1. WORK PROGRESS AND ACHIEVEMENTS DURING THE PERIOD

Progress towards objectives and details for each task

The project title is “Dynamic PET/MR – New reconstruction methods for Parametric Imaging”. The project has 4 Work Packages (WPs) related to the scientific work (and one related to management tasks): WP1 - Data acquisition and processing, WP2 - Image Derived Input Function methods, WP3 - Time Activity Curves methods, WP4 - Evaluation of new methods and WP5 - Dissemination activities.

For WP1 (Data acquisition and processing), the patient database in Jülich provides different acquisitions with the required protocol, that is, [18]F-FDG or [15]O-H2O with venous sampling and several MRI sequences acquired. There is a tool that allows the post-framing of the data with the desired frames and all the correction effects are estimated: random, scatter and attenuation. The reconstruction can be performed with scanner reconstruction program, but also with the reconstruction framework PRESTO (PET REconstruction Software TOolkit) by defining an appropriate script. Currently, all datasets are motion-corrected with PMOD software. This task is important for the clinical application of the developed methods in this project, because motion displaces the anatomical regions and therefore, Time-Activity Curves (TAC) are corrupted if not corrected for motion. The software results are accurate, but need user interaction. To save considerable time in processing data, it is important to automatize the motion-correction process. Therefore, at the same time, the researcher has supervised a Master Student in implementing such methods. For kinetic modelling, PMOD is also currently used and parametric maps using [18]F-FDG, [11]C-Raclopride and [15]O-H2O data can be obtained. Furthermore, PMOD allows extracting and importing TACs (Deliverable D1.1). For the interchange with the PRESTO reconstruction framework, these TAC can now be converted from one framework to the other. GATE (Geant4 Application for Tomographic Emission) has been used to realistically simulate [18]F-FDG data. A realistic dataset was simulated using partial volume effects (fuzzy segmented dataset) with three different brain tissues: White Matter (WM), Gray Matter (GM) and Vessels/Arterial Input Function (AIF). However, this framework computation time scales with activity and therefore, can only be used to simulate few examples (2 or 3). Therefore, the researcher extended the analytical simulation framework within PRESTO to allow the simulation of dynamic PET data. This has been tested with [18]F-FDG and [15]O-H2O data, but also [11]C-Raclopride data. The researcher has also learned JEMRIS (Jülich Extensible MRI Simulator) to simulate MRI data (Deliverable D1.2). Significant work has also been done in validating the PRESTO framework with Ordinary Poisson (OP) reconstruction methods using priors. This is an important part of the work for two reasons: 1) there has been few papers describing it, so it constitutes a novelty by itself, and 2) the results have shown to be very promising in terms of quantification and have been already applied to several patient data in Jülich. A clinical oriented paper using this method is currently under preparation by a colleague (Milestone M1.1). In general, this WP took more time than the expected time of 3 months, mainly due to the simulations and the validation of PRESTO. Furthermore, PRESTO has been recently re-designed and everything that has been already developed should and will be verified again.

For WP2 (Image Derived Input Function methods), the MRI-based MAP reconstruction algorithms have been integrated in the OP reconstruction within PRESTO and further validation needs to be performed. The MRI-based reconstruction algorithms include the Bowsher prior, but also segmentation based priors (Deliverable D2.1). Reduction of noise and partial volume effect has been assessed for dynamic PET (Conference Proceeding CP3 and Journal Paper JP2) and further assessment for MRI-based MAP reconstruction is going to be assessed (Deliverable D2.2) after the new PRESTO re-design has been validated. Unfortunately, this means that this task was not solved as initially proposed, but the initial proposal will be completed during the next year. For this reason, the Image Derived Input Function methods research line was further extended with a new methodology, but still completely integrated in the project Dynamic PET/MR. This method uses MRI-based AIF to estimate PET-based AIF. The MRI-based AIF is extracted from a dynamic MR sequence, which has been proposed by our institute. This sequence uses two different echoes (13 and 33 ms) and has reasonable spatial (approximately 2x2x5 mm3) and temporal (1.5s) resolution for AIF purposes. The PET-based AIF can then be estimated using the MRI-based AIF for the early frames. This early frames are the ones with less statistic because of the short time frame and therefore, the ones with high noise. Therefore, a new IDIF method was proposed (D 2.2) and a study with this new method in clinical setting (at the moment, there are more than 100 patients) is being performed (some results have already been published in conference proceeding CP 10 and CP 13) (M 2.1).

