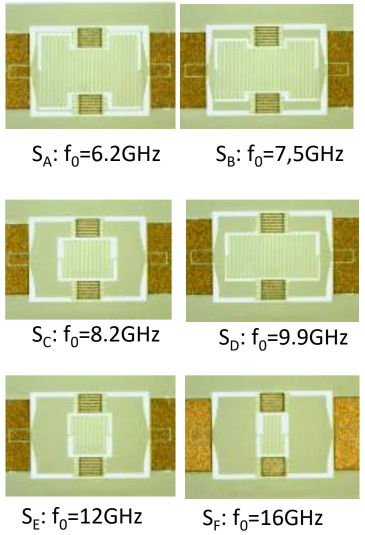


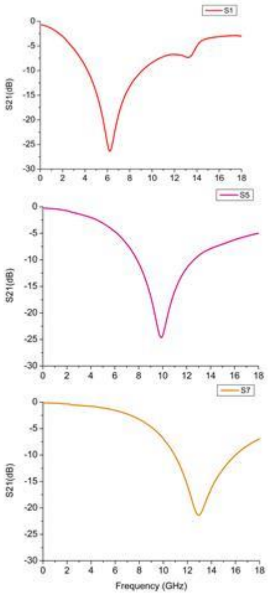
Cell Line	Stage	Morphology
WiDr	II	
SW480	II	
SW620	III	
DLD-1	III	
Colo 205	V	

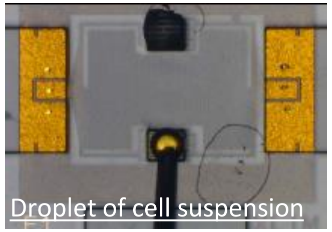


Dielectric signature established using Microwave resonating sensors







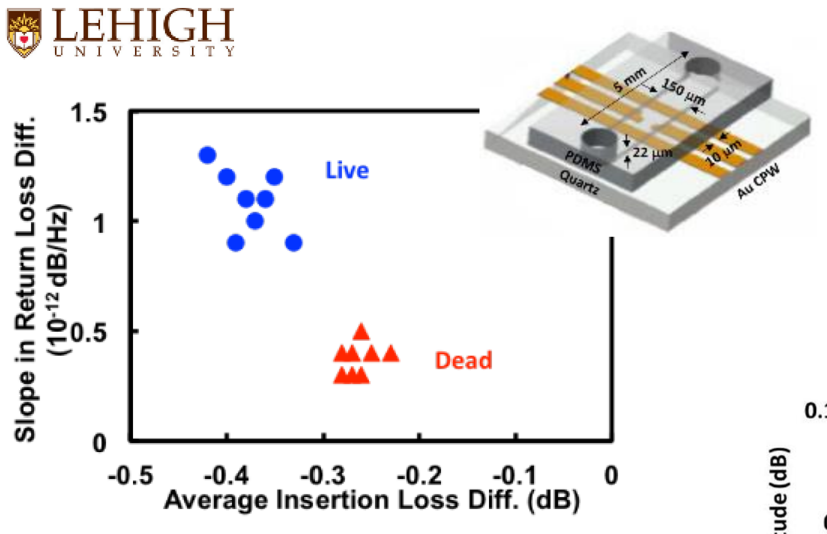


➡ *Correlation with the cell tumor grade*

L.Y. Zhang et al, Discrimination of Colorectal Cancer Cell Lines using Microwave Biosensors Sensors & Actuators: A. Physical, Vol 216, Sept 2014.

Dielectric spectroscopy on living cells: measurement inside a liquid

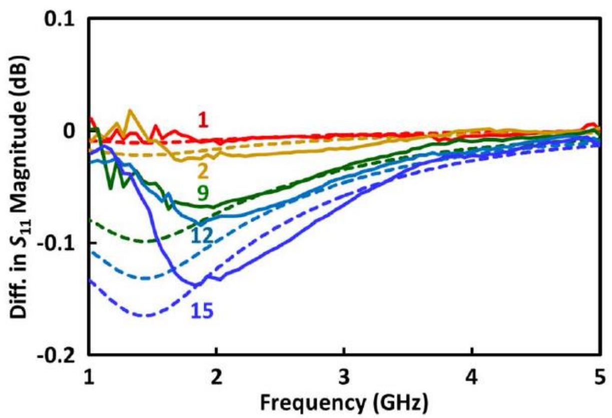
Probing living cells required sensors embedded in microfluidic channels

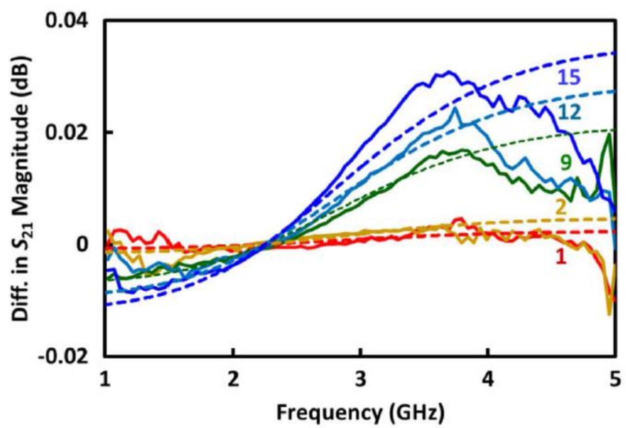


H. Li et al, DOI: 10.1109/TMTT.2017.2659736

<u>Measuring dielctric property of small particles suspended in liquid involved several challenges</u>:

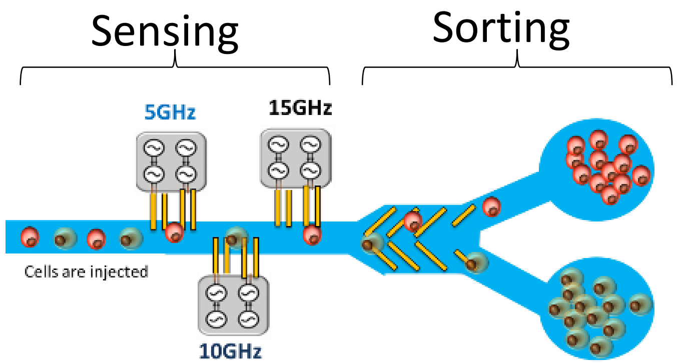
- Measurement accuracy and stability
- Choice of probing frequency
- Single cell measurement
- Requirement to be associated with cell trapping (especially for broadband meas)



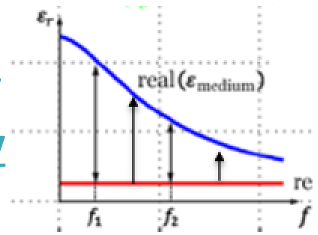


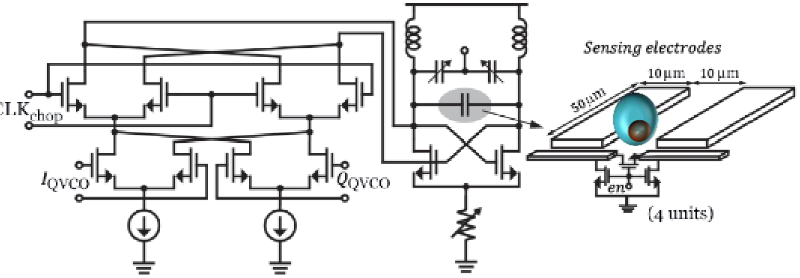
Toward to a dielectric spectroscopy cytometer concept

Potentially High-Throughput flowing cells microwave characterization



Based on measured EM signatures of each cell, they have then to be **individually sorted / isolated**

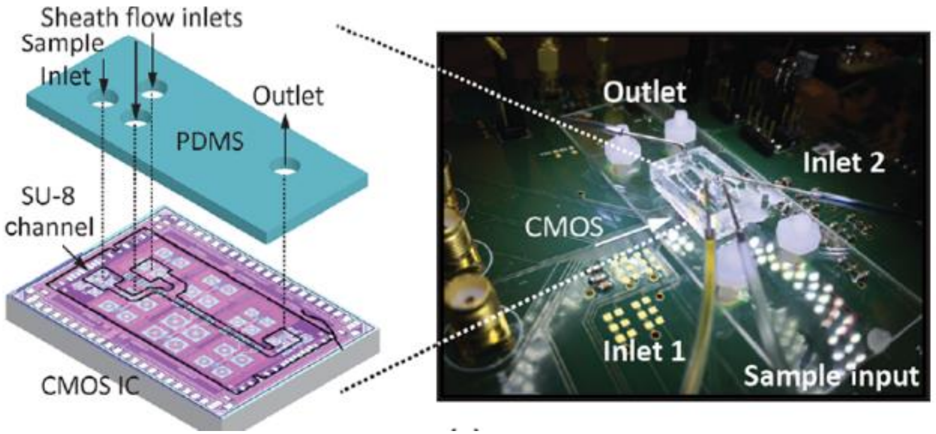




Challenges:

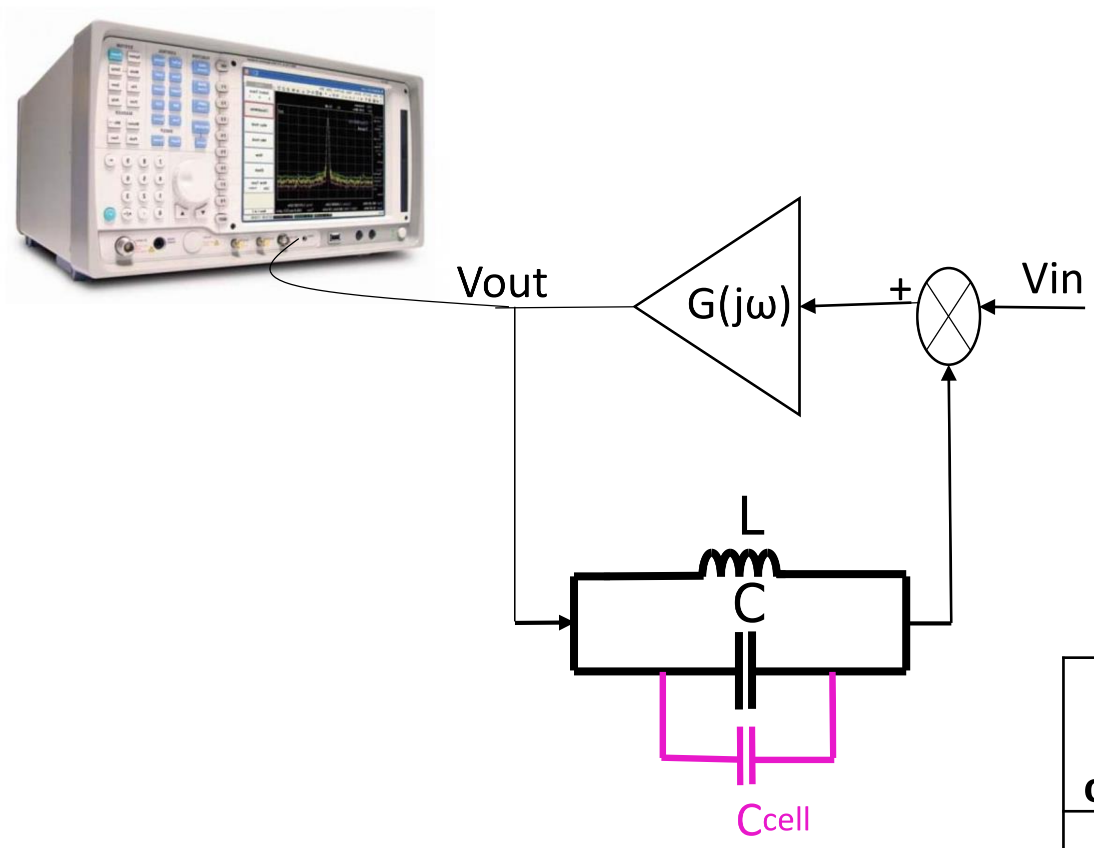
-Require strong sensitivity (ppm range!) sensor design with **attoF resolution** ➡ *A cell in liquid ~ 100-200 aF*

