Research in
BIOCHEMICAL ENGINEERING AND INDUSTRIAL BIOTECHNOLOGY

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BIOCHEMICAL ENGINEERING IS the application of biological and chemical engineering principles in the development and implementation of bio-process systems [1]. As such, it is the handmaiden of industrial biotechnology whereby these systems are put into commercial practice for the production of goods and services [2]. It is predicted that biotechnology will trigger the next industrial revolution [3] and that, within the next decade, more than 25% of new chemical engineering graduates will be involved in biotechnology-related activites [4]. These predictions are based on the current use and future potential of genetic manipulative techniques and biochemical engineering in the development of new and improved processes and products [5].

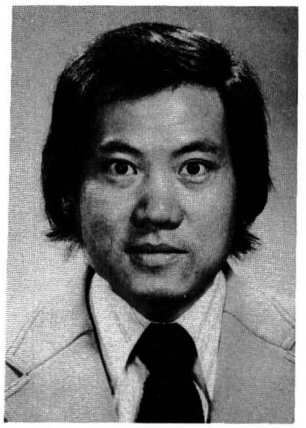
The following sketch of Waterloo's programs in biochemical engineering and industrial biotechnology highlights its graduate courses, its research activities and its technology transfer mechanism.

WATERLOO CONNECTIONS

For many years the University of Waterloo has been a pioneer in high-tech areas including micro-electronics, computer software, robotics, CAD/CAM and biotechnology. Last year, the Wall Street Journal featured it as the top computer school in North America, ahead of MIT and Stanford. In biotechnology, Waterloo has one of the oldest and largest programs in North America [6,7]. Started in 1966, the graduate program now involves 39 researchers, consisting of 7 of the 31 chemical engineering faculty members (see Table 1), 17 graduate students, 5 technicians, and 10 postdoctoral fellows, visiting scholars and research associates, in addition to collaborating faculty in the biology and chemistry departments. Waterloo is the first North American university to introduce a biotechnology core course in its chemical engineering program, which graduates about 100 students annually.

TABLE 1
ChE Faculty Members Involved In Biotech-Related Research

G. J. Farquhar, PhD (Wisconsin)
R. Y. M. Huang, PhD (Toronto)
R. L. Legge, PhD (Waterloo)
M. Moo-Young, PhD (London)
C. W. Robinson, PhD (UC Berkeley)
J. M. Scharer, PhD (Pennsylvania)
G. R. Sullivan, PhD (London)



Murray Moo-Young is a professor of chemical engineering and director of the Industrial Biotechnology Centre at Waterloo. He was educated at the universities of London (BSc, PhD), Toronto (MASc) and Edinburgh (postdoctorate). An active consultant worldwide, he is the chief editor of *Comprehensive Biotechnology*, a multi-volume reference treatise, and *Biotechnology Advances*, an international review journal.

In order to encourage the development of appropriate multidisciplinary "critical masses" in our biotech research, the activities have been incorporated into a research consortium, Guelph-Waterloo Biotech (GWB), which combines the resources of Waterloo with those at the neighbouring University of Guelph. At present, the consortium has 103 faculty members who belong to one or more of four constituent units: animal, industrial, microbial and plant biotech centres. Biochemical engineering research is under the general umbrella of the Industrial Biotechnology Centre (IBC), which is administratively located in the Waterloo chemical engineering department. The synergistic co-operation between several departments at the two universities has considerably expanded the versatility and comprehensiveness of our programs.

IBC has about thirty faculty members represent-

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ing 20% biological, 20% chemical, and 60% engineering-base expertise, and a rough 75/25 split between Waterloo and Guelph. Major aims of IBC include promotion of collaborative research among its faculty members and the provision of "windows" on biotech advances to GWB industrial affiliate members. Within its first year of operation, GWB has already signed up two European and three North American companies: Rhone-Poulenc, Drogocco, Liquid Air, Monsanto, and Allelix.

COURSES

Various courses are offered in biotechnology/biochemical engineering, and brief descriptions of these courses are given below. Except for the last course listed, all courses are given on a regular basis, annually. Throughout these courses, students are constantly reminded of the necessary multidisciplinary nature of biotechnology. It is noteworthy that graduates of honours non-chemical engineering technical programs are admitted to our programs provided they successfully complete a "qualifying" program of a pre-arranged set of courses usually lasting for one to two years of study.

Introduction to Biotechnology • Biological systems for the production of commercial goods and services. Properties of microbial, plant and animal cells, and of enzymes used in bioprocess applications. Classification and characterization of biological agents and materials. Quantification of metabolism, biokinetics, bioenergetics. Elementary aspects of molecular biology, genetic engineering, biochemistry, microbiology. (The material is based on Reference 8.)

