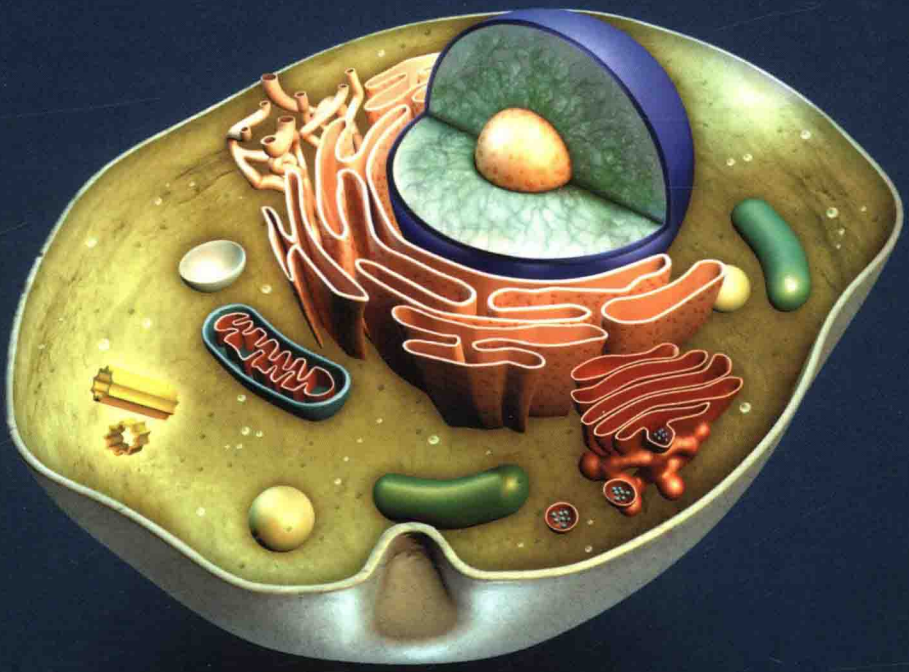
Bioreactors

Animal Cell Culture Control for Bioprocess Engineering



Goutam Saha
Alok Barua
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Bioengineering Science

Bioreactors

Animal Cell Culture Control for Bioprocess Engineering

Bioreactors: Animal Cell Culture Control for Bioprocess Engineering presents the design, fabrication, and control of a new type of bioreactor meant especially for animal cell line culture. The new bioreactor, called the "see-saw bioreactor," is ideal for the growth of cells with a sensitive membrane. The see-saw bioreactor derives its name from its principle of operation in which liquid columns in either limb of the reactor alternately go up and down. The working volume of the reactor is small, to within 15 L. However, it can easily be scaled up for large production in volume of cell mass in the drug and pharmaceutical industries.

The authors describe the principle of operation of the see-saw bioreactor and how to automatically control the bioprocess. They discuss different control strategies as well as the thorough experimental research they conducted on this prototype bioreactor in which they applied a time delay control for yield maximization.

To give you a complete understanding of the design and development of the see-saw bioreactor, the authors cover the mathematical model they use to describe the kinetics of fermentation, the genetic algorithms used for deriving the optimal time trajectories of the bioprocess variables, and the corresponding control inputs for maximizing the product yield. One chapter is devoted to the application of time delay control. Following a description of the bioreactor's working setup in the laboratory, the authors sum up their investigation and define the future scope of work in terms of design, control, and software sensors.

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Bioreactors

Animal Cell Culture Control for Bioprocess Engineering

Preface

Bioprocess engineering is the most important component for industries that produce commercial products such as industrial alcohol, organic solvent, and baker's yeast, special products such as antibiotics, antibodies, therapeutic proteins, vaccines, and recombinant products such as insulin. The bioreactor is where the bioprocess operation takes place, and its design and controlled operation are important for production aspects such as purity, quantity, efficiency, and safety.

Several excellent textbooks on bioprocess engineering are currently available; these generally are written almost exclusively with either biotechnology or chemical engineering in mind. However, these books do not cover the details of control system engineering. *Bioreactors: Animal Cell Culture Control for Bioprocess Engineering* will bridge the gap between control system engineering and biotechnology. The rigorous theoretical analysis it presents for the control of nonlinear systems such as bioprocesses is the major strength of the book.

Bioprocesses require effective control techniques due to increased demand on productivity, product quality, and environmental responsibility. This is especially important where the biomaterials are costly and require stringent control over product formation, as in animal cell cultures. Animal cell culture technologies are used for the production of many enzymes, hormones, vaccines, monoclonal antibodies, and anticancer agents. Among them, the most important product is monoclonal antibodies, which are produced by hybridoma cells.

Monoclonal antibodies have been used as diagnostic agents to develop many drugs, toxins, vitamins, and other biological compounds.

There are several types of bioreactors used in the laboratory as well as in large-scale industrial applications. Some of these are continuous stirred tank, bubble column, airlift, see-saw, and packed bed reactors. As their names indicate, they are meant for aerobic bioreaction processes. The technique used for fermentation of animal cells differs from that used with bacteria, yeasts, and fungi. The typical size of animal cells is 10–30 μm. Animal cells do not have a cell wall, but are surrounded by a thin and fragile plasma membrane, and therefore the cells are very sensitive to shear force. For the efficient growth of cells, the fermenter or bioreactor should operate with essentially no or minimum shear force.