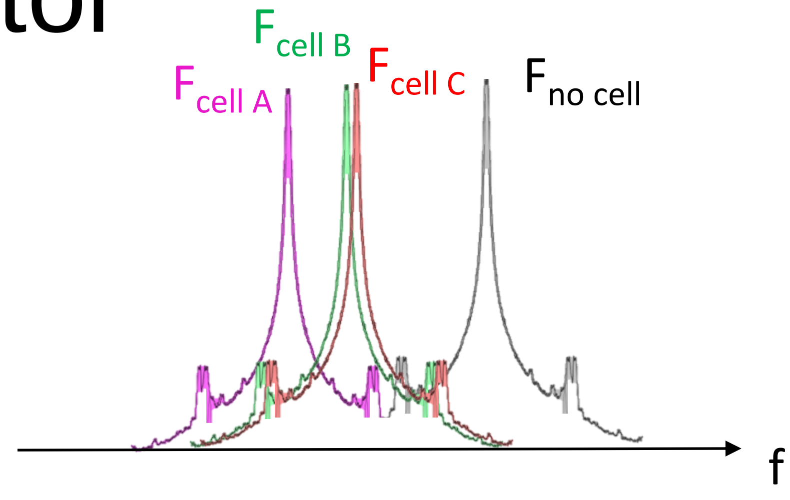
- Need to be associated with cell sorting system



J.C.Chien et al, DOI: 10.1109/JSSC.2015.2500362

From resonator to oscillator





No cell vs one single cell

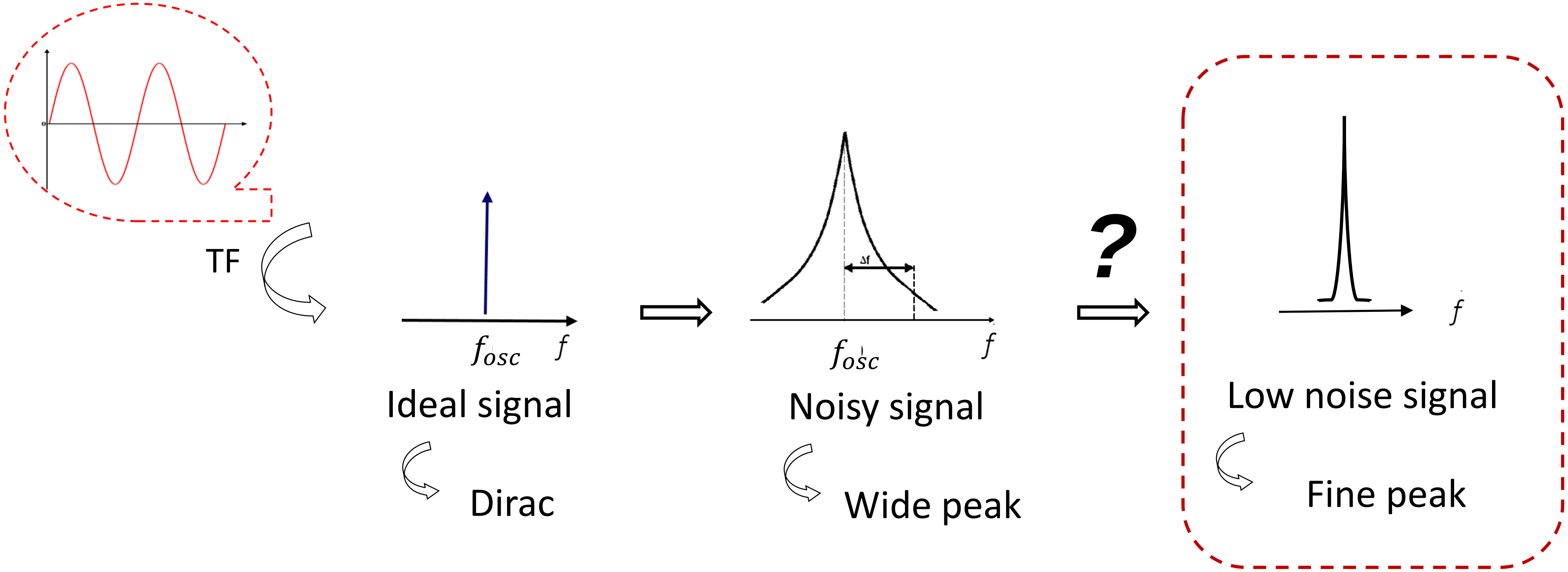
Cancerous cell vs another one with tumor grade difference

Estimated capacitance change (attoF)	200	95	31	10	3
Induced frequency shift (kHz)	500	300	100	32	10

Cancerous cell vs a different type one
Ex: Healthy vs cancerous cells

➡ *Oscillator based sensor might be more prone to detect such limited capacitance change*

Oscillator based sensor's major requirement



✓***Stability of the oscillation frequency***

✓***Spectral purity of the oscillator***

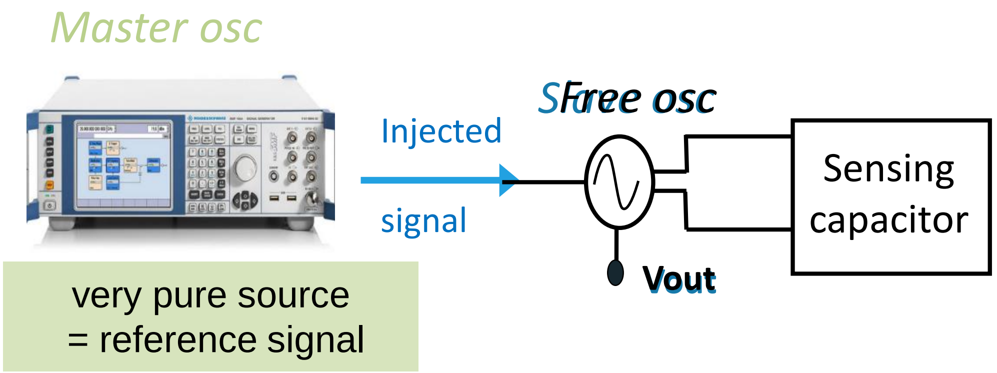
<u>*Objective:*</u> **Detect 10 kHz frequency shift around 5 GHz**

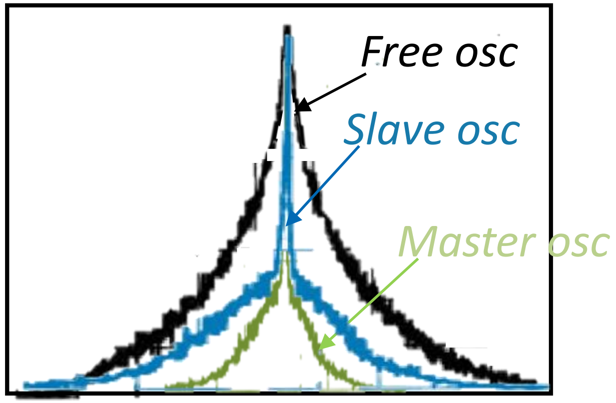
Principle of an Injection Locked Oscillator

Capacitive sensor with very high sensitivity

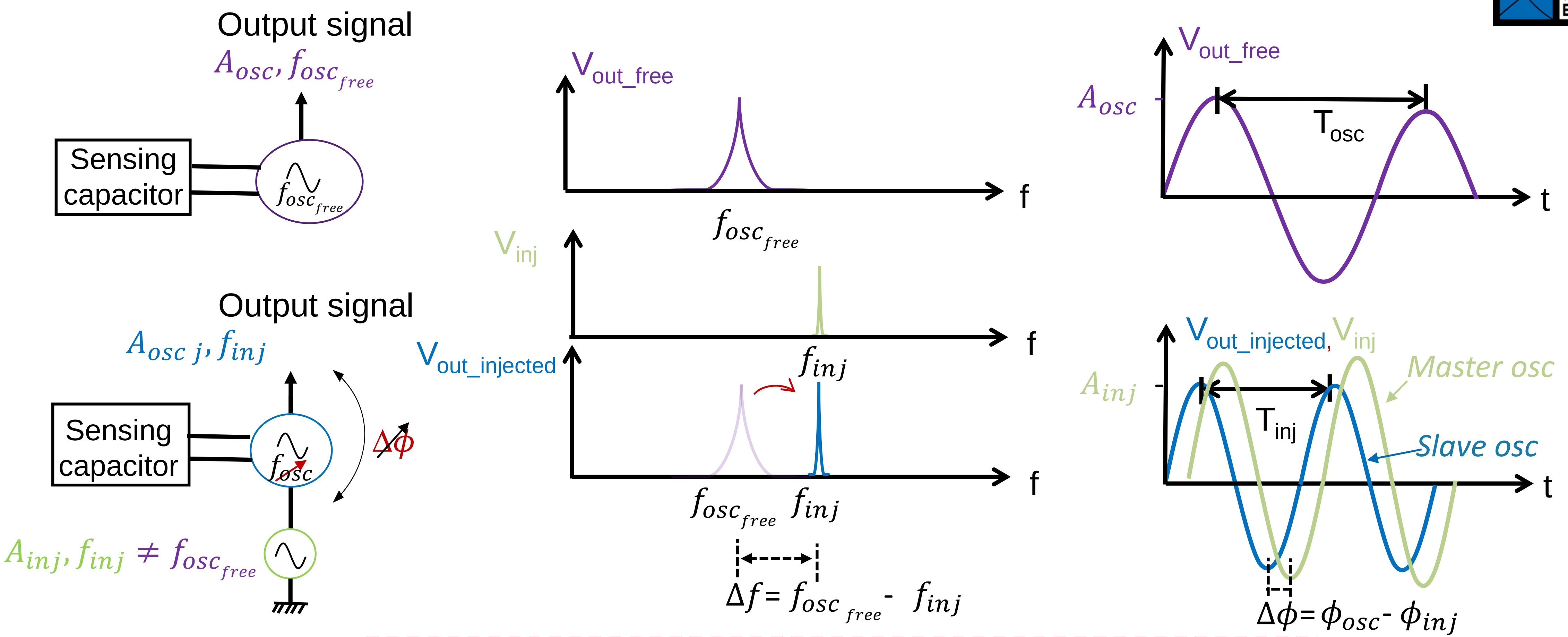
Injection Locked Oscillator

Principle: Reduce phase noise near the carrier





Principle of an Injection Locked Oscillator



<u>Adler's equation:</u> $f_{osc_{free}} - f_{inj} = \frac{f_{osc}}{2Q} \cdot \frac{A_{inj}}{A_{osc}} \cdot \sin(\phi_{osc} - \phi_{inj})$

Injection Strength

How using Injection Locked Oscillator as sensor?

