I3N Innovative Integrated Instrumentation for Nanoscience

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High Resolution Electronic Measurements in Nano-Bio Science

Differential measurements

When, why and how

Giorgio Ferrari

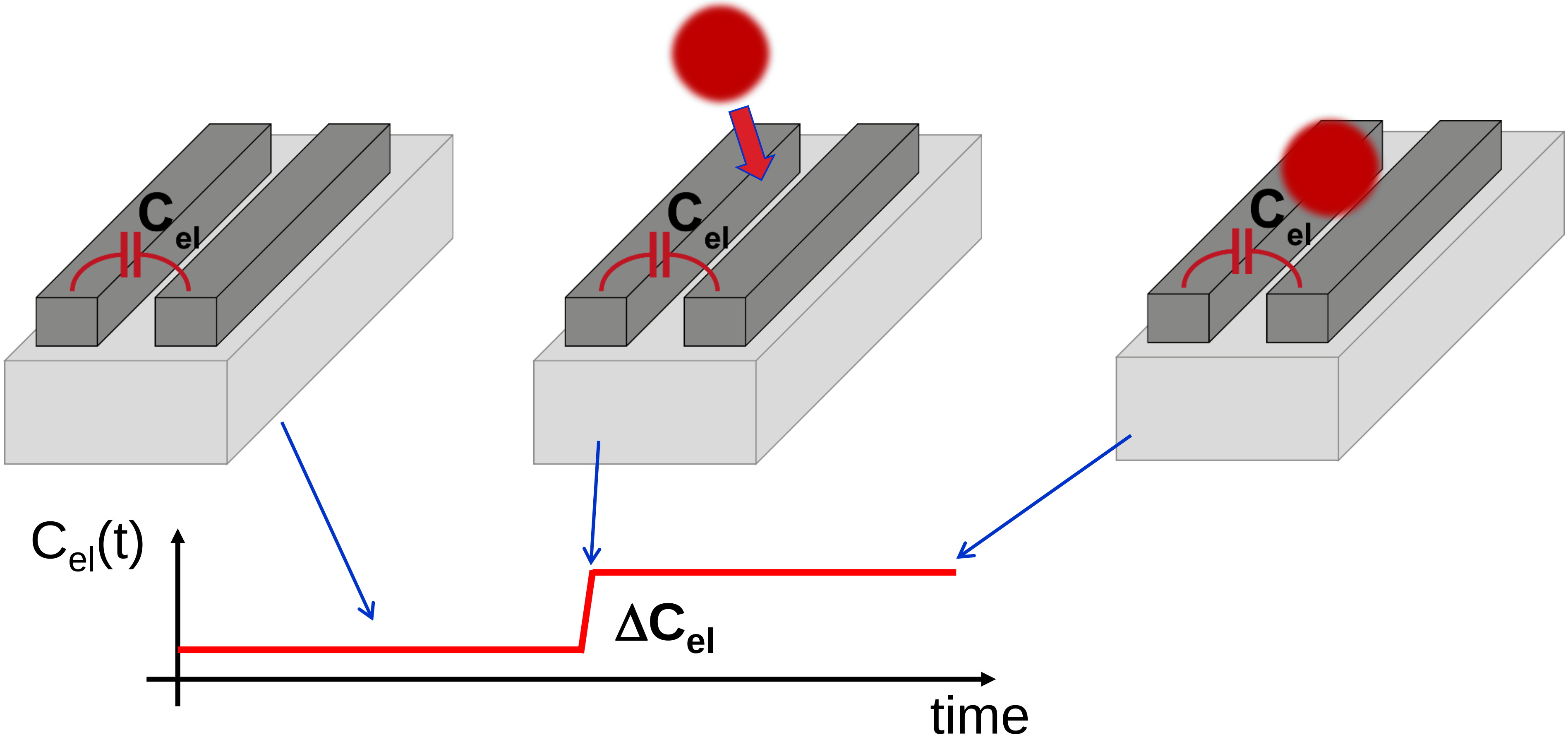
Milano, June 2023

OUTLOOK of the LESSON

- Motivation
- The differential approach
- Examples of implementation
- Limitations

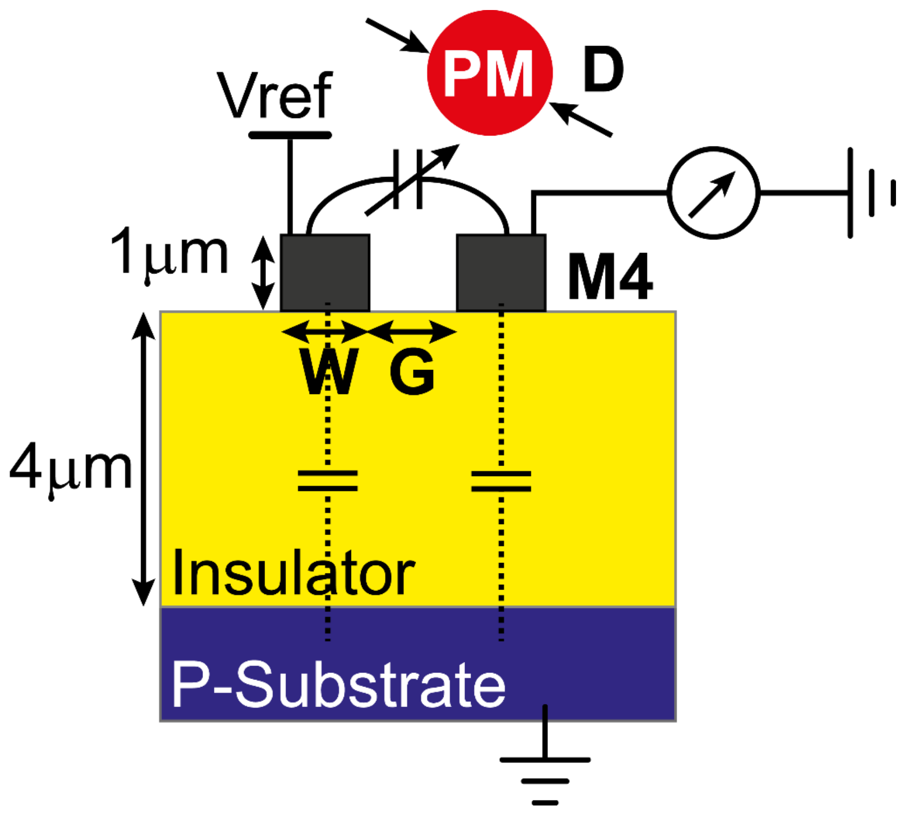
Example: capacitive detection of particles

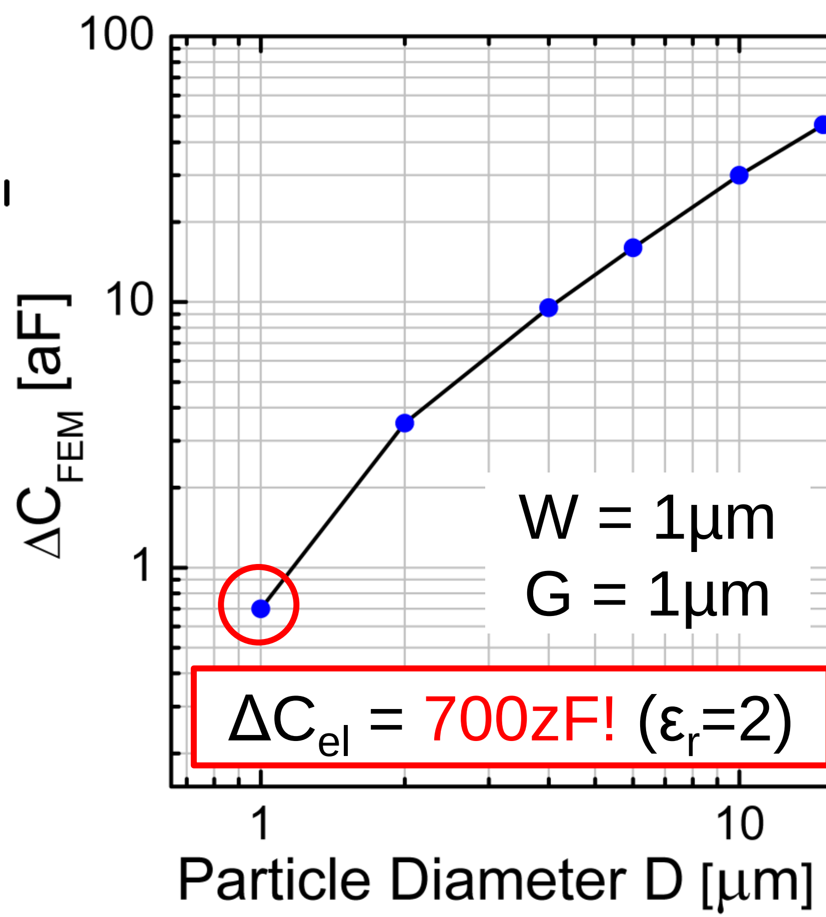
particle deposition on a surface (PM detector, cell monitor,…)



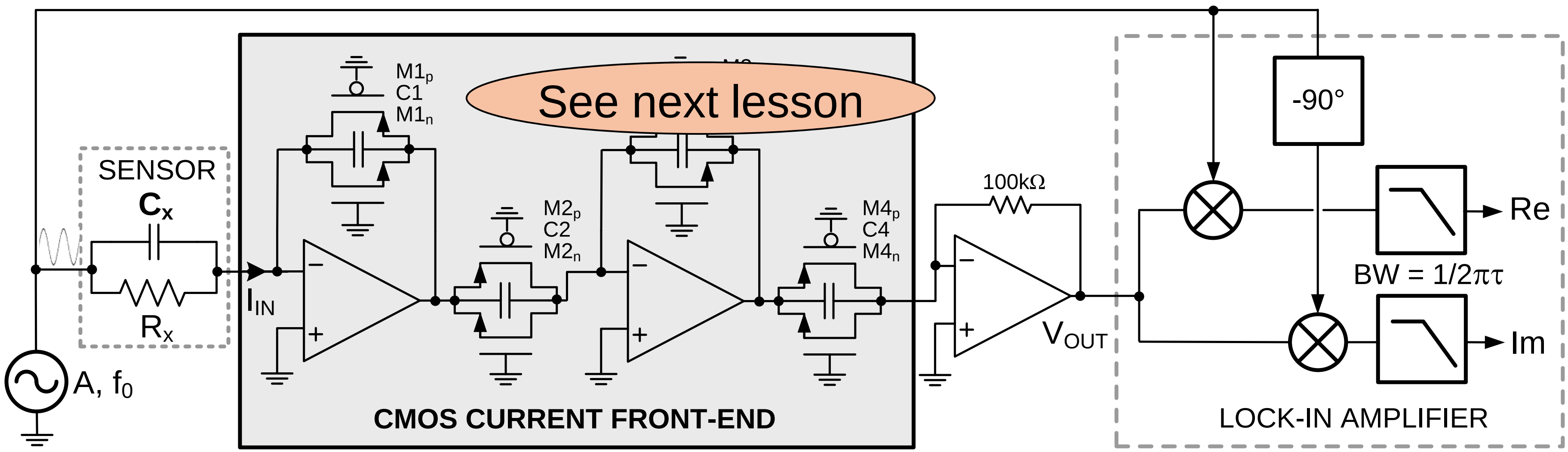
M. Carminati, Capacitive detection of micrometric airborne particulate matter for solid-state personal air quality monitors, *Sensors Actuators A* **219**, 2014.

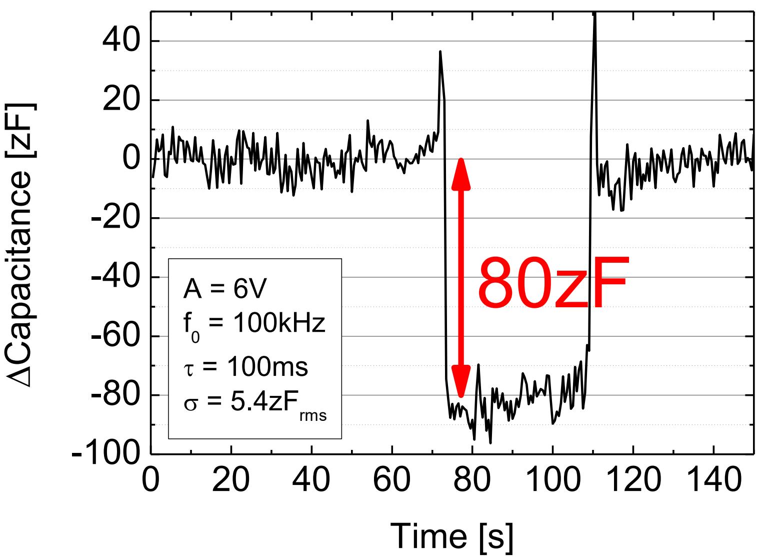
FEM Numerical Simulations

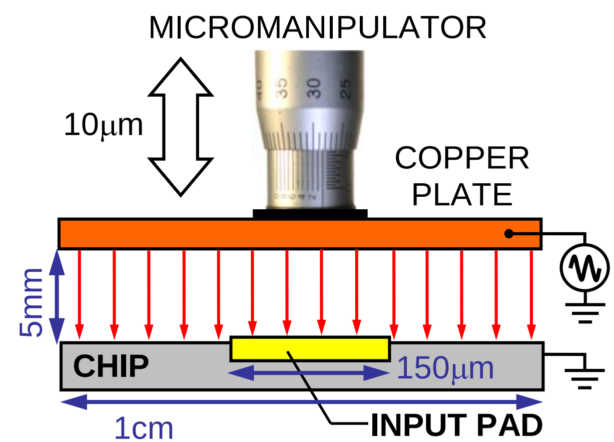




ZeptoFarad capacitance detection





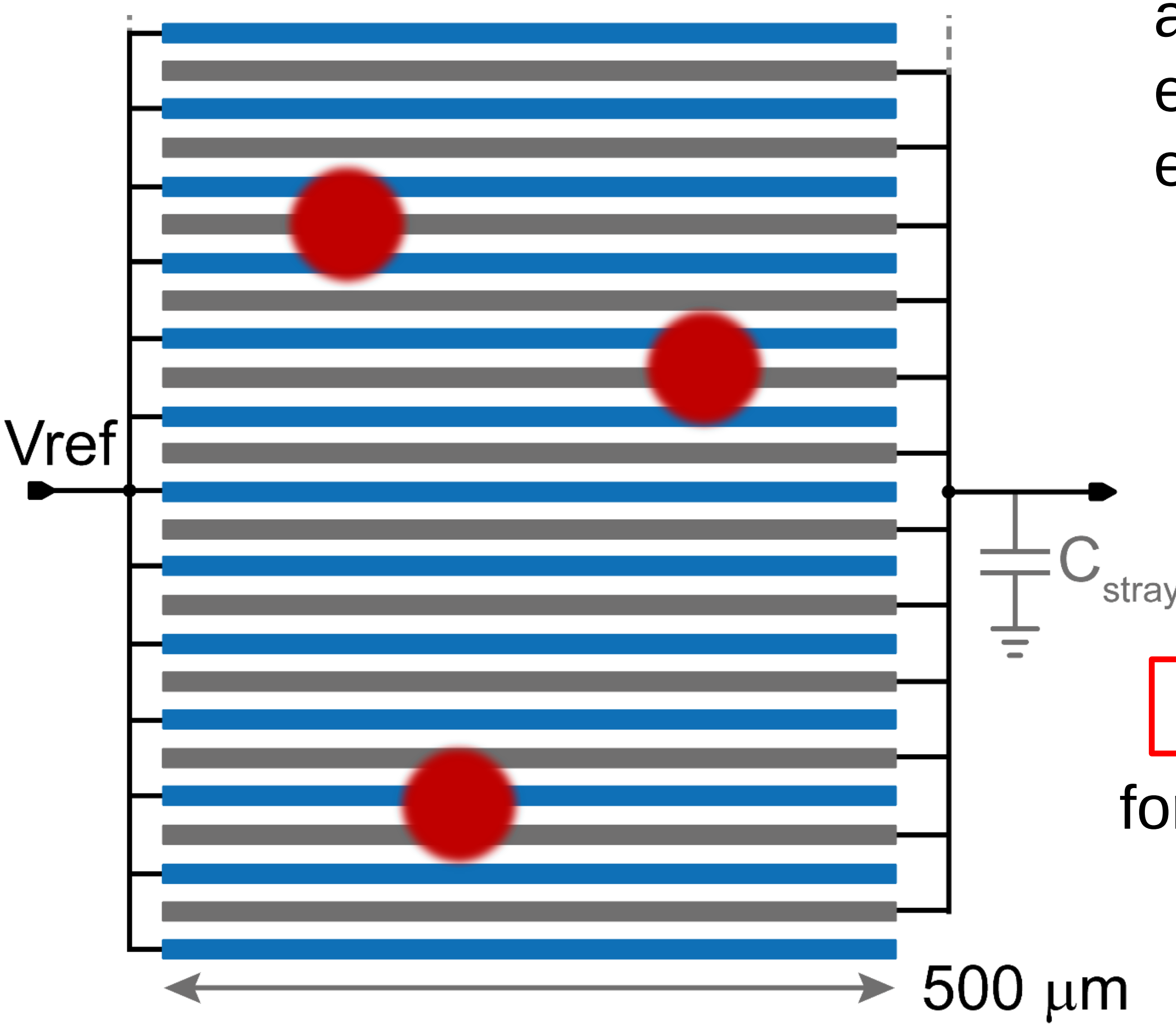


$C_x \approx$ 100 aF

M. Carminati, G. Ferrari, F. Guagliardo, M. Sampietro, "ZeptoFarad capacitance detection with a miniaturized CMOS current front-end for nanoscale sensors", Sensors and Actuators A: Physical, Vol. 172, pp. 117-123 (2011)

Large sensitive area

Interdigitated electrodes:



<u>Example:</u>

area 1 mm^2
electrode gap 1 μm
electrode length 500 μm

1000 electrodes!

