CHIMIA

CHIMIA 2017, Volume 71
ISSN 0009-4293
www. chimia.ch
Supplementa to Issue 7-8/2017

SCS
Swiss Chemical
Society

SCS Fall Meeting 2017
Lecture Abstracts

Symposium on PAT & Industry 4.0

August 21-22, 2017
University of Bern, Areal vonRoll
http://scg.ch/fallmeeting/2017

Swiss Chemical Society
Haus der Akademien
Postfach
3001 Bern
Switzerland
info@scg.ch
www.scg.ch

Symposium on PAT & Industry 4.0

T. Merz[1]

[1]Head of Process Analytical Technology, Lonza Ltd., Lonzastrasse, CH-3930 Visp

Process analytical technology (PAT) has been demonstrated as one of the key driver for the future plant automation. More and more smart sensors will be analyzing the critical quality attributes of your product and critical asset performance indicators will provide you a clear picture of your over-all plant fitness. All the collected information could result into a real-time release or “lights-out” manufacturing strategy. For the first time, the Swiss PAT community will meet on the SCS Fall Meeting.

The following companies generously sponsor this first edition of the PAT symposium

http://fm17.chemistrycongresses.ch/program/pat

Sensor Roadmap 4.0 – Prospects towards a uniform topology for process control and smart sensor networks

M. Maiwald[1], P. Gräßer[1], L. Wander[1], S. Guhl[1], K. Meyer[1], S. Kern[1]

[1]Bundesanstalt für Materialforschung und -prüfung (BAM), Richard-Willstätter-Str. 11, D-12489 Berlin, Germany - michael.maiwald@bam.de

Smart functions of sensors simplify their use and enable plug-and-play, even though they are more complex. This is particularly important for, self-diagnostics, self-calibration and self-configuration/parameterization. Intelligent field devices, digital field networks, Internet Protocol (IP)-enabled connectivity and web services, historians, and advanced data analysis software are providing the basis for the future project “Industrie 4.0” and Industrial Internet of Things (IIoT).

Important smart features include connectivity and communication ability according to a unified protocol (OPC-UA currently most widely discussed), maintenance and operating functions, traceability and compliance, virtual description to support a continuous engineering, and well as interaction capabilities between sensors. This is a prerequisite for the realization of Cyber Physical Systems (CPS) within these future automation concepts for the process industry. Therefore, smart process sensors enable new business models for users, device manufacturers, and service providers.

The departure from current automation to smart sensor has already begun. Further development is based on the actual situation over several steps. Possible perspectives will be via additional communication channels to mobile devices, bidirectional communication, integration of the cloud and virtualization. The integration of virtual runtime environments can provide a more flexible topology for process control environments.

The talk summarizes the currently discussed requirements to process sensors 4.0 [1] and introduces an online NMR sensor as an example, which was developed in the EU project CONSENS [2,3].

[1] Technologie-Roadmap 4.0 – Voraussetzungen für die zukünftigen Automatisierungskonzepte, Herausgegeben von VDI/VDE-Gesellschaft Mess- und Automatisierungstechnik (GMA) und NAMUR – Interessengemeinschaft Automatisierungstechnik der Prozessindustrie, Düsseldorf, November 2015.
[2] K. Meyer et al.: Process control with compact NMR, Trends in Analytical Chemistry 83 (2016), 39–52
[3] CONSENS – Integrated Control and Sensing for Sustainable Operation of Flexible Intensified Processes, funded by the European Union’s Horizon 2020 research and innovation programme under grant agreement N° 636942; www.consens-spire.eu

Machine Learning and Chemometrics: A contradictive approach or a good complement?

