CPAC Rome Workshop Summary

March 24-26, 2014
UW Rome Center

Achieving Process Optimization and Lower Costs via Technology Developments and Molecular Management

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CPAC (Center for Process Analysis and Control – University of Washington (UW)) conducted a workshop at the UW Rome Center, March 24-26, 2014, Rome, Italy, for the purpose of gathering US and European scientists and engineers of similar expertise in the field of instrumentation and data handling that enables process optimization. The goal was to catalyze transatlantic collaborations in the areas of unit operations (reaction, separation, purification) and the related enabling technologies of sampling and measurement science technologies.

These collaborations will advance research and educational aspects to enhance the discovery, development, and production of specialty chemical, pharmaceutical, bio-technology, and food products. The goal of these advances is to achieve technical developments that will improve the global issues of reduced energy use, a positive environmental impact, and reduced costs of quality products.

CPAC has an established track record in fostering academic and industrial interactions, which aim at bridging the gap between basic research and full-scale process / product development.

There were presentations and discussions at this Rome workshop on the make-up of the concept of Smart Manufacturing in achieving process intensification – and talks on technology advances from a variety of sources. The workshop provided continuing educational opportunities in the areas of Micro-Instrumentation (Micro-Reactor, Micro-Analytical, Micro-Separations, etc.), Process Intensification (Flow Chemistry, Separations, Environmental, Energy Reduction), and Approaches to Data Handling (Data Fusion, Big Data, etc.). It was a forum for presenting and discussing advances in continuous unit operations and measurement sciences linked to improved process control incorporating Quality by Design (QbD). The presentations included challenges in the selected areas, case studies, and new technical advances including emerging applications for NeSSI™ (New Sampling/Sensor Initiative).

The workshop attendees included: academic researchers, instrument manufacturers, engineering companies, and industrial ‘end-users’.

FORMAT

The Satellite Workshop was held over three days - beginning on Monday afternoon, March 24, and ending on Wednesday, March 26. The Workshop Presentations served as a basis for open discussions with a futuristic outlook toward the technology presented and its impact on the future of Process Analytical Technology (PAT). These discussions are facilitated by numerous networking opportunities the most significant of which is the Con Apertivo which was held each evening in the Director's suite overlooking old Rome. The official language for the workshop was English.

Rome Workshop 2014 Program

March 24-26, 2014, University of Washington (UW) Rome Center,

Piazza del Biscione, Rome, Italy

Workshop Sponsorship: UOP, ART Photonics, CPAC/UW, Infineum, Optimal Industrial Automation, Rollo Agro Enterprises, and UW Global Affairs

Monday, March 24, Conference Room, 1st Floor

12:30	Registration Opens
13:15	Introduction Mel Koch, CPAC/APL, University of Washington, USA
13:30	Welcome from the US Embassy in Rome, Italy

Day One "On a Process Scale - Production and Process Integration"

13:45	Chemical and Process-Design Intensification in Flow - seen Holistically (Abstract in Appendix) Kurt vandenBussche, UOP, USA, presented by Ray Chrisman, Atochemis
14:30	The Changing Face of Flow Chemistry: From Micro Reactors to Continuous Production (Abstract in Appendix) Paul Watts, Nelson Mandela University, South Africa
15:00	Case Study, Need for Process Monitoring for Process Control Giuseppe Caire, Infineum Italia, Italy
15:20	Break
15:45	University of Washington Rome Center Welcome, Sheryl Brandalik, Director, and Introduction of Participants
16:00	Analytics in Power to Gas Applications (Abstract in Appendix) Stefan Malcharek and Peter Berghauser, Siemens, Germany

16:30	Control Technologies for PAT / QbD and Process Improvements Marco Banti, ABB, Italy
17:10	Discussion: Ray Chrisman, ATOCHEMIS srl, Italy
17:30	Con Apertivo, UW Rome Center

Tuesday, March 25, Conference Room, 1st Floor

Day Two AM "Utilizing Developments in Continuous Process Units - Process Control, Sampling, and Sensing"

