Executive Summary:
The OPTICO project (http://www.opticoproject.eu/) aims at overcoming the present limitations on implementing Process intensification (PI) by establishing a new methodological design approach for sustainable, intensified chemical/biopharmaceutical plant design and operation through a flexible, integrated multi-scale modeling framework coupled with advanced process analytics tools and modern optimization/control techniques. The integrated framework was applied to four industrial processes, namely, a monoclonal antibodies production/purification system, a pharmaceutical crystallization process, a polymerization (i.e. suspension and inverse suspension) processes and an organic oxidation with hydrogen peroxide process.

The production of bio molecules is a constantly growing field in the biopharmaceutical industry. By developing simulation models for the upstream fermentation (production) and downstream (separation) part of the production, operating points for an overall process optimum can be determined. With the methods developed, ETH is able to monitor the upstream process sufficiently well, while for the downstream (purification) ETH and ChromaCon applied and calibrated different online sensors. For both antibody production (upstream) as well as antibody separation (downstream) two models were presented (ETH, Chromacon in collaboration with ICL). In line project objectives, ETH, ICL and ChromaCon intensified the production and purification process for monoclonal antibodies.

In crystallization processes, the work at DSM and TUDelft conceded on the current demands within industry with respect to the development of new crystallization processes focusing on a fast development on a smaller scale. For the multi sensor platform an in situ imaging probe was implemented and tested as an alternative, both in an 18 L air lift crystallizer as well as in a 5 L stirred tank crystallizer. Concentration or supersaturation monitoring has been tested in a membrane assisted crystallization process using an ultrasonic probe (SENSOTECH (Liquisonic concentration sensor)). An FBRM (Mettler Toledo) probe was also examined and compared
with off line CSD analysis using a laser diffraction instrument. The intensification of pharmaceutical crystallization processes has been focused on the application of the task-based design philosophy by using the integrated CAD/CAM platform for simulation of multi-compartment crystallization as one of the main tools.

In the frame of OPTICO project regarding the polymerization processes, the industrial research objectives (BASF), was to utilize the developed process analytical tools (RWTH, USTR and FPL) and modeling technologies (CERTH and UGENT) in order to optimize the suspension polymerization process for production of expandable polystyrene (EPS) and inverse suspension co-polymerization of acrylamide with cationic and anionic co-monomers. From work done for the polymerization process, within OPTICO project, BASF gained important building blocks for future work. More specifically, BASF obtained kinetic and PSD models for EPS and PAM processes (CERTH) and there is a good chance that together with Raman (RWTH, USTR) and Sopat probes they could be used for online process control in the very near future.

The oxidation process established by ARKEMA was optimized with respect the amount of hydrogen peroxide and the concentration of the aqueous solution keeping the reaction time and the addition time constant. For the fulfillment of this objective the role of RWTH was the experimental and theoritical investigation of the process so as to intensify and improve the reaction process without violating the critical operating conditions. At DTU, a mathematical model for the oxidation of unsaturated fatty acids with hydrogen peroxide in two-phase system has been developed. The process improved by 17% compared to base case operation recipe given by ARKEMA. These optimization results are very promising and showing the usefulness of modeling and optimization based approach for process optimization.

For all the selected processes, FPL had the responsibility to develop a customisable fibre optic multi-sensor platform suitable for use in industrial process monitoring. In collaboration with the consortium partners, a variety of different sensors and optical techniques have been explored, compared and assessed as to their suitability for a multi-function probe for the four processes of interest.

Project Context and Objectives:
The OPTICO project aims at establishing a new adaptive and integrated computational framework consisting of multi-scale, multi-phase phenomena-based modeling methodologies, advanced process analytics tools and advanced optimization/control techniques for intensified chemical/biochemical plant design and operation. The integrated framework will be applied to four industrial processes, namely, a pharmaceutical crystallization process, a polymerization (i.e. suspension) process, an organic oxidation with hydrogen peroxide process and a monoclonal antibodies production/purification system.

In order to advance process intensification in multi-scale particulate processes, a comprehensive understanding of the various physical/chemical/ biological phenomena (i.e. reaction kinetics, transport phenomena, thermodynamics, particle/crystal/cell size distribution and particle structure) occurring at different time and length scales is required.

The OPTICO project aims at the advancement of four key enabling technologies and their subsequent application to the four selected chemical/ biopharmaceutical processes. More specifically, in the OPTICO project the following four enabling technologies are advanced:

**Enabling Technology 1: Hardware Sensors Developments for Product Quality Monitoring**
Implementation of on-line sensors to the selected industrial processes for real-time monitoring of product quality. Compact fiber-optic multi-sensor systems consisting of different probes, such as transmission, reflectance, ATR absorbance, UV-MIR (550-55500 cm-1) and Raman scattering, will be utilized for the real-time measurement of “product quality” (e.g. particle size, chemical composition, etc.). The sensors robustness are assessed via the implementation of complementary sensor technologies (e.g. refractive index vs. FTIR, imaging vs. diffraction or attenuation measurements, etc.). Novel approaches are developed for in-line calibration and drift correction procedures to avoid elaborate pre- and post-process calibration procedures of the sensors.

Implementation of a PAT platform to the four selected industrial processes for sensor data interpretation, inferential analysis and control of key process parameters including particle/crystal size distribution, morphology, composition and degree of agglomeration, etc.

**Enabling Technology 3: A Multi-scale, Multi-phase Process Modeling Framework**
Development of a computational multi-scale, multi-phase model library for the simulation of the selected chemical/biopharmaceutical industrial processes. The library comprises models at different length/time scales (i.e. molecular models, reaction kinetics, micro-structure, particle population balances, mixing/CFD models, etc.). A generic modular structure is adopted so that a wide range of processes can be generated with little or no modification of the developed library models.

**Enabling Technology 4: Global Optimization & Control Tools**
Development of robust model predictive control (MPC) and explicit/multi-parametric non-linear process control (NPC) tools for optimization and control of the selected industrial processes. Robust dynamic optimization and model-predictive control methods is employed for the determination of optimal control policies to improve product quality, maximize plant productivity and minimize the production of off-spec products.

