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COMSOL CONFERENCE 2018 LAUSANNE

Optimizing Elastomeric Mechanical Cell Stretching Device

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Tampere, FINLAND

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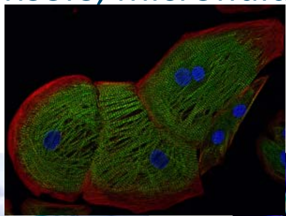

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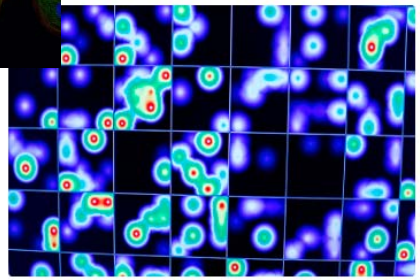
Heart Group



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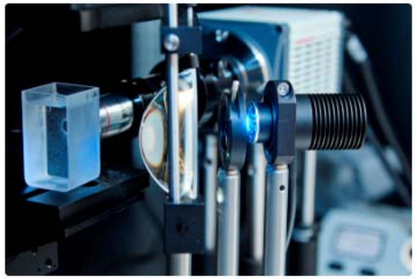

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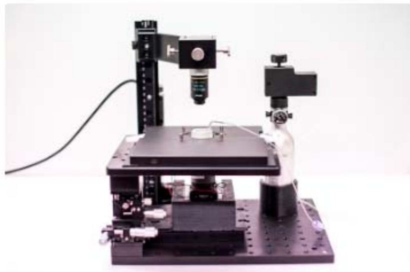

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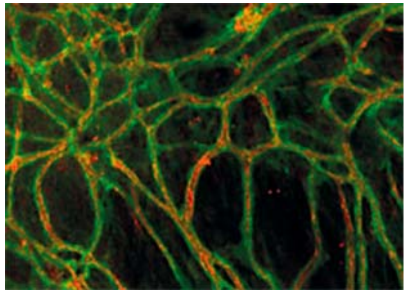

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CENTRES OF EXCELLENCE IN RESEARCH

ACADEMY OF FINLAND

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OUTLINE

- Introduction
- Methods
- Results
- Discussion and Future Outlook

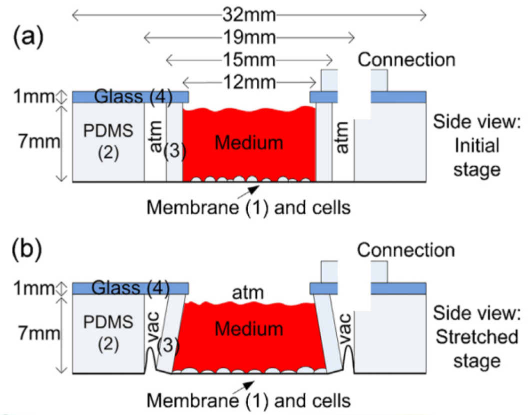
Introduction

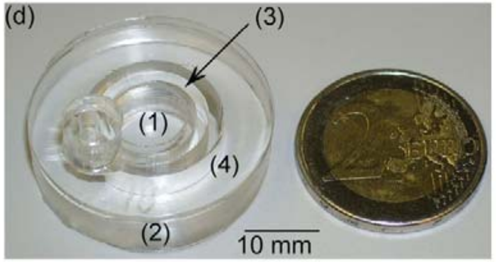
- Mechanical stimulation
  - ”**Gym for cells**” → Cell morphology, orientation, and fate of differentiated stem cells can be affected
  - Mechanobiological studies → to understand the molecular mechanism of cells
- Our ”gym” approach[1,2]
  - Equiaxial strain for cells on a coated polydimethylsiloxane (PDMS) membrane
  - Real-time observation of cells with a microscope

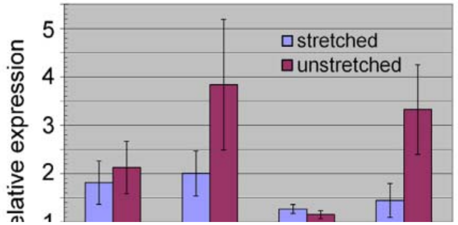
[1] Kreutzer, J, Ikonen, L, Hirvonen, J, Pekkanen-Mattila, M, Aalto-Setälä, K & Kallio, P 2014, 'Pneumatic cell stretching system for cardiac differentiation and culture' *Medical Engineering and Physics*, vol 36, no. 5, pp. 496-501. DOI: 10.1016/j.medengphy.2013.09.008

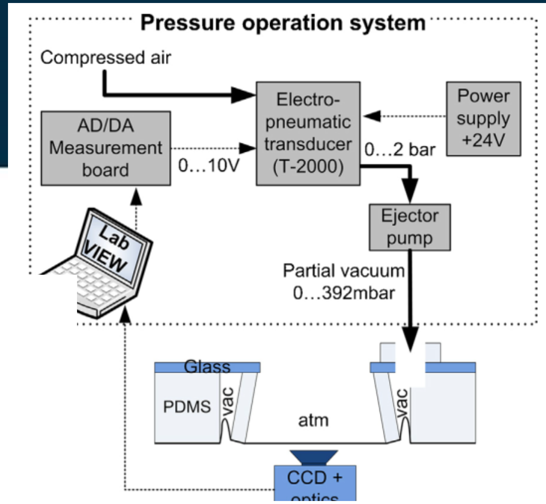
[2] Kreutzer, J, Viehrig, M, Maki, A-J, Kallio, P, Rahikainen, R & Hytönen, V 2017, Pneumatically actuated elastomeric device for simultaneous mechanobiological studies & live-cell fluorescent microscopy. in *International Conference on Manipulation, Automation and Robotics at Small Scales, MARSS 2017 - Proceedings.* IEEE, International Conference on Manipulation, Automation and Robotics at Small Scales (MARSS), 1/01/00. DOI: 10.1109/MARSS.2017.8001929

[1]









