台灣計算力學學會
專題演講 暨 會員交流活動

NTU, Taipei | March 28, 2023

Continuum Mechanics of Extreme Response Analysis and Measurement Noise Reduction for Stokes flow under Uncertainty

---

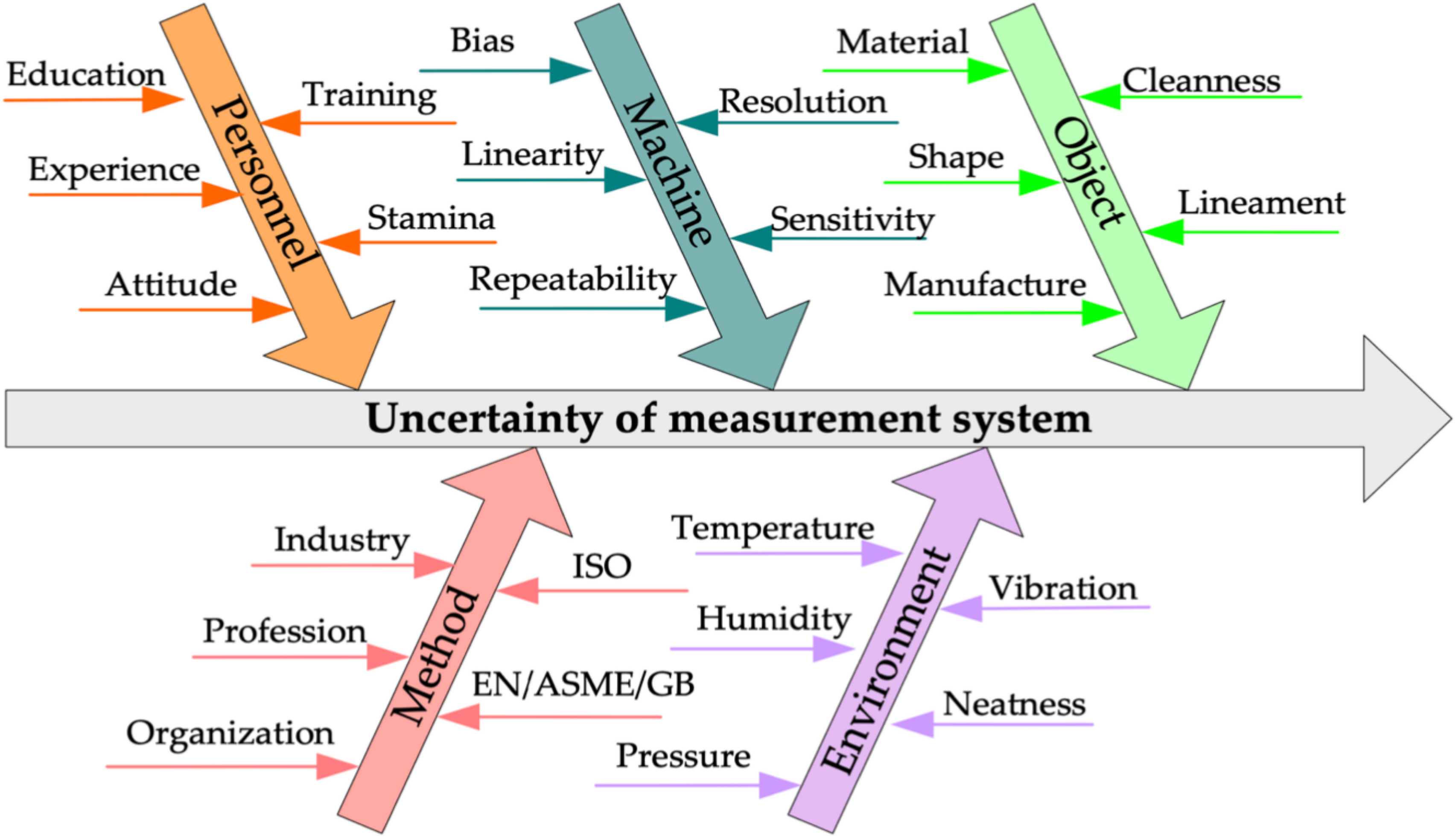
考慮不確定性於斯托克斯流場域
極值反應解析與量測數據降噪之連體力學研究

Po-Ting Lin (林柏廷), Qun-Yi Zhou (周峮毅), Chien-Kai Wang* (王建凱)

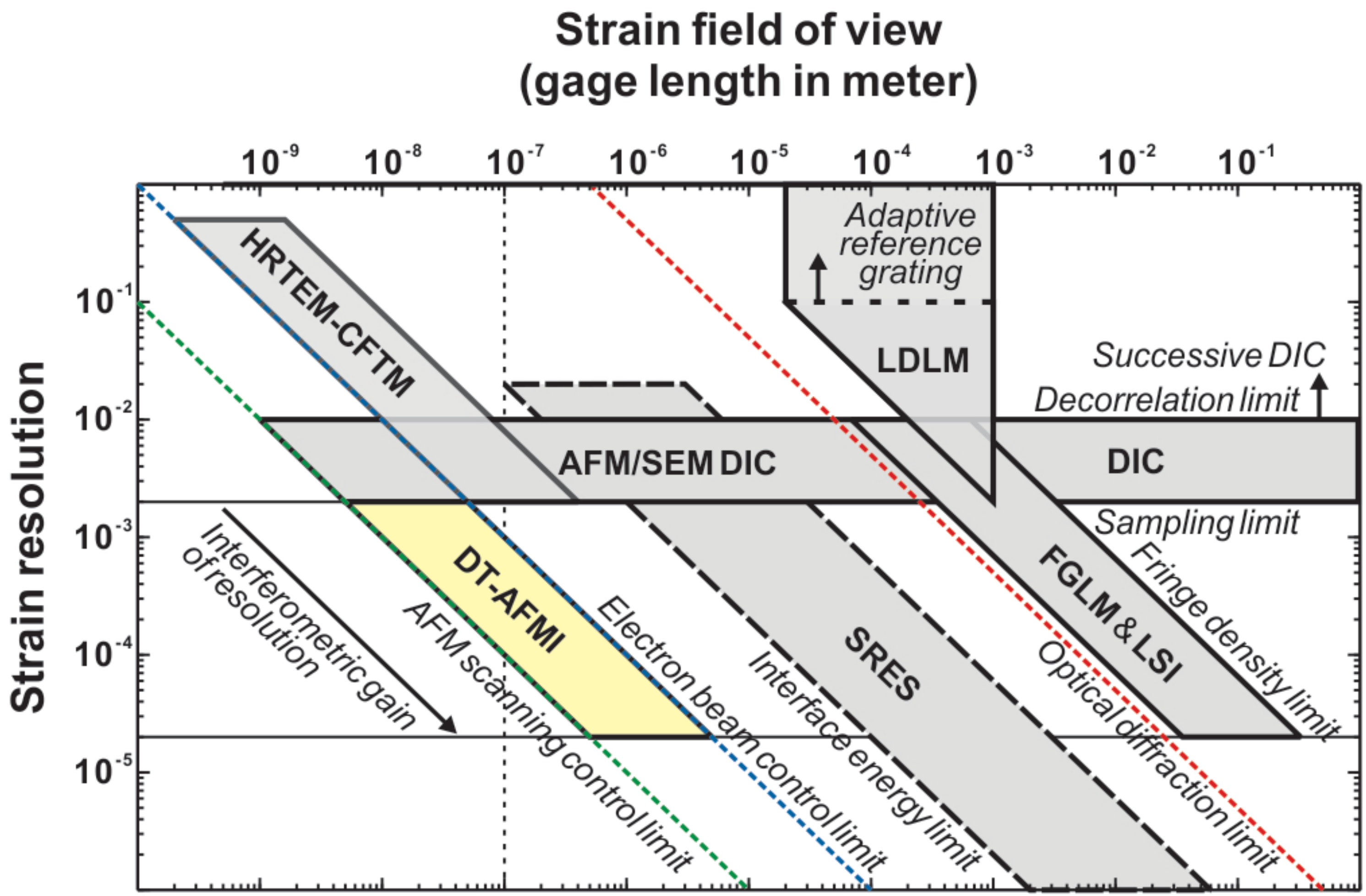
國立臺灣大學 機械工程學系

Contents

Introduction – Uncertainty of measurement system



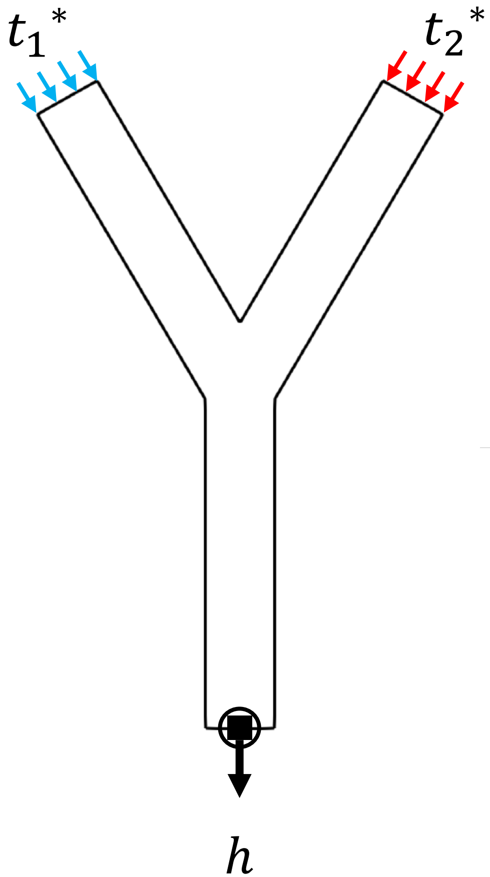
Deformation measurement map



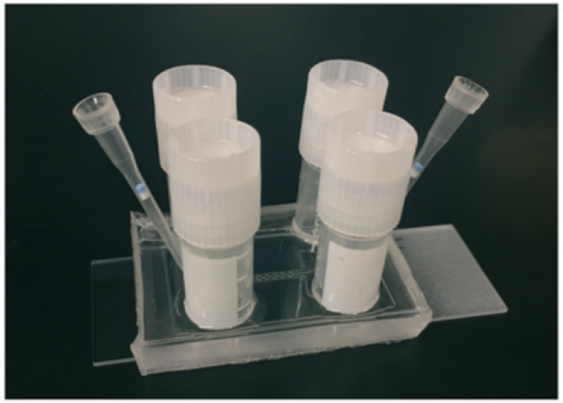
- **Strain resolution of measurements can be effectively gained from interferometry techniques.**
- **Interferometry utilizes precise lattice grating for deformation measurement with high strain resolution in small observation windows.**

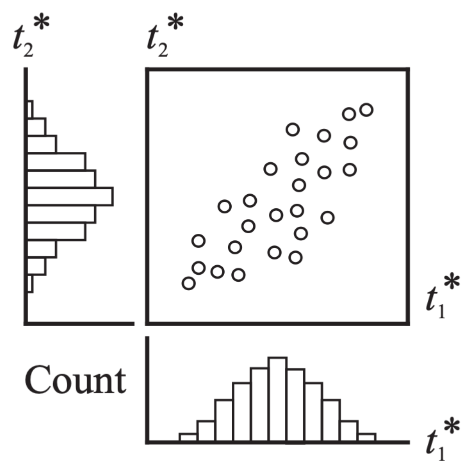
Motivation – Extreme response analysis for Stokes flow

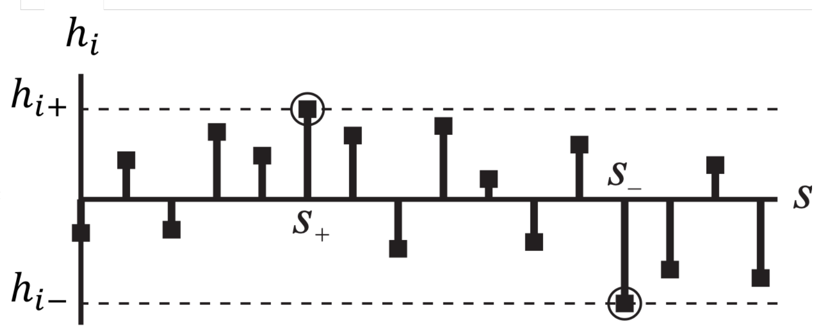
Microfluidic system



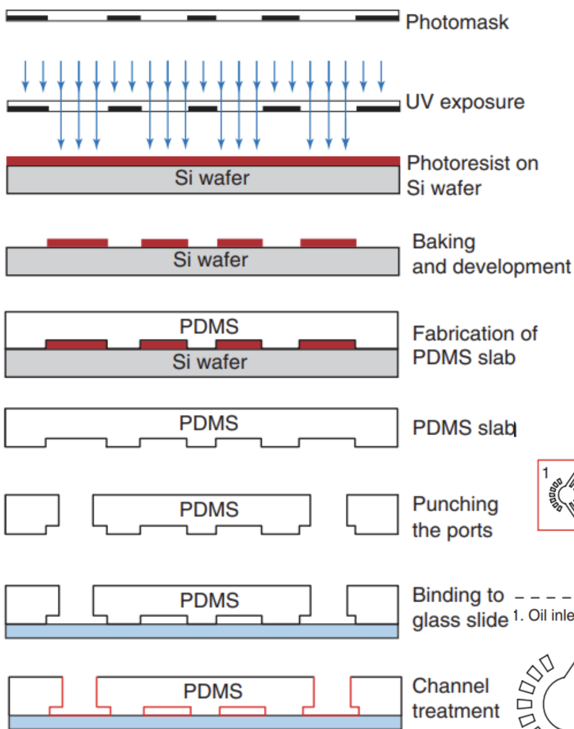
Uncertainty

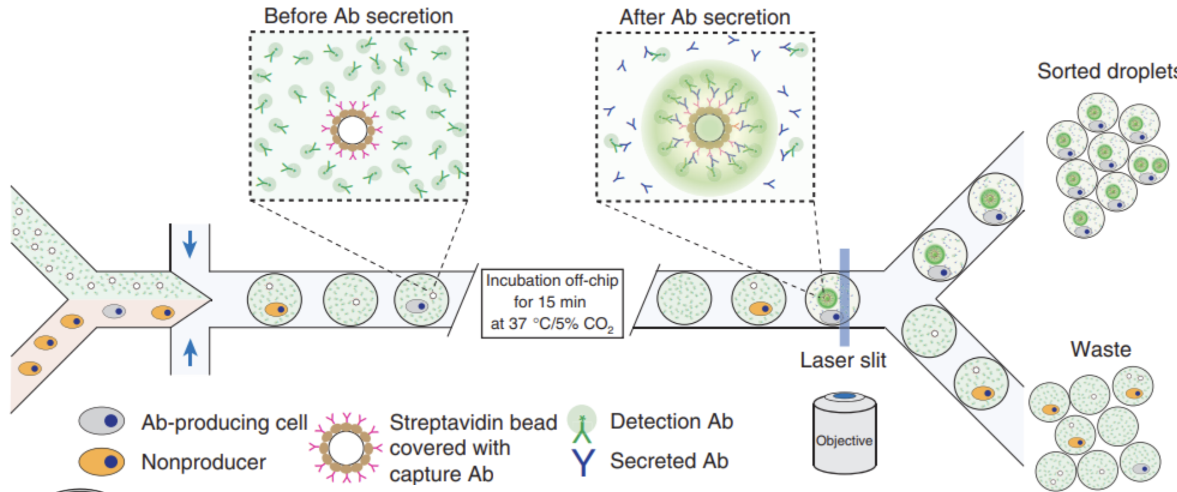


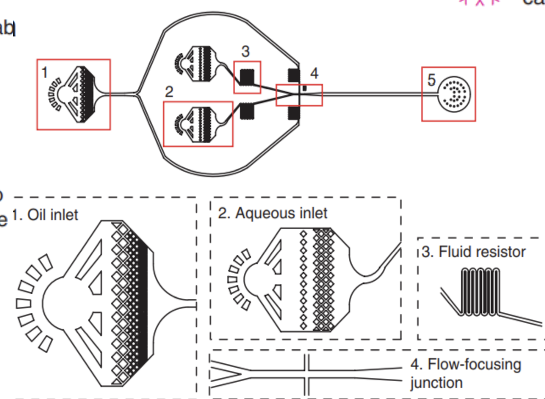


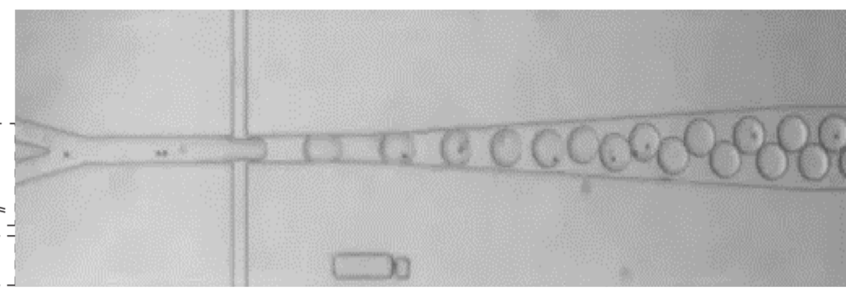


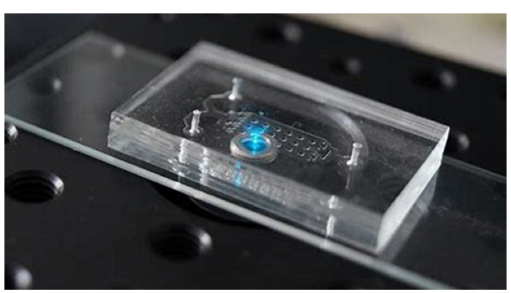
Fluorescence-activated droplet sorting experiment

