National Research Facility Annual Review Template

This Annual Review will be reviewed by the EPSRC National Research Facility High Level Group with any feedback provided by EPSRC. The report and any feedback should be made available to your advisory committee and will also be used within EPSRC by your individual EPSRC contact and the EPSRC NRF lead for information and discussion.

Timeline 2021/22:

- Reporting Period for this Annual Report: **1st September 2020 – 31st August 2021**
- Deadline for Annual Reports**: 11th February 2022**
- Assessment by Panel**: February/March 2022**
- Feedback to Facilities: **March/April 2022**

NRF ANNUAL REPORT

Facility Name:	**The UK High-Field Solid-State NMR Facility**
Director:	**Professor Steven P. Brown (University of Warwick)**
Start/End Dates	**5th January 2020 to 4th January 2025**
Funds awarded	**£2.4M (EP/T015063/1, to lead institution; related grants of total value £170k to Facility Executive PIs at other Universities: EP/T014121/1, EP/T01492X/1, EP/T014997/1, EP/T014911/1, EP/T014350/1)**

1) Value Proposition (max ½ page):

What is your facility uniquely placed to provide for UK research?

Much of the background policy context for the value proposition of the NRF to the UK's research landscape remained relatively unchanged during this period. The next period will likely see further developments with the updating of UKRI's overarching strategy expected soon in the context of the October 2021 Comprehensive Spending Review. The most relevant policy and strategy documents remain UKRI's Delivery Plan (10/20), the parallel more detailed infrastructure roadmap (to 2030), and EPSRC's Delivery Plan (6/19). The UKRI document translates key elements of the Government's ambitions (see BEIS roadmap document 7/20) which envisions the UK being at the forefront of attracting the highest quality researchers from around the world to carry out leading research. In addition, probably the most relevant new policy development is BEIS's Innovation Strategy (7/21). Four of the seven innovation priority areas it identified clearly directly map into research carried out at the Facility as indicated in the discussion of the Scientific Excellence (#2) and Publications (#3), demonstrating that the NRF contributes directly to both the UK's performance in scientific excellence and to key areas of innovation. It should be noted that a vibrant, well-equipped research environment that will help enable the best research and to attract the best talent to the UK is clearly stated in UKRI's Delivery plan, via '*…including technical and infrastructure…*as well as… *internationally competitive, high-quality and accessible facilities…*', with an almost parallel statement in BEIS's Innovation Strategy that '*…innovators often need access to expensive and specialist equipment…*'. The NRF plays directly into these aims and does so highly efficiently, therefore providing a strong value proposition through it being via a dedicated specialist centre. The Facility provides access to the whole of the physical sciences and life sciences communities to cutting-edge high-field solid-state NMR capability. With now two instruments (850 MHz, 1 GHz) backed up by a very wide range of state-of-the-art probe technology and highly trained, expert personnel, that a single university could not justify, this keeps the UK at the leading-edge internationally in a highly cost effective way compared to other ways one might contemplate providing such capability.

2) Scientific Excellence

For the reporting period, please provide examples of how the facility supports scientific excellence in the UK. This should be a short narrative, including information on:

- Important scientific breakthroughs that have been supported by the facility;
- New methodologies that have been developed;
- Case studies that have been produced, with links if possible;

The below highlights do not represent an exhaustive account of the scientific excellence supported by the NRF and new methodologies developed during the reporting period (see full listing with short summaries in #3), but serve to demonstrate how the world-class facilities are underpinning fundamental and applied research across a diverse range of fields and advancing the understanding of the technique itself.

The High-field Solid-State NMR NRF provides its users with access to high magnetic fields and specialist ancillary equipment (including ultrafast MAS, double rotation and a soon-to-be-installed laser heated MAS probe), resulting in a widely-used facility with internationally leading infrastructure. The high magnetic fields provide substantial gains in sensitivity and resolution; opening up the study of challenging isotopes in complex materials. During the reporting period, these attributes have enabled the NRF to support a range of scientific advances from the development of new methods for chemical analysis to the atomic-level understanding of molecular and extended solids.

Notable examples are in the study of metal-organic frameworks (MOFs), which are a very important class of materials with applications in areas such as gas storage and separation, catalysis and drug delivery. Despite the widespread interest in these materials, in many cases their complex structures and interactions with guest molecules remain poorly understood. Work carried out at the NRF has led to significant advances in understanding both the formation of MOFs themselves and how they function as catalysts. Harris, Easun and co-workers (*Chem. Sci.*, 2021, 12, 1486) implemented novel *in situ* experiments at 20.0 T to track the early stages of MOF formation during crystallisation from solution. Here, the high field was crucial for enabling high resolution spectra to be recorded with sufficient sensitivity to follow a nucleation process in real time. This exciting work has provided new insight into the fundamental process of MOF crystallisation and this information will be key in designing materials with tailored properties in the future. Schroder and co-workers (*J. Am. Chem. Soc.* 2021, 143, 29) used ^1H NMR to provide insight into the dispersion of Cu sites in a MOF and the role that these play in the catalytic reduction of NO_2. The increased resolution afforded by high field and fast (60 kHz) MAS in two-dimensional double-quantum correlation spectra was vital in resolving and assigning the different OH groups that provide insight on the nature and distribution of the defect sites present. This information enabled the catalytic performance to be rationalised in terms of the multiple different binding sites present in the structure to promote the adsorption and conversion of NO_2. These studies highlight the atomic-level detail that high-field solid-state NMR can provide for complex materials such as MOFs and how this can be used to understand material properties, paving the way for similar studies in the future.

The NRF has also made important advances in method development and structural understanding for systems of pharmaceutical relevance. The NRF's Technical Director, Iuga, and coworkers (*Magn. Reson. Chem.*, 2021, 59, 1089) demonstrated the successful implementation of ^{1}H-^{35}Cl correlation experiments for hydrochloride salts. Chloride salts have wide application in the isolation and purification of active pharmaceutical ingredients (APIs) and high-resolution structural characterisation is critical in order to understand and predict effects on properties such as solubility, stability and biological activity. Unfortunately, ^{35}Cl is notoriously difficult to study directly by NMR owing to its low receptivity and often large quadrupolar interactions. By using a through-space dipolar correlation NMR pulse sequence, and by exploiting the significant sensitivity and resolution gains afforded at 20.0 T, it was possible to indirectly observe ^{35}Cl via nearby ^{1}H nuclei, simultaneously enabling the local structure around the chloride ions to be characterised as well as ^{1}H-^{35}Cl proximities to be identified. With continued development, this methodology will be applicable to a wide range of pharmaceutical systems. In a separate study by Blanc and coworkers (*Mol. Pharm.*, 2021, 18, 3519), high-field NMR spectra recorded at the NRF were used to characterise formulations of paracetamol supported within amorphous hydroxypropylmethylcellulose acetyl succinate. Amorphous formulations are widely used to increase the bioavailability of APIs, but are very challenging to study owing to the absence of long-range order required for conventional crystallographic analysis. In this work the combination of high magnetic field and fast MAS rate enabled distinct chemical environments to be resolved, and API-polymer contacts to be identified through indirect observation of the low-receptivity ^{14}N nucleus in ^{1}H-^{14}N dipolar correlation experiments. In this way, it was possible to track recrystallisation of the API as a function of loading level, which is important for understanding the limiting solubility of the polymer.

The NRF makes all case studies available on its webpage: https://warwick.ac.uk/fac/sci/physics/research/condensedmatt/nmr/850/case_studies/ For this annual review, we are refreshing two (that dated back to 2016) concerning applications to, first, pharmaceuticals, and, second, plant cell walls (the latter corresponding research at the BBSRC/ EPSRC interface, as reflected by the additional partial funding of the NRF by BBSRC).

3) Publications

Please list the publications for the last 3 years of operation of the current award (by year), Please highlight the top publications for the year.

Also identify any publications that have been prepared for a wider audience.

How do you track publications and encourage users to inform you?

It is a condition of use of the NRF that users acknowledge the NRF and specifically the EPSRC and BBSRC funding in publications and that users report these publications via an online form on the NRF website. In preparing this annual review, users were contacted to check that the publication information is correct and complete. Information of publications from previous use of the NRF by a specific PI is provided to the time allocation panel when reviewing applications for time at the NRF. As detailed in #4, in this reporting period, we have started to produce Snapshot videos (made available online) to make the key results from publications presenting NRF data more widely available.

Concerning publications for a wider audience, the NRF was featured, including an interview with the Director, in a Chemistry World article in October 2020 to mark the delivery to the NRF of the first 1

GHz NMR magnet in the UK: https://www.chemistryworld.com/news/uk-reaches-the-gigahertz-nmr-level-behind-other-nations/4012642.article?adredir=1

To put the outputs of the UK High-Field Solid-State NMR Facility into context, the Facility Executive has compiled, based on information in annual reports and websites, the below Table that compares the number of publications per NMR instrument for the UK High-Field Solid-State NMR Facility to other NMR centres in the UK, Europe and North America. We note that a direct comparison is not straightforward since other centres have multiple instruments at different magnetic field strengths, and it may be that there is a higher publication statistic for the equivalent high-field solid-state NMR instruments. Most comparable to the operation of the UK High-Field Solid-State NMR Facility around one instrument (850 MHz, up to end 2020) is the French High-Field NMR network, which comprises 11 high-field solution- and solid-state NMR instruments in 7 centres, from 750 MHz to 1 GHz: the same number of papers per instrument per year of 16 is reported. This indicator is significantly lower for the MRC and Wellcome Trust funded NMR centres at the Crick Institute and in Birmingham in the UK, and 3 other centres in North America and Europe, though the above proviso about multiple instruments across a range of magnetic field strengths is to be noted.

Facility	Number of Instruments	*Papers per instrument per year
UK High-Field NMR Solid-State NMR Facility	**1**	**16.2**
IR-NMR (France)[a]	11	16.0
NHMFL (US)[b]	57	7.5
NANUC (Canada)[c]	2	5.5
Crick Biomolecular NMR Facility (UK)[d]	5	5.5
Swedish NMR Centre (Sweden)[e]	8	4.7
Birmingham Biomolecular NMR Facility (UK)[f]	5	3.6

a) IR-NMR Facility Report (last two years) https://www.ir-rmn.fr/en/ , b) NHMFL Reports (last three years) https://nationalmaglab.org/ , c) NANUC website (http://nanuc.ca/research/nanuc_rsch.php), d) Crick Biomolecular NMR Facility Annual Reports (last two years), e) Swedish NMR Centre website (https://www.gu.se/en/nmr/about-us/publications), f) Birmingham Biomolecular NMR Facility website (https://www.birmingham.ac.uk/facilities/nmr/research/publications.aspx)

In the below listing, we include a short summary to highlight the importance of each publication, also to illustrate the breadth of applications that are supported by the NRF; for 2020 papers, the NRF has invited the specific user to provide this summary.

