# BioProcessingDays 2019

## 18. – 20. Februar 2019 · Recklinghausen

Westfälische Hochschule
Gelsenkirchen Bocholt Recklinghausen

BIO PROZESSTECHNIK

APZ Applikationszentrum für angewandte Biotechnik

**Process Analytical Technology (PAT)**

**Process Intelligence**

BPDs 2019
BIOPROCESSINGDAYS

**CONFERENCE**

**WORKSHOPS**

Sponsoren:

aquila biolabs · BIOSTREAM · BlueSens · Fellab Validation Solutions · exputec · eppendorf · HAMILTON · I&L Biosystems · INFORS HT · Kuhner shaker · mp labs Microbioreactors · Märke Original OETTINGER SEIT 1731 · PlasmidFactory The Minicircle Company · PreSens PRECISION SENSING · Roche · TRACE Analytics

Informationen und Anmeldung:

**www.apz-rl.de/BioProcessingDays_2019**

# 1 MOTIVATION

Was kann die Prozessindustrie und Wissenschaft im Hinblick auf den Umgang mit großen Datenmengen, smarten Prozessen und dem Einsatz der künstlichen Intelligenz voneinander lernen? Mit dieser Frage schlagen die 4. „BioProcessingDays“ eine Brücke zwischen technologischen Bereichen, die für die chemisch/pharmazeutische Prozessindustrie aktueller denn je sind. Dabei beschränkt sich die Rolle der Prozessindustrie nicht allein auf die Entwicklung und Produktion von neuen Wirkstoffen. So lassen sich z.B. auch viele Aspekte der Sensorik übertragen bzw. kombinieren und bieten einen echten Mehrwert für die Anlagenbetreiber der Prozessindustrie.

Automation, Flexibilität und Formatwechsel, die in der Anlagentechnik schon zum Alltag gehören, werden angesichts der neuen Anforderungen – flexible Produktlinien, schnelle Chargenwechsel – auch für die chemische, pharmazeutische und biotechnologische Industrie immer wichtiger. Eine Antwort auf diese Herausforderung ist die intelligente Nutzung smarter Technologien und die Kombination von Möglichkeiten zu deren Umsetzung, die es in der Vergangenheit bisher nicht gegeben hat. Datenmanagement und Nutzung der Daten zum Betrieb der Anlagen gewinnen in der Prozess- wie in der Fertigungstechnik zunehmend an Bedeutung, bis hin zur datengetriebenen Anwendung von Produkten.

Die 4. BioProcessingDays werden all diese Themen beleuchten und damit eine Vortragsreihe und Diskussion entlang dieser Herausforderungen aufspannen. Es soll ein Überblick über die Technologien der Prozessindustrie, über Forschungsaktivitäten zur Prozessführung, über die Anforderungen von „PAT 4.0“ an neue Prozessanalytik und über die Werkzeuge für modellbasierte Regelung gegeben werden.

**M.Sc. David Bittner**

*Westfälische Hochschule*
*AG BioProzessTechnik*

**Dr. Holger Müller**

*BlueSens gas sensor GmbH*

**Prof. Dr.-Ing. Frank Eiden**

*Westfälische Hochschule*
*AG BioProzessTechnik*

# INHALTSVERZEICHNIS

# 2 AGENDA

| WISSENSCHAFTS-PROGRAMM | |
|---|---|
| 10:00 – 11:00 | Eintreffen und Registrierung |
| 11:00 – 13:00 | **Begrüßung durch die Organisatoren**<br>• **Sponsoren-Pitch** |
| 13:00 – 14:00 | Fingerfood |
| 14:00 – 15:00 | • **Sprecher Wissenschaft**<br>**Prof. Dr. Gesine Cornelissen** (HAW Hamburg)<br>Anwendung von PAT bei Bioprozessen mit *E. coli* und *P. pastoris* |
| 15:00 – 15:30 | Kaffeepause |
| 15:30 – 17:00 | • **Sprecher Industrie**<br>**Dr. Sebastian Schaepe** (BASF)<br>Industrial biotech applications for biological crop protection<br>**Dr. Hans-Georg Hennemann** (Evonik)<br>Datenerhebung und -verarbeitung in der industriellen Fermentationsentwicklung. Wie es bei uns (wirklich) aussieht… |
| 17:00 – 18:00 | freie Verfügung bzw. Austausch |
| 18:00 – 21:30 | • **Bio-Competition**<br>• **Postersession** |

| WISSENSCHAFTS-PROGRAMM | |
|---|---|
| 08:30 – 08:45 | **Begrüßung durch den Präsidenten der Westfälischen Hochschule Prof. Dr. Bernd Kriegesmann** |
| 08:45 – 10:45 | • **Sprecher Industrie**<br>**Dr. Jens Tränkle** (Bayer)<br>PAT for Monitoring and Control of Biotechnological Processes<br>**Dr. Christian Grimm** (Sartorius)<br>Paving the Road towards Real Time Release Testing<br>• **Sprecher Wissenschaft**<br>**Prof. Dr. Christoph Herwig** (TU Wien)<br>Workflows und Nutzen von Digital Twins |
| 10:45 – 11:15 | Pause und Austausch |

| WORKSHOP-PROGRAMM | |
|---|---|
| 11:15 – 12:45 | **WORKSHOPS *** |
| 12:45 – 14:00 | Mittagessen (Mensa) |
| 14:00 – 15:30 | **WORKSHOPS *** |
| 15:45 – 17:00 | **WORKSHOPS *** |
| 19:00 | **ABENDVERANSTALTUNG** |

| WORKSHOP-PROGRAMM | |
|---|---|
| 09:00 – 10:30 | **WORKSHOPS *** |
| 10:45 – 12:15 | **WORKSHOPS *** |
| 12:15 – 13:15 | Mittagessen (Mensa) |
| 13:15 – 14:45 | **WORKSHOPS *** |
| 15:00 | **Abschluss und Posterpreisverleihung** |
| 16:00 | Ende |

# 3 WORKSHOPS

**WORKSHOP 1**
**Raum 101**

**Exputec GmbH**
*Data management and data analytics accelerating bioprocess development*

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**WORKSHOP 2**
**Raum 102**

**Hamilton Bonaduz AG**
*PAT In-line CCP monitoring solutions with GMP paperless calibration and validation of process sensors*

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**WORKSHOP 3**
**Raum 103**

**Roche Diagnostics**
*Advanced multiparameter bioprocess analysis and seamless data management – close the loop from sampling to feed*

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**WORKSHOP 4**
**Raum 104**

**BlueSens gas sensor GmbH**
*How to determine and compensate a disturbance in a running fermentation process*

**AG BioProzessTechnik**
**(Westfälische Hochschule)**
*"ProcessShield"*
a modular, adaptive and intelligent soft-sensor based platforms

**WORKSHOP 5**
**Raum 105**

**TRACE Analytics GmbH** *&*
**TCI Universität Hannover**

*Lohnt sich eine Regelung der Glukosekonzentration auf 0,5 g/L? – Lösungsansätze für eine optimale Fütterungsstrategie*

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**WORKSHOP 6**
**Raum 106**

**Biostream International BV**
*Flexibility of fermentation control and more measurement by sensors*

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**WORKSHOP 7**
**Raum 107**

**m2p-Labs GmbH** &

**Microbial Bioprocess Lab**
**(FZ Jülich)**

*Accelerated Bioprocess Development: Integration of automated microbioreactor experimentation with interactive Python-based data analysis*

