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

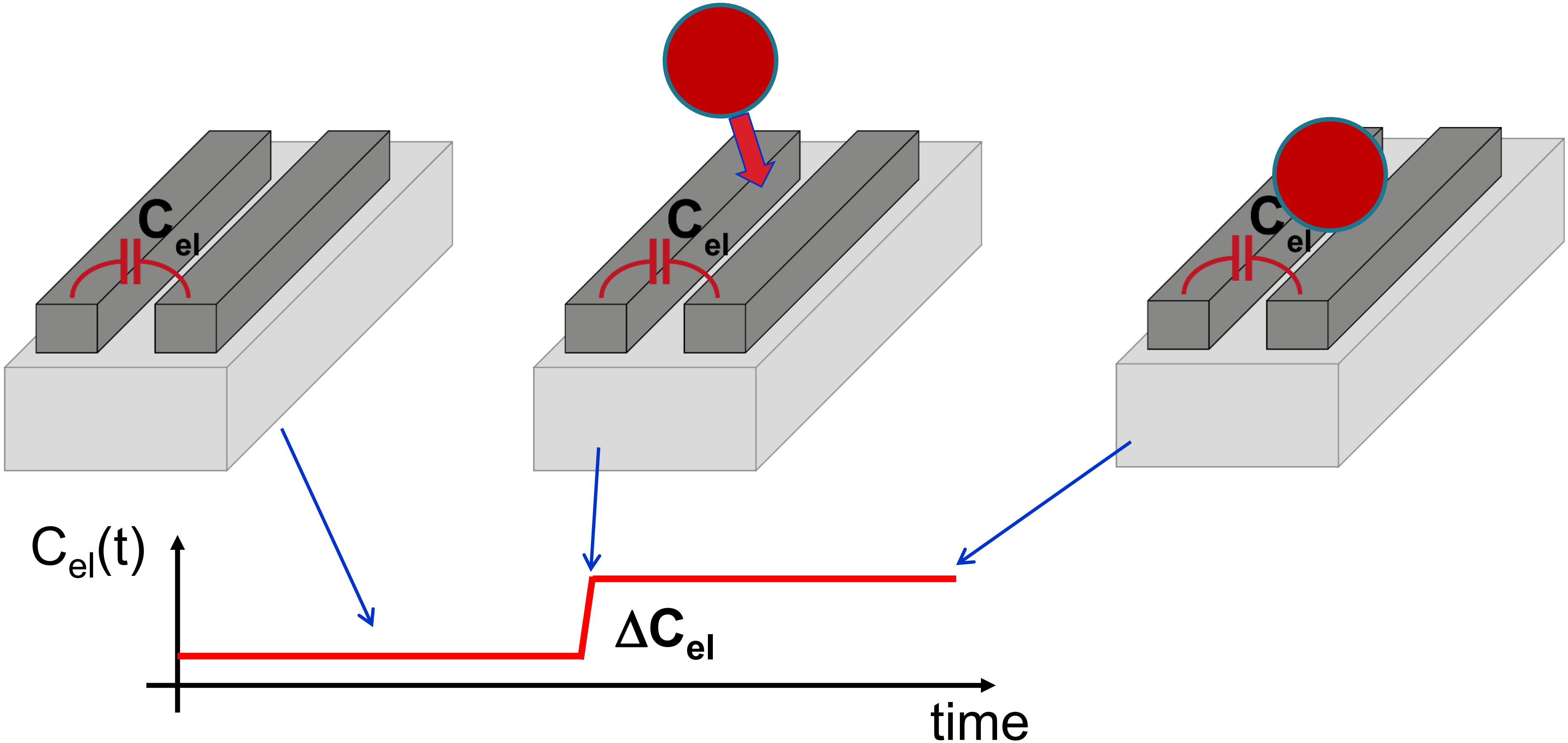
Milano, June 2025

OUTLOOK of the LESSON

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

Example: capacitive detection of particles

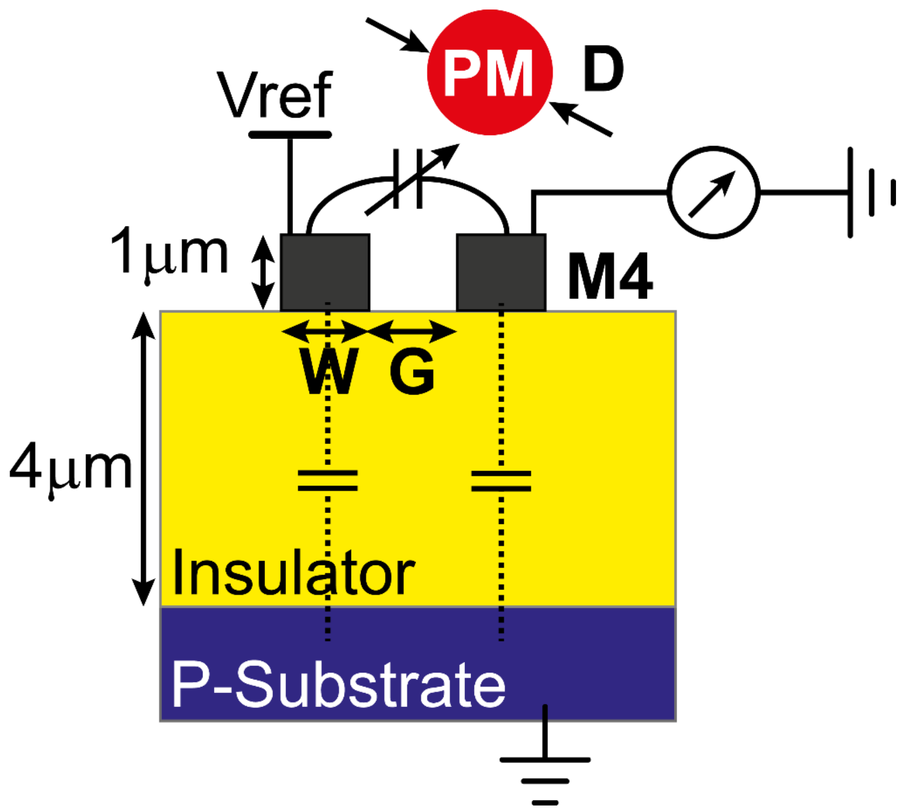
particle deposition on a surface (PM detector, cell monitor,…)

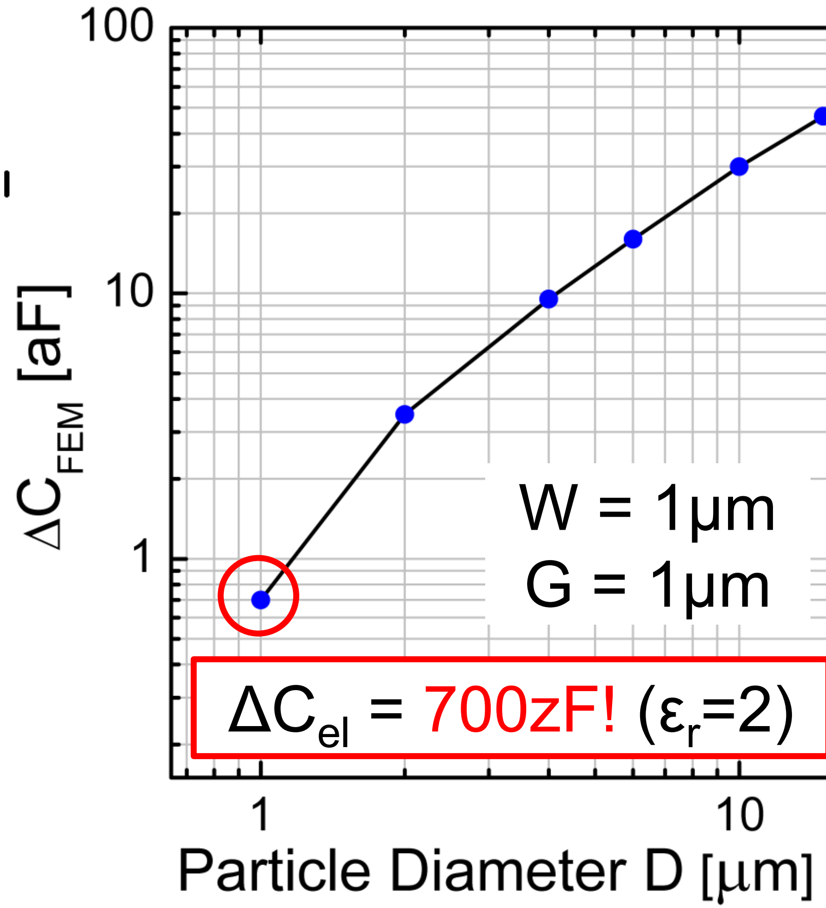


M. Carminati, Capacitive detection of micrometric airborne particulate matter for solid-state personal air quality monitors, *Sensors Actuators A* **219**, 2014.

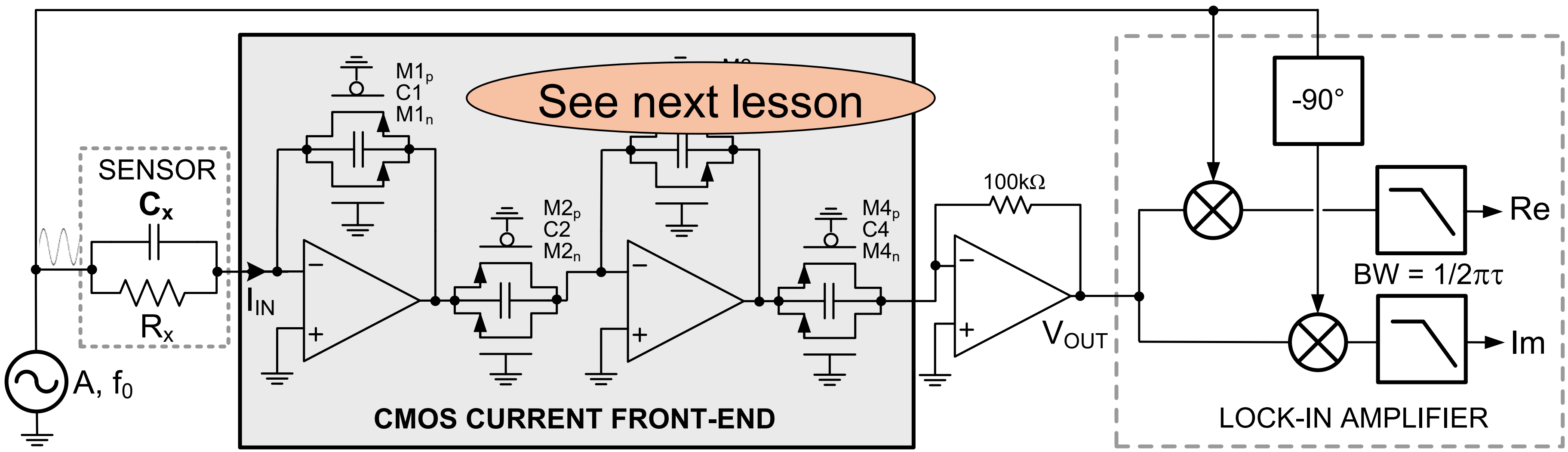
Electrodes Design

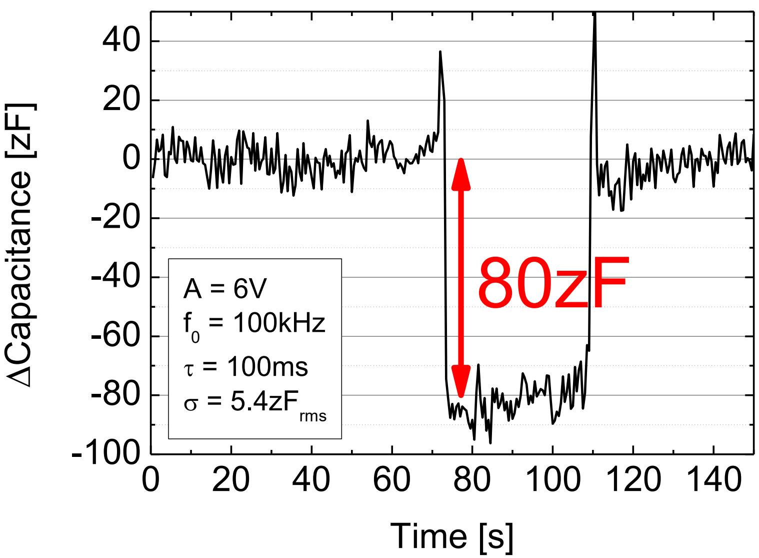
FEM Numerical Simulations

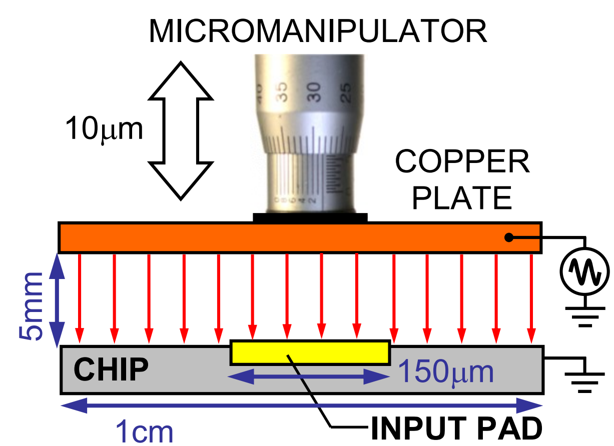




ZeptoFarad capacitance detection





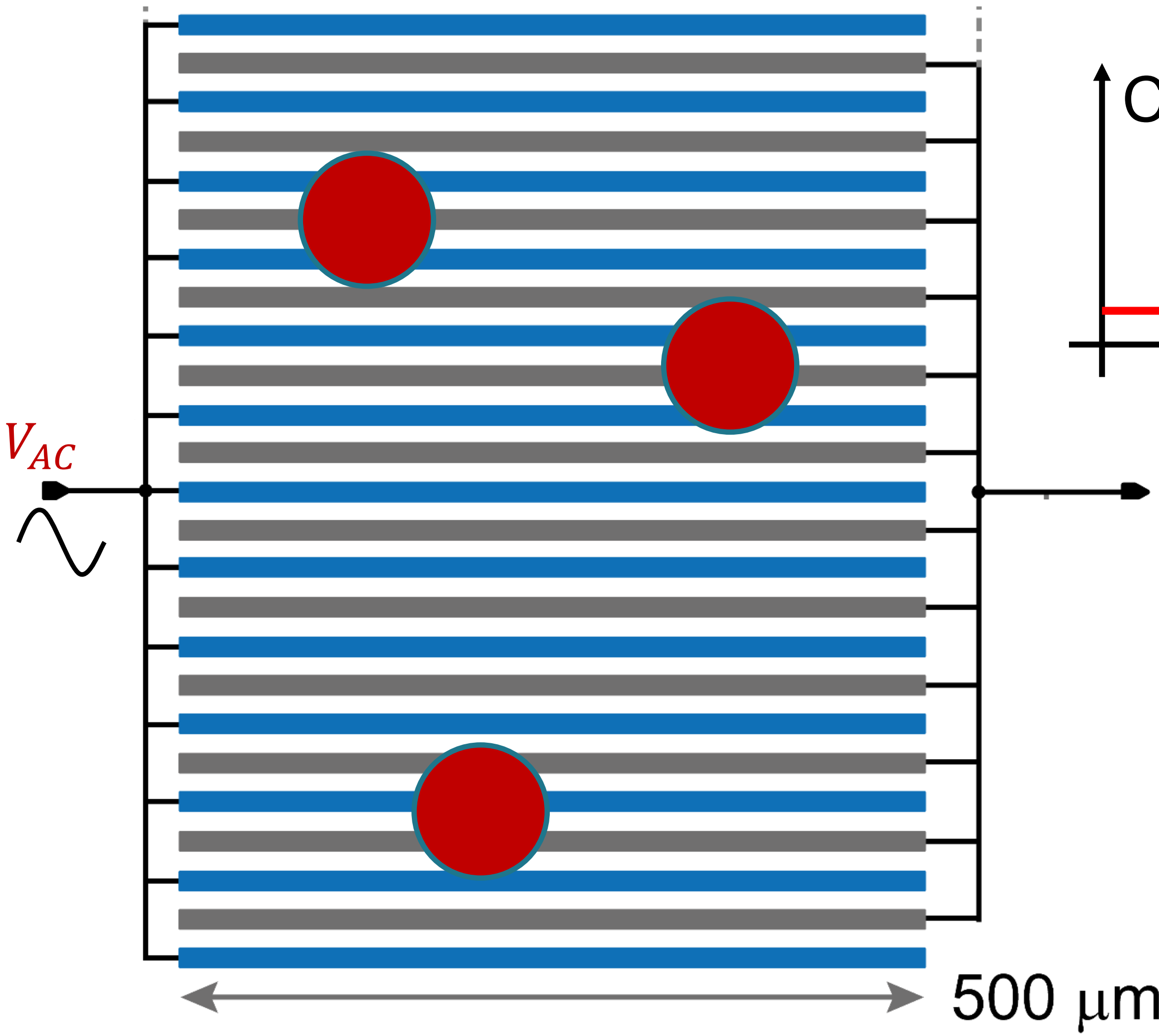


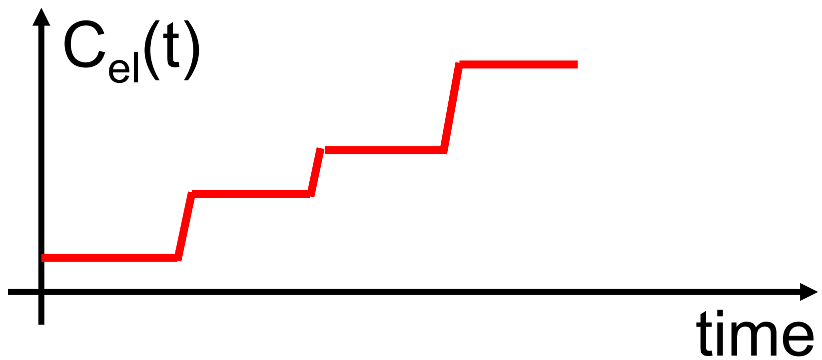
$C_x \approx$ 100 aF

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:

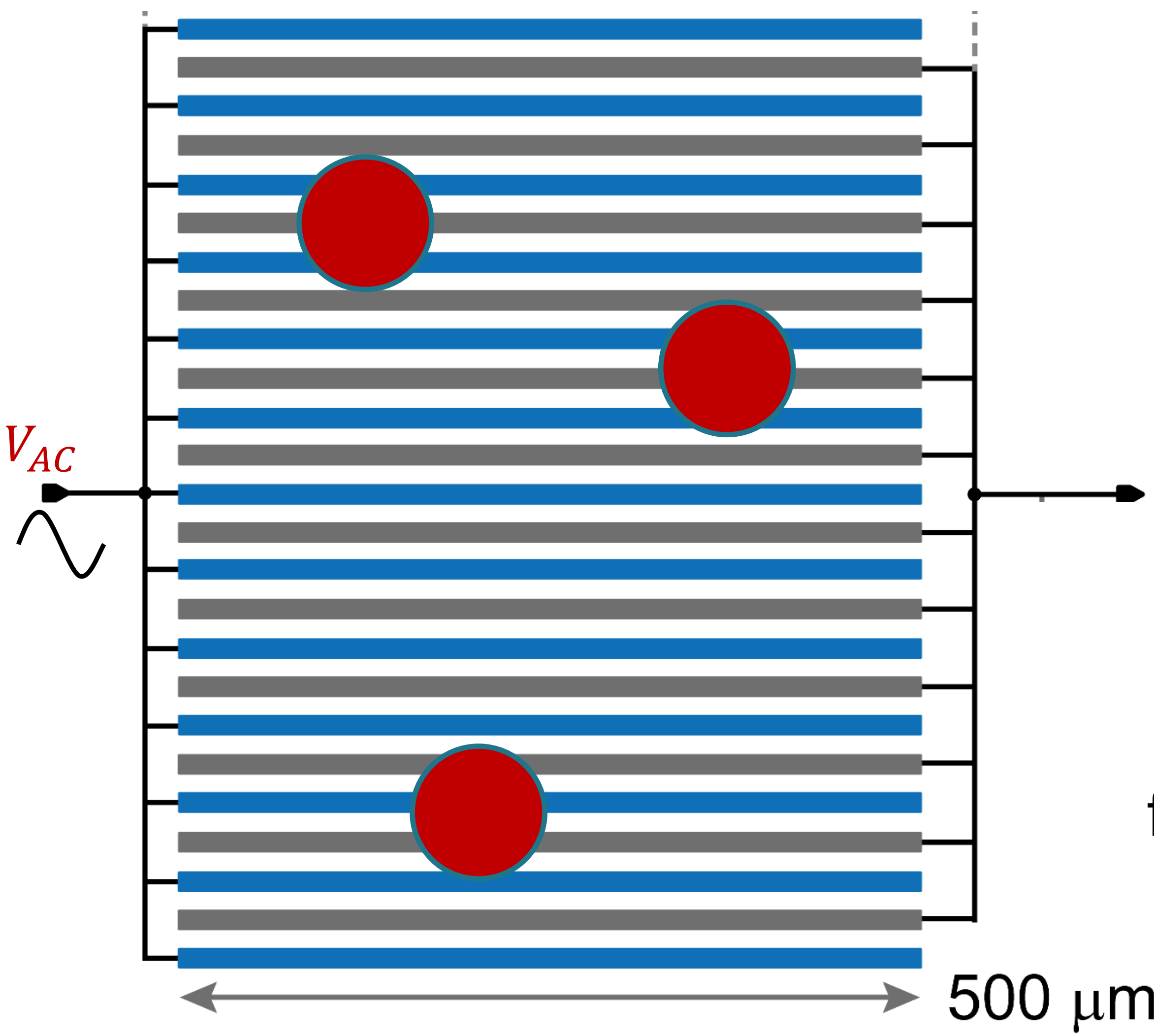




counting of single particles over a large active surface to increase the statistics

Large sensitive area

Interdigitated electrodes:



Example:

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

1000 electrodes!

C_{total} = 15pF

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

for particle size of 1 μm

0.07 ppm!

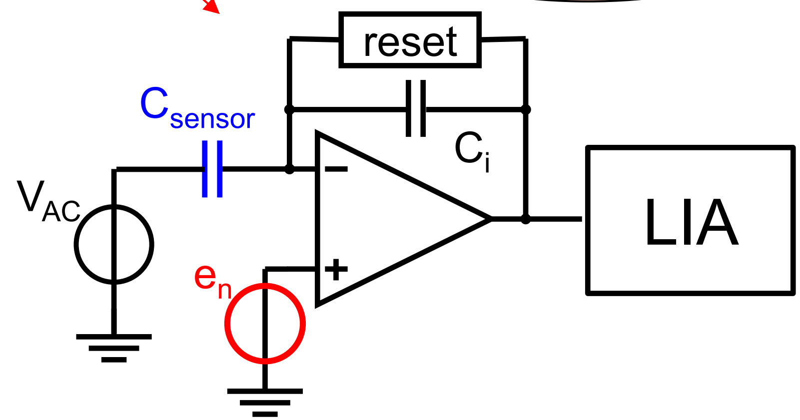
Small variations over large baseline: problems

1) Noise of the sensor and the preamplifier

see Sampietro lessons

Capacitance

"noiseless"
(air and SiO_2 are good dielectrics)
OK



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

Ex.:

$$V_{AC} = 3V, \overline{e_n^2} = \left(\frac{5nV}{\sqrt{Hz}}\right)^2, C_{sensor} = 15pF, BW = 100Hz$$

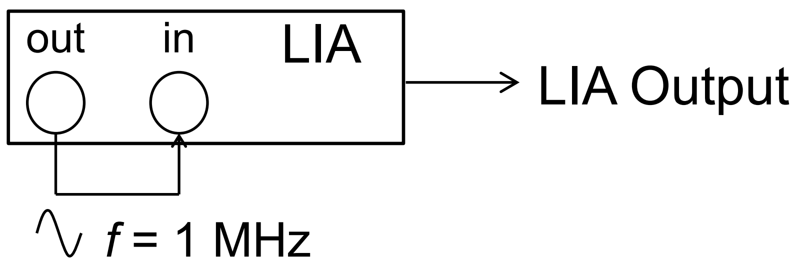
$$\Delta C = 0.5aF$$ **OK**

Small variations over large baseline: problems

1) Noise of the sensor and the preamplifier $\Delta C_{min} = 0.5\ aF$
2) Gain fluctuations (stimulus, acquisition chain)

see lesson on high-resolution lock-in amp.

Zurich Instruments, HF2LI



LIA resolution: 40 ppm

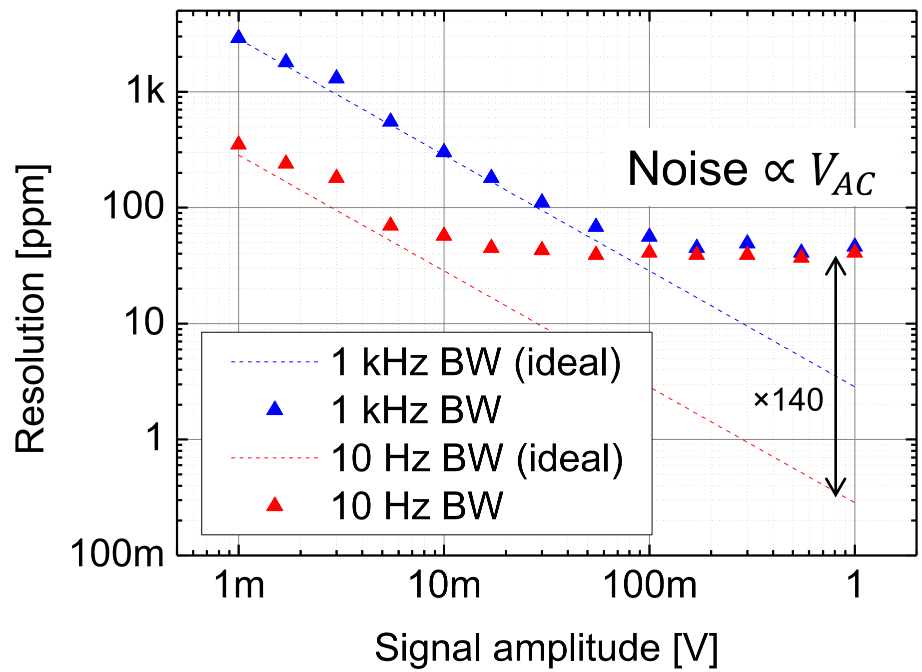
$C_{sensor} = 15pF$

$\boxed{\Delta C_{min} = 600aF}$

very bad!

Minimum particle size: > 50 μm

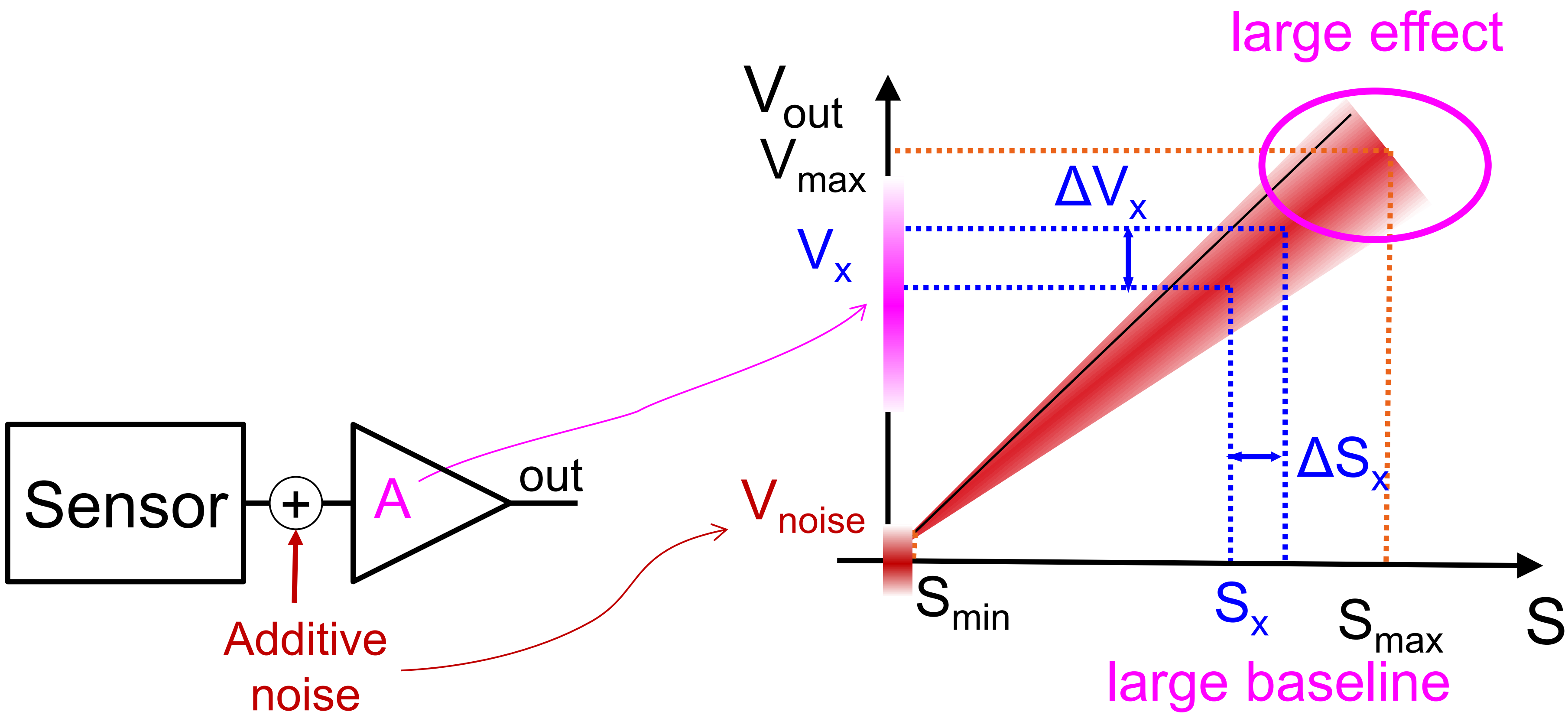
Resolution = Noise / Signal



ELIA: 0.5ppm → ΔC= 7.5aF, better but still not enough

How to improve the measurement?

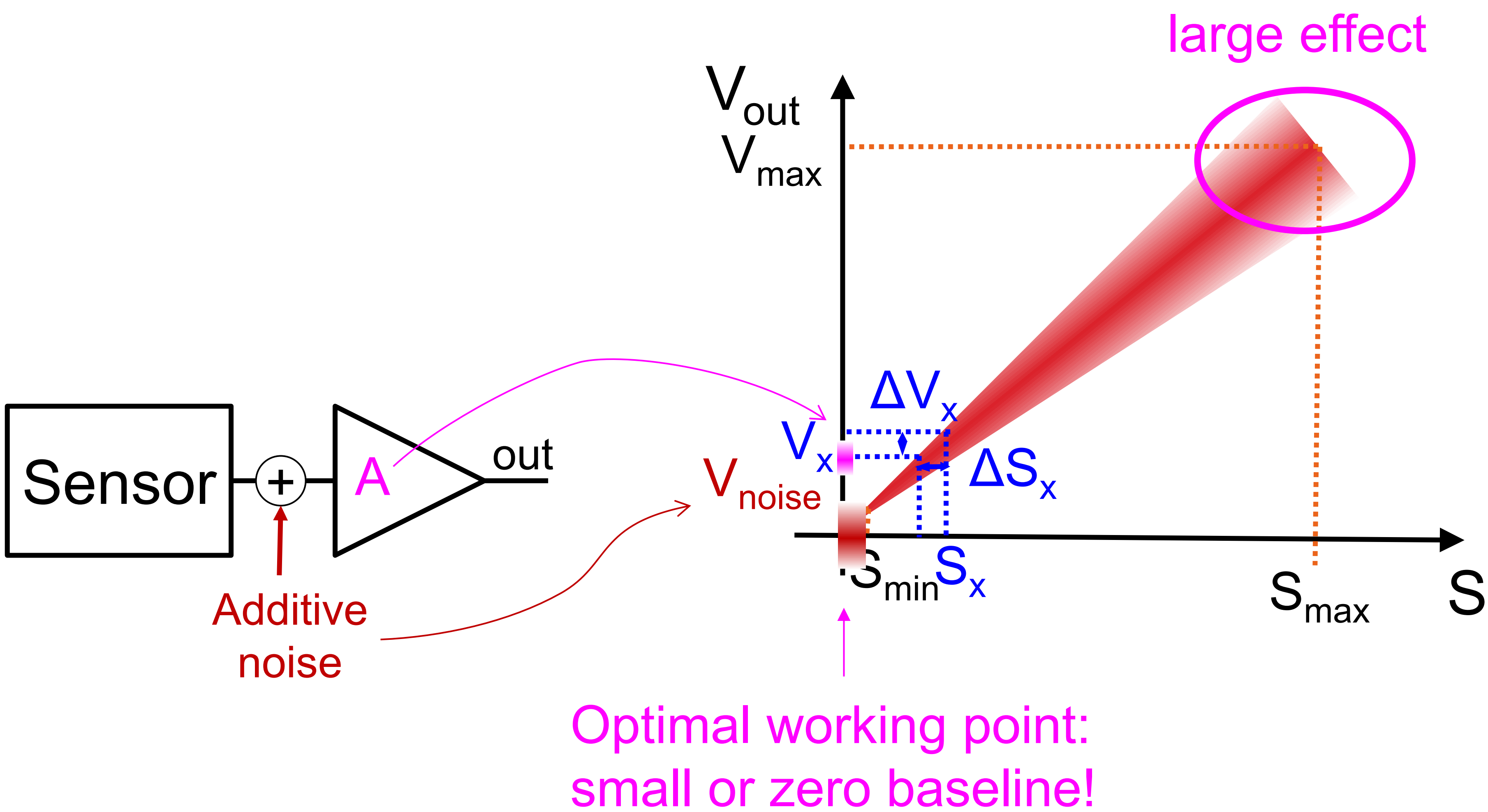
Slow measurements using low noise sensors and amplifiers could be limited by gain fluctuations (DAC, amp., ADC) + large baseline



The additional noise is proportional to the signal to be measured

How to improve the measurement?

