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To ensure that we capture all the important issues from across the research arena, we invite you to send us your ideas, comments and suggestions for future editions to contact@vph-dare.eu. Non-VPH-DARE@IT participants interested in receiving this newsletter can subscribe via the VPH-DARE@IT website at www.vph-dare.eu.
Editorial

Welcome to the first issue of the biannual newsletter of the VPH-DARE@IT project!

This first issue provides an overview of the project and looks at the role of 2 of the project partners: University of Sheffield (USFD) and the team in the University’s Department of Mechanical Engineering and Advanced Simulation & Design GmbH (ASD).

Our bi-annual newsletters will feature articles from partners in each issue with the aim of getting to know our partners, finding out what they do and how their work impacts and informs the project. We will also get to know the researchers working on the project with interviews and articles from students and researchers at different partner institutions. In this issue, we find out about the work of John Vardikas at University College London / University of Oxford and Stefan Klein tells us about the brain models being developed at Erasmus MC.

Since the kick-off meeting in April 2013, the VPH-DARE@IT project has already come a long way. We have welcomed new members of staff to the project, launched the project website www.vph-dare.eu and held a highly successful General Assembly meeting in Espoo, Finland. We are looking forward to seeing you all later this month at our second General Assembly meeting, to be held at IRCCS Fondazione Ospedale San Camillo, Venice, Italy.

This issue also includes an update from Jyrki Lötjönen about the progress made in Action Line 1, and Juan Arenas provides an overview of the Proof of Concept for the Research Platform which provides focus as we begin to prepare for the project’s first review meeting in June 2014.

The project continues to build on the momentum generated at the kick of meeting and we continue to develop links with other parallel initiatives in dementia related research and development. We are very fortunate to welcome Professor Martin Hofmann-Apitius, Coordinator of the AETIONOMY project to our General Assembly meeting in Venice, and in this issue of the newsletter we hear about this project and how the co-ordinated effort to establish a mechanism-based taxonomy which ultimately will result in improved diagnostic and therapeutic procedures compliments the work within our own project.

We hope you enjoy the first issue of the newsletter. We would love to hear your views, comments or suggestions for future articles or features. If you would like to make any comments or suggestions, please do not hesitate to contact us: contact@vph-dare.eu.

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Objectives of VPH-DARE@IT:

The “Virtual Physiological Human: DementiA Research Enabled by IT” (VPH-DARE@IT) project aims to provide a systematic, multifactorial and multiscale modelling approach to understanding dementia onset and progression and enable more objective, earlier, predictive and individualised diagnoses and prognoses of dementias to cope with the challenge of an ageing European society. This translates into five more specific objectives:

1. **Novel biomedical biomarkers of dementia**

   The project aims to define novel memory disorder biomedical biomarkers, available for predictive multi-scale model-building and personalisation, as well as for earlier differential diagnostics, to be made accessible through the VPH-SHARE infrastructure.

2. **Extend our basic understanding of dementia**

   We will extend our understanding of dementia, aided by a unified multi-scale modelling approach that fully accounts for environmental influences on metabolism, biophysics, physiology, clinical biomarkers and lifestyle.

3. **Deliver novel integrative modelling strategies and open source research modelling platforms**

   We will develop and disseminate novel integrative modelling strategies and Open Source research modelling platforms that unravel brain ageing processes and progression of dementias through high-throughput data analysis.

4. **Translate knowledge into clinical decision support platforms**

   We will turn know-how and methods into an innovative, integrative and objective clinical decision support platform for the early and differential diagnosis of memory disorders based on principles of evidence-based medicine and extensions of PredictAD technology (www.predictad.eu).

5. **Quantify the benefits and costs of using the VPH-DARE@IT platform**

   The project will quantify the benefits and costs of using the VPH-DARE@IT platform by both clinicians and industry and contribute to the competitiveness of our industrial partners.
The concept behind VPH-DARE@IT came about...
first year of the project, Alex’s view is that the project team has spent ample time discussing things thoroughly and have built an understanding across work packages. He feels that the general meetings have been particularly useful as well as the monthly teleconferences of the project board who lead the wider consortium through the work plan. Alex went on to comment “Most importantly: we are trying to create a truly innovative and inspiring atmosphere where people are not told what to do but rather the space is created to collaboratively and collegially come up with the best ideas.

When you lead clever people, it is not so much about managing them but about being an inspiring leader that creates space for meaningful conversations. Of course, there are always more grey tasks that need to be carried out (e.g. writing deliverables or formal progress reports) and people tend to dislike those. I hope that through effective support from the Project Management Team, people realise that those tasks are important for our stakeholders and that, in fact, can be carried out with minimal overhead.”

We asked Alex what he thinks have been the challenges for the project so far. Alex’s view is that the biggest challenge is the sheer complexity of dementias and neurodegeneration: “For every bit of knowledge we have on the disease, there are actually much more unknowns and questions that need to be unravelled. In particular, developing mechanistic models of dementia, and identifying the most relevant and feasible avenues for the personalisation of those models is far from trivial.” He went on to suggest that this is why we are incorporating in our project meetings ample time for interaction and discussion and we are bringing external invited speakers to complement our internal expertise.

According to Alex, the main strengths of the consortium are the excellence of the people on board and the interdisciplinary nature of the project: “the consortium is excellent – we have key people on board who not only provide key expertise but are well networked to other relevant initiatives”, he also commented that with the interdisciplinary nature of
the project “we have virtually all key disciplines represented in our cadre of partners and these two elements will ensure we advance in the understanding of this devastating disease and contribute to its improved management.