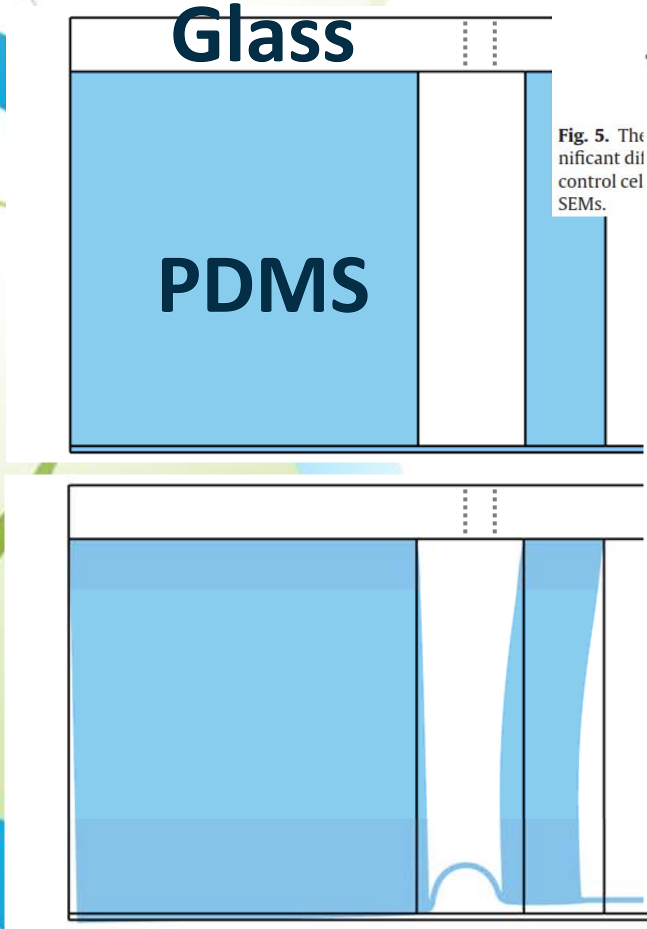


Fig. 5. The
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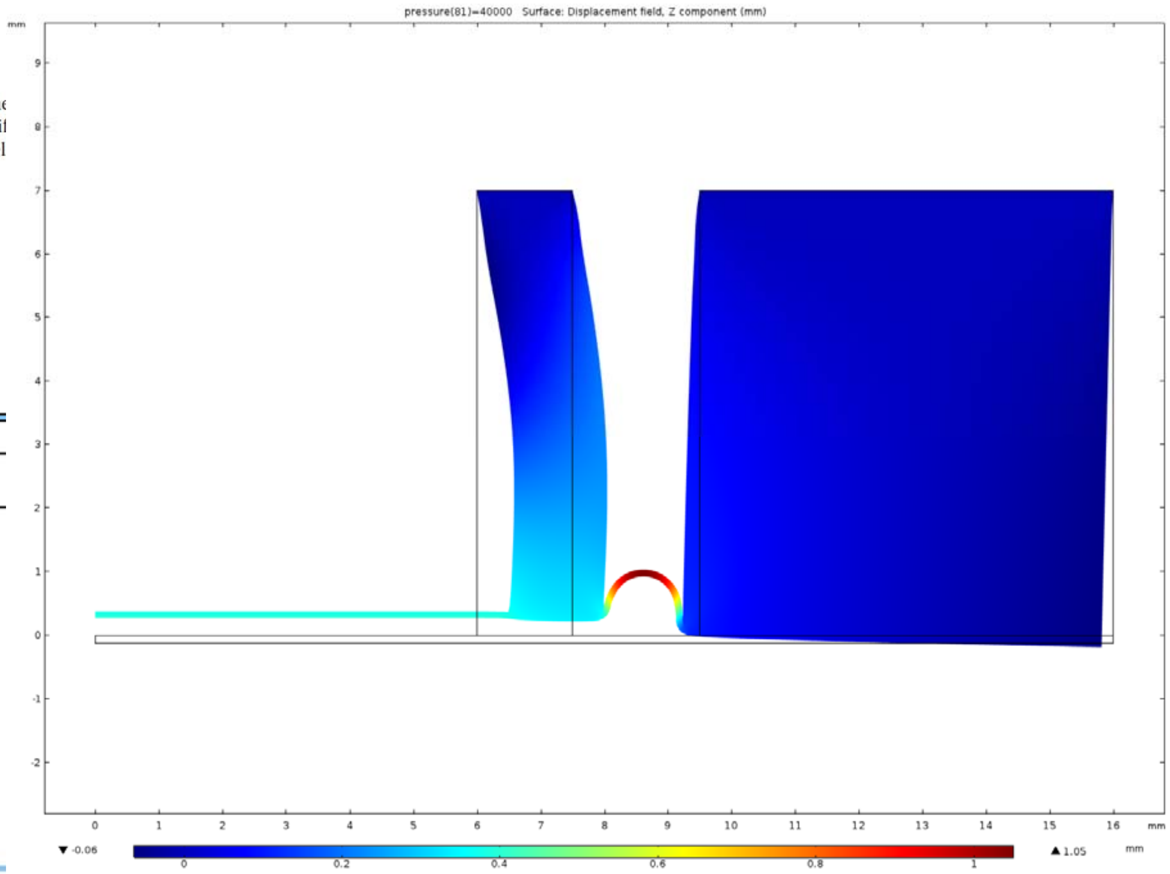


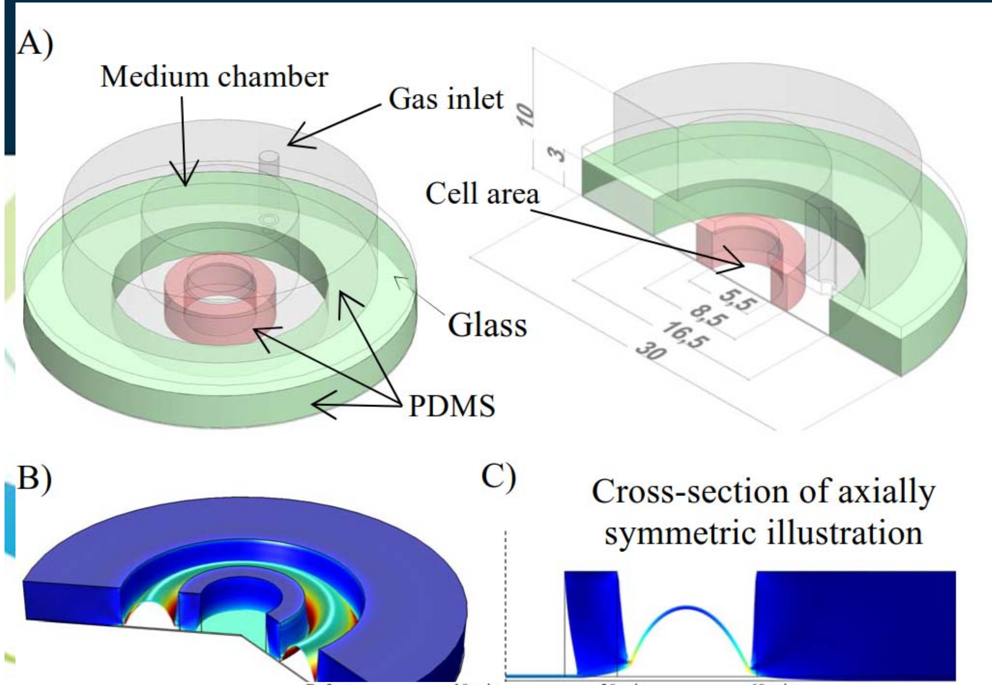
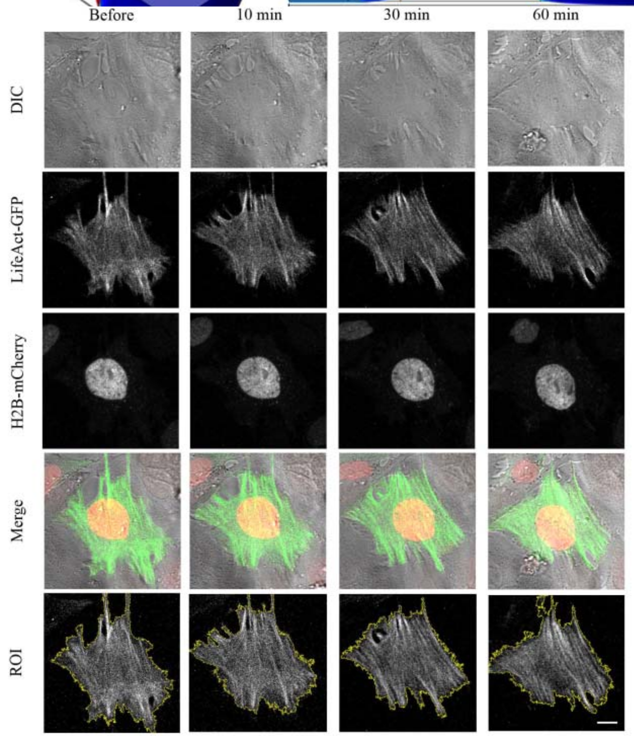


