A novel in situ measurement method of bubble sizes in bioreactors using a high speed camera

Mass transfer of oxygen from the gas phase to the liquid phase is the rate limiting phenomenon in many industrial aerobic fermentation processes. This phenomenon is often described by the rate constant $k_{La}$, which remains a key performance indicator for scale up and general operation of fermentation processes. The attributing variables to the rate constant, the mass transfer resistance $k_L$ and interfacial surface area $a$, are however very rarely individually identifiable from standard experimental analysis. This co-dependency of the variables on the rate constant limits the understanding of how process conditions affect the mass transfer rate, and hence a tool for identifying them individually is required. Available correlations for these variables are predominantly system dependent and therefore not necessarily valid in the process of interest. Currently available measurement techniques to identify bubble size require knowledge or assumptions regarding the gas flow direction to deduce the bubble size.

An optical method for determining the interfacial surface area, based on bubble size identification has been developed using a high speed camera and an endoscope. This novel method has been applied to bioreactors at different conditions in terms of power input, gas flow rate and viscosity. This in situ measurement illustrates the effect of process conditions on the size of the bubbles. The information on bubble sizes at different conditions is a valuable input to mechanistic models regarding gas-liquid mass transfer, for example computational fluid dynamics (CFD) models, in which the bubble size is a key input parameter.

General information

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Organisations: Department of Chemical and Biochemical Engineering, PROSYS - Process and Systems Engineering Centre, Novozymes A/S
Authors: Bach, C. (Intern), Albæk, M. O. (Ekstern), Krühne, U. (Intern), Gernaey, K. V. (Intern)
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Application of Iterative Robust Model-based Optimal Experimental Design for the Calibration of Biocatalytic Models

The aim of model calibration is to estimate unique parameter values from available experimental data, here applied to a biocatalytic process. The traditional approach of first gathering data followed by performing a model calibration is inefficient, since the information gathered during experimentation is not actively used to optimise the experimental design. By applying an iterative robust model-based optimal experimental design, the limited amount of data collected is used to design additional informative experiments. The algorithm is used here to calibrate the initial reaction rate of an $\omega$-
transaminase catalysed reaction in a more accurate way. The parameter confidence region estimated from the Fisher Information Matrix is compared with the likelihood confidence region, which is a more accurate, but also a computationally more expensive method. As a result, an important deviation between both approaches is found, confirming that linearisation methods should be applied with care for nonlinear models. This article is protected by copyright. All rights reserved.

**General information**

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Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.808 SNIP 0.931 CiteScore 2.2
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 0.764 SNIP 0.847 CiteScore 2.16
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 0.84 SNIP 0.868 CiteScore 2.35
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.918 SNIP 0.956 CiteScore 2.4
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.988 SNIP 0.947
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.965 SNIP 1.047
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 0.887 SNIP 0.992
Scopus rating (2007): SJR 1.011 SNIP 1.093
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 0.973 SNIP 1.108
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 0.905 SNIP 1.029
CFD Modeling of Flow and Ion Exchange Kinetics in a Rotating Bed Reactor System

A rotating bed reactor (RBR) has been modeled using computational fluid dynamics (CFD). The flow pattern in the RBR was investigated and the flow through the porous material in it was quantified. A simplified geometry representing the more complex RBR geometry was introduced and the simplified model was able to reproduce the main characteristics of the flow. Alternating reactor shapes were investigated, and it was concluded that the use of baffles has a very large impact on the flows through the porous material. The simulations suggested, therefore, that even faster reaction rates could be achieved by making the baffles deeper. Two-phase simulations were performed, which managed to reproduce the deflection of the gas–liquid interface in an unbaffled system. A chemical reaction was implemented in the model, describing the ion-exchange phenomena in the porous material using four different Sherwood number correlations. The simulations were overall in good agreement with experimental data.

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Organisations: Department of Chemical and Biochemical Engineering, CAPEC-PROCESS, Technical University of Denmark, SpinChem AB
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BFI (2015): BFI-level 2
Scopus rating (2015): SJR 0.949 SNIP 1.146 CiteScore 2.87
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 1.012 SNIP 1.292 CiteScore 2.85
Web of Science (2014): Indexed yes
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Scopus rating (2013): SJR 0.982 SNIP 1.243 CiteScore 2.6
CFD modelling of axial mixing in the intermediate and final rinses of cleaning-in-place procedures of straight pipes

The intermediate and final rinses of straight pipes, in which water replaces a cleaning agent of similar density and viscosity, are modelled using Computational Fluid Dynamic (CFD) methods. It is anticipated that the displacement process is achieved by convective and diffusive transport. The simulated agent concentrations show good agreement with the analytical axial mixing models from literature. The displacement time, minimum water consumption, minimum generation of wastewater and minimum requirement of intermediate rinsing water are evaluated using CFD. Practical empirical equations are derived from CFD results and applied to examine if the process is operated in an efficient and economic manner. It has been found that the displacement time can be predicted from the inner pipe diameter and the mean flow velocity using a power law relationship. Changing flow velocities does not significantly influence the minimum water consumption and the minimum wastewater generation for rinsing a pipe. Controlling the rinsing step based on a downstream measurement still consumes more water than the minimum requirement to reduce contamination risks. This article presents an innovative algorithm for optimizing the rinse steps with lower water consumption based on the above observations. A case of rinsing a 24 m long straight pipe describes the promising application of the CFD study. The recovery of cleaning agent can be up to 89.3% of the volume and the saving of intermediate rinsing water can be at least 55% compared to the conventional rinse method. The work in this article presents an example showing how to deal with more complex systems in the future.
General information
State: Accepted/In press
Organisations: Department of Chemical and Biochemical Engineering, PROSYS - Process and Systems Engineering Centre, Alfa Laval, Alfa Laval, Carlsberg
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BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.348 SNIP 1.908 CiteScore 3.1
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
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Scopus rating (2012): SJR 1.394 SNIP 1.993 CiteScore 2.84
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BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.329 SNIP 1.922 CiteScore 2.84
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BFI (2010): BFI-level 1
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Scopus rating (2009): SJR 1.411 SNIP 1.623
Web of Science (2009): Indexed yes
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Scopus rating (2008): SJR 1.301 SNIP 1.521
Scopus rating (2007): SJR 1.044 SNIP 1.958
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 1.101 SNIP 1.546
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 0.808 SNIP 1.441
Scopus rating (2004): SJR 0.857 SNIP 1.454
Web of Science (2004): Indexed yes
Scopus rating (2003): SJR 0.882 SNIP 1.6
Scopus rating (2002): SJR 1.202 SNIP 1.481
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Computational Fluid Dynamics - en genvej til procesindsigt

I artiklen gives der tre konkrete eksempler på, hvordan CFD kan bruges til at opnå procesindsigt på nuværende anlæg og på processer i udviklingsfasen.

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Authors: Bach, C. (Intern), Spann, R. (Intern), Larsson, H. K. (Intern), Pereira Rosinha Grundtvig, I. (Intern), Albæk, M. O. (Ekstern), Gernaey, K. V. (Intern), Krühne, U. (Intern)
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Development of in-situ product removal strategies in biocatalysis applying scaled-down unit operations

An experimental platform based on scaled-down unit operations combined in a plug-and-play manner enables easy and highly flexible testing of advanced biocatalytic process options such as in-situ product removal (ISPR) process strategies. In such a platform it is possible to compartmentalize different process steps while operating it as a combined system, giving the possibility to test and characterize the performance of novel process concepts and biocatalysts with minimal influence of inhibitory products. Here the capabilities of performing process development by applying scaled-down unit operations are highlighted through a case study investigating the asymmetric synthesis of 1-methyl-3-phenylpropylamine (MPPA) using ω-transaminase, an enzyme in the sub-family of amino transferases (ATAs). An on-line HPLC system was applied to avoid manual sample handling and to semi-automatically characterize ω-transaminases in a scaled-down packed-bed reactor (PBR) module, showing MPPA as a strong inhibitor. To overcome the inhibition, a two-step liquid-liquid extraction (LLE) ISPR concept was tested using scaled-down unit operations combined in a plug-and-play manner. Through the tested ISPR concept, it was possible to continuously feed the main substrate benzylacetone (BA) and extract the main product MPPA throughout the reaction, thereby overcoming the challenges of low substrate solubility and product inhibition. The tested ISPR concept achieved a product concentration of 26.5 gMPPA·L⁻¹, a purity up to 70% gMPPA·L⁻¹ and a recovery in the range of 80% mol·mol⁻¹ of MPPA in 20 hours, with the possibility to increase the concentration, purity and recovery further. This article is protected by copyright. All rights reserved

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Main Research Area: Technical/natural sciences

Development of in-situ product removal strategies in biocatalysis applying scaled-down unit operations

An experimental platform based on scaled-down unit operations combined in a plug-and-play manner enables easy and highly flexible testing of advanced biocatalytic process options such as in-situ product removal (ISPR) process strategies. In such a platform it is possible to compartmentalize different process steps while operating it as a combined system, giving the possibility to test and characterize the performance of novel process concepts and biocatalysts with minimal influence of inhibitory products. Here the capabilities of performing process development by applying scaled-down unit operations are highlighted through a case study investigating the asymmetric synthesis of 1-methyl-3-phenylpropylamine (MPPA) using ω-transaminase, an enzyme in the sub-family of amino transferases (ATAs). An on-line HPLC system was applied to avoid manual sample handling and to semi-automatically characterize ω-transaminases in a scaled-down packed-bed reactor (PBR) module, showing MPPA as a strong inhibitor. To overcome the inhibition, a two-step liquid-liquid extraction (LLE) ISPR concept was tested using scaled-down unit operations combined in a plug-and-play manner. Through the tested ISPR concept, it was possible to continuously feed the main substrate benzylacetone (BA) and extract the main product MPPA throughout the reaction, thereby overcoming the challenges of low substrate solubility and product inhibition. The tested ISPR concept achieved a product concentration of 26.5 gMPPA·L⁻¹, a purity up to 70% gMPPA·L⁻¹ and a recovery in the range of 80% mol·mol⁻¹ of MPPA in 20 hours, with the possibility to increase the concentration, purity and recovery further. This article is protected by copyright. All rights reserved
Knowledge and prediction of mixing and mass transfer in agitated bioreactors is fundamental for process development and scale-up. In particular, key process parameters such as mixing time and volumetric mass transfer coefficient are essential for bioprocess development. In this work, the mixing and mass transfer performance of a high power agitated pilot scale bioreactor has been characterized using a novel combination of computational fluid dynamics (CFD) and experimental investigations. The effect of turbulence inside the vessel was predicted using a standard RANS k-ε model. Mixing time was investigated by carrying out sodium chloride tracer experiments for both Newtonian and non-Newtonian fluids at various viscosities and agitation speeds, while tracking the conductivity. The mixing performance was simulated with CFD and the results showed good agreement with the experimental data. The mass transfer coefficients were determined from six Trichoderma reesei fermentations at different well-defined process conditions. Similarly, the mass transfer was predicted by Higbie’s penetration model from two-phase CFD simulations using a correlation of bubble size and power input, and the overall mass transfer coefficients were in accordance with the experimental data. This work illustrates the possibility of predicting the two-phase fluid dynamic performance of an agitated pilot scale bioreactor using validated CFD models. These models can be applied to illustrate the effect of changing the physical process conditions.
Experimental and computational evaluation of area selectively immobilized horseradish peroxidase in a microfluidic device

A microreactor with a square shaped reactor chamber was developed with the aim to correlate enzyme positioning with biocatalytic activity. The enzyme position as an important parameter to improve the contribution of the individual enzymes towards the overall reactor efficacy was therefore evaluated experimentally and by computational fluid dynamics (CFD) simulations. Ultimately, such a correlation would lead to faster development through computational pre-screening and optimized experimental design. In this proof-of-concept study, microreactors were prepared in a 2-step curing process of an off-stoichiometric thiol-ene-epoxy (OSTE+) mixture employing both a thiol-ene (TEC) and a thiol-epoxy curing reaction. Subsequent surface functionalization of the remaining thiol groups on the reactor surface through stenciled photoinitiated TEC enabled the preparation of specific surface patterns in the reactor. Patterns were visualized using an allyl-functional disperse red dye, illustrating the successful preparation of a fully reacted surface, a half covered surface and 2 checkerboard patterns. Similarly, allyl glycidyl ether was exploited to functionalize the microreactor surface with epoxide groups, which were used for covalent immobilization of horseradish peroxidase (HRP) in the same patterns. Biocatalytic activity measurements confirmed a clear dependency of the overall reactor performance depending on the spatial distribution of the immobilized enzymes, where specifically the two checkerboard motifs were identified as being particularly effective compared to enzymes covering homogeneously the entire reactor surface. The performance of the same configurations was additionally determined by 3-dimensional CFD simulations. The computational model predicted the same tendencies for the overall reactor performance as obtained from experimental determination. This good agreement between the obtained experimental and computational results confirmed the high potential of CFD models for predicting and optimizing the biocatalytic performance of such a reactor.
Oxygen Dependent Biocatalytic Processes

Enzyme catalysts have the potential to improve both the process economics and the environmental profile of many oxidation reactions especially in the fine- and specialty-chemical industry, due to their exquisite ability to perform stereo-, regio- and chemo-selective oxidations at ambient temperature and pressure. A significant number of enzymes carrying
out redox reactions (oxidoreductases) requiring molecular oxygen as an electron acceptor – those termed oxidases, monooxygenases and dioxygenases. These enzymes catalyze a range of industrially relevant reactions, such as oxidation of alcohols to aldehydes and ketones, oxyfunctionalization of C-H bonds, and epoxidation of C-C double bonds. Although oxygen dependent biocatalysis offers many possibilities, there are numerous challenges to be overcome before an enzyme can be implemented in an industrial process. These challenges requires the combined effort of protein engineering (i.e. modification of the amino acids sequence to improve activity, stability and selectivity) and reaction engineering (i.e. modification of reaction conditions to increase the yield and productivity) to be solved. The most important reaction engineering challenge is the requirement for oxygen, because the transfer of oxygen from the gas-phase (typically air) to the aqueous phase, where the reaction takes place, is notoriously slow due to the low aqueous solubility of oxygen at ambient conditions. Therefore, vigorous agitation and aeration is required to create a large interfacial area for mass transfer, which is not only expensive but also sets a limit to the maximum productivity of the reactor. The oxygen transfer problem is further complicated by gas-liquid interface induced enzyme deactivation, large dependency of the catalytic rate on the oxygen concentration in solution and stripping of volatile organic compounds from the reaction mixture.

