

Optical nanotweezers for single cell deformability measurements

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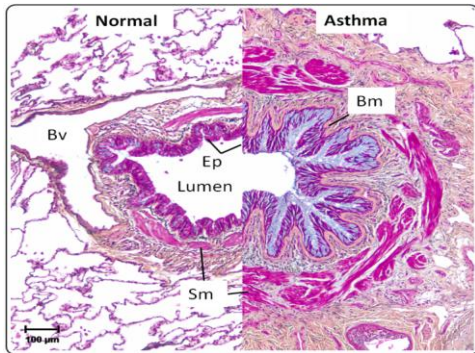
ÉCOLE
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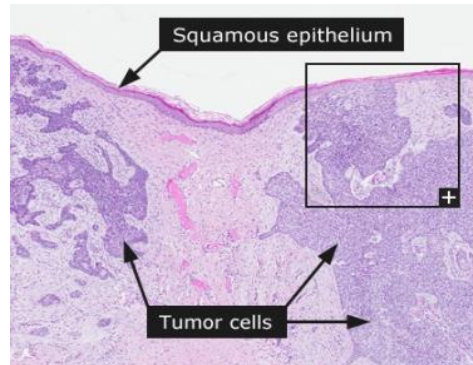
Mechanical phenotype for diagnostic applications

Asthma



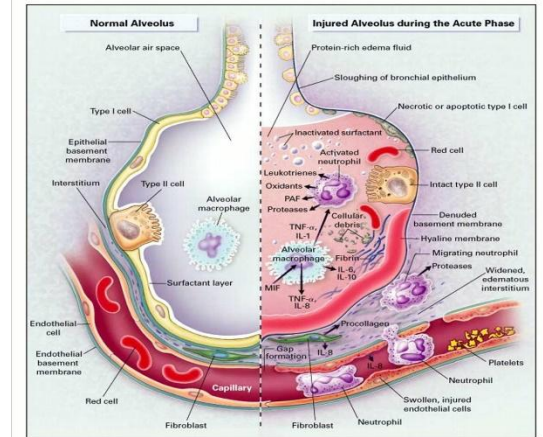
Wadsworth et al. *Asthma and Glycosylation in Airway Epithelial Repair*, (2012)