C_{total} = 15pF

$\Delta C_{target} \approx$ 1 aF

for particle size of 1 μm

Small variations over large baseline: problems

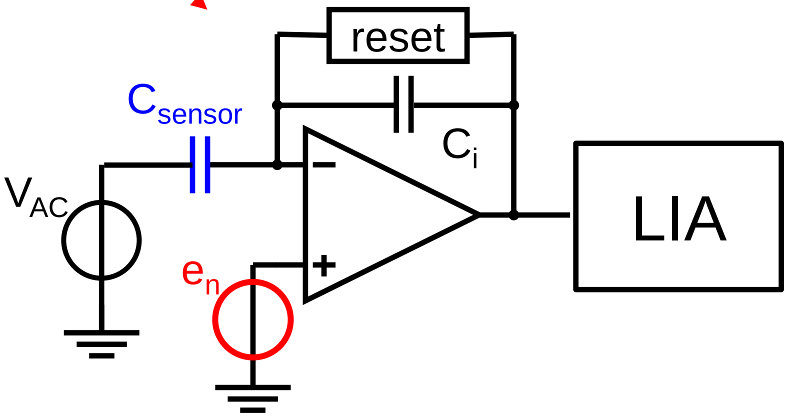
1) Noise of the sensor and of the preamplifier

see Sampietro lessons

Capacitance

"noiseless"

OK



$$(\Delta C \omega V_{AC})^2 > 2\, \overline{e_n^2}\, \omega^2 C_{sensor}^2\, BW$$

Ex.:

$$V_{AC} = 1V, \overline{e_n^2} = \left(\frac{5nV}{\sqrt{Hz}}\right)^2, C_{sensor} = 15pF, BW = 100Hz$$

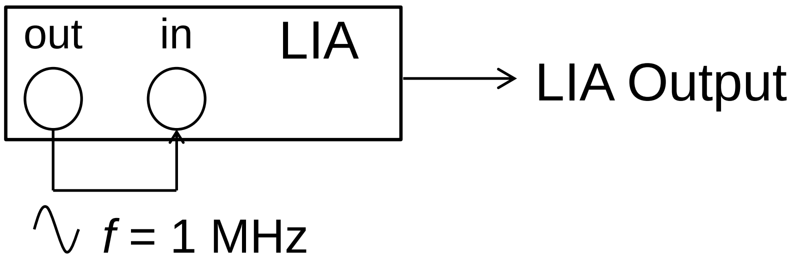
$$\Delta C > 1aF$$

Small variations over large baseline: problems

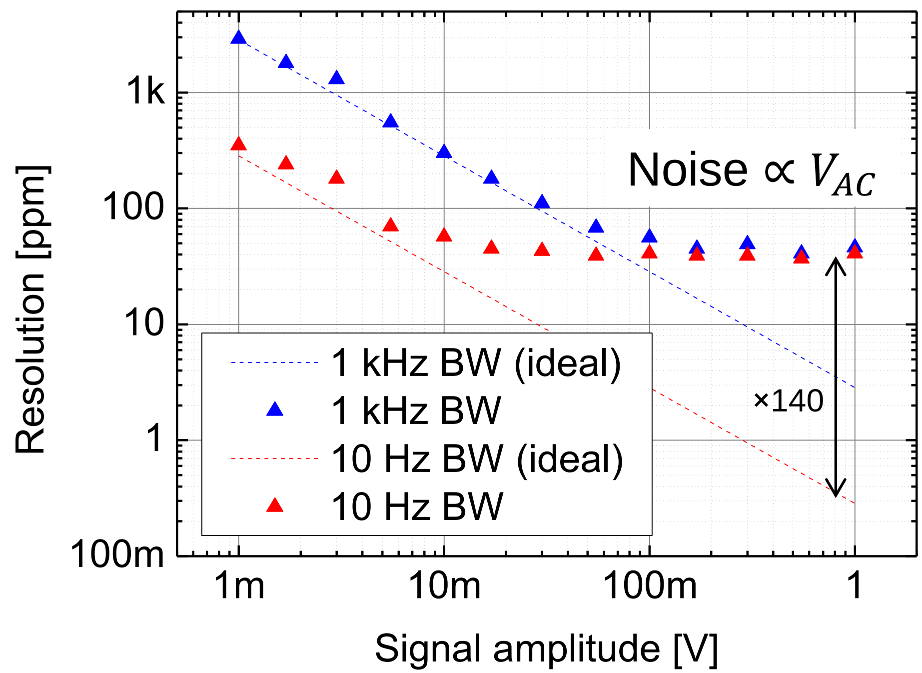
1) Noise of the sensor and of the preamplifier $\Delta C_{min} = 1aF$
2) Gain fluctuations (stimulus, readout)

see the lesson on high-resolution lock-in amp.

Zurich Instruments, HF2LI



Resolution = Noise / Signal



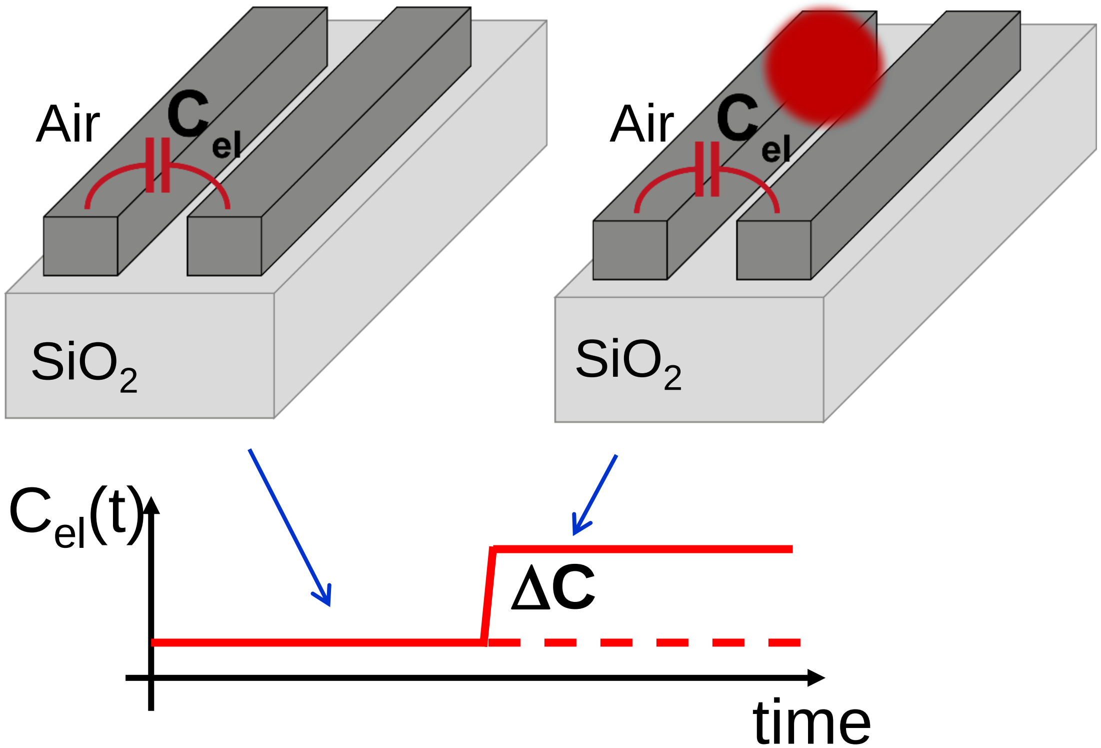
LIA resolution: 40 ppm

$C_{sensor} = 15pF$

$\Delta C_{min} = 600aF$

Minimum particle size:
> 50 μm

1) Noise of the sensor and of the preamplifier $\Delta C_{min} = 1aF$
2) Gain fluctuations (stimulus, readout) $\Delta C_{min} = 600aF$
3) Baseline fluctuations



$C_{baseline} = C_{el}(air) + C_{el}(SiO_2)$

Temperature:

$\Delta\epsilon_{air} \approx -2\ ppm/°C$

$\Delta\epsilon_{SiO_2} \approx 25\ ppm/°C$

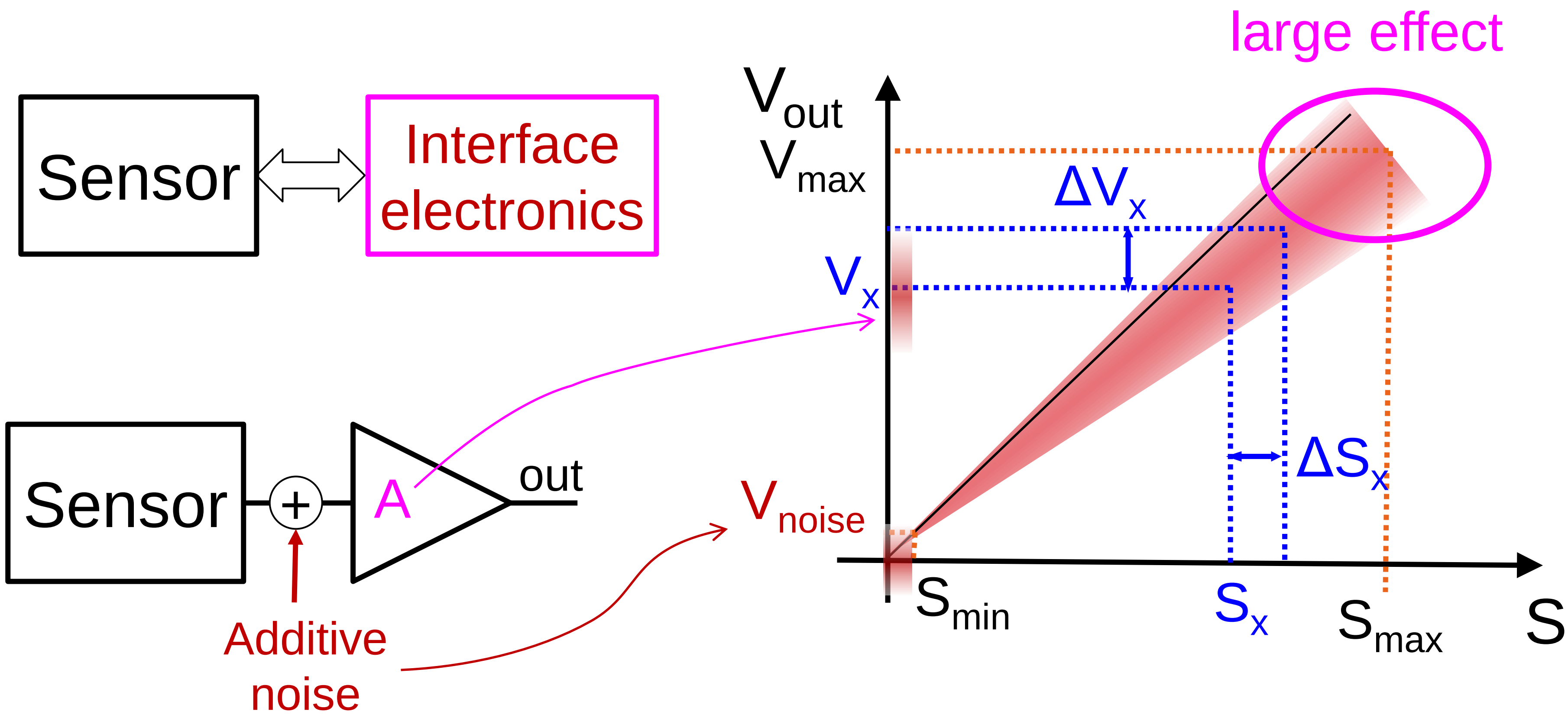
Humidity:

$\Delta\epsilon_{air} \approx 1\ ppm/\%RH$

$\Delta C \approx 250aF\ /°C$

How to improve the resolution?

Slow measurements using good amplifiers and low noise sensors could be limited by gain fluctuations (DAC, amp., ADC)



The additional noise is proportional to the signal to be measured

How to improve the resolution?

