Accelerating the adoption of continuous manufacturing and crystallisation processes, systems and plant for the production of high-value chemical products to higher quality, lower cost, more quickly and more sustainably.

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Welcome to our annual report which provides a summary of the EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation and highlights key events, activities and progress during its second year. The Centre’s collaborative programme is delivered by a multidisciplinary academic team that involves colleagues at the Universities of Bath, Cambridge, Edinburgh, Heriot-Watt, Glasgow, Loughborough and Strathclyde. The shared vision, scope and programme for the National Centre have been developed through close collaboration with industry and in particular our founding strategic partners GSK, AstraZeneca and Novartis who continue to provide significant input and support. Together the Centre partners have a shared long-term vision: to enable a step change from the current batch manufacturing paradigm to fully continuous manufacturing processes, systems and plants for the production of high-value chemical products to higher levels of quality, at a lower cost, more quickly and in a more sustainable manner.

The Centre has stimulated considerable growth in activities in this area since it was established in 2011 and during 2013 we have seen several exciting developments. Research has grown through new projects supported by EPSRC, TSB, EU and industry including a major new 5 year ICT project between Strathclyde and Loughborough Universities led by Prof Ivan Andonovic (Strathclyde) for Intelligent Decision support for Continuous Manufacturing and Crystallisation. The support and contributions from the Centre research team have been excellent and throughout 2013 we have also had a range of events to build on and embed the collaborative ethos and fellowship across the Centre, bringing together the academics and researchers with industrialists to share progress and develop new ideas. It has also been a pleasure to welcome our first Doctoral Training Centre (DTC) cohort into the Centre who have now successfully completed the innovative and challenging formal training programme. Training the next generation of scientists and engineers is vital to progress, and we are delighted to add a new SFC funded M.Sc. in Continuous Manufacturing and Crystallisation to our existing DTC programme. The substantial growth in funding, has seen the Centre grown from 33 Centre staff, RAs and research students in 2011 to 81 with the latest DTC cohort intake. This growth in the research community and scale of activity will help accelerate progress against some of the key manufacturing research challenges in this area.

I would like to thank a number of groups for their inputs and support over the last year. The Centre’s Independent Advisory Board, chaired by Prof Paul Sharratt, ICES Singapore provides advice on the direction and scope of all of the Centre activities and the Board’s efforts have been invaluable in ensuring the Centre’s activities are informed by leading academic and industry experience. The continued support from our industry partners has been at the core of our success and the CMAC Industry Members Board, chaired by Dr Clive Badman GSK and Industry Technical Committee continue to provide co-ordinated and sustained support for the Centre’s research, training and outreach programmes.

Strong academic and industrial partnerships are the foundation of the Centre and a key part of the Centre’s success depends on successful user engagement and through our Industry Director, Craig Johnston, we continue to develop excellent relationships with end-users and technology providers. These are exciting times for the Centre and our partners and we look forward to continue to work with the wider national community concerned with accelerating the adoption of continuous manufacturing and crystallisation.

Prof Alastair Florence,
Director
Overview of the EPSRC Centre 2012-13

Demand-led Scope

The research scope of the EPSRC Centre has been jointly defined by the academic team together with our industrial partners. The 10 key challenge areas against the scope are summarised in Figure 1 right and provide a focus for the academic engineering and physical science research activities.

Centre Mission

Through partnership and collaboration between academia, industry and public sector stakeholders we will establish a world-class Centre of Excellence in continuous manufacturing and crystallisation research. The programme will deliver continuous manufacturing research across three main thematic areas that are developing new understanding and supporting innovation across a range of products, processes and operations (Figure 2).

Products

Better particles through understanding particle formation and performance in continuous processes
- Innovative, safe, effective, high-value
- Nucleation, growth, agglomeration, breakage
- ‘dial-a’ ...form, size, shape, purity
- Tailored bulk and surface structure and function

Processes

Better technologies for continuous control, formation, isolation, and processing of particles
- Fast, efficient, sustainable, safe
- Controllable, scaleable, adaptable and agile
- Predictable, optimised
- Reconfigurable, modular, plug-play

Operations

Optimised high-value chemical manufacturing operations across the value chain
- Economic, efficient, lean, world class
- Wealth creating, sustainable
- Deliver regulatory compliance
- Reduced time to market
Multidisciplinary Research

Key to the success of the Centre is the multidisciplinary academic team supporting the research programme. Our initial team involved 12 academic investigators from 7 institutions working with 9 PDRAs, 8 PhDs, technical and administrative staff, harnessing expertise in chemical and process engineering, synthetic, physical, analytical, structural and materials chemistry, crystallisation science, pharmaceutical science, manufacturing and operations management, Figure 3. In year 2, the Centre retains the core 12 investigators and now has 26 PhD students and 14 PDRA’s with a management and support team of 7. The programme will also adapt to meet the challenges of the scope in years 3-5. The academic team also contribute to the innovative training programme developed for the new EPSRC Doctoral Training Centre in Continuous Manufacturing and Crystallisation that will train 45 doctoral researchers from 2012-2016. The first DTC cohort completed their specialist training in June of 2012 and we are looking forward to welcoming the next cohort in October 2013.

Flagship Projects – Years 1-2

Our foundation research activity is delivered via our flagship research projects against key areas of the research scope (Figure 4). Along with the Centre’s core researchers a platform RA and technician have also been appointed to carry out short-term feasibility projects and assist in evaluation of new technologies.
Over the past 12 months the Centre has been activity rich developing technology, techniques and understanding of continuous crystallisation processes. This work has involved several existing technology platforms at the University of Strathclyde, Loughborough, Heriot-Watt and Bath, including the mixed suspension mixer product removal (MSMPR) crystalliser, continuous stirred tank reactors (CSTRs), the meso-scale and full scale continuous oscillatory baffled crystalliser (COBC). Alongside these some new technologies have been developed including a filed patent for a device for inducing nucleation at Heriot-Watt University, bespoke nucleation units to obtain suitable seed suspension at the University of Strathclyde, the moving-fluid oscillatory baffled crystalliser for establishing parameters necessary as a precursor for continuous crystallisation and the design of a new flow crystallisation technology for the development of multi-component agrichemicals at the University of Bath.

**University of Strathclyde**

The Strathclyde team have made notabe progress in a range of areas of continuous crystallisation. Better understanding of heat transfer through a combination of modelling and experimental work and the implementation and interpretation of process analytical technologies, has led to more efficient cooling profiles and improved knowledge and understanding of the growth kinetics for model compounds within a NiTech continuous oscillatory baffled crystalliser (COBC). Alongside this researchers from the group of Dr Jan Sefcik, Dr Annan Jawor-Baczynska and Ulrich Schacht have been developing a bespoke nucleation unit for continuous anti-solvent precipitation to obtain suitable seed suspensions for feeding into a continuous growth unit. The controlled addition of seeds has allowed the development of continuous systems which produce products with desirable particle attributes including physical form and particle size distribution. For a more in depth case study of work performed in the continuous seeded crystallisation of L-glutamic acid in a COBC please refer to page 8. Other continuous crystallisation work has been performed by researcher Dr Humera Siddique on a Cambridge Reactor Design Rattlesnake oscillatory flow reactor, please refer to page 13.

**Loughborough University**

The research groups of Prof Chris Rielly and Prof Zoltan Nagy at Loughborough University are continuing to develop their understanding of continuous crystallisation over three crystallisation platforms; the mixed suspension mixer product removal (MSMPR) crystalliser, continuous stirred tank reactors (CSTR) and the meso-scale continuous oscillatory baffled crystalliser (meso-COBC). The MSMPR has been operated continuously for up to 12 residence times investigating cooling crystallisation, anti-solvent crystallisation, in-line seeded crystallisation, effect of impurities and polymorphism monitoring. These reactions have been monitored with the application of several PAT. An on-going collaboration between Loughborough University and the University of Bath is also studying the application of PAT for continuous co-crystallisation monitoring, control and scale-up.

The meso-scale COBC has now been rebuilt and fully commissioned with water testing, RTD studies and heat transfer measurements. Future work is looking to use heat transfer modelling to design and optimise the jacket configurations to give a target spatial temperature profile, using the minimum number of cold utility sources. Loughborough University researchers are developing a crystallisation monitoring and control framework for continuous processes, using a combination of mathematical modelling approaches and experimental investigations into a series of process analytical technologies (PAT).
Heriot-Watt University

Dr Cameron Brown at Heriot-Watt is investigating the expansion of available process monitoring tools and the creation of a model for crystallisation processes within a COBC incorporating concentration, temperature and particle size profiles.

