Master Thesis Presentation

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Title:	Towards Monitoring Tissue Stiffness in-Vitro
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Towards Monitoring Tissue Stiffness in-Vitro

Crystal Liou

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Introduction

Fibrosis is an excessive accumulation of extracellular matrix (ECM). It is caused by repeated tissue injury or dysregulated wound healing process. Myofibroblast is the main cell type involved in fibrosis. It produces ECM when activated by proinflammatory factors. The excessive ECM results in tissue hardening which further promotes myoflbroblast activation. As fibrosis becomes progressive, it can lead to organ dysfunction and even death. As the stiffness plays an important role in fibrotic disease, the aim of this study is to implement a stiffness measurement setup to experimentally measure stiffness of the cells cultured on chip and to develop a finite element (FE) simulation to give insight for future design improvement of the chip.

Materials and Methods

This project contains an experimental part for the deflection measurement of the setup and a FE simulation part to give insight for future design modification of the chip. Chips that were modified from lung–on-chip platform was used. The stiffness can be measured by the deflection of the membrane using a microscope with reflected light.

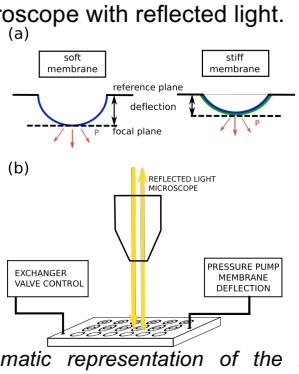

Fig. 1 Schematic representation of the measurement setup.

Measurement technique was applied on three different models. We started with inorganic model, pure PDMS membrane integrated in the chip, to characterize the measurement setup. Followed with collagen on chip model which is easier to handle and has a higher relevance. Finally, the hepatic stellate cells (HSC) were cultured on chip and the deflection measured. On the simulation part, a single membrane model and a simplified two membranes model was implemented. The simulation was done with different dimensions and membrane thicknesses to an idea for future optimization of the chip.

Results

The deflection of naked PDMS membrane was measured to calculate the Young's modulus. By fitting with an analytical Neo-Hookean hyperelastic model, the resulted E_{pdms} is 4.01MPa. The stiffness of 1mg/ml and 2mg/ml collagen concentration gel was characterized, it increased the stiffness of the chip membrane to 233% and 249%, respectively. The HSC cultured on chip had increase of collagen deposition when treated with AA2P inducer. Unfortunately, the stiffness of HSC could not be assed due to cell culture issues. The FE simulation results suggest that a reduction of membrane thickness only little improves the sensitivity, but an increase in membrane radius would significantly improve the sensitivity.

Discussion

The measurement setup was successfully applied to characterize the Young's modulus of PDMS and collagen gel on chip. HSC cell s were successfully cultured on chip and collagen deposition was quantified. Unfortunately, the cell layer was detached after the membrane deflection. Thus, the tissue stiffness could not be measured. The correlation between collagen deposition and stiffness could therefore not be acquired.
Suggested by the FE simulation results, the stiffness change of thin biological tissue with E~10KPa level is too small to be measured with the current chip design. Further modifications of the chip are needed to reduce the stiffness of the base membrane and increase the sensitivity of the system. Although the stiffness change of the cell layer and the collagen deposition could not be measured with the current setup, we made important progress towards a liver-fibrosis-on-chip model and give future perspectives for important design changes.

References

Stucki AO, Stucki JD, Hall SRR, Felder M, Mermoud Y, Schmid RA, Geiser T, Guenat OT: A lung-on-a-chip array with an integrated bio-inspired respiration mechanism. Lab Chip 2015.

Acknowledgements

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