For WP3 (Time Activity Curves methods), one of the goals is to extend the Median Root Prior (MRP) for temporal smoothing (Deliverable D3.1). There are two challenges to further address in this task:

1. Due to computational limits, it is not possible to reconstruct all the frames at the same time, or to load them all to the RAM memory. Therefore, it takes more than 24 hours to reconstruct one dataset. For efficiency, this computational time should be reduced before extensive testing. This challenging task has been the focus of work of the scientist in charge during this last year, Dr. Jürgen Scheins. At the moment, the re-design of PRESTO with these modifications is almost complete.
2. Temporal smoothing MRP enforces a monotonic TAC, which is not the case for all TACs. The solution that was already referred in the proposal is the use of Gibbs prior for temporal smoothing. For this solution, parameters have to be optimised to ensure that noise in the TAC is reduced, while dynamic changes in activity have to be preserved. Another solution is using anatomical information to define regions where TAC should be monotonic and which regions should not.

In this task, reduction of noise and partial volume effect has been assessed for dynamic PET (Conference Proceeding CP3 and Journal Paper JP 2) with spatial MRP (Deliverable D3.2).

For WP4 (Evaluation of new methods), kinetic parameters and parametric images using the different developed methods have to be evaluated. In this stage, the researcher has calculated parametric images for [18]F-FDG dynamic data (Patlak) and it was possible to see a clear reduction of noise in the parametric images (Conference Proceeding CP3 and Journal Paper JP2) (Deliverable D4.1). This kinetic evaluation has been also extended for [18]F-FET, which a tracer developed in Jülich. However, as this is still considered a new tracer, the kinetic model is still under discussion, but our group has been collaborating with the brain tumour group of our institute in this matter.

For WP5 (Dissemination activities), there has been a journal paper (Journal Paper JP2) and several conference proceedings directly related to the results of this project and several other proceedings related to this project (Deliverable D5.1). The Institute of Neuroscience and Medicine has updated the researcher as part of the MR-PET team [1], and the Helmoltz Association has a full page about the project “Dynamic PET/MR” [2]. COST Action TD1007 has also put on their webpage information about the project [3]. The researcher has presented her work in several places: IEEE NSS/MIC 2013 and 2014, STIR’s (Software for Tomographic Image Reconstruction) User meeting, TD1007 COST meeting Dec/2013, ISMRM (International Society of Magnetic Resonance in Medicine Conference) 2014 and 2015, First International Training School on PET/MR Engineering and PSMR 2014 and 2015 (3rd and 4th Conference on PET/MR and SPECT/MR). Furthermore, the researcher has also presented the Marie Curie project in several talks at: 1) TD1007 COST meeting. Gent, Belgium. 2013; 2) Athinoula A. Martinos Center for Biomedical Engineering at Massachussets General Hospital (MGH), Boston, USA. 2014; 3) Center for Advanced Imaging Innovation and research at New York University School of Medicine, New York, USA. 2014; 4) Translational and Molecular Imaging Institute at Mount Sinai Hospital, New York, USA. 2014; and 5) poster spotlight presentation in the topic “Neuroimaging”. INM retreat 2014.

The researcher has also been working on a project about Arterial Input Function using MRI. Recently, there have been published papers about arterial input functions in PET and MR, including comparison. In tumour patients, data is already acquired in which it is possible to extract AIF from both modalities. Therefore, the researcher started a project about this with MR colleagues and medical doctors. A paper is going to be re-submitted to a journal in the next few weeks (Title: Estimation of the Arterial Input Function using Accelerated Dual-Contrast EPIK) and several conference proceedings have already been published (CP).