Fig. 1. A) Schematic picture of the stretching device and dimensions in [mm]. B) Simulated illustration of a simplified stretching device used for computational simulations. C) 2D cross-section of axially symmetric simulated illustration. D) Real setup on Petri dish and on microscope. Connected stretching device in secured Petri dish holder. The tubing is secured to the heating insert of the microscope stage. A lid for CO_2 supply can be added on top.



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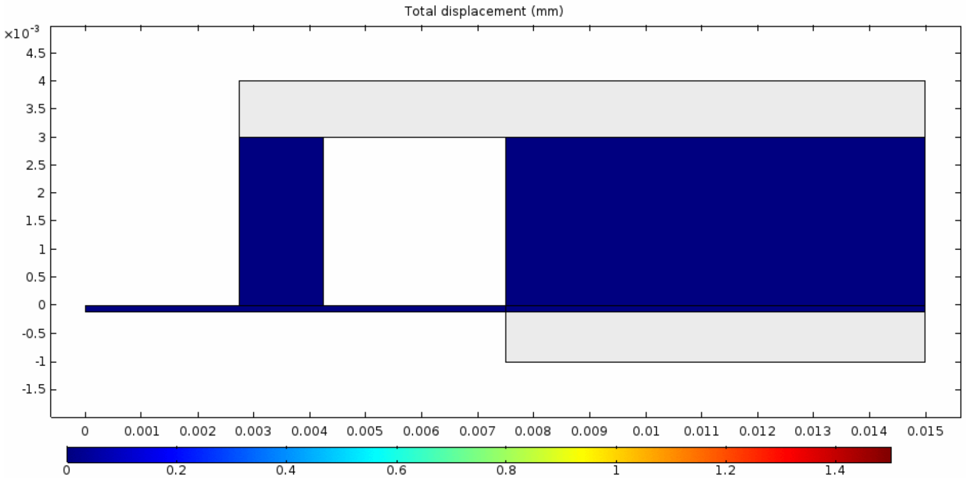
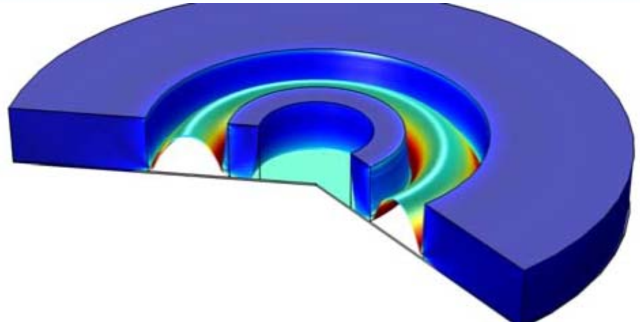
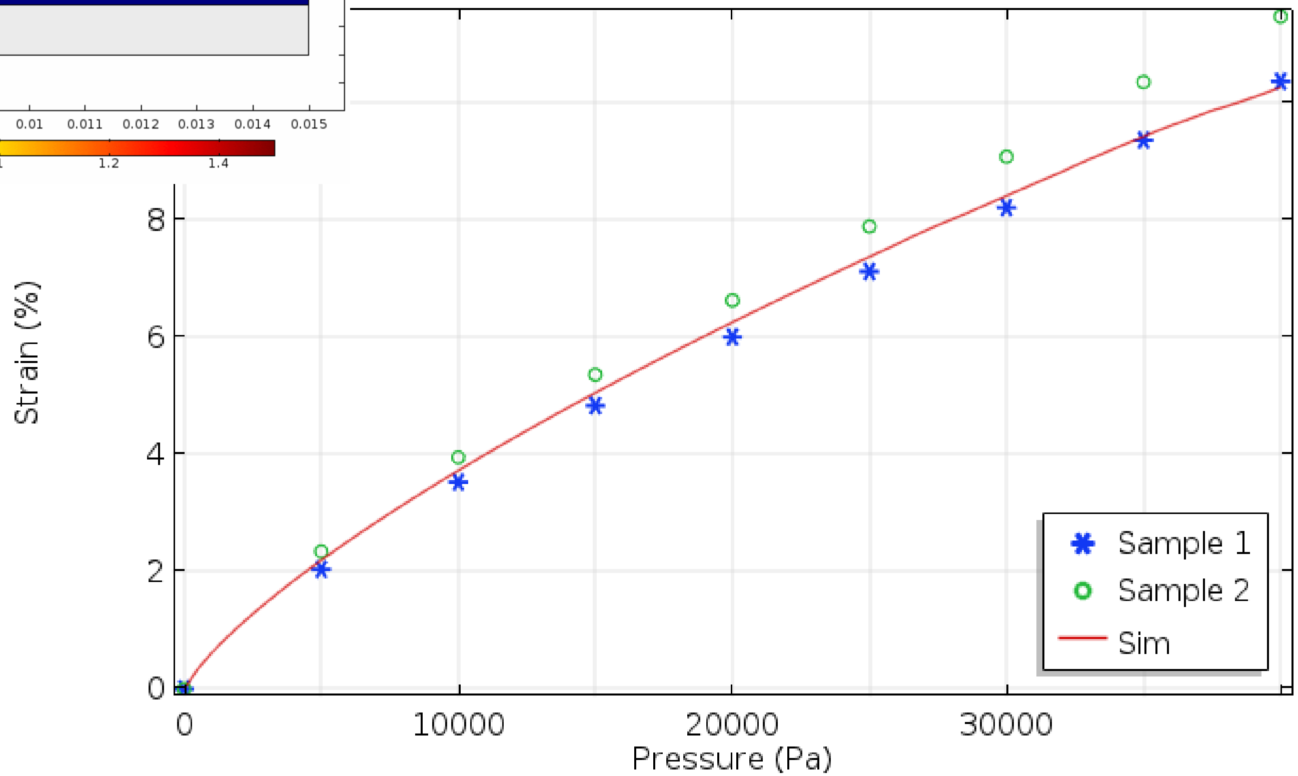
Model verification







