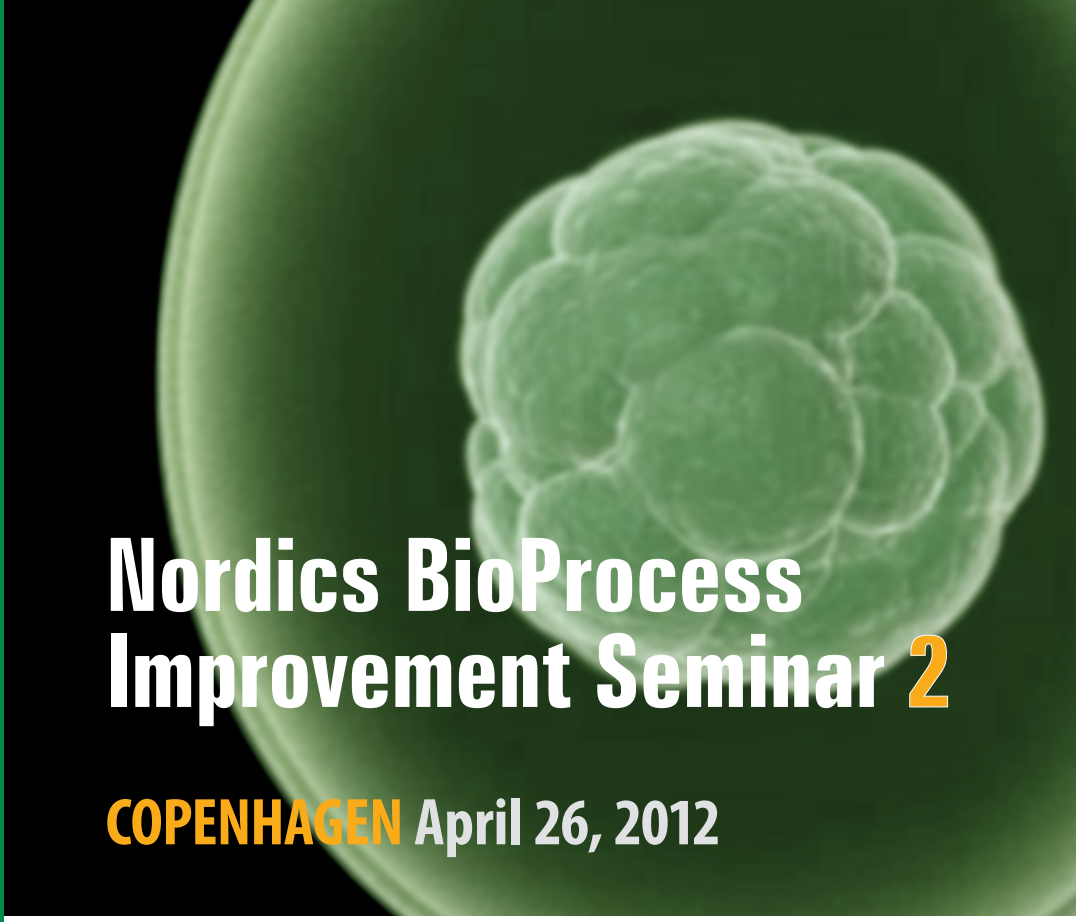

Nordics BioProcess Improvement Seminar 2

COPENHAGEN April 26, 2012

Process optimization from parallel micro bioreactors to large-scale bio-manufacturing

Interactive seminars for and by industrial and academic experts on the latest relevant developments in bioprocess innovation, with special focus on single-use technology and process intensification in upstream and downstream bioprocessing.

The low threshold opportunity for idea sharing, learning, networking and new partnerships building on bioprocessing improvement.

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Nordics BioProcess Improvement Seminar 2

Time & Venue

Thursday, 26 th of April, 2012

Technical University of Denmark, Anker Engelunds Vej Building 223 (room 207-213), 2800 Kgs. Lyngby, DENMARK