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

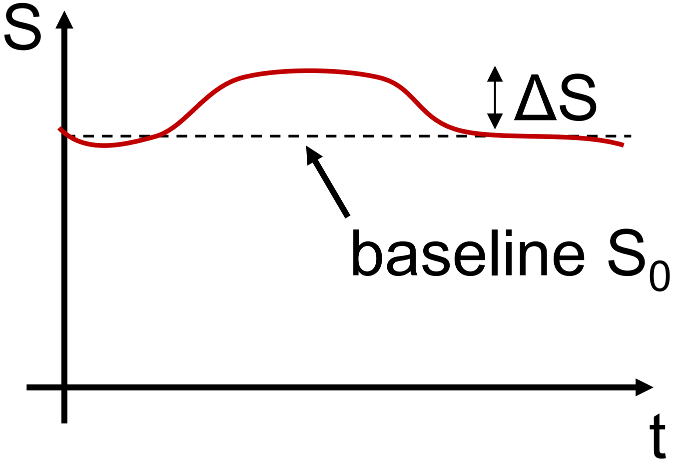


The differential approach

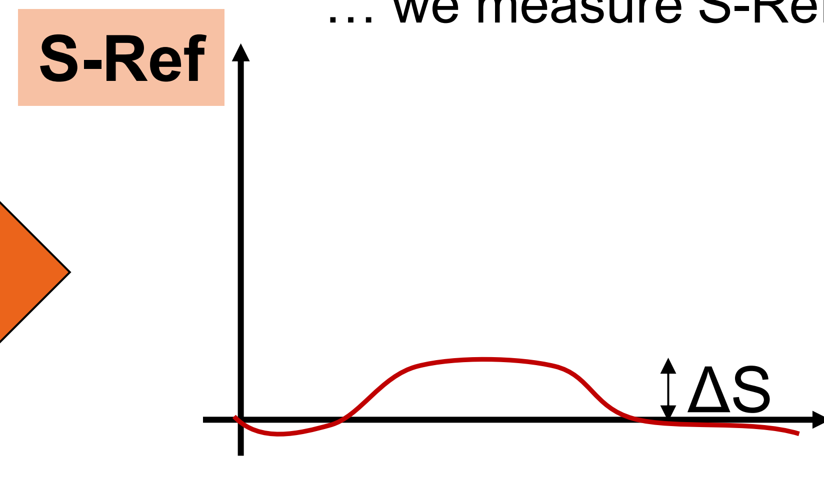
The additional noise is proportional to the input signal

keep only the useful signal!

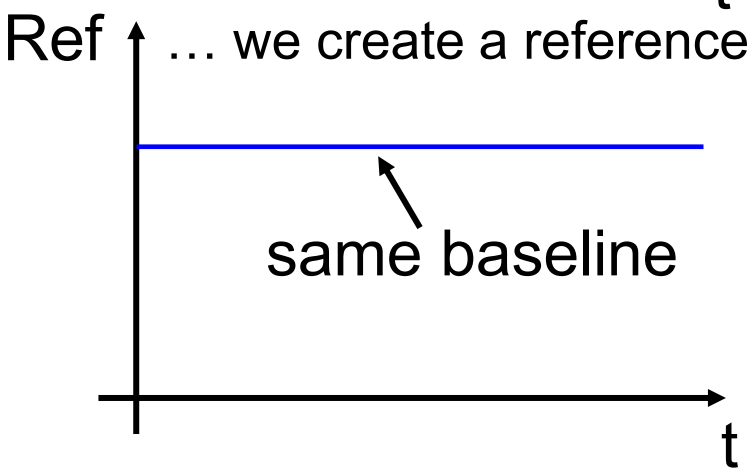
We want to measure this signal…



… we measure S-Ref



… we create a reference…



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

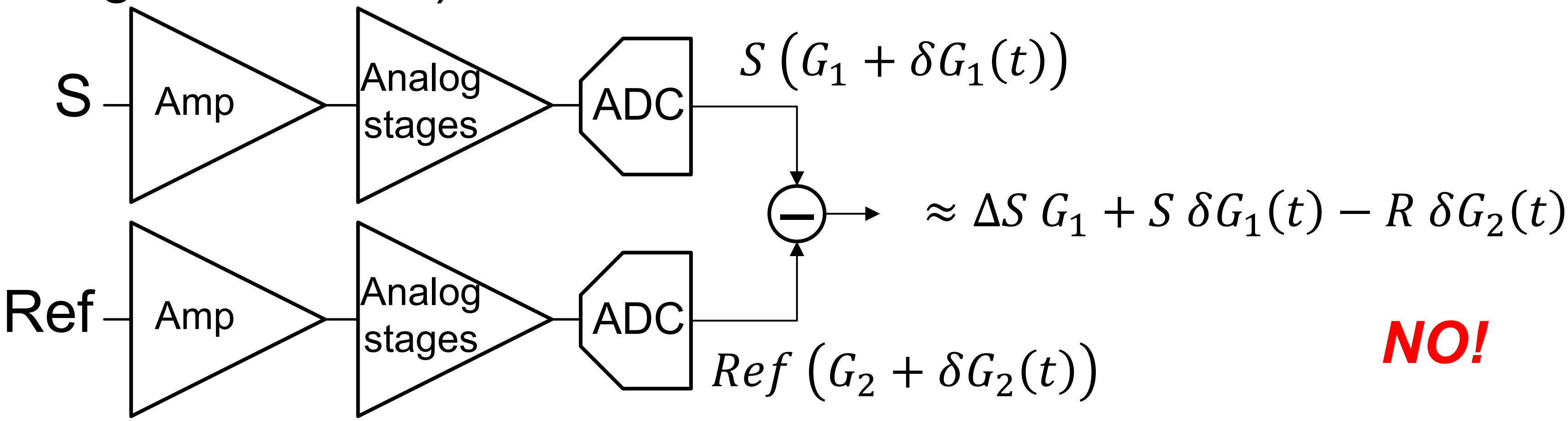
If $\Delta S << S_0$ ($Ref \approx S_0$):

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

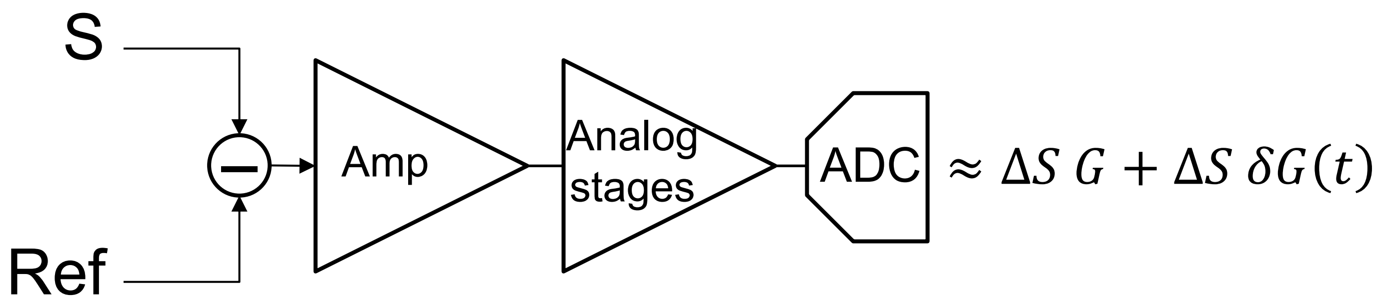
gain fluctuations prop. to $\Delta S \ll S_0$

The differential approach: 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!)



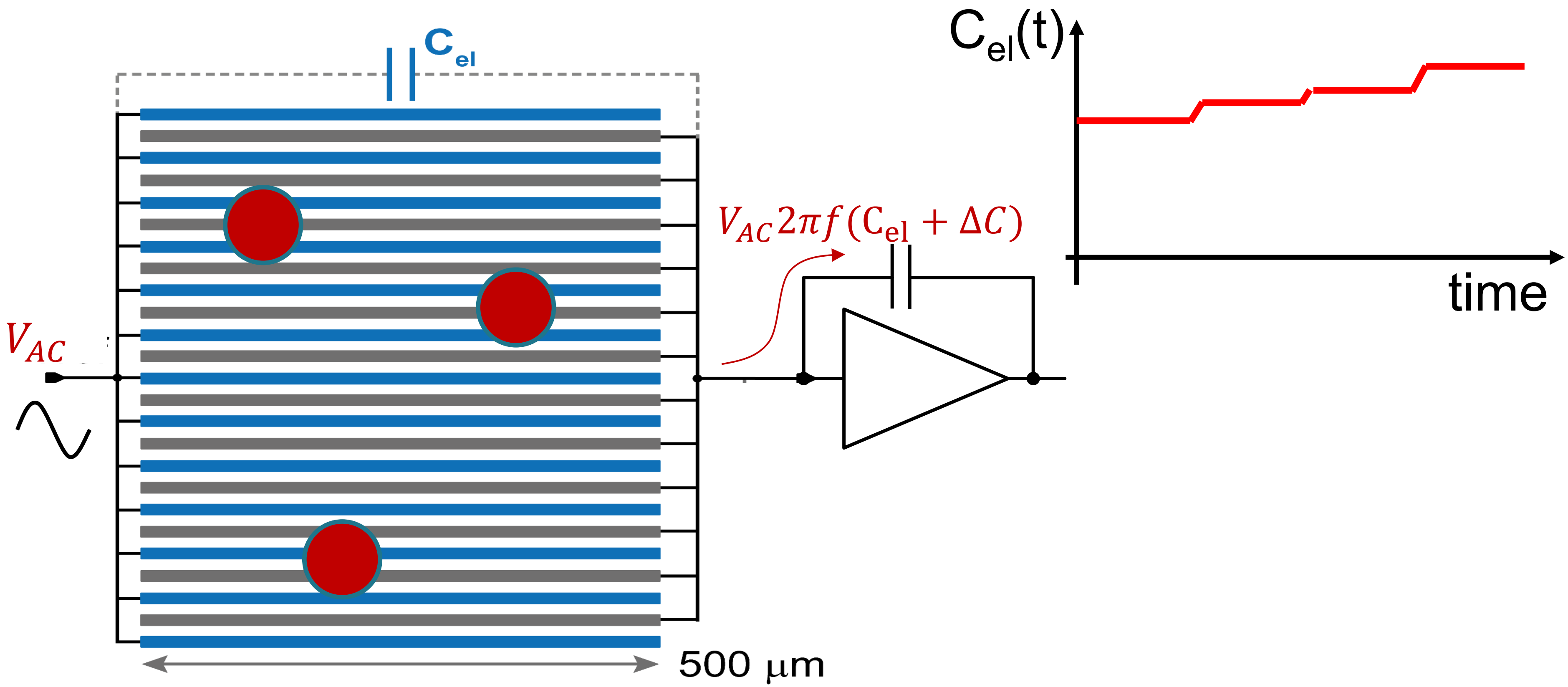
NO!



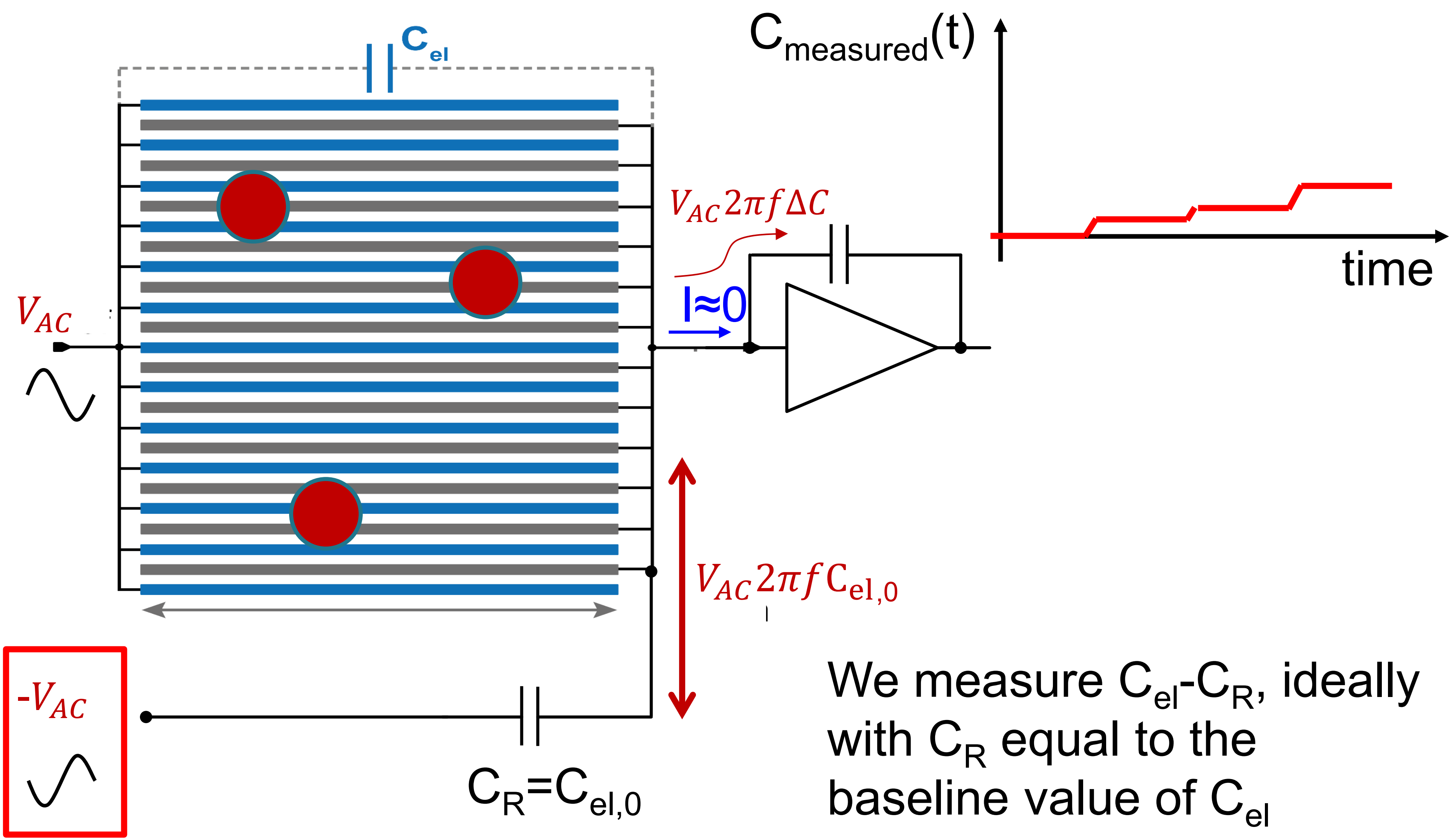
OK

However, if the limit is not the gain fluctuations of the acquisition chains, the first solution is more flexible (calibration of the reference path in the digital domain)