Cancer



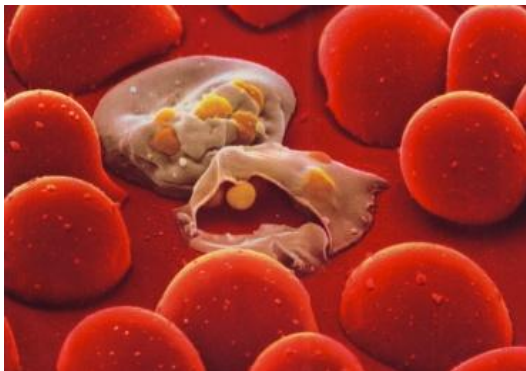
www.proteinatlas.org

ARDS



www.clinicaladvisor.com

Malaria



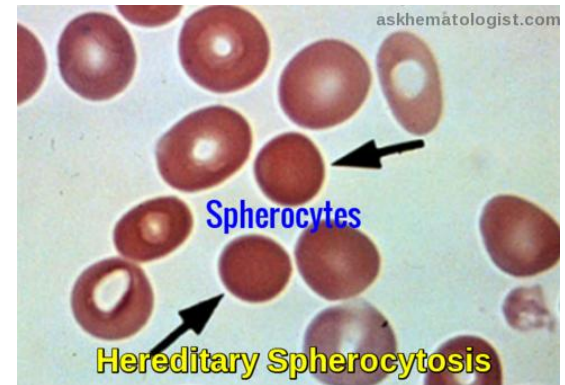
www.blog.rottenecards.com

Sickle Cell Disease



www.lifl.fr

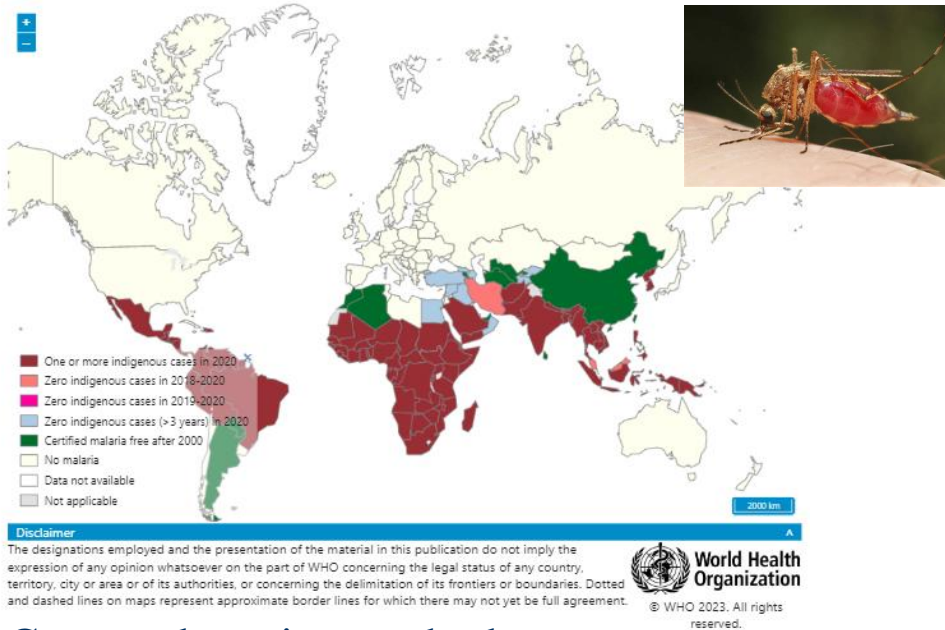
Hereditary Spherocytosis



www.askhematologist.com

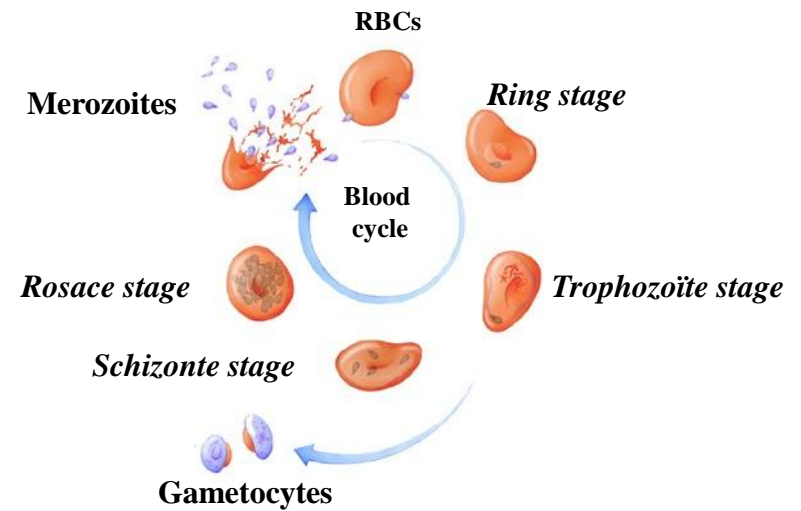
Mechanical signature of cells appears to be a relevant physical biomarker

For example: detection of malaria



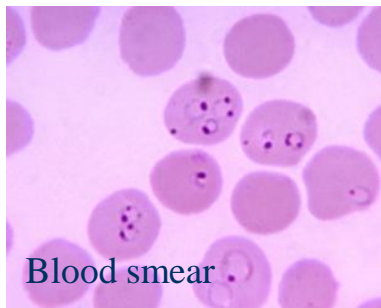
“247 million cases of malaria in 2021, and the estimated number of malaria deaths stood at 619 000. The WHO African Region carries a disproportionately high share of the global malaria burden.”

www.who.int/



www.pasteur.fr

Current detection methods:



Blood smear



Rapid Diagnostic Tests

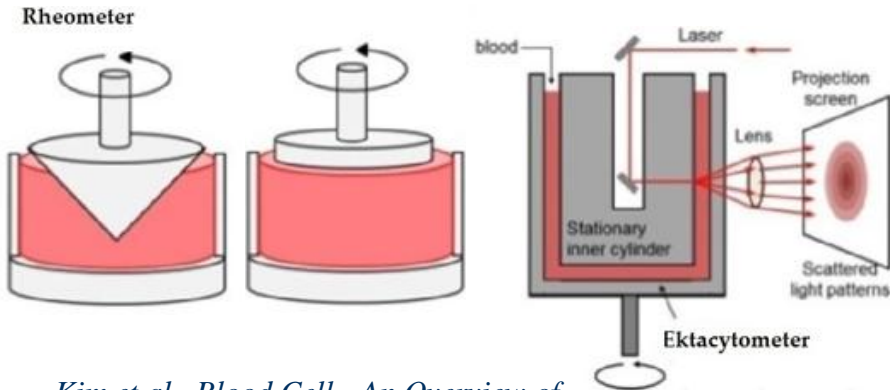
Not suitable for on field analysis

False-positive leading to unnecessary drug use which contributes to the emergence of treatment-resistant strains

Direct detection of the presence of parasites within the host cell → **mechanical phenotyping**

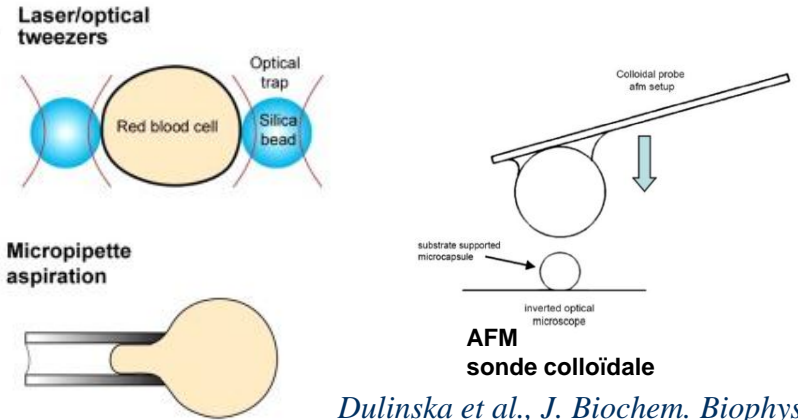
Mechanical phenotyping techniques

Collective techniques



Kim et al., Blood Cell - An Overview of Studies in Hematology - Chap10 (2012)