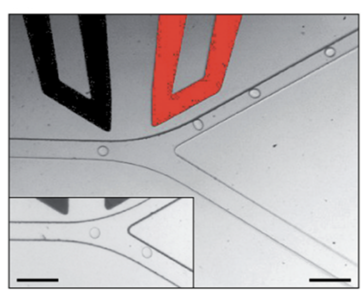


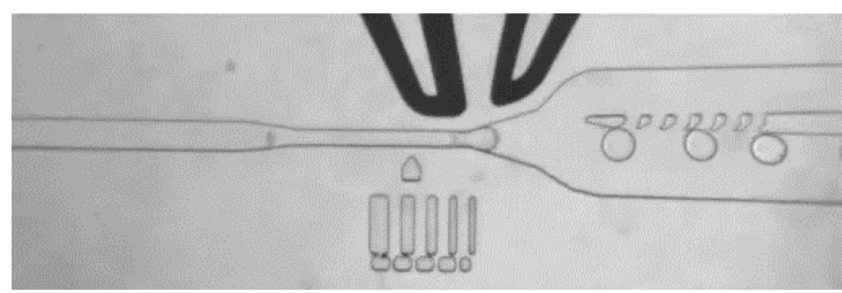






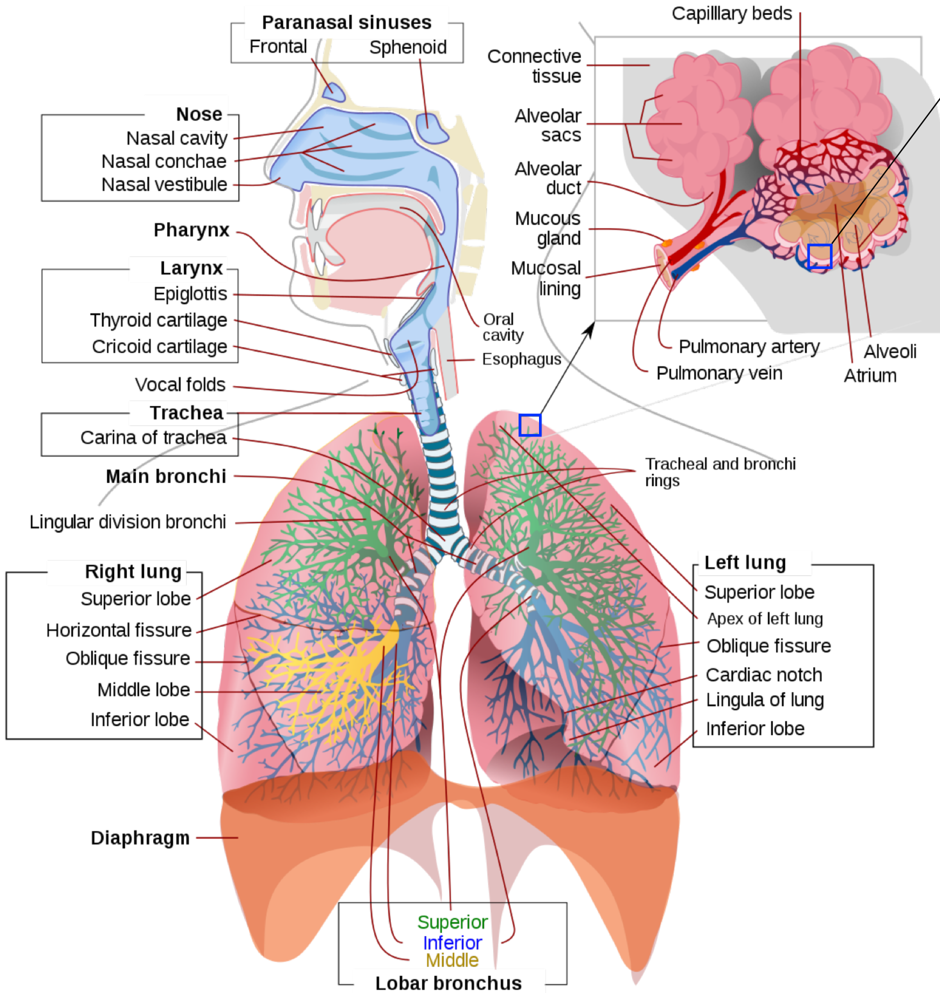


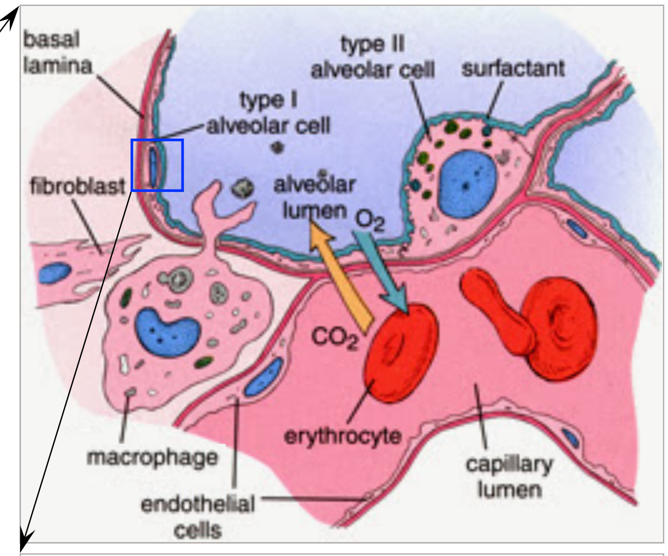


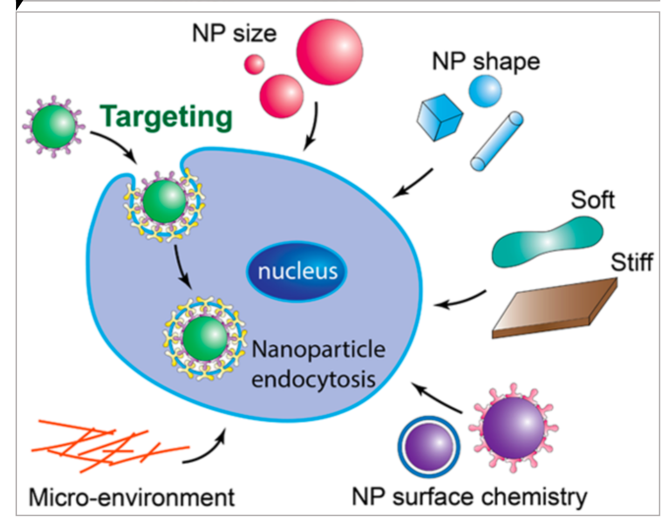


Measurement of oxygen diffusivity of live cell layers

Biological and environmental interactions



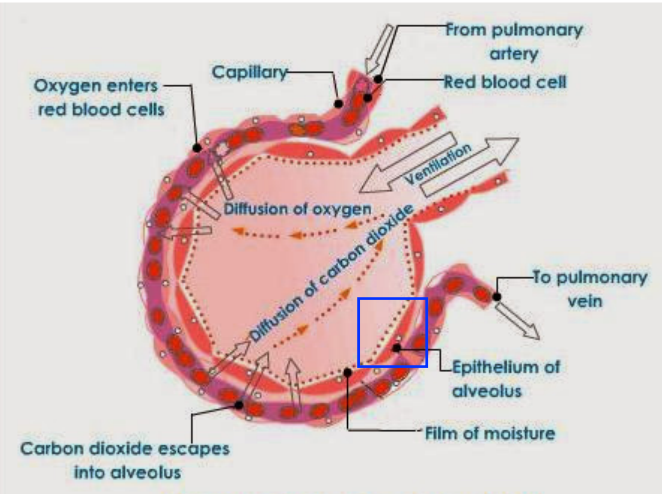


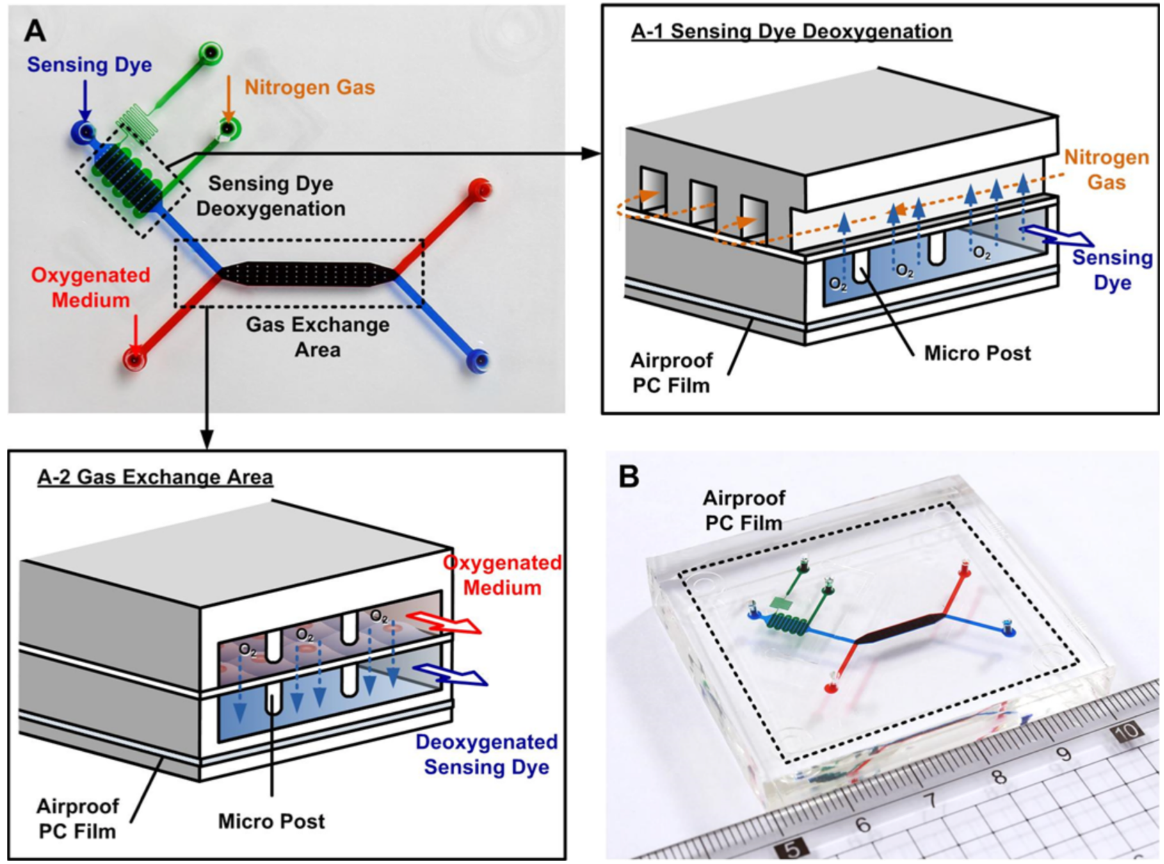


- Different studies have been reported to examine experimental oxygen diffusivity for simple membrane or single-celled organisms.
- However, proper investigation on oxygen transportation through cell layers have not been done.

Measurement of oxygen diffusivity of live cell layers

Biological and environmental interactions





(1) Fick's first law of diffusion

$$J = D\left[\frac{C_A - C(x)}{d}\right]$$

(2) Mass conservation

$$\frac{dC(x)}{dx} + \frac{D}{dhv}\left[C(x) - C_A\right] = 0$$

(3) Oxygen tension profile

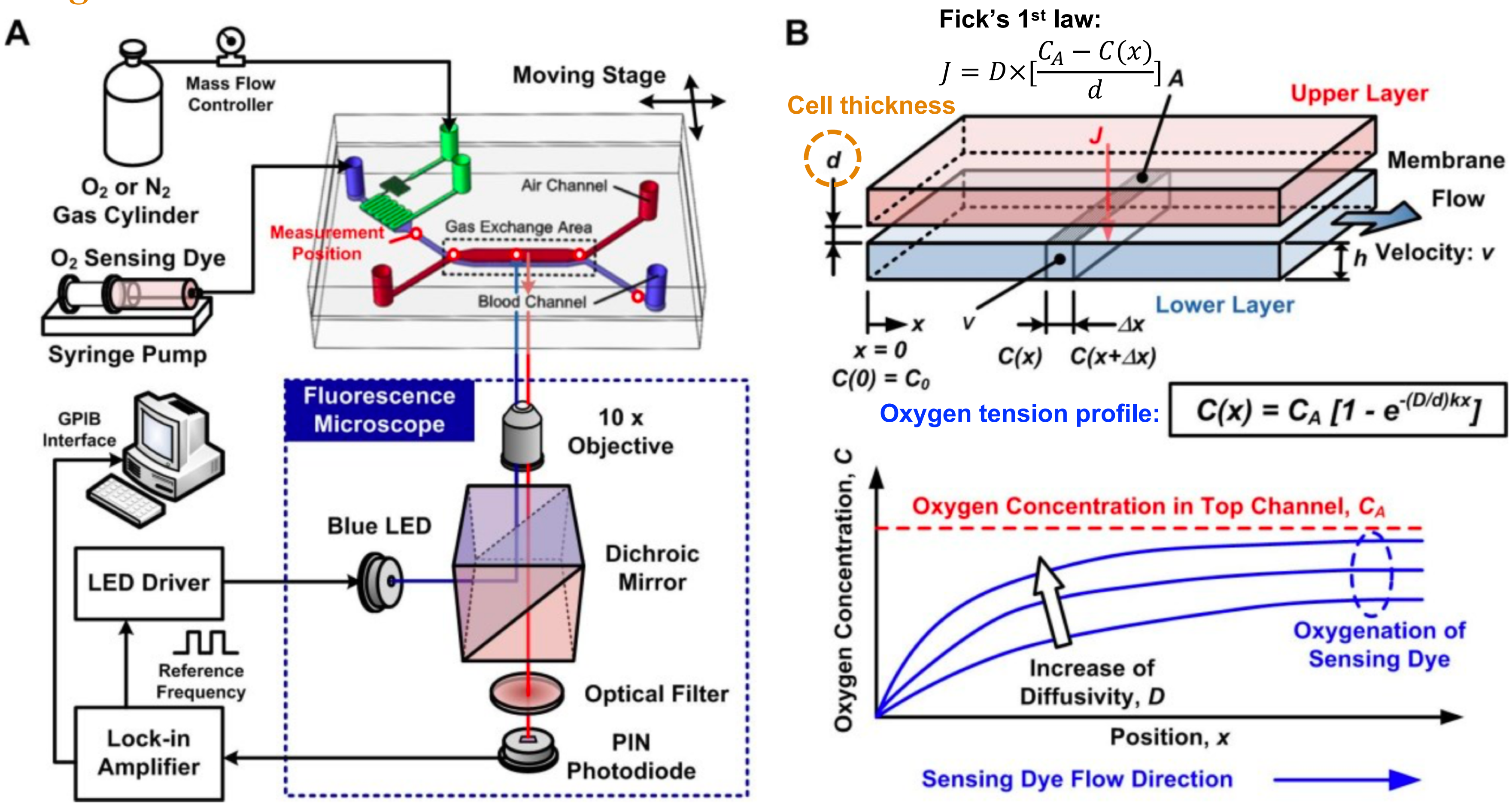
$$C(x) = C_A \times \left[1 - e^{-\left(\frac{D}{dhv}\right)x}\right]$$

- **Effects of environmental matter states (solid, liquid, gas, plasma) on cell uptake**
- **Cell entry pathways of gas diffusion**
- **Some particular cells might accelerate oxygen transportation**

Ref.: 1. *ACS Nano* **9** (9): 8655-8671 (2015); 2. Tung*, Wang*, et al. *Talanta* **236**: 122882 (2022)

Measurement of oxygen diffusivity of live cell layers

Biological and environmental interactions

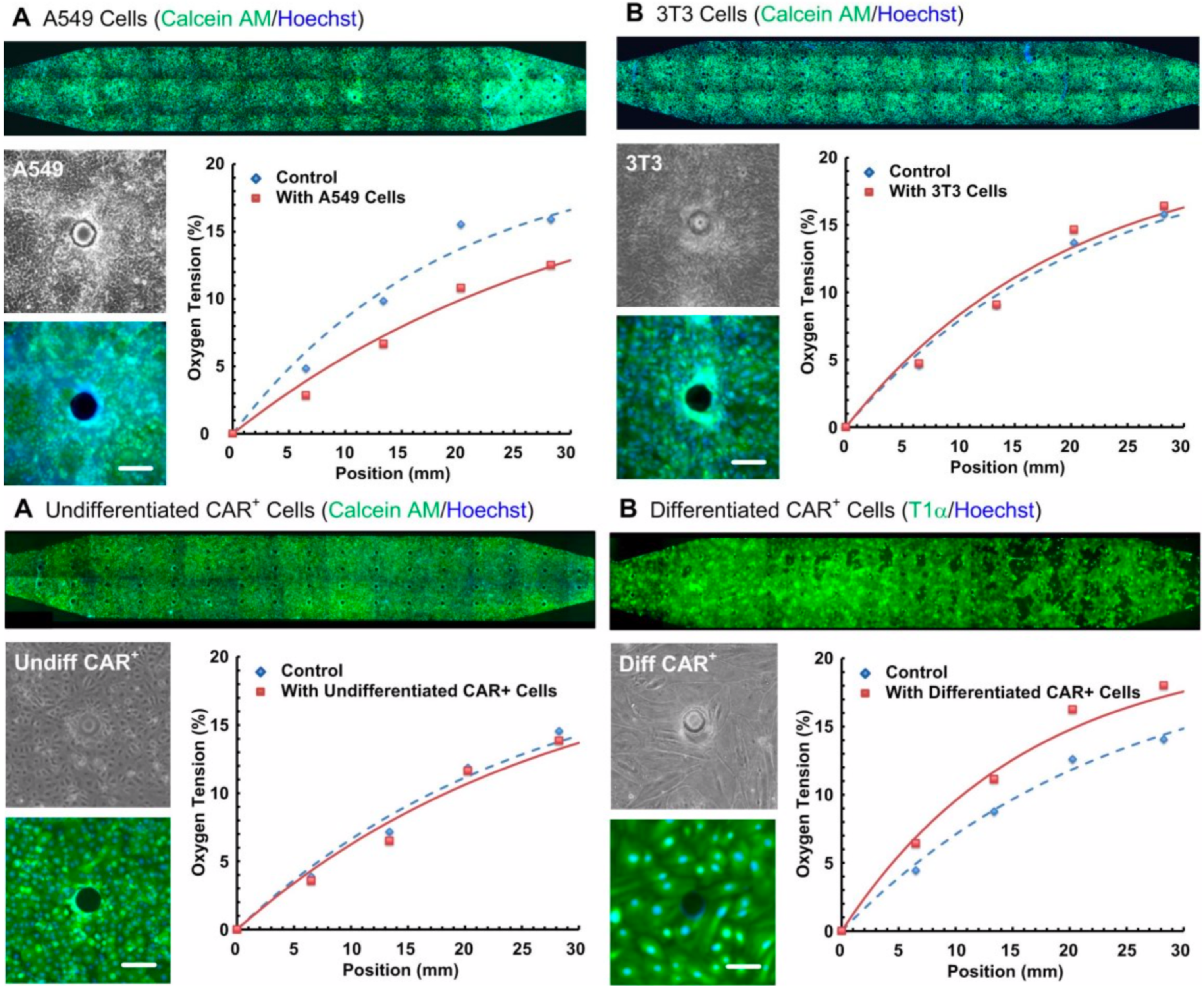


- **Lifetime fluorescence** measurement system for probing **oxygen tensions** in **microfluidic channel**
- **Fluidic actuation** achieved by a **computer-controlled syringe pump**
- **Theoretical model** for estimating **oxygen tension profile** in the bottom microfluidic channel with the **membrane of different oxygen diffusivity**

Ref.: 1. *ACS Nano* **9** (9): 8655-8671 (2015); 2. Tung*, Wang*, et al. *Talanta* **236**: 122882 (2022)