The first year has been primarily focussed on understanding the main tasks within each of the work packages and getting everyone to know their key partners with whom they will be working regularly. The next challenge, which is being addressed at the Project Board level, is to ensure that the project builds appropriate links and understanding across work packages, where the interdependencies, synergies and interdisciplinarity will be at their best display. Alex went on to say that “creating a sense of common purpose and making everyone understand how their piece makes the puzzle is the key to success in the coming year.”

We will be shortly entering the end of the first year and we will start to prepare for the first annual review. Alex welcomes this as an opportunity to inspire further team spirit which will require an effort of integration and holistic reflection as to where exactly we have reached in 12 months and what we have achieved. He went on to suggest that the team are planning to use the research and clinical platforms to drive this process in creating real scenarios on how such platforms will be used and how each of the work packages contributes to realising these scenarios.

Work package 10: Co-ordination, Communication and Outreach

As project manager, and WP10 leader, Dr. Mark Pullinger is charged with the smooth running of the project and the co-ordination of all its activities. The intention is to make partners’ lives as easy as possible; whilst putting in place communication and quality control procedures that will facilitate the delivery of the project’s outputs.

The first few months of the project have been dedicated to building the transnational team that will deliver the project’s activities. The kick-off meeting, held in Sheffield in April 2013, which brought together 52 researchers from the project’s 20 partners to hear a variety of presentations on the important topic of dementias, was the first step towards building the team. Subsequent project meetings have been similarly well attended and, whilst still an ongoing process, the consortium is beginning to jell and develop productive research links.

Monthly project board meetings have taken place via teleconference, with a face-to-face meetings held at various locations every quarter. The project board meetings have been well attended and are helping the project’s management team to keep track of the diverse activities taking place within the project and help to steer it towards its goals.

Now that the early deliverables have been completed, other parts of the project are beginning to ramp up their activities to ensure that project meets its challenging range of outputs over the next three years.

Mark feels that the project is running well and good collaborative teams are forming. Investment has been made in a new piece of project management software, EMDESK, which is currently being rolled out across the consortium. In addition to this, a robust quality control system for project outputs is currently being implemented. This will ensure project outputs and of high quality and produced the standards set by the project board.

The main challenge in the next six months is to prepare for the annual review of the project by the European Commission. Following the project board meeting in Zürich in January 2014, a core team has been formed in Sheffield to begin to put together the narrative that will be presented to the Commission’s appointed external reviewers. Mark and the management team will be working with all partners to ensure that work is on track and that the project is fully prepared for the first review.

Work Package 2 - Novel imaging disease biomarkers and methods for model personalisation

Dr. Zeike Taylor has responsibility for the activities in WP2, which has three overarching themes:
• Development of imaging protocols for the prospective data acquisition activities in WP1,
• Discovery of novel imaging biomarkers of dementia in support of the project’s clinical studies,
• Development of model personalisation techno-
logies to realise patient specific biophysical modelling of the ageing and degenerating brain.

When asked of the activities taking place in WP2, Zeike gave an overview of the various actions taking place: On the acquisition side, ETH Zürich, KCL, and Philips have been leading development of new protocols and devices for quantitative cerebral flow measurement, diffusion imaging, MR elastography, and quantitative susceptibility mapping. As well, the standard imaging protocols for the project were recently finalised. Zeike went on to say that Philips is leading development of cortical shape models and image registration techniques, which will allow, respectively, characterisation of disease-associated brain shapes and fusion of image data from the various modalities used in the project.

Novel approaches to MR elastography of the brain are being investigated by KCL and Sheffield. Zeike commented that KCL, in particular, has been investigating the effects of tissue microstructure on wave propagation patterns in the brain, while Sheffield is focusing on simulation-based methods for optimising the elastography configuration and development of physical brain phantoms. Imperial College London, also with Sheffield, has started to work on methods for generating normative models of brain images, for characterising patterns of degeneration.

Sheffield’s other activities have revolved around development of microstructure-based models of diffusion image signals, with the aim of characterising disease-related changes in the latter; and, with VTT, investigation of the potential of resting state fMRI in early dementia detection. We are also beginning to look at ways to leverage the shape modelling and image fusion developments of Philips for biophysical model personalisation (geometry, boundary conditions, tissue properties, etc.).

When asked what is going particularly well WP2, Zeike commented that the acquisition activities, necessarily, are the most progressed: the first draft deliverable, describing the standard acquisition protocols, has been circulated by ETH Zurich; the advanced protocol descriptions and MRE configurations will be published soon. Progress is being made in all of the WP's streams, and Zeike is particularly pleased to see the closer integration of efforts between the partners.

The priorities for WP2 in the next six months are further building of collaborative links between the various streams, a more focussed approach to the work based on the clinical studies set out in WP1, and construction of a cohesive narrative of the WP's activities for presentation at the 1st annual review in June 2014.

WP7: Biomedical Research Platform for Disease Modelling and Model Personalisation

Juan Arenas, Technology Officer, leads WP7. The aim of this work package is to deliver a research platform for the evaluation of the different types of dementias that will offer to researchers a powerful repository of data, algorithms and workflows with a friendly UI. The platform will also pay special attention to providing mechanism to incorporate new tools and to facilitate its extension.

The main deliverable for WP7 for the first year of the project is the architecture design and interoperability where all partners contribute in different ways. Juan and WP7 partners will focus on collaboration with linked projects such as VPH-Share, which provides the underlying infrastructure, and EMIF.

Since the Kick-off meeting in April 2013, it was clearly recognised the need to develop a proof of concept (PoC) that would validate the underlying platform (VPH-Share) while helping to identify gaps and areas for improvement. This PoC provides an end to end validation from the data upload up to the biomarkers extraction.

