Institution: Durham University

Unit of Assessment: 8 Chemistry

Title of case study: Structural science – software and solutions

Period when the underpinning research was undertaken: Between 2003 and 2015

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Prof. Judith A. K. Howard (JAKH)	Professor	1991–
Prof. John S. O. Evans (JSOE)	Professor	1998–
Prof. Ehmke Pohl (EP)	Professor	2007–
Prof. Jonathan W. Steed (JWS)	Professor	2004–

Period when the claimed impact occurred: Between August 2013 and the present

Is this case study continued from a case study submitted in 2014? Yes. In part.

1. Summary of the impact

Durham Chemistry research has led to many widely-used crystallographic tools, diagnostic routines, software packages and enhanced instrumentation. Examples include an array of powerful commercial software packages – *Olex*^{2}, *Autochem, LabSafe, TOPAS* and *NAMI*; new protein crystallisation screening kits (*Durham Screens);* supramolecular organogelators commercialised for pharmaceutical crystallisation; and the *pHeniX powder cryostat* apparatus. Associated software sales total [redacted] and equipment sales [redacted]. We have delivered complementary crystallographic research-based services ([redacted]) and training to enable the next generation of industrial and academic chemists to save time and money through using state-of-the-art analytical techniques.

2. Underpinning research

Durham Chemistry has a long track record of research into the structure-property relationships of functional materials, and these are core activities for several of our departmental research groupings.

The application of crystallographic methods to solve industrial and academic problems is 100% reliant on access to modern computational software packages. Durham research has led to two of the globally most widely-used software packages for small molecule single crystal refinements and powder diffraction analysis. Under EPSRC funding (C536274, GBP940k), the JAKH group, informed by their X-ray crystallography expertise and research, designed and coded a comprehensive software package (*Olex*^{2}) of Python-integrated modules combined with an intuitive scientist-friendly GUI. This platform has allowed the development of many new algorithms to address specific research needs and these are distributed via the open-access *smtbx* small-molecule Python toolbox [R1]. In powder diffraction, JSOE has been integral in the development of the innovative *TOPAS* [R2] suite of software, and his research has led to the incorporation of multiple new data analysis methods therein. These include methods for parametric fitting of huge bodies of diffraction data (e.g., 1000 patterns simultaneously analysed) [R3], for analysing time-of-flight neutron and energy dispersive diffraction data, distortion-mode modelling of functional materials, molecular distortion modes, magnetic diffraction and stacking fault analysis. These methods are used extensively by both industry and academics, with four of these research papers being submitted to REF2021.

The process of producing single crystals for diffraction analysis is challenging, particularly in the field of protein crystallisation, and often perceived as a black box operation. Grant support from the Wellcome Trust (WT094759AIA; GBP147,719) allowed EP to develop a platform technology based upon Thermal Shift Assay data processing that automatically identifies the optimal

conditions for protein crystallisation [R4]. This has been facilitated by the creation of bespoke software, *NAMI*, which can conduct automatic assessment of ThermoFluor assay data, generating melting points and phase transitions from fluorescence signals recorded as a function of temperature. The process has been optimised for high throughput operation in a 96-well format to suit industrial laboratory needs. Complementary research has also generated a series of protein stability screens (the *Durham Screens*). These accelerate research by providing an easy to follow protocol and an off-the-shelf kit to rapidly identify the optimal conditions to study protein-ligand interactions, thus enabling faster determination of key drug-target interactions [R4].

The control of small molecule crystallisation is also of tremendous importance. In particular, polymorph control of drug molecules allows the transformation of hard-to-control or amorphous active pharmaceutical ingredients (API) into readily-handled, predictable crystalline solids with appropriate physical properties. JWS has researched extensively into methods to induce specific polymorph crystallisation and has developed and published a series of supramolecular organogelators for pharmaceutical crystallization [e.g. R5], and contributed to research work underpinning new robotic crystallisation methods.

EPSRC-funded research into negative thermal expansion materials which contract on heating [e.g. R6] and on materials undergoing electronic phase transitions or light-induced phase transitions led to the design, prototyping and commercialisation (in 2003) of the *pHeniX* powder diffraction cryostat with Oxford Cryosystems (https://www.oxcryo.com/product/phenix). Its optimised design incorporated several novel features permitting integration with a range of lab-based instruments, and enable analysis of multiple different sample types.

3. References to the research

Citations according to Web of Science.