In this thesis, the supply of oxygen and the implications on the biocatalyst performance are studied. The important kinetics of the reaction between enzyme and oxygen are described in detail. In fact, it is found that most enzymes operate far below their potential maximum catalytic rate at industrially relevant oxygen concentrations. Detailed knowledge of the enzyme kinetics are therefore required in order to determine the best operating conditions and design oxygen supply to minimize processing costs. This is enabled by the development of the tube-in-tube reactor (TiTR) setup, capable of performing fully automated kinetic characterization of oxygen dependent enzymes - at oxygen concentrations allowing full saturation of the enzyme. The development of the TiTR enables us to characterize a range of enzyme variants developed through protein engineering. This not only exemplifies the importance of knowing the full enzyme kinetics when choosing an enzyme variant for further development, but also that it is in fact possible to change the oxygen reactivity of an enzyme through substitution of amino acid residues.

General information
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Shape optimization as a tool to design biocatalytic microreactors
Reactor design is commonly constrained to already well-known reactor shapes. This article presents an innovative application of shape optimization techniques to design biocatalytic microreactors. Currently, the optimization of reactor performance is often done by considering solely the process conditions. However, common reactor types used in (bio)chemical processes do not always give the optimal conditions for executing the reaction, and it is therefore necessary to look into new approaches to further improve the performance of reactors. The new application of shape optimization described in this paper has as its main goal the design of a reactor by compensating for the limitations of the reaction system by modifying the reactor configuration. Random search was the optimization method chosen for transforming the initial reactor configuration to a more optimal one.

The case study presented here investigates the impact of a change to the microreactor shape on the active mixing of two parallel streams (one containing an enzyme, amino transaminase, and the other the substrates, acetophenone and isopropylamine) and consequently its influence on the reaction yield. Compared to the original reactor configuration, the shape optimization resulted in changes of the microreactor wall surfaces leading to an 8.4 fold improvement of the reactor yield. This innovative optimization also offers the opportunity to obtain new structures which can later be tested experimentally.

General information
A CFD model for determining mixing and mass transfer in a high power agitated bioreactor

Prediction of mixing and mass transfer in agitated systems is a vital tool for process development and scale up in industrial biotechnology. In particular key process parameters such as mixing time and kLa are essential for bioprocess development [1]. In this work the mixing and mass transfer performance of a high power agitated pilot scale bioreactor has been characterized using a novel combination of computational fluid dynamics (CFD) and experimental investigations. The effect of turbulence inside the vessel was found to be most efficiently described by using the k-ε model with regards to
computational effort and required accuracy for industrial application. Mixing time was determined by carrying out sodium chloride tracer experiments at various bulk viscosities and agitation speeds, while tracking the conductivity. The mixing performance was predicted with one-phase CFD simulations and showed good agreement with the experimental data. The mass transfer coefficient was determined during three fed batch *Trichoderma reesei* fermentations at different process conditions previously described in [2]. Similarly the mass transfer was predicted by Higbie’s penetration model [3] from two-phase CFD simulations, and the overall mass transfer coefficient was found to be in accordance with experimental data. This work illustrates the possibility of predicting the hydrodynamic performance of an agitated bioreactor using validated CFD models. These models can be applied in the testing of new bioreactor configurations, and to illustrate the effect of changing the physical process conditions.

This is a showcase of how we have expanded our work in the area of mixing from microscale reactors to pilot scale industrial systems and we would like to present this work in order to receive feedback.

**General information**

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Organisations: Department of Chemical and Biochemical Engineering, PROSYS - Process and Systems Engineering Centre, Novozymes A/S
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A flexible well-mixed milliliter-scale reactor with high oxygen transfer rate for microbial cultivations

In order to choose the best strain and subsequently develop an optimal bioprocess many experiments need to be performed. Usually this process is expensive and labor intensive with a limited amount of data available. Small-scale bioreactors and high-throughput platforms are becoming an attractive solution and replacement for existing microtiter plates, shaken flasks and bench scale bioreactors. In this work, a new design of a milliliter-scale bioreactor system is presented and characterized. The entire system consists of a platform with gas connections, heater, temperature sensor and optical fibers on the one side and a bioreactor with special designed magnetic stirrer and non-invasive optical sensors for measurement of pH, dissolved oxygen and optical density on the other side. The system has a high level of flexibility in terms of volume (0.5–2 mL), aeration (sparging and surface aeration) and mixing (one- and bi-directional). Computational fluid dynamics (CFD) was employed in order to simulate the mixing times, the oxygen transfer rates and the appearance and size of the gas-liquid interfaces in the 1 mL-scale bioreactor with unidirectional mixing and surface aeration. Mixing performance was tested and the oxygen transfer rate was determined experimentally as well. The obtained results show a good mixing time (between 0.4 s and 2 s) and a high oxygen transfer rate (kLa > 1000 h−1). The milliliter-scale bioreactor platform was used to cultivate *Saccharomyces cerevisiae* and *Lactobacillus paracasei*.

**General information**

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Organisations: Department of Chemical and Biochemical Engineering, CAPEC-PROCESS, Department of Systems Biology, Technical University of Denmark
Authors: Bolic, A. (Intern), Larsson, H. K. (Intern), Hugelier, S. (Ekstern), Eliasson Lantz, A. (Intern), Krühne, U. (Intern), Gernaey, K. (Intern)
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A microfluidic toolbox for the development of in-situ product removal strategies in biocatalysis

A microfluidic toolbox for accelerated development of biocatalytic processes has great potential. This is especially the case for the development of advanced biocatalytic process concepts, where reactors and product separation methods are closely linked together to intensify the process performance, e.g., by the use of in-situ product removal (ISPR). This review provides a general overview of currently available tools in a microfluidic toolbox and how this toolbox can be applied to the development of advanced biocatalytic process concepts. Emphasis is placed on describing the possibilities and advantages of the microfluidic toolbox that are difficult to achieve with conventional batch-process-based technologies. Application of this microfluidic toolbox will potentially make it possible to intensify biocatalytic reactions and thereby facilitate the development towards novel and advanced biocatalytic processes, which in many cases have proven too difficult in conventional batch equipment.

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Organisations: Department of Chemical and Biochemical Engineering, CAPEC-PROCESS
Authors: Heintz, S. (Intern), Mitic, A. (Intern), Ringborg, R. H. (Intern), Krühne, U. (Intern), Woodley, J. (Intern), Gernaey, K. (Intern)
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Downstream bioprocess characterisation within microfluidic devices

Miniaturising bioprocess unit operation steps is a well-established approach to find novel routes for process intensification and improved process economics. While a number of microbioreactors have been presented over the last 15 years, miniaturised downstream unit operations (mDUO) are less developed which has, to some extent, hindered their implementation as early process development tools. Microfluidic devices are particularly attractive for using fewer resources, for having the possibility of parallelisation and for requiring fewer mechanical manipulations. The expectation is that these devices will facilitate the rapid definition of critical process parameters, and thus ultimately reduce production costs.

We have developed several microfluidic mDUOs and combined them with advanced and novel analytical approaches, resulting in devices that can potentially be employed for both analytical and preparative purposes; these include devices for cross-flow filtration, liquid–liquid extraction and flocculation. To accelerate in-depth process characterisation, we developed and implemented on-line monitoring approaches and image-processing algorithms.

In this contribution, we will present results for the liquid–liquid extraction of pharmaceuticals, for the purification and concentration of drug delivery vehicles, and for the flocculation of yeast cells in microfluidic devices. For the latter, we will present for the first time the capability to study flocculation-growth independent from the floc breakage phase; two phases which are in a state of equilibrium in larger scale systems, and can thus not be discerned in conventional systems. The applicability of these devices will be shown with the assembly of a train of mDUO for the enzymatic production of chiral pharmaceutical intermediates.

General information

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Organisations: Department of Chemical and Biochemical Engineering, CAPEC-PROCESS, University College London
Authors: Marques, M. (Ekstern), Krühne, U. (Intern), Szita, N. (Ekstern)
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Enzyme Characterization in Microreactors by UV-Vis Spectroscopy

In protein engineering mutants are often selected solely on the basis of activity [1], simplifying the analysis and enabling high throughput screening. At a later stage of development, several mutants show comparable performance and this basis for selection becomes indistinct. The basis for selection can at this point be improved by characterization of the enzyme performance where also inhibition and toxicity effects are taken into account. Enzyme characterization is here defined as the effect on initial rate of reaction with respect to pH, enzyme, substrate, co-substrate, product and co-product concentration [2]. From this investigation, it will be possible to determine whether the enzyme meets the criteria for process requirements or not. The development of the process will determine the requirements and this can also reach a state of maturity that resolves obstacles, lowers criteria and paves the way for implementation. As an example ω-transaminase is here investigated, which facilitates the exchange of an amine- and keto-group stereoselectively. The characterization will be carried out in a microreactor [3], this size is currently the only concept that can facilitate this thorough analysis, as the enzyme resource is scarce at this point of development. In the case where the reaction operates with UV active components, UV can be used to detect compounds with high sensitivity supplemented by multivariate data analysis. The spectra are here decorrelated and regressed to yield concentrations of individual compounds. HPLC systems are built for handling small quantities of liquids and the UV detectors for these proves to be fitting excellent. Enzyme characterization is therefore carried out by a combination of a microreactor with a diode array detector from an HPLC system.

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Geometry optimization of a fibrous scaffold based on mathematical modelling and CFD simulation of a dynamic cell culture

In tissue engineering, the development of a tissue essentially depends on supply of an adequate amount of nutrients and the design of a proper biophysical micro-environment for cells. The limitation of the available initial number of cells, expensive substances and time consuming experiments are the main bottlenecks in this type of processes. In this regard, mathematical modelling and computational fluid dynamics simulation (CFD) are powerful tools to identify an efficient and optimized design by providing reliable insights of the process. This study presents a mathematical model and CFD simulation of cartilage cell culture under a perfusion flow, which allows not only to characterize the supply of nutrients and metabolic products inside a fibrous scaffold, but also to assess the overall culture condition and predict the cell growth rate. Afterwards, the simulation results supported finding an optimized design of the scaffold within a new mathematical optimization algorithm that is proposed. The main concept of this optimization routine is to maintain a large effective surface while simultaneously keeping the shear stress level in an operating range that is expected to be supporting growth. Therewith, it should be possible to gradually reach improved culture efficiency as defined in the objective function.

Measurement of oxygen transfer from air into organic solvents: Oxygen transfer from air into organic solvents

Background: The use of non-aqueous organic media is becoming increasingly important in many biotechnological applications in order to achieve process intensification. Such media can be used for example to directly extract poorly water-soluble toxic products from fermentations. Likewise many biological reactions require the supply of oxygen, most normally from air. However, reliable on-line measurements of oxygen concentration in organic solvents (and hence oxygen transfer rates from air to the solvent) has to date proven impossible due limitations in the current analytical methods. Results: For the first time, we demonstrate on-line oxygen measurements in non-aqueous media using a novel optical sensor. The sensor was used to measure oxygen concentration in various organic solvents including toluene, THF, isooctane, DMF, heptane and hexane (which have all been shown suitable for several biological applications). Subsequently, we measured the oxygen transfer rates from air into these organic solvents. Conclusion: The measurement of oxygen transfer rates from air into organic solvents using the dynamic method was established using the solvent resistant optical sensor. The feasibility of online oxygen measurements in organic solvents has also been demonstrated, paving the way for new opportunities in process control.
Microfluidic device for continuous single cells analysis via Raman spectroscopy enhanced by integrated plasmonic nanodimers

In this work a Raman flow cytometer is presented. It consists of a microfluidic device that takes advantages of the basic principles of Raman spectroscopy and flow cytometry. The microfluidic device integrates calibrated microfluidic channels where the cells can flow one-by-one, allowing single cell Raman analysis. The microfluidic channel integrates plasmonic nanodimers in a fluidic trapping region. In this way it is possible to perform Enhanced Raman Spectroscopy on single cell. These allow a label-free analysis, providing information about the biochemical content of membrane and cytoplasm of the each cell. Experiments are performed on red blood cells (RBCs), peripheral blood lymphocytes (PBLs) and myelogenous leukemia tumor cells (K562).
Modelling and simulation of a U-loop Reactor for Single Cell Protein Production

In this work, two approaches of modelling a one phase U-loop reactor are presented. A simple CSTR model consisting of first-principles dynamic process equations was implemented in Matlab. The results give a good indication of the basic understanding of the effect of changing operation conditions on process performance. For a given product yield, the work investigates how process parameters such as dilution rate (D) or the methanol concentration should be selected to optimize the production. Nevertheless, this simple model exhibits some limitations hindering the development of the optimal operation procedure, such as the impact of the reactor geometry on the operating conditions. Some main hydrodynamic characterization parameters, like the mixing and the mass transfer coefficient $k_{La}$ are geometry dependent. The second modelling approach attempts to overcome the above-mentioned problems. A three-dimensional one-phase model using Computational Fluid Dynamics (CFD) methods is proposed. By introducing the momentum balances in the simulation, the results can capture the flow velocity fields in three dimensions. It is thereby possible to indicate the influence of the geometric design on the production yield. This methodology allows further research on the effect of design choices on optimal operation, such as the determination of where to locate the substrate input, the static mixer position or the gas injection position.
Online analysis of oxygen inside silicon-glass microreactors with integrated optical sensors