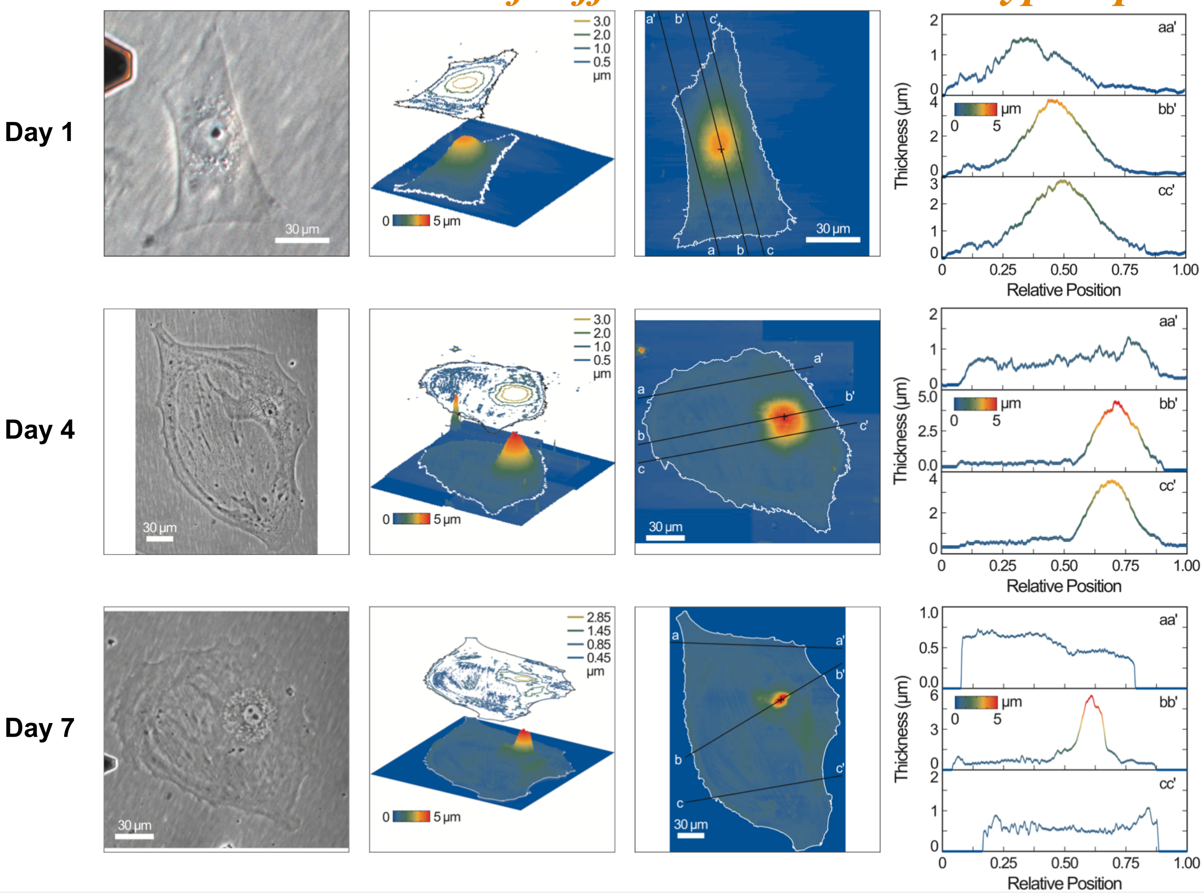
Measurement of oxygen diffusivity of live cell layers

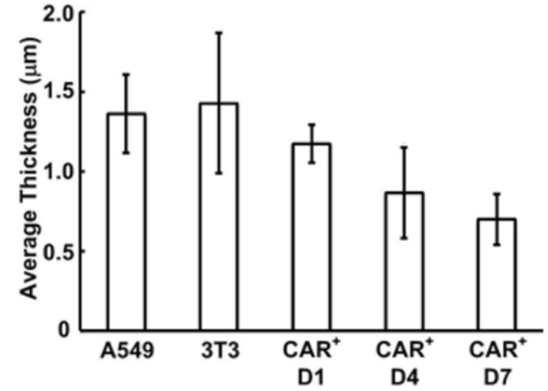
Biological and environmental interactions

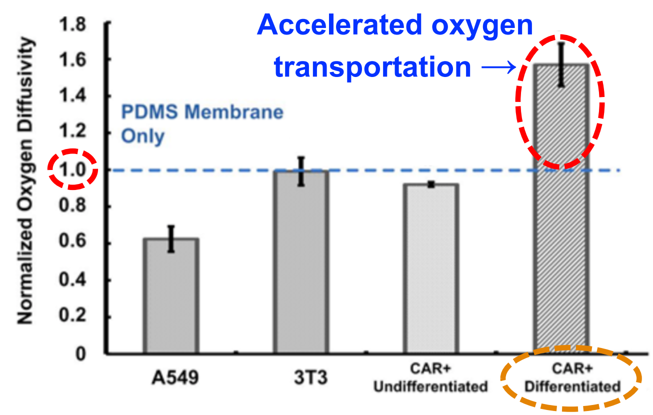


Bio-AFM & oxygen diffusivity of live cell layers

Bio-AFM measurement of differentiated alveolar type-I pneumocytes-like (dAT-I-like)/cells





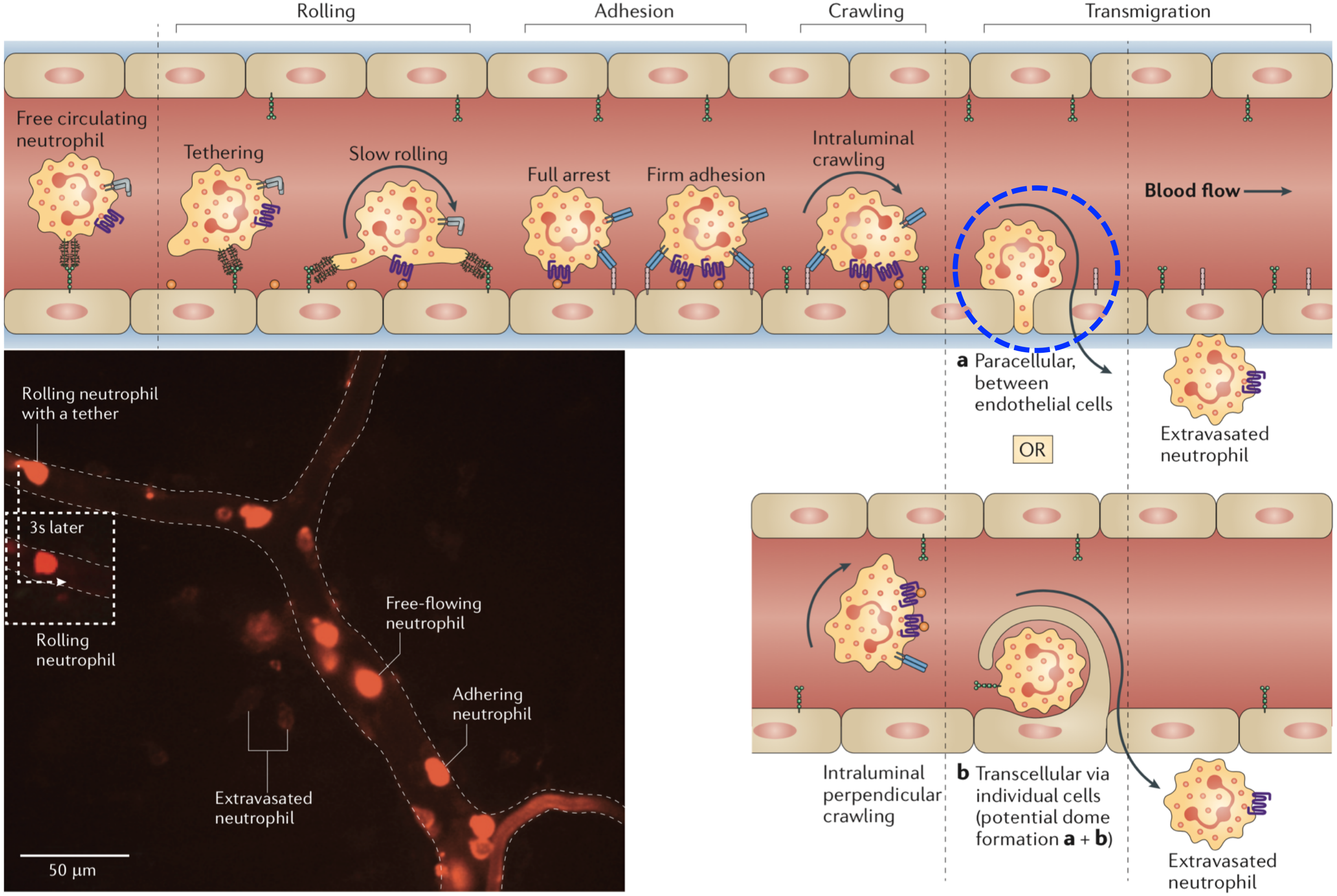


- ▸ **Distinct facilitated oxygen diffusion behavior of the dAT-I-like/cells**
- ▸ **Comparison with A549 cells (human adenocarcinoma originated from alveolar type-II pneumocyte) and 3T3 cells (murine fibroblast)**
- ▸ **Drug testing to seek possible therapeutic strategies to improve oxygenation in patients with pulmonary dysfunction, such as premature infants with bronchopulmonary dysplasia & adults with chronic obstructive pulmonary disease (COPD)**

Ref.: 1. *ACS Nano* **9** (9): 8655-8671 (2015); 2. Tung*, Wang*, et al. *Talanta* **236**: 122882 (2022)

Measurement of in-plane elasticity of live cell layers

Neutrophil recruitment cascade & extravasation

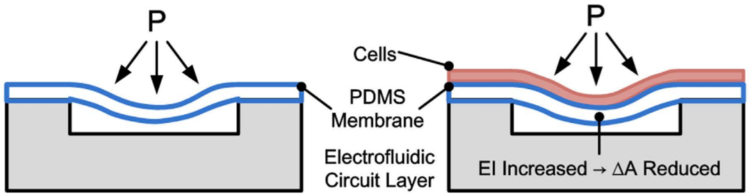


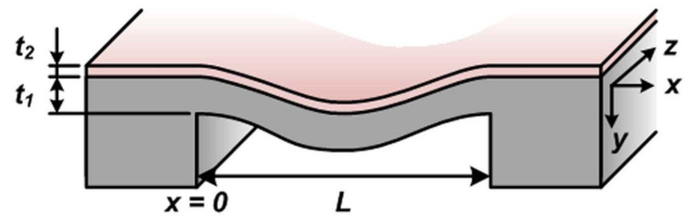
- **Endothelial membrane**: A continuous structure having ECM proteins - collagens & laminins
- **Neutrophils**: Releasing neutrophil **elastase** against ECM protein to **pass through** the membrane
- **Endothelium in-plane elasticity**: Having effects on the **interaction** between **vessel wall surfaces** and bloodstream carrying **white** and **red blood cells** in hemodynamic systems

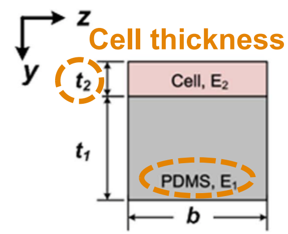
Ref.: 1. *Nature Medicine* **17**: 1381-1390 (2011); 2. *Nature Reviews Immunology* **13**: 159–175 (2013).

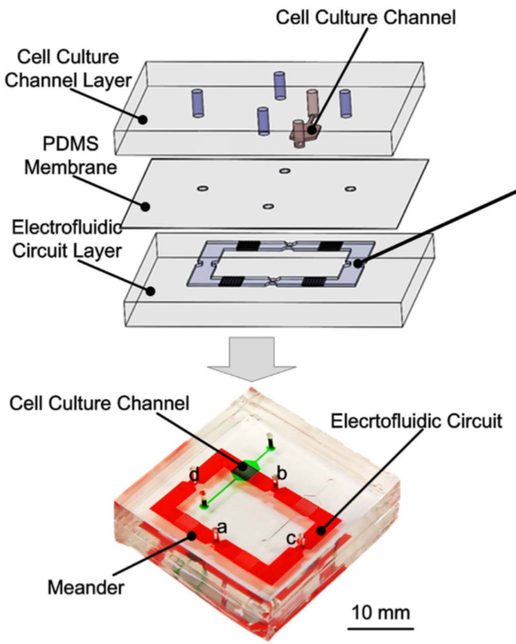
Measurement of in-plane elasticity of live cell layers

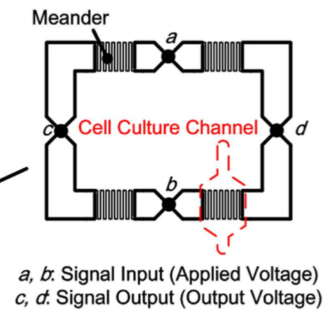
Microfluidic device development & mechanical model derivation

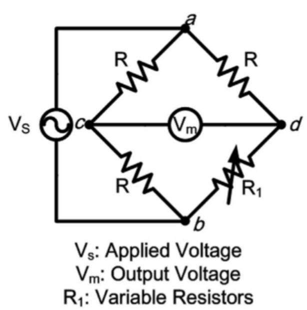






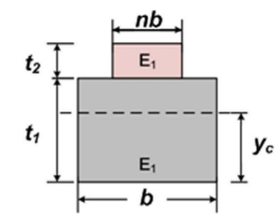






(1) Euler–Bernoulli beam theory

$$u_y(x) = \frac{P}{EI}\left(\frac{x^4}{24} - \frac{Lx^3}{12} + \frac{L^2x^2}{24}\right)$$



(2) Kirchhoff's s law on a Wheatstone bridge

$$V_m = \left[\frac{1}{2} - \frac{R}{(R+\Delta R_1)+R}\right] V_S \approx \left(\frac{\Delta R_1}{4R}\right) V_S \quad (\Delta R_1 \ll R)$$

(3) Sensitivity of output voltage variation to applied P

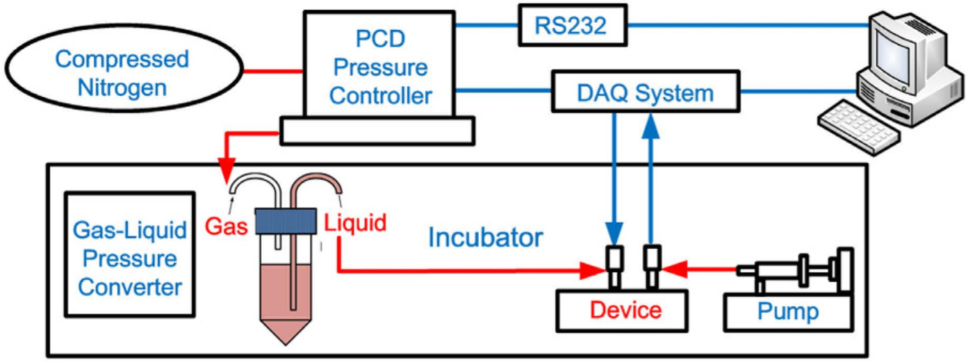
$$S_c \equiv \frac{\Delta V_m}{\Delta P} = \frac{L^4 V_s}{2880\, H\, E_1\, I(n)} \quad \left(n = \frac{E_2}{E_1}\right)$$

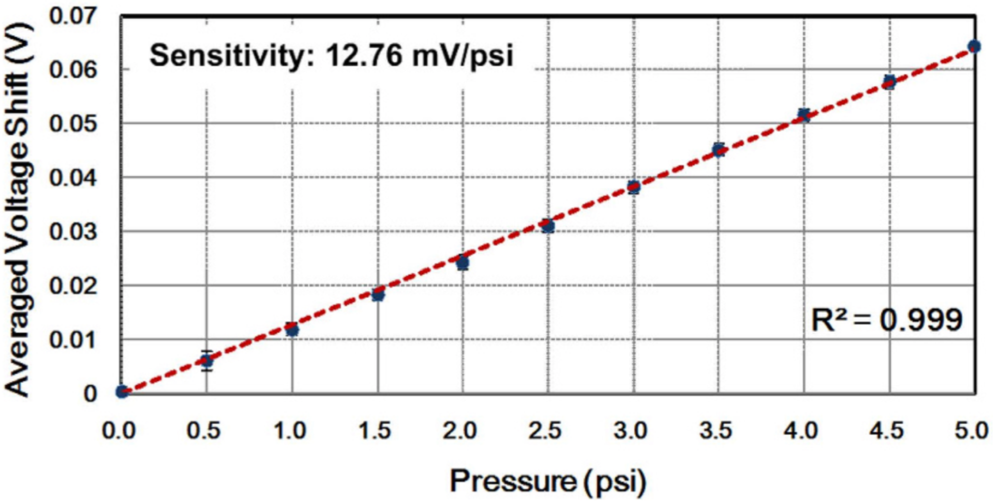
- ▸ Pressure sensor embedded microfluidic device: Measuring live cell layer in-plane elasticity
- ▸ Bio-AFM: Providing data of cell thickness and the elastic modulus of PDMS membrane
- ▸ Timoshenko beam theory needs to be utilized for the device with thick PDMS membrane

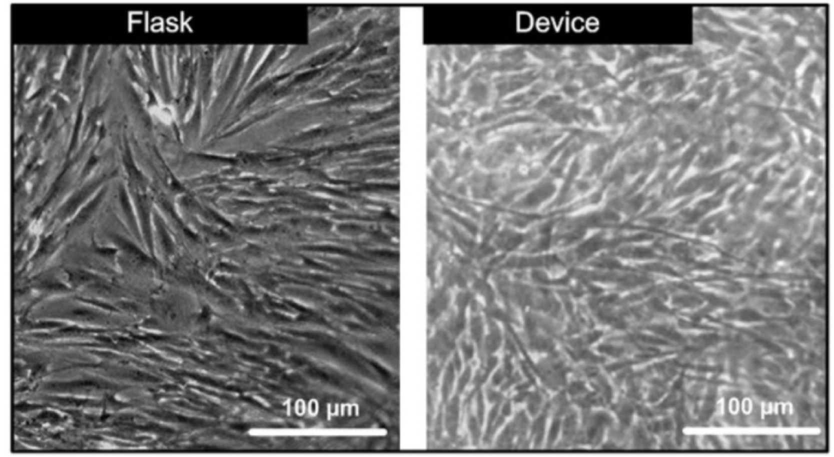
Ref.: 1. Lin*, Wang* et al. *Scientific Reports* **6**: 36425 (2016); 2. Hsu, Wang, et al. *Small* **17**: 2006091 (2021)

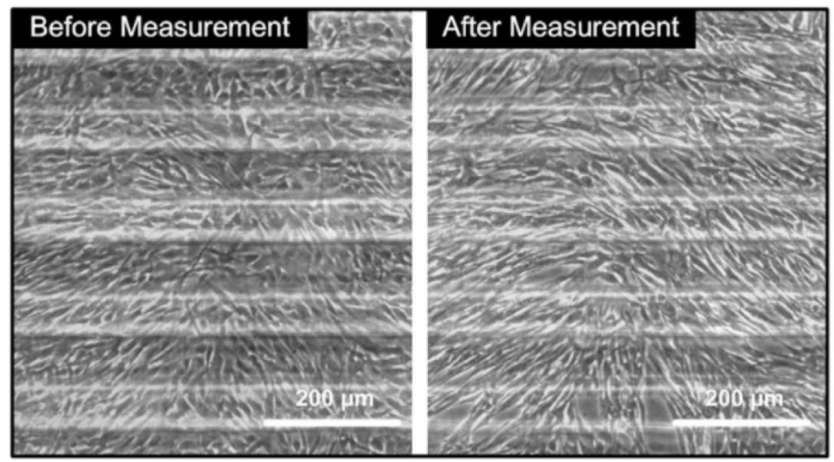
Measurement of in-plane elasticity of live cell layers

