Approach to an on-chip 3D neural-network in a hydrogel based bioreactor

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Research and development of drugs for the treatment of brain diseases require simple techniques that allow reliable high content screening in experimentally reproducible in-vitro hydrogel brain models [1],[2]. Here, a novel biomimetic based brain analog for *in-vivo* like neural cell culture with electrophysiological and biochemical read-outs is presented. We propose a 3D cell culture on top of a MEMS fabricated multi-electrode array as a solution to advanced brain models. By means of polydimethylsiloxane (PDMS) soft lithography, a bioreactor for neuronal cell culturing is realized in combination with a hydrogel.

The PDMS bioreactor is produced from a mold based on removable preconfigured 3D structures [3]. A hydrogel is inserted into the molded PDMS to form a semi-permeable cell culture chamber. Afterwards the 3D structures are removed to obtain microfluidic channels.

To test the utility of the hydrogel for its function as semi-permeable barrier, primary neurons dissociated from brains of newborn rats are cultured in agarose in a 96 well culture plate. Matrigel is used as positive control for cell growth and development. After staining the cells (Figure 1), the results indicate that agarose can indeed be used as a semi-permeable barrier preventing cells to migrate out of the culture chamber once integrated into the bioreactor.
The PDMS bioreactor with a agarose hydrogel and a cell culture compatible Matrigel is tested for fluid transport to the culture chamber (Figure 2). Agarose is stained after introduction of red dye into the coiled channel. The green stained Matrigel in the center becomes dark colored upon mixing of the red dye from the agarose.

The promising features of this bioreactor for 3D cell culturing will be further explored in future experiments. This also includes the possibility of combining the bioreactor with established micro-electrode arrays (MEA) for neuroelectrophysiological experiments with 3D neural networks, providing a novel brain model.

MIRA Institute for Biomedical Engineering and Technical Medicine of the University of Twente are greatly acknowledged, as well as financial support by the European Research Council within the MESOTAS project.

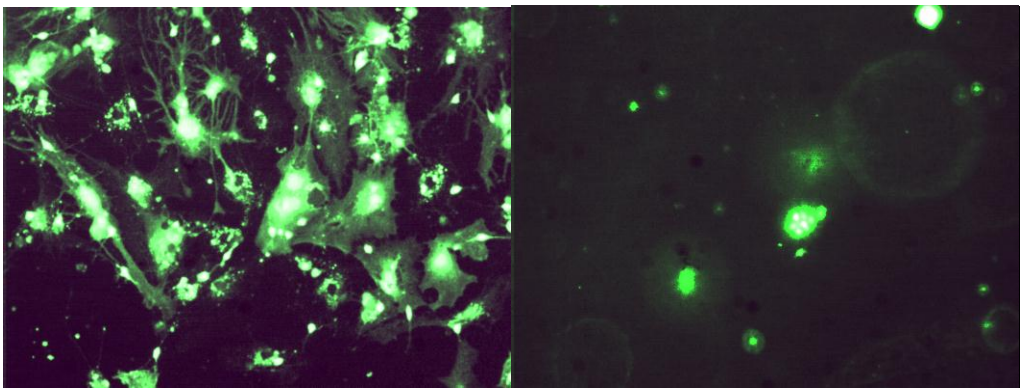

Figure 1:
Primary rat cortical brain cells (DIV 30 days) cultured in Matrigel (left) and agarose (2%)(Right). Migration, growth and cellular development of the cells in the Matrigel is higher in comparison to the agarose hydrogel, which only encapsulates the cells.

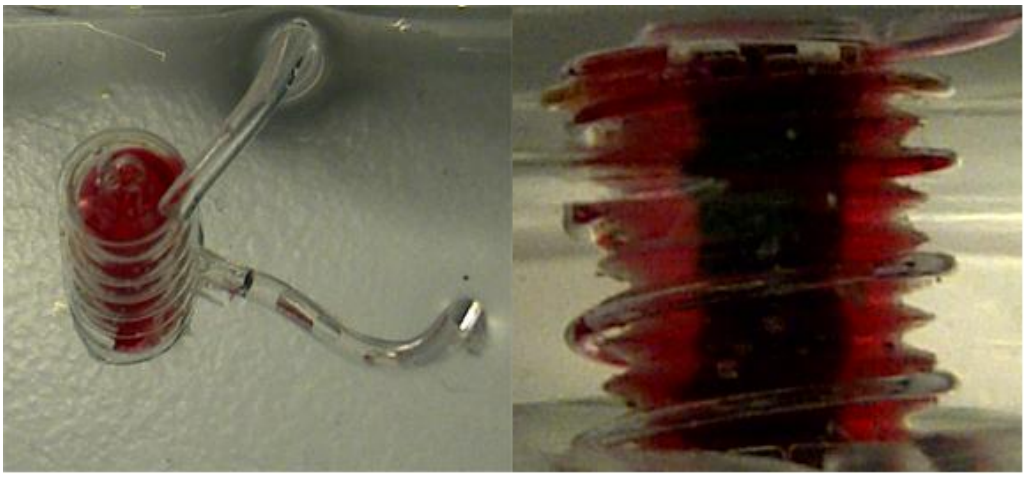

Figure 2:
The PDMS bioreactor with a coiled channel with inlet and outlet. The coiled channel is connected to the central reservoir in which the Matrigel (dark) is inserted into an agarose hydrogel (red).

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[3] Hongkai Wu,Teri W. Odom,Daniel T. Chiu, and, and George M. Whitesides. Fabrication of Complex Three-Dimensional Microchannel Systems in PDMS. Journal of the American Chemical Society 2003 125 (2), 554-559