Overview of the intended topics and presentations for The CPAC Rome Workshop 2020

The meeting was cancelled with the sentence below which unfortunately turned out to be a very appropriate decision

“At extensive discussions and assessment of the impact of the COVID-19 virus, we regret that the CPAC Rome Workshop, March 23-25, 2020 is postponed until March 22-24, 2021.”

However, given the exceptional strength of topics and speakers scheduled for the meeting it was decided to prepare an overview of the intended meeting based on abstracts and available slides to help encourage dialogue and interactions in these important areas. As a reminder the workshop focus is noted below and expanded on in the overview and theme statement.

Utilization of New Concepts in Supporting the Demand for Sustainable Materials by Developing Next Generation Materials, as well as Exploring New Reaction Routes that Benefit from the Growing Use of Continuous Flow Monitoring and Control Technology

Overview and Workshop Theme: A key enabler of the move to a Circular Economy will be process intensification which offers sustainable processing of lower volume distributed waste streams to generate a broad range of new platform chemicals including a growing list of biomass mass derived molecules. Using new catalysts for one pot syntheses and cascade chemistries, these new starting materials including nanomaterials are being converted to a range of new composites and materials with advanced properties. The 2020 Rome meeting was to build on this theme of sustainable production and focus on next generation materials. In addition, there was to be an emphasis on exploring new reaction routes that benefit from the growing use of continuous flow technology and effective monitoring and control concepts. The evolution of flow microscale reaction technology has led to a wide range of process intensification developments in the various steps that result in the ability to rapidly evaluate and optimize new reaction routes as well as offering more cost-effective processing. The key next step is the integration of these unit operations into end-to-end optimized continuous processes.
The Draft Program for the canceled CPAC Rome Workshop and an attendee list is attached – showing the diverse gathering of disciplines and countries that were planning to participate.

The meeting would have started with a review of the 2019 meeting which catalogues the progress documented in the meeting relative to flow chemistry development in various processing areas with goals, achievements and future needs. The general importance of flow chemistry was highlighted in one presentation that noted the International Union of Pure and Applied Chemistry (IUPAC) on April 1 2019 released their "Top Ten" List of emerging technologies that will contribute to the well-being of Society and the sustainability of Planet Earth in the 21st century (https://bit.ly/2HYAsSu). Flow chemistry is highlighted as critical technology to achieve the United Nation’s Sustainable Development Goals (SDGs) by 2030, for tackling SDG12: responsible consumption and production (https://bit.ly/2WM0mfk).

Continuous processing is cited as, among other things, minimizing the risk of handling hazardous substances and increasing productivity, both preventing harm and lowering the environmental impact. If you want to learn more about "why flow means green", in particular in the context of manufacturing pharmaceuticals, check out this recent review article: https://bit.ly/2VmbDD5.

The 2020 meeting was organized around several general concepts to insure broad coverage of the meeting theme. These themes were:

- **New Global Concepts that will Require Next Generation Processes and Approaches that will Facilitate Them**
- **Continuous Production for the Efficient Production of Complex Molecules**
- **Developing Process Understanding to Enable the Integration of Multiple Unit Operations for Continuous Processing**
- **Bio-based Projects as part of the path to a Circular Economy**
- **Solution Providers - Advances in Analytical Technologies and in Process Control**

In the first concept, **New Global Concepts that will Require Next Generation Processes and Approaches that will Facilitate Them**, there was a challenge. The general need for new concepts in manufacturing, and as importantly the way business is done, was rather forcefully demonstrated by Harald Sverdrup, University of Iceland and Norsemetal, Norway in a presentation titled **The Challenge of the Circular Economy, New Thinking in Product Purpose, Their Development and New Ways of Production**. His talk was to develop the argument that problems become opportunities for new thinking in product development and new approaches to production.
As Professor Sverdrup was to point out in his presentation the move to a sustainable circular economy will require new more efficient processes since energy is used and waste is generated in any production process. In additional, new materials are needed to increase the usable lifetime of manufactured products. Many of the presentations listed below are based on developing new more efficient processes as well as new more sustainable high performance materials. While these advantages will facilitate moving to a sustainable circular bioeconomy, they are not always noted in the short descriptions included in this overview. However it was a driving force for much of the work that is described and it is left to the reader to make the connection.

The next presentation was to describe a powerful new application of continuous sensing and control for the medical treatment field. *The Importance of Multiple Sensors in Evaluating Personalized Medicine*. It was based on a review article and presentation prepared by Babatunde A. Ogunnaike, University of Delaware, USA. It was then modified by Ray Chrisman, MK Optimization and Control LLC, USA, to include an expanded section on how the use of smart sensing as developed for process operations can provide significantly more information to process models by using the pattern of data from groups of simple sensors. This is particularly important where current treatment information comes from infrequent invasive sensing. It was to be pointed out that each individual is different and that extensive real time data that can be fused for more reliable information would provide better information about how an
individual is reacting to a medical condition and then in real time track the response to treatment. An example of a blood disease demonstrated that not only is real time response data needed but also multivariate process models are needed to characterize how a patient is responding such that an optimized treatment becomes possible long before more serious complications can develop. The data showed that multiple life processes must remain in balance for effective control and that without good data to moderate drug impacts it is impossible to have an effective treatment program at least for this blood disease.