Fermentation Engineering • Application of process engineering principles to the design and operation of fermentation reactors which are widely used in the pharmaceutical, food, brewing and waste treatment industries. Aspects of mass transfer, heat transfer, mixing and rheology with biochemical and biological constraints. (The material is based on References 8,9.)

Food Process Engineering • Applications of unsteady and steady-state heat and/or mass transfer operations to processing natural and texturized foods. Design and analysis of sterilization, low-temperature preservation, concentration, separation and purification processes. Effects of formulation, additives and processing on organoleptic and nutritional quality.

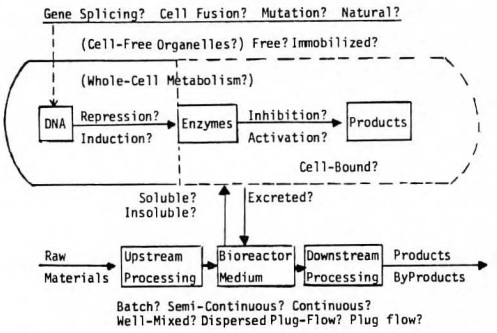

FIGURE 1. Bioreactor heart in industrial biotechnology: Biology selects it, biochemical engineering determines its performance.

(The material is based on Reference 10.)

Principles of Biochemical Engineering • Aspects of mass-transfer, heat-transfer, fluid flow, cell growth and enzyme kinetics related to the design of biological process equipment. Fermentations, sterilization techniques, specialized extraction methods, immobilized-enzyme reactor design. (The material is based on Reference 11.)

Advances in Biochemical Engineering • Design and control of continuous-flow processes for biological systems. Exploration of new methods of producing materials for food and medicinal purposes and of treating effluents. (The material is based on the current literature.)

Selected Topics in Biotechnology • Various courses deemed necessary at intervals. (The material is based on References 12, 13 and the current literature.)

CURRENT RESEARCH ACTIVITIES

A wide range of research projects is conducted in bioprocess and bioproduct developments. As indicated in Table 2 and Figure 1, we address problems involving principles and applications of a theoretical and experimental nature. In addition to the usual research facilities, we are well equipped with computers and a range of pilot-plants including a versatile 1,300-litre fermentation unit (the largest of its kind at a North American university) which is capable of various modes of operation (batch, fed-batch, continuous; stirred tank, air-lift). These facilities are available for graduate studies and contract research. Brief descriptions of a representative sample of our current research projects follow.

Transport Processes in Bioreactors

In this ongoing megaproject, multiphase contacting is used to promote transport processes for bioconversion. Novel contacting devices (recirculation loops, scraped tubes, packed beds) are being developed and compared to conventional stirred tanks and bubble columns for Newtonian and non-Newtonian systems. Transport phenomena and process control are the key elements of study.

Codeine Production

Medically important morphine alkaloids such as codeine are normally obtained from opium poppy cultivated in countries with fairly tenuous governments from which Canada (and the USA) import virtually all their supplies. Work is in progress on a bioreactor battery of immobilized enzymes derived from microbial and plant tissue cultures whereby readily available chemical feedstocks are converted into intermediates which are then chemically transformed to codeine.

Production of Monoclonal Antibodies

Animal cells in culture have the potential to be a source of macromolecules for diagnostic, therapeutic and processing applications. To address commercial scale production concerns, we are designing fully instrumented, computer-controlled, robust bioreactors for growing hybridomona cells in the production of monoclonal antibodies. Initially, MAb's with specificity against a cellulase complex enzyme antigen are being used as a model test system.

MBP Production

Agricultural and forestry residues represent potentially valuable renewable resources for fermentation processes which can be used to produce edible protein-rich microbial biomass products (MBP) for animal feed or human food. We are developing novel MBP processes which are based on the aerobic mass cultivation of yeasts and fungi. Computer process simulations, pilot plant evaluations and animal feeding trials are being used to test techno-economic scenarios for both developed and developing countries.

Ethanol Production

A continuous-flow, packed-bed bioreactor based on surface-immobilized yeasts attached to inexpensive wood chips has been developed, modelled and tested for the fermentation of hexose sugars. Stable operation has been achieved at productivities comparable to or greater than any previously reported. A process for fermenting enzymatically-transformed pentose sugars, another component of cellulosics, using the same yeasts is under investigation for possible process integration.

Anaerobic Digestion

The use of organic wastes is being tested for the production of energy (methane) and organic chemicals (fatty acids) under both mesophilic and thermophilic conditions. Bioreactor studies include continuous and intermittently-stirred tanks and fixed-film trickle beds. Performance is evaluated for retention time, loading rate, carbon-to-nitrogen ratio and several physico-chemical parameters.

