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Design and Fabrication of Disposable Microbioreactor

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Abstract

One area of interest in biotechnology is the parallelization of biological processes in a small-scale reactor system such as a microbioreactor. Microbioreactors are generally defined as a very small bioreactor system in which bioprocess operation take place under controlled operating conditions. This paper developed a model-based methodology in designing and fabricating a disposable microbioreactor system. The concept of attainable region was used to locate the optimal process design solution in terms of optimal condition of operation and from economic point of view. The target for this optimal solution was defined and selected at the maximum point of the attainable region diagram. It is expected that the solution target at the maximum point of the attainable region will show the highest value of the objective function, hence the optimal solution to determine the optimum operating volume for the microbioreactor system. Finally, the size and dimension of the microbioreactor vessel was determined at the optimum condition and then the microbioreactor was fabricated on this basis. The validity of this model-based methodology was confirmed by performing series of fermentation experiments in a microbioreactor setup that was fabricated in accordance to operating volume suggested by this method.

Keywords – attainable region, optimal process, optimal solution, operating volume

1. Introduction

Microbioreactors are generally defined as a very small bioreactor system in which bioprocess operation take place under controlled operating conditions [1]. Microbioreactor working volumes are usually between 50 to 800µL and due to their size, they offer a number of cost-reducing advantages for conducting fermentation processes. Advantages offered by microbioreactor include lower running cost of substrate and utilities, reduced space requirements for parallel experiments, and reduced labour and effort required to prepare fermentation experiment [2].

The capability of parallel operation couple with high through-put screen that can be achieved with microbioreactor system for specific experiment in bioprocess has been behind their transfer to large-scale application [3]. Due to the small size of microbioreactors, the fluid flow and the process conditions in the microbioreactor positively improved the transport phenomena and efficiency of the microbioreactor system. The microbioreactor system is classically used in process development of bioprocess and fermentation processes. These processes can either be aerobic or anaerobic. Microbioreactors are generally fabricated by using polymethylmethacrylate (PMMA) and polydimethylsiloxane (PDMS) polymeric materials. The advantages of fabricating microbioreactor with these materials include: they are cheap materials for microfabrication, easy to handle, and they offers the

possibility to fabricate two-dimensional and three dimensional microfluidic geometries through a rather straight forward fabrication procedures e.g. casting and micromachining [4].

Microbioreactors are often designed to work under bubble-free condition which means that, the reactor will be completely filled with liquid and operates at a constant volume. Therefore, it is important to consider and determine the total operating volume of the microbioreactor before fabrication phase. Generally, the shape of microbioreactors are designed in cylindrical form (i.e. volume = $\pi r^2 h$) and the operating volume is equal to the volume of the cylinder. In spite of the significant progress in microbioreactor technology, the working volume of a typical microbioreactor system is still a debatable issue. Until now, there is no well-established method for mechanical design and fabrication of microbioreactor system. Many of the researchers mention above designed and fabricated their microbioreactor without clear justification on the final volume selected. This paper presented a methodology for designing and fabricating a microbioreactor system with justifiable reasons for the volume selected. This method will enable microbioreactor designer to determine the optimum volume of the microbioreactor prior to fabrication phase.

II. METHODOLOGY

1.1 2.1 Algorithm of Design and Fabrication of Disposable Microbioreactor

A step-by-step algorithm of design and fabrication of disposable microbioreactor is presented below.

Step 1: Attainable Region (AR) Diagram Development: The attainable region diagram for the system is developed by plotting the concentration of the desired product as a function of the concentration of the substrate.

Step 2: Design-Control Target Selection: From the attainable region diagram developed in stage 1, the optimum point of the graph is located and set as a design target.

1.1.1 Step 3: Final Selection and Fabrication: The objective of this stage is to select the best candidates by analysing the value of the multi-objective function of the optimum point obtained at step 2. The best candidate is then selected and use for design and fabrication of the microbioreactor system. Fig.1 below is the flow diagram of the steps involved in design and fabrication of disposable microbioreactor.

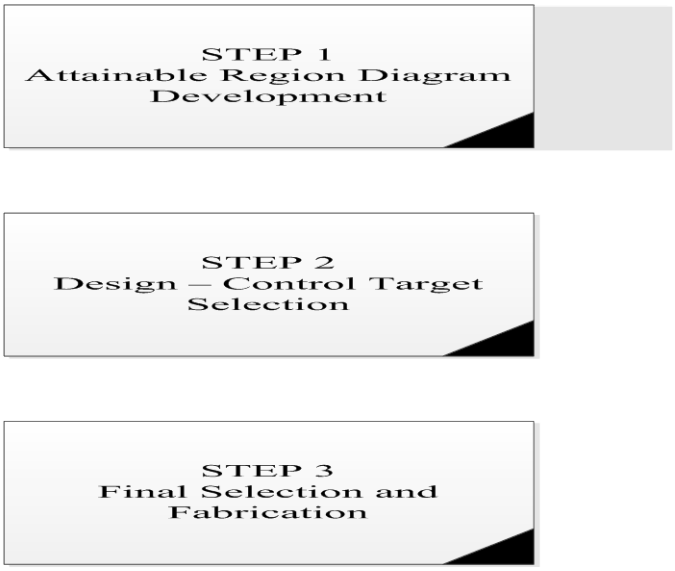

Figure 1: Flow diagram of the proposed method

III. Case Study

The capability of the proposed methodology was tested by determining the optimum operating volume of microbioreactor for conversion of glucose to lactic acid. The kinetic data obtained by [5] for conversion of glucose to lactic acid was adopted for this study. The attainable