F. Westad[1]

[1]CAMO Software AS, Oslo, Norway - fw@camo.com

One can hardly read the news these days without reading articles about how Big Data, Artificial Intelligence and Machine Learning are changing the world, the term disruptive technology is often used. How does this relate to the PAT community, product and process development and real-time process control? Obviously, computers can perform many tasks more efficiently than humans, e.g. searching through millions of records and looking for patterns. One frequently mentioned example is within medical diagnosis where scientific literature, patient journals and laboratory results are combined for diagnostic purposes where computers do it better than humans, who have difficulty in accessing and assessing all this information. Other examples are the ability to predict personality based on like-clicks on Facebook or to suggest travel destinations by analysing previous travel patterns and bookings. All these applications have thousands or millions of objects, which enables various algorithms to find patterns for classification purposes by use of deep learning. On the other side, the challenge within PAT is mostly that the number of *objects* is the limiting factor. How to we sample from our system to generate a good basis for the models with a minimum of effort? One example is prediction of the moisture content in lyophilisates directly through the glass vials with a required prediction uncertainty of < 0.2%. The models to be used within the PAT framework need to be applied on the *individual* object (sample) and a statistical significant correlation is not sufficient in itself: With enough objects, any pairwise correlation will be significant; however the important aspect is the *relevance* given the actual application.

Another important aspect is interpretation. The methods we use for exploratory data analysis, classification and prediction must be interpreted with the user's domain specific knowledge in mind. Therefore, human interaction in the modelling phase is mandatory. One reason is to prevent the inclusion of indirect correlation to make the model "better". These correlations may hold for the objects that were chosen to build the model but not for the future. Another reason is the need to set up the correct validation scheme for validating the model to account for future uncontrollable sources of variation such as raw material supplier, particle size, season, instrument etc. In most practical applications there will always be subgroups of objects in our data tables which invalidates the common procedure of splitting the objects 100 times randomly into calibration and test sets 60/40 [1]. When this is said, as long as the models can be interpreted and validated in the correct manner, there is no conflict between machine learning and chemometrics.

[1] F. Westad, F. Marini, *Analytica Chimica Acta*, **2015**, vol. 893, pp. 14-24.

Technological Challenges in the Production of Biopharmaceuticals

H. Engelking[1]

[1]Lonza Ltd., Rottenstrasse 6, 3930 Visp, Switzerland - Helge.Engelking@Lonza.com

The process development and custom manufacturing of biopharmaceutical products faces not only many regulatory challenges. In addition customer expectations to fulfil quality targets and to improve cost efficiency are increasing. Due to customer needs and increased regulatory requirements new approaches in process development and manufacturing are required. Concepts like "Quality by Design (QbD)", "Process Analytical Technology (PAT)", "Real Time Release", and “High Throughput Screening" are reflecting the cultural change in the industrial world.

Increasing process understanding, reducing process variation and thus increasing the product quality and reducing the production costs are the common goals of all these approaches. All these strategies rely on an increasing demand for data collection, storage, and analysis. Visualization and trending should ideally be performed real-time to allow immediate reaction on process shifts, trends or deviations.

A process for a recombinant protein for pharmaceutical applications will be used as an example to illustrate the different expectations in process development and production. The focus will be on the data management and analysis applied in both areas and different solutions will be outlined and discussed.

From process understanding to manufacturing process control with PAT

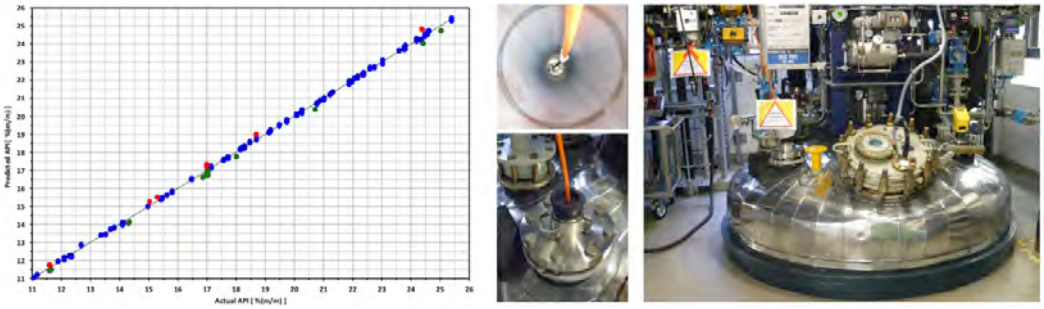
C. Lautz[1], M. Betschart[1]