A powerful online analysis set-up for oxygen measurements within microfluidic devices is presented. It features integration of optical oxygen sensors into microreactors, which enables contactless, accurate and inexpensive readout using commercially available oxygen meters via luminescent lifetime measurements in the frequency domain (phase shifts). The fabrication and patterning of sensor layers down to a size of 100 μm in diameter is performed via automated airbrush spraying and was used for the integration into silicon-glass microreactors. A novel and easily processable sensor material is also presented and consists of a polystyrene- silicone rubber composite matrix with embedded palladium(II) or platinum(II) meso-tetra(4-fluorophenyl) tetrabenzo porphyrin (PdTPTBPF and PtTPTBPF) as oxygen sensitive dye. The resulting sensor layers have several advantages such as being excitable with red light, emitting in the near-infrared spectral region, being photostable and covering a wide oxygen concentration range. The trace oxygen sensor (PdTPTBPF) in particular shows a resolution of 0.06-0.22 hPa at oxygen concentrations lower than 20 hPa (<2% oxygen) and the normal range oxygen sensor (PtTPTBPF) shows a resolution of 0.2-0.6 hPa at low oxygen concentrations (<50 hPa) and 1-2 hPa at ambient air oxygen concentrations. The sensors were integrated into different silicon-glass microreactors which were manufactured using mass production compatible processes. The obtained microreactors were applied for online monitoring of enzyme transformations, including d-alanine or d-phenylalanine oxidation by d-amino acid oxidase, and glucose oxidation by glucose oxidase.
Selective distribution of enzymes in a microfluidic reactor

Off stoichiometric thiol-ene mixtures are well suited for preparation of microfluidic devices with highly functional surfaces. Here a two stage process employing first thiol-ene chemistry (TEC) to prepare two opposite parts of a microfluidic system with a 30x30 mm reactor and subsequently a thiol-epoxy bonding was used to prepare a fully sealed microfluidic system. The reactor was surface functionalized in-situ with allyl glycidyl ether in different patterns (half-reactor, full-reactor, checkerboard structures) on the surface to provide a controlled distribution of epoxides. The method additionally enables the selective immobilization on either top-side or bottom-side or both sides of the reactor. Thereafter horseradish peroxidase was immobilized on the surface and activity tests illustrated how this distribution of the enzyme on the surface could be used to optimize the activity of the enzyme. The results were corroborated by CFD simulations.
Thiol-ene thermosets exploiting surface reactivity for layer-by-layer structures and control of penetration depth for selective surface reactivity.

Thiol-ene thermosets have been shown to be an efficient platform for preparation of functional polymer surfaces. Especially the effectiveness and versatility of the system has enabled a large variety of network properties to be obtained in a simple and straightforward way. Due to its selectivity, various thiols and allyl or other vinyl reactants can be used to obtain either soft and flexible or more rigid functional thermosets. The methodology permits use of either thermal or photochemical conditions both for matrix preparation as well as for surface functionalization. Due to excess reactive groups in the surface of thiol-ene thermosets, it is possible to prepare surface functional thermosets or to exploit the reactive groups for modular construction and subsequent chemical bonding. Here a different approach preparing monolithic layer-by-layer structures with controlled mechanical properties across freestanding samples is presented. The approach is further exploited for preparation of surface structures down to features of 25 µm scale by use of an absorber and simple masking. The combination of masking and absorbers were similarly used to prepare a reactor with controlled surface properties as shown in Figure 1. Here fully sealed reactors (Figure 1a) were prepared modularly by a combination of thiol-ene and thiol-epoxy curing reactions. The reactors were functionalized in different patterns on the top side of the assembled reactor, illustrating the effectiveness of absorbers in controlling the penetration depth and surface grafting. The methodology was used for surface immobilization of enzymes providing a direct link between the distribution of enzymes on the surface and the activity of the reactor.

A Numerical Procedure for Model Identifiability Analysis Applied to Enzyme Kinetics

The proper calibration of models describing enzyme kinetics can be quite challenging. In the literature, different procedures are available to calibrate these enzymatic models in an efficient way. However, in most cases the model structure is already decided on prior to the actual calibration exercise, thereby bypassing the challenging task of model structure determination and identification. Parameter identification problems can thus lead to ill-calibrated models with low predictive power and large model uncertainty. Every calibration exercise should therefore be preceded by a proper model structure evaluation by assessing the local identifiability characteristics of the parameters. Moreover, such a procedure should be generic to make sure it can be applied independent from the structure of the model. We hereby apply a numerical identifiability approach which is based on the work of Walter and Pronzato (1997) and which can be easily set up for any type of model. In this paper the proposed approach is applied to the forward reaction rate of the enzyme kinetics proposed by Shin and Kim (1998). Structural identifiability analysis showed that no local structural model problems were occurring. In contrast, the practical identifiability analysis revealed that high values of the forward rate parameter $V_f$ led to identifiability problems. These problems were even more pronounced at higher substrate concentrations, which illustrates the importance of a proper experimental design to avoid (practical) identifiability problems. By using the presented approach it is possible to detect potential identifiability problems and avoid pointless calibration (and experimental) effort.
Biocatalysis offers the ability to carry out important synthesis and production of valuable chemicals at benign conditions. In the development of new processes, enzymes are being engineered towards specific products with great success. Currently, mutations are introduced into enzymes, and mutants are formed thereof and a search among these is conducted. High throughput screening can deliver screening of mutants in the order of millions a day. Enzyme mutants with increased performance are therefore likely to be found. Here, the enzyme amine transaminases is evaluated since it offers a unique way of producing chiral amines. These amines are important as building blocks for pharmaceuticals and agrochemicals. A promising enzyme has been found, but it has been a problem to assess its performance and give process development direction. Common limitations are substrate and product solubility, unfavourable thermodynamics, inhibition and stability. It is a difficult task to assess where the current bottle neck is for a desired process. Moreover, it cannot be expected that a single solution to the limitations can be found and rather an integrated solution of all of the problems should be the future aim. All the limitations surround the reactor of a process, and with the performance of this being unknown, it is almost impossible to direct development. A focal point must therefore lie in the determination of kinetic models and how kinetic data can be obtained in a robust and generic way. Models for many enzymes already exist and can be found in common text books. These models do however require mutant specific data and must be collected with the target reaction. In this thesis a novel way of collecting kinetic data is created, this is carried out by combining existing technology and enables the analysis of aqueous solutions on-line. Furthermore, the use of a size exclusion column enables the simultaneous detection of enzymes and UV/VIS active compounds. The size exclusion chromatography does not provide baseline separated results, nor is this required. The application of chemometric tools enable detection of compounds in the collected retention time wavelength data. A major improvement over traditional techniques is the quantification of enzyme concentration and this makes it possible to use specific activities for model fitting. The setup takes advantage of microfluidic features and delivers semi-automatic experimentation, overall reducing both consumption of precious materials and costly labor.
Application of microfluidics for the development of intensified aminotransferase (ATA) processes

Development of biocatalytic processes is greatly dominated by well-established batch process based screening technologies, e.g. glass vials (mL) and microtiter plates (μL). However, there is still a need for improvement of currently available technologies and for new technologies enabling relatively easy screening and characterization of different process options. For example, small-scale microfluidic platforms enable testing of complex process options, by combining multiple process steps in a plug-and-play manner, that are difficult to assess with conventional methods. Early in the development of biocatalytic processes, most attention is given to developing and modifying the biocatalyst to reach required process targets. However, it is important to consider the downstream processing (DSP) early in the process development as well, i.e. the downstream costs and limitations to the separation steps will greatly influence the economic viability due to the constraints placed on the required process metrics. This thesis will therefore emphasise product recovery limitations and requirements in combination with the biocatalyst performance and limitations. Here the focus is mainly related to biocatalytic processes where it is found beneficial/necessary to implement in-situ co-product/product removal (IScPR/ISPR). For example, through combined operation of reactor and separation modules, as such applications require selective separation and sufficient driving force to influence the process significantly.

In recent years, many microfluidic applications have proven useful for process and synthesis development within the area of organic synthesis, i.e. flow chemistry. For example, the unique characteristics of the small scale enable safer and efficient handling and production of explosive and/or toxic compounds. Furthermore, development based on applying microfluidic platforms potentially enables easier introduction of continuous process aspects, when suitable. The motivation for this project is to investigate the potential of applying microfluidic technologies in the development and testing of biocatalytic processes. Within this thesis, microfluidic modules are applied as tools to screen, characterize, and test reactor and separation process options. Furthermore, multiple microfluidic modules are combined in order to test complex process configurations, i.e. reactor modules combined with separation modules, as a means of narrowing down and optimizing the most promising process options.

Throughout this thesis the applicability of microfluidics, as an integrated part of biocatalytic process development, is evaluated based on case studies focusing on the asymmetric synthesis of chiral amines using aminotransferases (ATAs). Chiral amines are valuable building blocks for many pharmaceuticals and precursors. The application of ATAs for asymmetric synthesis has many advantages, but it is also common that there are some challenges. In many cases it is found beneficial/necessary to apply various process engineering strategies, e.g. IScPR and ISPR, to overcome the challenges and ensure the economic feasibility of such processes. With economic process feasibility in mind, it can be extremely useful to apply microfluidic platforms to enable fast screening and characterization of various process options in order to overcome the challenges. Due to the physicochemical properties of the compounds involved in the case studies in this thesis, the focus will be on the application/development of liquid-liquid extraction modules to operate in combination with reactor modules. The main outcome of this PhD thesis is knowledge on the potential of applying microfluidics, in combination with conventional methods, for the development of biocatalytic processes. More specifically, microfluidics will enable testing of complex process options and strategies, which are very difficult to test with conventional methods, by combining microfluidic modules representing different process steps in a plug-and-play manner. The advantages and technology constraining disadvantages of microfluidics for biocatalytic process development are both identified in this thesis. Novel applications of microfluidic development of ATA processes are investigated in detail, i.e. first by characterization of single microfluidic process steps (reactor and liquid-liquid extraction modules) and afterwards by testing of complex processes by combining multiple microfluidic process steps. This is realized by putting in place a microfluidic demonstration system, a plug-and-play combination of a reactor module with two liquid-liquid extraction modules and settlers. Another novelty of this thesis, is the application of the integrated liquid-liquid extraction steps to both reactor and separation process options. Furthermore, multiple microfluidic modules are combined in order to test complex process configurations, i.e. reactor modules combined with separation modules, as a means of narrowing down and optimizing the most promising process options.

Throughout this thesis the applicability of microfluidics, as an integrated part of biocatalytic process development, is evaluated based on case studies focusing on the asymmetric synthesis of chiral amines using aminotransferases (ATAs). Chiral amines are valuable building blocks for many pharmaceuticals and precursors. The application of ATAs for asymmetric synthesis has many advantages, but it is also common that there are some challenges. In many cases it is found beneficial/necessary to apply various process engineering strategies, e.g. IScPR and ISPR, to overcome the challenges and ensure the economic feasibility of such processes. With economic process feasibility in mind, it can be extremely useful to apply microfluidic platforms to enable fast screening and characterization of various process options in order to overcome the challenges. Due to the physicochemical properties of the compounds involved in the case studies in this thesis, the focus will be on the application/development of liquid-liquid extraction modules to operate in combination with reactor modules. The main outcome of this PhD thesis is knowledge on the potential of applying microfluidics, in combination with conventional methods, for the development of biocatalytic processes. More specifically, microfluidics will enable testing of complex process options and strategies, which are very difficult to test with conventional methods, by combining microfluidic modules representing different process steps in a plug-and-play manner. The advantages and technology constraining disadvantages of microfluidics for biocatalytic process development are both identified in this thesis. Novel applications of microfluidic development of ATA processes are investigated in detail, i.e. first by characterization of single microfluidic process steps (reactor and liquid-liquid extraction modules) and afterwards by testing of complex processes by combining multiple microfluidic process steps. This is realized by putting in place a microfluidic demonstration system, a plug-and-play combination of a reactor module with two liquid-liquid extraction modules and settlers. Another novelty of this thesis, is the application of the integrated liquid-liquid extraction steps to both recover the product, using in-situ product removal (ISPR), and at the same time feed the main substrate, i.e. in-situ substrate supply (ISSS). Furthermore, guidelines for identifying suitable ISPR/IScPR options – and, importantly, for eliminating unfeasible options – for ATA processes are proposed.
Economic Considerations for Selecting an Amine Donor in Biocatalytic Transamination

The industrial implementation of biocatalysis for production of pharma and fine chemicals has grown substantially over recent years. An upcoming application is that of chiral synthesis of optically pure amines, a technology known for many years but that is now seeing a renewed and wider interest in industry. The technology has been demonstrated in a few selected cases, but widespread implementation and for a broader range of target molecules requires a deeper understanding of the underlying thermodynamic as well as economic constraints for the different choices that can be made in designing the process, in particular the choice of amine donor. This paper discusses these constraints and demonstrates, through simple thermodynamic and economic models, the process targets that need to be set and achieved for a process dependent on allowed process costs and quality targets.

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Hydrodynamic Characterization of Substrate Gradients in a Pilot Scale Fermenter Using CFD and Spatially Distributed Sensors

The prediction and understanding of mixing and oxygen mass transfer in fermenters and bioreactors is useful for bioprocess improvement as these dynamics govern production rates of the biotransformation. In particular heterogeneities occurring under process conditions is of interest as such gradients present challenges for process development and scale up [1]. Heterogeneities in substrate concentration have been identified in large scale fermenters [2] and reliable tools to identify and quantify these phenomena are required. This work utilizes the degradation of hydrogen peroxide to oxygen by catalase to illustrate and validate how substrate is distributed throughout the vessel by combining CFD and experimental data collected with spatially distributed sensors.