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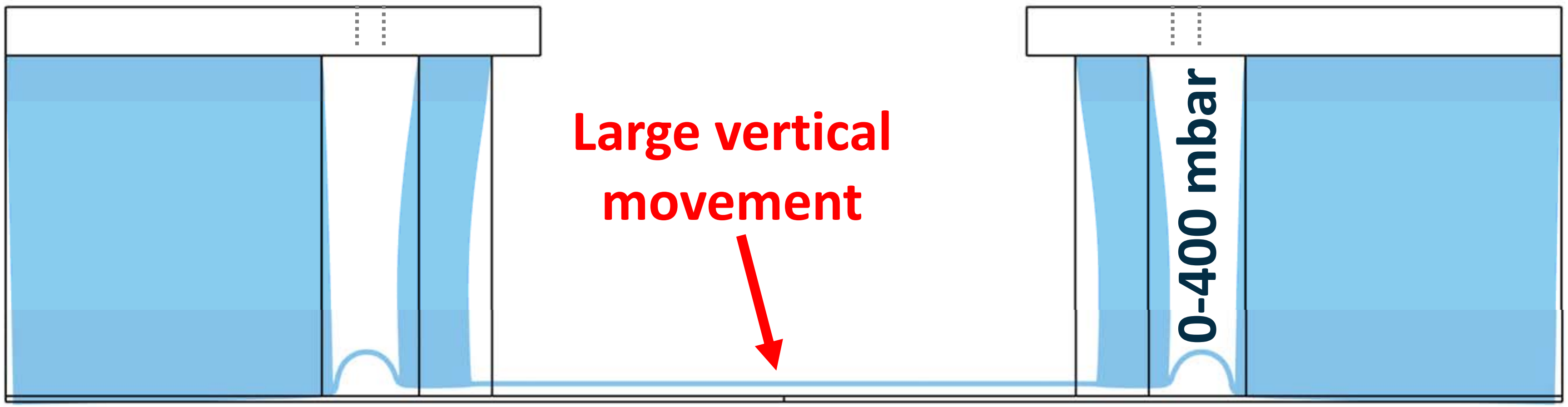
Problems with previous design

- Large z-movement[1] or small media volume[2]



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- **Approach to solve these problems**: Using COMSOL to desing the geometry that solves both

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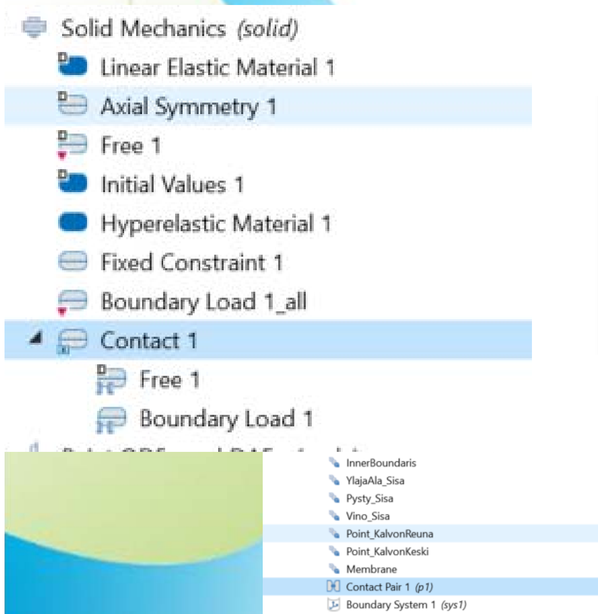
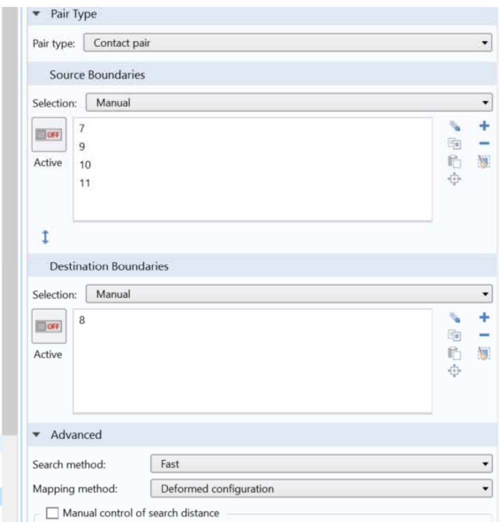
COMSOL implementation

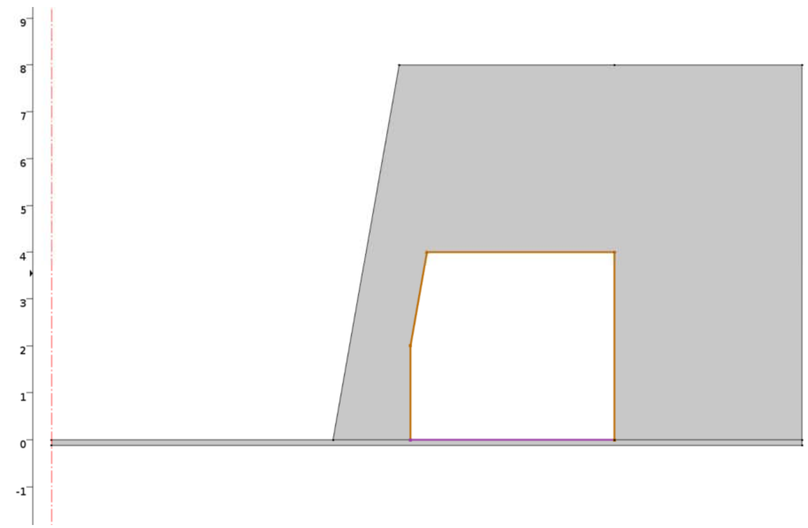
- Solid Mechanics (1/2)
  - Stationary, 2D symmetric model
  - Solid Mechanics physics for PDMS (silicone type elastomer)
    - Hyperelastic (Neo-Hookean model), nearly incompressible material property of PDMS
    - Used PDMS properties
      - Density: 971 kg/m^3
      - Young's modulus: 2 Mpa & Poisson's ration: 0.499 → Bulk modulus: 333.3 Mpa
      - Lamé parameter: 667e3 N/m^2