Speaking about the progress made during the first year of the project, Juan commented “I have to say that, even if it was not explicitly planned in the DoW, all partners involved were committed along the process, allowing us to make great progress and evolve the PoC to the next level where interoperability will be tested.”

The next challenge for Juan and the team is to identify the use cases for the research platform and guarantee that we meet all the requirements so they can be executed using the different components of the platform.

Partners in WP7 are currently exploring the best way to collaborate with EMIF at different levels: data, tools and platform. Juan believes there are several ways in which this collaboration will benefit both projects and hopes this collaboration will lead to concrete results in a relatively short time.
ASD Advanced Simulation & Design GmbH Germany

By Catrin Bludszuweit-Philipp

ASD Advanced Simulation & Design GmbH (ASD) is a private company focussed on the application of innovative, simulation-based methods primarily to the fields of bioengineering and biotechnology. ASD was founded in 1996 and is located in Rostock (Germany). The company’s core business is high-level computer simulations of flows, structure-mechanical systems, thermal and chemical processes as well as biological issues in complex systems. With its modern simulation technologies for biological processes, such as blood damage and coagulation, cell metabolism and tissue remodelling, ASD is an internationally recognised partner for biomedical, biotechnology and pharmaceutical industries which outsource related R&D and product design tasks to ASD.

Due to its focus on using highly innovative methods, ASD continuously engages itself in research activities to enhance its technologies. For example, the company has previously participated in European ICT research projects, e.g. BloodSim, GEMSS, @neurIST and ARTreat. With

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some of the partners from these previous projects, a continuation of modelling activities for the “Virtual Physiological Human”-project was envisaged, focussed on the modelling of the brain. These activities lead to the VPH-Dare@IT proposal where ASD contributes its long-term expertise and know-how in the complex modelling of coupled biochemical- biophysical systems.

The role of ASD in the VPH-DARE@IT project

ASD commits its know-how in the area of system analysis, metabolic activity and biophysical transport modelling to VPH-DARE@IT. The company provides its advanced simulation facilities to the project and contributes to the further development of simulation techniques within the project. ASD leads the work package on “Genetic, Biochemical and Metabolic Pathway Modelling” (WP4) and contributes to the “Multiscale Biophysical & Biochemical Modelling” (WP5). Two people will be the main contributors to the project.

Dr. Catrin Bludszuweit-Philipp, founder and managing director of ASD, coordinates activities of the partners in work package 4 and is a member of the project board. She has a degree in Mechanical Engineering and obtained her PhD in Bioengineering at Strathclyde University Glasgow (UK). Dr. Bludszuweit-Philipp has developed international reputation in the modelling of biomedical systems and the enforcement of virtual design technologies in medical applications. She focuses her research and development activities on the interactions between the metabolic modelling activities and transport mechanisms of substances in the brain on various scale-levels.

Felix Winter obtained his degree in business mathematics from the University of Rostock in 2009. He has since worked in several interdisciplinary projects related to the mathematical modelling of biological aspects of Alzheimer’s disease. Being part of the Systems Biology and Bioinformatics group of the University of Rostock for some years, he joined ASD GmbH at the beginning of 2013. He is a strong advocate for the use of standards in model development, simulation, storage and exchange. With regard to the VPH-DARE@IT project Mr. Winter is very actively involved in the mathematical modelling of the metabolism processes in the brain including the energy metabolism and to link them to metabolic alterations found in dementia. Additionally, he develops models for investigating the alterations in the amyloid-beta cascade and modifications in the tau-protein, both being closely linked to the manifestation and clinical prognosis of dementia.

“**The strong interaction between the involved clinicians and modelling experts within this project is particularly exciting because it builds on the integration of people with very different areas of know-how and background.**"
Key interests of ASD in the project

A very striking aspect of the project is the clear focus on the early prediction of dementia using a combination of imaging and modelling tools. In this respect, the strong interaction between the involved clinicians and modelling experts within this project is particularly exciting because it builds on the integration of people with very different areas of know-how and background. Working in such a large consortium therefore helps to put one’s own work into perspective. Also, it is enlightening to see how the different approaches come together and people try to find a common language. Especially for the junior researchers involved, the project provides very good possibilities to get to know other research groups and to become visible in this field.

As many prospects large collaborative projects may have, there are also challenges. One aspect is the great challenge in achieving a common project goal even if the partners are so diverse and everyone has his/her own research interest. If VPH-DARE@IT succeeds to integrate the results from the different areas into a comprehensive picture of dementia and its diagnosis, this will be a great achievement. Seeing that the worldwide activities and the permanent gain of new knowledge in understanding dementia is enormous, keeping track of these developments and consistently considering them in this project will be a challenging task.

“The project provides very good possibilities to get to know other research groups and to become visible in this field.”

For ASD the aim in this project is to develop a model which represents, simulates and predicts the complex interactions between the metabolic pathways, in terms of biochemical and energetic processes, including results from modern imaging and biomarkers for a patient-specific characterisation of dementia-related processes that is currently not available on the market. ASD with this hopes to expand in the future into new areas of simulation-based health care technologies with a very close clinical and pharmaceutical connection.
Action Line 1
By Dr. Jyrki Lötjönen

• Collaboration within Action Line 1

Action Line 1, consisting of work packages (WP) 1 to 3, is titled “Hypothesis, Biomarkers & Personalisation”. In work package 1 the key topic during the period has been the planning of the prospective studies by the clinical partners (UEF, USFD and HIRS). WP 2 has focussed on the development of novel MRI imaging protocols (ETHZ, KCL, HIRS, USFD, PRH). Collaborative efforts on MRE (KCL, USFD) have also commenced. WP 3 has been active both on planning and early implementation data sharing with the research platform (together with WP7) and on planning the high-throughput pipelines for image analysis (UCL, EMC, VTT, ICL).