9:00	Introduction Mel Koch, CPAC/APL, University of Washington, USA
9:15	Micro-structured Flow Reactors as a Versatile Lab-Tool for Two and Three- Phase Reactions Laurent Vanoye, Régis Philippe, Alain Favre-Réguillon, and Claude de Bellefon, University of Lyon, France
9:45	Developing Multi-Step Chemical Synthesis Using Micro-Reactors Frank Gupton, Virginia Commonwealth University, and Tyler McQuade, Florida State University, USA
10:15	Break
10:45	Developing Process Control for Flow Chemical Reactions – Using Unique Approaches to Sampling, Sensing, and Data Handling Brian Marquardt CPAC/APL University of Washington, USA
11:15	Choosing the Right Reactors for the Right Reactions: Implementing Flow Processes in Production Environments (Abstract in Appendix) Peter Poechlauer and Kai Dombach, DSM, Austria
11:45	A Case Study on the Conversion of a Batch to a Continuous Process Vincenzo Fusillo, Atochemis srl, Italy (Abstract in Appendix)
12:15	Lunch, Da Pancrazio, Palazzo Pio,

Day Two PM "On a Process Unit Scale - Reaction and Separation"

13:45 -	Following Successful Reactions There is a Need for Separation and Purification (Abstract in Appendix) Ray Chrisman, ATOCHEMIS srl, Italy
14;05	Micro-Extruder Technology Developments for Solids Handling Simone Maccagnan, GIMAC, Italy
14:35	Development of Predictive Model Control Approaches (Abstract in Appendix) Olav Martin Kvalheim, University of Bergen, Norway
15:15	Break
15:40	Data Fusion and Managing Big Data from the Laboratory to

	Manufacturing (Abstract in Appendix) Martin Gadsby, Optimal Industrial Automation Limited, UK
16:05	On-line Technology that Enables Process Control in the Food Industry Jens Petter Wold, Nofima, Norway
16:30	Discussion
17:30	Reception Con Apertivo, UW Rome Center

Wednesday, March 26, Conference Room, 1st Floor

Day Three "Solution Providers"

9:00	Introduction, Mel Koch, CPAC/APL, University of Washington, USA
9:10	Developments and Implementation of Smart Sampling Systems (Abstract in Appendix) Graham Johnson, Parker Hannifin Manufacturing, UK
9:35	Useful Applications of Smart Micro-Gas Chromatography with the NeSSI™ Platform Spencer Parker and John Crandall, Falcon Analytical, USA
9:50	Improvements in Sampling and Monitoring Bop-Processes Brian Marquardt. CPAC / APL, University of Washington, USA
10:15	Break
10:40	MEMS- Based Spectrometer and Fiber Probes for Process Spectroscopy (Abstract in Appendix) Slava Artyushenko, ART Photonics, Germany
11:05	Final Discussion and Action Plans
12:00	Conclusion of Rome Workshop
	Informal Reception, UW Rome Center

The topics of the discussion following the presentations are summarized below:

The workshop plenary talk was an update on challenges and successes in the refining and petrochemical industries. The application of concepts like 'big data' and 'data fusion' is making headway in the energy industry and is starting to impact both the overall optimization of processes and manufacturing complexes already in operation as well as the ways being developed for next generation technologies.

There were several industrial talks that focused on the potential value of monitoring industrial processes, both chemical and biological. There is a growing appreciation for the value of continuous processing, based on quality, energy, and environmental impact.

Continuous flow chemistry is showing continued success for effectively running chemical reactions. The reasons to pursue this are growing. Past emphasis has been on running reactions that were of concern from a safety point of view (exothermic condensations, nitrations, azide formations, etc.). Indeed this allows a safer path to studying new reaction parameters that could achieve increased reaction rates. The result is often allowing new synthetic steps to be considered. Also in the discussion are other areas being incorporated in the micro-reactors, including solvent switching, catalysis, continuous distillation, and extraction unit operations.

However, it has become increasingly obvious that micro-scale flow reactions are often a more effective way to run a process and / or to study process optimization. Interestingly, batch reactions can be optimized, as well as continuous processes – with the information gathered from these studies. A study was presented that involved a study funded by the US FDA where continuous micro- flow reactors could gather valuable process data – using effective sampling, measurement, and data handling. The results are indeed the ability to improve both batch and continuous processes.

Though most of the discussion has been focused on value of flow chemistry for the pharmaceutical industry, the impact on achieving the goals of green chemistry (energy efficiency, environmental impact, and lower cost) is still very relevant for chemical production in general. Of increased interest is the incorporation of catalysts – including enzymes – in these micro-flow devices.

