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Micro-fluidic integrated toolkit for micro-bioreactors and bio-catalytic processes

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Abstract

For true “Lab on a chip” applications, integration of microfluidics and analytical devices need to be realized. Here we report on 2D and 3D fabricated microfluidic “chips” based on unit operations (i.e. mixing, pumping, splitting and sensing) that can be combined and applied to the cell cultivation of saccharomyces cerevisiae in a 3D printed milli-bioreactor.

Keywords: microfluidics; 3D printed bioreactor; biosensor integration; “Lab on a Chip”; SPE; cultivation, PMMA

1. Introduction

Biosensors and microfluidics are ideal platform components to integrate for use in screening and online analysis applications. In order to sufficiently control individual channels in such devices, actuators have to be integrated into the system [1]. Microfluidic functions can be categorized into unit operations such as: micro-mixing, pumping, focusing, sorting and transfer [2]. Mastering these functions can lend themselves towards self-sufficient on-chip systems like multi-sensor microsystem for cancer research and drug screening. Here, we focus on a simplified miniaturized bioreactor platform, developing and characterizing all the sensors and actuators necessary for self-contained operation.

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2. Materials and methods

Electrochemical glucose biosensors are based on Prussian blue modified screen printed electrodes, glucose oxidase entrapped and protected by BSA and Nafion117 layer on the working electrode. Microfluidic devices were either engraved into PMMA by a CO2 laser cutter or build by stereo lithographic 3D printer. A modular approach is chosen for future “plug and play” systems towards building flexible integrated analytical bioreactor platforms. A 2.5 mL bioprocessing unit (“Milli-reactor”) is presented; Saccharomycescerevisiaeis cultivated with glucose concentrations and optical density monitored. The milli-bioreactor features an integrated magnetic mixer and external pumping and diluting system. Characterizations of active, magnetically actuated mixing, selective diluting system and a micro-centrifugal pump are presented. Mixing is evaluated using two syringe pumps, one filled with 5mM glucose and one with water. Guided through the mixing system, ratios of two different flow rates should yield expected concentrations of glucose monitored at the outlet if mixing is successful. Selective diluting system is evaluated in a similar manner with the same syringe pumps and their contents glucose is monitored at the outlet after a flow separator. The flow separator efficiency is visualized using a blue dye. Pumping is evaluated independence of potential fed to the actuating electric motor; flow rates and electrical currents are monitored. Cultivation was carried out in YPD medium, 20g/L glucose, in batch.

3. Results

Fig. 1. Evaluation of developed microfluidic tools developed to aid biosensor integration into microfluidics. (a) Micro-mixing: a mixing particle is magnetically actuated for active mixing as passive mixing is often inefficient. (b) Flow separator in tandem with a micromixer, evaluation with glucose solution and water at the two inlets. Laminar flow across the micromixer enables flow separation behind the mixer only when the mixer is turned on. (c) Color visualization of the separator – mixer is turned off on the left and on the right side. (d) Evaluation of the magnetically actuated micro-pump. A magnetic particle is spinning the fluid, causing centrifugal forces; hence, higher pressure at the radial outlet as opposed to axial inlet causes fluid propulsion.
4. Conclusion

Essential microfluidic tools for biosensor integration have been developed and characterized per unit operation, followed by an example of an integrated system. Pump, mixer and selective dilution system are modular and can be integrated into other applications.

- Mixing works with no restrictions. When used for diluting, the outlet concentrations correspond well with the expected values.
- Mixing also works well in the Milli-bioreactor for cultivations. Glucose sensors were successfully utilized for the monitoring of glucose concentrations in the fermentation broth.
- Mixing can be coupled with a flow separator, creating a selective dilution system. The Flow separator exhibits good efficiency at the flow rates around 400μL/min. The operation is highly reproducible.
- The micro-pump has a window where it works well approx. 50-380μl/min. When the potential is too low and the magnet is spinning too slowly, the generated pressure difference is insufficient for pumping. When the potential is too high, the magnetic wheel spins too quickly and the maximum momentum is exceeded, thus the pumping magnet can no longer spin.

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