Institution: University of Leeds

Unit of Assessment: 15 – General Engineering

Title of case study: Case 1. Particle Shape Measurement: Commercialisation and Applications

1. Summary of the impact (indicative maximum 100 words)

Research into on-line control of crystallisation at the University of Leeds started in 2002 which led to a collaboration being formed with Malvern Instruments Ltd (MIL) in 2006 and subsequently to the development of a new type of instrument capable of measuring particle shape and shape-distribution. The instrument range, *Morphologi*, launched in 2007 has since generated sales for MIL of approximately £11 million since January 2008. The instrument is now operational within many industrial sectors and used e.g. to optimise process efficiency and enhance product quality. The success of this instrument has contributed to providing secure employment at MIL and to obtaining the "Queen's Awards for Enterprise: International Trade" in 2011.

2. Underpinning research (indicative maximum 500 words)

Particulate based products are manufactured in many diverse industries such as, pharmaceutical, agro-chemical, dyes and pigments, food, detergent and formulation additives. Particle morphology, i.e. shape, is vitally important to achieve efficient manufacturing processes and produce a final product within its agreed specification. The morphology can directly affect, e.g., the flow of a product within a pipe or a hopper, it can affect the dissolution rate of ingredients within a chemical reactor and it can affect the final product end-user properties. In an extreme case, morphology can change the bio-availability (i.e. uptake within the body) of pharmaceutical ingredients, resulting in a company's loss of license to make a drug product. Given its importance, it would therefore be beneficial to many companies to have the ability to actively monitor particle morphology.

Previous efforts of monitoring particles have focused on optimising and controlling the particle size distribution but this clearly misses important information relating to particle morphology. Moreover, optimisation and on-line control of shape-distribution during formulation and manufacture has long been considered to be too challenging to achieve.

A multi-scale image analysis algorithm based on wavelet analysis [1] was developed by Professors **XZ Wang** and **KJ Roberts** at the University of Leeds, with PhD students J Calderon De Anda and C Ma and research assistant Dr J Chen. The research was conducted with research council and industrial support (AstraZeneca, Syngenta, GlaxoSmithKline, Pfizer, 3M HealthCare and MIL) over a number of projects such as EPSRC funded projects GR/R43860/01 (PI **Roberts**, 2002-2006, £969,560) and EP/C009541/1 (PI **Wang**, 2005-2009, £315,524) and was further developed and transferred to industry with two MIL funded projects. Using crystal edge detection and segmentation techniques, the algorithm enabled the fast on-line analysis of the crystallisation process where, in contrast to off-line techniques, the crystals were not necessarily within the camera depth of focus causing variation of clarity in the image. This method represents a milestone for progress in this specific area of research since it allows process images obtained on-line to be analysed quantitatively and used for closed-loop control of shape distribution of a particle population.

MIL, as an industrial partner to both research projects funded by EPSRC, were aware of the technology being developed at the University of Leeds. Collaborating on MIL's internal research and development programme '*Vision*' the research group at Leeds contributed to their programme through;

(1) the development of a multi-scale image analysis technique that is the only method that can effectively handle images obtained on-line from crystallisation processes [1];
(2) a 3D imaging probe (StereoVision imaging probe) that is the first on-line process imaging

probe that can provide real-time particle 3D shape ([2]; new 3-dimension technology being patented);

(3) development of a morphological population balance process model which for the first time allows modelling and simulation of the dynamic evolution of particle shape distribution subject to variation in process operational conditions [3,4,5];

As a result of the above developments, we have achieved closed-loop control of crystal shape distribution [6], a task long considered as almost impossible to achieve.

Key Researchers:
XZ Wang (Lecturer, 01/02/1995 - 31/07/2001, Senior Lecturer, 01/08/2001 - 31/07/2005, Reader, 01/08/2005 - 31/08/2006 and Professor, 01/09/2006 - present)
KJ Roberts (Professor, 01/01/2000 - present)

3. References to the research (indicative maximum of six references)

[1]. JA Calderon De Anda, **XZ Wang**, **KJ Roberts** (2005) "Multi-scale segmentation image analysis for the in-process monitoring of particle shape with batch crystallisers", *Chemical Engineering Science*, 60(4), 1053-1065, DOI: 10.1016/j.ces.2004.09.068.