More specifically, during the project lifetime the partners have been involved with the execution of the following S&T Workpackages and Tasks:

**WP 1: ON-LINE SENSORS AND PROCESS ANALYTICS TOOLS**
- 1.1: Hardware and software sensors developments
- 1.2: Development of a fibre-optic multi-sensor platform
- 1.3: Novel calibration methodologies
- 1.4: Data fusion and information extraction methods

**WP 2: MULTI-SCALE, MULTI-PHASE MODEL COMPONENTS LIBRARY**
- 2.1: Molecular, kinetic and thermodynamic models
- 2.2: Particle/crystal/cell structure models
- 2.3: Coupling of population balances with multi-compartment CFD models
- 2.4: Multi-scale, multi-phase modeling of selected industrial processes

**WP 3: NOVEL COMPUTATIONAL TOOLS FOR ON-LINE PROCESS OPTIMIZATION AND CONTROL**
- 3.1: Mixed-integer non-linear dynamic global optimization methods
- 3.2: Time-optimal trajectory control
- 3.3: Model-based non-linear predictive control methods

**WP 4: DEVELOPMENT OF AN INTEGRATED CAD/CAM SOFTWARE PLATFORM**
- 4.1: Software interoperability and specifications
- 4.2: Integration of modeling, PAT and control/optimization libraries
- 4.3: Development of an open-system software platform for PI

**WP 5: APPLICATION OF PROCESS INTENSIFICATION TO SELECTED INDUSTRIAL PROCESSES**
- 5.1: Intensification of polymerization processes
- 5.2: Intensification of an UFA oxidation with hydrogen peroxide process

**WP 6: DEMONSTRATION OF PROCESS INTENSIFICATION IN SELECTED INDUSTRIAL PROCESSES**
- 6.1: Intensification of a pharmaceutical crystallization process
- 6.2: Intensification of a monoclonal antibodies production/purification process

**Project Results:**

**On-line Sensors and Process Analytics Tools (WP1):**
For antibody production and purification, ETH tested online sensors developed by the OPTICO partners and ChromaCon applied online UV measurements during controlled multicolumn processes. In both cases the previously developed HPLC methods were used for calibration. With the methods developed within the 2nd half of the project, ETH is able to monitor the upstream process sufficiently well, while for the downstream (purification) ETH and ChromaCon applied and calibrated different online sensors. More specifically, for the bioreactor several on-line and off-line sensors are used. On-line sensors for pH value, temperature and dissolved oxygen were used during the whole cultivation process. For the downstream (purification of monoclonal antibodies) ETH and ChromaCon considered the use of IR measurement as an additional on-line sensor. The results showed that the amount of aggregates could be monitored on-line. UV and conductivity measurements were performed on-line and used for all chromatographic separations.

In crystallization processes, DSM and TUDelft worked on the current demands within industry with respect to the development of new crystallization processes (both new products as well as new production routes for existing products) focusing on a fast development on a smaller scale. Therefore, there was a need for high information lab tests using limited amounts of material. A methodology for measuring the crystallization kinetics using small scale automatic lab equipment (Avantium Crystal16 (1 mL) and Mettler-Toledo EasyMax (50 – 100 mL)) has been developed using turbidity measurements, the heat signal and the particle size distribution of the product. The Crystal16 can be used in a repetitive mode to measure the solubility and the primary nucleation behaviour of a compound. The EasyMax can be used to estimate, crystal growth, secondary nucleation and agglomeration behaviour. Measurement of crystallization kinetics requires a good control of the crystallization circumstances. Both the Avantium Crystal16 and the Mettler-Toledo EasyMax have the capability to perform a crystallization experiment with well controlled temperatures in the reactor compartment. Comparison with data from 5L stirred crystallizers and 18L airlift crystallizers gave similar kinetic data. This shows that most crystallization kinetics can be estimated on a small scale. One remaining crystallization aspect is crystal attrition.

For the multi sensor platform an in situ imaging probe was implemented and tested as an alternative, both in an 18 L air lift crystallizer...
as well as in a 5 L stirred tank crystallizer (reported previously). In addition, an FBRM (Mettler Toledo) probe was examined and compared with off line CSD analysis using a laser diffraction instrument. Both instruments provide information on some characteristics of the size and shape distribution of the crystals in the crystallizer. The image probe gives precise information on the shape of the crystals and on the occurrence of nucleation bursts. The FBRM probe appears to be a suitable probe for nucleation control in case of batch or continuous operation. Concentration or supersaturation monitoring has been tested in a membrane assisted crystallization process using an ultrasonic probe (SENSOTECH (Liquisonic concentration sensor)).

Since, FBRM is a very useful tool to quantify the crystal quality it has been implemented as a PAT tool and tested for the airlift crystallizer to specifically monitor the nucleation phenomena and evolution of CSD. More specifically, the FBMR probe which has been tested provides information on chord length distribution in-situ. For the online measurements made by the LiquiSonic concentration sensor, in order to obtain the concentration from the measured sonic velocity and the temperature, a correlation between them was made. As a conclusion, an inline image probe has been used in airlift and stirred crystallizer. The use of this in situ probe provides detailed information about the quality, size and shape of the crystals that are produced, as well as about the roughness of the crystal faces and the presence of small crystal nuclei. Offline concentration and CSD measurement has also been done during the experiments with airlift and stirred crystallizer. The results have been analysed and reported and are in good agreement off line analysis. A concentration sensor has been tested in the membrane unit to measure the concentration online. Measurements have been also done offline and results have been presented.

In the frame of OPTICO project regarding the polymerization processes, the industrial research objectives (BASF), was to utilize the developed process analytical tools and modeling technologies in order to optimize the suspension polymerization process for the production of expandable polystyrene (EPS) and the inverse suspension co-polymerization of acrylamide with cationic and anionic co-monomers. Thus, the processes of (i) suspension polymerization of EPS and (ii) inverse suspension polymerization of acrylamide with water soluble co-monomers were taken into account. To this direction, in polymerization process, the work (USTR, FPL and RWTH) was aimed at the utilization of Raman and Vis-spectrometry for the on-line monitoring of the monomer conversion and particle size distribution, respectively. More specifically, the work at BASF focused on the technical support of partners developing sensors and methods for their implementation in the selected polymerization processes. For the calibration of the Raman spectroscopic data and the estimation of the monomer conversion using liquid samples (not solid polymer particles) BASF has developed a method for the estimation of residual styrene in samples with undefined amount of water and organic phases.

At USTR the key focus has been the development and assessment of techniques for the monitoring of suspension polymerisation of styrene, where the specific requirement was to develop a sensor that can make in situ measurements of residual styrene at levels <2% and which can measure at least the mean particle size over the course of the reaction. To fulfil this goal, it was necessary to have the capability to perform EPS reactions and to assess the progress of reactions using off-line reference methods for determination of extent of conversion, residual styrene content and polystyrene bead size. Through assistance from BASF, reactions conditions for production of rigid EPS beads were identified at USTR. Having established that it was possible to measure the styrene content of beads down to approximately 0.2% w/w using the MR probe head in conjunction with the immersion probe, the residual styrene content was then monitored in the reactions. Raman spectra were pre-processed using multiplicative scatter correction and the styrene peak at 1630 cm⁻¹ was monitored during the reaction. In addition, during the final stages of the reaction when rigid EPS beads had been produced, samples of the beads were also taken for offline measurement of styrene content using HPLC. A comparison of the Raman styrene signal and the styrene content was determined using HPLC. While the residual styrene levels are relatively high (>2% w/w) in the reactions conducted at USTR, given the detection limit established in the previous section, it should be possible to monitor the residual styrene content in situ down to approximately 0.2% w/w. The data obtained can be used to build a model to predict the styrene content at concentrations below that currently detectable by in-line Raman spectrometry (with the MR immersion probe) and consequently, the end-point (when the styrene concentration is <0.1% w/w) could be determined.