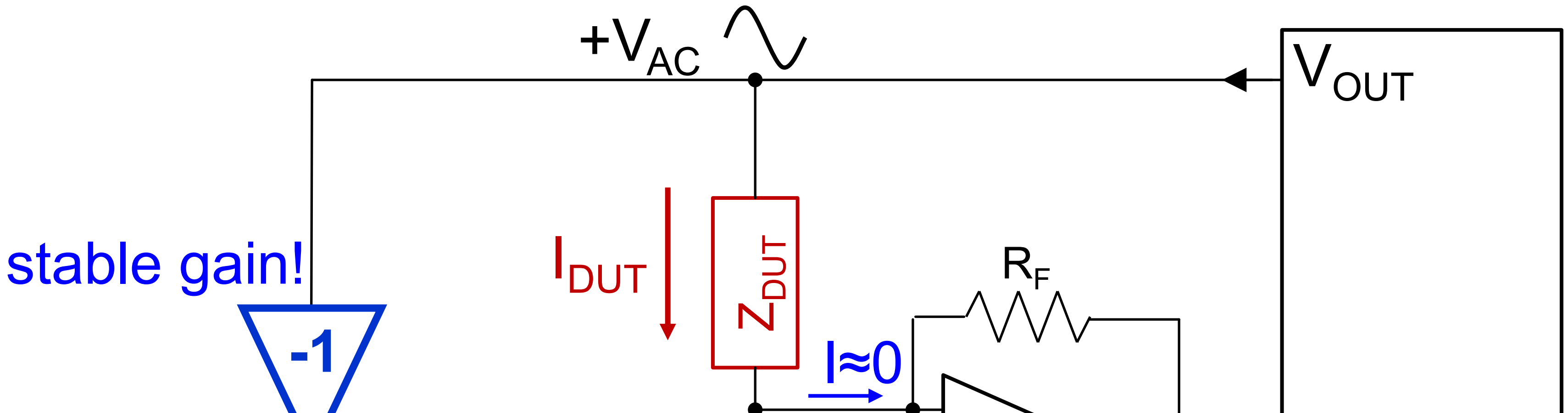
Single-ended measurement

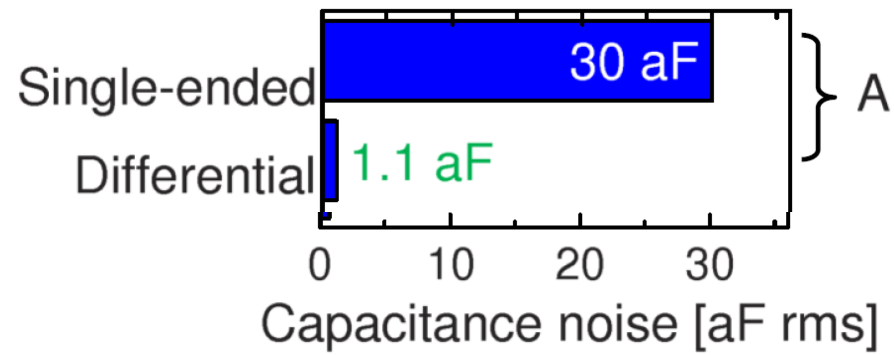


Differential measurement



We measure C_{el}-C_R, ideally with C_R equal to the baseline value of C_{el}





- Balanced structure:

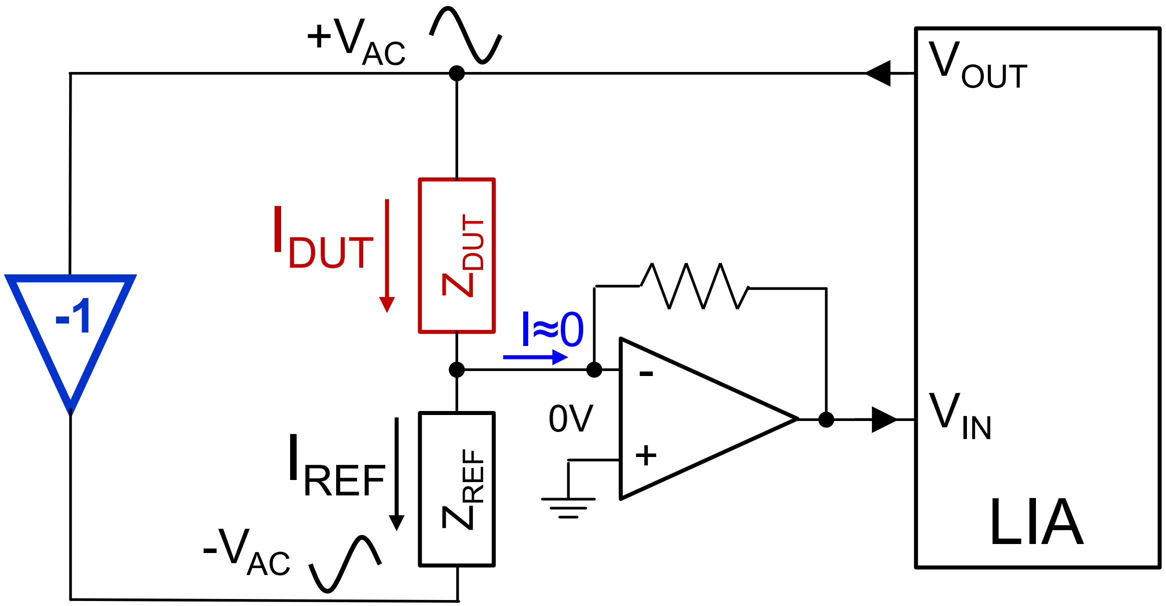
$$\boxed{Z_{REF} \approx Z_{DUT}} \Rightarrow \quad I = V_{AC}\left(\frac{1}{Z_{DUT}} - \frac{1}{Z_{REF}}\right) = V_{AC}(Y_{DUT} - Y_{REF}) \approx 0$$

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

✓ Amplifier optimization (gain, linearity, dynamic range)

M. Carminati, et al. "Differential configurations for the mitigation of slow fluctuations limiting the resolution of digital lock-in amplifiers," *Rev. Sci. Instrum.*, vol. 87, no. 2, p. 026102, Feb. 2016, doi: 10.1063/1.4941721.

Signal – reference matching: an example



Assuming:

- LIA resolution limit: 100ppm
- No other noise sources
- $Z_{DUT}(f_0)$ = 1MΩ, i.e. a $Y_{DUT}(f_0)$=1μS

Goal:

- Detection of $\Delta Z_{DUT}(f_0)$ of 1Ω, i.e. $\Delta Y_{DUT}(f_0)$=1pS

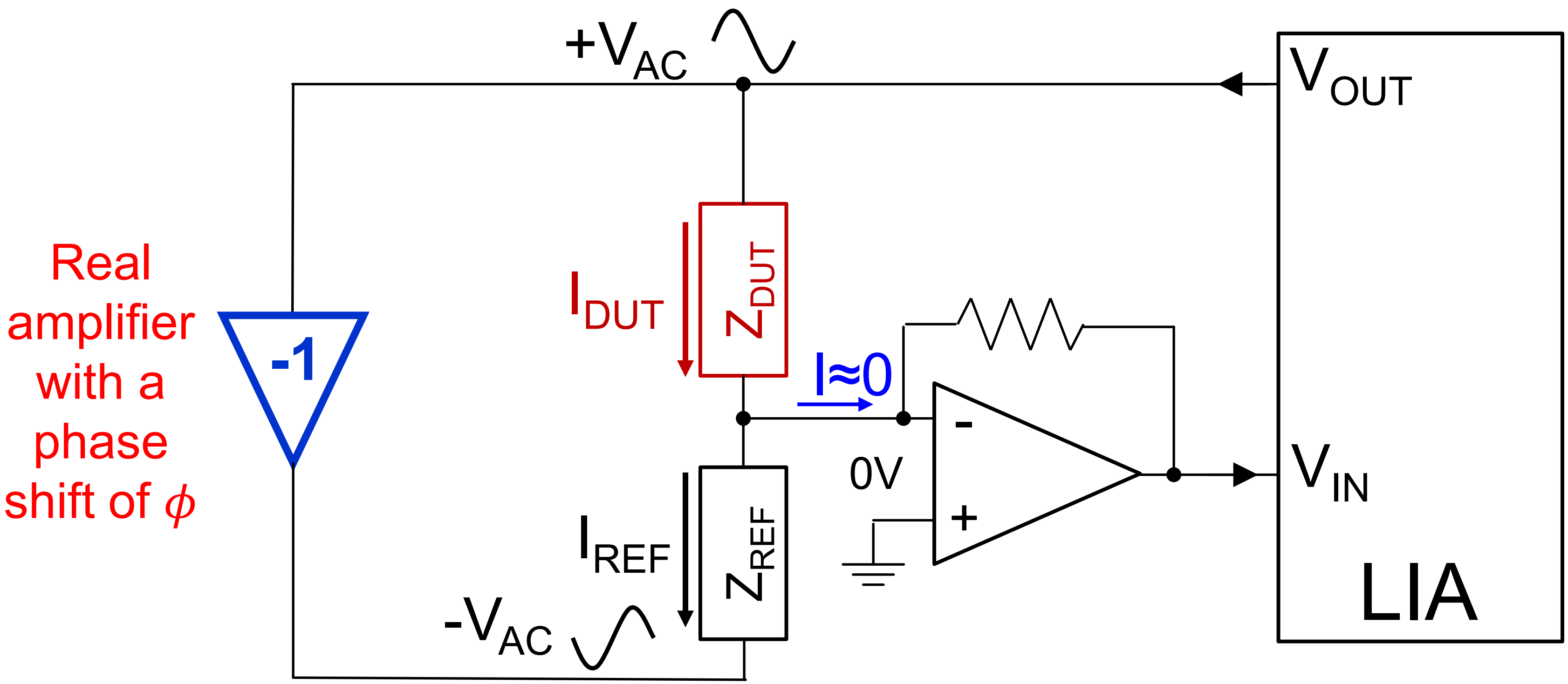
Current variation given by ΔY_{DUT}

Noise:

$$|\Delta I| \approx V_{AC}|\Delta Y_{DUT}| \quad > \quad \sigma \cong 100ppm \text{ of } I = 10^{-4} V_{AC} |Y_{DUT} - Y_{REF}|$$

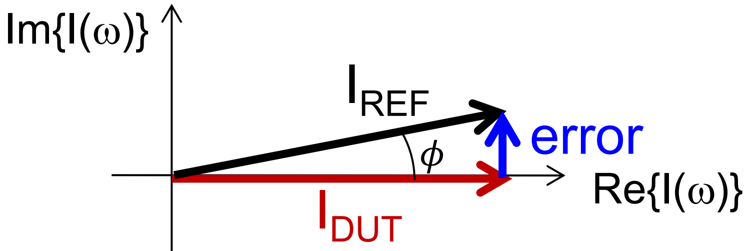
$$|\Delta Y_{DUT}| > 10^{-4}\, |Y_{DUT} - Y_{REF}| \quad \Rightarrow \quad Y_{REF} \approx Y_{DUT}(1 \pm 1\%)$$

Phase error



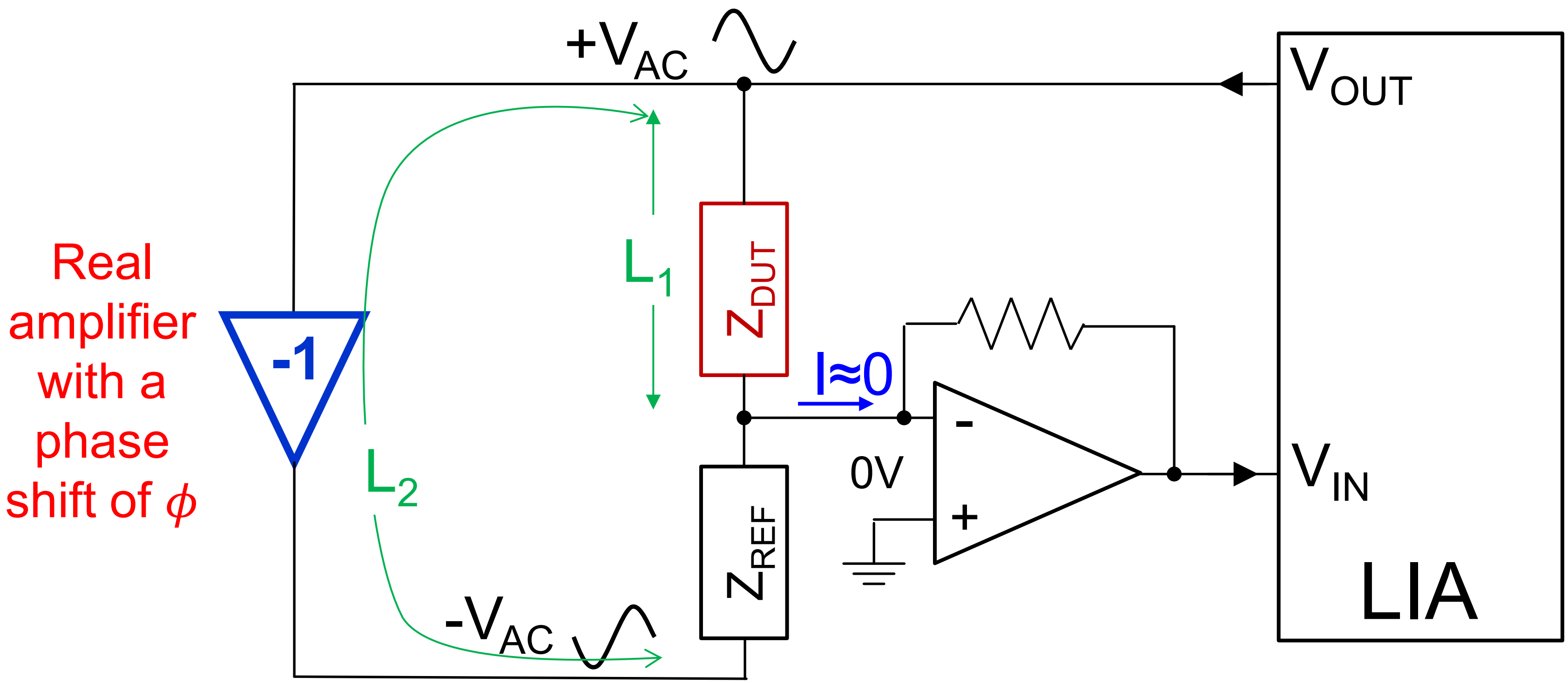
Assuming the ideal case of $Z_{REF} = Z_{DUT}$ we have a residual error:

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



In-quadrature error!

Phase error



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

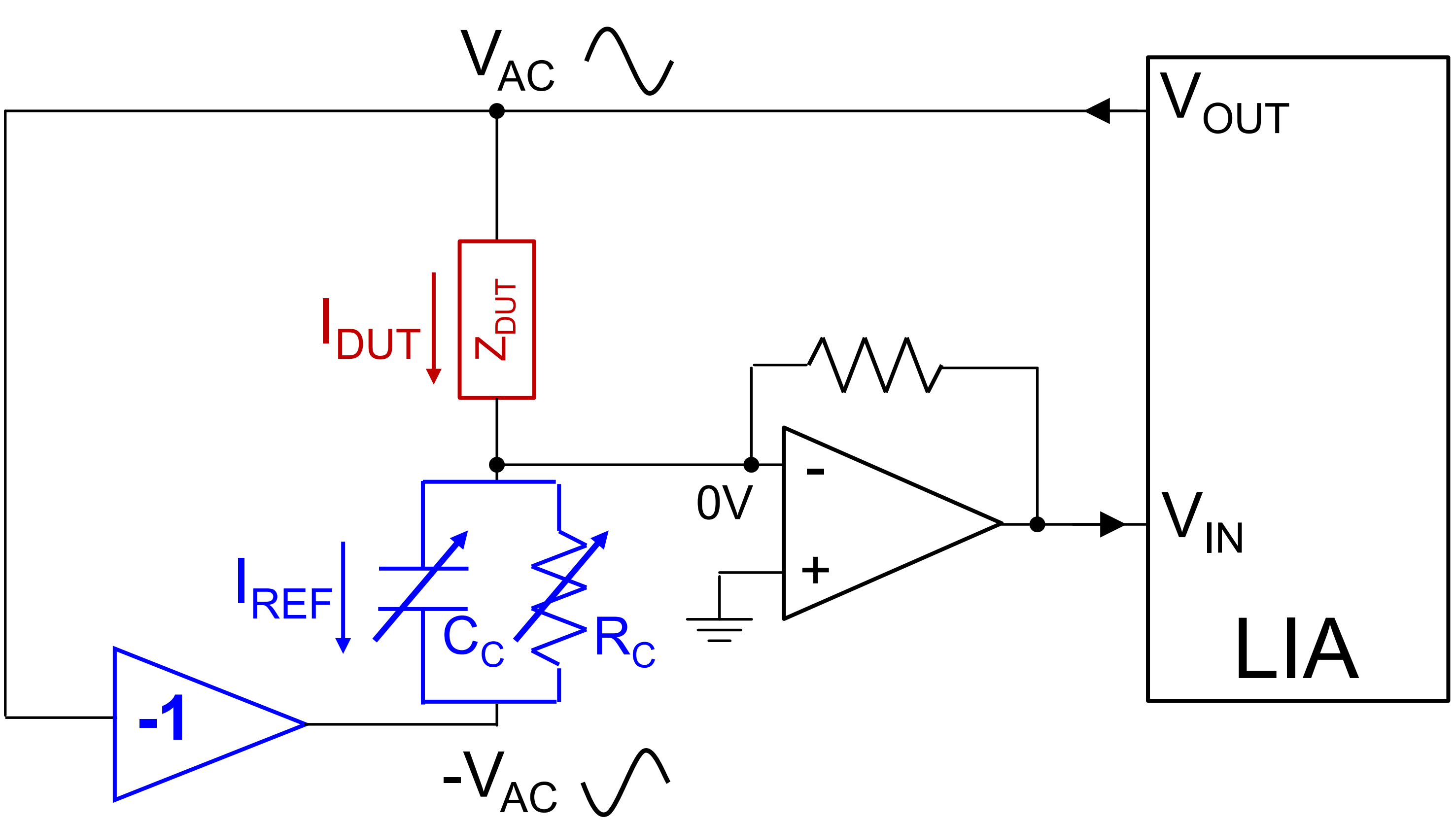
$$\frac{V_{AC}}{Z}\sin(\omega_0 t)-\frac{V_{AC}}{Z}\sin(\omega_0 t+\phi)=-2\frac{V_{AC}}{Z}\sin\left(\frac{\phi}{2}\right)\cos\left(\omega_0 t+\frac{\phi}{2}\right)$$