The next general concept **Continuous Production for the Efficient Production of Complex Molecules** was going to be demonstrated in several presentations.

The first was an update on the ongoing efforts of Frank Gupton’s research group at Virginia Commonwealth University, USA to dramatically reduce the cost of API’s by the use of new processing strategies for continuous production. His presentation was titled, **The Medicines for All Institute – Program Overview.** In his presentation he was to describe the basic concepts of the program and through the use of examples demonstrate the power of the program. The key first point is that access to global public healthcare is impacted by many technical, economic, and social factors since it is widely recognized that the resources required to deliver and improve global public health are currently constrained. A powerful way to increase access is to lower the cost of products and services that have already proven to be effective. Currently, the cost of producing a wide range of pharmaceutical products is higher than it needs to be. The mission of Medicines for All (M4All) is to transform active pharmaceutical ingredient (API) processes in order to reduce medication cost and improve patient access. To fulfil this objective, M4ALL has developed a set of core principles for API process development, which are derived from fundamental elements of process intensification. These principals are commonly known but often neglected. They have applied these principles to the preparation of several global health drugs yielding dramatic improvements in chemical efficiency. The development of novel and highly efficient heterogeneous catalysts for cross-coupling reactions that support this effort will also be presented.
The next presentation was to be focused on the major problems related to the cost of API’s in Africa. In his presentation *Process Intensification for API Synthesis in Africa Exploiting Continuous Manufacturing* Paul Watts Nelson Mandela University, South Africa planned to demonstrate the critical need to develop new much lower cost reaction routes for active pharmaceutical ingredients, API’s. After pointing out the almost overwhelming needs in Africa for much lower costs API’s to insure access to effective treatment Paul then intended to demonstrate several new multi-step synthetic routes for complex API’s. His approach is based on developing efficient new routes which can be coupled to enable more cost-effective production. The developed and evaluated routes demonstrate that it should be possible for API’s to be manufactured with much lower costs in Africa. The presentation planned to include examples in the area of AIDS, TB, and malaria.

The research group of Claude de Bellefon (Camille Méhault, Laurent Vanoye, Régis Philippe, Claude de Bellefon) Laboratoire de Génie des Procédés Catalytiques, Lyon – UCBL, France; was to deliver a presentation by Camile Méhault on *Could We Do More With Segmented Flow?* Gas/Liquid and Liquid/Liquid segmented flows have been widely investigated in the literature and have been identified as promising tools for process intensification. Indeed, segmented flow is characterized by high mass transfer efficiency due to high interfacial area and recirculation motions within the liquid slugs. In recent years, more complex multiphasic segmented flows have been explored. Examples of phase combination include Gas/Liquid/Liquid, Gas/Liquid/Solid, and Liquid/Liquid/Solid, with suspended solid particles inside the liquid slugs. Such diversity of multiphasic flows could have many applications for chemical reactions or material synthesis. As a practical example they demonstrated, in a Gas/Liquid/Liquid flow, gas/liquid reaction can be combined directly with the extraction by the second liquid phase.

To develop further the use of complex multiphasic segmented flow, a case study was conducted on a two-step cascade reaction where the two steps are both made in aqueous solutions but with incompatible catalysts. To perform the cascade reaction in flow, multiphasic segmented flow called the *alternated segmented flow* was developed (Figure 1a and b). The idea is to generate two aqueous droplets corresponding to the two mixtures used for each step. These two aqueous compartments

![Diagram](image1.png)
would be separated by an organic inert phase that would allow intermediate B to transfer. In the literature a few publications can be found on the formation of Aq./Aq./Org alternated segmented flow. However, no work has been done on how to maintain the alternated segmented flow for a long residence time (compatible with chemical applications) without having coalescence of aqueous droplets. The aim was therefore to develop such an operational flow system capable of performing the described cascade reaction by developing injection devices (Figure 1c and d) and a stabilization method.

Ernie Hillier, EH Consulting (former Waters Associates), USA was to present a more general overview of the needs for continuous processing in the pharma industry in a presentation titled **Liquid Chromatography Advances to Enhance Continuous Manufacturing**. In it he planned to note that over the past 15 years with guidance from the FDA regarding QbD, PAT, and Continuous Manufacturing (CM) the use of CM is rapidly growing within the Pharmaceutical and Biopharmaceutical industry. His discussion was to focus on an overview of CM with regards to the benefits and needs for the industry to implement this game changing direction. He planned to include examples of major companies that have deployed CM and incorporated advances in Liquid Chromatography PAT into their long-term business strategy. A summary overview of the benefits of CM to the company, to the patient, and to mankind was to be included.