Microfluidic device development & mechanical model derivation







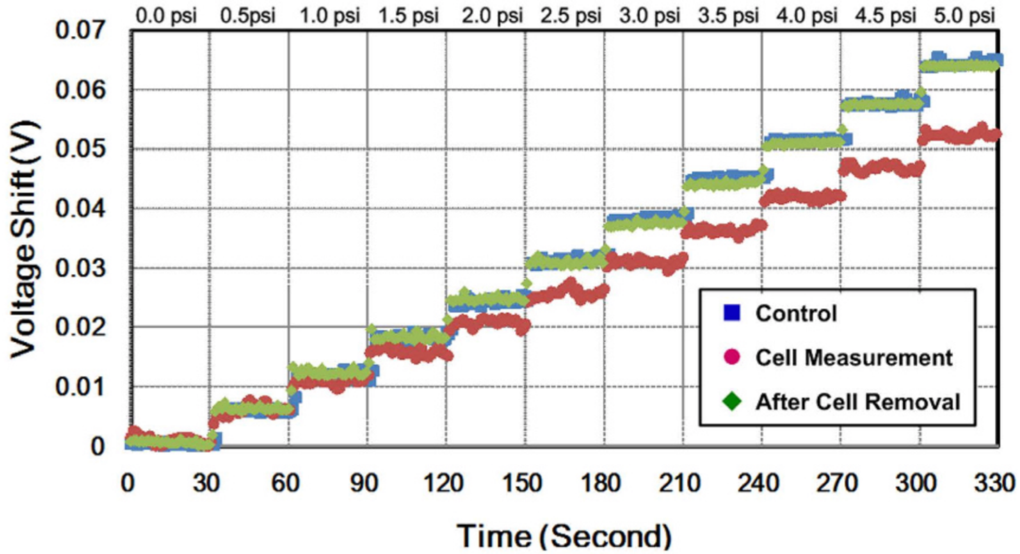


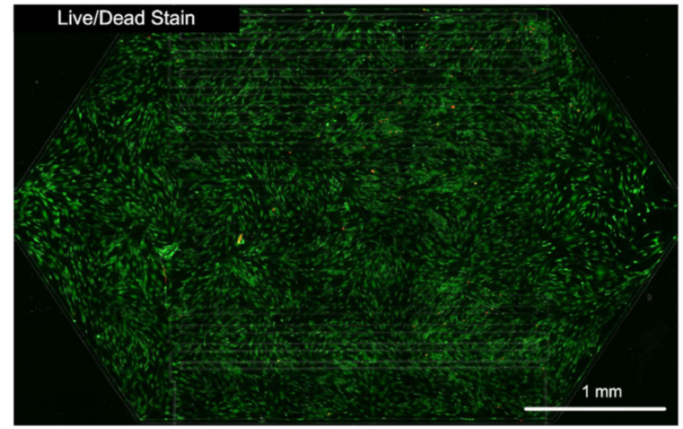
- **Experimental setup for the in-plane elasticity of cell layer measurement**
- **Pressure sensor calibration: Raw data of output voltage shifts from the pressure sensor under various applied pressures (0 ~ 5 psi)**
- **Sensitivity of output voltage variation to applied P is obtained by Linear regression of the results.**

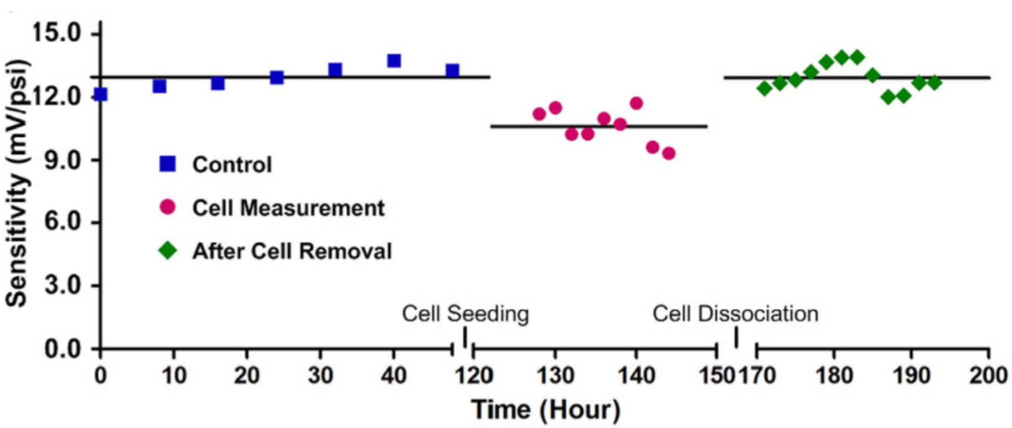
Ref.: 1. Lin*, Wang* et al. *Scientific Reports* **6**: 36425 (2016); 2. Hsu, Wang, et al. *Small* **17**: 2006091 (2021)

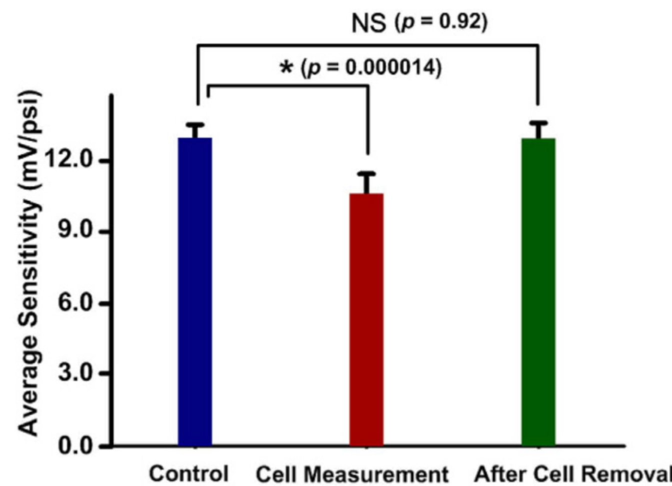
Measurement of in-plane elasticity of live cell layers

Microfluidic device development & mechanical model derivation







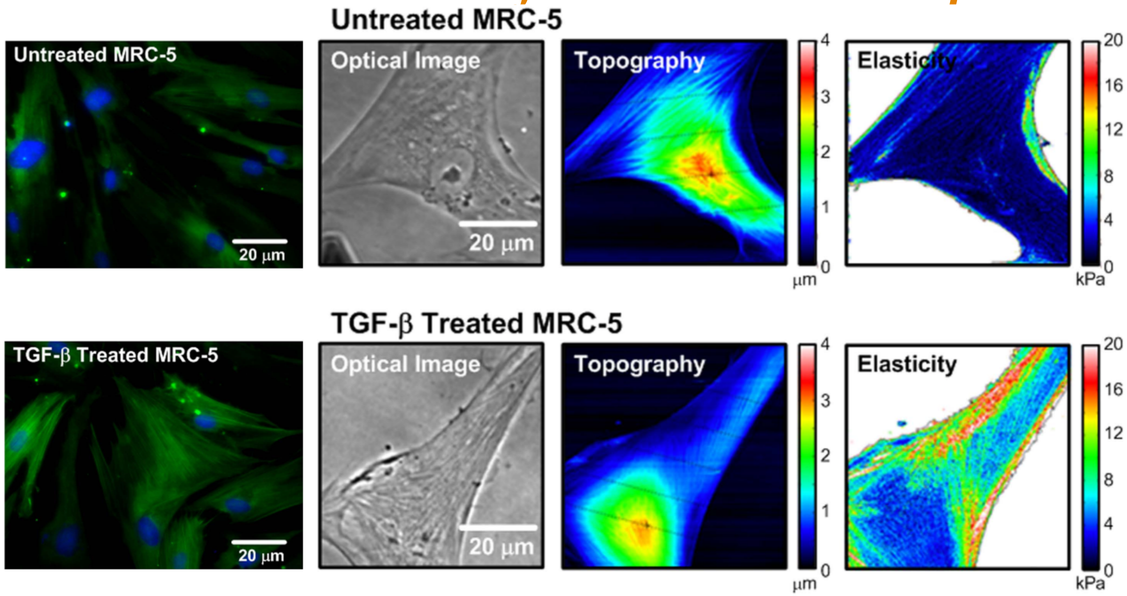


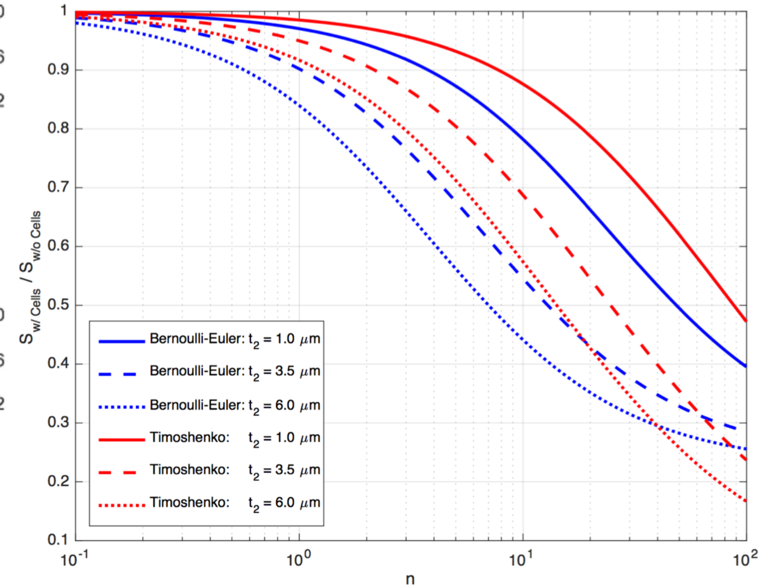
- **Raw data of output voltage shifts from the pressure sensor under various applied pressures.**
- **Sensitivity variation during a set of control experiment, cell measurement, and after cell removal.**
- **Comparison of the averaged sensitivities under the three experimental conditions.**

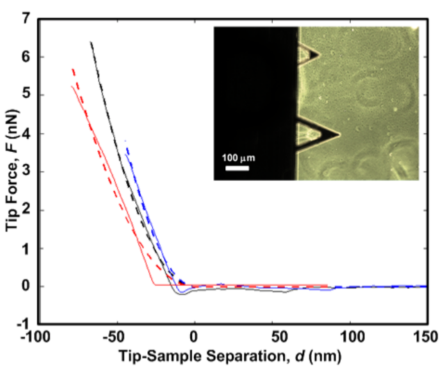
Ref.: 1. Lin*, Wang* et al. *Scientific Reports* **6**: 36425 (2016); 2. Hsu, Wang, et al. *Small* **17**: 2006091 (2021)

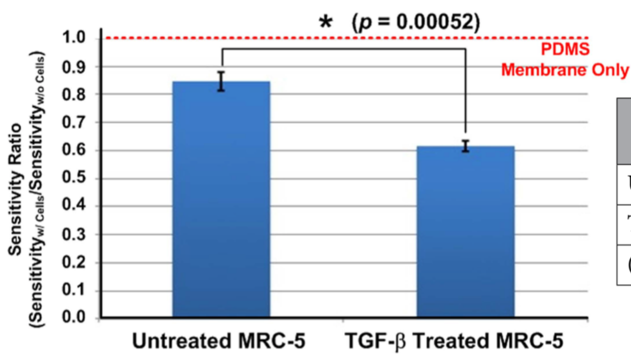
Bio-AFM & in-plane elasticity of live cell layers

Bio-AFM measurement of untreated and TGF-β treated MRC-5 cells







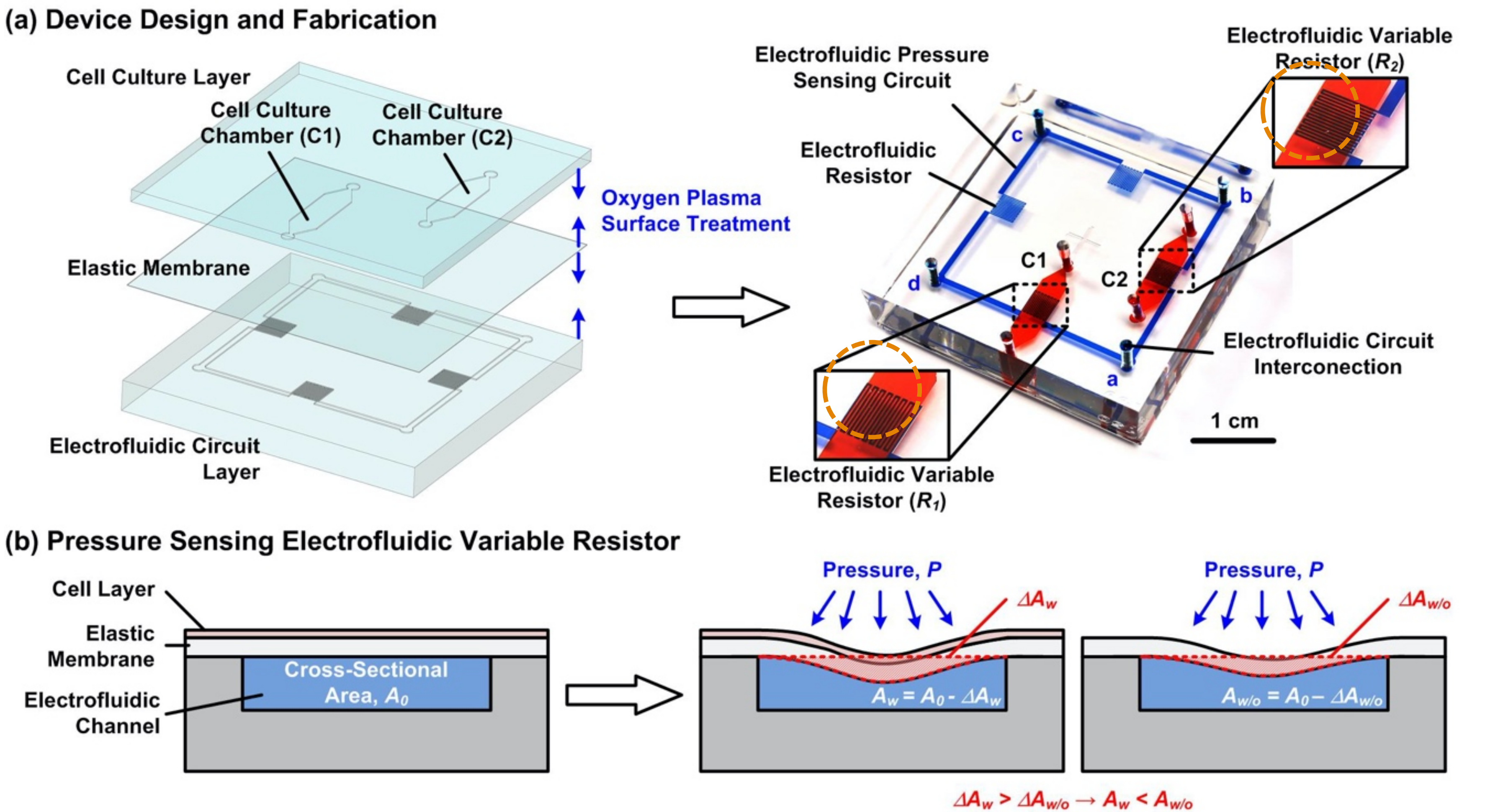


	In-Plane Elasticity by Microfluidic Device	AFM
Untreated MRC-5 (A)	6.38 ± 0.22 MPa	4.00 ± 1.34 kPa
TGF-β Treated MRC-5 (B)	33.78 ± 0.65 MPa	9.46 ± 0.71 kPa
(B)-(A)/(A)	429.3%	136.2%

- Young's modulus measured in normal direction: Cell membrane elasticity & enclosed cytoplasm
- Young's modulus measured in in-plane direction: Cell elasticity of cytoskeleton including microfilaments, intermediate filaments & microtubules
- Elasticity anisotropy of MRC-5 cells: In-plane elasticity directly affects physiological activities of vasodilation and lung expansion due to physically transformation (fibroblast to myofibroblast)

Measurement of anisotropic elasticity of live cell layers

Microfluidic device development & mechanical model derivation



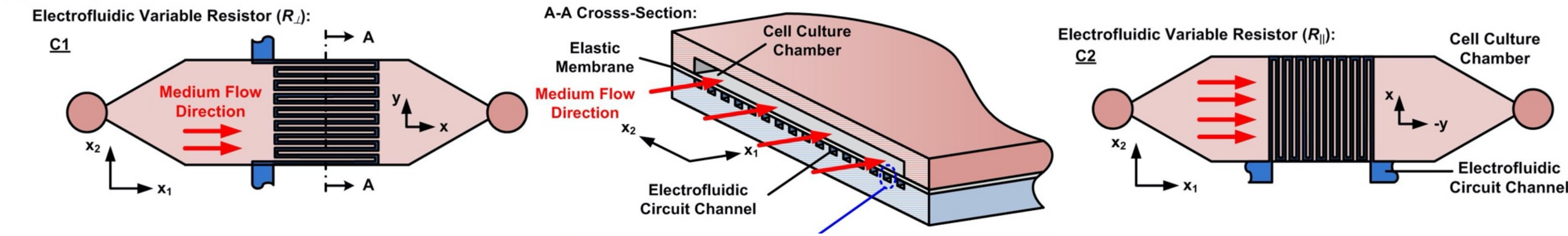
- A **microfluidic device** with the embedded electrofluidic pressure sensors for **measuring anisotropic elasticity of endothelial cells**
- **Operation principles of the microfluidic pressure sensor for the cell elasticity characterization**

Ref.: Ko*, Wang* et al. *Acta Biomaterialia* **145**: 316-328 (2022)

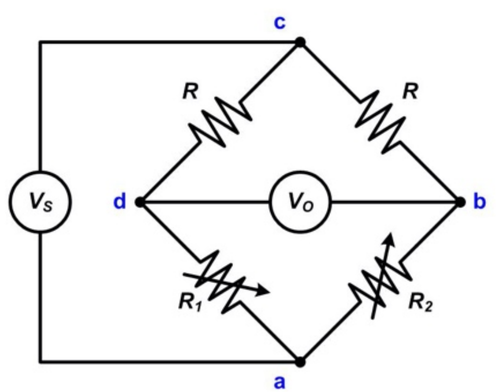
Measurement of anisotropic elasticity of live cell layers

Microfluidic device development & mechanical model derivation

(c) Arrangement of Electrofluidic Variable Resistors

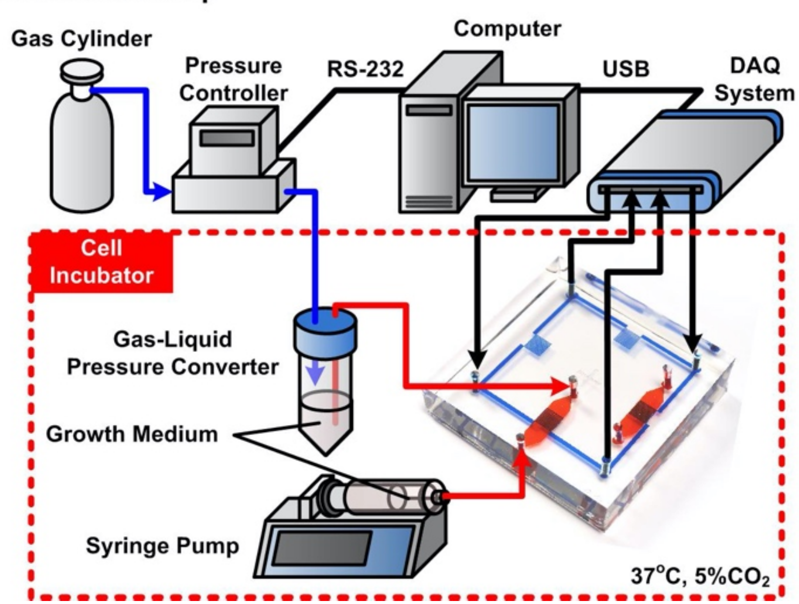


(d) Equivalent Electrical Circuit



V_s: Voltage source
V_o: Voltage output
R_1, R_2: Pressure Sensing Variable Resistors
R: Constant Resistors