Talks & Breaks

09.00-09.30	**Registration with coffee**
09.30-09.40	**Welcome**
09.40-10.40	❶ **Dr. Krist Gernaey, Dr. Anna Eliasson Lantz, Mads Albæk and Ulrich Krühne, DTU** *Towards improved bioprocess operation: monitoring, modeling and control*
	Short break
11.00-11.30	❷ **Dr. -Ing. Frank Kensy, m2p-labs** *High-throughput parallel bioprocessing in shaken microbioreactors –from clone screening to automated bioprocess development*
11.35-12.05	❸ **Dr. ir. Nico Oosterhuis, CELLution Biotech** *Mixing, mass transfer and bioprocess scaling up and down in new generation single-use bioreactors*
12.10-13.20	**Lunch**
13.25-13.40	❹ **MSc Ivana Dencic** *Exploring potential of enzymatic microreactors – enzyme immobilization and cost considerations (Ivana Dencic, Eindhoven University of Technology)*
13.40-14.10	❺ **Dr. Bram Bout, Bioceros** *Development of improved feed strategies for high performance cell cultures & online glucose/lactate measurement in a single-use system*
14.15-14.45	❻ **Dr. Nicolas Chaudet, Sanofi Pasteur** *Evaluation and application of single-use technologies with aerobic bacteria for upstream process intensification in the development of vaccines*
14.50-15.20	❼ **Christian Skjødt, CMC Biologics** *Disposable harvesting - designing a single-use approach for harvest clarification*
	Short break
15.30-16.00	❽ **Dr. Günter Jagschies GE Healthcare Life Sciences** *Future biologicals manufacturing, process integration with single-use technology*
16.05-16.35	❾ **Dr. Peter F. Pind Novozymes A/S / Alfa Laval** *Moving purification upstream in the recovery of proteins*
16.40-	**Coffee (or drinks) and general discussion**

Organizers: CELS Network/CEFFORT AB, ANL Life Sciences, Cellution Biotech, Bioprocess International

1

Towards improved bioprocess operation: monitoring, modeling and control

Dr. Krist Gernaey, Dr. Anna Eliasson Lantz, Mads Albæk and Ulrich Krühne, DTU

Short outline:

- Overview of modeling approaches and recent developments, Krist V. Gernaey
- Application of computational fluid dynamics across reactor scales, Ulrich Krühne
- Case story – Modeling enzyme production with *Aspergillus oryzae*, Mads Orla Albæk
- The use of advanced monitoring techniques to guide development and optimization of fermentation processes, Anna E Lantz

Krist V Gernaey is Associate Professor at the Department of Chemical and Biochemical Engineering, Technical University of Denmark with expertise within modeling of bioprocesses, includes fermentation, biocatalysis, wastewater systems and food production processes.

Ulrich Krühne is Senior Researcher at the Department of Chemical and Biochemical Engineering, Technical University of Denmark. He has more than 10 years experience with microfluidics and CFD modeling.

Mads Orla Albæk performs an industrial PhD with Novozymes and Department of Chemical and Biochemical Engineering, Technical University of Denmark. His PhD work focuses on applying modeling in the context of optimization and improvement of enzyme production processes.

Anna Eliasson Lantz is Associate Professor at the Department of Systems Biology, Technical University of Denmark. Her field of expertise lies within quantitative fermentation physiology and metabolic engineering of industrially important microorganisms, as well as Process Analytical Technology (PAT) projects.

2

High-throughput parallel bioprocessing in shaken micro-bioreactors – from clone screening to automated bioprocess development

Dr.-Ing. Frank Kensy, m2p-labs

The presentation will introduce into the BioLector technology and associated technologies. Due to continuous development of new technologies around the BioLector, the BioLector is now a full high throughput fermentation system allowing bioprocess development at microscale. Beside the capabilities of online monitoring of the most relevant fermentation parameters: biomass and fluorescent proteins as well as pH and DO; the system can also be operated in fedbatch mode. Data will be presented from fermentations with different glucose feeding rates and its effect on protein expression with microbial expression systems. Another advancement of the BioLector is the integration in standard liquid-handling systems. The so called RoboLector was developed to perform automated sampling and feeding with the BioLector. Examples will be given which demonstrate the power of the system in exploring induction profiling and fedbatch strategies. In conclusion, we believe that with the currently available microbioreactors a new era of bioprocess development

has begun. Today high-throughput fermentations provide deep insights into bioprocesses which cannot be explored with shake flasks or stirred tank fermenters within the common project timelines. Therefore, the new high-information content of process data provided by single-use microfermentation systems can pave the way towards high-speed bioprocess development and probably more productive bioprocesses.

Dr.-Ing. Frank Kensy studied Biochemical Engineering at the University Essen, Madrid and at RWTH Aachen. After receiving his diploma, he first started his professional career as fermentation scientist for new recombinant enzymes and pharmaceutical proteins at Rhein Biotech N.V. in Düsseldorf. In 2002 he decided to return to RWTH Aachen University for doing his PhD on shaken microbioreactors with Prof. Jochen Büchs. Since November 2005 he is founder and managing director of m2p-labs responsible for R&D and sales.