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**WORKSHOP 8**
**Raum 108**

**Infors GmbH & aquila biolabs GmbH**
*Shaked and stirred – new ways of bioprocess monitoring, controlling and planning*

**WORKSHOP 9**
**Raum 109**

**I&L Biosystems GmbH**
*Defining metabolites as critical parameters in mammalian cell cultivation*

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**WORKSHOP 10**
**Raum 110**

**Kuhner Shaker GmbH** & **PreSens GmbH**
*smart online+ Intelligentere Prozessführung in Screening und geschüttelten Kleinkulturmaßstaben mittels online pH, Sauerstoff und Biomassemessung*

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**WORKSHOP 11**
**Raum 111**

**AG BioProzessTechnik**
**(Westfälische Hochschule)**

***System FermSYS***
Datenmanagement - Datenvisualisierung – Prozessoptimierung

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**AUSSTELLUNG**

**Eppendorf AG**

**Ellab GmbH**

# 4 TEILNEHMER

| Nr. | | Titel | Vorname | Name | Institution |
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| 1 | Frau | Dr. | Karin | Ammon | PLATO AG |
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| 156 | Herr | B.Sc. | Jonathan | Sturm | Westfälische Hochschule |
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| 160 | Herr | | Niklas | Tenhaef | Forschungszentrum Jülich GmbH |
| 161 | Herr | Dr. | Jens | Traenkle | Bayer AG |
| 162 | Herr | M. Sc. | Burkhard M. | Trakowski | TU Dortmund |
| 163 | Herr | | Kevin | Ullmann | Medizinische Hochschule Hannover / LEBAO |
| 164 | Herr | B.Sc. | Dominik | Vogt | Westfälische Hochschule |
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| 166 | Herr | | Daniel | Waschestjuk | Westfälische Hochschule |
| 167 | Herr | | Patrick | Wegener | Richter-Helm-BioLogics GmbH & Co. KG |
| 168 | Herr | | Daniel | Wehrhahn | Eppendorf AG |
| 169 | Herr | Dr. | Christian | Weilke | Roche Diagnostics GmbH |
| 170 | Herr | | Lars | Widera | Westfälische Hochschule |
| 171 | Herr | Prof. Dr. | Philipp | Wiedemann | Hochschule Mannheim |
| 172 | Herr | | Maurits | Wienströer | Westfälische Hochschule |
| 173 | Herr | | Maurits | Wienströer | Westfälische Hochschule |
| 174 | Herr | | Matthias | Wiltfang | BlueSens gas sensor GmbH |
| 175 | Herr | Dr. | Thiemo | Zambanini | PLATO AG |
| 176 | Herr | Dr. | Thiemo | Zambanini | PLATO AG |
| 177 | Herr | | Christian | Zerhusen | TH Köln |
| 178 | Herr | | Carsten | Ziem | Evonik Nutrition & Care GmbH |
| 179 | Frau | | Irina | Zyuzin | Westfälische Hochschule |

# 5 REFERENTEN UND VORTRAGSABSTARCTS

## SPRECHER WISSENSCHAFT

Prof. Dr. Gesine Cornelissen

Hochschule für angewandte Wissenschaften Hamburg

### Anwendung von PAT bei Bioprozessen mit *E. coli* und *P. pastoris*

Zur Entwicklung, Analyse und Kontrolle von Herstellungsprozessen wurde 2004 von der FDA das Werkzeug *Process Analytical Technology* (PAT) eingeführt. PAT beinhaltet die Messung von kri- tischen Prozessgrößen (*Critical Process Parameters*, CPPs), welche die Qualität des Zielproduktes beeinflussen können, wie z. B. die Standardgrößen Temperatur, pH-Wert oder pO2. Daneben gibt es zahlreiche weitere In-, On- und Atline-Analyseverfahren, die für die Entwicklung, Analyse und Kontrolle eines Bioprozesses genutzt werden können. In diesem Beitrag werden verschiedene Anwendungen an Beispielen der Kultivierung von *E. coli* und *P. pastoris* vorgestellt.

Prof. Dr. Christoph Herwig

Technische Universität Wien

### „Workflows und Nutzen von Digital Twins“

Digitale Zwillinge sind ein zentraler Bestandteil im Lebenszyklus von Bioprodukten, um Wissen der Bioprozessentwicklung zu dokumentieren sowie dieses Wissen wieder bereit zu stellen. Aber: Welche Experimente braucht es, welche Workflows sind notwendig, um das Digital Twins zu erzeugen? Wie werden die die Erhöhung der Prozesstransparenz und Prozesskontrolle in Echtzeit implementiert? Der Vortrag beleuchtet diese Fragen anhand von Fallbespielen und Workflows und zeigt auf, dass Digitale Zwillinge ein zentrales Elemente von Industrie 4.0 ist.

## SPRECHER INDUSTRIE

Dr. Jens Traenkle

Bayer AG

### PAT applications in batch and continuous biotech processes

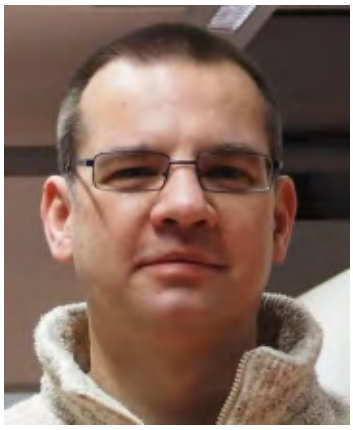
The manufacturing of biotechnological products puts up specific challenges to the control of production processes due to very tight operational ranges for certain process parameters, such as oxygen, temperature, pH, osmolarity or due to the very complex nature of the manufactured product itself. Process analytical technologies (PAT) help analyzing these process parameters today, but in addition, PAT also promises applications for measuring product quality attributes (cQAs) for online process optimization or product release in future.
Especially in recently used fully-closed, single-use or continuous processes moving from manually extracted samples measured at-line towards on-line or in-line measurements supported by PAT is desired for reducing contamination risk, ensuring process integrity and allowing timely adjustment of process parameters. Here, we will discuss the application of different PAT tools for the development and operation of batch and continuous upstream and downstream biotech processes for biopharmaceutical products.

Dr. Sebastian Schaepe

BASF

### Industrial biotech applications for biological crop protection

Industrial biotech offers attractive new business opportunities, that are more and more recognized in chemical industry. In times of increasing regulatory pressure towards chemical crop protection agents, biotechnology offers a variety of alternative solutions. These additional options contribute to meet the demand of high yield, low residue crop products. Fermentation processes are crucial element in the production process. Different fermentation technologies are highlighted, and the practical challenges throughout the process development, transfer to production scale as well as the regular operation are discussed.