Monitoring, or measurement, of continuous process steps is critical to developing the process understanding necessary to incorporate process control. As continuous reaction unit operations have gained a measure of success, the subsequent operations of continuous separation, purification, and formulation are being addressed – not only as unit operations that need to be connected but also the need to monitor and control their effectiveness. Separation unit operations like Simulated Moving Bed (SMB), membrane utilization, and process chromatography are being sized to interface with the micro-scale reaction components.

The needs for improvements in operations such as solids handling, cleaning validation, and purification operations are being discussed and addressed. There will be advances in these areas in the near future.

The use of Process Analytical Technology (PAT) is now being realized in continuous processes – and the use of PAT in batch processes must be expanded. Effective use of PAT requires a good understanding of the interaction of monitoring tools and processing conditions. Many process evaluation techniques are still evolving. There are exemplary systems that effectively involve sampling, measurement, data evaluation, and interface with process control (like the FDA funded study mentioned earlier). There were several other examples presented that pointed out the value of improved sampling using the NeSSI (New Sampling and Sensor Initiative) platform, including its use now in bio-processing.

Data Handling, or effective interpretation of instrumental data, is a key to process understanding and it was presented by several workshop participants. The ability to gather data, categorize it,

and incorporate data fusion of the various individual measurements for final product property predictions is valuable. There are also approaches to evaluate data bases for process predictions.

Given the range of chemistries being studied, new measurement tools for PAT are needed and approaches to these are being developed by the instrument vendors. In the Rome workshop there were presentations on advances in PAT that involved developments in areas in areas like: GC, NIR, Fiber Optic Sensors, Raman, and Laser Induced Breakdown Spectroscopy (LIBS).

Solids handling is important to most processes. New technology that involves micro-extruders was presented as an interesting approach to mixing solids and creating new dosage forms.

As the unit operations are being demonstrated, the need for process control is apparent. The developments by academic groups and engineering companies to handle complex measurement data and effectively control off the model developed from these measurements is impressive. In particular, the ability to link almost any measurement to the process control system via OPC UA ADI was very impressive and allowing for acceptance of multiple PAT interfaces.

New process interfaces – like novel spectral probes, particle sizing instrumentation, etc. is allowing for more complex data to be gathered and improved process understanding – resulting in improved process control. An approach to using adaptive model control was presented and examples given where it is showing value by continuously updating the process control model as measurements are taken.

Conclusions and Action Items:

The program was again strong technically, with speakers from key, global industrial, academic, and institutional research groups. The value of creating a forum for a multi-disciplinary and multi-industry meeting was very apparent. Cross fertilization of approaches to the needs and challenges between industries was again seen as positive. Continuing with this format was encouraged, even though some suggestions on focusing on particular solutions were made. Having demonstrations of new tools and hands-on experiments was also suggested.

During this workshop there were good case studies on the progress of process optimization using PAT. New monitoring tools and data handling advances were described – along with how these could lead to improved process control tools. With these topics being presented and discussed, it would have been nice to have had more participation of end user manufacturing groups. This is particularly true for those companies who would benefit from hearing these presentations and then be able to join the discussion on how they could take advantage of the successes in this field.

The planning for the next Rome workshop will work to increase the involvement of these organizations – by addressing the cultural changes needed to recognize the value of these advances. In the words of one of our Rome workshop participants: *'Just a quick thank you for a very enjoyable and technically rich event. It was a very rare mix of pleasure and business, and an event I shall long remember. I know that there were discussions relating to increasing the attendance and I wish you well with this, but hope that it in so doing it doesn't lose it's 'flavour' or ethos'.*

The next Rome workshop is scheduled for March 23-25, 2015.

Involvement with other CPAC sponsored events was encouraged as part of the action items. Membership in CPAC is encouraged as a way to get involved in the decision making process for developments in the field of PAT and Process Optimization. In particular, CPAC has a members meeting scheduled for May 12-13, 2014 in Seattle, where research progress reports and research proposals will be presented (guest participation is possible). CPAC will also have a Summer Institute July 22-24, 2014 in Seattle with a focus on advances in technology that demonstrate process optimization possibilities.

Note: PDF versions of selected presentations are available upon request to: kochm@uw.edu.