The next general concept of the theme of the meeting was; **Developing Process Understanding to Enable the Integration of Multiple Unit Operations for Continuous Processing**.

In her presentation in this section Amanda C. Evans, Los Alamos National Laboratory, USA was to demonstrate the production of new and better rocket fuels in **“The Power of Being Resourceful: Continuous Flow Biocatalysis Manufacturing Approaches for the Synthesis of Green Propellants”**. She was to point out the problems with the current fuels containing hydrazine and state that alternative propellant fuels for powering satellites and spacecraft offer greener and safer solutions that are more energetically dense and less expensive. Additionally, on-demand manufacturing approaches for green propellants could eliminate the need to stockpile and transport dangerous chemicals like hydrazine. This research deploys continuous flow biocatalysis approaches for making a key green rocket fuel from common biowaste starting materials.

Flow technologies have inherently homogeneous mixing and temperature control and scalability. This makes them ideal for the production of materials which may present a range of
structures dependent on the precise production conditions. Great opportunities of flow environments include non-invasive access to detailed monitoring of transient events in situ. When it comes to the active precipitation of solid materials in flow environments, there are however unique challenges to be addressed such as suspension and mixing of solids, blockages and encrustation. Karen Robinson of Nottingham University, UK was to present a talk on Flow Crystallisation: Controlled Self-Assembly and in situ Structural Analysis. A range of flow crystallisers was to be presented to address the challenges of flow synthesis and crystallisation showing how each apparatus can provide control on different scales (crystallisation time and resultant particle size). By employing these crystallisers they have exacted control in terms of polymorphic purity, crystal size and shape for organic materials (pharmaceuticals), discrete organometallic complexes and coordination polymers (spin-crossover materials). Using in situ structural analysis (powder and single crystal X-ray diffraction and Raman spectroscopy), they follow what is crystallising as it is crystallising enabling further understanding and control of the crystallisation process, uncovering polymorphic transitions and verifying relative polymorphic stabilities.

Timothy Noël of Eindhoven University of Technology, Department of Chemical Engineering & Chemistry, Micro Flow Chemistry & Synthetic Methodology, The Netherlands planned to address the advantages of flow technology in his presentation, Innovation in Synthetic Methodology through Use of Flow.

Until recently, many reactions have been exclusively performed in conventional batch LabWare. With the advent of microreactor technology, significant effort has been devoted to developing a wide variety of continuous-flow techniques to facilitate organic synthesis. Microreactor technology offers several advantages compared to traditional batch reactors, such as, enhanced heat- and mass-transfer, improved irradiation, safety of operation and the possibility to integrate several reaction steps and subsequent separations in a single streamlined process.

His group has taken a great interest in assisting chemists by developing automated and flow-based reaction technologies capable of reducing manual labor, increasing the reproducibility of the results and accelerating reaction discovery. In this presentation, he was going to give an overview of their synthetic methodology development, exemplified by photoredox catalysis, C–H activation chemistry and electrochemistry and how these synthetic methods were impacted by continuous-flow microreactor technology. Furthermore, he was going to discuss the developed technology and reaction models in detail.
C. Oliver Kappe, University of Graz and Research Center for Pharmaceutical Engineering GmbH (RCPE), Austria planned to present their new approach to gathering process analytical information for the needed process understanding for continuous production. His presentation Integration of PAT Tools in a Modular Flow Platform for the Monitoring and Optimization of Multistep Reactions demonstrates the complementary capabilities of three different analytical techniques within a highly modular microreactor system. Thus, in-line infrared (IR) spectroscopy, in-line nuclear magnetic resonance (NMR) spectroscopy and on-line ultra performance liquid chromatography (UPLC) have successfully been combined and integrated for control and monitoring. Although the system is based on the “plug and play” principle, which allows configuration of different flow setups within minutes, they showcased the initial setup using a multistep organometallic reaction, the likes of which are often problematic in flow (Fig. 1). This approach has the potential to be utilized for self-optimizing reactions or self-controlling systems in which machine-learning will play an important role for the development and improvement of models.

Richard A Bourne at the University of Leeds, UK based at the Institute of Process Research and Development (IPRD,) was planning to present a talk on the Rapid Optimisation of Pharmaceutical Processes Using Automated Systems that was focused on the development of automated continuous flow systems. In particular, recent research on self-optimising systems where the reactor and its process control instrumentation become an autonomous industry 4.0 unit into which the reactants are pumped, and from which products emerge with optimized processing conditions. The presentation planned to outline the recent grant ‘Cognitive Chemical
Manufacturing’ and the new approaches to synthesis of fine chemicals and pharmaceutical compounds. These automated systems work without human intervention and are capable of very robust experimentation and rapid optimisation of challenging processes. This talk was also going to describe optimisation of multiple unit operations including optimisation of telescoped reactions and reactions followed by continuous work-up.