2021

Al Rahal, O., Williams, P. A., Hughes, C. E., Kariuki, B. M., & Harris, K. D. M. (2021). Structure determination of multicomponent crystalline phases of (S)-ibuprofen and l-proline from powder X-ray diffraction data, augmented by complementary experimental and computational techniques. *Crystal Growth & Design*, *21*, 2498–2507 DOI: 10.1021/acs.cgd.1c00160

Two multicomponent crystalline phases of (*S*)-ibuprofen and L-proline are reported, with structure determination carried out directly from powder XRD data, augmented by information from high-field solid-state NMR, thermal analysis and periodic DFT-D calculations.

Chen, C. H., Mentink-Vigier, F., Trebosc, J., Goldberga, I., Gaveau, P., Thomassot, E., Iuga, D., Smith, M. E., Chen, K. Z., Gan, Z. H., Fabregue, N., Metro, T. X., Alonso B., & Laurencin D. (2021). Labeling and Probing the Silica Surface Using Mechanochemistry and ^{17}O NMR Spectroscopy. *Chemistry – A European Journal. 27*, 12574–12588 DOI: 10.1002/chem.202101421

Novel mechanochemical approaches to oxygen-17 enrichment were extended mixed SiO_2-TiO_2 systems. A comprehensive NMR methodology was employed which included exploiting the magnetic field variation of the spectra, as well as spatially dependent measurements to elucidate the labelling mechanism.

Cross, C., Cervini, L., Halcovitch, N. R., & Griffin, J. M. (2021). Solid-state nuclear magnetic resonance study of polymorphism in tris(8-hydroxyquinolinate)aluminium*. Magnetic Resonance in Chemistry 59*, 1024–1037 DOI:10.1002/mrc.5147

An aluminium coordination complex of interest for organic light-emitting diode technology is investigated by solid-state NMR and DFT calculations. This work resolves a long-standing debate about the polymorphic structures of this material which are subtly different and difficult to distinguish by diffraction. It also allows one proposed structure to be ruled out on energetic considerations.

Dawson, D. M., Macfarlane, L. E., Amri, M., Walton, R. I., & Ashbrook, S. E. (2021). The Thermal Dehydrofluorination of GaPO-34 Revealed by NMR Crystallography. *J. Phys. Chem. C. 125*, 2537-2545 DOI:10.1021/acs.jpcc.0c1087

High-field Ga NMR experiments were key in characterising an unusual phase transition in a gallophosphate framework, showing the new material is stabilised by the binding of the structure directing agent to give a five-coordinate Ga centre and a purely neutral, but templated, framework.

de Andrade, P., Muñoz-García, J. C., Pergolizzi, G., Gabrielli, V., Nepogodiev, S. A., Iuga, D., Fábián, L., Nigmatullin, R., Johns, M. A., Harniman, R., Eichhorn, S. J., Angulo, J., Khimyak, Y. Z., & Field, R. A. (2021). Chemoenzymatic synthesis of fluorinated cellodextrins identifies a new allomorph for cellulose-like materials. *Chemistry – A European Journal*, *27*, 1374-1382. https://doi.org/10.1002/chem.202003604

Fluorinated constituents are incorporated into self-assembled crystalline materials where a new allomorph is formed as characterized by ^{19}F, ^{1}H, and ^{13}C NMR experiments performed at the NRF.

Gamon, J., Dyer, M. S., Duff, B. B., Vasylenko, A., Daniels, L. M. Zanella, M., Gaultois, M. W. Blanc, F., Claridge, J. B., and Rosseinsky M. J. (2021). $Li_{4.3}AlS_{3.3}Cl_{0.7}$: A Sulfide-Chloride Lithium Ion Conductor with Highly Disordered Structure and Increased Conductivity. *Chemistry of Materials. 33*, 8733–8744 DOI: 10.1021/acs.chemmater.1c02751

The coordination environment of the Al sites in the computationally discovered and experimentally realised Cl-doped Li_3AlS_3 fast Li^+ ion conductor was solved using the enhanced resolution of the ^{27}Al NMR spectrum achieved at the high field facility.

Gardner, L. J., Walling, S. A. Lawson, S. M. Sun, S., Bernal, S. A., Corkhill, C. L., Provis, J. L., Apperley, D. C., Iuga, D., Hanna, J. V., & Hyatt, N. C. (2021). Characterization of and Structural Insight into Struvite-K, $MgKPO_4.6H_2O$, an Analogue of Struvite. *Inorganic Chemistry, 60*, 195-205 DOI: 10.1021/acs.inorgchem.0c02802

The NRF enabled recording of ^{25}Mg and ^{39}K solid-state NMR spectra of Struvite-K, a magnesium potassium phosphate mineral with naturally cementitious properties, which is finding increasing usage as an inorganic cement for niche applications including nuclear waste management and rapid road repair.

Hughes, A. R., Liu M., Paul S., Cooper A. I., & Blanc, F. (2021). Dynamics in Flexible Pillar[n]arenes Probed by Solid-State NMR. *J. Phys. Chem. C, 125*, 13370-13381 DOI: 10.1021/acs.jpcc.1c02046

Very high field ^{1}H NMR combined with very fast magic angle spinning and two-dimensional experiments revealed inter- and intra-molecular interactions in host-guest interactions in a new class of supramolecular assemblies.

Iuga, D., Corlett, E. K. & Brown, S. P. (2021). ^{35}Cl-^{1}H Heteronuclear correlation magic-angle spinning nuclear magnetic resonance experiments for probing pharmaceutical salts. *Magn. Reson. Chem. 59*, 1089-1100 DOI: https://doi.org/10.1002/mrc.5188

In a method development paper, two-dimensional ^{35}Cl–^{1}H solid-state NMR spectra recorded at the NRF are presented for a range of HCl salts, including for the pharmaceuticals cimetidine, amitriptyline and lidocaine.

Jones, C. L., Hughes, C. E., Yeung, H. H.-M., Paul, A., Harris, K. D. M., & Easun, T. L. (2021). Exploiting in-situ NMR to monitor the formation of a metal-organic framework. *Chemical Science*, *12*, 1486–1494 DOI: 10.1039/D0SC04892E

Formation of the MOF material MFM-500(Ni) was probed using an *in-situ* NMR strategy that gives information on the time-evolution of the reaction and crystallization processes, yielding detailed insights on the solution-phase processes and kinetics of crystallization.

Laurencin, D., Li Y., Duer M. J., Iuga D., Gervais C., & Bonhomme, C. (2021). A ^{43}Ca nuclear magnetic resonance perspective on octacalcium phosphate and its hybrid derivatives. *Magn. Reson. Chem. 59,* 1048-1061 DOI: 10.1002/mrc.5149

The NRF enables recording ^{43}Ca experiments, including using double-resonance ^{43}Ca-^{1}H and ^{43}Ca-^{31}P techniques, for octacalcium phosphate and hybrid derivatives involving intercalated metabolic acids namely, citrate, succinate, formate, and adipate, so yielding insight into complex hybrid biomaterials.

Leroy, C., Bonhomme-Coury, L., Gervais, C., Tielens, F., Babonneau, F., Daudon, M., Bazin, D., Letavernier, E., Laurencin, D., Iuga, D. Hanna, J. V., Smith, M. E., & Bonhomme C. (2021). A novel multinuclear solid-state NMR approach for the characterization of kidney stones. *Magn. Reson.,* 2, 653–671 DOI: 10.5194/10.5194/mr-2-653-2021

Understanding the underlying chemical processes that determine the structures of pathological calcifications such as kidney stones underpins better treatments. A fully multinuclear NMR approach was employed including ^{1}H-^{1}H SQ-DQ BABA experiments and ^{43}Ca MAS NMR at the National Facility where subtle variations of the calcium siting could be observed.

Ma, Y., Han, X., Xu, S., Wang, Z., Li, W., da Silva, I., Chansai, S., Lee, D., Zou, Y., Nikiel, M., Manuel, P., Sheveleva, A. M., Tuna, F., McInnes, E. J. L., Cheng, Y., Rudić, S., Ramirez-Cuesta, A. J., Haigh, S. J., Hardacre, C., Schröder, M., & Yang, S. (2021). Atomically Dispersed Copper Sites in a Metal−Organic Framework for Reduction of Nitrogen Dioxide. *Journal of the American Chemical Society*, *143*(29), 10977-10985. https://doi.org/10.1021/jacs.1c03036

The combination of high field and fast magic angle spinning available at the NRF enabled the nature of ^{1}H environments at defect sites of metal-organic framework UiO-66(Zr) to be determined. This helped locate the active sites responsible for efficient NO2 reduction in Cu/UiO-66(Zr).

Pawlak T., Sugden I., Bujacz, G., Iuga, D., Brown, S. P., & Potrzebowski, M. J. (2021). Synergy of Solid-State NMR, Single-Crystal X-ray Diffraction, and Crystal Structure Prediction Methods: A Case Study of Teriflunomide (TFM). *Cryst. Growth Des. 21*, 3328–3343 DOI: 10.1021/acs.cgd.1c00123

Low-temperature ^{13}C spectra recorded at the NRF allow the phase transition between two polymorphs of the pharmaceutical, teriflunomide, that has been approved for multiple sclerosis treatment to be observed directly.

Pugliese, A., Toresco, M., McNamara, D., Iuga, D. Abraham, A., Tobyn, M. Hawarden, L. E., and Blanc F. (2021). Drug–Polymer Interactions in Acetaminophen/Hydroxypropylmethylcellulose Acetyl Succinate Amorphous Solid Dispersions Revealed by Multidimensional Multinuclear Solid-State NMR Spectroscopy. *Mol. Pharm. 18*, 3519-3531 DOI: 10.1021/acs.molpharmaceut.1c00427

Well-resolved ^{1}H ^{14}N HMQC experiments at the high field facility recorded on several acetaminophen cellulose-derived amorphous solid dispersions were key to enable identification of spatial interactions that stabilisation these formulations.

Smith, M. E. (2021). Recent progress in solid-state nuclear magnetic resonance of half-integer spin low-gamma quadrupolar nuclei applied to inorganic materials *Magnetic Resonance in Chemistry 59*, 864–907 DOI: 10.1002/mrc.5116

Solid-state NMR of half-integer quadrupolar nuclei with small magnetic moments and their application to understanding inorganic materials are discussed in this invited review. It is clearly shown that through access to NMR capability such as provided by the National Facility that the utility of such nuclei has greatly expanded.

2020

Ashbrook, S. E., Dawson, D. M., Gan, Z., Hooper, J. E., Hung, I., MacFarlane, L. E., McKay, D., McLeod, L. K., & Walton, R. I. (2020). Application of NMR Crystallography to Highly Disordered Templated Materials: Extensive Local Structural Disorder in the Gallophosphate GaPO-34A. *Inorganic Chemistry*, *59*(16), 11616–11626. https://doi.org/10.1021/acs.inorgchem.0c01450

The multiple types and levels of disorder present in the material GaPO-34A can uniquely be probed using solid state NMR using ^{1}H, ^{13}C, ^{31}P, ^{19}F, and ^{71}Ga where the high field facility was used for ^{71}Ga satellite transition (STMAS) measurements.