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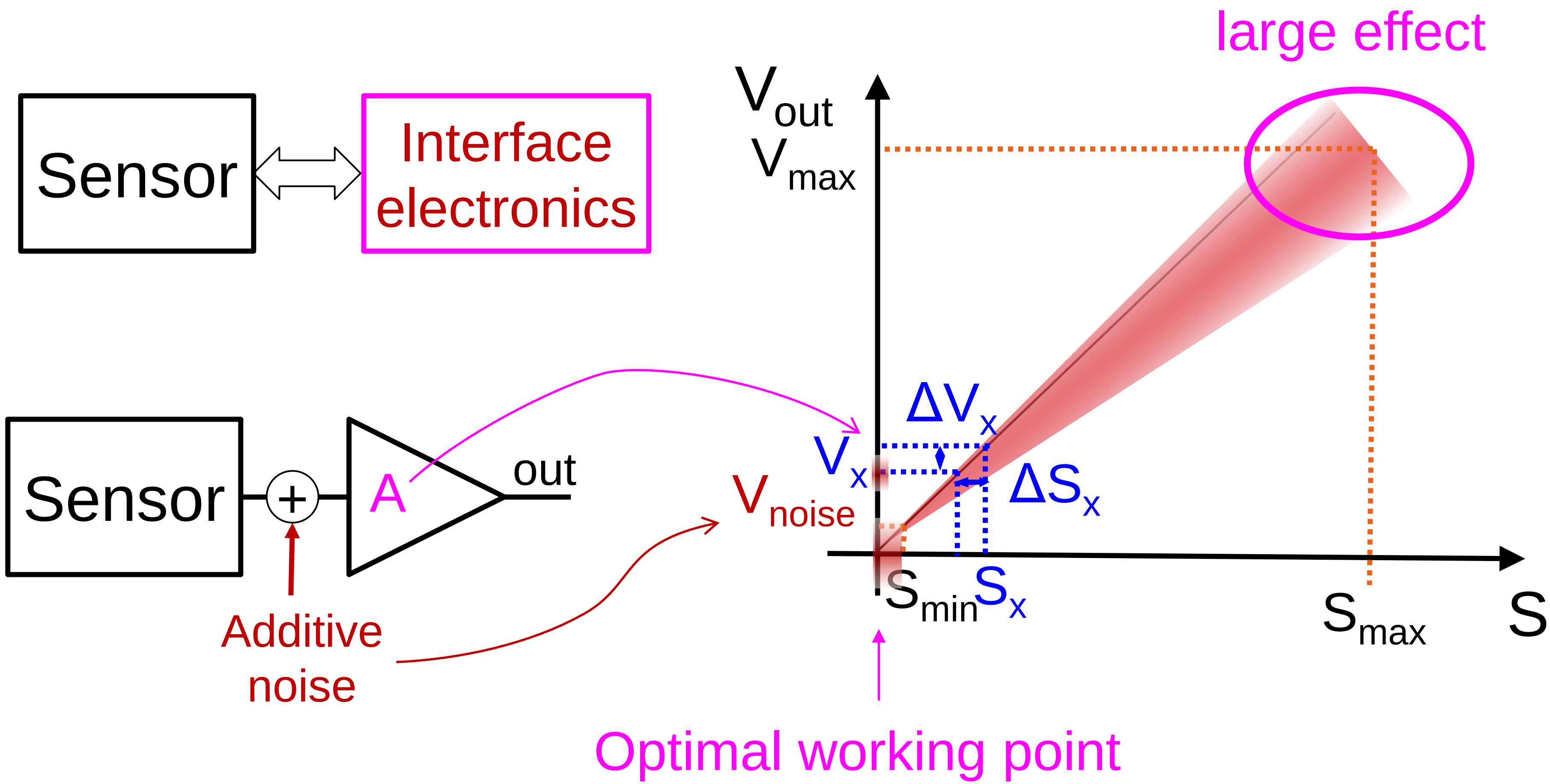


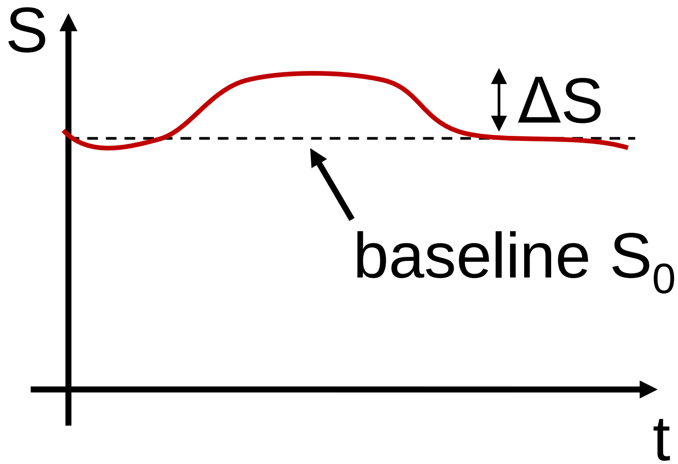
The additional noise is proportional to the signal

The differential approach

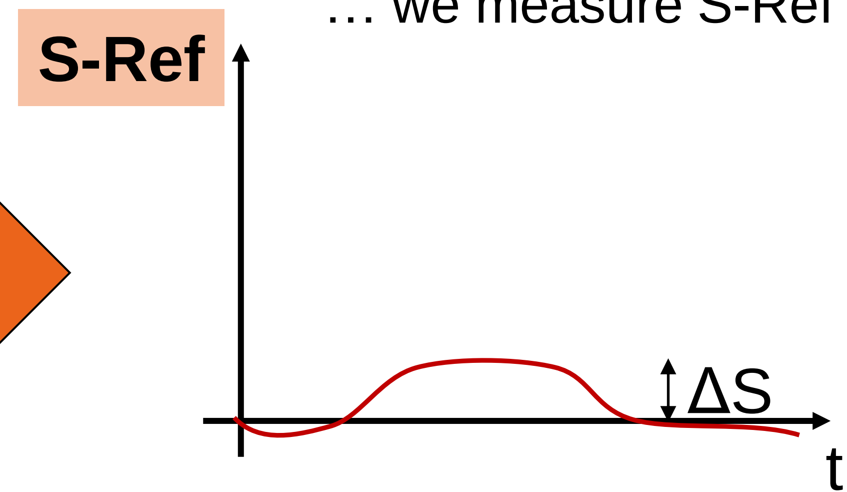
The additional noise is proportional to the signal

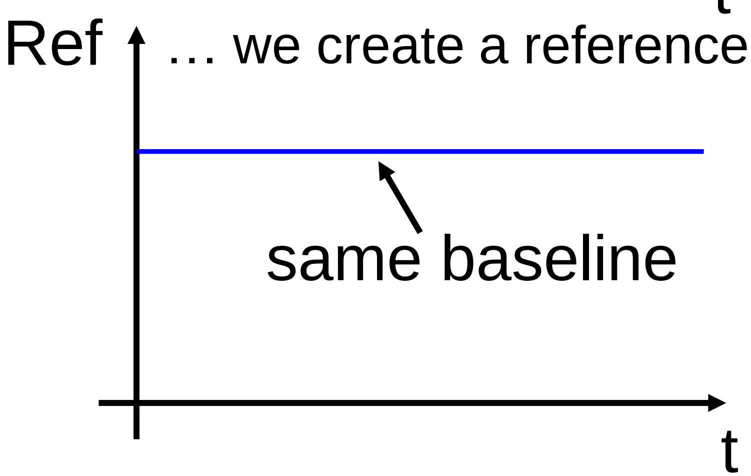
keep only the useful signal!

We want to measure this signal…



… we measure S-Ref





$$Out = (S - Ref) \cdot \left(G + \delta G(t)\right) \approx \Delta S \cdot (G + \delta G(t))$$

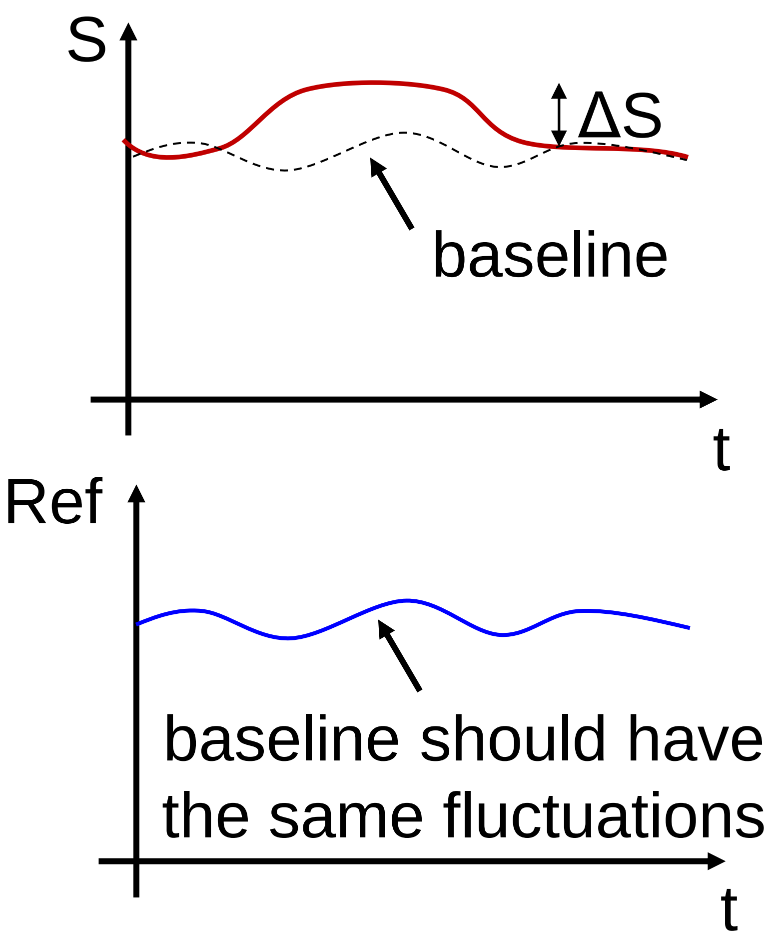
If $\Delta S << S_0$ ($Ref \approx S_0$):

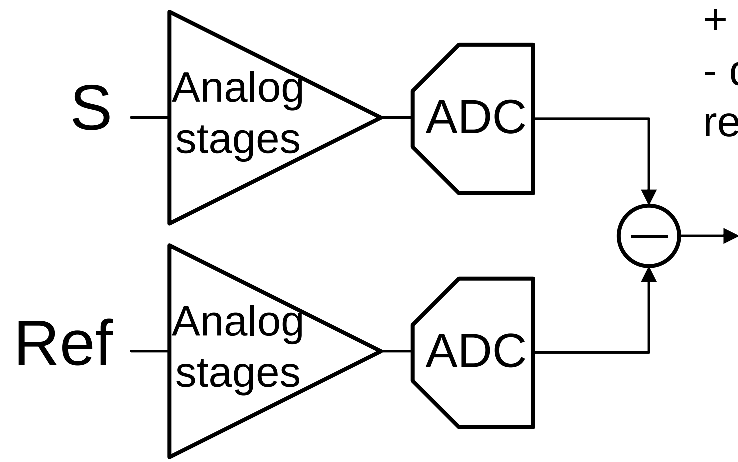
$$\text{noise}_{\text{diff}} = \Delta S \cdot \delta G(t) \ll \text{noise}_{\text{single}} = S_0 \cdot \delta G(t)$$

gain fluctuations prop. to $\Delta S \ll S_0$

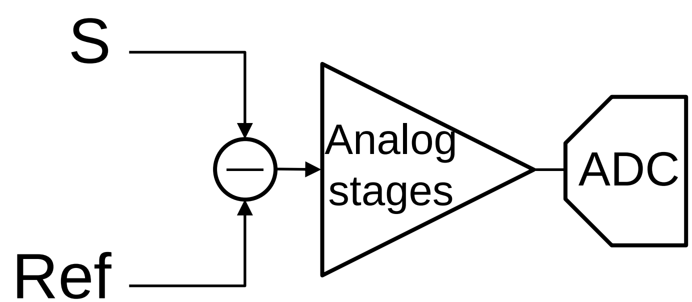
The differential approach: baseline fluctuations

The Reference must share the gain fluctuations of the baseline:





+ flexibility
- doubling of the resources

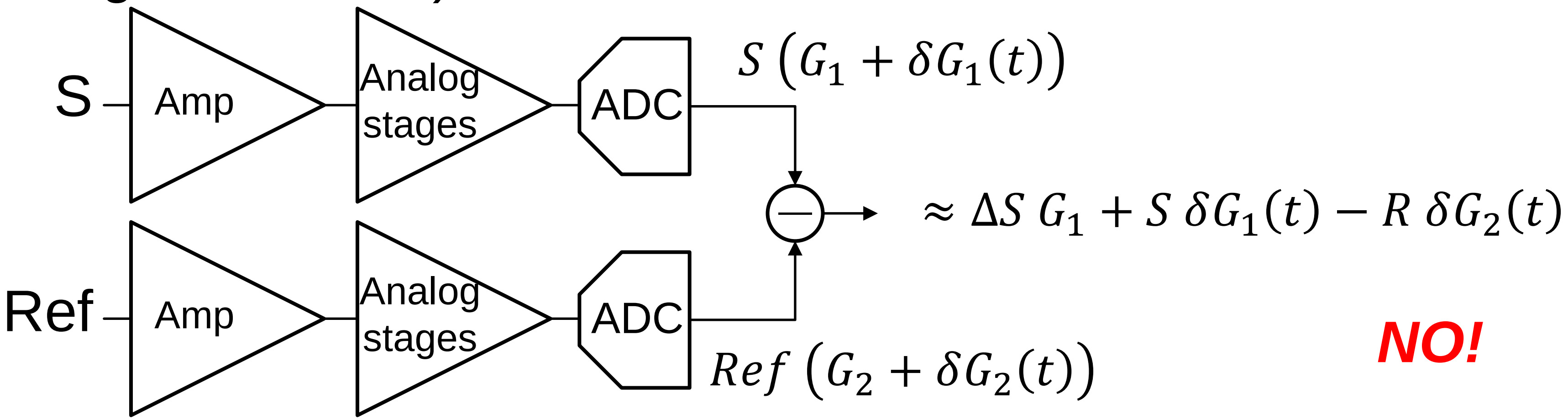


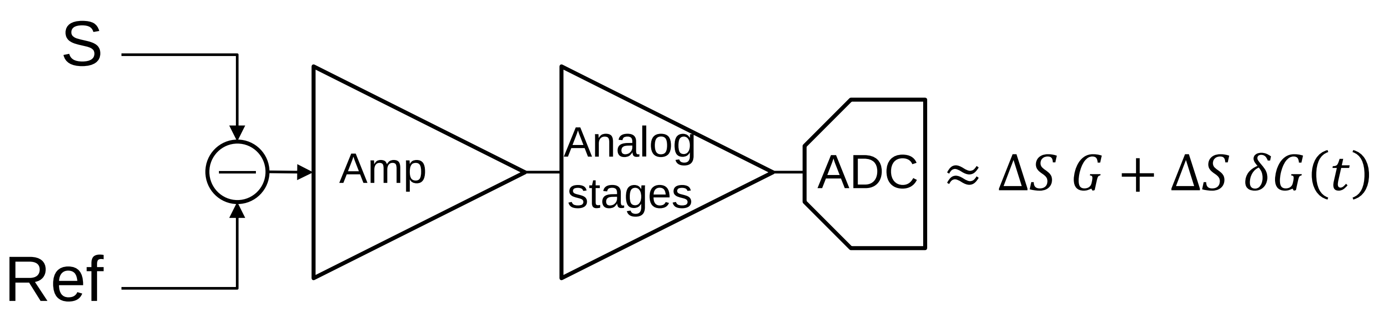
+ best working point of the amplifiers
- less flexibility (a calibration may be required)

If the baseline is the limiting factor, both solutions are OK

The differential approach: gain fluctuations

If the limitation is set by the **gain fluctuations of the acquisition chain** the subtraction should be implemented as soon as possible (no digital domain!)