COMSOL implementation

- Solid Mechanics (2/2)
  - Contact Pair and Contact nodes used to model contacts between the membrane and the device
    - Source: less convex (bulk material)
    - Destination: "softer“, more convex boundary (membrane)

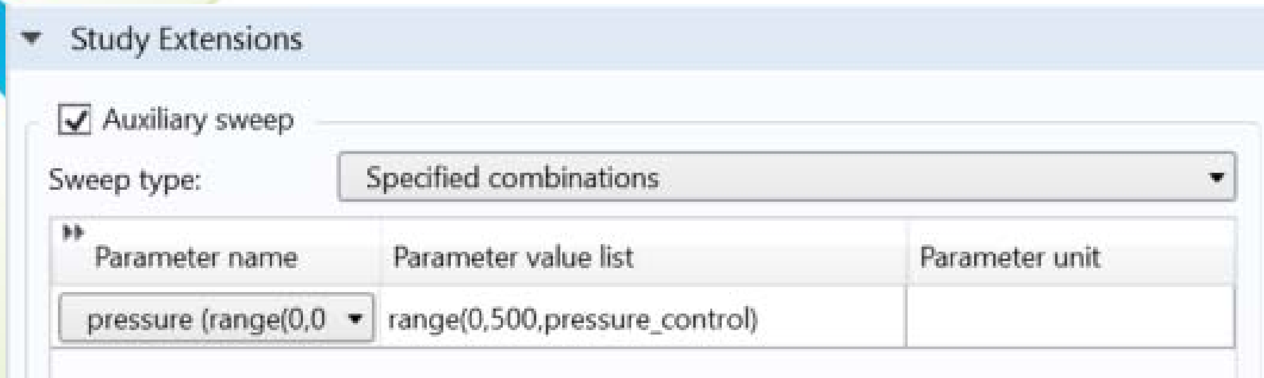




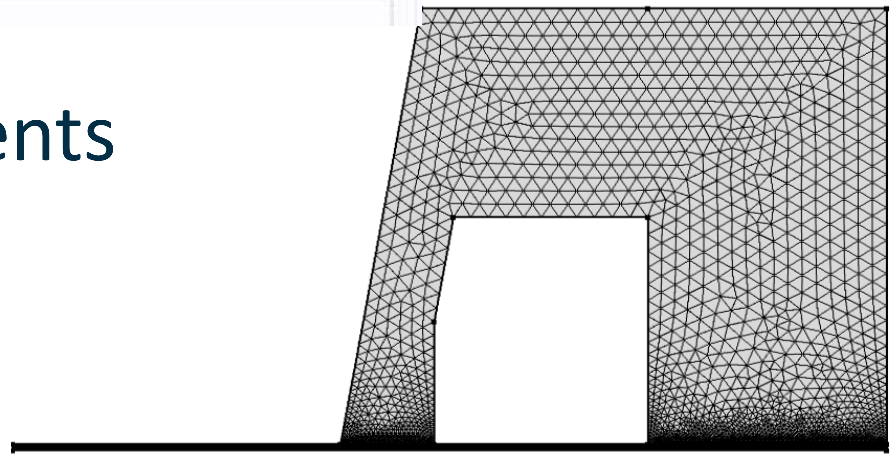


COMSOL implementation

- Stationary Solver
  - Problem is quite nonlinear → Auxilary sweep using previous solution as an initial value



- Mesh: Fine, ~7000 elements



Optimization

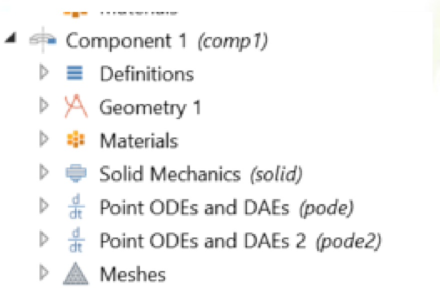
- Requirements for the device
  - Strain ≥ 10% with $p \le 400$ mbar
  - Membrane vertical movement ≤ 50 µm
  - Chamber volume ≥ 0.5 ml

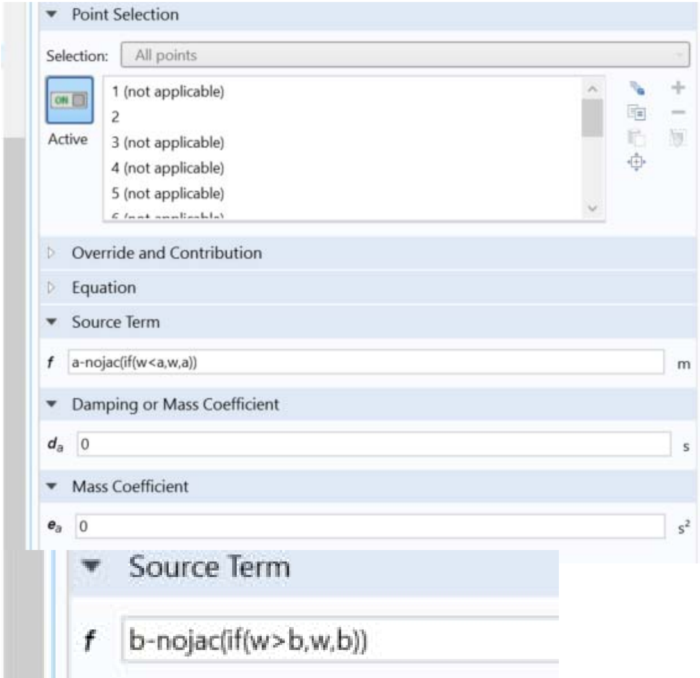
$$\varepsilon = \frac{l - l_0}{l_0} = \frac{\Delta l}{l_0}$$

- Optimization goal: minimize the objective function that included normalized
  - max vertical movement
  - required vacuum pressure