• Collaboration with other action lines

All action lines have participated in the planning the validation studies for VPH-DARE@IT, this output is visible in Deliverable 1.1 which was submitted in month 7 of the project. In addition, WP3 and WP7, especially UCL and USFD, have collaborated in data sharing with the research platform.

• Action Line Achievements

One of the key achievements since the kick off meeting in April 2014 has been the plans for the validation studies and prospective studies. One (out of two) prospective studies started in January 2014. To this end, the standard image acquisition protocols have been finalised, and advanced protocols are nearing completion.

• Planned activities

During the next 6 months Action Line 1 partners will be working on Deliverable 3.1 Detailed workflow specifications & component roadmap for high-throughput image analysis of large-scale studies. Work will also contribute to Milestone 21 Basic acquisition protocols standardised; detailed imaging specs consolidated which is due in month 12 of the project.

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One of the goals of VPH-DARE@IT is to demonstrate how true collaboration between European projects can help to reduce overall costs and time spent on common tasks, maximising the investment and results in areas where projects will add value and make a real difference to the community.

In this context, collaboration between VPH-Share (http://vph-share.eu) and VPH-DARE@IT (http://www.vph-dare.eu) was established with the aim of reducing effort usually spent at the infrastructural level. VPH-Share intends to provide all of the common IT services required by a VPH research project including: data management, security and authentication, workflow capabilities and HPC.

Since the beginning of VPH-DARE@IT, at the Kick-off meeting in April 2013, partners identified the need to validate that VPH-Share was capable of handling the VPH-DARE@IT requirements at the infrastructural level. At that point, an initial Proof of Concept (PoC) was defined as a joint effort between WP7 (USFD), WP3 (UCL) and WP8 (VTT), together with STH, which plays a major role in VPH-Share, but also in VPH-DARE@IT.

The initial proof of concept defined a use case where a user will:

1. Upload an external data set into VPH-DARE@IT underlying infrastructure (VPH-Share infostructure)
2. Publish a fully-automated processing component as a service to be used by the

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**PoC Implementation:** USFD, UCL, VTT, STH

1. **MIRIAD**
   - DPS + XNAT plugin
   - Clinical Info + Scans

2. **GIMIAS + Taverna**
   - GIMIAS + Wrapper + Pipeline
   - VM Image

3. **Pipeline execution**
   - Clinical Platform + External Repositories
   - Biomarkers

4. **Data Storage (Clinical Data, Images, Biomarkers,..) + VMs + Workflows**

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**VPH-DARE@VPH-Share**

www.vph-dare.eu
research community

3. Develop a workflow that runs the component across the imported dataset
4. Access the output of the process

After this initial definition and with the collaboration activities, we managed to:

- Import the annotated MIRIAD database using the Data Publication Services (DPS) tool, provided by VPH-Share and extended with an XNAT plugin developed by STH
- Publish the hippocampus segmentation component, provided by UCL, as a web-service of VPH-Share by using GIMIAS support for web-services and exposing the component as a command line extension
- Create a Taverna Workflow on VPH-Share that executes the component
- Run the workflow in the VPH-Share infrastructure using the dataset as input

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Background and research

I am assistant-professor at the Biomedical Imaging Group Rotterdam (BIGR), Erasmus MC, the Netherlands (www.bigr.nl). My research focuses on the development of advanced medical image analysis methods. I work with a team of 6 highly motivated PhD students. We develop and evaluate novel automated methods for quantitative analysis of medical images such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound scans.

I have an MSc in Mechanical Engineering from University of Twente, the Netherlands. I did my PhD study at the Image Sciences Institute, UMC Utrecht, the Netherlands. During my PhD study I developed open-source software Elastix (http://elastix.isi.uu.nl) for medical image registration, which is an important image processing task in many applications. This software is used by researchers worldwide, and will also be used within the VPH-DARE@IT project.

What is your specific role in VPH-DARE@IT?

I am involved in work package 6, in which we develop computer models of the ageing brain. Based on MRI scans acquired in large population studies, we construct a comprehensive model of how the average brain looks, and how it evolves with age. This model will serve as a reference against which new brain scans can be compared. Individuals whose brain morphology deviates significantly from the average healthy brain are suspected to suffer from a pathological condition such as Alzheimer’s disease. The brain models that we develop are expected to increase insight in the changes in the brain due to normal ageing processes, and ultimately, to improve the diagnosis and prognosis of patients with dementia in an early stage of the disease.

What do you find most interesting about the VPH-DARE@IT project?

The VPH-DARE@IT project is a highly multidisciplinary project, which makes it very interesting. It brings together people with very different backgrounds and expertise, such as epidemiology, radiology, image processing, informatics, and multi-scale modelling.

What do you as a researcher find most challenging about working in VPH-DARE@IT?

The multidisciplinary nature of the project brings also challenges: researchers with different backgrounds have different expectations of the project, use different terminology, and approach the scientific problems from a different view point. In a

“I believe that by sharing research data, software tools, knowledge and expertise with the other participants in VPH-DARE@IT, the research on dementia will be accelerated.”
large project like VPH-DARE@IT there is a risk that these challenges stand in the way of efficient collaboration.

**How do you find working as a part of a large collaborative project?**

The above mentioned strong multidisciplinary nature of VPH-DARE@IT makes it a very exciting project. I believe that by sharing research data, software tools, knowledge and expertise with the other participants in VPH-DARE@IT, the research on dementia will be accelerated.