Barney, E., Laorodphan, N., Mohd-Noor, F., Holland, D., Kemp, T., Iuga, D., & Dupree, R. (2020). Toward a Structural Model for the Aluminum Tellurite Glass System. *Journal of Physical Chemistry C, 124*(37), 20516–20529. https://doi.org/10.1021/acs.jpcc.0c04342

Neutron diffraction, thermal analysis, and ^{27}Al double-quantum MAS dipolar correlation NMR spectroscopy were performed on an Aluminium Tellurite glass leading to a charge balance model of the internal glass structure.

Cook, D. S., Hooper, J. E., Dawson, D. M., Fisher, J. M., Thompsett, D., Ashbrook, S. E., & Walton, R. I. (2020). Synthesis and Polymorphism of Mixed Aluminum-Gallium Oxides. *Inorganic Chemistry*, *6*, 3805-3816. https://doi.org/10.1021/acs.inorgchem.9b03459

Mixed Aluminum-Gallium oxides useful in electronics and catalysis are synthesized at low temperatures and characterized using ^{27}Al and ^{71}Ga solid state at the high field facility.

Griffiths, K., Halcovitch, N. R., & Griffin, J. M. (2020). Long-Term Solar Energy Storage under Ambient Conditions in a MOF-Based Solid−Solid Phase-Change Material. *Chemistry of Materials*, *32*, 9925-9936 DOI: 10.1021/acs.chemmater.0c02708

This study demonstrated a new mechanism for capturing and storing solar energy using photoresponsive molecules occluded within a metal-organic framework. Solid-state NMR was used to investigate the behaviour of the guest molecule, with high-field ^{1}H fast-MAS NMR supporting that it is highly dynamic when occluded within the MOF, thereby rationalising the efficient photoswitching that was observed.

Grüne, M., Luxenhofer, R., Iuga, D., Brown, S. P., & Pöppler, A. C. (2020). ^{14}N-^{1}H HMQC solid-state NMR as a powerful tool to study amorphous formulations-an exemplary study of paclitaxel loaded polymer micelles. *Journal of Materials Chemistry B*, *8*(31), 6827–6836. https://doi.org/10.1039/d0tb00614a

The quadrupolar coupling in ^{14}N-^{1}H HMQC experiments is shown to be helpful to resolve similar sites in amorphous samples where different magnetic fields shift the individual sites depending on their individual properties where the high field experiments were collected at the NRF.

House, R. A., Rees, G. J., Pérez-Osorio, M. A., Marie, J. J., Boivin, E., Robertson, A. W., Nag, A., Garcia-Fernandez, M., Zhou, K. J., & Bruce, P. G. (2020). First-cycle voltage hysteresis in Li-rich 3d cathodes associated with molecular O2 trapped in the bulk. *Nature Energy*, *5*(10), 777–785. https://doi.org/10.1038/s41560-020-00697-2

The voltage hysteresis of Li-rich cathode materials is explained by a loss of honeycomb structure and the formation of molecular O_2 as observed with a multi-technique analysis including ^{7}Li and ^{17}O NMR.

Kilpatrick, A. F. R., Rees, N. H., Turner, Z. R., Buffet, J. C., & O'Hare, D. (2020). Physicochemical surface-structure studies of highly active zirconocene polymerisation catalysts on solid polymethylaluminoxane activating supports. *Materials Chemistry Frontiers*, *4*(11), 3226–3233. https://doi.org/10.1039/d0qm00482k

The activation of zirconocene catalyst ornamentations on solid methylaluminoxane is characterized using polymerization experiments and ^{91}Zr NMR analysis consistent with surface Zr environments.

Koev, T. T., Muñoz-García, J. C., Iuga, D., Khimyak, Y. Z., & Warren, F. J. (2020). Structural heterogeneities in starch hydrogels. *Carbohydrate Polymers*, *249*(August), 116834. https://doi.org/10.1016/j.carbpol.2020.116834

Starch hydrogels, and the role of water in the formation of the gels, are characterized by multidimensional ^{1}H and ^{13}C solid state NMR that emphasize the static and dynamic portions of the samples.

Li, C., Pramana, S. S., Bayliss, R. D., Grey, C. P., Blanc, F., & Skinner, S. J. (2020). Evolution of Structure in the Incommensurate Modulated $LaNb_{1-x}W_xO_{4+x/2}$ (x = 0.04-0.16) Oxide Ion Conductors. *Chemistry of Materials*, *32*(6), 2292–2303. https://doi.org/10.1021/acs.chemmater.9b04255

The structural evolution between a modulated and unmodulated phase of an oxide ion conductor is revealed through high-field ^{17}O and ^{93}Nb spectra.

Mann, S. K., Pham, T. N., McQueen, L. L., Lewandowski, J. R., & Brown, S. P. (2020). Revealing Intermolecular Hydrogen Bonding Structure and Dynamics in a Deep Eutectic Pharmaceutical by Magic-Angle Spinning NMR Spectroscopy. *Molecular Pharmaceutics*, *17*, 622–631. DOI: 10.1021/acs.molpharmaceut.9b01075

Variable-temperature two-dimensional ^{1}H NOESY solid-state NMR spectra obtained at the NRF are key to distinguishing intermolecular from intramolecular contacts, showing the close association of ibuprofen and lidocaine in a deep eutectic pharmaceutical.

Page, S. J., Gallo, A., Brown, S. P., Lewandowski, J. R., Hanna, J. V., & Franks, W. T. (2020). Simultaneous MQMAS NMR Experiments for Two Half-Integer Quadrupolar Nuclei. *Journal of Magnetic Resonance*, *320*, 106831. https://doi.org/10.1016/j.jmr.2020.106831

Two MQMAS NMR experiments are simultaneously collected using a triply-tuned probe and multiple receivers.

Rees, G. J., Day, S. P., Barnsley, K. E., Iuga, D., Yates, J. R., Wallis, J. D., & Hanna, J. V. (2020). Measuring multiple ^{17}O-^{13}C: J-couplings in naphthalaldehydic acid: A combined solid state NMR and density functional theory approach. *Physical Chemistry Chemical Physics*, *22*(6), 3400–3413. https://doi.org/10.1039/c9cp03977e

Naphthaladehydic acid is characterized using multinuclear NMR with scalar coupling measurements to determine the multiple O functionalities of the lactone head group where high field data recorded at the NRF was needed for reducing quadrupolar linewidths and improving resolution in ^{17}O echo and MQMAS experiments.

Rice, C. M., Davis, Z. H., McKay, D., Bignami, G. P. M., Chitac, R. G., Dawson, D. M., Morris, R. E., & Ashbrook, S. E. (2020). Following the unusual breathing behaviour of ^{17}O-enriched mixed-metal (Al,Ga)-MIL-53 using NMR crystallography. *Physical Chemistry Chemical Physics*, *22*(26), 14514–14526. https://doi.org/10.1039/d0cp02731f

The structure, motion, pore size and shape, and composition of a terephthalate metal organic framework (MOF) is investigated by ^{17}O solid state NMR where the NRF provided a second field as required to fit the spectroscopic properties of the sample.

Rowlands, L. J., Marks, A., Sanderson, J. M., & Law, R. V. (2020). ^{17}O NMR spectroscopy as a tool to study hydrogen bonding of cholesterol in lipid bilayers. *Chemical Communications*. https://doi.org/10.1039/d0cc05466f

The hydrogen bonding environment of cholesterol in lipid bilayers is investigated using the solid state NMR provided by the high field facility and ^{17}O doped cholesterol.

Seymour, V. R., Griffin, J. M., Griffith, B. E., Page, S. J., Iuga, D., Hanna, J. V., & Smith, M. E. (2020). Improved Understanding of Atomic Ordering in $Y_4Si_xAl_{2-x}O_{9-x}N_x$ Materials Using a Combined Solid-State NMR and Computational Approach. *Journal of Physical Chemistry C*, 3–5. https://doi.org/10.1021/acs.jpcc.0c07281

The long range order indicated by neutron diffraction and the short-range disorder indicated by solid state NMR ^{15}N, ^{27}Al, and ^{29}Si spectra are reconciled, where the NRF was used to collect MQMAS ^{27}Al data for component analysis.

Vandeginste, V., Cowan, C., Gomes, R. L., Hassan, T., & Titman, J. (2020). Natural fluorapatite dissolution kinetics and Mn^{2+} and Cr^{3+} metal removal from sulfate fluids at 35 °C. *Journal of Hazardous Materials*. https://doi.org/10.1016/j.jhazmat.2020.122150

The kinetics of Mn^{2+}, Cr^{3+}, and acid removal from contaminated water using fluorapatite is monitored with ^{43}Ca NMR where Ca exchanges for the toxic heavy metals and can be is monitored through NMR.

2019

Al Rahal, O., Hughes, C. E., Williams, P. A., Logsdail, A. J., Diskin-Posner, Y., & Harris, K. D. M. (2019). Polymorphism of L-Tryptophan. *Angewandte Chemie International Edition*, *131*(52), 18964–18968. https://doi.org/10.1002/ange.201908247

A new crystalline polymorph of L-tryptophan is reported, prepared by crystallization from the gas phase. Structure determination was carried out directly from powder XRD data, facilitated by high-field solid-state ^{13}C NMR, which provided crucial evidence to confirm that the material has two independent molecules in the asymmetric unit.

Concistré, M., Kuprov, I., Haies, I. M., Williamson, P. T., & Carravetta, M. (2019). ^{14}N overtone NMR under MAS: Signal enhancement using cross-polarization methods. *Journal of Magnetic Resonance*, *298*, 1–5. https://doi.org/10.1016/j.jmr.2018.10.017

The Overtone Transition (OT) can be used to produce narrow spectral lines in an ^{14}N-^{1}H correlation spectrum but is not sensitive, so Cross Polarization (CP) is used to excite this transition: experiments recorded at the NRF complement those recorded at lower magnetic field.

Dawson, D. M., Moran, R. F., Sneddon, S., & Ashbrook, S. E. (2019). Is the ^{31}P chemical shift anisotropy of aluminophosphates a useful parameter for NMR crystallography? *Magnetic Resonance in Chemistry*, *57*(5), 176–190. https://doi.org/10.1002/mrc.4788

The use of ^{31}P Chemical Shift Anisotropy (CSA) is explored as a structural constraint, where the high field Facility is used for comparison with lower field because the magnitude of the CSA is greater at larger field.

