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Institut de Génie Chimique (IGC-II): Mass Transfer and Biochemical Engineering

Prof. Dr. **Urs von Stockar***

Born in Zurich in 1942, *Urs von Stockar* graduated at the Federal Institute of Technology Zurich (ETHZ) in 1967, became assistant in the Laboratory of Technical Chemistry and received his Ph.D. (silver medal) at the ETHZ in 1973. From 1973 to 1976, he worked at the Department of Chemical Engineering at the University of California where he lectured and participated in the development of a technical process for the biological conversion of cellulose to alcohol. In 1977, he was a chemical engineer with *Ciba-Geigy*. At the end of 1977, he was appointed professor at the EPF-Lausanne where he is head of the Institute of Chemical Engineering in 1978/79 as well as in 1989/90. In 1982 he becomes an ordinary professor. In 1982/83 and 1993/95, he was director of the Chemistry Department. The main subjects of his lectures and research are mass transfer and biotechnology. He is equally interested in questions of bioenergetics and biothermodynamics. In collaboration with the University of Lausanne (UNIL) and the ISREC, his group is developing manufacturing processes for special monoclonal antibodies, potentially capable of protecting human mucousal membranes. In 1990, he was appointed associated professor at the University of Geneva. He represents Switzerland in a group of experts of the European Federation of Biotechnology where he also sits on the board of directors. In the years 1996 and 1997, he serves as Chairman of this Federation. Since 1991 he has been head of the Swiss Coordination Committee for Biotechnology.

Mass Transfer and Fermentation Technology

The general topic of this broad research program can be summarized by the term integrated bioprocessing, which aims at integrating downstream elements and separation processes into the bioreactor in order to intensify the process. Special emphasis is placed on overcoming end product inhibition by *in situ* product recovery and on the use of similar techniques to obtain high product concentrations. Technologies that are studied to this effect include the use of hydrophobic porous membranes, extraction and complexion of products using tertiary and quaternary amines, the combination of these with perstraction through hydrophobic membranes, supercritical fluid extraction and the like. Another emphasis is given to continuous bioprocessing, and using cascaded reactors in order to adapt the residence time distribution of the resulting configuration to the fermentation kinetics. The process examples for which these techniques are developed include whey fermentations to produce alcohol and organic acids, methanogenesis, aroma production, and the production of antibiotics and bioinsecticides. Hydrophobic porous membranes have been used successfully to remove toxic ammonia from, and supply bubble-free aeration to, animal cell cultures.

Bioprocess Monitoring and Biocalorimetry

In this research area, special attention is given to the use of isothermal reaction calorimetry for on-line process monitoring. Heat generation is a universal feature of living systems. All metabolic events and metabolic states reflect themselves in the heat dissipation rates. Heat will also leave a culture system which is completely closed and thus offers absolutely no access for sampling and analysis. Such systems occur for instance in high density animal cell cultures in hollow fiber reactors. A major part of the work involves the development of an extremely sensitive biological reaction calorimeter (sensitivity < 20 mW l^{-1}), which operates under typical bioreactor conditions (STR/CSTR *etc.*), in association with *Mettler-Toledo AG*. Under the heading of biothermodynamics, the fundamental reasons are investigated why microorganisms and other cellular systems produce heat and how much they produce. In order to permit meaningful monitoring of the cellular physiology, however, the heat measurements have to be combined with as many other on-line signals and off-line analysis as possible during the culture. To this effect, a novel pH_2 probe has been developed and patented. Other important developments in on-line monitoring for the control of bioprocesses, often in association with calorimetry, includes the application of flow injection analysis for the measurement of glucose, glutamine, and ammonia concentrations in continuous mammalian cell cultures interfaced to *Macintosh* computers operating with *LabView* software for the control of hollow fiber reactors. The signals coming from batch, fed-batch, continuous, or transient continuous cultures are then evaluated using black box and metabolic flux analysis.