Professor Xiong-wei Ni (CMAC Co-investigator) and Craig Callahan (3rd year PhD researcher) at Heriot-Watt University have recently filed a patent for their device for inducing nucleation. (Ni, X.- W.; Callahan, C. J.: Device for Inducing Nucleation. 2013, WO 2013/088145.) The device, which separates the two operations of crystal nucleation and crystal growth, can be described as being similar to a two stage COBC.

University of Bath

The University of Bath have progressed with the implementation of continuous systems. Dr Karen Robertson is designing and developing a new flow crystallisation technology for the development of multi-component agrichemicals for physical property optimisation, e.g. solubility, mobility and degradation. The Bath team have now also fully commissioned their COBC and researcher Kate Wittering is developing crystallisation processes of multi-component molecular complexes to control polymorphic forms in continuous flow in collaboration with Dr Ali Saleemi, Loughborough University.

University of Edinburgh

Alasdair Mackenzie, a PhD researcher at the University of Edinburgh, has commenced his research in crystallisation using laser-induced nucleation for polymorph control. This research is investigating “non-photochemical laser-induced nucleation” (NPLIN) as a method of exerting control over polymorphism and incorporating the techniques into continuous crystallisation processes.

Related Crystallisation Technologies

Researchers at the University of Strathclyde and Heriot-Watt University are developing a workflow for moving from small-scale batch to a continuous oscillatory baffled crystallisation process. The batch vessel being developed is a moving fluid oscillatory baffled crystalliser (MF-OBC), which maximises similarity between batch and continuous OBC operation. For further information on the MF-OBC please refer to the case study on page 13.

University of Glasgow

Dr Greig Chisolm from Prof Cronin’s research group at the University of Glasgow has recently started a project to demonstrate that crystallisation conditions can be autonomously controlled via in-line analysis of the solution phase, and that evolutionary algorithms combined with analytical feedback can be used to optimise the desired product attributes.
Continuous seeded crystallisation of $\beta$ L-Glutamic Acid in a Continuous Oscillatory Baffled Crystalliser

**The Challenge**

To successfully develop a continuous seeded crystallisation of a model polymorphic compound in a NiTech continuous oscillatory baffled crystalliser (COBC), to a desired particle size with no encrustation or blockage of the crystalliser. L-Glutamic acid (LGA) was selected for this work as it has two known crystalline forms (meta-stable $\alpha$ and stable $\beta$) and there is existing literature providing background knowledge of LGA batch crystallisations and the ability to achieve polymorphic phase control under recognised process conditions.

**The Technology**

A continuous seeded crystallisation process was designed in a modular continuous crystallisation unit. The modular approach separates the two unit operations of crystal nucleation and controlled crystal growth. Crystal nucleation control is achieved with rapid antisolvent seed generation using a novel modular unit. Control of crystal growth is then managed with cooling crystallisation with the COBC.

Ulrich Schacht, a 3rd year Chemical Engineering PhD student working in the research group of Dr Jan Sefcik, designed and operated a novel seed generation unit, see Figure 5. Using the technique of rapid continuous antisolvent crystallisation, this unit can reproducibly provide a seed suspension of $\beta$ LGA with a mean particle size of 10 $\mu$m.

Naomi Briggs, a 3rd year Pharmaceutical Science PhD student working in the research group of Prof Alastair Florence operated and optimised the COBC crystal growth unit. The continuous growth unit operates using an optimised cooling profile, with continuous injection of the generated seed suspension into a hot saturated LGA solution, see Figure 6.
Measurement Techniques – online control and offline results

The COBC unit has been adapted to permit the insertion of process analytical technology (PAT) probes at the bends of the reactor which allows online monitoring techniques. Focused beam reflectance measurement (FBRM) was implemented to ascertain when steady-state of the reactor had been reached. The online FBRM results were verified with a series of offline techniques such as particle size distribution (PSD) analysis via Malvern laser diffraction, X-ray powder diffraction (XRPD) for characterisation of polymorphic phase purity and optical and electron microscopy for information on morphology of the isolated crystal product.

The Successful Outcome

The implementation of modeling and experimental verification of the desupersaturation profile along the COBC, optimal desupersaturation behaviour was ensured in the rig. The use of seeding allowed steady state operation to be reached after only one residence time with a desired PSD of 70 μm. The XRPD analysis confirms the phase purity with no unwanted primary nucleation of the meta-stable $\alpha$-LGA. With no issues of encrustation or sedimentation observed, this crystallisation unit has true 'dial a particle' characteristics.

**Figure 5.** Nucleator Set-up for antisolvent crystallisation of $\beta$ LGA seed crystals

**Figure 6.** Schematic of continuous oscillatory baffled crystalliser including insertion points for focused beam reflectance measurement (FBRM) and sample points (SP).

**Figure 7.** Malvern particle size distribution showing steady-state and particle size of 70 µm after one residence time (RT)

**Figure 8.** X-Ray powder diffraction of reference powder pattern of $\beta$ LGA (blue), seed suspension (green), product (black) and reference powder pattern of $\alpha$ LGA (red).
Sustainability is key to the Centre’s success and ability to impact in this field through strong industry engagement and leadership. Following the award of the EPSRC Centre, an industry led membership organisation (CMAC) was created to steer the development of user-led activities in this area, to inform basic research and develop higher TRL activity. The first CMAC board meeting was held in April 2011 and the 10th board meeting recently took place. In accordance with the Centre’s business plan, the aim is to populate the innovation landscape with parallel research activities across the TRL levels using a range of appropriate funding mechanisms to address industry needs in a structured manner.

The membership organisation operates under a pre-competitive, collaborative research and development model with senior level company support. The CMAC board (Figure 10) is chaired by Dr Clive Badman, OBE. A separate Technical Committee comprising industrial experts and representatives of the EPSRC Centre defines the core programme. The EPSRC Centre Director and Industrial Directors are members of these committees to ensure that optimal alignment of the programmes across TRLs is maintained. In addition to our Tier 1 partners, we are also working with a range of technology providers and companies from other chemical sectors who are contributing to the technical programme, for example, through access to new processing and measurement technologies. An example is the relationship with Mettler Toledo (Figure 9), which involves the provision of a suite of equipment that will be used and developed across the programme.

We are also continuing to develop further links with other companies that can contribute their expertise to advance the developing programme in continuous manufacturing research.

The Centre’s research direction is based on detailed academia-industry workshops which develop industry problem statements and identify research targets. These have been updated and expanded during this year. Further academia-industry links have also been developed through academic and student visits, workshops and secondments to industry. An innovative industry mentoring scheme has been initiated for 50+ PhD students from the Centre and the Doctoral Training Centre. There has also been broad UK and European dissemination including conferences jointly organised with the Royal Society of Chemistry. As students complete their studies we expect an outflow to industry positions using multidisciplinary skills.

At the Centre’s first annual open day there was over 130 delegates including 30 company representatives, exhibition space for technology companies and talks from senior industrialists. The second open day will be held on 12th September 2013.

The National EPSRC Centre also acts as a focal point for UK academic community with industry (fine chemicals and pharmaceutical). The Centre is very keen to establish new Knowledge Transfer Projects (KTPs).
The Institute for Manufacturing at the University of Cambridge (CMAC academic partner) co-ordinated the road-mapping for the Pharma ‘Deep Dive’ report, both with direct contribution and through engagement with CMAC companies. The Centre has worked very closely with the Technology Strategy Board during this year and it is pleasing to note that there are initial examples of the development of new technologies for direct exploitation with industrial partners. Engagement with TSB, SCI, IChemE, CIKTN, CIA and RSC in the following areas:

- influencing and participation regarding Horizon 2020 scope
- working with companies to contribute to Innovative Medicines Initiative consultation

The Centre has also engaged with HVM Catapult - Centre for Process Innovation (CPI) exchange visits, common skills agenda and both are involved in one of the current TSB projects, which is looking at developing links in complementary areas as well as building on the Centre capabilities at higher TRL that complement core CPI base.