Also, principal component analysis of the data collected by RWTH, BASF and Kaiser Optical Systems using a modified Raman spectrometer clearly shows that the Rayleigh scattered data are dominated by particle size information. A PLS model was also constructed with the Rayleigh scattered data in conjunction with the D50 values for the samples. Given the excellent fit of the model, it is suggested that the size values used are at the very least correlated to the actual values. If the particle size information can be confirmed, further PLS models can be built with data split into calibration and test samples, and utilising the size distribution information (rather than D50 values). In summary, the chemometric techniques applied here confirm the promise of the use of Rayleigh scattering data for particle size measurements.

For the development of a fibre-optic multi-sensor platform there were two parallel activities. First, a novel spatially resolved uv-visible-NIR probe was designed by USTR for measurement of the bulk optical properties of particulate media. While this activity was being undertaken, another probe with two rings of illumination fibres and a central collection fibre was constructed by FPL. The initial aim here was to use the FPL probe to measure the mean particle size of polystyrene beads and then to use any learning from research conducted using the USTR probe to advance the design of the FPL probe.
More specifically, the uv-visible-NIR probe that designed and constructed by USTR during the first half of the project has been evaluated further at the 2nd half of the project. The probe consists of 18 spatially resolved fibres (14 normal incident and 4 angular all with a diameter of 400 μm) with two different numerical apertures (0.11 and 0.22). It was shown that data collected using the normal incident fibres could be used to measure the mean particle size of polystyrene beads; the results obtained were comparable to those using the FPL probe. However, the primary focus of the research here was to determine the bulk optical properties of particulate samples to enable extraction of the bulk scattering coefficient. The bulk scattering coefficient can then, in conjunction with an appropriate model, be related to the particle size distribution. As it was difficult to utilise methods that rely on separation of absorption and scattering, research on the calibration methodologies focussed on more effective methods for removal of scattering effects from spectra when the requirement is to determine analyte concentration. The methods considered include: multiplicative scatter correction (MSC) and its variants, standard normal variate (SNV), derivatives and a new method termed optical pathlength estimation and correction (OPLEC). From all the previous methods the pre-processing method (OPLEC) removes scattering effects thus leading to more accurate results. Finally, the data fusion approaches in the development of a multi-sensor probe clearly demonstrated the benefits for measurement of particle size and concentration.

The results obtained using a partial least squares (PLS) model for prediction of mean particle size constructed from data collected using both the inner and outer illumination rings. Even though it was difficult to deploy the FPL probe in a styrene polymerisation reaction owing to incompatibility with the adhesive used to attach the window to the end of the probe and the reaction constituents it was possible to monitor the mean particle size of polystyrene beads in the required size range.

Regarding the oxidation process for the introduction of the epoxy function into the unsaturation system present in the fatty acid molecules, the development of reliable on-line measurement probes to measure the total peroxide concentration in the process not only would bring confidence to operators, but would also increase the productivity in existing units as well as support the application of new intensified production methods operating closer to the allowable explosion limit.

Since the oxidation of UFA is a multistep reaction opening also the way for multiple side reactions the main challenge was the determination of all species present and their quantification. While Raman spectroscopy was rapidly selected for H2O2 analysis, the choice of additional analytical methods for water, intermediates and final products had to be studied.

The first series of oxidative cleavage reactions carried out at ARKEMA was done with technical oleic acid grade, which contains only around 70% oleic acid and several other unsaturated fatty acids like palmitoleic (16:1). In order to simplify the exploitation of the results further experiments were done with an oleic acid grade containing ~90% of oleic acid. A special focus was set on the first hours of the reaction where the composition changes the fastest. The number of samples taken during this period were increased. After calibration, GC analysis allowed to quantify educts, intermediates and products during the reaction. These data were shared with RWTH and DTU. A phase transfer agent was tested and its impact determined.

For RWTH the scope of the work was to develop a methodology for monitoring HP and other species involved in the oxidation reaction using spectroscopy methods. During the work on this process, RWTH performed all the necessary experiments. The hydrogen peroxide was monitored by Raman spectroscopy in two phase oxidation reaction. The conversion of OA was followed by Raman spectroscopy. Moreover, RWTH developed a model, which could be used to monitor the concentration of all the species in the reaction mixture at any time, for different reaction conditions or operation modes. For this purpose, an indirect hard model (IHM) (with hard model and calibration model as sub models) of the components which are involved in the oxidation reaction was utilized. The concentration profile of the main components during the reaction was obtained. Patentable results have been obtained and licensing is discussed with the ARKEMA.

Multi-Scale, Multiphase Model Components Library (WP2):
For both antibody production (upstream) as well as antibody separation (downstream) two models were presented (ETH, Chromacon in collaboration with ICL). Both of them are connected by the outlet stream of the bioreactor, which defines the separation task for the downstream model. The upstream model takes the mass balance of the most important components as well as the cell number and state into account. For the chromatographic separation model parameters were determined and also presented. Both models were validated and were used for optimization and control development.

To get a better understanding of the crystallization process and especially the crystallization kinetics of L-ascorbic acid in an airlift crystallizer, a computational model was developed using gPROMS model builder. Growth and nucleation kinetics in the 18 L air lift crystallizer were estimated and compared to the kinetics in a 5 litre stirred crystallizer based on the measured experimental data. Different growth and nucleation models are compared with the goal to find evidence for different growth and nucleation mechanisms in the airlift compared to the stirred vessel crystalliser. Parameter estimation was used to find the optimal fit for the relative supersaturation during the experiment and the final crystal size distribution measured at the end of each experiment. The study allowed a quantitative comparison of the growth and nucleation rates in the airlift and the stirred crystalliser. The simulation confirmed the conclusions of the experimental data that only at low supersaturation levels the growth rate in both crystallisers were comparable due to the low sec nucleation rates.
In polymerization process, a comprehensive kinetic mechanism was employed (CERTH) to describe all the elementary reactions occurring in a chemically and thermally initiated free-radical homopolymerization. The capabilities of the present model are demonstrated by a direct comparison of model predictions with experimental data, provided by BASF, on monomer conversion, molecular weight averages and full molecular weight distribution. UGENT made a comparison between the CERTH model and Predici. A distinction is made by a comparison using intrinsic kinetics, i.e. neglecting diffusional limitations, and using apparent rate coefficients with preliminary parameters. It was concluded that the final version of the model is reliable. Regarding the PAM process, work both at CERTH and UGENT focused in theoretical and experimental work. In oxidation process, at DTU a multi-phase mechanistic model for the oxidation of unsaturated fatty acids with hydrogen peroxide developed and evaluated systematically. The influence of reaction parameters on the oxidation reaction studied via sensitivity analysis: the most important were found to be primary reaction mechanism parameters. The model calibrated and verified successfully against different experimental data. The model prediction of species in particular the dynamic trends were in agreement with the experimental data. The model ready for model-based optimization and scale-up with the constraints (in the specific cases) requires minimum two sets of experiments: for calibration and verification. This can be used to optimize operation conditions (e.g. loading, duration, etc.) and decrease the number of experiments. The developed model performance showed an acceptable match when DTU compare its prediction and published experimental data. The model parameter estimation has been performed for two simple cases, i.e. the epoxidation of unsaturated fatty acids and the dehydroxylation of the epoxide. The results of the experimental investigations show that using Raman spectroscopy together with available software tools (PEAXACT), • It is possible to monitor the conversion of oleic acid during the reaction • It can be monitored the accumulation of hydrogen peroxide in the reactor • Some species which are produced during the reaction may be observed