The general theme of **Bio-based Projects as Part of the Path to a Circular Economy** is addressed in the next section. The appreciation of the value of using bio-based materials as the source of raw materials is a key to future developments of building blocks for new materials of the future.

Advanced processing ideas to handle the challenges of moving to a sustainable economy were to be presented by Ludo Diels, VITO/Universiteit Antwerpen, Belgium, **The Role of Lignin as a Sustainable Replacement for Fossil-Based Aromatic Chemicals.** Aromatics are among the most important resources for the chemical industry. Many (especially construction and long lasting) materials are made from aromatics and lead to higher or better performance. However in some cases safety or toxicity is still an issue (e.g. bisphenol A). Brand owners are on the search for more sustainable molecules (e.g. bio-based), but also for safer materials of higher performance. In addition, the concept of circularity plays an increasing role in the effort to replace petrochemicals. Currently virtually all aromatic building blocks are made from fossil oil. His presentation described the anticipated growing shortage of aromatics from the petrochemical industry and the widely shared ambition to green the chemical industry. His lecture was to give an overview of the problems linked to wood-based refineries and the availability of lignin sources. Next, it planned to give an overview of the different approaches worldwide to valorize lignin and to produce bio-based aromatic molecules. It intended to indicate the hurdles, challenges and needs for value chain approaches. However, in order to use lignin, one of the big problems is its low reactivity, high polydispersity and heterogeneity which make it not very manageable. Efforts to fractionate, activate or depolymerize are under way by different consortia in order to solve these problems. In this respect, cost-effective downstream separation and purification processes are of utmost importance as well. State of the art of all these processes was to be presented with special attention to the future markets and applications. A large part of the work is done via the shared research center Biorizon. If interested you can join the community at: [www.biorizon.eu/community](http://www.biorizon.eu/community).
Giancarlo Cravotto Dipartimento di Scienza e Tecnologia del Farmaco and NIS–Centre for Nanostructured Interfaces and Surfaces, University of Turin, Turin, Italy, planned to describe a new range of heterogeneous catalysts in his presentation, **Cyclodextrin-Based Heterogeneous Catalysts in Batch and Continuous Flow Synthetic Processes**. In the last decade several authors reported catalytic applications of heterogeneous systems based on cyclodextrins (CDs). Heterogeneous catalysis is driven by surface phenomena and the contact between insoluble CD derivatives (complexes, supramolecular aggregates, self-assembling systems, polymers, micelles and hybrid materials) with the reacting solution. The role of CDs in catalytic systems is manifold in particular in organometallic reactions. Catalytic process intensification requires suitable reactors and conditions to promote the reaction steps of diffusion of the substrates on the catalyst surface, physical adsorption, chemical reaction at the surface, and desorption of the reaction products. Owing to the enhanced stability for reaction conditions for CDs, the amplification of reaction condition by the application of microwaves, ultrasound, hydrodynamic cavitation, ball milling, or flow reactors, enables faster and more efficient conversions. These fast-paced developments have provided valuable insights in the preparation of novel high-performance CD-based catalysts. Robustness, high selectivity, and easy scalability are the key demands for potential industrial application. His research group has developed the enabling technologies in green synthetic processes widely applied in CDs chemistry. They prepared several CD-based heterogeneous catalysts following different strategies: i) nano-dispersed metal cross-linked CDs (mono- or bimetallic); ii) metal-loaded CDs-grafted silica hybrid catalysts; iii) CD-grafted activated carbon (TiO₂, Ag doped). Solid supported Pd and Cu nanoparticles have been efficiently prepared and their homogeneous distribution was demonstrated by TEM and SEM analysis. These recyclable nanocatalysts combine the advantages coming from both, homogeneous (for selectivity and high yields) and heterogeneous catalysis (for easy catalyst recovery and negligible metal leaching).

The next presentation in this section was to be by the research group associated with Maurizio Galimberti (Vincenzina Barbera, Daniele Locatelli, Fatima Margani, and Lucia Rubino) Department of Chemistry, Materials and Chemical Engineering, Politecnico di Milano, Italy entitled, **Multifunctional Biosourced Ingredients for Elastomer Composites with Low Dissipation of Energy**. Their focus was to be elastomer composites which are fundamental materials for many key products. Applications such as compounds for tires (car, heavy trucks, airplanes), anti-seismic base isolators and anti-vibrating pads are highly demanding and can be satisfactorily obtained only with elastomers, i.e. with polymers with a molecular structure suitable for the entropic elasticity. However, elastomers are not enough. Composites have to be prepared, loaded with reinforcing fillers and with a considerable number of other ingredients: coupling, crosslinking, anti-aging, and processing agents. It would be highly desirable to develop new families of ingredients for elastomer composites, ideally from bio-sources, which are multifunctional and suitable to reduce the environmental impact of the final product. The
Objective of this work was to design and develop multifunctional ingredients for elastomer composites. In particular, multifunctional coupling agents are presented, suitable to promote chemical bonds between elastomer chains and both inorganic oxide and hydroxides and sp 2 carbon allotropes such as carbon black, carbon nanotubes and graphene and the related materials. These ingredients can play further roles, such as accelerators in sulphur based crosslinking. Moreover, they promote lower environmental impact during composite preparation and in the final application of the product. Such ingredients can be prepared from basic biosourced building blocks such as glycerol and glucose. Preparation of the ingredients, scale up of the synthesis, and then preparation and characterization of the composites were to be presented.