Diaz-Lopez, M., Shin, J. F., Li, M., Dyer, M. S., Pitcher, M. J., Claridge, J. B., Blanc, F., & Rosseinsky, M. J. (2019). Interstitial Oxide Ion Conductivity in the Langasite Structure: Carrier Trapping by Formation of $(Ga,Ge)_2O_8$ Units in $La_3Ga_{5-x}Ge_{1+x}O_{14+x/2}$ ($0 < x \leq 1.5$). *Chemistry of Materials*, *31*(15), 5742–5758. https://doi.org/10.1021/acs.chemmater.9b01734

Langasite is explored as a possible lower temperature solid oxide fuel cell, where ^{17}O, ^{71}Ga, and ^{73}Ga spectra acquired at the NRF point to carrier trapping in this material.

Gamon, J., Duff, B. B., Dyer, M. S., Collins, C., Daniels, L. M., Surta, T. W., Sharp, P. M., Gaultois, M. W., Blanc, F., Claridge, J. B., & Rosseinsky, M. J. (2019). Computationally Guided Discovery of the Sulfide Li_3AlS_3 in the Li-Al-S Phase Field: Structure and Lithium Conductivity. *Chemistry of Materials*, *31*(23), 9699–9714. https://doi.org/10.1021/acs.chemmater.9b03230

A new sulfide Li_3AlS_3 is discovered by a combined computational-experimental method to find a new lithium solid electrolyte, where ^{6}Li and ^{27}Al NMR data collected at the NRF are combined X-ray and neutron diffraction.

Halat, D. M., Britto, S., Griffith, K. J., Jónsson, E., & Grey, C. P. (2019). Natural abundance solid-state ^{33}S NMR study of NbS_3: Applications for battery conversion electrodes. *Chemical Communications*, *55*(84), 12687–12690. https://doi.org/10.1039/c9cc06059f

Wide-line natural abundance ^{33}S spectra collected at the NRF are presented using a frequency stepping approach including the first spectrum of a disulfide.

Heard, C. J., Ashbrook, S. E., Grajciar, L., Rice, C. M., Pugh, S. M., Nachtigall, P., & Morris, R. E. (2019). Fast room temperature lability of aluminosilicate zeolites. *Nature Communications*, *10*(10), 4690. http://dx.doi.org/10.1038/s41467-019-12752-y

Zeolites exchange framework oxygens with water at room temperature in under 24 hours but the framework is not broken as shown by ^{17}O, ^{27}Al, and ^{29}Si spectra, where the NRF was used to clearly resolve two similar Si-O-Al species.

Hughes, C. E., Walkley, B., Gardner, L. J., Walling, S. A., Bernal, S. A., Iuga, D., Provis, J. L., & Harris, K. D. M. (2019). Exploiting in-situ solid-state NMR spectroscopy to probe the early stages of hydration of calcium aluminate cement. *Solid State Nuclear Magnetic Resonance*, *99*(10), 1–6. https://doi.org/10.1016/j.ssnmr.2019.01.003

A high-field *in-situ* NMR study of the hydration of $CaAl_2O_4$ (the most important hydraulic phase in calcium aluminate cement). A variant of the CLASSIC NMR strategy, involving alternate recording of direct-excitation and MQMAS ^{27}Al NMR spectra, was used to monitor the ^{27}Al species present in both the solid and liquid phases as a function of time.

Ihli, J., Clark, J. N., Kanwal, N., Kim, Y. Y., Holden, M. A., Harder, R. J., Tang, C. C., Ashbrook, S. E., Robinson, I. K., & Meldrum, F. C. (2019). Visualization of the effect of additives on the nanostructures of individual bio-inspired calcite crystals. *Chemical Science*, *10*(4), 1176–1185. https://doi.org/10.1039/c8sc03733g

The mechanisms for controlling crystallization processes using soluble additives is explored in calcite crystals, where the NRF is used to confirm Mg substitution in calcite.

Jarvis, J. A., Concistre, M., Haies, I. M., Bounds, R. W., Kuprov, I., Carravetta, M., & Williamson, P. T. F. (2019). Quantitative analysis of ^{14}N quadrupolar coupling using ^{1}H detected ^{14}N solid-state NMR. *Physical Chemistry Chemical Physics*, *21*(11), 5941–5949. https://doi.org/10.1039/c8cp06276e

An efficient ^{14}N-^{1}H correlation experiment is presented that allows the determination of the quadrupolar coupling interactions, where the NRF was used to prove the method for a challenging system.

Kanwal, N., Colaux, H., Dawson, D. M., Nishiyama, Y., & Ashbrook, S. E. (2019). Sensitivity improvement in 5QMAS NMR experiments using FAM-N pulses. *Solid State Nuclear Magnetic Resonance*, *100*, 1–10. https://doi.org/10.1016/j.ssnmr.2019.03.002

A more efficient 5QMAS excitation and reconversion scheme is presented and subsequently implemented at the NRF (for ^{45}Sc), where the scheme is shown to greatly improve sensitivity.

Muñoz-García, J. C., Corbin, K. R., Hussain, H., Gabrielli, V., Koev, T., Iuga, D., Round, A. N., Mikkelsen, D., Gunning, P. A., Warren, F. J., & Khimyak, Y. Z. (2019). High Molecular Weight Mixed-Linkage Glucan as a Mechanical and Hydration Modulator of Bacterial Cellulose: Characterization by Advanced NMR Spectroscopy. *Biomacromolecules*, *20*(11), 4180–4190. https://doi.org/10.1021/acs.biomac.9b01070

The long-range order and local water affinity of bacterial cellulose hydrogels are found to be affected by the presence of arabinoxylan and xyloglucan, where the core, surface-bound, and surface domains are identified by NMR experiments performed at the NRF.

Öster, C., Kosol, S., & Lewandowski, J. R. (2019). Quantifying Microsecond Exchange in Large Protein Complexes with Accelerated Relaxation Dispersion Experiments in the Solid State. *Scientific Reports*, *9*(1), 1–11. https://doi.org/10.1038/s41598-019-47507-8

Relaxation dispersion experiments in proteins are accelerated using paramagnetic doping to overcome low sensitivity, where the resolution in the fingerprint ^{1}H-^{15}N spectrum is improved by the NRF instrumentation.

Seymour, V. R., & Smith, M. E. (2019). Distinguishing between Structural Models of β′-Sialons Using a Combined Solid-State NMR, Powder XRD, and Computational Approach. *Journal of Physical Chemistry A*, *123*(45), 9729–9736. https://doi.org/10.1021/acs.jpca.9b06729

One of four models of the replacement of silicon and nitrogen by aluminum and oxygen in β′-Sialons is found to be consistent with high field ^{29}Si and ^{27}Al NMR data collected at the NRF.

Terrett, O. M., Lyczakowski, J. J., Yu, L., Iuga, D., Franks, W. T., Brown, S. P., Dupree, R., & Dupree, P. (2019). Molecular architecture of softwood revealed by solid-state NMR. *Nature Communications*, *10*(1), 1–11. https://doi.org/10.1038/s41467-019-12979-9

The polymer interactions between cellulose, xylan, and galactoglucomannan suggest a model of the softwood molecular architecture where the NRF was necessary to unambiguously differentiate between 2-fold, and 3-fold xylan using ^{13}C correlation experiments.

Wang, L., Menakath, A., Han, F., Wang, Y., Zavalij, P. Y., Gaskell, K. J., Borodin, O., Iuga, D., Brown, S. P., Wang, C., Xu, K., & Eichhorn, B. W. (2019). Identifying the components of the solid–electrolyte interphase in Li-ion batteries. *Nature Chemistry*, *11*(9), 789–796. https://doi.org/10.1038/s41557-019-0304-z

The solid-electrolyte interphase responsible for the reusability of lithium ion batteries is shown to be lithium ethylene mono-carbonate by a multi-technique approach including ^{1}H and ^{7}Li spectra collected at the NRF.

4) Impact

Training, Outreach and Societal Impacts (max. 1 page): For the reporting period please provide evidence of the broader impact that the facility has through its outreach and training activities. This could include:

- Brief description of training courses and workshops held by the facility for its users / potential users and any benefits highlighted by the participants;
- Activities to promote the facility beyond its core user base;
- Facility staff training and career development;
- Public engagement;
- Examples of societal & economic impacts that the facility has created or been involved with.

The focus of the NRF's engagement with the userbase and wider NMR community was the 2021 annual symposium which was held online due to COVID-19 restrictions. As in previous years, no registration fee was charged in order to maximise the accessibility of the symposium. The online format had the benefit of reaching a much wider audience than previous symposia that had an average of 60 attendees in person, with 181 registered participants (peak attendance at any one talk was 100). The symposium was also significantly more diverse with 83 international registered participants, two international keynote speakers and 13 industry registered participants. The increased reach of the online format is a benefit that the NRF is keen to maintain moving forwards, with the 2022 annual symposium planned to take place in a hybrid format. In addition to the annual symposium, additional outreach to the industrial and materials communities was initiated through communication with the Society of Chemical Industries Materials Committee and the Metals in Biology BBSRC Network. These interactions resulted in plans being put in place for a joint one-day workshop on *Solid-State NMR for Materials Analysis* (held in October 2021, 260 registrations, peak attendance at any one talk was 200) and the Facility Management Team member Trent Franks giving a seminar introducing the NRF (held in January 2022, 30 participants). The NRF is also partnering with the EPSRC-funded ConnectNMR UK network to offer a training workshop for scientists with solution-state NMR expertise, but no or very little solid-state NMR experience, the day before the NRF annual symposium in March 2022.

To continue to reach a wider userbase and engage beyond the NMR community, the NRF Twitter feed @NrfHf was set up in the reporting period at the time of the installation of the new 1 GHz spectrometer in October 2020. In addition, during the reporting period, six "Research Snapshot" videos were produced by Facility users. This new format is hosted on the Facility Youtube channel to showcase research taking place at the Facility in an accessible format.

Throughout the reporting period, the NRF has continued to provide training to the userbase (see #6), in particular 19 PhD students and 14 PDRAs (with 9 and 4 respectively being first-time visitors) who gained valuable experience using the world-leading equipment. In-person visits to the Facility were not possible or of limited form for much of the reporting period due to COVID-19 restrictions. To mitigate this and to continue to offer a high-level service, remote access was introduced whereby users could control the spectrometer remotely via an online interface while at the same time receiving direct guidance from the Facility Management Team. This proved very successful, so much so that it has continued on an optional basis after formal restrictions were lifted in order to cater for users who have difficulty travelling. In particular, the capability of the facility to allow users to directly control the spectrometer and run their own experiments (rather than offering a sample analysis service) enabled student and PDRA users to continue receiving training and gaining experience in high-field solid-state NMR during a period when access to many experimental facilities was very limited. Looking forwards, the successful implementation of remote access puts the NRF in a strong position to react dynamically to any future restrictions, enabling both training and research to continue at the Facility with the minimum level of disruption. Remote access also has the advantage of facilitating access for those for whom an in-person visit to the NRF is harder to integrate with caring or family responsibilities, as well as reducing the NRF's carbon footprint.