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

Calibration of the reference path



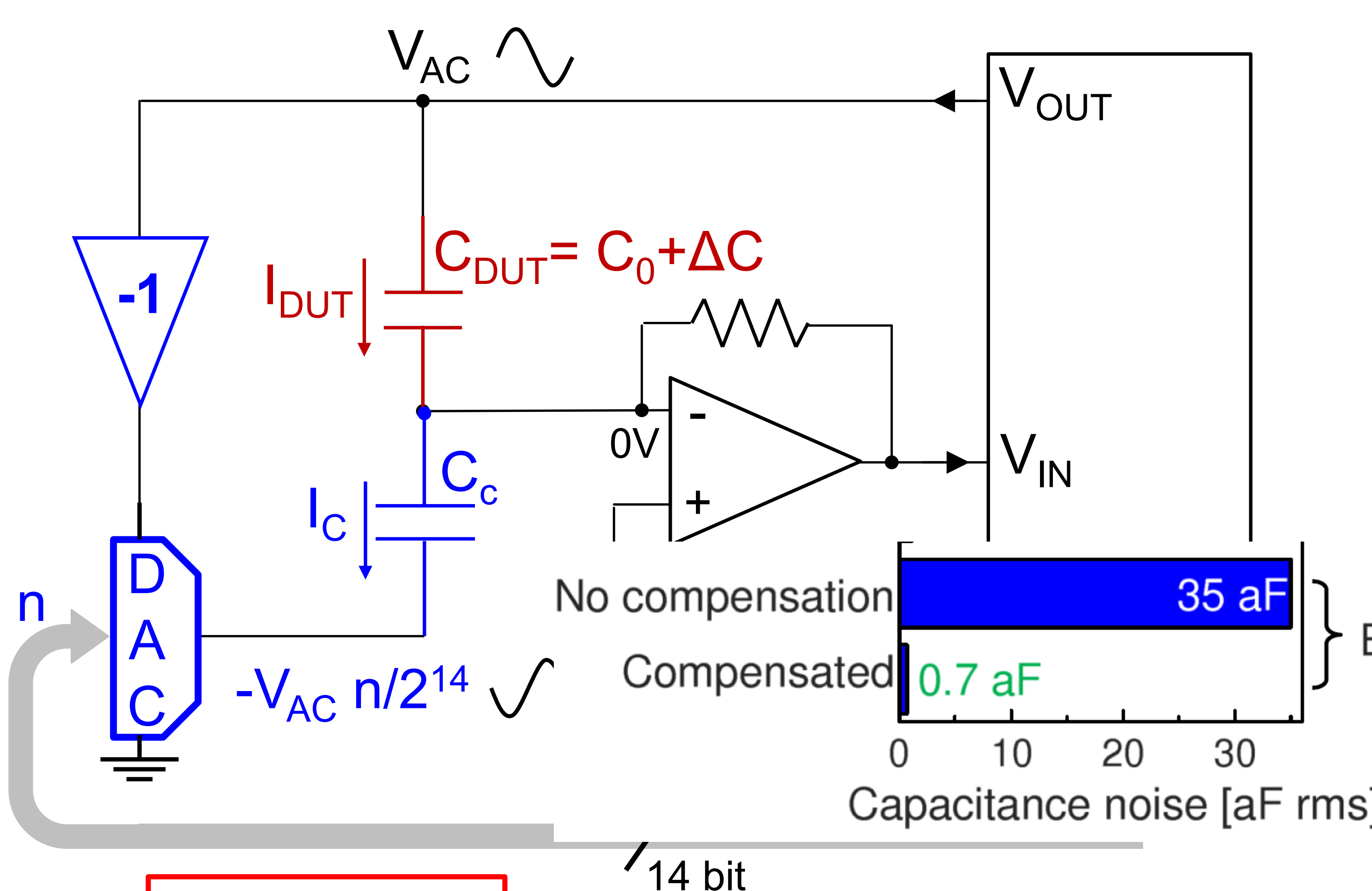
Calibration may be required to have $I_{DUT} \approx I_{REF}$ in *module and phase*

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

M. Carminati, et al. *Rev. Sci. Instrum.*, 2016, doi: 10.1063/1.4941721.



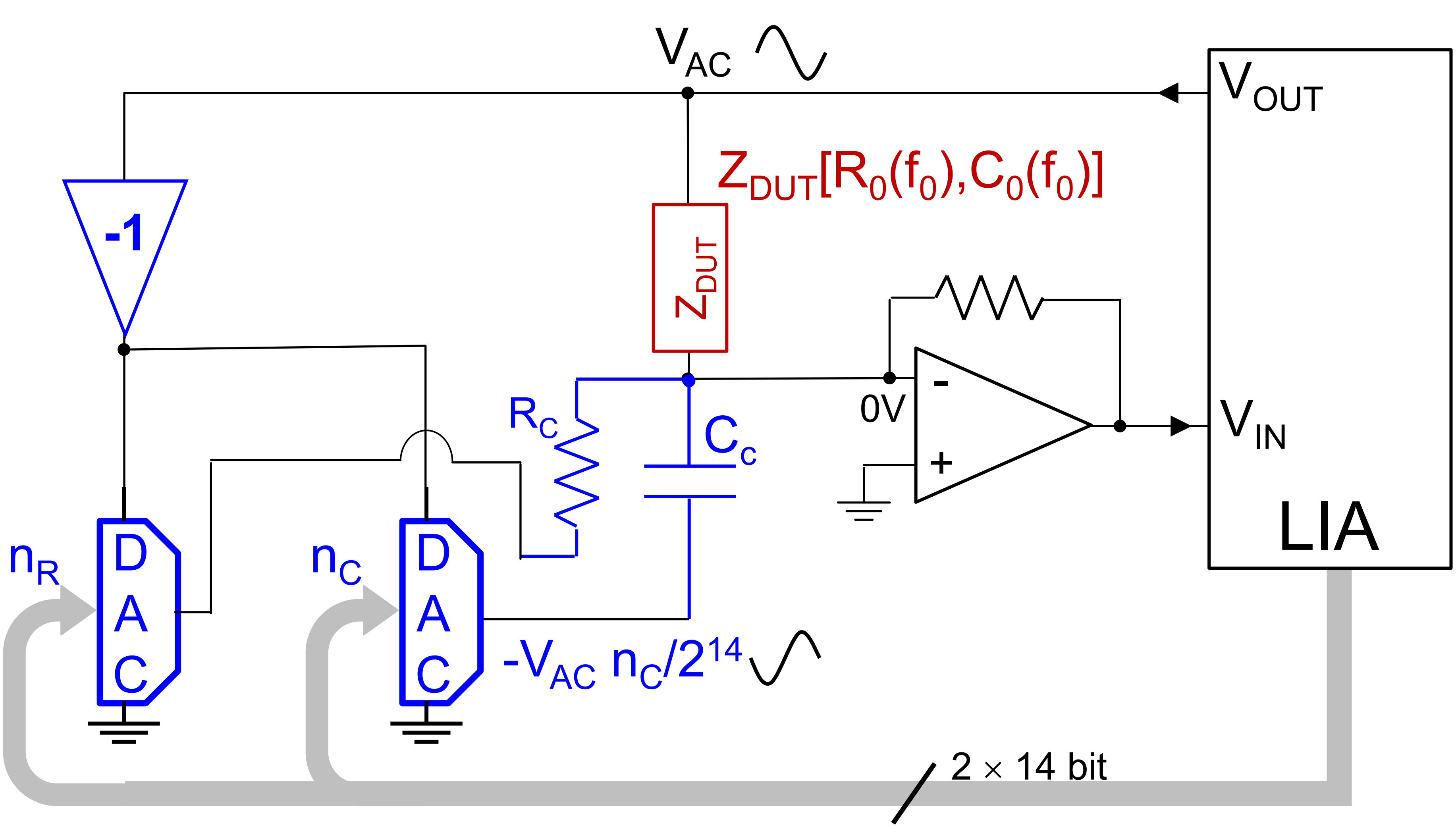
$$\frac{n}{2^{14}} C_C = C_0$$

C_c greater than C_0

(or use a higher inverting gain)

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

Digital control of the reference path

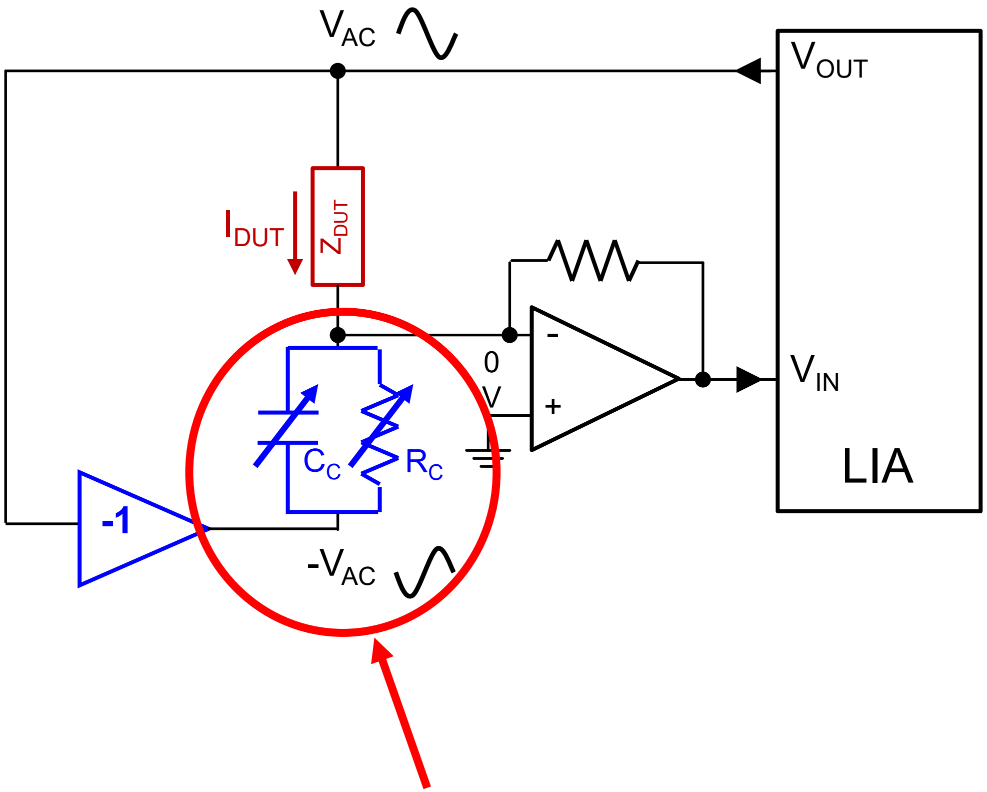


$$\boxed{\frac{n_R}{2^{14}}\frac{1}{R_c} = \frac{1}{R_0}}$$

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

AD5446: 14-bit multiplying DAC

Generation of the reference path



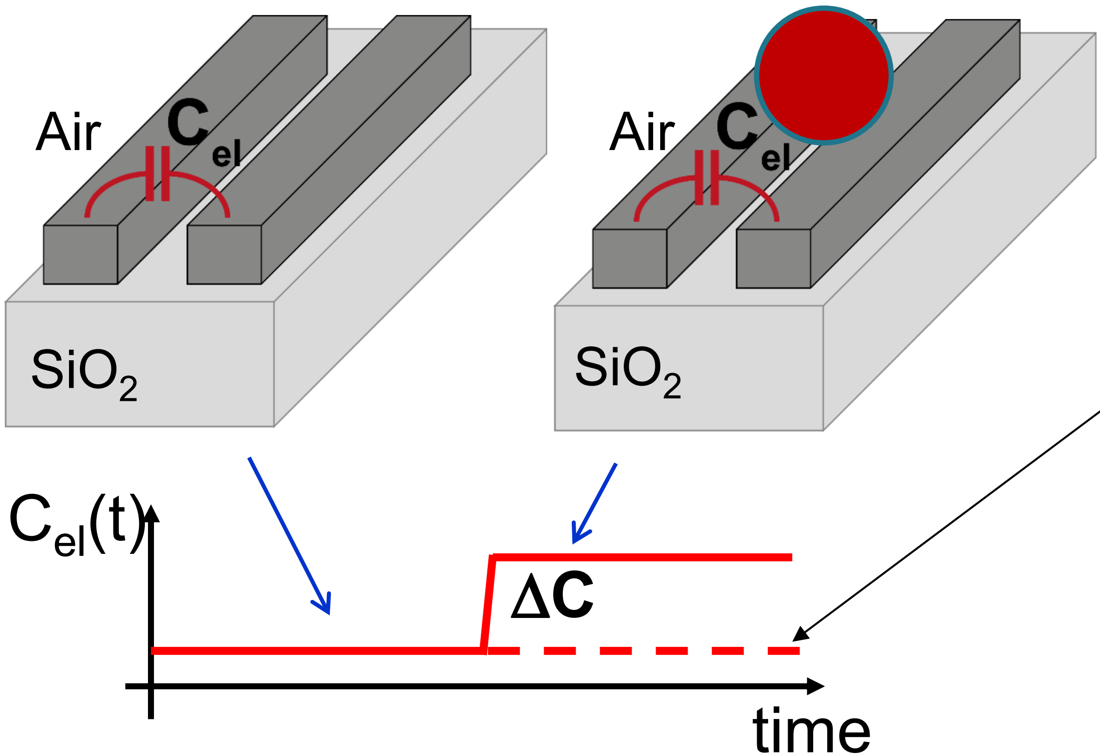
+ general approach
+ reduces the effect of gain fluctuations of acquisition chain and stimulus signal

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

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

Small variations over large baseline: problems

1) Noise of the sensor and of the preamplifier $\Delta C_{min} = 0.5aF$
2) Gain fluctuations (stimulus, readout) $\Delta C_{min} = 600aF$
3) Baseline fluctuations



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

Temperature:

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

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

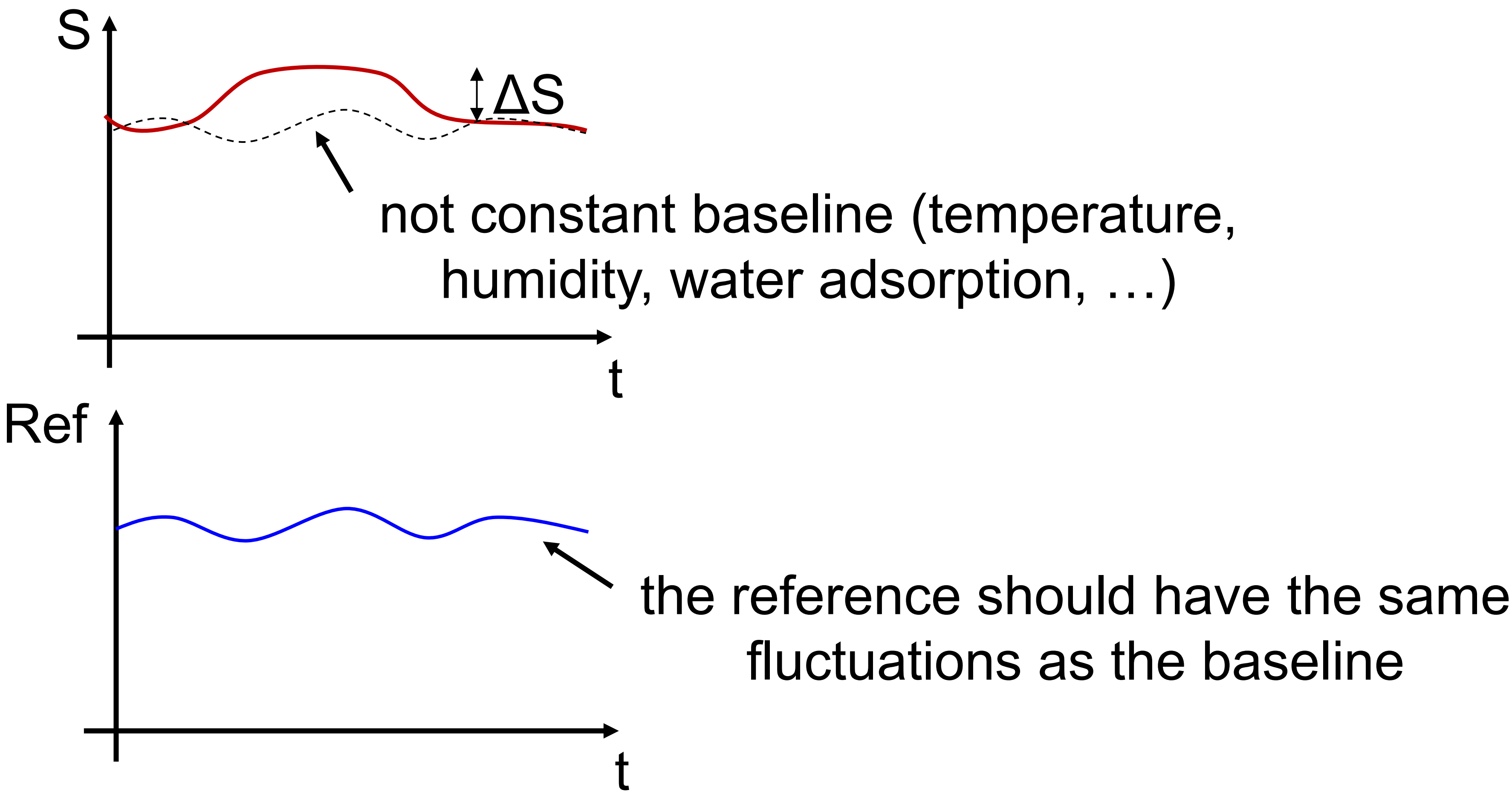
$\boxed{\Delta C_{baseline} \approx 250aF\ /°C}$

In addition: humidity

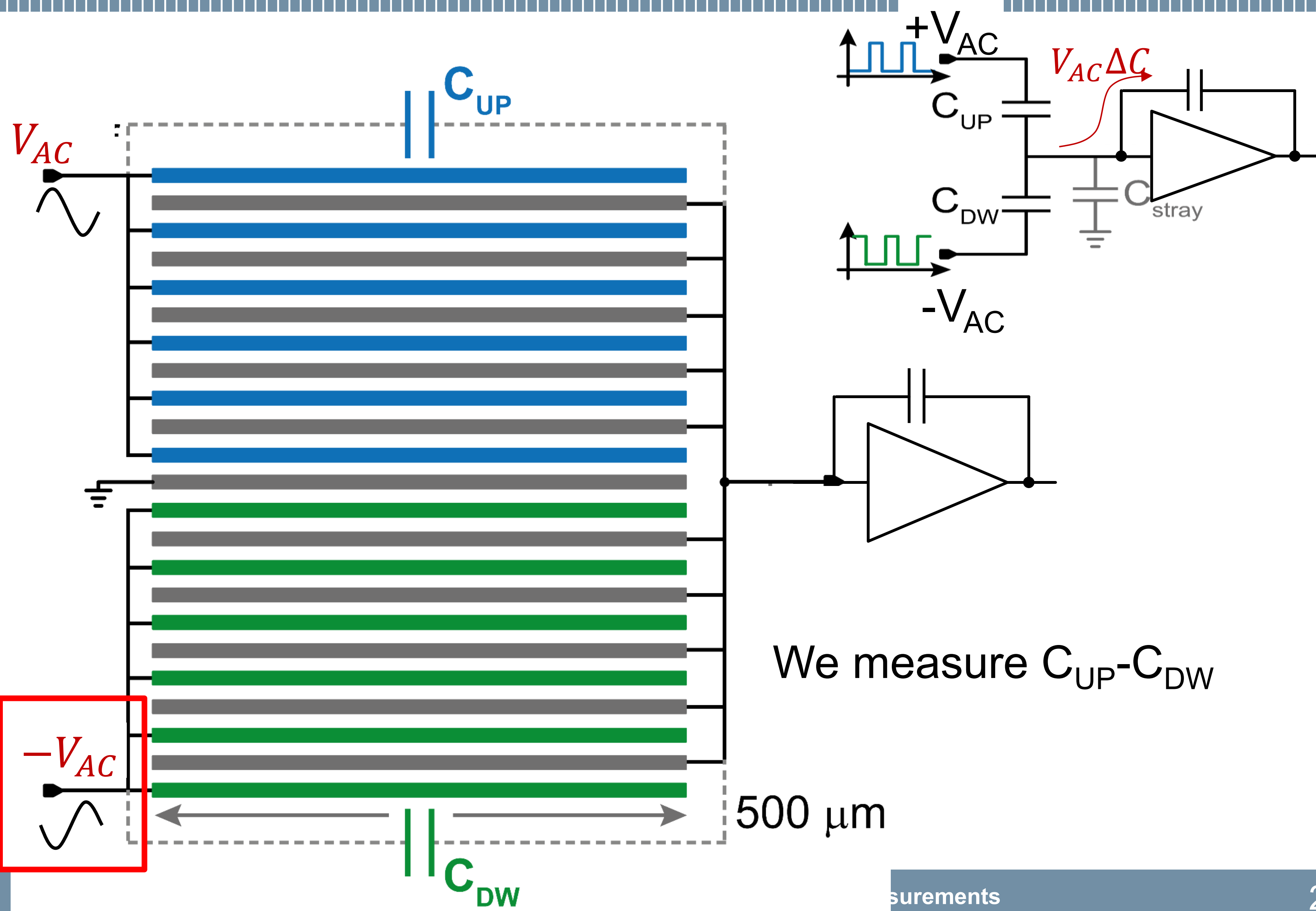
$\Delta\epsilon_{air} \approx 1\ ppm/\%RH$

The differential approach: baseline fluctuations

The Reference must share the fluctuations of the baseline:

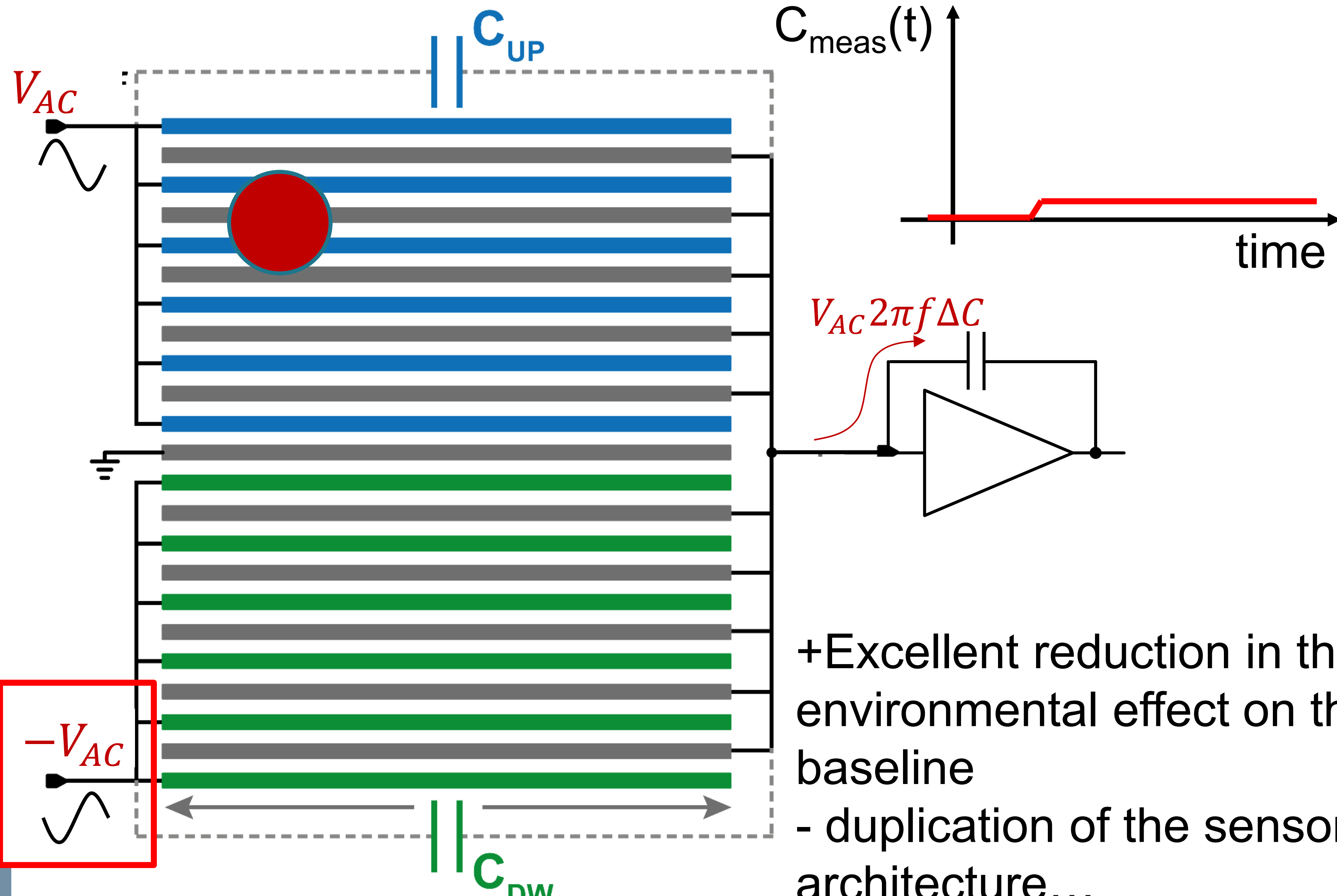


Differential electrode architecture



We measure C_{UP}-C_{DW}

Differential electrode architecture

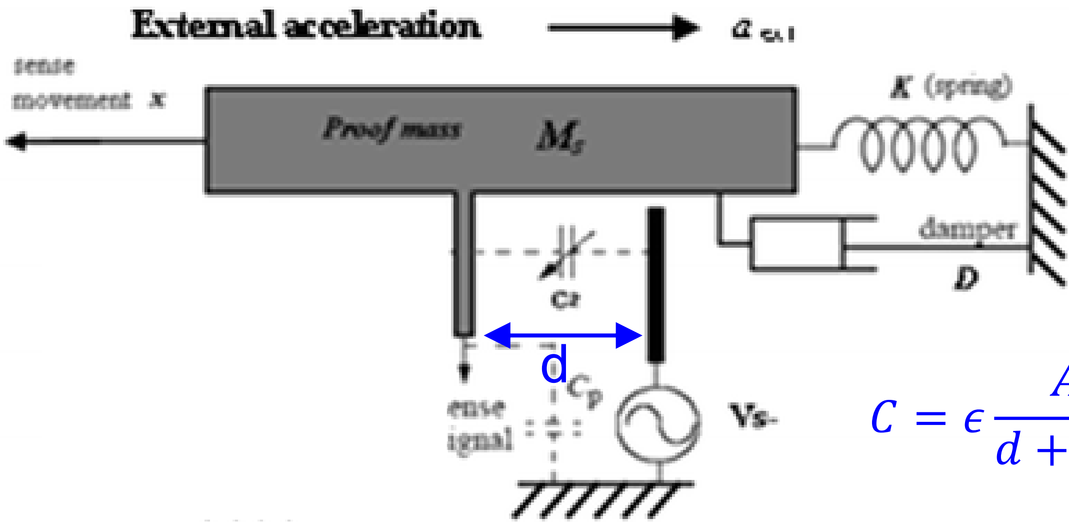


+Excellent reduction in the environmental effect on the baseline

- duplication of the sensor architecture…

Design differential sensors if possible

Example: MEMS capacitive sensors

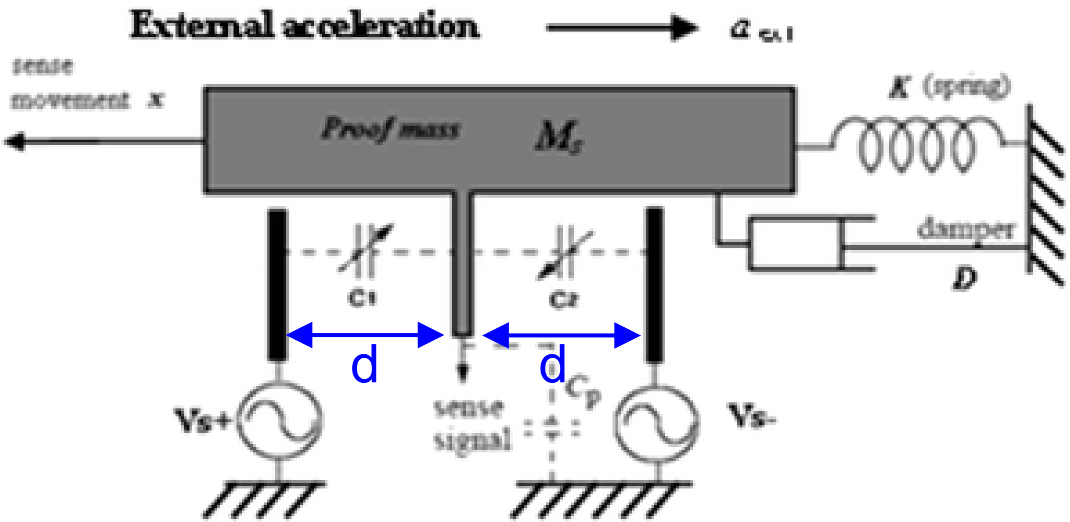


$$C = \epsilon \frac{A}{d + \Delta x} \cong C_0 - \Delta C$$

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

Design differential sensors if possible

Example: MEMS capacitive sensors



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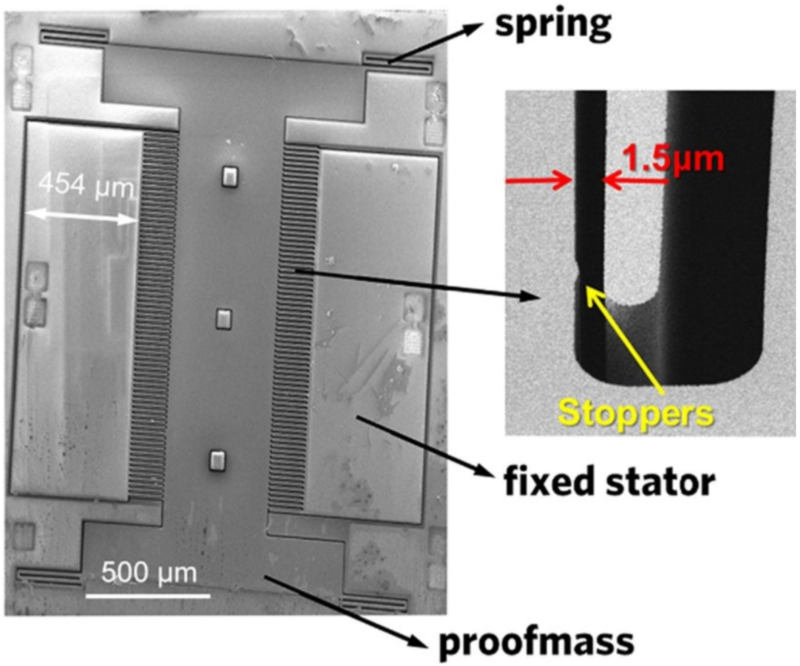


R. Li et al., Measurement, 2021

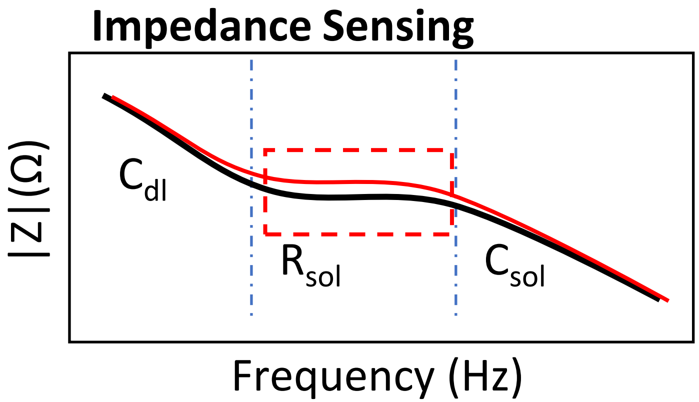
$$C_1 = \epsilon\frac{A}{d-\Delta x} \cong C_0 + \Delta C$$