Dr. Hans-Georg Hennemann

Evonik Industries

## „Datenerhebung und –Verarbeitung in der industriellen Fermentationsentwicklung. Wie es bei uns (wirklich) aussieht…“

Fermentation als Fachgebiet wird in der industriellen Prozessentwicklung genutzt, um so früh wie möglich Biokatalysatoren unter den Bedingungen zu testen und, die denen in der schlussendlich genutzten Großanlage am nächsten kommen. Dabei startet man mit einem auf dem Papier passenden Prozessprotokoll, das im Laufe der Projektentwicklung immer wieder den Anforderungen der angestrebten Produktion und des Biokatalysators angepasst wird. Im Fermentationslabor der Evonik Creavis GmbH ist dieser Prozess eng mit der Stammkonstruktion verknüpft, da auch der Biokatalysator selbst immer weiter verbessert werden muß. Biokatalysator- und Prozessentwicklung gehen dabei Hand in Hand. Um Prozessfortschritte und Verbesserungen am Biokatalysator sichtbar zu machen, müssen Zielmolekülkonzentration und die zur Produktion genutzten Prozessbedingungen gemessen bzw. dokumentiert und analysiert werden. Gerade in den Anfangsphasen von solchen Entwicklungen ist oft nicht bekannt, welche Parameter es genau sind, die die Prozessleistung beeinflussen, also die „Prozessbedingungen“ ausmachen. Man zeichnet also so viele Daten wie möglich auf, um auf alles zurückgreifen zu können, wenn sich dann Zusammenhänge zeigen. Dabei handelt es sich um Daten aus der offline-Analytik, die die Konzentrationen von Substraten, Zwischenprodukten, Nebenprodukten und Zielprodukten angeben, die gesamte online-Analytik der Fermentationssysteme, Entwicklung der Konzentration verschiedener Medienbestandteile, Wachstumskurven, ggf. Cytogramme usw.. Diese Fülle an Informationen muß idealerweise immer für alle möglichen Vergleiche von Experimenten sofort zur Verfügung stehen. Außerdem muß aus IP-Sicht sichergestellt sein, daß die erhobenen Daten so dokumentiert sind, daß klar beweisbar ist, wann welche Daten vorlagen. Weiterhin müssen die Dokumentationen den Anforderungen des Gentechnikgesetzes und der Biostoffverordnung genügen. Eine allumfassende Softwarelösung für diese Aufgaben, die unseren Ansprüchen standhielt, war bisher nicht zu bekommen. Man muß sich also behelfen….

Dr. Christian Grimm

Sartorius Stedim Biotech

## Paving the Road towards Real-Time Release Testing

The BioPhorum Technology Roadmap team, consisting of multiple end-user and supplier companies published a Biomanufacturing Technology Roadmap in July 2017. As part of the Roadmap process, the team has defined several working groups, one of which is the In-Line Monitoring / Real Time Release team (ILM/RTR).
This team was established with the ultimate goal of decreasing product release times while improving quality, efficiency and supply. The ILM/RTR team has been working to develop a prioritized list of process parameters and quality attributes that are required to be monitored or controlled within a typical biotech process. In addition to the prioritized parameter list a generic user requirement specification (URS) for the implementation of a new RTRT method was jointly created and worked out for a couple of parameters exemplarily. Besides the URS a cost modelling approach was discussed which is proposing a way of a business case estimation for implementing a new analytical method. During this session, the team goals, process, and status of priority list, URS and business case model will be reviewed. Feedback on the results and direction are appreciated. The team is actually working on releasing a white paper document in Q2/2019.

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Posternummer 1

# Gezielte $CO_2$-Konzentrationseinstellung mittels Berechnung der benötigten Glukoseeinwaage

Daniel Waschestjuk, Katharina Janneck, Richard Löffler,
Maurits Wienströer, Laura Kampl, Prof. F. Eiden

Die alkoholische Gärung mittels Hefen ist bereits seit Jahrhunderten bekannt und stellt auch in der modernen Fermentation eine wichtige Rolle dar. Im Rahmen der lifHack-BioCompetition sollte ein Programm entwickelt werden, mit dessen Hilfe eine bestimmte $CO_2$-Konzentration innerhalb einer bestimmten Zeit durch Berechnung der Glukoseeinwaage, erzielt werden kann. Die Hefe *Saccharomyces cerevisiae* setzt durch alkoholische Gärung die zugesetzte Glukose in $CO_2$, Ethanol und Acetat um. Dieser Prozess wird innerhalb eines batch-Fermenters durchgeführt und die $CO_2$-Entwicklung wird online gemessen. Durch Eingabe der verfügbaren Zeit und der zu erzielenden $CO_2$-Konzentration errechnet das Programm, auf Basis der Monod-Kinetik, die benötigte Glukosemenge, welche als Startkonzentration in den Fermenter eingewogen wird. Die Regelung des Prozesses findet in diesem Fall somit bereits im Vorfeld statt. In unserem Ansatz wurde die Substratfunktion als eine feste Funktion, welche nicht von der Biomassefunktion X(t) abhängig ist, definiert. Die Gleichung entspricht einer exponentiellen Abnahme, wobei der Faktor im Exponenten anhand der praktischen Messungen ermittelt wurde.

Posternummer 2

# Bioprocess Control through Process Analytical Technology and Tailored Software Scripts

*Marc Skoupi, Jens Schiffler, and Sebastian Kleebank*

*Eppendorf AG Bioprocess Center, Jülich, Germany*

To be competitive, industrial bioprocesses need to run robustly and need to deliver products at high yields and in consistent quality. For the implementation of advanced control strategies, including Quality-by Design approaches, it is crucial to understand how critical process parameters, culture growth, and product quality are interrelated. An increase of process understanding and the development of advanced control strategies can be reached by integrating process analytical technology (PAT) with the bioprocess control. Using proof-of-concept studies for feeding control as examples, we illustrate the implementation of advanced bioprocess monitoring and control strategies. With the first study we explain how the scripting functionality of DASware® control 5 bioprocess control software facilitated automation of user-defined feed control strategies. In the second study we describe how online glucose control was implemented by integrating an external Raman analyzer with a DASGIP® Parallel Bioreactor System using OPC connectivity.

Posternummer 3

# Microbial production of stereochemically defined poly-γ-glutamic acid

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Poly-γ-glutamic acid (γ-PGA) is an anionic, biodegradable, non-toxic polymer composed of D- and L-glutamic acid units linked by γ-glutamyl bonds.[1] Some applications of γ-PGA such as the use as drug carrier or food additive require chemically defined γ-PGA in terms of stereochemical composition and molecular weight. The stereochemical composition is influenced by: (1) the affinity of the γ-PGA synthetase towards the two alternative glutamate enantiomers and (2) the racemase activity, hence the availability of the monomers. Here, the production of stereochemically defined γ-PGA variants is presented. The integration of PGA synthetase and alternative glutamate racemase genes obtained from various *Bacillus* species into *B. subtilis* allowed the synthesis of alternative polymers. The stereochemical composition of the produced γ-PGA was determined by a LC-MS method established for D-/L-amino acid separation.[2] The engineered strains were further characterized by metabolomics. The novel combinations of synthetase and racemase genes enable the production of γ-PGA with altered stereochemical composition. The results are discussed in the context of polymer applications.