Novel Computational Tools for On-line Process Optimization and Control (WP3): In antibody production and purification, the computational tools for on-line process optimization and control developed by ETH Zurich focused on classical SMB for MPC for the MCSGP process. This novel multi-column chromatography process is able to achieve both high purity and yield by internally recycling overlapping regions of the chromatogram. For such a cyclic semi-continuous process a MPC control concept was developed. An objective is given to the MPC controller, which is predicting an optimal behavior with corresponding manipulated variables to the MCSGP process. Feedback is transferred to the controller via the online measurement and the Kalman filter. Depending on the manipulated variables a certain process performance in terms of purity and yield is achieved. However, this controller was not able to scope with the non-linearity of the process. Therefore, ICL was supported in developing an mp-MPC control concept.

More specifically, the focus of ICL was placed on three key areas: (i) advancement of the theory and application of robust optimization and explicit model predictive control (MPC), (ii) algorithmic developments in the area of multi-parametric mixed-integer programming and its application to operational optimization and explicit hybrid MPC and (iii) the software implementation of a unified framework for the step-wise application of such developments to real-world systems. These aims were achieved and surpassed as major contributions have resulted in all three areas. In the area of robust mp-MPC, a systematic approach for the incorporation of robustness into explicit MPC was developed featuring state-of-the-art techniques of robust optimization and multi-parametric programming. In the case of multi-parametric mixed-integer programming a general global optimization approach for multi-parametric mixed-integer programming problems was presented, which was successfully generalized to also include robust optimization. These results on robust mp-MPC as well as multi-parametric mixed-integer programming were put in context and made available to many applications via the development of the powerful software platform PAROC, which features high-fidelity modeling, model reduction and approximation, formulation and solution of the multi-parametric programming problem as well as closed-loop validation. In particular, the newly developed seamless interconnection of software tools allows for an effective and efficient application of theoretical concepts to real-world problems.

Within the newly created modeling framework several case studies which are actually mixed-integer linear and non-linear modeling problems have been tested. Through these case studies the modeling framework was also validated. The results showed that the developed structure works well. Using the task-function framework, newly developed tasks can be easily added, such that innovative Process Intensifications can be included in the model. The developed TBD model offers potential for model based process design of innovative task based crystallizers. This work has been done in TU Delft and the software is ready to be used for all kind of crystallization processes. It is implemented in gPROMS, which is in itself a generic modeling platform, making the integration of our approach into a more complex process relatively simple. Also, the presence of the advance crystallisation library gCRYSTAL, which is a dedicated modeling tool for industrial crystallisation processes running also on the gPROMS platform makes this platform attractive. An important aspect for the process intensification of polymerization processes is the availability of precise modeling tools for the reliable simulation of the polymerization kinetics (i.e. accurate equations used for the simulation of the polymerization reaction) for
various reaction conditions. The production of the expandable polystyrene (EPS) is a process that can be considered as one of the most complex studied polymerization processes from a kinetic point of view. To this direction, at CERTH a comprehensive kinetic mechanism was employed to describe all the elementary reactions occurring in a chemically and thermally initiated free-radical homopolymerization. The capabilities of the present model were demonstrated by a direct comparison of model predictions with experimental data, provided by BASF, on monomer conversion, molecular weight averages and full molecular weight distribution. Also, CERTH has developed the final version of the DSD/PSD Model which includes the simulation of droplet size distribution and particle size distribution in a non-isothermal experimental case. The model can simulate polymerization and non-polymerization case. Thus, the present DSD/PSD model can find application into different suspension processes.

Development of an Integrated CAD/CAM Software Platform (WP4):
In antibodies production and purification, PAROC was successfully applied for the development of multi-parametric controllers for the chromatographic separation MCSGP (ICL). To this end, the software platform PAROC (PARametric Optimization) has been developed. This framework is foreseen for the design, operational optimization and model-based control of process systems. Starting from a high-fidelity model in PSE's gPROMS® ModelBuilder, either system identification or model reduction techniques are applied resulting in an approximate state-space representation of the process in MATLAB®. This low-order model will serve the purposes of the design of the advanced multi-parametric controller, which is then tested in a ‘closed-loop’ validation process interconnecting MATLAB® and gPROMS® and the results are evaluated. Using the mAb from the first cultivation experiments done at ETH Zurich, and the HPLC methods developed by ChromaCon and ETH Zurich, parameters for the MCSGP model were obtained. Considering the control of this MCSGP process, which was one goal of this project, both ICL and ChromaCon developed control mechanisms. Also, the design of current industrial crystallizers was strongly focused on optimization of known types of crystallization equipment. To get a better control over the physical events governing crystalline product quality the TU Delft started with the development of a task based design (TBD) strategy, which is an example of a phenomena based approach. Task-based design uses physical phenomena to construct tasks, which are used as building blocks for design. A modeling tool for dynamic simulation of task based solution crystallization processes is developed. This is an important step towards the long term aim of model-based optimization driven process synthesis.

The developed TBD model can be applied to a wide range of crystallization processes: various crystallization methods, operation modes, configurations and a variety in number of streams, compartments and crystallization tasks. The modeling structure is based on compartmental modeling. A new way to connect tasks to this compartment model is developed. This framework supports rapid generation of consistent process models and facilitates analysis of the influence of individual tasks. The model is implemented in gPROMS.

At DSM an integrated CAD/CAM platform for simulation of multi-compartment crystallization processes has been extended with up-to-date nucleation model (surface activated secondary nucleation based on crystal-stirrer and crystal-crystal collisions) and design rules for airlift crystallizers. Key part of the surface activated secondary nucleation model is the breeding of new nuclei on the surface of crystals and release of nuclei from the surface by hydrodynamic forces. Design rules for the airlift crystallizer have been developed with special attention to the energy dissipation, gas hold-up and liquid circulation.

Regarding the development of an open-system software platform for polymerization process, the final version of the DSD/PSD Model includes the simulation of droplet size distribution and particle size distribution in a non-isothermal experimental case. The model can simulate polymerization and non-polymerization case. Thus, the present DSD/PSD model can find application into different suspension processes. The user can introduce the surface tension as well as the effect of agitation effects (impeller size and speed). Pentane can be added at the beginning of the execution. The model parameters are the reactor loading (monomer, water, surfactant, pentane), the agitation speed, the impeller size, the power number with volume relationship (mixing), surface tension, temperature profile and the numerical parameters regarding the domain size and the type of discretization.