Microfluidics in Chemical and Biochemical Engineering Applications

Microfluidics in Chemical and Biochemical Engineering Applications
Modelling of Mass Transfer Phenomena in Chemical and Biochemical Reactor Systems using Computational Fluid Dynamics

Computational fluid dynamics (CFD) is the application of numerical methods to solve systems of partial differential equations related to fluid dynamics. The continuity and the momentum equations are the most commonly applied equations within CFD, and together they can be used to calculate the velocity and pressure distributions in a fluid. CFD also enables the modelling of several fluids simultaneously, e.g. gas bubbles in a liquid, as well as the presence of turbulence and dissolved chemicals in a fluid, and many other phenomena. This makes CFD an appreciated tool for studying flow structures, mixing, and other mass transfer phenomena in chemical and biochemical reactor systems.

In this project, four selected case studies are investigated in order to explore the capabilities of CFD. The selected cases are a 1 ml stirred microbioreactor, an 8 ml magnetically stirred reactor, a Rushton impeller stirred pilot plant reactor, and a rotating bed reactor filled with catalytic porous material. A selection of the simulated phenomena includes the velocities and turbulent quantities in the reactors, as well as the distribution of the gas and liquid phases in them. Mixing times, oxygen transfer rates and an ion-exchange reaction are also modelled and compared to experimental data.

The thesis includes a comprehensive overview of the fundamentals behind a CFD software, as well as a more detailed review of the fluid dynamic phenomena investigated in this project. The momentum and continuity equations are presented as well as the theory behind the SST and the k-ε turbulence models. Modelling of additional variables, porous materials and two-phase flows are also introduced. The two-phase flows are modelled using the Euler-Euler method, and both dispersed and free-surface flows are simulated.

The importance of mass transfer with a focus on mixing, gas-liquid transfer of oxygen, and heterogeneous reactor systems is reviewed and mathematical models for these applications are presented. A review of how these mass transfer phenomena have been modelled in the scientific literature is also included.

The models are subsequently evaluated based on their applicability in the four case studies. The evaluations especially focus on the impact of the choice of turbulence model and other modelling decisions made by the user. The conclusion is that CFD is a highly valuable tool for modelling several important parameters in chemical and biochemical reactors but that the user must be well aware of the shortcomings with the applied models.
Shape and topology optimization of enzymatic microreactors

Structural optimization methods have been used by mechanical and civil engineers over the years to find the optimal structures. Structural optimization is a series of computational techniques which include shape and topology optimization. Shape optimization is directly applied to the boundaries of a structure and results in the deformation of the configuration. Topology optimization contributes to the improvement of the layout of the material in a domain. The mechanical performance of a structure is evaluated by an objective function which can be, for example, maximizing its stiffness. The need for effective and cost-efficient reactors for pharmaceutical processes forces the industry to search for better technologies. In biochemical engineering, the used reactor design in a given process is usually limited to a range of well-established configurations and layouts. Usually the implemented reactors in a chemical process do not always yield in the best reaction conditions. This thesis develops an innovative application of topology and shape optimization methods to a biochemical engineering problem. The main goal is to design a reactor according to the limitations of the reaction system by modifying the reactor configuration. In this thesis structural optimization methods were exclusively applied to enzymatic microreactors. The case studies were chosen such that they can be experimentally tested afterwards. In this way, the design of the reactor is customized to the reaction system and it contributes to the reduction of extensive experimental work to find the best reactor configuration. Shape optimization has been applied to an YY-microreactor with a rectangular cross-section with the intention to investigate the shape influence on the active mixing of substances and consequently in the reaction yield. The inlet and the outlet are located at the respective ends of the reactor. Both inlet and outlet have a Y shape where two streams meet at the entrance of the reaction chamber and two streams are split again at the exit. The optimization routine focuses on the modification of the microreactor shape parameters such as height and width. This is achieved by a computational fluid dynamic (CFD) simulation study, which investigates a biocatalytic reaction for the production of optically pure chiral amines in the reactor system. The routine implements kinetic models into a CFD framework (ANSYS CFX®), which is coupled with a self-programmed MATLAB® code. ANSYS CFX® performs the discretization of the microreactor into finite volume elements and calculates the main reactor outputs. The MATLAB® routine performs the optimization by changing the geometry. Furthermore, it includes the evaluation of the objective function, the new definition and execution of the next simulation for each new microreactor shape. Afterwards, the performance of the system is evaluated by comparing the objective function (reaction yield) with the previous best configuration. If the geometry changes result in a better reaction yield, this geometry is selected as the best and the old configuration is discarded. The optimization routine continues until a constraint is fulfilled or the optimization converges. The changes of the geometry are performed by a gradient-free method named random search. The random search modifies the design variables by sampling in an arbitrary manner from a vector which sets the variation limits. Subsequently, the same coupled routine between ANSYS CFX® and MATLAB® is applied to topology optimization. The method was used as a novel technique to computationally discover the best spatial distribution of an enzyme inside microreactors. Usually, the enzyme is uniformly distributed inside a reactor, which can mean either at a wall surface or in a packed bed reactor or free in solution. Therefore, these three applications are studied. The aim is to improve the product formation per same amount of enzyme in the reactor. The Evolutionary Structural Optimization (ESO) method is adapted to perform the optimization. The ESO method removes inefficient elements from a structure by a gradual and iterative procedure according to a rejection criterion which determines the elements that should be removed every iteration. The MATLAB® routine is featuring the adaptation of the ESO method to the biocatalytic reactor. The two-dimensional topology optimization is applied to a microreactor with immobilized enzyme on the wall surface. The selected reactor geometry is an adaptation of a previously scientific documented shape used in topology optimization of microreactors. The threedimensional topology is computationally applied to the distribution of enzyme in a miniaturized packed bed reactor as well as to a microreactor with free enzyme in the volume. In the last part of the thesis, the topology of microreactors is the experimentally studied. This is achieved by using the peroxidase-catalyzed oxidation of 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) to its radical form by reduction of hydrogen peroxide. The determination of the kinetic mechanism is required in order to validate the optimized microreactors. Two microreactor shapes are topology optimized for posterior experimental validation. The first shape corresponds to the shape with immobilized peroxidase on the wall surface. The experimental validation was attempted by using a photochemical reaction. The reaction attaches linkage molecules to a masked surface, which has an immobilization pattern. The linkage molecules will thereafter react with the enzyme molecules binding them covalently to the surface. The second microreactor configuration corresponds to a square shaped cross section microchannel with free enzyme in solution. For this case study, a well-mixed solution of enzyme and substrate is considered to enter the microreactor. The experimental comparison is performed by comparing an improved inlet configuration with a reference system. The configurations were selected and fabricated as a compromise considering the outcome of the topology optimization and the limitations of the fabrication process.

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Topology optimization for biocatalytic microreactor configurations

The aim of this study is to present an innovative strategy for selecting a reactor for a specific process. Instead of adapting the process to a well-known reactor shape, a topology optimization method is used to obtain the best reactor configuration, and is applied to a biocatalytic reaction system as a case study. The Evolutionary Structure Optimization (ESO) method is applied using an interface between Matlab® and the computational fluid dynamic simulation software ANSYS CFX®. In the case study, the ESO method is applied to optimize the spatial distribution of immobilized enzyme inside a microreactor. The results allow evaluating which regions in the microreactor have more importance for the product formation. In fact, it was possible to simulate the improvement of the outlet product concentration per same amount of enzyme by modifying the spatial distribution of the immobilized enzyme.

Biocatalytic process development using microfluidic miniaturized systems

The increasing interest in biocatalytic processes means there is a clear need for a new systematic development paradigm which encompasses both protein engineering and process engineering. This paper argues that through the use of a new microfluidic platform, data can be collected more rapidly and integrated with process modeling, can provide the basis for validating a reduced number of potential processes. The miniaturized platform should use a smaller reagent inventory and make better use of precious biocatalysts. The EC funded BIOINTENSE project will use ω-transaminase based synthesis of chiral amines as a test-bed for assessing the viability of such a high throughput biocatalytic process development, and in this paper, such a vision for the future is presented.
Challenges in industrial fermentation technology research

Industrial fermentation processes are increasingly popular, and are considered an important technological asset for reducing our dependence on chemicals and products produced from fossil fuels. However, despite their increasing popularity, fermentation processes have not yet reached the same maturity as traditional chemical processes, particularly when it comes to using engineering tools such as mathematical models and optimization techniques. This perspective starts with a brief overview of these engineering tools. However, the main focus is on a description of some of the most important engineering challenges: scaling up and scaling down fermentation processes, the influence of morphology on broth rheology and mass transfer, and establishing novel sensors to measure and control insightful process parameters. The greatest emphasis is on the challenges posed by filamentous fungi, because of their wide applications as cell factories and therefore their relevance in a White Biotechnology context. Computational fluid dynamics (CFD) is introduced as a promising tool that can be used to support the scaling up and scaling down of bioreactors, and for studying mixing and the potential occurrence of gradients in a tank. © 2014 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

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Authors: Ringborg, R. H. (Intern), Krühne, U. (Intern), Woodley, J. (Intern)
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Modeling and optimizing oxygen transfer in small scale reactors using computational fluid dynamics

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Authors: Larsson, H. (Intern), Gernaey, K. (Intern), Krühne, U. (Intern)
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Oxidase-based biocatalytic processes

Biocatalytic processes are gaining significant focus in frontiers where they offer unique advantages (selectivity and mild operating conditions) over chemical catalysts. It is therefore not surprising that there have been many industrial biocatalytic processes implemented. Despite past successes, the implementation of a new biocatalytic process still presents some challenges (demands placed on the biocatalyst) in terms of the requirements to make a viable industrial process. In order for a biocatalytic process to be economically successful, it is necessary that certain a set of target metrics (product titre, biocatalyst yield or space time yield and reaction yield) are achieved. Hence, the biocatalyst must be able to work at high substrate and product concentrations. Such constraints that arise from the biocatalyst are classified as biocatalyst-related limitations. In addition, other limitations can arise from the reaction species (substrate and product volatility for example) and the process (such as oxygen supply, ability to control pH) and are classified as reaction-related and process-related constraints respectively. Although the development of biocatalyst and process engineering tools offers a number of solutions to overcome the limitations, it is often complicated to identify the key limitation of the system that prevents economic scale-up. Hence, development of a systematic method for identifying the limitations during early-stage development of a biocatalytic process and potentially the order in which they need to be tackled would offer a valuable tool for process development. Biocatalytic oxidations are potentially of great value because of the selective chemistry that they offer, resulting in higher yields compared to those achievable through chemical catalysis. Oxidases are particularly interesting biocatalysts because they use a mild oxidant (oxygen) as a substrate opposed to their chemical counterparts which use strong oxidants such as permanganates. A class of oxidases called monoamine oxidases has been used as the central case study for the thesis. The rationale for choosing this system is that it has been shown to exhibit the potential for resolution of racemic amines, and is capable of producing industrially interesting imines which are rather difficult to synthesize by chemical routes. An important aspect for biocatalytic reactions would be the implementation of monitoring and control systems that allow for rapid data collection to gain process knowledge. For oxidase-based biocatalysis, oxygen is consumed in stoichiometric amounts for the reaction. Therefore, oxygen sensors which can measure the oxygen concentration can be a valuable tool for monitoring the process. The thesis exemplifies the use of novel solvent-resistant oxygen sensors as supporting technology for oxidase-based reactions using a glucose oxidase reaction system as an example. Implementation of biocatalytic oxidation at scale still requires process knowledge which includes systematic evaluation of the reaction system through the use of property prediction tools as well as experiments. The thesis presents a methodology for development of oxidase-based biocatalytic processes. Particularly important aspect of the methodology includes the use of in silico analysis where property prediction tools have been used to identify the potential limitations to the reaction system prior to experimentation. Such an analysis presents the opportunity to direct experimental work and therefore reduce the time and effort spent on process development, by eliminating unfeasible routes. The example chosen for the development of the methodology was a specific monoamine oxidase-based syntheses for the production of a pharmaceutical intermediate. This particular reaction system was chosen because of the potential use of the product of the biocatalytic reaction as a pharmaceutical intermediate. However, there was little information on the reaction system in the literature for the use of this biocatalyst for synthesis of chemicals. Therefore, early stage process understanding was required. The chapters of the thesis identify the potential limitations for the reaction system by systematic evaluation of the reaction system through the use of property prediction tools as well as experiments. The results obtained from the experiments are then used to identify the bottleneck for the implementation at scale. Furthermore, a discussion of the limitations and the order which they need to be tackled is presented.

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Programming language and tools for Multipurpose Lab-on-a-Chip Platforms

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Shape optimisation of a microreactor for biocatalytic synthesis of optically pure chiral amines

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Organisations: Department of Chemical and Biochemical Engineering, CAPEC-PROCESS
Authors: Pereira Rosinha, I. (Intern), Gernaey, K. (Intern), Woodley, J. (Intern), Krühne, U. (Intern)
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The focus of this work is on process systems engineering (PSE) methods and tools, and especially on how such PSE methods and tools can be used to accelerate and support systematic bioprocess development at a miniature scale. After a short presentation of the PSE methods and the bioprocess development drivers, three case studies are presented. In the first example it is demonstrated how experimental investigations of the bi-enzymatic production of lactobionic acid can be modeled with help of a new mechanistic mathematical model. The reaction was performed at lab scale and the prediction quality analyzed. In the second example a computational fluid dynamic (CFD) model is used to study mass transfer phenomena in a microreactor. In this example the model is not only used to predict the transient dynamics of the reactor system but also to extract material properties like the diffusion velocities of substrate and product, which is otherwise difficult to access. In the last example, a new approach to the design of microbioreactor layouts using topology optimization is presented and discussed. Finally, the PSE methods are carefully discussed with respect to the complexity of the presented approaches, the applicability with respect to practical considerations and the opportunity to analyze experimental results and transfer the knowledge between different scales.