The NRF has continued to support industrial research with 4 PhD students and one PDRA on industrially-funded projects using the Facility. During the reporting period, the Oversight Committee (OC) member Dr Nathan Barrow from Johnson Matthey stepped down from his position as he took on a new role within the company. In view of this, Dr Stephen Day (also from Johnson Matthey) was appointed as an OC member in order to ensure the continuation of industrial representation.

Concerning staff career development, the Facility Management Team was expanded with the appointment of Dr Trent Franks as Facility Manager and the promotion of Dr Dinu Iuga to Technical Director. The appointment of Dr Franks means the Facility can now offer users more focused training in biological solid-state NMR (in which Dr Franks has significant experience). Dr Franks appointment also represents progression within his own career, and as a user of the NRF during his previous postdoctoral research he is now in a position to integrate the training he has received into the day-to-day running of the Facility.

5) Cost Recovery

Please report on the sustainability returns for each year of operation of the current award, as an overall % recovery of running costs and also the actual figures. This includes headings of grant charges, other academic users, students, industry and Other charges for each year against the actual cost of running the facility. A narrative of future plans and issues is required below the table.

We present first a commentary why it is not straightforward to decide which expenditure and income costs to include in order to calculate the % cost recovery in any specific year.

Concerning running costs, we report in the below table for the reporting year (September 2020 to August 2021) the sum of NRF running costs (e.g., cryogens, consumables, accommodation, travel) of £114,401 and local management team (Dinu Iuga, Trent Franks, Charlie Whitewood) direct salary costs of £154,286, making the reported total in the Table of £268,687. (Note that when full FEC costs are included, the total rises to £457,410.)

Since 2016, i.e., the start of the previous funding award, PIs have been encouraged to request funding on UKRI grant applications for NRF time, using a per day rate that includes salary and running costs of £941 (2016-2020 NRF funding) or £917 (2020 onwards under current NRF funding), plus VAT where applicable. Under the previous funding award (5 years up to 4th January 2020), 60 days of grant funding, i.e., £56,460 (+VAT) was received for 4 grants (2 EPSRC, 2 BBSRC, 4 distinct PIs from Southampton and Warwick). In last year's NRF (2020) annual review, the reported income of £23,965 corresponded to income that was invoiced for these awards in year 1 of the current NRF funding. For the current funding period, the NRF has been informed of two successful grant awards, namely an EPSRC grant (EP/V002236/1, start date January 2021) to David Fengwei Xie (Newcastle, formerly Warwick) for 15 days and an NERC award (NE/V010778/1, start date November 2020) for 10 days to Thomas McDonald and Frédéric Blanc (Liverpool) for 10 days. In the below table, we then report grant income as (10+15)*£917 = £22,925.

Year	Running Costs	Grants	Other Academic	Students	Industry	Other	%
Sept 2020 to August 2021	£268,687	£22,925			£2,000		9.3%

What is the NRF's target cost recovery? Under the previous funding award, the NRF transitioned to partial cost recovery (80%) in years 4 and 5 (i.e., 2018 and 2019) from RCUK grants, with a per day rate that includes salary and running costs. In the current funding period (starting 5th January 2020), there is tapering of direct support from 80% to 75% to 70% to 65% to 60% in years 1, 2, 3, 4 and 5, respectively. So considering the 5-year grant as a whole (with an average direct support of 70%), and comparing to the usual 80% FEC as the baseline, for the reported year (September 2020 to August 2021), the stated 9.3% recovery is very close to the 10% per year recovery target.

That said, the Facility Executive is well aware that by the end of this funding award, 20% recovery needs to be achieved. From September 2021, 48 access days per year at the NRF 850 MHz and 1 GHz will be funded at a rate of 816€ / day on a 4-year EU transnational access grant (PANACEA, see #11). Moreover, the Facility Executive is pleased to see a steady increase in both the number of grant applications and the number of days requested on grant applications: 2021 (11 applications for 273 days), 2020 (10 applications for 161 days), 2019 (7 applications for 134 days), 2018 (5 applications for 104 days), 2017 (5 applications for 64 days). In addition, the Facility Executive is keen to increase the industry income; it is hoped that emerging from the pandemic in 2022 results in a return to more in-person user visits to the Facility, reducing the strain on the Facility Management Team associated with remote operation, thus allowing the, to take a more active role in reaching out to potential industry users.

6) Users

Please report on Users by year of operation of current award. This needs to broken down in category of user – student, academic, industry, other. We would like to know unique user numbers and repeat user figures. Indicate the research area split using a chart below the table and how this is measured (eg samples/project types etc). A narrative of future plans and issues is required below the table

How many of the users are new as a % of users this year?

We report from July 2020 to June 2021 that corresponds to the six-monthly time-allocation rhythm of the high-field solid-state NMR NRF. We present individual tables corresponding to the separate time-allocation periods and also for the separate 850 MHz and 1 GHz instruments, noting that the new 1 GHz system was first used in January 2021. We also present a table for the combined number of unique visitors across the whole year and both instruments. As well as stating the number and % of new users (the rest are returning users – we assume that this is what is meant by "repeat user figures" in the rubric), given the COVID disruption in the reporting period, we also indicate the number and % of remote access users.

850 MHz (July 2020 to December 2020)

July 2020 to Dec 2020	PhD Student		PDRA		Academic (PI)		Industry		Other	
Total unique users	6		8		17		0		1	
New users	3	50%	2	25%	3	18%	0	0%	0	0%
Remote	3	50%	7	88%			0	0%	1	100%

850 MHz (January 2021 to June 2021)

Jan 2021 to June 2021	PhD Student		PDRA		Academic (PI)		Industry		Other	
Total unique users	11		3		17		1		1	
New users	2	18%	0	0%	1	6%	1	0%	0	0%
Remote	6	55%	2	67%			1	100%	1	100%

1 GHz (January 2021 to June 2021)

Jan 2021 to June 2021	PhD Student		PDRA		Academic (PI)		Industry		Other	
Total unique users	12		6		13		0		3	
New users	4	31%	2	40%	0	0%	0	0%	0	0%
Remote	8	62%	3	60%			0	0%	3	100%

Total combined (July 2020 to June 2021, 850 MHz and 1 GHz)

July 2020 to June 2021	PhD Student		PDRA		Academic (PI[c])		Industry		Other	
Total unique users	19[a]		14[b]		27		1[d]		4[e]	
New users	9	45%	4	31%	4	15%	1	100%	0	0%
Remote[f]	15	75%	11	85%			1	100%	4	100%

[a] Funded by EPSRC (including a CDT in Molecular Analytical Science, CDT in Plastic Electronics & The Faraday Institution grant), BBSRC, ERC, The Allan Handsel Postgraduate Research Scholarship for Chemistry, Ernest Oppenheimer research studentship. 4 industrially-funded PhD students on projects involve companies across a range of sectors, namely AstraZeneca, Bruker, Pfizer, SG Chemicals Ltd.

[b] Funded by EPSRC (Including a Faraday Institution grant), BBSRC, Innovate UK KTP (with AstraZeneca), MRC, ERC, and an EU Marie Skłodowska-Curie award.

[c] PI numbers are reported for applications to the time allocation process.

[d] Johnson Matthey

[e] Including University research staff and an overseas academic collaborator of a UK-based PI

[f] For this COVID-disrupted reporting period, the only in-person users were from the University of Warwick.

The research split (by day of usage) is presented in this Table:

Research area split	Materials		Bio molecular Solids (including plant cell walls)		Methods		Pharmaceuticals and self-assembly	
	days	%	days	%	days	%	days	%
July to Dec 2020 (850 MHz)	89	52%	60	35%	12	7%	9	5%
Jan to June 2021 (850 MHz)	94	56%	26	15%	9	5%	40	24%
Jan to June 2021 (1 GHz)	78	50%	37	24%	14	9%	26	17%
Combined	261	54%	123	25%	25	5%	75	15%

7) User Surveys/Satisfaction

Please share a summary of any user surveys, including how many users asked and replied and how this has affected facility planning.

Average scores (July 2020 – June 2021, the NRF's time allocation periods)
Rating : 1 Low / 5 High

PI feedback questionnaires (23 sent, 16 responses received: requested once per year)

Q1. The ease of the application process	4.8
Q2. The transparency of the allocation procedure	4.8
Q3. The feedback on time requests	4.8
Q4. The scheduling of your time by the facility	4.8
Q5. Quality of results obtained at the facility	4.7

Visitors feedback questionnaires (45 sent, 23 responses received: requested after each visit. Scores are not provided for questions in italics about accommodation and expenses that were not applicable for remote access during the pandemic.)

Q1. Ease of arranging accommodation	
Q2. Quality of accommodation	
Q3. Location of accommodation	
Q4. Support from FM upon arrival	5.0
Q5. Support throughout your visit	4.9
Q6. Quality of NMR facilities	4.8
Q7. Quality of the sample preparation area and storage facilities	4.8
Q8. Ease of access to the facility out of hours	4.9
Q9. Your overall time at the facility	5.0
Q10. Arrangements for accessing data	4.7
Q11. Arrangements for returning any samples	4.7
Q12. Reimbursement of expenses	

During the reporting year, the Facility Executive decided to use an additional questionnaire related to the changed way of facility access during the pandemic: Remote visitor experience (45 sent, 22 responses: requested after each visit)

Q1. Ease of sending samples to the Facility	4.9
Q2. Assistance from the Facility prior to start of experiments (e.g., advising on experimental set-up)	4.5
Q3. Ease of establishing remote access via Teamviewer (this question is about any IT or connectivity issues)	4.6
Q4. Assistance from the FMT during experiments (e.g., FMT inserting probes, inserting and spinning rotors, and tuning probes)	4.7
Q5. Experience of running experiments remotely via Teamviewer	4.6
Q6. Ease of receiving samples back from the Facility [If applicable at time of completing survey]	4.7

Q7. When in-person visits to the Facility are possible again, indicate your preference for in-person visit (5) compared to remote access (1). 4.2

The Facility Executive and the Oversight Committee review questionnaire feedback at their six-monthly and annual meetings respectively, including specific comments entered into free text boxes. We continue to be pleased with the very high feedback scores received, and the feedback provided is very helpful to the Local Management Team to enhance the quality of the user experience.

8) Service Demand

Please include a chart showing demand and capacity per month by year of operation of the current award.