Also, the final version of the kinetic model included the non-isothermal polymerization case. The Marten-Hamielec gel-effect was used and tuned for the temperature range of 60 to 150 °C. A comprehensive kinetic mechanism was used and the gel- (and glass-) effect were tuned both at low and high temperatures. In addition to the kinetic model of the EPS process, CERTH has developed kinetic models for the initiator induced degradation of EPS as well as the effect of small quantities of a bifunctional comonomer (e.g. DVB) in the molecular weight developments of EPS. All the above codes have been unified into a single software code. The capabilities of the present model were demonstrated by a direct comparison of model predictions with experimental data, provided by BASF, on monomer conversion, molecular weight averages and full molecular weight distribution. The final version kinetic model is as a dll version so that it can be used from any open-architecture software platform.

In the oxidation process at DTU, concepts of phenomena-based process synthesis and phenomena-based building blocks had been developed. The concept and reasoning behind the phenomena-based synthesis method is analogous to computer-aided molecular design (CAMD). Combination of phenomena-based building blocks (PBBs) represents tasks, unit operations and flowsheets. PBBs are used to generate new alternatives for process intensification. The key computer-aided multi-level framework for process synthesis-
intensification has been developed. The complex synthesis-intensification problem is solved systematically using a decomposition approach. It has been shown, through application of the framework that intensified process alternatives can be generated by performing process synthesis and intensification together and operating at all three scales, operations, tasks and phenomena. ARKEMA provided analytical data to DTU for model development. Possible side reactions and concentration of different species in the oil and aqueous phase were estimated. Solubility data at the reaction temperature of reaction products in the aqueous phase were estimated.

Application of Process Intensification to Selected Industrial Processes (WP 5):
In polymerization processes, at UGENT, the accuracy of the CERTH model, neglecting branching reactions, was verified using the Predici software package, which is also available at BASF SE. For the intrinsic models, a good agreement was obtained, indicative of the numerical accuracy of the OPTICO model. An overview of the main results as came from the comparison between the CERTH model and the Predici model, where a distinction is made between a comparison using intrinsic kinetics (i.e. neglecting diffusional limitations, and using apparent rate coefficients obtained by regression to experimental data) proves that the two models are in conformity.

For the intensification of inverse suspension polymerization of acrylamide, CERTH has provided, in collaboration with UGENT, a detailed set of experimental polymerization data. At UGENT the main focus was on the copolymerization of acrylamide and sodium acrylate and at CERTH on copolymerization of acrylamide and dimethylaminoethyl acrylate. Since process intensification for inverse suspension copolymerization involving acrylamides, relies on the intrinsic kinetic parameters that were currently lacking, these parameters as well as the gel effect parameters were obtained by experimental studies. At CERTH and UGENT such model has been constructed for the copolymerization process involving as comonomers acrylamide and dimethylaminoethyl acrylate or sodium acrylate, respectively. Both at CERTH and UGENT the homopolymerization of acrylamide was extensively studied experimentally in solution (water) to identify optimal polymerization conditions and to obtain the intrinsic kinetic parameters, which are crucial for the process intensification. In addition, in CERTH, simulation results were compared using experimental data from literature (both solution and inverse suspension at high monomer concentration) and from CERTH's experimental work during the OPTICO project (solution and inverse suspension polymerization).

From the work done for the polymerization process, within OPTICO project, BASF gained important building blocks for future work. More specifically, BASF obtained kinetic and PSD models for EPS and PAM processes (CERTH) and there is a good chance that together with Raman (USTR, RWTH) and Sopat probes they could be used for online process control in the very near future.

Finally, regarding the intensification of an UFA oxidation with hydrogen peroxide process a reactor was modified in order to follow the reaction with different probes. Different addition modes of hydrogen peroxide were tested and the impact was followed by Raman spectroscopy and GC analysis.

At DTU, a mathematical model for the oxidation of unsaturated fatty acids with hydrogen peroxide in two-phase system has been developed. More specifically, at DTU investigation towards optimization and intensification of the oxidation process has been started based on the developed mathematical model of the process. Once the kinetic parameters had been identified and the kinetic model had been evaluated, the process could be optimized with respect to system variables, such as hydrogen peroxide concentration, hydrogen peroxide to UFA molar ratio, temperature, hydrogen peroxide addition time, stirring speed, and phase partitioning. As it had been showed in the qualitatively analysis of the model, the system variables affect the system and their optimum range of their values is essential in order to have the optimum operation. The conversion of the unsaturated fatty acid, the yield of the main products and the prevention of the formation explosive oligomers will be the objectives of the optimization. All the system variables had been tested except from the temperature. During the work on this process, RWTH performed all the necessary experiments and developed a model, which could be used to monitor the concentration of all the species in the reaction mixture at any time, for different reaction conditions or operation modes. The rest of the system variable had been tested qualitatively; the concentration of hydrogen peroxide solution should not be lower than 30% because the yield of the main products is low and the reaction should run for a long time in order to have high yields and not upper than the 70% because safety reasons arise. Hence, according to literature and the qualitatively analysis, the optimum range of the hydrogen peroxide solution should be between 30%-70%.

For all the selected processes, FPL has responsibility to develop a customizable fibre optic multi-sensor platform suitable for use in industrial process monitoring. In collaboration with the consortium partners, a variety of different sensors and optical techniques have been explored, compared and assessed as to their suitability for a multi-function probe for the four processes of interest. For finding a sensor capable of quantifying water in a bi-phasic system the presence of hydrogen peroxide and organics, ARKEMA received a NIR spectrometer from FPL. This equipment was used for tests for water measurements. Hydrogen peroxide/water mixtures with different concentrations were recorded. Data was shared with FPL for analysis. Oleic acid/water and ethanol/water mixtures were also analysed by NIR. Probe fouling was a major problem since oil forms a film on NIR sensors.
designed dividing the hydrogen peroxide flow so that only small H2O2 quantities come into contact with oleic acid. The ternary diagram of water, hydrogen peroxide and oleic acid was generated. The process was optimized with respect the amount of hydrogen peroxide and the concentration of the aqueous solution keeping the reaction time and the addition time constant. The process improved by 17% compared to base case operation recipe given by ARKEMA. These optimization results are promising and showing the usefulness of modeling and optimization based approach for process optimization.