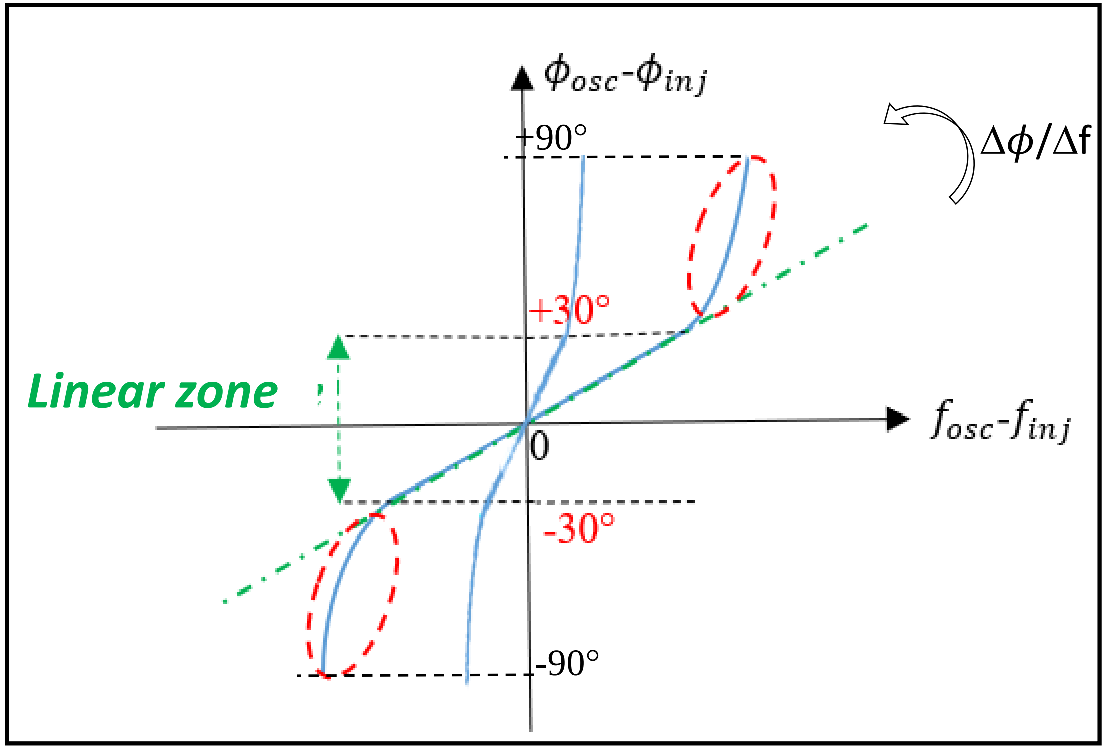
- ✓ Lock / synchronize the master / slave oscillators
- ✓ Lower the injection strength / the injection amplitude of the master oscillator

⇨ Increase the slope $\Delta\phi/\Delta f$:

Improve the sensitivity of the sensor

⇩

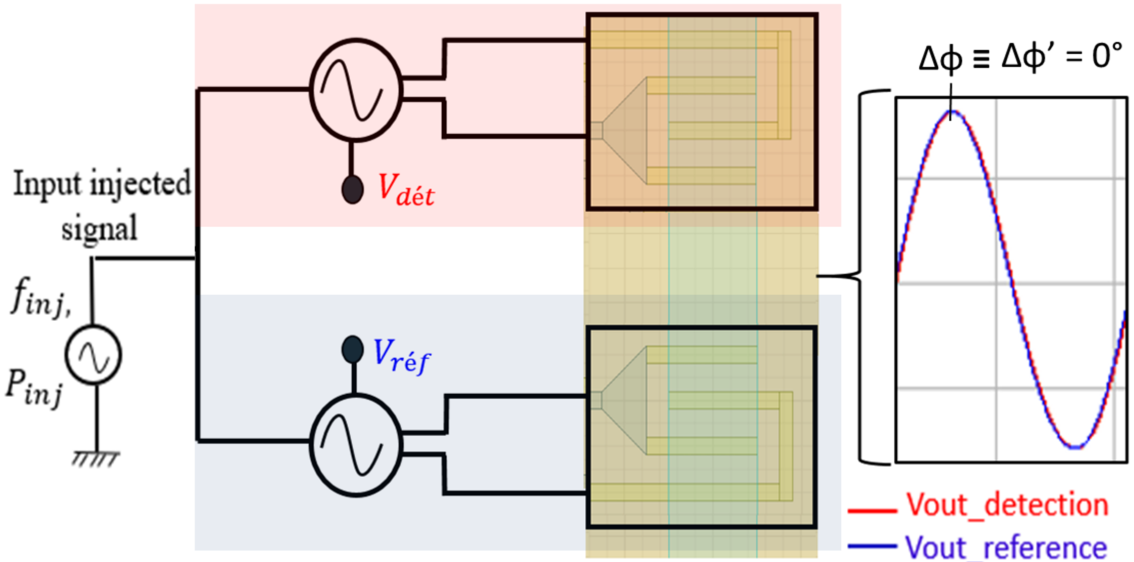
Significant phase shift

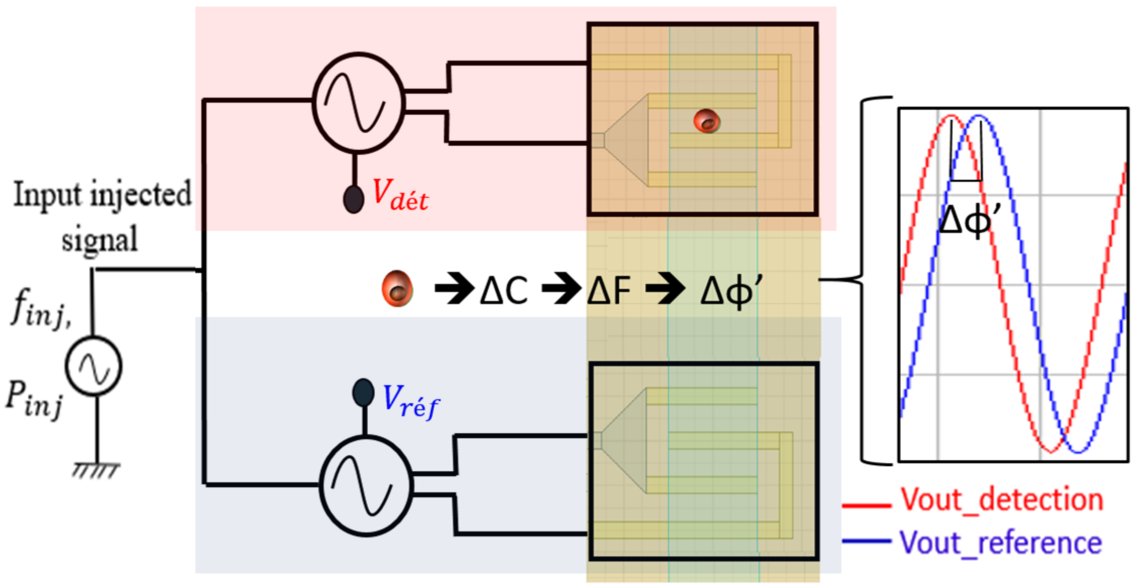


➢ **Adapt the injection strength to get the** required level of sensibility ➡ **Work in low injection regime**

Sensing system architecture

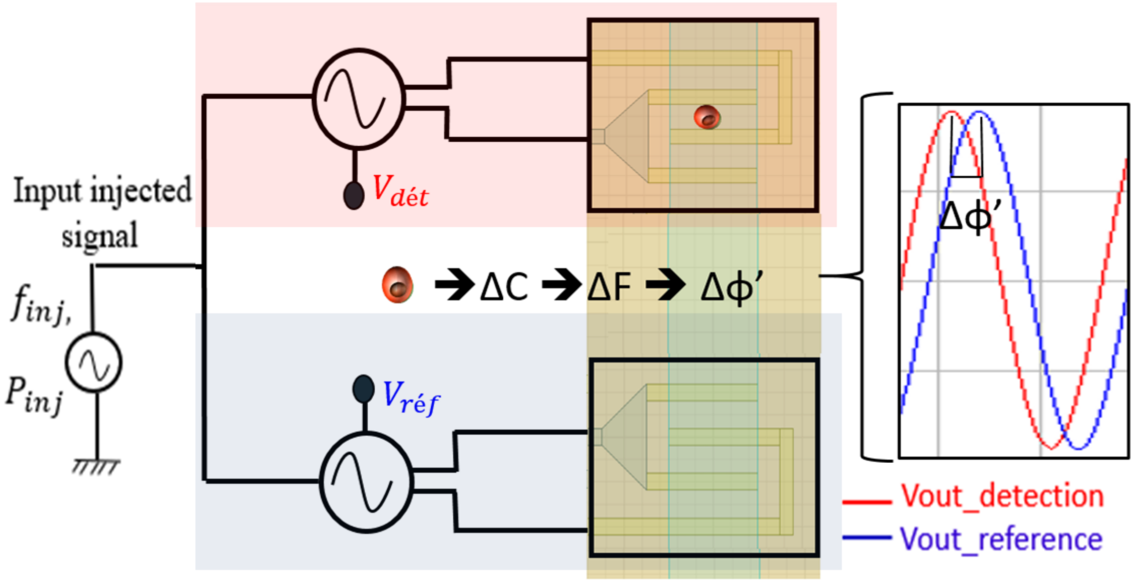
Two successive ILOs to enable differential measurement