OUTLOOK of the LESSON

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- The differential approach
- Examples of implementation
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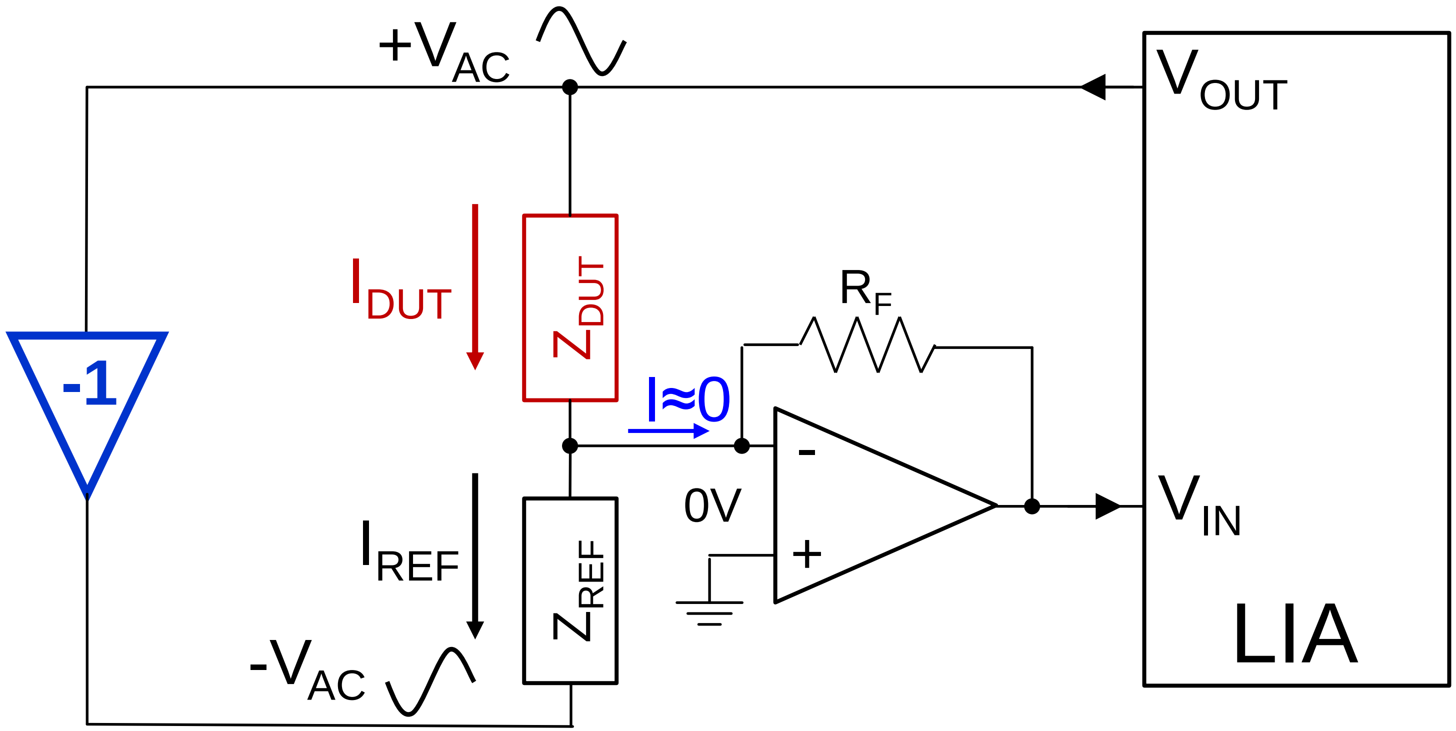
Differential current sensing



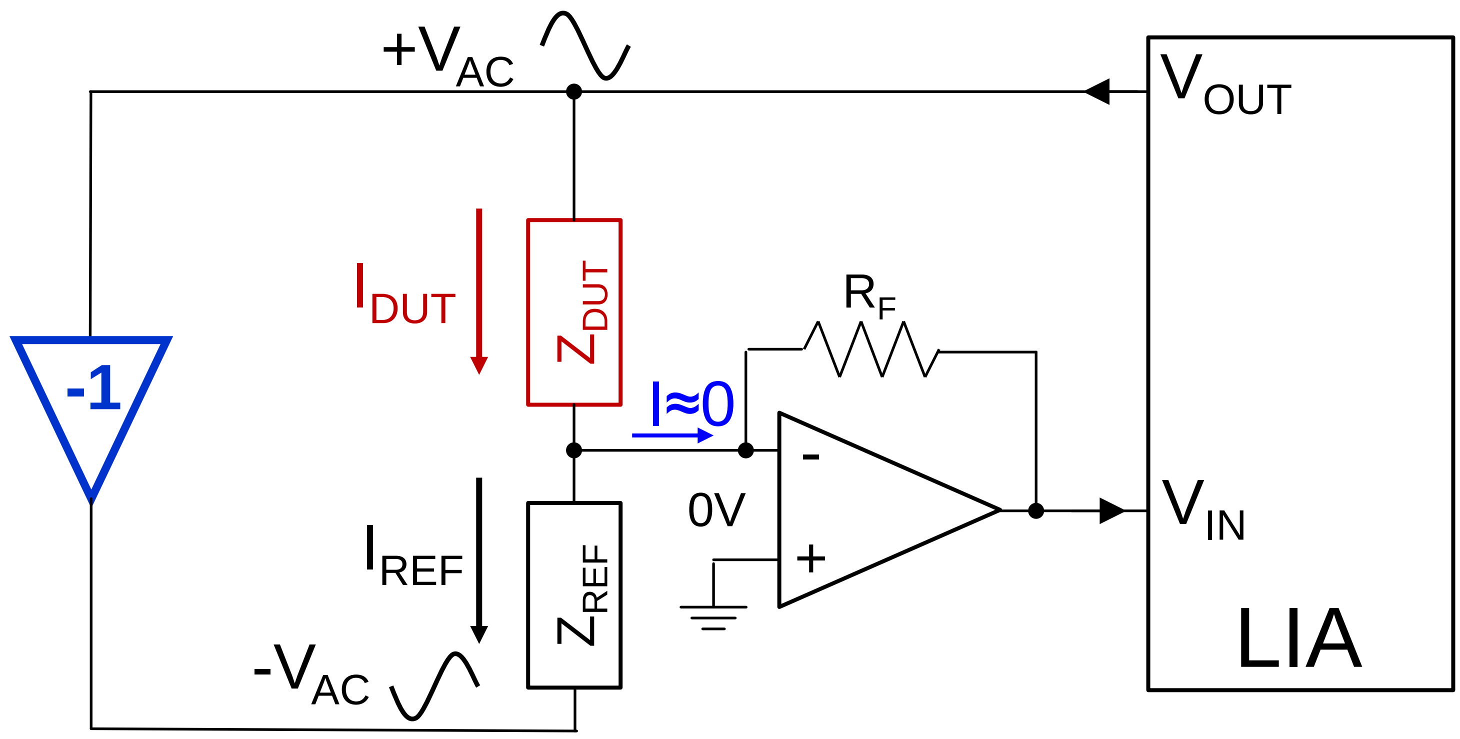
- Balanced structure:

$Z_{REF} \approx Z_{DUT}$ ⇨ $I = V_{AC}\left(\frac{1}{Z_{DUT}} - \frac{1}{Z_{REF}}\right) = V_{AC}(Y_{DUT} - Y_{REF}) \approx 0$

✓ Less noise given by gain fluctuations (V_{AC}, R_F, ADC,…)

✓ Amplifier optimization (gain, linearity, dynamic range)

Differential current sensing

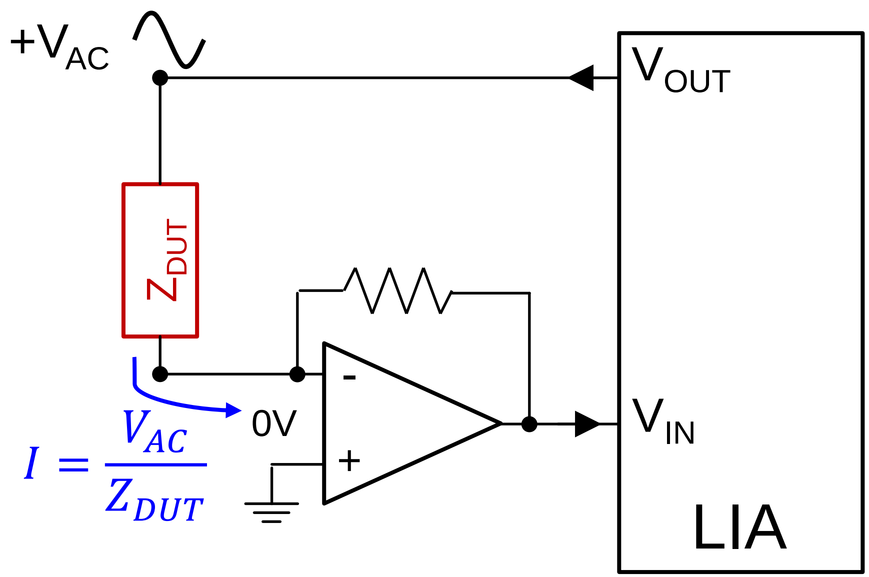


- Balanced structure:

$$Z_{REF} \approx Z_{DUT} \Rightarrow I = V_{AC}\left(\frac{1}{Z_{DUT}} - \frac{1}{Z_{REF}}\right) = V_{AC}(Y_{DUT} - Y_{REF}) \approx 0$$

- ❑ Z_{REF} adjacent to Z_{DUT} for sharing the same temp. fluctuations
- ❑ The inverting amplifier requires a stable gain!

Signal – reference matching: an example



Assuming:

- LIA resolution limit: 100ppm
- No other noise sources
- $Z_{DUT}(f_0)$ = 1MΩ

Goal:

- Detection of $\Delta Z_{DUT}(f_0)$ of 1Ω

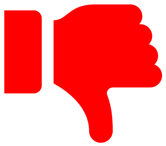
Current variation given by ΔZ_{DUT}

$$|\Delta I| \approx \left|\frac{\partial I}{\partial Z_{DUT}}\,\Delta Z_{DUT}\right| = \left|\frac{V_{AC}}{Z_{DUT}^2}\,\Delta Z_{DUT}\right| = \left|I\,\frac{\Delta Z_{DUT}}{Z_{DUT}}\right|$$

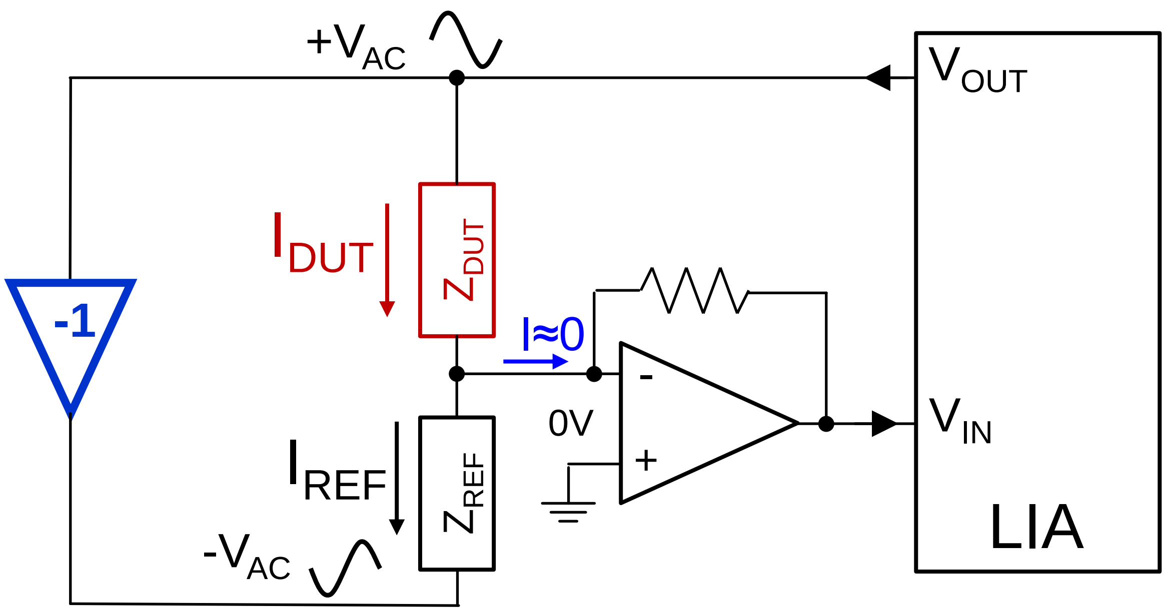
Minimum detectable impedance variation:

$$|\Delta I| > 10^{-4}\,I \quad \Rightarrow \quad \Delta Z_{DUT} > 10^{-4}\,Z_{DUT} = 100\Omega$$

(100ppm)



Signal – reference matching: an example



Assuming:

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- $Z_{DUT}(f_0) = 1M\Omega$

Goal:

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Current variation given by ΔZ_{DUT}

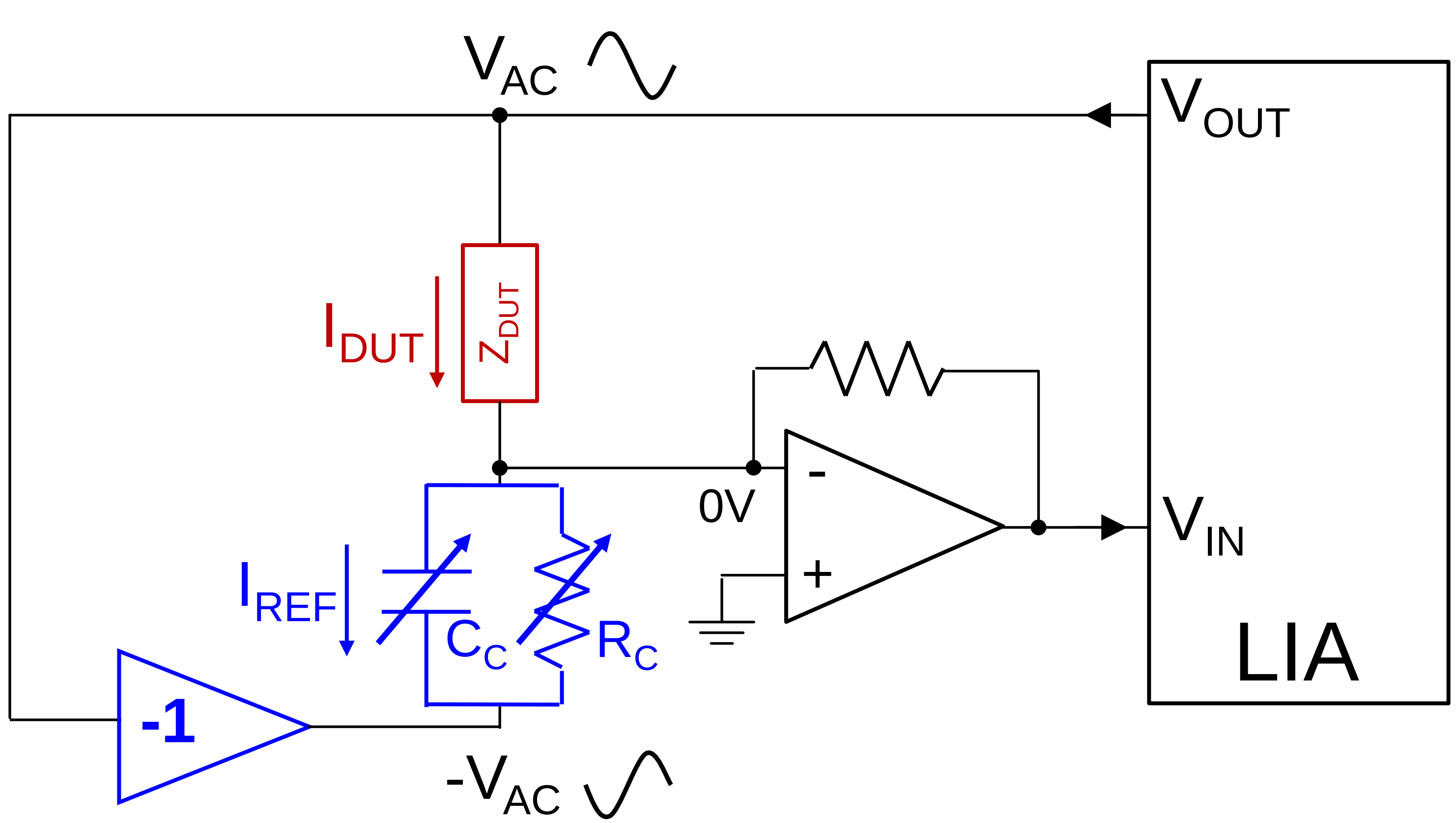
100ppm

$$|\Delta I| \approx \left|\frac{V_{AC}}{Z_{DUT}}\frac{\Delta Z_{DUT}}{Z_{DUT}}\right| > 10^{-4} I = 10^{-4}\left|\frac{V_{AC}}{Z_{DUT}} - \frac{V_{AC}}{Z_{REF}}\right|$$

$$\left|\frac{\Delta Z_{DUT}}{Z_{DUT}}\right| > 10^{-4}\left|1 - \frac{Z_{DUT}}{Z_{REF}}\right|$$