We report from July 2020 to June 2021 that corresponds to the six-monthly time-allocation rhythm of the high-field solid-state NMR NRF. We present information for the separate time-allocation periods and also for the separate 850 MHz and 1 GHz instruments. The reporting of the 850 MHz instrument time from July to December 2020 corresponds to the restart of operation after the COVID lockdown and the switch to remote operation with users sending in samples; as such, this includes time that had been allocated from March to June 2020 as well as a special direct allocation, where recent users were invited to send in samples (this ensured full usage of the spectrometer). The new 1 GHz system was first used on January 16th 2021 after the completion of the installation by Bruker: up to March 4th, time was used by a special direct allocation (again requesting recent users to send in samples), with time allocated by a special time allocation panel from March 5th onwards. Note that the spectrometers run 24/7, 365 days a year.

Service Demand (by day)	850 MHz July to Dec 2020		850 MHz Jan to June 2021		1 GHz Jan to June 2021		
Applicant type	*Round 21*	*Direct allocn*	*requested*	*granted*	*Direct allocn*	*requested*	*granted*
Outside Warwick (Facility Executive)	8	3	17	17	8	20	20
Outside Warwick (not Facility Executive)	35	66	106	106	9	44	36
Warwick (Facility Executive)	6	0	25	25	19	28	27
Warwick (not Facility Executive)	15	37	24	24	8	26	22
number of access days requested			172			118	
number of access days awarded	64	106	172		44	105	

Spectrometer time usage (% by day)	850 MHz July to Dec 2020	850 MHz Jan to June 2021	1 GHz Jan to June 2021
Time Allocation Panel (TAP) allocated days	35%	91%	67%
Direct allocation	58%		27%
Installation / calibration	7%		3%
Facility manager research			3%
Maintenance	1%	4%	1%
Compensation		2%	
Industrial (Paid-for contract research)#		2%	

#Johnson Matthey

9) Risks

Is there a Risk Register for the facility? How is this used, give some examples of changes that have been made as a result.

Risk mitigation has been inherent to the previous and current applications for NRF funding – this is summarised below. No changes to this risk register since the 2020 annual review.

1. MOST SEVERE: Likelihood Low/ Impact High / Risk rating High

1.1 Catastrophic loss (e.g., due to fire) of the magnet hall(s)

Covered by university insurance, but both would require facilitating access to other instruments in the UK and overseas with facility management team secondment, in person or online, to assist with remote experiments during rebuilding and reequipping.

1.2 Quench of magnet

Mitigation: Bruker have a 24/7 active monitoring system, informing the local management team and Bruker, embedded into the magnet design and operational software. The construction of the new 1 GHz building lab has incorporated necessary venting and emergency hardware & pipework required for a quench situation. The magnets require regular top-ups of liquid helium (and also liquid nitrogen): some mitigation of risk associated with helium shortages is provided by recovery of helium gas boil-off by means of a helium liquefier in the Department of Physics at the University of Warwick.

2. PERSONNEL, long-term unavailability of: Likelihood Medium/ Impact Medium / Risk rating Medium

The COVID pandemic increases the probability of personnel unavailability. However, the historical turnover of staff since the start of Facility operation (2010) or instances of absence is extremely low.

2.1 Director

The management of the NRF through the Facility Executive mitigates the impact if the Director is unavailable. A Deputy Director, Jeremy Titman, Nottingham, is in place along with the University of Warwick FE member, Jozef Lewandowski, who are empowered to act as required under the guidance of the FE.

2.2 Facility Management Team

The University of Warwick local team supporting the Millburn House Magnetic Resonance Laboratory can organise support & contingency plans for any disruptive events.

2.3 Administrator

Current processes are understood across the local management team as well as across the wider Physics department administration team as a fail safe.

2.4 Facility Executive

A reserve member named in grant application, Yaroslav Khimyak, UEA, is in place.

3. EQUIPMENT FAILURE: Likelihood Medium-High / Impact Low-Medium / Risk rating Medium

Manageable equipment failures during normal usage: duplication of equipment, notably probes, amplifiers, and pre-amplifiers; ability to carry out some in-house repairs, and close interaction with the suppliers.

10) Key Performance Indicators (KPIs) and Service Level (SLs) (max. 2 pages)

For the reporting period, please provide brief evidence of the facility's performance against its Key Performance Indicators and Service Levels. This information should tabulated where possible and include the following information:

- Brief description of each KPI or SL;
- Information or data associated with the facility's actual performance against each KPI or SL during this reporting period
- Target metric for each KPI or SL

For any targets that were not met, please provide a detail and describe the steps taken to mitigate negative impact on users and measures taken to improve performance. Often how an issue is dealt with is the more positive information for the panel.

July 20 - June 21				
QUERY LOG				
Respond to query within 5 working days: 99% and above, >90% < 99%; <90%				
Query Log KPI: A query log will be maintained by the NRF, split between active and completed queries. The log will include enquiries regarding the facility, advice for users, guidance to users etc. Respond to queries within 5 working days. Data reported every 6 months.	*July - Dec 20*		*Jan - Jun 21*	
	Queries	Replied within 5 working days	Queries	Replied within 5 working days
Queries from users (email threads, time for response, not FE)	377	100%	1014	100%
Fast-track applications by existing users (time for acknowledgement)	0	N/A	1	100%
Fast-track applications by new users (time for acknowledgement)	0	N/A	0	N/A
PhD travel fund applications (time for acknowledgement)	0	N/A	0	N/A
conference publicity fund applications (time for acknowledgement)	0	N/A	0	N/A
USAGE INFORMATION	Direct allocns	Round 22 (October 31st 2020 deadline, 850 MHz)	Round 23 (Feb. 18th 2021 deadline, 1 GHz)	Round 24 (April 30th 2021 deadline, 850 MHz and 1 GHz)
number of access days requested	N/A	172	118	268
number of access days awarded	N/A	172	105	296
% of access requests responded to within 10 wds of TAP	N/A	100%	100%	100%
number of distinct PIs	16	13	11	18
number of distinct universities	9	10	5	6
Department type				
Chemistry	9	7	5	10

Physics	3	2	1	4
Life Sciences		1		
Biochemistry	1			1
Centre for Host-Microbiome Interactions		1		
Chemical and Biological Engineering	1			
Chemical Engineering	1			1
Materials	1			
Material Science & Engineering		1		2
Pharmacy		1		
USERBASE DIVERSIFICATION				
The NRF will report the number of new PIs applying to the facility and their research backgrounds (subject field, current expertise in solid-state NMR or not). Data reported biannually after each TAP meeting.				
Round 22 (October 31st 2020 call)				
Research backgrounds: 2 in Chemistry (Solid-state NMR experts), 1 in Materials Engineering (not solid-state NMR expert)	3			
Round 23 (February 18th 2021 call, 1 GHz only)				
Research background: 1 in Physics (not solid-state NMR expert)	1			
Round 24 (April 30th 2021 call, 850 MHz and 1 GHz)				
Research backgrounds: 1 in Physics (Solid-state NMR experts), 2 in Engineering and 1 in Chemistry (not solid-state NMR expert)	4			
DOWNTIME				

Percentage downtime: <10%, >10% but < 20%, >20%						
Downtime KPI: Percentage downtime over period. Report reasons for downtime, Data reported every 6 months.	850 MHz: 2020 July 1st to Dec 31st (181 days)		850 MHz: 2021 Jan 1st to Jun 30th (181 days)		1 GHz: 2021 March 5th to June 30th (117 days)	
engineer installation days	13	7.2%			2	1.7%
maintenance days	1	0.6%	8	4.5 %	4	3.4%
user granted a compensation day	0		4	2.2 %		
Total	1	0.6%	12	6.7 %	4	3.4%
COMPLAINTS						
Complaints: The NRF will report the number of user complaints and response times. Data reported every 6 months.	No of Complaints		First response within 3 days			
3 working days for first response, 10 working days to resolve the issue: 95% and above; >90% but < 95%; <90%	0		N/A			
USER SATISFACTION						
USER SATISFACTION SCORES: 4; 3; 2	No:		Average score			
	16 (PI)		4.8			
	23 (Users)		4.7			
	22 (remote visitors)		4.6			
DISSEMINATION EVENTS						
Perform a minimum of one dissemination activity per year	Annual Symposium took place online on 22nd April 2021					
New snapshot videos hosted on youtube (prepared by users at St Andrews)	6					
Number of followers of Twitter account	303					
Information emails sent by the Facility to mailing list	3					
PUBLICATIONS						
The NRF will report the numbers of publications acknowledging the Facility. Data reported annually.						
KPI Number of outputs (per instrument) 15; 12; 10	16 (2020)					

RESEARCH OUTPUTS (talks and posters)	
Research Outputs Number of Research Outputs, including talks, posters etc. Data reported annually.	
KPI Number of outputs (per instrument) 50; 30; 20	25 (2020)*
* missing the target this year is explained by the absence of in-person scientific conferences in 2020 due to the COVID pandemic. There have been some presentations at online conferences, but this is far less than would otherwise have been.	
OUTREACH TO A WIDER USERBASE	
Number of distinct non-NMR meetings at which research outputs are presented by users. Data reported annually.	
KPI Number of outputs (per instrument) 15; 12; 9	9*
* missing the target this year is explained by the absence of in-person scientific conferences in 2020 due to the COVID pandemic. There have been some presentations at online conferences, but this is far less than would otherwise have been.	
GRANT APPLICATIONS FOR ACCESS	
Number of PIs submitting grant applications for access for which the Facility has provided a technical assessment. Data reported annually	Applications (in 2020)
KPI Number of applications 8; 6; 4	10

11) Links

What links does the facility have with other NRFs, institutes, Diamond etc? What international links does the facility have. What plans does the facility have to maintain, increase and strengthen such links? If your facility is based outside of the UK how is this a strength of the facility?

The capability and outputs of the NRF are at the cutting edge and are well-known internationally. Formally, the NRF's oversight committee (OC) provides an annual forum to review this and provide strategic guidance to the Facility Executive (FE). There are two eminent overseas solid-state NMR spectroscopists on the OC (for the reporting period: Tatyana Polenova, Maryland, USA, and Anne Lesage, Lyon, France), as well as a solid-state NMR spectroscopist from UK industry (Steven Day from Johnson Matthey) and a user representative, who is an early career researcher and user of the Facility (currently Greg Rees, Oxford). Wider input is provided by three further members who represent another NRF, a CDT and the Diamond synchrotron, namely, Rik Brydson (SUPERSTEM), Stephen Skinner (Imperial, Materials Characterisation CDT) and Julia Parker (beamline scientist at the Diamond Light Source), with Brydson the OC chair.

As noted in #4, outreach to the other research communities was initiated through communication with the Society of Chemical Industries Materials Committee and the Metals in Biology BBSRC Network. These interactions resulted in plans being put in place for a joint workshop on *Solid-State NMR for Materials Analysis* (held in October 2021) and the Facility Management Team member Trent Franks giving a seminar introducing the NRF (held in January 2022). The NRF is also partnering with the EPSRC-funded ConnectNMR UK network to offer a training workshop for scientists with solution-state NMR expertise but no or very little solid-state NMR experience, the day before the NRF annual symposium in March 2022. As the research community adapts to new ways of interacting, we look forward to working with other organisations that supported the current NRF funding application, notably the Faraday Institution, the Rosalind Franklin Institute and the Sir Henry Royce Institute for Advanced Materials. We note online training that FE members (Blanc, Liverpool, and Griffin, Lancaster) have provided in 2020 through the Faraday Institution.