Besides from working on the WPs described in the project, the researcher has worked on several other projects in parallel, but related to the project. Here is a brief description of these:

- The researcher has been supervising several students. She supervised a master student in the topic of Motion Correction for Dynamic PET. The student has finished her project and has presented her work in three different conferences: “Workshop on Biomedical Engineering 2014”, PSMR 2014 (Conference Proceeding CP4) and IEEE NSS/MIC 2014. She won best poster prize at the Workshop on Biomedical Engineering 2014. The student had a final grade of 18/20. The researcher supervised a bachelor student during July and August of 2013 about MRI artefact corrections, which can possibly affect PET reconstruction with anatomical priors. The student had a final grade of 18/20 in her bachelor thesis. The researcher has supervised a master student in the topic of semi-parametric images using PET and MR data. The student has presented her work in two different conferences: “Workshop on Biomedical Engineering 2014” and PSMR 2014 (Conference Proceeding CP5). The researcher has been supervising a master student from Fachhochschule Aachen during a mini-project internship about MR-PET AIF. She is also helping in another master thesis project of the PET group about LSO background radiation.

- The researcher has also been collaborating with Dr. Miguel Patrício from IBILI (Institute for Biomedical Engineering and Life Sciences, Coimbra, Portugal). We are studying [11]C-Raclopride protocol optimisation using iterative reconstruction methods. Filtered Back Projection (FBP) reconstruction is mostly used in receptor studies, but iterative reconstruction methods have shown in the last years their advantages. Dr. Miguel Patrício visited Jülich for 3 weeks under the COST action TD1007 and the researcher was the host supervisor. During his stay, he also presented a seminar in Jülich.

- The researcher has started collaborating with Dr. Kathleen Vunckx from Leuven University. Dr. Vunckx has been once visiting Jülich, where she presented a seminar and the researcher has been also once in Leuven University with scientist in charge, Dr. Jürgen Scheins. Dr. Vunckx is a recognised expert in anatomical priors for PET reconstruction and the collaboration started with an exchange of methods and data suitable for these methods.

[1] http://www.fz-juelich.de/inm/inm-4/EN/Forschung/MR-Physik/TeamMrPet/\_node.html

[2] http://www.helmholtz.de/en/helmholtz\_centres\_networks/eu\_projects/people/intra\_european\_fellowships\_ief/dynamic\_petmr/

[3] www.pet-mri.eu/news.html

Progress of the researcher training activities/transfer of knowledge activities/integration activities (as it applies for the Marie Curie action)