$$\Rightarrow \quad Z_{REF} \approx Z_{DUT}(1 \pm 1\%)$$

Calibration of the reference path

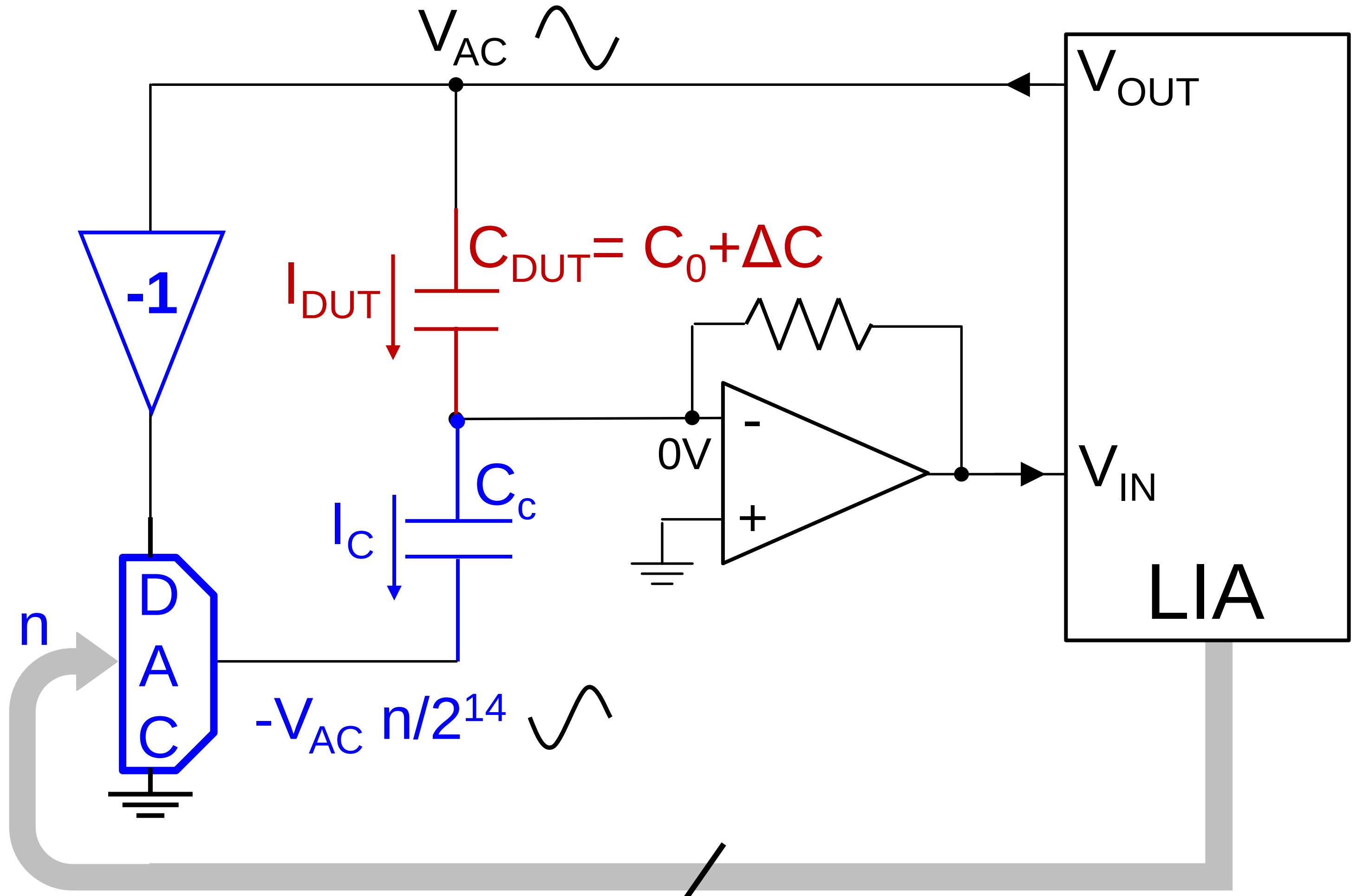


Calibration may be required to have $I_{DUT} \approx I_{REF}$ in *module and phase*

1) Manual setting of a capacitive trimmer C_C and resistive trimmer R_C

2) Digital setting of the reference path

Digital control of the reference path

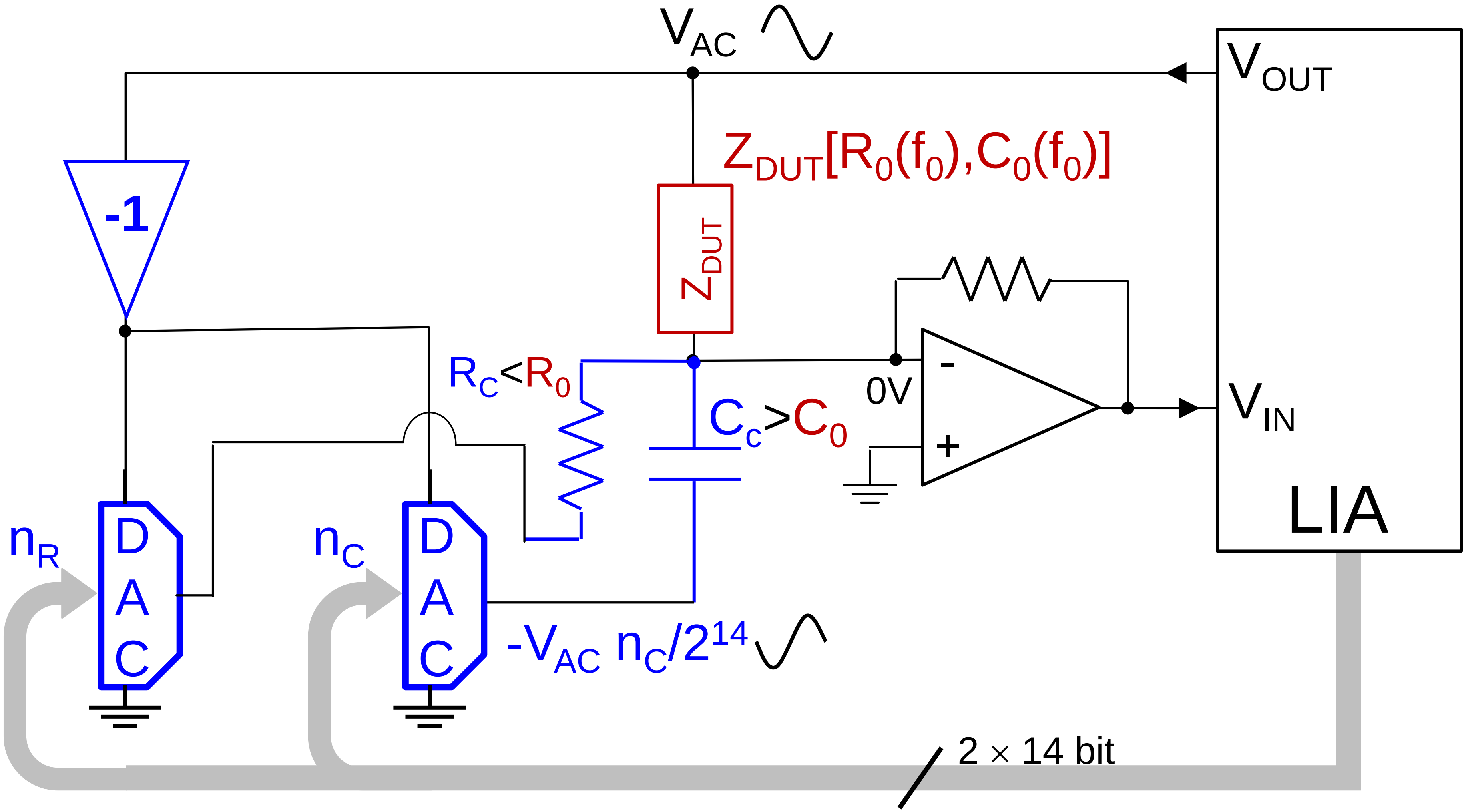


$$\frac{n}{2^{14}} C_C = C_0$$

C_c greater than C_0

AD5446: 14-bit multiplying DAC, BW= 12MHz, gain temp. coef. <20 ppm /°C

Digital control of the reference path

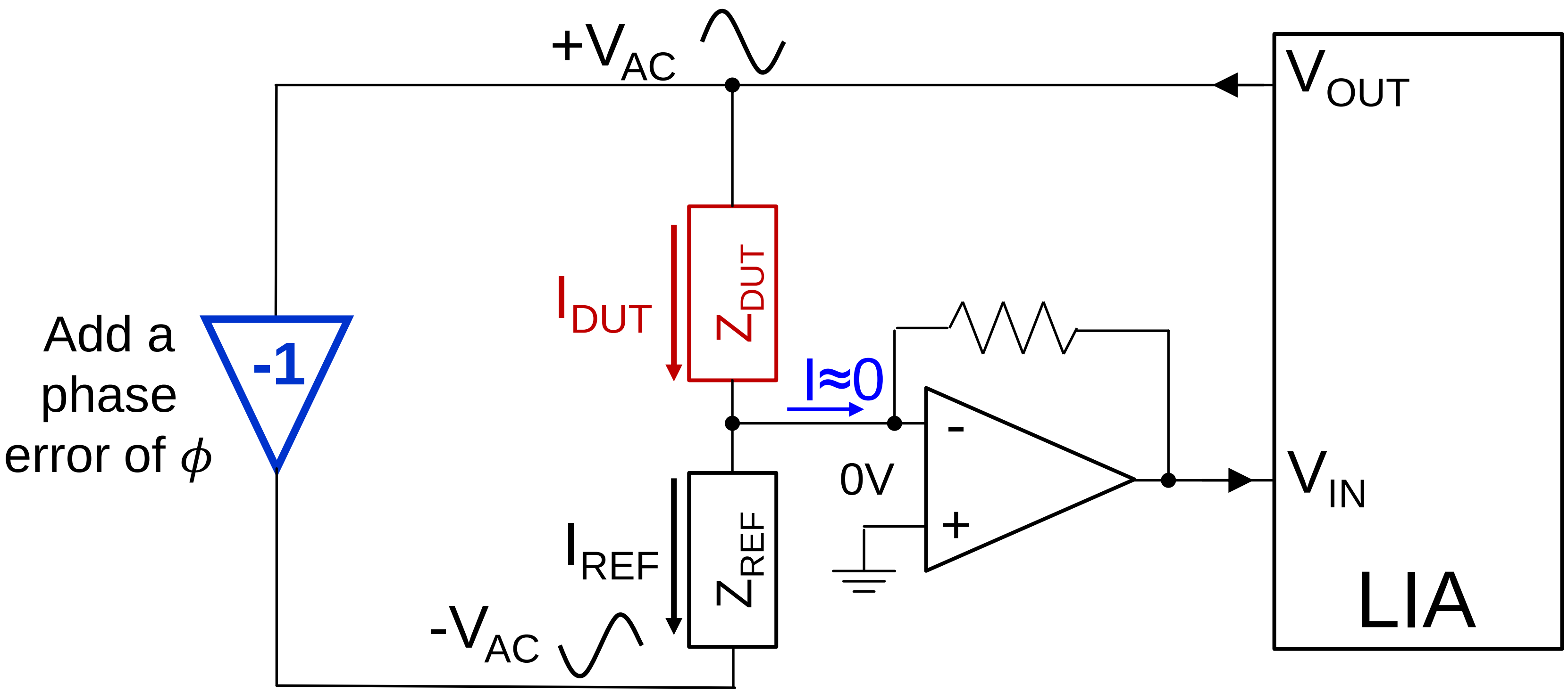


$$\frac{n_R}{2^{14}}\frac{1}{R_c}=\frac{1}{R_0}$$

$$\frac{n_C}{2^{14}}C_C=C_0$$

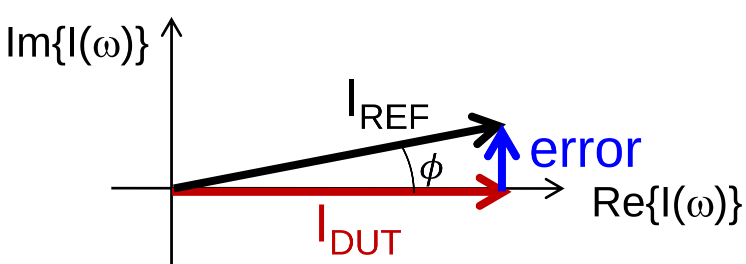
AD5446: 14-bit multiplying DAC

Phase error



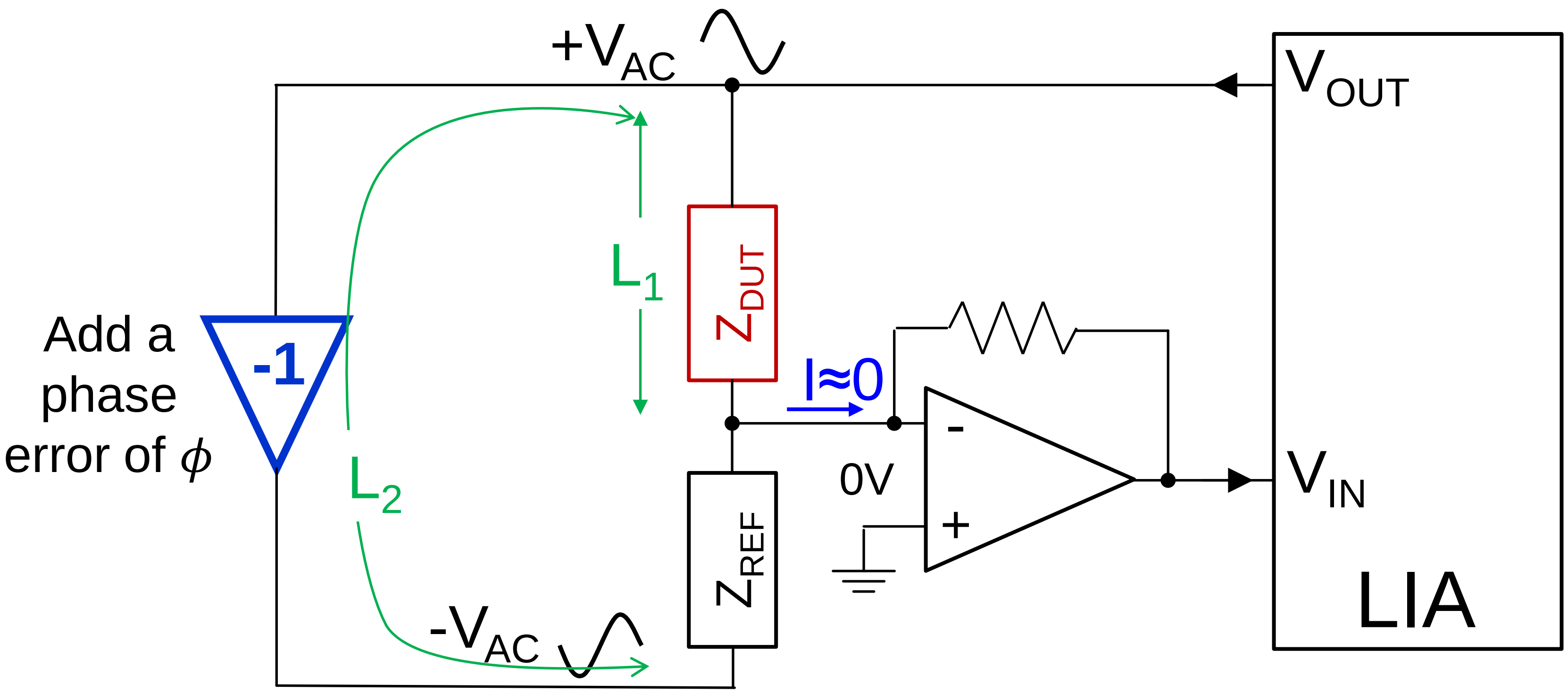
Assuming the ideal case of Z_{REF} = Z_{DUT} we have a residual error:

$$V_{AC}\sin(\omega_0 t) - V_{AC}\sin(\omega_0 t + \phi) = -2\,V_{AC}\sin\left(\frac{\phi}{2}\right)\cos\left(\omega_0 t + \frac{\phi}{2}\right)$$



It is an error in quadrature!