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Test design of particles for immobilization of ω-transaminase in a packed bed microreactor

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Authors: Pereira Rosinha, I. (Intern), Gernaey, K. (Intern), Woodley, J. (Intern), Krühne, U. (Intern)
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μ-structured devices as tools for screening process intensification in biocatalysis

Biocatalytic processes have been emerging as potential replacements of traditional chemical synthesis in many industrial relevant production processes. However the implementation of new biocatalytic processes can be a very challenging procedure which requires both biocatalyst and process screening and characterization for economic evaluation before scale-up. Microstructured devices have been used as screening tools that allow paradigm changes in process
development by shortening process development times through modularity and intensification. Customized reactor
designs and process configurations by integrating different modules can be developed at microscale. Such configurations
enable effective screening and rapid process development of biocatalytic reactions assuring economic viability and shorter
time to market for pharmaceutical products. Thus the work presented in this thesis is based on the application of
microstructured devices for screening and characterization of process options in biocatalytic processes. The thesis focuses
on interesting case studies like the asymmetric synthesis of chiral amines using ω-transaminases and synthesis of an
industrially relevant imine product using monoamine oxidase. The first part of the thesis is focused on the development of
novel reactor configurations for biocatalysis. A combination of micro reactors and computational fluid dynamics (CFD) has
been found to contribute significantly towards the understanding of diffusional properties of the substrate and the product.
Such knowledge is subsequently applied to design customized reactor configurations. It has been demonstrated that this
knowledge can be crucial for the choice and design of reactors. The second part focuses on developing μ-scale modules
for rapid screening and integrating process units. The increase in productivity is evaluated through process metrics. A
case study demonstrates the applicability of using a micro-scale packed bed column for screening synthetic resins for in-
situ product removal. CFD simulations were performed to guide the design of a packed column for efficient operation.
Further case studies demonstrate the development of modular set-ups with integrated processes at microscale to address
process limitations which were determined by initial experiments at lab scale. The degree of integration of functionalities
requires process optimization. Thus optimization studies were also performed by varying operational parameters. From an
academic point of view, a general methodology is desired and thus a systematic screening methodology is proposed that
relies on microstructured devices during process development. The methodology can be applied to other biocatalytic
reactions with some limitations.

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Biokatalysatoren veg til industrien

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Enzymatic process intensification across scales

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Main Research Area: Technical/natural sciences

Microreactors and CFD as Tools for Biocatalysis Reactor Design: A case study

Microreactors have been used for acquiring process data while consuming significantly lower amounts of expensive reagents. In this article, the combination of microreactor technology and computational fluid dynamics (CFD) is shown to contribute significantly towards understanding the diffusional properties of the substrate and the product of a biocatalytic reaction. Such knowledge is then applied to design reactor configurations. It has been demonstrated that this kind of knowledge is crucial for the choice and design of reactors. In the discussion, it is highlighted how microreactor-based platforms with similar dimensions to the ones tested here can be used as a screening tool for screening biocatalyst and process alternatives.

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Authors: Bodla, V. K. (Intern), Seerup, R. (Ekstern), Krühne, U. (Intern), Woodley, J. M. (Intern), Gernaey, K. (Intern)
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Miniaturized experimental toolbox for ω-transaminase technology (BIOINTENSE)

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Miniaturized Experimental Toolbox for ω-Transaminase Technology (BIOINTENSE)

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Simulation study of microbioreactor configurations for production of optically pure chiral amines

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Towards an integrated µ-factory: Integrated micro membrane packed bed reactor

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Towards an integrated µ-factory: Design and development of a microfluidic system to include fermentation and biocatalysis

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Organisations: Department of Chemical and Biochemical Engineering, Center for Process Engineering and Technology
Authors: Bodla, V. K. (Intern), Woodley, J. (Intern), Krühne, U. (Intern), Gernaey, K. (Intern)
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Towards an integrated μ-factory: Integrated micro membrane packed bed reactor

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Towards effective biocatalytic process development using microreactor technology

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Organisations: Department of Chemical and Biochemical Engineering, Center for Process Engineering and Technology
Authors: Woodley, J. (Intern), Heintz, S. (Intern), Ringborg, R. H. (Intern), Pereira Rosinha, I. (Intern), Tufvesson, P. (Intern), Krühne, U. (Intern), Gernaey, K. (Intern)
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Using micro technology in process screening for improved ω-transaminases

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Authors: Ringborg, R. H. (Intern), Krühne, U. (Intern), Gernaey, K. (Intern), Woodley, J. (Intern)
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Computational Fluid Dynamics at work - Design and Optimization of Microfluidic Applications
Computational Fluid Dynamics (CFD) is presented as a powerful tool to support design and optimization of microfluidic reactors. This is demonstrated by means of three case studies. First, a three-dimensional scaffold for tissue engineering purposes is investigated using a combination of CFD and a simple biological model. The result is a suggestion of an improved geometry design. In the second case study a microfluidic cartridge of a novel automated in vitro fertilization device is presented, where the CFD model has supported the fluidic design of the microfluidic network in which the stem cells are grown. In the last case study a biocatalytic microfluidic reactor design is presented in which the material characteristics of substrates and products of the catalytic reaction can be investigated. As model system the transaminase catalyzed formation of methylbenzylamine (MBA) from acetophenone is investigated and it is demonstrated how the experimental investigation along with the CFD model can be used for the characterisation of the performance of the reactor system.
Full in vitro fertilization laboratory mechanization: toward robotic assisted reproduction?

Objective: To describe the current efforts made to standardize different steps of assisted reproductive technology processes by the introduction of new technologies for the nonsubjective sperm selection process, oocyte denudation by mechanical removal of cumulus cells, oocyte positioning, sperm motility screening, fertilization, embryo culture, media replacement by microfluidics, and monitoring of embryo development by time-lapse photography, embryo secretions, and/or O₂ consumption. These technologies could be integrated in a unique and fully automated device.

Design: Pubmed database and research and development data from authors.

Setting: University-affiliated private center.

Patient(s): None.

Intervention(s): None.

Main Outcome Measurement(s): None.

Result(s): Several technologies would be useful for: 1) selection of sperm based on viability; 2) manipulation and removal of the cumulus cells' narrow channel regions combined with microfluidics; 3) advances in oocyte positioning precision through the use of joystick-controlled micromanipulators; 4) microfluidics allowing the gradual change of a culture medium, which might result in better embryo development as well as reduce the amount of embryo manipulation; 5) time-lapse, proteomic, and metabolic scoring of the developing embryo, allowing multiple and optimized selection of the embryos. The technologies described in this review have not yet reported reliable clinical proofs.

Conclusion(s): We already have available some of the technologies described, but we envisage an integrated device, i.e., an IVF lab-on-a-chip, by which oocyte and sperm would be processed to achieve a perfect embryo ready to be delivered into the uterus. With such a device, sample preparation, chemical or biologic reactions, and data collection would be integrated.
Lab on a chip automates in vitro cell culturing

A novel in vitro fertilization system is presented based on an incubation chamber and a microfluidic device which serves as advanced microfluidic cultivation chamber. The flow is controlled by hydrostatic height differences and evaporation is avoided with help of mineral oil. Six patient compartments allow six simultaneous temperature and pH controlled cultivations with 12 embryos with continuous logging of the monitoring data. Two media can be controlled with help of opening or closing of openings at the microfluidic disposable devices. The flow rates through the single cell compartments can be controlled up to 20μl/h. A common pH electrode is supplied by 14μl sample, which is expanded with help of DI water.

General information

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Organisations: Department of Chemical and Biochemical Engineering, Center for Process Engineering and Technology, Università “Magna Graecia” of Catanzaro, Smart Biosystems ApS, Italian Institute of Technology
Authors: Perozziello, G. (Ekstern), Møllenbach, J. (Ekstern), Laursen, S. (Intern), Di Fabrizio, E. (Ekstern), Gernaey, K. (Intern), Krühne, U. (Intern)
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Monitoring and control of microbioreactors: An expert opinion on development needs
This perspective article is based on an expert panel review on microbioreactor applications in biochemical and biomedical engineering that was organized by the M3C (measurement, monitoring, modelling and control) Working Group of the European Section of Biochemical Engineering Science (ESBES) in the European Federation of Biotechnology (EFB). The aim of the panel was to provide an updated view on the present status of the subject and to identify critical needs and issues for furthering the successful development of microbioreactor monitoring and control. This will benefit future bioprocess development and in vitro toxicity testing. The article concludes with a set of recommendations for extended use and further development of microbioreactors.

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Organisations: Department of Chemical and Biochemical Engineering, Center for Process Engineering and Technology, University College London, m2p-labs GmbH, Charité-Universitätsmedizin Berlin, Technical University of Berlin, Novo Nordisk A/S, Technische Universität Dortmund, Stem Cell Systems GmbH, Linköping University, Technische Universität Braunschweig
Authors: Gernaey, K. (Intern), Baganz, F. (Ekstern), Franco-Lara, E. (Ekstern), Kensy, F. (Ekstern), Krühne, U. (Intern), Luebberstedt, M. (Ekstern), Marx, U. (Ekstern), Palmqvist, E. (Ekstern), Schmid, A. (Ekstern), Schubert, F. (Ekstern), Mandenius, C. (Ekstern)
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Web of Science (2016): Indexed yes
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Web of Science (2015): Indexed yes
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Scopus rating (2014): SJR 1.189 SNIP 1.062 CiteScore 2.98
Web of Science (2014): Indexed yes
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Web of Science (2013): Indexed yes
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ISI indexed (2012): ISI indexed no
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Scopus rating (2010): SJR 0.787 SNIP 0.798
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BFI (2009): BFI-level 1
Multi-scale modeling for prediction of distributed cellular properties in response to substrate spatial gradients in a continuously run microreactor

In large-scale fermentors, non-ideal mixing leads to the development of heterogeneous cell populations. This cell-to-cell variability may explain the differences in e.g. yields for large- and lab-scale cultivations. In this work the anaerobic growth of Saccharomyces cerevisiae in a continuously run microbioreactor is simulated. A multiscale model consisting of the coupling of a population balance model, a kinetic model and a flow model was developed in order to predict simultaneously local concentrations of substrate (glucose), product (ethanol) and biomass, as well as the local cell size distributions.

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Multi-scale modeling for prediction of distributed cellular properties in response to substrate spatial gradients in a continuously run microreactor

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One-millilitre microbioreactor with impeller for improved mixing

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PSE opportunities in biocatalytic process design and development
Biocatalysis (the use of one or more isolated enzymes in soluble or immobilized form, as well as enzymes contained within resting whole-cells) is a rapidly growing area of process technology. The introduction of biocatalysis presents new opportunities to develop ‘green’ synthetic routes to pharmaceuticals and other chemical products, since enzymes usually work in an aqueous solution and under mild conditions. Nevertheless the implementation of a biocatalytic reaction and the integration of a biocatalytic reaction into an otherwise chemical catalytic sequence is a complex task where PSE tools have a particularly important role to play. In this paper we will present a variety of PSE tools including computational fluid dynamics (CFD), operating windows, kinetic modelling, economic analysis and environmental assessment to support the development of economically viable biocatalytic processes.

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Towards improved bioprocess operation: monitoring, modeling and control
A sample port of a cell culture system

Disclosed herein is a cell culturing system comprising a culturing chamber for culturing a biological cell in a growth medium and a sensor for measuring a signal in the spent growth medium, wherein the culturing chamber is provided in a mesoscale bioreactor platform with an inlet opening for an influent stream of growth medium and a outlet opening for an effluent stream of spent growth medium, said outlet opening, said spent growth medium being in fluid communication with a sample port for releasable adoption of the sensor. Furthermore, a method of measuring an effluent stream of spent growth medium from a culturing chamber in the cell culturing system is disclosed.

Chamber of a bioreactor platform

Disclosed herein is mesoscale bioreactor platform comprising an upwards open chamber for a biological cell, which chamber via a first port is in communication with a first channel for conducting an influent stream of a liquid into the chamber and via a second port is in communication with a second channel for conducting an effluent stream of a liquid away from the chamber, which chamber is provided with a closure comprising a water-immiscible liquid, and wherein said first channel is in fluid communication with a reservoir for a liquid and said second channel is in fluid communication with a waste container. Furthermore, a method for modifying the interaction of a content of a chamber with the surroundings is described as well as method of culturing a biological cell.
Lab on a chip automates in vitro cell culturing

General information
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Organisations: Department of Chemical and Biochemical Engineering, Università “Magna Graecia” of Catanzaro, Smart Biosystems ApS, Italian Institute of Technology
Authors: Perozziello, G. (Ekstern), Møllenbach, J. (Ekstern), Laursen, S. (Ekstern), Fabrizio, E. D. (Ekstern), Gernaey, K. (Intern), Krühne, U. (Intern)
Publication date: 2011
Event: Poster session presented at 37th International Conference on Micro and Nano Engineering, Berlin, Germany.
Main Research Area: Technical/natural sciences
Electronic versions:
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Bibliographical note
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Source: orbit
Source-ID: 313235
Publication: Research - peer-review › Poster – Annual report year: 2011

Mesoscale bioreactor platform for perfusion

General information
State: Published
Organisations: Technical University of Denmark
Authors: Larsen, J. M. (Ekstern), Krühne, U. (Intern)
Publication date: 2011

Publication information
Country: United States
IPC: C12M1/00
Patent number: US2011104730
Date: 05/05/2011
Original language: English
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Bibliographical note
Patent application number: US20080674762 20080801
Main Research Area: Technical/natural sciences
Source: dtu
Source-ID: u::9267
Publication: Research › Patent – Annual report year: 2007

Microfluidic enzymatic reactors using ω-transaminases

General information
A Transient 3D-CFD Model Incorporating Biological Processes for Use in Tissue Engineering

In this article a mathematical model is presented in which the fluid dynamic interaction between the liquid flow in a scaffold and growing cells is simulated. The model is based on a computational fluid dynamic (CFD) model for the representation of the fluid dynamic conditions in the scaffold. It includes furthermore a simple biological growth model based on Michaelis Menten type kinetics for the growth of cells. The model includes biomass, substrate and oxygen as the most important growth limiting components in the system. Furthermore the growth, decay and maintenance respiration of the cells are considered in the model. In a variation of the model the growth of the biomass is influenced by the fluid dynamic induced shear stress level, which the cells are exposed to. In parallel an experimental growth of stem cells has been performed in a 3D perfusion reactor system and the culturing has been stopped after 2, 8 and 13 days. The development of the cells is compared to the simulated growth of cells and it is attempted to draw a conclusion about the impact of the shear stress on the cell growth.