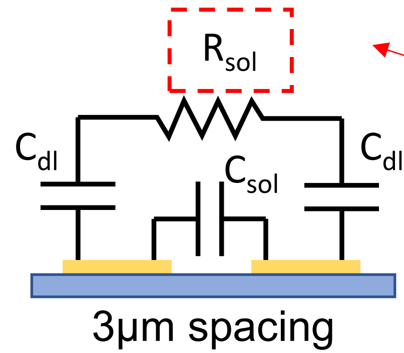
$$C_2 = \epsilon\frac{A}{d+\Delta x} \cong C_0 - \Delta C$$

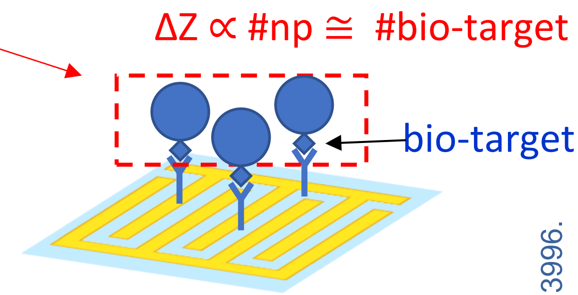
both arms of the differential structure are sensors

- 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,…)

Differential Impedance Biosensing





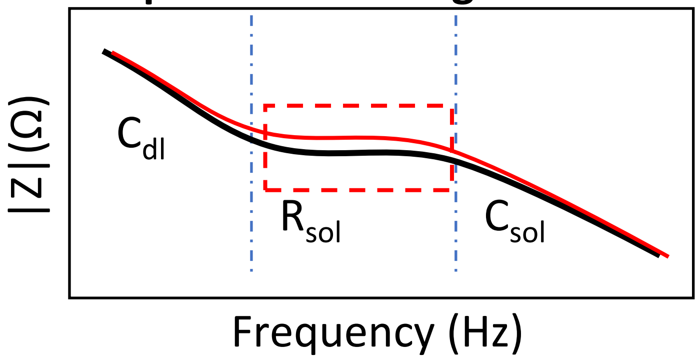


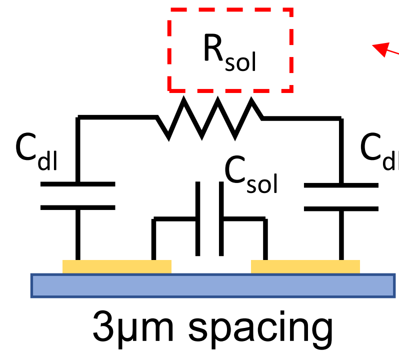
Resistance variation at the end of the experiment is related to the number of polystyrene NPs (diameter 800nm), i. e. to the specific nanosized biological target.

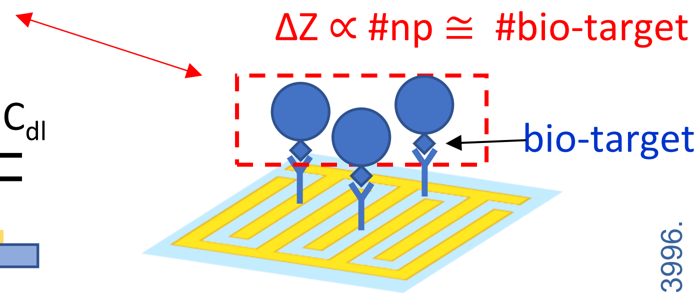
P. Piedimonte, et al, doi: 10.1016/j.bios.2022.113996.

Differential Impedance Biosensing

Impedance Sensing







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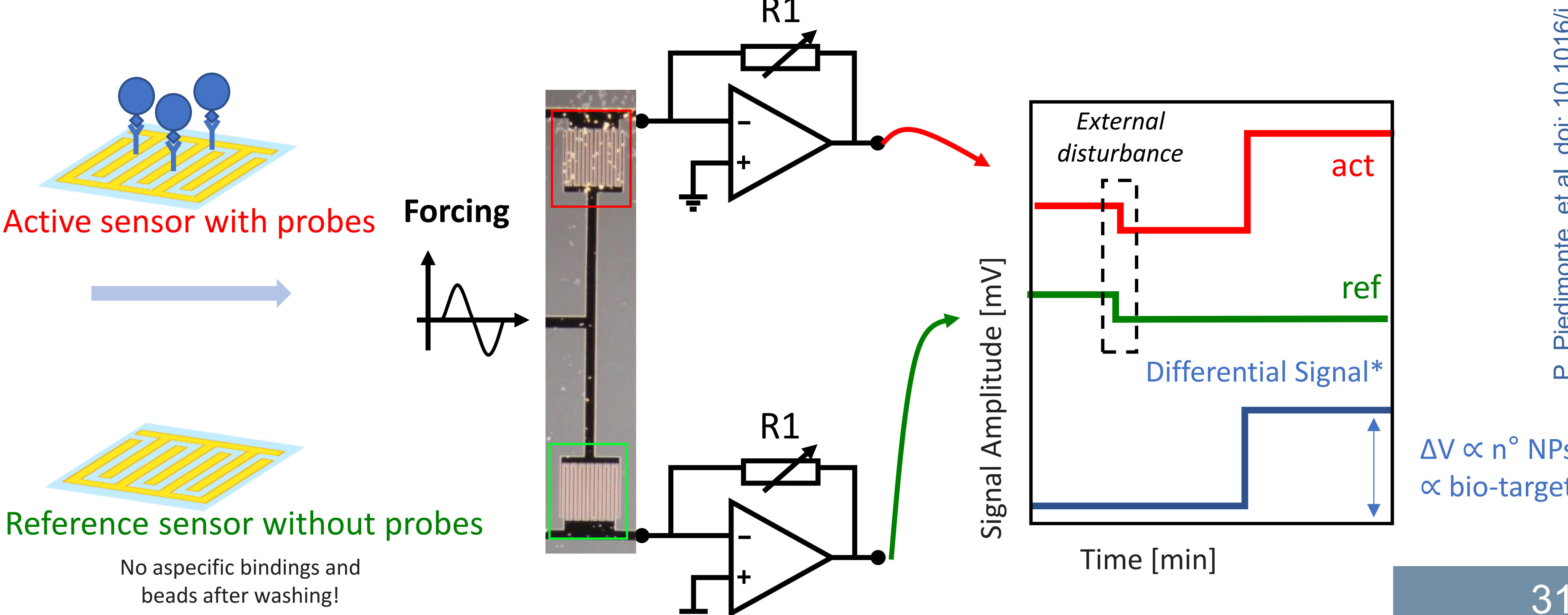
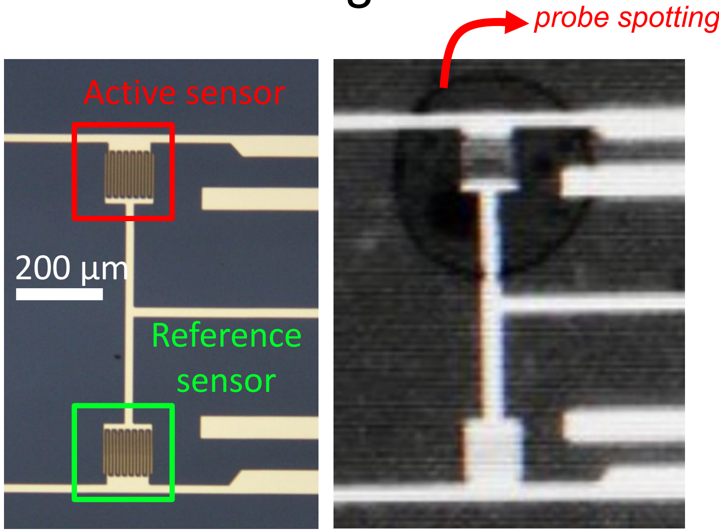


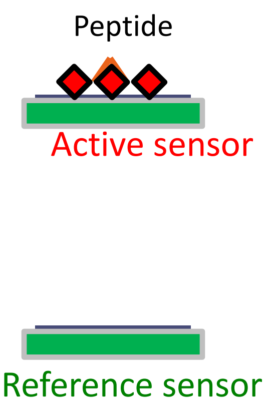
P. Piedimonte, et al, doi: 10.1016/j.bios.2022.113996.

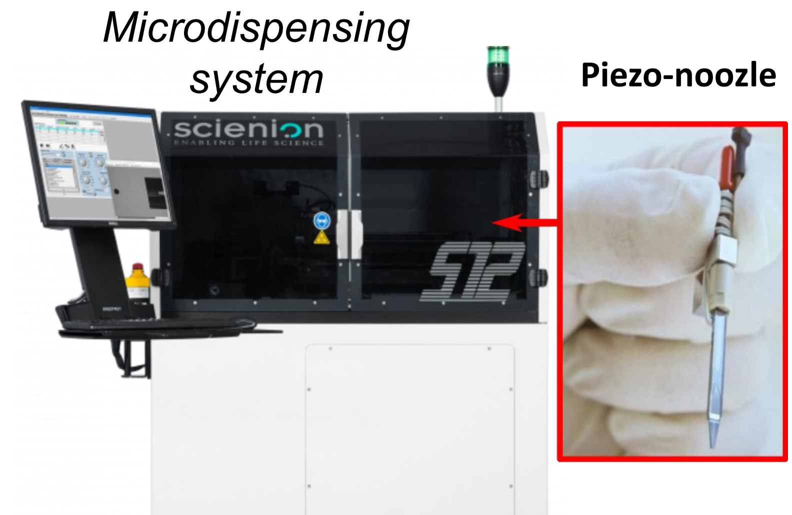
Biochip preparation for a Dengue test

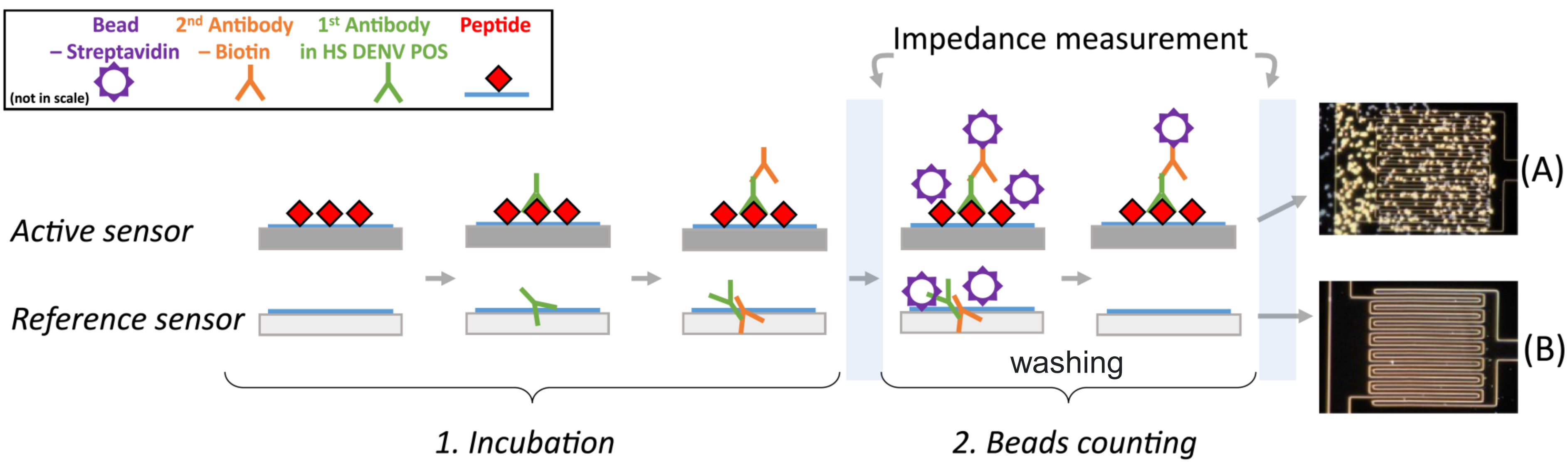
<u>Local functionalization of the **active sensor**</u> → avoid non-specific binding outside sensing area

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

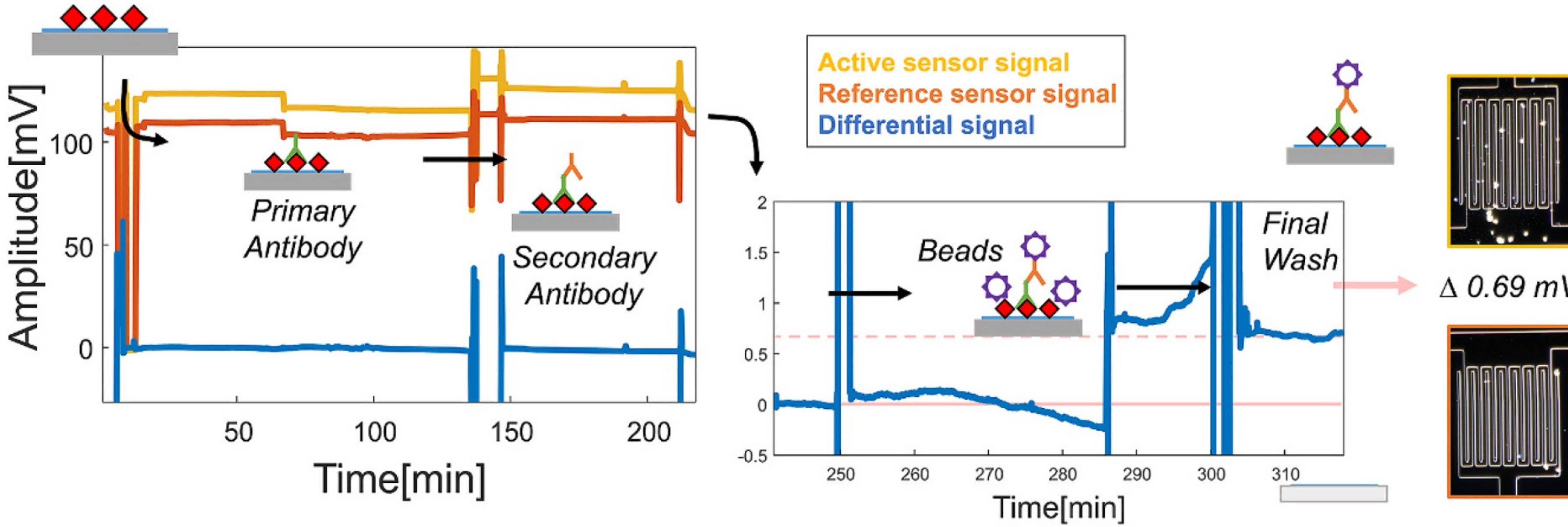




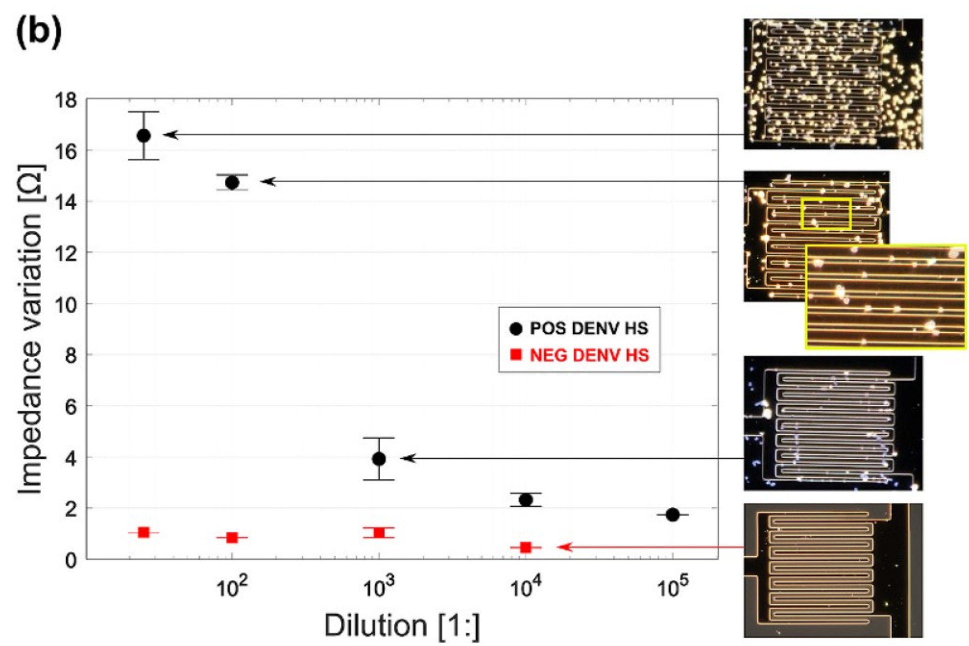




Results for Dengue Virus detection in human serum



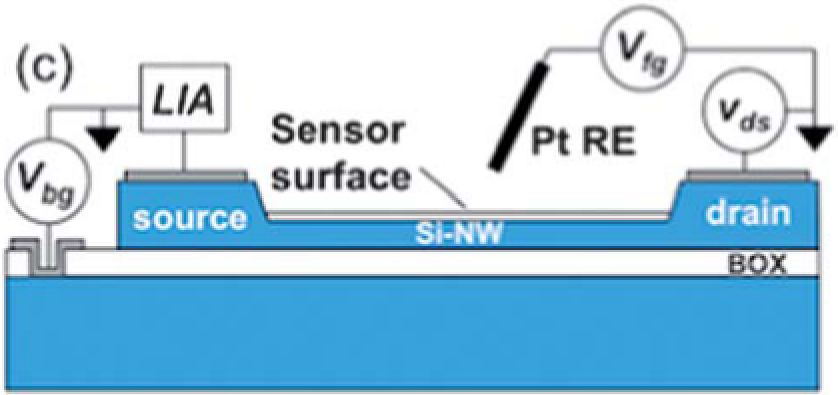
- **Human Serum** samples positive to anti-DNV IgG antibodies
- **Clinically relevant concentration**
- **Control**: HS negative to anti-DENV IgG antibodies



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.

