Case for Support

The UK has been at the forefront of many innovations in both positron emission tomography (PET) and magnetic resonance (MR) imaging, making the UK one of the world leaders in medical imaging since its inception. The recent integration of PET and MR into a single simultaneous imaging system opens up exciting potential for synergistic imaging, and this timely proposal of a collaborative computational project aims to bring together the best of the UK's PET and MR image reconstruction expertise to capitalise on this unique opportunity.

Part 1: Track Record

We have selected a team of investigators of enthusiastic mid- to early-career researchers with high international standing. They are fully supported by senior staff, all of outstanding international reputation, in the research groups at their universities.

Principal Investigator

Dr. Kris Thielemans is a Senior Lecturer in Medical Physics at **University College London**. He obtained his PhD in Theoretical Physics but switched in 1997 to research in image reconstruction of PET data at the MRC Cyclotron Unit where he was part of an EU-funded collaboration to develop iterative reconstruction techniques for PET on parallel hardware. The output of that work has grown into the Open Source Software for Tomographic Image Reconstruction [1], which he still co-manages. STIR is the only Open Source software that allows quantitative image reconstruction for PET and SPECT data and has around 250 users across the world. Dr Thielemans worked in industry from 2001 to 2011. He led the international team in GE Research that developed Q.Freeze™, the only commercial solution for respiratory motion correction in PET-CT. Since joining UCL in 2013, his research focus is PET-MR with an emphasis on motion correction and joint-reconstruction of PET-MR data. Dr Thielemans has 37 co-authored peer reviewed publications, 65 conference proceedings and holds 13 patents (3 patents pending).

Co-investigators

Dr. David Atkinson is a Senior Lecturer in Magnetic Resonance Imaging at **University College London** developing new MRI acquisition and reconstruction techniques to aid in clinical imaging and research. Dr Atkinson is well placed to understand the links between PET and MRI as he is an Investigator on EPSRC grant EP/K005278/1 *"Exploiting the unique quantitative capabilities offered by simultaneous PET/MR".* Additionally, as an Investigator on Programme Grant EP/H046410/1, techniques of direct parameter reconstruction from PET methodology have been applied to dynamic MR data.

Dr. Julian Matthews is a Senior Lecturer at the Centre for Imaging Science, **University of Manchester**. His research interests include the development of improved image reconstruction algorithms for PET data and the application of PET scanning to real problems in oncology, neuroscience and pharmacology. He is a CoI on a recently funded EPSRC PET-MR grant in dementia (EP/M005909/1) and will be involved in a funded PET-MR system to be installed in Manchester. His research career of 20 years has included positions both in academia (MRC Cyclotron Unit, University of Cambridge) and in industry (SmithKline Beecham/GlaxoSmithKline), in which he has published more than 40 peer reviewed papers and 35 conference records.

Dr. Claudia Prieto is a Lecturer in the Division of Imaging Sciences and Biomedical Engineering at **King's College London**. Her interests include the development of advanced undersampled reconstruction techniques to accelerate MR acquisition, and the incorporation of motion correction techniques directly in the reconstruction process. She has recently been awarded two MRC grants as PI in accelerated motion corrected cardiovascular MRI and is an Investigator on recently awarded EPSRC grant EP/M009319/1 "*PET-MR Motion Correction Based Purely on Routine Clinical Scans*" and on Programme Grant (EP/H046410/1). Dr. Prieto has published 27 peer-reviewed papers and 60 conference proceedings.

Dr. Andrew Reader returned from Canada (MNI) to the UK in March 2014 to take up the post of Reader in Imaging Sciences and Biomedical Engineering at **King's College London**. Dr. Reader has extensive experience in image reconstruction for PET, being one of the early pioneers in

iterative list-mode 3D image reconstruction. In the UK Dr. Reader's research has been funded by the EPSRC and by GE, which along with multiple successful grants in Canada, have led to a total of >£1.6 million being awarded to Dr. Reader in his capacity as PI, and >£2.2 million as Co-I (including a recently awarded EPSRC grant EP/M009319/1 "PET-MR Motion Correction Based Purely on Routine Clinical Scans"). Dr. Reader has published more than 60 peer-reviewed articles and >100 conference records/abstracts.