**Have you attended any of the VPH-DARE@IT project meetings and if so, what benefits did you get from attending these events?**

I have attended the kick-off meeting and found it very useful to get an overview of the project, to get to know the other participants, and to brainstorm together about the possible interactions between groups. I think the coordinators did a great job in creating an open atmosphere, stimulating discussion and collaboration. I am looking forward to the next meetings.

“I think the coordinators did a great job in creating an open atmosphere, stimulating discussion and collaboration.”

**How has working on VPH-DARE helped to develop your career?**

*The VPH-DARE@IT project enables me to extend my research on neuroimage analysis for improved diagnosis of dementia, which is an exciting research field with high relevance.*

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**Figure 1:** Anatomical brain change as a function of age. Construction of the model is presented in figure a). An empty frame indicates the population average at a certain age. Concatenation of all subsequent frames produces a model of the aging brain. Applying the model to the scan of a (randomly selected) individual yields the result of figure b). Note the typical white matter atrophy that can be distinguished.
Background and research

I’m a final year PhD student in Integrative Cerebral Dynamics (2010-2014) in the Institute of Biomedical Engineering & Department of Engineering Science at the University of Oxford. My PhD project is funded by the Digital Economy Programme; a RCUK cross-Council initiative led by the EPSRC and contributed to by AHRC, ESRC, and MRC, as well as from the VPH-DARE@IT project. My work is supervised by Prof. Yiannis Ventikos (who is now at University College London), and is part of a multidisciplinary research interface that combines computational fluid dynamics, Galerkin finite element methods, numerical analysis, high performance computing, surgical techniques, neuroscience and, surprisingly, soil mechanics.

During my PhD, I also completed the Science Innovation Plus programme in the Centre for Entrepreneurship and Innovation at the Saïd Business School, University of Oxford. In 2009, I joined the Centre for Doctoral Training (CDT) in Healthcare Innovation at the University of Oxford, where I completed research courses on a wide spectrum of topics from Cancer Therapeutics to Nanotechnology. During my time at the CDT, I was on a placement in the Department of Neuroradiology and Stroke Unit (part of the Oxford Radcliffe Hospitals), where I shadowed a Consultant Neuroradiologist and a Physician, observed detailed surgical interventions for the treatments of aneurysms and arteriovenous

A schematic outlining AQP4 channels in astroglial end-feet, which contact capillaries.

The cerebral ventricles of a diseased patient.
malformations and attended numerous multidisciplinary team meetings with both consultants, including further specialist meetings for very complex cases. In the same year, I also gained valuable product-specific market research experience with P2i, a leading company specialising in liquid repellent nano-coating technology with global headquarters in Oxford.

As I love travelling, prior to CDT, I was in Voro, Fiji, where I was in a team that won an Environmental Sustainability Award from Enactus for the best technical idea to implement for a rural community. We designed and built an environmentally sustainable desalination system for the island community in addition to surveying the formation of a town-sea wall and wind-turbine generator.

I grew up in London and Athens and I received a BEng (Hons) in Mechanical Engineering from King’s College London in 2008. I was awarded the Siemens Prize (1st), King’s College Engineering Society Centenary Prize and Gilbert Cook Bursary during my studies.

**What is your specific role in VPH-DARE@IT?**

I am part of WP5, namely: Multiscale Biophysical & Biochemical Modeling: Brain Substrate and its Evolution. My objectives include:

- The development and customisation of a computational modelling framework for a multicompartmental poroelastic model with a three-dimensional, spatio-temporally variable properties distribution.
- Casting of the model in an anatomically accurate, image-derived framework.
- Verification and validation of model predictions against clinical observations.
- Coupling this model with the metabolic models developed in WP4.

**What do you find most interesting about the VPH-DARE@IT project?**

There is a wide spectrum of unique expertise within the project, which makes every meeting highly motivating. The wealth of knowledge that is on offer creates a constantly evolving deve-
pment not only for the project itself, but as a platform to share ideas that in most cases create conduits into new and unexplored research.

What do you as a researcher find most challenging about working in VPH-DARE@IT?

As I'm involved in the mathematical modelling side of the project, the constant challenge that is faced is the inclusion of all the new ideas and proposals that come out of the meetings and developments in the area of dementia. The challenge is a positive one, and always leads to the advancement of our methods and insight, and so we embrace this challenge.

How do you find working as a part of a large collaborative project?

I find it very stimulating as the sheer spectrum of disciplines involved means everyone is highly focussed in trying to share their developments and proposals as frequently as possible. The project is managed in such a way that interdisciplinary knowledge is spread quickly and decisively.

Have you attended any of the VPH-DARE@IT project meetings and if so, what benefits did you get from attending these events?

Yes I have. The main benefit for me has been to gain experience in the level of planning and management required to conduct such meetings in order to achieve the desired objectives and ensure everyone's expectations are met. Attending such meetings also allows everyone present to feel confident that we are progressing at the required pace and accelerating whenever we have the opportunity.

How has working on VPH-DARE helped to develop your career?

As a PhD student, I feel I have gained invaluable experience thus far, and this can only serve to my benefit when working to develop our part of the project with the UCL team. The research that can be developed from such an interdisciplinary project is endless, and I can only think of one's desire as a limitation. The impact of Dementia research on the world stage is huge, and will be around for a long time. Tackling the long list of questions will require understanding of the complexity of wide-ranging collaborative arrangements, an aspect that VPH-DARE@IT has already excelled in.