Tier 1

| gsk GlaxoSmithKline | AstraZeneca | NOVARTIS |

Tier 2

- Cambridge Business School
- NiTech Solutions
- AMI Technology
- CLAIRET Scientific Limited
- PSE
- Avantium
- METTLER TOLEDO
- PERCEPTIVE Engineering Ltd
- Alconbury Weston Ltd
- WYATT Technology

Collaborators

- genzyme
- FUJIFILM
- AMBITUS CERN
- SMARTSOURCING
- CRODA
- LBRIZOL
- Johnson Matthey
- syngenta
- Pfizer
- P&G
- BRUKER
- SYMPA T
- GSE SYSTEMS
- Sympy
- CIP
- Infinity Photonics
- Gilden Photonics
- Cancer Research UK
Make To Order Processing Plants (MOPP) TSB funded project

The Challenge

This TSB/EPSRC funded project is being led by Perceptive Engineering with the HVM catapult Centre for Process Innovation (CPI) and AstraZeneca. This is a good representative example of research research supported by public and private sectors. The project aims to develop an adaptive ‘Dial a Product’ control system to deliver the precise control required for high value low volume manufacturing systems. Combining control design and analytical techniques will enable the reactors to reach optimum performance quickly and efficiently as manufacture switches between products and reactors.

The Technology

At CMAC, the automated control system is being installed on Cambridge Reactor Design’s Rattlesnake Oscillatory Flow Crystalliser. The system will be capable of fully automated running with model predictive control. The system will utilise in-line PAT (IR, UV-Vis, FBRM or Raman) for process monitoring and control. The control models are being developed for the heat/cool systems and full characterisation of the flow characteristics and residence time distribution have been carried out.

Next Steps

Initial work will focus on cooling crystallisation of lactose, from an aqueous solution, as a model compound focusing specifically on:-

- Long term continuous running (at least 72 hours building to 2 weeks)
- Understanding of the impact of process parameters on product attributes
- Use of model predictive control systems to provide consistent product quality as inputs and conditions vary.
- Ability to control and alter final product attributes “to order”

A more complex API molecule with an organic solvent will be selected for the second stage of the project. In parallel to the work at CMAC, an automated continuous reactor system with in-line PAT is being developed at CPI where an alkylation reaction will be carried out as a demonstrator.

*Figure 11. The automated control system user interface.*
The Challenge

The evaluation of a crystallisation process prior to continuous implementation is one of the key challenges for workflows across the Centre. Whilst some valuable thermodynamic and kinetic information may be obtained from traditional crystallisation platforms such as stirred tank crystallisers (STCs), there is still a vital gap with experimental considerations including primary and secondary nucleation, agglomeration and encrustation need to be investigated. Such factors will be affected by the notably different hydrodynamic environments between batch and continuous operation.

Current Technology

Traditionally for continuous oscillatory baffled crystallisers (COBCs) a moving baffle batch oscillatory baffled crystalliser (MB-BOBC) was used as an intermediate step prior to continuous experimentation. Optimised process conditions such as oscillation intensity and cooling profiles were then utilised in the COBC. The MB-BOBC tended to be operated with a stationary fluid and moving baffe arrangement, contrary to agitation mode in the COBC, where the fluid is oscillated through fixed baffles. The oscillating, tight-fitting baffles in a MB-BOBC generate scraping, a mechanism identified to give different outcomes to a seeded crystallisation experiment.

The Technology

Teams at the University of Strathclyde and Heriot-Watt University have developed a number of moving fluid batch oscillatory baffled crystallisers (MF-BOBCs), as evaluation platforms prior to continuous operation. With support from NiTech Solutions Ltd the new technology has been designed so that the generation of mixing mimics that of the COBC, with the use of bellows/piston configurations to generate the mixing at the interface between process fluids and crystalliser components. The MF-BOBC systems include a piston directly inserted into a precision-made jacketed glass tube and a set-up featuring a membrane material to separate a fluid filled bellows unit from the crystallising solution. These platforms will allow a much more realistic evaluation of a process on the batch scale, which should facilitate a smoother transition to continuous operation.

Figure 12. MF-BOBC platforms. Left and middle: oscillation driven by bellows and membrane assembly, right: piston-in-glass arrangement.
Manufacturing operations and supply chain management challenges in continuous manufacturing

Overall Project Vision
Accelerating adoption of continuous manufacturing across the pharmaceutical sector

The Challenge
To explore the manufacturing operations and supply chain management opportunities and challenges for continuous manufacturing. This theme is a joint collaboration between the research groups of Professor Umit Bititci at the University of Strathclyde and Professor Sir Mike Gregory and Dr Jag Srai at the Institute for Manufacturing, University of Cambridge.

Work developed by the Strathclyde team...
- Technological readiness of each manufacturing unit operation both for primary (API) and secondary (Formulation) manufacturing
- A technology road map:
  - capturing the key metrics and opportunities continuous manufacturing would bring
  - identifying technological and economic challenges to enable greater adoption of continuous manufacturing
  - mapping current CMAC projects attempting to address these challenges
  - identifying gaps where further research and development is required

Work developed by the Cambridge team...
- An understanding of the changing industrial landscape in pharmaceuticals and the opportunities for high value manufacturing solutions in Pharma/Biopharma
- Mapping current state supply network configurations in leading Pharma multinationals
- An industrial systems capability evolution approach for technology intense platforms in Pharma
- Value Chain Analytical Framework
  - to examine the interactions between the Value Network sub-systems in Pharma (e.g. Clinical, Primary Secondary Manufacturing, Packaging and Distribution, E2E Supply)
  - to inform the selection of Continuous Manufacturing candidates (therapies, patient populations, product-process archetypes, business case)
- Initial continuous manufacturing candidate profiles setting out transformation scenarios informed by Value Network analysis and technology roadmaps

Figure 13. Sub-system analysis of potential continuous manufacturing candidates
Drivers and Barriers for the Implementation of Continuous Manufacturing in Pharmaceutical Industry

Drivers and opportunities for continuous manufacturing
- Plant footprint reduction by 70%
- CapEx reduction by 25%
- Operating cost reduction by 30%
- Yield improvement by 10%
- More consistent quality
- More controllable, repeatable process

Barriers to the adoption of continuous manufacturing
- Regulatory uncertainties
- Under-utilisation of existing capacity
- Technological readiness and uncertainties
- No clear and specific vision as to how continuous manufacturing may impact on industry structure
- Transformation challenge and Behavioural issues

Integrating Research Theme 1 and Theme 2

A key role for Theme 1 is the facilitation of the discussion between Multi Discipline Research Teams (MDRT) and between MDRTs and Multi Agenda Industry Groups (MAIGs) on an on-going basis, as illustrated in the figure. It is believed that this conversation will become critical towards targeted innovation both in technology and the underlying supply chain and business models.

Figure 14. Integration of theme 1 and theme 2 research with Multi Discipline Research Teams (MDRT) and between MDRTs and Multi Agenda Industry Groups (MAIGs).
There is a great importance in being able to make in-process measurements as close to real time as possible in order to optimise, monitor and control high value industrial processes in the chemical and pharmaceutical industries. Real-time process control is well established in the petrochemical industry and has been growing in importance in the pharmaceutical industry over the last decade. Currently most processes where close to real-time measurements are made are batch operations but there is an additional challenge when making in-process measurements for continuous operations. In addition to making measurements it is important to validate and process data to produce information that can lead to understanding of process critical parameters and in this regard multivariate data is important for calibration building and process performance monitoring.

Presently, by far the most widely applied family of technologies used for in-process monitoring are spectroscopic techniques. There is a current focus of attention within the group in using non-invasive Raman to monitor crystallisation in a variety of reactors including mixed suspension mixed product removal (MSMPR) crystallisers and oscillatory baffled reactors, powder drying, powder blending and tablet analysis.

Presently the interest in mid-infrared spectroscopy is growing and there is an emphasis on helping vendor companies, such as Fibre Photonics and ART Photonics, in developing probe technologies for in-situ ATR-FTIR.

Although some spectroscopic techniques are suitable for non-invasive analysis there are other methods which can achieve this such as passive acoustic measurements – which are particularly useful for monitoring processes with phase changes or moving particles.

There has been recent emphasis on data analysis and improving calibration model transfer. This is especially useful for situations where spectrometers or probes have to be replaced, and offer a saving where calibration models do not need to be recreated.

At Loughborough University PAT tools are used not only for process monitoring, but also for process control. A full suite of PAT tools is available for techniques including ATR-UV/Vis absorption spectrometry, in-situ and non-contact Raman spectroscopy, focused beam reflectance measurement (FBRM) and particle vision microscopy (PVM). On-going work at Loughborough is focussed on crystallisation-related research and includes:
• Development and implementation of strategies such as automated direct nucleation control (ADNC) and supersaturation control (SSC) across different platforms.
• Integration of information from PAT arrays such as Raman, FBRM, ATR-UV/Vis, NIR etc.
• Crystallisation monitoring in different continuous processing systems such as MSMPR crystallisers, cascaded systems, oscillatory baffled reactors etc.
• Polymorphism monitoring and control for APIs and co-crystallisation.
• PAT for studying the effects of additives and impurities in crystallisation.
• In-situ imaging techniques for image analysis such as PVM.
• Population balance modelling and computational fluid dynamics (CFD) studies to investigate different phenomenon during crystallisation e.g. encrustation.