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# Posternummer 4

## Itakonsäure-Produktion mit *Ustilago*

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Itakonsäure ist ein wichtiger Synthesebaustein für eine Vielzahl von Chemikalien und Polymeren, die z.B. bei der Herstellung von synthetischen Fasern, Beschichtungen, Verdickungsmittel und im Pharmazeutischen Sektor genutzt werden. Weiterhin kann Itakonsäure in eine Reihe von hochwertigen Endprodukten umgewandelt werden. Die industrielle Fermentation von Itakonsäure erfolgt zurzeit mit *Aspergillus terreus*. Aufgrund des filamentösen Charakters erfordert der Prozess eine intensive Prozesskontrolle wodurch in der Herstellung von Itakonsäure hohe Produktionskosten entstehen. Neben *A. terreus* sind Brandpilze, wie z.B. *U. maydis* und *U. cynodontis*, für die Herstellung von Itakonsäure geeignete Organismen. Ein großer Vorteil von *U. maydis* ist sein Hefe-ähnliches Wachstum. Beide Organismen sind auf natürlicher Weise in der Lage eine große Anzahl von organischen Säuren unter Verwendung unterschiedlichster C-Quellen herzustellen. Sie zeigen eine hohe Stressresistenz, z.B. gegenüber hydromechanischem Stress bzw. Substratverunreinigungen. In diesem Projekt untersuchen wir die Anwendung von *Ustilago* Spezies, im Rahmen des Itakonsäureproduktionsprozesses mit Fokus auf Prozessbedingungen, wie pH-Optimum, Nebenprodukte und Morphologie. Im ersten Teil dieser Studie wurde *U. cynodontis* als neuer, pH-toleranter Produktionsstamm etabliert. Durch Fed-Batch-Fermentationen konnte der optimale pH-Wert von 3,6 für die Itakonsäureproduktion bestimmt werden. Dieser bietet zahlreiche Vorteile, wie z.B. autosterile Bedingungen während der Fermentation und vor allem eine erhebliche Reduzierung der Produktionskosten des anschließenden Downstreamprozesses. Des Weiteren konnte durch erste molekularbiologische Arbeiten, die Produktion von Nebenprodukten, wie 2-Hydroxyparakonat ausgeschaltet werden. Der zweite Teil dieses Projektes beschäftigte sich mit *U. maydis*, welcher bereits ein etablierter Itakonsäureproduzent ist. In dieser Arbeit konnten mittels „Metabolic engineering“ und *in situ* Produktabtrennung Itakonsäuretiter von über 200 g/L erreicht werden. Alles in allem konnte, ein *U. maydis* Stamm entwickelt werden, der konkurrenzfähig zum derzeit verwendeten *A. terreus* ist.

Posternummer 5

# Creating a program to determine the needed weighing of glucose, for a fermentation, in advance

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[1] Industrielle Biotechnologie - Gruppe: Die multiplen Organismen (DMO)

As part of the module „Industrial Biotechnology“, we combined theoretical facts with empiric data to create a program which is able to give an output of the weighing of glucose that is needed to reach a given Vol-% of $CO_2$ in a given time. As organism *Saccharomyces cerevisiae* is used in a standard batch fermentation, that is supervised by carbon dioxide measuring sensors. The data were collected during three active laboratory days and added to Python, the program we used for designing the program. As a result we selected two trend lines as boundary lines in order to establish an area of achievable data (in this case volume percent).

# Posternummer 6

# Sustainable and cost efficient sophorolipid production via biomass recycling and solvent free purification

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Sophorolipids (SLs) are glycolipid biosurfactants based on renewable resources (sugar + lipids). They are produced in high yields by non-pathogenic yeasts of the clade *Candida, Rhodotorula* and *Starmerella* [1,2]. Generally SLs possess a hydrophilic β-1-2-diglucoside head group and a hydrophobic lipid tail, which gives them an amphiphilic character. Accordingly they are mainly used in the cleaning, cosmetic and food industry as surfactants [3]. Structurally different types of SLs are synthesized by the individual species. Fermentation data will be presented for *Starmerella bombicola* and *Candida kuoi* including analysis of the SL product mixtures.
Currently SLs cannot compete with chemical produced bulk surfactants regarding cost - performance ratio and are therefore limited to niche applications. Cost estimation was done by the USDA for a 90.000 t/y SL production plant including fermentation, dehydration and solvent-based purification [4]. Raw materials glucose and oleic acid account for 65% of the overall manufacturing cost and 18% are needed for the solvent ethyl acetate used for extractive purification. Taking this into account cost saving potentials become obvious:
To save the overall glucose input a biomass recycling process was implemented. SL production was achieved in consecutive biomass centrifugal separation, washing and fermentation steps in 5 cycles over a period of 5 weeks. A modified solvent free downstream process, originally established by Roelants *et al*. [5], was analyzed. The process proved to be cost efficient and environmentally friendly. An optimized plant scheme for the production of SLs was designed from these data.

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Posternummer 7

# *Penicillium verruculosum* - Nachthaltige Produktion von Cellulasen

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Die Notwendigkeit nach alternativen Energiequellen zu suchen, hat eine große Auswahl an Möglichkeiten offenbart um fossile Brennstoffe zu ersetzen. Darunter auch die Nutzbarmachung von Ethanol als Kraftstoff. Bio-Ethanol wird bisher vorrangig aus stärkehaltigen Pflanzen, wie Mais oder Zuckerrüben, gewonnen. Jedoch ist diese Art der Kraftstoffgewinnung umstritten, da stärkehaltige Pflanzen vorrangig als Nahrungsmittel genutzt werden. Eine bessere Alternative ist die Gewinnung von Ethanol aus Cellulose bzw. Lignocellulose. Die benötigten Enzyme für die Aufspaltung von Cellulose in Glukose sind bereits seit Jahrzehnten bekannt aber noch nicht vollständig beschrieben. Diese Cellulasen, bestehend aus Endoglukanasen, Cellobiohydrolasen und β-Glukosidasen, werden vereinzelt von Bakterien, aber zum größten Teil von Pilzen gebildet. Der am besten untersuchte und genutzte cellulasebildende Pilz ist *Trichoderma reesei*. Die Mutanten des *Trichoderma reesei* sind aktuell die leistungsfähigsten Cellulase Produzenten, jedoch ist die Produktion des Enzymcocktails unausgeglichen. Um den Komplex im vollen Umfang industriel nutzen zu können müssen extern produzierte β-Glukosidasen zugesetzt werden. Um die Cellulaseproduktion wirtschaftlicher zu machen konzentrieren sich aktuelle Forschungen auf Mutanten des alternativen Produktionsstammes *Penicillium verruculosum.* Diese haben im Gegensatz zum *Trichoderma reesei* einen weitaus ausgeglicheneren Cellulasekomplex.

In der aktuellen Arbeit wird ein nachhaltiges System etabliert, welches die Cellulaseproduktion mittels Mutanten des *Penicillium verruculosum* ermöglicht. Hierbei wird Buchenholz als Ausgangsstoff im Labor- wie auch im Pilotmaßstab eingesetzt.

Posternummer 8

# Enzymatic synthesis of cyclic dinucleotides

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/The presence of deoxyribonucleic acids (DNA) in the cytosol of mammalian cells is a danger signal and triggers an innate immune response. Cytosolic DNA activates cyclic guanosine monophosphate (GMP) - adenosine monophosphate (AMP) synthase (cGAS), which catalyzes the synthesis of the cyclic GMP-AMP dinucleotide 2'3'-cGAMP [1, 2]. Recent studies have shown that 2'3'-cGAMP induces the production of interferons and appears to be promising for the use as a novel active ingredient to boost the innate immunity [3].
This study presents the synthesis of 2'3'-cGAMP and its derivatives using cGAS (Fig. 1). The activity of cGAS to synthesize 2'3'-cGAMP from guanosine triphosphate (GTP) and adenosine triphosphate (ATP) was proven. Design of experiments was used to establish a multivariable regression model which facilitates the description of basic catalytic mechanisms and moreover allows the identification of reaction optima. The results offer compelling evidence for the existence of two major substrate inhibition mechanisms. The inhibition of the biocatalytic reaction appears to be the result of substrate inhibition caused by ATP concentrations above 0.5 mM and substrate competition for side reactions. Interestingly, cGAS not only catalyzes the formation of 2’3’-cGAMP but also the formation of cyclic di-AMP and cyclic di-GMP.
Further experiments focus on the systematic analysis and characterization of cGAS and its application for new reactions. The development of libraries of such CDN analogs is thought to be a useful tool in future enabling to get a more detailed insight into the meaning of CDNs as second messenger.

