

## MOLECULAR IMAGING WITH POSITRON EMISSION TOMOGRAPHY

Mayneord Phillips Summer School  
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St Edmund Hall, Oxford

Lucy Pike, Addenbrookes NHS Trust, Cambridge.  
Elizabeth Harron, Regional Medical Physics Department, Newcastle Upon Tyne.  
Anne Dawson, Portsmouth Hospitals NHS Trust, Portsmouth.  
Anton Paramithas, St George's Hospital, London.  
Iain Murray, St Bartholomew's Hospital, London.

### Introduction

The Mayneord Phillips Trust is a charitable organisation that aims to promote the development of physical science techniques in medicine. It was founded by the Institute of Physics, the British Institute of Radiology and the Institute of Physics and Engineering in Medicine in 1991, and every two years the Trustees organise a week long summer school aimed at PhD level students. The subject for the week is chosen according to recent research interests and as such this year's topic was Molecular Imaging with Positron Emission Tomography (PET). The summer school was set in the beautiful surroundings of St Edmund Hall in Oxford and was attended by 24 students from across the globe (Figure 1). Further information on the Mayneord Phillips Trust and the next summer school (which will be devoted to '21<sup>st</sup> Century Radiotherapy' - see below) is available at <http://www.m-pss.org/index.html>.

### Day 1

The week started with a welcome to the summer school from organiser **Paul Marsden** (King's College London). The lectures on Monday provided an excellent introduction to the history and future uses of PET and to the scanner hardware. Uses of pre-clinical PET, and developments in multi-modality imaging, namely PET-CT and PET-MRI, were covered later in the day.

**Terry Jones** (University of Manchester) gave an enthusiastic first lecture, entitled "Meeting the Future Challenges of PET-based Molecular Imaging". He covered the development of PET since 1955, and went on to discuss recent innovations which have improved PET scanner performance, such as improvements in spatial resolution and increased axial field of view. Various reasons were given for why PET is such an exciting and useful imaging modality, and the challenges and potential solutions for future applications were outlined (see Figure 2).

This was followed by an overview of PET scanner hardware by **Sibylle Ziegler** (Technische Universität München, Germany). After covering the basics of PET hardware and the ideal characteristics of a scanner, Sibylle discussed the possible future developments in hardware that could lead to improvements in spatial and energy resolution as well as timing resolution. One example could be the use of avalanche photodiodes (APD) instead of photomultiplier tubes (PMT). These have the advantage of being unaffected in magnetic fields making them valuable in the development of PET-MRI.

**Tim Fryer** (University of Cambridge) moved away from clinical PET to microPET and the difficulties encountered with obtaining high resolution images of small animals. He described the stages required to obtain data for image quantification, right from

animal preparation through to the correction and analysis of the data using reference tissue models. There are numerous uses for small animal PET and Tim outlined some interesting research projects carried out at the University of Cambridge, such as the use of PET to study endothelin receptors by imaging the biodistribution of the radioligand [18F]-ET-1.

The ability to combine the functional information from PET with anatomical information from CT or MRI was the subject of lectures by **Thomas Beyer** (University Hospital Essen, Germany) and **Adrian Carpenter** (Wolfson Brain Imaging Centre, Cambridge). PET-CT scanners are becoming more widespread in Europe, and the combined modalities are of particular use for cancer diagnosis and staging, and for outlining tumours for radiotherapy treatment planning. Thomas discussed the challenges for PET-CT, such as respiration artefacts, and possible solutions to these. Adrian outlined the advantages and disadvantages of PET-MRI, compared to PET-CT (Figure 3). Although PET-MRI is technically more challenging than PET-CT due to problems such as interference between the two imaging modalities, Adrian was keen to point out that PET-MRI is a feasible option, with animal and human experiments taking place in 2007.

## Day 2

**Andrew Reader** (University of Manchester) started the morning off with two comprehensive lectures focussed on PET image reconstruction methods. The session benefited greatly from Andrew's decision to concentrate on the ML-EM (maximum likelihood-expectation maximisation) iterative reconstruction technique. This was based around a system matrix obtained using the Line Integral model. By providing step-by-step simulations of the stages involved the whole process was broken down into easily understood concepts, enabling the technique as a whole to be more fully appreciated. It also became very apparent how using such approaches to create the system model could be amended to incorporate new information such as Time of Flight and detector resolution/response models.