**Collaborative Expertise**

Together, the CMAC researchers at Strathclyde and Loughborough provide a wealth of experience in process monitoring and control, technique development and multivariate data analysis, contributing complementary skills and experience that support the development of continuous manufacturing from crystallisation through product recovery to secondary manufacturing operations.
Particle Isolation and Formulation

The Challenge

During the first year of the Centre the primary research focus was on continuous crystallisation, operation and supply chain research and process analytical technology, modelling and control. Over the past year the Centre’s scope has been expanded to include investment and capability in downstream operations with projects now covering filtration, drying and secondary formulation processing. This expansion of the Centre’s scope will allow us to gain better understanding and control of the complete journey to the final product.

Spray Drying

The Centre has recently purchased a Büchi Mini Spray Dryer B290.

Rebecca Halliwell, a DTC student at the University of Strathclyde under the supervision of Professor Alastair Florence, has commenced her research into Lab scale continuous crystallisers for control of pharmaceutical polymorphs and critical particle attributes. This research will be conducted on the Buchi Mini Spray Dryer B290, a compact bench-top device, see Figure 17. With the use of design of experiments and process modelling and optimisation Rebecca will investigate the ability of the spray dryer to consistently produce material with desirable particle attributes. This will include the ability to form composite powders of API and excipient as well as challenging the preconceptions of the spray dryer with research questions such as “Can spray drying be applicable for seed generation?” , “Can co-crystallisation occur within a spray dryer?” and “Can the spray dryer bridge the gap between primary and secondary processing?”.

Twin-Screw Extruder

Laura Martinez-Marcos, a DTC student at the University of Strathclyde under the supervision of Professor Gavin Halbert has commenced her research into the influence of solid form properties on formulation and extrusion processing. With the use of the Thermo Process twin–screw extruder, see Figure 18, hot melt extrusion (HME) will be studied with respect to improving physicochemical and biopharmaceutical properties. The advantages of HME over traditional granulation processes include:

- no requirement of solvent addition and subsequent drying steps
- the suitability for moisture sensitive drugs due to the short processing time
- the ability to combine several polymers into one formulation
- the ability to formulate sustained release APIs

Throughout this project the use of Process Analytical Technology (PAT) such as near-infrared spectrometry and Raman spectrometry will be implemented to understand and control the extrusion process.
Continuous Filter - Dryer

Denise Logue and Jaclyn Dunn, a PhD student and Research Associate at the University of Strathclyde under the supervision of Professor David Littlejohn and Dr Alison Nordon are researching in-situ and non-invasive measurement techniques for the monitoring and control of continuous manufacturing processes. This work is concentrated on secondary downstream process operations such as continuous isolation and drying, with the introduction of process analysis for optimisation and control. Denise’s current research is focussed on evaluating the use of broadband acoustic emission spectrometry, see Figure 19, to monitor drying processes and detect particle size changes in real time. This work is currently being optimised on a batch filter-dryer system (Figure 20) but will shortly be transferred to a continuous environment.

The advantages of continuous filtration and drying include

- Consistent particle properties, eliminating batch to batch variability, leading to lower cost drug options such as direct compression.
- Smaller equipment footprint allowing for portable fit for purpose equipment
- Higher efficiency and reduced energy consumption in comparison to batch systems
National Outreach

As a National Centre we have a role to work with and on behalf of the wider community and to engage with the wider community in this area. The Centre holds an important position in the collaborative Research and Innovation Landscape in the UK. To support this we are involved in a number of outreach activities to raise the profile of the Centre and to work with colleagues across the UK from different sectors. The Centre is linking with the external academic research community and will continue to evolve and grow the research programme over time to meet the needs of Centre’s research scope as wider engagement with the public.

iCON funding

With support from our National Centre Strategy funding we have developed mechanisms to engage with new academic groups to accelerate innovation in continuous manufacturing research. Our iCON project scheme call opened July 2013 and invited project proposal applications addressing key challenges or technological advances to continuous crystallisation and manufacturing that are not currently being applied within the Centre’s programme. Primarily the aim of this call was to increase expertise in the Work-up area of continuous processing but was open to all ideas that may impact on the Centre vision. Funds available will cover PDRA time and consumables for up to 6 month projects. Successful project proposals will be announced October 2013.

Figure 21. Centre researchers and investigators at 1st annual open day
The Centre has benefited from significant industry support with £60m funding. Our ambitions are now set at £100m by 2020.

Open day

The second Open Day is scheduled to be an international event and to take place September 12th at Glasgow’s Science Centre. It is shaping up to be a vibrant event with over 100 delegates and numerous technology exhibitors. Keynote presentations will be given from Dr Kevin Girard, Pfizer US, and Prof Paul Sharratt, Head of Process Science and Modelling, Institute of Chemical and Engineering Sciences, Singapore. We will also have presentations from a representative from our industrial consortium and researchers from all of the seven universities.

The Centre’s first annual Open Day took place in September 2012 at the Barony Hall, University of Strathclyde with over 130 delegates. The programme included invited industrial and academic speakers with participation of over 30 companies.

Academic engagement

The Centre has had preliminary visits with external groups including the Centre for Innovative Manufacturing in Emergent Macromolecular Therapies (UCL, Biochemical Engineering) and Brunel University (AMEE) on the Centre’s scope and research challenges and potential opportunities for cooperation and collaboration. We also have had discussions and joint workshops with the EPSRC’s Grand Challenge networks Dial-a-Molecule and Directed Assembly aimed at establishing functional links to support activities and mutual areas of research interest. Broadened academic involvement with the Centre has been achieved by CMAC hosting invited speakers for part of the annual seminar programme. Invited speakers have included Dr Jerry Heng from Imperial College London and Dennis Douroumis, University of Greenwich. Additionally, the Centre is working on an on-going basis with the HVM catapult (CPI Wilton) over existing projects and upcoming funding schemes.

Public engagement

The Centre has been publicised in the HM Government Strategy for UK Life Sciences newsletter. The Office for Life Sciences was launched by the Prime Minister in Dec 2011 and is part of BIS and fosters the sustainable long-term growth and global competitiveness of the sector. The Centre also participated in the CSS 3 day exhibition at the Scottish Parliament, which informed politicians and members of the public of the chemical industry’s platform for growth. Increasing public awareness of the importance of manufacturing research and the high value chemical industry in the UK has also been achieved by presentations and workshops with school children. Additionally, the Centre is working with it’s own artist in residence, Fiona McGurk. Fiona will be based at Strathclyde and create pieces that have been inspired by Continuous manufacturing research.

Social media

The Centre has been creating and building a social profile via the new website (www.cmac.ac.uk) that was launched earlier this year, our twitter feed (@EPSRC_CMAC), LinkedIn Group (EPSRC Centre of Continuous Manufacturing and Crystallisation) and our newsletter. To subscribe to our newsletter follow the link http://www.cmac.ac.uk//mailing_list.php. Keep up to date with all Centre news and activities and engage with us via these groups.
Researcher exchanges

• A researcher exchange took place between Rajni Miglani Bhardwaj (University of Strathclyde) and Maxwell Terban (Columbia University, New York) to enable research to be carried out that was additive to both of their projects.

• CMAC researcher Laura Palmer spent 3 months working with Professor Allan Myerson’s research group in the Department of Chemical Engineering at Massachusetts Institute of Technology (MIT) in Boston, who are actively involved in the Novartis-MIT Center for Continuous Manufacturing. Through this collaboration Laura gained experience with the mixed suspension mixed product removal crystalliser, with the implementation of in-line and off-line PAT.

• Researcher Laura Palmer also participated in an outward visit to the Institute of Chemical and Engineering Sciences (ICES), Singapore for a placement in the process science and modelling research group who have expertise in chemometrics and process analysis.

• Anna Jawor-Baczynska (University of Strathclyde) participated in an outwards visit to the University of Minnesota for a placement in the research group of Professor Alon McCormick. During the visit work was carried out on the direct visualisation and establishing the nature of mesostructures present in aqueous solutions of glycine and DL-alanine using CryoTEM technique.

• Professor Raj Suryanarayanan visited from his home institution at the University of Minnesota to develop collaborative research relationships. During his visit Professor Suryanarayanan met with several faculty members of both the Pharmacy and Chemical Engineering Departments. He also presented a guest seminar to researchers and academics.

• Professor Baron Peters visited from the University of Santa Barbara to develop collaborative research relationships and present a seminar at the University of Strathclyde.