UK Environment and Network

Clinical PET-MR systems have been available for only a few years with two installations in the UK at UCL and KCL. However, as part of its initiative on dementia, the UK government is expected to announce funding for five new PET-MR systems (at Cambridge, Edinburgh, Imperial College, Manchester and Newcastle), leading to the world's highest number of systems per capita. All of these groups have obtained substantial funding on PET-MR related projects (EPSRC, MRC, BRC, BHF, CRUK, Wellcome Trust, EU and industry). However, at present there has been little interaction between these activities, a problem that the proposed CCP aims to solve. This grant proposal is supported by key members of all UK institutions who have a vested interest in PET-MR:

- **UCL**: *Simon Arridge* (inverse problems), *Brian Hutton* (nuclear medicine, PET-MR and SPECT-MR), *Jenny Steeden* (MR reconstruction and interfacing to clinical systems), *Sébastien Ourselin* (software and data processing)
- **KCL:** *Jo Hajnal* (integrating MR data acquisition with reconstruction and image analysis), *Paul Marsden* (PET-MR instrumentation and clinical trials), *Tobias Schaeffter* (MR motion correction and reconstruction).
- **Manchester:** *Geoff Parker* (quantitative biomedical imaging)
- **Cambridge:** *Tim Fryer* (PET physics and PET-MR motion correction), *Martin Graves* (MR sequences and reconstruction)
- **Edinburgh:** *Edwin Vanbeek* (imaging to study cardiovascular and lung diseases)
- **Imperial:** *Peter Gatehouse* (interfacing Open Source software to clinical MR systems), *Daniel Rueckert* (image processing and image analysis).
- **Leeds**: *Charalampos Tsoumpas* (MR-based motion correction of PET, co-maintainer of STIR)
- **Newcastle:** *Ross Maxwell* (pharmacological imaging of cancer)
- **Imanova Ltd:** *Roger Gunn* (image analysis and kinetic modelling), *Rexford Newbould* (MR imaging)

who have all offered to join the Working Group (WG, see Management Structure). We anticipate that others sites in the UK will want to get involved in this initiative. The WG will be completed by:

- **VUmc** (Amsterdam, NL): *Ronald Boellaard* (PET reconstruction and clinical trial standardisation)
- CCP for Tomographic Imaging (CCPi) representative

We have contacted two international External Advisors who have the highest possible reputation in the field of PET-MR

- ***Jeffrey Fessler*** (Univ of Michigan, USA) is a world-authority in developing new image reconstruction algorithms and analysing their theoretical behaviour. Uniquely, he leads both the PET and MR reconstruction algorithm field.
- ***Ciprian Catana*** (Harvard Medical School, USA) is trained in both radiology and biomedical engineering and leads the PET-MR field in testing new methods in a clinical setting.

We have excellent relations with all three manufacturers of clinical PET systems, facilitated by the industrial experience of the PI.

References

[1] Thielemans et al. STIR: Software for Tomographic Image Reconstruction Release 2, Physics in Medicine and Biology, 57 (4), 2012 pp.867-883. See http://stir.sourceforge.net.

Part 2: Proposal and context

Motivation and background

Magnetic resonance (MR) and radionuclide imaging using positron emission tomography (PET) now have highly successful roles in medical diagnosis, clinical research and drug development. In recognition of the complementary and powerful capabilities of these two modalities, integrated simultaneous PET-MR scanners have now been designed and marketed by the major medical imaging scanner manufacturers. These devices open-up exciting new possibilities for exploitation of the synergy between these two modalities in many priority areas for human health, including dementia, cardiology, and oncology.

Whilst different and complementary to each other, both modalities use sophisticated algorithms to compute slices or volumes representing anatomical and functional properties of the patient. One of the key challenges is to combine the PET and MRI data so that the information obtained is more than the sum of PET and MRI collected separately. Our current research indicates that integrating image reconstruction of the multi-modal data will provide opportunities to achieve this, *e.g.* by using multi-modality motion information or cross-modality similarity (see Fig.1).