Demonstration of Process Intensification in Selected Industrial Processes (WP 6): In line with project objectives, ETH, ICL and ChromaCon intensified the production and purification process for monoclonal antibodies. With ChromaCon as main driver the different unit operations were successfully changed. The cultivation of CRL 1606 was changed from batch to fed-batch fermentation. Product isolation was successfully done with a two-column capture process, for which also a controller was developed. Product purification was changed from batch chromatography to the novel twin-column MCSGP process. In order to increase final mAb titer, a fedbatch process of CRL 1606 cells has been developed. In this way, the process duration could be increased from 4 days to 8 days. Applying a continuous feeding strategy of a mixed nutrient feed to avoid any limitation of amino acids and vitamins resulted in a doubling of the viable cell concentration and monoclonal antibody concentration. For the semi-continuous capture process ChromaCon developed a controller based on the online UV signal. The area of the elution peak is measured and compared to the amount of antibody loaded onto the column. From there on the error is calculated and the load amount is adjusted. For the MCSGP process a similar controller was successfully applied. This controller was able to reject different artificial disturbances during an experimental separation. Additionally, ETH Zurich used the previously developed model and optimization algorithms to compare the performance of the novel twin-column MCSGP process to batch chromatography. Since there is always a yield/productivity trade-off, pareto-optimal operation points are obtained. Purity was set as a constraint and results from steady-state operation were considered. A generalized differential evolution algorithm was used. As operation variables the switch times, flow rates gradient start and gradient slopes were optimized. As a result, 2-3 times higher productivity is obtained for the MCSGP process.

The intensification of pharmaceutical crystallization processes has been focused on the application of the task-based design philosophy by using the integrated CAD/CAM platform for simulation of multi-compartment crystallization as one of the main tools. The CAD/CAM platform has been applied on a number of existing processes of DSM to optimize the operation in order to improve the product quality and reduce process costs (e.g. energy costs) and to a number of new products/processes with the idea to design a process that is flexible and offers good control to generate a product that meets the high quality standards needed in the market for high value products.

One of the product groups of DSM has a strong dependence on continuous crystallization and is operated at different places around the world. Here a task-based approach has been applied to extend the operation of one of the plant to improve the flexibility of the product portfolio. The extension of the plant operation resulted in the addition of two functionalities in the plant, leading to an increase of the plant complexity. The CAD/CAM platform is used to identify the dynamic interaction between the different functionalities in the plant and support plant operations for good plant control. Here several steps have been taken: identification/calibration of crystallization kinetics, validation of crystallization kinetics, extension of plant model with new functionalities. Validation of new model functionalities, identification of functional interactions, design of addition control rules.

The process that is flexible and offers good control to generate a product that meets the high quality standards needed in the market for high value products. For the design of a crystallization process for a new product it is important to make sure that all product requirements are met from the moment the product is delivered to the market. One of the challenges is the fact that many new products are produced by biotechnological means because of the sustainability driver. This means that additional effort has to be done in order to remove the broad pallet of impurities (proteins, lipids and sugars).

At TUD, based on the experiences of the pilot airlift crystallizer and preliminary model simulation a design has been made for a flexible task-based crystalliser in which different crystallization tasks can be realised and integrated. The demonstration unit can be operated both batch wise as well as continuous and contains the units for airlift crystallisation, conventional crystallisation (draft tube crystalliser), membrane-assisted crystallisation, cooling and anti-solvent crystallisation, (continuously) seeding, ultrasonic seeding, which can be integrated into one integrated crystallisation process. This allows for a high flexibility in operation, production level and product quality. The unit is constructed and is tested for different crystallization processes. It is worth to mention that the unit is easy-to-transfer so that it can be easily transferred to a company for testing and validation. The units has been successfully tested batch wise using the airlift crystalliser and the membrane assisted crystallisation unit using the sweep gas membrane distillation with ascorbic acid as model material.

Dissemination-Exploitation of New Knowledge and Results (WP 7): With a number of ways, the results of the research within OPTICO Project have been distributed outside of the consortium. These include the standard practices of lectures and conference proceedings as well as poster presentations. The OPTICO website (www.opticoproject.eu) has been set-up and updated regularly, containing information relevant to the project objectives, structure, participants, achievements, publications, important links, etc. Basic information for young students interested in the enabling technologies and applications are included. Establishment of a separate secure area for the project participants has been foreseen to enable internal communication and exchange of documents. Diffusion of the research...
results through publications in international scientific journals and conference proceedings are pursued. For the efficient exploitation of the results, new potential applications related with the innovations of WPs1-6 are considered for future exploitation by the project’s partners. The aim of the work done was to extract value from the OPTICO project and promote the filing of patent applications that will demonstrate a real commitment to develop the technology that is being covered in the application. The partnership has successfully concluded a Consortium Agreement to take care of all IPR issues: i.e. organizational structure of the project, commercial exploitation of the R&D results, responsibilities and obligations of each partner, definition of market shape, and identification of rewards.

Project Management (WP 8): All Management activities realized during the project lifetime were in accordance to the Annex I (Discission of Work) and Annex II – Articles II.2.3 and II.16.5 (General Conditions) of the Grant Agreement.

**Potential Impact:**

Within the OPTICO project, thirteen European partners from eight different countries combine their efforts and expertise in complementary scientific fields to ensure accomplishment of the project objectives and transfer of the developed technology to a much wider European basis. More specifically, this three year project involved eight research institutes and academic partners: CERTH/CPERI (GREECE), Imperial College/ICL (UK), RWTH Aachen (GERMANY), ETH Zurich (SWITZERLAND), Technical University of Denmark/DTU (DENMARK), Technical University of Delft/TUD (NETHERLANDS), University of Gent/UGENT (BELGIUM) and University of Strathclyde/USTR (UK), three chemical industrial companies, one SME specialized in protein production/purification and one sensor-manufacturing SME: BASF (GERMANY), ARKEMA (FRANCE), DSM (NETHERLANDS), CHROMACON (SWITZERLAND) and FIBRE PHOTONICS (UK), respectively.

These research groups involved in OPTICO cover a wide variety of research fields, including: chemical and biochemical engineering, polymer reaction engineering, particle technology, computer aided process design, sensor development, etc. This resulted in a highly interdisciplinary consortium providing a collective expertise, extending over a broad range of scientific areas, tools (experiments, modeling, etc.) and interests (fundamental research, application and education). All the research teams have many years of experience in their respective scientific fields and have been in the forefront of the R&D worldwide as it is evident from their publications in leading scientific journals, presentations at international conferences, patents, etc.

The academic partners in the consortium carry out the vital task of educating highly skilled and well-trained scientists and researchers providing, thus, the skilled personnel for both industry and Universities. The close collaboration simulate new ideas and approaches to the technical problems being tackled, methods of work, etc. The exposure of academic research groups to important industrial problems and needs can help to focus their future strategic research plans.

On the other hand the consortium included industries that are ideally placed to commercialize and validate the technologies emanating from the project. Commercialization of the most promising results obtained from the present collaborative project is pursued by the industrial partners via the development of new intensified processes and products. Each industrial partner was responsible for the direct exploitation of the results obtained in the project. Furthermore, there is substantial potential for further commercial exploitation of the results by transferring the generic developments to other sectors outside the Consortium and particularly to knowledge-intensive SMEs.

The OPTICO consortium strode to exploit and commercialize the technology emerging from the project in a timely and effective manner. It was the consortium's intention to put in place a commercialization agreement for the OPTICO exploitable results which gives the industrial partners first right of technology exploitation. The partners considered the commercial significance of the results, and, in particular, the questions of patent/copyright protection of results in order to avoid premature disclosure. The exploitation of results and the protection of knowledge were defined in details in the Consortium agreement, which was signed by all the partners within the project lifetime.