View of the ventricular system along with the choroid plexus (CP) of the lateral (LV), 3rd and 4th ventricle. The arteries supplying these plexuses (not all are presented in the figure) are the anterior and lateral posterior choroidal arteries (ACA & LpCA), the P2 segment of the posterior cerebellar artery (PCA) and the medial posterior choroidal artery (MpCA).

CSF circulates through the four brain ventricles and in the subarachnoid space surrounding the brain and spinal cord.
The G8 dementia summit, held at Lancaster House in London on 11th December 2013, brought together G8 ministers, researchers, pharmaceutical companies and charities from around the world to discuss how to shape an effective international response to dementia. Speakers at the summit included, David Cameron, UK Prime Minister, Peter Dunlop, who is living with dementia, Dr. Margaret Chan, Director General of the World Health Organization (WHO) and Yves Leterme, Deputy Secretary General, The Organisation for Economic Co-operation and Development (OECD).

G8 Health and Science Ministers acknowledged the on-going work taking place globally to identify dementia as a major disease burden and the work being undertaken to address issues related to ageing and mental health. The summit ministers recognise that dementia is not a normal part of ageing, and that it is a condition that impairs the cognitive brain functions of memory, language, perception and thought and which interferes significantly with the ability to maintain the activities of daily living. They also acknowledged that dementia affects more than 35 million people worldwide, a number that is expected to almost double every 20 years.

During the summit, ministers noted the socio-economic impact of dementia globally and reported that 70 per cent of the estimated annual world-wide cost of US$604 billion (€446 billion) is spent on informal, social and direct medical care and identified that nearly 60 per cent of people with dementia live in low and middle income countries. This indicates how the economic challenge will intensify as life expectancy increases across the globe, and suggests how costs are expected to increase significantly if therapies to prevent dementia and improve care and treatment are not developed and implemented.

These facts highlight the importance of dementia research and VPH-DARE@IT and the need for the predictive models being developed in our project. The G8 dementia summit concluded with the publication of a declaration and communique setting out the agreements reached at the summit. During the summit, ministers agreed on the following priorities:

The countries agreed to:

- set an ambition to identify a cure, or a disease-modifying therapy, for dementia by 2025
- significantly increase the amount spent on dementia research
- increase the number of people involved in clinical trials and studies on dementia
- establish a new global envoy for dementia innovation, following in the footsteps of global envoys on HIV and Aids and on Climate Change
- develop an international action plan for research
- share information and data from dementia research studies across the G8 countries to work together and get the best return on investment in research
- encourage open access to all publicly-funded dementia research to make data and results available for further research as quickly as possible.

The publication of this declaration is a commitment made by the G8 to build an international effort to approach the problem of dementia. The communique sets out more information on future plans, including 3 legacy events planned for 2014.

To read the G8 dementia summit agreements in full, go to: https://www.gov.uk/government/publications/g8-dementia-summit-agreements
Overview on AETIONOMY

AETIONOMY is a project that is funded by the Innovative Medicine Initiative (IMI). The initial “expression of interest” was submitted in response to the 8th call of the IMI, which has the title “Developing an aetiology-based taxonomy for human diseases”. AETIONOMY proposes to develop a mechanism-based taxonomy for two major neurodegenerative diseases, namely Alzheimer’s Disease (AD) and Parkinson’s Disease (PD).

Background

In their 2011 Nature Reviews Drug Discovery paper “A call to reform the taxonomy of human disease” §, Ismail Kola and John Bell formulate an impressive plea for “A co-ordinated effort to incorporate advances in the understanding of the molecular and genomic variations in common diseases, such as hypertension, into their diagnosis and treatment could transform drug development and medicine.”

The two authors emphasise the need for a reclassification of diseases according to mechanisms that contribute to the aetiology of a disease at the molecular (“omics-”) level rather than the current phenotypic approach. They point out that several diseases that appear to be distinct at the clinical phenotype level may actually go back to one shared disease mechanism, or that diseases classified under one concept are in fact phenotypically similar manifestations of different, diverse disease mechanisms.

Kola and Bell underline that the concept of a mechanism-based taxonomy would also address the challenge of subgroup-specific or even individualised medicine, as an in-depth knowledge about the mechanisms underlying a disease inherently provides the basis for strategies to treat that disease in a dedicated, mechanism-specific way.

AETIONOMY is a response to the challenge they laid down and is a knowledge generation approach which can accommodate the specific data types and data structures for a broad variety of indication areas, whilst retaining the capacity to construct disease-specific taxonomies based on the underlying disease mechanisms. It is part of a larger, co-ordinated effort to establish a mechanism-
based taxonomy which ultimately will result in improved diagnostic and therapeutic procedures.

AETIONOMY is one of two projects in the “taxonomy call” of the IMI. The other project, “PRECI-SEADS” aims at generating a mechanism-based taxonomy for inflammatory diseases such as SLE and RA.

Vision Statement for AETIONOMY

The vision of the IMI project AETIONOMY is To generate a “mechanism-based taxonomy” of Alzheimer’s Disease and Parkinson’s Disease.

Currently, the established disease classification systems such as ICD (International Classification of Diseases) make use of phenotypes measured clinically or using standard laboratory and imaging techniques to establish major types and subtypes of diseases. In contrast to these established disease classification systems, a “mechanism-based taxonomy” is based upon the knowledge about the biological pathways involved in the aetiology of a disease to guide the classification of disease classes and subclasses. A specific challenge we face in the course of the AETIONOMY project lies in the fact that for most neurodegenerative diseases, the dysfunctional biological pathways underlying the disease are not known. AETIONOMY will therefore have to first define new ways of identifying the underlying disease mechanisms before organising these and proposing a rational disease taxonomy for Alzheimer’s and Parkinson’s disease. Moreover, we will validate the mechanism-based taxonomy, at least partially, in the course of a prospective clinical study.