* First of all, it is important to note that the researcher is now on post-doc contract with INM-4 after the Marie Curie grant ended to keep researching the same topic: Dynamic PET/MR. This means that the integration was very successful and that the topic of research is of interest.
* The researcher has attended several scientific meetings: 7th Erwin Hahn Lecture and fMRI workshop (September 2013), IEEE NSS/MIC 2013 and 2014, STIR’s User meeting, TD1007 COST meeting Dec/2013, ISMRM 2014 including the educational courses and ISMRM 2015, First International Training School on PET/MR Engineering and PSMR 2014 and 2015.
* As mentioned before, she has supervised one Bachelor student and two Master students. She was part of the jury for the defence of one of these master students. She is currently supervising a master student from FH Jülich for a summer internship. She is also helping in another master thesis project of the PET group about LSO background radiation.
* She has been recruited to start teaching in University of Wuppertal in the winter semester 2014/15 (exercises module). The course is entitled “Digitale Bildverarbeitung in der Medizinischen Physik”/”Digital Image Processing in Medical Physics”. She will teach again this exercises module in the next winter semester 2015/2016. In the summer semester 2015, she started teaching the course “Medizinische Physik”/“Medical physics” (exercises module).
* The researcher attends regularly meetings at the host institution: PET group (once per week), MR group (once per week), MR/PET team (once per month) and INM-4 meeting (once very three months). She also attended several seminars organised by the INM given by guest scientists.
* The researcher has also attended the “Introduction to the new employees” seminar in Jülich, and has attended four German levels (one per semester).
* She has also participated in the 2-day retreat of Institute of Neuroscience and Medicine of the Forschungszentrum (July/2013) and was also part of the organising team of this retreat in 2014 (July/2014).
* She has organized two seminars at the host institution: Dr. Kathleen Vunckx and Dr. Miguel Patrício, and has helped organise the Early Stage Researchers (ESR) Session in PSMR 2014 and 2015.
* She was part of the organising committee of “First International Training School on PET/MR Engineering”.
* She is at the moment part of the organising committee of PSMR 2016.
* She attended a post doc funding information seminar at RWTH Aachen in June 2015.
* She attended a coil workshop (1 afternoon in September 2014) and a Brain Voyager course (2 days in October 2014) organised in the INM-4.
* The researcher has performed MR scanner operator level 1 in Jülich, which allows entering the scanner room whenever necessary and started MR scanner operator level 2. Furthermore, the radiation protection officer also instructed her about radioactive material and the controlled area. She has also attended a refresher course about radiation and MR security during her second year.
* She has become a reviewer of Medical Physics Journal and also of COST actions.
* She visited the Institute of Biomedical Engineering and Biophysics in Lisbon, Portugal to discuss collaboration project along with colleagues from Jülich (September 2014).

Significant results

Here is a summary of the most relevant achievements during the two years of the Marie Curie:

Journal Papers (JP)

JP1. N Jon Shah, Hans Herzog, Christoph Weirich, Lutz Tellmann, Joachim Kaffanke, Liliana Caldeira, Elena Rota Kops, Syed M Qaim, Heinz H Coenen, Hidehiro Iida. [**Effects of Magnetic Fields of up to 9.4 T on Resolution and Contrast of PET Images as Measured with an MR-BrainPET**](http://dx.plos.org/10.1371/journal.pone.0095250). PloS One. 2014.

JP2. Liliana Caldeira, Nuno da Silva, Jürgen Scheins, Michaela Gaens, N Jon Shah. **Effects of Regularisation Priors and Anatomical Partial Volume Correction on Dynamic PET Data**. IEEE Transactions on Nuclear Science. (accepted for publication).

Conference Proceedings (CP)

CP1. Liliana Caldeira, Jürgen Scheins, Pedro Almeida, Hans Herzog. **Influence of MRI Artifats on PET Image Reconstruction Using MRI-Based Priors.** IEEE NSS/MIC 2013. Seoul, South Korea.

CP2. Raquel Conceição, João L. Tourais, Liane S. Canas, Gaspar Delso, Liliana Caldeira. **Image Processing Methods for PET/MRI Multi-modality Imaging.** IEEE NSS/MIC 2013. Seoul, South Korea.

CP3. Liliana Caldeira, Jürgen Scheins , Michaela Gaens, Nuno da Silva, N. Jon Shah. **Effects of Regularisation Priors on Dynamic PET Data.** PSMR 2014. Kos, Greece. (published as abstract in European Journal of Nuclear Medicine and Medical Imaging Physics)

CP4. Melissa Botelho, Liliana Caldeira, Jürgen Scheins, Nuno Matela, Elena Rota Kops, N. Jon Shah. **PET Motion Correction using PRESTO with ITK Motion Estimation.** PSMR 2014. Kos, Greece. (published as abstract in European Journal of Nuclear Medicine and Medical Imaging Physics)

CP5. Ana Morgado, Liliana Caldeira, Nuno da Silva, Christian Filss, Nuno Matela, Karl-Josef Langen, N. Jon Shah. **Dynamic analysis of MR-PET data on brain tumors.** PSMR 2014. Kos, Greece. (published as abstract in European Journal of Nuclear Medicine and Medical Imaging Physics)