Single cell techniques



Suresh, Acta Biomaterial (2007)

Dulinska et al., J. Biochem. Biophys. Meth. (2006)

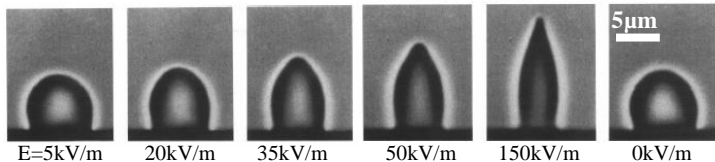
Not adapted for low number of pathological cells

High throughput

High sensitivity (single cell detection)

Low throughput

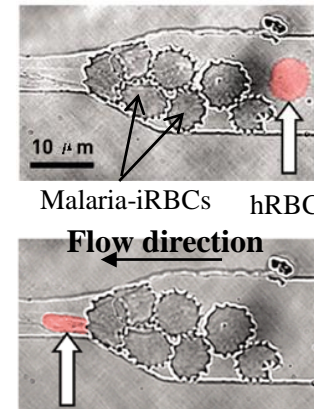
Microfluidic techniques



Engelhardt et al., Biophys. J.(1988)

actives

passives

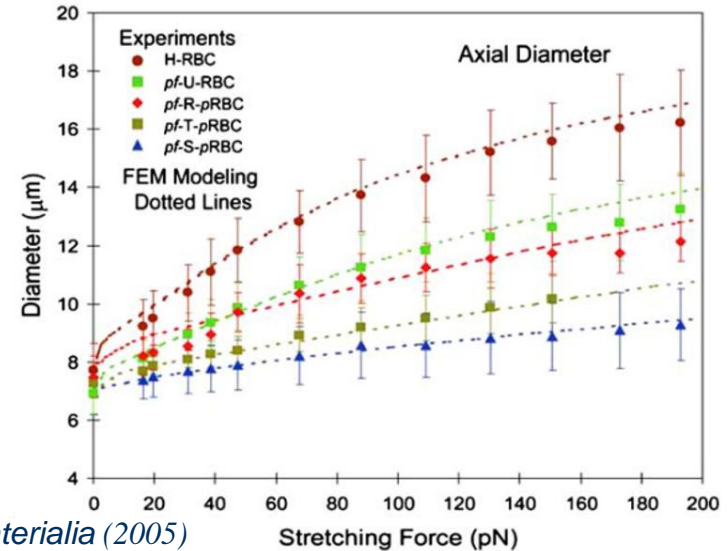
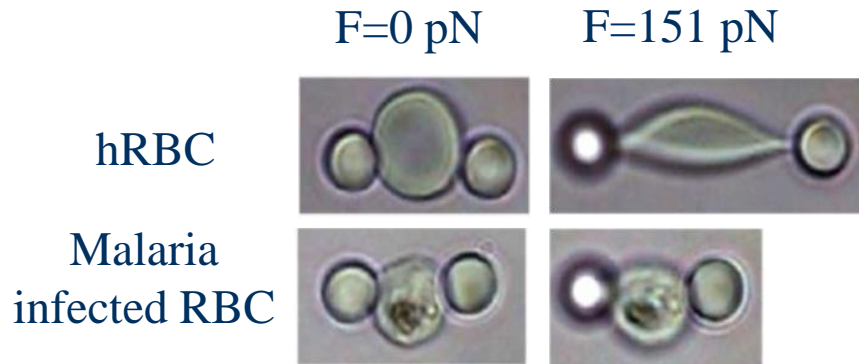


Malaria-iRBCs hRBC

Flow direction

Mechanical phenotyping using optical tweezers

Manipulation of microspheres diametrically attached to the RBCs membrane



Suresh et al., Acta Biomaterialia (2005)

Significant increase of malaria infected RBCs with parasite growth at different maturation stages