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Posternummer 9

# Moderate viscosity increases improve the oxygen supply in shake flasks

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The successful scale-up of aerobic biotechnological production processes relies on a defined oxygen supply of respective microbial cultures [1, 2]. Although stirred tank reactors and shake flasks are both well described regarding their oxygen transfer characteristics, the influence of increasing viscosity during microbial cultivations has hardly been investigated for the later [3, 4]. In this study, the oxygen transfer rate was measured for different viscosities using *Corynebacterium glutamicum* as microbial model system. Additionally, the shaking diameters were varied from 25 to 70 mm and tested at shaking frequencies from 200 to 450 rpm, covering common biotechnological screening parameters as well as more extreme conditions. The viscosity was adjusted with different polyvinylpyrrolidon (PVP) concentrations to achieve viscosities of 1 to 29 mPa·s. It was demonstrated that elevated viscosities in this range promote an increased oxygen supply in non-baffled shake flasks. For the first time, it was experimentally shown how an increasing viscosity from 1 to 5 mPa·s during the microbial cultivation can improve the oxygen supply by 35% and exceed the theoretical maximum oxygen transfer capacity of water-like viscosities by 20%. While even moderate viscosity increases decrease the $OTR_{max}$ in stirred tank reactors, the oxygen supply in shake flasks is improved. At a viscosity of 29 mPa·s the oxygen supply in a stirred tank reactor may decrease by about 90%. In contrast, the oxygen supply in shake flasks is similar to or only slightly reduced compared to a viscosity of 1 mPa·s. This dissimilarity between shake flasks and stirred tank reactors has significant implications for scale-up of viscous processes as e.g. production of biopolymers or degradation of viscous substrates.

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Posternummer 10

# Predicting industrial scale cell culture seed trains – considerations of input uncertainty, new process data and prognostic intervals using a Bayesian approach and sequential Bayesian updating

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The production of biopharmaceuticals in suspension cell culture up to 20 $m^3$ is state of the art. However, the generation of an adequate cell number for the inoculation of a production bioreactor is time- and cost-intensive. The cells need to be propagated by numerous passaging steps form cell thawing to large bioreactors. Seed train design, monitoring and optimization is important since cultivation conditions during the seed train have a significant impact on cell performance in production scale.

Model-assisted prediction methods can lead to advanced seed train monitoring and development of optimization strategies. The performance depends on a) the prediction accuracy, which can be improved by inclusion and quantification of prior process knowledge, especially when only few high-quality data is available, and b) description of inference uncertainty, i.e. providing, in addition to a 'best fit'-prediction, information about the probable deviation in form of a prediction interval, which contains the true values with a given probability.

This contribution illustrates the application of a probabilistic approach for seed train prediction to an industrial cell culture process, using Bayesian statistics in combination with a mechanistic model. This approach enables inclusion of prior knowledge as well as expression of predictive uncertainty and it was implemented using the Markov Chain Monte Carlo (MCMC)-method. In order to integrate information from new data for updating the prediction of the current seed train cultivation, the sequential Bayes method was applied. Prediction accuracy for large scales, only based on information from small scale data, are compared to prediction accuracy, taking new data into account.

Posternummer 11

# Engineering yeasts as platform organisms for cannabinoid biosynthesis

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During the last decade, the use of medical Cannabis has expanded globally and legislation is getting more liberal in many countries, facilitating the research on cannabinoids. The unique interaction of cannabinoids with the human endocannabinoid system makes these compounds an interesting target to be studied as therapeutic agents for the treatment of several medical conditions. However, currently there are important limitations in the study, production and use of cannabinoids as pharmaceutical drugs.
Here we reconstituted the final biosynthetic cannabinoid pathway in yeasts. The use of the soluble prenyltransferase NphB from Streptomyces sp. strain CL190 enables the replacement of the native transmembrane prenyltransferase cannabigerolic acid synthase from *C. sativa*. In pursuit of improved enzyme properties for a biotechnological cannabinoid production, we performed site-directed mutagenesis to investigate the glycosylation pattern, the C- terminal berberine-bridge-enzyme (BBE) domain, the active site and the product specificity of the $\Delta^9$-tetrahydrocannabinolic acid synthase (THCAS). Finally, we investigated the influence of the co-expression of 12 helper protein genes from *Komagataella phaffii* (formerly *Pichia pastoris*) on the functional expression of the THCAS.
These studies are important steps toward total biosynthesis of valuable cannabinoids and derivatives and demonstrates the potential for developing a sustainable and secure yeast bio-manufacturing platform.

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Posternummer 12

# Selbstbau-Photometer für Wissenschaft und Forschung

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Ein preiswertes Mikrocontroller-Board, ein Lichtsensor und eine LED als Lichtquelle - das sind die Zutaten für das selbst-baubare mobile Photometer der HAW Hamburg. Ein 3D Drucker fertigt das Gehäuse, die Elektronikkomponenten bedürfen einiger einfacher Lötarbeiten - die auch ungeübten Wissenschaftlern gelingen - und auch das Einspielen der benötigten Software ist mit wenigen Mausklicks erledigt. Dieses Photometer ist der ursprünglichen Intension mit einem spannenden High-Tech-Projekt Schüler und Schülerinnen für MINT Themen zu begeistern, entwachsen und konnte auch in Regelpraktika von Hochschulen einziehen sowie in biotechnologischen Forschungslaboren sein Einsatzgebiet finden. Vorgestellt wird die Konzeption des Photometers und eine Beispielapplikation zur Bestimmung des Kohlenhydratgehalts in Hefeextrakt.

Posternummer 13

# Production of Alginate with *Azotobacter vinelandii*

Sarah Stachurski[1], Elsa Gómez[2], Carlos Peña[2], Jochen Büchs[1]

[1]Biochemical Engineering, RWTH Aachen University

[2]Instituto de Biotecnologia, Universidad Nacional Autónoma de México

Alginate is an exopolysaccharide with a broad spectrum of applications in the food industry as well as in the medical field. High viscosity and shear-thinning behaviour make the production with microorganisms challenging. The fact, that the characteristics of the alginate may be modified by changes in cultivation parameters serves as a major benefit. *Azotobacter vinelandii* produces alginate naturally and can serve as an alternative to the production with algae. Characterizing the cultivation system with the RAMOS-device, advanced cultivation strategies under microaerobic conditions will be applied for a successful scale up to 50 L fermenters to maximize the formation of alginate with defined characteristics for specified applications.

Posternummer 14

# līfHack-BioCompetition:

Vanessa Mense[1], Annika Gutsche[1], Mareen Neuwald[1], Frederike Paß[1], Alena Strüder[1]

[1]BATCHelor of Science, Westfälische Hochschule

Im Mittelpunkt der Arbeit standen die Anforderungen der līfHack-BioCompetition an der Westfälischen Hochschule. Ziel des Projektes war es durch ein geeignetes Modell und eine damit verbundene Software eine Methode zu entwickeln, bei der abhängig von einer zu erreichenden $CO_2$-Konzentration und einer gewünschten Prozesszeit, die Berechnung der hinzuzugebenden Menge Substrat (Glucose) möglich ist.
Bei dem zugehörigen biotechnologischen Prozess handelt es sich um eine Fermentation im Batch mit Saccharomyces cerevisiae. Die Hefe wandelt den zugegebenen Zucker, unter Produktion von $CO_2$ und einer Zunahme der Biomasse, in Ethanol um. Die Reaktion erfolgt unter mikroaeroben Bedingungen.
Der entwickelte Ansatz basiert auf einem kinetischen Modell sowie Untersuchungen der Wachstumsrate μ der Bäckerhefe. Die Bestimmung der Wachstumsrate erfolgte mittels $CO_2$-Messungen. Die Programmierung der Software erfolgte mittels Python.