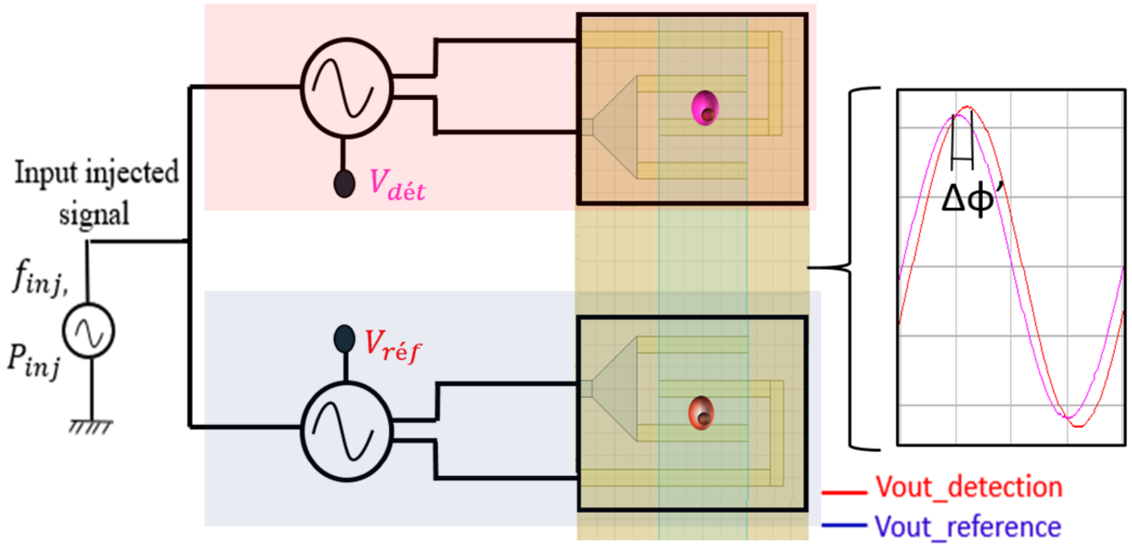




Sensing system architecture

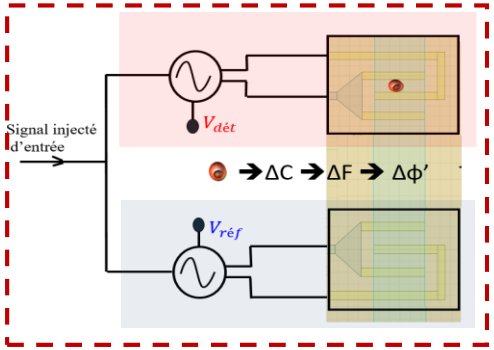
Two successive ILOs to enable differential measurement