Keyword: Computational fluid dynamics (CFD), Micro pores, Scaffold, Bioreactor, Fluid structure interaction, Tissue engineering

Design considerations and initial validation of a liquid microflow calibration setup using parallel operated syringe pumps

Danish Technological Institute (DTI) currently offers traceable calibration of liquid flow rates down to 5 L h⁻¹. However, the industry also requests traceable calibration below this point for flowmeters and pumps. Therefore, DTI is in the process of establishing a traceable calibration setup for such microfluidic devices. This paper addresses the design and uncertainty considerations for a setup based on gravimetric and volume traceability. The flow generation in the setup utilizes two
parallel operated syringe pumps with different syringe volumes. The two syringes are programmed so one syringe can replace the pumping action of the second syringe without influencing the resulting flow. In that way it is possible to generate flow rates for calibration in the range from 6 L h⁻¹ to 20 µL h⁻¹. Traceability is currently achieved gravimetrically using special-purpose toploader balances. The resulting expanded uncertainty is expected to be below 0.1% between 6 L h⁻¹ and 100 mL h⁻¹, gradually increasing towards 2% between 100 mL h⁻¹ and 1.2 mL h⁻¹. Furthermore, a concept is proposed to achieve traceability in the full flow range from 6 L h⁻¹ to 20 µL h⁻¹ based on delivered volume divided by time with glass syringes as reference and an expanded uncertainty expected to be below 2%.

Keyword: Uncertainty, Microfluidics, Microflow, Volume, Traceability, Calibration, Gravimetric, Syringe pump

General information
State: Published
Organisations: Danish Technological Institute
Authors: Melvad, C. (Ekstern), Krühne, U. (Intern), Frederiksen, J. (Ekstern)
Publication date: 2010
Main Research Area: Technical/natural sciences

Publication information
Journal: Measurement Science and Technology
Volume: 21
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Ratings:
  BFI (2017): BFI-level 2
  Web of Science (2017): Indexed yes
  BFI (2016): BFI-level 2
  Scopus rating (2016): SJR 0.668 SNIP 1.173 CiteScore 1.75
  BFI (2015): BFI-level 2
  Scopus rating (2015): SJR 0.687 SNIP 1.303 CiteScore 1.71
  BFI (2014): BFI-level 2
  Scopus rating (2014): SJR 0.657 SNIP 1.319 CiteScore 1.58
  Web of Science (2014): Indexed yes
  BFI (2013): BFI-level 2
  Scopus rating (2013): SJR 0.555 SNIP 1.244 CiteScore 1.53
  ISI indexed (2013): ISI indexed yes
  Web of Science (2013): Indexed yes
  BFI (2012): BFI-level 2
  Scopus rating (2012): SJR 0.716 SNIP 1.529 CiteScore 1.65
  ISI indexed (2012): ISI indexed yes
  Web of Science (2012): Indexed yes
  BFI (2011): BFI-level 2
  Scopus rating (2011): SJR 0.844 SNIP 1.703 CiteScore 1.77
  ISI indexed (2011): ISI indexed yes
  Web of Science (2011): Indexed yes
  BFI (2010): BFI-level 2
  Scopus rating (2010): SJR 0.679 SNIP 1.462
  Web of Science (2010): Indexed yes
  BFI (2009): BFI-level 1
  Scopus rating (2009): SJR 0.919 SNIP 1.573
  BFI (2008): BFI-level 1
  Scopus rating (2008): SJR 0.881 SNIP 1.494
  Web of Science (2008): Indexed yes
  Scopus rating (2007): SJR 0.823 SNIP 1.492
  Web of Science (2007): Indexed yes
  Scopus rating (2006): SJR 0.744 SNIP 1.58
  Web of Science (2006): Indexed yes
  Scopus rating (2005): SJR 0.82 SNIP 1.584
Microfluidic Prototyping for Biomedical Applications

General information
State: Published
Organisations: Danish Technological Institute, Biolab Oulu
Authors: Krühne, U. (Intern), Olesen, T. L. (Ekstern), Forsén, E. (Ekstern), Sesay, A. (Ekstern)
Publication date: 2010
Event: Abstract from Dansk Kemiingenriærkonference 2010, DTU, Kgs.Lyngby, :
Main Research Area: Technical/natural sciences
Electronic versions:
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Bibliographical note
Oral presentation
Source: orbit
Source-ID: 313247
Publication: Research - peer-review › Conference abstract for conference – Annual report year: 2010

The Development of a diagnostic test for the detection of drugs in saliva using a disposable sample preparation Micro-fluidic cartridge
In this paper we report on the development of a diagnostic test for the detection of illegal drugs in saliva using a disposable micro-fluidic sample preparation cartridge which was fabricated using CO2 and excimer laser ablation of a PMMA substrate assembly. The detection method is by immunoassay sensing on a surface plasmon resonance (SPR) platform. Experimental results shows that the immunoassay detection of the two illegal drugs tested are very sensitive and have a linear range for cocaine and MDMA of 0.01 pg/ml – 1 ng/ml and 0.1 pg/ml – 100 ng/ml respectively.

General information
State: Published
Organisations: University of Oulu, Danish Technological Institute
Authors: Sesay, A. M. (Ekstern), Krühne, U. (Intern), Sonny, S. (Ekstern), Olesen, T. L. (Ekstern), Virtanen, V. (Ekstern)
Pages: 1520-1522
Publication date: 2010

Host publication Information
Title of host publication: µTAS 2010 : The 14th International Conference on Miniaturized Systems for Chemistry and Life Sciences
ISBN (Print): 978-0-9798064-3-8
Main Research Area: Technical/natural sciences
Conference: 14th International Conference on Miniaturized Systems for Chemistry and Life Sciences, Groningen, Netherlands, 03/10/2010 - 03/10/2010
Electronic versions:
prod21365511353906.Adama_Sesay_cartdridge_1_.pdf
Publication: Research - peer-review › Article in proceedings – Annual report year: 2010
Toward user defined prototyping of µ-bioreactors

The development of alternative methods to animal testing is based in many experimental investigations on cellular assays, in which certain cell lines are tested for their response to drug candidates. Often the cells are grown in standard equipment like slide flasks or Petri dishes and exposed to the respective substances. In subsequent analysis the cells might be analysed by optical investigation, fluorescence microscopy, or other more complex standard processing methods. However, increasing scientific investigations show that certain cell types are sensitive to mechanical stimulation (e.g. shear stress). Therefore, important receptors can not be formed or developed in the absence of shear stress present in the in- vitro system. Hence, the success and relevance of static experiments is questionable. By applying lab-on-chip micro-fluidic technological solutions, µ-bioreactors can improve experimental design by allowing cells to experience shear stress in contained and sterile environments. The advantage of such systems is that they can be designed to use less reagents and chemicals, perform high throughput assays, have sensor integration and be automated. The presentation will focus on user designed micro- fabrication toolkits and prototyping of miniaturised µ-bioreactors systems. The presentation will show application examples, experimental results and fabrication methods of such miniaturised systems for performing more effective in-vitro assays and give the respective scientist the prospect to fulfill their more complex experimental ideas.

General information
State: Published
Organisations: Teknologisk Institut
Authors: Krühne, U. (Intern)
Publication date: 2008
Main Research Area: Technical/natural sciences
Electronic versions:
prod21322130656010_Royal_Society_Abstract[1].pdf

Magnetic separation in microfluidic systems

This Ph.D. thesis presents theory, modeling, design, fabrication, experiments and results for microfluidic magnetic separators. A model for magnetic bead movement in a microfluidic channel is presented, and the limits of the model are discussed. The effective magnetic field gradient is defined, and it is argued that it is a good measure, when comparing the performance of magnetic bead separators. It is described how numeric modelling is used to aid the design of microfluidic magnetic separation systems. An example of a design optimization study is given. A robust fabrication scheme has been developed for fabrication of silicon based systems. This fabrication scheme is explained, and it is shown how, it is applied with variations for several designs of magnetic separators. An experimental setup for magnetic separation experiments has been developed. It has been coupled with an image analysis program to facilitate real-time monitoring of the experiments. The set-up and experimental protocol are described in detail. Results are presented for ‘active’ magnetic bead separators, where on-chip microfabricated electromagnets supply the magnetic field and field gradients necessary for magnetic bead separation. It is shown conceptually how such a system can be applied for parallel biochemical processing in a microfluidic system. ‘Passive’ magnetic separators are presented, where on-chip soft magnetic elements are magnetized by an external magnetic field and create strong magnetic fields and gradients inside a microfluidic channel. Systems with the elements placed beside the microfluidic channel is combined with hydrodynamic focusing to demonstrate a magnetic bead microarray inside a microfluidic channel. Systems where the on-chip magnetic material is placed underneath the microfluidic channel are also presented. One of these designs feature multiple magnetic length scales, and it is shown that this enhances bead capture ability. A ‘hybrid’ magnetic separator design, where the magnetic field from on-chip current lines couples with an externally applied homogenous field to create strong fields and gradients is demonstrated. This gives extra magnetic bead manipulation possibilities compared to the passive designs. It is demonstrated how this can be used for magnetic bead microarrays. Finally, it is discussed, based on the research presented in this thesis, how to further develop magnetic separation systems in microfluidic systems, and recommendations are given for the choice of magnetic design based on the desired application.

General information
State: Published
Organisations: Magnetic Systems, Department of Micro- and Nanotechnology, Magnetic Systems Group, LabChip Section , Theoretical Microfluidics Group, Theory Section, Institute for Product Development, Department of Chemical and Biochemical Engineering
Number of pages: 188
Publication date: May 2007
"Cell metabolism inactivation in a microbioreactor"

General information
State: Published
Organisations: Department of Micro- and Nanotechnology, Department of Chemical and Biochemical Engineering
Authors: Fendt, S. (Intern), Werner, M. (Ekstern), Krühne, U. (Intern), Geschke, O. (Intern), Szita, N. (Intern)
Pages: 1377-1379
Publication date: 2005

Host publication information
Title of host publication: Proc. of Micro Total Analysis Systems 2005
Volume: 2
Place of publication: Boston, MA, USA
Main Research Area: Technical/natural sciences
Conference: Micro Total Analysis Systems 2005, Boston, MA, USA, 01/01/2005
Source: orbit
Source-ID: 183107
Publication: Research - peer-review › Article in proceedings – Annual report year: 2005

Refractive microlenses produced by excimer laser machining of poly(methyl methacrylate)
A method has been developed whereby refractive microlenses can be produced in poly (methyl methacrylate) by excimer laser irradiation at \( \lambda = 248 \) nm. The lenses are formed by a combined photochemical and thermal process. The lenses are formed as depressions in the substrate material (negative focal length), which makes replication necessary in order to obtain lenses with a positive focal length. The method allows for considerable flexibility with respect to the pattern of lenses and the properties of the individual lenses. In this investigation it was possible to vary the diameter of the lenses between 30 and 500 \( \mu \text{m} \) and the focal lengths between 300 \( \mu \text{m} \) and several mm.

General information
State: Published
Organisations: Department of Micro- and Nanotechnology, Department of Chemical and Biochemical Engineering, Danish Technological Institute
Authors: Jensen, M. F. (Intern), Krühne, U. (Intern), H., L. (Ekstern), Geschke, O. (Intern)
Pages: 91-97
Publication date: 2005
Main Research Area: Technical/natural sciences

Publication information
Journal: Journal of Micromechanics and Microengineering
Volume: 15
Issue number: 1
ISSN (Print): 0960-1317
Ratings:
BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 1.74 SJR 0.595 SNIP 1.017
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.64 SNIP 1.211 CiteScore 1.96
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.725 SNIP 1.224 CiteScore 1.84
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 0.611 SNIP 1.055 CiteScore 1.74
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
Refractive Microlenses produced by EXCIMER Lasermachining of poly(Methyl Methacrylate)

General information

State: Published
Organisations: Department of Micro- and Nanotechnology, Department of Chemical and Biochemical Engineering
Authors: Jensen, M. F. (Intern), Wu, J. (Intern), Krühne, U. (Intern), Christensen, L. H. (Ekstern), Geschke, O. (Intern)
Publication date: 2004

Host publication information

Title of host publication: Proceedings of µTAS 2004
Main Research Area: Technical/natural sciences
Conference: Proceedings of µTAS 2004, 01/01/2004
Source: orbit
Source-ID: 61634
Publication: Research - peer-review › Article in proceedings – Annual report year: 2004
Use of laminar flow patterning for miniaturised biochemical assays

Laminar flow in microfluidic chambers was used to construct low (one dimensional) density arrays suitable for miniaturized biochemical assays. By varying the ratio of flows of two guiding streams flanking a sample stream, precise focusing and positioning of the latter was achieved, and reactive species carried in the sample stream were deposited on functionalized chip surfaces as discrete 50 mm wide lanes. Using different model systems we have confirmed the method’s suitability for qualitative screening and quantification tasks in receptor-ligand assays, recording biotin-streptavidin interactions, DNA-hybridization and DNA-triplex formation. The system is simple, fast, reproducible, flexible, and has small sample requirements.