The exploitation strategy comprised the following steps that were carried out in parallel with the project development:

- Market evaluation and analysis for the developed products and technologies.
- Dissemination of results and trials to relevant industries.
- Issue of relevant patents and contacts with potential end-users.

The potential applications of the enabling technologies developed in the framework of OPTICO were quite numerous. Some important examples include:

- Prototype Multi-function Fibre Probe suitable for product quality monitoring for industrial processes
- A library of software tools (e.g. phenomena-based models, control & optimization software tools, PAT)
- A CAPE-OPEN unified modeling and computational software platform
- Intensification of industrial process via the optimized design and operation of process units
- Precision specification and engineering of product end-use properties

Within OPTICO Project a new adaptive, integrated methodological framework is developed for intensified chemical/ biopharmaceutical plant design and operation that offers concrete opportunities to chemical/biochemical enterprises in four areas: costs, safety, time to market, and company image. Intensification of a chemical/biochemical process can lead to a reduction of energy expenditure, decrease
by-product formation and substantial increase in productivity, resulting in further environmental, economical and employment benefits to our society.

In particular, intensification of a chemical/biochemical process can lead to a reduction of energy expenditure by 20-50%, decrease in by-product formation by up to 30% and substantial increase in productivity, resulting in further environmental, economical and employment benefits to our society.

Recombinant proteins production process: Within the protein-based therapeutics, monoclonal antibodies (mAbs) are the market leaders in terms of volume sales and the most common class of products. 15.8% annual increase in sales is forecasted so the sale of monoclonal antibodies is expected to reach $67.6 billion by 2015. The purification of mAbs for therapeutic use requires highly selective and robust technologies to achieve the very high purity required for biopharmaceutical applications. Also, large scale processing is a painful task that requires careful technology design as the feed stocks are variable in both product content and composition. Consequently, the downstream processing accounts for about 60%-80% of the mAbs production cost. Purification is presently performed in a cascade of multiple chromatographic separation methods carried out discontinuously whereas the optimization of the process is performed by a trial-and-error approach. The employment of the integrated process intensification platform for the design and operation of continuous downstream mAbs purification units, taking into account the variations in feed quality, is expected to reduce the overall production cost by 25-50%.

Pharmaceutical crystallization process: Batch crystallization is the workhorse of the pharmaceutical industry since almost 70% of the related products involves a crystallization step, at some point, in their production cycle. The design, optimization and control of crystallization processes is currently still performed by trial and error, causing large variations in product purity, crystal size distribution and downstream processing requirements. The integrated framework for intensified process design and operation to be developed within the OPTICO project will bring substantial improvements in the pharmaceutical crystallization processes that will enable faster product development (i.e. shorten times to market) as well as will ensure the consistent, reproducible production of high-quality products and eliminate the need for expensive downstream processing steps such as grinding and granulation.

Polymerization process: The key to the sustainability of polymer manufacturing companies lies in their capability to manufacture products which meet the product specifications in an efficient and safe manner. At present, the application of on-line optimal control policies is hindered by the inability to measure product properties in real time. The OPTICO project addresses this problem by developing advanced multi-scale soft sensor tools coupled with on-line analytical hard sensors for the real-time estimation of key product characteristics (e.g. molecular weight and particle size distributions). It is anticipated that the PI tools developed in the OPTICO project will make feasible the on-line estimation and control of the polymer properties and result in an increased productivity by 10%, a decrease of the off-spec amount of polymer by 20%, and, finally, a decrease in the downstream processing cost for removal of unreacted monomer(s) by 10%.

Organic oxidation process: The annual world production of hydrogen peroxide is approximately 3 million metric tons. With an annual market growth of 4%, hydrogen peroxide is widely used in almost all industrial areas. The on-line monitoring of H2O2 concentration is very important for the optimization and safety of the related oxidation processes. However, there is currently no reliable analytical device on the market for the on-line monitoring of its concentration in multi-phase reaction media. The development of reliable on-line measurement probes to measure the total peroxide concentration in the process will bring confidence to operators, and also increase the productivity. It is expected that the optimization of the equipment design will lead to a reduction of fixed costs by about 10%. Furthermore, the reduction of the residual H2O2 in the product will result in an economic benefit of another 10% on variable cost.

Dissemination of the Results
For the effective dissemination of the OPTICO Project results, a website (www.opticoproject.eu) has been set-up and updated regularly, containing information relevant to the project objectives, structure, participants, achievements, publications, important links, etc. Basic information for young students interested in the enabling technologies and applications are included. With a number of other ways, the results of the research within OPTICO Project have been distributed outside of the consortium. These include the standard practices of lectures and conference proceedings as well as poster presentations. Briefly the dissemination of knowledge outside the consortium has been made via

- Participation in international scientific conferences 20
- PhD theses related to the OPTICO project 10
- Papers to scientific journals 16
- Patents 2

Selected papers and/or dissemination activities are:
A Comprehensive Kinetic Investigation of the Inverse Suspension Copolymerization of Acrylamide: Theoretical and Experimental Studies, Olympia Kotrotsiou, Chrysoula Gkementzoglou, Prokopios Pladis and Costas Kiparissides, 2013 AIChE Annual Meeting, San

A Comprehensive Kinetic Investigation of the Inverse Suspension Copolymerization of Acrylamide: Theoretical and Experimental Studies, P. Pladis, O. Kotrotsiu, Ch. Gkementzoglou and C. Kiparissides, 10th Hellenic Congress of Chemical Engineering, Patra, Greece, June 4-6, 2015


A Framework for Hybrid Multi-parametric Model-predictive Control with Application to Volatile Anaesthesia, Ioana Nașcu, Richard Oberdieck, Efstratios N. Pistikopoulos, ESCAPE 25/PSE 2015

On the Development of Multi-parametric Controllers for the Twin-column MCSGP, Maria M. Papathanasiou, Fabian Steinebach, Nikolaos A. Diangelakis, Guido Stroehlein, Massimo Morbidelli, Athanasios Mantalaris, Efstratios N. Pistikopoulos, AIChE, November 2014, ATLANTA


Application of the Generic Modeling Template Approach to Unsaturated Fatty Acid Oxidation and Crystallization Systems, Fedorova, Marina; Papadakis, Emmanouil; Meisler, Kresten Troelstrup; Sin, Gürkan; Gani, Rafiqu, Computer Aided Chemical Engineering, 2014


The PhD Theses that initiated within the OPTICO Project are:

Ms Maria Papathanasiou (ICL):
Model-based Optimization and Control for the Production and Purification of Monoclonal Antibodies (Starting Date: 25/11/2012)

Mr Richard Oberdieck (ICL):
Advances in Multi-parametric Programming and Nonlinear MPC (Starting Date: 01/10/2013)

Mrs Marina Fedorova (DTU):
Systematic methods and tool for computer aided modelling (Starting date: 01/04/2012)

Mr Fabian Steinebach (ETH):
Continuous preparative chromatography for separation of monoclonal antibodies (Starting date: March 2013)

Mr Bastian Brand (ETH):
Developing of resin materials and intensification of chromatographic separation of biomolecules (Starting date: Apr. 2010)

Mr David Pfister (ETH):
Engineering biomolecules: Purification and Characterization (Starting date: Feb. 2012)

Mr Rushd Khalaf (ETH):
Modeling and Optimization of Chromatographic Purification Steps (Starting date: March 2012)
Exploitation of the R&D developments

For the efficient exploitation of the results, new potential applications related with the innovations of S&T results are considered. The aim of the work done was to extract value from the OPTICO project and promote the filing of patent applications that will demonstrate a real commitment to develop the technology that is being covered in the application. The partnership has successfully concluded a Consortium Agreement to take care of all IPR issues: i.e. organizational structure of the project, commercial exploitation of the R&D results, responsibilities and obligations of each partner, definition of market shape, and identification of rewards Task.