The last presentation is this general theme area was by the team of Giuseppe Ciccarella, (Department of Science and Technical Biology and The Environment, University of Salento, Italy) and selected Italian researchers and government officials (F. De Castro, F.P. Fanizzi, M. Benedetti, G.M. Balestra, A. De Stradis, G.P. Suranna, E. Dongiovanni, F. Piacente, F. Baldassarre, L. Faifer, D. Bonassi, A. Truppi, C. Loporto, M. R. Taurino, M. Stefanelli, C. Giliberti, F. Mottola, A. Rollo, F. Manzari, G. Brillante). The presentation was to be focused on solving the challenges described in the title The DEMETRA Project: Design and Testing of Innovative Technologies for the Early Diagnosis and Treatment of Olive Quick Decline Syndrome (OQDS). They have been focused on a problem that has been getting worse in recent years due to climate change and globalization which seem to have encouraged the spread of different plant pathogens in Italy as well as globally, causing serious economic damage to agriculture. In particular, the Puglia Region has recently been a protagonist due to the spread among the olive trees of the pathogen Xylella Fastidiosa, the causative agent of the Olive tree Quick Decline (OQDS).

In this context, the present project is centered on the testing of new technologies for early diagnosis and nano-technological phytotiatric treatments for OQDS. The project activities include the production of different nano-formulated agrochemicals. The goal is to obtain phytoterapeutic protocols for OQDS characterized by the application of nano-structured products with high bioavailability, controlled release over time, maximum effectiveness and low environmental impact. The effective fight against the pathogen also presupposes the need to detect its presence from the early stages of the disease. The approach chosen for early diagnosis is that of metabolomics, that is, the study of small molecules expressed by the target pathogen or by the plant itself following the triggering of the defense response. The detection of metabolites allows the presence of the pathogen to be identified even in the initial stages, regardless of the area of the plant sampled, minimizing false negatives. Previous research activities have allowed the development of the new analytical method. The planned testing activity will allow the evaluation of the official method certification conditions.
The last general theme of the meeting was, Solution Providers - Advances in Analytical Technologies and in Process Control. This is the section where advances in technology are presented – that will enable the progress required to reach our goal of a sustainable circular economy. Less waste, more efficient energy, improved cost, etc. are the main metrics of proceeding on this course.

In his presentation Viacheslav Artyushenko Art Photonics GmbH, Berlin, Germany was planning to describe, Fiber Solutions in Life Science & Process Control. He planned to point out that there are several key spectroscopy methods: absorption, reflection, fluorescence or Raman scattering, - which can be selected to monitor media composition in chemical reactions or medical diagnostics. Fiber optic probes enable remote monitoring, in real time and under harsh conditions in industry: with toxic or aggressive reagents, at high or low temperature/ pressure, under vibrations, in electromagnetic field, etc. In addition, medical diagnostics needs very tiny, highly flexible and biocompatible spectral probes of low cost – to use them in endoscopes. To compare all the positive and negative features of the 4 different spectral methods the R&D Multi-Spectral Fiber (MSF-) System was made for a very broad spectral range: 400nm to 16μm, - and then it was tested to select the best methods based on sensitivity, specificity and accuracy. When there was no single outstanding method found - then 2 or 3 methods have been united in one combi-fiber probe to enable the synergistic fusion of multi-spectral data. This approach enables finding the most sensitive and precise way to control process parameters on-line or even in-line. Experimental test of the MSF-system made for the selected process provides double benefit: a) selection of the best method from trials of all of them and b) good basics in design of the customized Spectral Fiber Sensor (SFS) for process control. The difference between the MSF-system dedicated for R&D testing using 4 spectral methods in a broad spectral range and the SFS-concept is to use only a few of the most information rich spectral features – with the consequent substantial cost and size reduction. At the same time the SFS customized for a selected process will use the best method or an optimal combination of methods to enable the use of SFS with an LAN or VLAN data transfer to process-cloud. This IoT concept allows the use of multiple SFS in all critical points of any reactor or plant and enables fully automated process control to increase yields, to reduce risk of malfunction and reduce cost of service, while improving product quality.

