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Design and development of microbioreactors for long-term cell culture in controlled oxygen microenvironments

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Abstract:

The ability to control the oxygen level to which cells are exposed in tissue culture experiments is crucial for many applications. Here, we design, develop and test a microbioreactor (MBR) for long-term cell culture studies with the capability to accurately control and continuously monitor the dissolved oxygen (DO) level in the cell microenvironment. In addition, the DO level can be controlled independently from other cues, such as the viscous shear-stress acting on the cells. We first analyze the transport of oxygen in the proposed device and determine the materials and dimensions that are compatible with uniform oxygen tension and low shear-stress at the cell level. The device is also designed to culture a statistically significant number of cells. We use fully transparent materials and the overall design of the device is compatible with live-cell imaging. The proposed system includes real-time read-out of actual DO levels, is simple to fabricate at low cost, and can be easily expanded to control the concentration of other micro-environmental solutes. We performed control experiments in the absence of cells to demonstrate that the MBR can be used to accurately modulate DO levels ranging from atmospheric level to 1 %, both under no flow and perfusion conditions. We also demonstrate cancer cell attachment and viability within the MBR. The proposed MBR offers the unprecedented capability to perform on-line measurement and analysis of DO levels in the microenvironment of adherent cultures to correlate them with various cellular responses.

Key-words: microfluidics, hypoxia, cell culture, microenvironment control