• Dr Dimitrios Lamprou visited the National Institute of Pharmaceutical Education and Research (NIPER) and the University of Hyderabad, India, to interact with academics and establish some new collaboration with the EPSRC Centre and the possibility of establishing a student exchange programme.
• Professor Alastair Florence, Craig Johnston, Dr Andrea Johnston, Dr Thomas McGlone and Dr Anna Jawor-Baczynska all visited ICES, Singapore to partake in workshops with the academics and researchers within the Process Science and Modelling group which is managed by Professor Paul Sharratt.

• Professor Alastair Florence, Craig Johnston and Dr Andrea Johnston visited Professor Mary Chan at Nanyang Technological University (NTU), Singapore to identify potential areas of research overlap between the EPSRC Centre and the Department of Bio and Chemical Engineering, potential future funding schemes and the possibility of student exchanges relating to the Centre for Doctoral Training. As a result of these visits an academic workshop between Strathclyde and NTU academics is being hosted at Strathclyde in September. We also look forward to hosting NTU academics at our annual open day in September 2013.

• Prof Alastair Florence and Craig Johnston visited Purdue who are one of the main academic partners of NSF ERC C-SOPS (http://ercforsops.org/) to discuss common areas of research interests, view facilities and identify possible future collaborations.

• CMAC participated in academic road-shows in Singapore, Japan and China with other leading research groups from the University of Strathclyde, that was funded by the EPSRC’s Global Engagements award.

International workshop – Purdue

In January 2013, University of Strathclyde hosted an international engagement event to visitors from Purdue University in order to build new research links between the two institutions. The two day event included presentations, research challenge workshops and a collaborative research sandpit event. Following on from this event several new research partnerships have ensued between researchers from both institutions.

1. Dr Dimitrios Lamprou (University of Strathclyde) visited Prof Stephen Beaudoin (Purdue University) to follow up on possible collaborative work relating to the study of the adhesion properties of molecules to surfaces in relation to fouling.
2. A joint project is taking place remotely between the institutes on developing work flows for batch and continuous crystallisations.
3. Collaborations between Brad Rider (Purdue University) and Naomi Briggs (University of Strathclyde) are currently underway on experimental and modelling of plug-flow systems in continuous crystallisers.

International workshop - MIT

CMAC hosted an academic workshop at Strathclyde between MIT-Novartis Centre and CMAC academics. The workshop focussed around supply chain activity relating to the EPSRC Centre Theme 2 research and the opportunities available for future collaborative work.

Figure 22: Participants at an international workshop between University of Strathclyde and Purdue University
Creativity@home and internal research day at Lancaster House Hotel 14-15 May

With the award of the EPSRC creativity@home funding, the Centre held a creative workshop in May to assist researchers in discussing and exploring innovative approaches to tackling research challenges. This was an opportunity for all levels within the Centre from DTC student to Director to come together and generate and nurture creative thinking. Three Times Three Consultancy Ltd delivered a programme emphasising team work/collaboration and facilitated everyone to draw on strengths and recognise weaknesses while having some fun.

The Centre’s Internal Research Day followed on from the creativity workshop and allowed for the sharing of current research activities across the Centre. The day involved poster presentations from all researchers and a selection of oral talks from across the research groups. The day also included workshop sessions on particular challenge areas from the Centre’s scope including nucleation monitoring and control, PAT implementation and integration of Theme 1 and Theme 2. These events were deemed a success by all with a flood of resulting cross Centre collaborations, see Figure 23.

![Figure 23. Cross-Centre collaborations currently taking place between Centre researchers](image-url)
DTC Summer School 10-14 June 2013
at Crieff Hydro Hotel

The Centre’s first DTC cohort’s residential training was concluding with a week long summer school at Crieff Hydro. The cohort showed off their transferable skills with presentations and posters on both their group and proposed individual research projects. They also defended their formulated business plans as entrepreneurs within the Dragon’s Den, which consisted of the Centre’s Craig Johnston and Ian Houson, AstraZeneca’s Phil Shering and GSK’s Chris Price acting as the Dragons.

Communities of Practice – CoP

This year the Centre has set up several Communities of Practice (CoP) which bring together researchers with common interests from across the Centre portfolio of programmes. These monthly tele-cons provide a forum in which to:

- discuss new project proposals to ensure new activity is informed by all related experience
- discuss on-going projects based on presentations from researchers to inform and advise on future directions
- Involve academics, RAs and PhDs and Tier 1 industry experts in discussions

The four established communities of practice are:

1. Continuous work - up
2. Continuous crystallisation
3. Bridging continuous processes: primary into secondary
4. Operations management and supply chain

Materials and/or measurement and modelling underpinning all four areas will initially be addressed within these Communities of Practice.
CMAC in the press

CMAC receive £34.2 M for capital investment

In June CMAC was awarded a £34.2m funding boost. This was composed of a £11.4 million cash injection by the Higher Education Funding Council for England (HEFCE) under the UK Research Partnership Investment Fund (UKRPIF), supported with £22.8 million industry and charity contributions. This substantial investment will further develop and enhance the leading facilities supporting the Centre’s cutting-edge manufacturing research programme. In strengthening the national Centre’s capabilities, and broaden engagement with industrial partners, from multi-national pharmaceutical companies to small and medium-sized enterprises. This news story alone was reported in over 90 press outlets. For further information and more details of these stories please visit, http://www.cmac.ac.uk/press.html.

Other Press Highlights

- Centre Director, Professor Alastair Florence was interviewed at the Chemspec Europe conference about his experiences with continuous crystallisation
- Holyrood Online, May edition, ‘Chemistry Set’
- Chemical & Engineering News, May edition, ‘Europeans seek competitive advantage from continuous processing’
- The Times Business Insight, January 29th, ‘More hands make less work’
- HM Government Strategy for UK Life Sciences newsletter, July 2013

Publications

- Kitson, P. J.; Symes, M. D.; Dragone, V.; Cronin, L.: Combining 3D printing and liquid handling to produce user-friendly reactionware for chemical synthesis and purification. Chemical Science 2013, 4, 3099-3103.
Patents


Conference Proceedings


• Jawor-Baczynska, A.; Sefcik, J.: Development of continuous crystallisation processes of pharmaceutical compounds to achieve better control over final product attributes. In 17th International Conference on Crystal Growth and Epitaxy: Warsaw, Poland, 2013.


Invited Speakers


Sponsorship

• Flow Chemistry Symposium organised jointly with CMAC and RSC at Chemspec Europe 2013, Munich Germany

• CrystallisAbility, Syngenta Jealott’s Hill, Bracknell

• Dial a Molecule Grand Challenge: Next-Generation Reaction Platforms Technology Showcase, Brunel University, UK

• Manufacturing the Future 2014 – conference hosts @ University of Strathclyde

Other News

• Professor Alastair Florence invited to join the board of Chemical Innovation Knowledge Transfer Network (CIKTN).

• CMAC joins A.SPIRE (an international non-profit association formed to represent the private sector as a partner in the Sustainable Process Industry through Resource and Energy Efficiency).

• Professor Alastair Florence has been appointed conference chair of the Academy of Pharmaceutical Science (APS) 2013.

• Craig Johnston has been appointed to the Scottish Technology Advisory Group.

• Professor Alastair Florence has been named as the new chair of the British Association of Crystal Growth (BACG).

• Dr Thomas McGlone, postdoctoral research associate @CMAC University of Strathclyde was shortlisted for the CIA Young Ambassador Award.
The CMAC Doctoral training Centre commenced in October 2012 with the first cohort completing their first year’s residential training in May 2013. The second cohort of 20 students will commence their studies in October 2013 and will benefit from inputs from all of the EPSRC Centre universities (Bath, Cambridge, Edinburgh, Glasgow, Heriot-Watt, Loughborough and Strathclyde).

The DTC provides a cohort approach to deliver the required skills with:
- **Interdisciplinary training** – fresh approach to problems
- **Team working** – e.g. group design project, summer schools
- **Meeting student aspirations** – industry relevant, excellent facilities, exciting projects
- **Establish life-long links** – create a community of practice in continuous manufacturing

The DTC PhD Training Programme

The DTC four year programme combines a dynamic, multi-disciplinary training spanning the breadth of the Centre’s research scope. The programme combines taught formal training and research (Figure 25). The formal training programme is co-ordinated by Dr Jan Sefcik. There are three elements to the taught component: (i) a range of taught modules covering the different aspects of the programme; (ii) individual and group miniprojects; (iii) transferable skills training. On completion of the 1st year training programme students move into the research phase of their projects.