Phase error



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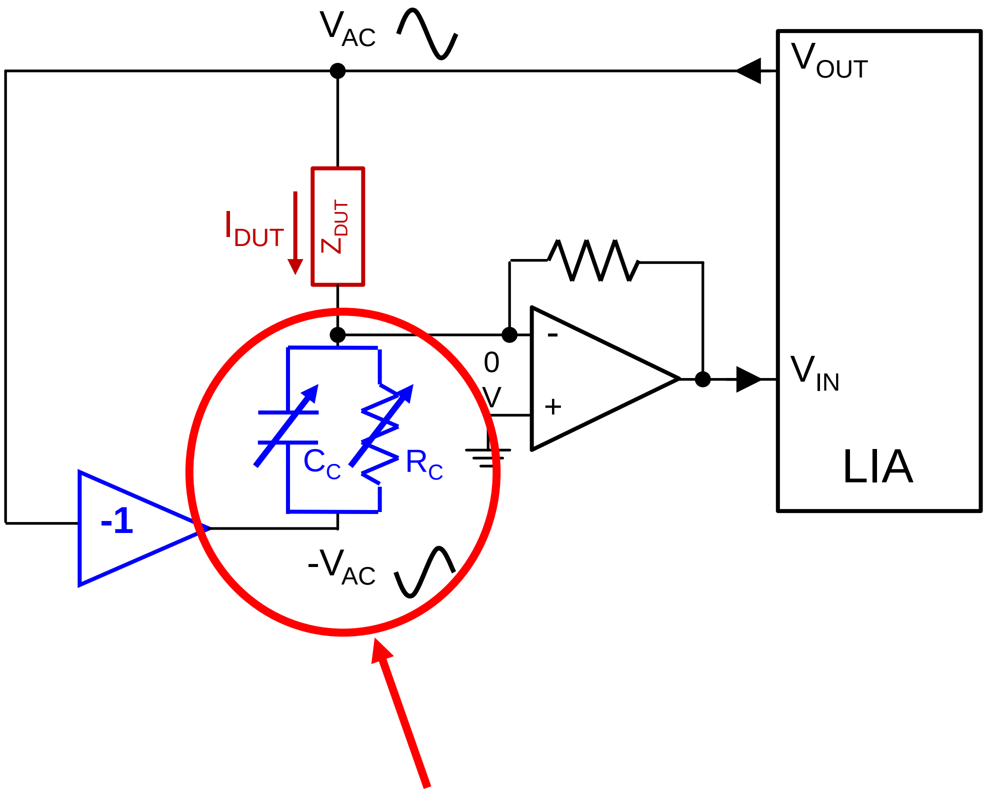
It is an error in quadrature!

For an error <1% $\rightarrow \phi < 0.6°$

- BW >100·f_0
- If f_0=10MHz → connection length: $|L_2-L_1|$< 3.3cm

Generation of the reference path

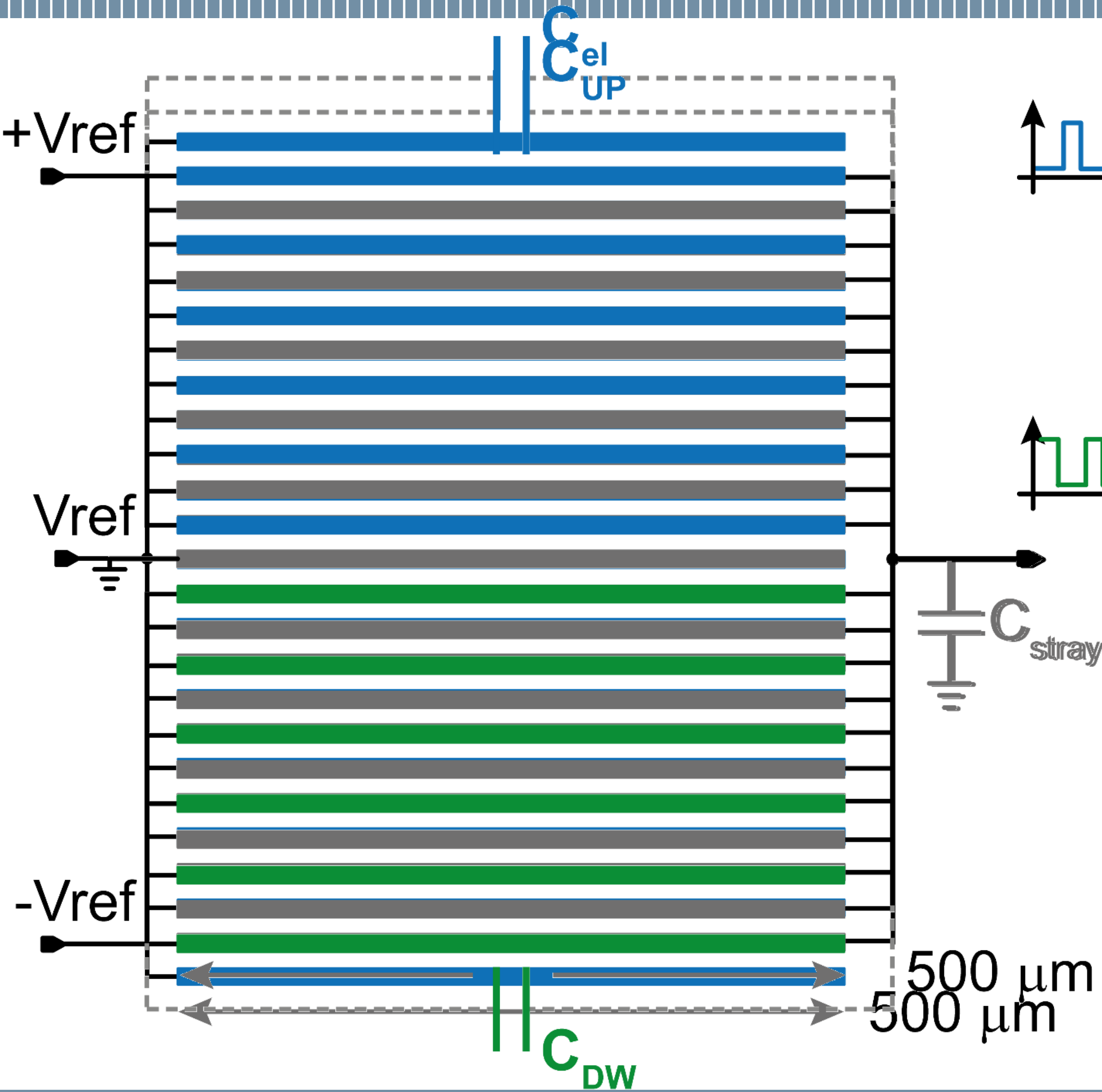


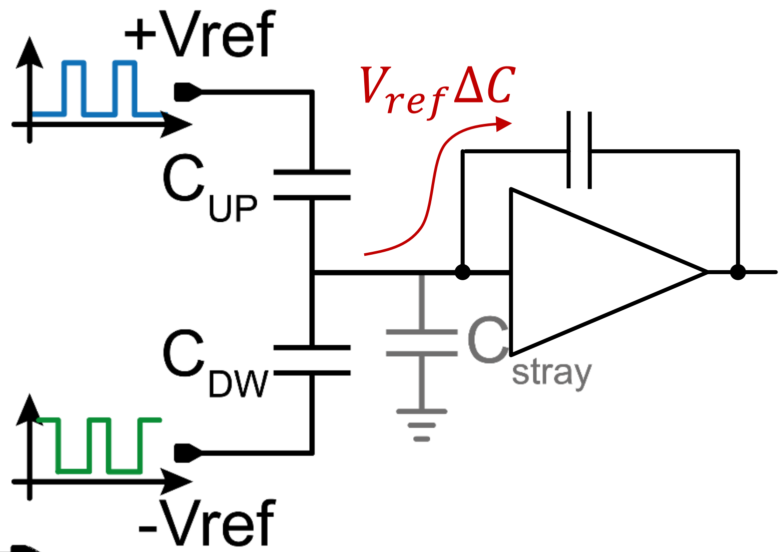
\+ general approach
\+ reduces the effect of gain fluctuations of the acquisition chain and the stimulus signal

\- limited compensation for the environmental effects (temperature, humidity,…)
\- long-term stability

Fabricate the reference path with the same technology as the DUT, if possible!

Differential electrodes architecture





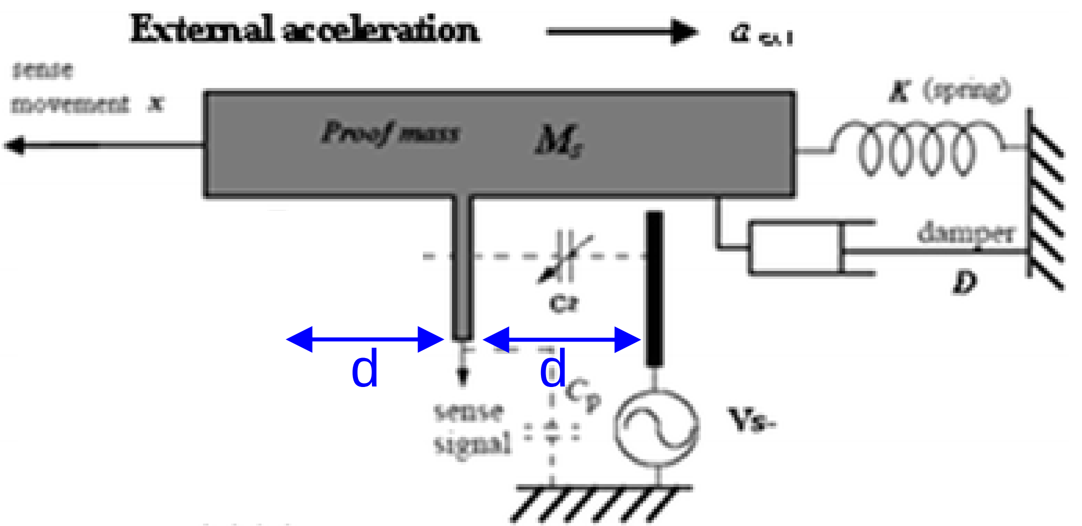
Differential structure

- Common mode rejection
- Gain fluctuations
- Environment

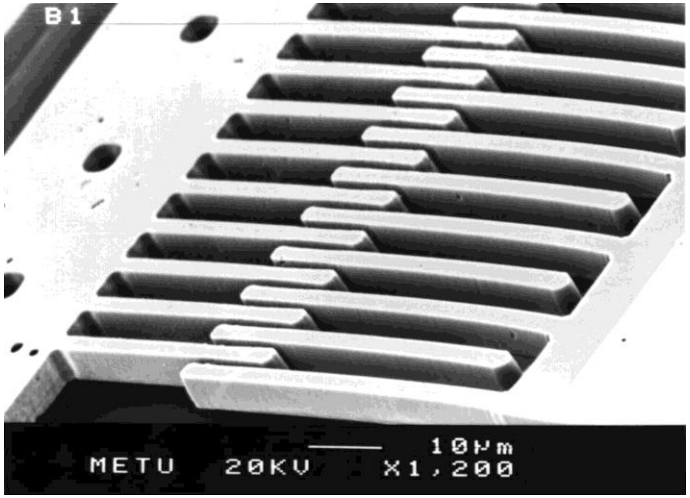
more electronic details in the next lesson

Design differential sensors if possible

Example: MEMS capacitive sensors



Microsystem Technologies, 2013, pp 713–720, DOI: 10.1007/s00542-013-1741-z



http://www.microsystems.metu.edu.tr/gyroscope/gyroscope.html

$$C_1 = \epsilon \frac{A}{d + \Delta x} \cong C_0 - \Delta C$$

$$C_2 = \epsilon \frac{A}{d - \Delta x} \cong C_0 + \Delta C$$

both arms of the differential structure are sensors

- Doubling the signal: C_2-C_1=2ΔC
- Better linearity: compensation of even non-linearity
- Well-balanced structure
- Excellent rejection of common-mode interferences (temperature,…)

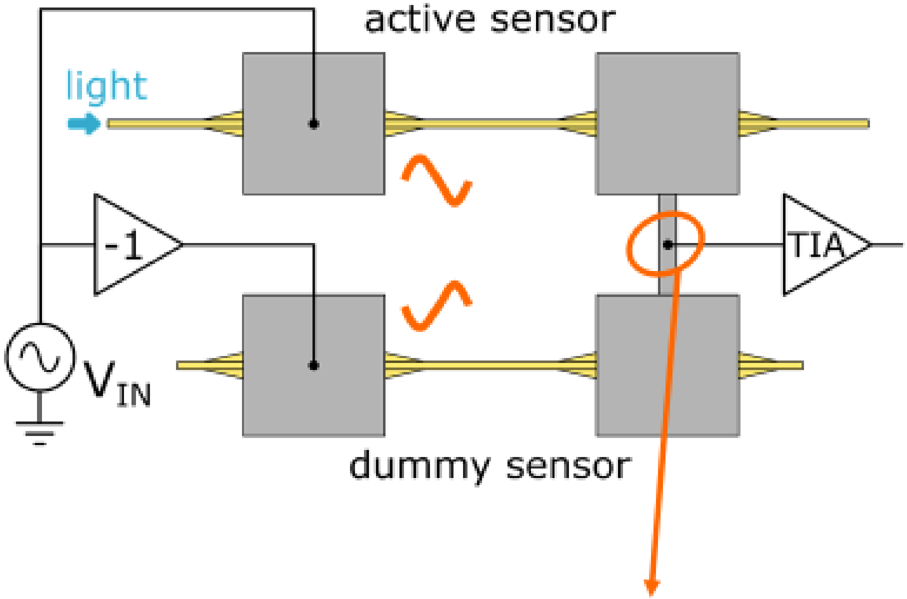
Dummy sensor

Differential sensor topology

Main CLIPP problems:

- The coupling between the electrodes generates a current much larger than the small variations to be measured.
- Sensitivity to temperature variations.
- Crosstalk between CLIPPs on different waveguides due to light in the oxide and substrate.

Differential topology to solve them all!

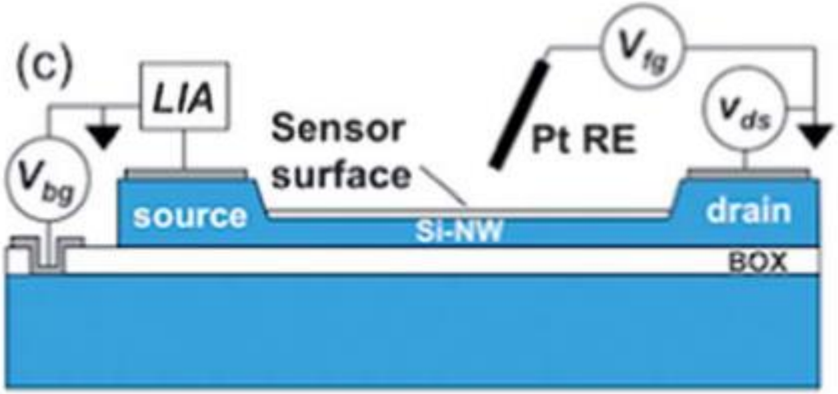


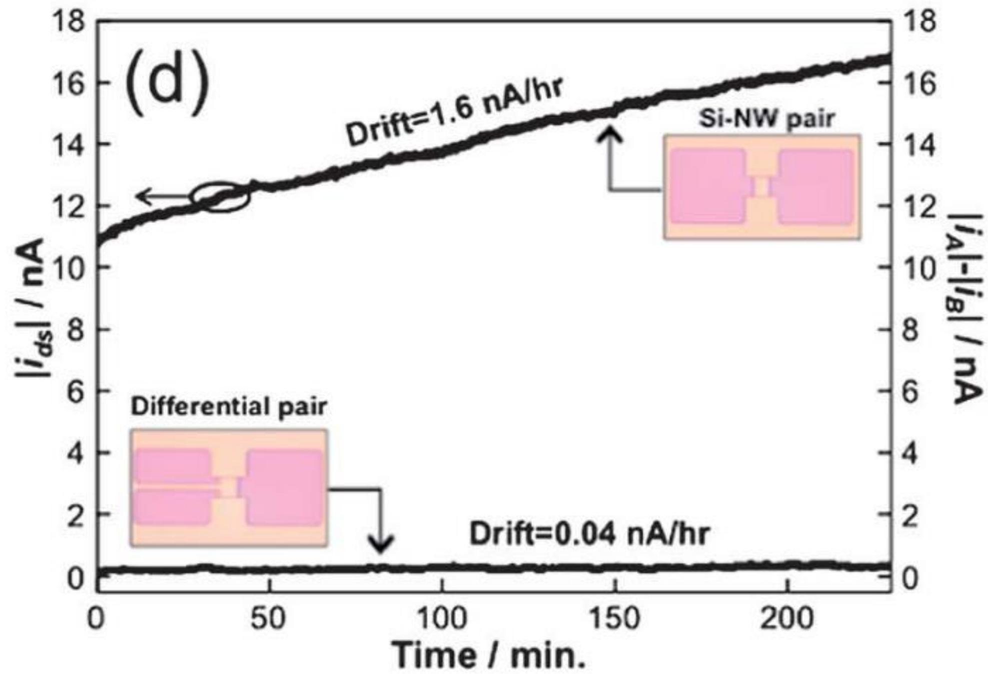
Any commod-mode current is steered away from the virtual ground of the TIA.