3

Mixing, mass transfer and bioprocess scaling up and down in new generation single-use bioreactors

Dr. ir. Nico Oosterhuis, CELLution Biotech

The application of single-use equipment is common practice now in the biopharmaceutical industry. Compared to the traditional glass or stainless steel stirred tanks, single-use bioreactors offer clear advantages: a quicker turnaround time; minimal utilities required; greatly reduced potential of cross contamination; greater operational flexibility; reduced validation requirements.

The CELL-tainer® single-use bioreactor creates a superior oxygen mass-transfer compared to other single-use bioreactors, making the system suitable for high density mammalian cell cultures, but especially also for microbial and viscous mycelia cultures.

Comparison of the CELL-tainer® performance with the standard stirred bioreactor and of cultivation results of different cell-lines like CHO-cells, PER.C6®-cells, and also microbial cultures like *E.coli* and *Pichia* shows the opportunity to design high-performance processes in single-use equipment. As the $k_l a$ value in the CELL-tainer® can be controlled, the equipment also can be used for process development.
The CELL-tainer® bioreactor opens a new area for bioprocesses optimization in a single-use system and using the advantages thereof. As a single-use bioreactor is less sensitive to contamination, the system could also be applied in seed trains for large-scale bulk fermentations.

Dr. ir. Nico Oosterhuis is CTO/CSO and co-owner of CELLution Biotech. Started the company in 2005, he has been involved in the development from the start. Before, Dr. ir. Oosterhuis has had several project management and R&D management positions in both the bio-pharmaceutical as food processing companies, Dr. ir. Oosterhuis is also a consultant to several companies in the biotech industry and as such involved in a large-scale biotechnology project in Russia. Dr. Oosterhuis achieved his PhD at the TU Delft on "Scale-up of bioreactors" and studied food process technology before at the Wageningen University.

4

Exploring potential of enzymatic microreactors – enzyme immobilization and cost considerations

MSc Ivana Dencic, Eindhoven University of Technology

In the lab of Microflow chemistry and process technology at Eindhoven University of Technology we explore enzyme immobilization in a way that it is suitable for implementation in a microreactor. I will present covalent immobilization on a silica nanospring support, immobilization on Eupergit, and absorption on a mixed matrix membrane. This support is suitable for a micro plate and micro/mili packed bed reactor design. Novel Nanospring support enable very good and stable enzyme binding, while activity retention needs to be improved. We consider further costs associated with these preparations, concluding that although costs of enzyme immobilization are high they can be tolerated if they are used in the synthesis of high added value products.

MSc Ivana Dencic is a PhD candidate at the Technical University Eindhoven, Netherlands. She is specializing on 'Ex ante process and cost analysis for intensification of fine chemicals production'.

5

Development of improved feed strategies for high performance cell cultures & online glucose/lactate measurement in a single-use system

Dr. Bram Bout, Bioceros

Many therapeutic antibodies have successfully entered the market and many more are currently in development. In general, cost for treatment with monoclonal antibodies are viewed as high and hence reducing cost of goods while maintaining biological activity is imperative. This can be achieved by:

- ***reducing development timelines***
  during selection of high antibody producing cell lines (e.g. CHO derived), not only production levels are important but screening high producing cells in an early phase for responsiveness to standard feed solutions saves much development time effort later on.
- ***reducing manufacturing cost***
  disposable bioreactors allow cost effective production of biopharmaceuticals, including monoclonal antibodies. In the early research phase when many pivotal scientific data are collected, research batches are produced in a fed-batch process in small shaker flasks. It is therefore important that product quality is maitained during the intensification and upscaling of the process. Online monitoring of multiple parameters, especially glucose and lactate, are needed for optimal process control.

Bram Bout CEO and Chairman of the Management Board of Bioceros BV
Prior to joining Bioceros he was employed by Crucell (from 1993 till March 2007), where he held several management positions with increasing responsibility. His last position at Crucell was Vice President, Protein Production. Dr. Bout is co-inventor of the human PER.C6® production platform which is used for the

development and manufacturing of vaccines, monoclonal antibodies, therapeutic proteins and gene therapy products. He studied Chemistry at the University of Amsterdam and his PhD thesis was on peroxisomal storage disorders. Dr. Bout is also Chief Technology Officer at ProFibrix BV (Leiden, The Netherlands).