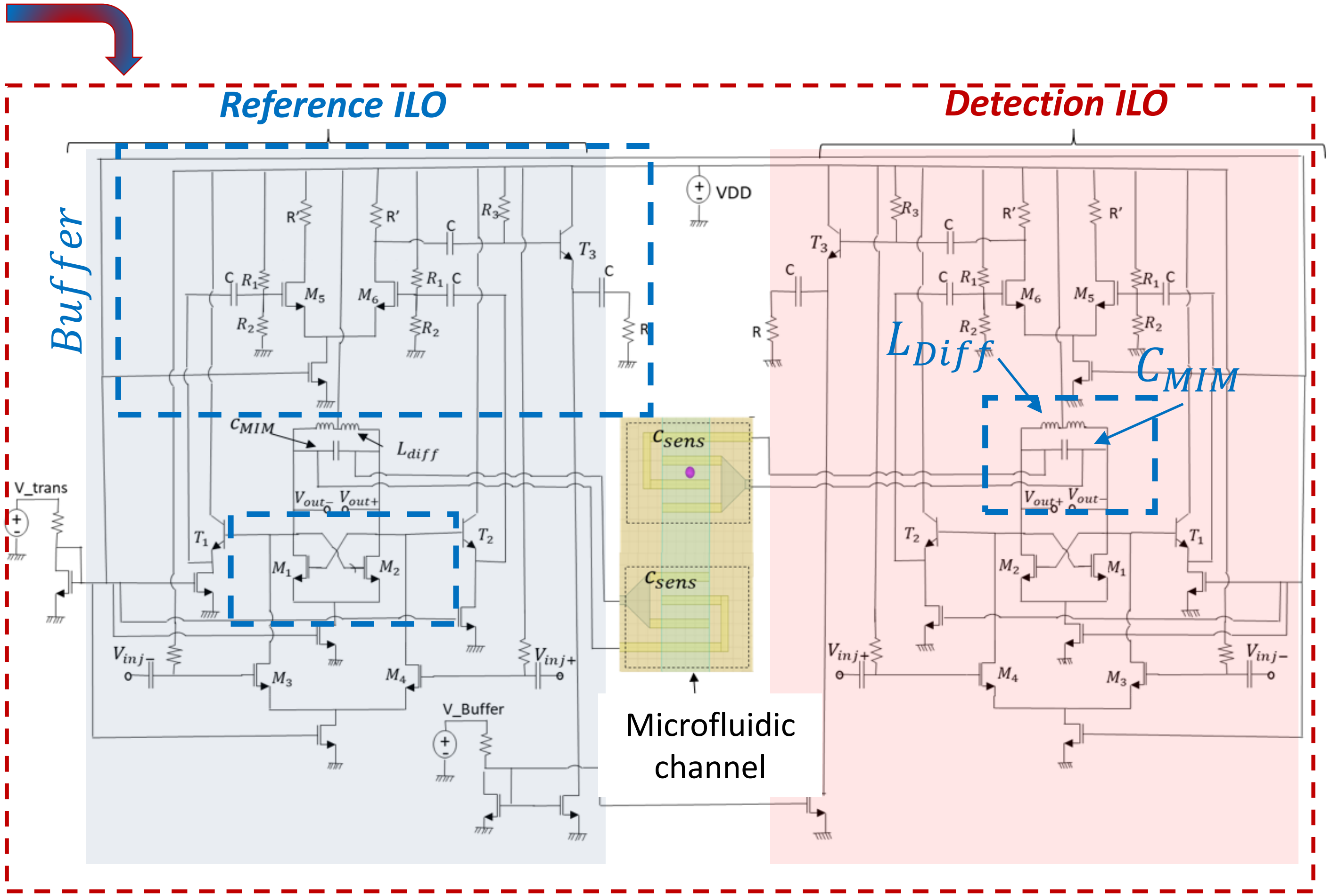




Lower injection regime required

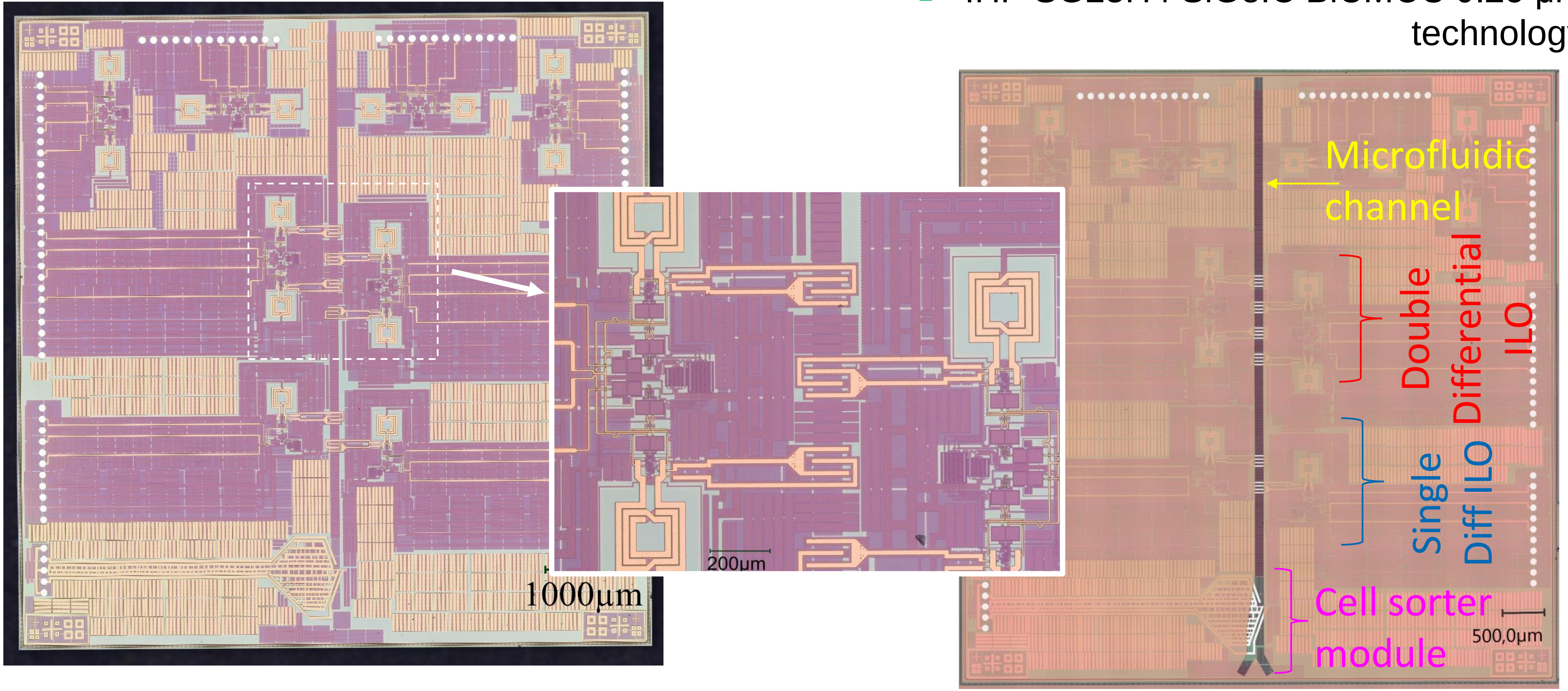
Design of the sensing system



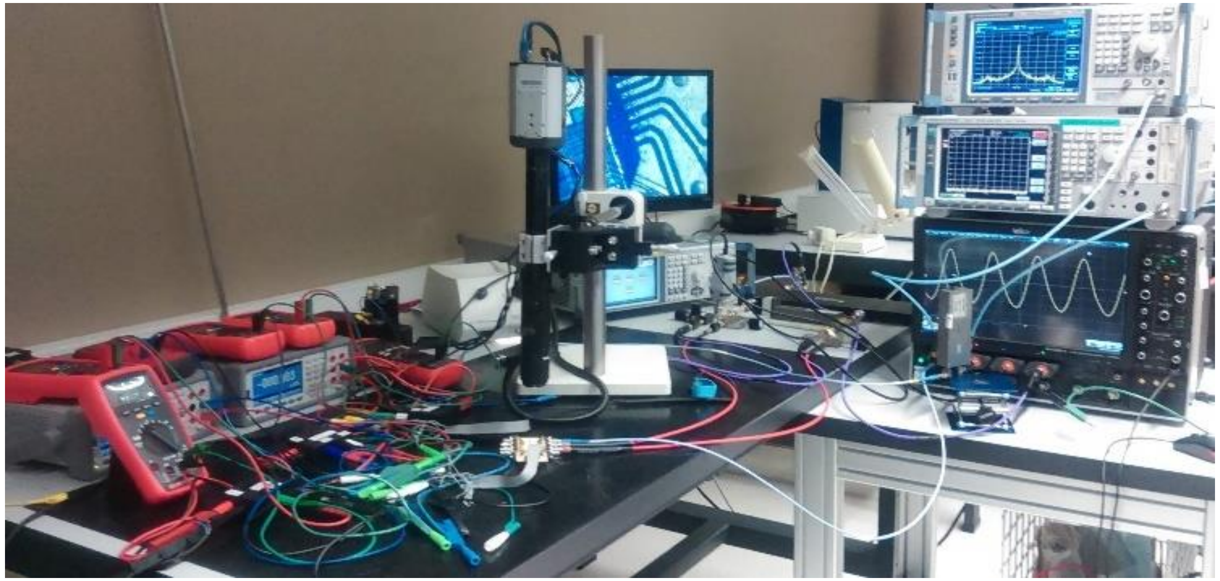


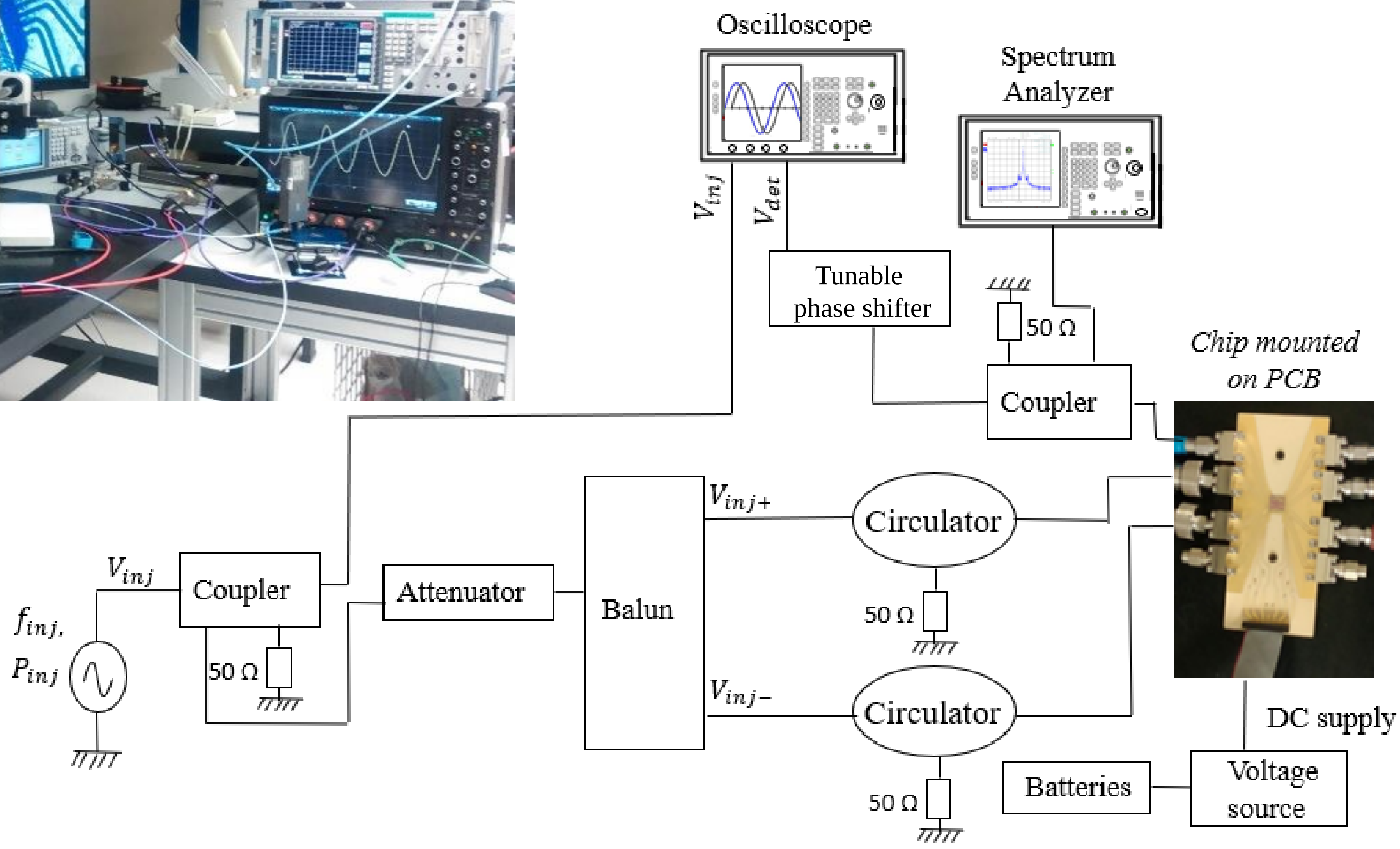
Fabricated chip photo

- Chip size: 7× 7 mm^2
- IHP SG25H4 SiGe:C BiCMOS 0.25 µm technology



Measurement setup

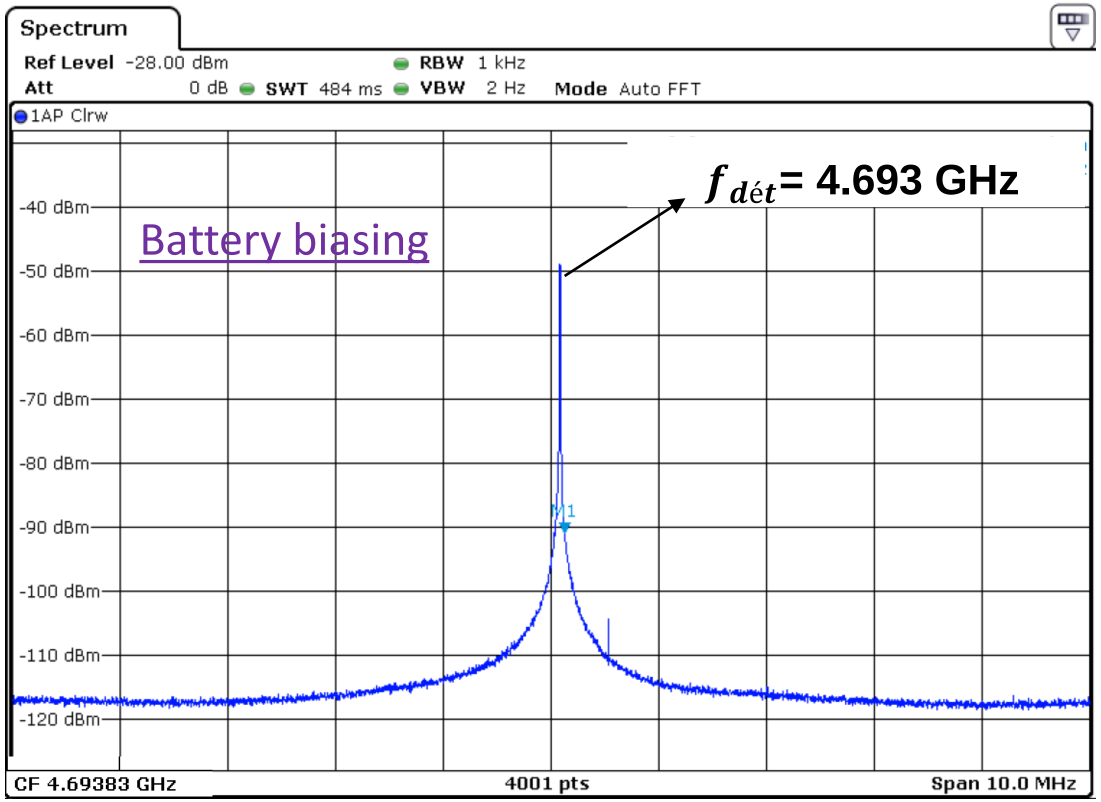




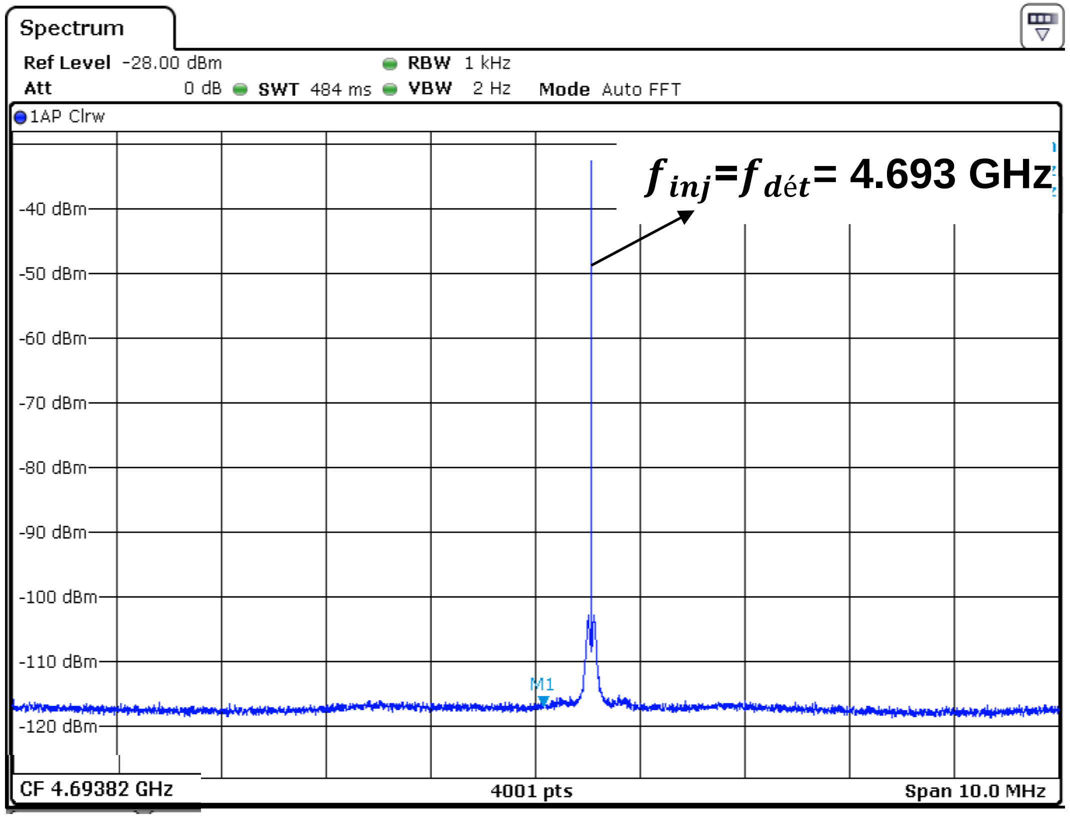
Measured output spectra

❖Output spectrum of the sensing oscillator