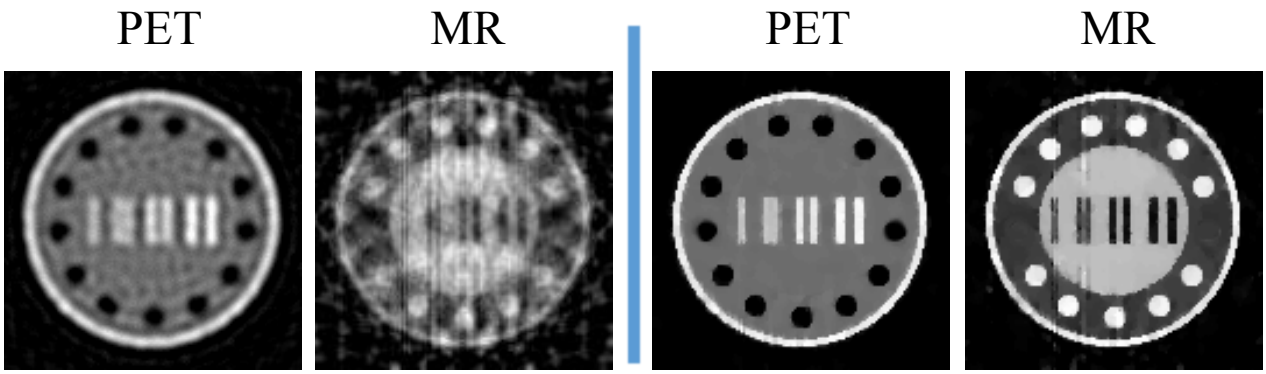

Fig. 1. Example reconstructions from simulated PET-MR data (Poisson noise for PET, Gaussian noise for MR, radial sampling with 15 lines).
Left*:* independent reconstructions. ***Right***: joint-reconstruction using a Quadratic Parallel Level sets prior. (After Fig. 5 in Ehrhardt, Thielemans *et al*, *Joint reconstruction of PET-MRI by exploiting structural similarity*, Inverse Problems (accepted).

However, the development and testing of novel algorithms on patient data requires considerable effort in software implementation. Often, algorithms are developed at local research groups with each group needing to resolve significant technical challenges in interfacing their software with manufacturer's data and proprietary software. This often prevents porting the software to other centres, preventing evaluation with sufficient clinical data, historically resulting in very little translation of novel reconstruction algorithms into clinical research/practice.

There is therefore considerable potential to increase the impact of the UK in PET-MR by having researchers who are equally knowledgeable about the reconstruction of both modalities and who have access to an offline reconstruction capability so that researchers are not restricted by the turnkey software implemented by manufacturers and have a platform on which they can develop and explore alternative approaches. We therefore propose to establish a new Collaborative Computational Project (CCP) to enhance the UK's overall effectiveness in realizing the potential that combined PET and MR provides. **The overarching vision is the formation of a new UK-wide unified PET-MR community, centred on shared and collaborative software development, which brings together the collective UK expertise in these areas. This will enable researchers across the UK to rapidly develop novel integrated PET-MR reconstruction algorithms and to share such developments for validation and exploitation.**

Such a network will, of course, also be highly useful for researchers in image reconstruction in PET or MR only, and of some interest to other tomographic modalities. Therefore, we intend to provide opportunities to link-up with the existing, but differently focused, CCP for Tomographic Image

Reconstruction (CCPi). Since CCPi is largely dominated by computed tomography (CT) in a non-medical context, a distinct CCP which facilitates access to the new PET-MR technology in the medical context is essential, but interaction with the existing CCPi would provide beneficial added value.

Aims and Objectives

The proposed CCP has two primary aims: to bring together researchers from different institutions, imaging modalities and systems, and, to provide a solid software infrastructure to enable implementing and testing of new ideas.