Figure 25. The new DTC will create a new community of continuous manufacturing researchers.
Meet the DTC 2012 cohort……

Juliet Adelakun  
**Home University:** Heriot-Watt University  
**Supervisor:** Professor Xing-wei Ni  
**Project:** ‘Characterisation of concentration and size profiles in a Continuous Oscillatory Baffled Crystalliser (COBC)’. My research will gain better understanding and control over cooling crystallisation in a continuous crystalliser, by using experimental data to build up models to predict operational and quality parameters.

Georgi Alekseiev  
**Home University:** University of Strathclyde  
**Supervisor:** Professor David Littlejohn and Dr Alison Nordon  
**Project:** ‘Real-time analytical technologies for optimisation and control of continuous processes’. My research will combine data analysis and monitoring and control of multi-step continuous operations for enhanced process understanding and real-time optimisation.

Rebecca Halliwell  
**Home University:** University of Strathclyde  
**Supervisor:** Professor Alastair Florence  
**Project:** ‘Lab scale continuous crystallisers for control of pharmaceutical polymorphs and critical particle attributes’. My research will aim to investigate the spray drying technique for continuous pharmaceutical crystallisation.

Anneke Klapwijk  
**Home University:** University of Bath  
**Supervisor:** Professor Chick Wilson  
**Project:** ‘Inducing layered solid-forms and controlling defects in multi-component continuous crystallisation’ My research will targets the introduction of disorder defects in molecular materials for enhanced physical properties, such as solubility and compressibility.

Fraser Mabbott  
**Home University:** University of Strathclyde  
**Supervisor:** Professor Alastair Florence  
**Project:** ‘The ‘Exquisite Particle’ – Understanding Fouling’. The principal aim of this project is to investigate a selection of different materials of construction that are commonly encountered within the pharmaceutical industry and the effect they have upon crystallisation fouling.

Laura Martinez Marcos  
**Home University:** University of Strathclyde  
**Supervisor:** Professor Gavin Halbert  
**Project:** ‘Influence of solid form properties on formulation and extrusion processing’. My research will investigate the application of hot-melt extrusion to develop and manufacture solid dosage forms with the aim of improving oral bioavailability of poorly soluble drugs.

Iyke Onyemeluwere  
**Home University:** Loughborough University  
**Supervisor:** Professor Chris Rielly and Professor Zoltan Nagy  
**Project:** ‘Comparative investigation of continuous crystallisation approaches using process analytical technology’. My research will aim to develop a crystallisation monitoring and control framework for continuous manufacturing using complementary process analytical technology tools.

**2013-2014 DTC Project Themes**

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<tr>
<th>Institution</th>
<th>Name of Student</th>
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<tbody>
<tr>
<td>Glasgow</td>
<td>Lorna Christie</td>
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<tr>
<td>Edinburgh</td>
<td>Daniel Ward</td>
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<td>Loughborough</td>
<td>Dimitros Fysicopoulos</td>
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<td>Glasgow</td>
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<td>Cambridge</td>
<td>Mark Phillips</td>
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<td>Strathclyde</td>
<td>Albarah Al-Afandi</td>
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<td>Emmauel Kimuli</td>
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<td>Heriot-Watt</td>
<td>Guillermo Jimeno Millor</td>
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<td>Strathclyde</td>
<td>Maria Lucia Briuglia</td>
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<tr>
<td>Bath</td>
<td>Lauren Agnew</td>
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<td>Strathclyde</td>
<td>Elanor Brammer</td>
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<td>Glasgow</td>
<td>Jamie Purcell</td>
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<td>Strathclyde</td>
<td>Thomas Kendall</td>
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<td>Strathclyde</td>
<td>Leda Todorova</td>
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<td>Joanna Lothian</td>
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<td>Edinburgh</td>
<td>Fraser Keir</td>
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<td>Strathclyde</td>
<td>Rajesh Gurung</td>
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The Electronic Lab: Notebooks and Databases

Electronic Lab Notebooks (ELN)

This year the Centre’s researchers will be provided with cutting edge scientific ICT in the form of Electronic Lab Notebooks (ELN). ELN are designed to replace traditional paper-based notebooks and will allow users to analyse and report scientific findings, facilitating the research data lifecycle from collection to publication and subsequent digital storage for re-use. Experimental procedural workflows and SOPs developed in the Centre will be made available to all researchers, across all sites, by implementing within the ELN platforms enabling systematic, common streamlined approaches to research activities such as continuous crystallisation approaches or PAT monitoring and control. Data will be made searchable to avoid the duplication of experiments, with data and reports being shared amongst the Centre, and with third parties where appropriate, to ensure that as much value can be extracted from resources as possible. Wherever possible, web-based content delivery will ensure that data are readily accessible from any PC or smart devices such as tablets and phones, ensuring maximum access to researchers as they visit different labs in the Centre to perform experiments. This is particularly relevant for the new TIC facility, where it is anticipated we will have visiting researchers from collaborators on an on-going basis. Scientific insight from researchers captured in the ELN will be integrated with data from equipment to provide Intelligent Decision Support (IDS) systems developed as a part of the £3 million EPSRC ICT CMAC award and the £34.2 million RPIF award from HEFC. This platform will be built around Accelrys’ iLabber ELN, Pipeline Pilot and Materials Studio with currently discrete functionality being interwoven to provide a useful and rapidly evolving IDS system for continuous manufacturing processes.

Equipment database

ULab is a unique web-based laboratory and equipment management system developed at the University of Strathclyde with an EPSRC Institutional Sponsorship award. It enables users to catalogue and visualise their key laboratory equipment on fully customisable floor plans, monitor their activity as well as handling complex booking, both within their own research groups and with other institutions within the Centre. Managers are able to gain an overview of their systems ensuring that equipment is utilised in the best manner possible. Equipment from the Centre’s labs at Strathclyde has already been added to ULab with additional functionality being developed as a part of the EPSRC ICT CMAC award.
Figure 26. Electronic Lab Notebooks make the headlines in Chemistry World

Figure 27. Researchers’ experimental data are captured using Electronic Lab Notebooks (ELN) and then stored in databases alongside real-time data from process equipment. Scientific workflows developed in conjunction with researchers analyse data and generate reports to facilitate Intelligent Decision Support (IDS). A web-based IDS Portal provides users with targeted information depending on their role within the Centre and also provides a means of sharing data with external collaborators.
Funding highlights 2012-13

Building a Sustainable Centre: Funding Highlights

Overall funding secured is now £60m, well ahead of business plan with an additional £40m secured over the last year across EPSRC, TSB and EU. This is significantly ahead of initial business plan of £36m. The major funding from HEFCE was a £34m project to provide state of the art facilities. This and other funding streams are outlined. Alastair Florence and Craig Johnston are working closely with the Advisory and CMAC Board to ensure sustainability.

RPIF

In June CMAC was awarded a £34.2m funding boost. This was composed of £11.4 million cash injection by the Higher Education Funding Council for England (HEFCE) under the UK Research Partnership Investment Fund (UKRPIF), supported with £22.8 million industry and charity contributions.

The Chancellor of the Exchequer said:

“By bringing together our Nobel Prize winning scientists, our world-class companies and our entrepreneurial start-ups, we can drive innovation and create the economic dynamism Britain needs to win in the global race.

“And today, I can announce five new projects through our £300 million UK Research Partnership Investment Fund - using public money to secure private investment so our world-class science also delivers jobs and growth.”
Minister for Universities and Science David Willetts said:

“The UK’s world-class universities are at the forefront of our economic recovery. It’s vital we do everything we can to encourage collaboration with the private sector and boost funding for research. These excellent projects will not only deliver new knowledge and applications for industry, but will accelerate growth and foster innovation between the research base and business, keeping the UK ahead in the global race."

Sir Alan Langlands, Chief Executive of HEFCE, said:

“These five projects highlight yet again the success that UK universities have in working with commercial partners and charities to raise funds and deliver vital initiatives to stimulate research in critical areas vital to the economy. In challenging times, the higher education sector consistently demonstrates its key role in delivering growth.”