Under free-running condition



Under locked condition: P_{inj} = - 25 dBm

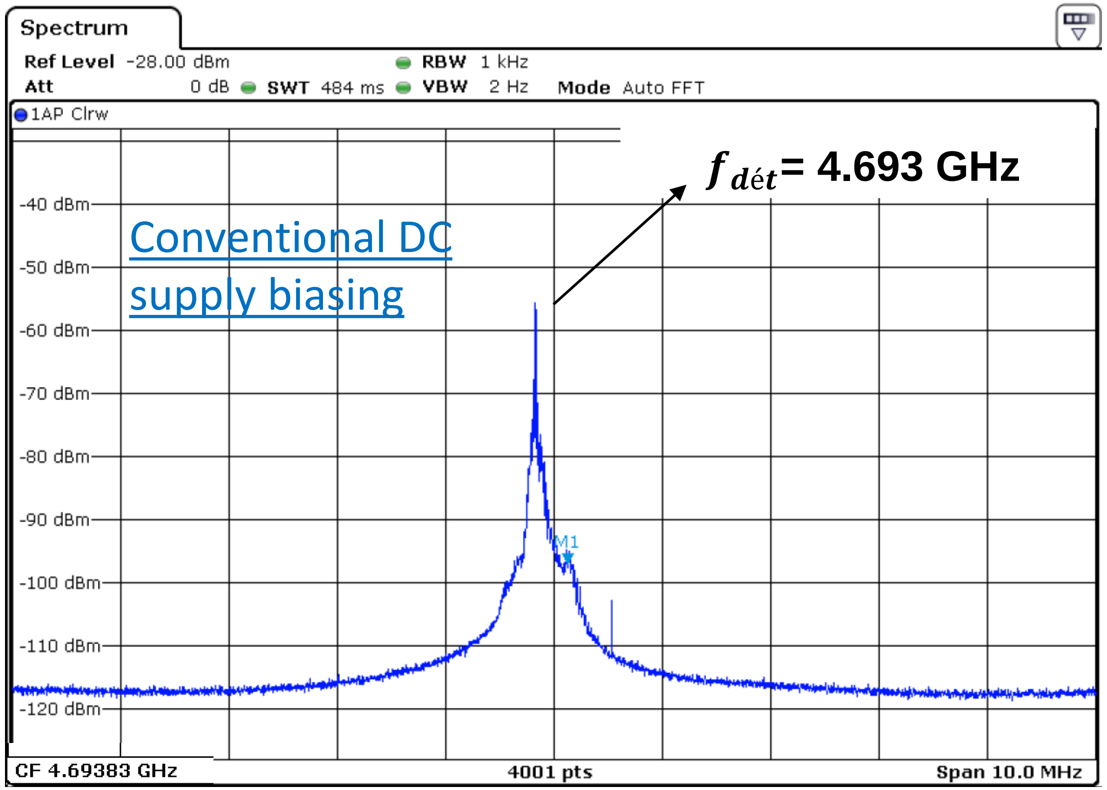


✓ Lock on the injection frequency ✓ Phase noise is reduced near the carrier

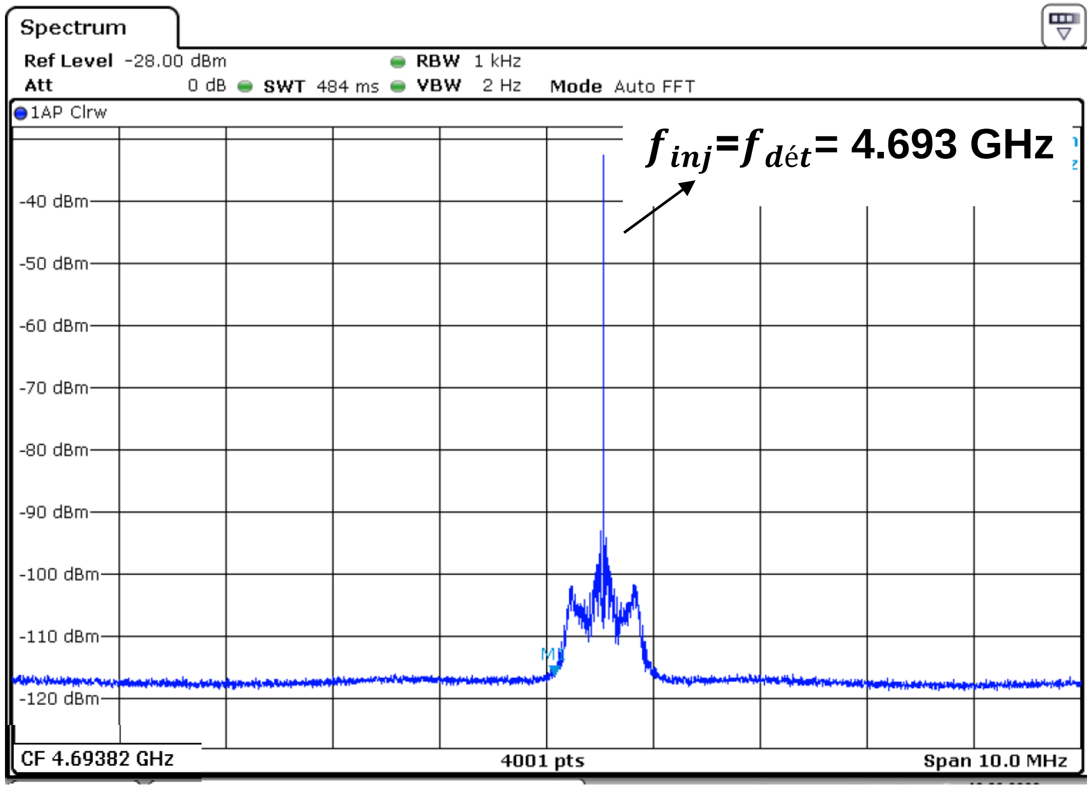
Measured output spectra

❖Output spectrum of the sensing oscillator

Under free-running condition

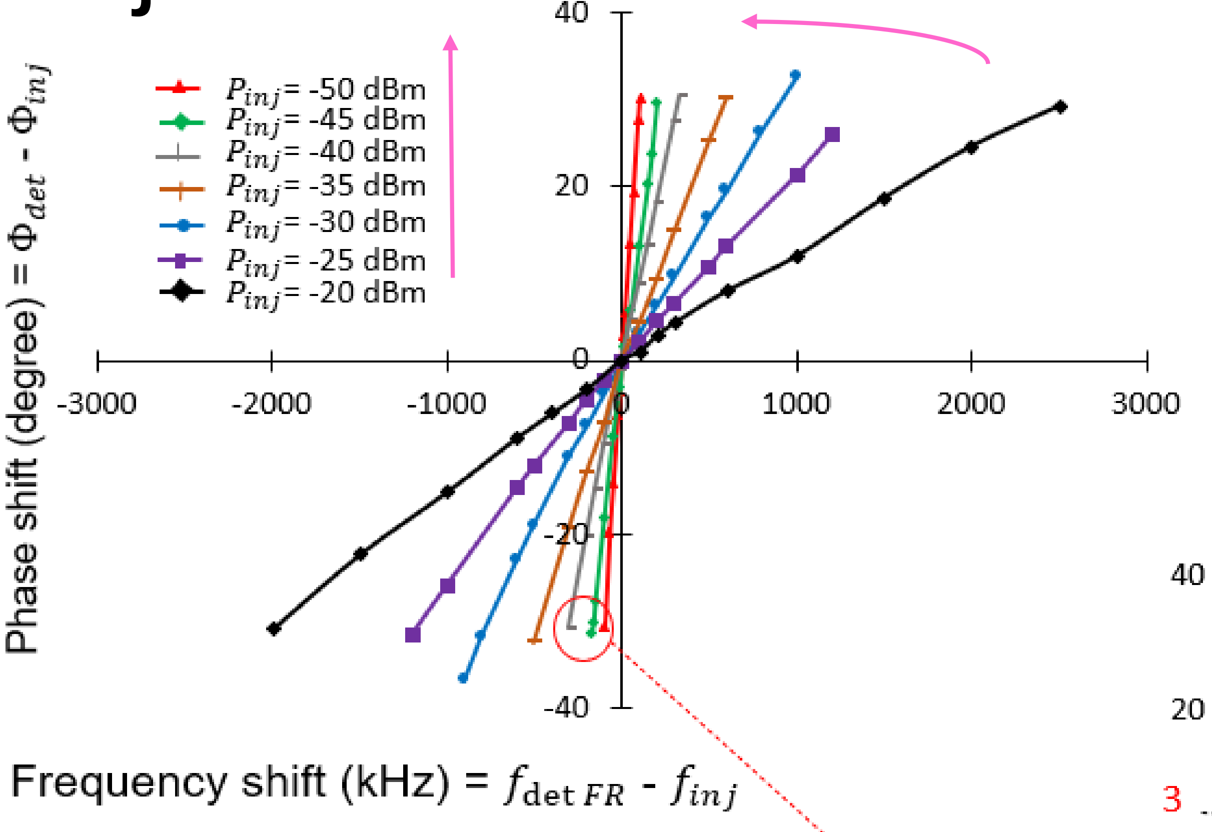


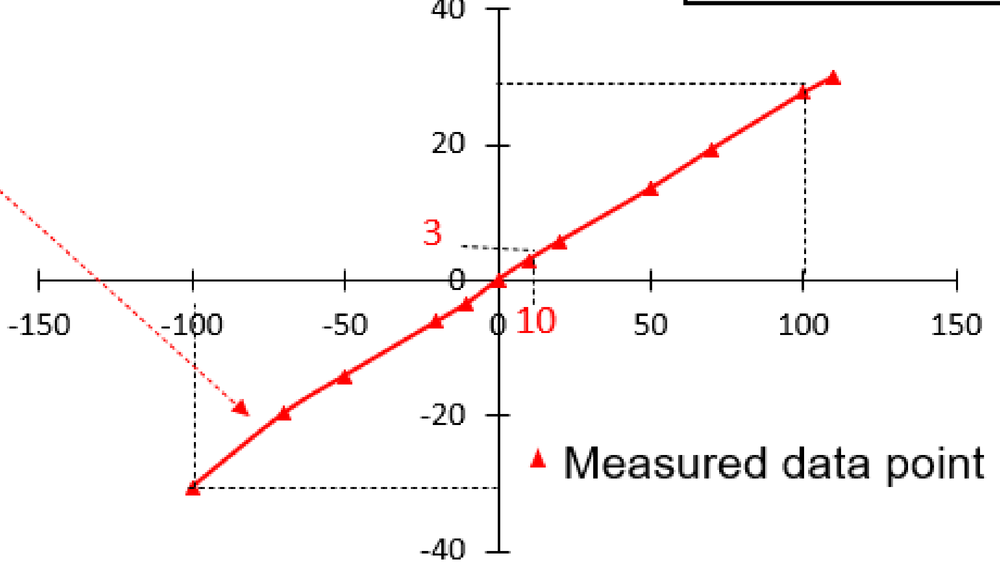
Under locked condition: P_{inj} = - 25 dBm