[1]F. Hoffmann-La Roche Ltd, CH-4070 Basel - christian.lautz@roche.com

In an early phase of drug substance development, Process Analytical Technology (PAT) tools can help to generate deeper process understanding by real-time insight into chemical processes. With a maturing project and its improved process chemistry, some of the PAT tools applied in laboratory may be used on scale-up and transferred to pilot plant or even full-scale manufacturing.

The requirements and demands for PAT applications grow with the projects, regarding their ruggedness as well as all aspects of technical and GMP compliance.

The presentation will focus on current examples from Roche Small Molecule Development and Manufacturing, covering the range from laboratory PAT experiments for increased process understanding and troubleshooting to fully validated spectroscopic GMP applications substituting classical chromatographic in-process samples.



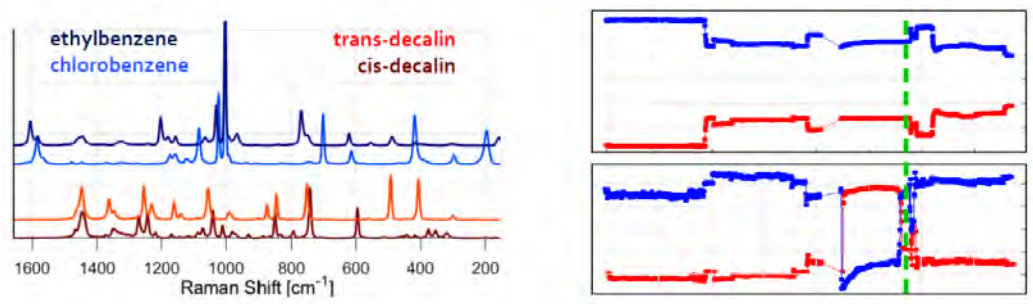
Real-time Insights: Inline Raman monitoring of distillation columns

C. Minnich[1], C. Uerpmann[2]

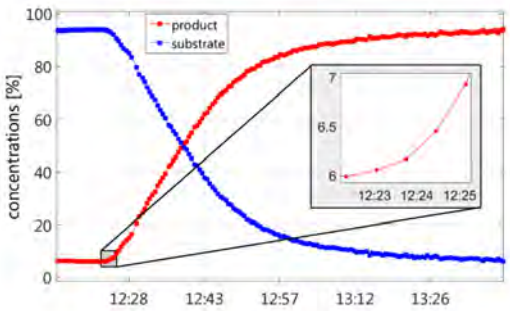
[1]S-PACT GmbH, Burtscheider Str. 1, 52064 Aachen/DE - clemens.minnich@s-pact.de, [2]Kaiser Optical Systems S.a.r.L., 16 rue de Lombardie, 69800 Saint-Priest/FR

Process Raman spectroscopy was successfully employed for the monitoring of both batch and continuous distillation processes in pilot and production scale. Fibre-coupled immersion probes were mounted inline, i.e. into the condenser/boiler reflux or into the transfer lines towards the downstream processing units. Recorded spectra were immediately subjected to quantitative analysis in order to calculate real-time mixture composition for monitoring and control purposes. An inline method like Raman spectroscopy avoids external sampling which can be detrimental to the analysis e.g. of high-melting liquids or volatiles and supports optimal operation of the plant.

The separation capacity of columns is typically determined in steady-state operation. Isomer mixtures typically employed for the characterisation of columns are well resolved with Raman spectroscopy (e.g. cis-/trans-decalin, left image) and allowed for the detection of concentration changes below the 0.5 % level e.g. in feed or load changes (right image, condenser and boiler).