- Network formation: bringing together expertise in each modality: the UK has a number of research groups with high international standing, working on image reconstruction for either PET or MR, but these groups have historically not worked closely together. With this network, we aim to bring these communities together towards the goal of synergistic PET-MR reconstruction by
  - advancing understanding of PET-MR: collective learning about the two imaging modalities to understand their similarities and differential strengths and weaknesses and the scope for synergy.
  - enhancing understanding of the algorithms used for each modality: iterative reconstruction algorithms are widely used on commercial PET systems, while they have not yet been incorporated in the software of most MR vendors. Both the PET and the MR communities actively research iterative reconstruction algorithms but with different emphases; for instance the PET field is more developed in handling noise while the MR field has more experience with modelling image sparsity. We aim to improve communication between the relevant researchers to combine expertise.
- Developing software infrastructure: this will enable researchers to use a common framework to tackle the specific challenges of simultaneous PET-MR. Examples include the lack of tissue density information for PET attenuation correction, possibility for motion estimation and correction, and the opportunity for joint reconstruction as both modalities measure different aspects of the same function and anatomy. This will be achieved by
  - creating an Open Source software platform for integrated PET-MR image reconstruction. This will enable reconstructions to be performed across UK sites on data from different manufacturers, and enable developments at one site to be readily transferable to other sites. This platform will be based on Open Source software, but will include generic interfaces to other third party software commonly used by the two communities such as the (commercial) MATLAB™ package (MathWorks). The platform will be developed using sustainable software practices and include High Performance Computing techniques.
  - standardisation of data formats. Agreement on a standard data format will allow researchers to share raw data from PET-MR scanners. We will work with manufacturers to create tools to export data in these data formats. For MR, we will continue to support and contribute to efforts by the International Society for Magnetic Resonance in Medicine (ISMRM) for creation of a standard data format. For PET, our proposal will be based on previous work by the PI and others on the extension of the Interfile standard to PET, currently partially supported by Siemens. We have obtained agreement from Siemens, Philips and GE that they will provide the necessary information or tools to convert to this standard format (see Letters of Support).

An additional aim is to link with the wider communities of PET-CT, MR and other tomographic modalities to allow cross-fertilisation.

Software strategy

Image reconstruction is a computationally demanding task. We will therefore implement the core functionality of the image reconstruction algorithms in C++ as a library with a clearly documented Application Programming Interface (API). The library will use High Performance Computing (HPC) techniques. To maximise usability and take-up by the community, we will create an interface to this library from MATLAB and Python. This will allow, for instance, researchers to quickly implement a new algorithm for joint-reconstruction of PET-MR data by implementing a gradient function for a

joint-prior in MATLAB, combining this with gradient functions for PET and MR from the API, and using this in an optimisation algorithm (either in MATLAB or the API).

Where possible we will exploit existing Open Source initiatives such as: STIR; NiftyRec (UCL); the UK CCP in Tomographic Imaging software; Gadgetron; NCIGT Fast Imaging Library; codeare (all for image reconstruction); NifTk; and the Insight Toolkit (ITK) for image registration and segmentation. Existing software will be selected based on (in order of priority) user requirements and feedback, licensing, adherence to sustainable software practices and active community. We will use a structure with sub-projects and interfaces/translators between these packages. This strategy will free-up resources for new developments, ensure that the efforts of the network will benefit the wider community and vice versa, and increase the longevity of our software.

Sustainable software techniques will be used throughout (see also the *Core support* and *Pathway for Impact: Sustainable Software* sections). Our experience growing STIR as collaborative Open Source has shown that modularity, version tracking and automatic building and testing procedures are crucial for large projects.

Our software platform will be designed in close consultation with the users in the network via yearly surveys. We have a team of experts that will determine initial requirements.

Networking and Widening Participation

Network activities: A number of activities are proposed designed to facilitate education, interactions and collaborations between researchers based at multiple sites across the UK. Through the provision of a common software platform, the aim is to initially enable researchers but then to further develop them to enable others through the contribution to software development.