The NRF Director and Deputy Director know well other NRF Directors (as facilitated by very useful and beneficial regular EPSRC events bringing together the NRF leadership teams that have continued online during the pandemic). As an example, the NRF is supporting the Physical Sciences Data Infrastructure (PSDI) initiative, following an initial email from the Physical Sciences Data-science Service (PSDS) NRF Director, Simon Coles, Southampton.

The NRF instrumentation at 850 MHz and 1 GHz are integrated into the PANACEA project, A Pan-European solid-state NMR Infrastructure for Chemistry-Enabling Access, that started in September 2020 with funding from the European Union Horizon 2020 INFRAIA-02-2020: Integrating Activities for Starting Communities call. This 4-year €5M initiative links together high-field solid-state NMR laboratories in Europe (Denmark, France, Italy, the Netherlands, Portugal, Sweden, Switzerland and the U. K.) as well as the National High-Field Magnet Laboratory in the U.S.A. The NRF is also represented, with the University of Warwick one of 26 partners, within the REMOTE NMR (R-NMR): Moving NMR Infrastructures to Remote Access Capabilities 3-year €1.5M project that has been recommended for funding (subject to contract negotiation) under the HORIZON-INFRA-2021-DEV-01 call.

12) Improvements and future plans

Please indicate steps that have been taken to improve the access, user experience and ensure the long term sustainability of the facility. This can include plans for achieving ISO accreditation and any proposed equipment upgrades etc.

The NRF's key role is to provide researchers with access to state-of-the-art instrumentation and the reporting period has seen a significant expansion of the Facility's capabilities with the installation of the 1 GHz solid-state NMR spectrometer in its newly built, purpose-designed laboratory (£1.5M investment by the University of Warwick), located adjacent to the main hall that has housed the 850 MHz since the start of facility operation in 2010. This is the first 1 GHz NMR magnet at field in the UK as featured in Chemistry World,). The system is equipped with a range of probes with diameters from 0.7 to 7 mm, providing users with a wide choice of sample volumes and spinning frequencies (5 to 111 kHz). This facilitates a large variety of studies from high-spinning-frequency proton-detected measurements of biomolecules and pharmaceuticals to low-gamma studies of inorganic materials. Installation by Bruker was completed in January 2021, since when time has been allocated to NRF users, first by an informal request for samples from recent NRF users, and then from March 2021 time allocated via a normal independent time-allocation panel (TAP) process. Time allocation since July 2021 has been via a joint TAP with a single call for both the 850 MHz and 1 GHz instruments to maximise efficiency.

Significant investment has been maintained in the 850 MHz system, responding to user requests and demand. Using £494k funding from the current NRF award, three new probes were ordered in Summer 2020: a 1.6 mm (H/F)XY probe to enhance the Facility's ability to conduct fluorine NMR: the latter purchase is from a new supplier, Phoenix NMR, diversifying the range available to users (installation completed February 2022); a high-temperature laser heated broad banded 7 mm probe which will enable Facility users to access temperatures up to 1000 K, doubling the temperature range currently accessible (installation planned February 2022); an additional 1.3 mm HXY probe (delivery expected February 2022). In addition, with £250k funding from a Core Equipment Award, EP/V03622X/1, a very-fast MAS probe, capable of 150 kHz MAS, was ordered in August 2021 from Darklands, Estonia, for the 1 GHz instrument (delivery expected March 2022).

The Covid-19 pandemic has resulted in a major change to how users interact with the Facility. Pre-pandemic, nearly all users visited in person to carry out experiments independently with often only limited input from the Facility Manager Team (FMT) being required. Since the restart of NRF operation in June 2020, nearly all access has been remote: users with time allocated mail samples to the Facility, and the FMT pack rotors and set up the experiment. The Facility has implemented remote access such that an experienced user can then run the experiments remotely on the spectrometer computer using the Teamviewer software. While this has permitted continued usage of the NRF instruments during the pandemic by users, this new way of working is imposing a significant workload on the FMT: specifically, an experienced in-person user would themselves pack and unpack rotors, insert the probe, including inserting and ejecting the packed rotor, into the magnet, and tune the *rf* probe electronics themselves for each experiment, while under remote operation the FMT must do all this. One consequence in rebalancing the work distribution is much less time has been available to pursue outreach work to broaden the user base and increase industry usage as was envisaged in the 2019-submitted NRF application.

As a result of the expansion of the NRF, a second Facility manager Trent Franks was appointed in 2020 to assist Dinu Iuga in the running of the instruments. Trent's background is in the field of biological solid-state NMR, complementing Dinu's expertise that is primarily in materials science. In addition, a dedicated administrator, Charlie Whitewood, joined the Local Management Team (LMT) in July 2020, at 40% FTE. Using savings generated by less user travel expenditure, this allocation has been increased to 80% FTE for 12 months from October 2021, to assist with the extra burden associated with the changed remote operation model for the NRF.

13) Website

Please include a link to your website. What plans do you have to develop this space and what web analytics data do you have from visits?

Website and Social Media Platforms

The UK High-Field Solid-State NMR Facility (warwick.ac.uk)

The UK High-Field Solid-State NMR Facility - YouTube

The UK High-Field Solid-State NMR Facility (@NrfHf) on Twitter (since October 2020), 336 followers.

The main website is currently being used as both an information resource hub for new and established users as well as an administration tool for the LMT (Local Management Team). Since July 2020, a number of operational improvements have been made to the web site including:

a. Appropriately reorganise the collection of data from users for example, the visitor check-in process or the accommodation request booking process using webform tools.

b. Use of the webform data to implement a smoother booking experience for users and importantly has enabled the management of operational information and data to be provided to the Facility Executive, the Oversight Committee and the funding agencies as simple as possible.

c. Expanded the use of social media platforms (Twitter/YouTube) to reach a wide potential future audience to ultimately generate future requests for access from a broad spectrum of potential users both within the academic & industrial community, as well as to generate awareness within the student population and beyond.

For the next review period the focus for the development of the website will be the improvement of the User interface with the intention to implement a visitor portal. The visitor portal will operate as a self-service resource that will allow users to manage their unique information as well as that which relates to their planned or actual time at the facility.

Analytics

Website Hits (July 2020 – June 2021)

Total Hits	On-Campus Hits	External Hits	Student Hits	Staff Hits	Not logged-in user hits
16074	189	15885	60	817	15197

Top Website Pages (Total Hits from July 2020 –June 2021)

1.	Homepage	1119
2.	The Symposium 2021	1057
3.	Call for Applications	628
4.	Publications	566
5.	Annual symposia	325
6.	850 MHz Probes	302
8.	1 GHz Probes	285
9.	Publicity	205
10.	Online application form	192
11.	PhD theses	191
12.	Service Level Agreement	181
13.	Applications for access	178
14.	Dinu Iuga CV	171
15.	UK Solid-State NMR	166
16.	Contact	152
17.	Acknowledgement	130
18.	User Report	128
19.	NRF Video Snap-Shots	115
20.	Reporting	100
21.	Information for Users	80
22.	Presentations	65
23.	Symposium 2020	60
24.	DOR	28
25.	Facility Executive	24
26.	0.7 mm HXY H148429	22
27.	Funding	22

The UK High-Field Solid-State NMR Facility - YouTube
6 snapshot videos currently uploaded onto the channel.
(1) Tracking Defects by MAS NMR. Presenter: Dr Frédéric Blanc, University of Liverpool
(2) Research from Phys. Chem. Chem. Phys., 2020, 22, 14514 - 14526. Published by the PCCP Owner Societies. Presenters: Zachary Davies and Cameron Rice, University of St Andrews.
(3) Oxygen-17 NMR: Dr Frédéric Blanc, University of Liverpool
(4) Gain structural insight from ^{27}Al. Presenter: Valerie Seymour, Lancaster University.

(5) The use of the NMR facility to study magnesium acetate. Presenter: Valerie Seymour, Lancaster University.
(6) ^{14}N–^{1}H HMQC solid-state NMR as a powerful tool to study amorphous formulations – an exemplary study of paclitaxel loaded polymer micelles. Presenter: Prof. Ann-Christin Pöppler, University of Würzburg, Germany (research with the NRF Director, Brown, Warwick).

Video	**Views**	**Watch time (hours)**	**Impressions**	**Impressions Click through rate %** [a]
Total	350	4.52	605	26.25
1	94	1.02	88	22.46
2	34	0.67	46	34.67
3	36	0.31	91	19.35
4	41	0.41	82	22.22
5	42	0.32	132	16.2
6	96	1.76	166[b]	35.35

[a] Views per impression shown. This measures how often viewers watched a video after seeing an impression.
[b] Note that a tweet publicising video 6 on the NRF twitter account garnered 15.1k impressions

14) Case Studies

Please include up to 3 case studies. One of which should focus on less traditional case study areas such as: working with other facilities/institutes, resolving a major issue, outreach. (EPSRC is currently in the midst of a total UKRI web overhaul, so we hope to start linking these in).

The NRF makes all case studies available on its webpage: https://warwick.ac.uk/fac/sci/physics/research/condensedmatt/nmr/850/case_studies/ For this annual review, we are refreshing two (that dated back to 2016) concerning applications to, first, pharmaceuticals, and, second, plant cell walls (the latter corresponding research at the BBSRC/ EPSRC interface, as reflected by the additional partial funding of the NRF by BBSRC).

1. Title of Case Study: Solid-State NMR of Pharmaceuticals

2. Grant Reference Number: EP/F017901/1, NS/A000061/1 & EP/T015063/1

3. One sentence summary: ^{1}H, ^{13}C and ^{14}N two-dimensional Nuclear Magnetic Resonance (NMR) spectra obtained at the UK High-Field Solid-State NMR Facility provide structural and dynamic insight at atomic resolution for pharmaceuticals, often employing an NMR crystallography approach that combines experiment with calculation of NMR parameters.

4. One paragraph summary:

Nuclear magnetic resonance (NMR) spectroscopy is a powerful analytical tool for characterising the structure of molecules with atomic resolution via the chemical shift and quadrupolar interaction (for spin $I \geq 1$) that are sensitive to the local electronic environment of the atomic nucleus and dipolar and J couplings of nuclear spins that inform on through-space proximities and through-bond connectivities. Employing the technique of magic-angle spinning (MAS) enables NMR analysis to be performed for samples in the solid state. This case study describes the application of experimental MAS NMR to characterise the structure and dynamics of molecules of an active pharmaceutical ingredient in the solid state, notably benefitting from the enhanced resolution and signal to noise provided by working at the high magnetic field of the UK High-Field MHz Solid-State NMR Facility. By combining experiment with calculation of NMR parameters using density-functional theory, the output of a single-crystal X-ray diffraction analysis can be validated. By focusing in on key hydrogen atoms, valuable insight is obtained into the intermolecular hydrogen bonding that governs the adopted structure. Such fine detail in structural analysis is of importance for regulatory approval, as well as for predicting stability of the active ingredient when delivered as a medicine.