✓ Lock on the injection frequency ✓ Phase noise is reduced near the carrier

Sensing oscillator locked by injection





- ✓ f_{det} = f_{ref} = 4.693 GHz
- ✓ P_{inj} = - 50 dBm

⇩

- Detection of Δf =**10 kHz** around the operation frequency **4.693 GHz**

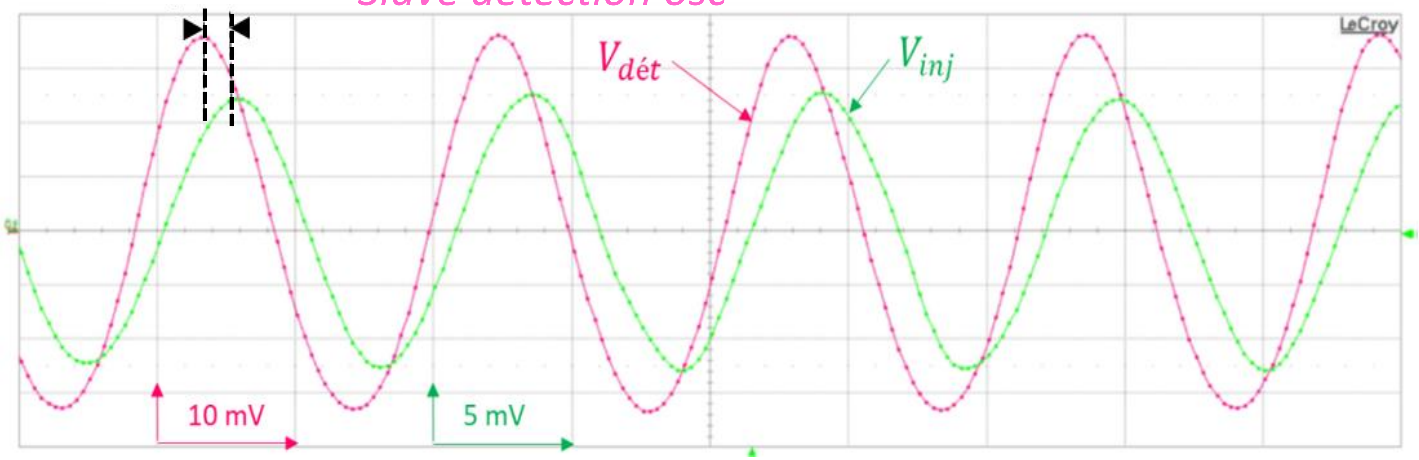
Sensing oscillator locked by injection

- ✓ P_{inj}=-50 dBm
- ✓ f_{inj} = 4.693 GHz

Δf= -100 kHz
$\Delta\phi$ = -31.6°

⟺

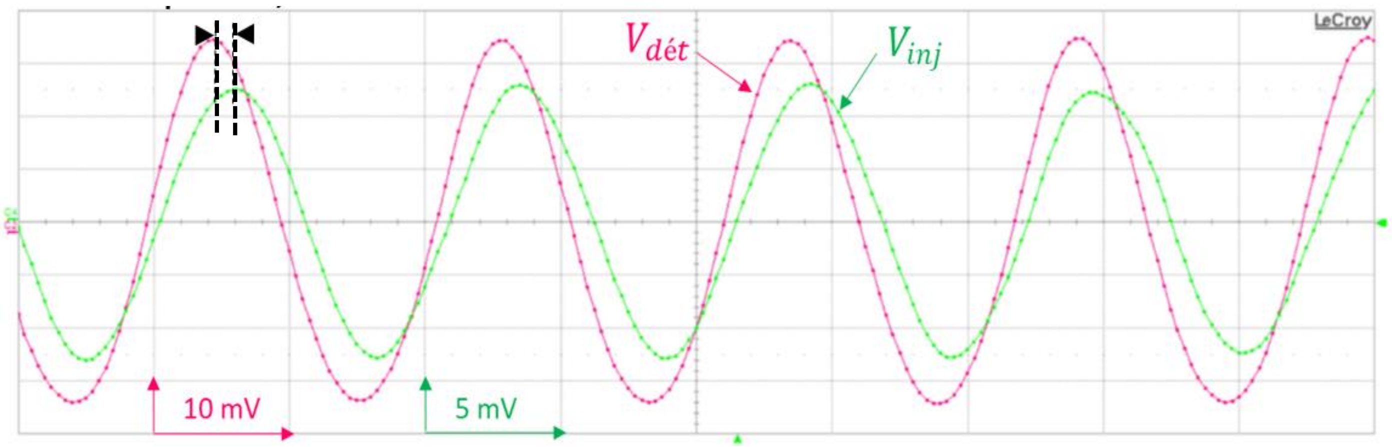
$\Delta\phi$ = -31.6°



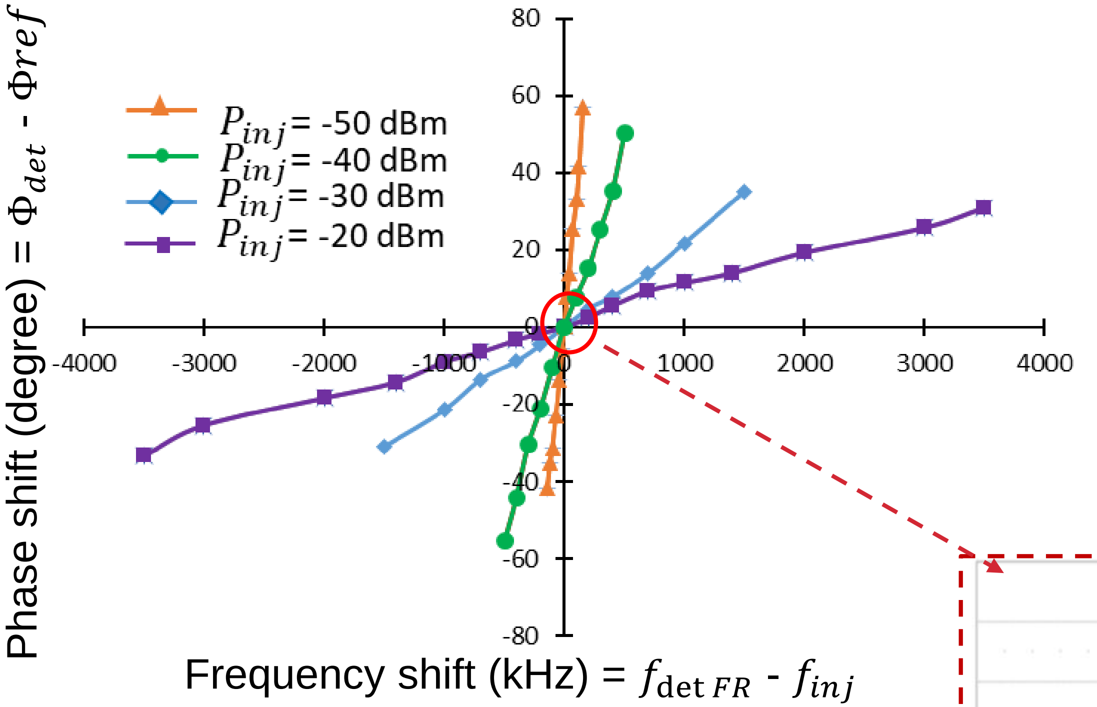
Δf= -40 kHz
$\Delta\phi$ = -14.1°

⟺

$\Delta\phi$ = -14.1°



Measured phase shift between ILO outputs



<u>Without any dielectric disturbance</u> on the detection oscillator

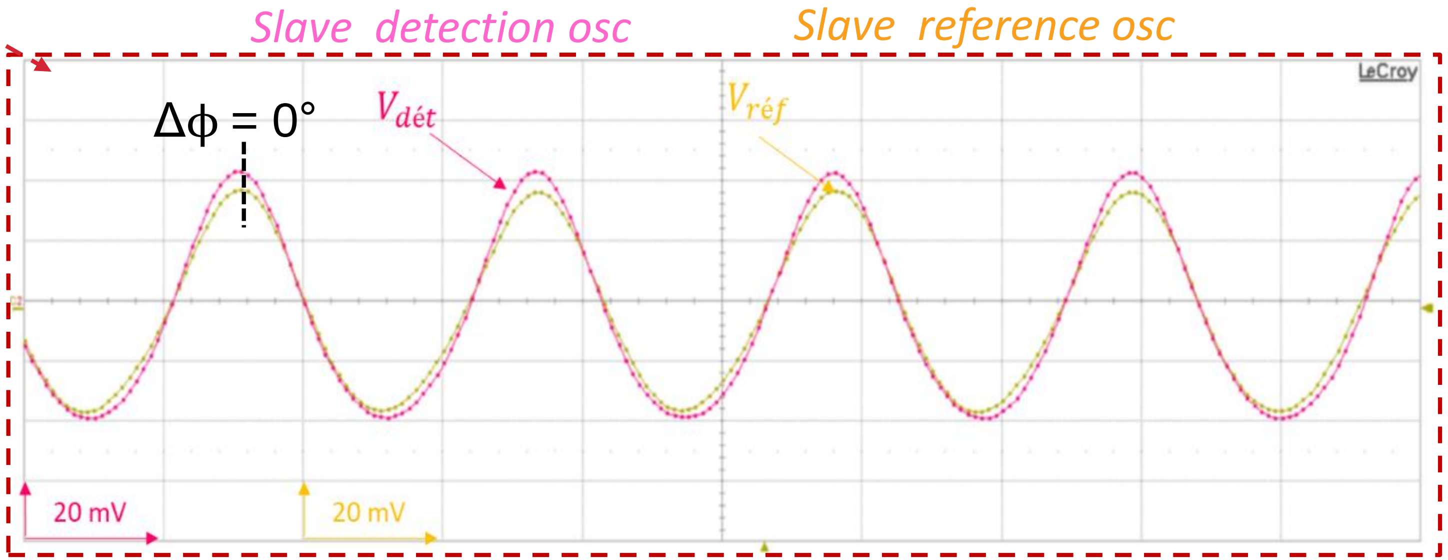
⇩

<u>No</u> frequency shift **<u>Δ*f*</u>**

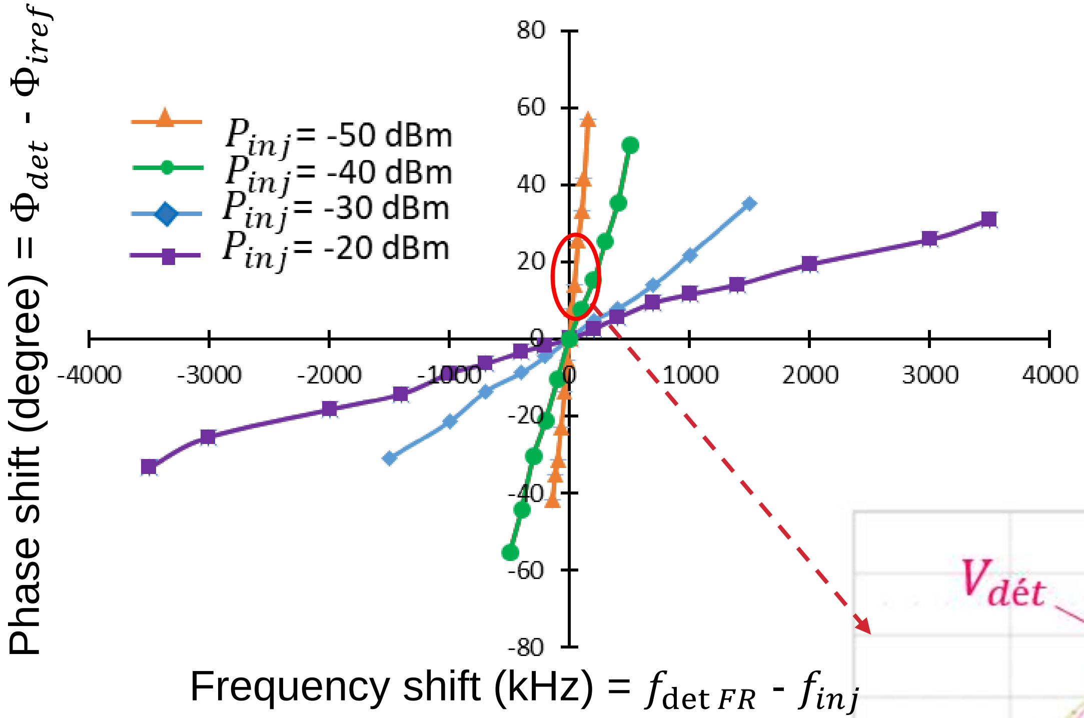
⇩

Phase shift **Δϕ** = $\boldsymbol{\Phi_{det\,FR}} - \boldsymbol{\Phi_{inj}}$ **= 0°**

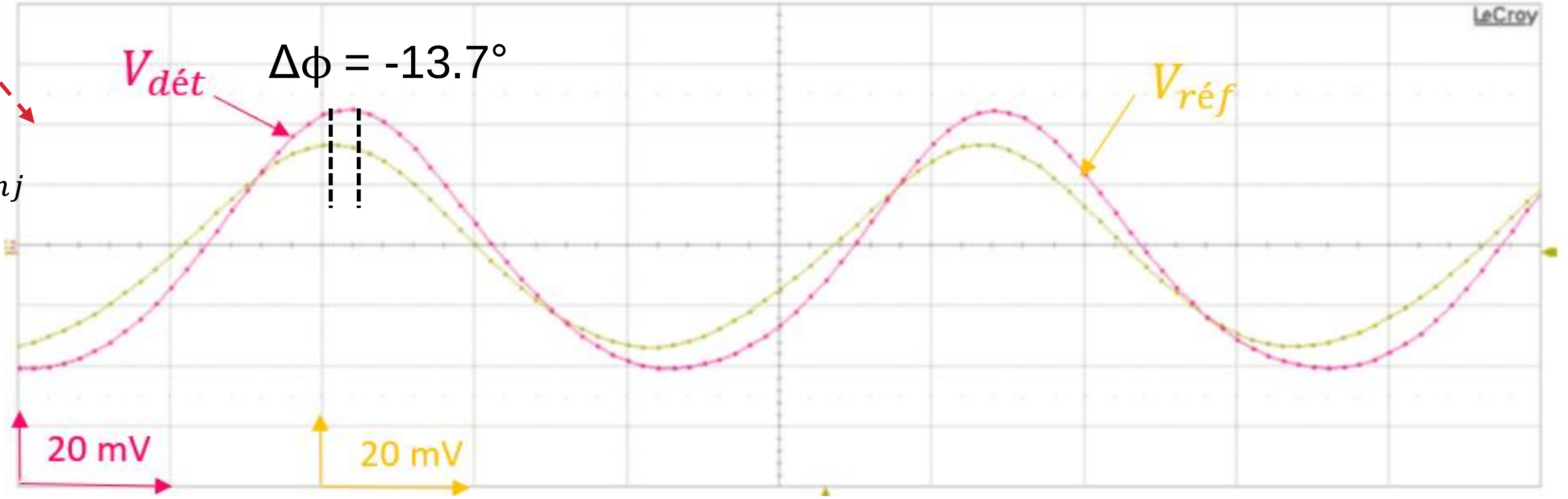
- ✓ P_{inj}=-50 dBm
- ✓ $f_{inj} = f_{ref} = f_{det}$ = 4.693 GHz



Measured phase shift between ILO outputs



When dielectric perturbation occurs
on the detection oscillator
⇩
Frequency shift $\mathbf{\Delta f = +40}$ **kHz**
⇩
Phase shift $\mathbf{\Delta\phi = -13.7°}$

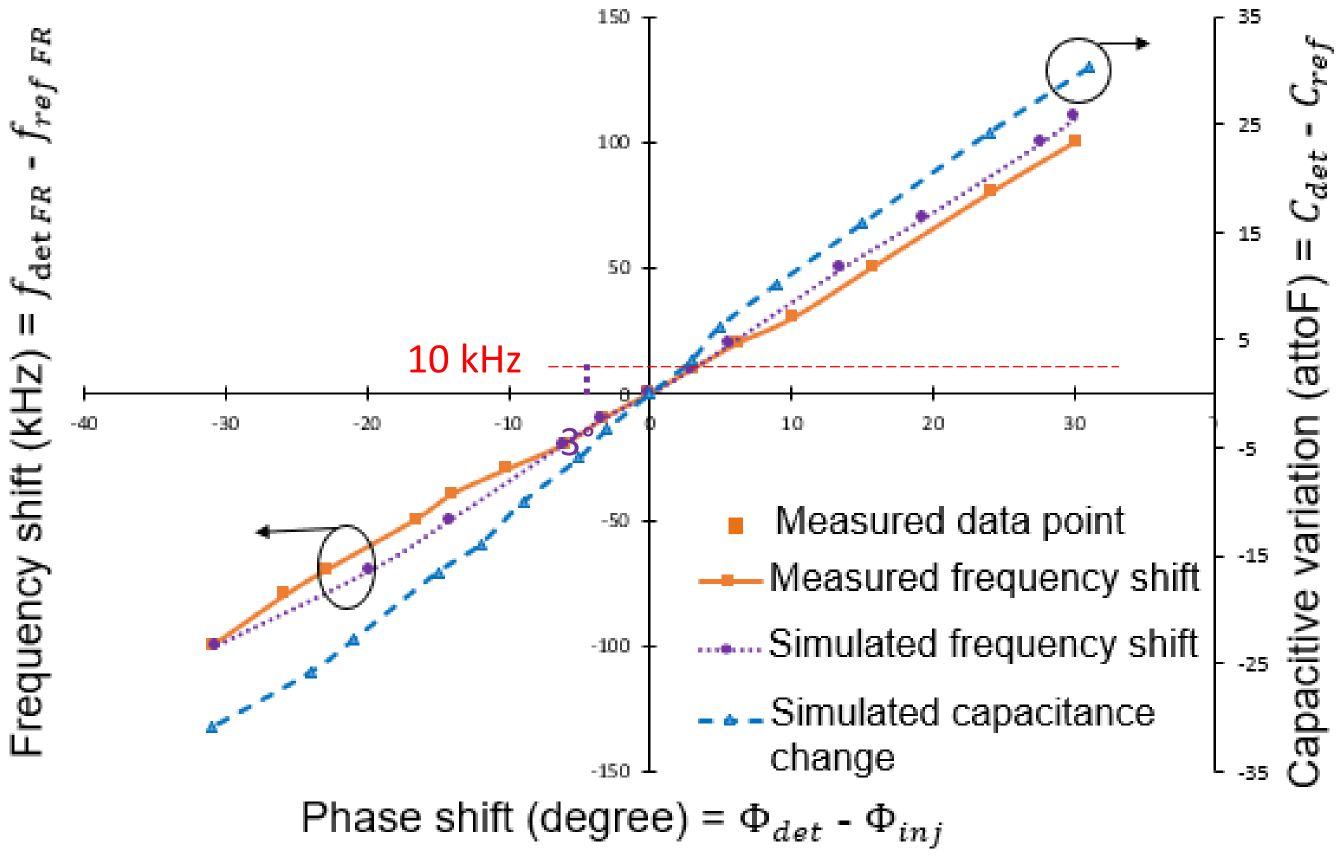