- Annual 2 day meetings will be organised and delivered consisting of: plenary lectures from international invited speakers; scientific presentations of activities facilitated through the network; as well as a significant emphasis on cross modality education and training. This training will aim to provide integrated theoretical and practical hands-on training, enabling attendees to both understand and implement ideas. These workshops will be organised to allow online attendance and presentation whenever possible.
- A series of online (~2/annum) and in person (~2/annum) smaller group meetings will be held focussing on particular topics. These topics will be driven by the interests and requirements of the network but it is envisaged that they include: training in sustainable software development, focused software development “hackathons”; modality specific topics such as attenuation correction; and modality integration topics such as resolution matching. The aim of these meetings will be to facilitate community progress in an identified topic.
- Webinars (~6/annum) by experts using WebEx online meetings.
- We will contribute to workshops and summer schools associated with major UK and international conferences (IEEE Medical Imaging Conference, PSMR, ISMRM, British Chapter ISMRM). Training in using and extending the software will be incorporated into existing general image reconstruction courses. This will help increase the network participation and impact beyond the UK.
- Mailing lists/fora for announcements and community discussion will be created and maintained. These mailing lists will also be used to solicit general network needs and interests and coordinate activities such as data format standardisation. We also hope that members of the network will use this facility to self-support each other through requests for information and help. To encourage interaction and collaboration, a small yearly prize will be awarded (to student or RA) for the individual with the most useful contributions to the community.
- We will provide resources and information through a network website which will include: software platform documentation and download; information on, and content from, the annual and focus group meeting; and a community led software repository and information source (wiki). In addition, the website will provide user and developer tutorials (including videos showing installation and usage procedures), together with information on common problems and frequently asked questions.
- We will encourage exchanges within the network by sponsoring travel and living expenses.
- We will select internationally-renowned Visiting Researchers; commitment from Prof. J. Fessler (Michigan, USA) and Prof. M. Burger (Muenster, Germany).

- We will acquire example data sets of both simple geometric objects and patient data for network participants for testing of the provided and/or their own algorithms.

In addition to these specific activities the network will interact with other groups including other CCPs such as the CCP in tomographic image reconstruction who have an interest in computer tomography. Where identified interests overlap, joint meetings will be arranged.

Outreach

Medical image reconstruction provides visually impressive and emotive images that can be used in outreach activities. To help collecting this material via the network, we will have a small award for "Image of the Year". Atkinson has previously been a Co-Investigator on two EPSRC Public Engagement grants (EP/D070163/1 PPE Medical imaging resources for the school curriculum, and, GR/S83197/02 PPA: Science, Maths and ICT in Medical Imaging). Material from the networking events will be selected and offered to organisations such as the Institute of Physics who maintain educational resources for teachers. Additionally, we will maintain on our website a lay section with state-of-the-art images to enhance public engagement.

Core support

Core support will be essential to the network. We are asking for 1.5 FTE spread between 1 FTE for programming and 0.5 for administration.

The 0.5 FTE person will help with networking activities, including web-site management (with Wiki), mailing lists and fora, maintaining a databases of example PET-MR data-sets and training videos contributed by the project partners but also administration and organisation of workshops and meetings (both in–and online). We will use CPPForge as our main platform for internal communication and outward presence. In addition, 1 FTE will help the software development in the network by support (provide training in sustainable software techniques, establish and enforce coding standards, OS and compiler independence, release management, installation support, creation of a virtual machine with pre-installed packages and environment ready for further development) and coding, including maintaining documentation.

Core support will create the interfaces between selected independent packages and provide a consistent API. IO routines to support the standard data formats and High Performance Techniques (including multi-threading via OPENMP and GPU support) will be added to the packages as necessary.

To help the large proportion of the community that is unfamiliar with C++, core support will investigate the use of tools that (almost) automate the *wrapping* of the API. For example, the Open Source tool SWIG can currently wrap C++ to many different languages and has an active community. SWIG is currently used by STIR and ITK for their Python interfaces. At the time of writing, SWIG is being extended to create an interface to MATLAB is being added (with contributions by the PI). Core support will assist with both maintaining the wrapper tools and wrapping the C++ library. In addition, selected algorithms contributed by users with an implementation in, *e.g.* MATLAB, will be added to the C++ library.

