Real-time direct cell concentration and viability determination using a fully automated microfluidic platform for standalone process monitoring

The industrial production of cells has a large unmet need for greater process monitoring, in addition to the standard temperature, pH and oxygen concentration determination. Monitoring the cell health by a vast range of fluorescence cell-based assays can greatly improve the feedback control and thereby ensure optimal cell production, by prolonging the fermentation cycle and increasing the bioreactor output. In this work, we report on the development of a fully automated microfluidic system capable of extracting samples directly from a bioreactor, diluting the sample, staining the cells, and determining the total cell and dead cells concentrations, within a time frame of 10.3 min. The platform consists of custom made stepper motor actuated peristaltic pumps and valves, fluidic interconnections, sample to waste liquid management and image cytometry-based detection. The total concentration of cells is determined by brightfield microscopy, while fluorescence detection is used to detect propidium iodide stained nonviable cells. This method can be incorporated into facilities with bioreactors to monitor the cell concentration and viability during the cultivation process. Here, we demonstrate the microfluidic system performance by monitoring in real time the cell concentration and viability of yeast extracted directly from an in-house made bioreactor. This is the first demonstration of using the Dean drag force, generated due to the implementation of a curved microchannel geometry in conjunction with high flow rates, to promote passive mixing of cell samples and thus homogenization of the diluted cell plug. The autonomous operation of the fluidics furthermore allows implementation of intelligent protocols for administering air bubbles from the bioreactor in the microfluidic system, so that these will be guided away from the imaging region, thereby significantly improving both the robustness of the system and the quality of the data.

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