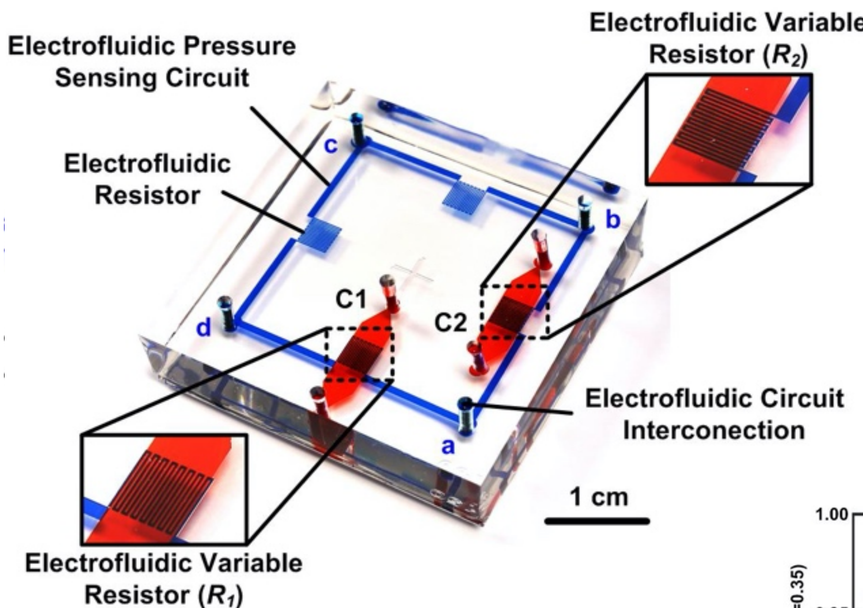
(e) Experimental Setup

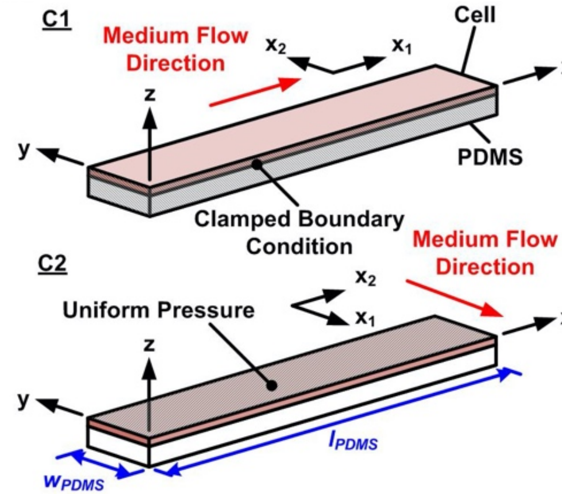


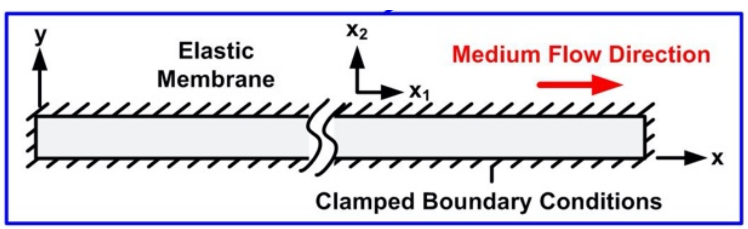
- Arrangement of the pressure sensors to measure the transverse cell elasticities
- Diagram of the experimental setup for the elasticity measurement

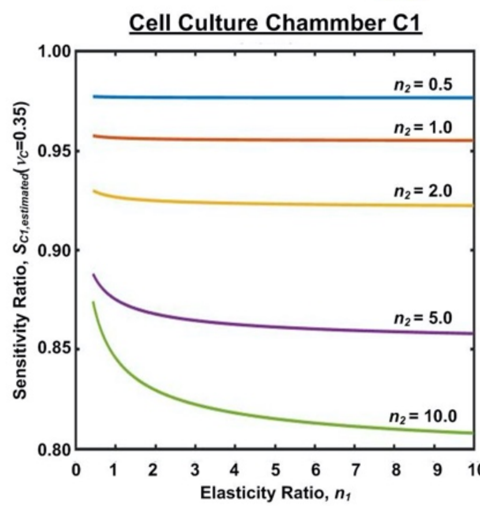
Measurement of in-plane elasticity of live cell layers

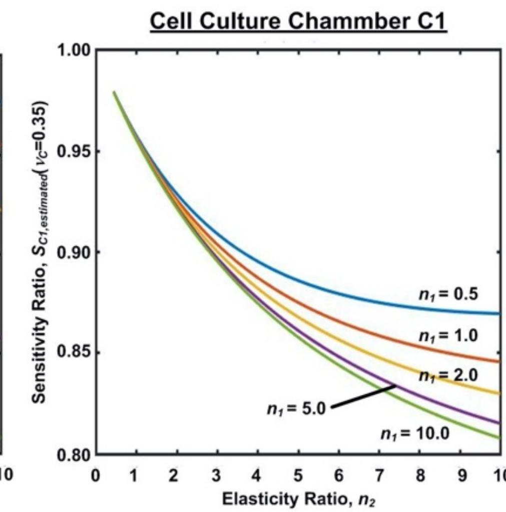
Microfluidic device development & mechanical model derivation









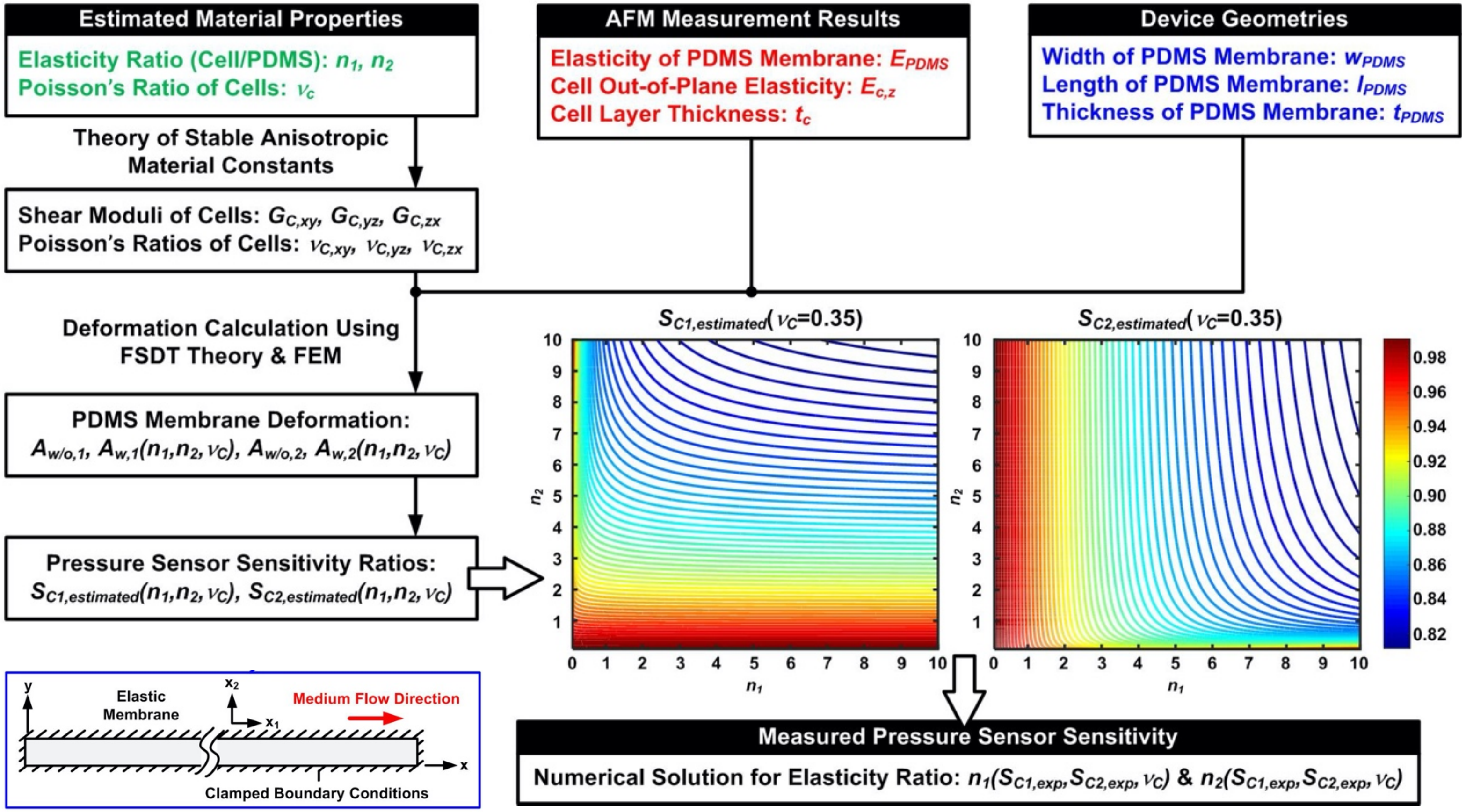


- The theoretical mechanics model constructed for the cell elasticity estimation.
- The theoretically derived results for the sensitivity ratios under various elasticity ratio combinations for the cell culture C1.

Measurement of in-plane elasticity of live cell layers

Microfluidic device development & mechanical model derivation

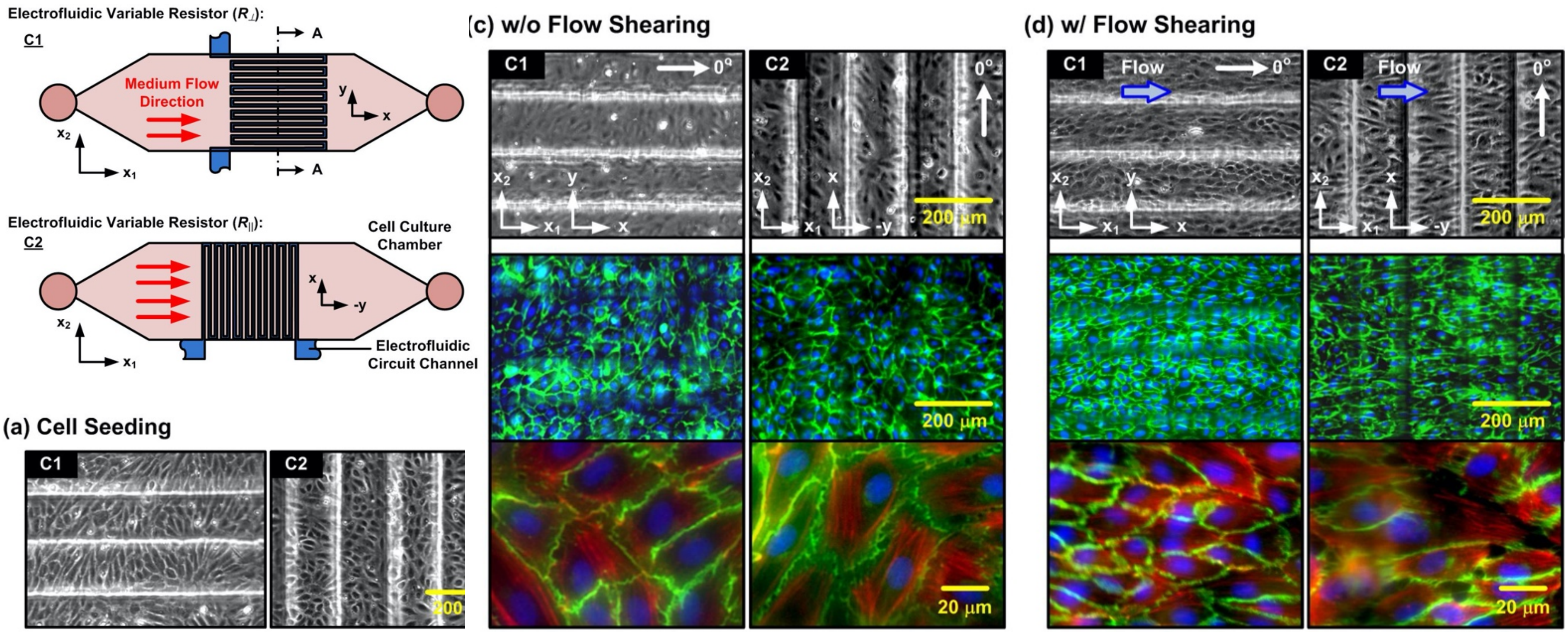
Material Property Estimation Process



- **The flowchart of the cell transverse elasticity estimation process taking advantage of the experimental data obtained in AFM analysis and pressure sensor-embedded microfluidic device measurement results.**
- **The elasticity calculation process is constructed based on the FSDT theory and FEM analysis.**

Measurement of in-plane elasticity of live cell layers

Microfluidic device development & mechanical model derivation

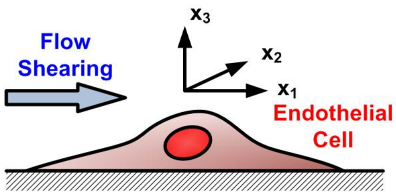


- The brightfield microscopic images of the HUVECs seeded in the microfluidic device after the cell seeding and attachment.
- The brightfield and fluorescence images of the HUVECs which are stained: blue for nuclei, green for VE-cadherin, and red for F-actin.

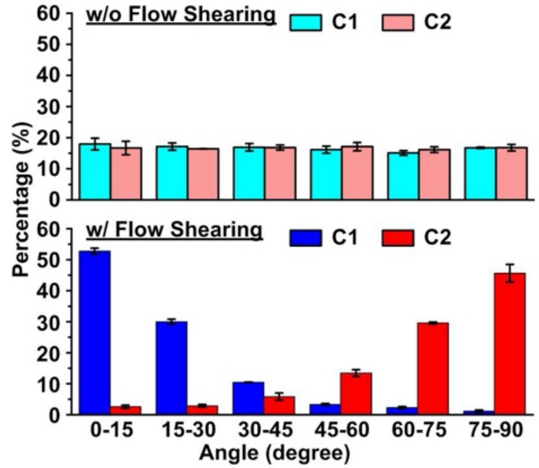
Measurement of in-plane elasticity of live cell layers

Microfluidic device development & mechanical model derivation

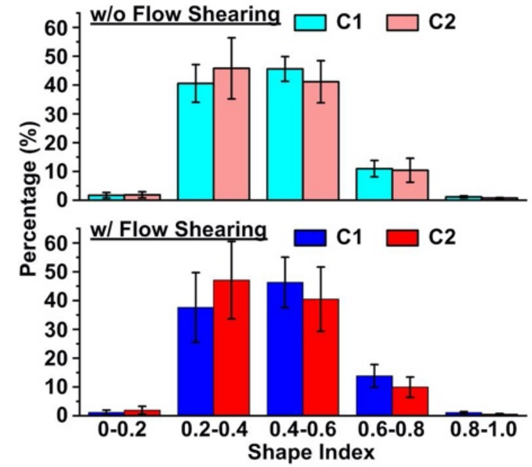
(c) Elasticity Comparison



(e) Cell Alignment

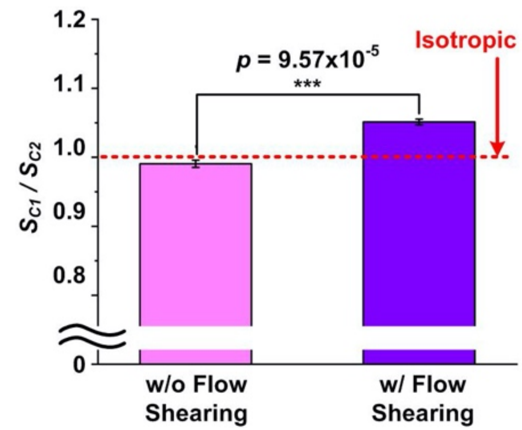


(f) Cell Morphology



$$\text{Sensitivity Ratio } (S) = \frac{\text{Sensitivity (w/ cells)}}{\text{Sensitivity (w/o cells)}}$$

	w/o Flow Shearing			w/ Flow Shearing		
	S_{C1}	S_{C2}	S_{C1} / S_{C2}	S_{C1}	S_{C2}	S_{C1} / S_{C2}
Experiment 1	0.886	0.889	0.997	0.895	0.848	1.055
Experiment 2	0.904	0.913	0.990	0.852	0.814	1.047
Experiment 3	0.905	0.918	0.986	0.878	0.835	1.051
Mean	0.898	0.907	0.991	0.875	0.832	1.051
SEM	6.17×10^{-3}	8.95×10^{-3}	3.14×10^{-3}	1.25×10^{-2}	9.91×10^{-3}	2.53×10^{-3}



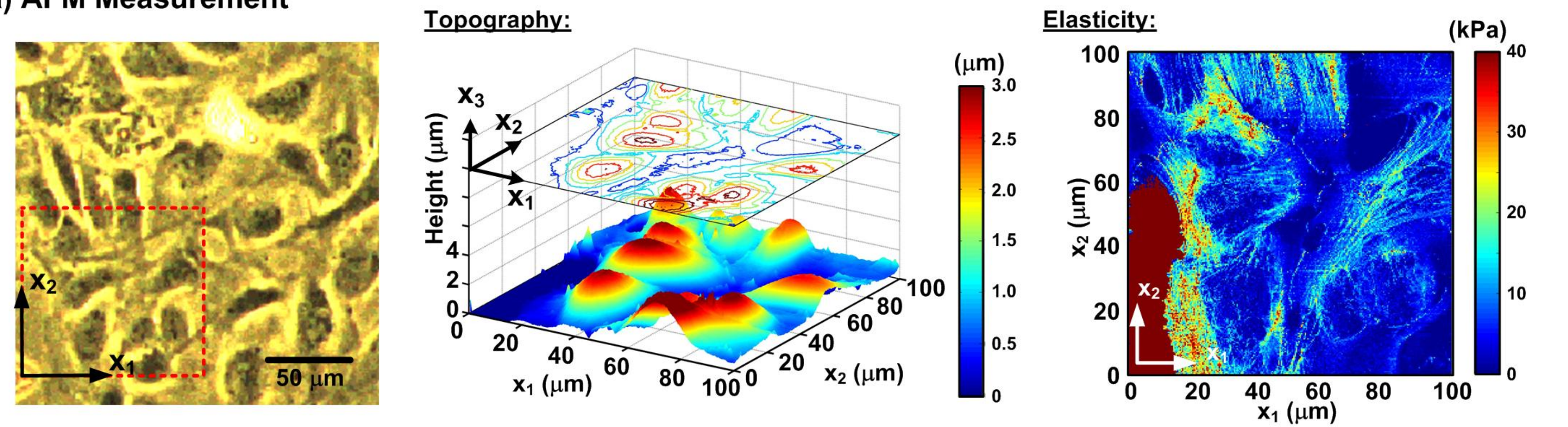
- **Cell alignment and morphology analysis results from the microscopic images. (The flow direction is defined as 0 degree.)**
- **The summarized sensitivity ratios calculated from the experiments with and without the HUVECs cultured in the devices.**

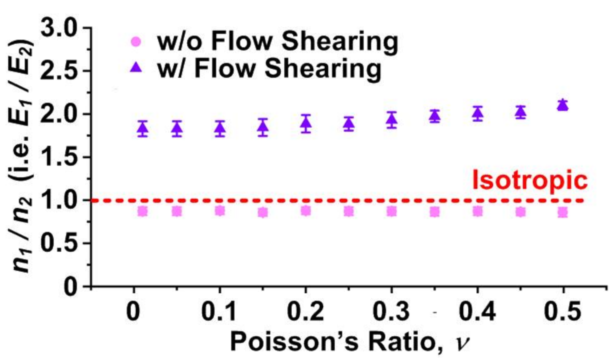
Ref.: Ko*, Wang* et al. *Acta Biomaterialia* in revision.

