

A Fluid Dynamics Approach to Bioreactor Design for Cell and Tissue Culture

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Abstract: The problem of controlling cylindrical tank bioreactor conditions for cell and tissue culture purposes has been considered from a flow dynamics perspective. Simple laminar flows in the vortex breakdown region are proposed as being a suitable alternative to turbulent spinner flask flows and horizontally oriented rotational flows. Vortex breakdown flows have been measured using three-dimensional Stereoscopic particle image velocimetry, and non-dimensionalized velocity and stress distributions are presented. Regions of locally high principal stress occur in the vicinity of the impeller and the lower sidewall. Topological changes in the vortex breakdown region caused by an increase in Reynolds number are reflected in a redistribution of the peak stress regions. The inclusion of submerged scaffold models adds complexity to the flow, although vortex breakdown may still occur. Relatively large stresses occur along the edge of disks jutting into the boundary of the vortex breakdown region. © 2006 Wiley Periodicals, Inc.

Keywords: bioreactor technology; fluid dynamics; particle image velocimetry; cell culture; scale-up

INTRODUCTION

Improving the outcomes of cell and tissue culture through the use of bioreactors is a goal that has recently received substantial research interest (Darling and Athanasiou, 2003; Freed and Vunjak-Novakovic, 2000; Martin et al., 2004; Shachar and Cohen, 2003). This has partly been generated by strong advancements in the fields of tissue engineering and cell culture based research. In particular there is now the need to produce therapeutically relevant cell yields or tissue constructs on a scale that goes far beyond what is typically required for laboratory use (Carrier et al., 1999; Martin et al., 2004; Wu et al., 1999). Cell culture bioreactors range from, among other designs, highly specialized microscale perfused vessels (Nielsen, 1999; Nilsson et al., 1999), to larger rotating wall annular flow vessels (Begley and Kleis, 2000, 2002; Freed and Vunjak-Novakovic, 1995, 2000; Goodwin

et al., 2003; Kleis et al., 1990), to simple upright tanks stirred either by impeller or magnetic stirrer (Cherry and Papoutsakis, 1986; Leckie et al., 1991; Kallos et al., 1998; Vunjak-Novakovic et al., 1996). Bioreactor design requirements are numerous and varied, and include hydrodynamic stress conditions, nutrient delivery, gas transfer, sterility, heat transfer, and maintenance. Where adherent cells (e.g., endothelial cells, epithelial cells, or chondrocytes) are cultured, surface properties and the flow around bluff bodies also become important.

The process of generic bioreactor design is impeded by the range of hydrodynamic requirements, which vary on a case-by-case basis. For example, different phenotypes will respond in different ways to a certain shear exposure. Furthermore, in the case of cell culture for tissue engineering purposes, a high cell yield and a complex aggregate structure may be required. These complications limit mammalian cell bioreactor technology, as the expertise of the cell culturer rarely encompasses all the disciplines necessary to adequately meet all the design requirements. Consequently, the fluid dynamics of the system is one area that has lacked thorough attention. Despite a few attempts to predict bioreactor flows using both experimental and computational fluid dynamics (Begley and Kleis, 2000, 2002; Curran and Black, 2004; Sadosky et al., 2004; Venkat et al., 1996; Williams et al., 2002), there are relatively few recorded cases where the hydrodynamic force considerations have been given prominence.

The approach usually exercised in the previous bioreactor fluid dynamics studies has been to commence with a measurement or adaptation of an established bioreactor technology. Our approach proceeds from a different angle, with an investigation of more fundamental flows derived as idealizations of mixed flask bioreactor flows. The intention is to demonstrate that appropriate shear and mixing conditions can be better located within flows using a spatially resolved three-component velocimetry technique. A wider aim is to demonstrate the merits of characterizing bioreactor flows in terms of independent, non-dimensional parameters. By linking models that describe the manner in which the internal physical properties are determined by certain input

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Table of Contents **Bioreactor And Bioproceb Fluid Dynamics**

1. Understanding the eBook **Bioreactor And Bioproceb Fluid Dynamics**
 - The Rise of Digital Reading **Bioreactor And Bioproceb Fluid Dynamics**
 - Advantages of eBooks Over Traditional Books
2. Identifying **Bioreactor And Bioproceb Fluid Dynamics**
 - Exploring Different Genres
 - Considering Fiction vs. Non-Fiction
 - Determining Your Reading Goals
3. Choosing the Right eBook Platform
 - Popular eBook Platforms
 - Features to Look for in an **Bioreactor And Bioproceb Fluid Dynamics**
 - User-Friendly Interface
4. Exploring eBook Recommendations from **Bioreactor And Bioproceb Fluid Dynamics**
 - Personalized Recommendations
 - **Bioreactor And Bioproceb Fluid Dynamics** User Reviews and Ratings
 - **Bioreactor And Bioproceb Fluid Dynamics** and Bestseller Lists

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 - Bioreactor And Bioproceb Fluid Dynamics Public Domain eBooks
 - Bioreactor And Bioproceb Fluid Dynamics eBook Subscription Services
 - Bioreactor And Bioproceb Fluid Dynamics Budget-Friendly Options
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 - ePub, PDF, MOBI, and More
 - Bioreactor And Bioproceb Fluid Dynamics Compatibility with Devices
 - Bioreactor And Bioproceb Fluid Dynamics Enhanced eBook Features
7. Enhancing Your Reading Experience
 - Adjustable Fonts and Text Sizes of Bioreactor And Bioproceb Fluid Dynamics
 - Highlighting and Note-Taking Bioreactor And Bioproceb Fluid Dynamics
 - Interactive Elements Bioreactor And Bioproceb Fluid Dynamics
8. Staying Engaged with Bioreactor And Bioproceb Fluid Dynamics
 - Joining Online Reading Communities
 - Participating in Virtual Book Clubs
 - Following Authors and Publishers Bioreactor And Bioproceb Fluid Dynamics
9. Balancing eBooks and Physical Books Bioreactor And Bioproceb Fluid Dynamics
 - Benefits of a Digital Library
 - Creating a Diverse Reading Collection Bioreactor And Bioproceb Fluid Dynamics
10. Overcoming Reading Challenges
 - Dealing with Digital Eye Strain
 - Minimizing Distractions
 - Managing Screen Time
11. Cultivating a Reading Routine Bioreactor And Bioproceb Fluid Dynamics
 - Setting Reading Goals Bioreactor And Bioproceb Fluid Dynamics
 - Carving Out Dedicated Reading Time
12. Sourcing Reliable Information of Bioreactor And Bioproceb Fluid Dynamics
 - Fact-Checking eBook Content of Bioreactor And Bioproceb Fluid Dynamics
 - Distinguishing Credible Sources
13. Promoting Lifelong Learning

- Utilizing eBooks for Skill Development
- Exploring Educational eBooks

14. Embracing eBook Trends

- Integration of Multimedia Elements
- Interactive and Gamified eBooks

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