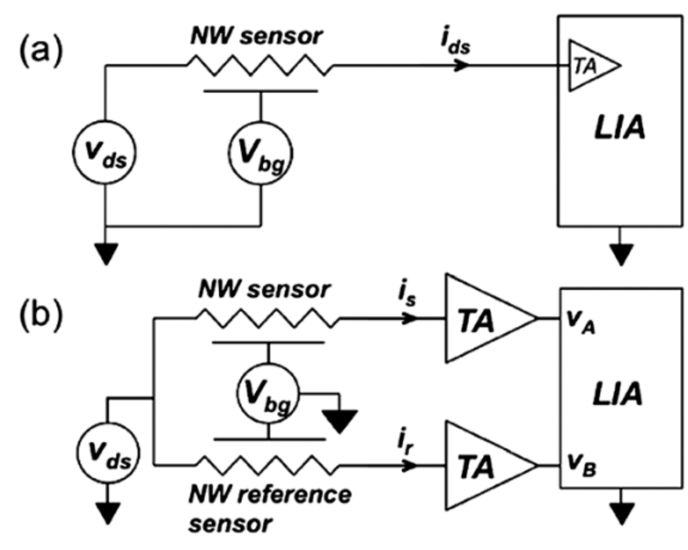
F. Zanetto's lesson

Differential biosensors

<u>*Ex.:* silicon nanowire DNA sensor</u>



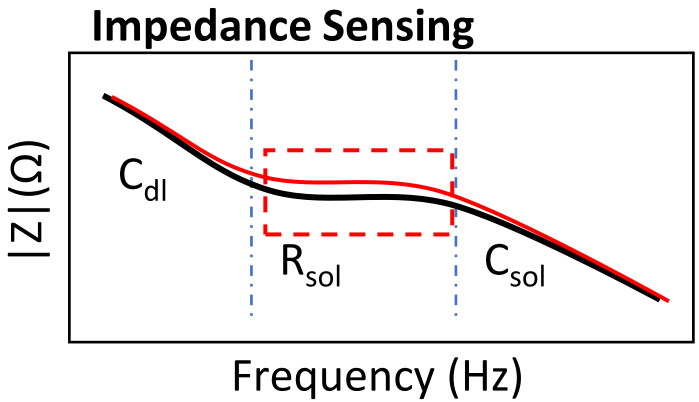


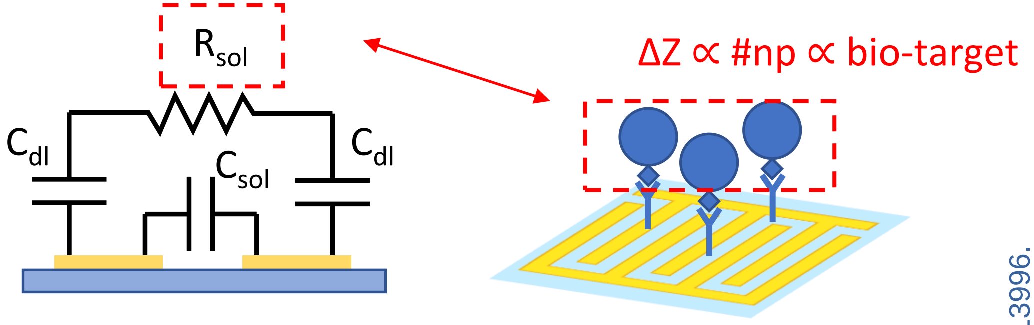


- AC measurement (LIA) for reducing the 1/f noise of the nanowire
- suffer from drift due to ion migration at the gate-oxide interface → differential meas.

A. De, et al. "Integrated label-free silicon nanowire sensor arrays for (bio)chemical analysis," *Analyst*, vol. 138, no. 11, pp. 3221–3229, 2013, doi: 10.1039/c3an36586g.

Differential Impedance Biosensing



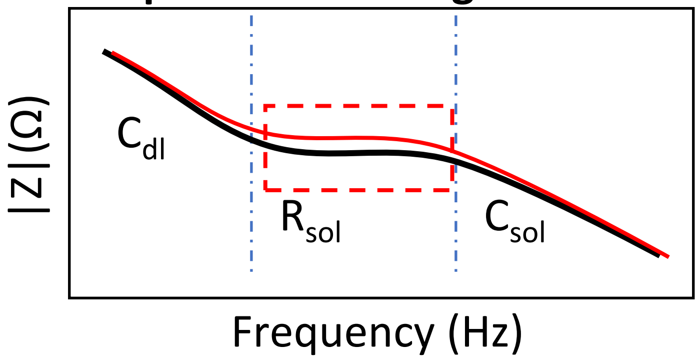


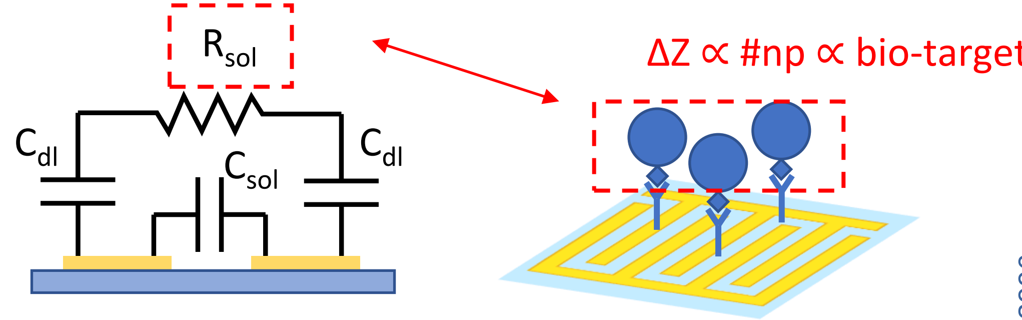
Resistance variation at the end of the experiment is related to the number of polystyrene NP's, i. e. to the specific nanosized biological target.

P. Piedimonte, et al, doi: 10.1016/j.bios.2022.113996.

Differential Impedance Biosensing

Impedance Sensing





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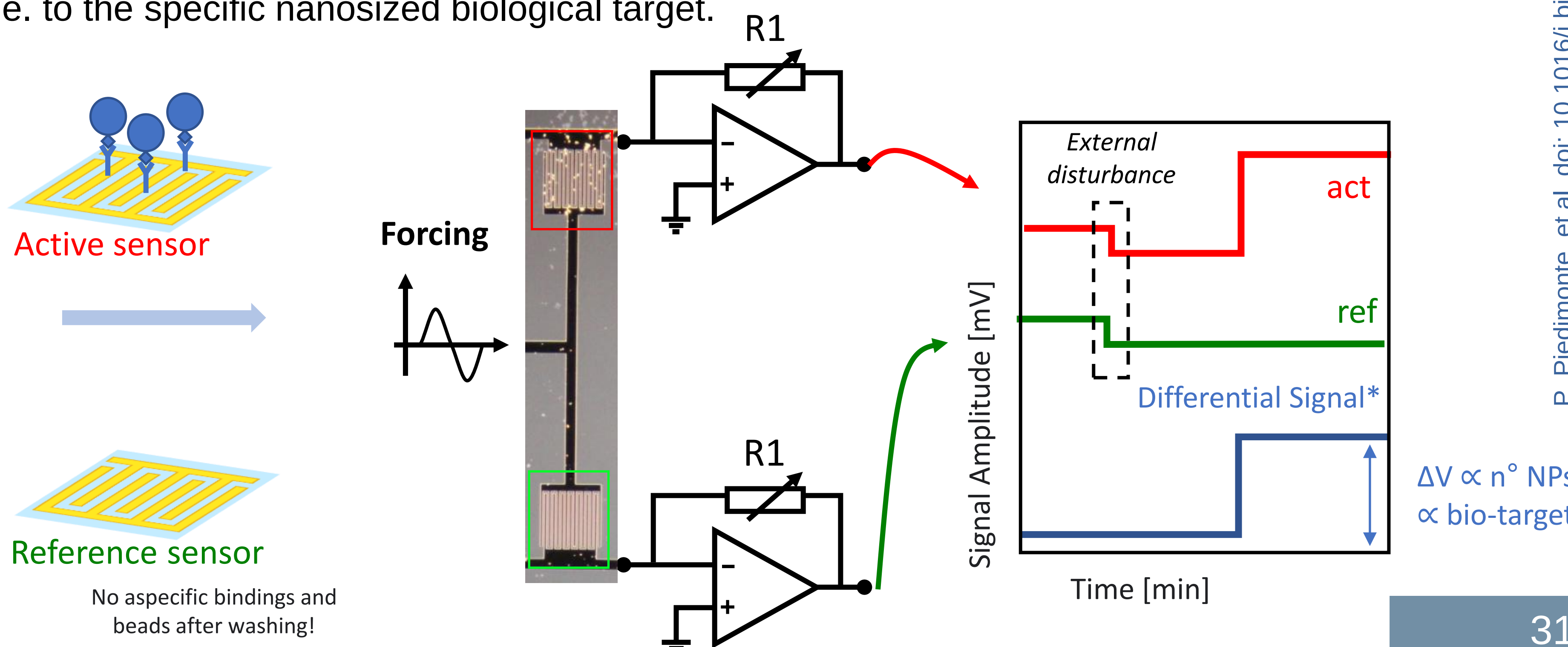

P. Piedimonte, et al, doi: 10.1016/j.bios.2022.113996.

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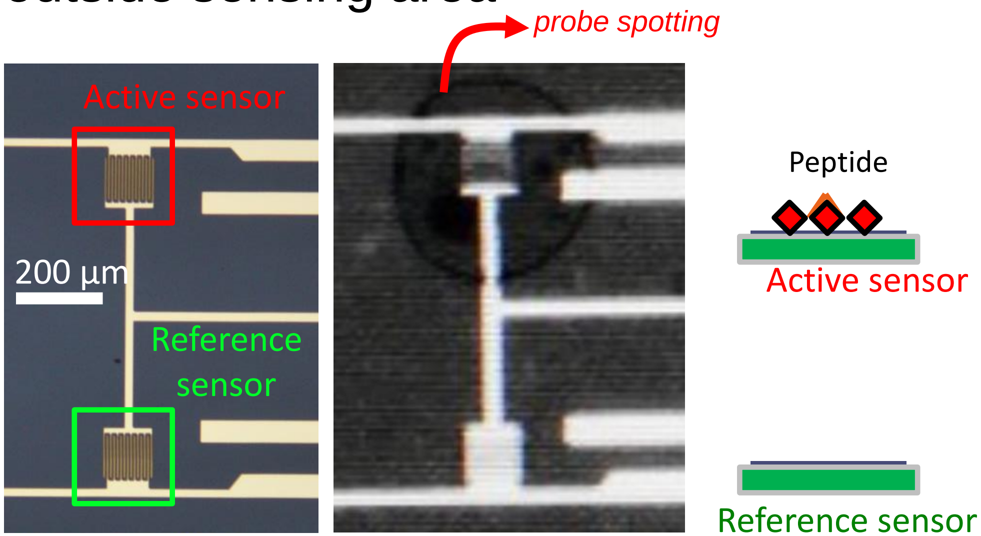
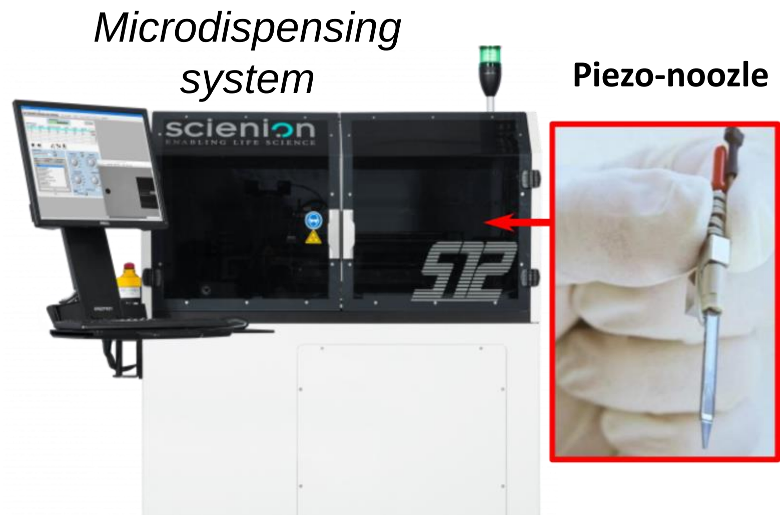
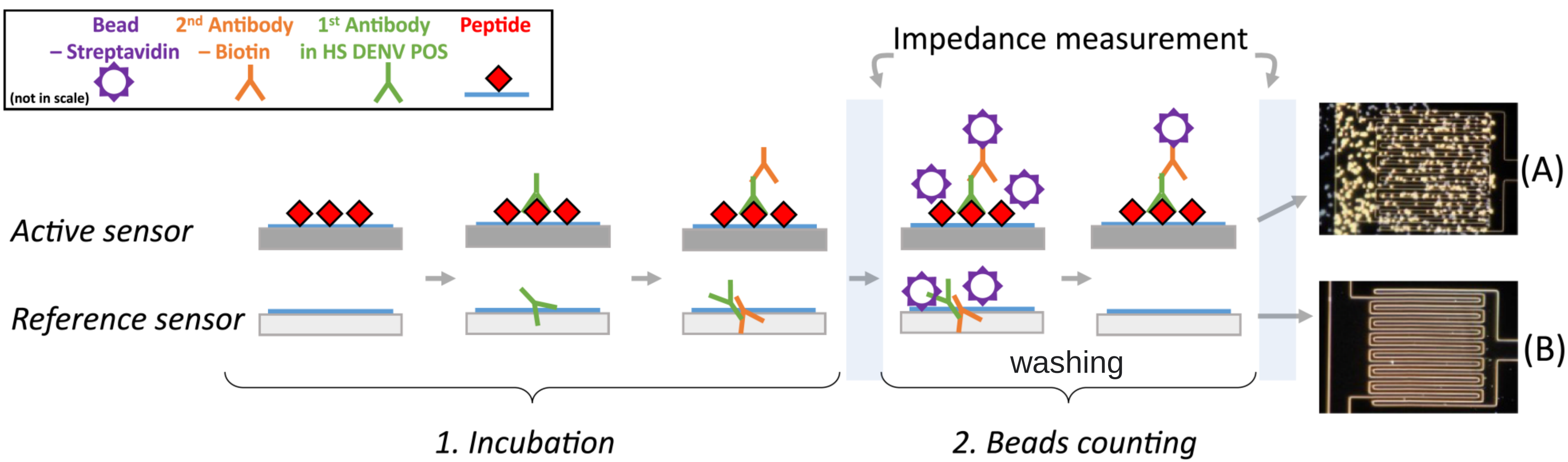
Biochip preparation