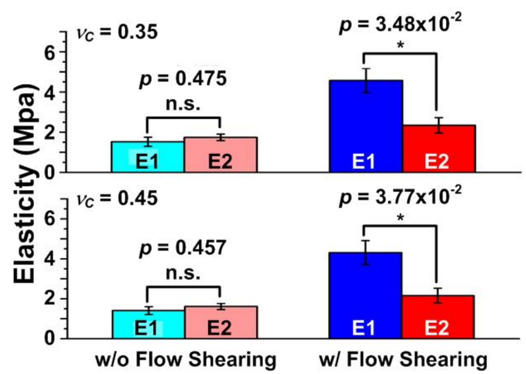
Measurement of in-plane elasticity of live cell layers

Microfluidic device development & mechanical model derivation

(a) AFM Measurement





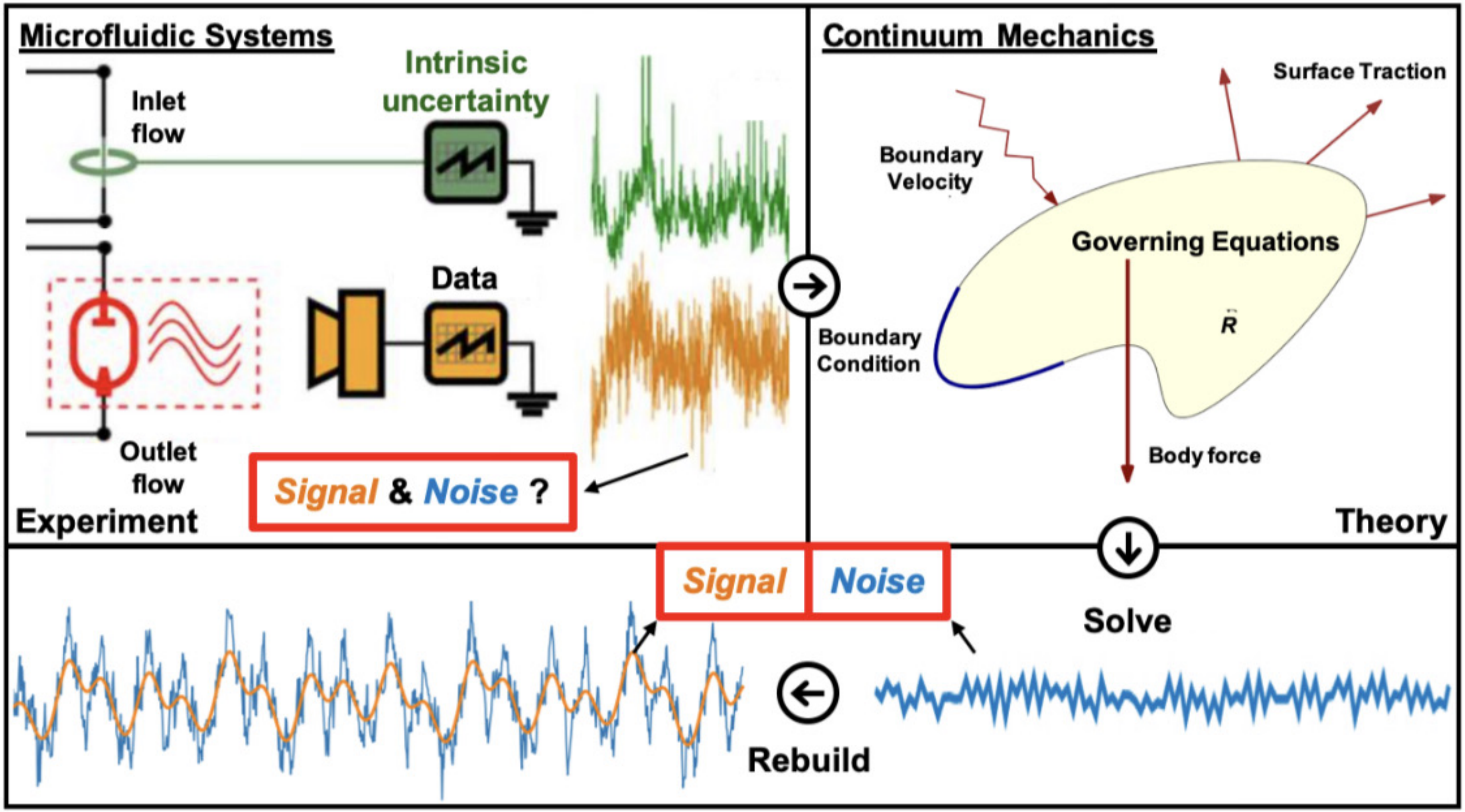


	w/o Flow Shearing		w/ Flow Shearing	
	ν = 0.35	ν = 0.45	ν = 0.35	ν = 0.45
E_1	1.52 ±0.23 MPa	1.41 ±0.20 MPa	4.57 ±0.60 MPa	4.31 ±0.60 MPa
E_2	1.74 ±0.16 MPa	1.61 ±0.16 MPa	2.34 ±0.38 MPa	2.16 ±0.37 MPa
E_3	9.39±0.76 kPa (AFM Measurement)			

- The microscopic and AFM topographic images of the HUVECs cultured in a Petri-dish.
- Cell transverse elasticities in different directions are estimated for different Poisson's ratios.
- Summary of experimental results obtained in the AFM analysis and microfluidic device measurements based on the developed process without and with flow shearing.

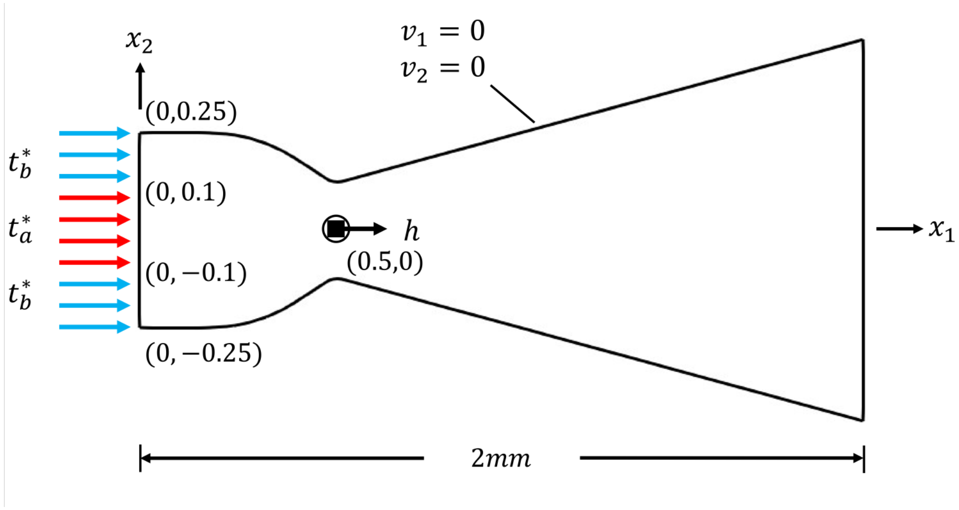
Ref.: Ko*, Wang* et al. *Acta Biomaterialia* in revision.

Motivation – Measurement noise reduction for Stokes flow



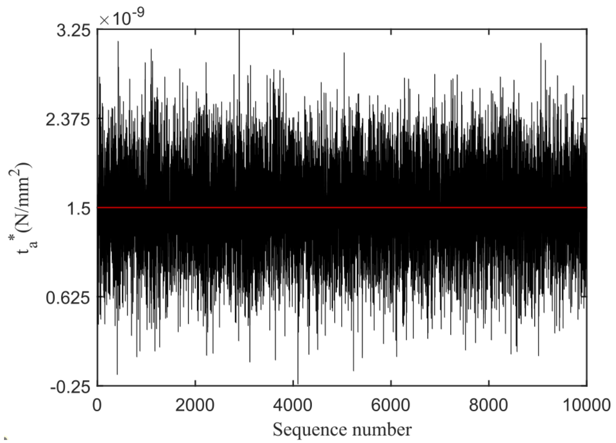
Numerical examples – CD nozzle

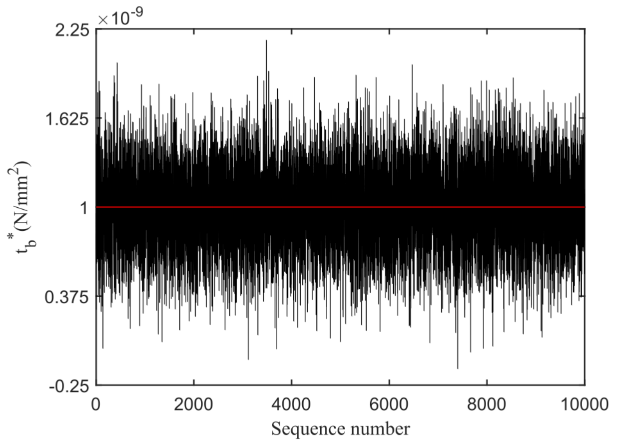
Uncertainty conditions: $t_a^* \& t_b^*$
Observation pt: h (0.5, 0), in horizontal dir.

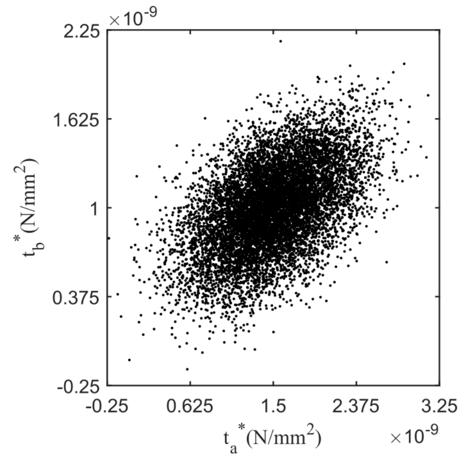


Length: 2 (mm)
Inlet diameter: 0.5(mm)
t_a^*: 1.5 (mPa)
t_b^*: 1 (mPa)
Fluid: water, at 20°C
Dynamic viscosity: $1\times10^{-9}(N \cdot s/mm^2)$
Kinematic viscosity:$1(mm^2/s)$

$\sigma_{t_a^*} = 0.45(mPa)$
$\sigma_{t_b^*} = 0.3\times(mPa)$
$\rho_{t_a^* t_b^*} = 0.5$

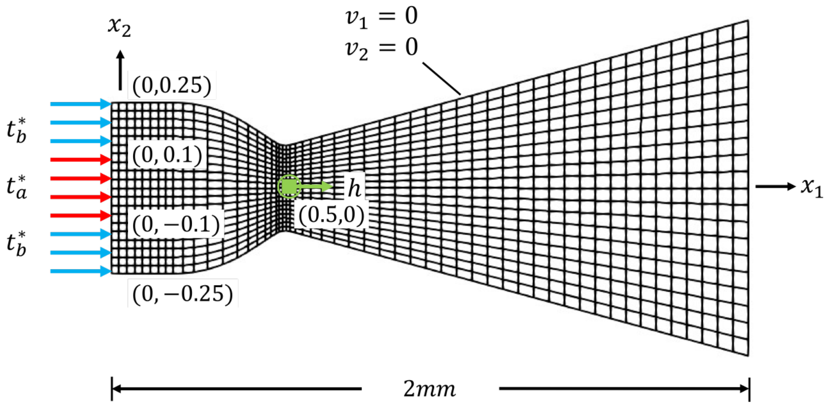


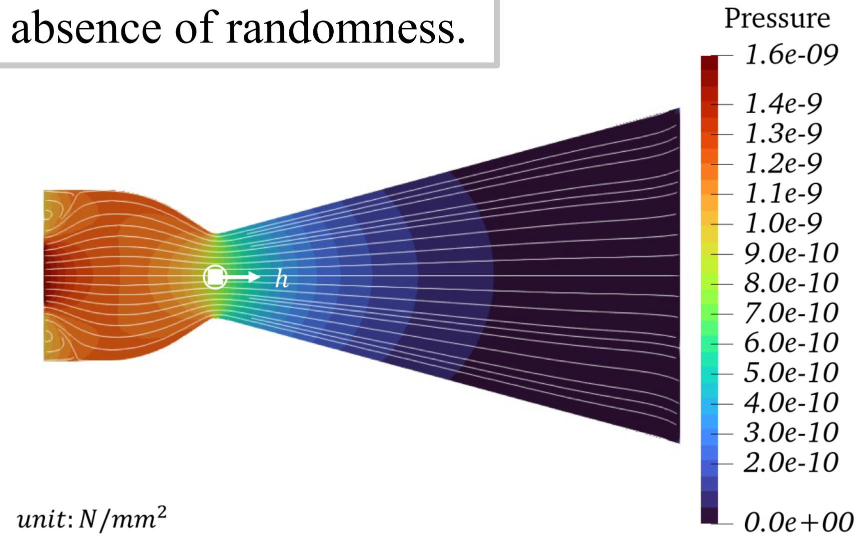


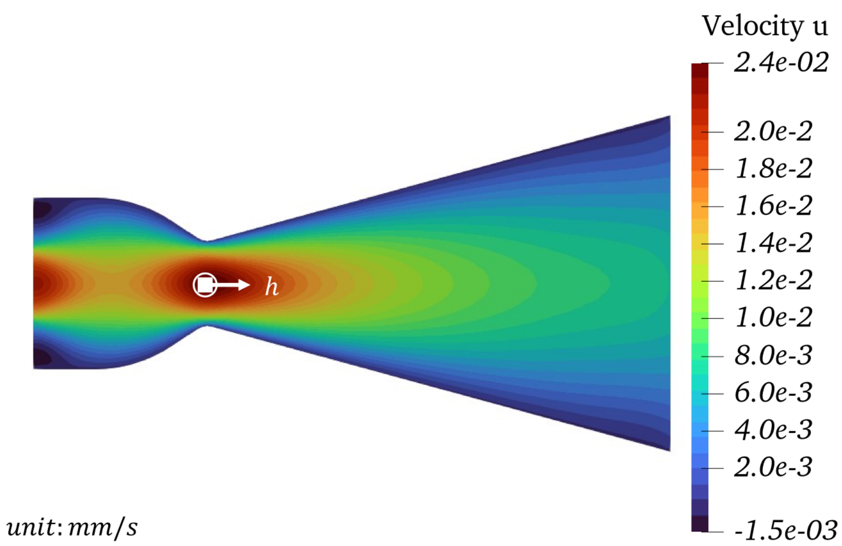


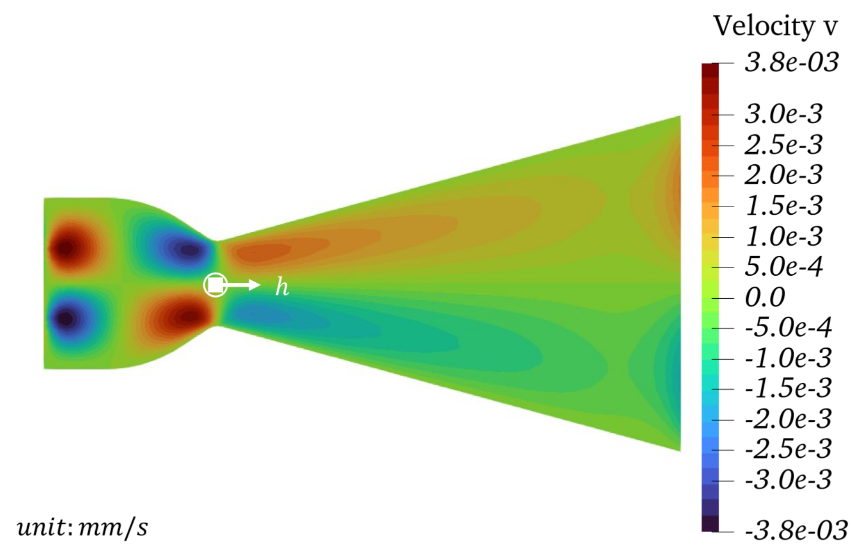
Numerical examples – CD nozzle

The computation result in the absence of randomness.