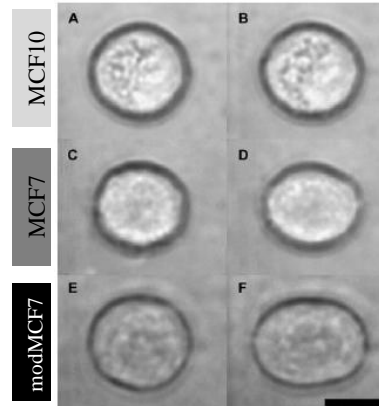
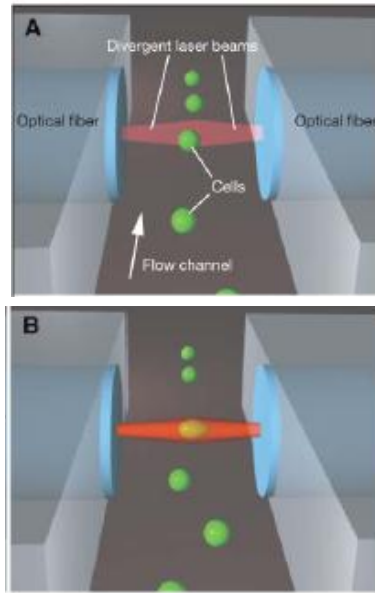


Single cell scale measurement

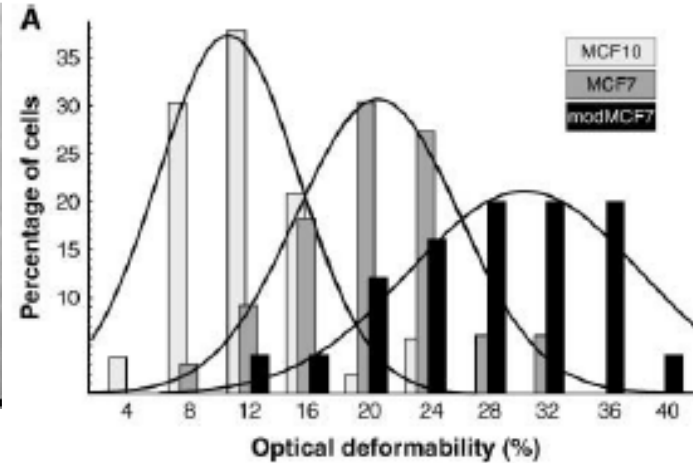


Low throughput analysis (~ 100 cells/hour)

Optical tweezers coupled with microfluidics



Guck et al., *Biophys. J.* (2005)



Single cell scale measurement

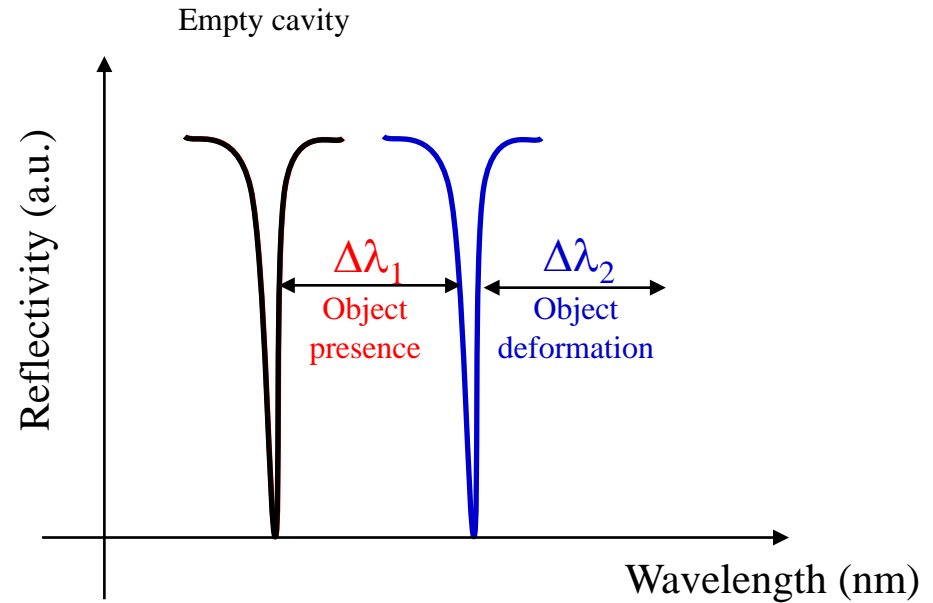
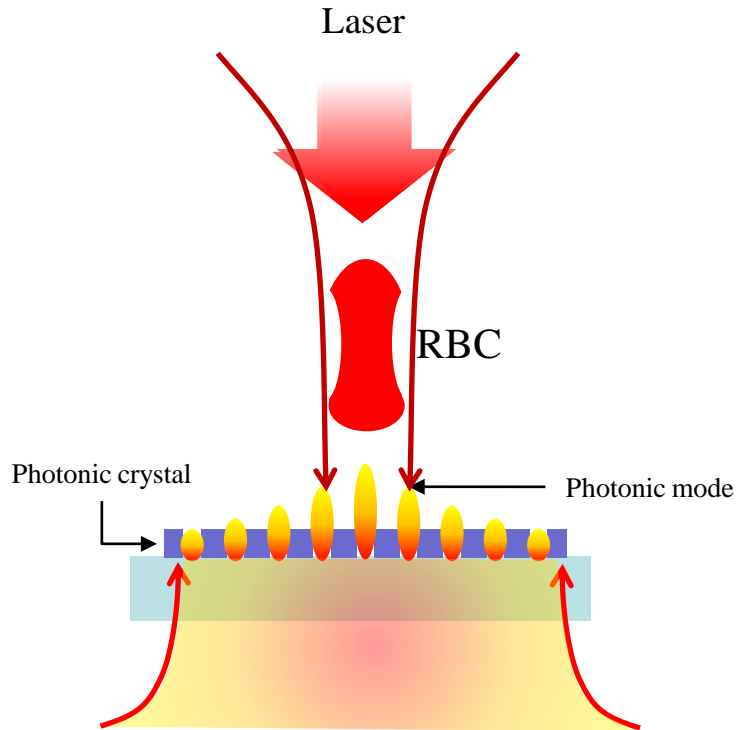