There was going to be a presentation on Raman Spectroscopy for Bioprocesses: How Hardware, Sampling and Data Analysis Decisions Drive Success by Brian Marquardt of MarqMetrix and CPAC, University of Washington, USA. This presentation was to focus on the practical aspects of applying Raman spectroscopy for the measurement and control of biological processes. A successful application of Raman starts with selecting the correct hardware for the required application and measurement. Selection of the system laser
wavelength, spectral range and detector response function was to be covered. Other factors such as system temperature and intensity stability were to be discussed with regards to calibration and model transfer. Once the hardware system has been determined the next and probably most critical decision is determining the correct sampling interface for the application. The correct sampling interface drives both the capability and reproducibility of the Raman system for accurately measuring the bioprocess attributes. This is especially true in many bioprocessing applications where the sample is heterogeneous. The final consideration is the modeling approach to take with the bioprocess Raman data. The discussion was to include effective data pretreatment algorithms, best modeling approaches to determine both consumption of reactants and formation of products and how to use the information for improved process understanding and control.

The presentation from the group, Sophia Fricke, Matt Augustine, and Mike McCarthy at the University of California, Davis, USA Portable, Low Field NMR for Industrial Applications: The Next Generation demonstrated recent technological advancements have now made portable nuclear magnetic resonance (NMR) spectroscopy economically and practically feasible. The ease with which it can be customized to address unique problems makes portable NMR an extremely desirable analytical technique. A selection of case studies was to be explored to demonstrate its widespread utility to study a variety of systems. The studies have a unified focus of improving portable, low field NMR from the standpoints of data processing and theory, as well as broadening its immediate applications in industry. Special emphasis was to be given to areas of industry with high economic impact, such as agriculture, medicine, and materials chemistry. This is particularly important given the need to utilize highly variable biomass to achieve the goals of the circular bio-economy. Sarah E. Prebihalo, and Robert E. Synovec University of Washington, Department of Chemistry, USA were to describe another powerful process characterization technique in their presentation, Comprehensive Two-Dimensional Gas Chromatography Coupled with Time-of-Flight Mass Spectrometry (GC×GC-TOFMS). The system is a powerful instrumental platform capable of separating complex mixtures. Due to the enhanced peak capacity provided by a second separation, highly dimensional, GC×GC-TOFMS is more frequently being used for the discovery of biomarkers in samples of biological origin such as human plasma. To date, analyses of large sample sets have been hampered due to shortcomings in data analysis software, however, significant effort has recently investigated the development of automated data analysis software such as targeted and untargeted chemometrics to solve this problem. In this research project, discovery-based chemometrics was employed to provide a comprehensive view of the changes in the human metabolome associated with injury of the anterior cruciate ligament (ACL) as compared to healthy controls. For this purpose, in-house developed Fisher ratio (F-ratio) software was applied, which facilitates a supervised untargeted analysis for the discovery of metabolites and other interesting analytes with a statistically significant variance between samples classes.
Traditionally, the interpretation of subsequent F-ratio results has increased data processing as manual peak decomposition and analyte identification and quantification is performed with commercial software such as parallel factor analysis (PARAFAC). However, our in-house F-ratio software provides mass spectral selectivity information in the form of F-ratio spectra, a feature which has been previously underutilized. Following the discovery of potential ACL injury biomarkers via the F-ratio software, the mass spectral selectivity provided in the F-ratio spectra is exploited using a novel algorithm which calculates analyte signal for chromatographic features identified during F-ratio analysis. By utilizing the chromatographic and mass spectral information provided from the F-ratio software, automated and rapid quantification of 42 potential ACL injury biomarkers is provided without requiring chemometric decomposition.

Bill Nelson from Tetracore, USA was planning to make a presentation on Advances in Point of Care testing for SARS-CoV-2. This presentation was an update on the development of an instrument the T-COR 8™ that has been presented at previous CPAC Rome workshops. The current coronavirus pandemic has been exacerbated by the lack of testing capabilities - especially at Point-of-Need testing. Diagnostic testing for viral diseases was revolutionized by the invention of polymerase chain reaction technology (PCR) and its evolution to Real-Time-PCR. The T-COR8 was designed to operate outside of a “high complexity laboratory” in pharmacies, clinic, and doctors’ offices. It incorporates inexpensive BK Ball lens, off-the-shelf optical sensors, inexpensive small single board computers designed for the hobbyist, and architectural grade LEDs. The instrument is using an in-house design reverse transcriptase Real-Time-PCR assay targeting three genes from the SARS-CoV-2 at the point of care. Its internal lithium batteries allow it to be used in drive through curb-side testing sites providing an answer in 20 to 30 minutes.