Concept

The AETIONOMY concept is based on an inversion of the common research process. In the traditional research process, independent researchers generate a hypothesis and then design an experiment to test or validate their hypothesis. Hypothesis-generation is often an individual process in this workflow and is built on the individual “belief” in a certain paradigm. This determines the experimental design and the entire scientific data generation and analysis workflow. If there is a clear “disease model” underlying the hypothesis, it usually only exists in the brain of the individual scientist conducting the research. As a result, a systematic validation of the model underlying the hypothesis is nearly impossible.

Conventional scientific knowledge discovery workflow

In contrast to the approach sketched above, AETIONOMY follows a model-driven approach that puts the generation and articulation of the disease model at the centre of the project. We start first with a co-ordinated and comprehensive approach to the identification, re-annotation, curation and semantic harmonisation of all data available to the public and inside of the consortium. Over the enti-
All the data and knowledge relevant for the generation of the mechanism-based taxonomy will be organised in a dedicated data cube. In parallel to the semantic harmonisation and curation work, dedicated disease models based on different modelling strategies will be generated. The disease models will capture and represent knowledge about causal and correlational relationships in AD and PD (based on the biological expression language, OpenBEL). In an independent modelling approach, features (indices) derived from -omics data, imaging data and other knowledge sources including expert knowledge will be assembled in a “pathophysiology graph” based on the ApiNATOMY framework developed in the Virtual Physiological Human (VPH) project.

Model-driven mining approaches will be used to identify “disease mechanisms”, which in essence are subgraphs representing entire chains of causal or correlative relationships. These sub-graphs again contain “measurables”, which are quantifiable molecular or cellular readouts or indices derived from brain image analysis. Existing or new -omics data as well as data from epidemiological studies or clinical trials will be tested for their concordance with essential features of the models; in particular we will test, to what extent independent data sets provide supportive evidence for newly identified candidate disease mechanisms.

The “mechanism-based taxonomy” will be generated by representing “chains of causation” or entire pathophysiology graphs in a semantically meaningful way; the consortium is experienced in the generation of disease-specific ontologies as exemplified by the recently published Alzheimer Disease Ontology (ADO), which appeared in “Alzheimer’s & Dementia” in 2013 (Malhotra et al.).

AETIONOMY will not have the resources to validate the entire set of mechanisms linked to the taxonomy in the given time and within the budgetary limits. We have therefore carefully designed a validation strategy that will guide the final prospective clinical study meant to demonstrate the validity of the aetiology-based taxonomy. The consortium brings together four leading clinical centres with proven expertise in conducting these types of studies; addressing effectively the need to validate the mechanism-based taxonomies for both PD and AD. The taxonomy and pathophysiology maps will be publicly available and will allow other groups to also validate parts of the classification.

A dedicated AETIONOMY work package on ethical and legal aspects has a clear European perspective and scope and is set up in a way that reaches out beyond the AETIONOMY project and actively seeks the co-ordination with other projects funded under the same theme.
AETIONOMY makes extensive use of developments made in and funded by other IMI or EU projects. In the area of knowledge and data management, we build largely on the work done in OpenPHACTS [www.openphacts.org]; and we will re-use the entire data curation pipeline developed in the course of eTRIKS [http://www.etriks.org]. Modelling and mining principles learned from VPH projects will guide our work [http://www.apinatomy.org], leveraging on our involvement in other large EU research initiatives. Finally, the substantial effort made on the side of clinical data integration in the course of EMIF, the European Medical Information Framework [http://www.emif.eu], will be accessible to AETIONOMY.

Implementation

AETIONOMY is an ambitious project that intends to deliver its promises. Besides facing a significant scientific challenge, the AETIONOMY project has to integrate efforts from heterogeneous groups and stakeholders: biomedical informatics experts will work together with experts in clinical neurology; industrial researchers join forces with academic scientists. There are 20 partners from 11 different countries directly involved in the project.

To enable efficient collaboration and to ensure that the overall concept for AETIONOMY is turned into tangible outcomes, an efficient management and work package structure has been generated.

- **WP1** deals with all management and communication aspects of the project
- **WP2** brings together all partners involved in the design, implementation and population of the AETIONOMY Knowledge Base
- **WP3** deals with all data modelling and mining activities
- **WP4** focuses on ethical and legal aspects and involves the partners representing patient interest groups
- **WP5** is the “clinical work package” where all the taxonomy validation work will be organised.

A series of well-defined deliverables and milestones ensures that all partners in the AETIONOMY project will work closely together following the work plan and deliver according to the promise by 2018.

AETIONOMY will have 5 years to achieve its ambitious goal to generate a mechanism-based taxonomy for Alzheimer’s Disease and Parkinson’s Disease. Approximately 45% of the budget will be spent on data curation, modelling and mining (WP 2 and 3); 45% of the budget will be spent on the clinical validation of the taxonomy.

The remaining 10% of the budget will be distributed amongst the ethical / legal work package (WP4) and the management & communication work package (WP1).

A series of well-defined deliverables and milestones ensures that all partners in the AETIONOMY project will work closely together following the work plan and deliver according to the promise by 2018.