ICT - Intelligent Decision Support and Control Technologies for Continuous Manufacturing and Crystallisation of Pharmaceuticals and Fine Chemicals

The goal of this £3M project is to develop a comprehensive intelligent decision support platform for continuous manufacture of crystalline products comprising monitoring, signal processing, data analysis, communications and control technologies. Although continuous crystallisation provides significant benefits for innovative manufacture, the key challenge of real-time, robust monitoring of quantitative attributes (form, shape, size) of particulate products still remains a massive challenge. While particle attributes are crucial for downstream processing of products, no current solution allows the processing of data from in-line sensors to reliably extract these attributes in real time across multiple manufacturing steps and the subsequent use of this knowledge for intelligent decision support and control of processes. The development of solutions for the sector requires expertise across many technologies driven by end user requirements. The industrial co-creators will provide the requirements, the range of expertise within the applicants ensuring that the goals of the programme are met. The grant will enable the establishment of a process test-bed which as the project matures will be made available to a range of national and international user and application communities. This activity will support the creation of a requirement and technology roadmap, in so doing informing both the research and commercial communities on future opportunities. The project will also yield the following added value to the community:

- the cross-disciplinary nature of the project and participating teams will stimulate new solutions and promote creativity through sharing best practice in executing research from different perspectives
- the PDRAs will be applying their know-how to joint development tasks, allowing them to gain comprehensive knowledge and expertise across a range of field and in so doing provide trained, talented engineers that will fuel the deployment of these innovative solutions
- the project addresses the integration of a number of distinct architectural layers to transform a physical infrastructure into a flexible platform which supports a range of applications whilst accessible to users

TSB Funded Projects

CMAC has started 2 industry-academia projects jointly funded by the TSB and EPSRC.

- The Make To Order Processing Plants (MOPP) project is being led by Perceptive Engineering with the Centre for Process Innovation and AstraZeneca. The project aims to develop an adaptive ‘Dial a Product’ control system to deliver the precise control required for high value low volume manufacturing systems. Combining control design and analytical techniques will enable the reactors to reach optimum performance quickly and efficiently as manufacture switches between products and reactors. CMAC is providing expertise in continuous processing and has a novel demonstrator crystallisation unit from Cambridge Reactor Design.

- The second project, led by Syrris, in collaboration with GSK, AMRI UK and CMAC will develop an innovative modular system for continuous chemical processing at the 10s to 100s kg scale. It will develop modules that can be used by any chemical industry to perform unit operations such as liquid-liquid, liquid-solid and liquid-solid-gas phase reactions, crystallisations and aqueous work-up in a continuous process, with analysis. The modules will be scalable, easy to use, automatable and able to be quickly reconfigured into hundreds of conceivable single or multi step process systems.

The projects have a total value of ~ £0.7 and 1.0million respectively.

Other related funding

- Centre Co-Investigator (Prof Halbert) is involved in a successful IMI project, Orbito, that is relevant to the EPSRC Centre scope providing fundamental understanding of physic-chemical properties of pharmaceutical particles.
- Centre Co-Investigators (Prof Sir Mike Gregory and Dr Jag Srai) are involved in an EPSRC project entitled Terpene-based Manufacturing for Sustainable Chemical Feedstocks. The overall objective of the project is to develop sustainable and integrated pathways to manufacture for industrial chemicals based on renewable biological terpenoid feedstocks.
Meet the Teams

Principle Investigator: Professor Alastair Florence
Home Institution: University of Strathclyde
E-mail: alastair.florence@strath.ac.uk

Researchers:
- Dr Lihua Zhao, Senior Research Associate, Centre Platform RA. Feasibility studies and continuous crystallisation projects.
- Dr Thomas McGlone, Research Associate, Constructing exquisite particles (growth, transport, fouling and controlling agglomeration)
- Dr Humera Siddique, Research Associate on TSB funded projects, Made to order process plants (Perceptive Engineering, CPI and AstraZeneca) and Development of an innovative modular system for continuous chemical processing (Syrris, GSK and AMRI)
- Naomi Briggs, PhD Researcher, Controlling nucleation, growth and polymorphism in continuous oscillatory baffled crystallisers.
- Francesca Perciballi, PhD Researcher, Continuous formation of optimised particles for formulation and processing.
- Rebecca Halliwell, DTC Researcher, Lab scale continuous crystallisers for control of pharmaceutical polymorphs and critical particle attributes.
- Fraser Mabbott, DTC Researcher, The exquisite particle—understanding fouling.

Co-Investigator: Dr Jan Sefcik
Home Institution: University of Strathclyde
E-mail: jan.sefcik@strath.ac.uk

Researchers:
- Dr Anna Jawor-Baczynska, Research Associate, Modular test bench for continuous crystallisation.
- Ulrich Schacht, PhD Researcher, Control of nucleation in continuous crystallisation processes.
- Rachel Sheridan, PhD Researcher, Understanding and mitigation of fouling in continuous crystallisation.

Co-Investigator: Professor David Littlejohn
Home Institution: University of Strathclyde
E-mail: d.littlejohn@strath.ac.uk

Researchers:
- Jaclyn Dunn, Research Associate, The introduction of analytical measurements for control of continuous filtration and drying.
- Laura Palmer, PhD Researcher, Development of in-situ and non-invasive measurement techniques for the monitoring and control of crystallisation.
- Denise Logue, PhD Researcher, In-situ and non-invasive measurement techniques for the monitoring and control of continuous manufacturing processes.
- Natalia Dabrowska, DTC Researcher, Real-time analytical technologies for optimisation and control of continuous processes.
- Joanna Lothian, DTC Researcher, In-situ imaging and optical spectroscopic monitoring of crystallisation processes.

Co-Investigator: Dr Alison Nordon
Home Institution: University of Strathclyde
E-mail: alison.nordon@strath.ac.uk

Researchers:
- Dr Anna Jawor-Baczynska, Research Associate, Modular test bench for continuous crystallisation.
- Ulrich Schacht, PhD Researcher, Control of nucleation in continuous crystallisation processes.
- Rachel Sheridan, PhD Researcher, Understanding and mitigation of fouling in continuous crystallisation.

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- Jaclyn Dunn, Research Associate, The introduction of analytical measurements for control of continuous filtration and drying.
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- Denise Logue, PhD Researcher, In-situ and non-invasive measurement techniques for the monitoring and control of continuous manufacturing processes.
- Natalia Dabrowska, DTC Researcher, Real-time analytical technologies for optimisation and control of continuous processes.
- Joanna Lothian, DTC Researcher, In-situ imaging and optical spectroscopic monitoring of crystallisation processes.
Co-Investigator: Professor Gavin Halbert
Home Institution: University of Strathclyde
E-mail: g.w.halbert@strath.ac.uk

Researchers:
- Laura Martinez-Marcos, DTC Researcher, Influence of solid form properties on formulation and extrusion processing.

Co-Investigator: Professor Umit Bititci
Home Institution: University of Strathclyde
E-mail: u.s.bitici@strath.ac.uk

Researchers:
- Rajan Talati, Researcher, Manufacturing operations and supply chain management challenges in continuous manufacturing of solids.
- Colin Andrews, Researcher, Manufacturing operations and supply chain management challenges in continuous manufacturing of solids.
- Georgi Aleksiev, DTC Researcher, Exploring supply network reconfiguration opportunities arising from more continuous processing in Pharma.

Co-Investigator: Professor Chick Wilson
Home Institution: University of Bath
E-mail: c.c.wilson@bath.ac.uk

Researchers:
- Dr Karen Robertson, Research Associate, Multi-component crystallisation of agrichemicals and development of flow crystallisers.
- Kate Wittering, PhD Researcher, Multi-component crystallisation in the continuous flow environment.
- Anneke Klapwijk, DTC Researcher, Inducing layered solid-forms and controlling defects in multi-component continuous crystallisation.

Co-Investigator: Professor Sir Mike Gregory
Home Institution: University of Cambridge
E-mail: mig@eng.cam.ac.uk

Researchers:
- Dr Jag Srai, Research Associate, Manufacturing operations and supply chain management challenges in continuous manufacturing.
- Leila Alinaghian, PhD Researcher, Manufacturing operations and supply chain management challenges in continuous manufacturing.

Co-Investigator: Professor Colin Pulham
Home Institution: University of Edinburgh
E-mail: c.r.pulham@ed.ac.uk

Researchers:
- Craig Henderson, PhD Researcher, Co-crystals of energetic materials – a new route to insensitive munitions.
- Paul Coster, PhD Researcher, Investigating the polymorphism of energetic materials.
- Alasdair Mackenzie, PhD Researcher, Non-photochemical laser-induced nucleation of pharmaceuticals and fine chemicals.