Medium throughput analysis (~ 1 cell/min)

In order to improve further the throughput performances it would require avoiding image analysis step

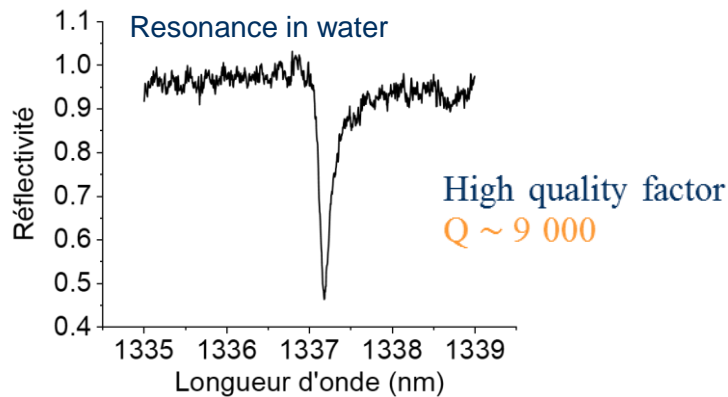
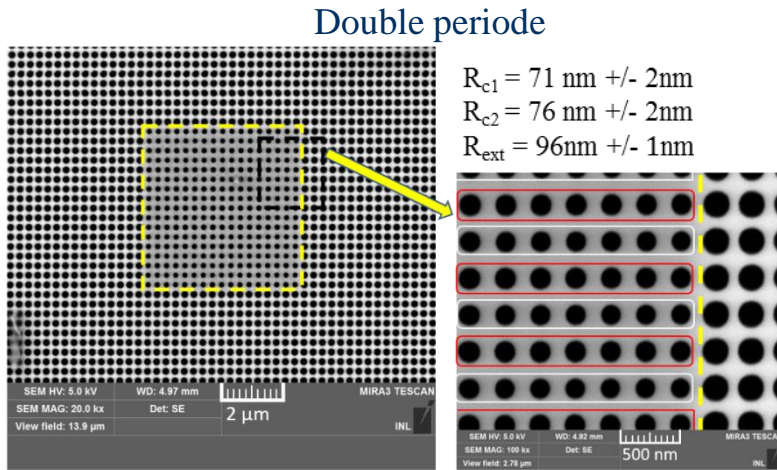
Our approach : Optical Nanotweezers based on Photonic Crystal