Appendix

Data Fusion in Energy Supply: Concepts and Applications in Chemical Engineering and Catalysis

Kurt VandenBussche. UOP LLC, A Honeywell Co., Des Plaines, IL

The application of concepts like 'big data' and 'data fusion' is making headway in the energy industry and is starting to impact both the overall optimization of processes and manufacturing complexes already in operation as well as the ways we develop next generation technologies.

In this presentation, we will at first introduce the concept of data fusion and how it applies to the world of chemical conversion, discussing elements of catalysis, feed and product analysis, process control and techno-economics. A number of typical query statements will be used to illustrate the intrinsic power of processing 'big data' streams, which can often be sparse in nature.

The paper will then discuss the analytical challenges around **crude oil processing** and the associated feedstock reconstruction techniques, before moving into the characterization of petroleum processing catalysts. The impact of data fusion and sensing techniques on process design, optimization and control will be shown by means of case studies from the area of fluid catalytic cracking and Hydroprocessing of renewable and fossil feedstocks. A discussion of remote process monitoring and crude trading scenarios will conclude this part of the presentation. Similar considerations will subsequently be shown for **natural gas clean-up and conversion**, looking at the production of LNG and the impact of shale gas on the production of petrochemicals and energy.

The paper will conclude by showing an overall hierarchical approach to decision making based on various levels of data, and will introduce the topic of correlative transfer between hierarchies for further discussion throughout the meeting.

The Changing Face of Flow Chemistry: From Micro Reactors to Continuous Production

Paul Watts, Nelson Mandela University, South Africa

When micro reactor technology was first introduced it was seen as being a research and development tool suitable for small scale production. However the most topical examples discussed in the literature include the Ritter reaction performed on an industrial scale by DSM (Austria) which has to date generated over 4000 tonnes of product and the synthesis of nitroglycerine in China. The key driver in these examples being safety, where the excellent mixing and heat transfer characteristics of micro structured reactors enables these highly exothermic reactions to be safely performed.

Nevertheless there is now a plethora of commercial reactors on the market, which means that most companies are investigating this technology to rapidly screen reactions utilizing continuous flow, leading to the identification of reaction conditions that are suitable for use at a production level. Furthermore the inherent safety associated with the use of small reactor volumes enables users to employ reaction conditions previously thought to be too hazardous for use within a production environment; such as extreme reaction conditions or the use of hazardous compounds. Consequently, the types of reactions available to the R&D chemist increases through the use of this technology. It is this system flexibility that has the potential to reduce both the time taken and risk associated with transferring reaction methodology from research to production. A review of the technology will be outlined.

Analytics in Power to Gas Applications

Stefan Malcarek, Siemens, Karlsruhe, Germany

The presentation contains the operation of gas chromatography in the field of renewable energy. Renewable energy comes from resources which are naturally replenished on a human timescale (like wind or solar power) and should replace conventional fuels in different areas such as electricity generation, hot water heating or motor fuels. The main challenge of renewable energy is the fact that is not possible to store the energy effectively.

A new process called Power to Gas (PtG) is described in the presentation. This process enables the storage of energy in the form of hydrogen coming from wind or solar power. The existing network infrastructure can be utilized by linking existing power and natural gas grids. For quality control and custody transfer of newly built PtG processing plants, a new gas chromatography solution from Siemens is mandatory to determine the extended natural gas composition including hydrogen, oxygen and Helium.

Choosing the Right Reactors for the Right Reactions – Using Unique Approaches to Sampling, Sensing, and Data Handling

Peter Poechlauer, DSM, Austria

The essence of the presentation was to show the necessity of taking a holistic approach to implement intensified processes in a chemical production environment.

Not only the chemical reaction itself (starting materials, yield) determines the efficiency, but also environmental balance and ease of implementation:

It takes a strong interaction of many disciplines such as chemists, process technologists and engineers to be successful and to reach a degree of process understanding required by authorities.

The ability of this approach to respond efficiently to needs of speedy, quick, safe and affordable process implementation is elucidated by various examples.

A Case Study on the Conversion of a Batch to a Continuous Process

Vincenzo Fusillo, Atochemis srl, Italy

Microreaction technology has asserted itself as a powerful technique to conduct chemical processes, with distinct advantages in terms of purity and conversion compared to batch processes (in more and more cases nowadays).

By combining flow chemistry and photochemistry, it would be possible to explore a wider range of chemical transformations and, in some cases, this paradigm has already been demonstrated. This presentation will show examples of the approach, some of them developed within Atochemis.