Optimization

- 2 x Point ODEs and DAEs



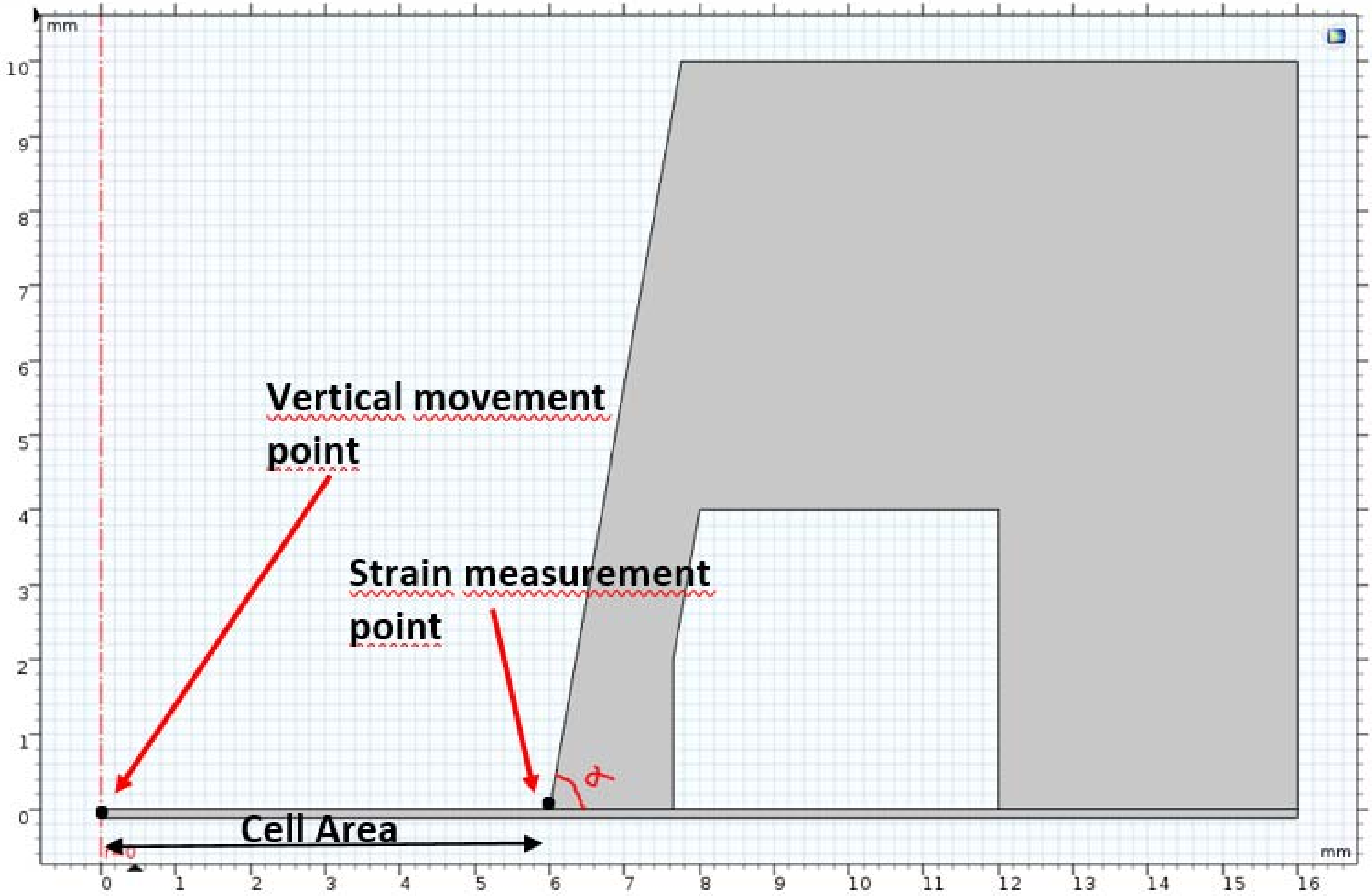


Variables

Name	Expression	Unit
min_w	min(a,w)	m
max_w	max(b,w)	m
diff_z	max_w-min_w	m

Optimization

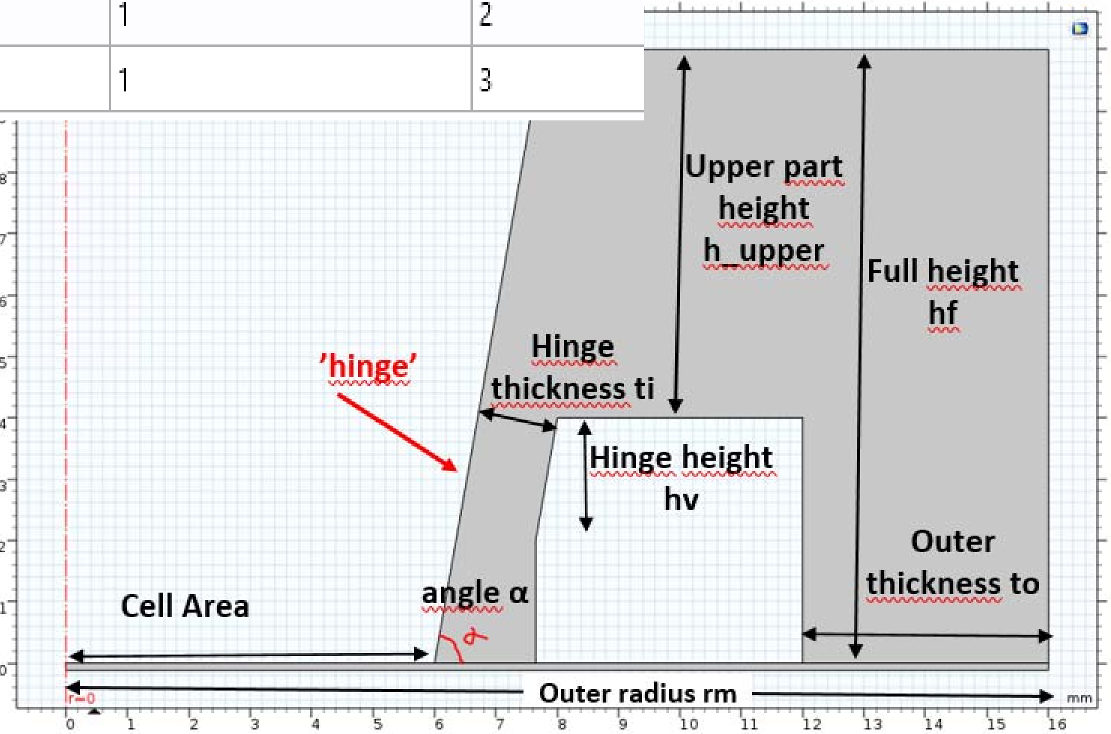
- Points that are monitored



Control variables & parameters

Control Variables and Parameters

Parameter name	Initial value	Scale	Lower bound	Upper bound
to (to=4.3706 mm Strain	4	1	2	6
pressure_control	35e3	1	25e3	40e3
hf (opt: 8.3487mm, 6-15)	8	1	6.1	15
af (degrees)	80	1	65	89.9
hupper	4	1	1	5
ti	1.3	1	1	2
hv	2	1	1	3