General information
State: Published
Organisations: Center for Microbial Biotechnology, Department of Systems Biology, Department of Chemical and Biochemical Engineering, NanoNord, Bioneer A/S, Radiometer Medical ApS
Authors: Regenberg, B. (Intern), Krühne, U. (Intern), Beyer, M. (Ekstern), Pedersen, L. (Ekstern), Simon Soria, M. (Intern), Thomas, O. R. T. (Intern), Nielsen, J. (Intern), Ahl, T. (Ekstern)
Pages: 654-657
Publication date: 2004
Main Research Area: Technical/natural sciences

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Journal: Lab on a Chip
Volume: 4
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Ratings:
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 5.98 SJR 2.147 SNIP 1.611
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.26 SNIP 1.764 CiteScore 5.74
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.534 SNIP 1.801 CiteScore 5.6
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 2.374 SNIP 1.703 CiteScore 5.9
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 2.382 SNIP 1.738 CiteScore 5.35
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 2.535 SNIP 1.791 CiteScore 5.76
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 2.64 SNIP 1.846
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 2.575 SNIP 2.115
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 2.792 SNIP 1.853
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 2.444 SNIP 1.819
Web of Science (2007): Indexed yes
Experimental and model assisted investigation of an operational strategy for the BPR under low influent concentrations

The behaviour of a pilot scale biological phosphorus removal process (BPR) of the alternating type was investigated during periods of low influent concentrations and increased hydraulic load. A process disturbance of this type result in an increase in the phosphate concentration level in the anoxic/aerobic reactors and in the plant effluent shortly after the influent wastewater returns to normal strength. The accumulation of phosphorus in the system was avoided by the addition of an external carbon source either to the influent or to the effluent from the anaerobic reactor in form of sodium acetate. With the help of such an addition, the internal carbon storage compounds could be maintained at a high level, which is shown by poly-hydroxy-alcanoates (PHA) measurements. Several levels of acetate addition were investigated experimentally in order to determine a minimal amount of internally stored carbon, which could ensure the stabilization of BPR during such dynamic influent conditions. Furthermore reduction of aeration time during periods of low influent concentrations was investigated. It was observed that BPR was stabilized by combining a reduction of aeration time with carbon source addition, which maintained the internal stored carbon at a higher level. This combined control action resulted in a desired high BPR activity when the normal strength of the influent wastewater was reestablished. The failure of the BPR process was sometimes observed even when comparatively high concentrations of PHA could be detected and an identification of a minimal PHA level was not possible. During this investigation an extended version of the activated sludge model No. 2 (ASM2), which includes denitrification by phosphate accumulating organisms, is used for the detailed analysis of the experiments. The model predicted the phosphorus build-up after the process disturbance as well as the performance during the stabilized experiments. Assisted by the model, the investigations indicate that a PHA limitation is not the only factor affecting the recovery of the BPR process during periods of low influent concentrations.
Hydrodynamic guiding for addressing subsets of immobilized cells and molecules in microfluidic systems

Background: The interest in microfluidics and surface patterning is increasing as the use of these technologies in diverse biomedical applications is substantiated. Controlled molecular and cellular surface patterning is a costly and time-consuming process. Methods for keeping multiple separate experimental conditions on a patterned area are, therefore, needed to amplify the amount of biological information that can be retrieved from a patterned surface area. We describe, in three examples of biomedical applications, how this can be achieved in an open microfluidic system, by
hydrodynamically guiding sample fluid over biological molecules and living cells immobilized on a surface. Results: A microfluidic format of a standard assay for cell-membrane integrity showed a fast and dose-dependent toxicity of saponin on mammalian cells. A model of the interactions of human mononuclear leukocytes and endothelial cells was established. By contrast to static adhesion assays, cell-cell adhesion in this dynamic model depended on cytokine-mediated activation of both endothelial and blood cells. The microfluidic system allowed the use of unprocessed blood as sample material, and a specific and fast immunoassay for measuring the concentration of C-reactive protein in whole blood was demonstrated. Conclusion: The use of hydrodynamic guiding made multiple and dynamic experimental conditions on a small surface area possible. The ability to change the direction of flow and produce two-dimensional grids can increase the number of reactions per surface area even further. The described microfluidic system is widely applicable, and can take advantage of surfaces produced by current and future techniques for patterning in the micro- and nanometer scale.
The invention relates to methods and devices for forming a concentration gradient of a reagent for use in chemotactic evaluation. A flow passage is provided and defined at least in part by a substrate having a target region on a surface thereof. A concentration gradient of a reagent is formed over the target region by controlled delivery of a fluid containing the reagent in laminar flow through the flow passage and over the target region. The concentration gradient is suitable for chemotactic evaluation. Typically, the inventive methods and devices are employed to evaluate the chemotactic interaction between a candidate compound and a monolayer of immobilized cells.
Stabilisation of Biological Phosphorus Removal from Municipal Wastewater

The biological phosphorus removal (BPR) from wastewater has developed considerably during the last decades and is applied in many present wastewater treatment plants (WWTP) all over the world. The process performance and the control of the BPR are under the influences of daily and seasonal variations of the influent wastewater concentrations and are not yet always guaranteed. Even though the scientific knowledge and practical experience has reached a high level of understanding of the involved key-processes it is still necessary to apply chemical precipitation of phosphorus during the time periods, where the complete BPR can not be achieved. The understanding of the main phenomena involved into such failure of BPR and the development of operational or control strategies to overcome these deficiencies are the main areas of investigation of this thesis. Investigations of the failure of BPR have been performed on an alternating pilot plant,
receiving municipal wastewater. The pilot plant is equipped with an automatic measurement system based on the flow injection analysis (FIA) principle. Continuous analysis of the ammonium (NH4-N), nitrate (as NOx-N) and phosphorus (PO4-P) was performed in all important places of the plant. Based on literature studies and investigations of the available pilot plant measurement data experimental designs were developed to produce operational conditions where the BPR failed. The process was investigated during periods of low influent concentrations and increased hydraulic load, with subsequent re-establishment of normal conditions. A process disturbance of this type results in an increase in the phosphate concentration level in the effluent, shortly after the wastewater returns to normal strength. During the first part of the thesis it was examined if an extended version of the activated sludge model No. 2 (ASM2) including denitrification by phosphate accumulating organisms (PAO) can be calibrated and validated on the existing system. A set of parameter was determined through a simple evolutionary parameter estimation strategy. This parameter set was used during the whole investigation. The prediction of the dynamic model was used for development of new operational and control strategies. Based on the model simulations an external carbon source addition (ECSA) was designed in order to overcome the BPR process failure. With the help of such addition, the internal carbon storage compounds could be maintained at a high level, indicated by poly-hydroxyalcanoate (PHA) measurements and the accumulation of phosphorus in the effluent could be avoided. Experimental investigations imply that the ECSA together with a reduction of aeration time during periods of low organic influent concentration could improve and stabilise the BPR. The identification of a minimum PHA level, necessary to ensure complete BPR, was however not possible. The failure of BPR was sometimes observed even when comparatively high internal PHA concentrations were present. The experiments where therefore further investigated with help of the model. The study indicates that a PHA limitation is not the only factor affecting the recovery of the BPR process during such periods. The actual amount of PAO present in the system during and after such disturbance can play a role in the deterioration of BPR. In the last part of the thesis the obtained understanding through the operational investigations was used for the design of a model predictive control (MPC) strategy for the BPR system under low influent concentrations. The MPC strategy is based on the addition of an ECSA keeping the internally stored carbon products at a high level. A simple model-based observer estimating the unmeasured influent soluble organic or internal PHA concentrations is used. This observer improves the robustness operation of the addition significantly. The MPC control performance is compared to a simple feed-forward control design, which also is based on the estimated organic influent concentrations. It is shown that the simple feed-forward as well as the more advanced MPC strategies can improve the BPR without major interference with the other biological processes. With increasing complexity of the strategy the amount of external added carbon could be significantly reduced while the effluent PO4-P concentration could be kept below the required concentration of 1mgP/L.
Control design for a periodic cycled activated sludge plant using ASM 1

General information
State: Published
Organisations: Department of Chemical and Biochemical Engineering, Computer Aided Process Engineering Center
Authors: Jensen, J. L. (Ekstern), Meinhold, J. (Intern), Krühne, U. (Intern), Jørgensen, S. B. (Intern)
Pages: 231-238
Publication date: 1998

Host publication information
Title of host publication: Control design for a periodic cycled activated sludge plant using ASM 1
Main Research Area: Technical/natural sciences
Conference: European Conference for New Advances in Biological Nitrogen and Phosphorous Removal Plant for Municipal or Agroindustrial Waste Waters, Narbonne, France, 01/01/1998
Source: orbit
Source-ID: 174601
Publication: Research - peer-review › Article in proceedings – Annual report year: 1998

Modeling of biological phosphorus removal data with the activated sludge model No.2 and an extended version incorporating denitrifying PAO

General information
State: Published
Organisations: Department of Chemical and Biochemical Engineering
Authors: Krühne, U. (Intern), Isaacs, S. H. (Intern), Jørgensen, S. B. (Intern)
Pages: 239-246
Publication date: 1998

Host publication information
Title of host publication: Proceeding of European Conference on New Advances in Biological Nitrogen and Phosphorus Removal for Municipal or Industrial Wastewaters
Main Research Area: Technical/natural sciences
Conference: European Conference on New Advances in Biological Nitrogen and Phosphorus Removal for Municipal or Industrial Wastewaters, Narbonne, France, 01/01/1998
Source: orbit
Source-ID: 174521
Publication: Research - peer-review › Article in proceedings – Annual report year: 1998

Model Predictive Control Design for an Alternating Nutrient Removal Process

General information
State: Published
Organisations: Department of Chemical and Biochemical Engineering, Department of Informatics and Mathematical Modeling, Scientific Computing, Computer Aided Process Engineering Center
Authors: Jensen, J. L. (Ekstern), Meinhold, J. (Intern), Krühne, U. (Intern), Jørgensen, J. B. (Intern), Jørgensen, S. B. (Intern)
Publication date: 1998
Main Research Area: Technical/natural sciences
Source: orbit
Source-ID: 224398
Publication: Research - peer-review › Conference abstract for conference – Annual report year: 1998

Projects:

Continuous Biocatalytic Alkene Hydrogenation
Department of Chemical and Biochemical Engineering
Period: 01/11/2017 → 31/10/2020
Number of participants: 4
Phd Student:
Decolorization, Desalination and Purification of Molasses by Nanofiltration
Department of Chemical and Biochemical Engineering
Period: 15/02/2017 → 15/09/2017
Number of participants: 4
PhD Student:
Tan, Sheng (Intern)
Supervisor:
Krühne, Ulrich (Intern)
Luo, Jianquan (Intern)
Main Supervisor:
Pinelo, Manuel (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Eksternt finansieret virksomhed
Project: PhD

CFD Modelling of dynamic microfiltration for application in biotechnology processes
Department of Chemical and Biochemical Engineering
Period: 01/02/2017 → 31/01/2020
Number of participants: 4
PhD Student:
Marke, Henrik Sander (Intern)
Supervisor:
Hansen, Ernst (Intern)
Pinelo, Manuel (Intern)
Main Supervisor:
Krühne, Ulrich (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Stipendie fra udlandet
Project: PhD

Development of Strategies for More Efficient CIP Cleaning
Department of Chemical and Biochemical Engineering
Period: 01/12/2015 → 30/11/2018
Number of participants: 3
PhD Student:
Yang, Jifeng (Intern)
Supervisor:
Gernaey, Krist V. (Intern)
Main Supervisor:
Krühne, Ulrich (Intern)

Financing sources
Automating Experimentation in miniaturized reactors

Department of Chemical and Biochemical Engineering
Period: 15/08/2015 → 14/10/2018
Number of participants: 4
Phd Student:
Tajsoleiman, Tannaz (Intern)
Supervisor:
Gernaey, Krist V. (Intern)
Huusom, Jakob Kjøbsted (Intern)
Main Supervisor:
Krühne, Ulrich (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Samfinansieret - Andet
Project: PhD

Consistent Scale-up of the Freeze-drying Process

Department of Chemical and Biochemical Engineering
Period: 01/08/2015 → 31/07/2018
Number of participants: 5
Phd Student:
Teresa de Melo Machado Simoes Carvalho, Ana (Intern)
Supervisor:
Clausen, Anders (Intern)
Krühne, Ulrich (Intern)
Madsen, Michelle Milling (Ekstern)
Main Supervisor:
Gernaey, Krist V. (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Marie Curie (EU-stipendium)
Project: PhD

Modeling of gradients in large scale bioreactors

Department of Chemical and Biochemical Engineering
Period: 01/03/2015 → 12/04/2018
Number of participants: 3
Phd Student:
Bach, Christian (Intern)
Supervisor:
Krühne, Ulrich (Intern)
Main Supervisor:
Gernaey, Krist V. (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Eksternt EU-finansieret
Project: PhD

Development of Optimal Operating Conditons for Producing Single Cell Protein

Department of Chemical and Biochemical Engineering
Period: 15/12/2014 → 16/03/2018
Number of participants: 4
Phd Student:
Wu, Mengzhe (Intern)
Supervisor:
Huusom, Jakob Kjøbsted (Intern)
Krühne, Ulrich (Intern)
Main Supervisor:
Gernaey, Krist V. (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Forskningsrådsfinansiering
Project: PhD