The design, fabrication, and control of a new type of bioreactor meant especially for animal cell culture are covered in this book. Existing bioreactors like the continuous stirred tank reactor, bubble column reactor, and airlift reactors are briefly discussed. However, these conventional reactors are not suitable for fermentation of animal cells, as they cause shear damage to the cells. Moreover, large support material surface areas are to be provided for anchorage of dependent cells. The laboratory-scale cultivation of animal cells is carried out in T-flasks, spinner flasks, and other extremely small reactors, and these are not suitable for any commercial production.

The new bioreactor is called the see-saw bioreactor and is ideal for the growth of cells with a sensitive membrane. The name is derived from its principle of operation, in which liquid columns in either limb of the reactor alternately go up and down. The oxygen transfer in this type of bioreactor has been studied by a distributed parameter model. The working volume of the reactor is small, to within 15 L. However, it can be easily scaled up for large production in volume of cell mass in the drug and pharmaceutical industries. The see-saw bioreactor was developed at the Indian Institute of Technology Kharagpur. The authors neither experimented on animal cells nor made any animal cell culture in the prototype reactor developed and patented due to limited facilities in the department; however, its description and analysis clearly command its suitability for the said culture.

The primary aim of this book is to describe the principle of operation of a new type of bioreactor and how to automatically control the bioprocess. In this context different control

strategies have been discussed. The authors have conducted thorough experimental research on this prototype bioreactor and applied a time delay control for yield maximization. Emphasis has been placed on the development of a suitable control strategy and mode of operation such that more products can be made from this bioreactor. However, the model that is developed from the mass balance concept does not describe the bioprocess completely. The model parameters often vary with time due to metabolic variations and physiological and genetic modifications. The reproducibility of the biotechnological experiments is also poor. Thus a bioprocess, in general, is a nonlinear, undermodeled multivariable system with uncertainties.

The limitations of conventional control such as proportional-integral-derivative have been discussed here. Time delay control, which has never before been used as a controller in bioreactor control, has been applied. It is designed as a tracking controller such that the process variables allow optimal trajectories within finite error bounds. In a bioprocess some of the process variables are not measurable. A suitable observer, or "software sensor," has been designed. The optimal trajectories of different bioprocess variables have been derived using genetic algorithms. However, separate controllers are used for controlling the temperature and pH of the bioreactor fluid.

The authors would like to express their appreciation and gratitude to the many individuals who have contributed to the development of the see-saw bioreactor. Our best wishes go to the students and researchers who are the ultimate users of this book.

Goutam Saha
Alok Barua
Satyabroto Sinha
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Goutam Saha earned his BE in electrical engineering, his ME in electronics and telecommunication engineering, and his PhD in electrical engineering from Bengal Engineering and Science University (formerly known as B.E. College) and IIT Kharagpur in 1984, 1989, and 1999, respectively. He worked as a postdoctoral research fellow at Ben Gurion University, Israel, from January to August 2002. He is currently a full professor in the Department of Information Technology, North-Eastern Hill University, Shillong, India. With more than 25 years of teaching experience in various engineering colleges including the National Institute of Technology (Durgapur), the National Institute of Technical Teachers Training and Research (Kolkata), and other government engineering colleges of West Bengal. He has published several papers in the areas of instrumentation, bioreactor design and control, bioinformatics, and system biology. He has supervised many MS theses and five PhD theses on bioinformatics and system biology. He is also one of the team members holding a patent for the design of a see-saw bioreactor. He is a member of the Sixth Reconstituted Task Force Committee on Bioinformatics, Computational and System Biology for the Government of India.

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Professor Barua is the author or coauthor of several books: *Computer Aided Analysis, Synthesis and Expertise of Active Filters* (Dhanpat Rai, New Delhi, 1995), *Fault Diagnosis of Analog Integrated Circuit* (Springer, the Netherlands, 2005), *Fundamentals of Industrial Instrumentation* (Wiley India, New Delhi, 2011), and *Analog Signal Processing: Analysis and Synthesis* (Wiley India, New Delhi, 2014). He also coauthored a research monogram, *3D Reconstruction with Feature Level Fusion* (Lambert Academic, Germany, 2010).

Satyabroto Sinha (deceased) earned a PhD in electrical engineering from the Indian Institute of Technology (IIT) Kharagpur. He taught electrical engineering at IIT Kharagpur from December 1963 to May 2005 (professor, 1982–2002; professor emeritus, 2002–2005). He advised 13 doctoral students, coauthored several books, and published approximately 60 conference and journal papers, nationally and internationally. His area of specialization was instrumentation and control. He was a national coordinator for the Technology Development Mission on Communication, Networking and Intelligent Automation for the Government of India from 1995 to 2000. He was a senior member of the Institute of Electrical and Electronics Engineers and a chartered engineer and fellow of the Institution of Engineers (India).

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