This led nicely into the next talk given by **Kris Thielemans** (GE Healthcare, London) concerning quantification in PET with both iterative and back projection based algorithms. Kris's concise talk around the subject of bias and variance in these settings made it clear that in clinical situations the accuracy and precision of any parameters derived from PET images should not be taken for granted, particularly as quantitative measurements are increasingly used. Kris also covered the effects of motion in some detail. He explained the effects of blurring and attenuation mismatch due to respiratory motion on standardised uptake values (SUV) and included some very interesting results from NCAT simulations and clinical data looking into the effect of respiratory motion on solitary pulmonary nodules (Figure 4).

The afternoon session started with a talk from **Dimitris Visvikis** (INSERM, France) on Monte Carlo simulations in PET. After outlining the general principles of Monte Carlo the focus moved onto specific codes for emission tomography and in particular GATE. (GEANT4 Application for Tomographic Emission). GATE is freely available and as well as modelling energy deposition can also model such processes as radioactive decay, object and detector movement and tracer kinetics.

To finish the day, two talks from outside the immediate world of PET were given. **Derek Hill** (IXICO, London) gave an insightful and informative perspective on advanced image processing techniques such as automatic region definition, segmentation and registration.

**Tobias Schaeffter** (King's College London) then gave a talk on Molecular Imaging with MRI. The principal development in this field has been around vascular targets. Impressive results from a range of compounds, such as  $\alpha_v\beta_3$ -integrin used in the imaging of angiogenesis, were demonstrated. On the other hand it was also made clear that the higher concentration of tracer compounds required in MRI was a limiting factor on developments in this area – after all this was a PET meeting!

### Day 3

The principles of image analysis and modelling in PET were covered on Wednesday morning. This comprised of two lectures given by **Vin Cunningham** and **Roger Gunn** (GlaxoSmithKline, London). The first lecture concentrated on the fundamentals of compartmental models. It provided a valuable overview of the subject with a series of common examples such as the Kety blood flow model and the Sokoloff deoxyglucose model. The talk then went on to demonstrate the use of the models in occupancy studies.

The second of the two lectures gave a review of some common PET compartmental models for the plasma input and the reference tissues. A general equation for plasma and reference input models was then derived that can be theoretically applied to model “any” PET experiment. The last part of the talk concentrated on showing how different data driven fitting methods are derived from this general equation. This included graphical methods such as Logan and Patlak plots, spectral analysis and basis function methods.

The lecture was followed by an interactive session where example spectra mimicking real situations were shown. The audience was then encouraged to select the appropriate model that best fit the scenario including parameterisation of the suggested models drawing on the fundamentals that had been taught in the preceding lectures. The audience's fitting parameters were then input into a software modelling programme in real-time so that the accuracy of the audience's suggestions could be determined. The session was very beneficial as it allowed one to consolidate the theory and appreciate the practical implementation.

The afternoon was left free to give the attendees a chance to enjoy the historical city of Oxford and some of the students took advantage of this time to go punting along the river Thames. Then in the evening the students and lecturers all enjoyed a superb dinner alongside the river in picturesque Moulsoford.

### Day 4

The Thursday morning session focussed on radiopharmaceuticals for PET imaging. **John Clark** (University of Cambridge) started the session with a presentation about PET radionuclide production. He described how a cyclotron produces positron emitting radionuclides, in particular the GE PETtrace cyclotron which is used at the Wolfson Brain Imaging Centre in Cambridge (see Figure 5).

**Tony Gee** (GlaxoSmithKline, London) talked about tracers labelled with  $^{11}\text{C}$  and  $^{18}\text{F}$ . **Phil Blower** (King's College London) then talked about metallic radionuclides and tracers. He described the advantages of metals over organic positron emitters, such as the wider choice of half life and the potential for radionuclide therapy using metallic positron emitters. Particularly interesting was the use of  $^{60}\text{Cu}$ -ATSM for imaging hypoxia. Studies are being carried out using this radiopharmaceutical to identify hypoxic tumours or ischaemic regions of the heart.