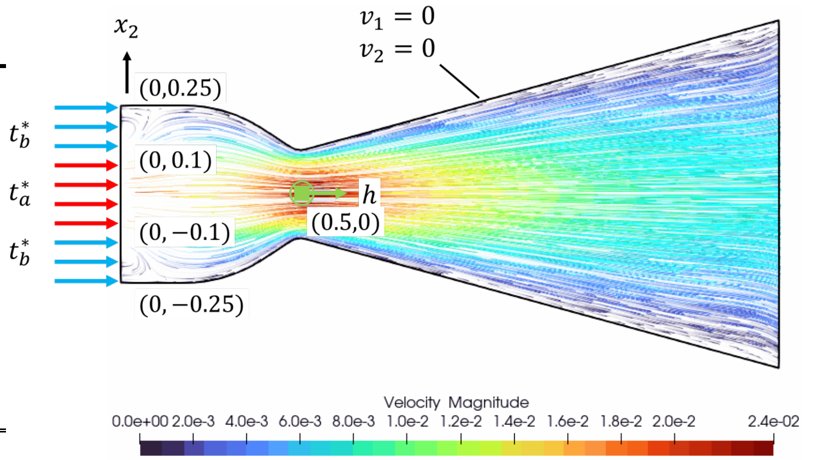


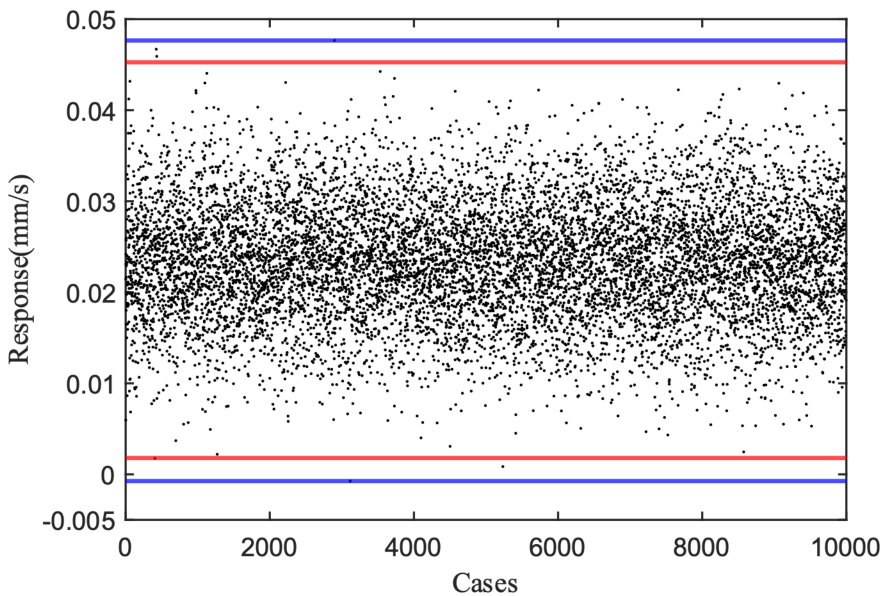


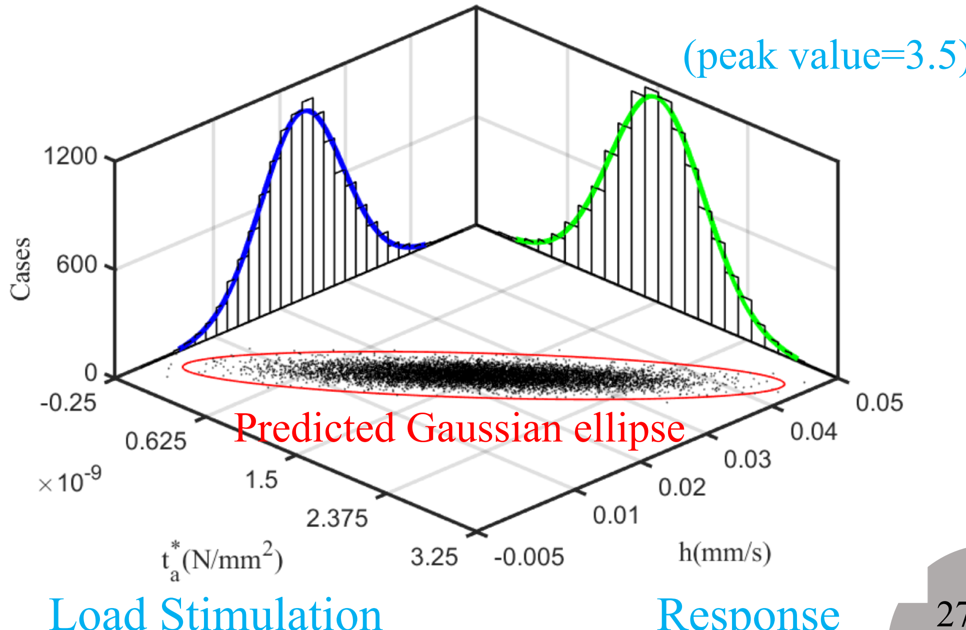
Numerical examples – CD nozzle

	Sampling test	FLRC	Error (%)
Response avg. (mm/s)	0.02345	0.02353	0.34
Response std. (mm/s)	0.006269	0.006209	0.95
Correlation coef. (h, t_a^*)	0.9419	0.9402	0.18
Pos. peak response(mm/s)	0.04766	0.04526	10.22
Neg. peak response(mm/s)	−0.0007387	0.001797	10.82

	Pos. peak response	Neg. peak response
Fail prediction(%)	0.03	0.02





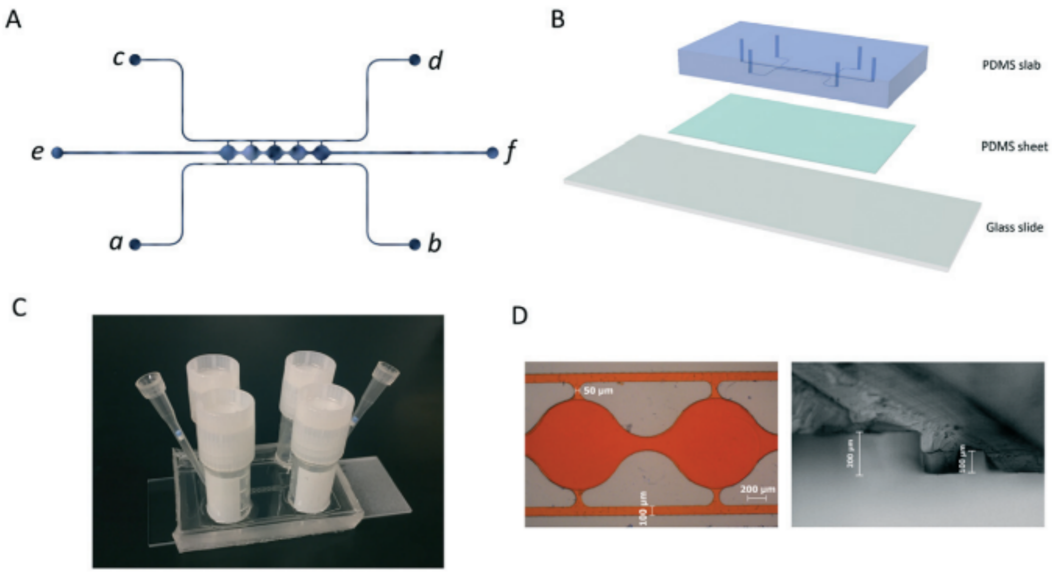


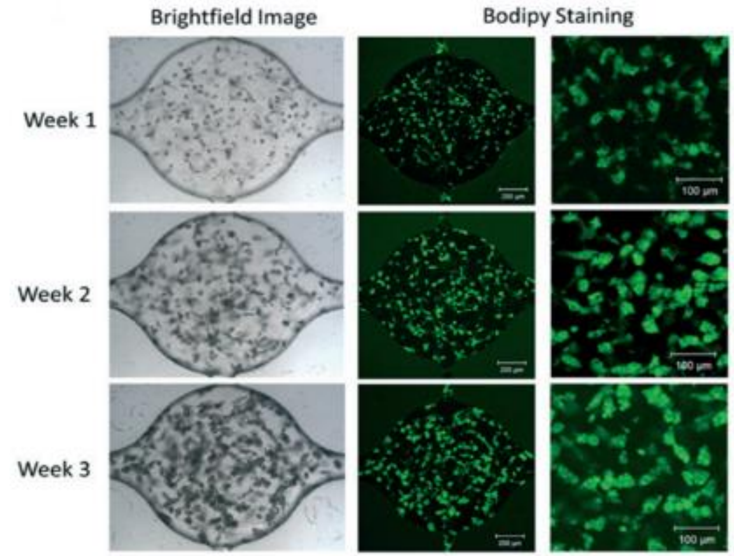
Numerical examples – Microfluidic chamber

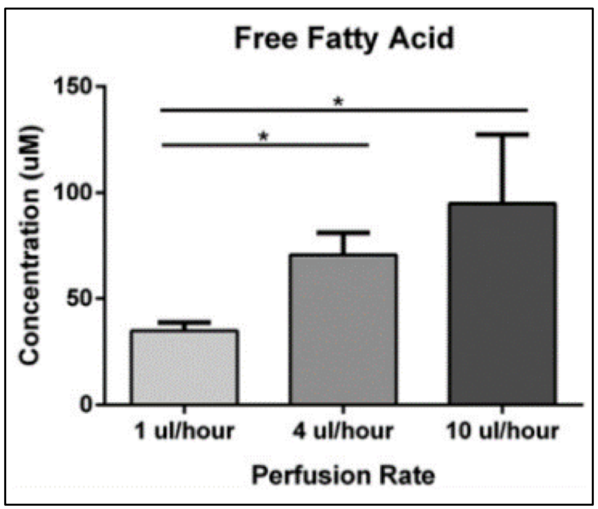
A 3D human adipose tissue model within a microfluidic device

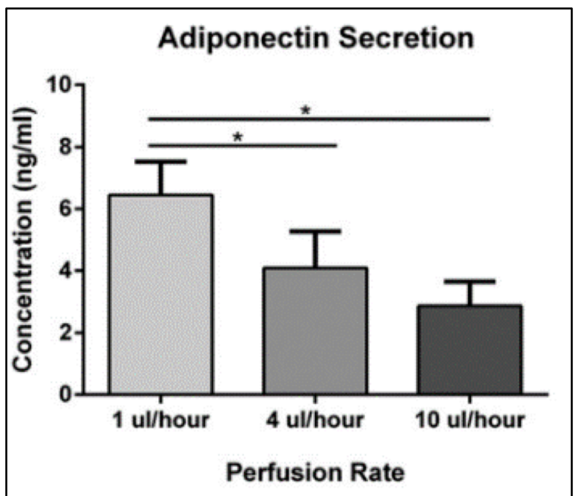
Lab on a Chip 2021 Vol. 21 Issue 2 Pages 435-446

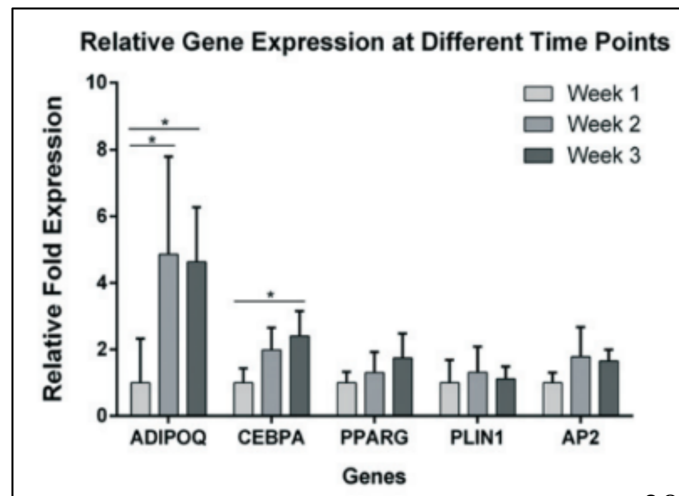
Investigating the effects of shear stress at different flow rates in a cell culture chamber on cellular physiological responses.



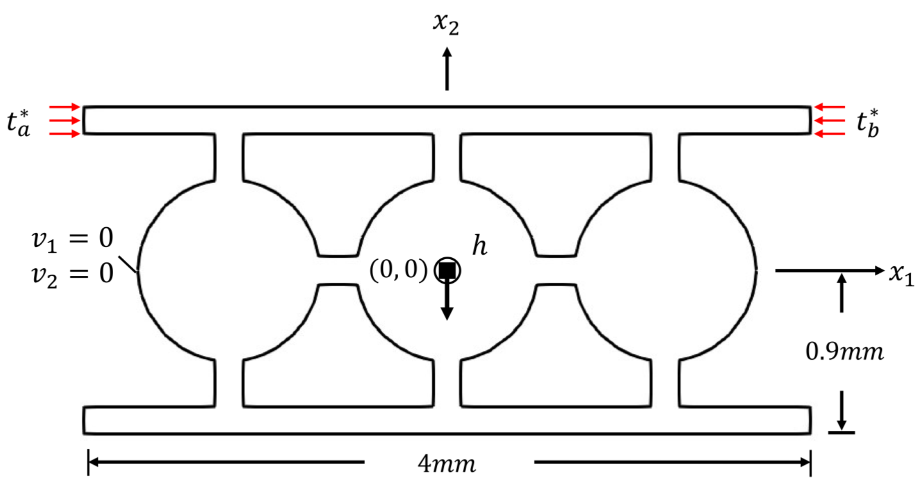








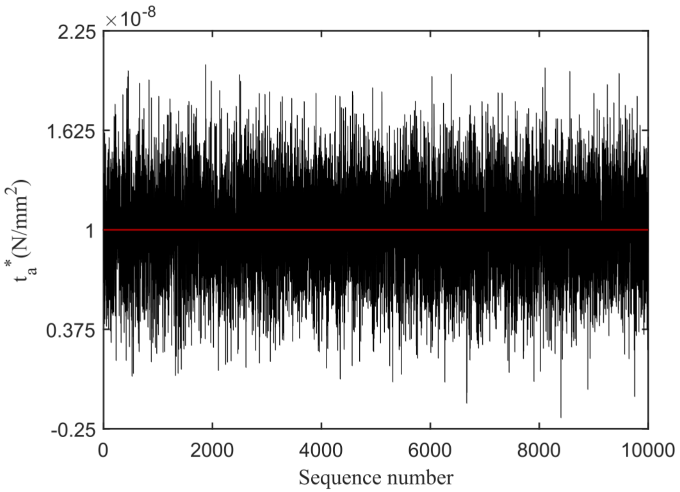
Numerical examples – Microfluidic chamber

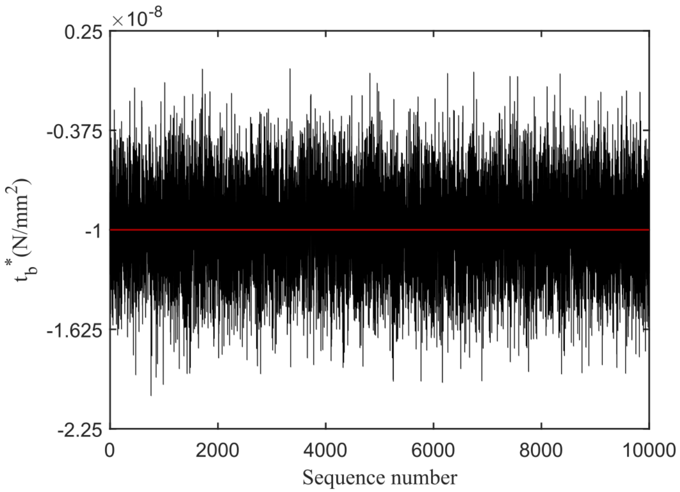


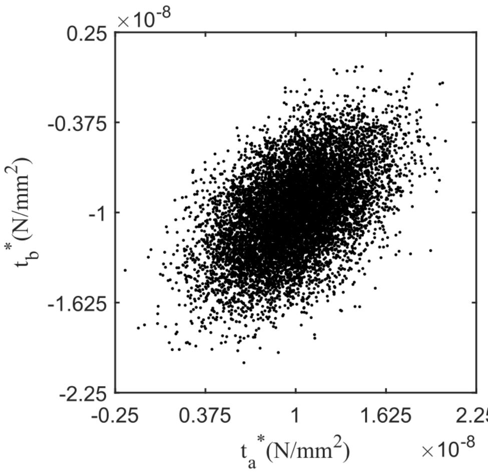
Uncertainty conditions: $t_a^* \& t_b^*$
Observation pt: h (0, 0), in vertical dir.

Chamber diameter: $1(mm)$
Pipe diameter: $0.2(mm)$
t_a^* : $10(mPa)$; t_b^*: $-10(mPa)$
Fluid : water, at 20°C
Dynamic viscosity: $1\times10^{-9}(N\cdot s/mm^2)$
Kinematic viscosity: $1(mm^2/s)$

$\sigma_{t_a^*} \& \sigma_{t_b^*} = 3(mPa)$
$\rho_{t_a^* t_b^*} = 0.5$

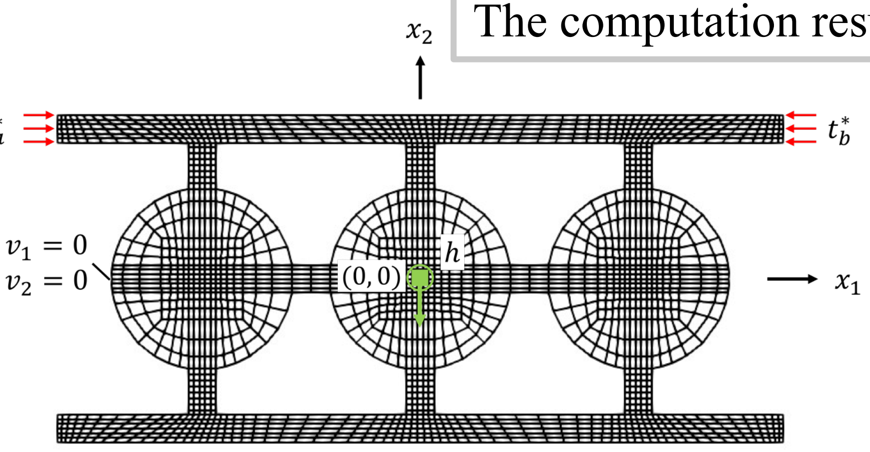


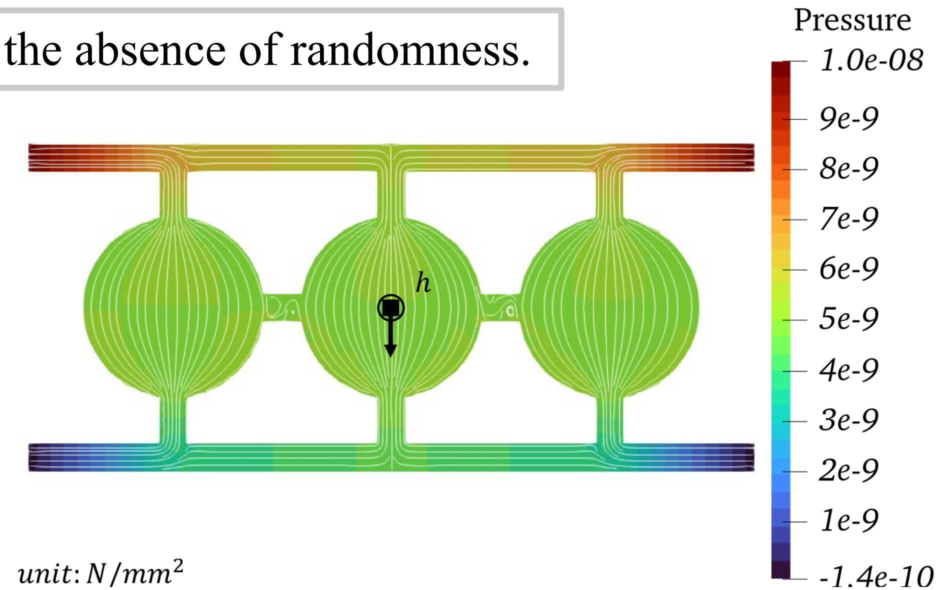


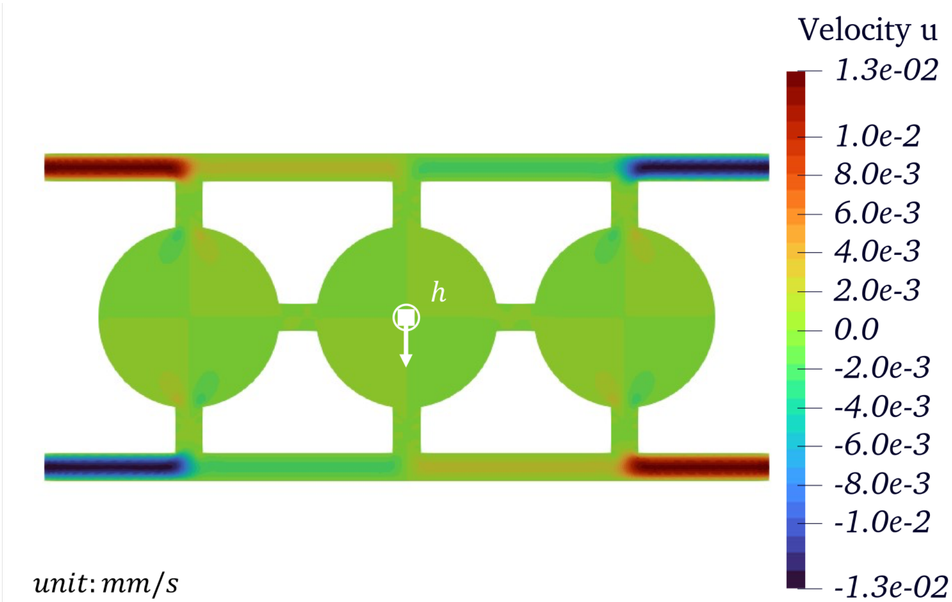


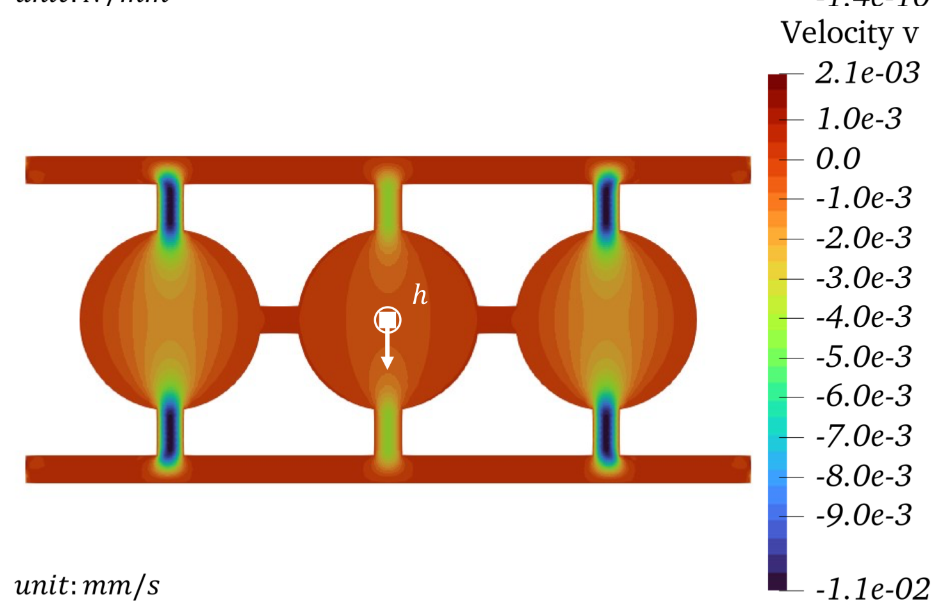
Numerical examples – Microfluidic chamber

The computation result in the absence of randomness.