Model-based interpretation of microbioreactor data
Department of Chemical and Biochemical Engineering
Period: 15/08/2014 → 15/02/2018
Number of participants: 4
Phd Student:
Semenova, Daria (Intern)
Supervisor:
Krühne, Ulrich (Intern)
Zubov, Alexandr (Intern)
Main Supervisor:
Gernaey, Krist V. (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Marie Curie (EU-stipendium)
Project: PhD

Micro Scale Reactor System development with integrated advanced sensor technology
Department of Chemical and Biochemical Engineering
Period: 01/07/2014 → 31/08/2017
Number of participants: 6
Phd Student:
Oliveira Fernandes, Ana Carolina (Intern)
Supervisor:
Gernaey, Krist V. (Intern)
Krühne, Ulrich (Intern)
Examiner:
Eliasson Lantz, Anna (Intern)
Kockmann, Norbert (Ekstern)
Wohlgemuth, Roland (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: Marie Curie (EU-stipendium)
Project: PhD

Biooxidation reactor and process design
Department of Chemical and Biochemical Engineering
Period: 01/04/2014 → 12/07/2017
Number of participants: 6
Phd Student:
Pedersen, Asbjørn Toftgaard (Intern)
Investigation of Aspergillus niger aggregation behaviour and its relationship to industrial fermentation

Department of Chemical and Biochemical Engineering
Period: 15/11/2013 → 08/08/2018
Number of participants: 4
Phd Student:
Hagemann, Timo (Intern)
Supervisor:
Krühne, Ulrich (Intern)
Stocks, Stuart M. (Ekstern)
Main Supervisor:
Gernaey, Krist V. (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Samfinansieret - Andet

Relations
Publications:
Oxygen Dependent Biocatalytic Processes
Project: PhD

Exploring biochemical process performance limits through topology optimization

Department of Chemical and Biochemical Engineering
Period: 01/12/2012 → 16/06/2016
Number of participants: 7
Phd Student:
Larsson, Hilde Kristina (Intern)
Supervisor:
Gernaey, Krist V. (Intern)
Skov, Anne Ladegaard (Intern)
Main Supervisor:
Krühne, Ulrich (Intern)
Examiner:
Sin, Gürkan (Intern)
Drønen, Nils Kjetil (Intern)
Nopens, Ingmar (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: Grundforskningsfonden

Relations
Publications:
Modelling of Mass Transfer Phenomena in Chemical and Biochemical Reactor Systems using Computational Fluid Dynamics
Topology optimization in biocatalytic reactions using miniaturized reactors

Department of Chemical and Biochemical Engineering
Period: 01/11/2012 → 20/04/2016
Number of participants: 7
Phd Student:
Pereira Rosinha Grundtvig, Ines (Intern)
Supervisor:
Gernaey, Krist V. (Intern)
Woodley, John (Intern)
Main Supervisor:
Krühne, Ulrich (Intern)
Examiner:
Abildskov, Jens (Intern)
Maier, Petra (Ekstern)
Perozzello, Gerardo (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: 1/3 FUU, 1/3 inst 1/3 Andet
Project: PhD

Mastering bioprocess Integration and Intensification across scales

Department of Chemical and Biochemical Engineering
Period: 01/10/2012 → 02/12/2015
Number of participants: 7
Phd Student:
Ringborg, Rolf Hoffmeyer (Intern)
Supervisor:
Gernaey, Krist V. (Intern)
Krühne, Ulrich (Intern)
Main Supervisor:
Woodley, John (Intern)
Examiner:
Nordblad, Mathias (Intern)
Hessel, Volker (Ekstern)
Jensen, Klavs F. (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: 1/3 FUU, 1/3 inst 1/3 Andet
Project: PhD

Process intensification in biocatalytic reactions

Department of Chemical and Biochemical Engineering
Period: 01/09/2012 → 22/02/2016
Number of participants: 7
Phd Student:
Heintz, Søren (Intern)
Supervisor:
Krühne, Ulrich (Intern)
Woodley, John (Intern)
Main Supervisor:
Gernaey, Krist V. (Intern)
Examiner:
Abildskov, Jens (Intern)
Modelling and Simulation of Wastewater Treatment Plants

Department of Chemical and Biochemical Engineering

Period: 01/05/2012 → 01/07/2015

Number of participants: 9

Phd Student:
Snip, Laura (Intern)

Supervisor:
Alsina, Xavier Flores (Ekstern)
Jeppsson, Ulf A. C. (Ekstern)
Krühne, Ulrich (Intern)
Plósz, Benedek G. (Intern)

Main Supervisor:
Gernaey, Krist V. (Intern)

Examiner:
Sin, Gürkan (Intern)
Ort, Christoph (Ekstern)
Pons, Marie-Noelle (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: 1/3 FUU, 1/3 inst 1/3 Andet
Project: PhD

Bioprocess engineering for the application of P450s

Department of Chemical and Biochemical Engineering

Period: 01/02/2012 → 02/12/2015

Number of participants: 6

Phd Student:
Lundemo, Marie Therese (Intern)

Supervisor:
Krühne, Ulrich (Intern)

Main Supervisor:
Woodley, John (Intern)

Examiner:
Eliasson Lantz, Anna (Intern)
Hayes, Martin (Ekstern)
Schmid, Andreas (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: Marie Curie (EU-stipendium)
Project: PhD

Computer aided framework for synthesis, design and retrofit of water networks in processing industries

Department of Chemical and Biochemical Engineering

Period: 16/12/2011 → 13/05/2015

Number of participants: 6

Phd Student:
Bozkurt, Hande (Intern)
Novel greener and lean processes using integrated microfactories
This project is focusing on efficient and sustainable production of organic-synthesis based active pharmaceutical ingredients (API) by use of novel microfluidic based concepts to biocatalytic and fermentation processes. Major challenges are met since many of these processes have complex reaction mechanisms with equilibrium limited conversions, often substrate and/or product inhibition and material transport challenges along with slow heterogenic reaction kinetics. In this project it is hypothesized that much faster process development could be achieved by studying bioprocesses in continuous flow mode already from the laboratory stage. Well characterized (fast mixing and heat transmission) small reactors with low dead volumes will facilitate dynamic experiments, while non-invasive, real-time, in-line monitoring technologies will provide high quality data, with potential for automation, real-time optimization and rapid modeling of reaction kinetics.

Department of Chemical and Biochemical Engineering
Center for Process Engineering and Technology
Period: 01/03/2011 → 28/02/2014
Number of participants: 3
biocatalysis, in situ product removal, CFD, microfluidics, kinetic investigations
Acronym: μ factories
Number of related Ph.D. students: 1
Project participant:
Krühne, Ulrich (Intern)
Bodla, Vijaya Krishna (Intern)
Gernaey, Krist V. (Intern)

Project
Integrated microfactories for enzyme production
Department of Chemical and Biochemical Engineering
Period: 01/03/2011 → 11/03/2015
Number of participants: 7
Phd Student:
Bodla, Vijaya Krishna (Intern)
Supervisor:
Krühne, Ulrich (Intern)
Woodley, John (Intern)
Main Supervisor:
Gernaey, Krist V. (Intern)
Examiner:
Nordland, Mathias (Intern)
Baganz, Frank (Ekstern)
Bouwes, Dominique (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: Forskningsrådsfinansiering
Project: PhD

Multi-dimensional population balance models of crystallization processes
Department of Chemical and Biochemical Engineering
Period: 01/03/2011 → 04/02/2015
Number of participants: 7
Phd Student:
Meisler, Kresten Troelstrup (Intern)
Supervisor:
Gernaey, Krist V. (Intern)
von Solms, Nicolas (Intern)
Main Supervisor:
Gani, Rafiqul (Intern)
Examiner:
Krühne, Ulrich (Intern)
Mazzotti, Marco (Ekstern)
Seidel-Morgenstern, Andreas (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: Institut stipendie (DTU) Samf.
Project: PhD

Scale-up of biocatalytic cascade reactions for the synthesis of chiral amines
Department of Chemical and Biochemical Engineering
Period: 01/12/2010 → 24/09/2014
Number of participants: 7
Phd Student:
Janes, Kresimir (Intern)
Supervisor:
Tufvesson, Pär (Intern)
Woodley, John (Intern)
Main Supervisor:
Gernaey, Krist V. (Intern)
Examiner:
Krühne, Ulrich (Intern)
Pedersen, Lars Haastrup (Ekstern)
Vasic-Racki, Durda (Ekstern)
Validation of Structures Model for Autotrophic Nitrogen Removal in High Strength Wastewater

Department of Chemical and Biochemical Engineering
Period: 01/09/2010 → 12/11/2013
Number of participants: 7
Phd Student:
Vangsgaard, Anna Katrine (Intern)
Supervisor:
Gernaey, Krist V. (Intern)
Smets, Barth F. (Intern)
Main Supervisor:
Sin, Gürkan (Intern)
Examiner:
Krühne, Ulrich (Intern)
Lemaire, Romain (Ekstern)
Morgenroth, Eberhard (Ekstern)

Process Considerations for Asymmetric Synthesis of Chiral Amines using Omega-Transaminase

Department of Chemical and Biochemical Engineering
Period: 01/06/2010 → 11/12/2013
Number of participants: 6
Phd Student:
Lima Afonso Neto, Watson (Intern)
Supervisor:
Tufvesson, Pär (Intern)
Main Supervisor:
Woodley, John (Intern)
Examiner:
Krühne, Ulrich (Intern)
Adlercreutz, Patrick (Ekstern)
Howard, Roger M. (Ekstern)

Modelling controlled release of substrate and removal of products in biocatalysis

Department of Chemical and Biochemical Engineering
Period: 01/11/2009 → 21/05/2013
Number of participants: 7
Phd Student:
Al-Haque, Naweed (Intern)
Supervisor:
Gani, Rafiqul (Intern)
Tufvesson, Pär (Intern)
Main Supervisor:
Woodley, John (Intern)
Examiner:
Krühne, Ulrich (Intern)
Daugulis, Andrew J. (Ekstern)
Spiess, Antje C. (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: 1/3 FUU, 1/3 inst 1/3 Andet
Project: PhD

Magnetisk Separation i mikrofluide Systemer
Department of Micro- and Nanotechnology
Period: 01/02/2004 → 29/05/2007
Number of participants: 7
Phd Student: Smistrup, Kristian (Intern)
Supervisor: Bruus, Henrik (Intern)
Krühne, Ulrich (Intern)
Tang, Peter Torben (Intern)
Main Supervisor: Hansen, Mikkel Foug (Intern)
Examiner: Jacobsen, Claus Schelde (Intern)
Gijs, Martinus A. M. (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: Eksternt finansieret virksomhed
Project: PhD

Electric DNA chips for bioprocess control
Department of Systems Biology
Period: 01/03/2000 → 26/01/2004
Number of participants: 6
Phd Student: Barken, Kim Bundvig (Intern)
Supervisor: Wumpelmann, Mogens (Ekstern)
Main Supervisor: Molin, Søren (Intern)
Examiner: Tolker-Nielsen, Tim (Intern)
Holmstrøm, Kim (Intern)
Krühne, Ulrich (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Samarbejdsaftalefinans
Project: PhD

B.7 Modelling and simulation of biological waste water treatment processes
Biological phosphorous removal
Department of Chemical and Biochemical Engineering
Period: 01/05/1997 → ...
Number of participants: 3
Project participant: Meinhold, Jens (Intern)
D.5 Control of biological waste water treatment process

Biological wastewater treatment processes using activated sludge may be operated as a periodic cycled plant to enable better possibilities for manipulating the process. The operational task is complicated by the desire to remove Carbon, Nitrogen and Phosphorous to fulfil requirements upon effluent quality. These requirements render this task a typical multivariable control problem. The number of handles in conventional waste water plants is rather limited, therefore there is considerable interest in exploiting the additional degrees of freedom available in periodically operated plants. The activated sludge process consists of two reactors alternating between aerobic and anoxic conditions. As this process is operated periodically it is highly non-linear. In a first phase of this project a period-to-period linearized model of the plant will be investigated concerning its ability to predict the inter-periodic plant performance. Subsequently, both model verification and state estimation will be investigated. One key aspect is the model detail that is required to obtain reliable predictions several periods ahead. Subsequently it is intended to investigate the achievable inter-periodic control performance of the plant using a linear state space MPC controller.
Harremoës, Poul (Intern)
Dupont, René (Ekstern)
Olsson, Gustaf (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: Anden Forskningsrådsfinan.-SU
Project: PhD

Control of Biological Waste Water Treatment Plants
Department of Chemical and Biochemical Engineering
Department of Biotechnology
Period: 01/01/1996 → 31/01/1997
Number of participants: 6
Project participant:
Isaacs, Steven Howard (Intern)
Krühne, Ulrich (Intern)
Meinhold, Jens (Intern)
Løfvall, Jan Michael (Intern)
Seeberg, Henrik (Intern)
Project Manager, organisational:
Kymmel, Mogens (Intern)

Financing sources
Source: Unknown
Name of research programme: Ukendt
Amount: 898,000.00 Danish Kroner
Project

Activities:

A Biocatalytic Microreactor – Dynamic CFD Modelling and Experimental Analysis
Period: 27 Sep 2016
Ulrich Krühne (Lecturer)
Department of Chemical and Biochemical Engineering
CAPEC-PROCESS

Description
Keynote lecture
Documents:
ECCE ECAB3 Nice 2016 Abstract

Related event
3rd European Congress of Applied Biotechnology
27/09/2015 → 01/10/2015
Nice, France
Activity: Talks and presentations › Conference presentations

Microfluidics in Chemical and Biochemical Engineering Applications
Period: 23 Sep 2014
Ulrich Krühne (Lecturer)
Department of Chemical and Biochemical Engineering
CAPEC-PROCESS

Related event
8th Workshop "Low Flows in Medical Technology"
23/09/2014 → 24/12/2014
Lübeck, Germany
Activity: Talks and presentations › Conference presentations