Martin Gadsby of Optimal Industrial Technologies, UK was to present a talk on “Using a PAT System to Increase Flexibility in Raw Material Selection and Optimize the Performance and Quality Output of your Process” After a 20+ year gestation period, PAT systems are now extensively used to great benefit in a wide range of process types including batch and continuous, small and large molecules. A well applied, holistic PAT system will not only improve the development and manufacturing processes but will also allow greater flexibility in the selection of raw material sources, as the system capability to accept larger variations in raw material specification will have been enhanced. Furthermore, whilst PAT is widely employed in continuous OSD manufacturing and increasingly in continuous biotech manufacture, its take-up and use in flow chemistry systems, with some notable exceptions, is slower than expected, especially so as they can now be used to automatically measure trace materials in your process. The presentation was to attempt to explore why the use of PAT in a flow chemistry system can deliver significant benefits not only in terms of quality, cost and time of manufacture, but also in terms of raw material sourcing flexibility and trace contaminant measurement. Using a tool
like the Optimal synTQ can help to show which functions - such a tool needs - to provide, in order to enable success. It also shows that PAT can be implemented for simple QA monitoring or full control and in batch or continuous processing. Indeed, Continuous processing needs on-line PAT in ‘realtime’. Data management is critical and synTQ acts as the interface between the PAT data and the IT systems.

Olav Martin Kvalheim from the University of Bergen, Norway was to present a paper co-authored by, Bjørn Grung, U of Bergen, Tarja Rajalahti, Fjordomics, and Reidar Arneberg, Pattern Rognition Systems on the topic of Preprocessing, Wavelength Selection and Modelling of Process Raman Data. Maintaining optimal process conditions at all times with a minimum of operator interaction is a key goal for companies. This requires on-line sensors and optimal use and modelling of available data. They are involved in an innovation project with the Norwegian omega-3 producer GC Rieber Oil and the Raman supplier MarqMetrix on automating process control using on-line Raman data sampled at two different locations in a distillation process of fish oil to produce oil with a high content of the omega-3 fatty acids, EPA and DHA. The feed to the distillation process is varying over time due to raw material variation and due to differences in product specifications. When the feed or product specification is changed, the process has to adjust to the new conditions as quickly as possible in order not to lose product, time, and ultimately money. Software was developed by Pattern Recognition Systems for this project. Three steps are essential in this operation: i) optimal preprocessing of the Raman data, ii) optimal use of the preprocessed data, and, iii) optimal automated procedures for model selection for prediction of set points for the process control variables. Raman spectra of fish oils shows a varying and strong fluorescence that has to be removed. Furthermore, the information about EPA and DHA is located to certain regions of the spectra and thus wavelength selection is crucial to remove interferents that complicate the models. In this lecture, they were comparing various options for pretreatment and variable selection and show how different choices impact the model performance.

Marco Banti, ABB IAEN Business Development & System Sales, Fine Chemicals & Pharma Industries, Italy was to present a talk on Data Analytics for Governing Big Data in Continuous Process Operations in a Digital Factory. Unit operations and process skids are typically designed as autonomous systems equipped with their own local controls. Such local controls are usually enough in batch processing, where the unit operations are disconnected from each other. While local control is also essential in continuous processing, the integration of unit operations and modular units requires global coordination of the entire process flow. Tightly associated with process automation and control is the need for adequate PAT measurements. Reliable long term operation of the continuous system can be accomplished if adequate real-time PAT information is available for each unit operation and if globally coordinated along process or single manufacturing steps. Such PAT systems can be positioned at several strategic
points along the process flow, supplying control systems with the required product quality information. Physical and physico-chemical parameters are reliably monitored (e.g., UV absorbance, pH, conductivity, flow rate, pressure, etc.) using technologies that are well established in batch processes. What is missing, however, is the adequate amount of real-time information about product’s Critical Quality Attributes (activity, aggregation, etc.). Consequently, continuous systems have to be equipped with a “second level software control system” that supervises and aligns the work of the individual unit operations, providing oversight functions like coordination of flow rates, event-based control, exception handling, high degree of open and integrated controls, requiring minimal operator involvement. A potential challenge here is that different vendors often use different control systems, which can make such kind of integration difficult. Emerging trends in process controls drives to new “vendor-neutral automation layer” concepts. The "Modular Automation", developed by Namur W1.12 consortium and led by TUV, chemical & pharmaceutical manufacturers and automation firms, is perhaps in the most advanced industrial stage at European level, compared to similar initiatives still in a consolidation phase. It already has significant references to plant-wide orchestration of multiple process units that use local automations and analytical measurements. The ABB presentation was to focus on deployment of Namur W1.12 concepts in a real “second level control system”, that streamlines local and global controls, facilitates continuous operations and reduces engineering & integration efforts. A case study was to be presented on how the “Orchestration layer” and “MTP modules” are integrated in a fine chemicals industrial project, showcasing benefits for end users and OEM manufacturers, and providing an overview of the today available control infrastructures to truly support a 4.0 factory.