References: Hass, Pörtner: Praxis der Bioprozesstechnik. Spektrum-Verlag.

Posternummer 15

# Bioprocess design for surfactant production with *Pseudomonas putida* KT2440 in an innovative multiphase loop reactor

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3 Institute of Biochemical Engineering, University of Stuttgart, 70569 Stuttgart, Germany

The production of biosurfactants in an aerated fermentation process leads to excessive foaming, which hinders an efficient production in a conventional fermenter. To prevent foam formation, an innovative reactor setup for a microbial fermentation process is developed (Figure 1). This loop reactor realizes continuous *in situ* product removal by integrating a countercurrent liquid-liquid extraction in the downcomer [1]. The multiphase loop reactor (MPLR) and the producing microorganism, *Pseudomonas putida* KT2440, will be iteratively adapted to each other to find optimal process conditions. Therefore, the current organism-caused constraints need to be identified. Two potential constraints have been analyzed in this work.

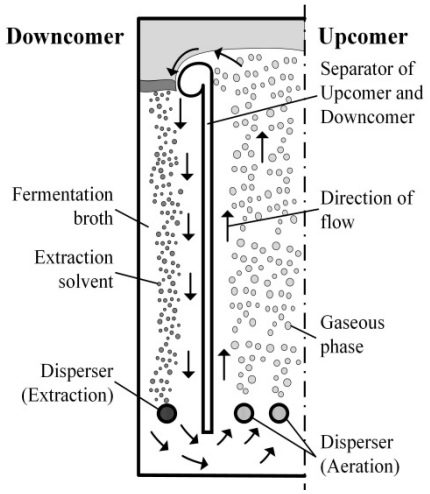


**Figure 1: Multiphase loop**

First, the impact of temporary oxygen limitation on the obligate aerobic microorganism *P. putida* KT2440 is investigated. Passing the oxygen-deficient downcomer of the MPLR causes the organism to encounter constantly altering conditions. Oscillations of the dissolved oxygen tension were mimicked in stirred tank reactors by controlling the stirrer speed and the aeration rate in an on-off mode. *P. putida* KT2440 showed a decreased maximal growth and production rate in batch cultivations in which the dissolved oxygen tension was oscillated. However, final biomass and product titers reached the same levels as in undisturbed control cultivations. Corresponding continuous cultivations in a stirred tank reactor coupled to a plug-flow reactor confirmed initial findings of a robust cultivation at oscillating oxygen levels.

Second, an experimental set-up for a comprehensive selection of a suitable extraction solvent for *in situ* rhamnolipid recovery was developed. The number of possible candidates was reduced stepwise by an initial *in silico* solvent screening focusing on physicochemical properties, followed by testing extraction efficiencies, biocompatibilities and the performance at process conditions.

The poster shows that *P. putida* KT2440 is a suitable production host for a fermentation process in the MPLR as its performance values at repeated oxygen limitations are similar to a non-limited cultivation. Further, a solvent screening for the liquid-liquid extractions of rhamnolipids in the downcomer is presented. The results are used to define first constrains for the operational window.

Posternummer 16

# Kuhner Shaker Feeding Technology

Bei der Entwicklung neuer Produktionsstämme in der Biotechnologie ist das Screening und Scale-Up unter prozessnahen Bedingungen entscheidend für die Auswahl des optimalen Produktionsstamms. Dabei sollte die Betriebsweise bereits im Screening an die Bedingungen im Produktionsprozess angeglichen werden.

Die Kuhner Feeding Technology ermöglicht eine verlässliche Fed-batch Betriebsweise im Screening Maßstab. Durch die Annäherung der Betriebsbedingungen im Screening an die Bedingungen im Produktionsprozess, können präzise Aussagen über die tatsächliche Produktivität eines Klons getroffen werden. Negative Effekte der Batchkultivierung, wie Crabtree Effekt, Overflow-Metabolismus, hoher osmotischer Druck oder Sauerstoff-limitierungen werden vermieden.

Die Substratfreisetzung dieser innovativen Technolog erfolgt über eine inerte Silikonmatrix, in welche ein Nährstoff eingebracht wurde. Dieses System zeichnet sich durch seine hohe Flexibilität hinsichtlich Substrate, Freisetzungsraten und Kulturgefäße aus.

Weiterhin ist das System kosteneffizient und kann leicht in bestehende Screening-Prozesse integriert werden. Die Nutzung in einer bereits bestehende Standard-Laborausstattung ist genauso möglich wie die Nutzung in automatisierten Hochdurchsatz-Kultivierungsanlagen. Durch die sterile Verpackung bietet die Kuhner Feeding Technology ein hohes Maß an Sicherheit und kann als ready-to-use-Produkt unmittelbar eingesetzt werden.

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Posternummer 17

# An application to calculate the glucose mass for a Batch-Fermentation

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As a part of the lifHack Competition, a software tool was created. With the help of this method, it is possible to calculate the amount of glucose, which is needed for the organism Saccharomyces cerivisiae to produce a certain volume of CO2 after a certain period of time.

This Python-based tool uses experimental data as its basis. This data was divided by a time limit at 60 minutes. As a consequence two empirical building rates have been build. One for the data which was gathered before the time limit of 60 minutes and the other for the data that was gathered after the 60 minutes time limit. The more data is available for the calculation of these, the greater is the reliability of the results.

Posternummer 18

# Novel inhibitor-resistant lignocellulolytic enzymes from Indian fungal ressources

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[2]VTT – Technical Research Centre of Finland Ltd
[3]VINSTROM - Vivekananda Institute of Tropical Mycology
[4]University of Tartu, Chair of General and Microbial Biochemistry

Sustainability is one of the greatest future challenges on Earth, along with increasing demand for energy and for reducing the greenhouse effect. Therefore, fuels produced from renewable raw materials, as lignocellulosic wastes and residues are of particular interest. The most environmentally sustainable technology to convert lignocellulosic biomass to fermentable sugars is enzymatic hydrolysis.

Despite recent developments, the enzyme costs remain a bottleneck to the process feasibility. High-temperature pretreatments of biomass prior enzymatic hydrolysis are used to overcome the resistance of the materials. As a result, inhibitory compounds such as phenolics, furans and organic acids are produced that inhibit both enzymes and fermentation organisms. In the biorefinery processes, the high solids concentrations required for hydrolysis process efficiency emphasize enzyme inhibition. Forest-fire residues contain chemicals similar to the inhibitors found in lignocellulose materials that have been processed at high temperatures. Microbes extracted from fire-prone areas have been shown to adapt for these chemicals, such as furans, and have improved thermotolerance.

This project aims at discovery of novel inhibitor-tolerant cellulases and improvement in the efficiency of biomass processing through understanding the complex interactions between the enzymes and lignocellulose-derived compounds. The unique culture collection of VINSTROM (India) containing fungi isolated from fire-prone forests was used as a source for enzyme screening. Novel screening methods are developed based on lignocellulose-derived compounds, produced and characterized jointly between VTT (Finland) and RWTH (Germany). Molecular biology expertise at VTT is utilized for identification and production of then novel enzymes, which will be then characterized together by VTT and University of Tartu (Estonia).