CP6. Jürgen Scheins, Christoph Weirich, Liliana Caldeira, Philipp Lohmann, Elena Rota Kops, Lutz Tellman, Michaela Gaens, Hans Herzog, Uwe Pietrzyk, N. Jon Shah. **High/resolution Quantitative 3D PET Image Reconstruction for the Siemens hybrid MR/BrainPET Scanner using the PET Reconstruction Software Toolkit (PRESTO).** PSMR 2014. Kos, Greece. (published as abstract in European Journal of Nuclear Medicine and Medical Imaging Physics)

CP7. Miguel Patrício and Liliana Caldeira. **Optimisation of PET framing sequences.** PSMR 2014. Kos, Greece. (published as abstract in European Journal of Nuclear Medicine and Medical Imaging Physics)

CP8. Liliana Caldeira, Seong Dae Yun, Nuno da Silva, Christian Filss, N. Jon Shah. **Estimation of the arterial input function using accelerated dual-contrast EPIK: a multi-modality MR-PET study.** ISMRM 2014. Milan, Italy.

CP9. Melissa Botelho, Liliana Caldeira, Jürgen Scheins, Nuno Matela, Elena Rota Kops, N Jon Shah. **PET/MR Motion Estimation using ITK**. IEEE NSS/MIC 2014. Seattle, USA.

CP10. Liliana Caldeira, Seong Dae Yun, Nuno da Silva, Christian Filss, Jürgen Scheins, Lutz Tellmann, Hans Herzog, N Jon Shah. **Simultaneous acquisition of dynamic PET-MRI: arterial input function using DSC-MRI and [18F]-FET**. PSMR 2015. Elba, Italy. (published as abstract in European Journal of Nuclear Medicine and Medical Imaging Physics)

CP11. Nuno da Silva, Liliana Caldeira, Hans Herzog, Lutz Tellmann, Christian Filss, Karl-Josef Langen, N Jon Shah, **Automatic derivation of an MR-PET image-based input function for quantification of 18F-FET**. PSMR 2015. Elba, Italy. (published as abstract in European Journal of Nuclear Medicine and Medical Imaging Physics)

CP12. Elena Rota Kops, André Ribeiro, Liliana Caldeira, Hubertus Hautzel, Matthias Lukas, Geral Antoch, Christoph Lerche, N Jon Shah. **Attenuation correction for hybrid MR/PET scanners: a comparison study**. PSMR 2015. Elba, Italy. (published as abstract in European Journal of Nuclear Medicine and Medical Imaging Physics)

CP13. Liliana Caldeira, Seong Dae Yun, Nuno da Silva, Christian Filss, N Jon Shah. **Conversion of the arterial input function using accelerated dual-contrast EPIK: a multi-modality MR-PET study**. ISMRM 2015. Toronto, Canada.

CP14. Nuno da Silva, Liliana Caldeira, Jörg Mauler, Hans Herzog, N Jon Shah. **Automatic Internal Carotid Segmentation for estimation of an Image Derived Input Function with MR-PET**. ISMRM 2015. Toronto, Canada.

CP15. Theodoros Kaltsas, Liliana Caldeira, Jürgen Scheins, Lutz Tellmann, Elena Rota Kops, N Jon Shah, Christoph Lerche. **Reconstruction of attenuation maps for a PET/MR scanner based on the LSO background activity**. IEEE NSS/MIC 2015. San Diego, USA. (accepted)

Other communications:

- Liliana Caldeira. **Reconstruction of PET data acquired with the BrainPET using STIR**. STIR User’s meeting. Seoul, South Korea. 2013

- Liliana Caldeira. **Dynamic PET/MR: Marie Curie Project**. TD1007 COST meeting. Gent, Belgium. 2013.

- Miguel Patrício, Liliana Caldeira, Nuno da Silva, Francisco Caramelo, Nuno Ferreira. **Protocol optimisation for PET quantification.** IBILI meeting. 2014.