[R1] L. J. Bourhis, O. V. Dolomanov, R. J. Gildea, J. A. K. Howard, H. Puschmann, "The anatomy of a comprehensive constrained, restrained refinement program for the modern computing environment-Olex2 dissected", *Acta. Cryst. A – Foundations and Advances* **2015**, *71*, 59–75. DOI: 10.1107/S2053273314022207. **[530 + 11,601 citations of a 2009 paper describing the software package with less detail on the algorithms developed.]**

[R2] A. A. Coelho, J. S. O. Evans, I. R. Evans, A. Kern, S. Parsons, "The TOPAS symbolic computation system", *Powder Diffraction*, **2011**, *26*, S22–S25. DOI: 10.1154/1.3661087. **[150]**

[R3] G. W. Stinton, J. S. O. Evans, "Parametric Rietveld refinement", *J. Appl. Cryst.*, **2007**, *40*, 87–95. DOI: 10.1107/S0021889806043275. **[125]**

[R4] M. K. Grøftehauge, N. R. Hajizadeh, M. R. Swann, E. Pohl, "Protein-ligand interactions investigated by thermal shift assays (TSA) and dual polarization interferometry (DPI)." *Acta Cryst*. **2015**, *D71*, 36–44. DOI: 10.1107/S1399004714016617. **[41]**

[R5] J. A. Foster, K. K. Damodaran, A. Maurin, G. M. Day, H. P. G. Thompson, G. J. Cameron, J. Cuestra, J. W. Steed, "Pharmaceutical Polymorph Control in a Drug-Mimetic Supramolecular Gel" *Chem. Sci.*, **2017**, *8*, 78–84. DOI: 10.1039/C6SC04126D. **[56] [Front cover]**

[R6] S. Allen, J. S. O. Evans, "The kinetics of oxygen migration in $ZrWMoO_8$", *J. Mater. Chem.*, **2004**, *14*,151–156, RSC Hot Article. DOI: 10.1039/B310137A. **[29]**.

4. Details of the impact

Durham research has helped create world-leading software for both single crystal and powder diffraction analysis (both sold commercially), delivered commercial crystallisation kits and diffraction hardware and has had direct impact on companies and the research community.

OlexSys software: EPSRC funding to JAKH enabled the development of *Olex*^{2} [R1], a software suite dedicated to solving, refining and visualising structures from single crystal diffraction data. *Olex*^{2} is commercialised via Durham Chemistry spinout OlexSys which employs 2 PhD-level developers (GBP700k economic impact in period) [E1], and which enables an open source version of the software to be provided to academia available free of charge. *Olex*^{2} has over 12,000

registered users and 800 new installations are registered per month. The software is launched once every two minutes (29k times per month) [E1] and we estimate that over 10,000 crystal structures are solved with *Olex*^{2} a year (currently ~45%, COD-data). The original paper describing the software [R1] has been cited >10,000 times in the REF period, demonstrating its impact on the global chemical community. OlexSys also provides bespoke commercial software to industry: Rigaku-Oxford Diffraction (ROD) sells a branded version of *Olex*^{2} with expanded functionality as part of their X-ray systems (unit cost >GBP300k, with an estimated [redacted] being assigned to the software). ROD have also contracted OlexSys to create an exclusive product *AutoChem* to provide automated, intelligent, real-time structure refinement during data collection as a core component of the *CrysAlis*^{Pro} control software which is supplied with all ROD diffractometers. The latest update, *Autochem5.0* was commissioned in 2020 and will be released with all new diffractometers in 2021. Although sales figures have not been released, we understand >650 units have been installed worldwide (2014–2020), equating to [redacted] in assignable software sales.

OlexSys has used its expertise in research data management from structural research to launch "LabSafe" (https://www.labsafe.org/index.html), a laboratory management package co-developed with Durham Chemistry (2015) that is used for safety assessment, purchasing, tracking and disposal of chemicals. It is now used across the whole of Durham Science Faculty (purchased for [redacted] 2017) it currently tracks 82,500 chemicals for 1500 users. Regensburg University have recently purchased the system (2019, [redacted]) and it is being evaluated by several major universities around the world [E1].