Constraints

Constraints

Expression	Lower bound	Upper bound
comp1.maxop1(u/r_c*100)	10	
comp1.maxop2(diff_z*1[1/m])/50e-6		1

Constraint handling method: Penalty

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Optimization settings

Settings
Optimization
Compute   Update Solution

Label: Optimization

Optimization Solver

Method:
Monte Carlo

Optimality tolerance:
0.01

Random seed:
0

Maximum number of model evaluations in each Parametric Sweep:
1

Maximum number of model evaluations:
1000

Study: Study 1_DefaultCase_w_ulko=4mm {std1}
Step 1: Stationary: Stationary {stat}
Solver Configurations
Solution: Solution 1 {sol1} {sol1}
Compile Equations: Compile Equations: Stationary {st1}
Dependent Variables: Dependent Variables 1 {v1}
Field: Auxiliary pressure (comp1.solid.pw) {comp1_solid_p
Field: Contact pressure (comp1.solid.Tn_p1) {comp1_solid_
Field: Displacement field (comp1.u) {comp1_u}
Field: Dependent variable a (comp1.a) {comp1_a}
Field: Dependent variable b (comp1.b) {comp1_b}
Stationary Solver: Stationary Solver 1 {s1}
Direct: Direct {dDef}
Advanced: Advanced {aDef}
Parametric: Parametric 1 {p1}
Previous Solution: Previous Solution 1 {ps1}
Segregated: Segregated 1 {se1}
Job Configurations

Objective Function

Expression	Description	Evaluate for
comp1.maxop2(diff_z*1[1/m])/50e-6	Max_z_norm	Stationary
pressure_control/40e3	Max_pres_norm	Stationary

Type:
Minimization

Multiple objectives:
Sum of objectives

Solution:
Use last

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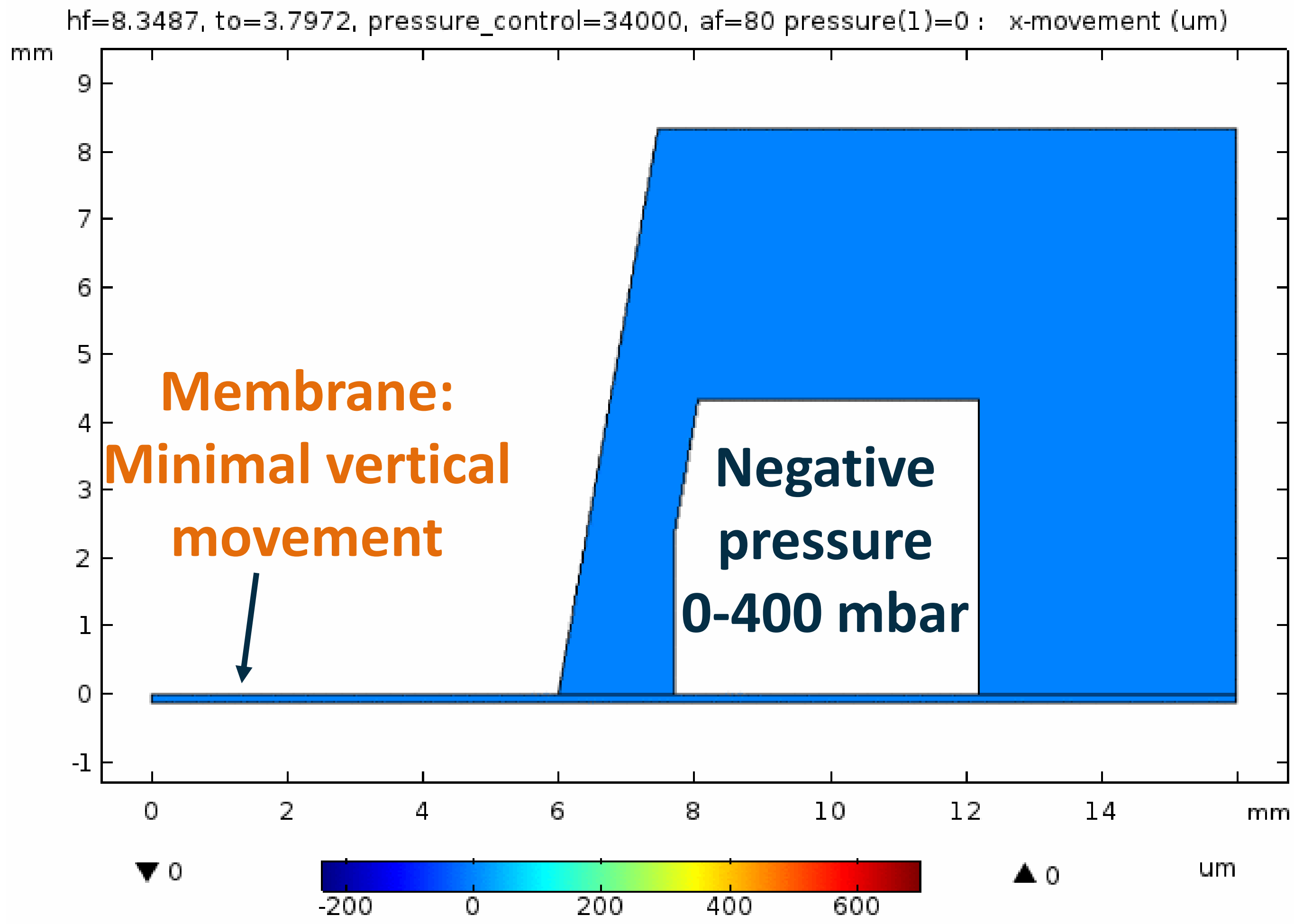
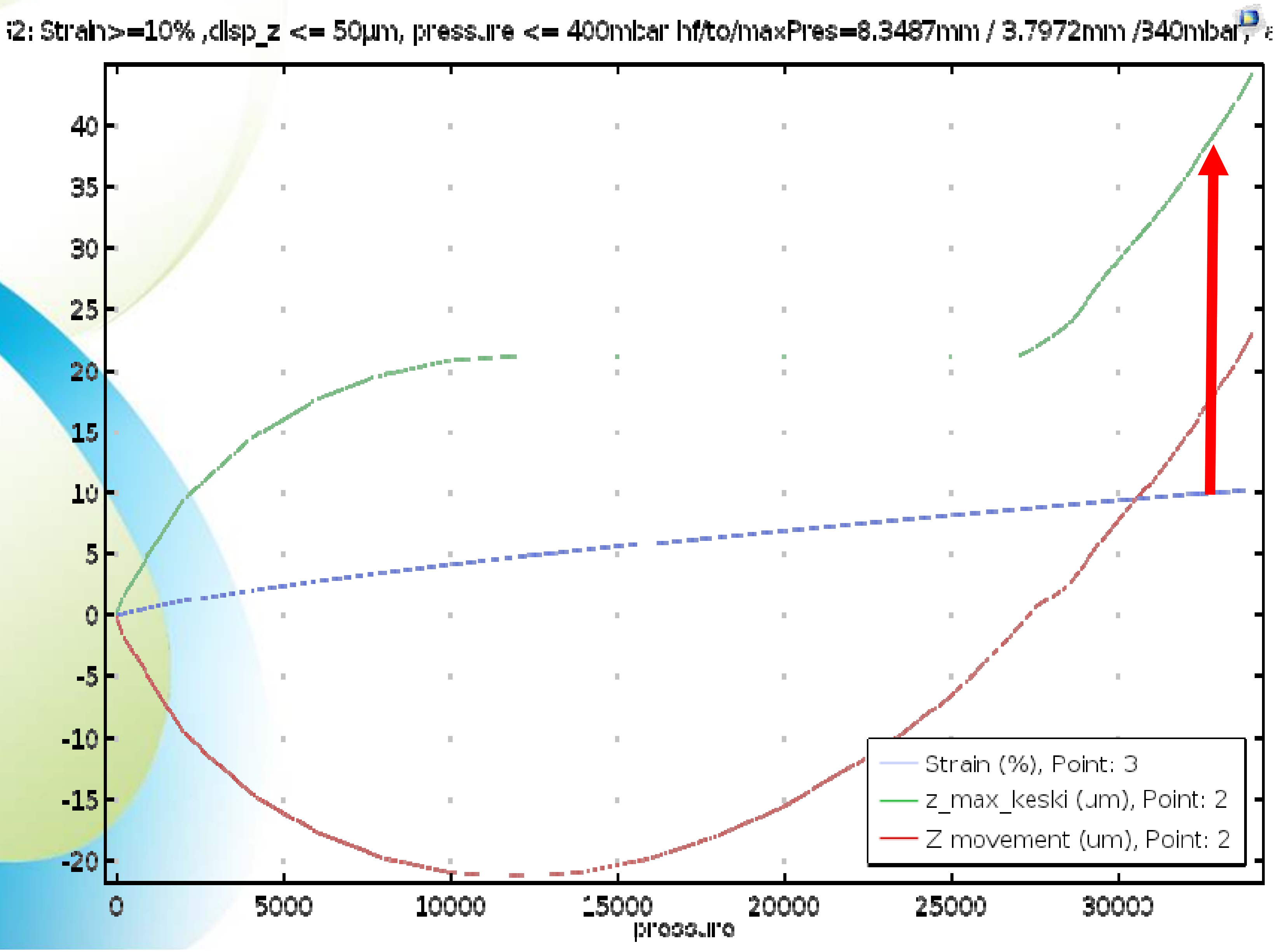
- Strain > 10% when p = ~330 mbar
- Vertical movement: ~37 µm