AETIONOMY Partners

- **UCB Pharma**, Belgium
- **Fraunhofer-Gesellschaft e.V.**, Germany
- **Erasmus Medical Center**, The Netherlands
- **Universitätsklinikum Bonn**, Germany
- **ICM - Institut du Cerveau et de la Moelle épinière**, France
- **Consorci Institut D’Investigacions Biomèdiques August Pi i Sunyer**, Spain
- **Leibniz Universität Hannover**, Germany
- **University College London**, United Kingdom
- **NeuroRad**, Romania
- **Pharmacoidea Ltd.**, Hungary
- **University of Luxembourg**, Luxembourg
- **Alzheimer Europe**, Luxembourg
- **European Brain Council**, Belgium (official registration of partnership under way)
- **European Parkinson’s Disease Association**, United Kingdom (partnership planned, registration under way)
- **Karolinska Institutet**, Sweden
- **Novartis**, Switzerland
- **Sanofi**, France
- **Boehringer Ingelheim**, Germany
Virtual human modelling, binaural sound immersion and enhanced living space approaches added to the more classical areas of dementia research of neuropathology, neuropsychological profiling and quality of life interventions at the “Dementia Research Forum” held on 10 January 2014 at the Sheffield Institute for Translational Neuroscience (SITraN). More than 80 dementia research and care professionals took part in an afternoon of multidisciplinary talks and networking organised in partnership with the Academic Directorate of Neuroscience at the Sheffield Teaching Hospitals NHS Foundation Trust, Clinical Academic Staff from the Department of Neuroscience and researchers from the Institute for in silico Medicine (INSIGNEO) at the University of Sheffield. The event tackled a wide range of topics in dementia research and patient care, and was widely praised by participants for creating an opportunity for interdisciplinary exchange and for showcasing the multidisciplinary nature of the research already being carried out across Sheffield. The event had the scope to promote essential collaborations among researchers involved in different types of dementia research in Sheffield and to build on the synergies between their scientific approaches and expertise to advance dementia research and care to make a real difference to the lives of dementia patients and their families.

Talks were divided into four sessions covering basic science, dementia research, clinical trials, quality of life studies and computer modelling in dementia research. Break-out sessions led by representatives of each subject area enabled participants to discuss the state of the current research and what action is needed to accelerate progress in each field. Insights from these focus groups were summed up for the forum.

Dr. Stephen Wharton, Reader in Neuropathology, SITraN, concluded the neuropathology focus. He stressed the need to strengthen work in biological dementia science in Sheffield, including developing increasing collaboration between research groups, and for basic science research to provide relia-
ble biological markers for early diagnostics which allow distinction between dementia versus “normal” ageing pathologies.

Consultant neurologist Dr. Daniel Blackburn highlighted the “massive demand” for patient assessment due to the increase of patients with benign non-progressive memory disorders presenting to the NHS memory clinics. His focus group identified the current challenge of finding ways to communicate and collaborate with primary care providers to differentiate between patients suffering stress and anxiety related memory disorders and patients with progressive dementia.

Lead of the psychosocial research focus, Professor Gail Mountain, Chair in Health Services Research, ScHARR, stated that “psychosocial research plays a Cinderella role in terms of dementia research funding” and argued that more local initiatives for skills and knowledge transfer are needed to improve patient’s quality of life and psychosocial care.

Finally, Professor Iain Wilkinson from the University of Sheffield’s Academic Radiology Unit urged dementia researchers to come forward to identify and discuss projects that could be solved or benefit from computer modelling and other IT solutions. As an example of such collaboration VPH-DARE@IT researchers presented to the group. Dr. Leandro Beltrachini gave an overview of the VPH-DARE@IT project, Dr. Luigi Di Marco discussed cardiovascular variability accounting for dementia risk factors and Dr. Deirdre McGrath presented Magnetic Resonance Elastography applied to dementia.

Participants welcomed the opportunity to make new contacts and further discuss future collaborations at a following wine reception with music from Nigel Humberstone’s “In the Nursery”. The Dementia Research Forum was part of a series of events intended to foster collaborations and identify areas for interdisciplinary exchange in the Neurosciences.

For information about this event please contact the Academic Directorate of Neuroscience (http://www.sheffieldclinicalresearch.org/clinical-research-activity/sheffield-teaching-hospitals/academic-directorate-of-neuroscience)

For more information on the Virtual Physiological Human Project (VPH-DARE@IT) please visit www.vph-dare.eu.
Deliverables and Milestones completed

**D 1.1** UEF  Clinical evaluation studies and hypotheses design

**D 1.2** UEF  Database inventory, governance, and data access policies

**D 8.1** VTT  Specification of clinical platform – 1st version

**D 5.3** USFD  Literature review on lifestyle and circadian factors

**D 10.1** USFD  Communication strategy

**D 10.2** USFD  First six-monthly progress report

**MS101** USFD  Web site available

**MS 11** UEF  Study and hypotheses design completed

**MS 81** VTT  Specifications ready

**MS 31** STH  Connectivity to first external distributed database of retrospective data

**MS 21** USFD  Basic acquisition protocols standardised; detailed imaging specs consolidated
Upcoming events

• **ECR 2014** - *Vienna, 6th - 10th March 2014*

• **The Dementia Challenge** - *London, 8th April 2014*
  http://www.dementia-challenge.co.uk/event-home

• **ISBI IEEE International Symposium on Biomedical Imaging** - *Beijing, 28th April 2014*
  http://biomedicalimaging.org/2014/

• **WBIR 6th International Conference on Biomedical Image Registration** - *London, 7th - 8th July 2014*
  http://wbir2014.cs.ucl.ac.uk/

• **AAIC** - *Copenhagen, 12th - 17th July 2014*
  https://www.alz.org/aaic/

• **MICCAI 2014** - *Boston, 14th to 18th September 2014*
  http://miccai2014.org/

• **FTD** - *Vancouver, 23th - 25th October 2014*
  http://www.ftdvancouver2014.com

In the next issue...

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VTT Technical Research Centre of Finland
The University of Sheffield Faculty of Medicine

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