# Posternummer 19

# Automated Bioprocess Analysis using the Bio HT Analyzer Coupled with In-Line Auto Sampling Systems

Stephen Grimme, Neera Sammeta, and Oliver Strobel
Roche CustomBiotech, Roche Diagnostics USA

Cedex Bio HT Analyzers were developed based ob industry-proven technology and designed to support the daily anaytical needs of bioprocessing with high robustness and low need for manual interaction. Although the Cedex Bio HT is known for its high throughput capacity of up to 90 at-line samples onboard at one time, the analyzer has a number of features that make it well suited for automated in-line sampling and analysis. Roche CustomBiotech has collaborated with several leaders in automated bioprocess sampling to pair their in-line auto-sampling systems with the analytical capabilities of the Bio HT. This poster shares the general capabilities of those systems and the automated analysis of the Bio HT.

Posternummer 20

# ProcessShield – A software for different machine learning and neural network approaches in biotechnology

Jonathan Sturm[1], Alexander Beer[1], Frank Eiden[1]

[1] AG Bioprozesstechnik Westfälische Hochschule Recklinghausen

In the context of industry 4.0, analysis of bioprocess data is becoming an increasingly challenging task. High throughput experiments using robotics and advanced analytics can produce an immense amount of high-dimensional data in short amounts of time. Traditional evaluation of process data is at risk of becoming a bottleneck in further progression because of the large timeframe needed. Therefore, the use of modern data analytics tools is key to keep up with this development [1].

Shallow artificial neural networks (ANNs) offer a set of different techniques to model target variables with no prior knowledge, completely data driven. This allows to construct easy-to-use, precise mathematic models to control and optimize bioprocesses.

Deep neural networks (DNNs) are a more advanced method to model more complex target functions. They are suited for analyzing diverse data and pattern recognition but are computationally expensive. Both these approaches have the advantage that they do not require mechanistic understanding of the process at hand.

In our work, we show that the different models can be used to generate knowledge, e.g. learn about the current status of a process variable not traditionally measurable in real time via regression models or classify data into subgroups. But neural networks are also able to predict the further development of bioprocesses for short time frames, making complex control strategies possible.

The models built using these techniques can therefore be used to achieve predictive process control, so that processes always reach their maximum potential through automated actions of an artificial intelligence agent in the future. In these systems, the control loop is closed, and sensor input is used in machine learning models to determine the optimal operation parameters for every process.

[1] S. Charaniya, W.S. Hu, G. Karypis, Mining bioprocess data: opportunities and challenges, Trends Biotechnol. 26 (2008) 690–699.

Posternummer 21

# "FermSYS" - a new software-framework for user-friendly and systematic data management, data visualization and optimization of bioprocesses

Christopher Gora[1], Frank Eiden[1]

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The software framework "FermSYS" serves the optimal management and evaluation of process data. It enables easy reading, sorting, processing and output of data generated during the bioprocess or from own simulations. In addition, the calculation of process parameters that cannot be measured directly, such as growth and specific substrate uptake and product formation rates, is supported. A function for comparing and evaluating the measured and calculated data of several bioprocesses enables the generation of ranked lists. In these, the processes are compared based on user-defined specifications and arranged accordingly. In addition, the framework has a module for the graphical representation of all the above-mentioned functions, including the plotting of the optimal bioprocess found by the rankings. Furthermore, a module for kinetic modelling of the bioprocesses will be implemented. An optimization algorithm will be used to calculate a model with the associated parameters that matches the measured process values on the basis of an exemplary cultivation.

Posternummer 22

# Influence of stirring rate on induced pluripotent stem cell expansion in stirred tank bioreactors

Kevin Ullmann[1,2] , Felix Manstein[1,2], Caroline Halloin[1,2], Wiebke Löbel[1,2], Henning Kempf[1,2], Annika Franke[1,2], Ulrich Martin[1,2], Robert Zweigerdt[1,2]

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Human pluripotent stem cells (hPSCs) are a unique source for the production of tissue-specific human cell types, fueling the development of advanced *in vitro* drug screening, toxicity analysis, disease modelling and novel regenerative therapies. Most applications will require the constant supply of billions of cells generated by robust, economically viable bioprocesses. Conventional expansion strategies for hPSCs rely on adherent monolayer culture (2D) in plates or flasks utilizing artificial extracellular matrices. However, 2D cultivation cannot fulfil the requirements for a reliable large-scale production of hPSCs. Alternatively, expansion of hPSCs in suspension culture (3D) is a potentially superior strategy for producing required cell numbers applying industry-compliant stirred tank bioreactor technology. These 3D cultivation processes are inoculated with hPSC single cell suspensions. However, hPSCs cannot be expanded as single cells, therefore they can either be cultivated on microcarriers mimicking a 2D growth mode in suspension or form matrix-free cell-only aggregates with continuous growth in size.

We have recently established expansion of hPSCs at the pluripotent stage as cell-only aggregates. Subsequently, efficient differentiation into specific mesodermal lineages including cardiomyocytes, endothelial cells or macrophages in stirred tank bioreactors was established, demonstrating the universal utility of these systems for the mass production of hPSC-progenies. Moreover, perfusion-based medium exchange was established. This advancement resulted in more homogeneous culture conditions, enabled significantly increased cell yields, and opened new possibility for process control. However, average aggregate size is also increased drastically up to potentially growth limiting dimensions.

Here we started to use the full range of opportunities offered by instrumented stirred tank bioreactors. Next to the combination of perfusion-mode with the control of specific process parameters such as pH and dissolved oxygen (DO) we further optimized the process by controlling the cell aggregate diameter. Aggregate size control in 150 mL bioreactor scale resulted in more homogenous and more reproducible process conditions and substantially elevated cell yields compared to published data. Detailed analysis of process indicators will also be presented, including comprehensive assessment of hPSCs' pluripotency status and the energy metabolism.

Together, the study highlights the enormous potential for process development in hPS cell manufacturing, particular by using well monitored and controlled bioreactor systems, which also facilitates straightforward upscaling.

Posternummer 23

# Modellbasierte Prozesssteuerung von Biogasanlagen

Thomas Kirner[1], Ellen Euchner[1], Carolin Griese, Bettina Manns, Udo Schmale[2], David Wehmeyer[2], Thomas Frank[3], Heribert Insam[4], Andreas Walter[4], Maraike Probst, Marcus Stiemer[5], Michael Dudzinski[5], Werner Sternad[6], Barbara Waelkens[6], Marcus Kiuntke[1], Dieter Bryniok[1]

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Nobelstraße 12, D-70569 Stuttgart

The anaerobic biological metabolic processes of the complex microbial mixed cultures in a biogas plant are still not fully understood and there are no reliable, easy-to-measure indicators for the early detection of disorders in the degradation process. Easy-to-detect parameters like pH-Value or decreasing gas production show the disturbance too late. The associated biological processes are at this point already so disturbed that a strong decline up to the complete stop in biogas production can no longer be avoided.

The interdisciplinary project „MOST“ (“Model Based Process Control of Biogas Plants”), funded by the German Ministry for Education and Research aims at an optimized process control of biogas production plants. Based on literature data of kinetic parameters a mathematical model of the anaerobic digestion process has been used to identify key parameters. In bench scale experiments with different substrates analytical parameters like VOA-TAC (volatile organic acid -to- buffer capacity ratio), pH-value, VFAs (volatile fatty acids), biogas and methane yields and other parameters are measured to compare the results to the mathematical model. Additionally, the microbial community composition was identified using Illumina Amplicon sequencing.