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region diagram is shown in Fig. 2. Three different points were located on the AR diagram and at each point, the volume of the microbioreactor was calculated and subsequently their dimension was determined. The microbioreactor setup consisted of three layers (i.e. reactor vessel, PDMS layer, and top layer). The reactor vessels and tops layers were fabricated by using PMMA polymers. The PDMS layers were molded with PMMA material and casted by using PDMS substrate and curring agent in the ratio of 10:1 respectivey . The shape and size of these layers were achieved by using CNC milling maching (model-MDX40A). The microbioreactor was equiped with on/off temperature control, PI agitation rate controller and integrated with one-way valve for feeding. Process automation for the reactor setup was achieved by interfacing the sensors and actuators to National Instruments (NI) data acquisition device NIUSB6343.

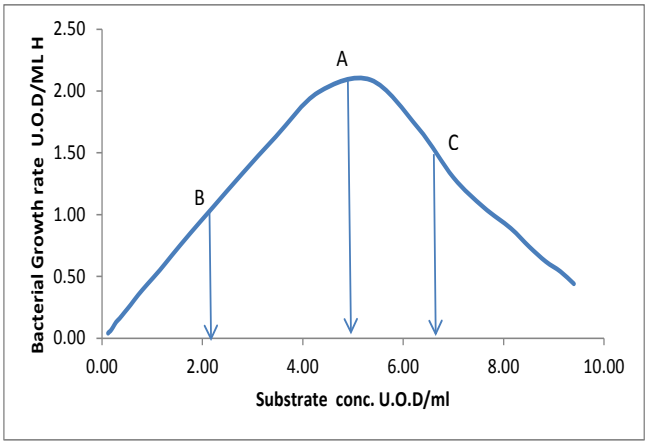

Figure 2: AR diagram for fermentation of glucose to lactic acid

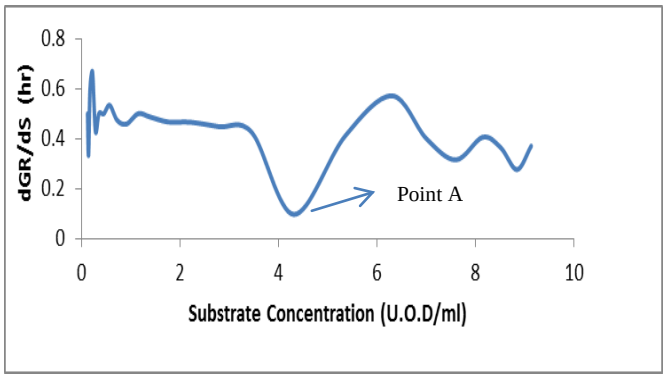

Figure 3: Disturbance rejection analysis.

Figure 6: 19

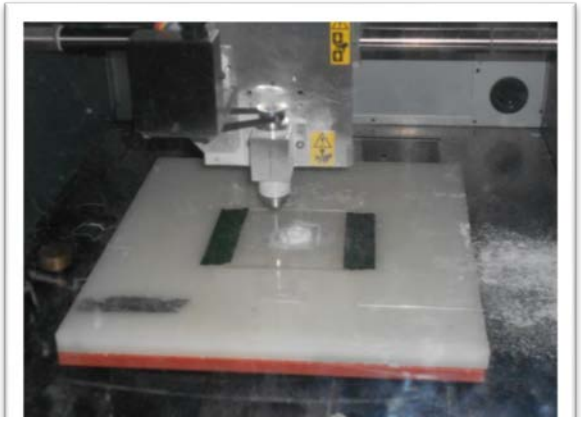

Figure 4: Pictorial views of computer numerical control milling machine used for the fabrications

Figure 5: Middle layer preparation

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4. Discussion of Result

At the maximum point of Fig.2, which is at the 2.09 U.O.D. /ml bacteria growth rate (dN/dt), 18.2 mg/ml concentration of product (P) can be obtained. Even though this is not the highest yield, but at this point is the best in terms of controllability performance. At this point, the sensitivity of the bacterial growth rate with respect to disturbance (change in the substrate) will be smaller. Thus, will have smaller effect on the bacterial growth rate and the rate can be easily maintained in the presence of disturbance. A microbioreactor should be designed at the maximum point of the attainable region because at this point the controllability performance of the system is best satisfied [6]. To establish this, the absolute value of derivatives of rate of bacterial growth with respect to substrate concentration is plotted for the sensitivity analysis as shown in Fig. 3. From control point of view, any changes in the substrate concentration will give smaller changes in bacterial growth at point A compared to any other points. Therefore, by maintaining the substrate at point A, the product can easily be obtained and control than for the other points. Hence, the optimum volume for this microbioreactor is the volume of the microbioreactor at point A. The diameter of the microbioreactor was calculated to be 19mm and 4mm depth. The optimum volume was calculated to be approximately 1.2 ml.

5. Conclusion

A design and fabrication of disposable microbioreactor methodology relying on the use of attainable region approach has been developed and presented in this paper. The method is capable of determining the optimum operating volume of microbioreactor system before the fabrication phase of the microbioreactor. The method has the additional advantage that it also offers clear justification for the size of the designed disposable microbioreactor.

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