Justification of resources

1.5 FTE of core support is requested for administration and software development. Resources are requested for travel and accommodation to enable attendance at the annual, focus group and Working Group meetings, for visiting researchers and for exchange between UK centres, including visits of the STFC programmer to sites with relevant software expertise. The budget also provides a contribution towards the acquisition, preparation and storage of the example data sets. A small amount is set apart for web-hosting, impact-related activities and consumables. The outline as described in the justification of resources allocates full financing for the activities from the grant. However, the network will seek additional industry support for events through sponsorship. Depending upon the strength of the support the events may change format or frequency.

Management Structure

An Executive Committee (EC) composed of the PI (chair) and Co-Investigators will be responsible for the running of the network and software activities. The EC will keep track of software licensing and will keep the network within budget. The EC will meet monthly.

A Working Group (WG) will decide on workshops, network activities and software efforts. The WG will propose an Open Source license for all contributions to the software platform, although exceptions will be allowed if necessary. The WG will also invite visiting researchers and decide on intra-network exchanges to stay within budget. The WG will suggest and coordinate application for funding from research councils, charities and industry. Membership of the working group can change during the project with any disputes resolved by the Executive Committee. The working group will meet in person or electronically approximately twice per year.

Two External Advisors (EA) will provide a yearly check on the project and give independent advice. This will be based on reports provided to the Executive Committee either in person or electronically. The EAs will be highly respected members of the international community, one with a computational and one with a clinical PET-MR background. The EAs will also be able to contribute to workshops and meetings as appropriate. In case one of the EAs resigns, the WG will propose a replacement.

Targets and performance indicators

	Mid-term	End of grant
Networking		
UK User base	• 20 UK members of network	• 40 UK members of network • 6 UK contributors to software • Outreach beyond PET-MR
International links	• 2 International Researcher visits • 5 International members • Participation in 1 international training course	• 4 International Researcher Visits • 4 International contributors to software • 10 International members • Participation in 2 international training courses
Workshops/training	• 40 different people have attended	• 80 different people have attended
Software developer community	• 5 active contributors • 1 educative hackathon	• 10 active contributors • 3 hackathons
Example data sets and instructions	• 4 phantom and 5 patient data sets from 2 PET-MR scanners	• 8 phantom and 20 patient data sets from 5 PET-MR scanners
Outreach	• Lay-section of the web-site including before/after images	• Updated lay-section • Suitable material from Network meetings packaged and offered to organisations such as Institute of Physics.
Software development		
Available software (fully documented and tested)	• C++ library with core functionality for PET and MR reconstruction in 3D allowing cross-modality information to be used • Wrappers in MATLAB	• Extended C++ library for 4D data allowing cross-modality use of information including motion • Integration with external library for motion estimation • Wrappers in MATLAB and Python
High Performance Computing	• Multi-threading for most intensive calculations	• Updated multi-threading • GPU version, callable from MATLAB

		and Python
Distribution	• Source code and documentation • Virtual machine with pre-installed software • Precompiled libraries and wrappers for Linux	• Source code and documentation on github or equivalent open to non-members • Updated virtual machine • Precompiled libraries and wrappers for Linux, MacOS and Windows

Long-term Sustainability

Funding for activities identified as being effective will be incorporated into future related grants. The STIR community already uses satellite events at major meetings to bring people together and this model will be adopted. The software will be hosted as Open Source on a major accessible site such as GitHub and thus should be self-sustaining for as long as it proves useful.

Work plan prioritisation

In the event that cuts are required, we would prioritise funding for networking activities over the (EPSRC cost) for core support. Cuts to networking activities would be applied approximately evenly across all activities, pro-rata to the cuts. If the FTEs had to be cut, we would maintain administrative support and reduce the amount of software included within the core support. An extra means of saving manpower costs that would not lead to a loss of outputs would be to combine certain roles with CCPi (Tomographic Imaging; Prof. Phil Withers, Manchester) with whom we have already had some discussions. We are already proposing to share some meetings and activities. See the Justification of Resources for more detail.