7

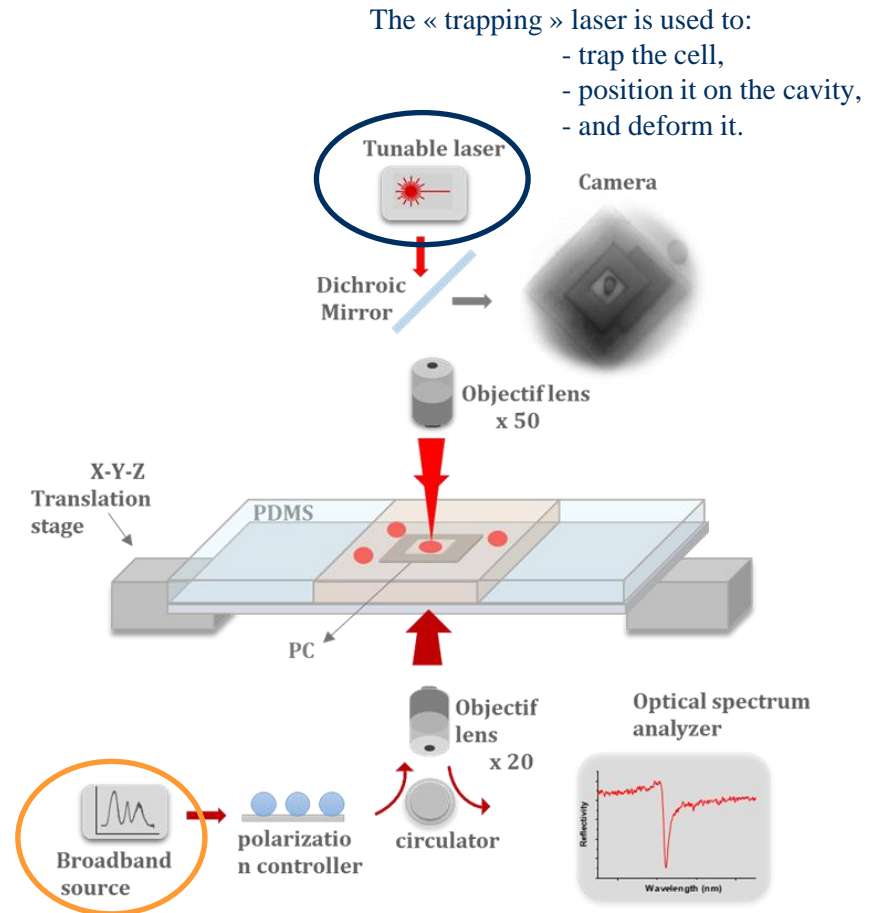


• Measurement of a reference on an empty cavity,

The 5 μm wide Photonic Cristal (PhC) cavity



The setup



The SLED is a broadband source is used to:

- measure the reflectivity of the PhC

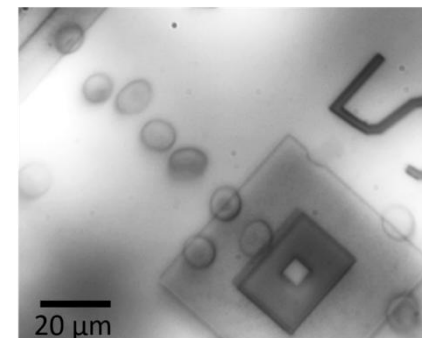
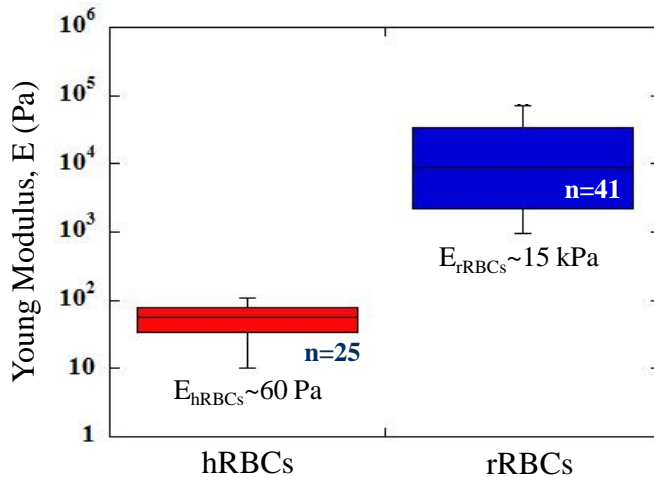
□ The samples

rRBC	hRBC
Chemical treatment ~ 12 % glutaraldehyde for 1H00	no treatment
Young's modulus : $E_{rRBC} = 1,5 * 10^4$ Pa	Young's modulus : $E_{hRBC} = 0,5 * 10^2$ Pa

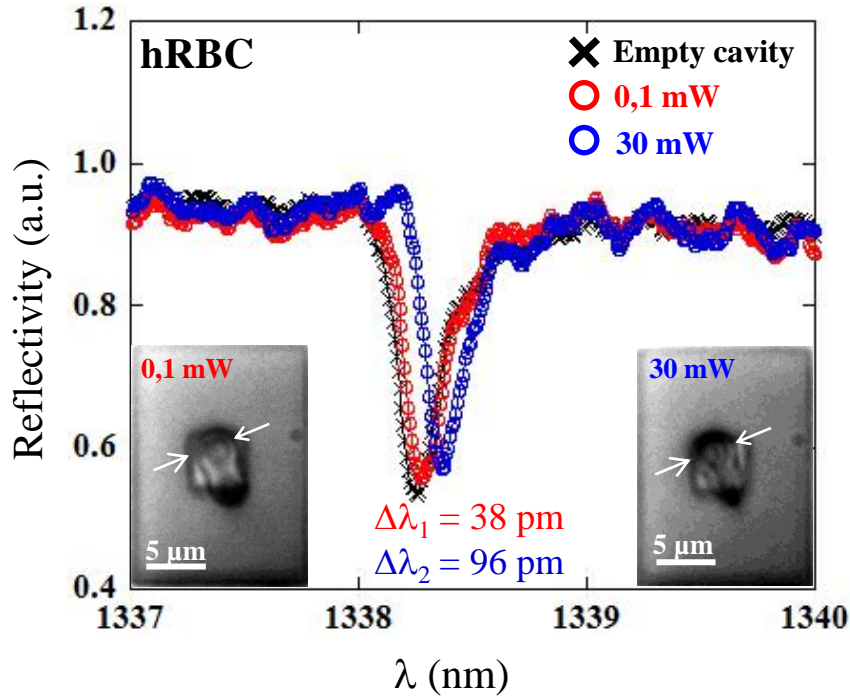
□ The buffer

Due to electrostatic interactions, non specific adhesion of RBCs on SOI substrates is observed despite passivation treatment (Bovin Serum Albumin or silane)