- ✓ P_{inj}=-50 dBm
- ✓ $f_{inj} = f_{ref}$= 4.693 GHz

Measured phase shift between ILO outputs

- ✓ P_{inj}=-50 dBm
- ✓ f_{inj} = $f_{réf}$ = 4.693 GHz

❖ Differential measurement of the free running frequency change between detector and reference ILOs according to the measured phase shift between both output signals



- ✓ ***ΔC* = 3 aF** around 670 fF of the overall LC tank capacitor
- ✓ ***Δf* = 10 kHz** around 4.693 GHz
- ✓ Detected phase shift ***Δϕ* = 3°**

Capacitive sensing sensitivity

5 ppm

Conclusion

- ✓ Implementation of an ultra-sensitive capacitive sensor based on an injection-locked oscillator architecture on a BiCMOS SiGe 0.25µm technology,.

- ✓ The detection system is able to detect **capacitance changes in the range of few attoF**, induced by **dielectric disturbance** occurring on on-chip integrated sensing capacitors.

- ✓ Measurement results show that such an architecture is able to achieve **5 ppm** sensing sensibility.

- ✓ Such detection level are especially required for future lab-on-chip development for biomedical diagnosis purpose.

THE ART OF MICROWAVES
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Thank you for your attention

Sumcastec

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