In what follows the actions of each Partner in this task are presented.

At USTR, owing to the considerable promise of the spatially resolved uv-visible-NIR probe, which was partially demonstrated during the OPTICO project, Yi-Chieh (Claudia) Chen has created a start-up company, Savitur Metrics, which will be spun out from USTR later in 2015. The background of the IP to uv-vis NIR probe belongs to Thennadil SN and Yi-Chieh Chen and concerns an apparatus and method for estimating bulk optical properties of suspensions. (UK patent application no. 112 0075.5 led on November 21st, 2011). It is worth mentioning that Savitur Metrics won the 2014 Converge Challenge, which is a prestigious national contest that champions enterprise and entrepreneurial innovation from within Scotland's academic community. Company aims to become a leading global supplier of monitoring technology for effective quality control across pharmaceutical and chemical plants around the world.

FPL has demonstrated the potential during OPTICO for compact multi-sensor portable systems which will provide sophisticated on-line monitoring suites at affordable price tags (£40-100k). This will open up the market and drive future growth. A product development program needs follow which is estimated in the range £250-500k. Funding for this is being sought now from partners, trade bodies, government enterprise agencies, and further EU funding. Future sales of ~ 15-20 systems would allow FPL and future development partners to recover their investment in OPTICO. It is expected there is potential for additional sales of £1m per annum for FPL and will create in the near term up to 5 new jobs in Europe; more growth is expected as the company diversifies in to new applications and market sectors.

At ARKEMA the results obtained for the oxidation process have the potential to be adapted to other processes using hydrogen peroxide. ARKEMA launched discussions with internal and external clients for the development of online analysis for other processes using hydrogen peroxide. The challenges faced during the oxidation process and the discussions under partners of the oxidation process and experiments carried out allowed Fibre Photonics to gain important insights in water and hydrogen peroxide measurements. This opens up for Fibre Photonics applications and markets beyond the oleic acid oxidation process. Many other industries are looking for water measurements including the paper industry, food & drink, agriculture, biopharma, medical etc. So, the knowledge gained during OPTICO has unexpectedly opened up new avenues and markets to explore. The purpose will be to promote the use of hydrogen peroxide under safe conditions in organic chemistry. By giving an analytical method to optimize organic reactions with hydrogen peroxide under safe conditions, ARKEMA would sell H2O2 with service (Analytical method/Model/Know how). IPR exploitable measures include patent know-how or publication.

Based on the work done by ETH/Chromacon, through the use of internal recycling, the intrinsic purity-yield tradeoff of batch chromatography is avoided and challenging separation tasks can be fulfilled with high purity and yield. Like in batch chromatography the product purity depends on the pooling policy. However, recycling impure product streams can increase the yield of the collected product, while keeping the purity at least at the same level of a batch process. Further to work done in collaboration with ETH, ChromaCon implemented an improvement for the control software of the Contichrom system. Here a new software tab allows loading of external control parameters to the software and thereby control and optimize any process. This new interface was included in the ChromIQ operating software allowing online control and implementation of process control parameters obtained from different algorithms. For ChromaCon, the OPTICO project is expected to have important economic impact in the sales.

At DSM, the exploitation of the intensification of pharmaceutical crystallization processes is focussed on two items:

- Application of the Task-based design tool to optimize existing processes.
- Application of the Task-based design tool, including the newly developed technology for the design of new crystallization processes.

Another expected exploitation of the OPTICO results is the development of the simplified spectroscopic devices by FPL. Industrial
application of in-line technology (particle size and concentration determination) is still hampered a lot by the costs of current equipment. Although the new equipment has less resolution than the existing equipment, it is not a problem for modern process control opportunities.

A separate exploitation action that has been started is the testing of the PSE/gProms platform (main platform for the Task-Based design) inside DSM.

The design of new processes will benefit in two ways from the Task-Based design and additional technology. First of all a reduction of energy usage is foreseen. The separation of tasks and the homogeneous mixing of the airlift crystallizer will result in a production process that uses less mixing energy and results in a smooth product with a particle size distribution with less fines. The effect of the improved particle size and morphology will be that the solid/liquid separation will be easier with less liquid attached to the crystals and less energy requirements for the drying. Overall a energy saving in the order of 25 % is expected. A second benefit is the fact that the methodology promotes the production of right-first-time material. Our customers will get premium material right from the start. This will give an additional commercial benefit, especially when cost-prices are comparable or lower (less energy costs) and because many new products are produced in a sustainable way.

At CERTH exploitable R&D developments include the Kinetic Model of EPS process, the EPS Degradation Model, the PSD/DSD Model for the EPS Process software tools and the acrylamide kinetic model. Using these models it will be possible for BASF or other companies to produce polymers with desired properties with respect to the MWD and PSD.

At BASF the kinetic and PSD models, developed by CERTH during the duration of the OPTICO Project, will be intensively tested in the following time period and the optical measurements with the probe from company SOPAT may have potential for successful online monitoring of PSD in EPS case.

As a conclusion, the consortium showed both strength in depth of expertise of individual members and the excellent integration between them to realize the objectives of the project. Commercialization of the most promising results obtained from the present collaborative project was pursued by the industrial partners via the development of new intensified processes and products. Each industrial partner was responsible for the direct exploitation of the results obtained in the project. Furthermore, there was substantial potential for further commercial exploitation of the results by transferring the generic developments to other sectors outside the Consortium and particularly to knowledge-intensive SMEs.

FIBRE PHOTONICS provided a novel compact fibre-optic multi-sensor system with capability of providing simultaneous measurements through different probe technologies for the real-time monitoring of the multi-phase processes. CHROMACON developed a mini pilot-scale unit for mAb production/purification.

On the other hand, the three large companies of the consortium were directly involved in the implementation of the integrated PI framework to three industrial-scale processes: BASF implemented the integrated intensification methodology to the suspension and inverse suspension polymerization processes aiming at the optimization of processes with respect to desired particle size and molecular weight distributions. ARKEMA utilized the sensor technology and PAT tools to monitor and control the UFA epoxidation process. DSM used the design and optimization tools for the intensification of a pharmaceutical crystallization process.

List of Websites:
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