The fed-batch experiments were performed in 2-L bioreactors equipped with gas meters and sensors for methane and carbon dioxide. Digestate from a biogas plant treating fruit and vegetable wastes was used for inoculation. Total solids and total volatile solids, VOA-TAC (volatile organic acid -to- buffer capacity ratio), and pH were measured. VFAs. For the experiments different substrates were used.

Posternummer 24

# Analysis of Microbial Cultivations Using the Cedex Bio HT Analyzer

B Gutschmann[1], SL Riedel[1], A Sawatzki[1], E Anane[1], L Santolin[1], K Pellicer Alborch[1], S Hans[1], MN Cruz Bournazou[1], S Junne[1] and P Neubauer[1]*

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…

*Off line* analysis throughout microbial cultivations is a very time consuming procedure, especially when various analytes are quantified. Using automated robotic pipetting platforms, such as the Cedex Bio HT Analyzer (Roche Diagnostics, Switzerland), allows rapid sample analysis, predominantly performing enzymatic tests, during and/or after the cultivations. At the Bioprocess Engineering laboratory at TU Berlin, the Cedex Bio HT Analyzer is used for various analysis throughout aerobic and anaerobic bioprocesses with yeast and bacteria from lab- to pilot- scale (0.5 – 150 L) and during high throughput cultivations in parallel mini-bioreactors (8 – 12 mL)1,2. In the Bachelor bioprocess engineering practical course, the device is used to introduce students to the latest technology and provide reliable data for computational modeling of the performed *Escherichia coli* batch cultivation.

It was shown in multiple experiments, that the Cedex Bio HT Analyzer results are matching with reference analyses, as e. g. HPLC measurements. Therefore, a much faster methodology to determine process relevant metabolite changes can be provided, which results in an improvement of the process control. By a capacity of up to 180 tests per hour, the robot was used to determine various analytes as substrates (e.g. glucose, ammonia), metabolites (e.g. lactate, acetate) or co-factors (e.g. magnesium, calcium) of parallel cultivations in a short time to generate high-qualitative data for multivariate data analysis. In addition, the Cedex Bio HT was used during high-cell-density fed-batch cultivations of *E. coli* to determine robust and reproducible values for the optical density up to OD583 180.

**References**

**1** Sawatzki, A. *et al. Bioengineering* 5, 101 (2018)

**2** Anane, E. *et al. N. Biotechnol.* 44, S60–S61 (2018)

Posternummer 25

# Fantastic Yeasts and How to Feed Them

## How different glucose concentrations affect the production of $CO_2$ by yeast

B. Badia Roigé[1*], S. Frings[1], E. Recker[1], E. Richter[1]

[1] Institut für Angewandte Mikrobiologie iAMB, Blockpraktikum Mikrobiologie und Genetik, RWTH Aachen University. * Corresponding Author: bielbadia3@gmail.com

*Saccharomyces cerevisiae* has two pathways for ATP production from glucose: respiration and fermentation. Both start with glycolysis, which results in the production of two molecules of pyruvate and ATP per glucose. In fermentation, pyruvate is then turned into ethanol. In respiration, pyruvate is completely oxidised to $CO_2$ through the TCA cycle and oxidative phosphorylation, which yields additional ATP but requires oxygen [1].

The approaches with different glucose concentration showed at first the same progression: The concentration rises linearly and increases more rapidly, the more glucose is in the medium. The only exception is the culture with 10 % glucose, which produces less $CO_2$ than the culture grown on 7,5 % glucose (Crabtree effect).

What is noticeable is the insignificant levels of $CO_2$ production during the first 20 minutes. This might be due to rehydration of the dry yeast and media assimilation of the cells. Following this the yeast‘s metabolism is activated and $CO_2$ production increases rapidly.

To phrase an ultimative statement about how different glucose concentrations affect the production of $CO_2$ by yeast, a new graph with the $CO_2$ production over glucose concentration at different times between 10 minutes and 120 minutes was created (Fig.3).

After the results some conclusions about this experiment were drawn: The production of $CO_2$ with higher glucose concentrations than 1,5 % shows a similar progression, the pathway for the utilisation of glucose is partially unknown, rehydration and activation of dry yeasts takes about 25 min and control over temperature or oxygen input and foam formation would improve the regulation of the $CO_2$ production.

**References:**

**[1]** Rehm HJ. (1967) Backhefe. In: Industrielle Mikrobiologie. Springer, Berlin, Heidelberg

Posternummer 26

# Biobench BioBased fermentor (BBF), a single vessel for hydrolysis and fermentation

Biostream International BV, Doetinchem

Lignocellulosic (waste) streams are increasingly used as feedstock for the industrial production of “green” chemicals or fuels through fermentation. "Bio-based" processes, such as SSF (simultaneous saccharification and fermentation) or CBP (consolidated bioprocessing), generally involve high solid loads. Although this may not be a major issue on a large scale, on a laboratory scale the limitations of the currently available equipment readily become apparent. The Biobench BioBased Fermenter (BBF) from Biostream now offers a unique platform for handling high solid loads at laboratory scale. As illustrated in this application note, the BBF is equally suited for hydrolysis of cellulosic feedstocks and fermentation.

# 7 RAUMPLANUNG / WEGSKIZZE


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B1.2.101 – Exputec GmbH

B1.2.102 – Hamilton Germany GmbH

B1.2.103 – Roche Diagnostics Deutschland GmbH

B1.2.104 – BlueSens gas sensor GmbH / ProcessShield (AG BPT)

B1.2.105 – Trace Analytics GmbH

B1.2.106 – Biostram International B.V.

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**TRACE Analytics GmbH**
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**Oettinger Brauerei**
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http://www.apz-rl.de/BioProzessTechnik


APZ Applikationszentrum für angewandte Biotechnik

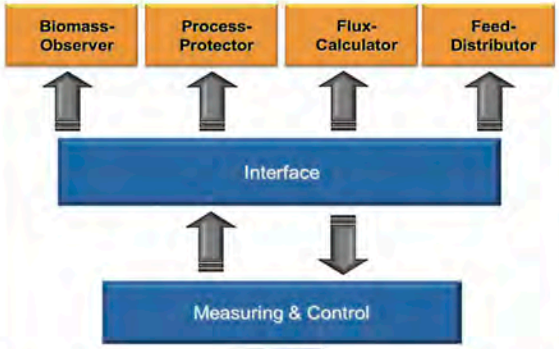
**Workshop ProcessShield Raum 104**
**Workshop FermSYS Raum 111**

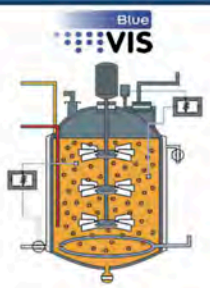
## “Biomass-Observer”

- calculation of biomass in real-time
- based on a mathematical model
- via soft-sensors using online data ($CO_2$, $O_2$ & glucose)

# ProcessShield

adaptive intelligent environment




## “Flux-Calculator”

- online calculation of metabolic fluxes
- stoichiometric approach based on biochemical reactions
- online graphic display of calculated metabolic flux rates

## “Process-Protector”

- online process surveillance tool
- detection of differing process parameters from pre-set values
- error alerts and automated process regulation

## “Feed-Distributor”

- adapted substrate feeding tool
- measurement of current glucose consumption
- prediction of glucose demand

adaptive BRAIN POOL module

Using offline- and online-data for bioprocess optimization:
Modeling fermentation characteristics using artificial neural networks and archived process information

**Contact: info@agbioprozesstechnik.de**