Biomass Pretreatment

A techno-economic comparison is made of existing and potential chemical and biochemical strategies for cellulosic biomass utilization in the production of fermentation feedstocks suitable for replacing or supplementing traditional substrates, *e.g.*, molasses, starch. In particular, cellulosic materials generated as paper-pulp mill sludge and wood remnants are being studied.

TABLE 2
Current Research Areas in Biotechnology/Biochemical Engineering

BIOREACTOR DESIGN
- mass transfer
- heat transfer
- mixing
- stirred tanks
- air lifts
- packed beds
- biokinetcs
- bio-immobilization

BIOCONVERSION AGENT
- microbial cells
- plant cells
- animal cells
- rDNA cells
- hybridoma cells
- psychrophiles
- thermophiles
- enzymes

PRODUCT TYPES
- SCP/MBP
- alcohols
- methane
- organic acids
- enzymes
- biopolymers
- monoclonal antibodies
- morphinans

INSTRUMENTATION
- computer control
- biosensors
- data logging
- modelling
- product assays
- economic analysis
- CAD/CAM

BIOPROCESSING TECHNIQUES
- hydrolysis
- sterilization
- membrane separations
- chromatography
- flotation
- drying
- cell disruption

FEEDSTOCK TYPES
- cellulosics
- starches
- sugars
- oils
- forestry biomass
- agricultural biomass
- biomass pulps
- xenobiotics

Additional benefit in reduced disposal costs and environmental pollution control may be realized.

Desulphurization of Petroleum Crudes

Conventional physiochemical desulphurization methods would add a prohibitive $10+ per barrel to the cost of producing fuel oil from crudes containing 3% or more sulphur. We are evaluating the technoeconomic potential of biotechnology processes for upgrading bitumen and heavy oils in a Canadian environment in terms of microbial desulphurization, demetallization and viscosity reduction.

Delaying Fruit Ripening

This project is focussed on increasing our understanding of the physiological mechanisms underlying fruit ripening as well as chilling injury sustained during low temperature storage. Using this information, we wish to develop suitable treatment and/or containment strategies for extending the storage life of chilling-sensitive fruits such as tomatoes.

Lignocellulosic Materials

Various approaches are being taken to scale up the production of microbial cellulose and to alter its physical characteristics during the process in an attempt to develop unique products. In addition, various white rot fungi, which are capable of lignin degradation, are being studied to produce ligninases. These are earmarked for use in the production of more fermentable feedstocks and for biobleaching.

Disruption of Microbial Cells

Microbial products such as intracellular proteins and hormones require cell wall disruption for recovery. Little or no information is currently available to allow rational design of large-scale cell disruption devices. Cell wall disruption is being studied in a high-pressure capillary-flow device producing stresses of known type and magnitude. Various cell types (bacteria, yeast, algae) are being studied.

rDNA Downstream Processing

Studies are currently in progress to optimize an integrated 8-step process involving fermentation, recovery and purification for the production of protein gene products based on rDNA technology. Investigation of a unique continuous fermentation strategy which, by operating at different temperatures in each stage, will result in maximum expression of the proteins, forms a key part of this study. It is expected that the results will produce an overall optimized process model which has general applicability.

Separation Membranes

In fermentation technology, improved downstream processing techniques are required for the recovery and purification of intracellular bioproducts. We are synthesizing and testing a steam-sterilizable polymeric thin-film composite-membrane micro-filtration system, conceptualized for the separation of whole single cells (bacterial and yeast) and of cell debris (after cell disruption) from fermentation broths without undue damage of protein products left in the liquid fraction required for further processing refinement.

Biological Waste Management

This is a multi-faceted project. One aspect involves examination of some unique microbial systems as potentials for breaking down recalcitrant pollutants such as polychlorinated compounds as found in landfills. Another aspect deals with dynamic modelling of the activated sludge process for handling inlet perturbations of xenobiotics. Finally, a major aspect deals with microbial regeneration of activated carbon often used for the adsorptive removal of water contaminants in industrial effluents, *e.g.* phenols, aromatics.

CONCLUDING REMARKS

The sheer size of the Waterloo programs allows us to cover a full range of graduate interest in biochemical engineering and industrial biotechnology. This comprehensive multidisciplinary mileau is rare in chemical engineering departments. We hold an enviable record of technology transfer via the Waterloo Centre for Process Development (WCPD) (also located in our department) and through Waterloo-trained personnel in virtually every major organization involved in biotechnology in Canada, and in parts of the USA, Europe and Japan.

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