The final morning talk was given by **Steve Mather** (St Bartholomew's and Royal London Hospitals, London) who talked about biological targets for radiopharmaceutical development in cancer. He described the molecular targets for radiopharmaceuticals in two categories – functional and non-functional. Non-functional targets include neuropeptide receptors such as the somatostatin receptors expressed by neuroendocrine tumours. Functional targets include metabolic pathways such as the glucose pathway used for  $^{18}\text{F}$ -FDG imaging.

The afternoon session covered clinical uses of PET imaging and cancer research. **Michael O'Doherty** (King's College London) began with a presentation on the clinical uses of PET-CT. The presentation focussed on oncology imaging, which accounts for the majority of scanner workloads. The speaker described the potential targets for oncology imaging, with the most common being glucose metabolism. However, other targets are being investigated, including imaging apoptosis, blood flow and hypoxia. Eric Aboagye (Imperial College, London) then described how PET could be used in the development of new cancer therapies.

**Tony Ng** (King's College, London) finished the Thursday session with a talk about the establishment of multimodal imaging in cancer research. The presentation focussed on optical imaging techniques for imaging cancer cells. One of the methods was the detection of Förster Resonance Energy Transfer (FRET), which is the exchange of energy between interacting molecules. Using optical imaging to study the cancer cell protein network can give information on how the network is formed and biochemically regulated.

## Day 5

The last day began with another talk from **Tony Gee** on the applications of PET imaging in drug discovery and development. This talk covered the use of PET in the early stages of drug development and testing. He gave examples of how drug microdosing in combination with PET can identify drugs that have a different distribution from expected prior to clinical trials. This can potentially lead to significant time and money savings as well as reducing the risks to volunteers.

**Laurence Reed** (King's College London) then spoke about the neuropsychiatric applications of PET. He highlighted several recent studies carried out at the PET Imaging Centre at St Thomas' Hospital in collaboration with the Institute of Psychiatry, where they have been using FDG-PET to research appetitive motivational networks. This has important uses in a number of areas such as addictions, psychiatric disorders, medical disorders and adolescence.

The subject for the next talk by **Paul Marsden** was PET-CT Quality Control. He went through the performance parameters that should be measured at acceptance and their significance. Paul also explained the protocols for daily QC procedures and interpretation of the results.

The final lecture was given by **Brian Hutton** (University College London). His lecture covered the principles of both PET and SPECT along with a comparison of the attributes of the two modalities. The talk also gave an overview of the new D-SPECT<sup>TM</sup> Cardiac Imaging System (Spectrum Dynamics) which included a description of the new collimation system and how it compared to a conventional LEHR collimator. He also discussed recent developments in small animal imaging,

such as the work carried out at the University Medical Centre in Utrecht in developing multi-pinhole SPECT and how this may be applied to clinical SPECT systems in the future.

The week was rounded off with a general session for the students to present some of their own work. **Reynold Cooper** and **David Oxley** (Liverpool University Imaging Group) gave a fascinating presentation on their work as part of the SmartPET project which is investigating the development of Compton Camera PET imaging. **Matthew Miller** (GE Healthcare, UK) spoke about his work in the research and development of new radiopharmaceuticals that target angiogenesis for use in oncology. The session also gave the students an opportunity to ask speakers questions and **Paul Marsden** kindly provided a tutorial on the calculation of standardised uptake values (SUV) at their request.

### **2009 Summer School**

The next Mayneord-Phillips Summer School will take place in July 2009 and will be devoted to '21<sup>st</sup> Century Radiotherapy'. Topics to be covered will include: Tumour imaging and localisation, biological effects and outcome prediction, beam generation and delivery, proton and heavy ion therapy and radiotherapy planning and verification. An international faculty will provide teaching and lead discussion in these areas. Look out for further announcements. To register your interest in this event, please contact Colin Baker ([colin.baker@liverpool.ac.uk](mailto:colin.baker@liverpool.ac.uk))

Figure 1. The students and course organiser, Paul Marsden, in the courtyard of St Edmund Hall, Oxford.

Figure 2. Reasons for using PET imaging (courtesy of Terry Jones).

Figure 3. Advantages and disadvantages of PET-MRI versus PET-CT imaging (courtesy of Adrian Carpenter).

Figure 4. Comparison of gated and ungated PET/CT data to illustrate the problems caused by respiratory motion (courtesy of Kris Thielemans).

Figure 5. GE PETtrace cyclotron opened for service (courtesy of GE and John Clark).