6

Evaluation and application of single-use technologies with aerobic bacteria for upstream process intensification in the development of vaccines

Dr. Nicolas Chaudet, Sanofi Pasteur

Single-use bioreactors have many advantages for R&D fermentation process : rapid implementation, increased flexibility and turn-around, reduced infrastructure needs and time
Yet, due to oxygen and heat transfer limitations, few number disposable bioreactors (labscale ≥ 1 liter) are available to perform high density bacterial fermentation with aerobic strains such as *E. coli.*

An evaluation and characterization of the CELL-tainer system has been done and then compared to results obtained with standard stainless steel reactor with recombinant *E. coli.*

Besides and for DOE purpose an other disposable system was developed and implemented as a high throughput scale down model : the Micro-24 bioreactor system allowing to perform 24 simultaneous cultures with individual temperature, DO and pH regulations. Presentation of a case of study on the improvement of culture parameters of an established industrial aerobic process (1000 liters scale) with a combination of micro24 system with DOE approach will be detailed.

Nicolas Chaudet is Scientist-Upstream platform, Bioprocess R&D department, SANOFI Pasteur (vaccine division of SANOFI) (Marcy l'Etoile, France). Expertise; 15 years in production of proteins and polysaccharides from aerobic or anaerobic process with recombinant, pathogenic strains.
Development of bacterial processes for new vaccines, Industrial process support and GMP production. Expertise in DOE.

7

Disposable harvesting - designing a single-use approach for harvest clarification

Christian Skjødt, CMC Biologics

Cell culture harvest clarification is performed in the industry on a number of different established platforms, including centrifugation, hollow fiber and depth filtration. At CMC Biologics A/S a portable, disposable harvest clarification system accommodating Sartorius depth filters has been designed to fit into CMCs generic clarification platform. The system was designed to have a small footprint, to have zero turnaround time and to be applicable up to 2000L disposable productions.

Christian Skjødt, MSc, Scientist, Cell Culture Manufacturing. Civil engineer/M.Sc. biotechnology/medical molecular biology (DTU 2007). Engineering business administration (Copenhagen engineering college expected graduation 2012).

8

Future biologicals manufacturing, process integration with single-use technology

Dr. Günter Jagschies GE Healthcare Life Sciences

The presentation concerns

- Productivity of bioreactors has reached levels where operation at scales feasible for single-use technology is a reality
- New possibilities to integrate all parts of drug substance manufacturing with much greater efficiency and lower cost

Günter Jagschies is Senior Director, Strategic Customer Relations at GE Healthcare Life Sciences in Uppsala. He has 27 years of experience with GE Healthcare in the Bioprocess business working with global industrial collaborations and expert support to the biopharma industry and GE Healthcare teams from R&D to Commercial.

9

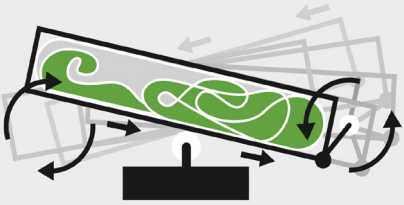
Moving purification upstream in the recovery of proteins

Dr. Peter F. Pind Novozymes A/S / Alfa Laval

Novozymes has together with Alfa Laval developed a new process for recovering precipitated proteins directly from fermentation broth liquids. By doing so we have created a step change within Novozymes for the recovery of protein in production scale. Exploiting the differences of density and size they have developed and new classification process for centrifuges – dos separating precipitated proteins from bacterial cells in a continuous setup with high efficiency.

The presentation will show the state of the art centrifuge technology from Alfa Laval used for this new type of process and present the results obtained during the development of the new process. The process has been demonstrated in production scale with a feed flow of several tons fermentation broth per hour.

Peter F. Pind is a technology specialist within Novozymes, working on developing and optimizing solid liquid separation processes for fermented proteins. Peter has worked for more than 10 years within Novozymes within production, optimization and development of protein production. For the last 3 years he has been working closely together with Alfa Laval on developing a step change recovery technology for Novozymes.



Binding Registration

SEMINAR 2 - COPENHAGEN DTU
Process optimization from parallel micro bioreactors to large-scale bio-manufacturing
Thursday 26th April 2012

Registration fees

Copenhagen meeting registration **2012-04-23** 80€ + VAT 25% (750 SEK + moms)
VAT (25%) will be added for Swedish participants and participants without an international VAT registration number.
Lunch, coffee, tea and snacks is included in the fee.

Payment

to ANL Produkter AB, Life Sciences. ANL will send you an invoice after registration.

Needed information

- Company / University / Organisation
- Name, e-mail, telephone and address of Participant
- International VAT reg number (non Swedish participant)

Register by e-mail

Send e-mail with the information to:
ake@anl.se
Question on registration: Call +46 8 99 00 90

Note: *The number of participants are limited. ´First registered are first served´ applies.*

Confirmation of Meeting and Registration (Disclaimer)
A formal confirmation of the meeting will be sent via e-mail to participant. The organizers take no responsibility for travel and other costs in the case an unconfirmed meeting is moved to a different venue, cancelled or postponed.

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