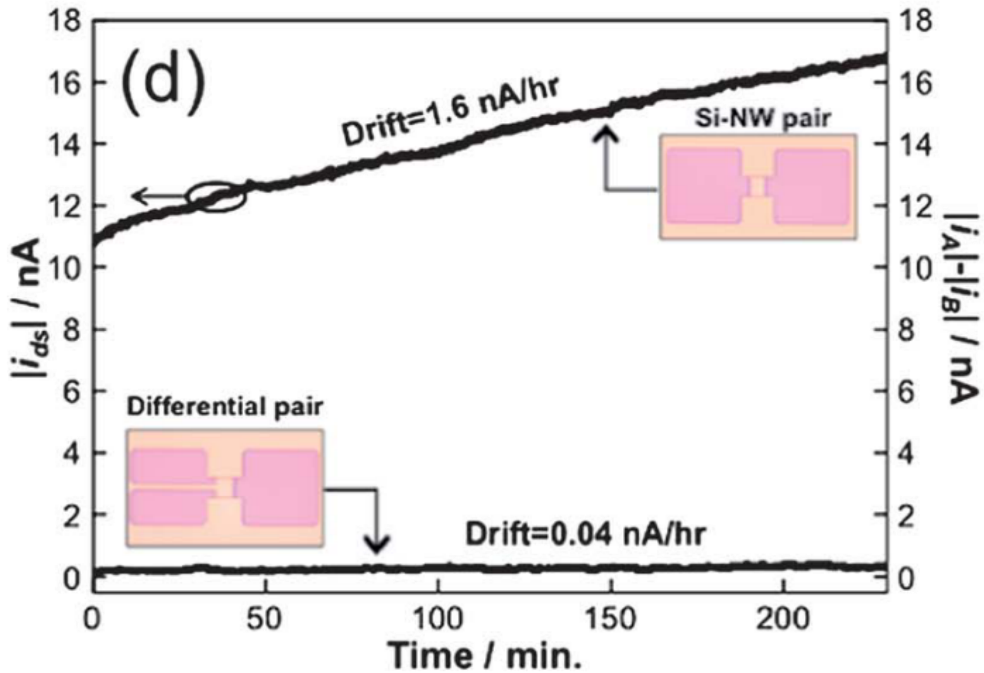
Differential biosensors

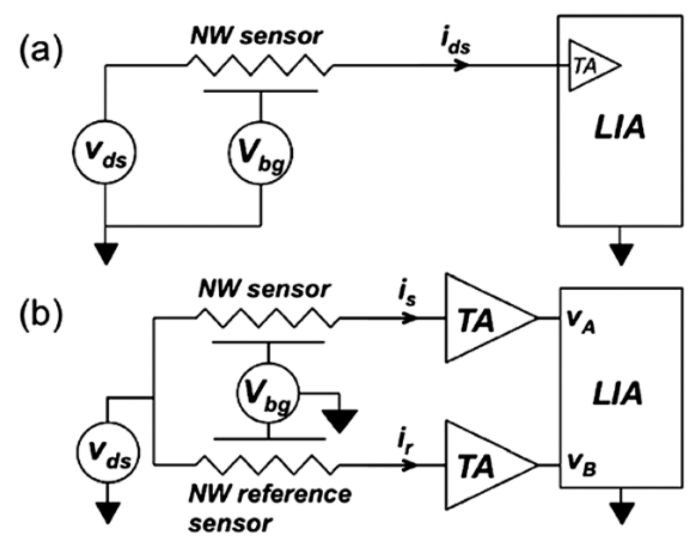
<u>*Ex.:* silicon nanowire DNA sensor</u>



- AC measurement (LIA) for reducing the 1/f noise of the nanowire

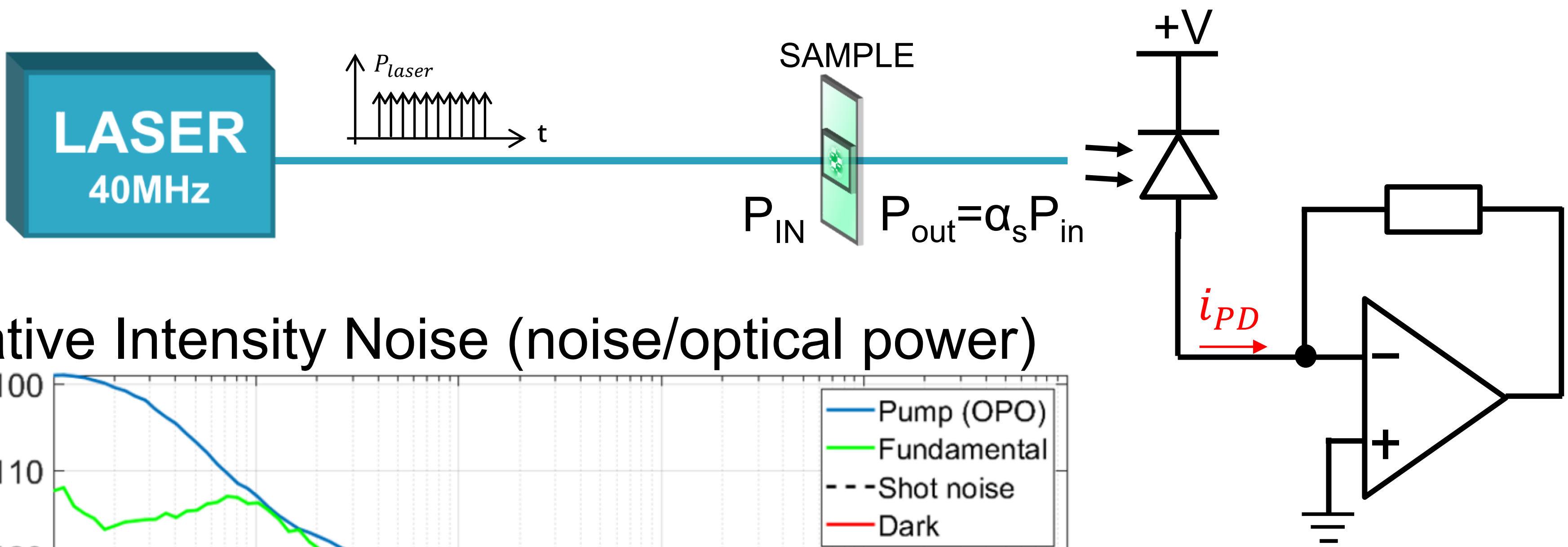
- suffer from drift due to ion migration at the gate-oxide interface → differential meas.



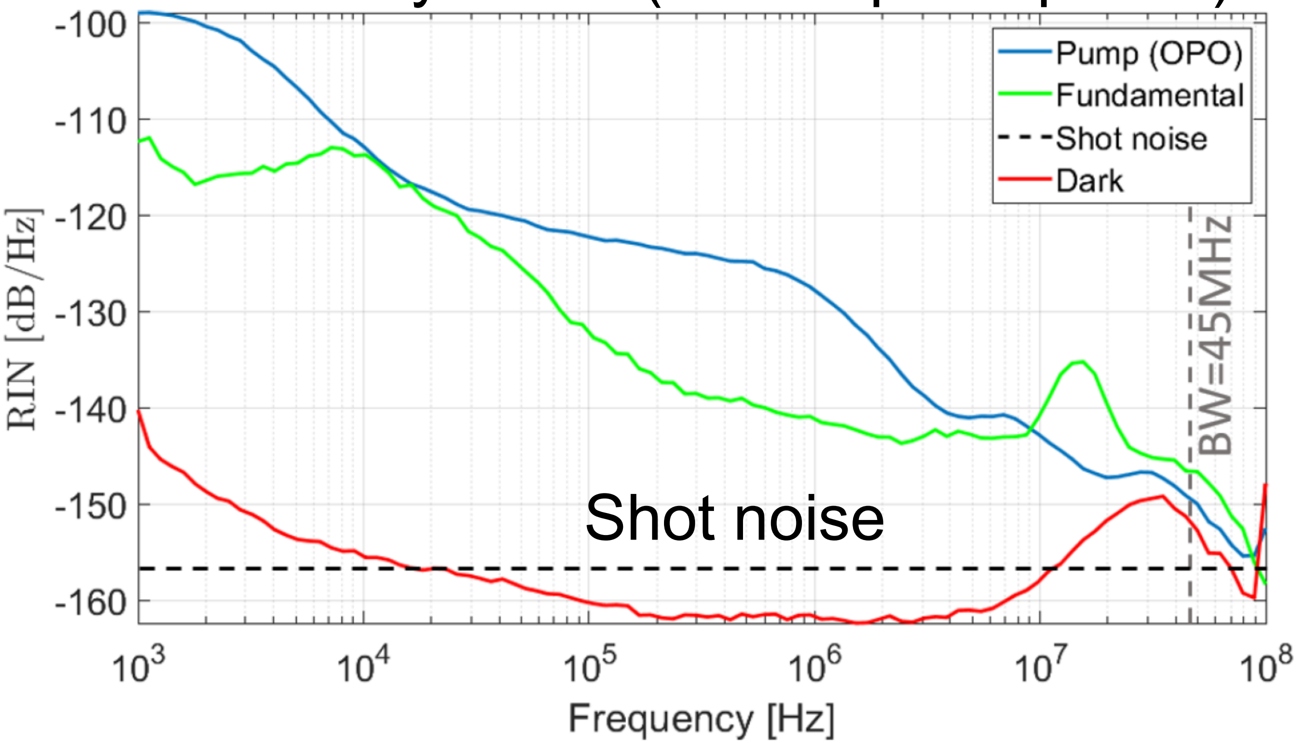


A. De, et al. "Integrated label-free silicon nanowire sensor arrays for (bio)chemical analysis," *Analyst*, vol. 138, no. 11, pp. 3221–3229, 2013, doi: 10.1039/c3an36586g.

Laser-based optical spectroscopy



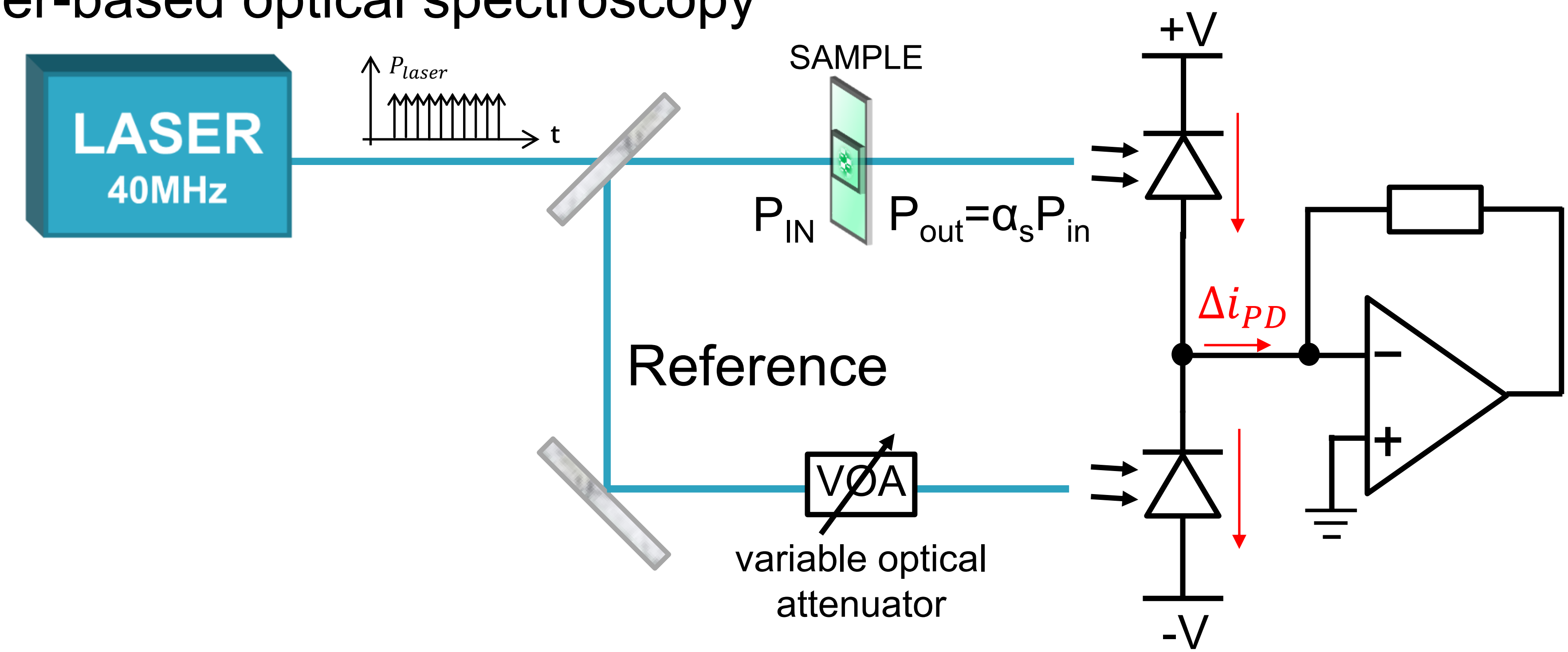
Relative Intensity Noise (noise/optical power)



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

Balanced optical detection

Laser-based optical spectroscopy



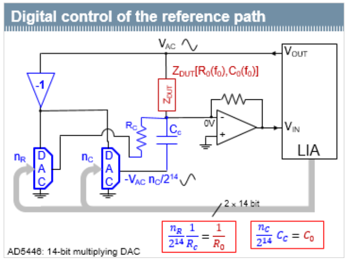
- \+ Cancellation of the optical intensity fluctuations
- \+ Optimization of the readout circuits
- \- Require a calibration for any change in the sample
- \- Each photodiode has an independent shot noise

  → doubling the minimum theoretical noise

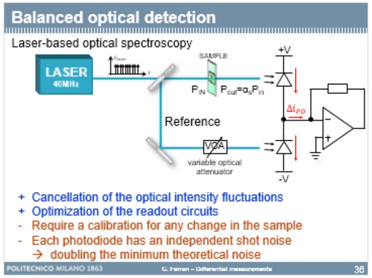
Drawbacks of the differential approach

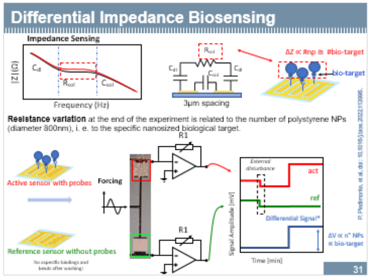
While differential measurements offer several advantages, there are also some drawbacks to consider:

- 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

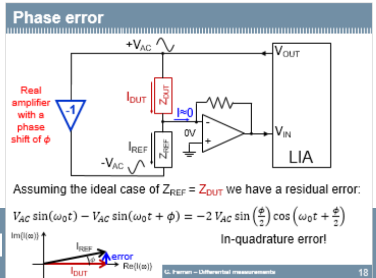


- Increase the minimum theoretical noise
  - ✓ Use a differential approach when you are limited by gain fluctuations or environmental effects
  - ✓ design a differential sensor with a doubling of the signal!





- 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.