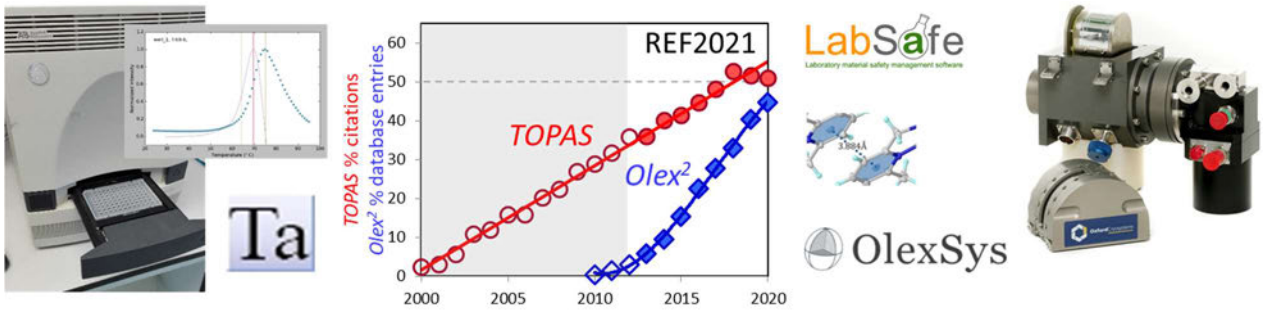

Figure (Left to Right): Molecular Dimensions 96 well assay and NAMI analysis screenshot, TOPAS and Olex^2 *field dominance, and the pHeniX cryostat*

Rietveld software: Powder-diffraction based research has also led to major developments in the *TOPAS* [R5] Rietveld package, with associated financial impact [E2]. *TOPAS* is now the most widely used software for Rietveld analysis by academic and (particularly) industrially users as evidenced by the >50% (and rising) share of global citations in the area shown in the figure and evidenced in [E3]. The similar market dominance to *Olex*^{2} is clear. Over [redacted] copies of the academic version of TOPAS have been sold in the REF period and around [redacted] upgrade licences (1st licence GBP1400; [redacted] total sales) [E2]. Bruker AXS sell a commercial version of the software (stand-alone industry price ~GBP25,000) approximately 50:50 to industry and academia, often as part of a much larger diffractometer purchase. While sales figures are commercially sensitive, Durham University estimate a similar number of sales in-period and total sales around [redacted]. We support the software through the Durham *TOPAS* wiki [E3] and discussion forum (Topas - Topas Wiki (dur.ac.uk)), which has a vibrant and expanding community with >1,000 members from industries in the chemicals (e.g. Johnson Matthey, BASF), cement, pharmaceutical and mining sectors and academia.

Crystallisation kits: We have also exploited our structural research to provide several commercial solutions to the production of crystalline samples suitable for diffraction studies. EP has developed and commercialised a ThermoFluor kit for rapid Thermal Shift Analysis to optimise crystallisation conditions to study protein-small molecule interactions [R4]. He has also developed the associated *NAMI* software application (launched 2014, available from GitHub), which helps users automatically optimise conditions [E4]. *NAMI* has had >7,500 installations. The team has also devised three additional screening kits (pH, salt and osmolytes). Combined they provide a comprehensive indication of protein stability for a wide range of buffer and additive systems. The pH and salt kits were commercialised in 2017 by Molecular Dimensions (MD), followed in 2019 by the osmolytes screen [E5]. All are sold globally with steadily increasing sales reported: **2017**; 29-

kits=[redacted], **2018**; 36 kits=[redacted], **2019**; 65-kits=[redacted], **2020**;139-kits=[redacted] [E5]. The growing influence of the kits has recently been extended using the new nanoDSF system, the accompanying video tutorial has >12,600 views (~17 views per day: Dec 2020) from around the world [E6].

JWS's research into gel crystallisation media for controlling pharmaceutical polymorphism [R5] has led to crystallisation kits being sold by TCI chemicals [E7] and more recently contributed to nanodroplet crystallisation techniques commercialised through SPT Labtech's mosquito liquid-handling robot and Indicatrix Crystallography Ltd [E7].

Powder cryostat sales: Impact through diffraction hardware includes the *pHeniX* powder cryostat co-developed with Oxford Cryosystems (OC) in 2003 and sold to industries, national facilities and academic institutions worldwide [R6, E7]. Around [redacted] units have been sold in the REF period [E8] at a list price of [redacted] ([redacted] total). OC confirm in E8 that: "*without the research excellence of Durham University, we would not be manufacturing and selling these cooling devices as we are today.*" Their other technologies now use some of the ideas developed in the *pHeniX*.