5. Key outputs in bullet points:

- *Access for leading UK and international pharmaceutical companies to state-of-the-art solid-state NMR experimental characterisation*
- *Atomic-level understanding of key intermolecular hydrogen-bonding interactions that govern the packing of an active pharmaceutical ingredient molecule in the solid state; this insight is critical information for predicting stability during manufacture, and for regulatory approval*
- *Use of NMR crystallography (comparison of experiment to NMR chemical shifts and quadrupolar parameters calculated using density-functional theory) to refine and validate crystal structures solved by X-ray diffraction, and quantify the effect of specific key intermolecular interactions, hydrogen bonding and pi interactions, on NMR parameters*

6. Main body text

Solid-state NMR characterisation was performed at a magnetic field strength of 20 Tesla (corresponding to a ^{1}H Larmor frequency of 850 MHz) for active pharmaceutical ingredients, in projects of relevance to AstraZeneca, Bristol-Meyers Squibb, Daiichi Sankyo, and GlaxoSmithKline. One-dimensional ^{1}H and ^{13}C MAS NMR spectra and two-dimensional ^{1}H-^{1}H, ^{1}H-^{13}C, ^{14}N-^{1}H and ^{35}Cl-^{1}H MAS NMR correlation spectra allow the resolution and assignment of ^{1}H and ^{13}C chemical shifts and the determination of ^{14}N and ^{35}Cl quadrupolar parameter, as well as the identification of specific H-H, C-H and N-H proximities, notably key intermolecular proximities associated with

hydrogen bonding.
In an NMR crystallography analysis, starting from the output of a single-crystal X-ray diffraction structure determination, NMR parameters can be calculated using density functional theory. Considering a comparison between experimental and calculated NMR parameters, a particular focus is on the NMR parameters for hydrogen and nitrogen atoms involved in intermolecular hydrogen bonding interactions that drive the adopted packing of the molecules in the solid state. As an example, this is important for understanding of the co-crystal/ salt categorisation of a system – this comes down to a question as to whether a particular hydrogen atom is close to one of two different heteroatoms. Since X-rays are diffracted by electrons, it is a challenge, as in this case, to determine precisely such hydrogen atom positions in an X-ray diffraction experiment; by comparison, the NMR parameters are very sensitive to such a change in the structure.
References:

Al Rahal et al, Crystal Growth & Design, 21, 2498–2507, 2021 DOI: 10.1021/acs.cgd.1c00160
Iuga et al, Magn. Reson. Chem. 59, 1089-1100, 2021 DOI: https://doi.org/10.1002/mrc.5188
Pawlak et al, Mol. Pharm. 18, 3519-3531, 2021 DOI: 10.1021/acs.molpharmaceut.1c00427
Pugliese et al, Mol. Pharm. 18, 3519-3531, 2021 DOI: 10.1021/acs.molpharmaceut.1c00427
Grüne et al, J. Mater. Chem. B, 8, 6827-6836, 2020. https://doi.org/10.1039/d0tb00614a
Mann et al, Mol. Pharm., 17, 622-631, 2020. DOI: 10.1021/acs.molpharmaceut.9b01075
Maruyoshi et al, J. Pharm. Sci., 106, 3372, 2017. http://dx.doi.org/10.1016/j.xphs.2017.07.014

7. Names of key academics and any collaborators:

Professor Steven P. Brown, University of Warwick
Dr Frédéric Blanc, University of Liverpool
Professor Kenneth D. M. Harris, University of Cardiff
Dr Leslie P. Hughes, AstraZeneca UK
Dr Anuji Abraham, Dr Lucy E. Hawarden, Dr Micheal Tobyn, Bristol-Meyers Squibb, UK and USA
Dr Keisuke Maruyoshi, Daiichi Sankyo Japan
Dr Tran N. Pham, GlaxoSmithKline UK

8. Sources of significant sponsorship (if applicable):

EPSRC funding for the High-Field Solid-State Nuclear Magnetic Resonance Facility
AstraZeneca, Bristol-Meyers Squibb, Daiichi Sankyo, GlaxoSmithKline

9. Who should we contact for more information?

Professor Steven P. Brown, Department of Physics, University of Warwick
S.P.Brown@warwick.ac.uk

1. Title of Case Study: The Molecular Architecture of Plant Cell Walls

2. Grant Reference Number: Contract: PR140003

3. One sentence summary: The arrangement and molecular interactions of polymers within plant cell walls as evidenced by high-field solid-state NMR.

4. One paragraph summary:

Dupree and co-workers have made use of the improved resolution obtained at high magnetic field to investigate cell wall architecture in the model plant *Arabidopsis* and in spruce wood grown in air containing ^{13}C-enriched CO_2. The aim of this study was to understand the molecular basis of plant cell wall properties, such as strength and recalcitrance, which influence the use of plant biomass for timber, paper and pulp, renewable materials and fuel. Wild-type *Arabidopsis,* cell wall-defective mutants and spruce were investigated using multi-dimensional ^{13}C MAS NMR. Specifically, we showed that the structure of xylan is important for assembly of the cell wall. We substantially revised the understanding of softwood molecular architecture, proposing an arrangement of xylan-coated cellulose embedded with mannan and lignin. The work is important for improving the processing and application of wood-derived materials.

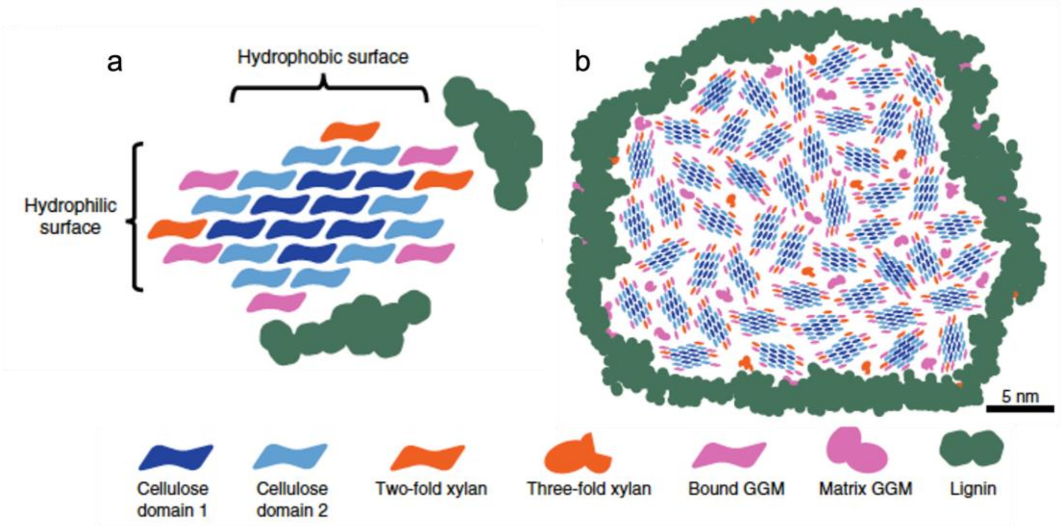
5. Key outputs in bullet points:

- *A model was derived for the molecular architecture of softwood*
- *Deeper insight into the structure of cellulose fibrils was obtained*
- *Discoveries will allow increased use and improved applications of woody materials for building construction, energy, materials and food*
- *Training, notably in solid-state NMR of plant cell walls, of a postdoctoral worker Dr Rosalie Thompson and Ph.D. students Oliver Terrett and Jan Lyczakowski*
- *Instigated a new collaboration with Dr Mathias Sorieul, Scion, New Zealand, on NMR studies of wood*
- *Further funding to develop smart sustainable plastics from plants (UKRI: NE/V010565/1)* with *Prof J Elliott, Dr J Cullen*

6. Main body text

Materials from plants have been used by humans over millennia for their food, to feed animals, for clothing, and for building construction as timber. As the largest available resource of renewable carbon on the planet, in the future plants are likely to provide sustainable ways to avoid fossil fuel use. However, increased exploitation of this plant cell wall biomass is hampered by our ignorance of the molecular basis for its properties such as strength and digestibility. Cellulose is the main component of the plant cell wall material, and it is present as long, strong fibrils, set like steel reinforcement rods within a mixture of other components. These other components include long chains of other sugars, such as xylan and galactoglucomannan (GGM). Xylan is the principal hemicellulose in many plant secondary cell walls where it binds tightly to cellulose microfibrils. The precise atomic-scale nature of this interaction remains unclear, despite the likely importance in providing strength to timber and in preventing digestion of woody plants.

In this project our aim is to study plant cell walls, to determine their molecular architecture, and to obtain information about how cellulose binds to xylan. We have developed techniques to study intact plant cell walls with solid-state NMR spectroscopy so that information on the shape of the components and the distance between them could be obtained. The very high resolution obtained at the 850 MHz NMR Facility enabled us to distinguish many of the different components in the cell wall. We showed (*Nature Plants* **3** 859–865(2017)) that an even pattern of xylan substitution is critical for its interaction with cellulose in plant cell walls, and were able to present a model (see the figure) for the cell wall architecture of softwood (N*at. Comm*. **10**, 13902 (2019). (This paper is already highly cited being in the top 1% in plant sciences according to the Web of Science)



A possible model of the molecular architecture of softwood. a) A microfibril showing the two cellulose domains with 2-fold xylan and GGM bonded to the surfaces. b) A model of the macrofibril containing groups of cellulose microfibrils with bound GGM and xylan. Lignin is localised mainly to the surface of the macrofibril and interacts predominantly with GGM, xylan and cellulose domain 2

The discovery of how polysaccharides influence plant cell wall assembly provides new principles to understand woody cell wall properties. This method and discovery will now lead to development of better processes for paper and packaging production, and also in improvements to digestion of plant materials for animal feed and bioenergy. Since timber is used widely for building construction, we believe this model will also allow development of better methods for wood modification and preservation.

7. Names of key academics and any collaborators:

Professor Paul Dupree (University of Cambridge)
Professor Ray Dupree (University of Warwick)
Professor Steven P. Brown (University of Warwick)

8. Sources of significant sponsorship (if applicable):

Contract for the High Field Solid State Nuclear Magnetic Resonance Facility (EPSRC)
BBSRC (The BBSRC Sustainable Bioenergy Cell Wall Sugars Programme, and BB/R015783/1)

9. Who should we contact for more information?

Professor Paul Dupree, pd101@cam.ac.uk