Solution	Morphologie de RBCs	Non-adh�sion sur la surface
sucrose (285 mM)	☹️	98 % de RBCs libres
sucrose + PBS $\frac{V_{sucrose\ 285\ mM}}{V_{PBS}} = 3.3$	☺️	56 % de RBCs libres
sucrose + PBS $\frac{V_{sucrose\ 285\ mM}}{V_{PBS}} = 0.4$	☺️	16 % de RBCs libres
PBS 1X	☺️	0% _ 0.5 % de RBCs libres



Reflectivity spectrum

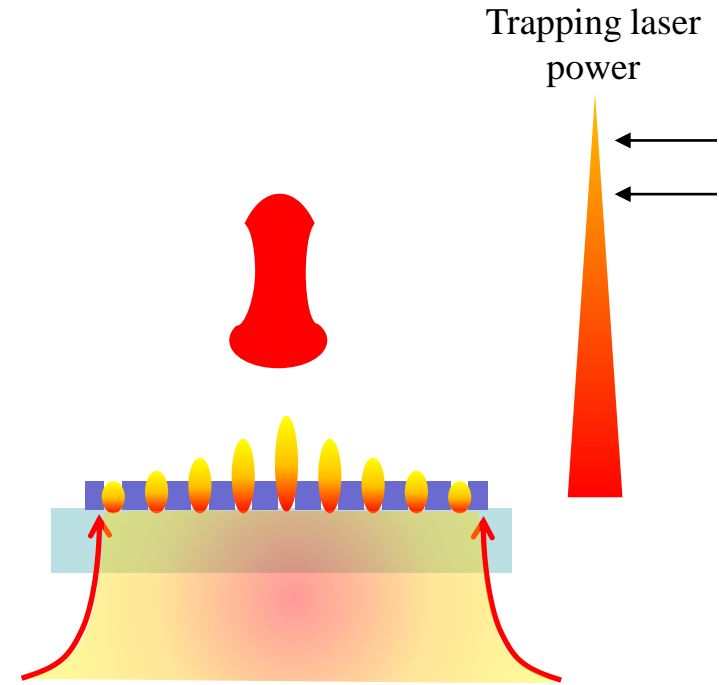
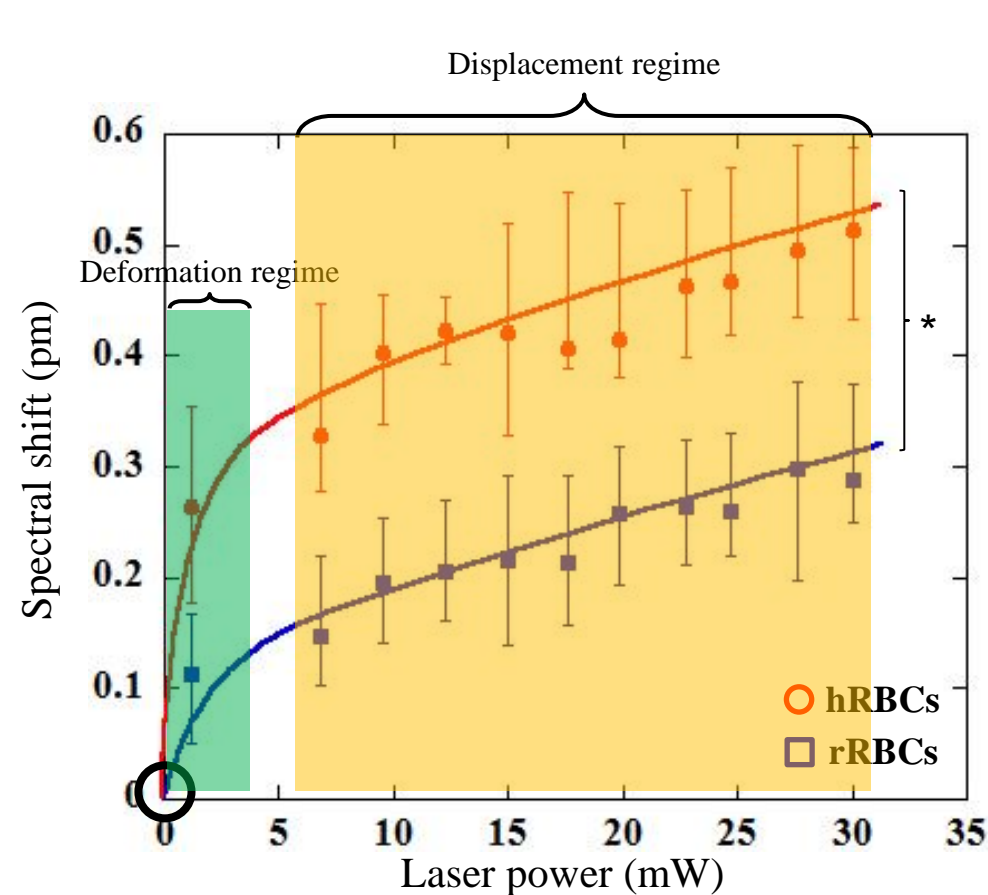


➤ $\lambda_{\text{resonance}}$ varies with :

- optical indice at the PhC surface vicinity,
- distance between object and PhC surface,
- object surface area interacting with Ph mode.