Co-Investigator: Professor Xiong-Wei Ni
Home Institution: Heriot-Watt University
E-mail: x.ni@hw.ac.uk

Researchers:
- Dr Cameron Brown, Research Associate, Characterisation and development of continuous oscillatory baffled crystalliser.
- Craig Callahan, PhD Researcher, Probing into nucleation of cooling crystallisation in an oscillatory baffled crystalliser.
- Natalia Falenta, PhD Researcher, A study of the effect of mixing mechanisms in cooling crystallisation of adipic acid.
- Hannah McLachlan, PhD Researcher, Investigations into parameters affecting purity in the oscillatory baffled crystalliser and stirred tank reactor.
- Juliet Adelakun, DTC Researcher, Characterisation of profiles and steady states in a continuous oscillatory baffled crystalliser (COBC) using cooling crystallisation process.
Phase I of the programme has seen excellent progress in developing a range of continuous crystallisation technologies and platforms. With the success of the RPIF bid and the new TIC facility coming into place these are exciting times for the Centre and our partners as we develop our plans for Phase II of the research programme.”

Prof. Alastair Florence, The Centre Director
Phase II of the Centre will commence in October 2013 and will be focused on the three themes of products, processes and operations around the 3 main work packages:

- “lab scale continuous process capabilities to support end-to-end manufacturing ”
- “tools and workflows for rapid product assessment and continuous process selection”
- “product-process archetypes that support supply chains of the future”

These areas have been used extensively through our original Centre plan and developed in Phase I of the programme. The general aims will continue to be: to study inherent properties of particles that impact on their processing and performance, develop understanding of how to manipulate, retain and control these during continuous processing; develop tools and workflows to allow rapid assessment of these for different molecules to inform continuous process selection; to develop a range of laboratory scale continuous processing technologies to enable manufacture of particles and formulated product; develop models of supply chain configurations that are suitable for different product-process archetypes, optimising the benefits of continuous operations on the industry. Lab-scale is an important driver for the Centre and to implement at smaller scale the process for understanding and process development.

The EPSRC Centre has secured a dedicated new 500m² laboratory facility in the new £100m Technology and Innovation Centre (TIC) at Strathclyde. The Technology and Innovation Centre will enable world-leading academics and researchers to partner in delivering ground-breaking and viable solutions for energy, manufacturing, health and smart cities. The TIC Lab will act as a physical hub for the National Centre and will house world-class capabilities for crystallisation, process development, materials characterisation, secondary processing and analysis. The recent RPIF award will be used to establish these world class facilities. Importantly, this new building will allow us to co-locate multi-disciplinary teams of PhDs, RAs and academics and specifically industrial researchers across the Centres projects.

The move to the Strathclyde Technology and Innovation Centre will be key to the Centre meeting the research challenges in the three work packages outlined above for Phase II.

Also key to the success of the Centres future is the mid-term review scheduled to take place in March 2014. The mid-term review will be conducted by a panel of independent members from the international academic and industrial communities as well as representatives from the EPSRC. The mid-term review will be a fantastic opportunity for the Centre as a whole, including academics and researchers, to showcase its research and progress in continuous manufacturing to a target audience. The Centre will further showcase its outputs to a wider audience at the 3rd annual Open Day scheduled for September 2014 at the University of Strathclyde. Open days have proven to be a great success as judged by feedback from the public and particularly from the Centres Advisory Board and Technical Committee. The Centre is also proud to host EPSRC’s Manufacturing the Future conference in September 2014. This will be third consecutive year the conference will be held and it is the only national manufacturing research conference focusing on the leading edge, taking a broad perspective on manufacturing. The conference is open to all from academia and industry and will have representatives from EPSRC Centres for Innovative Manufacturing, the Technology Strategy Board High Value Manufacturing programme and the High Value Manufacturing Catapult.

Looking Forward...
The Centre’s key activities are overseen by the Advisory Board and the Centre Management Committee. The Centre Advisory Board is chaired by Prof Paul Sharratt from ICES Singapore. Full membership is shown below. Centre representation on the board includes the Director, Industry Director and EPSRC. Additional members of the board are an experienced grouping of academics and industrialists. The board meets three times per year with at least two meetings face to face. Responsibilities of the board include:

1) Provide independent input from leading academics and industrialists not directly involved in the Centre;
2) Gather views that will influence the running of the research of the EPSRC Centre and DTC;
3) Advise on strategy, reporting, project monitoring etc.;
4) Provide input from researchers from different fields and from stakeholders from sectors other than pharmaceuticals;
5) Carry out an annual review of Centre performance.

### Centre Management Committee

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
<th>Status</th>
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<tbody>
<tr>
<td><strong>Chair</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prof Paul Sharratt</td>
<td>ICES, Singapore</td>
<td>International independent academic</td>
</tr>
<tr>
<td>Dr Clive Badman OBE (deputy-chair)</td>
<td>GSK</td>
<td>Non-independent industry</td>
</tr>
<tr>
<td><strong>EPSRC Centre Representatives</strong></td>
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<tr>
<td>Prof Alastair Florence</td>
<td>EPSRC Centre</td>
<td>Centre Director</td>
</tr>
<tr>
<td>Craig Johnston</td>
<td>EPSRC Centre</td>
<td>Industry Director</td>
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<tr>
<td><strong>Independent Academic Members</strong></td>
<td></td>
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<tr>
<td>Prof Brian Glennon</td>
<td>University College Dublin (SSC)</td>
<td>International independent academic</td>
</tr>
<tr>
<td>Prof Nigel Titchener-Hooker</td>
<td>UCL</td>
<td>Independent academic; EPSRC Centre Emergent macromolecular therapies</td>
</tr>
<tr>
<td>Prof Kevin Roberts</td>
<td>Leeds University</td>
<td>Independent academic</td>
</tr>
<tr>
<td>Prof William Jones</td>
<td>Cambridge University</td>
<td>Independent academic</td>
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<tr>
<td><strong>Non-independent Industrial Members</strong></td>
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<tr>
<td>Dr Jon-Paul Sherlock</td>
<td>AZ</td>
<td>Non-independent industry</td>
</tr>
<tr>
<td><strong>Independent Industrial Members</strong></td>
<td></td>
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<tr>
<td>Kenny Gilmour</td>
<td>Victrex</td>
<td>Independent industry</td>
</tr>
<tr>
<td>Dr Colin Groom</td>
<td>CCDC</td>
<td>Independent non-academic</td>
</tr>
<tr>
<td>Dr Kevin Girard</td>
<td>Pfizer (US)</td>
<td>International independent industry</td>
</tr>
<tr>
<td>Ian Laird</td>
<td>Moorbrook Textiles</td>
<td>Independent industry</td>
</tr>
<tr>
<td>Dr Paul Stonestreet</td>
<td>Roche</td>
<td>Independent industry</td>
</tr>
<tr>
<td><strong>EPSRC/TSB Members</strong></td>
<td></td>
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<tr>
<td>Dr Richard Bailey</td>
<td>EPSRC</td>
<td>EPSRC representative</td>
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<tr>
<td>Dr Malcom Hannaby</td>
<td>TSB</td>
<td>TSB representative</td>
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<tr>
<td><strong>Observer</strong></td>
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<tr>
<td>Dr Andrea Johnston</td>
<td>EPSRC Centre</td>
<td>Centre Manager</td>
</tr>
</tbody>
</table>

The Management Committee consists of the core management team plus co-investigators. The committee meets monthly and responsibilities of the committee include:

1) Review project progress against milestones;
2) Refine and shape the vision and research programmes in line with user needs
3) Conduct an annual review and assess proposals for future work packages/DTC themes;
4) Responsible for wider functions such as ensuring that the work of the Centre is appropriately disseminated/published and ensure exploitation pathways are optimised;
5) Oversee the financial aspects of the programme;
6) Grow activities and secure future funding towards delivering the Centre vision.
“The Centre continues to progress well – not only in terms of its portfolio of research achievements but also the growing sense of community among the researchers. An impressive feature among those researchers I have talked to has been their clear understanding of and commitment to the aims of CMAC. This bodes well for the future when such engagement will increasingly be a prerequisite for delivering effectively on the research challenges.”

Professor Paul Sharratt, Division Head at ICES and Chair of the Centre Advisory Board.

“The supply chain of the future, for pharmaceuticals, draws nearer as a result of a splendid second year for CMAC. The collaboration across universities and industry continues to focus on innovative research in continuous manufacturing and crystallisation and supplying the skills for the new supply chain through the Doctoral Training Centre and new Masters programme and. The team continue to work with GSK, AZ, Novartis and the other partners to progress innovative research against a well defined, user led scope. For GSK this has resulted in a deepening and broadening engagement over the year. The successful RPIF bid will provide much needed capital equipment for the Centre’s new facility opening in the Technology Innovation Centre in 2014 and across the network. Here we will see industrialists and academics working together to capitalise on new manufacturing technology , creating a new supply chain to meet the increasing need of patients worldwide.”

Dr Clive Badman OBE, VP Investigational Material Supply, GSK and Chair of the CMAC Board.