FRAUNHOFER INSTITUTE FOR MATERIAL AND BEAM TECHNOLOGY IWS

Supporting your vision

REGULATING MICROFLUIDIC-BASED CELL CULTURE SYSTEMS WITH THE USE OF NETWORK MODELS

Mathias Busek[1], Kevin Hofmann[2], Uwe Grätz[2], André Rudolph[1], Stefan Grünzner[1], Florian Schmieder[1], Frank Sonntag[1]

[1]Fraunhofer Institute for Material and Beam Technology IWS Dresden; [2] ITI GmbH, Dresden

Kontakt: mathias.busek@iws.fraunhofer.de

INTRODUCTION

Microfluidic-based cell culture systems are getting more and more important in biotechnology especially for the recently developed "organ-on-a-chip" [1] systems with several human tissues in one branched microvascular system [2]. Due to the high complexity of those systems flow and nutrient regulations are essential. Hereby presented is an approach which uses a mathematical model of the microfluidic system to calculate how fluidic actuators like valves and pumps have to be set to ensure specific nutrient and growth factor gradients.

SETUP

The oxygen content in a branched, polymer multilayer cell cultivating device [3] with integrated micro pumps, valves and tissue chambers was measured in two parallel fluidic pathes (see Fig. 2). By operating the pneumatic pump with different process gases (nitrogen, air) the amount of dissolved oxygen can be varied. Furthermore the perfusion of each cell culture chamber was regulated with the help of closing valves positioned in each fluidic branch.

RESULTS

Due to permeation processes the oxygen content in the fluidic system could be slightly reduced within several minutes by operating the pump with nitrogen. The flow directing valves are sequentially actuated so that repeatedly n pump cycles are pumped in chamber A and k cycles are flowing in chamber B. By varying the n/k ratio one can influence the deoxygenation curve or keep the cell culture at a certain oxygen level. The last operating mode can be used for repeated hypoxia assays which are currently performed in animals [4]. Bye dying the cells for example with CYTO-ID® one can observe the oxidative stress for the cultivated cells under different hypoxic conditions.

[1] S. N Bhatia and D. E Ingber: "Microfluidic organs-on-chips", Nature biotechnology, Vol 32 No. 8,760-772, 2014.

[2] I. Wagner et al: "A dynamic multi-organ-chip for long-term cultivation and substance testing proven by 3D human liver and skin tissue co-culture", Lab Chip, 13, 3538-3547, 2013.

[3] U. Klotzbach et al: "Multilayer-based lab-on-a-chip systems for perfused cell-based assays", Advanced Optical Technologies, 3 No. 5-6, 515-521, 2014.

[4] J. R. McColm et al: "VEGF isoforms and their expression after a single episode of hypoxia or repeated fluctuations between hyperoxia and hypoxia: Relevance to clinical ROP" Relevance to clinical ROP

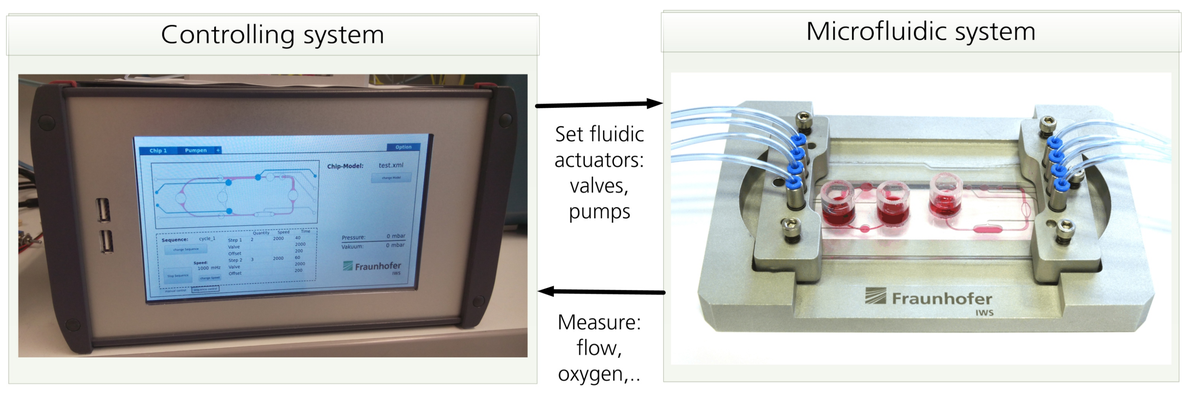

FIGURE 1: Cell cultivating device consisting of a microfluidic system and a controlling system which sets fluidic actuators and measures oxygen content. A mathematic model of the fluidic can be implemented.