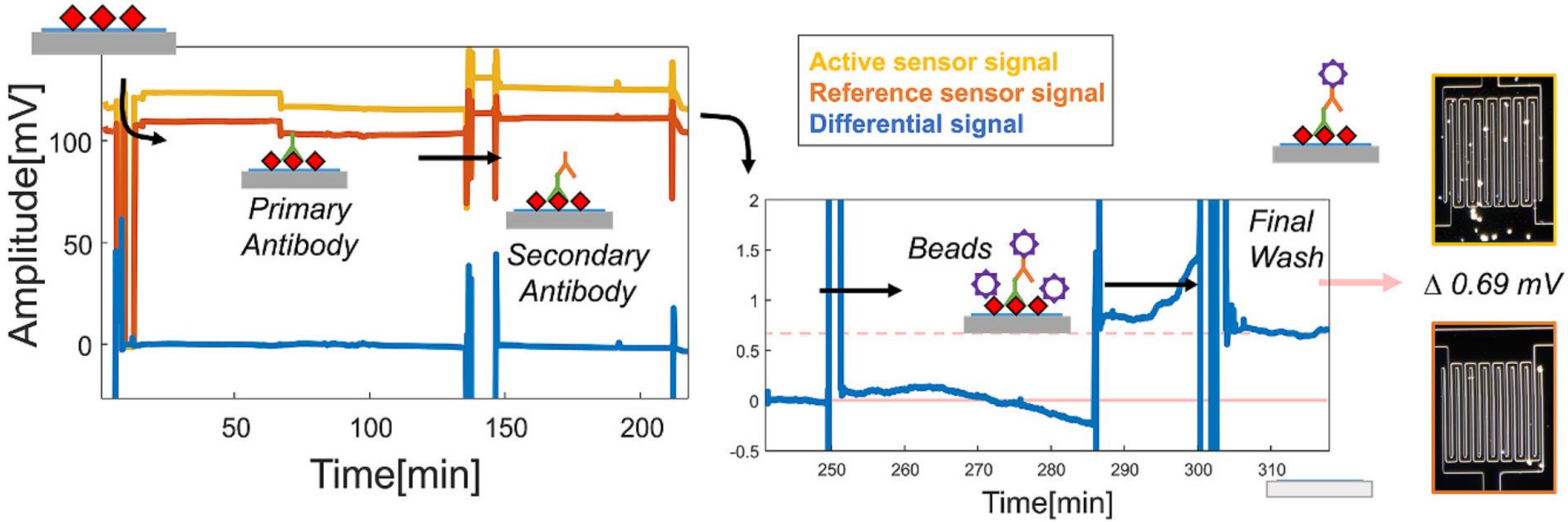
Local functionalization of the **active sensor** → avoid non-specific binding outside sensing area



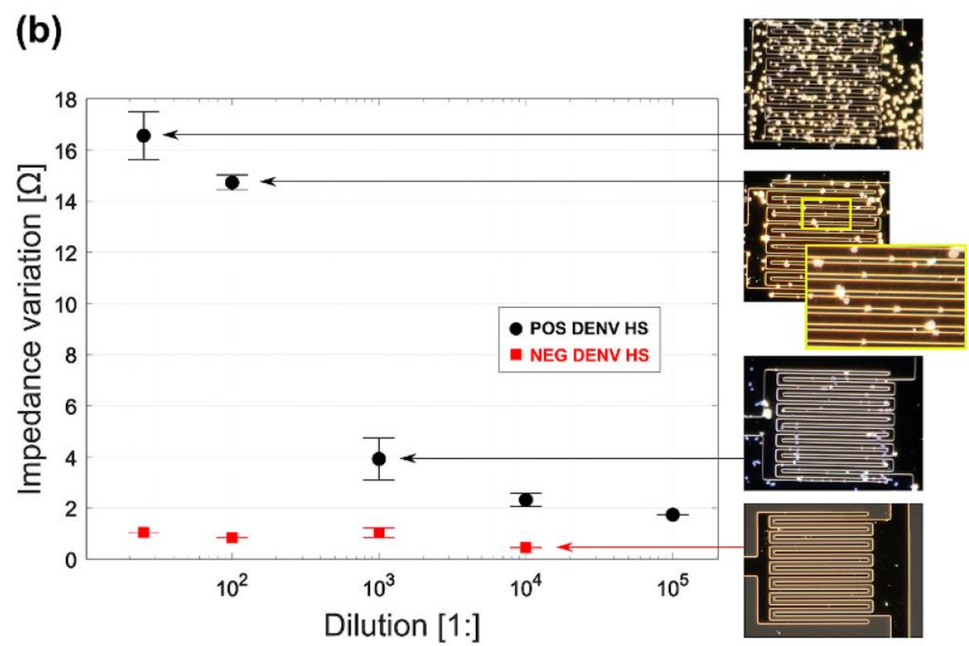




Results for Dengue Virus detection in human serum

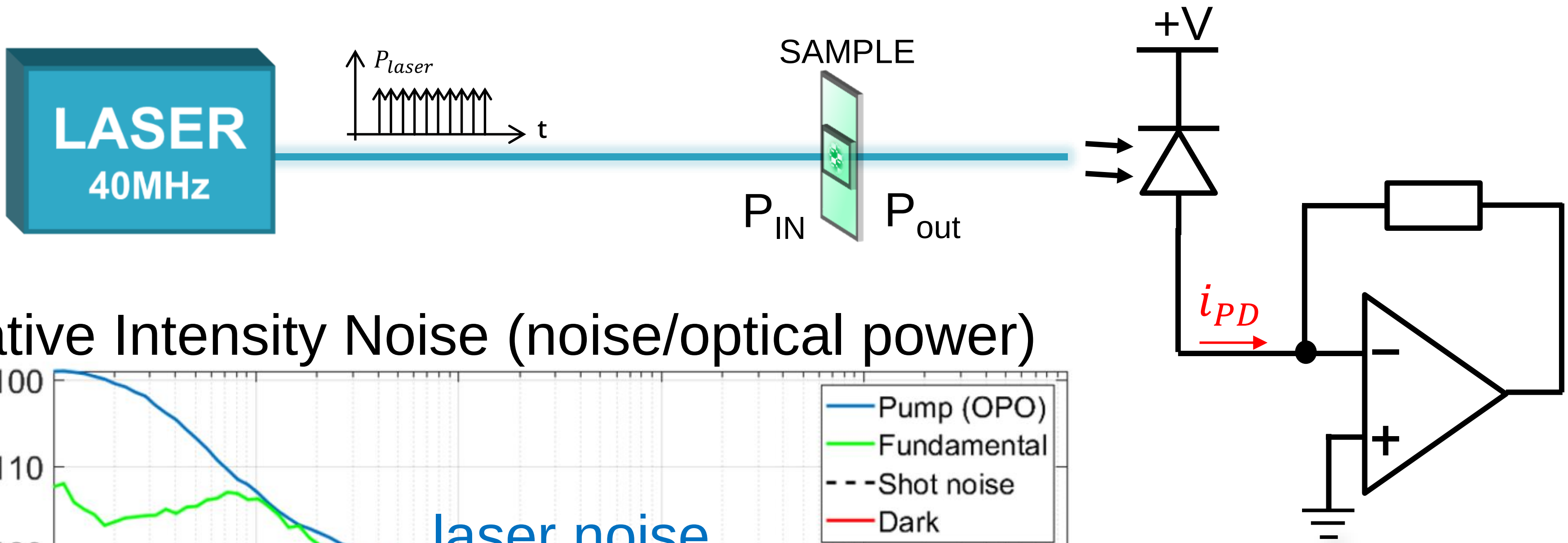


- **Human Serum** samples positive to anti-DNV IgG antibodies
- **Clinically relevant concentration**
- **Control**: HS negative to anti-DENV IgG antibodies

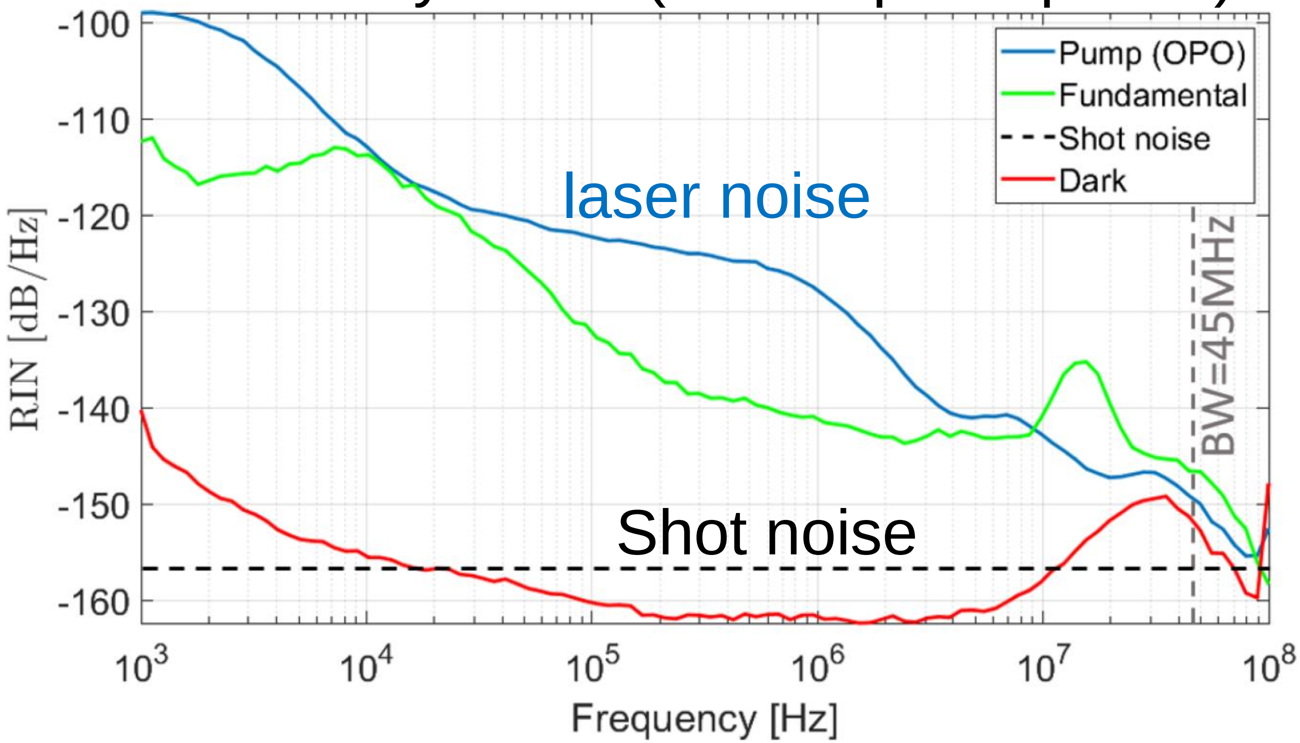


P. Piedimonte, et al, “Differential Impedance Sensing platform for high selectivity antibody detection down to few counts: A case study on Dengue Virus,” Biosens. Bioelectron., vol. 202, p. 113996, Apr. 2022, doi: 10.1016/j.bios.2022.113996.

Laser-based optical spectroscopy



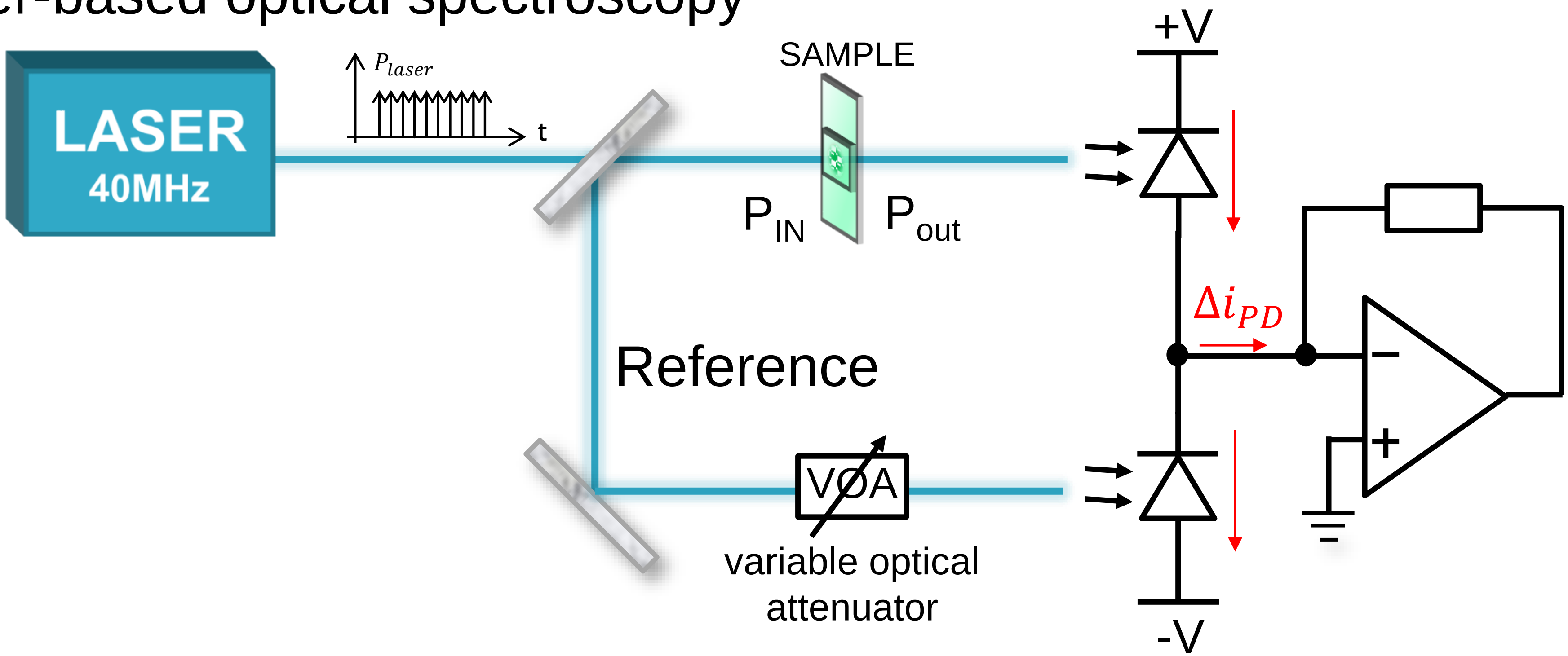
Relative Intensity Noise (noise/optical power)



The instability in the power level of the laser may be the limiting factor!

Balanced optical detection

Laser-based optical spectroscopy

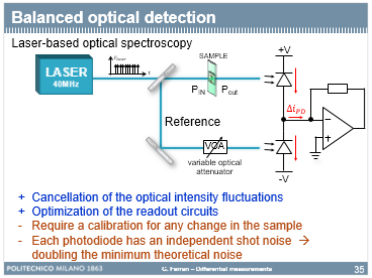


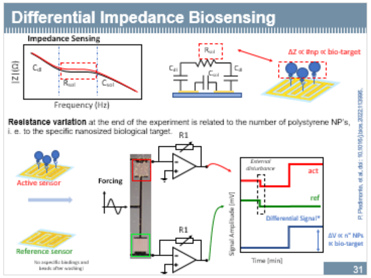
+ Cancellation of the optical intensity fluctuations
+ Optimization of the readout circuits
- Require a calibration for any change in the sample
- Each photodiode has an independent shot noise → doubling the minimum theoretical noise

Drawbacks of the differential approach

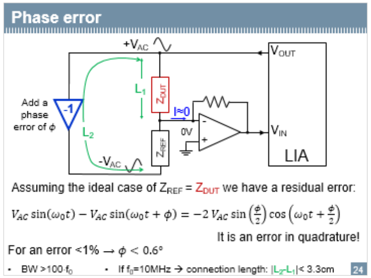
While differential measurements offer several advantages, there are also some drawbacks to consider:

- Additional complexity for the generation of the reference path
- Calibration may be required for a well-matched structure
- Sensor response vs. frequency (spectroscopy) or temperature or bias,… could be difficult
- Increase the minimum theoretical noise





- Pay attention to the phase response and propagation delays



Summary

- A large baseline causes difficulties:
  - Gain fluctuations
  - Baseline fluctuations
  - Gain, linearity, and dynamic range of the acquisition chain
- Differential approach
  - Subtract the large baseline
  - Design a differential sensor if possible! (or use a dummy sensor)
  - A calibration may be required
- Alternative: ratiometric approach

see lessons on high-resolution LIA and impedance meas.