[2]. **XZ Wang**, **KJ Roberts**, CY Ma (2008) "Crystal growth measurement using 2D and 3D imaging and the perspectives for shape control", *Chemical Engineering Science*, 63(5), 1173-1184, DOI: 10.1016/j.ces.2007.07.018.

[3]. CY Ma, **XZ Wang**, **KJ Roberts** (2008) "Morphological population balance for modelling crystal growth in face directions", *AIChE Journal*, 54(1), 209-222, DOI: 10.1002/aic.11365.

[4]. CY Ma, **XZ Wang** (2008) "Crystal growth rate dispersion modeling using morphological population balance", *AIChE Journal*, 54(9), 2321-2334, DOI: 10.1002/aic.11549.

[5]. **XZ Wang**, CY Ma (2009) "Morphological Population Balance Model in Principal Component Space", *AIChE Journal*, 55(9): 2370-2381, DOI: 10.1002/aic.11860.

[6]. J Wan, **XZ Wang**, CY Ma (2009) "Particle Shape Manipulation and Optimization in Cooling Crystallization Involving Multiple Crystal Morphological Forms", *AIChE Journal*, 55(8), 2049-2061), DOI: 10.1002/aic.11892.

Of the above, reference [1] best indicates the quality of the underpinning research. This paper has been extensively cited and demonstrates the capability of analysing crystal morphology with varying image quality. This capability was crucial for the development of Malvern's *Morphologi* instrumentation.

4. Details of the impact (indicative maximum 750 words)

Context
UK SME Malvern Instruments Ltd (MIL) is one of the world's leading developers and manufacturers of particle characterisation instruments. Its products are used during R&D and manufacturing to understand and control the properties of dispersed systems ranging from proteins and polymers in solution, particle and nanoparticle suspensions and emulsions, through to sprays and aerosols, industrial bulk powders and high concentration slurries.

In 2005-2006, concurrent with the EPSRC projects (EP/C009541/1 and GR/R43860/01), MIL invested £130k in image analysis and crystallisation research and £300k to sponsor Prof **XZ Wang**'s Readership position. The insights from the *Vision* project fed into MIL's development of *Morphologi G2*, the first instrument in the world able to measure particle shape and shape distribution in real time. Leeds research "*contributed notably*" in three areas [A]:

1. "*The selection of appropriate analysis algorithms leading to improved correlation between*

measured parameters and material performance

2. *Designing and carrying out crystallisation experiments to generate data for system testing and validation*
3. *Using the multi-scale image analysis algorithm developed at Leeds to process the images obtained in experimentation in order to do further analysis of the particles such as texture analysis and classification.*"

The first *Morphologi G2* was launched at the end of 2005 and was superseded in September 2007 by the *G3*.

Impact

The innovative step to which research conducted at the University of Leeds has contributed has had a range of impacts during the eligible period on MIL and also on Morphologi users around the world in a range of industrial sectors and applications, much of which is regarded by MIL as proprietary information. However, public sources of information shows MIL to have a truly global outreach with over 50 international subsidiaries and distributors of their instrumentation.

MIL

Impacts on MIL are both strategic and financial, the Company strengthening its competitive advantage in markets around the world and winning significant new business since 2008:

- Establishing Morphologi as a key product in its portfolio, helped by extending the range in October 2012 with the launch of the G3-ID [B], which added chemical identification of particles using Raman spectroscopy to the core imaging functionality of Morphologi
- Generating revenue of nearly £11m from Morphologi since 2008, "*leading to revenues of £12 million, about 90% of it was generated since January 2008*". [A]
- Strengthening its position in all of its important markets (Europe, USA, Asia and the Far East) through "*increased sales and continued growth worldwide*" [A]
- Helping "*secure a number of people in employment at Malvern*". [A]

As such Morphologi also contributed to the Queens Award for Enterprise, International Trade in 2011. [A, G]