Vicenzo Fussillo of the H.E.L group, Germany was then going to present a talk on Maximizing Chemical Productivity with the HEL FlowCAT. All chemical companies work nowadays to develop more efficient processes, that could be also more environmentally friendly given the mounting concern on waste managing and consequent “cradle-to-grave” approaches. On this line, a sustainable use of resources for energy, chemical and material production could be achieved by heterogeneous catalysis.

On a different line, Continuous flow processing has proven to be a robust and efficient technology able to deliver significant benefits in terms of process efficiency, low side product generation, safety and sustainability in general. With better control over reaction/process parameters (e.g. mixing, heating or throughput) and superior product properties in terms of product quality, selectivity and reliability, continuous flow processes are rapidly replacing batch operations (wherever possible) in chemical synthesis. H.E.L has put considerable efforts in developing a continuous flow reactor, the FlowCAT, that could exploit heterogeneous catalysts in a trickle bed configuration. Solid catalysts can be packed directly into the column as powder
particles (mixed with inert materials such as glass beads for spacing), allowing the use of either commercially “off-the-self” catalysts or conventionally synthesized bulk catalysts in the laboratory. Thanks to its flexibility and versatility, the FlowCAT could be initially used for small scale studies to characterize the reaction parameters. These conditions could then be translated to large scale using larger columns.

Examples of how FlowCAT systems have helped to achieve all these goals were to be reported in three case studies from different companies/institutions. In the first case study, full reduction of ethyl nicotinate was achieved under process intensification conditions and the robust protocol developed was then applied to multikilogram scale, obtaining the fully reduced product with high purity.

In the second case study, in the course of an API synthesis an aliphatic nitro intermediate had to be reduced to amine: several catalysts were screened and, having found the right one, a reductive reaction optimization was conducted. The parameters were then tested at higher scale, with the possibility of reusing the same catalyst bed several times without loss of productivity.

In the third case study, the FlowCAT was successfully coupled with analytical equipment (a gas chromatographer with mass spectroscopy/Barrier Ionization Discharge detector) for online analysis of ethanol upgrading reactions to higher oxygenates. This increasing in chain length was completed by a multi-stage reaction that took place in a single catalyst bed. It was demonstrated that it is possible to monitor the product distributions and the catalyst deactivation over time, as well as to identify different products at different temperature regimes. With its robustness, flexibility and ease of use, the FlowCAT is a powerful tool for R&D investigations and scale-up studies alike.

A valuable resource to industry as a solution provider is Axel’One. A presentation was to be made by Dr. Franck Baco-Antoniali, Axel’One, France The Link They Provide Between Suppliers of Innovative Technologies (Online Analysis & Digital Solutions) and Industrial End-users. Axel’One is a collaborative innovation platform in the Chemistry and Environment sector created in 2011 and dedicated to clean processes and innovative materials, located in Lyon, Auvergne-Rhône-Alpes Region. Axel’One is an independent association whose main missions are to provide shared facilities, tools and services (characterization tools and online analysis, Kilo labs, chemistry laboratories, scale up pilots) for collaborative research and development projects. These services are open to all stakeholders including SMEs and enable users to carry out R&D projects, tests, scale-up, pre-series production etc. In 2019, Axel’One hosted 17 SMEs and provided its services to 40 collaborative projects representing more than 250 people located on the platform, with a staff of 27 people.
Axel’One Analysis (part of smart processes’ department) is strongly involved in on-line analysis, monitoring and process control, digital solutions and data management. This covers a large range of techniques in order to answer market needs and issues on sampling, industrial analysis, instrumentation, metrology and data processing. Axel’One Analysis is specialized in separation techniques, spectral techniques, specific sensors and data analysis (chemometrics, MSPC, Artificial Intelligence). The platform mutualizes skills and tools for numerous R&D projects. It provides a perfect interface between instrumentation suppliers, industrial end-users of these new technologies and academic laboratories. The activity of Axel’One works for industrial companies from the chemical, petrochemical, pharmaceutical sectors, but also with other industrial sectors such as steel, textile and building industries.

Again, the goal of the organizers of the 2020 CPAC Rome workshop was to build a program around the theme of the need for achieving the goal of a Sustainable Circular Economy – and to develop it so that it demonstrates the technology being developed that will allow for approaching that goal.

The purpose of this summary report is to keep the thoughts and discussion on the 2020 topics alive until we meet again in 2021. As we gathered the abstracts to create this summary report, we received a strong response from the participants who planned to be there in 2020 – to reserve the dates in 2021 (March 22-24, 2021). If there are particular questions with regard to content of the abstracts, please let us know and we will work to provide references and/or contact information for the authors.

We look forward to having our next meeting in Rome on March 22-24, 2021. We anticipate that it will again be a memorable gathering in a peaceful setting – where technical and social discussions occur freely. As a reminder, here are some photos from the CPAC Rome workshop in 2019 and from the friendly environs of Rome in normal times.
See you next March 22-24, 2021 at the CPAC 2021 Rome Workshop