Mass Production of Secretary IgA Monoclonal Antibody

Secretary IgA antibodies are produced in large amounts in mammals and secreted onto the mucosal surfaces (lungs, mouth, digestive tract, *etc.*), where they act as a first line defense against pathogenic invaders that try to enter the body through these mucosal surfaces. The production of large amounts of these substances in bioreactors would possibly permit to immunize people against pathogens for which no practical vaccination strategy exists. This immunization could be done by oral or nasal administration of the antibodies. The production of IgA antibodies directed against *V. cholerae, H. pylori*, and other pathogens are studied in various types of bioreactor configurations operating under different feeding strategies including STR, CSTR, hollow fibers and fluidized bed reactors. Process optimization is an important aspect of this work including the development of serum- and protein-free media together with adaptation of cells with high growth rates and productivities

**Correspondence*: Prof. Dr. U. von Stockar
Département de chimie
Institut de génie chimique II
EPFL
CH–1015 Lausanne

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to them. A number of such media have been commercialized in association with *Cell Culture Technologies*, Glattbrugg, Switzerland. A special emphasis is placed on the quality of the product obtained (state of oligomerization, activity against the target antigen, glycosylation) and how the reactor configuration and physicochemical parameters may influence these. Purification of the IgA antibodies to pilot scale using both conventional separation/chromatographic techniques as well as the development of novel procedures including immunoaffinity chromatography is also undertaken.

Cell Immobilization/Encapsulation

In a new development, in association with *Nestec* and *Inotech AG*, a novel extrusion, device based upon a vibrating nozzle principle, is being developed for commercialization in 1996/97. This system is capable of producing perfectly spherical beads of immobilized microbial and animal cells within the range 150–4000 μm with a very defined size distribution under perfectly sterile conditions. Various polymers may be used to produce the beads (including alginate, collagen *etc.*) which may subsequently be coated with a second polymer such as poly-L-lysine and the initial bead dissolved to leave encapsulated cells. The latter have important potential for use as implants (*e.g.* of pancreatic islet cells) as well as for the industrial production of medically important proteins in fluidized bed reactors.

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Institut de Génie Chimique (IGC-III): A. Chemical Reaction Engineering

Prof. Dr. **Albert Renken***

The main research interests concern heterogeneous catalysis including the unsteady state operation of chemical reactors and polymer reaction engineering.

Heterogeneous Catalysis

The research is mainly dedicated to the extension and refinement of the unsteady state experimentation with the main interest focused on *in situ* measurement of adsorbed intermediates and the mathematical modelling of catalytic reactors for application to catalyst modification [1][2]. An experimental set-up has been developed to investigate simultaneously the surface and gas-phase concentrations (*Fig. 1*). The heart of the installation is a fixed-bed reactor which is directly coupled to a diffuse reflectance (DRIFTS) cell *via* an external recycle loop. The effluent from the reactor is continuously analysed by a mass spectrometer. As only a small amount of catalyst is present in the DRIFTS cell,

*Correspondence: Prof. Dr. A. Renken
Département de chimie
Institut de génie chimique III
EPFL
CH-1015 Lausanne

Albert Renken was born in 1941 in Hannover, Germany. From 1961 to 1966 he studied Chemistry at the University of Hannover and earned his Ph.D. in Chemical Engineering in 1968 and the *venia legendi* for Chemical Engineering in 1973. In 1973, he joined the *Hoechst* company in Frankfurt am Main and became group leader in the Department of Chemical Engineering. At the same time, he was appointed as 'Privatdozent' at the University of Hannover where he directed a research group in Chemical Reaction Engineering. In 1977, he became full professor at the Swiss Federal Institute of Technology in Lausanne where he is actually head of the Institute of Chemical Engineering. *Albert Renken* is author or co-author of *ca.* 200 papers published in scientific journals, 14 patents and he is co-author of a textbook in Chemical Reaction Engineering. He is member of several working parties of the European Federation of Chemical Engineering, member of the advisory board of the *Journal Chemical Engineering Technology* and member of the research council of the Swiss National Science Foundation.