- Melissa Botelho, Liliana Caldeira, Jürgen Scheins, Nuno Matela, Elena Rota Kops, N. Jon Shah. **PET Motion Correction using PRESTO with ITK Motion Estimation.** Workshop on Biomedical Engineering. Science Faculty of Lisbon. 2014

- Ana Morgado, Liliana Caldeira, Nuno da Silva, Christian Filss, Nuno Matela, Karl-Josef Langen, N. Jon Shah. **Dynamic analysis of MR-PET data on brain tumors.** Workshop on Biomedical Engineering. Science Faculty of Lisbon. 2014.

- Kaveh Vahedipour and Liliana Caldeira. **MR Simulation Practical**. “First International Training School on PET/MR Engineering”. Athens, Greece. 2014

- Liliana Caldeira. Oral presentation **Dynamic PET/MR** at Athinoula A. Martinos Center for Biomedical Engineering at Massachussets General Hospital (MGH), Boston, USA. 2014.

- Liliana Caldeira. Oral presentation **Dynamic PET/MR** at Center for Advanced Imaging Innovation and research at New York University School of Medicine, New York, USA. 2014.

- Liliana Caldeira. Oral presentation **Dynamic PET/MR** at Translational and Molecular Imaging Institute at Mount Sinai Hospital, New York, USA. 2014.

Awards:

- Award of IEEE NSS/MIC/RTSD Conference Trainee Grant 2013. Seoul, South Korea, October/November 2013.

- Award for Best Paper NuklearMedizin 2013: H Herzog, KJ Langen, C Weirich, E Rota Kops, J Kaffanke, L Tellmann, J Scheins, I Neuner, G Stoffels, K Fischer, L Caldeira, HH Coenen, NJ Shah **High Resolution BrainPET Combined with Simultaneous MRI**.

- Award for Best Poster for supervised Master student Melissa Botelho on Workshop on Biomedical Engineering. Science Faculty of Lisbon. 2014.

- Best poster award in the topic “Neuroimaging” in INM retreat 2014.

- ISMRM merit award Magna Cum Laude for abstract: Nuno da Silva, Liliana Caldeira, Jörg Mauler, Hans Herzog, N Jon Shah. **Automatic Internal Carotid Segmentation for estimation of an Image Derived Input Function with MR-PET**. ISMRM 2015. (CP 14)

2. ADDITIONAL INFORMATION

3. PROJECT MANAGEMENT

* Project planning and status – from the management point of view

The first WP1 has been completed. WP2 methodology has been changed, which means that the initial methods were not used, because it took more time to re-design the PRESTO software than expected. However, a new IDIF method which has been accepted by the community was proposed. Therefore, the major goal of this WP was fulfilled. Nevertheless, the researcher is still working on the methods initially proposed. WP3 focused mainly in post-reconstruction anatomical partial volume correction methods, which have shown to improve the TAC and consequently, kinetic modelling. There is still space for more evaluation and developments to be done in this WP. In terms of management, WP2 and WP3 have been done simultaneously and not sequentially as initially planned, because time can be used more efficiently. WP4 has evaluated the new methods in the clinical setting, but it still needs to be evaluated against parametric image reconstruction. Initially, this would use STIR reconstruction software, but so far this software is incompatible with our data, so we will implement our own PIR, but this will of course require more time.,WP5 was done simultaneously to all the other WPs and has been fulfilled (less Journal papers, but more conference proceedings).

- Problems which have occurred and how they were solved and envisaged solutions

Nothing to report.

- Changes to the legal status of any of the beneficiaries, in particular, SME status

(not applicable)

- Impact of possible deviations from the planned milestones and deliverables, if any

No negative impact expected.

- Development of the project website (if applicable)

(not applicable)

- Gender issues, Ethical issues

Nothing to report.

- Justification of subcontracting (if applicable)

(not applicable)

- Justification of real costs (management costs)

Only costs related to the research activities have been claimed.