In batch distillations, finding the optimum point for the fraction change is typically the optimisation target. The short response time of Raman spectroscopy (here ~40 sec) allowed to reliably identify this point so that cross-contamination of the product fractions could be avoided.



Our presentation will discuss the approaches to address the specifics of the two applications and give recommendations for the use of Process Raman spectroscopy to similar processes.

Online Proton-transfer-reaction and Resonance-enhanced multiphoton ionization mass spectrometry for monitoring the coffee roast process

S. Opitz[1], M. Wellinger [1], S. Smrke[1], C. Yeretzian[1]

[1]Institute of Chemistry and Biotechnology, Zurich University of Applied Sciences, Einsiedlerstrasse 31, 8820 Wädenswil, Switzerland) - opit@zhaw.ch

Coffee is one of the most traded commodities and is one of the most consumed beverages worldwide with an estimated coffee consumption of 4 kg per capita in Switzerland. Coffee, e.g. Arabica coffee (*Coffea arabica*) is harvested and processed in the origin countries to produce the green beans. The roasting process transforms then the green beans into roasted coffee and thereby producing a drinkable product. Coffee roasting itself is an extremely complex chemical and physical process leading to the formation of a large number of (semi)volatile organic aroma compounds. However, the dynamics and mechanisms of these formation processes are not completely understood and specific characteristics of the roast process such as the actual roast degree are often determined empirically or based on individual experience. Hence, on-line monitoring of the roasting process is important to understand the underlying chemical reactions and to ensure an optimum product. Direct mass spectrometry applying soft ionization techniques is a powerful method to study the roast process in real time. We have applied direct mass spectometry to coffee roasting in the form of proton-transfer-reaction mass spectrometry (PTR-MS) and photo-ionization time-of-flight mass spectrometry (PI-TOF-MS).[1]

On the one side we used PTR-ToF-MS, where we sample and analyse the roast gas and with it the produced volatile organic compounds (VOCs). This is an indirect method, which allows the real-time monitoring of the formation pattern of important coffee aroma compounds along the roasting process. By varying the time-temperature roasting parameters (roast degree and length of roasting process) as well as the coffee species and coffee origin reveals then changes in the coffee flavour formation: (i) different VOCs were formed differently while roasting the same type of coffee along the same time-temperature roasting profile, (ii) these formation pathways changed when changing the time-temperature roasting profile, and (iii) roasting different coffee origins led to different flavour formation pathways for the same VOCs. From a technical perspective, this study underlines the importance of taking into account the roasting parameters like flow of hot air for the different roaster configurations. A proper normalization of the VOC intensities with the flow parameters, pressures and temperatures is indispensable for a comparison of VOC formation between different roaster configurations.

A different way to detect VOCs can be carried out be resonance-enhanced multiphoton ionization time-of-flight mass spectrometry (REMPI-ToF-MS). Photo-ionization was employed to investigate more fundamental questions to examine chemistry and kinetics of VOC formation in individual single coffee beans.[2] The observed chemistry in single bean experiments reflects bulk roasting processes well, thus both approaches, PTR and PI, may be combined to improve the understanding of the chemical mechanisms during coffee roasting. This approach takes into account that the integrity of individual beans plays a decisive role for the formation of coffee flavour.

[1] Biasioli, F.; Yeretzian, C.; Gasperi, F.; M„rk, T. D., PTR-MS monitoring of VOCs and BVOCs in food science and technology. *Trends in Analytical Chemistry* **2011,** *30* (7), 968-977.
[2] Hertz-Schönemann, R.; Dorfner, R.; Yeretzian, C.; Streibel, T.; Zimmermann, R., On-line process monitoring of coffee roasting by resonant laser ionisation time-of-flight mass spectrometry: bridging the gap from industrial batch roasting to flavour formation inside an individual coffee bean. *Journal of Mass Spectrometry* **2013,** *48* (12), 1253-1265.