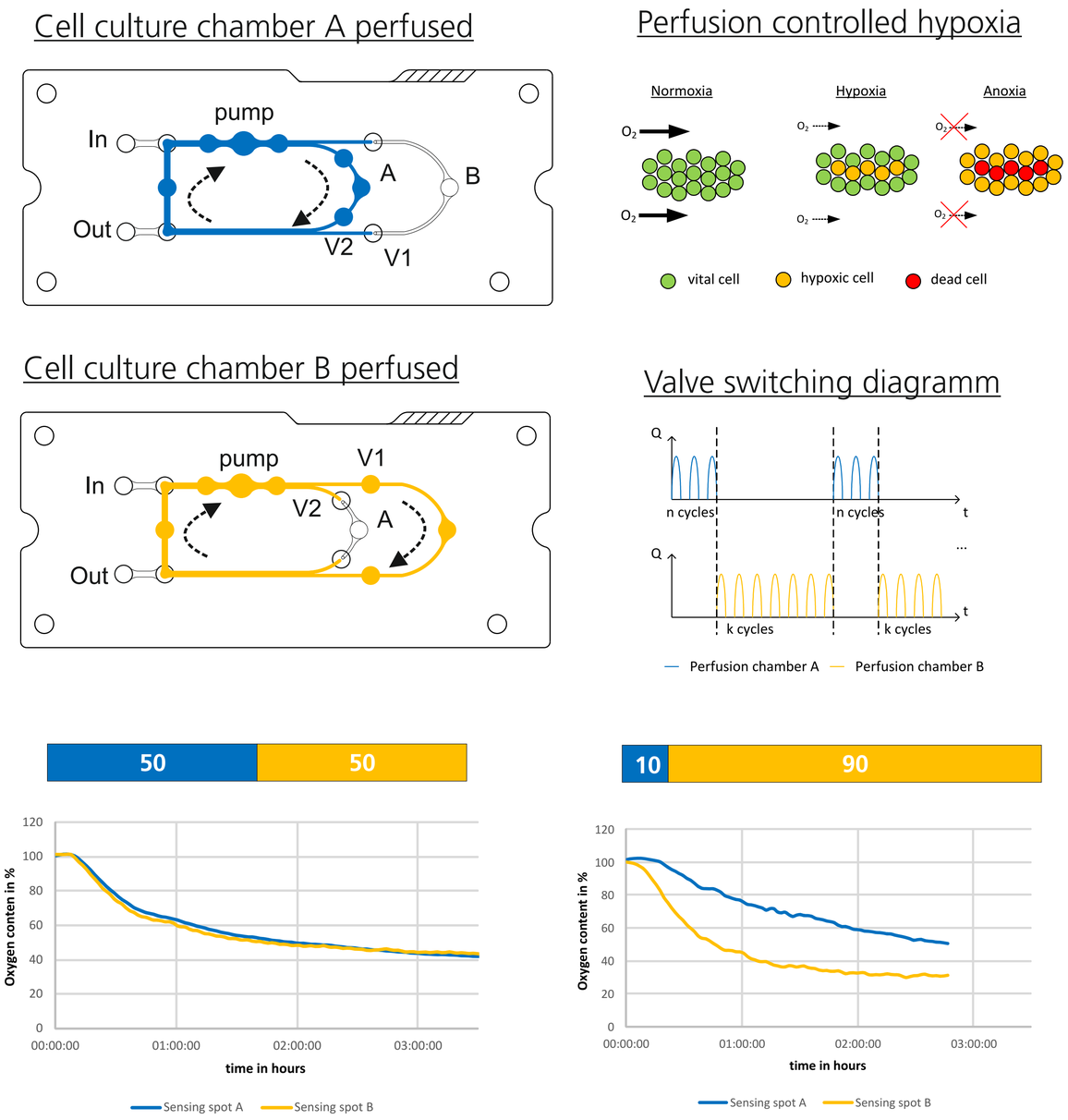

FIGURE 2: Top: Principle of perfusion controlled hypoxia assay with two parallel cell culture chambers A and B controlled by the closing valves V1 and V2. Bottom: Measured oxygen content in both chambers for different actuation cycles of V1 and V2 (50/50 and 10/90) under deoxygenation with nitrogen as process gas mimicing two different hypoxic states.