Morphologi Users

Morphologi products provide industrial users with critical information that helps accelerate R&D, enhance and maintain product quality, and optimise process efficiency. They are used in both traditional (e.g. cement) and advanced manufacturing sectors (e.g. pharmaceuticals) in applications including:

- Discovery/R&D screening
- Crystallisation engineering
- Formulation development and optimisation
- Process scale-up and optimisation
- Troubleshooting and root cause analysis in manufacturing
- Automation of microscopy methods e.g. detection and enumeration of foreign particulates
- Validation of quality control particle sizing methods (e.g. laser diffraction)

Examples of Morphologi's impact on users include the following (note that quotes *in italics* are taken directly from the relevant web pages shown in the corroboration section that detail the business advantages these companies experienced since using the instrument):

- **Mo-Sci Corporation (Missouri, USA)** regards the Morphologi G3 as unique, testing several systems and finding that "*while able to characterise our specialised glass materials from a size distribution standpoint, other systems couldn't separate out and identify individual particles that overlapped within the view of the microscope*". And in terms of productivity: "*During the development of the unique glass beads used in blood typing cards (almost half a million glass microspheres per card), it could take three operators four days to look at the beads in a single card.*" "*The Morphologi G3 can accurately measure all the beads on a card in around 15 minutes, and that includes setting up the sample. The measurements themselves take only a few minutes and produce enormous amounts of information*". [C]
- The Morphologi G3 is used by **Solvay Pharmaceuticals (Georgia, USA)** during R&D: "*By*

analysing shape as well as size, the Morphologi G3…helps us more fully understand the materials we are working with and what we can do with them". The company previously contracted out much of its particle characterisation work and has benefited from "*shortened R&D times and much richer data*". The R&D team also studies wet granulation: "*Being able to look at the continuum in terms not only of granule size, but also of shape was a useful exercise in determining granule growth*". [D]

- **Particle Technology Labs (Chicago, USA)**, a full service particle characterisation lab, uses the Morphologi G3 and G3S (G3 with an integrated sample dispersion unit) to analyse clients' materials: "*Not only has the Morphologi G3 allowed us to move away from manual imaging methods, we can now process large numbers of images in many different ways and examine a wide variety of parameters to provide more detailed information and the extra insight required*". [E] The ability to "*investigate sample-to-sample differences or R&D applications…is very important for a cGMP compliant laboratory with a primary client base in the pharmaceutical, nutraceutical, and food & beauty industries*". And the G3S "*provides the highest level of automation, and the greatest variety of measurement parameters*". [F]

As one of MIL's "*key products*" [A] the success of this innovative range of instruments has made an obvious contribution toward MIL being awarded the prestigious Queen's Award for Enterprise: International Trade 2011 [G]. This award adds significantly to the national and international reputation of MIL, to pursue excellence within its business sector.

5. Sources to corroborate the impact (indicative maximum of 10 references)

A. Letter of corroboration from Technology Leader, Malvern Instruments Ltd, Malvern
B. '*Malvern Instruments launches Morphologi G3-ID to global markets*', PR2953, released 3rd October 2012, http://www.malvern.com/malvern/pr.nsf/id/pr2593
C. '*Malvern's Morphologi G3 helps Mo-Sci Corporation produce precision glass*', PR1910, released 30th November 2009, http://www.malvern.com/malvern/pr.nsf/id/pr1910
D. '*Morphologi G3 "adds new dimension" to Solvay Pharmaceuticals R&D*', PR1924, released 9th February 2010, http://www.malvern.com/malvern/pr.nsf/id/pr1924
E. '*PTL adds Malvern's Morphologi G3 to its testing technologies*', PR1960, release date 4th May 2010, http://www.malvern.com/malvern/pr.nsf/id/pr1960
F. '*Morphologi G3 supports the expansion of Particle Technology Labs*', PRPTL, release date 26th February 2010, http://www.malvern.com/malvern/pr.nsf/id/prptl
G. '*The Queen's Awards for Enterprise Magazine*', Winners 2011, International Trade http://www.queensawardsmagazine.com/winners2011

All web-sites successfully accessed on 22nd October 2013.