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Microbioreactor for lower cost and faster optimization of protein production

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Abstract:

Optimisation of bioprocesses relies on approaches that are either labour intensive or require expensive robotic systems. There is a need for fluidic processing at low volume that can be integrated with existing bioprocess analytics to provide analytical information for the development and optimization of bioprocesses. We demonstrate a 1 mL polymer inkjet 3D printed (i3DP) microbioreactor with integrated sensing (pH, oxygen and cell density) for optimization of recombinant protein production with different feeds. A pressurized fluid driving system was used to control flow rates down to 0.7 µL min^{-1} with fluid switching from four reservoirs using a manifold controlled by solenoid valves. Oxygen transferred from a headspace via a gas-permeable membrane achieved a k_La of up to 90 h^{-1} at 1500 rpm. Cultivation of *E. coli* within the microbioreactor was comparable with a 2 L bench scale bioreactor, with optical densities of respectively 7.1 ± 0.4 and 6.5 ± 0.35. Triplicate batch cultivations within the microbioreactor of *Pichia pastoris* with diauxic growth on glycerol (0.20 ± 0.02 h^{-1}) and methanol (0.02 ± 0.04 h^{-1}), showed good control of pH and DO and achieved a maximum dry cell weight of 10 ± 1 g L^{-1}. For continuous cultivations, recombinant protein production was higher in pure methanol (314 ± 23) than methanol-sorbitol (202 ± 17) but reduces over time with lower cellular viability for methanol-glucose mixed feed, with less total protein produced and increases in DNA and proteases released. The developed system could be used in different applications including within synthetic biology, cell and gene therapy and organ-on-chips.

Keywords: microfluidic microbioreactor, oxygen transfer efficiency, recombinant protein production, gas-permeable membrane, process optimization, i3DP