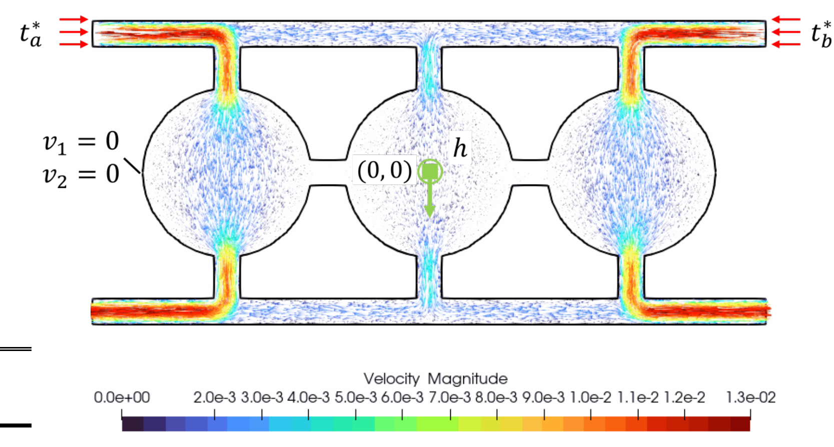


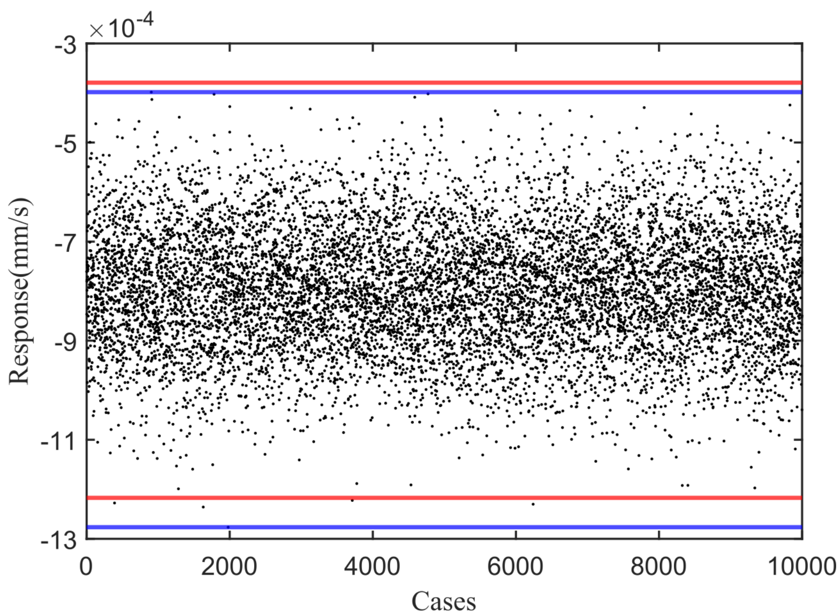


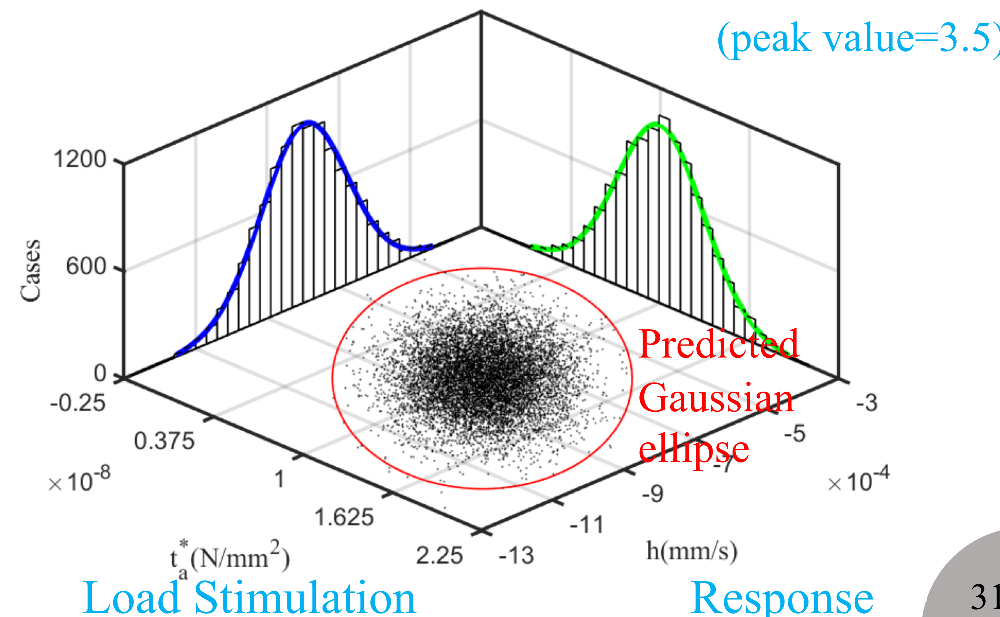
Numerical examples – Microfluidic chamber

	Sampling test	FLRC	Error (%)
Response avg. (mm/s)	−0.0007955	−0.0007982	0.34
Response std. (mm/s)	0.0001198	0.0001197	0.058
Correlation coef. (h, t_a^*)	−0.5014	−0.5005	0.17
Pos. peak response(mm/s)	−0.0003983	−0.0003792	2.40
Neg. peak response(mm/s)	−0.001277	−0.001217	7.45

	Pos. peak response	Neg. peak response
Fail prediction(%)	0.00	0.05



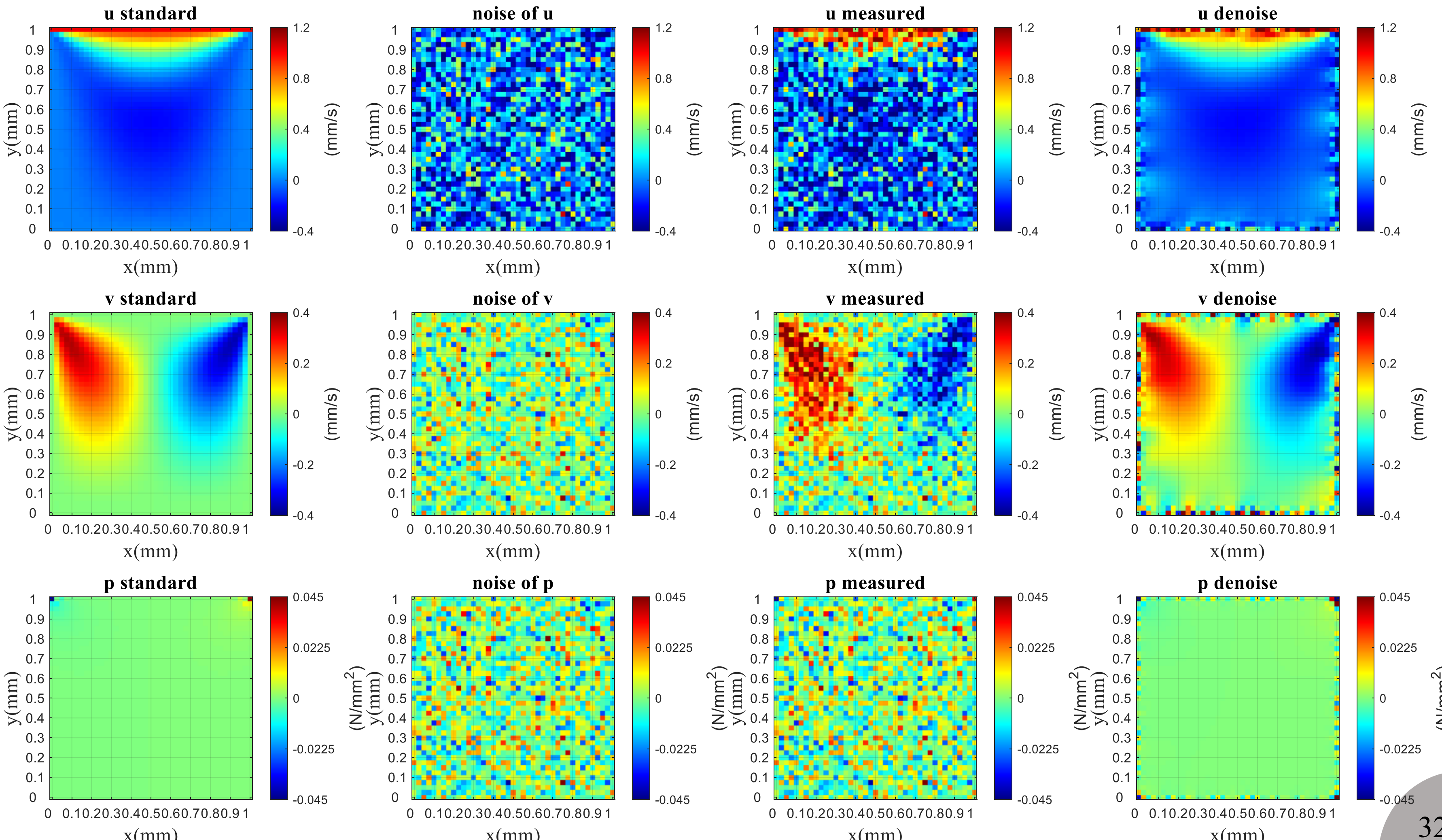




Noise reduction example – cavity flow

Marginal length: 1 mm ; Upper border BC: $1mm/s$(x-dir.)
SAE 80W-90 oil Dynamic viscosity: $1.36\times10^{-4}\ N\cdot s/mm^2$
Std. of simulation noise: 30% field maximum

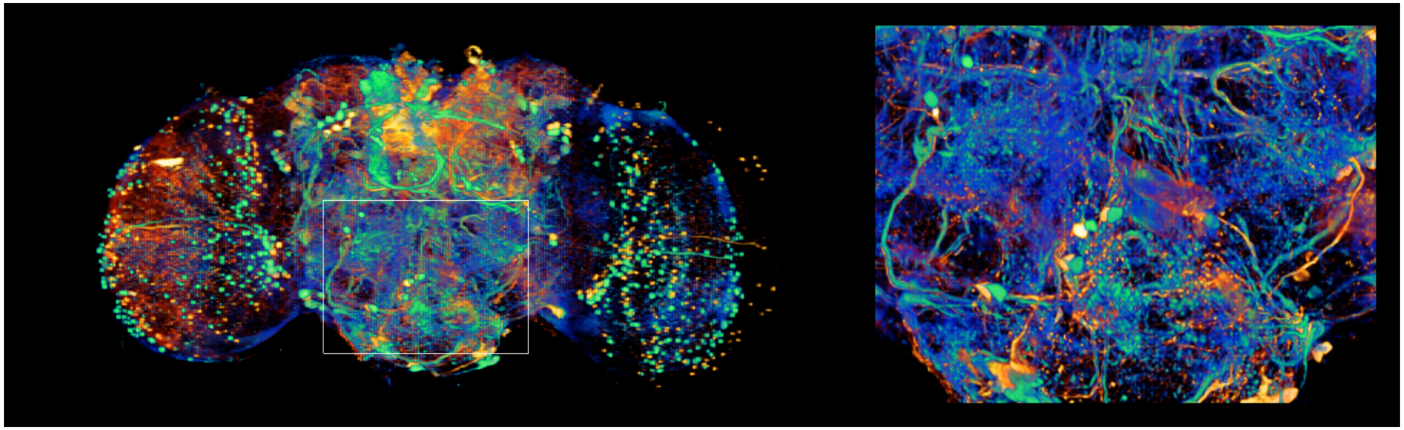
$\boldsymbol{h} = \left(\boldsymbol{I} + \boldsymbol{Q}^{-1}\widetilde{\boldsymbol{A}}^{T}\Delta^{-1}\widetilde{\boldsymbol{A}}\right)\widehat{\boldsymbol{h}}$	Noise reduce (RMSE)(%)
Velocity u(mm/s)	85.92
Velocity v(mm/s)	73.68
Pressure(N/mm^2)	97.70



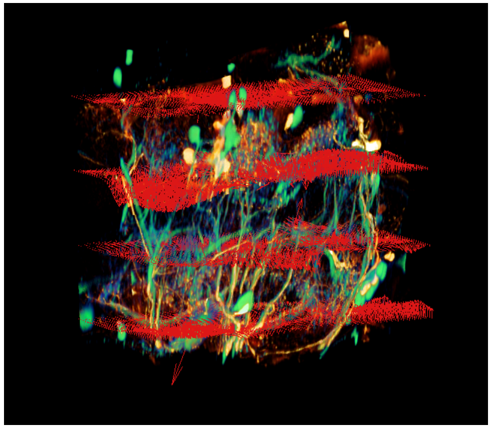
3D example

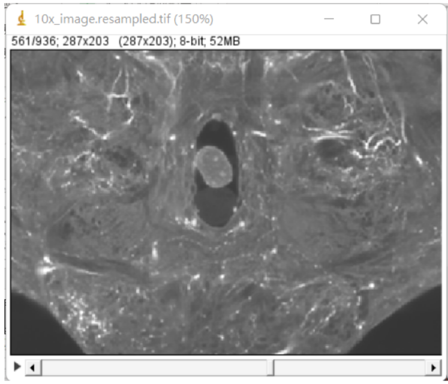
- Applications in Biological Imaging - Fly Brain(3D)

Overlay of Fluorescent Images Before and After motion. Blue: Before motion, Orange: After motion.

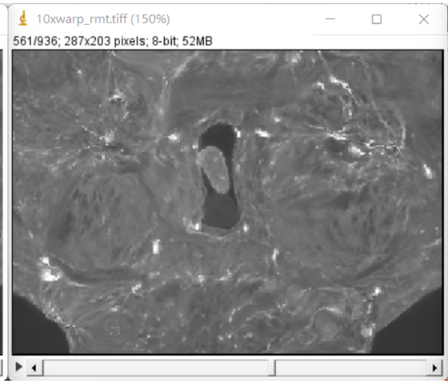


Result of 3D Image Velocity Field Calculation

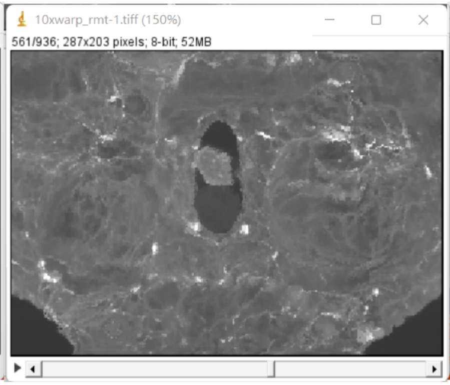




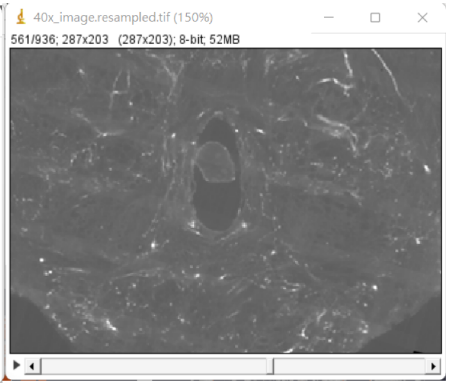
Source image: Before motion



Register image 1



Register image 2



Target image: After motion

Conclusion

1. Based on continuum mechanics, this research develops a novel finite element method for computational mechanics and conducts scientific experimental research on related microfluidic systems.
2. It is possible to derive the uncertain response of a Stokes flow in Euler space for any degree of freedom under random external conditions. Therefore, it is possible to predict and control the service performance and quality of mechanical system design effectively and efficiently.
3. By performing actual measurements, it is possible to analyze the measurement error of any degree of freedom of a Stokes flow in Euler space. This allows the measured data of the fluid field to comply with the fluid governing equations and eliminates concerns regarding distorted signals due to noise reduction.

Acknowledgements

Division of Applied Mathematics &
Solid Mechanics, School of Engineering,
Brown University

Research Center for Applied Sciences,
Academia Sinica
108-2-1-09-21
107-1-1-09-23

Division of Solid Mechanics,
Dept. of Mechanical Engineering
National Taiwan University

110-2221-E-002-142-MY2
108-2221-E-002-172
106-2221-E-032-018-MY2
105-2221-E-032-006
104-2218-E-032-004
103-2221-E-001-001

111-HT512038

Many thanks for the supports from my families and friends.

Thank you.

Chien-Kai Wang, NTU ME Dept.

E-Mail: ckwang@ntu.edu.tw (臺大機械 王建凱)