2: Strain>=10% ,disp_z <= 50µm, pressure <= 400mbar hf/to/maxPres=8.3487mm / 3.7972mm /340mbar,
40
35
30
25
20
15
10
5
0
-5
-10
-15
-20
0
5000
10000
15000
20000
25000
30000
pressure
Strain (%), Point: 3
z_max_keski (um), Point: 2
Z movement (um), Point: 2

OUTLINE

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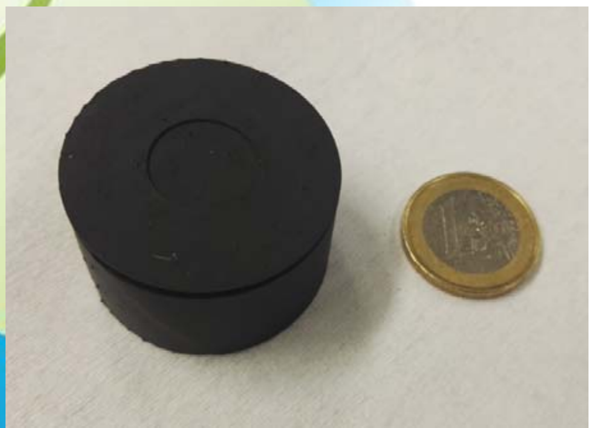
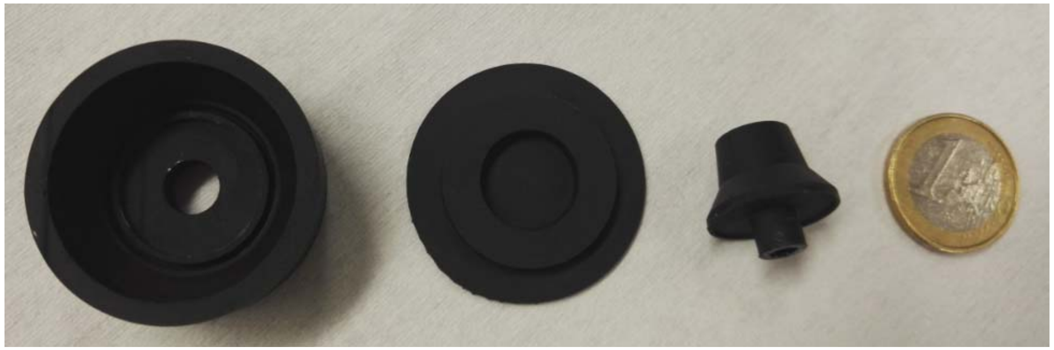
Discussion & challenges

- Modeling method to optimize cell streching device was presented
- Some issues related to modeling strain of membrane
  - PDMS parameters (*E*, *ρ*, …) vary
  - Stationary (modeling) vs. time-dependent (1 Hz sine) experiments
  - Hyperelastic material → very non-linear
    - Neo-Hookean model used → some more sophisticated?
  - Liquid (cell media) not included
- Optimization: Finding really optimized structure difficult
  - Best results vs fabrication
  - Between geometry ranges, not all combinations possible → need to do optimization simulations in steps
  - Highly non-linear problem
    - Cobula etc solver→ typically only local maximum
    - Monte Carlo solver used → is really ”optimized”?

Future work

- For the future
  - Fabricate the optimized device
  - Verify the strain and z-movement
  - Streching cells
    - Study different strecthing parameters (e.g. different input signal frequencies and amplitudes)





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  - Prof. Pasi Kallio, researchers Joose Kreutzer and Leena Koistinen
  - COMSOL support
  - Financial: Academy of Finland, Finnish Society of Automation

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