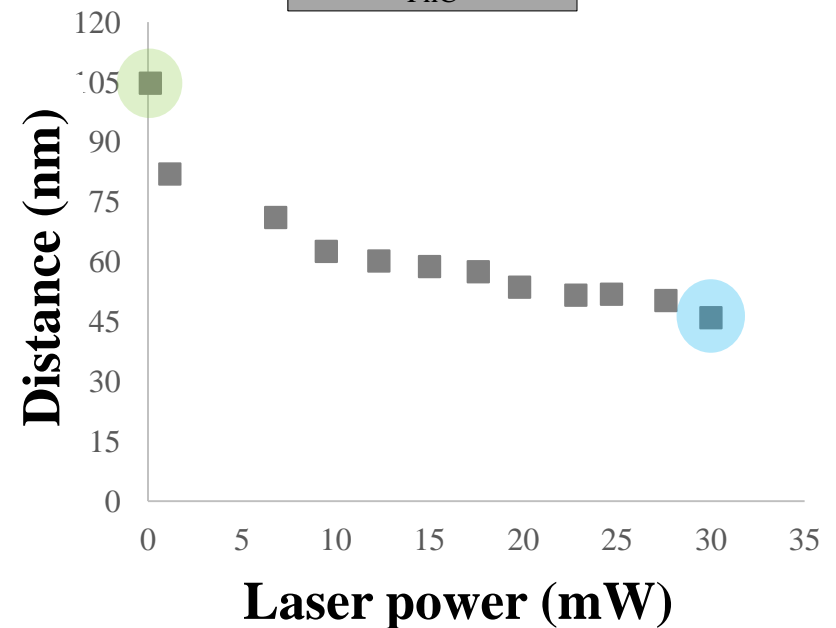
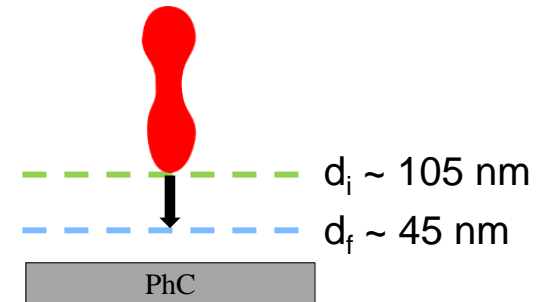
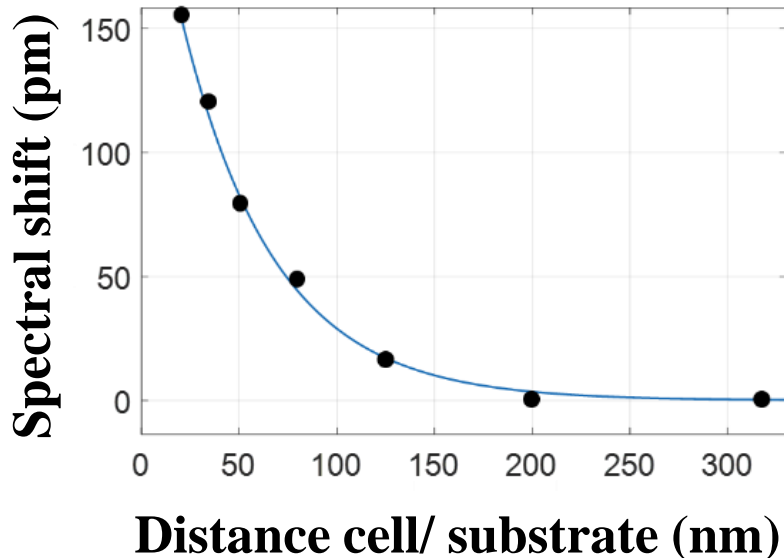
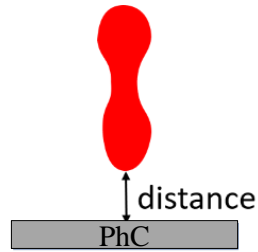
➤ $\Delta\lambda_{1_{\text{hRBC}}} = \Delta\lambda_{1_{\text{rRBC}}} \rightarrow$ no difference in optical indice

➤ **Discrimination possible between hRBCs and rRBCs without imaging**



- In the deformation regime: Combinaison of **displacement + deformation**
- In the displacement regime: Pure **displacement**

Numerical simulations



➤ Approach of the rRBCs of roughly 60 nm

□ Conclusions:

- ✓ We developed a biosensor device able to probe without imaging the deformability of RBCs
- ✓ We demonstrated that $\lambda_{\text{resonance}}$ can be used to detect cell deformation
→ It's a premiere !!
- ✓ We were able to discriminate hRBCs from rRBCs



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