Following Successful Reactions: There is a need for Separation and Purification; PAT can help

Ray Chrisman, Atochemis

This presentation describes the need for the development of post reactor unit operations to enable the implementation of completely continuous microscale processing. The justification is that a significant part of the value to be gained from converting to continuous processing such as reduced labor costs and higher quality are often lost if the whole process is not continuous. Unfortunately continuous microscale separations and purification are still not as well developed as the reactor technology. This presentation demonstrates that post reactor processing could benefit from the same increases in mass transfer and heat transfer that has benefited the reactor section. It then gives an overview of the current state of development of several of the approaches to continuous purification with techniques such as extraction, distillation, crystallization, membranes, and chromatography. It also discusses the combination of reaction and separation that is needed to achieve high levels of conversion with equilibrium reactions. Through the entire presentation it mentions the value of PAT to the various steps and demonstrates how PAT can be used to couple a group of unit operations for a much more efficient process. Finally the presentation finishes with a discussion of the need for better solids handling and describes the use of microextruders as one possible solution.

Optimal Strategies and Tools for Interpretation and Variable Selection in Spectral Profiles from Process Analysers

Olav M. Kvalheim[1], Reidar Arneberg[2,3], Olav Bleie[1,3], Tarja Rajalahti[4,5], Age K. Smilde[6] and Johan A. Westerhuis[6]

This contribution discusses various strategies available for model interpretation and variable selection in spectral profiles. Latent variable regression (LVR) modelling represents a key technology to obtain information and predictive models for continuous monitoring of composition and properties of manufacturing processes.

We discuss new tools to extract knowledge and reduce latent variable regression models in a way that meet both the claims of interpretation of models and models with optimal prediction performance. In particular, we focus on the problem of orthogonal variation for interpretation and variable selection and strategies and tools to handle this problem.

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[6]Swammerdam Institute for Life Sciences, University of Amsterdam, Amsterdam

Data Fusion and Managing Big Data from the Laboratory to Manufacturing

Martin Gadsby, Optimal Industrial Automation Limited, UK

Managing the huge data sets associated with a PAT based process system poses significant challenges, this starting in the development phase and continuing through to closed loop control during manufacturing. By using a PAT Data Manager such as synTQ all the data gathered and generated as part of your PAT system can be managed in a 21 CFR Part 11 compliant way and allow more rapid development of models and your process understanding, this leading to real time closed loop control, continuous improvement and Real time Release.

Development and Implementation of Smart Sampling Systems

Graham Johnson, Parker Hannifin, UK

Development and implementation of smart sampling systems: This presentation gives a brief introduction into NeSSI principles, then explains how Parker has designed their products to ensure full compliance with the intent of the NeSSI objectives. Parker has successfully addressed a multitude of challenging applications some of which are outside of the original design intention. In addition to this some of the latest Parker innovations are presented.

Fiber MEMS Sensors for Process Control

V. Artyushenko[1], J. Mannhardt[1], J. Suhonen[2]

Within the last 2 decades the synergy of fiber optics with UV-Vis-NIR-spectroscopy enables fast growth of fiber spectroscopy applications in lab and industry, but in a limited spectral range as silica glass fibers are transparent till 2.2-2.4µm only. The other types of Mid IR-fibers enable remote process-control for a longer wavelengths from 2 to 17µm, including "finger-print" spectral range - the most informative for molecular vibration analysis. Flexible bridge between chemical reactor and IR-spectral systems and sensors of various type (FTIR, Fabry-Perot, LED, QCL, IR-filter, etc.) can be based on Polycrystalline IR-fibers from Silver Halides, chalcogenide glass IR-fibers or hollow waveguides.

While fiber coupled spectral systems using FTIR, Diode Array, CCD or other type spectrometers are needed to monitor various reactions and to investigate different process parameters in labs, their volume application for industrial process control (even at pilot plants) is limited due to their high cost, sophisticated software and demand on highly qualified and well-trained personal. That´s why pragmatic need is growing for customized fiber spectral sensors to be dedicated for real time control of few specific wavelengths – with a simple task to keep process-parameters in so called "green corridor". Such small, robust and low cost sensors should replace expensive broad band spectral system in industrial plants. One type of such a sensor based on tunable MEMS Fabry-Perrot filters will be described.

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