Impacting industry: Our structural expertise has also impacted on industry through their exploitation of research consultancy work. Within period, single crystal and powder diffraction analyses with contract values over [redacted] were performed. For example, JSOE developed a novel automated analytical approach based on [R3] research methods for a Finnish mining company (via Stenman Minerals). The method was used by them to analyse >50,000 samples in the first month [E9]. We have also supported industrial users with solid state structure-related problems via Durham's industry-funded solid state NMR service, helping 53 companies with work charged at [redacted]. JWS and JSOE have also acted as expert witnesses and advisors for pharmaceutical companies on several cases in involving multi-billion-dollar drugs, including major court cases in the US and Canada [E9].

Outreach and training: We place significant importance on outreach activities to maximise impact of our structural research through training the next generation of scientists. JSOE co-authored the 2019 text book on "Rietveld Refinement" [E3] and provides a suite of ~200 heavily-used online training examples [E10]. JSOE and IRE ran biennial training schools in Powder Diffraction and Rietveld Refinement in period ([redacted] turn over), training ~200 international PhD+ delegates (10% from industry) [E10]. They have delivered additional training in Australia (2015) and Sweden (2017). The Durham-based BCA X-Ray Single Crystal School trained >250 delegates. Olexsys staff have run over 44 international workshops in period reaching >3500 delegates, their YouTube Channel has >1200 subscribers; evidence for the effectiveness of these activities comes, in part, from the ensuing software citations (see figure).

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

[E1] Olex^2 from OlexSys (http://www.olexsys.org); UK registered company 07465154. Olex^2 and Autochem: Oliver Presley, Program Marketing Manager (XRD), Agilent (www.agilent.com). Labsafe: https://www.labsafe.org/index.html; CPI integration: https://www.uk-cpi.com/news/innovation-integrator-olexsys-labsafe

[E2] TOPAS: Bruker AXS's, Head of Global Product Management XRD, and the owner of Coelhosoft have provided testimonials confirming JSOE's contribution to *TOPAS* and sales figures. Data to support the figure citations is provided.

[E3] TOPAS software-associated links: TOPAS academic software link http://www.topas-academic.net/; Commercial offering via Bruker https://www.bruker.com/products/x-ray-diffraction-and-elemental-analysis/x-ray-diffraction/xrd-software/topas.html. Rietveld book: http://www.degruyter.com/books/978-3-11-045621-9.

[E4] The launch of the Durham screens is given in: https://www.lubio.ch/media/news/article/molecular-dimensions-presents-their-newest-protein-stability-screen-the-durham-osmolyte-screen/. Molecular Dimensions Ltd (Company No. 01794026) is a world-leading supplier of modern screens, reagents, other consumables and instrumentation for protein structure determination by X-ray crystallography. Their Head Quarters

are in Newmarket, Cambridge, England. Details of the Durham Screens can be found on their website: http://www.moleculardimensions.com/products/durham-screens. Molecular Dimensions are owned by the American parent company Annatrace Products LLC who distribute the Durham screen products in the USA, Mexico, Brazil and Canada: https://www.anatrace.com/Workflow/CryoEM. The *NAMI* software is free to download and readily available on the Durham website – https://github.com/grofte/NAMI

[E5] Molecular Dimensions royalty statements copies provided by Research and Innovation Services - Durham University.

[E6] (https://www.jove.com/video/58666/how-to-stabilize-protein-stability-screens-for-thermal-shift-assays) On-line statistics (30 December 2020, show 12,602 views, including from UK, Europe, US, China, Brazil etc. Locations of the views can be seen on the website).

[E7] TCI, SPT Labtech and indicatrix crystallography websites referencing JWS research contributions to crystallisation work.

[E8] Oxford Cryosystems testimonial on pHeniX cryostat (https://www.oxcryo.com/product/phenix), brochures and sales statement.

[E9] Example open court records as expert witness. Testimonials from Stenman Minerals Ab, established 2011: website https://stenmanminerals.fi/etusivu/about-us/?lang=en.

[E10] Powder diffraction and Rietveld refinement school: website and delegate numbers. The International Union of Crystallography powder commission described it as a "school others should aspire to". The problem-based learning example set for the powder school features many examples derived from Durham research to help train others in our methods. (http://community.dur.ac.uk/john.evans/topas_workshop/pcg_workshop_menu.htm)